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From presence to provenance: Building substantive infrastructure for China's rare disease ecosystem

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SUMMARY: International collaboration is indispensable in rare diseases, yet its depth and impact vary widely. In recent years, China has expanded its engagement in global rare-disease initiatives, but not all efforts translate into lasting progress. This Policy Forum examines China's evolving role through the lens of symbolic versus substantive collaboration. While symbolic efforts enhance visibility, substantive collaboration builds durable infrastructures—such as standardized terminologies, interoperable data systems and registries, and sustained clinical and research networks. Drawing on policy-relevant case examples, this article shows how patient-centered, infrastructure-building approaches can transform episodic engagement into systemic capacity. Looking ahead, the next phase of collaboration must focus on embedding global standards into health information systems, registries, and reimbursement frameworks. With its population scale, growing scientific capacity, and expanding global interaction, China is well positioned to evolve from a participant to a co-shaper of a truly global rare-disease ecosystem.

Keywords: rare disease innovation, China's rare disease advantage, patient-initiated research, Lesch-Nyhan Syndrom (LNS), Hemophilia Home of China (HHC), rare disease infrastructure building

1. Introduction

Rare diseases, though individually "rare", represent a global public health priority of staggering proportions (*1-3*). No single nation possesses the patient volume or specialized expertise to address these conditions in isolation, and international collaboration is not merely an advantage; it is a necessity.

In China, the sheer scale of the population (1.4 billion) transforms rare prevalence into high absolute patient numbers regardless of which definition is used (*3-5*). While these conditions remained on the periphery of the national health agenda for decades, the last ten years have marked a radical policy pivot (*6-9*). Beginning with the 13th Five-Year Plan for Health and Wellness (2017) (*10*) and the landmark release of the National Rare Disease Catalog (2018) (*11*), the Chinese government embarked upon a systematic, cross-sectoral approach. This era of "explosive growth" was underscored by the allocation of substantial state funding to initiatives such as the National Rare Disease Cohort Study (*12,13*).

The initial phase of China's rare disease evolution was characterized by "inbound" collaboration—a vital period of knowledge importation where Chinese stakeholders adopted global best practices in patient care, clinical guidelines, advocacy, and genomics from the U.S., Europe, and Japan. This foundation was solidified through pivotal international engagements. Academic research collaboration and the "Haigui" (returnee) phenomenon have successfully ignited China's biotech infrastructure (*14*), yet a critical distinction must be made between isolated research successes and substantive, systemic progress.

This Policy Forum argues that the next frontier for China—and the global community—lies in moving beyond symbolic gestures toward collaborative infrastructure-building. By analyzing unique case studies in patient-led networks and technology standards, this article examines the structural and regulatory shifts necessary to build an enduring, interoperable rare disease collaborative ecosystem.

2. Symbolic *vs.* substantive efforts

Not all forms of collaboration deliver equal impact. In rare diseases, where data is scarce and time is a luxury, it's important to distinguish between symbolic and substantive efforts (Table 1).

Symbolic collaborations, are often highly visible but

Table 1. Comparison of symbolic *vs* substantive collaboration in rare diseases

Feature	Symbolic Collaboration	Substantive Collaboration
Primary goal	Visibility, prestige, short-term wins	Utility, scalability, long-term efficiency
Type of output	Press release, conference, MOUs, halo publication	Shared data standards, shared protocol/ methodology, clinical trial network, registry useful for research and drug development
Data strategy	Siloed or proprietary	Interoperable, sharable *via* open data standards
Duration	Transient, dissipates once the event or funding ends	Durable, outlasts the initial project or individuals
Barrier to entry	Low, requires consensus on a public message	High, requires legal, technical and regulatory alignment
Policy implication	Low	High, generate evidence base for standard of care or reimbursement changes
Impact on patient	Indirect, unsubstantiated hope rarely changes patient outcomes	Direct, reduction in the diagnostic odyssey, access to global trials/ treatment, and improved standard of care

functionally shallow. They generate headlines and short-term visibility, but rarely "move the needle" on patient outcomes. In many cases, they create an opportunity cost—consuming precious resources and stakeholder attention while leaving little behind once the spotlight fades.

By contrast, substantive collaborations produce durable infrastructure and systems with far-reaching effects. These initiatives prioritize what can be described as "the plumbing of progresses": inherently harder, slower, and often less glamorous than symbolic gestures. It often requires navigating complex regulatory frameworks and aligning disparate institutional interest. However, it is precisely this groundwork that enables progress to be systematic, scalable, and reproducible across borders.

The substantive collaboration efforts can originate as grassroots initiatives but snowball into institutional forces that could shape policy changes.

2.1. Patient advocacy

Patient advocacy in rare diseases is born of necessity. Historically, in the United States and Europe, advocacy was the fundamental prerequisite for establishing medical and legislative recognition (*15,16*). Prior to formal mobilization, rare diseases were often dismissed as "marginalized problems" lacking commercial or clinical visibility (*17*). In China, this trajectory is compressed but equally transformative. As recent as 30 years ago, the healthcare system was ill-equipped to recognize or treat most rare conditions, with expertise concentrated in a few tertiary hospitals in big cities. Patients were medically underserved and subjected to social stigma (*17*). Within this environment, patient advocacy emerged as the first "visible bridge" connecting Chinese patients to global expertise.

2.2. From patient support to trial-ready networks

China's patient advocacy evolved from grassroots support to "trial-ready" infrastructure, exemplified by the Hemophilia Home of China (HHC) (*18-20*). Supported by the World Federation of Hemophilia (WFH), and buoyed by favorable policy tailwinds, HHC collaborated with clinical experts to establish China's Hemophilia Treatment Center Collaborative Network of China (HTCCNC) (*19*). The network expanded from 6 centers in 2004 to 115 in 2019, building a National Hemophilia Registration System with tens and thousands of patients (*19,20*).

Leveraging its registry for patient identification and enrollment, HHC partnered with Belief Biomed (BBM). Their partnership enabled the 2025 NMPA approval of BBM-H901, China's first domestically developed gene therapy (*21*). Today, HHC's digital platforms facilitate centralized recruitment and standardized AAV antibody testing—shifting the role from "support beneficiary" to "sophisticated co-development partner."

2.3. Lesch-Nyhan syndrome (LNS) – From serendipity to leading global research

While HHC illustrates the power of national networks for higher-prevalence rare diseases, Lesch-Nyhan Syndrome (LNS)—with an incidence of 1 in 380,000—demonstrates how substantive collaboration can achieve global impact in ultra-rare, resource-constrained contexts.

The China LNS Patient Group emerged from the "Wonder Sir" digital platform (*22*), founded by Dr. Yiwei Chen, a molecular geneticist and "returnee" (haigui) from Heidelberg University in Germany. Her academic background bridged the gap between laboratory research and clinical needs, enabled her to grow a small WeChat group with just three families into the world's largest LNS community with over 100 patients in just eight months.

Beyond providing mutual support, the community has

built a robust medical infrastructure: a national clinical and research network in China, and LNS Diagnostic Guidelines, aligned with GeneReviews standards (*23*). With direct support from the world's top LNS expert, Dr. Hyder A. Jinnah, the initiative now entered into a new phase: advancing basic research and co-designing clinical trials with Chinese clinicians and researchers. The resulting work is currently being developed into a graduate thesis under the supervision of a principal investigator (PI) (*24*). Serving as an outside graduate advisor, Dr. Chen plays a key role in ensuring that grassroots data collection is translated into academically rigorous output capable of meeting international peer review standards.

As a trail blazer, LNS group has encountered a range of structural challenges. Securing funding for patient-initiated research remains particularly difficult. Despite her strong academic background, Dr. Chen is at disadvantage when applying for government grants, which are typically awarded to PIs affiliated with established institutions. Regulatory barriers further complicate the landscape: strict rules governing human genetic materials, along with limitation on non-for-profit organizations receiving foreign funding, significantly restrict access to diverse funding sources.

Collaboration with hospital-based researchers presents an additional hurdle as rare disease research is perceived as a "non-essential" clinical activity. Neither institutions nor physicians are incentivized to engage deeply as existing rare disease reporting mandates focus solely on avoiding penalties for "non-compliance" rather than awarding excellence. Consequently, hospital participation remains largely performative, fulfilling administrative quotas without advancing clinical depth.

This systemic apathy, however, is not merely a failure of wills, but a failure of infrastructure. The friction encountered by the LNS case reveals the structural gaps in our current healthcare infrastructure – gaps that cannot be bridged by advocacy alone but require a fundamental shift on how rare disease research is recognized and valued.

2.4. The infrastructure of visibility: Standardized terminologies

To move rare disease collaboration from symbolic gestures to substantive impact, data must be both visible and computable across disparate systems and throughout the disease lifecycle. A shared global vocabulary is the only mechanism capable of transcending technical and linguistic barriers to aggregate these rare and highly valuable data points. By standardizing clinical data, we transform isolated anecdotes into a powerful engine for timely diagnosis, treatment development, and for deepening our understanding of the physiology and pathology of cellular networks (*25-30*). Furthermore, this standardization enables insights on disease prevalence, the natural history of rare conditions, and the socioeconomic burdens on families and health systems. The Human Phenotype Ontology (HPO) (*25-27*) and Orphanet Nomenclature of Rare Diseases (ORPHACode) (*28-30*) serve as the two foundational pillars of this global infrastructure.

2.4.1. CHPO: Standardizing the clinical narrative

The Human Phenotype Ontology (HPO) was constructed with the goal of covering all phenotypic abnormalities that are commonly encountered in human monogenic diseases (*25-27*). Originally developed in English, its usage in China was limited until the grassroots creation of the Chinese Human Phenotype Ontology (CHPO) (*31*). Led by a volunteer consortium of experts including Professors Weihong Gu, Shangzhi Huang, and Kai Wang—with the direct support of HPO creator Peter Robinson—the CHPO allows Chinese clinicians to document phenotypes in their native language while remaining fully interoperable with the global system.

CHPO is more than a language translation; it is a reciprocal infrastructure. As CHPO updates in parallel with HPO, Chinese clinical feedback flows back into the global data registry, ensuring that the diverse phenotypic expressions of 1.4 billion people are represented in world science (*32*).

The Chinese Human Phenotype Ontology (CHPO) is being used to support rare disease research, genomic analysis, and emerging AI-driven diagnostic tools (Table 2) (*33-35*). Its strongest adoption is in leading academic and clinical centers, where it enables structured phenotyping, facilitates genotype–phenotype correlation, and improves data interoperability in research settings (*33-35*). However, CHPO is not yet widely integrated into routine hospital information systems, which continue to rely on ICD-based coding and local clinical terminologies. As a result, its clinical use is often indirect, supported by natural language processing and AI-based tools that map unstructured Chinese clinical records to CHPO terms (*34-35*). This reflects a broader transitional model in China, where ontology-based standards are advancing rapidly in research and data infrastructure, while clinical implementation is being enabled through intermediary technologies rather than direct system-level integration.

2.4.2. Orphanet Nomenclature of Rare Diseases (ORPHACode): Making the invisible visible

While CHPO standardizes symptoms, ORPHACode is the gold standard for rare disease nomenclature (Table 2) (*28-30*). It is formalized in key institutional documents, such as The WHA Resolution (May 24, 2025) (*36*), and European Commission Guidelines (2024) (*37,38*).

ICD10 is notoriously poor for rare diseases. Most conditions are lumped to "Other Specified" catch-all codes (*e.g.* Q87.8). The result is rare disease patients become invisible in health statistics. "For rare diseases to

Table 2. Comparison of the CHPO and ORPHACode translation projects

	HPO Localization (CHPO)	ORPHACode Chinese Translation
Description	Record Chinese phenotypes in the native Chinese languages leveraging HPO's interoperable and computable data structure	Label rare disease in registry or public health system
Current status	Continue to be updated, and locally maintained	No update since the initial release in June 2021; Centrally maintained by Orphanet
Features	Used in leading academic and research centers in rare disease research, genomic analysis and AI diagnostics. Chinese data flow back into the global registry	Currently no recorded implementation in China. Only used as a reference in NRDRS: when a new case is submitted to NRDRS, the disease name needs to be consistent with the ORPHACode translation
Future direction	Implement in the electronic medical record (EMR) systems	Implement in the health systems, registries, and reimbursement systems

Table 3. Comparison – Electronic vehicle industry *vs* rare disease research

Feature	Electronic Vehicle (EV) Industry	Rare Disease (RD) Ecosystem
Initial market status	Niche, high-cost, "unprofitable" for traditional automakers	Niche, "non-essential", high risk / low return for traditional hospital / pharma
Strategic value	Testing ground for battery tech, AI and autonomous driving	Testing ground for gene and cell therapy, AI diagnosis, precision medicine
The plumbing	National charging networks and standardized battery connectors	Standardized terminologies (HPO / ORPHACode), and interoperable data repositories
Role of policy	From subsidiaries (symbolic / initial) to mandatory fleet shifts and infrastructure (substantive)	From "direct report" mandates (symbolic) to integrated "trial-ready" networks and stimulative measures for innovations (substantive). System-wide implementation of terminology maximize data intelligence
Grassroots influence	Early adopters and tech-disruptor (*e.g.* Tesla/NIO forcing policy change	Grossroot initiative (HHC, LNS) fill critical gaps and brings valuable patient insight, drive regulatory changes
Global dynamics	China's manufacturing prowess creates global export standards	Chinese vast patient data generates global scientific evidence

count, we need to count rare diseases" (*30*).

ICD-11 was developed in close collaboration with Orphanet. It adopts a much more granular approach that mirrors the ORPHACode structure. Compatibility between the systems is a major driver for the adoption of ICD-11 (*36*).

In December 2020, I initiated and led the Chinese translation of ORPHACode, supported by the China Alliance for Rare Diseases (CHARD). Teams at Fudan University Children's Hospital and Peking Union Medical College Hospital (PUMCH) completed the translation work in June 2021. However, a critical gap remains: while the translation is complete, it has yet to be implemented in China's National Rare Disease Registration System (NRDRS) or hospital information systems, which are still using ICD-10.

3. Conclusion and recommendations: Toward a substantive global ecosystem

To realize the full potential of the rare disease ecosystem, China should transition from a compliance-driven regulatory model toward an "Innovation-First" framework. In much the same way that the electric vehicle industry served as a catalyst for transforming the broader automotive and energy infrastructure, rare disease research acts as the "EV sector" of healthcare—a high-tech laboratory for the next generation of precision medicine and digital health systems (Table 3).

Investing in the "plumbing" of this sector—from standardized terminologies to patient - initiated rare disease research and to trial-ready networks, —offers far-reaching strategic value that transcends the rare disease community. I propose that policy incentives be redesigned to foster innovation at both the institutional and grassroots levels.

3.1. Elevate rare disease to "National Strategic Asset"

Policy must evolve beyond baseline administrative mandates toward a framework that integrates rare disease research into the fundamental value proposition of the

national healthcare system. By recognizing rare disease research and clinical trials as primary drivers of medical innovation-analogous to "New Energy" benchmarks in the industrial sector—the government can incentivize hospital leaders to prioritize these efforts as core institutional strengths rather than peripheral "nice-to-have" obligations.

Rare disease research represents a unique "frontier territory" where the boundaries between basic science and clinical care dissolve. They provide an unparalleled window into human biology, offering insights that catalyze breakthroughs in common diseases, oncology and regenerative medicine.

China possesses a distinct structure advantage in this global race: the high concentration of healthcare resources within major tertiary hospitals in mega-cities. While this centralization presents access challenges for patients, it has created an unparalleled density of rare disease cohorts that exists nowhere else in the world. This "concentration effect" allows for the rapid recruitment of patient groups even in the ultra-rare conditions like LNS - effectively turning China's leading medical centers into global hubs for accelerated clinical validation, treating these concentrated patient populations as vital resources for national scientific sovereignty and global biopharmaceutical leadership.

3.2. Incentivize the "grassroots-to-institution" pipeline

Strategic value is often generated at the initiation level by "trail-blazers" like the LNS and HHC groups. The future of rare disease research may depend on recognizing and integrating these grassroots, yet highly substantive, forms of collaboration into formal policy and funding frameworks. Future policy should provide clear pathways for these grassroots, patient-led initiatives to access government research grants and formalize their role as "trial-ready" partners. By allowing more flexible regulatory pathways for patient-initiated research and facilitating international data-sharing, China can empower its local talent to lead global scientific discourse.

Traditional market and policy incentives often fail in ultra-rare diseases, as progress depends less on scale than on the ability to integrate data, expertise and patient communities across borders. The LNS community could serve as a good pilot case to illustrate how grassroots efforts, when coupled with scientific leadership and international expertise can generate research-ready infrastructure that rivals formal systems. Grassroots innovation, when substantively organized, can transcend structural limitations and reshape the landscape of ultra-rare disease research both in China and abroad.

3.3. Build the infrastructure of scalability

Just as the rapid expansion of electric vehicle (EV) industry required a national charging network, the rare diseases "innovation engine" requires a standardized data infrastructure. Implementing CHPO and ORPHACode at the system level is not a technical formality, but a strategic necessity. This standardized plumbing will ensure that the high-quality longitudinal data generated within China's population is interoperable, computable, and primed for global R&D investment.

Furthermore, building this infrastructure of scalability provides the empirical bedrock for sustainable healthcare financing. By rendering rare conditions visible within health care systems, policymakers can perform high-precision analysis of disease prevalence, direct and indirect treatment costs, and the real social economic burden on families and societies. This level of data granularity is the prerequisite for moving from speculative budgeting to evidence-based forecasting, enabling both social and commercial insurers to design risk-sharing models that are actuarially sound and socially equitable.

By investing in building the infrastructure for rare disease, China is not only addressing the needs of its own 20 million rare disease patients but is providing the world with a scalable model for collective scientific and social progress. The spotlight on rare diseases must be used to illuminate the structural path toward a truly universal healthcare ecosystem.

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