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CONTENTS

Volume 15, Number 1, 2026

Editorial

Policy Forum

Review

Original Article

Topic:
Rare Diseases and Orphan Drugs in China: From System Building to Global Engagement

Guest Editors:
Chunlin Jin
Da He

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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Policy Forum

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The imperative for national legislation on rare diseases in China: A policy review and call to action

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SUMMARY: Rare diseases represent a significant public health challenge in China, affecting an estimated 20 million individuals. Despite incremental policy improvements over the past decade, including the publication of two National Rare Disease Lists, an increasing number of available treatments, and the inclusion of some therapies in the Nationally Reimbursed Drug List (NRDL), patients continue to face systemic challenges in diagnosis, treatment access, and sustainable protection. That said, China has very limited rare disease research & development (R&D) and industrial development, so the market potential is far from being tapped. This policy review argues that the lack of a national legal definition for rare diseases and orphan drugs, an unsustainable payment mechanism for high-value innovative therapies, and insufficient incentives for domestic research and development have collectively hindered the creation of a sustainable rare disease ecosystem. Drawing on an analysis of patient registry data, policy documents, and proposals from China's National People's Congress (NPC) sessions, we demonstrate a growing societal consensus on the need for comprehensive national legislation on rare diseases, which is not only a moral imperative to safeguard the rights of patients but also a strategic necessity for a national population strategy and biomedical industrial development. We consider systemic rare disease legislation in China to be imperative, and now is the optimal time to promote rare disease legislation in China. We propose nine key initiatives, including establishment of a working committee on national legislation, creating a standardized definition of rare diseases and orphan drugs, creating a dedicated national rare disease fund, and robust R&D incentives.

Keywords: rare diseases, health policy, legislation, China, orphan drug, biomedical industry

1. Introduction

Rare diseases collectively impact approximately 20 million people in China, creating substantial challenges for patients, families, and the healthcare system within a rapidly changing healthcare landscape (*1*). The Chinese Government has acknowledged this challenge, enacting pivotal measures since 2018 such as the creation of the two installments of National Rare Disease Lists, which consist of 207 diseases to date (*2-4*), the establishment of a national diagnosis and treatment collaboration network, facilitation of the market entry for over 100 rare disease drugs, and around two-thirds of in-market rare disease drugs have been included in the Nationally Reimbursed Drug List (NRDL).

However, these well-intentioned efforts, often siloed within individual ministries or regional governments, lack the cohesion and authority of overarching legislation. This policy fragmentation has resulted in persistent gaps in diagnosis and care, treatment accessibility, social inclusion, and a stagnant domestic innovation landscape. This article reviews the limitations of the current policy framework, underscores the strategic opportunity the rare disease sector presents, and makes the case that comprehensive national legislation is the essential next step to transform the lives of millions and secure China's position as a leader in biomedical innovation.

2. The persistent challenges for patients

Despite significant advances over the past years, rare disease patients in China still confront persistent and multifaceted challenges to their survival and well-being.

2.1. Diagnostic odyssey

Of the over 7,000 known rare diseases globally, only 207 are listed in China's Rare Disease List (*2-4*). The path to a definitive diagnosis could be notoriously long and fraught with errors. A cross-sectional analysis

of the 2018 national rare disease survey in China, involving 1,010 adult patients with rare diseases, indicated that the average diagnostic odyssey was 4.30 years, with a misdiagnosis rate of 72.97% (*5*). This is compounded by a critical shortage of medical expertise; an article published in 2021 indicates that only 5.3% of physicians reported being "moderately or well aware" of rare diseases while the majority suspected rare diseases in patients fewer than 3 times (*6*).

2.2. Therapeutic desert – poor treatment availability

Although therapies for an increasing number of rare diseases have been approved internationally, fewer than 10% of the 7,000+ known rare diseases have specific treatments worldwide, and access in China remains limited (Table 1). For China's First Rare Disease List, which includes 121 conditions, 116 drugs approved by the U.S. Food and Drug Administration (FDA), European Medicines Agency (EMA), or China's National Medical Products Administration (NMPA) are available on the Chinese market, effectively addressing 53 distinct rare diseases (*7*). Among the 86 conditions on China's Second List of Rare Diseases, only 37 (43%) have drugs with approved indications domestically, and 10 diseases have therapies approved by the FDA or EMA that are used off-label in China (*8*). Together, these figures highlight the persistent challenges in providing timely and equitable access to rare disease treatments across the country.

2.3. Limited treatment accessibility – lack of a systematic payment solution for innovative therapies

China has established a national social insurance system, Basic Medical Insurance (BMI), which covers approximately 98% of the population. The NRDL plays a critical role in determining which therapies are eligible for reimbursement under BMI. However, treatment solutions with annual costs exceeding RMB ¥500,000 (USD $70,000) for negotiation or RMB ¥300,000 (USD $42,000) for reimbursement are typically excluded from NRDL coverage (*9*). Although the inclusion of rare disease therapies in the NRDL has increased in recent years, reflecting growing but still selective efforts to cover the reimbursement of these drugs, significant gaps in access remain (*10*). A recent analysis found that 34 approved rare disease drugs are not reimbursed by health insurance (*11*), including many high-cost, specialized treatments that

Table 1. 33 Rare diseases for which there are "drugs approved abroad but not yet approved in China"*

No.	Disease	FDA approval	EMA approval
1	Hereditary epidermolysis bullosa	√	√
2	Hypophosphatasia	√	√
3	Laron syndrome	√	√
4	Leber hereditary optic neuropathy	×	√
5	Lysosomal acid lipase deficiency	√	√
6	Porphyria	√	√
7	Very long-chain acyl-CoA dehydrogenase deficiency	√	×
8	Achondroplasia	√	√
9	Adult-onset Still's disease	√	√
10	Alpha-1 antitrypsin deficiency	√	×
11	Bardet-Biedl syndrome	√	√
12	Renal clear cell sarcoma	√	×
13	Cold agglutinin disease	√	√
14	Merkel cell carcinoma	√	√
15	Cystinosis	√	√
16	Eosinophilic gastroenteritis	√	√
17	Epithelioid sarcoma	√	×
18	Fibrodysplasia ossificans progressiva	√	×
19	Progeria	√	√
20	Leber congenital amaurosis	√	√
21	Limbal stem cell deficiency	×	√
22	Metachromatic leukodystrophy	√	√
23	Neuronal ceroid lipofuscinosis	√	√
24	Osteosarcoma	×	√
25	Pheochromocytoma	√	×
26	PIK3CA-related overgrowth spectrum	√	×
27	Primary insulin-like growth factor-1 deficiency	√	√
28	Recurrent pericarditis	√	×
29	Rett syndrome	√	×
30	Tenosynovial giant cell tumor / pigmented villonodular synovitis	√	×
31	Thrombotic thrombocytopenic purpura	√	√
32	Tumor necrosis factor receptor-associated periodic syndrome	√	×
33	Von Hippel-Lindau syndrome	√	×

*Data originally from *Reference 14*, and updated by the authors of this article.

may be the only effective options for certain conditions (Table 2). These gaps exacerbate the financial burden on patients, who often rely heavily on family support. A 2021 Chinese patient survey reported that only 4.7% of rare disease patients held full-time employment, while 43.8% were children or otherwise dependent, highlighting the ongoing accessibility challenges faced by patients even when therapies are approved and available on the Chinese market (*12*).

2.4. Socioeconomic marginalization and intergenerational impact

The consequences of inadequate care extend far beyond health. From 2014 to September 2024, 26,304 rare disease patients have registered with the Chinese Organization for Rare Disorders (CORD). An analysis of 5,810 patients in the registry in 2019 revealed that the lack of timely treatment led to high rates of disability; over half of registered patients reported varying degrees of physical disabilities, indicating that disability is a major burden among this population (*13,14*). This, combined with pervasive stigma and a lack of support systems, creates a vicious cycle of illness-induced poverty, illness-induced unemployment, and recurring poverty due to illness, resulting in significant unemployment among patients. Without effective intervention, nearly one-third of children with rare diseases die before the age of five, a tragic outcome for the affected. The economic impact could be devastating. Data from the CORD registry also revealed that over 80% of families have an annual income below USD 7,000 (RMB 50,000), yet annual treatment costs consume 80% or more of their household income (*13,14*). This far exceeds the World Health Organization's threshold for catastrophic health expenditure (40%) (*15*), forcing families to make the difficult choice between treatment and basic sustenance.

This triad of challenges — inaccessible diagnosis, unaffordable treatment, and debilitating socioeconomic marginalization — underscore the urgent need for a systematic solution through national legislation.

3. The unrealized market potential of the rare disease sector

Evaluate Pharma projects that orphan drugs will make up a fifth of the forecasted USD 1.6 trillion in worldwide prescription drug sales by 2030 (*16*). Over half of new drugs approved in the US and EU are now designated as orphan drugs, driving a significant portion of biomedical innovation. Many blockbuster drugs began with a rare disease indication before expanding into broader markets. China possesses unique advantages to capitalize on this trend, with the world's largest patient population for clinical research, a rapidly advancing biotech infrastructure, and sufficient resources to make a significant impact. Many rare diseases are ideal targets for cutting-edge modalities like gene therapy, offering China a chance to leapfrog as the leader for the next generation of medicines. Moreover, breakthroughs in rare diseases frequently provide insights and therapeutic platforms applicable to common diseases, helping to propel the entire biomedical sector. An analysis from Boston Consulting Group (BCG) projects that, drawing from

Table 2. 16 Rare diseases for which "drugs are available but not reimbursed" and the "cost of treatment"*

Disease	Estimated Prevalent Patient #	Treatment	Annual cost of treatment (RMB 10,000)	
			Adult	Pediatric
Pompe disease	35,000	Alglucosidase alfa for injection	175	98
Mucopolysaccharidosis I	18,900	Laronidase solution for injection	311	139
Mucopolysaccharidosis II	27,440	Idursulfase injection	333	111
Mucopolysaccharidosis IVa	4,667	Elosulfase alfa injection	234 (withdrawn)	110 (withdrawn)
X-linked hypophosphatemia	70,000	Burosumab injection	156	106
Primary hemophagocytic lymphohistiocytosis (HLH)	28,000	Emapalumab injection	256	106
Primary light chain Amyloidosis	14,000	Daratumumab injection (subcutaneous)	45.7	—
Neuroblastoma	14,000	Dinutuximab beta injection	—	—
Neuroblastoma	14,000	Naxitamab injection	—	—
Alagille syndrome	46,667	Odevixibat oral solution	—	—
Transthyretin amyloid polyneuropathy (ATTR-PN)	7,600	Tafamidis meglumine soft capsule	47	—
Neurotrophic keratitis	700,000	Cenegermin eye drops	14 (withdrawn)	—
Neonatal hypoxic respiratory failure with pulmonary hypertension	—	Inhaled nitric oxide	—	155
Argininemia	4,000	Glycerol phenylbutyrate oral solution	60	36
Citrullinemia type I	6,363	Glycerol phenylbutyrate oral solution	60	36
Ornithine transcarbamylase deficiency	25,000	Glycerol phenylbutyrate oral solution	60	36
HHH syndrome	4,000	Glycerol phenylbutyrate oral solution	60	36

*Data originally from *Reference 14 and 22*, and updated by the authors of this article. #Numerical values here are based on average weights per disease area.

China's proportion of the global oncology market (approximately 5% to 7%), China's rare disease drug market is expected to reach a scale of 60–90 billion RMB by 2030 (*17*).

However, the huge market potential has not yet been tapped in China. Lacking legislation and policy support, few researchers have incentives to conduct research and development in the area of rare diseases, and few companies are willing to develop or market rare disease drugs. According to an analysis by the CORD, only 42% of the marketed 252 rare disease drugs are domestic products, and more than 80% of these domestic products are generics or biosimilars.

4. Root cause: Lack of systematic policy support

The root cause behind the persistent challenges for patients and the untapped market potential of the rare disease sector is the same: lack of systematic policymaking. China's existing responses can be characterized as decentralized, department-specific initiatives that lack synergy and long-term stability.

4.1. Lack of rare disease definition & listing dilemma

Since 2018, China's National Health Commission (NHC) has released two installments of Rare Disease Lists, which is a landmark step toward defining rare diseases in the country. However, as efforts in the rare disease field continue to progress, we also see that the limitations of this list-based approach have become increasingly apparent. First, the two installments include only 207 conditions — accounting for just 3% of the approximately 7,000 rare diseases identified worldwide. Secondly, the Rare Disease List remains a reactive and clinically-oriented policy tool that focuses primarily on conditions that are "diagnosable and treatable" (*18*). This creates a disincentive for research and development of new therapies for many rare diseases. Last but not least, the updating cycle has been slow and unpredictable. The second installment was published 5 years after the first installment. The Rare Disease List's exclusion criteria leave thousands of rare conditions unrecognized and thus ineligible for supportive policies.

4.2. Unsustainable payment models

The absence of a patient-centric and dedicated funding mechanism has created huge barriers to not only patient access but also industry development. China's BMI is primarily budget control-driven, and it is ill-equipped to finance innovative or ultra-high-cost therapies. The price cap of NRDL (an annual cost of no more than 300,000 RMB) has excluded most life-saving rare disease drugs, leaving patients in a predicament of extremely poor access (*10*). Moreover, the multi-tier payment system is based on the BMI and NRDL, if a therapy is not covered by NRDL, it is impractical for it to be funded by critical illness insurance, medical assistance, or commercial insurance within the existing institutional framework.

4.3. Insufficient research & development (R&D) incentives

Critical policies like the definition of rare disease and rare disease drugs, market exclusivity periods, and enhanced data protection for orphan drugs, though proposed in drafts, have not been formally enacted in China (*19*). This regulatory uncertainty fails to provide the long-term predictability needed for companies to commit to high-risk, high-investment rare disease R&D (*20,21*).

4.4. Uncoordinated ministries & central-local dynamics

On one hand, different ministries operate with conflicting priorities, hampering the creation of synergy. The NHC emphasizes "diagnosable and treatable" with the Rare Disease List, the National Healthcare Security Administration (NHSA) operates under a constrained budget, wary of formulary expansion that would increase financial pressure, while the National Medical Products Administration (NMPA) encourages broader "rare disease" drug development far beyond the Rare Disease List. This misalignment could stand in the way of cohesive policy development. On the other hand, the division of responsibilities between the central and local governments in rare disease development remains vague (*22*). Provincial-level rare disease funds in Zhejiang and Jiangsu used to be "best practices" in China but have now been suspended due to a lack of central guidance and support.

5. A consensus for legislative action

After more than 10 years of exploratory efforts, China needs to shift from fragmented actions to systematic legislation for rare diseases. First, China has amassed decades of experience in the rare disease field, with various government departments and local authorities having developed relatively mature policy-making expertise. Second, rare diseases have become a high-profile topic for proposals at the annual National People's Congress (NPC) and Chinese People's Political Consultative Conference (CPPCC) sessions, and a preliminary consensus has emerged across society regarding the necessity and urgency of legislation. Last but not least, drawing from the experiences of other regions globally, China now possesses the socioeconomic foundation required for enacting rare disease legislation. Most countries enacted rare disease legislation when their per capita GDP approached or

exceeded $10,000 — a threshold China had already reached by 2022. Moreover, several countries with lower per capita incomes than China have also successfully enacted rare disease legislation, such as Colombia and the Philippines.

Analysis shows that the number of publicly announced motions and proposals calling for rare disease legislation grew more than tenfold from 2019 to 2024 (*23-31*). The proponents of these proposals have expanded from primarily clinical experts to biopharmaceutical industry leaders, policy researchers, economists, and representatives from various social sectors (Figure 1). The content of these proposals has evolved from general calls for awareness to actionable policy blueprints. This multi-sectoral consensus underscores that rare disease legislation is now widely recognized not as an isolated healthcare issue, but as a critical national priority intertwined with China's social stability, economic development, and strategic positioning in the global biopharmaceutical industry. The collective voice from the NPC and CPPCC provides a powerful mandate and a clear roadmap for policymakers to initiate the legislative process.

6. Conclusion and recommendations: A framework for national legislation

National legislation for rare diseases can help harmonize disparate policies, guarantee sustainable funding, and send an unambiguous signal for innovation to the global community. Based on our extensive analyses and benchmarking, we propose a legislative framework built upon nine pillars:

i) Systemic rare disease legislation in China is imperative: Systemic legislation is the foundation for safeguarding the various social rights of rare disease patients and serves as a driving force for promoting quality population growth in China. At the same time, using rare diseases as an entry point can stimulate innovation in R&D, production, and services related to the rare disease industry, thereby advancing the development of new quality productive forces in biomedicine and fostering societal progress.

ii) Now is the optimal time to promote rare disease legislation in China: Rare disease legislation began globally in the 1980s, with most regions enacting it after their per capita GDP exceeded $10,000. China's level of economic development and social system have matured, fully meeting the conditions for rare disease legislation. Against the backdrop of intensifying geopolitical tensions and widespread critical reflection on Western systems due to global political and economic instability, China should seize the opportunity to demonstrate its soft power and value orientation by enacting legislation for minority groups, tailored to its national conditions.

iii) Nominate a national rare disease legislation working committee: A high-level task force or committee should be established at the central level to coordinate and promote rare disease legislation, break down inter-departmental barriers, pool collective wisdom, and develop a timeline and roadmap for the legislative process.

iv) Clarify the legal definitions of rare diseases and orphan drugs: Defining rare diseases and orphan drugs is the cornerstone of legislative efforts. The current mechanism for updating the Rare Disease List can no longer meet industry development needs. The definitions of rare diseases and orphan drugs should be

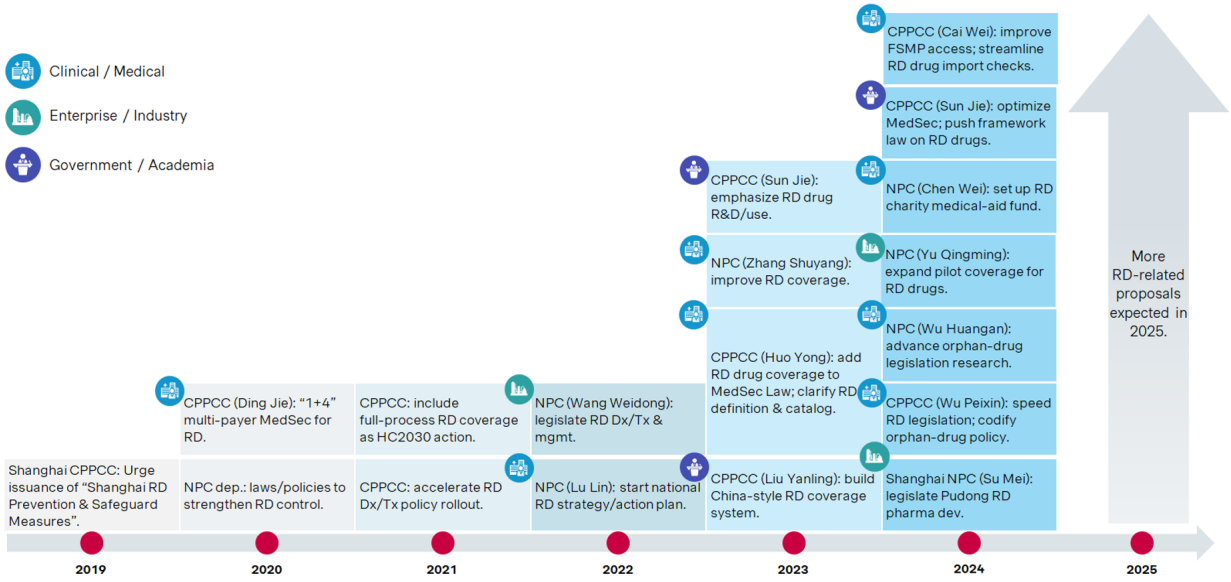

Figure 1. Trends in proposed legislation dealing with rare diseases in China. *Data Source: Ref. (23-31). Abbreviations*: RD, rare disease; Dx, diagnosis; Tx, treatment; R&D, research & development; NPC, National People's Congress; CPPCC, Chinese People's Political Consultative Conference; MedSec, medical security; HC2030, Healthy China 2030; FSMP, foods for special medical purposes.

swiftly discussed and confirmed under the leadership of the legislative task force, providing a legal basis for safeguarding the rights of rare disease patients and promoting industrial growth.

v) Establish a national special rare disease security fund: A national fund should be established specifically for rare diseases as soon as possible, integrating resources from various sectors (*e.g.*, the Ministry of Finance, Ministry of Civil Affairs, National Health Commission, and National Healthcare Security Administration) for fundraising and operation. In the meantime, local initiatives for special rare disease funds or other innovative payment models should be encouraged.

vi) Devise incentive policies for rare disease R&D and industrial development: Rare diseases sit at the pinnacle of medicine and addressing them involves tackling high-precision medical technologies and seizing the commanding heights of medical innovation. Rare disease legislation should explicitly outline incentives for R&D and industrial development, promoting the drafting and enactment of laws and regulations in key areas such as patent compensation, data protection laws, market exclusivity periods, and R&D tax benefits.

vii) Strengthen the national network for rare disease diagnosis, treatment, and rehabilitation: In recent years, China's national collaborative network for rare disease diagnosis and treatment has become an exemplary model globally. Legislation should further encourage the construction of a medical system for rare disease diagnosis, treatment, and rehabilitation, enhancing capabilities for early screening, diagnosis, and treatment. This will ensure rapid and accurate diagnosis of rare diseases and guarantee the accessibility and effectiveness of treatments.

viii) Fully safeguard the social rights of rare disease patients: Rare disease patients and families are deeply concerned not only with medical treatment but also with needs related to education, employment, and social integration. In formulating relevant regulations, the uniqueness of rare disease patients should be fully considered, ensuring their rights in healthcare, education, employment, movement, and social participation. These efforts will undoubtedly contribute to the further development of China's modern cities.

ix) Seize every opportunity to promote rare disease legislation at all levels: All government departments concerned with rare diseases should explore the formulation or revision of departmental regulations based on their functions. Regions with socio-economic conditions conducive to the drafting of legislation should examine their needs and capitalize on their resources to consider laws and regulations that protect the rights of rare disease patients and promote industrial development. When every department and region recognizes and responds to the needs of rare disease patients, taking actionable steps, these cumulative efforts will ultimately converge into a wave of progress for the era.

The moment to act is now. By enacting thoughtful and comprehensive rare disease legislation, China can secure the right to health for millions of its citizens, foster a world-leading biopharmaceutical industry, and demonstrate its commitment to building a truly equitable, innovative, and modern society.

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Progress in the research and pharmacoeconomic evaluation of drugs and devices for rare diseases in China

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SUMMARY: The development, importation, and reimbursement of drugs and medical devices for rare diseases have become critical issues within China's healthcare system. Since 2018, China has issued two national Rare Disease Lists, covering 207 diseases. As of December 2025, 223 drugs for rare diseases have been marketed domestically, with 136 (61.0%) included in the national list for reimbursement by basic medical insurance scheme. Advances have also been made in diagnostic technologies and treatment equipment. This article also examines the issues with and factors influencing the pharmacoeconomic evaluation of rare disease therapies. Additionally, over 100 registered patient organizations contribute substantially to care, education, research, and advocacy. China has piloted multi-level healthcare security system, including national and local healthcare security systems. The introduction of a list of innovative drugs covered by commercial insurance in 2025 further supplements this system. These measures have collectively expanded reimbursement coverage. Despite progress in drug development, insurance coverage, and evaluation of drugs in terms of health economics, continued efforts are needed to enhance treatment accessibility and equity. Key measures include putting forward rare disease legislation, promoting research on health technology assessment, improving health utility measurement, encouraging domestic orphan drug development, and strengthening international collaboration. China's experience offers valuable insights for global rare disease prevention and treatment initiatives.

Keywords: rare diseases, orphan drugs, rare disease medical devices, pharmacoeconomic evaluation, pharmaceutical policy

1. Introduction

Rare diseases in China are officially defined as conditions meeting any of the following criteria: an incidence of less than 1 in 10,000 among newborns, a prevalence below 1 in 10,000 in the general population, or a total patient population under 140,000 (*1*). Based on these definitions, the estimated number of rare disease patients in China is approximately 20 million. This definition is more stringent than that of the European Union (EU) and the United Kingdom (UK), which set the prevalence threshold at 5 in 10,000, and it suggests a lower absolute patient count than in the United States (US), where the benchmark is 200,000 individuals (*2*).

In 2018, China's National Health Commission, along with four other ministries, jointly issued the first national Rare Disease List, listing 121 conditions (*3*). A second installment was published in 2024, adding 86 more rare diseases, bringing the total to 207 (*4*). Additionally, regional initiatives such as the Shanghai Rare Disease List (2025 edition) have expanded the scope to 278 conditions, offering supplementary guidance for clinical practice and insurance coverage (*5*).

Most rare diseases are characterized by high rates of disability and mortality. The drafting of rare disease lists plays a critical role in guiding public health, regulatory, and insurance authorities in prioritizing prevention and treatment efforts. It also facilitates the regulatory review and approval of orphan drugs and stimulates pharmaceutical innovation. The Center for Drug Evaluation (CDE) under the National Medical Products Administration (NMPA) has established a priority review pathway, through which 15 rare disease drugs were approved for marketing in 2023 (*6*). Moreover, the CDE continues to publish lists of urgently needed imported drugs, allowing certain rare disease therapies to bypass Phase III clinical trials and proceed directly to market authorization (*7*).

The development, importation, and reimbursement of drugs and medical devices for rare diseases have emerged as key issues within China's evolving healthcare system. This paper aims to examine the progress made in

rare disease drug and device research, analyze the current landscape of pharmacoeconomic evaluation, and explore the role of patient organizations and policy innovation, with particular attention to the development of a multi-level healthcare security system, in improving access and equity for rare disease patients in China (Figure 1).

2. Progress in the development of rare disease drugs in China

China has made notable strides in the research and development (R&D) of rare disease drugs. According to publicly available information (*8,9*), as of December 2025, a total of 223 rare disease drugs had been approved for marketing in mainland China. While treatments exist, the lack of insurance coverage remains a barrier to access. Over two-thirds of these drugs are imported, with limited domestic innovation, resulting in unstable supply and high prices.

In 2025, China approved its first domestically developed gene therapy product — Dalnacogene Ponparvovec Injection (Chinese brand name: Xinjuning) — for moderate to severe hemophilia B. Developed by Belief Biomed Inc, this Class I innovative drug fills a critical gap in China's gene therapy landscape (*10*). Hemophilia B affects approximately 20,000 patients in China (*11*). The therapy uses a hepatotropic recombinant adeno-associated virus (rAAV) vector to enable long-term expression in liver cells. Initial clinical trials with 10 patients involving a median follow-up of 58 weeks indicated that average FIX activity reached 36.9 IU/dL and there were no Grade 3–4 adverse events (*12*). Long-term follow-up data from 26 patients, presented at the 66th American Society of Hematology (ASH) meeting, showed an annual bleeding rate (ABR) of 0.6 and average FIX activity of 55 IU/dL, with 80.8% of patients experiencing no bleeding episodes post-treatment (*13*). In 2023, Belief Biomed Inc. entered a strategic partnership with Takeda China, enabling more patients to receive this therapy (*14*).

As of 2025, Chinese companies have launched 52 gene therapy R&D projects targeting 28 rare

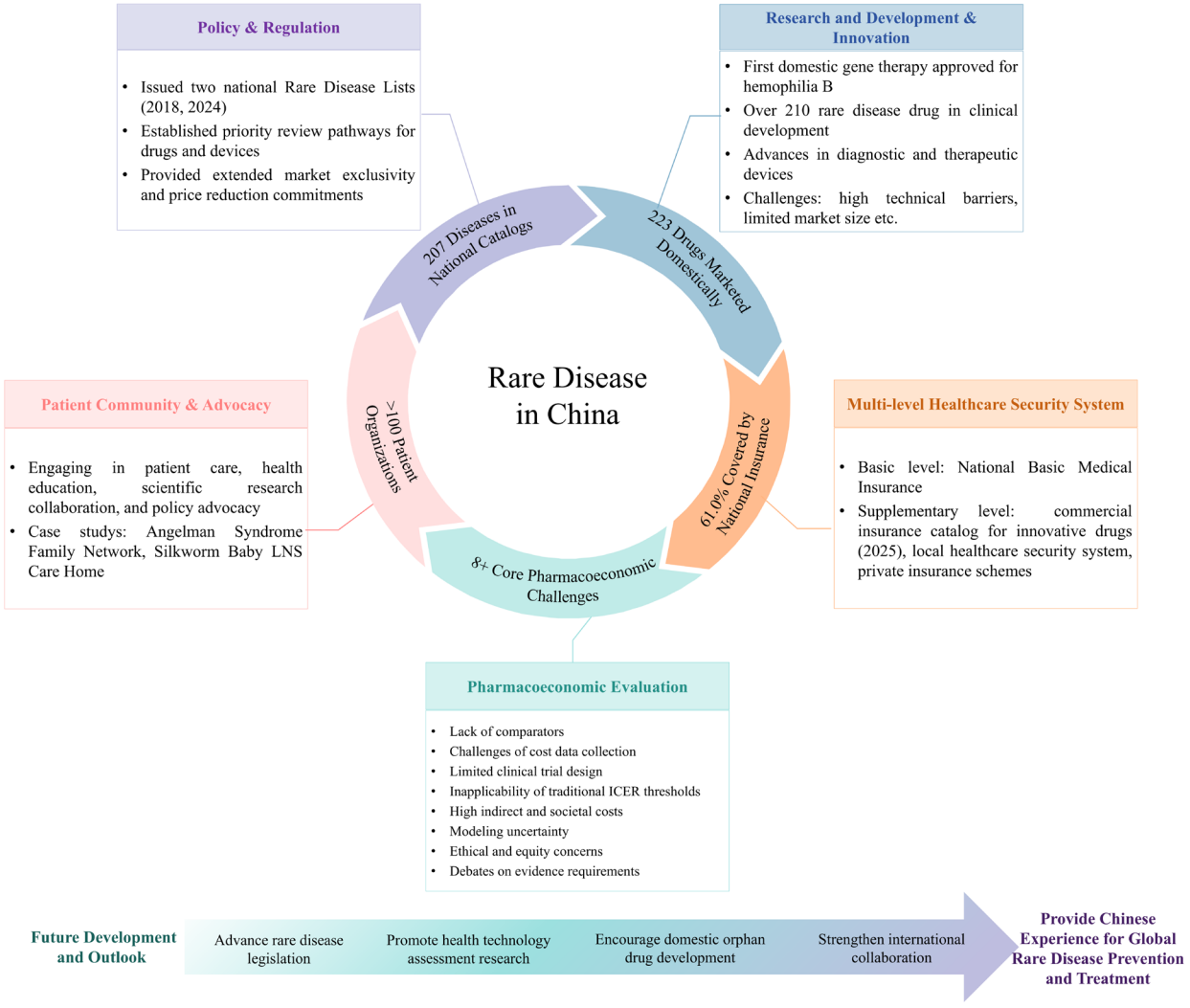

Figure 1. China's rare disease prevention and treatment system. ICER, incremental cost- effectiveness ratio; LNS, Lesch-Nyhan syndrome.

diseases, with five therapies in Phase III trials (*15*). Approximately 210 rare disease drugs are currently in clinical development (*9*). Overall, China's rare disease drug research is entering a phase of rapid expansion.

Generic drug policies have also been introduced, including priority review, extended market exclusivity, and price reduction commitments. For instance, the annual cost of velaglucerase beta for Gaucher disease was reduced to 50% of the imported drug price (*16*). Given the higher R&D costs of orphan drugs compared to common disease treatments, special policy support is essential — such as accelerated approval, tax incentives, and extended exclusivity periods (*e.g.*, 10 years in the EU, 7 years in the US).

3. Progress in the development of rare disease medical devices in China

China has provided substantial policy support for the R&D of medical devices targeting rare diseases. The release of the first national Rare Disease List in 2018 explicitly outlined directions for device innovation in this field (*17*). The National Medical Products Administration (NMPA) has encouraged the registration of innovative devices, with some rare disease-related products granted access to expedited approval pathways.

3.1. Diagnostic technologies

On the diagnostic front, China has launched a nationwide newborn genetic screening initiative using a combined approach of tandem mass spectrometry and next-generation sequencing (NGS), now implemented across 29 provinces (*18*). The National Health Commission issued the "Guidelines for Equipment Configuration in the Rare Disease Diagnosis and Treatment Network", recommending the deployment of high-throughput sequencers, mass spectrometers, and neuroimaging navigation systems. Provinces and municipality such as Shanghai, Zhejiang, and Jiangsu have begun including certain in vitro diagnostic reagents for rare diseases in their medical insurance reimbursement schemes.

3.2. Therapeutic devices

In terms of treatment technologies, deep brain stimulation systems have been used to treat primary dystonia. High-quality evidence from long-term follow-up studies has demonstrated that deep brain stimulation systems provides substantial and sustained improvements in motor function and quality of life (*19*). Exoskeleton robots (*e.g.*, the "Maibu Robot") have entered clinical trials for spinal muscular atrophy (SMA) patients at Peking Union Medical College Hospital. Brain-computer interface technologies, based on neuromorphic chips, have been deployed for precision interventions in pediatric brain tumors, refractory epilepsy, and neurodeveopmental disorders.

3.3. Challenges and barriers

Despite these advances, several challenges persist: *i*) high technical barriers: device development requires interdisciplinary integration and long R&D cycles; *ii*) limited market size: the small patient population leads to a low return on investment, dampening industry enthusiasm; *iii*) regulatory gaps: There is currently no dedicated approval pathway for rare disease devices, necessitating further regulatory refinement; and *iv*) health technology assessment (HTA) limitations: comparator selection is difficult, often relying on composite interventions as the "standard of care". Modeling studies involve a high level of uncertainty and risks of biased parameter assumptions.

4. Current status of the pharmacoeconomic evaluation of rare disease drugs in China

Orphan drugs are characterized by high pricing and increased R&D costs, with premiums largely driven by monopolistic pricing mechanisms. Due to the small patient population size, demand elasticity is limited. The pharmacoeconomic evaluation of rare disease drugs in China faces numerous challenges:

First is the lack of comparators, more than 95% of rare diseases lack effective treatments (*20*). The standard of care (SOC) often consists of palliative therapies or off-label use, resulting in either no comparator or multiple, inconsistent comparators.

Second is the challenge of collecting cost data, cost data are highly heterogeneous and difficult to standardize.

Third is limited clinical trial design. Most trials are single-arm with small sample sizes, leading to uncertainty in treatment effect estimations. Mixed treatment comparisons (MTC) and network meta-analyses are recommended to compensate for the lack of head-to-head trials, along with the use of global patient registries and real-world data (RWD) to construct synthetic control arms.

Fourth is the inapplicability of traditional incremental cost-effectiveness ratio (ICER) thresholds. The commonly used ICER threshold of three times per capita GDP (cost per QALY) is difficult to apply to rare diseases. Strict adherence to this threshold standard may result in inequitable access for rare disease patients.

Fifth are high indirect and societal costs. Rare disease patients often require long-term caregiving, and yet current evaluations lack any consideration of the caregiver burden and productivity loss.

Sixth is modeling uncertainty. Utility values and the probability of disease progression are unavailable for most rare disease. Survival curves often require long-term extrapolation. For gene or cell therapies with

high upfront costs, traditional pay-as-you-go insurance models are insufficient, necessitating innovative payment mechanisms.

Seventh are ethical and equity concerns. The high cost of orphan drugs raises ethical questions. Allocating limited resources to rare diseases may be perceived as unfair to patients with more common conditions.

Finally, there are debates on evidence requirements. There have been proposals to exempt orphan drugs from traditional economic evidence requirements, shifting the focus toward budget impact analysis (*21*).

To address these complexities, value assessment of orphan drugs should adopt a multi-criteria decision analysis (MCDA) framework, incorporating non-economic dimensions such as disease severity, unmet medical need, innovation level, and equity considerations. Manufacturers often seek to expand indications to maximize commercial value.

5. The role of patient organizations in orphan drug research

Over the past decade, China has established multiple rare disease advocacy organizations, including the China Organization for Rare Diseases (CORD), the China Alliance for Rare Diseases (CHARD), the Illness Challenge Foundation (ChinaICF), and the Shanghai Foundation for Rare Diseases. According to CORD statistic data, there are currently over 100 officially registered rare disease patient organizations nationwide (*22*). These groups play a vital role in patient care, health education, scientific research collaboration, and policy advocacy.

The Golden Snail Award is a grassroots honor in China's rare disease community, established by CORD to recognize individuals, teams, patient organizations, and research institutions that have made outstanding contributions to the field. The following two case studies are from the "2025 Golden Snail Award".

5.1. Case Study 1: Angelman Syndrome Family Network

Founded in 2011, this organization supports 1,522 families affected by Angelman syndrome, a condition listed in China's first national Rare Disease List. In collaboration with Roche Inc, the group participated in a National Natural Science Foundation project and conducted extensive outreach and education. It collected genotype data from 150 patients and conducted natural history and survival studies on over 500 cases. The organization helped establish a dedicated clinic at Fudan University Children's Hospital and proposed to establish "Children's Brain Health Centers" at a certain tier of care. The Network's 25-member management team includes physicians, rehabilitation specialists, and patient parents. In 2022, a market shortage of clonazepam was resolved swiftly following advocacy efforts by the organization and public support (*23*).

5.2. Case Study 2: Silkworm Baby Lesch-Nyhan Syndrome (LNS) Care Home

LNS is a rare X-linked recessive purine metabolism disorder characterized by motor dysfunction, intellectual disability, and self-injurious behavior. Cases have been identified across 19 provinces with a prevalence of 1 in 380,000. The organization was established in 2008, it has registered over 100 cases and launched the "China LNS Diagnosis and Research Alliance". It conducts natural history and genotype-phenotype studies, maintains a literature database of over 800 publications from 32 countries spanning 45 years, and developed China's first expert consensus on the diagnosis of LNS. The group pioneered HPRT enzyme activity testing, initiated a digital disease tracking tool, and built a national LNS patient registry system, fostering international collaboration (*24*).

6. Multi-level healthcare security system for rare diseases

In addition to the National Basic Medical Insurance (NBMI), China has explored multi-level local healthcare security system in terms of payment reform experience. In 2019, for example, Zhejiang Province established a provincial rare disease drug fund, financed by an annual contribution of 2 RMB per person from the critical illness insurance pool. The fund prioritized four ultra-rare diseases: Gaucher disease, phenylketonuria, Pompe disease (mucopolysaccharidosis type II), and Fabry disease. Over 90% of treatment costs were reimbursed, with an annual out-of-pocket capping out at 100,000 RMB per patient (*25*). In 2021, Jiangsu Province developed a mechanism linking rare disease drug coverage with national insurance negotiations, initially covering Gaucher disease, Pompe disease, Fabry disease, spinal muscular atrophy (SMA), and mucopolysaccharidosis type IVA (*26*).

Starting in 2025, a list of innovative drugs covered by commercial insurance has been developed to supplement coverage through urban inclusive supplementary commercial health insurance (Huiminbao) and other private insurance schemes. The latest medical insurance list, released in 2025, added a total of 114 new drugs. Ten of those drugs were for rare diseases, accounting for about 9% of the total. By the end of 2025, the total number of rare disease medications on the list had reached 136, covering 69 diseases on the First and Second Installments of the Rare Disease List. Medical coverage for rare disease drugs is expected to continue to expand (*27,28*).

7. Future development of and outlook for rare disease research in China

At the 78th World Health Assembly (WHA) in 2025, the World Health Organization (WHO) adopted a landmark resolution recognizing rare diseases as a global health priority. The resolution aims to enhance equity, inclusion, and access to care, thereby improving universal health coverage for over 300 million individuals living with rare diseases worldwide (*29,30*). This initiative is expected to significantly advance China's efforts in rare disease prevention, treatment, and drug development.

China is promoting legislation in the area of rare diseases, expanding the number of orphan drugs included in the NBMI reimbursement list and exploring commercial insurance pathways. For high-cost cell and gene therapies (CGTs), efforts are underway to include them in the national list of innovative drugs, along with the development of novel payment mechanisms to improve affordability and access.

China has also established the National Rare Disease Registry System (NRDRS), which currently includes data on 218 rare diseases and more than 100,000 registered cases (*31*). A nationwide network of 419 hospitals has been formed to provide collaborative diagnosis and treatment for rare diseases at the provincial level, and further improvements in clinical capacity are expected (*32*).

In the future, China should prioritize legislation for rare diseases and promote research on health technology assessment frameworks and methodologies for rare disease drugs and medical devices. Particular emphasis should be placed on promoting high-quality approaches to measuring health utilities, encouraging domestic orphan drug development, and fostering international collaboration. Breakthroughs in the field of rare diseases are not only a reflection of medical progress but also a testament to social equity and humanitarian care. China's exploration of and practical experience in rare disease prevention and treatment can make a meaningful contribution to the global advancement of rare disease initiatives.

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Review

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Health technology assessment and medical insurance access for rare disease drugs in China: A policy review with quantitative insights from publicly available data

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SUMMARY: To ascertain the status and propose optimization strategies for rare disease drugs (RDDs) value assessment in the scenario of the National Reimbursement Drug List (NRDL) dynamic adjustment in China, we conducted a narrative policy review that synthesized published literature and policy documents, supplemented by a secondary descriptive statistical analysis of publicly available 2022–2024 year NRDL negotiation data to contextualize recent reimbursement practices for rare disease drugs in China. This study found that value assessment of RDDs largely aligned with the traditional framework, encompassing five key dimensions: safety, efficacy, economic evaluation, innovation, and equity. Considering disease severity and the competitive landscape, innovative RDDs tend to receive higher clinical value ratings, higher willingness-to-pay thresholds, and broader policy support across the healthcare system. Between 2022 and 2024, a total of 60 RDDs applied for NRDL inclusion, with 43% successfully reimbursed. Most applicants were either original research drugs already approved overseas or modified new drugs launched domestically and abroad. Notably, 42% of the drugs had achieved global first launches before 2015, thereby accumulating extensive clinical evidence, and 58% submitted randomized controlled trial (RCT) data. The proportion of drugs supported by RCT evidence in the reimbursed group was significantly higher than the figure in the non-reimbursed group, whereas the proportion of drugs with pediatric indications were relatively lower in the reimbursed group. No significant differences were observed in other value assessment dimensions between successful and unsuccessful applicants. It is recommended that China develop detailed health technology assessment (HTA) guidelines and real-world evidence (RWE) guidance tailored for RDDs, facilitating the generation of high-quality evidence and decreasing decision-making risks associated with the value assessment of innovative RDDs.

Keywords: rare disease, health technology assessment, marketing access, medical insurance reimbursement

1. Introduction

Rare diseases impose a substantial burden on patients and their families, and improving the quality of life for individuals living with rare diseases requires concerted public efforts across society. In China, government agencies, academic institutions, charitable organizations, and patient groups have collaboratively advanced the development of a more comprehensive security system for rare diseases. At the national level, the government has continuously strengthened top-level design and provided end-to-end support for the research, market entry, and utilization of innovative rare disease drugs (RDDs). Since 2018, the National Health Commission has released two editions of the National Rare Disease List, covering a total of 207 diseases (*1,2*). In 2024, the State Council Executive Meeting reviewed and approved the Implementation Plan for End-to-End Support of Innovative Drug Development, which reinforced comprehensive policy measures, integrating pricing regulation, reimbursement policies, commercial insurance, drug availability and use, as well as financing mechanisms, while optimizing regulatory review and hospital performance assessment to accelerate the development of innovative medicines. In 2025, the General Office of the State Council issued the Opinions on Deepening the Reform of Drug and Medical Device Supervision to Promote High-Quality Development of the Pharmaceutical Industry, which emphasized accelerating the review and approval of drugs and devices for rare diseases, exempting eligible innovative drugs for rare diseases from clinical trials, and prioritizing review for urgently needed therapies, including cell and gene therapies (*3*). In the same

year, the National Healthcare Security Administration (NHSA) and the National Health Commission (NHC) jointly introduced Measures to Support High-Quality Development of Innovative Drugs, which explicitly provided end-to-end support for RDDs in priority areas such as R&D, market entry, hospital adoption, and multi-source payment mechanisms (*4*). At the practical level, China has established demonstration zones, including the Boao Lecheng International Medical Tourism Pilot Zone in Hainan, the "Hong Kong–Macao Medicine and Device Connect" policy in the Guangdong–Hong Kong–Macao Greater Bay Area, and the Beijing Tianzhu Rare Disease Drug Security Pilot Zone, further addressing unmet clinical needs for RDDs.

With the accelerated launch of innovative RDDs, particularly cell and gene therapies, the traditional health technology assessment (HTA) framework faces significant challenges (*5*). These challenges mainly arise from immature clinical trial evidence, limited sample sizes, reliance on surrogate endpoints, uncertainty regarding long-term benefits, and extremely high drug prices (*6-10*). To address these challenges, HTA bodies worldwide have adapted their pathways to better accommodate treatments for rare diseases (*11-15*). For example, the National Institute for Health and Care Excellence (NICE) in the United Kingdom has incorporated additional elements of value, such as severity, rarity, equity, unmet need, and innovation. Innovative drugs for rare diseases are eligible for higher willingness-to-pay thresholds, or a severity modifier that increases the weight of quality-adjusted life years (QALYs) for severe conditions (*16,17*). In Germany, the Federal Joint Committee (Gemeinsamer Bundesausschuss, G-BA) assesses rare disease treatments through an orphan medicine pathway that simplifies evidence requirements. To strengthen data collection, France has developed the National Rare Disease Database (Banque Nationale de Données Maladies Rares, BNDMR), while Italy has established multiple monitoring registries to routinely collect product utilization data (*18*).

Unlike other countries, China has yet to establish a separate HTA institution at the national level. Instead, the NHSA directly oversees both purchasing and technical appraisal processes, relying on a network of affiliated research and academic institutions. The HTA of RDDs is primarily conducted by universities and research institutes, and the findings are directly translated into supporting evidence for reimbursement applications. To clarify the current status and challenges of value assessment for RDDs, this study reviews and summarizes the value dossiers of RDDs that participated in National Reimbursement Drug List (NRDL) price negotiations between 2022 and 2024.

The plan is to clarify the value assessment elements of RDDs that support reimbursement decisions, identify the challenges encountered in value assessment and reimbursement processes, and propose future optimization pathways by drawing on international experience.

2. Policy review and analysis

2.1. Literature and policy review about HTA-informed NRDL for rare diseases

A narrative review was conducted using the keywords "rare diseases", "orphan drugs", "health technology assessment", "reimbursement access", "National Reimbursement Drug List negotiations", and "comprehensive clinical evaluation of drugs" in PubMed, China National Knowledge Infrastructure (CNKI), and the official website of the NHSA from inception to 1st August, 2025, without limitation on article types. This review identifies publicly available Chinese and English literature and policy documents related to HTA and reimbursement access for RDDs in China, which constitutes the core of the review. We included health or medical insurance policy research related to NRDL price negotiation and HTA of RDDs, aiming to summarize the dimensions and elements of HTA applied to RDDs during the reimbursement process. Studies focusing on a single disease area (*e.g.*, oncology) regarding NRDL negotiation impacts on price or clinical benefits of drugs were excluded.

2.2. Policy document synthesis

Since the establishment of the NHSA in 2018, the NRDL has undergone annual dynamic adjustments in charge of NHSA. NHSA publishes yearly NRDL adjustment work plans, in which the adjustment scope and work procedure were elucidated. The scope of adjustment includes newly approved drugs with generic names, as well as drugs with significant changes in indications or therapeutic functions approved by the National Medical Products Administration (NMPA). The adjustment work procedure consists of five phases: preparation, application, expert evaluation, price negotiation or bidding, and publication of the final results. NHSA published the drug value dossiers submitted by pharmaceutical companies during the application stage and released the updated NRDL after the negotiation or bidding stage. These public disclosures were major sources of policy practice information. Starting in 2022, RDDs approved by the NMPA were listed as a separate category within the NRDL adjustment scope. To avoid bias, this study focuses solely on RDDs that participated in NRDL adjustments between 2022 and 2024 (*19-21*).

2.3. Secondary descriptive quantitative analysis

Based on the list of drugs that passed formal review and the publicly available drug value dossier released

by the NHSA, a secondary descriptive analysis was conducted to provide contextual quantitative support for the narrative review and was not intended to identify determinants, predictors, or causal mechanisms of reimbursement outcomes. Thus, this study analyzed the characterization of the RDDs involved in NRDL adjustments and the current status of their value assessment evidence, with results presented as drug counts and the percentages of each value feature. Drugs were grouped according to reimbursement success, and Pearson's chi-squared test was applied to categorical data for intergroup comparisons to explore drug value features differences between reimbursed group and non-reimbursed group. Two-tailed p values < 0.05 were considered statistically significant. All descriptive analysis were performed using Excel (Microsoft 365) and intergroup comparative analysis were performed using STATA/MP 16 (Stata Corp).

3. Value assessment framework and current status for rare diseases drugs applying for NRDL

3.1. Value domains and key considerations in each domain for rare diseases drugs

The value assessment of RDDs for reimbursement is conducted within the traditional value assessment framework. In addition to basic drug information, the value assessment of drugs primarily encompasses five key dimensions: safety, efficacy, economic evaluation, innovation, and equity, each with distinct connotations (*22*) (see Table 1). These evaluation criteria apply to all drugs seeking reimbursement access. Absolute safety and efficacy, as well as relative safety and efficacy compared with reference drugs, constitute the foundation of drug value assessment and reimbursement decision-making.

Economic evaluation of drugs, in addition to

Table 1. Overview of value assessment domains and items of the National Reimbursement Drug List (NRDL) price negotiation

Domain	Items
Basic information	• Generic name of the drug • Registered formulation • Indications/therapeutic functions as described in the package insert • Dosage and administration • First marketing approval date in mainland China • Current market status of drugs with the same generic name in mainland China • Country/region of the first global marketing approval and the corresponding approval date • Whether the drug is over-the-counter (OTC) • Recommended reference drugs, and comparative advantages and disadvantages relative to reference drugs or other drugs in the same therapeutic area already on the market • Basic information on the treated disease, unmet medical needs addressed, and disease prevalence in mainland China
Safety	• Safety information reported in the drug's package insert • Incidence of adverse reactions for the drug domestically and internationally • Major safety advantages and disadvantages compared with other drugs in the same therapeutic area listed in the NRDL
Efficacy & Effectiveness	• Efficacy advantages and disadvantages of the drug compared with comparator drugs in clinical trials and real-world studies • Recommendations in clinical guidelines or treatment protocols • Description of the drug's efficacy in the Technical Review Report issued by the Center for Drug Evaluation (CDE) of the National Medical Products Administration (NMPA) • Comparative efficacy advantages and disadvantages relative to other drugs in the same therapeutic area listed in the NRDL • Rationale for the formulation of traditional Chinese medicine (TCM) products and relevant descriptions of how the formulation leverages TCM therapeutic benefits
Economy	• Drug sales revenue in mainland China from January 1, 2021, to June 30, 2023 (including all formulations; if not exclusive, focus primarily on the company's own products) • Current pricing and cost information • Projected sales over the next three years • Impact on the health insurance fund • Cost-effectiveness and other economic evaluations
Innovation	• Key innovative features • Efficacy or safety advantages resulting from the innovation • Whether the drug is supported by national major scientific and technological initiatives (*e.g.*, "Major New Drug Creation" projects) • Whether the drug is an innovation with independent intellectual property rights • Drug registration category • (For traditional Chinese medicine products) Degree of heritage or lineage of the formulation
Equity	• Public health impact of the treated disease • Compliance with the "basic insurance coverage" principle • Whether the drug can address gaps in the NRDL • Clinical management complexity and other relevant considerations

cost-effectiveness and budget impact analyses, also considers publicly available drug prices domestically and internationally (including post-charity donation prices) and the historical sales data in mainland China over the past three years. Assessments of innovation and equity are closely linked to Chinese government policies supporting innovative drugs, reflecting the integration of reimbursement policy with regulatory approval and clinical use policies. Factors such as first-in-class innovative drugs, drugs supported by national major scientific and technological initiatives (*e.g.*, "Major New Drug Creation" projects), urgently needed overseas drugs, encouragement for pediatric drug development, and rare diseases with high severity are considered as additional positive factors during the evaluation process.

3.2. Add-on value considerations for rare disease drugs

The specificity of value assessment for RDDs is mainly reflected in both the evaluation content and the preferential weighting given to RDDs during the review process due to the disease severity and highly unmet clinical needs. For example, innovative RDDs tend to receive more policy support from various regulatory authorities, and many drugs listed in the NHC's catalogue of urgently needed medicines are RDDs. Drugs for rare diseases with higher severity often receive higher clinical value scores. In economic evaluations, elevated willingness-to-pay thresholds are applicable to pediatric drugs, RDDs, end-of-life treatments, and first-in-class medicines (*23*). This approach aligns with adjustments made by international HTA bodies for value assessment of rare diseases (*16,17*).

3.3. Various value characteristics of rare disease drugs applied for and reimbursed by national basic healthcare insurance

The success rate of negotiations for RDDs was not high. Between 2022 and 2024, a total of 77 value dossiers were submitted. After excluding duplicate submissions in the same year, 60 RDDs applied for reimbursement, of which fewer than half (43%) were successfully included in the NRDL (see Table 2). Most of the submitted RDDs were exclusive products (n = 51, 85%).

Both older drugs that have been on the market for many years and high-value innovative drugs with a relatively short market history applied for NRDL price negotiation. Fewer than half of the drugs (n = 25, 42%) had their first global marketing approval more than 10 years ago. Regarding innovation, the majority of submitted RDDs were original drugs already marketed abroad or improved new drugs marketed domestically and internationally (n = 33, 55%), followed by generics (n = 21, 35%). Among these generics, some were based on original drugs not yet marketed in China (n = 8, 13%), while innovative drugs not yet marketed either domestically or internationally were rare (n = 6, 10%). This phenomenon was partially because the NRDL dynamically adjusted annually began from 2018, with several older drugs on the market for many years without opportunity to be included in the NRDL before that. Therefore, for RDDs that have been available for many years, the traditional value assessment framework remains applicable. To date, no cell or gene therapies for rare diseases have applied for reimbursement in China. Currently, a gene therapy for Leber's hereditary optic

Table 2. Value characteristics distribution of rare diseases drugs passing the formal review of national reimbursement drug list price negotiation during 2022–2024

Characteristics	Total (n = 60)	Reimbursed (n = 26)	Non-reimbursed (n = 34)	p-value
Exclusive products	51 (85%)	23 (88%)	28 (82%)	0.51*
Drugs with multiple indications	14 (23%)	4 (15%)	10 (29%)	0.20*
Drugs with non-rare disease indications	11 (18%)	3 (12%)	8 (24%)	0.23*
Innovation				0.23*
Innovative drugs not yet marketed domestically or internationally[a]	6 (10%)	5 (19%)	1 (3%)	
Innovative drugs marketed abroad or improved new drugs[b]	33 (55%)	13 (50%)	20 (59%)	
Generics based on original drugs not marketed in China[c]	8 (13%)	3 (12%)	5 (15%)	
Other generics[d]	13 (22%)	5 (19%)	8 (24%)	
Reported randomized controlled trials (RCTs)	35 (58%)	21 (81%)	14 (41%)	< 0.01*
Reported patient-reported outcomes (PROs)	11 (18%)	5 (19%)	6 (18%)	0.88*
Pediatric indications	32 (53%)	10 (38%)	22 (65%)	0.04*
Applications citing a blank reference drug	28 (47%)	9 (35%)	19 (56%)	0.10*
First global marketing approval before 2015	25 (42%)	14 (54%)	11 (32%)	0.09*
Priority review	28 (47%)	13 (50%)	15 (44%)	0.65*
Breakthrough therapy designation	9 (15%)	5 (19%)	4 (12%)	0.42*
Orphan drug designation	20 (33%)	9 (35%)	11 (32%)	0.85*
Listed as urgently needed, encouraged for development, or encouraged for generic submission	21 (35%)	11 (42%)	10 (29%)	0.30*

Note: [a] Innovative drugs not yet marketed domestically or internationally: Chemical drugs, Class 1 ; Therapeutic biologics, Class 1. [b] Innovative drugs marketed abroad or improved new drugs: Chemical drugs, Class 5.1 ; Therapeutic biologics, Class 3.1; Chemical drugs, Class 2.2. [c] Generics based on original drugs not marketed in China: Chemical drugs, Class 3. [d] Other generics: including Chemical drugs, Class 4; Chemical drugs, Class 5.2; Original chemical drugs, Class 5; Original chemical drugs, Class 6. *Pearson's chi-squared.

neuropathy has been approved for priority use in Boao but has not yet received formal approval domestically. With high-value and clinical uncertainty innovative drugs applying for NRDL, the current value assessment framework needs to be adjusted to comprehensively assess the innovative drugs.

Multiple indication RDDs drove the value assessment framework adjustment. About 23% of drugs were indicated for multiple conditions, of which 79% (n = 11) had non-rare disease indications. Typically, the main indication should be designed for multi-indication drugs to assess drug value and form the basic medical insurance payment price, with drug indication for rare diseases as an add-value factor.

Clinical evidence quality raises decision-makers' and reviewers' concerns. Fifty-three percent of the drugs had pediatric indications. Forty-seven percent of applications cited a blank reference drug, and 58% submitted randomized controlled trial (RCT) data, while patient-reported outcomes (PROs) were infrequently reported (n = 11, 18%).

Full-chain policy supports drug authority and clinical rational use for RDDs. In terms of policy support, approximately half (47%) of the drugs received priority review, 15% were designated as breakthrough therapies, 33% were granted orphan drug status, and 35% were included in the National Health Commission's lists of urgently needed, encouraged for development, or encouraged for generic submission drugs.

Among the RDDs, higher submission/reimbursement frequencies were observed for multiple sclerosis (4 submitted, 3 reimbursed), myasthenia gravis (4; 2), pulmonary arterial hypertension (3; 2), and neuromyelitis optica (2; 2) (see Figure 1 and Figure 2). The reimbursed RDDs and corresponding indications are shown in Table 3.

3.4. Comparisons of value characteristics between reimbursed and non-reimbursed drugs groups

Clinical value remains the major factor for reimbursement of RDDs. The proportion of RDDs with RCT evidence in the reimbursed group was significantly higher (81% *vs.* 41%, $p < 0.01$). The proportion of drugs with pediatric indications was higher in the reimbursement failure group (65% *vs.* 38%, $p < 0.05$). No significant differences were observed between the success and failure groups in terms of exclusivity, first global approval date, drug innovation, multiple indications, blank reference drug application, PRO submission, or policy support (see Table 2). These findings provide contextual quantitative insight for HTA of RDDs applying NRDL pricing negotiation.

3.5. Economic evaluation of RDDs requires more detailed guidance

Currently, reimbursement assessments consider elements such as treatment course costs, historical and projected sales, budget impact, and cost-effectiveness. Model-based cost-effectiveness analyses are optional. According to China's pharmacoeconomic evaluation guidelines, the discount rate applied in economic models for RDDs is the same as for other drugs, with both costs and outcomes discounted at 5%. By contrast, NICE allows lower discount rates (1.5%) for drugs with long-term patient benefits (*16*). With the anticipated market entry of one-time, lifelong-benefit therapies such as cell and gene therapies, China will need to issue more detailed HTA guidelines specifically for rare disease drugs (*22*).

4. Moving forward

4.1. Exploring real-world evidence (RWE) applications and standards for RDDs

The application scenarios and standards for RWE of RDDs are being explored, particularly for innovative RDDs granted conditional approval based on single-arm clinical trial data due to immature trial evidence. Historical data indicate that statistical differences of the proportion of drugs with RCT evidence between reimbursement and non-reimbursement group were noted. In 2025, national policymakers issued guidance encouraging the use of RWE to support the inclusion of innovative drugs in the NRDL, as well as their renewal and adjustment of reimbursement coverage. However, quality standards and specific application scenarios for RWE have not yet been publicly defined (*24*). Currently, the International Society for Pharmacoepidemiology (ISPE) working group, in collaboration with HTA experts, has developed a bias assessment tool for real-world studies of drug safety and effectiveness. Potential for bias is assessed across three domains: *i*) bias due to study design (including time-related bias, inappropriate adjustment for causal intermediaries, depletion of outcome-susceptible individuals, reverse causation, detection bias, and informative censoring), *ii*) misclassification bias (exposure, outcome), and *iii*) bias due to confounding (residual confounding) (*25*). Innovative RDDs already used in demonstration zones have accumulated clinical data, with 42% of drugs having more than ten years of clinical use. Therefore, it is recommended that China establish RWE quality standards for RDDs, drawing on international experience, to provide evidence for drug safety and effectiveness in real-world clinical settings, as well as data on dosage and treatment duration, thereby supporting value assessment of RDDs.

4.2. Building rare disease data systems to support value assessment

Immature clinical evidence for innovative RDDs and unclear disease trajectories pose high decision-making

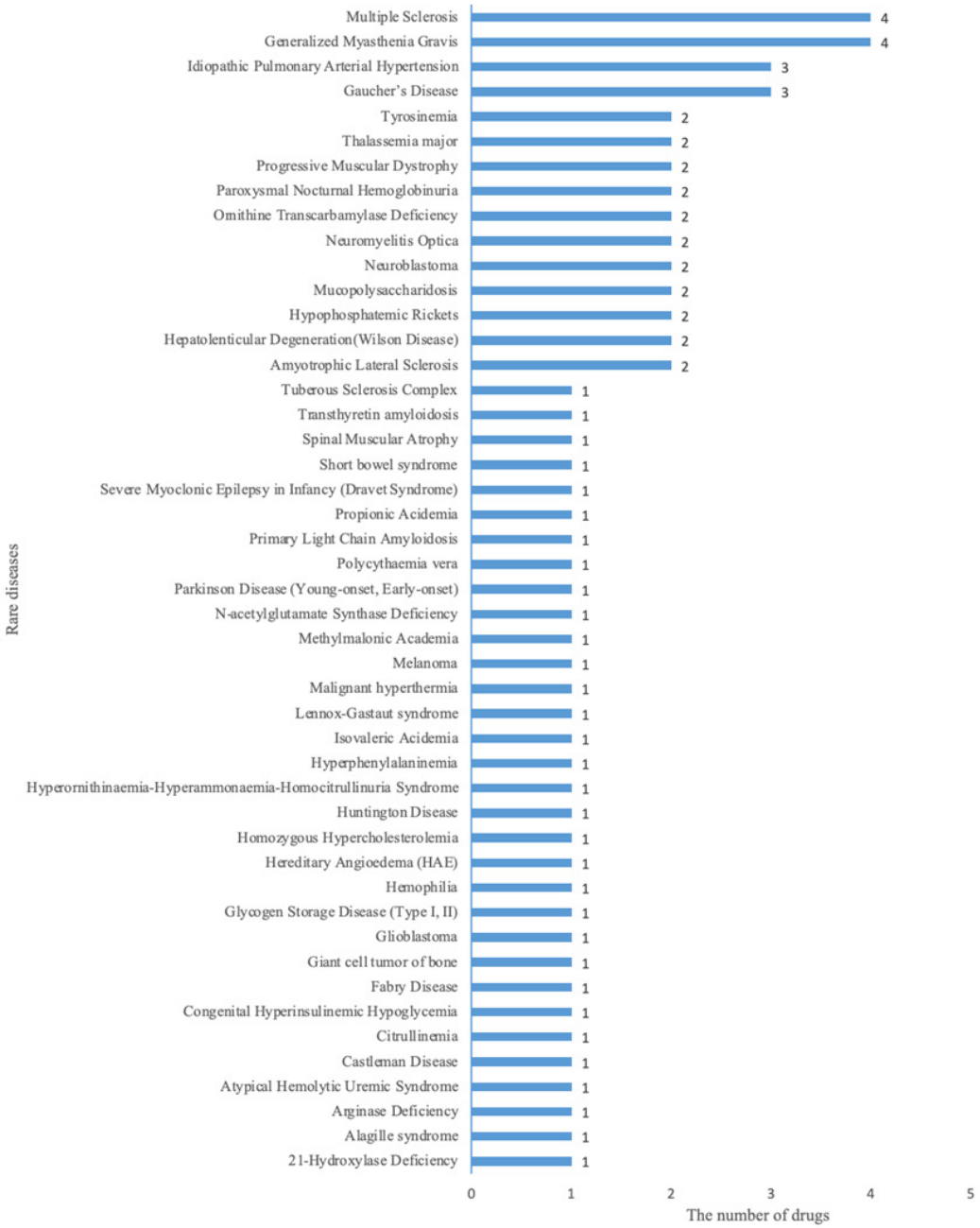

Figure 1. Distribution of drug indications among those drugs applying for national reimbursement drug list price negotiation during 2022–2024.

risks for reimbursement authorities, clinicians, and patients, making it difficult to evaluate long-term risk-benefit profiles. The China Alliance for Rare Diseases has been actively promoting the development of rare disease databases, including the national rare disease registry system, which integrates patient treatment data, drug data, hospital data, expert data, and disease data. Disease-specific cohorts, such as for achondroplasia, are currently being constructed. These data systems enable epidemiological analysis and disease trajectory mapping, including patient sociodemographic, genotyping, treatment regimens, and outcomes, providing critical support for RDD value assessment.

4.3. Introducing commercial health insurance and innovative payment mechanisms

To address the challenges posed by high-cost innovative therapies, such as cell and gene therapies, international HTA bodies have implemented innovative payment mechanisms, including outcome-based reimbursement, to mitigate the budget impact of high-value drugs (*6,26*). In 2025, the NHSA proposed establishing a commercial health insurance innovative drug catalog, focusing on drugs with high innovation, substantial clinical value, significant patient benefit, and coverage beyond basic health insurance, thereby improving China's multi-tiered

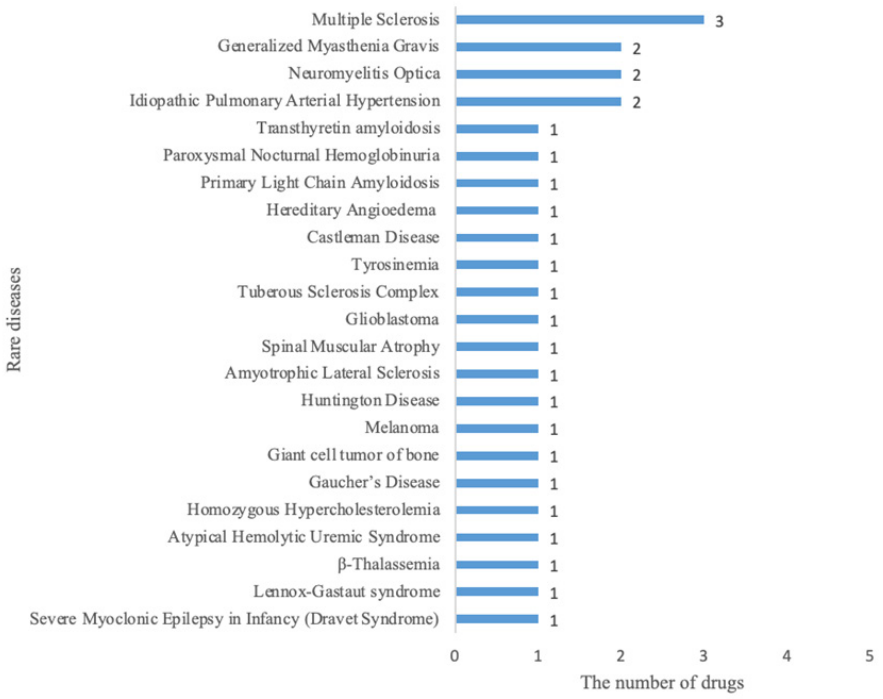

Figure 2. Distribution of drug indications among those drugs listed in national reimbursement drug list *via* price negotiation during 2022–2024.

Table 3. Rare diseases drugs and corresponding drug indications listed in National Reimbursement Drug List (NRDL) *via* price negotiations during 2022 to 2024.

Drug Generic Name	Indication
Beraprost Sodium Sustained-release Tablets	Idiopathic Pulmonary Arterial Hypertension
Bozitinib Enteric Capsules	Glioblastoma
Daratumumab Injection (Subcutaneous Injection)	Primary Light Chain Amyloidosis
Deferasirox Granules	Thalassemia major
Clobazam Tablets	Lennox-Gastaut syndrome
Tafamidis Meglumine Soft Capsules	Transthyretin amyloidosis
Narlumosbart Injection	Giant cell tumor of bone
Stiripentol For Suspension	Severe Myoclonic Epilepsy in Infancy (Dravet Syndrome)
Tunlametinib Capsules	Melanoma
Ezetimibe and Atorvastatin Calcium Tablets (II)	Homozygous Hypercholesterolemia
efgartigimod alfa-fcab injection	Generalized Myasthenia Gravis
Tetrabenazine Tablets	Huntington Disease
eliglustat tartrate capsules	Gaucher's Disease
Nitisinone Capsules	Tyrosinemia
Satralizumab Injection	Neuromyelitis Optica
Sirolimus Gel	Tuberous Sclerosis Complex
Ozanimod Hydrochloride Capsules	Multiple Sclerosis
Eculizumab Injection	Paroxysmal Nocturnal Hemoglobinuria; Atypical Hemolytic Uremic Syndrome; Generalized Myasthenia Gravis
Siltuximab for Injection	Castleman Disease
Ofatumumab Injection	Multiple Sclerosis
Dimethyl Fumarate Delayed-release Capsules	Multiple Sclerosis
Lanadelumab Injection	Hereditary Angioedema (HAE)
Riluzole Oral Suspension	Amyotrophic Lateral Sclerosis
Risdiplam Powder for Oral Solution	Spinal Muscular Atrophy
Treprostinil Injection	Idiopathic Pulmonary Arterial Hypertension
Inebilizumab Injection	Neuromyelitis Optica

Data source: This table was compiled based on the annal lists of declared medicines that passed form review, along with and updated NRDL from 2022 to 2024 published on the National Healthcare Security Administration website.

healthcare security system.

4.4. Encouraging patient engagement in HTA

Patient engagement is becoming increasingly relevant in regulatory decision-making and HTA for rare diseases (*27-29*). On one hand, it provides insight into the disease and patient needs; on the other hand, traditional cost-effectiveness models often fail to capture the full impact of these conditions. Between 2022 and 2024, only 18% of drugs reported PROs, indicating that the patient voice has not yet been formally incorporated into reimbursement decisions. However, China's drug evaluation authorities have issued guidance outlining how to collect patient experience data throughout the drug lifecycle — including the research planning stage, pre-clinical trial stage, pre-key study stage, pre-marketing application/ marketing application stage, and post-marketing stage — how to apply these data in drug development, and how to implement clinical trials that account for patient experience (*30*). With the integration of regulatory review and HTA reimbursement evidence, HTA agencies may consider incorporating the patient perspective more systematically during reimbursement evaluation, such as patients' previous treatment experiences, disease impact on daily life, and patient-reported quality of life (*31*).

5. Limitations of this review

This study is limited to RDDs that applied for reimbursement between 2022 and 2024. Information on drugs undergoing formal review for NRDL inclusion in 2018–2019 was not published on the NHSA website, and the formal review data for 2020–2021 did not separately identify RDDs. Therefore, only RDDs from 2022 to 2024 were included in this study. Since the submitted drug dossiers did not change during this period, this limitation does not affect the analysis of value assessment elements and the overall evidence profile of RDDs.

Furthermore, in the empirical analysis of reimbursement outcomes, this study did not summarize or analyze economic evidence of reimbursed drugs. This limitation is primarily due to the lack of publicly available information. The NHSA has not disclosed the complete value assessment dossiers or expert review reports submitted by companies after comprehensive review. Consequently, it is not possible to determine whether RDDs that passed comprehensive review included model-based cost-effectiveness analyses. However, based on publicly available information, the main evaluation criteria for economic assessment of RDDs — such as treatment course costs, cost-effectiveness, and budget impact — can be identified.

6. Conclusions

In China, the HTA of RDDs should integrate both traditional and innovative assessment frameworks. To better support reimbursement decisions, the traditional assessment framework is sufficient to demonstrate the clinical, economic, and social value of RDDs that have been marketed internationally for many years or face well-established competitive landscapes. For high-cost innovative RDDs with uncertain long-term clinical benefits, the reimbursement value assessment process should explore incorporation of additional elements, including disease severity, real-world evidence, patient involvement, and innovative payment models, to address uncertainties in value assessment and mitigate associated decision-making risks.

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Review

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Foods for special medical purposes for the dietary therapy of rare diseases: Current status and future prospects

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SUMMARY: Foods for special medical purposes (FSMPs) is a type of products that provides targeted nutritional support for specific diseases or physiological conditions. Compared with conventional dietary therapy, FSMPs are more targeted, safer, and applicable in clinic. When FSMPs are used to treat rare diseases, their core principle is to bypass or alleviate metabolic disorders. With the increasing recognition of clinical treatment effectiveness and the growing demand from patients, the types and market scale of commercial rare disease FSMPs continue to expand. However, there are currently no article summarized and analyzed the characteristics of diverse commercial products. Based on this, this review collected and collated the vast majority of commercial rare disease FSMPs in the global market, and summarized the characteristics of these products by categorizing them into protein substitutes, nutritional modules, ketogenic diets (KDs), and special low protein foods (SLPFs). Following the comprehensive analysis of the global commercial rare disease FSMPs landscape, this review shifted focus to China and provided suggestions from product diversity, technological innovation, and policy optimization. It aims to offer available suggestions and references for the healthy development of rare disease FSMPs in China.

Keywords: rare disease, foods for special medical purposes (FSMPs), protein substitutes, nutritional modules, ketogenic diets (KDs), special low protein foods (SLPFs)

1. Introduction

Rare diseases are characterized by extremely low individual prevalence but a large global patient base. This feature presents a major challenge in diagnosis and treatment to the global public health system. Under the collective efforts of researchers and clinicians worldwide, treatment strategies for rare diseases have become increasingly diversified, including small molecule drug therapy, antibody therapy, oligonucleotide therapy, gene therapy, and cell therapy (*1,2*). Since the enactment of the "Orphan Drug Act" in 1983, over 7,000 orphan drugs have been developed, but only about 500 rare diseases have approved treatments (*3,4*). Narrow disease coverage, lack of specific therapeutic drugs, and low accessibility of some medications remain prominent issues for the management of rare diseases. Eighty percent of rare diseases are hereditary. A significant number of these hereditary conditions are inborn errors of metabolisms (IEMs), such as amino acid metabolic disorders, organic acid metabolic disorders, urea cycle disorders (UCDs), carbohydrate metabolism defects, and fatty acid oxidation disorders (*5,6*). The core of IEM treatment lies in correcting metabolic imbalances to prevent acute or chronic metabolic crises and support normal growth and development (*7*). Nevertheless, the vast majority of IEMs lack effective pharmacotherapeutic options.

In the 1950s, a low-phenylalanine diet was first used to prevent or alleviate clinical symptoms in patients with phenylketonuria (PKU). Since then, dietary therapy has gradually become the preferred and primary treatment for various IEMs (*8*). But it was soon to be found that dietary therapy achieved by adjusting the combination of natural foods may fail to meet the extreme nutrient needs of rare disease patients. Fortunately, FSMPs with precisely controllable formulas make up for the shortcoming of dietary therapy. In 1991, Codex Alimentarius Commission (CAC) provided the clear definition of FSMP in *CODEX STAN 180-199*, "Foods for special medical purposes are a category of foods for special dietary uses which are specially processed or formulated

and presented for the dietary management of patients and may be used only under medical supervision. They are intended for the exclusive or partial feeding of patients with limited or impaired capacity to take, digest, absorb or metabolize ordinary foodstuffs or certain nutrients contained therein, or who have other special medically-determined nutrient requirements, whose dietary management cannot be achieved only by modification of the normal diet, by other foods for special dietary uses, or by a combination of the two" (*9*). For non-IEM rare diseases, FSMPs can also be customized into easy-to-swallow and highly absorbable formulations according to patient needs. These formulations ensure patients' basic nutritional requirements and provide nutritional support for pharmaceutical treatment and rehabilitation training. According to market data, the global market size of rare disease FSMPs reached 1.33 billion US dollars in 2024, and it is expected to grow to 1.41 billion US dollars in 2025, with a projected compound annual growth rate of 6.1% (*10*). Modern medicine has been gradually recognized the important value of FSMPs in the clinical treatment of rare diseases. Therefore, the demand for rare disease FSMPs will continue to grow in the future.

Numerous articles have emphasized the importance and necessity of dietary therapy in IEMs. Some of them have elaborated on the mechanisms, applications, and therapeutic efficacy of dietary therapy for different rare diseases (*6,11-14*). For patients with rare diseases, commercial FSMPs are an indispensable component of their daily dietary therapy. However, after conducting literature searches on Web of Science, Google Scholar, China National Knowledge Infrastructure (CNKI), and Wanfang Data using the terms "rare disease", "foods for special medical purposes/medical foods", "dietary therapy", and "commercial product", we found that no any review has detailly summarized and analyzed the characteristics of commercial FSMPs. Based on this, we collated product information from nine global brands (Ajinomoto Cambrooke, Mead Johnson, Nutricia, Nestlé Health Science, Abbott, Prekulab, Eton Pharmaceuticals., PIAM Farmaceutici S.p.A., Orpharma) that market FSMPs. Then, products were categorized into four types (protein substitutes, nutritional modules, ketogenic diets and special low protein foods) to take the overviews of their characteristics and applicable patients. Finally, based on the comprehensive summary of currently commercial products, we provided insights into the future development of FSMPs in China. It aims to help researchers and companies identify current market gaps and promote the research and development of rare disease FSMPs.

2. Therapeutic strategies of rare diseases

The World Health Organization (WHO) defines rare diseases as specific health conditions with an incidence rate of less than 1 per 2,000 of the population (*15*). China proposed three criteria for judging rare diseases in 2021: *i*) the incidence rate of newborns is less than 1 per 10,000; *ii*) the prevalence rate is less than 1 per 10,000; *iii*) the affected population is less than 140,000. If one of them is met, it can be defined rare disease (*16*). In order to better manage rare diseases, China has released two batches of the "List of Rare Diseases" in 2018 and 2023, which included a total of 207 rare diseases. According to statistics, rare diseases affect hundreds of 300 million people worldwide, with over 20 million patients in China alone (*17*). However, the low incidence rate, clinical rarity, diverse types, and difficulty in diagnosis and treatment render rare diseases a public challenge for global healthcare. In recent years, through the collective efforts of researchers around the world, rare disease managements have witnessed significant breakthroughs. More potential and effective treatment strategies are emerging.

2.1. Small molecule drug therapy

Small molecule drug therapy is a therapeutic approaches that interferes with abnormal signaling pathways, inhibits enzyme activity, or blocks intermolecular interactions by binding small molecules to specific targets (*2*). Small molecule drugs typically have a relative molecular mass of less than 1,000 Da (*18*), featuring simple molecular structures and diverse chemical architectures. They have been successfully used in the treatment of rare diseases, like cystic fibrosis (*19*), lysosomal storage disorders (*20*), Duchenne muscular dystrophy (DMD) (*21*), and PKU (*22,23*). Small molecule drugs possess irreplaceable advantages compared to many advanced therapies, including convenient administration routes, a broad range of therapeutic targets, the ability to cross the blood-brain barrier and low production costs (*21*). However, identifying small molecules with favorable pharmacological effects, optimal pharmacokinetic profiles, and minimal off-target effects remains the primary challenge (*2*). With the advancement of artificial intelligence technologies, as well as progress in chemistry and biology, problems faced by small molecule drugs are being increasingly well addressed (*18,24*).

2.2. Antibody therapy

Antibody therapy is a therapeutic approach that confers specific immunity through the passive transfer of antibodies (*25*). Antibodies play a role by modulating signaling pathways, recruiting cells or proteins to specific sites, delivering cytotoxins, neutralizing or modulating circulating factors (*2*). Soliris, the first antibody drug for the treatment of paroxysmal nocturnal hemoglobinuria was approved by the U.S. Food and drug administration (FDA) in 2007 (*25*). Since that, antibodies have gained increasing attention in rare disease therapy.

Canakinumab, a monoclonal antibody targeting the key proinflammatory cytokine IL-1β has been used to treat cryopyrin-associated periodic syndromes (*26*). Emicizumab, a specific monoclonal antibody that binds both activated coagulation factors IX and X has been employed for the routine prophylaxis of hemophilia A (*27*). High specificity, high affinity, and low off-target toxicity are the advantages of antibody therapy. However, inconvenient administration routes, poor tissue and cellular penetration, and high costs have limited their application in rare disease treatments, which are critical issues requiring urgent resolution (*2*).

2.3. Enzyme replacement therapy

Given that the pathogenic mechanisms of numerous rare diseases are associated with enzyme deficiency or dysfunction, enzyme replacement therapy has long served as a critical therapeutic modality for rare diseases (*28*). Enzymes can be purified from human or animal tissues, or produced *via* recombinant technology (*29*). Enzyme replacement therapy restores normal metabolic function by exogenously supplementing the missing or abnormally functional enzymes. For example, Gaucher disease is caused by the deficiency of glucocerebrosidase, which leads to the accumulation of glucocerebroside in the body and causes the disease. Injecting recombinant glucocerebrosidase can replace the enzyme deficient in the body, catabolizes accumulated substrates, alleviates symptoms, and improves patient quality of life (*28*). Enzyme replacement therapy exhibits high target and favorable safety profiles in clinic. However, this therapeutic approach still faces several challenges, such as the high manufacturing and purification costs of recombinant enzymes and the long lead time required to establish manufacturing capacity for new products (*2*).

2.4. Oligonucleotide therapy

Oligonucleotide therapy regulates gene expression *via* synthetic nucleic acid sequences that bind to RNA targets through sequence-specific base pairing (*2*). Small molecule drug therapy, antibody therapy, and enzyme replacement therapy mentioned above are all interventions acting at the protein level. Oligonucleotide therapy acts at the RNA level, belonging to upstream regulation (*30*). In rare disease treatments, antisense oligonucleotide (ASO) and small interfering RNA (siRNA) have been the most extensively studied, and both of them have achieved significant efficacy in treating rare neuromuscular diseases. For example, Nusinersen acted as an ASO is used to treat spinal muscular atrophy (*31*). Eteplirsen is indicated for patients with DMD exon 51 skipping (*32*). Patisiran, the first FDA-approved siRNA drug, is applicable for the treatment of hereditary transthyretin amyloidosis (*33*). Oligonucleotide therapy can target molecules inaccessible to traditional therapies and reduces drug toxicity due to limited body's exposure. However, poor blood-brain barrier penetration remains a critical challenge to oligonucleotide therapy. In the future, this issue is expected to be better addressed with breakthroughs in chemical modification technologies and delivery systems (*2,30,34*).

2.5. Gene therapy

Gene therapy refers to a therapeutic approach that modifies or manipulates gene expression to alter the biological properties of living cells for therapeutic purposes (*35*). Adeno-associated virus is currently the most commonly used and successful vector for *in vivo* gene therapy, with proven therapeutic efficacy in rare diseases including spinal muscular atrophy, hemophilia A, hemophilia B, and hereditary retinal dystrophy caused by RPE65 gene mutations (*36-38*). Gene-editing represents the most cutting-edge gene therapy strategy, achieving in situ repair of genes at pathological sites by directly delivering gene-editing systems (such as CRISPR/Cas9) into the body. Casgevy is the first FDA-approved gene-editing therapy, used for treating sickle cell disease (*39*). Gene therapy exhibits high targeting specificity and precision, holding promise for achieving one-time cure of rare diseases. However, challenges such as the complexity of the technology itself, uncertainty in efficacy, safety risks, and high costs are issues that must be addressed in the development of gene therapy (*40*).

2.6. Cell therapy

Cell therapy involves transplanting autologous or allogeneic cellular materials into patients to replace, repair, or enhance the function of damaged tissues or cell (*41*). The most representative modalities in rare disease treatments are hematopoietic stem cell transplantation (HSCT) and chimeric antigen receptor T (CAR-T) cell therapy. Currently, multiple HSCT-based therapies are used to treat rare diseases such as childhood cerebral type of Adrenoleukodystrophy (*42*) and β-thalassemia (*43*). CAR-T cell therapy also shows great promise in treating autoimmune diseases like systemic lupus erythematosus (*44*) and multiple sclerosis (*45*). Cell therapy is a dynamic therapeutic strategy. Once viable cells are administered into the body, they can activate, proliferate, and establish immune memory, thereby providing long-term protection to patients. This dynamic action is unmatched by any chemical drugs. Furthermore, cell therapy also exhibits high targeting specificity and precision. However, like gene therapy, cell therapy faces many challenges including technological complexity, high safety risks, and substantial costs (*2*).

2.7. Dietary therapy

Dietary therapy plays a crucial role of saving lives and

maintaining health in the field of rare diseases. While distinct from pharmacotherapeutic interventions, gene therapy, and cell therapy, it remains an unshakable cornerstone in managing numerous rare diseases owing to its directness, relative accessibility, and safety. The core concept of dietary therapy is to bypass or alleviate metabolic disorders, thereby maintaining the stability of the body's internal environment through strict control of dietary composition. Of the 121 rare diseases showed in China's "First List of Rare Diseases", 32 rare diseases are amenable to dietary therapy, and 18 of them mentioned in Figure 1 require timely, lifelong, and adequate use of FSMPs (*46,47*).

2.8. The importance of FSMPs in rare disease treatment

FSMPs represent a pivotal dietary intervention for rare disease management. According to nutritional compositions, FSMPs are usually divided into three categories: *i*) nutritionally complete food with a standard nutrient formulation, which can serve as the sole source of nutrition; *ii*) nutritionally complete food with a disease-specific nutrient-adapted formulation that can serve as the sole source of nutrition; *iii*) nutritionally incomplete food with either a standard or disease-specific nutrient-adapted formulation intended for partial feeding or use as a dietary supplement (*48*). It should be noted that there are some different names for FSMPs in different countries, for instance, medical foods in the U.S. (*49*), foods for a special dietary use (FSDU) in Canada (*50*).

From the standpoint of rare disease treatment, FSMPs bypass specific metabolic defects by providing formulations devoid of the problematic components, rendering them potent etiological interventions that directly target the pathogenic mechanisms of disease. Furthermore, FSMPs can function as adjuvant therapeutic agents, acting in synergy with pharmacotherapy, gene therapy, and enzyme replacement therapy to prime a more favorable physiological milieu for these interventions.

From the standpoint of nutritional support, the stringent dietary restrictions imposed by treatment regimens for rare disease patients frequently predispose them to malnutrition. By eliminating or severely restricting problematic substrates while precisely fortifying all other essential nutrients, FSMPs ensure patients receive comprehensive and balanced nutrition. This is particularly critical for safeguarding the normal physical and intellectual development of infants and children with rare diseases. Additionally, FSMPs broaden the dietary repertoire of rare disease patients, alleviating dietary monotony. This not only enhances treatment compliance but also enables patients to experience a dietary pattern analogous to that of healthy individuals, thereby improving their quality of life.

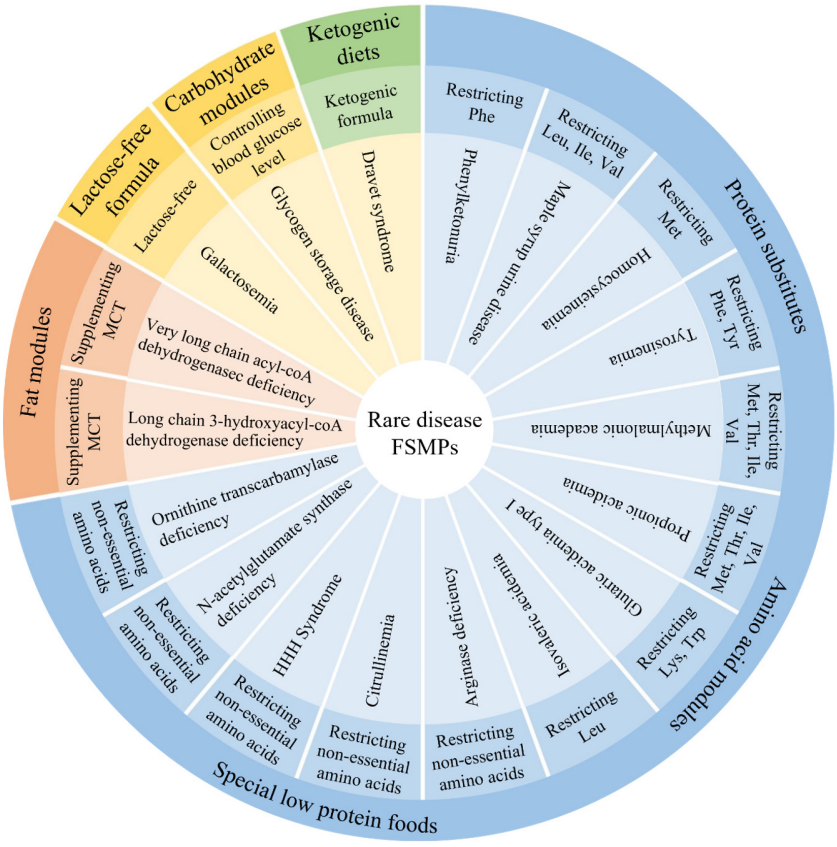

Figure 1. Eighteen rare diseases requiring long-term foods for special medical purposes (FSMPs) use and their product characteristics.

Within the integrated rare disease diagnosis and management framework, FSMPs constitute an indispensable pillar of the "screening-diagnosis-treatment" continuum. For many rare diseases for which no effective therapeutic interventions exist, FSMPs currently serve as the sole therapeutic modality capable of mitigating symptoms and extending survival. During the diagnostic phase, FSMPs function as life-saving emergency interventions. In the treatment phase, they act as core therapeutic tools for disease management, exerting a direct impact on patient prognosis. Throughout the long-term management phase, FSMPs provide a critical safeguard for sustaining lifelong health and quality of life.

3. Commercial product status of rare disease FSMPs

FSMPs are edible products designed for patients with special nutritional needs, and their therapeutic efficacy in rare disease management has been globally recognized. This rare disease management model that integrates clinic therapy with patients' daily dietary requirements has endowed FSMPs with substantial market potential. To cover a broader spectrum of rare diseases and provide more diverse options for patients, an increasing number of products have emerged. Protein substitutes, nutrient modules, KDs, and SLPFs are main four commercial rare disease FSMPs.

3.1. Protein substitutes

Protein substitutes, also termed amino acid metabolism disorder formulas, are a class of FSMPs tailored to the dietary management of amino acid or protein metabolism disorders. Protein substitutes are nutritionally incomplete FSMPs. They are specifically intended for target groups with specific nutritional needs and cannot act as the only protein source (*51*). Protein substitutes strictly restrict amino acid(s) that patients cannot consume while selectively providing other essential amino acid(s), non-essential amino acid(s), vitamins, minerals, and other nutrients (*52*). Thus, they need to be combined with natural proteins and other nutrients. This combination can support growth and development, maintains metabolic homeostasis, micronutrient balance, and normal neurological and psychosocial functions (*53,54*).

3.1.1. Design concepts of protein substitutes

Protein substitutes have been acted as treatment strategies for PKU, Tyrosinemia (TYR), Maple syrup urine disease (MSUD), Methylmalonic academia (MMA), Propionic acidemia (PA), Homocysteinemia (HCY), Glutaric acidemia type I (GA I), Isovaleric acidemia (IVA), and UCDs (Table 1). According to the composition of FSMPs, the design concept of protein substitutes can be divided into two types: *i*) totally without restricted amino acid(s) while containing other essential amino acid(s), non-essential amino acid(s), vitamins, minerals, and other nutrients; *ii*) totally without restricted amino acid(s) while containing large neutral amino acids (LNAAs), non-essential amino acid(s), vitamins, minerals, and other nutrients.

Protein substitutes adopting the first design concept dominate the commercial market of rare disease FSMPs. These formulations strictly control intake of the restricted amino acid(s) and have demonstrated efficacy in managing patients' health status. PKU infants treated with phenylalanine (Phe)-free FSMP (PKU Start, Nestlé Health Science) have been shown to maintain normal growth and satisfactory blood Phe control, with early gastrointestinal symptoms (constipation, colic, vomiting, and poor feeding) improving over time (*55*). A case report of a 29-year-old male with MSUD documented that his leucine (Leu) levels normalized (66 to 170 μmol/L) within 5 days when he ate a branched-chain amino acid (BCAA)-free FSMP named Ketonex-2 from Abbott and supplemented with 20 mg/kg L-isoleucine (L-Ile) and 20 mg/kg L-valine (L-Val) at the same time (*56*).

LNAAs mentioned in the second design concept refer to Phe, Tyr, Ile, Leu, Val, tryptophan (Try), threonine (Thr), methionine (Met), arginine (Arg), lysine (Lys), and histidine (His), sharing same transporter proteins in the brain and intestinal mucosae (*57*). LNAAs compete with and inhibit Phe transport across the intestinal mucosa and blood-brain barrier. Based on this mechanism, LNAAs have also become one of the methods for designing PKU FSMPs (*58*). Currently, only three LNAA-based products are approved for PKU, all three of which are manufactured by Prekulab. The first LNAAs product is PreKUnil® tablets. When six subjects aged 20-34 year were treated with it at 0.4 g/kg/day and consumed "relaxed" diets approaching to ordinary people, their blood Phe concentrations essentially unchanged, but brain Phe concentrations gradually decreased toward the carrier range (*59*). NeoPhe® tablets and NeoPhe® powder are two products modified from PreKUnil® by adjusting the concentrations of certain amino acid(s) and supplementing. NeoPhe® can reduce elevated blood Phe levels by 50% (*57*). Furthermore, NeoPhe® extends eligibility to pediatric patients. Notably, LNAA-based products enable PKU patients to obtain up to 80% of their protein intake from regular diets, making them particularly beneficial for patients with poor dietary adherence (*60*).

3.1.2. Dosage forms of protein substitutes

With the rapid development of the FSMP industry, the product formats of protein substitutes have expanded rapidly. Patients have more diversified choices, which is beneficial for improving compliance.

Powdered protein substitutes are currently the most prevalent FSMPs on the market, suitable for all age groups. These protein substitutes require reconstitution

Table 1. A part of common protein substitutes in global commercial market*

Rare disease	Product	Dosage form	Brand
Phenylketonuria (PKU)	Phenyl-Free® 1 Infant Formula & Medical Food, Phenyl-Free® 2 Medical Food, Phenyl-Free® 2HP Medical Food, PKU Anamix Infant, PKU Anamix Junior, PKU Lophlex LQ Powder, PKU Maxamum, PKU Synergy, PKU start™, PKU gel™, PKU explore™, PKU express™ plus, PKU express™ (newly renovated), PKU express®, PKU sphere®, Phenex-1®, Phenex-2®, Afenil 2, Afenil Gel, Afenil Medi 15, Afenil Buddy, Afenil Lime, NeoPhe Powder, PKU Go	Powder	Mead Johnson, Nutricia, Nestlé Health Science, Abbott, PIAM Farmaceutici S.p.A., Prekulab, Orpharma
	PKU Anamix Junior LQ, PKU Lophlex LQ 10, PKU Lophlex LQ 20, PKU Lophlex Select 20, Easiphen, PKU cooler®, PKU air®, PKU Motion, PKU sphere® 20 liquid, PKU sphere™ NEXT15, Afenil 1, Afenil Squash 15, PKU Easy Shake & Go, PKU Easy Liquid, PKU Baby	Ready-to-drink	Nutricia, Nestlé Health Science, PIAM Farmaceutici S.p.A., Orpharma
	NeoPhe Tablets, PreKUnil Tablets, Afenil Micro 3H, Neutrafenil Micro R, PKU Microtabs, PKU Microtabs Plus, PKU Easy Tablets, PKU EASY Microtabs	Tablet	Prekulab, PIAM Farmaceutici S.p.A., Orpharma
	PKU Anamix First spoon, PKU Lophlex Sensation 20, PKU squeezie™	Semi-solid	Nutricia, Nestlé Health Science
	PKU GOLIKE PLUS®, PKU GOLIKE KRUNCH	Granules	Eton Pharmaceuticals
Tyrosinemia (TYR)	TYROS 1 Infant Formula & Medical Food, TYROS 2 Medical Food, TYR Anamix infant, TYR Anamix junior, TYR Lophlex LQ Powder, TYR Maxamum, XPHEN TYR Tyrosidon, TYR gel™, TYR explore5™, TYR express™, TYR express™ plus, TYR express™ newly renovated, TYR sphere®, Tyrex-1®, Tyrex-2®, TYR medi 2, TYR medigel, TYR medi 15	Powder	Mead Johnson, Nutricia, Nestlé Health Science, Abbott, PIAM Farmaceutici S.p.A.
	TYR Anamix junior LQ, TYR Lophlex LQ 10, TYR Lophlex LQ 20, TYR cooler™, TYR Easy Shake & Go Leaflet	Ready-to-drink	Nutricia, Nestlé Health Science, Orpharma
	TYR medimicro 3H, TYR Easy Tablets	Tablet	PIAM Farmaceutici S.p.A., Orpharma
Maple syrup urine disease (MSUD)	BCAD 1 Infant Formula & Medical Food, BCAD 2 Medical Food, MSUD Anamix infant, MSUD Anamix junior, MSUD Lophlex LQ Powder, MSUD Maxamum, MSUD gel™, MSUD explore5™, MSUD express™, MSUD express™ plus, MSUD express™ newly renovated, Ketonex-1®, Ketonex-2®, MSUD medi 2, MSUD medigel, MSUD medi 15	Powder	Mead Johnson, Nutricia, Nestlé Health Science, Abbott, PIAM Farmaceutici S.p.A.
	MSUD Anamix junior LQ, MSUD Lophlex LQ 10, MSUD Lophlex LQ 20, MSUD cooler®	Ready-to-drink	Nutricia, Nestlé Health Science
	MSUD medimicro 3H, MSUD Easy Tablets	Tablet	PIAM Farmaceutici S.p.A., Orpharma
Methylmalonic academia (MMA) / Propionic acidemia (PA)	OA 1 Infant Formula & Medical Food, OA 2 Medical Food, MMA/PA Anamix infant, MMA/PA Anamix junior, MMA/PA Maxamum, XMTVI Asadon, MMA/PA gel™, MMA/PA explore5™, MMA/PA express™, Propimex-1®, Propimex-2®, MMA/PA medi 2, MMA/PA medigel, MMA/PA medi 15	Powder	Mead Johnson, Nutricia, Nestlé Health Science, Abbott, PIAM Farmaceutici S.p.A.
	MMA/PA cooler™	Ready-to-drink	Nestlé Health Science

*Data were collected from: Mead Johnson (https://www.enfamil.com/products/metabolic-special-medical-needs/); Nutricia (https://www.nutricia.co.uk/hcp/products.html); Nestlé Health Science (https://www.nestlehealthscience.com/vitaflo); Abbott (https://www.abbottnutrition.com/our-products); Prekulab (https://www.prekulab.com/); Eton Pharmaceuticals (https://www.etonpharma.com/products/); PIAM Farmaceutici S.p.A. (https://www.piamfarmaceutici.com/en/product-category/foods-for-special-medical-purposes/); Orpharma (https://www.orpharma.com/).

Table 1. A part of common protein substitutes in global commercial market* (continued)

Rare disease	Product	Dosage form	Brand
	MMA/PA medimicro 3H	Tablet	PIAM Farmaceutici S.p.A.
Homocysteinemia (HCY)	HCY 1 Infant Formula & Medical Food, HCY 2 Medical Food, HCU Anamix infant, HCU Anamix junior, HCU Lophlex LQ Powder, HCU LV, HCU Maxamum, HCU gel™, HCU explore5™, HCU express™ newly renovated, HCU express™, HCU express™ plus, Hominex-1®, Hominex-2®, HOM medi 2, HOM medigel, HOM medi 15	Powder	Mead Johnson, Nutricia, Nestlé Health Science, Abbott, PIAM Farmaceutici S.p.A.
	HCU Anamix Junior LQ, HCU Lophlex LQ 10, HCU Lophlex LQ 20, HCU cooler™	Ready-to-drink	Nutricia, Nestlé Health Science
	HCU Easy Tablets, HOM medimicro 3H	Tablet	PIAM Farmaceutici S.p.A., Orpharma
Glutaric acidemia type I (GA I)	GA Infant Formula & Medical Food, GA1 Anamix infant, GA1 Anamix junior, GA1 Maxamum, GA gel™, GA explore™ 5, GA express™, Glutarex-1®, Glutarex-2®, GA medi 2, GA medigel, GA medi 15	Powder	Mead Johnson, Nutricia, Nestlé Health Science, Abbott, PIAM Farmaceutici S.p.A.
	GA medimicro 3H	Tablet	PIAM Farmaceutici S.p.A.
Isovaleric acidemia (IVA)	LMD Infant Formula & Medical Food, IVA Anamix infant, IVA Anamix junior, I-Valex-1®, I-Valex-2®, IVA medi 2, IVA medigel, IVA medi 15	Powder	Mead Johnson, Nutricia, Abbott, PIAM Farmaceutici S.p.A.
	IVA cooler™	Ready-to-drink	Nestlé Health Science
	IVA medimicro 3H	Tablet	PIAM Farmaceutici S.p.A.
Urea cycle disorder (UCD)	WND® 1 Infant Formula & Medical Food, WND® 2 Medical Food, EAA supplement, UCD trio™, Cyclinex-1®, Cyclinex-2®, UCD medi 2, UCD medigel, UCD medi 15	Powder	Mead Johnson, Nestlé Health Science, Abbott, PIAM Farmaceutici S.p.A.
	UCD medimicro 3H	Tablet	PIAM Farmaceutici S.p.A.
long chain 3-hydroxyacyl-coA dehydrogenase deficiency (LCHADD)	Enfaport™ Infant Formula	Ready-to-drink	Mead Johnson

*Data were collected from: Mead Johnson (https://www.enfamil.com/products/metabolic-special-medical-needs/); Nutricia (https://www.nutricia.co.uk/hcp/products.html); Nestlé Health Science (https://www.nestlehealthscience.com/vitaflo); Abbott (https://www.abbottnutrition.com/our-products); Prekulab (https://www.prekulab.com/); Eton Pharmaceuticals (https://www.etonpharma.com/products/); PIAM Farmaceutici S.p.A. (https://www.piamfarmaceutici.com/en/product-category/foods-for-special-medical-purposes/); Orpharma (https://www.orpharma.com/).

with water at an appropriate temperature, and detailed preparation guidelines must be provided in each product's instructions. Powdered protein substitutes typically have suboptimal palatability, which significantly impacts treatment adherence. To address this, many manufacturers have developed products with diverse flavors (such as vanilla, lemon, orange, raspberry, tropical, and chocolate) for patient selection.

Ready-to-drink protein substitutes are convenient ready-to-use formulations that require no reconstitution, allowing immediate consumption after opening and offering portability. These protein substitutes are suitable for patients aged over one year old. A study investigating adherence to protein substitutes among PKU patients demonstrated that liquid formulations reduced self-consciousness and facilitated out-of-home use. Additionally, they reduced product wastage (*61*). Notably, ready-to-drink protein substitutes typically have hyperosmolar concentrations in a small volume, which increases the risk of abdominal discomfort (*62*). Therefore, it is recommended that patients consume water or permitted beverages after ingesting liquid FSMPs.

Tablet protein substitutes are administered similarly to pharmaceutical tablets and are suitable for older children and adults. PKU patients received at least 40% of their protein requirements from amino acid tablets, and showed better compliance. 70% subjects preferred incorporating tablets into their usual protein substitute regimen (*63*). Tablet protein substitutes have good stability and long-shelf-life. This dosage form of protein substitutes can be carried by patients and is easy to consume when going out.

Semi-solid protein substitutes currently include two types: *i*) products supplied in a semi-solid state, which can be consumed with a spoon or directly sucked from a pouch; *ii*) Powdered products that can be easily reconstituted into a gel or paste with a small amount of water. These formulations are suitable for patients ranging from 6-month-old infants to adults. Importantly, semi-solid protein substitutes facilitate the transition of weaned infants from exclusive liquid diets to solid foods, as their consistency is analogous to weaning foods (*62,64,65*). Like liquid formulations, semi-solid protein substitutes are concentrated, so consumption of water or permitted beverages afterward is recommended.

Slow-release protein substitutes are novel FSMPs developed in recent years, typically formulated as granules or tablets. The core technology of these formulations involves embedding amino acid(s) within hydrophilic coatings. A novel slow-release protein substitute prepared using Physiomimic Technology™ extended the duration of amino acid elevation in plasma compared to free amino acid(s) (*66*). Patients consumed slow-release protein substitutes reported fewer gastrointestinal symptoms (diarrhoea, constipation, bloating, nausea or vomiting) compared to baseline (*67*). Furthermore, the coatings can mask the bitter taste and odor while reducing the osmolarity of free amino acid(s), which enhances product acceptability and patient adherence (*67,68*).

3.2. Nutrient modules

Nutrient modules are single-nutrient FSMPs that are usually used as supplements in the dietary management of rare diseases, providing nutritional support for patients (*5,69*). It is important to emphasize that nutrient modules are nutritionally incomplete products and cannot be used as the sole source of nutrition.

3.2.1. Amino acid modules

In addition to protein substitutes, amino acid modules can also be used in dietary therapy for patients with inborn errors of amino acid metabolism. Amino acid modules offer greater flexibility in application, as they can be used independently or in combination with other dietary therapeutic strategies (*70*). Commercial amino acid modules can be either single amino acid or amino acid mixtures, and present in powder. Patients usually supplement amino acid modules for two purposes, avoiding the intake of restricted amino acid(s) or supplementing specific amino acid(s).

When amino acid modules are used for avoiding the intake of restricted amino acid(s), their functions are similar to that of protein substitutes. Compared to protein substitutes which have more complex nutritional compositions and focus on fulfilling overall protein nutritional functions, amino acid modules can precisely adjust the types and contents of amino acids according to patients' specific conditions. This characteristic is particularly important for infants, toddlers, and children with rare diseases (*71,72*). On the one hand, amino acid modules can completely eliminate restricted amino acids while precisely provide other amino acids required for growth and development (*72*). On the other hand, younger rare disease patients may have weak digestive functions or prone to allergies in the gastrointestinal tract. Amino acid modules are carefully screened and designed for composition, without complete protein molecules and can be fully absorbed without digestion, which can reduce the burden on the gastrointestinal tract and have higher safety (*73,74*). Nestlé Health Science has already come up several amino acid modules without restricted amino acids, including UCD amino5™, MSUD amino5™, MMA/PA amino5™, and GA amino5™. Nutricia has launched XMTVI Asadon and XPHEN TYR Tyrosidon targeting MMA/PA and TYR, respectively.

Avoiding to intake of restricted amino acid(s) is the key strategy for dietary therapy of amino acid metabolism disorder, but attention should also be paid

to the disruption of metabolic pathways caused by the absolute deficiency or functional insufficiency of specific amino acids (*75*). For example, Arg and/or citrulline (Cit) impairs urea synthesis in UCDs. Supplementation of these amino acids is not only essential for correcting metabolic defects but also maximizes ammonia excretion during the acute phase of metabolic decompensation (*76*). Beyond supplementing specific amino acid(s) due to impaired synthesis, specific amino acid(s) can also be supplemented to compete with other amino acid(s). For instance, Arg can compete with Lys for the blood-brain barrier transporter *SLC7A1*. Compared with GA I patients on conventional Lys-restricted diets, those supplemented with Arg in their diets exhibit lower Lys concentrations in the plasma and reduced the urinary excretion of 3-hydroxyglutaric acid (*77*). There have been systematic reviews and meta-analyses summarized rare diseases that can be supplemented with one or several specific amino acid(s) (*75,78*). To meet the needs of rare disease patients for supplementation, Ajinomoto Cambrooke, Nutricia, and Nestlé Health Science have launched single amino acid powders.

3.2.2. Fat modules

Fat modules are FSMPs with fat (fatty acid) as the core functional ingredients, specifically designed to supplement or adjust fat (fatty acid) intake in specific populations. They primarily consist of long-chain fatty acid (LCT), medium chain fatty acid (MCT), and other permitted fatty acids. Fat modules deliver core nutritional support to rare disease patients by precisely supplementing fat sources, optimizing energy provision, and correcting metabolic imbalances, thereby helping alleviate symptoms, maintain physiological functions, and improve prognosis. Commercial fat modules include powdered product (MCTprocal™, Nestlé Health Science) and oil-based product (MCT Oil and Liquigen®, Nutricia).

Fatty acid metabolism disorders (such as long chain 3-hydroxyacyl-coA dehydrogenase deficiency (LCHADD) and very long chain acyl-coA dehydrogenase deficiency) urgently require fat modules to treat. Patients with these disorders cannot convert fatty acids into tricarboxylic acid cycle intermediates and subsequently into energy, due to disrupted fatty acid transport *via* the mitochondrial β-oxidation pathway or the carnitine transport pathway. In addition, fat modules can also apply in the dietary management of other rare diseases, including short bowel syndrome, cystic fibrosis, PKU, and refractory epilepsy. MCT is essentially pure trioctanoylglycerol, thereby its daily dose should be evenly distributed across all meals. Infants fed MCT-containing formula milk typically tolerate MCT without adverse symptoms. However, elderly patients supplementing MCT at the first time often experience gastrointestinal symptoms, including abdominal discomfort, cramping, flatulence, bloating, and diarrhea. Fat modules can be consumed alone or mixed into a variety of foods and beverages. To avoid gastrointestinal symptoms caused by the use of fa modules, patients are usually required to consume them on a non-fasting status.

3.2.3. Carbohydrate modules

Carbohydrate modules are classified as nutritionally incomplete FSMPs intended for patients with well-defined medical conditions that necessitate targeted carbohydrate supplementation to address specific nutritional requirements and provide energy. Carbohydrate sources encompass a broad range of compounds, including monosaccharides, disaccharides, oligosaccharides, polysaccharides, maltodextrin, glucose polymers, and other raw materials adhering to relevant regulatory guidelines. Commercial carbohydrate modules are currently in powder.

Glycogen storage disease type I (GSD I) is one of the rare diseases with the highest demand for specific carbohydrate supplementation. GSD Ia and GSD Ib are caused by mutations in the *G6PC* gene and *SLC37A4* gene, respectively, and both of them can lead to a deficiency of glucose-6-phosphatase translocase (*79*). Since GSD patients experience significant fasting hypoglycemia, the therapeutic principle is to maintain blood glucose within the normal range and maximize the duration of stable glycemia following carbohydrate supplementation (*80*). The clinical application of uncooked corn starch (UCCS) represents a key breakthrough in the foundational treatment regimen for GSD I. UCCS is slowly hydrolyzed into glucose by gastrointestinal amylases, with sustained glucose release over approximately 4 hours, thereby effectively preventing fasting hypoglycemia (*81*). Glycosade® is currently the most effective FSMP approved for the treatment of GSD I, and it has been validated to prolong the fasting tolerance of GSD I patients to more than 8 hours (*82-85*). Long-term follow-up studies have shown that the dosage of Glycosade® is lower than that of UCCS, but metabolic indicators are more stable. Furthermore, the average daily administration frequency of Glycosade® has decreased from 3.95 times to 3 times (*82*), which contributes to improve compliance. Recently, the *in vitro* dynamic small-intestine mode has demonstrated the therapeutic potential of sweet manioc starch (SMS) for GSD Ia (*86*). A randomized, triple-blind, Phase I/II cross-over study also confirmed that the duration of maintaining normal blood glucose with SMS (8.2 ± 2.0 h) is longer than that with UCCS (7.7 ± 2.3 h) (*87*). FSMPs targeting blood glucose maintenance in rare diseases are relatively scarce. In the future, more slow-release starch products with diverse carbohydrate sources and longer blood glucose stability durations should be developed.

3.3. Ketogenic diets

KDs are dietary therapies rather than FSMPs. Specific formula foods used to implement KDs are FSMPs and serve as critical interventions for certain rare diseases. KDs are characterized by high fat, low carbohydrate, and moderate protein and other nutrients, which have been utilized for epilepsy treatment since 1921 (*88*). KDs have been proven to be highly effective alternative therapies and are even considered the last resort for refractory epilepsy (*89*). Currently, KDs have been incorporated into the clinical management of various rare diseases, including Angelman syndrome, complex 1 mitochondrial disorder, Dravet syndrome, epilepsy with myoclonic-atonic seizures, febrile infection-related epilepsy syndrome, glucose transporter type 1 deficiency syndrome, infantile epilepsy spasms syndrome, Ohtahara syndrome, pyruvate dehydrogenase deficiency, super-refractory status epilepticus, tuberous sclerosis complex (*88*). These diseases are often accompanied by uncontrollable epileptic seizures. A range of FSMPs for KDs are commercially available (Table 2). To maximize tolerability, enhance palatability, achieve dietary diversification, and improve compliance, five distinct types of KDs have been developed (*88,89*).

3.3.1. Classic ketogenic diet

Classic ketogenic diet (CKD) is the most restrictive diet, typically maintaining the ketogenic ratio (the ratio of fats to carbohydrates and proteins combined) at 4:1 (*88*). CKD shows excellent clinic efficacy on refractory epilepsy, but is poorly tolerated in the gastrointestinal tract, particularly in infants and adolescents. For these populations, the ketogenic ratio of CKD can be adjusted to 3:1 (*90*), and even 2:1 (*91*). In a randomized controlled trial involving 76 children with refractory epilepsy, 30.5% of those on the 3:1 ratio achieved seizure freedom, compared with 55.0% of those on the 4:1 ratio (*92*). The 2:1 diet has a notably lower proportion of fat than 4:1 diet or 3:1 diet but nonetheless exhibits favorable efficacy in both short- and long-term follow-up (*91*).

3.3.2. Medium-chain triglyceride diet

Medium-chain triglyceride diet (MCTD) is an alternate version for CKD (*88*). The main source of fats in MCTD is saturated fatty acids with 6~12 carbons, mainly including octanoic acid (C8:0) and decanoic acid (C10:0). MCT is more readily hydrolyzed by gastrointestinal lipases and can rapidly and efficiently

Table 2. A part of common FSMPs implemented KDs in global commercial market*

Product	Ketogenic ratio	Dosage form	Brand
KetoCal 4:1, KetoVie Café Kwik Mix	4:1	Powder	Ajinomoto Cambrooke, Nutricia
K.Flo™, KetoCal 4:1 LQ, KetoVie 4:1, KetoVie Peptide 4:1, KetoVie 4:1 Plant-Based Protein	4:1	Ready-to-drink	Ajinomoto Cambrooke, Nutricia, Nestlé Health Science
K.Yo™	3:1	Semi-solid	Nestlé Health Science
KetoCal 3:1	3:1	Powder	Nutricia
KetoVie 3:1	3:1	Ready-to-drink	Ajinomoto Cambrooke
KetoCal 2.5:1 LQ	2.5:1	Ready-to-drink	Nutricia
KetoVie Café Cinnamon Donut Delights, KetoVie Café Pizza Petites	2.5:1	Solid	Ajinomoto Cambrooke
KetoVie Café Creamy Cereal, KetoVie Café Wholesome Bread	2:1	Solid	Ajinomoto Cambrooke
MCTprocal™	10 g MCT per 16 g	Powder	Nestlé Health Science
MCT oil	100% MCT	Oil	Nutricia
K.Quik™	20 g MCT and 1 g LCT per 100 mL	Ready-to-drink	Nestlé Health Science
KetoVie Café Raspberry Muffins	3.5:1	Solid	Ajinomoto Cambrooke
K.Vita	40 g MCT per 120 mL	Ready-to-drink	Nestlé Health Science
Liquigen	50% MCT	Ready-to-drink	Nutricia

*Data were collected from: Ajinomoto Cambrooke (https://www.cambrooke.com/); Nutricia (https://www.nutricia.co.uk/hcp/products.html); Nestlé Health Science (https://www.nestlehealthscience.com/vitaflo).

produce ketones (*93*). This property enables MCTD to have lower total fat content while incorporating higher amounts of carbohydrates and proteins (*89,94*). A study comparing CKD (n = 73) and MCTD (n = 72) for the treatment of childhood epilepsy found no significant differences between the two groups in terms of ≥ 50% and ≥ 90% reductions in seizure frequency or reduction in antiepileptic drug dosage after 3 months (*95*). MCT exhibits higher oxidative capacity than LCT, thereby enhancing thermogenesis and decreasing fatty acid accumulation in adipose tissue (*96,97*). Furthermore, studies have shown that adherence to MCTD leads to a significant reduction in the total cholesterol-to-high-density lipoprotein cholesterol ratio (*98*). An important consideration in the design of MCT-based FSMPs is using an appropriate ratio of C10 to C8. Most current products adopt a 60:40 (C10:C8) ratio, while K.Vita (Nestlé Health Science) utilizes an 80:20 (C10:C8) ratio. K.Vita significantly reduced seizure frequency and was associated with mild gastrointestinal adverse effects (*99*). Given that MCT is rapidly hydrolyzed, potential manifestations resulting from rapid ketogenesis (such as ketosis) require monitoring (*100*).

3.3.3. Low glycemic index treatment

The glucose stability during KD therapy is closely associated with seizure control (*101*). Low glycemic index treatment (LGIT) is a KD variant emphasizing low-glycemic foods, and has been validated for effective blood glucose regulation. LGIT imposes less stringent carbohydrate restriction, permitting 40–60 g of low glycemic index (GI) foods or limiting low-GI foods to no more than 10% of total caloric intake (*102,103*). A study involving 36 epilepsy patients with Lennox-Gastaut syndrome or Dravet syndrome undergoing LGIT demonstrated that 56% of patients achieved a ≥ 50% reduction in seizure frequency after 3 months. Only 6% of patients reported adverse events, and no patients developed symptoms such as vomiting, constipation, abdominal pain, or kidney stones (*104*). Maintaining an appropriate blood ketone level is critical for effective refractory epilepsy control. However, during LGIT for refractory epilepsy, researchers observed that seizure control could still be achieved even without strictly maintaining blood ketone levels (*105*). The underlying reason may be that the higher carbohydrate allowance under LGIT facilitates the maintenance of blood glucose within an optimal range, thereby enabling the production and functional efficacy of ketone bodies (*103,106*).

3.3.4. Modified Atkins diet

Modified Atkins diet (MAD) is a KD adapted from the Atkins diet (*107*), characterized by high fat, low carbohydrate, and minimal restrictions on protein intake (*88*). MAD does not require a fixed ketogenic ratio, though the typical ratio ranges from 1:1 to 2:1 (*88,108*). MAD can induce ketosis, thereby producing anti-epileptic effects. A study comparing MAD with anti-epileptic drug therapy found that 30% of patients in the MAD group had > 90% seizure reduction, 52% of patients had > 50% seizure reduction, while the drug group only had 7.7% and 11.5% (*109*). The MAD exhibits greater flexibility than other KD variants. Owing to the absence of a fasting period, faster initiation, and relative ease of implementation, it is convenient for clinicians to prescribe for outpatient emergency management (*107*). Its less restrictive nature also makes MAD the preferred dietary intervention for adult patients (*110*). A more recently developed alternative, the modified ketogenic diet, incorporates many design principles of MAD (*88*) and is regarded as the least restrictive KD variant (*111*).

3.4. Special low protein foods

For many rare diseases classified as inborn errors of intermediary protein metabolism, such as protein/amino acid metabolism disorders, organic acid metabolism disorders, UCDs, dietary management constitutes a pivotal therapeutic strategy (*112*). SLPFs are an integral component of such dietary therapy (*113,114*). SLPFs are considered indispensable for managing these disorders, which not only meet nutrients and energy requirements but also sustain anabolism and enhance dietary diversity. SLPFs are beneficial for maintaining metabolic parameters within target ranges.

One of the most special features of SLPFs is that they can be made into many different types. This feature renders them more similar to regular foods. Protein substitutes and amino acid supplements often have poor taste, which may affect patients' mood and autonomy in eating, thereby reducing compliance with products. SLPFs effectively address these challenges by offering greater dietary options, enabling patients to experience a sense of well-being analogous to that of healthy individuals during mealtimes (Table 3).

4. Prospects for China's rare disease FSMPs

The development of rare disease FSMPs in China is now in the stage of rapid growth. Since the registration of rare disease FSMPs was incorporated into the priority review and approval procedure in 2023, researchers and companies have invested greater efforts in rare disease FSMPs. Encouraged by this policy, two domestically developed rare disease FSMPs were launched in 2025. However, due to the relatively late start of China's rare disease FSMPs, there remain numerous gaps to be addressed and aspects to be optimized. Based on the statistical and analytical summary of commercial FSMPs status of rare diseases in the word, this part presents prospects for the development of China's rare disease

FSMPs from three aspects: product diversity, technology and process, and management policy.

4.1. Expanding the diversity of China's rare disease FSMPs

Insufficient product diversity remains a critical challenge in rare disease FSMPs industry. For instance, of the 32 rare diseases explicitly identified in China as requiring FSMPs to treat, only a subset have accessible products. And these products mainly target amino acid metabolic disorders, organic acid metabolic disorders, fatty acid oxidation disorders, carbohydrate metabolic disorders, and refractory epilepsy. A large number of patients who need FSMPs to treat still face the situation of no available products. For example, patients suffered from galactosemia need long-term use of lactose-free FSMPs, but there are no related products available. In the future, more FSMPs tailored to different rare diseases should be developed.

Expanding product diversity can be achieved not only by broadening the range of applicable diseases but also by exploring new raw materials. Currently, the use of raw materials still focuses on safety and compliance, so raw materials that meet the standards of various countries or organizations are prioritized in production. This has significantly constrained innovation in rare disease FSMPs. Going forwards, more sources of raw materials can be explored, such as plant-based ingredients (*48*), insect proteins (*115*), and marine bioactive compounds (*116*). In addition, rare diseases FSMPs have extremely strict restrictions on raw materials, requiring ingredients to be pure, effective, safe, and not induce metabolic disorders in patients. This poses a huge challenge to production technologies of raw materials. Synthetic biology offers a potential solution to this challenge (*117*). In the future, it should be used for the targeted synthesis of proteins/peptides with specific amino acid compositions, functional carbohydrates, and other substances required for rare disease FSMPs.

4.2. Accelerating innovation in technology and process

Regarding product manufacturing technology, innovations such as 3D/4D printing and targeted delivery systems have already been employed (*12*). Moving forward, these emerging technologies should be further leveraged to produce FSMPs with precisely designed modular dosage forms and enhanced slow or controlled-release profiles. FSMPs formulation imposes extremely stringent requirements on micronutrient content control. Thus, ensuring precise micronutrient dosing and uniform mixing at the industrial scale remains a major challenge. Future efforts should focus on advancing continuous production processes and developing more accurate real-time monitoring technologies.

In terms of product dosage forms, FSMPs in China's market are mainly in powder and liquid forms at present. More portable and edible dosage forms of rare disease FSMPs need to be designed to expand patients' choices in the future. SLPFs are an important product type for enriching patients' choices. A research group from China have developed steamed buns with a low protein content (0.50 g/100 g) for the potential nutritional treatment of abnormal amino acid and organic acid metabolism, urea cycle disorders, and chronic kidney disease (*118*). The design concept of SLPFs requires them to be more closely related to daily diets (*13,113*). Therefore, localized SLPFs can be developed by integrating traditional dietary cultures from different regions to enhance patients' appetite and happiness in the future.

Many ingredients used in rare disease FSMPs have bad tastes, which may greatly reduce the patient's acceptance of the product. Some rare disease FSMPs have been adjusted for flavor by using seasonings. In the future, it is recommended to use more advanced technologies to enhance the flavor of products, such as encapsulation technology (*119*), bio-enzymatic debittering technology (*120*) and odor-taste cross-modal interaction (*121*). Using advanced technologies is beneficial for accelerating the optimization process of rare disease FSMPs from functional priority to sensory pleasure.

4.3. Optimizing China's management policy

Due to variations in food production standards, healthcare systems, regulatory traditions, and risk perceptions, different countries or organizations have developed distinctly different management frameworks. The U.S., Canada, and Australia-New Zealand adopt relatively lenient regulations for FSMPs, with no pre-market registration or notification required. The U.K. and the E.U. implement a pre-market notification system for FSMPs. Japan employs a registration and approval system, though the process from application to approval takes at least six months (*122*). China implements a registration and approval system for FSMPs (*47*), establishing a comprehensive regulatory framework covering formula design, production, market access, and post-market supervision. In China, foods for special medical using are classified into two categories according to whether registration is required or not: *i*) foods with special medical using needed registration, including special medical purpose infant formula foods and FSMPs for one year onwards; *ii*) other foods for special medical purposes exempt from registration, including SLPFs, low glycemic index foods, nutrient supplements, easy-to-chew foods, and nutritionally formulated meals. Under this stringent registration policy framework, China has established the priority review and approval procedure to encourage the research and development and accelerate the market entry for rare disease FSMPs and urgently needed new FSMPs (*123*). Before the implementation of

Table 3. A part of common SLPFs in global commercial market*

Category	Product	Protein content/100 g	Brand
Pasta	Pierogi, Ravioli, Aproten Ditalini, Aproten Fusilli, Aproten Linguine, Aproten Penne, Aproten Pipe, Aproten Rigatoni, Aproten Sedani, Aproten Spaghetti, Pasta Duets, Pasta Solo - Elbows, Dital, Fusilli, Spaghetti, Penne, Loprofin Fusilli, Loprofin Penne, Loprofin Tagliatelle, Loprofin Macaroni, Loprofin Lasagne, Loprofin Spaghetti, Loprofin Animal Pasta, Promin Low Protein Lasagne, Promin Low Protein Pasta Spirals, Promin Low Protein Pasta in Sauce - Cheese & Broccoli, Promin Low Protein Pasta in Sauce – Tomato, Pepper & Herb, Promin Low Protein Cous Cous, Promin Low Protein Alphabets, Promin Low Protein MacPot - Macaroni Cheese, Promin Low Protein MacPot - Tomato Macaroni, Sineamin	0–3.03	Ajinomoto Cambrooke, Nestlé Health Science, Nutricia, Orpharma, PIAM Farmaceutici S.p.A.
Mix (baking, cake, cookie, sugar, bread, soup)	Baking Mix, Blueberry Scone Mix, Chewy Fudgy Brownie Mix, Chocolate Chip Cookie Mix, Gingerbread Mix, MixQuick, Sugar Cookie Mix, Wel-Made Baking Mix, Blueberry Scone Mix, Chewy Fudgy Brownie Mix, Chocolate Chip Cookie Mix, Gingerbread Mix, Sugar Cookie Mix, Alfredo Sauce Mix, Bread Mix, Loprofin Mix, Loprofin Chocolate Cake Mix, Promin Low Protein Hot Breakfast, Promin Low Protein Chocolate Hot Breakfast, Promin LowProtein Scrambled Egg & Omelette Mix, Promin Low Protein XPot - All Day Scramble, Promin Low Protein Burger Mix – Original Flavour, Promin Low Protein Sausage Mix - Original, Promin Low Protein All Purpose Baking Mix, Promin Low Protein Potato Cake Mix, NEC	0–4	Ajinomoto Cambrooke, Nestlé Health Science, Nutricia, Orpharma, PIAM Farmaceutici S.p.A.
Bread	Bagel Bars French Toast, Bagels, Brookelyn Dog Buns, Camburger Buns, Cinnamon Raisin Swirl Bread, Focaccia Sticks - Italian Style, HomeStyle Bread, Pita Pockets, Toaster Topz - Banana Chip, Tuscan Pizza Crusts, The Bigger Bagel, GO! Pockets, Ciabattine, Pane Casereccio	0.34–1.9	Ajinomoto Cambrooke, Nestlé Health Science
Biscuit	Cookies, Mini Crackers, Vitabite, Cookies, Frollini, Loprofin Crackers, Loprofin Herb Crackers	0.22–0.7	Ajinomoto Cambrooke, Nestlé Health Science, Nutricia
Cereal	Loprofin Flakes, Loprofin Loops, Creamy Hot Cereal, Malt-O-Meal	0.32–4	Ajinomoto Cambrooke, Nutricia
Cheese	Cheddar Shreds, Cheddar Wizard, Cheese Singles, Cream Cheese Plain, Mozzarella Shreds	1.8–2.14	Ajinomoto Cambrooke
Bar	Fruit Bar, Apple Breakfast Bars, Blueberry Breakfast Bars	0.32–0.6	Ajinomoto Cambrooke, Nestlé Health Science
Rice	Rice, Loprofin Rice, Short Grain Rice	0.4–0.6	Ajinomoto Cambrooke, Nestlé Health Science, Nutricia
Pizza	Pizza Base, Pizza	0.9–1.45	Ajinomoto Cambrooke, Nestlé Health Science
Chocolate	Chocotino, Chocolate Cha-Cha's	0.4–1.25	Ajinomoto Cambrooke, Nestlé Health Science
Flour	Wheat Starch	0.3	Ajinomoto Cambrooke
Snacks	Yuca Tater Home Fries, Wise Onion Rings, Promin Low Protein Potato Pot – Onion and Croutons, Promin Low Protein XPot - Beef & Tomato	0.2–2.14	Ajinomoto Cambrooke, Orpharma
Sauces	Marinara Minis	1.41	Ajinomoto Cambrooke
Spread	Pea-Not Butter	3.57	Ajinomoto Cambrooke
Meat replacer	Tweekz	1.15–3.44	Ajinomoto Cambrooke

*Data were collected from: Ajinomoto Cambrooke (*https://www.cambrooke.com/*); Nutricia (*https://www.nutricia.co.uk/hcp/products.html*); Nestlé Health Science (*https://www.nestlehealthscience.com/vitaflo*); PIAM Farmaceutici S.p.A. (*https://www.piamfarmaceutici.com/en/product-category/foods-for-special-medical-purposes/*); Orpharma (*https://www.orpharma.com/*).

Table 3. A part of common SLPFs in global commercial market* (continued)

Category	Product	Protein content/100 g	Brand
Egg replacer	Loprofin Egg Replacer, Loprofin Egg White Replacer, Eggz	0–1.88	Ajinomoto Cambrooke, Nutricia
Milk replacer	ProZero, Loprofin Sno-Pro, Loprofin Drink LQ, Milco	0–0.4	Nestlé Health Science, Nutricia, PIAM Farmaceutici S.p.A.

*Data were collected from: Ajinomoto Cambrooke (*https://www.cambrooke.com/*); Nutricia (*https://www.nutricia.co.uk/hcp/products.html*); Nestlé Health Science (*https://www.nestlehealthscience.com/vitaflo*); PIAM Farmaceutici S.p.A. (*https://www.piamfarmaceutici.com/en/product-category/foods-for-special-medical-purposes/*); Orpharma (*https://www.orpharma.com/*).

Table 4. Fourteen rare disease FSMPs entered the priority review and approval procedure*

Announcement time	Acceptance number	Product	Applicant for registration
May 15, 2024	TY20240024	Kairuntai® Special Medical Purpose Intant Amino Acid Metabolism Disorder Food PKU Formula	Jiangsu Daisy Special Medical Food Co., Ltd.
Oct. 18, 2024	TY20240076	Teaibingjia Special Medical Purpose Intant Amino Acid Metabolism Disorder Formula Food	Qingdao Sainte Nutritional Food Co., Ltd.
Oct. 18, 2024	TY20240077	Teaibenjia Special Medical Purpose Intant Amino Acid Metabolism Disorder Formula Food	Qingdao Sainte Nutritional Food Co., Ltd.
Mar. 13, 2025	TY20250032	Enruiyoute Special Medical Purpose Intant Amino Acid Metabolism Disorder Formula Food	SINOFN (Tianjin) Pharmaceutical Technology Co., Ltd.
Mar. 21, 2025	TY20250033	Enzhuoyoute Special Medical Purpose Amino Acid Metabolism Disorder Formula Food	SINOFN (Tianjin) Pharmaceutical Technology Co., Ltd.
Mar. 21, 2025	TY20250034	Enboyoute Special Medical Purpose Amino Acid Metabolism Disorder Formula Food	SINOFN (Tianjin) Pharmaceutical Technology Co., Ltd.
Jun. 11, 2025	TY20250054	Aizhizun Special Medical Purpose Amino Acid Metabolism Disorder Formula Food	Chifeng Sunrise Pharmaceutical Co., Ltd.
Jun. 11, 2025	TY20250055	Aizhixi Special Medical Purpose Amino Acid Metabolism Disorder Formula Food	Chifeng Sunrise Pharmaceutical Co., Ltd.
Jun. 11, 2025	TY20250060	Aifuxi Special Medical Purpose PKU Amino Acid Module Formula Food	Heilongjiang Bright Songhe Dairy Co., Ltd.
Jun. 20, 2025	TY20250062	Ruibaoan® Amino Acid Metabolism Disorder PKU Infant Formula Food	Inner Mongolia Tekangrui Nutritional Food Co., Ltd.
Nov. 15, 2025	TY20250120	Nuobaowei® PKU Formula Food	Hebei Aisheng Technology Co., Ltd.
Nov. 25, 2025	TY20250130	Nuobaorui® PKU Formula Food	Hebei Aisheng Technology Co., Ltd.
Dec. 31, 2025	TY20250155	Kairuntai® Special Medical Purpose Intant Amino Acid Metabolism Disorder Formula Food	Jiangsu Daisy Special Medical Food Co., Ltd.
Jan. 8, 2026	TY20250151	Teyiwei Special Medical Purpose PKU Formula Powder	Shandong Ruoyao Special Medical Food Co., Ltd.

*Data were collected from: Center for Food Evaluation, State Administration for Market Regulation (*https://www.cfe-samr.org.cn/*).

the priority review and approval procedure, there were only three rare disease FSMPs from Nutricia that applied for registration. Fortunately, since the implementation of this procedure, 14 rare disease FSMPs have been included (Table 4), and two of them from Qingdao Sainte Nutritional Food Co., Ltd. have been approved (*124*). It is expected that more high-quality, reasonably priced domestic FSMPs will enter the market in the future.

While the priority review and approval procedure has significantly facilitated the development of China's FSMP industry, the types and quantities of FSMPs still fails to meet patient needs and problems such as complex registration processes, lengthy approval cycles, and insufficient corporate innovation incentives persist still exist. These indicate that the regulatory policy framework of FSMPs requires optimization. Going forward, under guaranteeing high standards for product safety, it will be necessary to establish clear and flexible technical standards for different FSMP categories to reduce approval uncertainties and accelerate market access. For overseas FSMPs that have been marketed but not registered, it is recommended to implement different

approval criteria based on their overseas safety record and clinical research data. This approach would not only ensure the safety of products but also accelerate the entry of overseas products into the China's market.

5. Conclusion

In summary, FSMPs play a crucial role in rare disease management. This review focuses on the commercial rare disease FSMPs around the word. By analyzing the design of products, applicable diseases, and treatment effects, we proposed suggestions for the development of China's rare disease FSMPs in terms of product diversity, technology and process, and management policy.

It should be pointed out that this review only collected commercial rare disease FSMPs. Although this can help researchers and companies understand current market gaps and promptly fill in the shortage of product types, it fails to fully cover and track products that have been studied but not yet marketed. Future studies may consider using systematic review and meta-analysis to comprehensively evaluate rare disease FSMPs that have been launched and are currently under developing. This can provide a more detailed understanding of product development trends and scientific basis for clinical decision-making.

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Review

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Current status and challenges of biologic targeted therapy for myasthenia gravis in China

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SUMMARY: Myasthenia gravis (MG) is an autoimmune neuromuscular disorder posing substantial disease burden in China, with significant impacts on patient quality of life. While conventional immunosuppressants remain fundamental therapy, biologic targeted agents—including B-cell targeting drugs, complement C5 inhibitors, FcRn antagonists, and IL-6R inhibitors—have brought major advances, especially for refractory and MuSK-antibody–positive MG. Increasing availability in China has demonstrated promising clinical outcomes, yet substantial barriers remain. Challenges include high drug costs, limited insurance access, insufficient multicenter clinical evidence, and disparities in physician adoption. China's research is improving, exemplified by local innovation with telitacicept and active participation in global trials, though most biologics remain imported. To maximize benefits, clinical application should be guided by antibody subtype and immunopathology, with individualized, dynamic regimens balancing efficacy, safety, and affordability. High-quality randomized trials, updated guidelines, broader insurance coverage, and R&D investment are urgently needed to promote individualized and accessible MG care in China.

Keywords: myasthenia gravis, biological targeted therapy, FcRn antagonist, C5 inhibitor, chimeric antigen receptor T-cell therapy

1. Introduction

Myasthenia gravis (MG) is an acquired autoimmune disease affecting the neuromuscular junction, characterized by fluctuating muscle weakness and fatigability (*1*). It is caused by autoantibodies that attack components of the neuromuscular junction (NMJ). About 85% of patients have antibodies against the nicotinic acetylcholine receptor (AChR), while the rest mainly have antibodies to muscle-specific kinase (MuSK) or lipoprotein receptor-related protein 4 (LRP4). A small proportion lacks detectable antibodies and is classified as seronegative MG (SNMG) (*2*).

Conventional immunosuppressive treatments, such as glucocorticoids, azathioprine, tacrolimus, and mycophenolate mofetil, can achieve good symptom control in most patients (*3,4*). However, about 20% of patients fail to respond to or cannot tolerate conventional treatments, thus becoming refractory MG (*5*). And 10–20% of patients may have acute onset with rapidly worsening symptoms like dysphagia and weakness in swallowing, chewing, limbs, or neck, which may lead to myasthenic crisis (MC) (*5,6*). These patients often experience significantly impaired quality of life and functional prognosis due to recurrent relapses, drug side effects, and long-term immunosuppressive status.

In recent years, the clinical application of biological targeted therapy has brought new breakthroughs in the treatment landscape of MG. Targeted drugs represented by B cell depleting agents (Rituximab and Inebilizumab) (*7,8*), complement C5 inhibitors (eculizumab, ravulizumab and zilucoplan) (*9-11*), and FcRn inhibitors (efgartigimod, rozanolixizumab, batoclimab and nipocalimab) (*12-15*) have shown favorable efficacy and safety in studies.

In China, some biological agents have been gradually applied in clinical practice, and preliminary results indicate that they have good effects in patients with refractory MG and MuSK antibody-positive MG, providing a new option for patients who do not respond significantly to conventional treatments. However, China still faces many challenges in the promotion of biological targeted therapy for MG, including insufficient independent research and development, high treatment costs, limited medical insurance coverage, and lack of multi-center clinical research data. Therefore, this article aims to review the current status and challenges of biological targeted therapy for MG in China, which is of great significance for promoting standardized and precise treatment.

2. Disease burden of MG in China

The annual incidence of MG in China is about 0.68 per 100,000 population, with a prevalence of 7.3 per 100,000. Nationwide, the total number of patients is estimated at approximately 650,000 (*16,17*). The median length of hospital stay was 8 days with median hospitalization cost US$1,037 (*16*). A recent Chinese nationwide registry-based study indicated the median annual direct medical cost was US$2,219.0, with a median of US$1,860.2 contributed by medical costs and a median of US$248.2 for non-medical costs (*18*).

Despite the continuous advancement of treatment methods, the mortality rate associated with MG remains at a relatively high level. Limited evidence showed the crude mortality rate of MG varied from 0.43 to 2.7 per million people over the past three decades. A national population-based study in China indicated that the age-standardized mortality rate of MG was 1.86 per million people and markedly higher in males than in females (2.37 *vs.* 1.31 per million). The median age at death from MG was 59.45 years, significantly lower than that in the general population (75.47 years) (*19*).

MG has a significant impact on the quality of life of both patients and caregivers. The overall quality of life (QoL) scores for patients with MG are lower than those of the general population, with significant impairments particularly evident in physical functioning and daily activities. Greater disease severity, as reflected by higher MG-ADL and QMG scores, is associated with a poorer quality of life. Patients with less social support and greater economic burden experience a more pronounced decline in QoL (*20*). A cross-sectional study conducted in China showed that approximately one-third of patients exhibited clinically significant fear of disease progression (FoP), which is higher than that observed in some other chronic disease populations. Higher FoP was more likely in patients with more severe MG, shorter disease duration, higher levels of anxiety and depression, lower levels of social support, and among female patients (*21*). Additionally, a recent study investigated the family burden experienced by caregivers of patients with MG in Northwest China. The results showed that a significant proportion of caregivers reported notable family burden, with financial strain and daily activity disruption being the most prominent (*22*).

Although most patients with MG can be definitely diagnosed based on clinical symptoms, antibody tests, and repetitive nerve stimulation (RNS), certain atypical presentations are prone to misdiagnosis. These mainly include distal limb weakness, onset confined to bulbar muscles, unilateral or asymmetric manifestations, as well as initial symptoms of non-specific manifestations such as respiratory failure. These features can easily lead to clinical misdiagnosis as stroke, myopathy, peripheral neuropathy, or amyotrophic lateral sclerosis (*23*).

In China, taking a comprehensive approach that includes medical staff education, standardized diagnosis procedure and auxiliary examinations, patient education, and multidisciplinary collaboration can significantly reduce misdiagnosis and missed diagnosis of MG, facilitating early diagnosis and treatment, and thereby improving patient prognosis.

3. Immunopathological mechanisms of MG

The emergence of biologic targeted therapies has been driven by a deeper understanding of the immunopathological mechanisms of MG. According to current immunological perspectives, thymic abnormalities (such as thymic hyperplasia or thymoma) result in aberrant expression of acetylcholine receptor (AChR) or related antigens within the thymus. In this context, self-reactive $CD4^+$ T cells escape central tolerance mechanisms and are activated by AChR antigen-presenting cells (such as dendritic cells and macrophages). These antigen-presenting cells process AChR peptides and present them to naïve $CD4^+$ T cells, thereby initiating T cell activation (*24*).

Activated $CD4^+$ T cells (primarily Th1 and Th17 subsets) facilitate B cell activation by providing secondary signals through cell surface molecule interactions and secretion of various pro-inflammatory cytokines. Additionally, the increased number and enhanced function of Th17 cells, coupled with impaired Treg function, lead to dysregulation of the immune regulatory network, further promoting persistence and progression of autoimmune responses (*25*).

With T cell help, self-reactive B cells recognizing self-antigens such as AChR become activated and subsequently proliferate and differentiate within germinal centers into memory B cells and long-lived plasma cells. Interleukin-6 (IL-6) serves as a key cytokine, promoting B cell differentiation into antibody-secreting cells while simultaneously inhibiting Treg cell generation and function (*26*). The differentiated plasma cells migrate to the bone marrow or inflamed tissues, where they continually produce high-affinity anti-AChR and other autoantibodies (anti-MuSK antibodies).

After AChR antibodies enter the circulation and reach the neuromuscular junction, they disrupt synaptic transmission *via* multiple mechanisms: *i*) upon binding to AChR, they activate the complement cascade (especially the C5b-9 membrane attack complex), directly damaging the postsynaptic membrane; *ii*) they induce cross-linking and accelerated internalization and degradation of AChR, reducing the number of functional receptors; *iii*) they directly block acetylcholine binding sites, thereby interfering with neurotransmitter-receptor interactions (*27*).

In MuSK antibody-positive MG, the pathogenic mechanism differs somewhat. Anti-MuSK antibodies are primarily the non–complement-activating IgG4

subclass and mainly disrupt the post-synaptic membrane organization by blocking the agrin–LRP4–MuSK signaling pathway, affecting formation and stability of the neuromuscular junction, with less reliance on complement activation (*28*).

Understanding this complex cascade of immunopathological processes provides a theoretical basis for targeted interventions at various immune stages and explains why targeted therapies against B cells, FcRn, the IL-6 pathway and the complement system have demonstrated clinical efficacy in MG (Figure 1).

4. Progress in biological targeted therapy for MG in China

4.1. B-cell targeted therapies

As an anti-CD20 monoclonal antibody, Rituximab is currently off-label widely used in domestic clinical practice for the treatment of refractory generalized MG (gMG). Several Chinese prospective and retrospective studies have shown that low-dose Rituximab can alleviate patient symptoms, reduce the concurrent use of glucocorticoids, and achieve better treatment outcomes in patients with refractory gMG, especially patients with MuSK antibody appear to have an even better therapeutic response (*29-32*). Additionally, the use of low-dose Rituximab in new-onset gMG patients in China has also achieved favorable efficacy, and real-world research data support the findings of the RINOMAX study that Rituximab demonstrates superior efficacy over placebo in new-onset patients (*7,33,34*). Although there is a lack of support from high-level large, multicenter, prospective randomized controlled trials (RCTs), real-world data have demonstrated the efficacy of rituximab, and European treatment guidelines have recommended it as an alternative first-line option for gMG (*35*). However, a unified standard for individualized medication strategy for Rituximab has not yet been established, and further research is needed to explore an optimal treatment regimen.

Inebilizumab, an innovative anti-CD19 monoclonal antibody targeting B-cells and partial $CD19^{+}$ plasma cells, has completed a pivotal global Phase III clinical trial with positive results (*8*). Through more thorough B-cell depletion, this drug may provide more potent treatment for MG patients with high-titer antibodies. Inebilizumab has been approved in China for treatment of neuromyelitis optica spectrum disorder (NMOSD), but its indication for gMG is still under review by the National Medical Products Administration (NMPA).

Telitacicept is a dual-target recombinant fusion protein that blocks the BAFF (BLyS) and APRIL pathways, broadly suppressing B cells and antibody production. Due to positive results in pivotal phase II and III clinical trials, the drug was approved in China in 2025 for treatment of gMG (Phase III data have not yet been published) (*36*). This is the first biologic targeted therapy for gMG independently developed and approved for marketing in China.

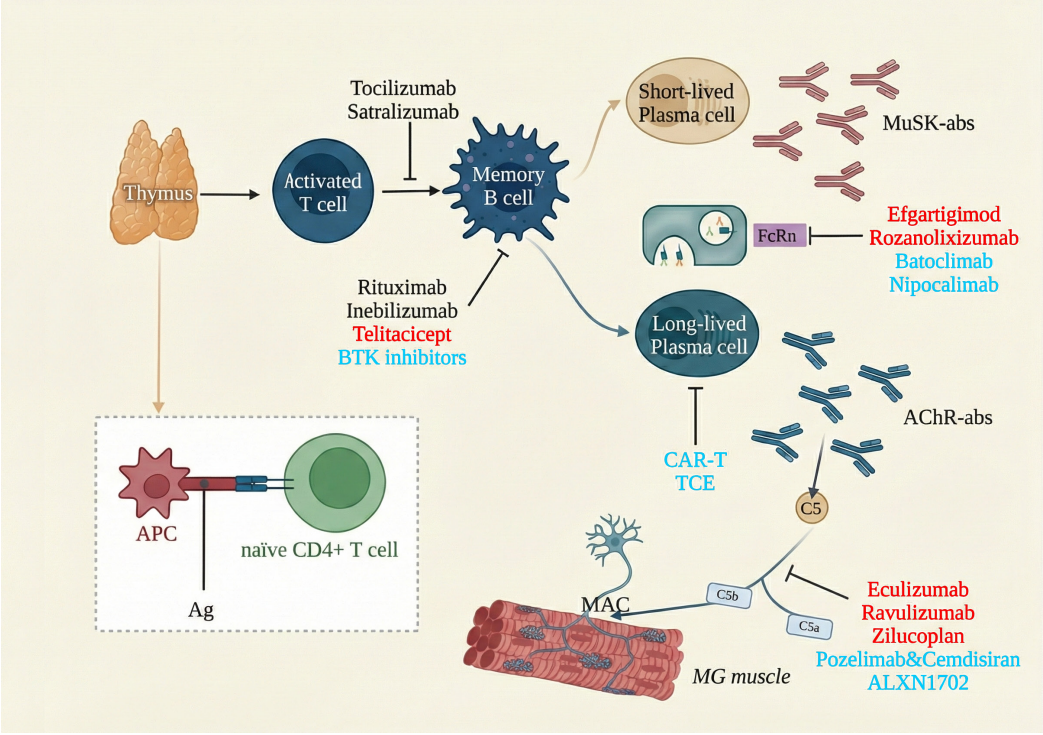

Figure 1. Schematic diagram of the immunopathological mechanisms of myasthenia gravis. APC: antigen presenting cell; Ag: antigen; MAC:membrane attack complex; CAR-T: chimeric antigen receptor T; TCE: T-cell engager. *Red-labeled agents*: biologic targeted drugs approved in China for the treatment of MG. *Black-labeled agents*: biologic targeted drugs approved in China for other indications and used off-label for MG.

4.2. Complement inhibitors

Eculizumab, the first C5 complement inhibitor, blocks terminal complement activation to protect the neuromuscular junction, reduce AChR loss, and improve neuromuscular transmission. It was approved in China in 2023 for the treatment of refractory AChR-positive gMG. Several Chinese prospective observational studies showed favorable efficacy and good tolerability in myasthenic crises, and thymoma-associated MG (TAMG) (*37,38*). Other case reports indicate that eculizumab can be used in special situations such as those involving severe infections and pembrolizumab-induced impending crisis (*39,40*).

Another C5 complement inhibitor, ravulizumab, has been approved in China in 2025 and is soon to be applied in clinical practice. As a long-acting C5 inhibitor, ravulizumab requires maintenance dosing only every 8 weeks after the loading dose (compared to every 2 weeks for eculizumab), which significantly reduces frequency of infusions and associated healthcare burden (*10*). Zilucoplan is a subcutaneously injected macrocyclic peptide targeting C5 with demonstrated efficacy and good safety in global Phase III trials (*11*). As a peptide inhibitor, its binding site differs from that of monoclonal antibodies, offering potential inhibitory advantages against certain C5 variants—such as the p.Arg885His mutation reported in PNH—that limit monoclonal antibody binding (*41*). Zilucoplan has already submitted a marketing application to the NMPA and is expected to receive approval to enter the Chinese market in 2026.

4.3. FcRn antagonists

FcRn binds to IgG within endosomes, mediating recycling and prolongation of IgG half-life. FcRn antagonists bind to FcRn with high affinity, competitively inhibiting the binding and recycling of IgG—including pathogenic autoantibodies such as anti-AChR/MuSK IgG—thereby leading to reduced circulating total IgG levels and decreased titers of pathogenic autoantibodies. FcRn antagonists have become a new milestone in the treatment of gMG. Efgartigimod (Fc fragment) and rozanolixizumab were approved in China in 2023 and 2025, respectively. Multiple real-world studies from China have explored use of efgartigimod in myasthenic crisis, impending crisis, TAMG, new-onset MG, ocular MG, and seronegative MG, providing Chinese evidence for application of efgartigimod in different subtypes of MG patients (*42-47*). However, experience with rozanolixizumab in China is still very limited, and there are currently no relevant data.

Both batoclimab and nipocalimab are monoclonal antibodies targeting FcRn. Their pivotal phase II and III clinical trials have yielded positive results (*13,15*), and both have already been submitted for pre-market review to the NMPA. Notably, the registration clinical trial for batoclimab was conducted independently in China, and it is the first published drug in China to demonstrate positive results in RCT for the treatment of gMG.

4.4. IL-6R inhibitors

Satralizumab is a humanized monoclonal antibody administered *via* subcutaneous injection that binds to and blocks both membrane-bound and soluble IL-6 receptors (IL-6R), thereby inhibiting both the classical and trans-signaling pathways of IL-6 and reducing downstream inflammatory and immune activation signals such as JAK/STAT. A recent phase III clinical study involving China demonstrated that satralizumab is well tolerated and, compared with placebo, led to modest improvements in both patient-reported and clinician-assessed outcomes at week 24 in patients with AChR antibody positive gMG (*48*). It has been approved for the treatment of NMOSD in China, but Roche terminated the open-label extension study after the phase III trial, possibly due to the perception that its efficacy was not sufficiently remarkable.

Additionally, two prospective cohort studies conducted in China have indicated that another IL-6R inhibitor, Tocilizumab, can improve symptoms of gMG and reduce dosage of glucocorticoids. However, the use of IL-6R inhibitors in treating gMG in China is considered off-label, and further evidence is needed to support their efficacy (*49,50*).

4.5. Frontiers in cell therapy

China has made rapid progress in the field of cellular immunotherapy such as Chimeric Antigen Receptor T (CAR-T) cell therapy, and some projects have taken the lead in clinical exploration for MG. Zhang *et al.* used bispecific BCMA/CD19-targeted CAR-T cell therapy to treat a case of refractory AChR-MG, achieving significant and sustained efficacy with no occurrence of severe cytokine release syndrome or neurotoxicity (*51*). Tian *et al.* used BCMA9-targeted CAR-T cell therapy to treat one case of refractory AChR-MG and one case of refractory MuSK-MG, both of which demonstrated significant and durable efficacy with favorable safety profiles (*52*). These valuable cases suggest that CAR-T therapy holds potential to provide a "functional cure" for MG.

4.6. China's active participation in global R&D of biologically targeted drugs

China's participation in global multi-center clinical trials of biologically targeted drugs has increased significantly. The ongoing phase III trials include Pozelimab/Cemdisiran (C5 inhibitor, Regeneron), ALXN1720 (C5 inhibitor,AstraZeneca), and Remibrutinib (BTK inhibitor, Novartis). A phase Ib clinical trial of a BCMA-

targeting bispecific T cell-engaging antibody (Cizutamig, Candid Therapeutics, Inc.) for the treatment of gMG is also ongoing. This proactive involvement has not only accelerated local adoption of innovative drugs but also enhanced China's international influence in the field of neuroimmunology. In the future, as more domestic enterprises join global research and development networks, China is poised to transform from a "follower" to a "leader", contributing Chinese expertise to treatment of rare diseases worldwide.

At present, targeted therapeutic drugs approved for marketing in China have formed two core therapeutic directions: complement C5 inhibitors and FcRn antagonists. According to the latest data in September 2025, 6 targeted drugs have been approved for the treatment of gMG, and another 3 drugs are under review by the NMPA (Table 1 and Table 2).

5. Challenges and perspectives

5.1. Optimizing the clinical application of conventional and biologic targeted therapies

Conventional agents (including corticosteroid and other immunosuppressants) still remain as fundamental status in MG, but the cumulative risks associated with long-term use—particularly infections—should not be overlooked. The advent of biologic targeted therapies has expanded precision treatment and partially reshaped the treatment landscape; however, stratified, population-specific guidance for Chinese patients is still lacking. Inappropriate combination regimens may increase adverse events and financial burden. One of the main challenges at present is how to optimize conventional therapies and biologic targeted therapies in the context of balancing economic considerations and clinical efficacy.

Combination therapy should be based on MG immunopathology. FcRn antagonists and complement

Table 1. Biological targeted drugs approved for marketing in China for gMG

Drug Name	Mechanism of Action	Indication	Approval Time	Route of Administration
Efgartigimod	FcRn antagonist	Used in combination with conventional drugs for the treatment of adult patients with AChR antibody positive gMG	July 2023	Subcutaneous / Intravenous
Rozanolixizumab	FcRn antagonist	Used in combination with conventional drugs for the treatment of adult patients with AChR antibody or MuSK antibody positive gMG	May 2025	Subcutaneous
Eculizumab	Complement C5 inhibitor	Used for the treatment of adult patients with refractory AChR antibody positive gMG	June 2023	Intravenous
Ravulizumab	Complement C5 inhibitor	Used in combination with conventional drugs for the treatment of adult patients with AChR antibody positive gMG	April 2025	Intravenous
Zilucoplan	Complement C5 inhibitor	Used in combination with conventional drugs for the treatment of adult patients with AChR antibody positive gMG	Oct 2025	Subcutaneous
Telitacicept	BLyS/APRIL dual-target fusion protein	Used in combination with conventional therapy for the treatment of adult patients with gMG	May 2025	Subcutaneous

Data Source: https://www.nmpa.gov.cn/

Table 2. Biological targeted drugs for gMG under review by NMPA

Name	Mechanism of Action	Indication	Review Stage	Clinical Trial Progress
Batoclimab	FcRn antagonist	Used in combination with conventional drugs for the treatment of gMG	New Drug Application (NDA) submitted	Phase III clinical trial was completed in January 2023, results have been published, showing significant efficacy
Inebilizumab	Anti-CD19 monoclonal antibody	Treatment of adult patients with AChR antibody positive gMG	New Drug Application (NDA) submitted	Results of the global pivotal Phase III MINT trial have been published, showing significant efficacy
Nipocalimab	FcRn antagonist	Used in combination with conventional therapeutic drugs for the treatment of adult patients with gMG	New Drug Application (NDA) submitted	Results of the global pivotal Phase III Vivacity-MG3 trial have been published, showing significant efficacy

Data Source: https://www.nmpa.gov.cn/; data up to Nov 27, 2025.

C5 inhibitors can rapidly and substantially improve symptoms in AChR-positive gMG, yet their targets lie downstream and do not directly deplete upstream memory B cells or plasma cells responsible for autoantibody production. Although efgartigimod may exert an "educational" effect on upstream immune networks (*53,54*), current data suggest this effect is insufficient to reconstitute B-cell compartments or restore immune homeostasis. In clinical practice in China, FcRn antagonists or C5 inhibitors are often used for weeks to months during the acute or induction phase, combined with low-dose glucocorticoids and/or nonsteroidal immunosuppressants. Once stable, biologics are tapered or discontinued while conventional therapies are continued. This approach reflects a concurrent use of upstream conventional agents with downstream biologics. Relevant Investigator-initiated trials (IITs) are ongoing and are expected to refine clinical decision-making. For refractory MG with poor response to conventional therapy, B-cell–targeting agents or C5 inhibitors may be prioritized, though optimal dosing and duration remain to be defined. If response to available biologics is inadequate, participation in CAR T-cell therapy trials may be considered.

Treatment decision making should be guided by antibody subtype (AChR, MuSK, LRP4), clinical classification (ocular *vs.* generalized), and thymoma status. A stratified and rational combination of conventional drugs and biologics, with dynamic assessment of efficacy and safety, is essential to achieve individualized care. In the future, a biomarker-driven, subtype-based therapeutic framework with adaptive strategy adjustment will be vital to realizing precision medicine.

5.2. Restrictions on accessibility and affordability

Biologic targeted therapies offer meaningful clinical benefit, but high costs and limited medical insurance reimbursement restrict access for some patients. Even after efgartigimod entered the reimbursement list, patients still bear approximately 20–30% out-of-pocket costs, and those in economically disadvantaged rural or remote regions may have no practical access.

Delays in updating the National Reimbursement Drug List (NRDL) have also widened disparities to access. Rozanolixizumab is a humanized monoclonal antibody approved and launched in China for MG. However, although eligible MuSK-MG patients meet the clinical indications, they currently cannot obtain reimbursement because the drug has not yet been listed in the NRDL. There is an urgent need to accelerate the inclusion of novel biologic agents in the NRDL and to explore diversified payment models—such as basic medical insurance combined with commercial insurance—to reduce patients' financial burden and improve equitable access.

5.3. Lack of high-quality evidence

The current evidence base for the treatment of MG in China remains limited. Most available studies are small-sample, retrospective analyses rather than RCTs. For example, domestic investigation of tocilizumab in refractory MG is a single-center cohort study with inadequate sample sizes and insufficient long-term follow-up.

Furthermore, systematic evaluations of how genetic diversity within the Chinese population influences therapeutic efficacy of biological targeted therapy have not been conducted, constraining localization of existing guidelines. Lack of real-world registry studies also impedes development of efficacy prediction models and advancement of individualized treatment strategies. There is an urgent need to establish a national MG database and to initiate high-quality, multidisciplinary RCTs to address evidence gaps and standards of care tailored to Chinese patient characteristics.

5.4. Lag in physicians' practice and academic consensus

There are marked regional disparities in management of MG across China. Tertiary centers in major cities have broadly adopted biologic targeted therapies, whereas primary healthcare institutions largely rely on conventional regimens and demonstrate limited awareness of novel agents such as FcRn antagonists. Although an updated Chinese clinical practice guideline was released in 2025 (*55*), many clinicians have not yet integrated these advances into routine care and remain uncertain about treatment selection.

To address these gaps, it is essential to strengthen academic training and disseminate the latest guidelines through national continuing medical education programs, while establishing regional multidisciplinary platforms to support experience sharing. In parallel, consensus-building among Chinese experts on the use of biologic targeted therapies in MG is needed to clarify treatment prioritization and monitoring indicators across MG subtypes, thereby narrowing disparities in treatment.

5.5. Challenges in innovative Drug R&D for Chinese biotechs

Among drugs approved or under review in China for the treatment of MG, only telitacicept represents a domestically originated innovation. Moreover, of the many RCTs conducted to date, telitacicept and batoclimab remain the sole two studies completed independently in China. Collectively, these observations highlight current limitations in China's research and development capacity for biologic targeted therapies.

This embarrassing situation is due to inadequate accumulation of cutting-edge originality and core technologies. Owing to longstanding dependence on

clinical demand–driven and generic drug pathways, independent innovation capabilities remain relatively limited, with suboptimal investment in basic research and world-leading breakthrough technologies. As a result, "me-too" and "me-better" drugs continue to dominate the market, while truly first-in-class or best-in-class innovative therapies remain uncommon.

Additionally, the evolving policy landscape, difficulties in market access, and complexities of internationalization further challenge Chinese biotechs innovators. Ongoing adjustments in areas such as drug review, pricing, and reimbursement constrain promotion and payment for new therapies and elongate return cycles. At the same time, the overseas regulatory registration, intellectual property barriers, and limited access to global collaborative resources collectively heighten competitive pressures on Chinese biotechs in the global high-end pharmaceutical innovation arena.

6. Conclusion

Biologic targeted therapies have reshaped the MG management landscape in China, offering new hope for refractory patients. However, optimizing clinical use, improving access and affordability, investing in domestic innovation, and generating robust local evidence remain critical for achieving equitable and precise MG treatment nationwide.

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How to evaluate rare disease policy effectiveness based on policy modeling consistency (PMC) index model: A quantitative assessment of policy implementation in China

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SUMMARY: Based on the Policy Modeling Consistency (PMC) index model, this study systematically evaluates 19 national-level and 13 regional-level rare disease policy documents from 2016 to 2025, aiming to reveal the structural characteristics and consistency level of China's rare disease policy system. Using ROSTCM 6.0 software, high-frequency keywords and semantic networks from the policy texts were extracted to identify policy focus and thematic evolution. A PMC evaluation system was constructed to assign values and conduct a visual analysis of the sample policies. Results show that the average PMC index for China's rare disease policies is 5.31 (national level) and 4.94 (local level), falling within the "excellent–acceptable" range overall, indicating that the structure of China's rare disease policy system is well-developed. Among the indicators, policy nature (X2), policy function (X8), and outcome orientation (X4) scored higher, reflecting strategic planning and institutional characteristics at the national level. In contrast, incentive measures (X5), patient support (X6), and social support (X9) scored lower, highlighting deficiencies in research and development incentives, social integration, and long-term support mechanisms. Further comparisons reveal that national policies emphasize top-level design and institutional development. In contrast, local policies focus more on exploratory efforts in medical assistance and policy innovation. To optimize China's rare disease policy system, it is essential to improve incentive and social support systems, promote coordinated legislation between national and local levels, establish a national rare disease information platform and a dedicated fund, and build a comprehensive policy chain.

Keywords: policy evaluation, PMC index, rare diseases, policy evaluation

1. Introduction

Rare diseases are conditions with extremely low prevalence and small patient populations, most of which are chronic, severe, or life-threatening. No unified international definition exists, with classification typically based on prevalence or patient numbers (*1*). Over 10,000 rare diseases have been identified to date, accounting for approximately one-tenth of all human diseases (*2*). By the end of 2024, the global rare disease patient population had exceeded 300 million, with a trend toward earlier onset and longer disease duration (*3*). The Chinese Medical Association has proposed reference criteria for rare diseases: conditions with a prevalence below 1/500,000 or a neonatal incidence rate below 1/10,000 are classified as rare diseases (*4*).

To address rare disease challenges, multiple countries have established systematic policy frameworks. The United States enacted the Orphan Drug Act in 1983, promoting drug development through tax incentives, R&D support, and market exclusivity (*5*). The European Union implemented the Orphan Medicinal Products Directive in 2000, establishing cross-border collaboration mechanisms to harmonize drug approvals, clinical guidelines, and social security provisions (*6*). Japan and South Korea have also improved patient access to medications and diagnostic services through catalog recognition, research funding, and healthcare coverage (*7*). In contrast, China's policies began later but have gradually formed a system centered on catalogs, drugs, diagnostics, and coverage, in recent years (*8*). In 2018, China's National Health Commission released the "First Batch of Rare Disease Catalog", listing 121 diseases, which for the first time defined the scope of rare diseases and promoted drug development, standardized diagnostics, and medical insurance coverage (*9*).

In 2019, the Ministry of Finance and the General Administration of Customs introduced tax incentives to reduce drug prices (*10*). The same year saw the release of the "Guidelines for Diagnosis and Treatment of Rare Diseases (2019 Edition)", providing standardized clinical protocols for all 121 diseases and mandating their implementation by network hospitals (*9*). In 2023, the "Second Batch of Rare Disease Catalog" added 86 new conditions, bringing the total to 207, further expanding policy coverage and public awareness (*11*).

Existing research primarily focuses on policy content, international experiences, specific diseases, or regional cases, commonly employing literature reviews, comparative studies, and qualitative interviews (*12*). Systematic, standardized tools for quantitative assessment and visualization of national and provincial policies are rarely utilized. This study employs the Policy Modeling Consistency (PMC) index model and text mining methods to conduct quantitative analysis of policy texts at the national and regional levels in China. It aims to reveal the current status and shortcomings of China's rare disease policies, provide empirical evidence for policy optimization, and offer insights for the international community to understand China's rare disease governance practices.

2. Materials and Methods

2.1. Data sources

To ensure the representativeness and authority of the policy documents studied, this research employed the keyword "rare diseases" to conduct searches on the official websites of the State Council of the People's Republic of China and various ministries, as well as specialized policy databases such as "Peking University Law Database". Given the relatively limited number of specialized rare disease policies and China's overall late start in this field, the following criteria were applied for inclusion and exclusion:

Inclusion Criteria: *i*) Issuing authorities limited to the State Council of the People's Republic of China, ministries and commissions, provincial/municipal people's governments, and relevant government departments (*e.g.*, National Health Commission, local health commissions); *ii*) Document types restricted to plans, opinions, notices, and other policy-normative or directive documents; *iii*) Policy content must be closely related to the research theme. Exclusion criteria: *i*) Policy documents unrelated to the research theme; *ii*) Non-official documents such as bulletins, responses, or speeches.

China entered a phase of concentrated policy issuance in the rare disease sector starting in 2016, with a significant increase in policy density. This study selected policy documents issued between January 1, 2016, and June 1, 2025, as research texts. At the national level, a total of 19 policy documents were included (Table 1). At the local level, this study did not comprehensively cover all provinces but selected representative regions, such as those leading in rare disease diagnosis and treatment system development, medical insurance coverage, and drug accessibility, including a total of 13 policy documents (Table 2).

2.2. Policy text mining and analysis

Extracting the smallest analytical units highly relevant to the research theme from policy texts enhances the focus and scientific rigor of analysis, providing support for revealing core issues and evolutionary logic within rare disease policies. This study retained the smallest paragraphs highly relevant to the research theme from each policy text to construct a rare disease policy corpus. A combined qualitative and quantitative approach was employed to conduct a multi-perspective, multi-dimensional analysis of national and regional rare disease and drug-related policy texts. Following the compilation of national and regional policy texts, ROSTCM Content Mining 6.0 software was employed to perform text mining on 32 policies. This process involved filtering out non-specific policy indicators like "reduce" and "enhance", merging synonyms such as "evaluation" and "assessment", systematically removing function words and redundant general expressions, and generating a high-frequency word list (Table 3) and a semantic network diagram (Figure 1). This process identified policy focal points and intrinsic connections, establishing a data foundation for subsequent content analysis.

The high-frequency words reveal that rare disease policy texts predominantly focus on terms like "hospital", "patient", "treatment", "medical care", "clinical", and "disease". Policy emphasis centers on establishing diagnostic and treatment systems and providing patient healthcare services. Simultaneously, terms like "medicines", "drugs", "trials", and "review" reflect the state's high priority on drug R&D and regulatory approval processes. Conversely, terms related to financial burdens and social support, such as "guarantee" and "insurance", appear with lower frequency.

The semantic network diagram reveals that patients, clinical practice, and genetics occupy central positions within the social network. This indicates that clinical work, drug supply security, and genetic screening are the primary focuses of China's current rare disease policies. Furthermore, these three core high-frequency terms radiate out to multiple keywords, including treatment, disease, testing, mutation, drugs, and genetics. Consequently, enhancing the diagnostic and therapeutic standards for rare diseases, encouraging the market launch of rare disease drugs, and promoting innovative technological approaches represent the primary directions for China's current rare disease prevention, treatment, and policy safeguards.

Table 1. National-level policies on rare diseases in China

Policy Code	Policy Title	Issuing Authority	Date Issued
P1	Guiding Opinions on Promoting the Development of the Pharmaceutical Industry Chain (*37*)	General Office of the State Council	March 4, 2016
P2	Key Tasks for Deepening Healthcare System Reform in 2016 (*38*)	State Council	April 21, 2016
P3	Notice on Issuing the "Guidelines for Pharmaceutical Industry Development Planning" (*39*)	Ministry of Industry and Information Technology, National Development and Reform Commission, Ministry of Science and Technology	October 26, 2016
P4	Opinions on Deepening Reform of Review and Approval Systems to Encourage Innovation in Pharmaceuticals and Medical Devices (*40*)	State Council	October 8, 2017
P5	Notice on Publishing the First Batch of Rare Disease Catalog (*41*)	National Health Commission, Ministry of Science and Technology, Ministry of Industry and Information Technology	May 11, 2018
P6	Announcement on Optimizing Matters Related to Drug Registration Review and Approval (*42*)	National Medical Products Administration, National Health Commission	May 23, 2018
P7	Technical Guidance Principles for Accepting Overseas Clinical Trial Data for Drugs (*43*)	National Medical Products Administration	July 6, 2018
P8	Announcement on Issuing Guidance Principles for the Registration Review of Medical Devices Used in the Prevention and Treatment of Rare Diseases (*44*)	National Medical Products Administration	October 12, 2018
P9	Notice on Issuing the Diagnosis and Treatment Guidelines for Rare Diseases (2019 Edition) (*45*)	National Health Commission	February 27, 2019
P10	Notice on Establishing the National Rare Disease Diagnosis and Treatment Collaborative Network (*46*)	National Health Commission	February 12, 2019
P11	Notice on Value-Added Tax Policies for Rare Disease Medicines (*47*)	Ministry of Finance, General Administration of Customs, State Taxation Administration, National Medical Products Administration	February 20, 2019
P12	Notice on Implementing the Registration of Rare Disease Case Diagnosis and Treatment Information (*48*)	National Health Commission	October 10, 2019
P13	State Administration for Market Regulation (*49*)	State Administration for Market Regulation	March 30, 2020
P14	Technical Guidance Principles for Clinical Development of Rare Disease Drugs (*50*)	Drug Evaluation Center, National Medical Products Administration	December 31, 2021
P15	Guidance Principles for Natural History Studies in Rare Disease Drug Development (*51*)	Drug Evaluation Center, National Medical Products Administration	July 27, 2023
P16	Notice on Announcing the Second Batch of Rare Disease Catalog (*52*)	National Health Commission	September 18, 2023
P17	Technical Guidance Principles for Clinical Trials of Rare Disease Gene Therapy Products (*53*)	Drug Evaluation Center, National Medical Products Administration	January 12, 2024
P18	National Reimbursement Drug List for Basic Medical Insurance, Work Injury Insurance, and Maternity Insurance (2024 Edition) (*54*)	National Healthcare Security Administration, Ministry of Human Resources and Social Security	November 27, 2024
P19	Notice on Issuing Diagnosis and Treatment Guidelines for 86 Rare Diseases, Including Achondroplasia (2025 Edition) (*55*)	National Health Commission	June 17, 2025

Data Source: Compiled based on publicly available information from the official websites of the National Health Commission, the National Healthcare Security Administration, and other relevant authorities. For detailed references, see the bibliography at the end of this document.

Table 2. Policies related to rare diseases in typical regions

Region	Policy Code	Policy Title	Issuing Authority	Date Issued
Qingdao	P1	Qingdao Supplementary Medical Insurance Directory of Special Medicines, Special Medical Consumables, and Precision Diagnosis and Treatment Projects (*56*)	Qingdao Municipal Human Resources and Social Security Bureau	July 26, 2018
	P2	Notice of Qingdao Municipal Health Commission on Forwarding Document Lu Yibao Fa [2020] No. 84 Regarding Inclusion of Certain Rare Disease Specialty Medicines into Provincial Critical Illness Coverage (*57*)	Qingdao Municipal Medical Security Bureau, Qingdao Municipal Finance Bureau, Qingdao Municipal Health Commission	January 26, 2021
Shanghai	P3	Shanghai List of Major Rare Diseases (2025 Edition) (*58*)	Shanghai Municipal Health Commission and Four Other Departments	March 3, 2025
	P4	Shanghai Municipal Medical Security Regulations (*59*)	Standing Committee of the Shanghai Municipal People's Congress	December 31, 2024
Beijing	P5	Implementation Plan for Beijing's Pilot Zone Construction on Rare Disease Drug Coverage (Trial) (*60*)	Beijing Municipal Drug Administration and Five Other Departments	September 14, 2024
	P6	Capital Health Development Special Research Program on Rare Diseases (*61*)	Beijing Municipal Health Commission	May 27, 2025
Guangzhou	P7	Guangzhou Municipal Medical Security Development Plan for the 14th Five-Year Period (*62*)	Guangzhou Municipal Medical Security Bureau	December 28, 2021
Foshan	P8	Foshan Municipal Medical Assistance Measures (*63*)	Foshan Municipal Medical Security Bureau	February 28, 2025
	P9	Foshan City Catalog of Medicines, Therapeutic Foods, and Medical Institutions for Rare Disease Medical Assistance (2020 Edition) (*64*)	Foshan Municipal Medical Security Bureau	May 29, 2020
Jiangsu	P10	Jiangsu Province Implementation Plan for Rare Disease Diagnosis and Treatment (*65*)	Jiangsu Provincial Health Commission	April 2, 2019
	P11	Notice on Clarifying Matters Related to Diagnosis, Medication Treatment, and Benefit Eligibility for Rare Disease Medication Coverage Recipients (*66*)	Jiangsu Provincial Medical Security Bureau	July 6, 2021
Zhejiang	P12	Notice on Establishing the Zhejiang Province Rare Disease Medication Security Mechanism (*67*)	Zhejiang Provincial Medical Security Bureau, Zhejiang Provincial Department of Civil Affairs, Department of Finance	December 30, 2019
	P13	Notice on Strengthening Medical Security for Rare Diseases (*68*)	Zhejiang Provincial Department of Human Resources and Social Security, Zhejiang Provincial Department of Civil Affairs, Zhejiang Provincial Department of Finance, Zhejiang Provincial Health and Family Planning Commission	May 13, 2016

Data Source: Compiled based on publicly available information from the official websites of local health commissions, medical insurance bureaus, and other relevant authorities. For detailed references, please see the appendix at the end of this document.

2.3. PMC index model

The PMC index model was proposed by Estrad (*13*). Based on the Omnia Mobilis theoretical framework, it serves as an effective tool for measuring policy impact. This theory advocates prioritizing the influence of every relevant variable during policy evaluation. The PMC index model enables in-depth analysis of policy strengths and weaknesses across multiple dimensions, thereby facilitating quantitative assessment of policy texts.

2.3.1. Variable selection and configuration

Variable selection and indicator configuration are critical for policy analysis using the PMC Index Model. Based on high-frequency vocabulary and referencing existing

Table 3. High-frequency word list

No.	Term
1	Hospital
2	Patient
3	Treatment
4	Healthcare
5	Clinical
6	Disease
7	Gene
8	Drug
9	Diagnosis
10	Coverage
11	Mutations
12	Drugs
13	Neurological
14	Syndrome
15	Cell
16	Research
17	Institution
18	Rare
19	Abnormal
20	Test
21	Screening
22	Internal Medicine
23	Symptoms
24	Associated
25	Causes
26	Differential Diagnosis
27	Genetic
28	Metabolic
29	Management
30	Level
31	Pediatric
32	Disorder
33	Service
34	Developmental
35	Standard
36	Insurance
37	Protein
38	Immune
39	Endocrine
40	Diagnosis and Treatment
41	Data
42	System
43	Defect
44	Nation
45	Center
46	Development
47	Review
48	Severe
49	Quality
50	Chromosome

literature on the PMC Index Model construction, a quantitative evaluation system for China's rare disease policies was developed after expert consultation. This system comprises 9 primary variables and 32 secondary variables to comprehensively and specifically analyze China's rare disease policies (Table 4).

2.3.2. Calculation method for the PMC index model

Following Estrada's proposed calculation method for the PMC index model, the process primarily involves the following steps: First, assign values of 0 or 1 to secondary variables; second, calculate the scores for primary variables using Equation (3); finally, aggregate the scores of all primary variables for each policy using Equation (4).

$$X \sim N[0,1] \quad (1)$$

$$X = \{XR[0 \sim 1]\} \quad (2)$$

$$X_i = [\sum_{j=1}^{n} \frac{X_{ij}}{T(X_{ij})}] \quad (3)$$

$$PMC = \sum_{i=1}^{19} (X_i[\sum_{j=1}^{n} \frac{X_{ij}}{T(X_{ij})}] \quad (4)$$

Referencing existing evaluation metrics, policies are categorized into four grades: Perfect (7 ≤ PMC Index ≤ 9), Excellent (5 ≤ PMC Index < 6.99), Acceptable (3 ≤ PMC Index < 4.99), Poor (0 ≤ PMC Index < 2.99) (Table 5).

2.3.3. PMC surface plot construction

The PMC surface plot is constructed based on a 3 × 3 PMC matrix, with the specific construction method shown in Equation (5). The PMC surface plot visually presents policy evaluation results more intuitively. It substitutes the mean values of each policy's primary variables, imports the data into Excel, and generates the overall mean PMC surface plot for the policy. In this surface plot, 1, 2, and 3 represent the horizontal coordinates of the matrix, while Series 1, 2, and 3 denote the vertical coordinates. The PMC surface plot uses different colors to distinguish index scores, enabling visual assessment of policy refinement. Convex regions indicate higher scores for corresponding evaluation indicators, while concave regions reflect lower scores.

$$PMC = \begin{Bmatrix} x1 & x2 & x3 \\ x4 & x5 & x6 \\ x7 & x8 & x9 \end{Bmatrix} \quad (5)$$

3. Results

3.1. Overall evaluation of national policies

By constructing an input-output analysis model for national rare disease policies and calculating the PMC Index, the rationality and maturity of the policy system can be systematically assessed, providing empirical evidence for optimizing policy design and enhancing implementation effectiveness. Based on the variable system of national rare disease policies, an input-output analysis model was developed to calculate the PMC Index and evaluation grades for 19 policies (Table 6). The average PMC Index across all policies was 5.31, earning an Excellent rating. This outcome reflects China's significant progress in rare disease policy development, demonstrating overall rational policy design with a stratified rating distribution: 2 policies rated Perfect, 8

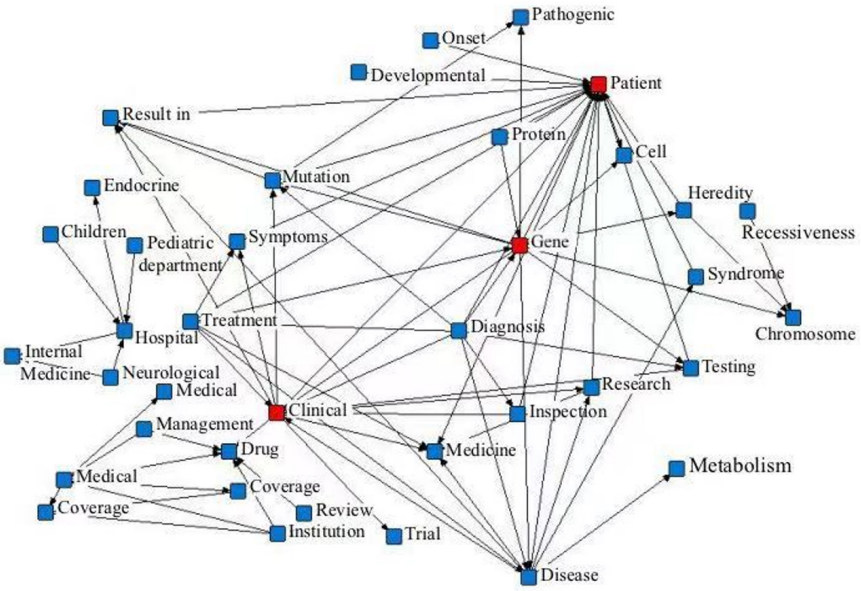

Figure 1. Semantic network diagram.

rated Excellent, and 9 rated Acceptable, with no Poor ratings. China's rare disease policies have thus reached a mature stage.

A radar chart was constructed using the mean values of the 19 primary variables for rare disease policies (Figure 2). Examining specific policy dimensions reveals higher average scores for Policy Nature (X2) and Policy Outcome Evaluation (X4). Currently, China's rare disease policies demonstrate strong strategic planning and outcome orientation, with clear long-term objectives. The strategic planning dimension (X2,1) indicates that policies generally provide a guiding framework for future development. Additionally, the high score for Policy Functionality (X8) suggests that China's policies emphasize oversight and accountability during implementation, effectively driving policy execution. Issuing Authority (X1) reflects that China's rare disease policies are primarily developed through multi-departmental leadership, with active participation from various government agencies.

The incentive measures (X5) scored the lowest, indicating that China's policy measures in areas such as R&D funding support and clinical trial incentives are relatively inadequate, affecting the development and market access of innovative drugs. Furthermore, the scores for patient support (X6) and social support (X9) were 0.42 and 0.39, respectively, reflecting that patient protection and social integration mechanisms remain weak. In particular, social integration measures have not effectively eliminated the social discrimination and employment barriers faced by rare disease patients.

3.2. Analysis of typical national policy cases

By comparing high-scoring and low-scoring policies, we can reveal differences in strategic levels, coverage scope, and implementation effectiveness in policy design. This provides a reference for optimizing the rare disease policy system and formulating more targeted and scientifically grounded policies. Among policies issued at the national level, we selected the two highest-scoring and the two lowest-scoring policies for case analysis, constructing a surface plot accordingly (Figure 3, and Supplementary Figure S1, *https://www.irdrjournal.com/action/getSupplementalData.php?ID=283*). Policy P1, "Guiding Opinions on Promoting the Development of the Pharmaceutical Industry Chain", focuses on strengthening technological innovation, advancing industrial restructuring and cluster development, enhancing production and supply capabilities for generic drugs, essential medicines, and clinically urgent drugs; improving quality standards and testing systems; establishing fast-track review and market access channels for shortage drugs and innovative drugs; and aligning the registration system with international standards. Overall, it exhibits a high strategic level, broad coverage, and a comprehensive system. Policy P4, "Opinions on Deepening the Reform of the Review and Approval System to Encourage Innovation in Pharmaceuticals and Medical Devices", explicitly proposes deepening the review and approval system and establishes a regulatory framework tailored to innovative drugs. It enables accelerated review for urgently needed medicines and simultaneous submission of new drugs from overseas, significantly shortening time-to-market. Its incentive measures are relatively comprehensive in scope.

However, Policy P11, "Notice on Value-Added Tax Policies for Rare Disease Drugs", focuses solely on tax reductions and serves as a supplementary, supporting measure. Policy P9, "Notice on Issuing the Diagnosis

Table 4. National-level policy evaluation system

Primary Variable	Code	Secondary Variable Name	Secondary Variable Evaluation Criteria	Indicator Source
Issuing Agency (X_1)	X_{11}	State Council	Whether the policy issuing body is the State Council itself.	Modified from Jin Chen's (*69*) article
	X_{12}	General Office of the State Council	Whether the policy issuing body is the General Office of the State Council.	
	X_{13}	State Council Constituent Departments (Ministries and Commissions)	Whether the policy issuing body is a ministry-level agency.	
	X_{14}	State Council Directly Affiliated Agencies	Whether the policy issuing body is a directly affiliated agency.	
	X_{15}	Internal Departments and Subordinate Units	Whether the policy issuing body is a subordinate unit.	
	X_{16}	Multi-Agency Joint Release	Whether the policy is jointly issued by two or more of the above agencies.	
Policy Nature (X_2)	X_{21}	Strategic Planning	Whether the policy proposes long-term goals, development directions, or top-level design frameworks.	Modified from Ruiz Estrada (*13*) and Zhang Yong'an (*70*) articles
	X_{22}	Guidance and Coordination	Whether the policy provides action guidelines, cross-department collaboration mechanisms, or multi-party coordination requirements.	
	X_{23}	Supervision and Control	Whether the policy specifies regulatory bodies, accountability mechanisms, or mandatory constraint clauses.	
	X_{24}	Prediction and Evaluation	Whether the policy includes risk warnings, effect evaluations, or dynamic adjustment mechanisms.	
Drug Security (X_3)	X_{31}	Market Access and Incentives	Focuses on how to encourage pharmaceutical companies to research, produce, and quickly bring drugs to market.	Modified from rare disease policy texts
	X_{32}	Medical Insurance Payment and Accessibility	Focuses on how to ensure patients have access to and can afford these drugs.	
Policy Outcome Evaluation (X_4)	X_{41}	Clarity of Goal Setting	Whether the goals set by the policy are clear.	Modified from Wang Jinfu (*71*) and Zhang Li (*72*) articles
	X_{42}	Rationality and Sufficiency of Basis	Whether the basis for policy formulation is sufficient.	
	X_{43}	Practicality of Planning	Whether the policy planning is feasible to implement.	
Incentive Measures (X_5)	X_{51}	Resource Sharing	Whether the policy relates to resource sharing.	Modified from Zhang Yong'an's (*70*) article
	X_{52}	Institutional Guarantees	Whether the policy relates to institutional guarantees.	
	X_{53}	Talent Development	Whether the policy relates to talent development.	
	X_{54}	Finance and Taxation	Whether the policy relates to finance and taxation.	
	X_{55}	Clinical Trial Support	Whether the policy supports the conduct of clinical trials.	
	X_{56}	R&D Funding	Whether the policy relates to research and development funding support.	
	X_{57}	Other	Whether the policy relates to other incentive measures.	
Patient Support (X_6)	X_{61}	Diagnosis, Treatment, and Survival Support	Whether it provides support directly benefiting individual patients, such as diagnosis, medication, rehabilitation, and living subsidies.	Modified from rare disease policy texts
	X_{62}	Rehabilitation and Social Adaptation Support	Whether it provides psychological counseling, vocational skills training, social adaptation guidance, *etc*., for individual patients to enhance their social participation ability.	

Table 4. National-level policy evaluation system (continued)

Primary Variable	Code	Secondary Variable Name	Secondary Variable Evaluation Criteria	Indicator Source
Technological Innovation (X_7)	X_{71}	R&D Drive and Translation	Measures whether the policy systematically incentivizes the translation of cutting-edge basic research into clinical applications.	Modified from rare disease policy texts
	X_{72}	Early Screening System Construction	Measures the policy's efforts in building a comprehensive, life-cycle rare disease prevention and early detection network.	
	X_{73}	Accelerated and Inclusive Review	Measures the innovation and flexibility of the drug regulatory system.	
	X_{74}	Data Empowerment and Collaboration	Measures the policy's support for scientific research infrastructure and collaborative ecosystems.	
Policy Function (X_8)	X_{81}	Supervision and Constraints	Whether it supervises and constrains rare disease treatment.	Based on Xuan Tianhui's (*73*) article, modified
	X_{82}	Standardization and Guidance	Whether it standardizes and guides rare disease treatment.	
	X_{83}	Quality Improvement	Whether it improves the quality of rare disease treatment.	
Social Support (X_9)	X_{91}	Information Platform and Data Construction	Whether a unified rare disease information sharing system has been established.	Modified from rare disease policy texts
	X_{92}	Emergency Assistance and Medical Security	Whether a rare disease acute episode treatment channel has been established.	
	X_{93}	Rights Protection and Anti-Discrimination	Whether it explicitly prohibits genetic discrimination in employment/education/insurance fields.	
	X_{94}	Other	Whether it includes other macro-level social support policies not covered above.	

Table 5. Rare disease policy evaluation grades

Policy modeling consistency (PMC) index	0–2.99	3.0–4.99	5.0– 6. 99	7.0–9.0
Evaluation Grades	Poor	Acceptable	Excellent	Perfect

Table 6. Policy modeling consistency (PMC) index of national-level rare disease policy documents

Policy Code	X1	X2	X3	X4	X5	X6	X7	X8	X9	PMC Index	Ranking	Policy Level
P1	0.83	1.00	1.00	1.00	1.00	0.50	0.75	1.00	0.75	7.83	1	Perfect
P2	1.00	0.75	0.50	0.67	0.14	0.00	0.25	1.00	0.25	4.56	14	Acceptable
P3	1.00	1.00	0.50	1.00	0.43	0.00	0.75	1.00	0.50	6.18	5	Excellent
P4	1.00	1.00	1.00	1.00	0.57	0.50	0.75	1.00	0.25	7.07	2	Perfect
P5	1.00	0.50	1.00	1.00	0.14	0.50	0.25	1.00	0.50	5.89	6	Excellent
P6	0.92	1.00	0.50	1.00	0.71	0.50	0.50	1.00	0.75	6.88	3	Excellent
P7	0.50	0.25	0.50	1.00	0.29	0.00	0.75	0.67	0.25	4.20	17	Acceptable
P8	0.50	0.25	0.50	1.00	0.14	0.50	0.50	1.00	0.00	4.39	16	Acceptable
P9	0.67	0.50	1.00	1.00	0.14	0.50	0.00	1.00	0.25	5.06	9	Excellent
P10	0.67	0.75	0.50	1.00	0.57	0.50	0.50	1.00	0.75	6.24	4	Excellent
P11	0.87	0.25	0.00	1.00	0.29	0.50	0.00	1.00	0.25	4.16	18	Acceptable
P12	0.67	0.25	0.50	1.00	0.29	0.50	0.00	1.00	0.25	4.46	15	Acceptable
P13	0.50	0.50	0.00	1.00	0.29	1.00	0.50	1.00	0.25	5.04	10	Excellent
P14	0.33	0.75	0.00	1.00	0.86	0.50	0.50	1.00	0.50	5.44	8	Acceptable
P15	0.33	0.50	1.00	1.00	0.29	0.50	0.25	0.67	0.50	5.03	11	Excellent
P16	0.67	0.25	1.00	1.00	0.00	0.50	0.25	0.67	0.25	4.58	13	Acceptable
P17	0.33	0.50	0.50	0.67	0.14	0.50	0.75	1.00	0.25	4.64	12	Acceptable
P18	1.00	0.50	1.00	1.00	0.29	0.50	0.25	0.67	0.50	5.70	7	Excellent
P19	0.67	0.50	0.00	1.00	0.50	0.00	0.00	0.33	0.50	3.50	19	Acceptable
Mean	0.71	0.58	0.58	0.96	0.37	0.42	0.39	0.89	0.39	5.31	—	Excellent

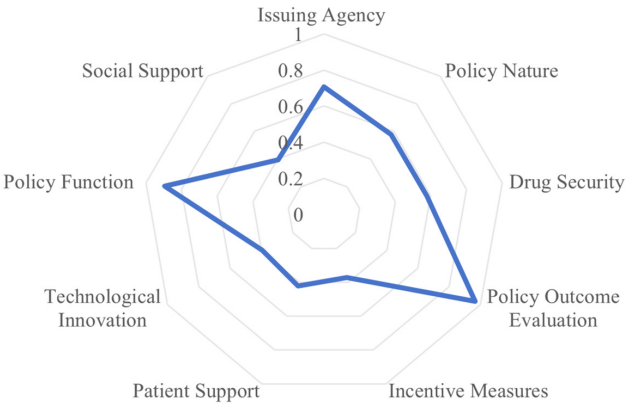

Figure 2. National rare disease policy modeling consistency (PMC) mean radar chart.

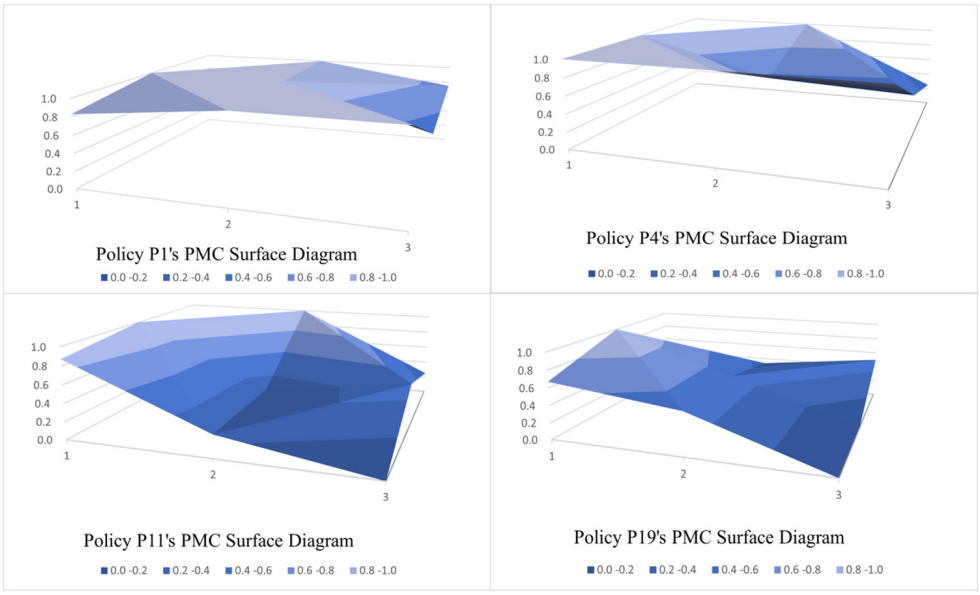

Figure 3. Policy modeling consistency (PMC) surface plot of national rare disease policies.

and Treatment Guidelines for 86 Rare Diseases Including Achondroplasia (2025 Edition)", primarily addresses medical practice and has limited coverage, resulting in a lower score.

3.3. Overall evaluation of regional policies

The analysis of provincial policy cases reveals the strengths and weaknesses of China's provincial-level regional policies by assessing the design characteristics and implementation effectiveness of rare disease policies across regions. This provides reference for optimizing local policy systems, promoting differentiated policy innovation, and advancing scientific decision-making. Based on the variable system of provincial rare disease policies, an input-output analysis model was developed to calculate the PMC index and evaluation grade for 13 policies (Table 7). The average PMC index for all policies was 4.94, with policy ratings showing a stratified distribution: 4 policies rated Excellent, 9 rated Acceptable, and none rated Poor. This indicates that the sampled policies were generally well-designed, with rare disease policies in typical regions becoming increasingly refined. This reflects an overall pattern where, under national strategic guidance, localities are exploring distinctive models.

A radar chart was constructed using the mean values of the primary variables for the 13 rare disease policies (Figure 4). Analysis of specific dimensions reveals that policy nature (X2) generally scored highly, particularly in Beijing and Shanghai. Their policies demonstrate strong strategic and long-term planning capabilities, reflecting robust top-level design and organizational coordination by governments in advancing rare disease policies. Additionally, high scores for policy functionality (X8) indicate these regions possess strong oversight mechanisms and implementation capacity, ensuring policy execution and enforcement.

Incentives (X5) and Patient Support (X6) represent weaknesses in most regional policies. The average score

Table 7. Policy modeling consistency (PMC) index of rare disease policy documents in representative regions

Policy Code	X1	X2	X3	X4	X5	X6	X7	X8	X9	PMC Index	Ranking	Policy Level
P1	0.60	0.25	1.00	1.00	0.27	0.00	0.00	1.00	0.25	4.37	9	Acceptable
P2	0.80	1.00	1.00	1.00	0.14	0.50	0.25	1.00	0.25	5.94	3	Excellent
P3	1.00	0.25	0.00	0.67	0.00	0.50	0.50	1.00	0.25	4.17	12	Acceptable
P4	1.00	1.00	1.00	1.00	0.29	0.50	0.25	1.00	0.25	6.29	2	Excellent
P5	1.00	1.00	1.00	0.67	0.43	0.50	0.50	1.00	0.25	6.35	1	Excellent
P6	1.00	0.25	0.50	1.00	0.29	0.00	0.67	1.00	0.25	4.96	6	Acceptable
P7	0.80	0.50	0.00	1.00	0.43	0.00	0.25	1.00	0.25	4.23	11	Acceptable
P8	0.60	0.25	0.50	0.67	0.29	0.50	0.00	1.00	0.50	4.31	10	Acceptable
P9	0.60	0.25	0.50	1.00	0.00	1.00	0.00	0.33	0.25	3.93	13	Acceptable
P10	0.60	1.00	0.00	1.00	0.57	0.50	0.25	1.00	0.25	5.17	5	Excellent
P11	0.60	0.75	1.00	0.67	0.14	0.50	0.00	0.67	0.25	4.58	8	Acceptable
P12	0.80	1.00	1.00	0.67	0.14	0.50	0.00	1.00	0.25	5.36	4	Acceptable
P13	0.80	0.25	1.00	0.67	0.14	0.50	0.00	1.00	0.25	4.61	7	Acceptable
Mean	0.78	0.60	0.65	0.85	0.24	0.42	0.21	0.92	0.27	4.94	-	Acceptable

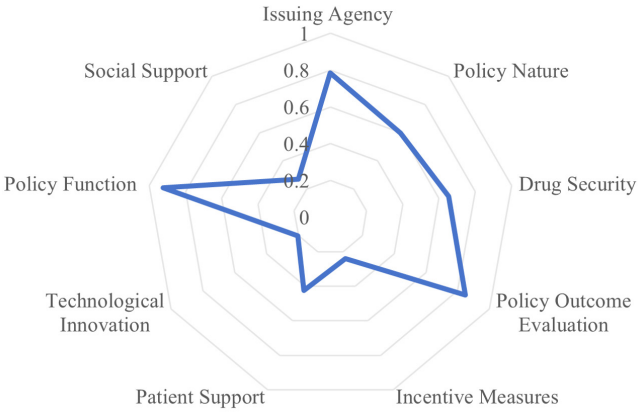

Figure 4. Radar chart of average policy modeling consistency (PMC) for rare disease policies in representative regions.

for local policy X5 (Incentives) is 0.24, significantly lower than the national policy average of 0.37. Both X6 (Patient Support) scores are low, though local measures demonstrate greater operational feasibility—such as Qingdao's specialized drug coverage program.

Shanghai, Beijing, and Zhejiang exhibit more systematic policy design. These economically developed regions with concentrated medical resources generally achieve higher policy scores. Jiangsu and Qingdao perform well in medical insurance payments and treatment protocols — Jiangsu's implementation plan specifies diagnostic pathways. At the same time, Qingdao explores incorporating certain specialty drugs into major illness insurance, though research and incentive measures remain inadequate. Foshan and Guangzhou focus their policies on medical assistance and insurance planning, emphasizing a "safety net" function, but lack systematic design and have room for refinement.

3.4. Analysis of typical regional policies

Since 2005, Shanghai, Qingdao, and Zhejiang Province have successively explored rare disease drug coverage models independent of the basic medical insurance system, which have, to some extent, alleviated patients' payment burden (*14*). Shanghai stands as one of China's pioneers in addressing the unique needs of the rare disease community, consistently leading domestic efforts in rare disease healthcare coverage. Both Shanghai and Beijing score highly in innovative drug support and patient protection policies. Shanghai's release of the Shanghai Catalogue of Major Rare Diseases (2025 Edition) and the Shanghai Medical Security Regulations not only enhances drug accessibility but also clarifies social support and policy safeguards for patients. Beijing, through its Capital Health Development Rare Disease Research Special Project policy, provides robust financial backing for rare disease research and drug development, ensuring policy effectiveness. Qingdao has established a multi-tiered healthcare security system prioritizing rare disease patients, incorporating over 20 rare diseases into outpatient critical illness management, and implementing specialized coverage for three rare disease-specific drugs (*15*). Guangzhou has constructed a multi-tiered support system covering diagnosis, treatment, medical insurance, and assistance. It features a Major Complex and Rare Disease Diagnosis and Treatment Center integrating Chinese and Western medicine, while leveraging provincial collaborative network hospitals like Guangzhou Medical University Women and Children's

Medical Center to promote early screening and diagnosis. Beyond implementing the national medical insurance catalog, it supplements coverage with insurance that does not restrict pre-existing conditions. Foshan City has included all diseases listed in the "First Batch of Rare Diseases Catalog" within its medical assistance coverage, extending this support to cover outpatient specialty and therapeutic food expenses for rare disease patients beyond basic medical insurance. The proactive explorations in rare disease medical coverage in regions like Zhejiang and Jiangsu provide practical models for achieving nationwide coverage, offering highly valuable reference points (Supplementary Table S1 and Supplementary Figure S2, *https://www.irdrjournal.com/action/getSupplementalData.php?ID=283*).

4. Discussion and recommendations

4.1. Comparison and implications of national and local rare disease policies

Based on the quantitative results of the Policy Management Center (PMC) analysis, differences exist between national and local policies in terms of functional positioning and implementation pathways. These variations not only reveal the structural characteristics of China's rare disease policy framework but also provide entry points for subsequent institutional optimization.

Among the 32 policy documents evaluated, 19 were national-level policies and 13 were local-level policies. Overall, national policies exhibit broad coverage and high institutionalization, primarily focusing on foundational institutional designs such as establishing drug directories, drug registration and review, medical insurance reimbursement, and diagnostic and treatment guidelines. They perform notably well in the Institutional Foundation (X2) and Policy Tool Completeness (X3) dimensions of the PMC index. Local policies, however, are more targeted and exploratory, often focusing on supplementary medical insurance payments, establishing relief funds, expanding patient assistance channels, and innovating multi-tiered security systems. They demonstrate certain advantages in the areas of safeguard measures (X4) and incentive mechanisms (X5).

This divergence reflects the complementary relationship between national and local policies in their functional roles. National-level policies are responsible for top-level design and establishing institutional frameworks, providing unified standards and fundamental safeguards for rare disease governance. While local policies conduct differentiated explorations based on economic conditions and social resources, they offer more targeted support to patients. However, national policies still need to enhance their specificity in implementation, while local policies, constrained by fiscal capacity and institutional authority, exhibit weaker coverage and sustainability (*16*). Future policy optimization should establish tighter coordination mechanisms between national and local levels. The national government should strengthen institutional safeguards and resource coordination. In contrast, local governments should serve as "policy testing grounds", accumulating practical experience and feeding it back to the national level to drive the continuous improvement and balanced development of the rare disease policy system.

4.2. Pathways for improving institutional frameworks and policy safeguards

Since the release of the "Guidelines for Diagnosis and Treatment of Rare Diseases (2019 Edition)", China became the first country to define rare diseases through a catalog system, laying a crucial institutional foundation for subsequent policy development and drug review and approval processes. However, comparisons with international experiences reveal gaps in China's policy safeguarding system, particularly in policy stability, interdepartmental coordination, and legal enforceability. Current policies primarily rely on departmental regulations and technical guidelines, lacking unified national legislation. This leads to fragmented implementation and inconsistent standards across regions. Additionally, oversight and dynamic evaluation mechanisms remain underdeveloped, with some localities exhibiting weak enforcement and inadequate interdepartmental coordination during implementation (*17*).

To address these issues, it is recommended to enhance the rare disease policy framework through legislative and institutional measures (*18*). At the macro level, national efforts should advance the enactment of a "Rare Diseases Law" or other specialized legislation (*19*), incorporating fundamental patient healthcare rights, orphan drug R&D incentive mechanisms, rules for establishing and allocating dedicated rare disease funds, interdepartmental collaboration protocols, and information-sharing systems into the legal framework. At the local level, tailored approaches should be adopted to establish robust policy implementation and oversight mechanisms, considering China's context of substantial economic scale but relatively low per capita income (*20*). Transparency and fairness can be ensured by involving third-party institutions and social organizations. Throughout this process, policies should be optimized and revised based on implementation outcomes. This institutional design enhances policy transparency and accountability while providing evidence-based support for dynamic adjustments, thereby fostering a virtuous cycle of "legislation-implementation-evaluation-revision".

4.3. Regional disparities and optimization of policy coordination mechanisms

Regional disparities have become a prominent issue in the practical implementation of China's rare disease policies. Economically developed regions have demonstrated a leading advantage in institutional development, research investment, and innovation safeguards (*21*). However, policy frameworks in small and medium-sized cities and underdeveloped areas remain weak. Local initiatives heavily depend on regional economic development levels, policy implementation speed, and local sociocultural traditions, preventing them from extending assistance beyond the nationally mandated drug directory (*22*). Within the framework of basic medical security, benefit levels under basic medical insurance, critical illness insurance, and medical assistance remain constrained by existing policy structures, making it difficult to implement special protective policy adjustments for rare disease patients (*17*). This results in significant regional disparities in diagnostic accessibility, insurance reimbursement rates, and assistance levels for rare disease patients. Concurrently, China's household registration system and local coordination mechanisms further exacerbate coverage inequities, creating substantial gaps in access to rare disease medical services and pharmaceutical support across different regions.

To enhance policy universality and sustainability, the national level should promote cross-regional policy coordination and resource integration, providing preferential support to underdeveloped areas to improve local diagnostic capabilities and coverage levels. Establishing a unified national rare disease collaboration network would enable cross-regional sharing of research platforms, clinical resources, and referral networks, thereby institutionally facilitating the decentralization of superior resources (*23*). Thus strengthening fiscal burden-sharing and technical support between central and local governments, while guiding local authorities to develop tailored, localized measures. Promoting a "best practices" model that integrates Shanghai's institutional innovations, Beijing's research strengths, and multi-tiered coverage experiences from Guangdong, Qingdao, and other regions—while institutionalizing and scaling these approaches within a national framework—can progressively narrow regional disparities. This shift from "isolated experimentation" to "networked collaboration" in rare disease governance enhances overall fairness and sustainability, offering valuable pathways for refining China's distinctive health governance model.

4.4. Incentive system development and strategies to promote orphan drug R&D

Rare disease drug development is central to improving patient care and drug accessibility. Despite recent national policies encouraging innovation, support remains insufficient in R&D funding, clinical trial incentives, and market access for innovative drugs. This results in weak corporate R&D motivation, clinical trial bottlenecks, and inefficient drug commercialization. High drug prices reduce patient access, while low prices may deter innovation, ultimately compromising patient outcomes (*24*). Systematic legal and policy incentives are crucial drivers for orphan drug development. The U.S. Orphan Drug Act significantly boosted new drug development output through market exclusivity, tax incentives, and R&D funding. The EU similarly advanced orphan drug innovation *via* multinational collaboration mechanisms, centralized approval processes, and financial incentives. These experiences demonstrate that combining institutional incentives with market mechanisms can stimulate corporate innovation in rare disease areas.

China should establish a more comprehensive national R&D system and build a national rare disease research and clinical data sharing platform. This platform should enable standardized sharing of patient registries, real-world evidence, and multicenter clinical trial data, thereby reducing research costs and enhancing R&D efficiency (*18*). Establishing priority review and approval pathways, coupled with granting orphan drugs a certain period of market protection, would improve the feasibility and economic returns of drug development and market launch. A dedicated talent development program for rare diseases should be launched, offering research funding preferences and incentives to young scientists and clinicians to encourage greater participation in this field. National-level policy design should refine supportive measures, enhance corporate social responsibility, and ensure the production and supply accessibility of rare disease medications (*25*). International collaboration should be promoted by sharing technologies, evaluation standards, and clinical research evidence with global orphan drug agencies to address data gaps and inconsistencies in evaluation during R&D. Concurrently, China should enhance public awareness of rare diseases, stimulate societal engagement, and incentivize pharmaceutical companies to engage in orphan drug development (*26*). These measures will progressively establish a comprehensive system encompassing financial support, institutional incentives, and talent cultivation. This framework will foster a conducive regulatory environment for orphan drug research and development, thereby enhancing innovation capacity and clinical accessibility for rare disease medications (*27*).

4.5. Establishing patient support systems and specialized insurance for rare diseases

Rare diseases pose significant challenges not only in medical and physiological aspects but also profoundly impact patients' and their families' economic and social lives. Although some rare diseases have been included in medical insurance coverage, the scope and level of protection remain limited. The prolonged treatment

cycles and need for multiple medications result in persistent financial burdens, placing heavy economic and psychological strain on patients during long-term care (*28*). A study assessing the accessibility of definitive diagnosis for rare diseases among Chinese adults revealed that approximately 72.97% of patients received misdiagnoses. On average, patients endured 4.30 misdiagnoses and visited 2.97 hospitals before receiving a correct diagnosis (*27*). In China, very few rare disease patients possess commercial insurance, with the majority lacking any commercial coverage (*27*). Few commercial insurers are willing to include high-cost, low-volume, rare disease-specific medications within their coverage scope (*29*).

In addressing this issue, the United States, the European Union, Japan, and Taiwan have implemented various financing models, including commercial insurance, social charitable funding, medical assistance programs, and government subsidy funds (*30*). Therefore, to further enhance the patient support system, it is essential to expand medical insurance coverage and increase reimbursement rates for rare disease medications to meet patients' survival and developmental needs better. Incorporating rare diseases into basic medical insurance and critical illness insurance can alleviate patients' financial burdens. A dedicated rare disease protection fund should be established under critical illness insurance, achieving comprehensive provincial coordination for this specific category. Drawing from Zhejiang's experience, annual contributions to this fund could be allocated from the critical illness insurance pool within each coordinated region. However, given the limited capacity of government medical insurance funds, supplementary security mechanisms like commercial insurance are crucial for addressing the high costs associated with rare disease treatment (*31*). Special insurance plans should be established to cover treatment and long-term management expenses for rare diseases, and promote the establishment of specialized psychological support and rehabilitation service centers to provide patients with counseling and social adaptation guidance. Social organizations should be encouraged and public welfare foundations be engaged in patient services, forming a multi-tiered support network. Expanding medical insurance coverage, establishing a dedicated rare disease fund, gradually increasing reimbursement rates, and actively providing patients with living allowances, rehabilitation subsidies, and long-term medication assistance to alleviate family burdens is necessary. Through concerted efforts from multiple stakeholders, enhancing patient support capabilities is essential(*32*).

4.6. Synergistic effects of social support systems and multi-stakeholder collaboration

Rare disease patients face not only medical challenges but also heightened survival pressures due to inadequate social support. While the government has provided basic medical coverage to some extent, social-level support remains insufficient, particularly in areas like social adaptation and employment, where patients encounter significant difficulties (*33*). China's current social support system remains in its early stages, with low social participation rates among rare disease patients. Constrained by societal misconceptions, educational barriers, and employment discrimination, patients endure significant psychological and financial pressures (*34*). For instance, some EU countries utilize charitable funds and social security programs to provide living allowances and rehabilitation support for rare disease patients, while the United States encourages collaborations between social organizations and corporations to advance rare disease research and drug development, promoting broader drug accessibility.

Therefore, a unified national rare disease information platform should be established to facilitate the sharing of patient registries, diagnostic guidelines, drug directories, and other critical information. Enhanced big data applications should support precision in scientific research and policy formulation. Concurrently, an emergency "green channel" should be created for acute episodes of rare diseases, ensuring priority treatment during emergency care and hospitalization. A temporary relief fund should be established to provide safety-net coverage for sudden high medical expenses. Legislation should explicitly prohibit discrimination in education, employment, and insurance. Public awareness campaigns and science education should be promoted to enhance public understanding of rare diseases and reduce stigma. Charitable organizations, public welfare funds, and social enterprises should be encouraged to participate in rare disease patient assistance, forming a multi-faceted social support system (*35*) that pools diverse resources to address medication accessibility for rare disease patients collectively.

4.7. Limitations of the study

This study analyzed the shortcomings of existing policies. However, upon examining the content, it was found that the research exhibits the following limitations in terms of sample coverage, methodological constraints, and practical evaluation. At the macro level, the representativeness of regional samples is limited. The study selected only 13 policy documents at the local level, concentrated in typical regions such as Shanghai, Beijing, and Qingdao. Compared to China's 34 provincial-level administrative regions, the coverage of these 13 local documents is narrow, making it difficult to fully reflect the diversity of local policies. The selected regions predominantly represent economically developed cities or provinces with concentrated healthcare resources. This selection bias may lead to

overly optimistic evaluation outcomes, failing to fully reflect the genuine gaps in rare disease policies within central, western regions, or areas with weaker healthcare infrastructure.

Second, while the PMC index model enables quantitative evaluation, its methodology inherently involves certain simplifications. The selection of secondary variables relies on expert consultation, and the assignment of variable values (0 or 1) carries a degree of subjectivity. Any discrepancies in interpreting and understanding policy provisions during scoring will directly impact the final score. Furthermore, when calculating primary variable scores, the model typically assumes equal importance across all secondary variables without employing weighted scoring. In practice, however, a fiscal subsidy policy may carry significantly greater weight and provide stronger policy support than a mere work notice. Such weighting differences cannot be captured by simple binary scoring.

Finally, the disconnect between policy texts and implementation outcomes is significant. Research primarily focuses on the consistency and structural completeness of policy texts rather than their actual effectiveness. The PMC model evaluates the textual quality of policies themselves. However, certain high-scoring policies (such as those rated P1 or P4 as perfect) may face practical challenges in implementation, including difficulties in cross-departmental coordination and inadequate funding allocation. Empirical analysis of such real-world outcomes remains limited in this paper.

5. Conclusion

This paper employs the Policy Modeling Consistency (PMC) index model and text mining methods to conduct a systematic quantitative evaluation of rare disease-related policies issued at the national level (19 policies) and in representative regions (13 policies) in China from 2016 to 2025. Regarding research methods and tools, ROSTCM 6.0 software was used to extract high-frequency vocabulary, identifying policy focal points primarily concentrated on "hospitals", "patients", "treatment", "clinical", and "medicines". An evaluation framework was constructed comprising nine primary variables—issuing authority, policy nature, drug coverage, outcome evaluation, incentive measures, patient support, technological innovation, policy function, and social support—along with 32 secondary variables. Policy strengths, weaknesses, and refinement levels were visually represented through PMC surface plots and radar charts.

Findings revealed high scores for policy nature (X2), policy function (X8), and outcome orientation (X4), indicating robust strategic planning and regulatory rigor. Conversely, incentive measures (X5), patient support (X6), and social support (X9) emerged as weak points with generally low scores, revealing deficiencies in R&D funding, social integration, and long-term security mechanisms. Regionally, developed areas like Shanghai, Beijing, and Zhejiang exhibited more systematic policy design, while Guangzhou and Foshan emphasized the safety net function of medical insurance.

Finally, the article recommends establishing a comprehensive policy framework covering R&D, diagnosis/treatment, medical insurance, and social support. This includes strengthening coordinated legislation to advance the Rare Disease Law, incorporating patient rights, orphan drug R&D incentives, and dedicated fund establishment into the legal system. Enhancing incentives and support requires building a national R&D system and information-sharing platform, while implementing market protection periods and fiscal/tax incentives for orphan drugs. Furthermore, regional coordination should be optimized to narrow coverage disparities, promote "best practice" models, and enable cross-regional sharing of research resources and clinical data. A multi-tiered insurance system should be developed, including a dedicated rare disease fund, while encouraging participation from commercial insurers and social welfare organizations to alleviate patients' financial burdens.

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Original Article

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Visualization analysis of the use of traditional Chinese medicine in the diagnosis and treatment of rare diseases in mainland China based on CiteSpace

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SUMMARY: This study used CiteSpace (version 6.4.R1) to perform a visualization analysis of 3,058 articles on traditional Chinese medicine (TCM) diagnosis and treatment of rare diseases retrieved from the China National Knowledge Infrastructure (CNKI) database, the VIP Chinese Science and Technology Periodical Database (VIP), the Wanfang database (Wanfang), and the Chaoxing database (Chaoxing). The goal was to ascertain the current status of research, hotspots in research, and trends in the development of TCM for rare disease diagnosis and treatment in mainland China, providing insights for future TCM research in this field. Visual maps of annual publication volume, authors, institutions, keywords, and other content have revealed that TCM demonstrates prominent advantages in 5 out of 207 defined rare diseases: idiopathic pulmonary fibrosis, hepatolenticular degeneration (Wilson's disease), osteosarcoma, retinitis pigmentosa, and multiple sclerosis. Potential advantages are identified in treating melanoma, amyotrophic lateral sclerosis, homocysteinemia, primary biliary cholangitis, and lymphangioleiomyomatosis. TCM research on rare diseases focuses on etiology, pathogenesis, and syndrome differentiation-based treatment. Case-control studies and mechanism investigations have been initiated for some conditions, while clinical research is gradually incorporating integrated TCM-Western medicine approaches. However, enhanced team and institutional collaboration, development of multicenter networks, exploration of multidisciplinary research, and clinical studies yielding high-level evidence are still needed to provide quality evidence-based support for clinical decision-making in the TCM treatment of rare diseases.

Keywords: CiteSpace, China, rare diseases, traditional Chinese medicine

1. Introduction

The World Health Organization (WHO) defines rare diseases as those with a prevalence of 0.65 to 1% of the total population (*i.e.*, 6.5 to 10 individuals per 100,000 people) (*1*). In China, the First (*2*) and Second Lists (*3*) of Rare Diseases were issued in 2018 and 2023 by six government entities in China (*4*), including the National Health Commission, the Ministry of Science and Technology, the Ministry of Industry and Information Technology, the National Medical Products Administration, the National Administration of Traditional Chinese Medicine, and the Logistics Support Department of the Central Military Commission. These lists cover a total of 207 types of diseases (*5*). The updated 2024 list of member hospitals in the National Rare Disease Diagnosis and Treatment Collaboration Network includes 10 traditional Chinese medicine (TCM) or integrated Chinese and Western medicine units (*6*).

This study used the co-occurrence analysis function in the software CiteSpace to visualize authors, institutions, and keywords in TCM literature on rare disease diagnosis and treatment in order to explore the historical context and current status of research while predicting future trends in this field, identifying research hotspots and frontiers.

2. Materials and Methods

2.1. Retrieval strategy

Since information on TCM diagnosis and treatment of rare diseases is primarily located in TCM databases, the sources examined in this study were all found in Chinese databases, namely the China National Knowledge Infrastructure (CNKI) database, the VIP Chinese

Science and Technology Periodical Database (VIP), the Wanfang database (Wanfang), and the Chaoxing database (Chaoxing). Searches were conducted using the keywords "rare diseases" and "traditional Chinese medicine"; the search query used was "specific rare disease name" AND "traditional Chinese medicine". Based on the first and second national lists of rare diseases issued by the government, we searched for 207 names of rare diseases across all of the databases, ensuring comprehensive coverage. The search covered articles indexed in these databases from their inception until July 31, 2025. Information was collected from the literature, and a total of 5,243 sources were saved in RefWorks text format.

The literature review revealed that the earliest source was from 1958, so the year span for the graphs ranges from 1958 to 2025. This starting year aligns with the history of rare disease research in mainland China, and the TCM diagnosis and treatment of rare diseases has gradually emerged over the past 70 years. After rounds of screening to remove all duplicate entries, sources with incomplete information, and other types of literature, 3,058 papers were ultimately included.

2.2. Research methodology

The software CiteSpace (version 6.4.R1) was used in this study. Software parameters: *i*) Time slicing from January 1958 to July 2025, with a 1-year Time analysis slice; *ii*) Term source: Title, Abstract, Author Keywords (DE), Keywords Plus (ID); *iii*) Term type: "Noun phrase" was selected in maps of keywords, otherwise it was not selected; *iv*) Node types: Author, Institution, Keyword; and *v*) Selection criteria were set to g-index, k = 25.

Pruning was done using the Pathfinder and Pruning sliced networks. This resulted in the generation of the following networks: an author collaboration network map, an institution collaboration network map, a keyword co-occurrence network map, a cluster map, a timeline map, and a citation burst map. These networks provide insights into research hotspots, evolutionary trajectories, collaborative dynamics among entities, and the distribution of research capabilities within the field of TCM diagnosis and treatment for rare diseases.

3. Results

3.1. Annual publication volume

Publications in the field of TCM diagnosis and treatment for rare diseases have tended to increase since 1958. Publications surpassed single digits in 1987, exceeded 30 in 1994, reached over 60 in 2005, stabilized between 80 and 89 from 2008 to 2011, broke the 100-article mark in 2012 by 120, and continued climbing to 158, 141, and 165 articles respectively from 2017 to 2019. A slight decline occurred during the period of the 2020–2022 pandemic, but new highs were consecutively reached after 2023. As of July 2025, 118 articles have been published in 2025 (Figure 1).

3.2. Author analysis

In the co-occurrence network of authors, there was a total of 1,236 nodes (N), 1,284 links (E), and a network density (Density) of 0.0017 (Figure 2). Each node represents an author, with node size reflecting the co-occurrence frequency of his or her publications. Links between nodes indicate collaborative relationships among authors. The map reveals that the top authors by publication volume include Wenming Yang, Han Wang, Hui Han, Meixia Wang, Yongzhu Han, Yuanchen Bao, Jiyuan Hu, Juan Zhang, Renmin Yang, Hong Chen, and Wenbin Hu. Node color variations reflect temporal dimensions: orange-yellow nodes represent early authors, while deep red nodes denote recently active authors. The predominance of red nodes indicates that the author collaboration network for TCM treatment of rare diseases has grown annually.

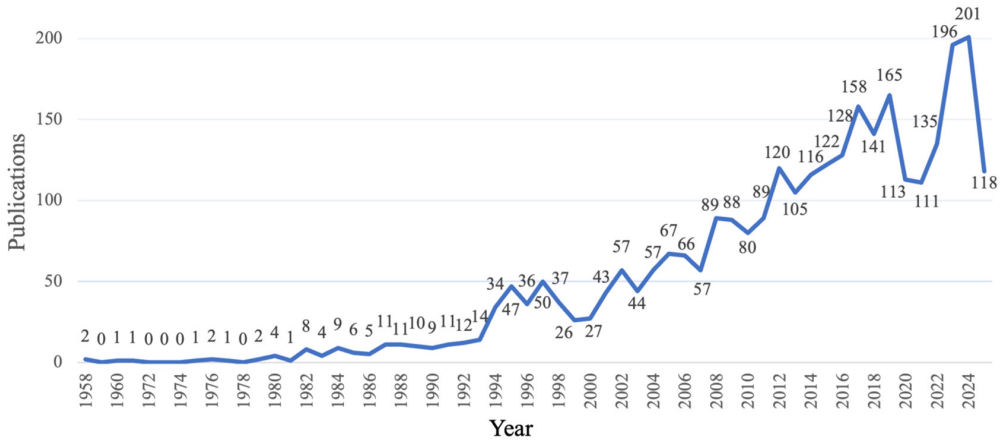

Figure 1. Annual number of publications for rare disease-related studies.

3.3. Institution analysis

The institutional network map reveals that research on TCM treatment of rare diseases is primarily concentrated in TCM universities and their affiliated hospitals. The network consists of 721 nodes, 337 links, and a density of 0.0013 (Figure 3). Each node in the diagram represents an institution, with node size proportional to the institution's co-occurrence frequency in the literature. Links indicate collaborative relationships between institutions. The top 3 institutions are Beijing University of Chinese Medicine, Tianjin University of Traditional Chinese Medicine, and Henan University of Chinese Medicine, with research focusing on rare diseases such as multiple sclerosis and idiopathic pulmonary fibrosis. There is close collaboration between universities and

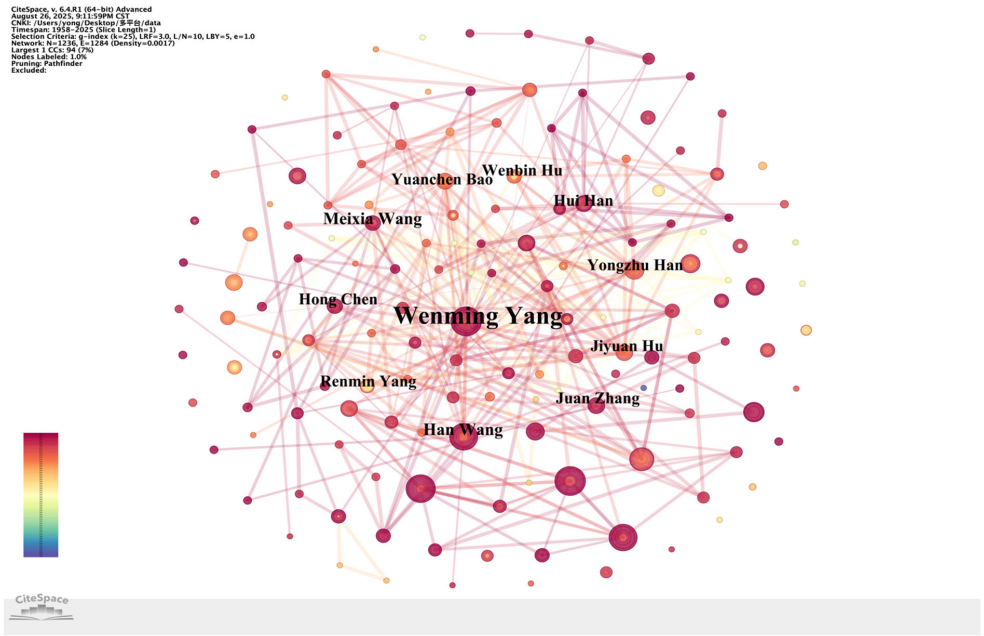

Figure 2. A network knowledge map of authors in the field of traditional Chinese medicine diagnosis and treatment of rare diseases obtained using the software CiteSpace6.4.R1 based on mainstream Chinese databases (CNKI, VIP, Wanfang, and Chaoxing).

Figure 3. A network knowledge map of institutions in the field of traditional Chinese medicine diagnosis and treatment of rare diseases obtained using the software CiteSpace6.4.R1 based on mainstream Chinese databases (CNKI, VIP, Wanfang, and Chaoxing).

their affiliated hospitals, but cooperation between institutions in different regions remains limited.

3.4. Keyword analysis

3.4.1. Keyword co-occurrence analysis

Keywords concisely summarize article themes. This map reveals co-occurrence relationships among high-frequency keywords in the literature. There were 1,086 total nodes, 2,619 links, and a network density of 0.0044 (Figure 4). The size of each keyword node correlates positively with its frequency of occurrence. Colors ranging from yellow to purple reflect temporal distribution (yellow indicating earlier years, and purple indicating more recent years). Links between nodes represent the co-occurrence of keywords within the same source; more lines indicate stronger associations. The top five keywords are "TCM therapies", "idiopathic pulmonary fibrosis", "multiple sclerosis", "hepatolenticular degeneration", and "TCM syndrome patterns". The map also highlights names of diseases like "Behcet's disease" and "Retinitis Pigmentosa" and research orientations like "Review", "Treatment based on syndrome differentiation", "Famous doctor's experience", "TCM syndrome", "Etiology and pathogenesis", which to some extent represent the research hotspots in the field of TCM diagnosis and treatment of rare diseases.

3.4.2. Keyword clustering analysis

Noun phrases were selected as the term type, and a keyword cluster map was generated. After displaying the co-occurrence map of keywords through co-word clustering, the log-likelihood ratio algorithm (LLR) was used to generate multiple significant clusters. Each cluster consists of nodes of similar color, with node size reflecting the keyword frequency in the literature. Cluster labels are automatically identified by the algorithm, representing the research themes of each keyword category. The network had an overall modularity (Q) of 0.6158 (Q > 0.3), indicating a significant clustering structure with relatively clear thematic distribution. The weighted mean silhouette (S) was 0.8354 (S > 0.7), demonstrating high internal consistency and reliability within the clusters (Figure 5).

The circular view function was used, and the map clearly displays 15 clusters, including #0 Idiopathic Pulmonary Fibrosis, #1 Hepatolenticular Degeneration, #2 Traditional Chinese Medicine therapy, #3 Multiple Sclerosis, #4 Medication regularity, #5 Syndrome differentiation and treatment, #6 Amyotrophic Lateral Sclerosis, #7 Primary Biliary Cholangitis, #8 Case record, # 9 Retinitis Pigmentosa, #10 Traditional Chinese Medicine intervention, #11 Famous doctor's experience, #12 Traditional Chinese Medicine constitution, #13 Polycythemia Vera, and #14 Gandou Decoction (Table 1). Disease-related clusters include #0 Idiopathic Pulmonary Fibrosis, #1 Hepatolenticular Degeneration, #3 Multiple Sclerosis, #6 Amyotrophic Lateral Sclerosis, #7 Primary Biliary Cholangitis, #9 Retinitis Pigmentosa, #13 Polycythemia Vera, and #14 Gandou Decoction. The corresponding rare diseases, sorted by average publication year in ascending order, are multiple sclerosis (2002), retinitis pigmentosa (2002), polycythemia vera (2007), amyotrophic lateral sclerosis (2010), primary

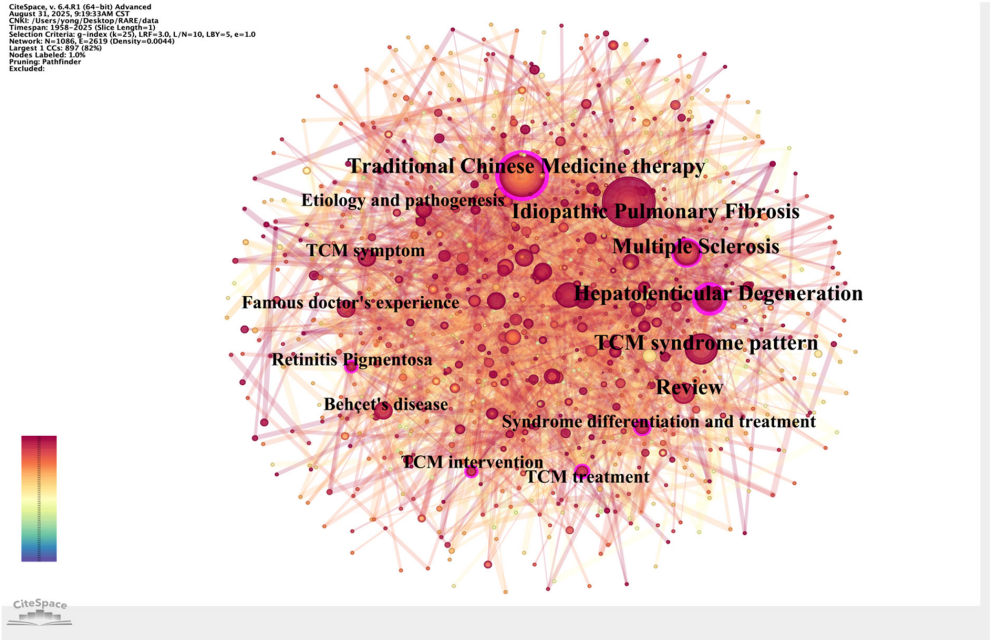

Figure 4. A network knowledge map of keywords in the field of traditional Chinese medicine diagnosis and treatment of rare diseases obtained using the software CiteSpace6.4.R1 based on mainstream Chinese databases (CNKI, VIP, Wanfang, and Chaoxing).

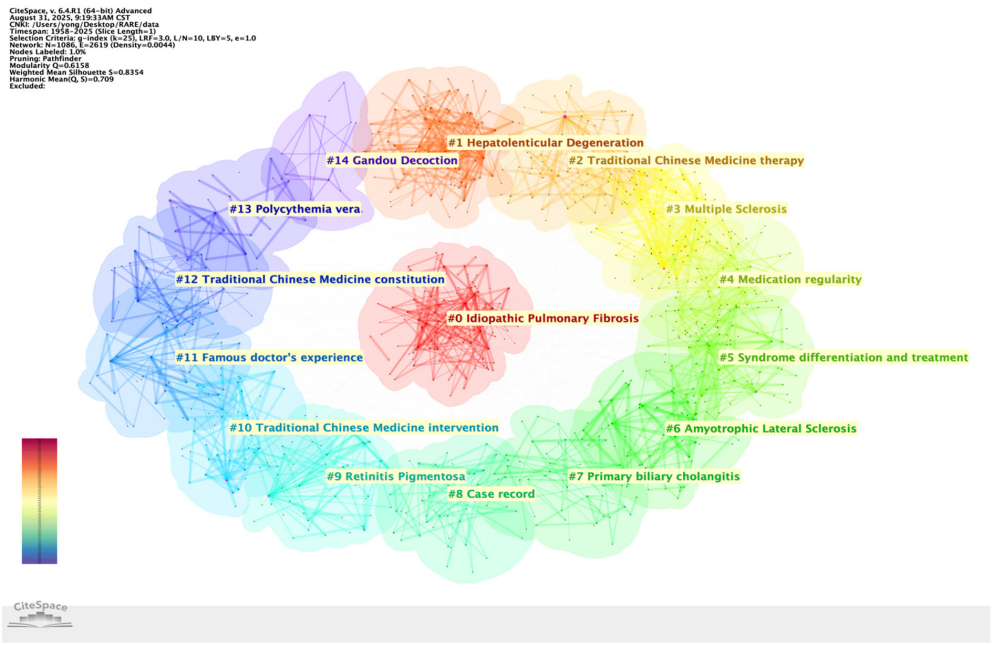

Figure 5. A clustering map of rare disease keywords obtained using the software CiteSpace6.4.R1 based on mainstream Chinese databases (CNKI, VIP, Wanfang, and Chaoxing).

idiopathic pulmonary fibrosis (2012), hepatolenticular degeneration (2012), and primary biliary cholangitis (2017).

3.4.3. Keyword timeline analysis

The keyword timeline map uses clustering as the horizontal hierarchy, with node size representing keyword frequency, color gradient indicating time, and arcs depicting cross-year co-occurrence relationships.

#0 Idiopathic Pulmonary Fibrosis emerged around 1995 and remains prevalent to the present. Related nodes include "experimental research, lung bi (肺痹, fei bi), pulmonary atrophy (肺痿, fei wei), pathogenesis", indicating a high level of interest in rare pulmonary disease topics that was sustained. Key nodes for #1 Hepatolenticular Degeneration emerged after 1985, with "TCM syndrome patterns" appearing after 2000; the last two decades saw the emergence of "hyperhomocysteinemia, homocysteine, H-type hypertension". #2 Traditional Chinese Medicine therapy emerged around 1990, and was associated with keywords like "recurrence, nursing, proven case, bullous pemphigoid, academic research". #3 Multiple Sclerosis appeared before 1985, and was linked to keywords such as "TCM treatment, TCM clinical experience, preventive medicine (治未病, zhi wei bing), latent pathogen theory (伏邪学说, fu xie xue shuo)". #4 Medication regularity: The node "Behçet's disease" emerged before 1990; "osteosarcoma, syndrome differentiation, clinical efficacy" appeared in around 2005; "multiple sclerosis, data mining, medication rules" emerged around 2015; and "network pharmacology, mechanism of action" appeared after 2020. #5 Syndrome differentiation and treatment emerged around 1990, with the node "adult-onset Still disease" appearing around 1995; in around 2000, it was associated with "integrated Chinese and Western medicine, TCM therapy" and was later linked to nodes such as "Behçet's syndrome, systemic sclerosis, quality of life". #6 Amyotrophic Lateral Sclerosis emerged after 1990, with nodes clustering after 2000 alongside "TCM syndrome, Flaccidity Syndrome (痿证, wei zheng), etiology and pathogenesis", indicating the trajectory of research. #7 Primary Biliary Cholangitis appeared in around 1995 and was associated with "clinical observations, clinical experience". #8 Case record emerged in around 1990 and was associated with "Multiple System Atrophy, Neuromyelitis Optica, etiology and pathogenesis, acupuncture". #9 Retinitis Pigmentosa appeared in around 1990 and was linked to nodes such as "Primary Retinitis Pigmentosa, acupuncture therapy, acupuncture, acupuncture treatment". #10 Traditional Chinese Medicine intervention spanned from before 1990 to after 2020 and was associated with "Primary sclerosing cholangitis, Narcolepsy, vessel bi-disease (脉痹, mai bi)". #11 Famous doctor's experience emerged in 1990 and continues to this day, with subsequent nodes including "Multiple Sclerosis, POEMS syndrome, pediatric neuroblastoma, lung flaccidity (肺痿, fei wei), and Retinitis Pigmentosa". #12 Traditional Chinese Medicine constitution emerged in 2000 and was associated with "TCM pathogenesis, acupuncture, clinical characteristics, lung function, syndrome factors, risk factors". #13 Polycythemia Vera appeared in 1985 and was linked to "Chinese medicine, veteran TCM

Table 1. Summary of major clusters

ID	Size	Silhouette	Year	Keywords	Label (LLR)
0	100	0.806	2012	Idiopathic pulmonary fibrosis	Idiopathic pulmonary fibrosis, traditional Chinese medicine, progress of research, clinical research
1	89	0.936	2012	Hepatolenticular degeneration	Hepatolenticular degeneration, traditional Chinese medicine syndrome patterns, hyperhomocysteinemia, Wilson's disease
2	80	0.73	2002	Traditional Chinese medicine therapy	Traditional Chinese medicine therapy, pemphigus, case reports, nursing care, pemphigus vulgaris
3	77	0.895	2002	Multiple sclerosis	Multiple sclerosis, traditional Chinese medicine treatment, integrated Chinese and Western medicine treatment, preventive medicine
4	71	0.763	2012	Medication regularity	Medication regularity, data mining, Behçet's disease, Chinese herbal medicine, cluster analysis
5	69	0.826	2007	Syndrome differentiation and treatment	Syndrome differentiation and treatment, traditional Chinese medicine, adult Still's disease, systemic sclerosis, experience
6	65	0.831	2010	Amyotrophic lateral sclerosis	Amyotrophic lateral sclerosis, ALS, traditional Chinese medicine syndrome, motor neuron disease
7	52	0.82	2017	Primary biliary cholangitis	Primary biliary cholangitis, clinical experience, ursodeoxycholic acid, traditional Chinese medicine therapy
8	51	0.812	2015	Case record	Case record, multiple system atrophy, pathogenesis, multiple system atrophy, neuromyelitis optica
9	51	0.869	2002	Retinitis pigmentosa	Retinitis pigmentosa, primary retinitis pigmentosa, Gaofeng cataract, traditional Chinese medicine ophthalmology
10	49	0.831	2002	Traditional Chinese medicine intervention	Traditional Chinese medicine intervention, narcolepsy, Takayasu arteritis, primary sclerosing cholangitis
11	41	0.79	2009	Famous doctor's experience	Famous doctor's experience, multiple sclerosis, inflammatory myofibroblastic tumor
12	33	0.806	2016	Traditional Chinese medicine constitution	Traditional Chinese medicine constitution, Leber's hereditary optic neuropathy, neuromyelitis optica, clinical features, risk factors
13	26	0.895	2007	Polycythemia vera	Polycythemia vera, malignant melanoma, experiences of veteran TCM practitioners, Longdan Xiegan decoction
14	16	0.923	2019	Gandou decoction	Gandou decoction, internal damp-heat pattern, Wilson's disease, hepatolenticular degeneration

doctor's experience". #14 Gandou Decoction emerged in 2000, with nodes including "research strategies, combination of disease and syndrome, Wilson's disease" (Figure 6).

3.4.4. Keyword emergence analysis

Detecting citation burst terms can provide an intuitive visualization of historical shifts in research hotspots within Chinese literature on TCM treatments for rare diseases. The figure indicates that disease-related keywords — "Retinitis Pigmentosa", "Multiple Sclerosis", "Primary Biliary Cholangitis", and "Idiopathic Pulmonary Fibrosis" — emerged as research focal points during the periods 1993–1999, 2004–2013, 2017–2025, and 2023–2025, respectively. Regarding research methodology-related keywords, "experiences of renowned physicians" emerged as a hot topic from 2010 to 2017, while "data mining" and "medication patterns" gained prominence from 2021 to 2023 (Figure 7).

4. Discussion

4.1. TCM's primary advantages in diagnosing and treating rare diseases are limited to specific conditions

Based on the above descriptive analysis of 207 rare diseases, TCM demonstrates diagnostic and therapeutic advantages primarily in five conditions: idiopathic pulmonary fibrosis, multiple sclerosis, hepatolenticular degeneration, retinitis pigmentosa, and osteosarcoma. These will now be discussed in detail.

4.1.1. Idiopathic pulmonary fibrosis was studied the most

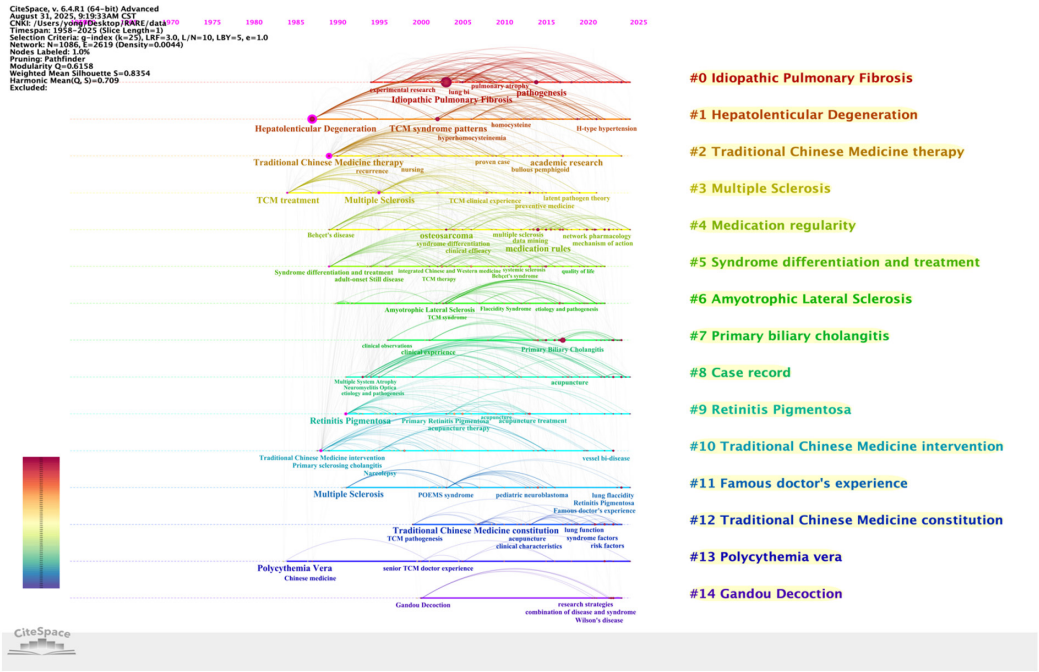

Figure 6. A timeline map of rare disease keywords obtained using the software CiteSpace6.4.R1 based on mainstream Chinese databases (CNKI, VIP, Wanfang, and Chaoxing).

Top 10 Keywords with the Strongest Citation Bursts

Keywords	Year	Strength	Begin	End
TCM therapy	1989	65.39	**1992**	2010
Retinitis Pigmentosa	1991	14.66	**1993**	1999
Multiple Sclerosis	1995	15.02	**2004**	2013
Famous doctor's experience	2003	9.38	**2010**	2017
Primary biliary cholangitis	2017	14.79	**2017**	2025
Traditional Chinese Medicine	1998	9.11	**2020**	2025
Data mining	2014	13.82	**2021**	2023
Medication regularity	2015	9.82	**2021**	2023
idiopathic pulmonary fibrosis	2014	18.5	**2023**	2025
traditional chinese medicine	2014	16.75	**2023**	2025

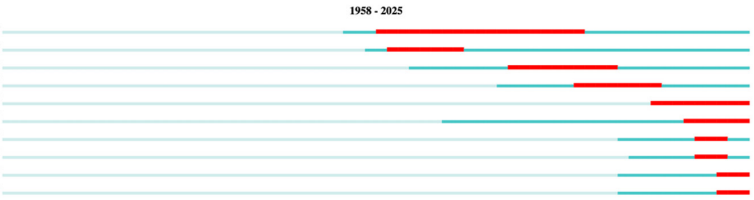

Figure 7. A citation burst map of rare disease keywords obtained using the software CiteSpace6.4.R1 based on mainstream Chinese databases (CNKI, VIP, Wanfang, and Chaoxing).

Idiopathic pulmonary fibrosis is a terminal-stage lung alteration in interstitial lung disease (*7*) and falls under pulmonary system diseases in TCM. The primary research institution studying this disease is the Liaoning University of Traditional Chinese Medicine and its affiliated hospitals. The team led by Xiaodong Lyu (core members include Lijian Pang and Li Yang) has significantly influenced research on this disease. In 2007, this team proposed that pulmonary fibrosis falls under the TCM category of pulmonary atrophy (肺痿, fei wei) (*8*) and it suggested treating pulmonary fibrosis based on the principles of pulmonary atrophy. The disease's location is in the lungs, spleen, and kidneys (*9*). Its pathogenesis involves a fundamental deficiency and superficial excess (本虚标实, ben xu biao shi): a lung-kidney deficiency constitutes the fundamental deficiency, while phlegm, dampness, toxins, and blood stasis represent the superficial excess (*10*). Guided by the collateral disease theory (络病理论, luo bing li lun) after 2014, the team proposed that lung heat and collaterals stasis (肺热络瘀, fei re luo yu) constitutes the fundamental pathogenesis of idiopathic pulmonary fibrosis (*11*). Subsequent research identified a qi yin deficiency and phlegm and blood stasis collateral (肺气阴虚, fei qi yin xu, 痰瘀伏络, tan yu fu luo) as the primary pathogenesis (*12*). TCM herbal compounds are commonly based on the therapeutic principles of benefiting qi and nourishing yin (益气养阴, yi qi yang yin), activating blood and dredging collaterals (活血通络, huo xue tong luo), resolving phlegm and dredging collaterals (化痰通络, hua tan tong luo), and regulating the lungs and dredging collaterals (理肺通络, li fei tong luo) (*13*). Potential common therapeutic targets include transforming growth factor-beta 1 (TGF-β1), tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), vascular endothelial growth factor (VEGF), and the balance between matrix metalloproteinases and tissue inhibitors of metalloproteinases (MMPs/TIMPs) (*14*). The combination of Shenlong Decoction (primarily containing radix Glehniae and Pheretima)

with pirfenidone serves as a prognostic protective factor for this disease ($p < 0.05$) (*15*). Application of plasters to acupoints is the main method of external treatment, using acupoint combinations focusing on Feishu (BL13) and the Bladder Meridian of Foot-Taiyang, with Semen Sinapis Albae and Asarum as core drugs (*16*). Traditional Chinese nursing specifically proposes methods to enhance healthy Qi, resolve phlegm, remove stasis, and dredge collaterals (*17*). Basic research on the TCM diagnosis and treatment of this disease has amassed nearly 20 years of findings. In recent years, Xiaodong Lyu's team has focused primarily on standardizing TCM pattern differentiation and treatment protocols (*18*). Future research, such as randomized controlled trials (RCTs), may gradually yield high-level evidence following the establishment of standardized TCM diagnostic and therapeutic criteria.

4.1.2. Diagnosis and treatment standards for multiple sclerosis have been devised

Multiple sclerosis is a central nervous system (CNS) disease (*19*), and it falls under the category of brain diseases in TCM. The primary research institution studying this disease is Beijing Tiantan Hospital affiliated with Capital Medical University, where Yongping Fan's team has significantly influenced its study. In 2005, Fan reviewed over two decades of TCM literature, confirming that TCM's advantages in treating this disease lie in effectively alleviating neurological symptoms, regulating immune function, alleviating relapse symptoms, and reducing episode frequency (*20*). He analyzed the medical records of 500 multiple sclerosis patients and summarized 6 combinations of TCM syndrome factors as Liver-Kidney Yin Deficiency, Spleen-Kidney Yang Deficiency, Spleen Qi Deficiency, Blood Stasis, phlegm dampness and phlegm heat, and engendering wind (*21*). This led to the development of the Clinical Diagnosis and Treatment Guidelines for Multiple Sclerosis in Traditional Chinese Medicine, which identified four primary syndromes: a Liver-Kidney Yin Deficiency, a Spleen-Kidney Yang Deficiency, Phlegm-Damp-Heat, and a Qi Deficiency with Blood Stasis. The guidelines also recommended Chinese patent medicines, decoction prescriptions, and acupuncture treatment protocols (*21*). In 2024, an integrated Chinese-Western medicine treatment plan for this disease was further proposed (*22*). Analysis of renowned TCM practitioners' treatment experiences has revealed that the most frequently used categories of drugs are tonics, heat-clearing drugs, and blood-activating stasis-removing drugs. Herbs such as Astragalus, Angelica, Poria, Coix Seed, and Atractylodes demonstrate specific therapeutic effects (*23*). TCM has certain advantages in managing this condition, though future research requires higher-level clinical trials and studies of its mechanisms.

4.1.3. There are effective TCM formulas for hepatolenticular degeneration

Hepatolenticular degeneration is an autosomal recessive inherited copper metabolism disorder (*24*), and it falls under the category of brain diseases in TCM. The primary research institution studying this disorder is Anhui University of Chinese Medicine and its affiliated hospitals, with Wenming Yang's team significantly influencing this field. Yang posits that the TCM pathological nature of hepatolenticular degeneration involves a complex interplay of deficiency and excess. Copper toxicity consistently permeates the disease process, while internal accumulation of damp-heat, phlegm-turbidity, blood stasis, and a deficiency of qi and blood are common pathogenic factors or pathological products. Treatment should focus on resolving phlegm and stasis (*25,26*). Through case-control studies, Yang's team demonstrated that Gandouling decoction improves liver function in patients with this disease (*27*). Combined with swallowing rehabilitation training, it can ameliorate swallowing dysfunction in pseudobulbar palsy caused by hepatolenticular degeneration (*28*); Combined with repetitive transcranial magnetic stimulation, it alleviates depressive disorders (*29*) and enhances cognitive function (*30*) in hepatolithiasis patients. When taken by patients with a liver-kidney deficiency and phlegm-blood stasis, Gandou Fumu granules significantly improved TCM syndrome scores, enhanced clinical efficacy, boosted copper-excretion effects, and demonstrated anti-inflammatory and antioxidant properties (*31*). There is extensive TCM clinical practice regarding this condition, warranting further research into its mechanisms.

4.1.4. TCM's effectiveness at treating retinitis pigmentosa is close to 80%

Retinitis pigmentosa is an inherited retinal neurodegenerative disease (*32*), and it falls under the category of ophthalmological diseases in TCM. The primary research institutions studying this disease include Hunan University of Chinese Medicine and its affiliated hospitals as well as the China Academy of Chinese Medical Sciences. In 1993, Qinghua Peng and Chuanke Li from the First Affiliated Hospital of the Hunan University of Chinese Medicine proposed that the pathogenesis of retinitis pigmentosa involves a deficiency combined with blood stasis. They treated 769 patients using methods to alleviate deficiency and promote blood circulation, achieving an efficacy exceeding 80% (*33*). In 2020, the team categorized syndromes into four patterns: a kidney yang deficiency, a liver-kidney yin deficiency, a spleen qi deficiency, and a qi deficiency with blood stasis. Use of comprehensive TCM therapies in 297 cases yielded an overall efficacy of 78.12% (*34*). A 2021 retrospective analysis of their comprehensive TCM treatments in 973 cases revealed

an overall efficacy of 74.15% (*35*). The Ophthalmic Hospital of the China Academy of Chinese Medical Sciences treated 35 cases with TCM integrated therapy, achieving an overall response rate of 55.37% (*36*). In 2024, a team from Hebei University of Chinese Medicine proposed applying zang-fu syndrome differentiation based on the "Five Wheels Theory" as an approach to this disease's treatment (*37*), though it has yet to be verified clinically. TCM treatment demonstrates distinct advantages in treating this condition, with higher-level clinical studies likely to be conducted in the future.

4.1.5. TCM interventions for osteosarcoma have practical effects

Osteosarcoma is a primary malignant bone tumor (*38*), and it falls under the renal system in TCM. The current study identified 115 TCM-related articles on this condition. The literature indicates that TCM research teams across various regions of China are studying this disease, and yet no mainstream consensus has been reached. Current research primarily involves literature reviews and summaries of renowned physicians' experiences, though it has provided numerous insights into TCM interventions. In 2015, Fuchun Si and Shuaiwei Ding proposed four primary syndromes: a Kidney Yin Deficiency, a Spleen-Kidney Yang Deficiency, Qi and Blood Stagnation, and Phlegm-Heat interaction. Key treatment methods include tonifying a deficiency, activating blood and resolving stasis, and clearing heat (*39*). Professor Guizhi Sun from Guang'anmen Hospital of the China Academy of Chinese Medical Sciences has demonstrated particular expertise in treating this condition. She believes that based on a deficiency in origin and excess in manifestation, syndrome differentiation and treatment should be conducted depending on whether the patient has a spleen and kidney deficiency, the cold or heat nature of the cancer toxin, and the presence of phlegm-dampness and blood stasis (*40*). Professor Yunxia Liu from Hangzhou Third People's Hospital emphasizes distinguishing between Yin patterns (phlegm-dampness and blood stasis obstructing the bones) and Yang patterns (heat-toxin accumulation in the bones) in diagnosis and treatment. She proposes applying the theory of preventive treatment to control lung metastases in this condition (*41*). Ding *et al.* analyzed the role of TCM in bone sarcoma radiotherapy and chemotherapy, finding that TCM enhances immune function, improves liver function, sensitizes bone sarcoma cells to radiotherapy, reverses multidrug resistance in bone sarcoma cells undergoing chemotherapy, promotes hematopoietic function recovery, and prevents distant metastasis of bone sarcoma cells; these effects have been verified (*42*). In recent years, experts from Shanghai, Guangdong, and Henan have collaborated to study this disease. Yin *et al.* analyzed and categorized TCM syndromes in osteosarcoma (*43,44*) and conducted studies on the molecular mechanism of Yiqi-Sanyu-Jiedu Formula (*45*). Further clinical research may follow.

4.2. TCM provides auxiliary support for multiple conditions

Research indicates that TCM can play a supplementary role in specific stages or in particular aspects of managing rare diseases. Numerous conditions fall under this category, including pemphigus, polycythemia vera, Takayasu arteritis, amyotrophic lateral sclerosis, homocysteinemia, primary biliary cholangitis, and lymphangioleiomyomatosis.

4.2.1. TCM can reduce the steroid dosage in pemphigus patients

Pemphigus is a rare and serious autoimmune bullous disease mediated by a group of pathogenic autoantibodies mainly targeting desmoglein 2 (*46*). In TCM, pemphigus is defined as a type of bullous skin disease characterized by initial skin lesions as small as semen Euryales or as large as chess pieces, potentially extending all over the body and causing an intense burning pain (*47*). Unruptured blisters remain firm, while ruptured ones discharge toxic fluid with no foul odor. TCM research on this condition began in the 1990s and was initially dominated by clinical reports of individual case treatments and care. The first case-control study involving 120 cases appeared in 2007 and concluded that while glucocorticoids remain the first-line treatment for pemphigus and pemphigoid, integrating TCM syndrome differentiation can reduce glucocorticoid dosage (*48*). Literature from the 2010s continued to emphasize case reports, including contributions from nationally renowned physicians (*49-51*). These practitioners used pattern differentiation to prescribe internal herbal decoctions or combined them with external herbal washes. Such approaches enabled reduced steroid usage and even prolonged steroid-free periods. Recent studies increasingly emphasize integrated Chinese-Western medicine, elucidating key synergistic points at the protein level (*52*).

4.2.2. There are guidelines for the TCM treatment of polycythemia vera

The main characteristics of polycythemia vera are erythrocytosis, thrombotic and hemorrhagic predisposition, various symptoms and cumulative risks of fibrotic progression and/or leukemic evolution over time (*53*). TCM treatment for polycythemia vera began in the 1970s, and the literature was initially dominated by case reports (*54,55*). Clinical studies emerged after the 1990s. In 2011, Zhejiang Province issued an Evaluation of the

Pathogenesis of Polycythemia Vera and the Efficacy of Combined TCM-Western Medicine for Its Treatment (*56*), proposing standardized diagnosis and treatment criteria from the perspective of the mechanisms of TCM and Western medicine and evaluation of their efficacy. The accumulated experience of famous doctors has also significantly contributed to the TCM management of this condition (*57,58*). In 2022, multiple national academic organizations jointly issued the Expert Consensus on Integrated Chinese and Western Medicine Diagnosis and Treatment of Polycythemia Vera (2022) (*59*), which clearly defines TCM's understanding of this disease and provides specific clinical guidelines.

4.2.3. Staged TCM treatment for Takayasu arteritis can alleviate clinical symptoms

Takayasu arteritis presents as systemic vasculitis (*60*), predominantly affecting the aorta and its major branches (*61*). Clinical reports on TCM treatment for Takayasu arteritis emerged as early as the 1980s (*62*). Treatment outcomes demonstrated that TCM therapy can alleviate clinical symptoms, eliminate a low-grade fever, lower blood pressure, improve renal function, and restore the erythrocyte sedimentation rate (ESR) and anti-streptolysin O (ASO) titer to normal levels, thereby controlling disease activity. Famous doctors have generally had good results in treating this disease. For instance, Jiuyi Xi uses a three-phase approach emphasizing dispelling wind, consolidating the exterior, and fortifying the body's defenses (*63*); Shikui Guo treats the disease and its complications based on the theory of blood stasis (*64*); Baogui Chen focuses on expelling pathogens during the acute phase and fortifying the body during the stable phase, with both methods restoring blood flow in patients (*65*). However, an expert consensus has not yet been reached, and high-level case-control studies still need to be conducted.

4.2.4. TCM tonifying methods can reduce syndrome scores in amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a fatal CNS neurodegenerative disease (*66*) that includes motor decline and cognitive and/or behavioral symptoms (*67*). Chinese ALS cohorts have distinct epidemiological features, including a younger mean age of onset and prolonged median survival (*68*). Famous doctors from Guangzhou University of Chinese Medicine and its affiliated hospitals have influenced research on this disease to an extent. They posit that a spleen-kidney deficiency constitutes the root cause of this disease, while internal wind due to a deficiency and phlegm-stasis obstructing collaterals represent its manifestations (*69,70*). Treatment primarily involves tonifying formulas (*71*) intended to delay disease progression and improve TCM syndrome scores.

4.2.5. TCM can alleviate homocysteinemia and its secondary conditions

An elevated level of homocysteine in the body is known as homocysteinemia (*72*). TCM views a congenital constitutional insufficiency and acquired deficiency of vital substances as primary etiologies, with phlegm-stasis obstruction as the core pathogenesis. Both blood stasis and phlegm turbidity are pathologies that further trigger new pathological changes. Treatment focuses on resolving phlegm, clearing turbidity, promoting blood circulation, and removing stasis (*73*). TCM treatment for this condition has demonstrated efficacy in improving blood pressure and reducing the associated stroke risk (*74,75*) as well as in alleviating angina pectoris in coronary heart disease (*76*).

4.2.6. TCM can alleviate symptoms in non-responders to drugs to treat primary biliary cholangitis

Primary biliary cholangitis (PBC) is a chronic liver disease characterized by an autoimmune attack on the small bile ducts (*77*). Currently, ursodeoxycholic acid (UDCA) is recognized as an effective treatment that significantly alters the natural course of PBC. The advantage of TCM lies in its ability to improve outcomes in 30 to 40% of patients who fail to respond to UDCA (*78*).

4.2.7. TCM can alleviate respiratory symptoms in lymphangioleiomyomatosis

Lymphangioleiomyomatosis is a rare neoplastic disease characterized by the presence of diffuse thin-walled cysts in lungs and angiomyolipomas in kidneys (*79*), and it falls under the category of pulmonary diseases in TCM. By soothing the liver and regulating Qi, tonifying the kidney and astringing the lungs, modified Sini Powder can significantly alleviate clinical symptoms such as dyspnea, coughing, wheezing, and tightness of the chest (*80*).

4.3. Advantages of TCM in diagnosing and treating rare diseases

4.3.1. Comprehensive TCM approaches offer advantages in treating rare diseases

This study has revealed that TCM for rare diseases is rarely a singular treatment. TCM has a holistic advantage in treating rare diseases, guided by theories such as collateral disease theory and preventive treatment theory and adopting comprehensive treatment modalities including Chinese herbs, acupuncture, tuina, and traditional exercises throughout the long course of rare diseases. These comprehensive approaches have been confirmed to improve the quality of life of some rare

disease patients.

4.3.2. TCM interventions offer unique benefits and complement Western medicine in treating rare diseases

An analysis of the clinical research literature on TCM for treatment of various rare diseases has revealed that case-control studies using TCM or integrated TCM-Western medicine approaches primarily observe improvements in TCM syndrome scores and alleviation of specific symptom clusters. Organ structures do not typically differ significantly. Conversely, many Western pharmaceutical interventions fail to improve TCM syndrome scores, indicating that TCM offers a distinct perspective and unique role in treating rare diseases. For instance, TCM can alleviate respiratory symptoms in lymphangioleiomyomatosis, enhancing patients' quality of life; it can also alleviate symptoms in 30 to 40% of patients with primary biliary cholangitis who are unresponsive to standard medications. These cases demonstrate the efficacy of integrated Chinese-Western medicine in treating rare diseases and represent a promising direction for the future management of rare diseases.

4.4. Limitations of TCM in diagnosing and treating rare diseases

4.4.1. Lack of a scaled team for TCM diagnosis and treatment of rare diseases

As rare diseases in mainland China are primarily treated in general hospitals, only about 10 TCM institutions are involved in rare disease care. Consequently, epidemiological data on rare diseases in China are currently limited (*81,82*), and TCM institutions and teams specializing in rare diseases remain scarce. An analysis of 207 rare diseases revealed that, based on Price's law, core authors involved in the TCM treatment of rare diseases should publish more than 4 papers. However, there are only 54 core authors in this field, accounting for approximately 4.4% of all publishing authors. These core authors published 547 papers, accounting for 22.8% of the literature. Since the output of core authors in this field did not reach 50% of the literature, this indicates that a team of core authors has not yet formed in this area. This suggests that TCM research on rare diseases is still in its infancy and that the scope of TCM integration into rare disease diagnosis and treatment should be further expanded.

4.4.2. Lack of high-level evidence-based clinical research on rare diseases in TCM

TCM's involvement in the diagnosis and treatment of rare diseases appears as a scattering of distributed points. Keyword clustering analysis revealed that literature review and data mining are the primary methods used in TCM research on rare diseases. In clinical research, studies typically begin with the long-term clinical experience and accumulated efficacy of famous doctors over decades. From this foundation, research progresses from literature to famous doctors' experience, focusing on TCM classifications of rare diseases to investigate pathogenesis, syndrome patterns, and effective formulas. Building upon this foundation, case-control studies are conducted. For conditions that have been sufficiently studied, their mechanisms are researched—for instance, there is support from the National Natural Science Foundation of China for study of both idiopathic pulmonary fibrosis and retinitis pigmentosa. However, clinical research yielding high-level evidence has yet to be conducted, representing a key direction for the future development of TCM in the area of rare diseases.

5. Conclusion

TCM plays a unique role in the diagnosis and treatment of rare diseases in mainland China. Institutions are scattered across the country, with their primary strengths focused on alleviating specific clinical symptoms and improving quality of life. For rare diseases where TCM demonstrates distinct therapeutic advantages, research teams remain relatively singular, concentrating on etiology, pathogenesis, and syndrome differentiation. Case-control studies and studies of mechanisms have been initiated for certain conditions. Clinical research has shifted from purely TCM studies to integrated TCM-Western medicine approaches. However, further efforts are needed to strengthen team and institutional collaboration, develop multicenter networks, explore multidisciplinary research, and conduct high-level clinical studies. This will provide quality evidence-based support for clinical decision-making with regard to the TCM treatment of rare diseases.

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Original Article

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Medical security for rare disease patients in China: Insights from patients with Dravet syndrome

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SUMMARY: The high costs of diagnosing and treating rare diseases impose a substantial financial burden on patients and families, underscoring the need to understand reimbursement experiences and unmet needs to improve medical security. Using Dravet syndrome, a severe and lifelong epileptic encephalopathy, as a representative rare disease, this study conducted an online questionnaire survey completed by 161 respondents, including family members or caregivers of patients with Dravet syndrome. The results revealed that most families had insufficient income to cover treatment costs, with patients' annual treatment expenses generally approaching or even exceeding their families' financial capacity, while 41.67% reported that out-of-pocket payments after reimbursement accounted for more than half of their total treatment expense. Surveyed respondents expressed general satisfaction with various medical security models (over 75%), including basic medical insurance, critical illness insurance, medical assistance, commercial health insurance, and charitable aid. However, challenges remain: the limited funding pool and reimbursement capacity of basic medical insurance, the ongoing development of commercial insurance products (*e.g.*, region-specific Huimin insurance), and the lack of guaranteed scale and sustainability of charitable funding. Thus, further improvements in China's medical security for rare disease are imperative. Key priorities include enhancing policy coherence, improving coordination across security models, and increasing the depth of coverage at all levels to alleviate the financial burden on patients.

Keywords: rare diseases, multi-tiered medical security, Dravet syndrome, policy recommendations, China

1. Introduction

Dravet syndrome, previously known as Severe Myoclonic Epilepsy of Infancy (SMEI), is a drug-resistant developmental and epileptic encephalopathy that begins in infancy and proceeds with accumulating symptom burden that significantly impacts individuals throughout their lifetime (*1,2*). Patients typically experience gradual developmental delay or regression, with most developing varying degrees of intellectual disability, behavioral abnormalities, sleep disorders, and mental health issues by adolescence (*3*). The syndrome carries a high mortality rate of 15–20%, primarily due to sudden unexpected death in epilepsy, prolonged seizures, seizure-related accidents (*e.g.*, drowning), and infections (*4,5*).

China currently lacks large-scale epidemiological data on Dravet syndrome. Existing literature reports its prevalence between 1/40,900 and 1/15,700, estimating approximately 20,000 to 50,000 affected families (*6,7*). Currently, the main therapeutic approaches for Dravet syndrome include antiepileptic drugs, dietary therapies such as a ketogenic diet for children aged 6 years and younger or a modified Atkins diet for adolescents and adults, and neuromodulation techniques like vagus nerve stimulation and deep brain stimulation. Additionally, novel therapies such as serotonergic drugs and gene-modifying therapies are under development (*8,9*). Overall, existing therapies have limited efficacy. While they may reduce seizure severity and frequency, managing non-epileptic episodes remains challenging. Complete cure is currently unattainable, and patients require lifelong medication (*7*). Concurrently, patients often experience developmental delays or intellectual disabilities, necessitating round-the-clock family care. This imposes multidimensional medical demands, high treatment costs, and long-term caregiving challenges on families. These factors severely impact quality of life for patients and their families, causing immense psychological stress and financial burdens (*10*), placing

households at significant risk of falling into poverty or relapsing into poverty due to illness (*7*). A systematic review of Dravet syndrome published in 2023 showed that the mean annual direct medical costs for patients were consistently high across studies, ranging from USD 11,048 to USD 77,914 per patient per year (*7*). For these reasons, Dravet syndrome patients urgently require access to new therapies, along with healthcare coverage and supportive systems to ensure treatment accessibility and long-term continuity.

In May 2018, Dravet syndrome was included in China's inaugural Rare Disease Catalog, qualifying for policy support such as accelerated review and medical insurance reimbursement. Related products have since been approved for market release (*11*). Currently, medical coverage for patients with Dravet syndrome in China primarily relies on a multi-tiered medical security system, including basic medical insurance, critical illness insurance, commercial health insurance, medical assistance, and charitable aid. However, despite ongoing policy advancement, systematic evidence at the patient level regarding actual medical burdens and coverage benefits under different insurance systems remains lacking, necessitating practical evaluation.

This study employs a patient-centered approach, selecting Dravet syndrome patients through questionnaire surveys. It examines coverage scope, actual benefits, and unmet needs of patients with Dravet syndrome across multiple insurance models. This study aims to provide empirical support for evaluating the actual effectiveness of China's multi-tiered medical security system for rare diseases, reveal gaps between existing healthcare policies and patient needs, and offer actionable recommendations for refining policies, optimizing healthcare resource allocation, and improving patient quality of life.

2. Respondents and Methods

2.1. Study design

This study employed a cross-sectional design utilizing a self-developed online questionnaire to investigate medical security experiences of patients with Dravet syndrome within China's multi-tiered healthcare protection system. Its design was grounded in the framework of China's multi-tiered medical security system and informed by a review of national policy documents, alongside prior studies on economic burden of rare diseases and health insurance evaluation. Content validity was established through review by a panel of experts specializing in health policy, rare disease management, and health economics. A pilot test was subsequently conducted with 15 caregivers of Dravet syndrome patients (excluded from the main survey) to assess clarity, comprehensibility, and completion time. Utilizing survey data from a national sample of affected individuals and their caregivers, the research examined coverage scope, realized benefits, and unmet needs associated with diverse insurance models, including basic medical insurance, critical illness insurance, medical assistance, commercial health insurance, and charitable aid.

The analytic framework integrated descriptive and comparative methods to evaluate the performance of the multi-tiered medical security system from the perspective, providing empirical evidence to inform policy refinement and resource allocation.

2.2. Questionnaire collection and data analysis

This cross-sectional survey distributed questionnaires online in collaboration with the "CHN Dravet Syndrome Patient Support Group". This patient organization has long provided disease management and information support to patients with Dravet syndrome and their families, and has a relatively stable and representative patient base. Given the nature of Dravet syndrome, all responses were provided by the patient's primary caregiver/family member based on the actual situation to ensure authenticity and accuracy.

Convenience sampling was employed for participant recruitment. Inclusion criteria were as follows: *i*) patients with a confirmed diagnosis of Dravet syndrome established by a qualified medical institution; *ii*) patients or their primary caregivers who were fully informed of the study objectives and voluntarily consented to participate.

Exclusion criteria included: *i*) questionnaires with unclear diagnostic information or missing key data related to disease characteristics or medical costs; *ii*) incomplete questionnaires or those containing evident logical inconsistencies; *iii*) duplicate submissions identified as originating from the same patient.

The questionnaire comprised two sections: basic patient information and issues related to the multi-tiered medical security system for rare diseases, totaling 45 items. The basic information section covered demographic characteristics (age, region, average annual household income), commonly used medications, annual treatment costs, insurance coverage status, *etc.* The security system section addressed economic burden, utilisation of benefits, and reimbursement experiences (including benefit entitlements, reimbursement experiences, and satisfaction levels). Question types included multiple-choice and open-ended fill-in-the-blank items.

The survey was conducted from March 13 to March 24, 2025. Data were processed using SPSS 26.0, with descriptive statistics applied and categorical data were described using frequencies (*n*) and percentages (%). In addition, all costs were assessed in US dollars (USD), using the average RMB/USD exchange rate of 7.1217 in 2024 (*12*).

2.3. Ethical approval

This study, which employed an online questionnaire,

received ethical approval from the Ethics Committee of China Pharmaceutical University (Approval no. 2025-09-010). Prior to participation, electronic informed consent was obtained from all participants. They were assured that collected data would be used exclusively for academic purposes, that all provided information would remain strictly confidential, and that their privacy would be protected through anonymization of any personal data. This study also conforms to the provisions of the Declaration of Helsinki.

3. Results

3.1. Basic patient information

A total of 161 online questionnaires were completed by primary caregivers or family members of patients with Dravet syndrome from 27 provinces, including Guangdong, Shandong, Henan, and Jiangsu. The survey results showed that 69.56% (112/161) of the patients were infants or young children aged 0–12 years. Regarding medication use, in addition to valproic acid and clobazam, patients commonly used more than ten other antiepileptic drugs, indicating a high level of treatment complexity.

3.2. Economic disease burden

Patients with Dravet syndrome typically require lifelong treatment, with medication being the primary therapeutic option. The most commonly prescribed drugs include valproic acid, clobazam, and stiripentol (Table 1), though medication choices may vary among patients. The survey showed that 77.36% of respondents reported that the medications required by patients were included in the national reimbursement drug list. However, as detailed in Table 1, 58.49% of respondents indicated that not all medications required by patients were fully covered by insurance.

The survey findings revealed that most patient's families didn't have sufficient income to cover the costs associated with treatment. Among the families, 42.86% (69 families) reported an annual income of less than 7,020.80 USD, while 78.26% had an annual income below 14,041.59 USD. However, 55.28% (89 respondents) reported that patient's annual treatment costs ranged from USD 0 to 7,020.80, and 44.72% indicated annual treatment costs ranged from USD 7,020.80 to 14,041.59. Overall, the treatment expenses borne by many patient families approached or even exceeded their financial affordability (Figure 1).

3.3. Patient insurance coverage and benefits

As detailed in Table 1, enrollment rate for basic medical insurance was 98.14% (158/161), surpassing the national coverage rate of 95% in 2024. In contrast, the uptake of commercial health insurance was 7.45% (12/161), which included "Huimin insurance" (9, 5.59%) and other commercial health insurance (9, 5.59%).

Table 1. Age, geographical distribution, and medication information of the 161 respondents*

Characteristics	Number	Percentage (%)
Age (year)		
0–6	64	39.75
7–12	48	29.81
13–17	12	7.45
18–24	4	2.48
25–40	25	15.53
41–65	7	4.35
> 65	1	0.62
Province		
Guangdong	20	12.42
Shandong	14	8.7
Henan	13	8.07
Jiangsu	12	7.45
Anhui	10	6.21
Sichuan	10	6.21
Others	82	50.94
Commonly Used Medications		
Valproic acid	140	86.96
Clobazam	105	65.22
Topiramate	55	34.16
Stiripentol	41	25.47
Levetiracetam	34	21.12
Clonazepam	22	13.66
Perampanel	16	9.94
Insurance Coverage		
Basic Medical Insurance	159	98.76
Critical Illness Insurance	12	7.45
Huimin Insurance	9	5.59
Other Commercial Insurance (excluding Huimin Insurance)	9	5.59
Medical Assistance	3	1.86
Charitable Aid	3	1.86
Inclusion of Required Medications in Basic Medical Insurance		
None included	36	22.64
Partially included	93	58.49
All required medications included	30	18.87

*All questionnaires were completed by patients' family members or caregivers, who reported patient-related information based on their caregiving experience. Commonly used medications are listed individually only if reported by more than 14 patients (frequency > 14).

With regard to insurance benefits, all enrollees in basic medical insurance had access to corresponding benefits. Furthermore, 7.45% (12/161) of respondents received support through critical illness insurance, and 1.86% (3/161) benefited from medical assistance. Despite these reimbursements, a considerable proportion continued to bear a high out-of-pocket share of total medical expenses. Specifically, 41.67% of respondents reported being responsible for over half of their medical costs, highlighting a persistent financial burden (Figure 2).

Recipients of medical assistance included individuals from low-income households, those on the margin of poverty, and patients affected by catastrophic health

expenditures. Assistance was delivered in the form of subsidies for basic medical insurance premiums and inpatient treatment costs. Respondents reported a noticeable reduction in their financial burdens after receiving this support.

Among respondents who had purchased commercial health insurance (including Huimin insurance), 75% (9/12) enjoyed the relevant benefits. However, only 33.33% (3/9) of these insured respondents reported a substantial reduction in treatment costs as a result of insurance claims. Furthermore, 22.22% (2/9) indicated they would not renew any commercial health insurance policies in the future, with the exception of Huimin insurance.

Additionally, 1.86% (3/161) of respondents benefited from charitable aid. Support mechanisms included targeted assistance from rare disease foundations (reimbursing out-of-pocket expenses exceeding 421.25 USD with a maximum subsidy of 702.08 USD) and specialized rare disease medical assistance programs.

3.4. Satisfaction and challenges of multi-tiered medical security

Surveyed respondents generally expressed satisfaction or a neutral stance toward the various tiers of medical security, including basic medical insurance, critical illness insurance, medical assistance, commercial health insurance, and charitable aid (Figure 3). Overall, respondents acknowledged the advancements in China's multi-tiered medical security system for rare diseases and the protection it affords, while also underscoring several persistent challenges that require further attention.

Regarding satisfaction with basic medical insurance, 81.13% (129/159) of insured respondents held a positive view. However, they also reported several concerns during reimbursement, including: *i*) limited reimbursement rates, which inadequately alleviated financial burdens (114/159, 71.7%); *ii*) difficulties in reimbursing cross-provincial medical expenses due to discrepancies between local and treatment-site insurance catalogs (67/159, 42.14%); *iii*) stringent eligibility criteria for chronic or critical illness recognition, hindering access to appropriate treatments (65/159, 40.88%); *iv*) high deductibles that impeded reimbursement (59/159, 37.11%); and *v*) low reimbursement caps, leaving

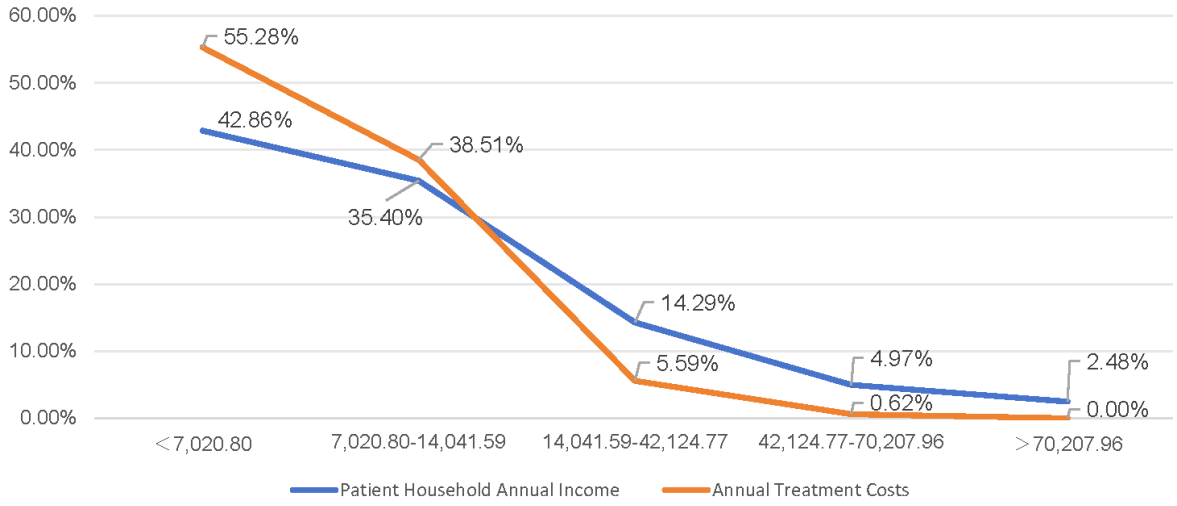

Figure 1. Patient household annual income *vs.* annual treatment costs. Values are presented in US Dollars (USD), converted from Chinese Yuan (RMB) using the average 2024 exchange rate of USD 1 = RMB 7.1217.

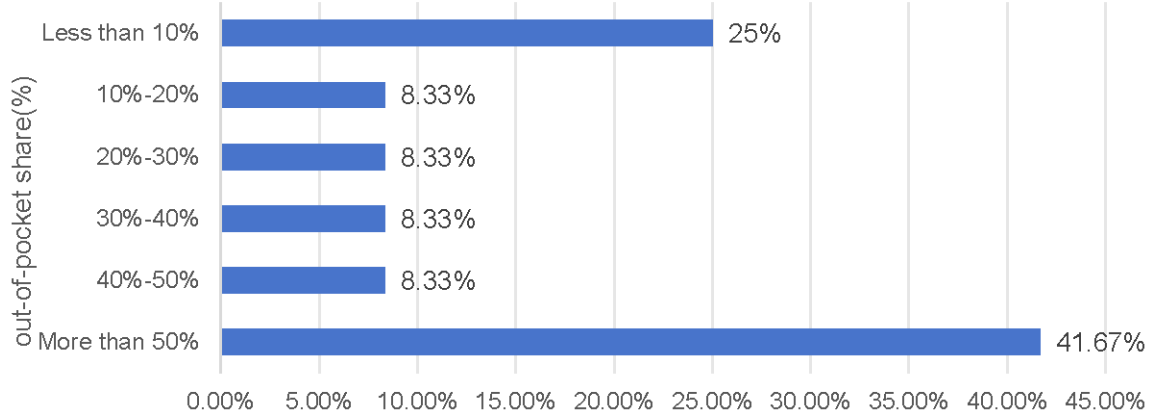

Figure 2. Patient's out-of-pocket share after basic medical insurance and critical illness insurance reimbursement.

substantial out-of-pocket expenses (53/159, 33.33%) (Figure 4).

For critical illness insurance, 91.67% (11/12) of insured respondents expressed satisfaction. Nevertheless, they highlighted several issues: *i*) high deductibles (8/12, 66.67%); *ii*) limited reimbursement rates providing insufficient financial relief (6/12, 50%); *iii*) low reimbursement caps (3/12, 25%); *iv*) financial pressure from prepaying cross-provincial medical expenses (3/12, 25%); and *v*) the need for better integration with basic medical insurance (5/12, 41.67%) (Figure 5).

All respondents receiving medical assistance were generally satisfied with the benefits but noted specific challenges, such as: *i*) cumbersome qualification verification procedures requiring multiple certifications across regions and institutions, and *ii*) high deductibles and low reimbursement rates that limited the overall reduction of financial burden (Figure 6).

As a supplementary layer to basic medical insurance, commercial health insurance was viewed positively by 77.78% (7/9) of insured respondents. Huimin insurance emerged as a commonly used plan among rare disease respondents. However, 77.78% (7/9) cited issues such as limited coverage and high deductibles or reimbursement thresholds (Figure 7). For other commercial health insurance products (excluding Huimin insurance),

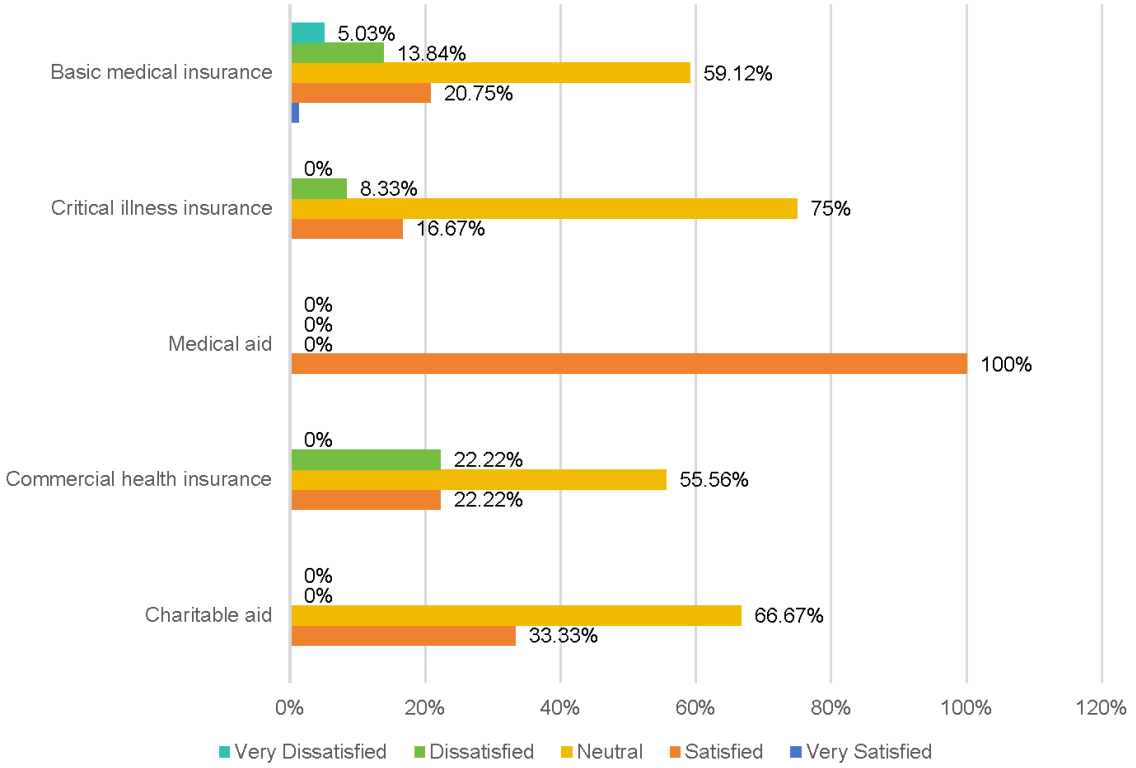

Figure 3. Patient satisfaction with the multi-tiered medical security system for rare diseases.

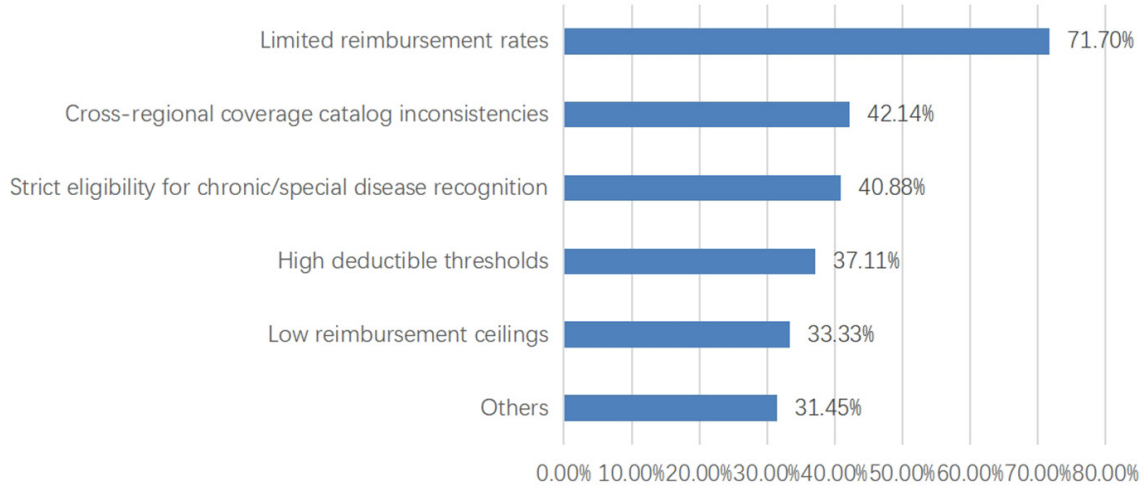

Figure 4. Challenges and issues faced by patients in reimbursement and services under basic medical insurance.

55.56% (5/9) reported exclusions related to pre-existing conditions, while 44.44% (4/9) highlighted high out-of-pocket costs, elevated deductibles, and expensive premiums — all contributing to additional financial strain on families (Figure 8).

Charitable aid is a form of support provided through foundation grants, medication assistance, and medical aid. Respondents who have received such benefits have expressed satisfaction with them.

Furthermore, in relation to the overall multi-tiered medical security system for rare diseases, 80.75% (130/161) of respondents emphasized the need to

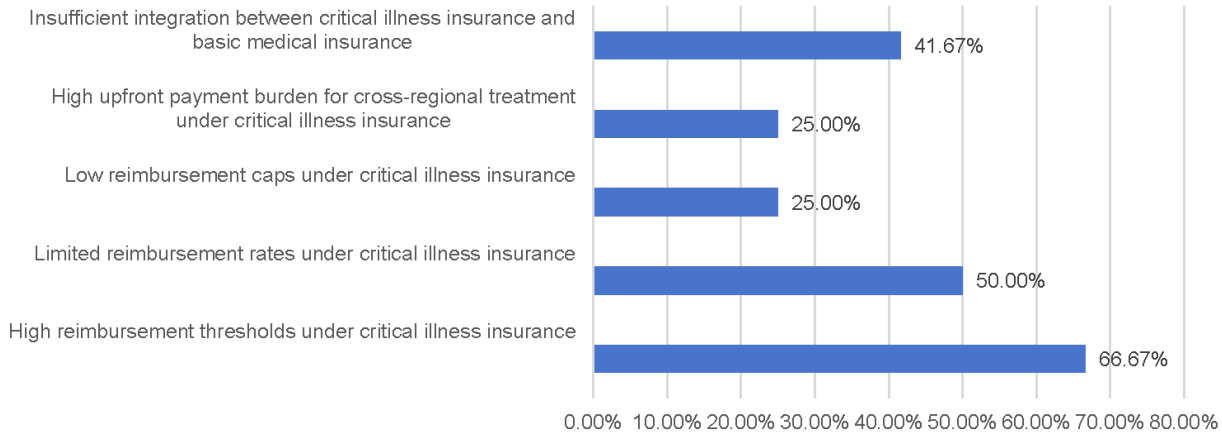

Figure 5. Challenges and issues faced by patients in reimbursement and services under critical illness insurance.

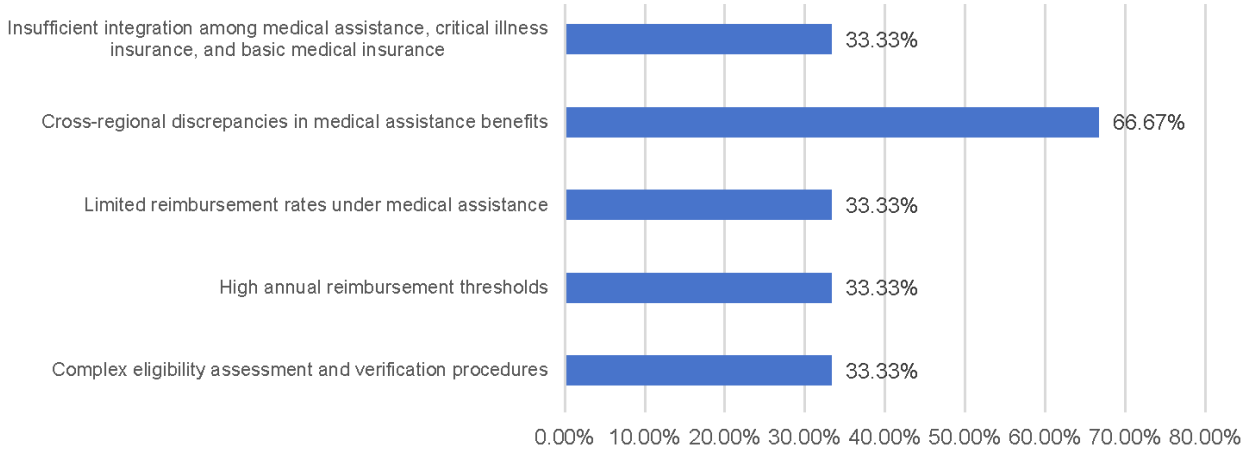

Figure 6. Challenges and issues faced by patients in reimbursement and services under medical assistance.

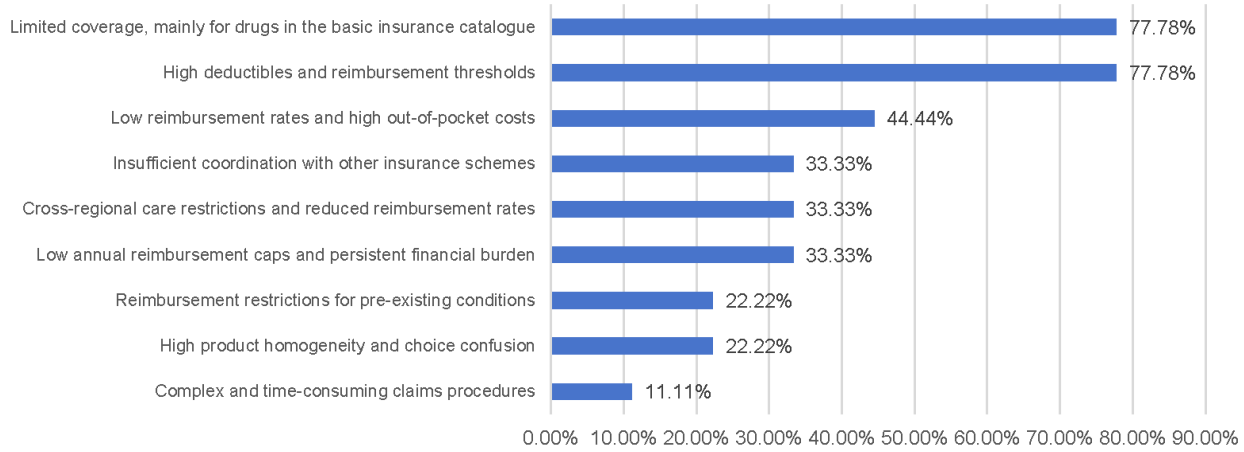

Figure 7. Challenges and issues faced by patients in reimbursement and services under Huimin insurance.

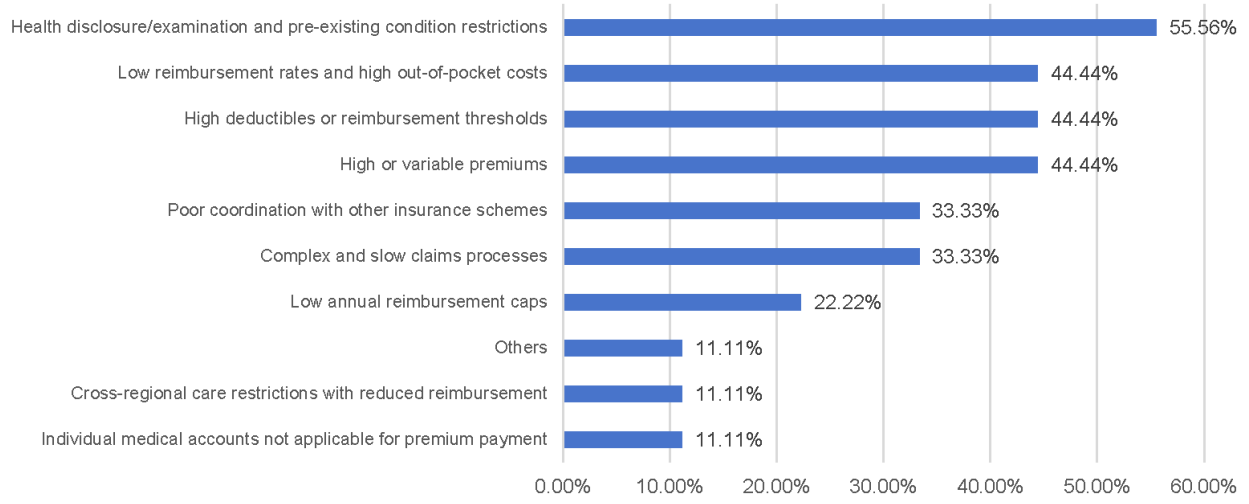

Figure 8. Challenges and issues faced by patients in reimbursement and services under other commercial health insurance (excluding Huimin insurance).

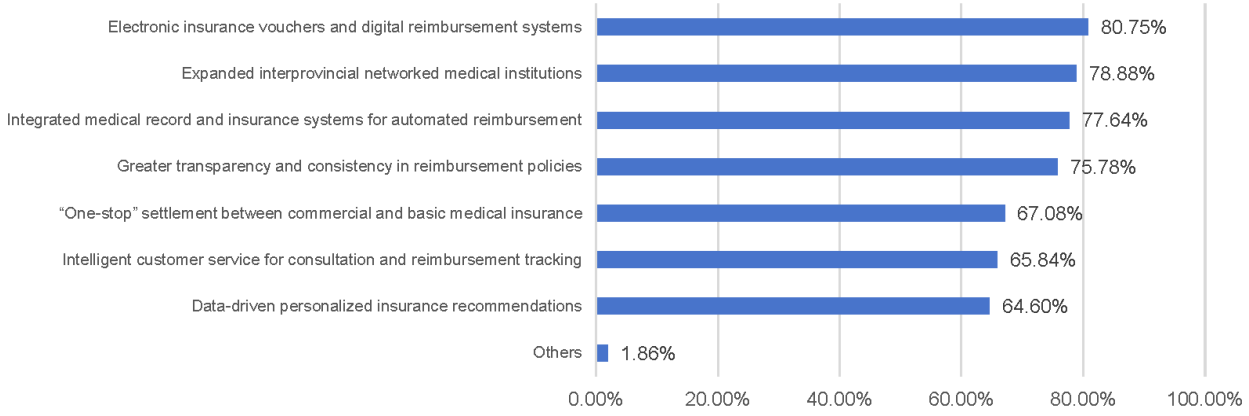

Figure 9. Patients' perceptions of areas for improvement in multi-tiered medical security systems (reimbursement convenience, information sharing, *etc.*).

improve reimbursement convenience and called for accelerating the rollout of electronic medical insurance systems. In addition, 78.88% (127/161) suggested enhancing the convenience and accuracy of cross-regional insurance settlement to alleviate difficulties associated with seeking medical care outside their home regions. Moreover, 77.64% (125/161) considered the interoperability of medical insurance information essential (Figure 9).

4. Discussion

The findings of this study indicate that although China has initially established a multi-tiered medical security system for rare diseases, respondents still report a significant lack of satisfaction with the reimbursement experience and an insufficient sense of financial relief. This result, to some extent, corroborates conclusions drawn by domestic and international scholars, who think the medical security system for rare diseases is universally plagued by insufficient coverage and uneven accessibility. This study, however, diverges from research that highlights institutional progress. Its main contribution lies in elucidating the disparity between the designed system and patients' reimbursement experiences, a disparity that manifests most significantly in limited coverage and high out-of-pocket expenditures. The finding reveals that proliferation of different models (*e.g.*, basic insurance, commercial insurance) has not been fully translated into effective protection for patients.

However, this study has several limitations. First, this research employed a cross-sectional design and convenience sampling through an online survey distributed *via* a patient support group, which may limit the generalizability of the findings. The sample, though national in scope, may not fully represent all patients with Dravet syndrome in China, particularly those without access to online patient communities or with varying socioeconomic backgrounds. Additionally, the study focuses solely on Dravet syndrome, and while informative, the results may not be fully transferable to other rare diseases with different treatment patterns and

cost structures. Future research could further conduct cross-regional and cross-disease comparative studies to uncover the heterogeneity in the fairness and accessibility of security among different rare disease populations.

The following sections will provide an in-depth analysis based on survey data, covering four aspects: basic medical insurance, critical illness insurance, medical assistance, commercial insurance.

4.1. Three shortcomings of basic medical insurance: limited coverage, regional imbalances, and high out-of-pocket burden

Although China's basic medical insurance coverage has reached 98.76%, patients with Dravet syndrome continue to experience a disproportionate economic burden. The core challenge lies not in insurance enrollment but in the depth of coverage and the alignment of existing schemes with the long-term, high-cost nature of Dravet syndrome treatment. Coverage of high-cost orphan drugs within the national reimbursement drug list remains limited (*13*) and substantial regional variation in outpatient policies for chronic and special diseases further increases uncertainty in long-term medication management and cross-regional healthcare utilization. Moreover, low reimbursement rates, high deductibles, and strict reimbursement caps mean that a considerable proportion of patients must still bear substantial out-of-pocket costs even within the insurance framework, pushing some families toward sustained financial strain at or beyond their economic capacity (*13*).

4.2. Critical illness insurance: high deductibles and low reimbursement rates undermine its supplementary role

In theory, critical illness insurance is designed to complement basic medical insurance by alleviating catastrophic health expenditures. However, for patients with Dravet syndrome, its supplementary role remains largely unrealized. The extremely low participation rate suggests limited accessibility, while high deductibles substantially weaken its protective capacity, particularly for families facing long-term and continuous medication needs. Although many regions have adopted tiered reimbursement mechanisms, the reimbursement gradients remain insufficient to meaningfully offset costs during high-expenditure phases. More importantly, the persistence of high out-of-pocket payments even after dual reimbursement highlights structural misalignment between critical illness insurance and basic medical insurance, resulting in fragmented protection rather than cumulative risk pooling.

4.3. Medical assistance: inadequate safety-net coverage for rare disease patients

Medical assistance is intended to serve as the last line of defense within China's healthcare security system. However, its actual protective effect for patients with rare diseases is constrained by both systemic design and implementation barriers. Strict eligibility thresholds based on household income and assets exclude the majority of families affected by Dravet syndrome, many of whom, while not meeting conventional poverty criteria, endure prolonged financial pressure from high and continuous medical expenses. In addition, medical assistance is limited in both coverage and funding amount, typically only reimbursing a portion of costs specified under basic medical insurance policies (*14*). For patients with Dravet syndrome who rely on high-cost, long-term medication, the risk-mitigation effect is very limited, making it difficult to establish an effective economic safety net. Therefore, within the multi-tiered medical security system for rare diseases, the role of medical assistance remains largely supplementary and constrained, highlighting an urgent need for institutional optimization in terms of coverage, funding standards, and application accessibility.

4.4. Commercial health insurance: challenges in balancing market incentives and public good for rare diseases

Commercial health insurance has the potential to supplement gaps in the public insurance system, particularly in financing innovative therapies for rare diseases. However, for patients with Dravet syndrome, its practical impact remains constrained by market-driven incentive mechanisms. Risk-selection practices, such as exclusion of pre-existing conditions, high deductibles, limited reimbursement ceilings, and restrictions on policy renewal, substantially reduce both accessibility and financial protection. Although inclusive products, such as public-benefit insurance schemes, have modestly expanded coverage, their depth of protection remains limited and out-of-pocket costs remain relatively high, constraining their overall effectiveness. This structural tension between profitability and social protection highlights the inherent difficulty of relying solely on market-based mechanisms to address long-term, high-cost medical needs of individuals with Dravet syndrome (*15*).

5. Suggestions

5.1. Enhancing policy coherence in China's multi-tiered medical security system for Dravet syndrome

China's multi-tiered medical security system for Dravet syndrome faces dual challenges in policy coherence and regional equity (*13*). There is an urgent need to strengthen institutional coordination, establish a nationally integrated multi-tiered security network, and gradually narrow regional gaps to improve system-wide

integrity and equity.

In the short term, the government can refine implementation of the medical insurance benefits list by allowing greater flexibility in local policy execution while maintaining centralized coordination. For provinces that have already established specialized local coverage schemes for Dravet syndrome, a transitional period of three to five years could be granted to ensure a smooth integration into a nationally unified policy and prevent interruptions in patient coverage (*16*). This approach would maintain continuity of care for patients while enabling gradual alignment with nationwide standards.

In the long term, the government can strengthen legislative safeguards for Dravet syndrome and establish a dedicated national fund for this condition. Resource allocation can be dynamically adjusted based on patient numbers and regional fiscal capacity, with priority given to Dravet syndrome cases that remain unaffordable at the local level. In addition, the government can introduce appropriate payment and intergovernmental transfer incentives to support economically disadvantaged regions.

5.2. Enhancing coordination in China's multi-tiered medical security system for Dravet syndrome

China's medical insurance system for Dravet syndrome continues to face coordination challenges, which significantly affect patients' diagnostic pathways, treatment continuity, and medication management. To address these challenges, policy efforts should prioritize strengthening cross-departmental coordination and promoting synergies across all levels of the healthcare security system, thereby establishing a more sustainable, accessible, and predictable framework for drug coverage.

A centralized platform should be established to systematically collect patient experiences, clinical data, and input from multiple stakeholders, including government agencies, healthcare providers, insurers, pharmaceutical companies, and patient organizations. Such a platform would facilitate evidence-based decision-making, support long-term planning, enhance stakeholder awareness, guide development of unified national guidelines, and foster multi-stakeholder consensus in the governance of Dravet syndrome.

5.3. Building an equitable and sustainable multi-tiered medical insurance system for Dravet syndrome

To address the three main shortcomings of basic medical insurance, which is limited catalog coverage, regional disparities, and high out-of-pocket burdens, it is essential to strengthen national-level coordination and reinforce its central role in systematically optimizing the rare disease security system. The supplemental function of critical illness insurance should be enhanced by optimizing deductibles and reimbursement structures and strengthening linkages with basic insurance to reduce patients' financial burden. Medical assistance, as a safety net, requires broader eligibility criteria and expanded coverage to secure its foundational role (*17*).

A better balance between market orientation and social function of commercial health insurance should be pursued through stronger government guidance and oversight, encouraging inclusion of high-cost drugs and reasonable off-catalog expenses. At the same time, improving data interoperability and mutual recognition between basic and commercial insurance would support actuarial soundness and "one-stop" settlement, thereby enhancing product inclusivity and service efficiency (*18*).

Finally, to foster sustainable development of charitable aid and social mutual assistance, functional boundaries should be clarified and collaborative mechanisms established for targeted and shared responsibility. Expanding stable funding channels, optimizing the policy environment, and channeling social resources toward high-leverage, systematic supports can help shift away from fragmented aid toward integrated assistance (*19*), strengthening the role of charitable medical aid within the multi-tiered security system.

6. Conclusion

This study reveals a critical gap within China's multi-tiered medical security system for rare diseases, as experienced by patients with Dravet syndrome. Despite high enrollment in basic medical insurance, the financial burden remains severe due to limited reimbursement depth, regional disparities, and high out-of-pocket costs. Critical illness insurance, medical assistance, and commercial health insurance each exhibit structural limitations, such as high deductibles, restrictive eligibility, and inadequate coverage, that collectively fail to provide sufficient, coordinated protection.

These findings underscore the need to shift from expanding coverage models to deepening protection and enhancing policy coherence. Strengthening national coordination, optimizing reimbursement mechanisms, and better integrating all security tiers are essential to alleviate the financial burden on rare disease families and ensure sustainable, equitable healthcare access.

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Comparative analysis of adverse event reporting signals between Satralizumab and Inebilizumab in neuromyelitis optica spectrum disorder: A pharmacovigilance study using the FDA Adverse Event Reporting System

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SUMMARY: Neuromyelitis optica spectrum disorder (NMOSD) is a relapsing autoimmune disorder predominantly driven by anti-aquaporin-4 immunoglobulin G (AQP4-IgG), which mediates astrocyte injury, neuroinflammation, and demyelination. Satralizumab and Inebilizumab represent two promising therapeutic options with distinct mechanisms of action and clinical profiles. This study conducted a retrospective pharmacovigilance analysis of data from the U.S. FDA Adverse Event Reporting System (FAERS) from January 2020 to June 2025 to assess and compare adverse event (AE) reporting signals associated with Satralizumab and Inebilizumab. The analysis revealed a higher number of reported adverse events for Satralizumab compared to Inebilizumab (1,114 cases *vs.* 349 cases). A higher reporting proportion of AEs was observed in female patients for both drugs, with no statistically significant difference between them (exploratory $p = 0.760$). The reported AEs for both agents were primarily categorized under System Organ Classes (SOCs) such as infections and infestations and nervous system disorders. Urinary tract infection and pneumonia were among the most frequently reported preferred terms (PTs) for Satralizumab, whereas headache and COVID-19 were prominent for Inebilizumab. Reports classified as serious were more frequent for Satralizumab than for Inebilizumab (exploratory $p < 0.01$), noting that "seriousness" in FAERS may encompass outcomes related to underlying disease activity. This signal detection study highlights distinct adverse event reporting profiles for these biologics and offers insights that may inform clinical monitoring and personalized treatment strategies in NMOSD. Further studies with rigorous prospective designs are recommended to validate these findings and elucidate the mechanisms underlying the observed adverse events.

Keywords: NMOSD, Satralizumab, Inebilizumab, adverse events, FAERS

1. Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is a rare autoimmune disease characterized by optic neuritis and transverse myelitis, typically causing devastating outcomes such as blindness and paralysis (*1*). Infiltration of anti-aquaporin 4 (AQP4) antibodies into the central nervous system (CNS) contributes critically to the pathogenesis of NMOSD by inducing astrocyte injury (*2*). Epidemiological studies indicate an estimated prevalence in Europe of approximately 1 per 100,000 individuals. In contrast, East Asian populations exhibit a higher prevalence, reported at around 3.5 per 100,000, suggesting that genetic or ancestral background may influence susceptibility to NMOSD (*3*). The primary goal of NMOSD treatment is to mitigate the risk of irreversible neurological damage through relapse prevention and attenuation of acute attack severity (*4*). Among the emerging therapeutic agents, Satralizumab and Inebilizumab have become notable additions to the pharmacological management of NMOSD (*5*). Satralizumab exerts its therapeutic effect by reducing inflammation and inhibiting interleukin-6 (IL-6) mediated activation of autoimmune T and B cells, thereby preventing the differentiation of B cells into AQP4-IgG-secreting plasmablasts. In June 2020, Satralizumab received its first global approval in Canada for the treatment of NMOSD as a monotherapy or as combination therapy with immunosuppressant in adults and children aged ≥ 12 years who are AQP4-IgG seropositive. Subsequent approvals were granted in Japan, Switzerland, and the

United States (*6*). Inebilizumab is a humanized, affinity-optimized, afucosylated IgG1 kappa monoclonal antibody that targets the B-cell surface antigen CD19. It is indicated for the treatment of a range of autoimmune diseases associated with CD19-expressing B cells (*7*). Inebilizumab received its first global approval on 11 June 2020 in the USA for the treatment of adult patients with NMOSD who are seropositive for IgG autoantibodies against AQP4 (*8*).

Satralizumab and Inebilizumab were respectively approved in China for the treatment of adult patients with AQP4-IgG positive NMOSD in May 2021 and March 2022. The accumulation of real-world evidence for Satralizumab and Inebilizumab has led to their designation as first-line therapies in the Chinese Guidelines for the Diagnosis and Treatment of NMOSD. Separately, the Chinese Evidence-Based Guidelines for the Diagnosis and Treatment of Demyelinating Optic Neuritis, incorporating cost-effectiveness analyses, propose Satralizumab or Inebilizumab (Level of evidence 2B) as options for patients whose disease is refractory to prior immunosuppressant therapy (*e.g.*, azathioprine, mycophenolate mofetil, or rituximab) (*9-11*).

However, the introduction of these novel therapeutic agents underscores the need for a comprehensive understanding of their safety profiles. Although Satralizumab and Inebilizumab have demonstrated significant clinical efficacy, the spectrum of associated AEs raises pertinent clinical concerns that necessitate careful evaluation (*12,13*). For Satralizumab, reports have surfaced indicating potential risks such as nasopharyngitis, upper respiratory tract infection, and headache (*14*). AEs associated with Inebilizumab treatment have been reported to include urinary tract infections, arthralgia, and infusion-related reactions. Notably, a case of severe respiratory failure was documented in a patient with NMOSD following inebilizumab administration, which was subsequently diagnosed as Pneumocystis jirovecii pneumonia (*15*). The occurrence of such adverse reactions may compromise patient compliance and present clinical challenges in balancing therapeutic efficacy with safety considerations.

Addressing this critical gap, the present study utilizes the extensive repository of the FDA Adverse Event Reporting System (FAERS) database to conduct a comprehensive analysis of adverse events associated with Satralizumab and Inebilizumab. The FAERS is a publicly accessible database maintained by the FDA. All data within FAERS are freely available and can be downloaded directly from the official FDA website without any registration or application process. To protect patient privacy, all case data undergo de-identification, removing personal identifiers such as names and contact information. As such, the dataset primarily comprises demographic information (*e.g.*, age, gender), drug exposure details, and adverse event reports, with no content that could directly reveal a patient's identity. Consequently, the use of this database typically does not require additional ethical approval. With its broad coverage and real-time reporting of adverse drug events (ADEs), FAERS plays a crucial role in identifying and evaluating potential safety signals (*16*). This study aims to systematically assess ADE signals related to Satralizumab and Inebilizumab following their market approval, using data extracted from the FAERS database. The findings are expected to enhance the clinical management of NMOSD by supporting informed treatment decisions based on a balanced evaluation of therapeutic benefits and associated risks.

2. Materials and Methods

2.1. Study design and data acquisition

This retrospective pharmacovigilance analysis covered the period from Q1 2020 to Q4 2024, a timeframe selected to accommodate the market availability of the two drugs. The corresponding ASCII data packages were downloaded from the FAERS database and imported into SAS 9.4 software. The FAERS data were obtained on a quarterly basis and comprised seven files: demographic and administrative information (DEMO), drug information (DRUG), adverse events (REAC), patient outcomes (OUTC), report sources (RPSR), start and end dates for reported drugs (THER), indications for use (INDI). The FAERS data were retrieved from the FAERS quarterly data extract files, which can be accessed at *https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html*. The analysis focused on identifying and comparing AE signals associated with Satralizumab and Inebilizumab, taking into account their distinct pharmacodynamic profiles.

2.2. Data mining

The target drugs were defined as "satralizumab", "enspryng", "inebilizumab", "upliznatm". We used CASEID to remove duplicate reports and verified the FDA_DT date to ensure the uniqueness of each patient's record. In the database, each report is assigned a single Primary Suspect (PS) drug. To identify the target drug user population, only cases in which a target drug was designated as the PS were considered. Thus, if a patient's PS drug in the analyzed dataset matched one of the target drugs, the patient was included in the target drug cohort; all other patients were assigned to the non-target drug cohort. Each report underwent thorough review to confirm relevance; essential information collected included demographic characteristics (such as age and gender), descriptions of AEs, event outcomes, and the type of reporter (healthcare professional or consumer). Data extraction and management were performed using R 4.3.2 and OpenVigil, which facilitated efficient

processing of large datasets and improved accuracy in the identification of duplicate records.

2.3. Adverse event codification

AEs were coded in accordance with the terminology established by the Medical Dictionary for Regulatory Activities (MedDRA), version 25.0. The hierarchical framework of MedDRA supports the systematic categorization of AE information, thereby promoting consistency in reporting across diverse pharmacovigilance studies. AEs were classified based on the principal System Organ Classes (SOCs) and Preferred Terms (PTs) as specified in MedDRA, enabling a granular analysis of the AE profiles for both therapeutic agents.

2.4. Statistical methodology

In this study, four disproportionality analysis methods were employed for signal detection: Reporting Odds Ratio (ROR), Proportional Reporting Ratio (PRR), Bayesian Confidence Propagation Neural Network (BCPNN), and Multi-item Gamma Poisson Shrinker (MGPS). The integration of these methods aims to leverage their respective advantages to broaden the scope of signal detection, enable multi-perspective validation, and enhance the comprehensiveness and reliability of identified safety signals (*17*). By combining multiple algorithms, cross-validation can be performed to mitigate false positives, while the adjustment of thresholds and variance parameters facilitates the identification of potential rare adverse reactions. The ROR was applied to evaluate the disproportionality in reporting between a target drug-event pair and all other events. A higher ROR value suggests a potential safety signal (*18*). The PRR measures the proportion of reports for a specific drug-event combination relative to all other drugs reported with the same event. A PRR significantly greater than 1 is indicative of a signal (*19*). The BCPNN method computes the Information Component (IC) within a Bayesian framework, where a positive IC value reflects a statistically relevant association (*20*). MGPS, as an empirical Bayesian data mining approach, calculates the Empirical Bayes Geometric Mean (EBGM) to quantify association strength, with higher EBGM values pointing to stronger signals (*21*). A signal was considered significant when it met all the following criteria: *i*) ROR $\geq$ 3 with the lower limit of the 95% confidence interval (95% CI) > 1; *ii*) PRR $\geq$ 2 with the lower limit of the 95% CI > 1; *iii*) IC025 > 0; and *iv*) EBGM05 > 2. Detailed algorithms and formulas are provided in the Appendix (Supplementary Tables S1-S2, *https://www.irdrjournal.com/action/getSupplementalData.php?ID=284*). Furthermore, we used χ^2 tests to compare demographic characteristics between the two drug groups. A p-value < 0.05 was considered statistically significant for these comparisons. Given that FAERS data are derived from a spontaneous reporting system without a defined population denominator, these statistical tests are considered descriptive. While p values are reported, they are intended for exploratory comparison and should not be interpreted as indicating population-level significance.

3. Results

3.1. Descriptive analysis

The extensive dataset compiled by FAERS is depicted in Figure 1, showcasing a total of 23,168,942 AE reports collected from the first quarter of 2020 to the second quarter of 2025. After cleaning the data, FAERS collected a total of 19,252,329 AE reports, of which 1,114 were related to Satralizumab and 349 were related to Inebilizumab. Both Satralizumab and Inebilizumab were launched in 2020; however, the number of adverse reaction reports associated with Inebilizumab was substantially lower than that of Satralizumab.

Table 1 presents a detailed demographic analysis of AE reports associated with Satralizumab and Inebilizumab in the treatment of NMOSD. The data indicate a slight predominance of AE reports among females. Specifically, males accounted for 12.39% and 7.45% of AE reports for Satralizumab and Inebilizumab, respectively, reflecting a subtle gender disparity in AE reporting patterns; however, no statistically significant difference was observed in gender distribution between the two treatment groups (exploratory $p = 0.760$). With the exception of gender, significant differences were observed between the two drugs in terms of age, report year, reporter, reporter country, indications, serious reports, and adverse event occurrence time ($p < 0.01$). The details are presented in Table 1.

The AEs associated with Satralizumab and Inebilizumab both peaked in 2024, with 360 and 120 cases reported, respectively. Physicians constituted the primary source of reports. The majority of these reports originated from the United States, followed by Japan and other countries, including China.

The specific indications for Satralizumab and Inebilizumab, primarily in NMOSD and myasthenia gravis, are supported by the data presented in Table 1, which show that these conditions collectively account for more than 60% of all AE reports. The substantial proportion of reports with unspecified indications points to potential gaps in documentation or possible off-label use, introducing additional complexity into drug safety monitoring.

Furthermore, the proportion of reports classified as serious was higher for Satralizumab than for Inebilizumab. It is important to note that the "serious" designation in FAERS is based on outcomes such as hospitalization and may reflect disease relapse. We evaluated reported outcomes to assess the prognosis

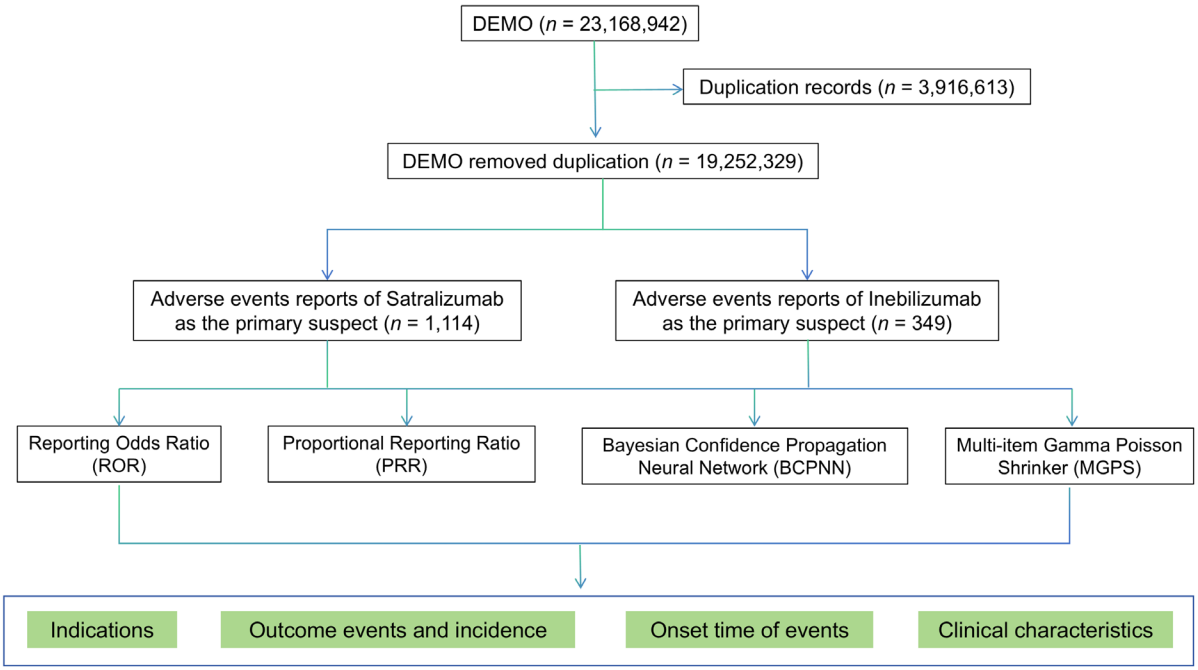

Figure 1. Flowchart of the research. The study comprises data collection and cleaning, disproportionality analysis methods to calculate signal strength, and presentation of results.

of patients experiencing AEs following treatment with either agent. Among all documented AEs, congenital anomalies were the least frequently reported (0.18% for Inebilizumab and 0.29% for Satralizumab), whereas initial or prolonged hospitalization represented the most common outcome (37.25% and 27.79%, respectively). Time-to-onset (TTO) analysis indicated that both Satralizumab and Inebilizumab exhibited a higher proportion of adverse reactions occurring within 30 days after treatment initiation

3.2. Disproportionality analysis

A comprehensive disproportionality analysis of AE reports associated with Satralizumab and Inebilizumab was conducted using data extracted from the FDA's FAERS database, providing significant insights into the safety profiles of these therapeutic agents. Based on a robust statistical framework, Satralizumab reported 874 PTs, while Inebilizumab reported 373 PTs, with 221 PTs shared between them. This analysis identified 64 and 28 strong disproportionality signals for Satralizumab and Inebilizumab, respectively, using four distinct algorithms (ROR, PRR, BCPNN, and MGPS).As shown in Supplementary Table S3 (*https://www.irdrjournal.com/action/getSupplementalData.php?ID=284*), these signals, indicative of a statistically significant disproportionality between the observed and expected number of AE reports, highlight potential areas of concern and necessitate a deeper examination of the drugs' safety profiles.

The top 20 PTs associated with Satralizumab and Inebilizumab are presented in Table 2. Apart from NMOSD, AEs related to Satralizumab were predominantly infection-related, including urinary tract infection (*n* = 79, ROR = 10.16, 95% CI: 8.12–12.70), pneumonia (*n* = 58, ROR = 3.66, 95% CI: 2.8–4.75), COVID-19 (*n* = 46, ROR = 5.49, 95% CI: 4.1–7.34), and sepsis (*n* = 25, ROR = 4.78, 95% CI: 3.22–7.09). In contrast, AEs associated with Inebilizumab were more frequently related to pain, such as headache (*n* =28, ROR = 3.11, 95% CI: 2.14–4.53), pain (*n* = 21, ROR = 2.34, 95% CI: 1.52–3.61), arthralgia (*n* = 17, ROR = 2.87, 95% CI: 1.78–4.64), and back pain (*n* = 9, ROR = 2.63, 95% CI: 1.37–5.08).

A statistical analysis of adverse events was performed across two drugs based on SOC standards. The results indicate that Infections and infestations had the highest reporting proportion among overall adverse events (*n* = 681, 18.81%) (Table 3). This was followed by nervous system disorders (*n* = 582, 15.22%), general disorders and administration site conditions (*n* = 485, 12.69%), injury, poisoning and procedural complications (*n* = 343, 8.97%), and musculoskeletal and connective tissue disorders (*n* = 265, 6.93%).

3.3. Comparison of safety signals in serious group

In the analysis, 60 serious AEs associated with Satralizumab and 11 with Inebilizumab met the criteria across four statistical methods, the top 20 serious AEs are shown in Figure 2. Unique serious AEs specific to Satralizumab included pyelonephritis, compression fracture and lymphocyte count decreased. In contrast,

Table 1. Data of reports associated with Satralizumab and Inebilizumab From Q1 of 2004 to Q2 of 2025

Characteristic	Satralizumab (*n* = 1,114) Reports, *n* (%)	Inebilizumab (*n* = 349) Reports, *n* (%)	χ^2/Z	*p*
Gender			0.093	0.760
Female	886 (79.53)	179 (51.29)		
Male	138 (12.39)	26 (7.45)		
Not Specified	90 (8.08)	144 (41.26)		
Age			16.097	0.01
< 18	17 (1.53)	1 (0.29)		
18–44	171 (15.35)	52 (14.90)		
45–64	344 (30.88)	81 (23.21)		
≥ 65	269 (24.15)	34 (9.74)		
Not Specified	313 (28.10)	181 (51.86)		
Report year			124.641	0.00
2020	4 (0.36)	19 (5.44)		
2021	77 (6.91)	71 (20.34)		
2022	163 (14.63)	21 (6.02)		
2023	278 (24.96)	45 (12.89)		
2024	360 (32.32)	120 (34.38)		
2025	232 (20.83)	73 (20.92)		
Reporter			68.481	0.00
Consumer	383 (34.38)	111 (31.81)		
Pharmacist	99 (8.89)	90 (25.79)		
Physician	625 (56.10)	148 (42.41)		
Not Specified	7 (0.63)	0 (0)		
Reporter country			158.052	0.00
United States	431 (38.69)	269 (77.08)		
Japan	468 (42.01)	51 (14.61)		
China	58 (5.21)	5 (1.43)		
Other	157 (14.09)	24 (6.88)		
Indications (TOP 3)			113.029	0.00
Neuromyelitis optica spectrum disorder	988 (88.69)	235 (67.34)		
Product used for unknown indication	78 (7.00)	98 (28.08)		
Myasthenia gravis	9 (0.81)	2 (0.57)		
Other	39 (3.50)	14 (4.01)		
Serious Report			462.577	0.00
Serious	820 (73.61)	180 (51.58)		
Non-Serious	294 (26.39)	169 (48.42)		
Outcome			5.502	0.358
Life-Threatening	26 (2.33)	7 (2.01)		
Hospitalization - Initial or Prolonged	415 (37.25)	97 (27.79)		
Disability	23 (2.06)	4 (1.15)		
Death	55 (4.94)	23 (6.59)		
Congenital Anomaly	2 (0.18)	1 (0.29)		
Other	424 (38.06)	111 (31.81)		
Adverse event occurrence time - medication date (days)			20.960	0.04
0–30 d	140 (12.57)	64 (18.34)		
31–60 d	38 (3.41)	8 (2.29)		
61–90 d	34 (3.05)	5 (1.43)		
91–120 d	29 (2.60)	5 (1.43)		
121–150 d	28 (2.51)	2 (0.57)		
151–180 d	16 (1.44)	2 (0.57)		
181–360 d	57 (5.12)	19 (5.44)		
> 360 d	87 (7.81)	18 (5.16)		
Missing	685 (61.49)	226 (64.76)		

Inebilizumab was associated with distinct serious AEs such as blood immunoglobulin G decreased, COVID-19 pneumonia and acute respiratory distress syndrome.

Comparative analysis of serious AE reports revealed that reports of NMOSD, urinary tract infection, and optic neuritis were more frequently associated with Satralizumab. It should be noted that terms such as "NMOSD" and "optic neuritis" may reflect underlying disease activity rather than drug-induced toxicity. Conversely, reports of pneumonia, COVID-19, herpes zoster, blindness, and COVID-19 pneumonia showed a stronger association with Inebilizumab. Refer to Table 4 for further details.

4. Discussion

Comparative efficacy analyses provide valuable evidence to support informed decision-making. For healthcare

Table 2. The top 20 ADE signals of Satralizumab and Inebilizumab

Satralizumab						Inebilizumab					
PT	Case Reports	ROR (95% CI)	PRR (Chi_Square)	IC (IC025)	EBGM (EBGM05)	PT	Case Reports	ROR (95% CI)	PRR (Chi_Square)	IC (IC025)	EBGM (EBGM05)
Neuromyelitis optica spectrum disorder	178	3132.92 (2,664.56–3,683.60)	2941.61 (455,078)	11.32 (7.15)	2558.43 (2,175.95)	Neuromyelitis optica spectrum disorder	42	2,093.24 (1,528.66–2,866.34)	1,996.57 (81,198.0)	10.92 (4.94)	1,935.21 (1,413.25)
Urinary tract infection	79	10.16 (8.12–12.70)	9.91 (634.23)	3.31 (2.83)	9.90 (7.92)	Headache	28	3.11 (2.14–4.53)	3.05 (38.86)	1.61 (0.96)	3.05 (2.09)
Pneumonia	58	3.66 (2.82–4.75)	3.61 (110.02)	1.85 (1.41)	3.61 (2.78)	COVID-19	26	10.07 (6.82–14.88)	9.81 (206.37)	3.29 (2.32)	9.81 (6.64)
COVID-19	46	5.49 (4.10–7.34)	5.42 (166.10)	2.44 (1.88)	5.42 (4.05)	Pneumonia	22	4.47 (2.93–6.83)	4.39 (57.89)	2.13 (1.32)	4.39 (2.87)
No adverse event	41	4.96 (3.64–6.75)	4.90 (127.76)	2.29 (1.72)	4.90 (3.60)	Pain	21	2.34 (1.52–3.61)	2.31 (15.73)	1.21 (0.50)	2.31 (1.50)
Hypoaesthesia	27	3.80 (2.60–5.55)	3.77 (55.19)	1.92 (1.23)	3.77 (2.58)	Arthralgia	17	2.87 (1.78–4.64)	2.83 (20.32)	1.50 (0.67)	2.83 (1.75)
Sepsis	25	4.78 (3.22–7.09)	4.75 (74.07)	2.25 (1.48)	4.75 (3.20)	Product storage error	14	9.97 (5.88–16.90)	9.83 (111.21)	3.30 (1.88)	9.83 (5.80)
Infection	21	3.18 (2.07–4.89)	3.1 7(31.17)	1.66 (0.91)	3.16 (2.06)	Hypoaesthesia*	13	5.90 (3.41–10.19)	5.83 (52.08)	2.54 (1.34)	5.82 (3.37)
Cellulitis	20	8.36 (5.39–12.99)	8.31 (128.72)	3.05 (1.99)	8.31 (5.35)	Urinary tract infection	12	4.87 (2.76–8.62)	4.82 (36.47)	2.27 (1.09)	4.82 (2.73)
Muscular weakness	19	3.56 (2.27–5.59)	3.54 (34.70)	1.82 (1.00)	3.54 (2.25)	Pyrexia	11	2.17 (1.20–3.94)	2.16 (6.88)	1.11 (0.14)	2.16 (1.19)
Septic shock	19	9.56 (6.09–15.01)	9.50 (144.62)	3.25 (2.09)	9.50 (6.05)	Back pain	9	2.63 (1.37–5.08)	2.62 (9.03)	1.39 (0.25)	2.62 (1.36)
Hepatic function abnormal*	18	10.58 (6.66–16.82)	10.52 (155.11)	3.39 (2.14)	10.52 (6.62)	Muscle spasms	8	2.95 (1.47–5.91)	2.93 (10.19)	1.55 (0.30)	2.93 (1.46)
Herpes zoster	17	6.29 (3.90–10.13)	6.25 (75.09)	2.64 (1.59)	6.25 (3.88)	Vision blurred*	8	4.05 (2.02–8.12)	4.02 (18.19)	2.01 (0.62)	4.02 (2.00)
Lymphocyte count decreased	16	19.14 (11.71–31.29)	19.04 (273.28)	4.25 (2.50)	19.02 (11.63)	Infusion related reaction	8	8.83 (4.40–17.71)	8.76 (55.04)	3.13 (1.27)	8.76 (4.37)
Syringe issue	15	18.05 (10.87–29.99)	17.96 (240.13)	4.17 (2.40)	17.95 (10.80)	COVID-19 pneumonia	8	45.93 (22.89–92.15)	45.53 (348.26)	5.51 (1.97)	45.50 (22.68)
Compression fracture*	14	22.20 (13.13–37.55)	22.10 (281.80)	4.46 (2.45)	22.08 (13.06)	Burning sensation*	7	6.82 (3.24–14.34)	6.77 (34.46)	2.76 (0.95)	6.77 (3.22)
Optic neuritis	14	32.09 (18.97–54.27)	31.94 (418.95)	4.99 (2.63)	31.89 (18.85)	Paraesthesia*	7	3.00 (1.43–6.32)	2.99 (9.27)	1.58 (0.23)	2.99 (1.42)
Pyelonephritis	14	34.89 (20.63–59.01)	34.73 (457.83)	5.12 (2.67)	34.67 (20.50)	Visual impairment*	7	3.78 (1.80–7.95)	3.76 (14.20)	1.91 (0.46)	3.76 (1.79)

*Note: *indicated the PT was not included in the specification.*

Table 2. The top 20 ADE signals of Satralizumab and Inebilizumab (continued)

	Satralizumab					Inebilizumab					
PT	Case Reports	ROR (95% CI)	PRR (Chi_Square)	IC (IC025)	EBGM (EBGM05)	PT	Case Reports	ROR (95% CI)	PRR (Chi_Square)	IC (IC025)	EBGM (EBGM05)
Blindness*	13	6.89 (4.00–11.89)	6.87 (65.18)	2.78 (1.50)	6.86 (3.98)	Circumstance or information capable of leading to medication error	7	14.56 (6.92–30.64)	14.46(87.73)	3.85 (1.41)	14.46 (6.87)
Cystitis	13	8.53 (4.95–14.72)	8.50 (86.03)	3.09 (1.69)	8.50 (4.93)	Intercepted product administration error	7	56.08 (26.65–118.01)	55.66 (375.44)	5.80 (1.80)	55.61 (26.43)

*Note: *indicated the PT was not included in the specification.*

providers, this evidence aids in developing patient care plans, while payers and fundholders utilize it to inform coverage and reimbursement policies. The most credible source of comparative evidence comes from head-to-head randomized controlled trials (RCTs). However, conducting such trials with adequate statistical power to compare all relevant treatments is often not feasible, particularly for rare diseases like AQP4-IgG-seropositive NMOSD, which is characterized by low prevalence and incidence. In this study, we performed a comprehensive analysis and comparison of ADE reports associated with two widely used biological agents, Satralizumab and Inebilizumab, using the FDA FAERS database. Our findings confirm previous reports (*22*) of a higher reporting proportion of ADEs for both Satralizumab and Inebilizumab in females (79.53% *vs.* 12.39% and 51.29% *vs.* 7.45%, respectively). This disparity may be attributed to the higher prevalence of NMOSD in females, as well as their potentially greater awareness or reporting of adverse reactions (*23*). Additionally, since the FAERS database is largely dominated by reports from the United States, the majority of ADEs originated from this country — particularly for Inebilizumab (Satralizumab: 38.69%; Inebilizumab: 77.08%) — suggesting a possible geographical bias. With the increasing incidence of NMOSD, ADE reports linked to Satralizumab and Inebilizumab have risen annually.

Based on our analyses, Satralizumab and Inebilizumab generated signals in urinary tract infection, pneumonia and COVID-19 similarly in the results of Top 20 PTs. Meanwhile, signals for terms such as NMOSD and hypoaesthesia were also detected. It is important to interpret these signals cautiously, as they may reflect the underlying relapsing nature of NMOSD rather than direct drug toxicity. The primary clinical manifestations of the disease, such as paresthesia and limb numbness, often reflect this refractory disease course (*24*). Furthermore, these AEs mentioned in labels may be linked to the drug's pharmacological mechanism. Satralizumab, a monoclonal antibody targeting the interleukin-6 receptor, works by inhibiting IL-6 signaling — a pathway central to the pathology of NMOSD. As IL-6 is a key pro-inflammatory cytokine, its inhibition can suppress classical signs of inflammation such as fever and an elevated C-reactive protein level. This effect poses a risk of concealing or delaying the diagnosis of infections, which are critical complications requiring vigilant monitoring following the initiation of biologic therapy. Particular attention should be paid to the potential exacerbation of urinary tract and respiratory infections (*25*). Consistent with its mechanism of action, Inebilizumab depletes B lymphocytes, leading to a reduction in lymphocyte counts. As is observed with other B-cell depleting therapies, this effect is associated with an increased risk of infection. Among the associated adverse events with an incidence greater than 10%, urinary tract infection was the most notable, occurring

Table 3. System organ classes (SOCs) for adverse events of Satralizumab and Inebilizumab

SOC	*n* (%)	Satralizumab *n* (%)	Inebilizumab *n* (%)
Infections and infestations	681 (17.81%)	558 (19.15%)	123 (13.53%)
Nervous system disorders	582 (15.22%)	432 (14.82%)	150 (16.50%)
General disorders and administration site conditions	485 (12.69%)	330 (11.32%)	155 (17.05%)
Injury, poisoning and procedural complications	343 (8.97%)	244 (8.37%)	99 (10.89%)
Musculoskeletal and connective tissue disorders	265 (6.93%)	191 (6.55%)	74 (8.14%)
Investigations	222 (5.81%)	189 (6.49%)	33 (3.63%)
Gastrointestinal disorders	194 (5.07%)	141 (4.84%)	53 (5.83%)
Eye disorders	135 (3.53%)	98 (3.36%)	37 (4.07%)
Respiratory, thoracic and mediastinal disorders	135 (3.53%)	97 (3.33%)	38 (4.18%)
Psychiatric disorders	100 (2.62%)	87 (2.99%)	13 (1.43%)
Skin and subcutaneous tissue disorders	108 (2.83%)	81 (2.78%)	27 (2.97%)
Hepatobiliary disorders	74 (1.94%)	69 (2.37%)	5 (0.55%)
Blood and lymphatic system disorders	78 (2.04%)	63 (2.16%)	15 (1.65%)
Product issues	56 (1.46%)	55 (1.89%)	1 (0.11%)
Metabolism and nutrition disorders	61 (1.60%)	52 (1.78%)	9 (0.99%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	57 (1.49%)	51 (1.75%)	6 (0.66%)
Renal and urinary disorders	56 (1.46%)	43 (1.48%)	13 (1.43%)
Vascular disorders	61 (1.60%)	42 (1.44%)	19 (2.09%)
Cardiac disorders	32 (0.84%)	28 (0.96%)	4 (0.44%)
Immune system disorders	29 (0.76%)	21 (0.72%)	8 (0.88%)
Social circumstances	12 (0.31%)	10 (0.34%)	2 (0.22%)
Surgical and medical procedures	14 (0.37%)	8 (0.27%)	6 (0.66%)
Reproductive system and breast disorders	13 (0.34%)	8 (0.27%)	5 (0.55%)
Endocrine disorders	11 (0.29%)	7 (0.24%)	4 (0.44%)
Ear and labyrinth disorders	8 (0.21%)	4 (0.14%)	4 (0.44%)
Pregnancy, puerperium and perinatal conditions	8 (0.21%)	4 (0.14%)	4 (0.44%)
Congenital, familial and genetic disorders	3 (0.08%)	1 (0.03%)	2 (0.22%)

in 20% of patients (*26,27*). These findings are consistent with our results.

Our analysis further revealed a distinct profile of treatment-emergent AEs between the two biologics. AEs associated with Satralizumab were predominantly infectious in nature, whereas those linked to Inebilizumab were more strongly correlated with pain-related disorders. This observation is consistent with published literature indicating that pain — including headache, back pain, extremity pain, and chest pain — is a recognized side effect of certain immunosuppressive agents such as Inebilizumab (*28*). In contrast, findings from Ikeguchi *et al*. suggest a potential therapeutic benefit of Satralizumab in pain management (*29*). This analgesic effect may be mechanistically explained by the blockade of IL-6, a pronociceptive cytokine critically involved in the pathogenesis of neuropathic pain. By inhibiting IL-6 signaling, Satralizumab not only reduces immunological activity but may also directly attenuate neuropathic pain (*30*). Consequently, for patients with a pre-existing risk or clinical presentation of neuropathic pain, Satralizumab may represent a more favorable therapeutic option compared to Inebilizumab.

There are slight differences in the SOC distribution between Satralizumab and Inebilizumab. Infections and infestations, nervous system disorders, general disorders and administration site conditions, injury, poisoning and procedural complications, and musculoskeletal and connective tissue disorders remain key concerns. This is similar to the results reported in previous literature (*31*).

The most frequently reported serious events associated with both Satralizumab and Inebilizumab were terms corresponding to the disease itself, such as "NMOSD" and "optic neuritis". This observation can be explained by the recurrent nature of NMOSD, in which disability accrual is primarily attributable to acute relapses (*32,33*). Literature reports indicate that Satralizumab was superior to Inebilizumab in reducing relapse rate (*34*). This finding contrasts with the trend observed in the present study, which indicated a higher reporting frequency of serious adverse event reports with Satralizumab compared to Inebilizumab. Furthermore, our signal detection analysis indicated that reports of COVID-19 and COVID-19 pneumonia showed a stronger association with Inebilizumab. It is unknown if Inebilizumab increases the susceptibility to SARS-CoV-2 or if it predisposes to a more severe infection. B-cell lymphopenia may impact T-cell activation which is involved in the early immune response against SARS-CoV-2 but more importantly may influence antibody-mediated long-term immunity against the virus potentially increasing reinfection risk. Furthermore, it is possible that Inebilizumab may impact the efficacy of viral protein vaccines including future SARS-CoV-2 vaccines when they become available (*35*). However, given the small case numbers and the nature of spontaneous reporting, this finding should be considered hypothesis-generating. Potential explanations include

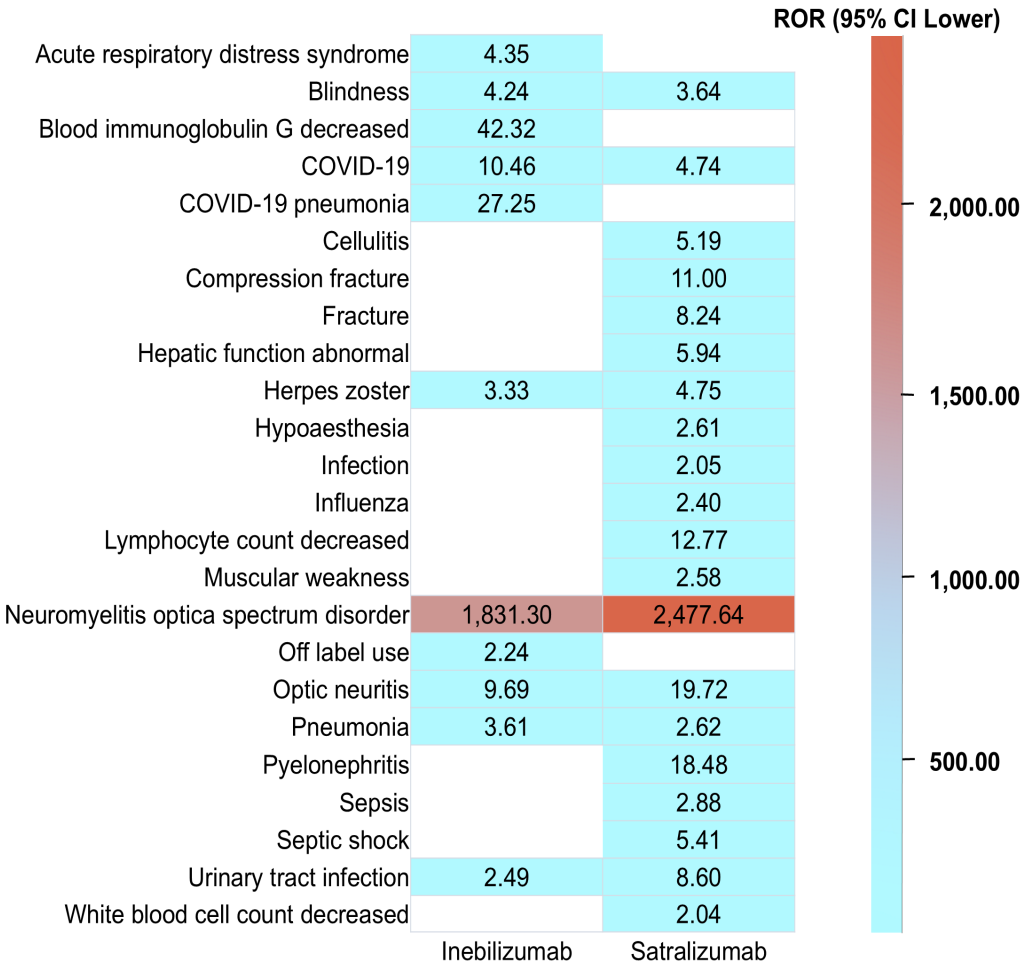

Figure 2. The top 20 serious AEs of Satralizumab and Inebilizumab.

Table 4. Comparison of ADE PTs in serious group between Satralizumab and Inebilizumab

ADE	Satralizumab		Inebilizumab		ROR (Satralizumab)/ ROR (Inebilizumab)
	Case Reports	ROR (95% CI)	Case Reports	ROR (95% CI)	
Neuromyelitis optica spectrum disorder	178	2918.23 (2477.64–3437.16)	41	2530.34 (1831.30–3496.20)	1.15
Urinary tract infection	72	10.88 (8.60–13.76)	8	5.01 (2.49–10.08)	2.17
Pneumonia	58	3.40 (2.62–4.41)	22	5.53 (3.61–8.48)	0.61
COVID-19	35	6.62 (4.74–9.25)	20	16.35 (10.46–25.55)	0.40
Herpes zoster	15	7.90 (4.75–13.12)	4	8.90 (3.33–23.79)	0.89
Optic neuritis	14	33.38 (19.72–56.48)	3	30.14 (9.69–93.77)	1.11
Blindness	13	6.27 (3.64–10.82)	5	10.22 (4.24–24.66)	0.61
COVID-19 pneumonia	4	6.40 (2.40–17.07)	8	54.79 (27.25–110.17)	0.12

reporting bias, temporal coincidence, and differential exposure during the pandemic, rather than a definitive causal relationship.

Given that both therapies were approved in 2020, differences in time since market introduction are unlikely to account for this discrepancy. Meanwhile, variations in trial designs, methodologies, treatment durations, and comparator groups limit the reliability of direct comparisons between these two agents (*36*). Therefore, further research is necessary to validate and extend these findings and to address remaining questions in this field.

Our analysis of the FAERS database provides valuable insights into the safety signals associated with Satralizumab and Inebilizumab. However, it is crucial to acknowledge the inherent limitations of spontaneous reporting systems. FAERS data are not derived from a defined population and are subject to significant reporting bias, under-reporting, and lack of

denominator data. Consequently, while we observed a trend toward lower SAE reports for Satralizumab, these findings are exploratory and should not be over-interpreted as conclusive evidence of a superior safety profile in the broader patient population. Second, due to the retrospective nature of the study, we can only identify associations between the drugs and adverse events rather than establish causal relationships. Third, FAERS data do not allow for the calculation of adverse event incidence rates or medication error frequencies in the monitored population; they are primarily useful for generating hypotheses rather than confirming them. Fourth, the effects of combination therapy, patient health status and disease progression cannot be excluded, although these are often inherent characteristics of patients.

5. Conclusion

Our comprehensive analysis underscores the critical role of pharmacovigilance in optimizing the management of NMOSD. As Satralizumab andInebilizumab remain pivotal therapeutic options for this condition, our findings provide valuable insights into their long-term safety profiles. This knowledge is essential for supporting evidence-based clinical decisions and ultimately improving patient outcomes. Future research, complemented by more robust pharmacovigilance methodologies, will be crucial to refine our understanding and advance the goal of safe and effective NMOSD therapy.

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Original Article

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Multidisciplinary approach to the assessment and management of children with Fabry disease: Insights from the Chinese Children Genetic Kidney Disease Database

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SUMMARY: Fabry disease (FD) is a rare multisystemic lysosomal storage disorder with diverse pediatric manifestations. This multicenter study analyzed 64 children with FD from the Chinese Children Genetic Kidney Disease Database following establishment of the first national pediatric FD multidisciplinary team (MDT) in April 2020, which expanded to 15 centers by January 2022. Median diagnostic age was 11.4 years in males and 9.4 years in females, with diagnostic delays of 4.4 and 4.0 years, respectively. Family screening accounted for most female diagnoses (72.2%), while 6.5% of males were incidentally detected during genetic testing for other diseases. Missense variants predominated (65.2% males, 66.7% females). Biochemically, males had markedly reduced α-Gal A activity (0.6 ± 0.4 μmol/L/h), and most patients showed elevated globotriaosylsphingosine (Lyso-GL-3), including 87.0% of males and 83.3% of females. Neuropathic pain was the most common initial symptom (52.2% males, 27.8% females; median onset 8 years), primarily acroparesthesia (92.1% and 85.7%, respectively). Other frequent features included anhidrosis/hypohidrosis (58.7% males, 11.1% females). Multisystem involvement included cardiac (arrhythmia n = 11, left ventricular hypertrophy n = 3), pulmonary (obstructive airway disease in 24.2% of males), skeletal (low bone mineral density in 4/7 tested males), and renal manifestations (reduced glomerular filtration rate (GFR) in 3). Thirty-seven patients received enzyme replacement therapy at median ages of 12.9 years (males) and 11.7 years (females). This first nationwide pediatric FD cohort highlights substantial diagnostic delays and underscores the importance of MDT collaboration, family screening, and early recognition to improve outcomes in affected children.

Keywords: Fabry disease, children, multidisciplinary team

1. Introduction

Fabry disease (FD) is a rare X-linked lysosomal storage disorder characterized by reduced or complete absence of the enzyme α-galactosidase A (α-Gal A) due to mutations in the GLA gene. In 2018, FD was included in the first official list of 121 rare diseases in China (No. 27). Clinical symptoms frequently emerge in childhood or adolescence (*1-5*). With the accumulation of the substrate globotriaosylceramides (GL-3) and its derivative deacetyl GL-3 (globotriaosylsphingosine, Lyso-GL-3), early symptoms can develop into life-threatening complications, leading to serious clinical events including renal, cardiac, cerebrovascular complications or death. However, the initial symptoms of FD are atypical, the clinical manifestations are diverse, and there is a significant delay from the onset of symptoms to diagnosis, which can be as long as 14-16 years (*6*).

The approval of enzyme replacement therapy (ERT) in China in 2019 positioned FD as one of the few genetic metabolic diseases amenable to targeted therapy. With advances in enzymatic assays and genetic testing, early diagnosis provides a crucial opportunity for timely intervention before irreversible organ damage occurs. To address diagnostic challenges, the Children's Hospital of Fudan University established the first pediatric multidisciplinary diagnosis and treatment (MDT) team for FD in April 2020. A tertiary referral framework was introduced, incorporating risk-based symptom and family screening, dried blood spot (DBS) triple testing (α-Gal A activity, lyso-GL-3 levels, and GLA sequencing), and targeted newborn genetic testing for high-risk metabolic disorders (*7*).

The Fabry Aim Children Early (ACE) Project, jointly initiated by the Chinese Association for Improving Birth Outcome and Child Development and the Children's Hospital of Fudan University, expanded MDT implementation to 21 institutions between July 2021 and January 2022 (Supplementary Table S1 and Supplementary Figure S1, *https://www.irdrjournal.com/action/getSupplementalData.php?ID=281*). These teams were established in tertiary hospitals across China to improve early detection and provide effective interventions for children and families with FD.

A clearer understanding of pediatric FD phenotypes in China is essential for guiding both diagnosis and long-term management. This study summarizes the clinical characteristics and treatment status of children diagnosed through the MDT network.

2. Patients and Methods

2.1. Study design and data sources

This retrospective multicenter study enrolled pediatric patients (≤ 18 years) diagnosed with FD before March 2025 from the Chinese Children's Genetic Kidney Disease Database (CCGKDD, *www.ccgkdd.com.cn*) – a national multicenter registry systematically documenting genotypic and phenotypic data of children with inherited kidney diseases in China (*8*).

Inclusion criteria: *i*) Age ≤ 18 years at diagnosis; *ii*) Confirmed FD diagnosis meeting one of the following criteria (*9*):

Identification of a pathogenic or likely pathogenic (P/LP) GLA gene variant according to the American College of Medical Genetics and Genomics (ACMG) guidelines (*10*);

For males: Presence of a GLA gene variant of uncertain significance (VUS) combined with deficient α-Gal A activity (< 2.4 μmol/L/h);

For females: Presence of a GLA VUS with elevated plasma Lyso-GL-3 (≥ 1.11 ng/mL) and/or deficient α-Gal A activity.

Exclusion criteria: *i*) Absence of essential biochemical data—specifically, α-Gal A activity or Lyso-GL-3 levels—required for diagnostic confirmation; *ii*) Initiation of ERT before collection of baseline clinical data.

Clinical information was collected using a standardized questionnaire to ensure uniform data acquisition across centers. Collected data included demographics, presenting symptoms, organ involvement, genetic test results, and treatment status.

2.2. Data collection and management

A standardized, web-based electronic case report form (e-CRF) was specifically designed for this study to ensure uniform and comprehensive data collection across all participating centers. The e-CRF captured the following domains:

i) Demographics: Age, sex, family history.

ii) Diagnostic data: Age at first symptom onset, age at diagnosis, reason for diagnostic testing (symptoms *vs.* family screening), diagnostic delay.

iii) Genetic data: GLA gene variant (nucleotide and protein change), zygosity, ACMG classification, segregation analysis within the family.

iv) Biochemical data: α-Gal A enzyme activity (reference: > 2.4 μmol/L/h), plasma Lyso-GL-3 level (reference: < 1.11 ng/mL).

v) Clinical manifestations: A comprehensive review of systems was conducted to document involvement across neurological (pain characteristics: acroparesthesia, Fabry crises, burning sensation, tingling, numbness), dermatological (angiokeratoma), ophthalmological (cornea verticillata, cataracts), gastrointestinal (abdominal pain, diarrhea, constipation), renal (microalbuminuria, proteinuria, estimated glomerular filtration rate - eGFR), cardiac (arrhythmias, left ventricular hypertrophy, valvular abnormalities), respiratory (pulmonary function tests), auditory (hearing loss), and skeletal (bone mineral density) systems.

Severe clinical events were defined as: cardiac events

(atrial fibrillation, admission for any rhythm disturbance or congestive heart failure), stroke, and the need for dialysis and transplantation.

vi) Treatment data: Use of ERT (agalsidase alfa or beta), age at ERT initiation, duration of ERT, adjunctive therapies (analgesics, RAAS inhibitors, *etc*.), and reported adverse events.

All data extracted for analysis were collected prior to the initiation of ERT to accurately represent the natural history of the disease.

2.3. Statistical analysis

Descriptive statistics were used to summarize the patient characteristics. Categorical variables were presented as numbers and percentages (*n*, %). Continuous variables were expressed as mean ± standard deviation (SD) and median with range (min-max). Data visualization was conducted using GraphPad Prism (version 9.0, GraphPad Software, San Diego, CA, USA).

2.4. Ethical approval

The study was approved by the Institutional Review Board of Children's Hospital of Fudan University (No. 2021241) and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all legal guardians and from patients aged ≥ 8 years. All personal identifiers were anonymized to protect participant privacy.

3. Results

A total of 64 pediatric patients with FD from the Chinese Children Genetic Kidney Disease Database were included in this study (Supplementary Table S2, *https://www.irdrjournal.com/action/getSupplementalData.php?ID=281*), comprising 46 males (71.9%) and 18 females (28.1%).

3.1. Baseline demographic and diagnostic characteristics

The baseline demographic and diagnostic characteristics, stratified by sex, are presented in Table 1.

The median age at diagnosis was 11.4 years (range: 0.1–18.2) for males and 9.4 years (range: 1.7–16.7) for females. Family screening accounted for 72.2% of female and 34.8% of male diagnoses, highlighting a marked sex difference in diagnostic pathway. In three males (6.5%), GLA variants were identified incidentally during genetic testing for unrelated conditions.

The median age at symptom onset was slightly earlier in males (6.4 years) than in females (7.0 years), with corresponding diagnostic delays of 4.4 years and 4.0 years, respectively.

Neuropathic pain was the most frequent presenting symptom, observed in 52.2% of males and 27.8% of females, with a median onset age of 8 years.

3.2. Genetic and biochemical characteristics

Genetic and biochemical features are summarized in Table 1.

Missense variants were the predominant mutation type in both sexes (males: 65.2%; females: 66.7%). Male patients exhibited markedly reduced α-Gal A enzyme activity (0.6 ± 0.4 μmol/L/h), while females showed variable but generally normal enzyme levels (2.3 ± 0.9 μmol/L/h).

Despite this, elevated plasma Lyso-GL-3 levels were detected in the majority of both sexes (males: 87.0%; females: 83.3%), indicating significant substrate accumulation even among females with normal enzymatic activity.

3.3. Clinical manifestations and multisystem involvement

The spectrum and frequency of organ system involvement are detailed in Table 2, with further visualization provided in Figure 1 and Figure 2. Key systemic manifestations are summarized below:

i) Neurological involvement: During follow-up, 90.5% of symptomatic males and 38.9% of females experienced neuropathic pain. Acroparesthesia was predominant (males: 92.1%; females: 85.7%) and manifested as burning (52.6% *vs.* 14.3%), tingling (31.6% *vs.* 57.1%), or numbness (10.5% *vs.* 14.3%). Fabry crises were reported in 63.2% of males and 28.6% of females.

ii) Renal involvement: Although overt kidney disease was uncommon, early renal abnormalities were evident. Among 41 males with evaluable data, 14.6% had renal abnormalities, most commonly microalbuminuria (12.2%) and reduced estimated GFR (7.3%). One patient presented with renal tubular dysfunction, suggesting early tubular involvement.

iii) Cardiac manifestations: Cardiac abnormalities were observed in both sexes. Arrhythmias occurred in 27.5% of males and 44.4% of females. Left ventricular hypertrophy (LVH) was noted in 7.5% of males, while valvular dysfunction and conduction disturbances were reported across both groups.

iv) Additional organ system involvement: Notable involvement was also found in other organ systems. Ophthalmological examination revealed cornea verticillata in a substantial proportion of both males and females (48.7% and 53.8%, respectively). Respiratory function testing identified obstructive airway disease in 24.2% of the male patients. Furthermore, sensorineural hearing loss was detected in 10.8% of males. Involvement of other systems included: skeletal, with low bone mineral density found in 4 out of 7 (57.1%) tested males.

3.4. Treatment status

Table 1. Summary of demographic and disease characteristics by sex

Characteristic	Male (*n* = 46)	Female (*n* = 18)
Age at Fabry diagnosis (years)		
Mean ± SD	10.6 ± 4.6	9.8 ± 4.0
Median age (range)	11.4 (0.1–18.2)	9.4 (1.7–16.7)
Diagnostic Data		
Age at first onset of symptom (years)		
Patients with symptoms, *n* (Percentage)	42 (91.3%)	9 (55.0%)
Mean ± SD	5.5 ± 4.5	5.5 ± 4.8
Median age (range)	6.4 (0–16.0)	7.0 (0–13.0)
Diagnostic delay (years)		
Mean ± SD	5.6 ± 5.1	4.5 ± 5.5
Median age (range)	4.4 (0–17.5)	4 (-4.8–13.5)
Reason for testing, *n* (%)		
Symptoms	27 (58.7%)	5 (27.8%)
Family screening	16 (34.8%)	13 (72.2%)
Patients at risk of genetic metabolic disorders	3 (6.5%)	0
Family members diagnosed with Fabry, *n* (%)		
Yes	41 (89.1%)	11 (100%)
No	3 (6.5%)	0
Unknown/not reported	2 (4.3%)	0
Genetic Data		
GLA variants Type, *n* (%)		
Missense	30 (65.2%)	12 (66.7%)
Truncating	6 (13.0%)	3 (16.7%)
Deletion	6 (13.0%)	1 (5.6%)
Splicing	2 (4.3%)	1 (5.6%)
Intron	2 (4.3%)	1 (5.6%)
Biochemical Data		
GLA activity, Mean ± SD (μmol/L/h)	0.6 ± 0.4	2.3 ± 0.9
Elevated plasma lyso-GL-3, *n* (%)	40 (87.0%)	15 (83.3%)

Treatment details are summarized in Table 3.

A total of 37 patients (31 males, 6 females) received ERT, initiated at median ages of 12.9 years in males and 11.7 years in females. The median interval from symptom onset to ERT initiation was 7.3 years in males and 4.0 years in females.

Most patients received agalsidase beta (Fabrazyme®). ERT was generally well tolerated; only two males (6.5%) experienced grade 3 adverse events, with no grade ≥ 4 reactions reported.

Adjunctive medications included analgesics (41.3% of males) and renin–angiotensin–aldosterone system (RAAS) inhibitors (13.0%), reflecting proactive nephroprotective management within multidisciplinary care frameworks.

3.5. Severe clinical events

During the study observation period, severe clinical events were rare. Only one male patient (2.2%) experienced a significant renal event requiring transplantation. There were no reported deaths, cardiac, or cerebrovascular events.

4. Discussion

This nationwide study, conducted through China's first MDT network dedicated to pediatric FD, provides the first comprehensive overview of its clinical spectrum, diagnostic patterns, and management practices in Chinese children. The key findings include diagnostic delays, early multisystem involvement, sex-related clinical differences, and the increasing adoption of early enzyme replacement therapy within MDT care frameworks.

4.1. Diagnostic delay and the critical role of family screening

Diagnostic delay remains a key challenge in FD, particularly in pediatric populations. International registries have documented prolonged intervals between symptom onset and diagnosis—reaching 13.7 years in males and 16.3 years in females (*11*). Against this global background, our study demonstrates meaningful progress within China's emerging MDT framework: the median diagnostic delay in our pediatric cohort was 4.4 years for males and 4.0 years for females.

This substantial reduction reflects the early success of the national pediatric FD MDT network, underscoring the benefits of systematic family screening, cascade genetic testing, and improved clinician awareness. Notably, 72.2% of female patients in our cohort were diagnosed through family screening, highlighting the decisive role of this strategy in shortening the diagnostic odyssey. This approach aligns with both Chinese expert consensus (*12*) and international recommendations from European (*13,14*) and the United States (*15*) guidelines, which emphasize cascade testing as the most effective

Table 2. Prevalence of organ system involvement and clinical manifestations

Parameter	Male	Female
Total number	46	18
Organ system, *n* (%)	42 (91.3%)	9 (50.0%)
Neuropathic pain symptoms	38 (82.6%)	7 (38.9%)
Age at acroparaesthesia onset, Mean ± SD (years)	8.4 ± 3.0	9.0 ± 2.1
Age at acroparaesthesia onset, (years)	8	8
Median age (range)	(0–16)	(7–13)
Acroparaesthesia in hands	27 (58.7%)	4 (22.2%)
Acroparaesthesia in feet	36 (73.5%)	7 (38.9%)
Fabry crises	24 (52.2%)	2 (11.1%)
Burning pain	24 (52.2%)	1 (5.6%)
Tingling	12 (26.1%)	4 (22.2%)
Numbness	4 (8.7%)	1 (5.6%)
Headache/migraine	3 (6.5%)	1 (5.6%)
Anhidrosis or hypohidrosis	27 (58.7%)	2 (11.1%)
Angiokeratoma	21 (45.7%)	2 (11.1%)
Gastroenterological	9 (19.6%)	3 (16.7%)
Abdominal pain	6 (13.0%)	2 (11.1%)
Constipation/Diarrhea	5 (10.9%)	1 (5.6%)
Nausea/Vomiting	2 (4.3%)	1 (9.1%)
Ophthalmology (*NA = 7/5)	23 (59.0%)	7 (53.8%)
Cornea verticillata	19 (48.7%)	7 (53.8%)
Posterior subcapsular cataract	3 (7.7%)	0
Visual impairment	1 (2.6%)	0
Retinal vascular tortuosity	1 (2.6%)	0
Sensorineural hearing loss (*NA = 9/7)	4 (10.8%)	0
Depression (*NA = 37/16)	1 (1.1%)	0
Respiratory (*NA = 13/7)	8 (24.2%)	0
Obstructive respiratory diseases	8 (24.2%)	0
Restrictive respiratory diseases	1 (3.0%)	0
Renal (*NA = 5/6)	6 (14.6%)	0
Microalbuminuria	5 (12.2%)	0
Low glomerular filtration rate	3 (7.3%)	0
Renal tubular dysfunction	1 (2.4%)	0
Cardiovascular (*NA = 6/7)	23 (57.5%)	4 (44.4%)
Arrythmias	11 (27.5%)	4 (44.4%)
Valvular dysfunction	3 (7.5%)	0
Conduction abnormalities	3 (7.5%)	0
Left ventricular hypertrophy	3 (7.5%)	0
T-wave inversion on electrocardiogram	2 (5.0%)	0
Congenital heart disease	2 (5.0%)	0
Low bone mineral density (*NA = 39/17)	4 (57.1%)	0

*NA = number of patients with no data available in groups of male and female.

means of early identification.

To further narrow this gap, the integration of systematic family-based cascade screening with expanded newborn and high-risk population screening programs is critical. Such coordinated efforts within the MDT framework will be pivotal in realizing true early detection and timely intervention for children with FD in China.

4.2. Sex differences and clinical relevance in females

As expected, given FD's X-linked inheritance, male patients in our cohort presented with earlier symptom onset and more severe clinical manifestations, notably neuropathic pain and anhidrosis/hypohidrosis. However, a significant proportion of female children (nearly half) were symptomatic, some exhibiting severe features like Fabry crises and cardiac arrhythmias.

The recent consensus review by Hopkin *et al.* (*16*) demonstrated that over two-thirds of female patients develop multisystem involvement, and more than one-third experience severe clinical features in adults. The clinical heterogeneity observed in females primarily arises from random X-chromosome inactivation and the lack of effective cross-correction of the enzymatic defect between cells. These pathophysiological mechanisms explain the potential for significant tissue and organ damage even with normal plasma α-Gal A activity (*16*). Therefore, female children with confirmed GLA variants or relevant clinical symptoms should receive equally rigorous monitoring and longitudinal assessment as males, independent of their enzyme activity levels.

4.3. Early organ involvement and expanding the monitoring paradigm

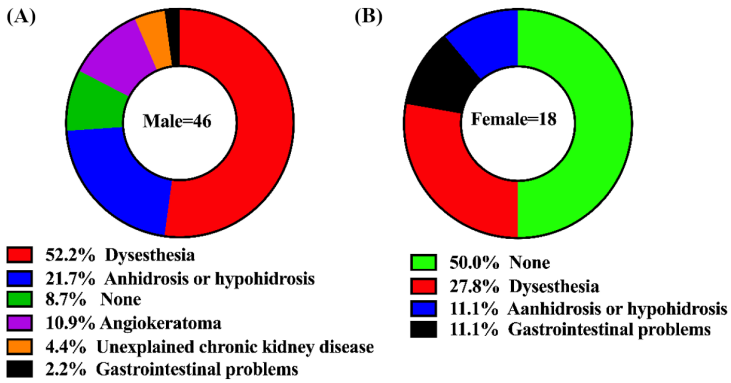

Figure 1. The first symptoms in male and female patients diagnosed with Fabry disease. (A) Proportion and type of first symptoms reported in male patients (n = 46); **(B)** Proportion and type of first symptoms reported in female patients (n = 18). Symptom categories include: Angiokeratoma, Unexplained chronic kidney disease, Anhidrosis or hypohidrosis, Dysesthesia, Gastrointestinal problems and none. Data are presented as percentage of patients reporting each symptom as their first manifestation.

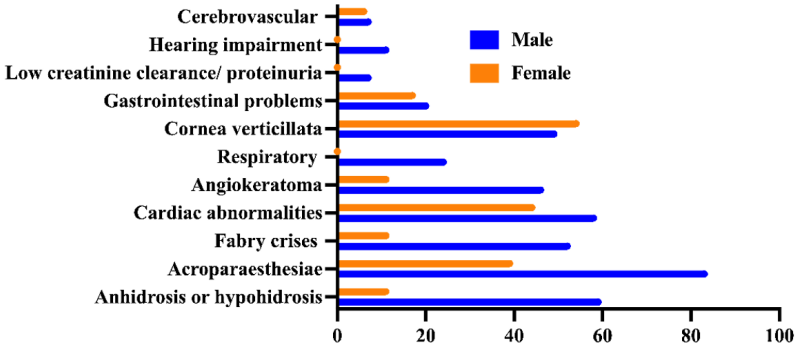

Figure 2. Proportion of male and female patients with Fabry disease showing different clinical manifestations at diagnosis. Bar chart comparing the prevalence of various clinical manifestations at the time of diagnosis between male (n = 46) and female (n = 18) patients. Manifestations shown: Cerebrovascular, Hearing impairment, Low creatinine clearance/proteinuria, Gastrointestinal problems, Cornea verticillata, Respiratory, Respiratory, Angiokeratoma, Cardiac abnormalities, Fabry crises, Acroparaesthesia, Anhidrosis or hypohidrosis. Data are derived from the same cohort as in Figure 1.

Table 3. Treatment patterns and details of enzyme replacement therapy

Parameter	Male	Female
Total number	46	18
Medication, *n* (%)	31 (67.4%)	7 (38.9%)
ERT, *n* (%)	31 (67.4%)	6 (33.3%)
Fabrazyme®, agalsidase beta 1 mg/kg/14 days (*n*)	24	6
Replagal®, agalsidase alfa 0.2 mg/kg/14 days (*n*)	7	0
Switch between therapies (*n*)	2	1
Age at first ERT (years), Mean ± SD	12.92 ± 2.88	11.73 ± 2.78
Age at first ERT (years), Median age (range)	12.9 (7.7–18.6)	12.9 (7.2–14.1)
Symptom onset to first ERT (years), Mean ± SD	7.40 ± 4.85	5.11 ± 4.91
Symptom onset to first ERT (years), Median age (range)	7.25 (0.8-17.8)	3.95 (0.3–13.7)
Duration of ERT (years), Mean ± SD	2.90 ± 1.37	2.55 ± 1.16
Patients with grade 3 adverse event, *n* (%)	2 (6.5%)	0
Patients with grade 4-5 adverse event, *n* (%)	0	0
Analgesics	19 (41.3%)	1
RAAS blockers	6 (13.0%)	0
Potassium citrate	1 (2.2%)	0

Abbreviations: ERT, enzyme replacement therapy; RAAS, Renin-angiotensin-aldosterone system.

Consistent with previous studies (*1,3,15,17*), our findings reaffirm that FD is a multisystem disorder from early childhood, with neuropathic pain as the earliest and most prevalent symptom. In our cohort, 90.5% of symptomatic males and 38.9% of females reported pain. This manifestation, primarily in the form of acroparesthesia (affecting 92.1% of symptomatic males and 85.7% of females), often exhibits gender-specific characteristics, with a predominant burning sensation in males (52.6%) and tingling in females (57.1%). Notably, Fabry crises occurred in 63.2% of males and 28.6% of females, underscoring the severe and episodic nature of this neuropathic phenotype. These results echo previous pediatric reports (*3,18*) and highlight the need for proactive surveillance rather than reactive symptom management.

Neuropathy in FD often coexists with subclinical injury in other organ systems, progressing silently during childhood. Renal involvement—manifested as microalbuminuria or early GFR reduction—can precede overt nephropathy, supporting the use of sensitive biomarkers (*e.g.*, urinary podocyte markers, advanced imaging) to detect preclinical injury (*17,19*). Cardiac abnormalities, including arrhythmias and LVH, were also observed, aligning with data that identify cardiac disease as the leading cause of mortality in FD (*20*). Therefore, annual ECG and echocardiographic monitoring from diagnosis are warranted.

This study identifies additional features contributing to the pediatric phenotype, beyond neurologic, renal, cardiac, ophthalmologic, and angiokeratoma presentations. Low bone mineral density in over half of tested males and obstructive pulmonary dysfunction in nearly one-quarter indicate previously underappreciated skeletal and respiratory involvement. These findings, consistent with emerging evidence (*21,22*), suggest Fabry pathology may extend to mesenchymal and connective tissues, warranting integration of skeletal and pulmonary assessments into routine follow-up. Sensorineural hearing loss, detected in 10.8% of males compared with 6.4% in prior reports (*23*), further supports inclusion of audiologic evaluation in comprehensive care. Gastrointestinal symptoms, though less frequently reported here, are likely underrecognized due to nonspecific presentations (*24,25*); structured and targeted assessment should thus be part of pediatric evaluation.

Collectively, these findings emphasize that multisystem involvement—including renal, cardiac, skeletal, respiratory, auditory, and gastrointestinal systems—can emerge in early childhood, even before overt decline. We therefore advocate an expanded, integrated monitoring paradigm that addresses neuropathic pain as a sentinel feature while systematically screening for subclinical organ injury. Such a holistic, anticipatory approach is essential to delay disease progression and optimize long-term outcomes in pediatric FD.

4.4. Timing of therapy and indications for early intervention

The rationale for early treatment is firmly supported by pathological and clinical evidence. Gb3 accumulation and podocyte injury begin in early childhood, preceding overt albuminuria or renal function decline (*26*). A recent study (*27*) further suggests that early diagnostic kidney biopsies should be considered irrespective of biochemical findings, to facilitate timely ERT initiation in pediatric FD.

The median age of ERT initiation in our cohort (12.9 years in males, 11.7 years in females) was slightly higher than the recommended early-intervention window. Current disease-specific therapies include agalsidase beta—approved in Europe for patients aged ≥ 8 years and in the U.S. for those aged ≥ 2 years; agalsidase alfa—approved in Europe from age ≥ 7 years; and pegunigalsidase alfa—approved in both Europe and the US in 2023 for adults. Migalastat was additionally approved in Europe in 2021 for patients aged ≥ 12 years (*28*).

International and national guidelines consistently advocate early intervention once Fabry-related symptoms or biomarkers appear. In the United States, the 2016 Fabry Pediatric Expert Panel recommends ERT for any symptomatic boy or girl, regardless of age, with neuropathic pain, renal or cardiac disease, or gastrointestinal involvement. For asymptomatic boys with classical mutations, treatment is discussed by 8–10 years, while asymptomatic girls are followed longitudinally (*15*). The French 2019 consensus recommends initiating ERT in symptomatic patients with neuropathic pain, albuminuria ≥ 3 mg/mmol, or cardiac/gastrointestinal involvement, and considering earlier therapy in asymptomatic boys with classic GLA variants and Lyso-Gb3 > 20 nmol/L (*29*). Similarly, a Portuguese review advises treatment for classic males from 8–10 years and for females or late-onset males once organ involvement is evident (*30*).

The 2021 Chinese Expert Consensus on the Diagnosis and Treatment of Fabry Disease (2nd edition) aligns with these recommendations, suggesting ERT initiation in boys and girls presenting with Fabry-related symptoms, though without a defined age threshold (*12*). This symptom-based, individualized approach reflects a growing national emphasis on early recognition and timely management of pediatric FD.

Collectively, these perspectives underscore that early ERT initiation, guided by genotype, biomarkers, and subclinical organ involvement, is essential to prevent irreversible progression. The modest delay in treatment initiation in our cohort highlights the ongoing need to improve early diagnosis and therapy access within China's developing pediatric FD network.

4.5. Study limitations

This study has limitations inherent to its retrospective design. The modest sample size, recruited from specialized centers, may limit generalizability. The analysis focused exclusively on pre-ERT data, which, while informative of the natural history, does not allow for assessment of treatment response. Future prospective, longitudinal studies are needed to evaluate the impact of early ERT initiation on long-term outcomes.

5. Conclusion

In summary, this study—based on the Chinese Children Genetic Kidney Disease Database—confirms that pediatric FD in China manifests as a multisystem disorder with significant renal, cardiac, skeletal, respiratory, and auditory involvement from an early age. Findings from this Chinese cohort underscore the importance of MDT-driven strategies, family screening, and early therapeutic intervention to improve long-term outcomes in Chinese children with FD.

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From co-creation to compounding value: A new model of rare disease science communication in China

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SUMMARY: For the vast rare disease patient community in China, science communication is crucial for bridging the information gap. However, the traditional, expert-led knowledge distribution model has proven insufficient to address the dual challenges of resource scarcity and low efficiency in the rare disease field. This paper introduces a new science communication model derived from practice in China. With "Patient-Driven Co-Creation" as its core, this model's ultimate goal transcends traditional information dissemination, aiming to empower the entire ecosystem through systematic value creation. Through an analysis of the practical model of the *Wonder Sir* platform, this paper proposes for the first time the "Patient Compounding Value Model". This model demonstrates how intangible patient-lived experiences can be systematically transformed into tangible assets capable of driving scientific research, clinical optimization, and public policy, thereby providing a sustainable value-generation mechanism for the resource-scarce rare disease field.

Keywords: rare diseases, science communication, patient engagement, co-creation, China

1. Introduction

For the vast rare disease patient community in China, science communication is crucial for bridging the information gap and addressing systemic challenges. These challenges are pervasive, exemplified by a diagnostic odyssey averaging more than five years and extremely low awareness among clinicians (*1,2*). The core challenge confronting the rare disease community lies not only in the scarcity of information but, more fundamentally, in how to translate their unique lived experience into an effective force for advancing the entire ecosystem. While global discourse on patient engagement is intensifying, most practices remain confined to consultative or lower levels of involvement (*3,4*), lacking a systematic theoretical framework to guide and measure how deep patient participation can be converted into sustainably appreciating core assets. This theoretical void is particularly pronounced in low- and middle-income countries (LMICs) where resources are scarce (*5,6*).

These persistent systemic challenges themselves prove the insufficiency of the traditional knowledge distribution model followed by conventional science communication. This model, which presumes patients are passive recipients of information and aims to solve an information deficit, is inherently a unidirectional process that consumes existing expert and institutional resources. This paper argues for a paradigm shift: from mere knowledge distribution to systematic value creation. Based on an analysis of the practice of *Wonder Sir*, a rare disease education and innovation platform in China (*7*), this paper introduces the "Patient Compounding Value Model". This theoretical framework elucidates how intangible patient experiences can be systematically transformed into tangible assets capable of driving scientific research, clinical optimization, and public policy. The core of the "Patient Compounding Value Model" is that it functions as a generative system that activates latent resources—the patients—to continuously create new assets.

2. Theoretical framework: The "Patient Compounding Value Model"

The "Patient Compounding Value Model" is philosophically rooted in the concept of coproduction, wherein the value of healthcare services is co-created by professionals and patients (*8*). The model comprises a driving engine ("Patient-Driven Co-Creation") and a value-transformation mechanism (the compounding growth of six core assets).

2.1. The engine: "Patient-Driven Co-Creation"

"Patient-Driven Co-Creation" serves as the core methodological engine for value transformation. It applies the foundational principles of Community-Based Participatory Research—such as recognizing the community as a unit of identity, building on community strengths, and fostering equitable partnerships (*9,10*) — to the rare disease context. Transcending unidirectional knowledge dissemination, "Patient-Driven Co-Creation" is a systematic process that empowers patients, transforming them from passive information recipients into active value co-creators (*7*).

The operational flow of this engine, exemplified by the creation of the "Born to Challenge" science communication comic series produced by *Wonder Sir*, has been presented as an innovative model at international conferences (*e.g.*, World Orphan Drug Congress 2024, Boston, MA) and can be summarized in four stages (Figure 1):

(1) Strategic Framing & Community Consensus: The process begins with a clear strategic objective: to enhance public empathy through a layperson's perspective. Based on this, the platform proactively collaborates with patient communities, upgrading the engagement model from story collection to co-creation, thereby fundamentally acknowledging the expert status of the patient community.

(2) Multi-stakeholder Content Creation: Initiated by the community, a creative triangle comprising the protagonist, community representatives, and clinical experts is formed. A pre-consensus on the script is achieved through in-depth interviews and joint reviews before production begins, ensuring accuracy, empathy, and efficiency.

(3) Embedded Expert Review: Clinical experts, recommended and invited by the patient community, are involved throughout the process from inception, establishing a trust-based, collaborative relationship rather than a traditional final-stage approval.

(4) Joint Dissemination & Asset Empowerment: The final output is jointly disseminated by the platform and the community. Crucially, all materials are provided royalty-free to the community, empowering them with sustainable tools. This act transforms dissemination from mere amplification into asset empowerment. (An English example of a science communication comic is available as Supplementary Figure S1, *https://www.irdrjournal.com/action/getSupplementalData.php?ID=280*).

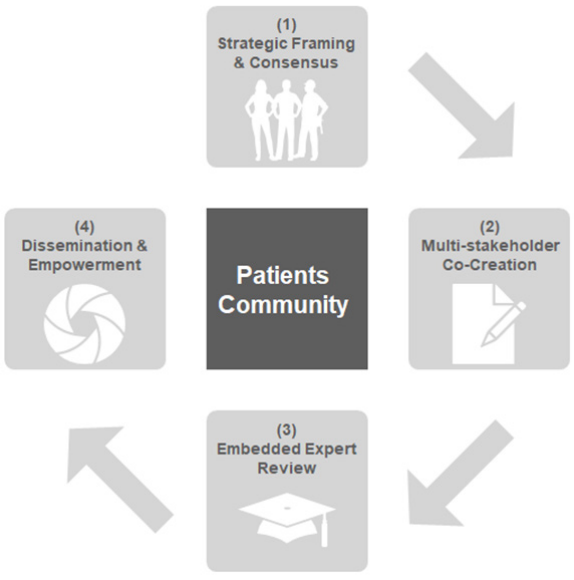

Figure 1. The "Patient-Driven Co-Creation" Process Model. The model illustrates a cyclical, four-stage process with the patient community as the central engine. The process begins with (1) Strategic Framing & Consensus to align goals, followed by (2) Multi-stakeholder Co-Creation to jointly develop content. (3) Embedded Expert Review ensures accuracy throughout the process. The cycle concludes with (4) Dissemination & Empowerment, where the output is transformed into a sustainable asset for the community, initiating a new cycle of value creation.

2.2. The output: Compounding growth of the six core assets

The output of the "Patient-Driven Co-Creation" engine is not a one-off piece of content but the systematic generation of six cumulative and reusable core assets. The formation of these assets reflects the construction of social capital—features of social organization such as networks, norms, and trust that facilitate coordination and cooperation for mutual benefit (*11*). These assets can be categorized into three logically progressive tiers based on their nature and evolutionary stage, enabling a compounding growth of value (*12*). The hierarchical structure and compounding value growth of this model are illustrated in Figure 2.

Tier 1: Social Assets - The Foundation of Value Creation

i) Narrative & Communication Assets: The capability to transform intangible lived experiences into tangible, scalable tools for empathetic communication. This asset is not merely content; it is the primary lever for building community identity, combating social stigma, and attracting external resources.

ii) Community Mobilization Assets: The aggregate social capital of a rare disease community, encompassing trust networks, shared identity, and the organizational capacity to mobilize individuals for collective action. This asset serves as the organizational infrastructure upon which all other assets are generated and transformed. Without robust community mobilization capacity, systematic data collection or biospecimen banking is inconceivable.

Tier 2: Knowledge Assets - The Transformation from Experience to Evidence

iii) Data Assets: Patient community-led, structured information collections that reflect the real-world panorama of a disease. Compared to traditional clinical trial data, this asset places greater emphasis on long-term,

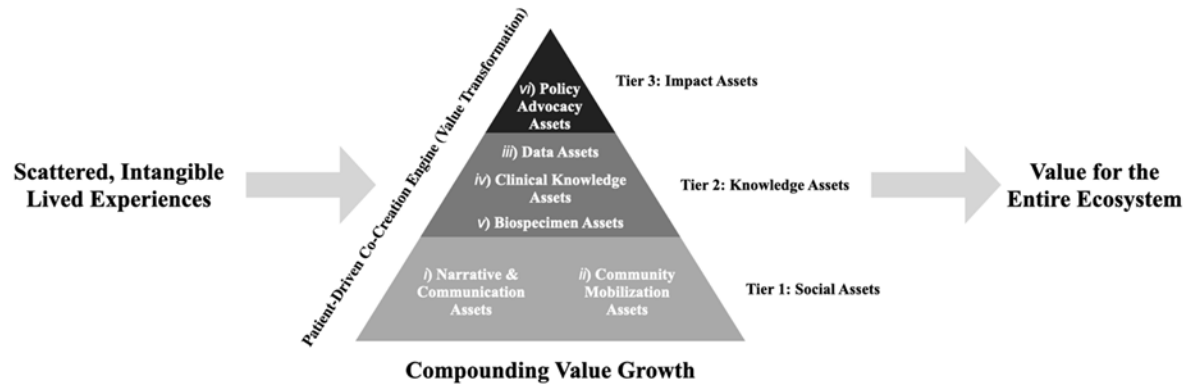

Figure 2. The "Patient Compounding Value Model". The model illustrates how the "Patient-Driven Co-Creation" engine transforms scattered, intangible lived experiences into tangible value for the ecosystem. This process demonstrates a compounding value growth, visualized as a pyramid of three hierarchical tiers. **Tier 1**, the foundation, consists of Social Assets: *i*) Narrative & Communication, and *ii*) Community Mobilization. These enable the creation of **Tier 2**, Knowledge Assets: *iii*) Data, *iv*) Clinical Knowledge, and *v*) Biospecimen. At the apex is **Tier 3**, Impact Assets: *vi*) Policy Advocacy, which leverages the lower-tier assets to drive systemic change.

continuous quality of life, disease burden, and patient-reported outcomes, offering a unique and indispensable perspective for understanding natural history and evaluating real-world treatment effectiveness.

iv) Clinical Knowledge Assets: An experiential knowledge system, accumulated and validated by the patient community through long-term practice. It includes non-pharmacological intervention techniques for specific symptoms, side-effect management strategies, and nuanced observations of treatment responses not found in textbooks. This knowledge is crucial for optimizing clinical practice guidelines and developing more patient-centric therapeutic approaches.

v) Biospecimen Assets: The collective capacity of a community, built on trust and mobilization, to provide well-characterized, ethically sourced biospecimens for research. The value of such specimens extends far beyond the biological material itself, as they are linked to the rich data and clinical knowledge assets held by the community, offering researchers an invaluable specimen-data-knowledge triad.

Tier 3: Impact Assets - The Driver of Ecosystem Change

vi) Policy Advocacy Assets: The ability of a community to leverage its accumulated assets to engage with policymakers, transforming its role from passive recipients to active co-creators of policy. When a community can present its own narratives, data, and knowledge in policy discussions, it evolves from being a mere supplicant to an evidence-based participant in the policy agenda-setting process.

2.3. A compelling case: The Lesch-Nyhan syndrome community

The efficacy of the "Patient Compounding Value Model" is compellingly demonstrated by the trajectory of the Chinese Lesch-Nyhan Syndrome (LNS) Association. The model was initiated by a high-impact Narrative & Communication Asset—a science communication article on LNS (*13*). This asset acted as a lighthouse, connecting several isolated families on the day of its publication and leading directly to the formation of China's first LNS patient WeChat group, marking the birth of the first Community Mobilization Asset. The significance of this step lies in its use of emotional resonance to transform atomized, powerless individuals into a collective with a shared identity (*14*).

This community container then began to precipitate value. Through internal communication, members systematically generated and accumulated Data Assets and Clinical Knowledge Assets. For instance, caregivers collectively identified patterns and intervention strategies for the self-injurious behaviors characteristic of LNS—experiential knowledge that even top specialists had not observed. This knowledge represents an invaluable scientific clue for understanding the disease's core mechanisms. Subsequently, the community independently produced the "Survey Report on the Current Status of Chinese Patients with Lesch-Nyhan Syndrome (2021)" and the "100 Questions and Answers on Lesch-Nyhan Syndrome handbook", formally converting dispersed experiences into structured knowledge assets. This step marked the community's evolution from a peer support network into a knowledge production hub (*15,16*).

Ultimately, this rich foundation of social and knowledge assets empowered the community to make a decisive leap. It has grown into the world's largest LNS patient cohort, possessing significant potential to build a Biospecimen Asset. More importantly, it has begun converting its internal value into external Impact Assets. The community leader, as the sole representative of a single-disease patient community from China, attended the 2024 World Orphan Drug Congress and hosted an exhibition booth, engaging with executives from top pharmaceutical companies and leading researchers, thereby gaining international recognition.

This recognitions is not merely honorary; it signifies that the community has earned a seat at the table for dialogue with top-tier global resources, marking its emergence onto the global stage as a professional and equal partner (*14*).

3. Discussion and Conclusion

The "Patient Compounding Value Model" proposed in this paper offers a novel, operational framework for conceptualizing and measuring the true value of patient engagement, elevating patients from passive research subjects to active co-builders of the ecosystem. Unlike Western models, which are often driven bottom-up by politically powerful Patient Advocacy Groups such as NORD in the US and EURORDIS in Europe (*17,18*), the rare disease ecosystem in China is predominantly constructed through top-down state guidance, with stakeholders participating as collaborative partners (*19*). While this collaborative partner model may possess less direct political influence than its Western counterparts, its high degree of alignment with national strategy affords it a unique efficiency in mobilizing centralized resources and rapidly advancing specific agendas.

As the practice of *Wonder Sir* demonstrates, a professional third-party platform plays a crucial role as infrastructure and an enabler in this model (*7*). Its true advantage lies not in the volume of content it produces unidirectionally, but in its pioneering and validation of the replicable "Patient Compounding Value Model", which systematically empowers patient communities to create value for themselves. This enabling role represents a fundamental transcendence of the traditional knowledge distribution model.

The central tenet of the "Patient Compounding Value Model" is that science communication should be elevated from a mere promotional activity to essential infrastructure for ecosystem-building. Against the backdrop of global sustainability challenges in the rare disease field (*20*), this model, originating from China and rooted in low-cost digital platforms, demonstrates high replicability in resource-constrained environments (*5,6*). It thus offers an innovative and sustainable solution for other LMICs facing similar challenges. We therefore propose that global health policymakers and funding agencies consider shifting investment from traditional information-dissemination programs to supporting and cultivating such value-creation infrastructures that can systematically generate, manage, and transform patient value. Such an investment shift would not only endorse a new model but would also represent a strategic commitment to a more equitable, effective, and human-centered future for global health.

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Conflict of Interest: The author is the founder of *Wonder Sir*, which is discussed in this paper. No financial or commercial conflicts of interest are declared.

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