Review

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Rare but not to be overlooked: Epidemiology and strategies for rare dermatological diseases in China

Yue Han[1], Qianwei Zhuo[1], Nuo Chen[1], Haosong Zhang[1], Lihang Lin[1], Peipei Song[2,3,*]

[1] Department of Dermatology, The Union Hospital, Fujian Medical University, Fuzhou, Fujian, China;
[2] Center for Clinical Sciences, Japan Institute for Health Security, Tokyo, Japan;
[3] National College of Nursing, Japan, Tokyo, Japan.

SUMMARY: Rare skin diseases in China, recognized through the 2018 National Rare Disease List (121 conditions), pose substantial epidemiological and systemic challenges. The National Rare Diseases Registry System (NRDRS) documented 62,590 cases (2016–2020) of 166 diseases, and yet data remain fragmented: only 53.1% of rare diseases are prevalent and they are found in 94.1% of regions. Eight diseases have an incidence of ≥ 1/1,000. Regional disparities persist, as 60% of cases originate from affluent East/North China, contrasting with lower utilization of genetic testing in Western regions (71.9% *vs*. 79.2% in the East). Diagnostic delays average 1.4 years, with patients visiting 3.2 hospitals and enduring 1.6 misdiagnoses, exacerbated by limited physician awareness — only 5.3% of clinicians report moderate familiarity with rare diseases. Therapeutic advances, including B cell-targeted therapies (*e.g*., rituximab), coexist with barriers like orphan drug affordability, exemplified by projected annual budgets exceeding CNY 179 million for 98 patients. Clinical trials increased at a rate of 28.2% annually (2013–2022), yet China lags behind its global counterparts in trial diversity. Policy initiatives, such as the 2019 Drug Administration Law, prioritize orphan drug development but face challenges in regional implementation and insurance coverage. Critical needs include equitable healthcare access, standardized registries, and clinician education. Collaborative networks (*e.g.*, NRDRS-linked biobanks) and media-driven awareness campaigns are vital to alleviating systemic gaps for China's estimated 20 million patients with rare diseases.

Keywords: rare skin diseases, genetic testing, healthcare policy, diagnostic challenges, therapeutic advances

1. Epidemiological overview of rare dermatological diseases in China

1.1. Definition and classification of rare skin diseases

Rare dermatological diseases are defined based on their low prevalence in the general population. In China, the classification of rare diseases gained significant attention following the release of the first national list of rare diseases in 2018, which included 121 conditions. This list aimed to enhance societal awareness, improve diagnostic and treatment capabilities, and promote research and development of orphan drugs (*1*). While the list encompasses a broad spectrum of rare diseases, specific dermatological conditions are included, reflecting the growing recognition of their impact on public health (Table 1).

The classification of rare skin diseases often involves a combination of clinical presentation, genetic factors, and epidemiological data. For instance, anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), which includes microscopic polyangiitis (MPA) and granulomatosis with polyangiitis (GPA), is not uncommon in China. Among GPA patients, myeloperoxidase (MPO)-ANCA is markedly more prevalent than proteinase 3 (PR3)-ANCA (*2*). This highlights the importance of molecular and immunological markers in the classification and diagnosis of rare dermatological diseases.

The establishment of the National Rare Diseases Registry System (NRDRS) in China has further contributed to the classification of rare diseases. Between 2016 and 2020, the NRDRS registered 62,590 cases involving 166 diseases or disease types (*3*). This registry provides a structured framework for categorizing rare diseases, including dermatological conditions, based on clinical and demographic data. Such efforts are critical to understanding the epidemiological landscape and guiding healthcare policies.

1.2. Prevalence and incidence in different regions of China

Table 1. Rare skin diseases in China (Top 30)

No.	Disease
1	Epidermolysis bullosa (EB)
2	Ichthyosis (*e.g.*, Harlequin ichthyosis and Lamellar ichthyosis)
3	Porphyria cutanea tarda
4	Hereditary angioedema
5	Scleroderma (Systemic sclerosis)
6	Dermatomyositis
7	Xeroderma pigmentosum (XP)
8	Neurofibromatosis (Type 1 and 2)
9	Tuberous sclerosis complex (TSC)
10	Necrobiosis lipoidica
11	Pseudoxanthoma elasticum (PXE)
12	Darier disease (Keratosis follicularis)
13	Hailey-Hailey disease (Familial benign pemphigus)
14	Erythropoietic protoporphyria (EPP)
15	Lichen sclerosus
16	Pachyonychia congenita
17	Goltz syndrome (Focal dermal hypoplasia)
18	Incontinental pigmenti
19	Sturge-Weber syndrome
20	Ehlers-Danlos syndrome (Vascular or Dermatosparaxis types)
21	Cutaneous T-cell lymphoma (Mycosis fungoides/Sézary syndrome)
22	Hidradenitis suppurativa (Severe/rare subtypes)
23	Aplasia cutis congenita
24	Congenital melanocytic nevus syndrome
25	Mastocytosis (Systemic or Cutaneous)
26	Paraneoplastic pemphigus
27	Blau syndrome
28	Lipoid proteinosis (Urbach-Wiethe disease)
29	Erythrokeratodermia variabilis
30	Progeria (Hutchinson-Gilford syndrome)

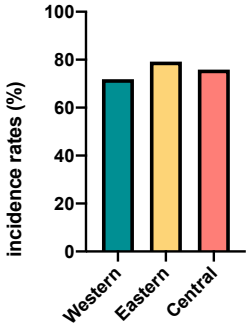

Figure 1. Regional disparities in the prevalence and incidence of rare diseases in China.

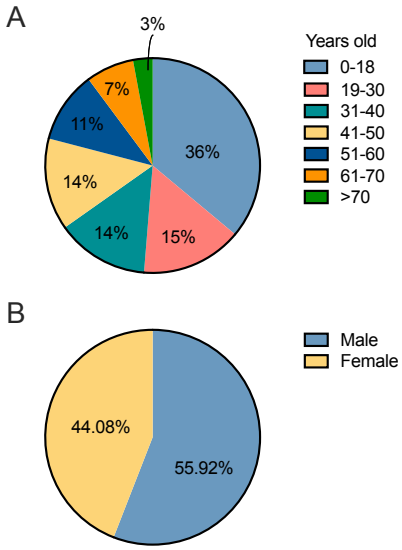

Figure 2. Characteristics of patients with rare diseases in China. (A) Age; (B) Sex.

Epidemiological data on rare diseases in China remain limited, with only 1,264 data points on prevalence and incidence found in 277 studies, guidelines, and official websites. These data cover 110 rare diseases (53.1%) and 32 regions (94.1%), excluding the Tibet Hui Autonomous Region and Macao Special Administrative Region. Eight of these diseases have an incidence equal to or greater than 1,000 patients per million (*4*). This highlights the uneven distribution of epidemiological data and the need for comprehensive studies to address gaps in knowledge, particularly for rare dermatological diseases.

Regional disparities in the prevalence and incidence of rare diseases are evident. For example, the NRDRS data indicate that 60% of registered cases are from the wealthier regions of East and North China, underscoring disparities in access to quality care (*3*). Similarly, the rate of genetic testing for rare diseases is highest in the Eastern region (79.2%), followed by the Central (75.9%) and Western regions (71.9%) (Figure 1) (*5*). These disparities reflect broader socioeconomic inequalities that influence the availability and quality of healthcare for rare disease patients.

Rare disease patients in China often face significant challenges in being accurately diagnosed. On average, patients experience a diagnostic delay of 1.4 years and 1.6 misdiagnoses across 3.2 hospitals. Moreover, diagnoses are highly concentrated in 10 large hospitals (43.8%) and 5 major cities (42.1%) (*6*). This concentration of medical resources further exacerbates regional disparities and highlights the need for equitable distribution of healthcare infrastructure.

1.3. Demographic and genetic factors influencing disease distribution

Demographic and genetic factors play a crucial role in the distribution of rare dermatological diseases in China. The NRDRS data reveal that the average age of definitive diagnosis for rare diseases is 30.88 years, with 36.07% of cases diagnosed in individuals under 18 years of age (Figure 2) (*3*). This age distribution underscores the importance of early diagnosis and intervention, particularly for pediatric patients who may face lifelong challenges associated with rare dermatological conditions.

Genetic testing has emerged as a vital tool for diagnosing and understanding rare diseases. In China, the overall rate of genetic testing for rare diseases is 76.0%,

with pediatricians performing testing at the highest rate (94.1%) and surgeons performing it at the lowest rate (58.3%). The high rate among pediatricians reflects the critical role of genetic testing in diagnosing congenital and hereditary conditions, which are common among rare dermatological diseases. However, the high cost of genetic testing remains a significant concern for medical personnel (*5*), potentially limiting its accessibility for patients in less affluent regions.

Specific genetic markers have been identified in certain rare dermatological diseases, further elucidating their distribution. In AAV, for instance, there is a significant predominance of MPO-ANCA over PR3-ANCA in Chinese patients. This genetic predisposition highlights the need for targeted diagnostic and therapeutic strategies tailored to the unique genetic landscape of the Chinese population.

Demographic and genetic factors significantly influence the distribution and diagnosis of rare dermatological diseases in China. Efforts to address disparities in access to genetic testing and healthcare are essential for improving outcomes for patients affected by these conditions.

2. Clinical features and diagnostic challenges

2.1. Key clinical manifestations of rare skin disorders

Rare dermatological diseases in China have varied clinical presentations, often hampering their recognition and diagnosis. For instance, the clinical manifestations of hand, foot, and mouth disease (HFMD), which can occasionally present with dermatological symptoms, vary significantly depending on the causative pathogen. Among 5115 HFMD inpatients analyzed, 4.3% presented with severe symptoms, and there were significant complications in 4.1% of severe cases. While HFMD is not exclusively a dermatological condition, its skin-related symptoms, such as vesicular eruptions, highlight the importance of pathogen identification in understanding disease severity. Coxsackievirus A6 was identified as the predominant pathogen, accounting for 63.5% of mild cases and 36.2% of severe cases. This serotype's association with more severe dermatological manifestations underscores the need for pathogen-specific diagnostic approaches. In contrast, EV-A71, previously considered a major serotype, was responsible for only 15.6% of severe cases and 1.2% of mild cases. Sporadic detection of Coxsackievirus A10 (CV-A10) and A16, with CV-A10 infections tending to increase, further complicates the clinical landscape (*7*).

The variability in clinical presentations among rare dermatological diseases poses significant challenges for clinicians. For example, the overlapping symptoms of different pathogens, such as vesicular eruptions and systemic complications, can lead to misdiagnosis or delayed diagnosis. This complexity is compounded by the lack of standardized diagnostic criteria for many rare skin disorders, which often rely on clinical observation and pathogen-specific laboratory tests. The findings from HFMD studies highlight the importance of understanding pathogen-specific clinical features to improve diagnostic accuracy and patient outcomes (*7*).

2.2. Barriers to early and accurate diagnosis

The diagnosis of rare dermatological diseases in China is hindered by several systemic and educational barriers. A survey of physicians revealed that only 5.3% were moderately or well aware of rare diseases, indicating a significant knowledge gap. This lack of awareness is further reflected in clinical practice, where 80.1% of physicians reported suspecting rare diseases in their patients fewer than three times throughout their careers (*8*). Such limited exposure to rare diseases may result in delayed recognition and misdiagnosis, particularly for conditions with subtle or atypical dermatological manifestations.

Physicians with longer careers were more likely to believe that their medical education had not provided sufficient information about rare diseases. This suggests that conventional medical curricula may inadequately address the complexities of rare dermatological conditions, leaving clinicians ill-equipped to identify and manage these diseases. Moreover, the lack of continuing medical education programs focused on rare diseases exacerbates this issue, as practicing physicians have limited opportunities to update their knowledge and diagnostic skills.

The importance of rare disease awareness was emphasized by nine rare disease experts, who highlighted the role of awareness in facilitating early diagnosis and timely treatment (*8*). Increased awareness among healthcare personnel could lead to more proactive diagnostic approaches, reducing the time to diagnosis and improving patient outcomes. However, achieving this requires systemic changes in medical education and training as well as the development of targeted educational campaigns.

2.3. Role of advanced diagnostic tools and biomarkers

Advances in diagnostic technologies and biomarker research offer promising solutions to the challenges of diagnosing rare dermatological diseases. The establishment of the NRDRS represents a significant step toward standardizing rare disease registration and improving diagnostic accuracy. This system integrates genomic biobanks and fosters partnerships to share data and collaborate in research, enabling the identification of disease-specific biomarkers and genetic variants (*9*).

Innovative informatics technologies, including ontological and knowledge bases, have been implemented to facilitate the standardization of

diagnostic criteria and enhance diagnostic precision. These tools allow clinicians to access comprehensive databases of rare disease information, facilitating the identification of atypical clinical features and rare genetic mutations associated with dermatological conditions. By using these technologies, healthcare personnel can improve diagnostic accuracy and reduce the reliance on subjective clinical observations.

Long-term research collaboration is encouraged to create additional national rare disease networks, which could further enhance diagnostic capabilities and translate research findings into clinical practice (*9*). Such networks would enable the development of novel diagnostic tools and biomarkers, alleviating the current gaps in rare disease diagnosis. Moreover, the integration of these networks into clinical workflows could streamline the diagnostic process, ensuring that patients with rare dermatological diseases receive timely and accurate diagnosis.

The role of advanced diagnostic tools and biomarkers is pivotal in overcoming the challenges associated with rare dermatological diseases. By integrating genomic data, informatics technologies, and collaborative research efforts, the NRDRS and similar initiatives provide a framework for improving diagnostic accuracy and patient care (*9*).

3. Current therapeutic approaches and management strategies

3.1. Existing treatment modalities: Efficacy and limitations

The treatment landscape for rare dermatological diseases in China has developed markedly over the past few years, reflecting both advances in therapeutic strategies and persistent challenges. Among the notable developments, the refinement of treatment protocols for AAV, a rare dermatological condition with systemic implications, has been a key focus. In China, a rapid tapering of glucocorticoids has been used to minimize long-term exposure and associated adverse effects. This approach has shown promise in reducing treatment-related complications while maintaining disease control. Additionally, B cell-targeted therapies, such as rituximab, have gained traction as effective options for inducing remission in AAV patients. However, the use of rituximab is not without risks, as infection-related complications and associated mortality remain significant concerns (*2*).

Complement-targeted therapies are another emerging modality for AAV management in China. These therapies aim to modulate the complement system, which plays a critical role in the pathogenesis of the disease. While these approaches are still being developed, they offer the potential for improving outcomes in patients with refractory or severe disease. Moreover, a modified renal risk score model has been validated for early risk prediction in Chinese AAV patients, enabling more personalized and timely interventions (2). Despite these advances, the treatment of rare dermatological diseases in China continues to face challenges, including limited access to specialized therapies, high treatment costs, and the need for more robust clinical evidence to guide practice.

In the broader context of rare diseases, orphan drugs have been a focal point of research and development. These include traditional antibodies, small molecule drugs, gene therapy, stem cell therapy, and small nucleic acid drugs. Clinical breakthroughs in these areas have provided valuable references for the treatment of rare diseases in China, including dermatological conditions. However, the availability and affordability of these therapies remain significant barriers to widespread clinical use (*10*).

3.2. Emerging therapies and innovations

The development of innovative therapies for rare dermatological diseases in China has been bolstered by national initiatives and an increasing emphasis on clinical research. Since 2013, China has implemented a pilot project targeting 20 representative rare diseases, which has facilitated the establishment of a national network of approximately 100 provincial or municipal medical facilities. This network has been instrumental in fostering collaboration among clinicians, researchers, and patient organizations, thereby accelerating the development and application of medical guidelines and clinical pathways for rare diseases (*11*).

One of the key outcomes of this initiative has been the promotion of molecular testing for rare genetic disorders, which has significant implications for the diagnosis and treatment of rare dermatological diseases. By enabling precise genetic characterization, molecular testing facilitates the development of targeted therapies and the formulation of personalized treatment plans. Additionally, the establishment of a rare disease patient registry and data repository system has provided a valuable resource for tracking disease progression, treatment outcomes, and long-term patient needs (*11*).

Clinical trials have also played a pivotal role in advancing therapeutic options for rare diseases in China. Between 2013 and 2022, 481 clinical trials on rare diseases were conducted, with an average annual increase of 28.2%. This surge in clinical research has been driven, in part, by supportive policy measures, such as the 2015 policy document that led to an 80% increase in clinical trial applications for rare diseases in 2016 compared to the previous year (Figure 3). Despite these achievements, the number of clinical trials for rare diseases in China remains lower than in the United States, Europe, and Japan, highlighting the need for continued investment and international collaboration (*12*).

Emerging therapeutic modalities, such as gene

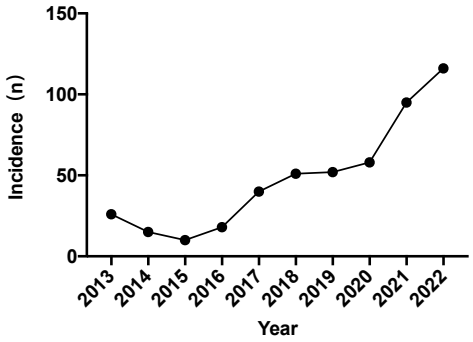

Figure 3. Annual numbers of clinical trial applications for rare diseases in China.

therapy and stem cell therapy, have shown particular promise in addressing the unmet needs of patients with rare dermatological diseases. These approaches offer the potential for long-term disease modification and, in some cases, curative outcomes. However, their clinical application is still in the early stages, and further research is needed to establish their safety, efficacy, and cost-effectiveness (*10*).

3.3. Patient-centered care and quality of life considerations

In the management of rare dermatological diseases, patient-centered care is increasingly recognized as a critical component of therapeutic strategies. This approach emphasizes the importance of addressing not only the clinical aspects of the disease but also the broader psychosocial and quality of life impacts experienced by patients. Rare dermatological conditions often impose significant physical, emotional, and financial burdens on patients and their families, necessitating a holistic approach to care.

The establishment of a collaborative network among medical facilities, clinicians, and patient organizations in China has been a significant step toward improving patient-centered care. By fostering communication and collaboration, this network has facilitated the development of tailored treatment plans that align with patients' individual needs and preferences (*11*). Moreover, the integration of patient-reported outcomes into clinical practice and research has provided valuable insights into the real-world impact of therapies, enabling more informed decision-making and resource allocation.

Efforts to enhance patient-centered care have also included initiatives to improve access to specialized treatments and reduce the financial burden associated with rare diseases. Government-funded biomedical research programs have been proposed to address challenges such as the high cost of treatment and the shortage of effective drugs for rare diseases (*13*). These programs aim to bridge gaps in care and ensure that patients with rare dermatological conditions receive timely and appropriate interventions.

While significant progress has been made in the therapeutic management of rare dermatological diseases in China, ongoing efforts are needed to address the remaining challenges. By utilizing emerging therapies, fostering collaboration, and prioritizing patient-centered care, the healthcare system can continue to improve outcomes and quality of life for this vulnerable patient population.

4. Healthcare and policy challenges in addressing rare dermatological diseases

4.1. Access to specialized care and medications

Access to specialized care and medications for rare dermatological diseases in China remains a significant challenge, influenced by factors such as regional disparities, limited healthcare infrastructure, and high costs. The NRDRS, established in 2016, has made strides in standardizing rare disease data collection and promoting research collaboration. This registry includes genomic biobanks and uses innovative informatics technologies to improve rare disease diagnosis and care (*9*). Despite these advances, regional disparities persist, with 60% of registered cases originating from wealthier regions, highlighting inequities in access to quality care (*3*).

The National Network to Collaborate on Diagnosis and Treatment of Rare Diseases, launched in 2019, includes 324 hospitals and aims to create a tiered healthcare alliance for rare diseases. This network focuses on improving collaboration and resource allocation, which is critical to addressing the needs of patients with rare dermatological conditions (*14*). However, physicians in China exhibit a low awareness of rare diseases, with only 5.3% moderately or well aware of those diseases. This lack of awareness underscores the need for improved education in medical schools and the establishment of an online information hub to enhance early diagnosis and treatment (*8*).

Genetic testing plays a pivotal role in diagnosing rare diseases and is performed at an overall rate of 76.0% across China. Regional differences are evident, with testing performed at the highest rate in the Eastern region (79.2%), followed by the Central (75.9%) and Western regions (71.9%). Pediatricians perform genetic testing at the highest rate (94.1%), while surgeons perform it at the lowest rate (58.3%). High costs remain a major concern for physicians, limiting the widespread use of genetic testing in rare disease diagnosis and treatment (*5*).

China's First List of Rare Diseases, established in 2018, includes 121 diseases, with 83 treatments available domestically and 50 covered by national medical insurance. However, challenges such as the lack of a clear definition and coding for rare diseases, difficulty in calculating their economic burden, and limited diagnostic

and rehabilitation services persist. Policy implementation varies across regions, and pilot programs in qualified areas are recommended before national rollout (*15*).

The amended Drug Administration Law of 2019 prioritizes the review and approval of new drugs for rare diseases and encourages domestic development of such drugs. This legal framework provides a basis for improving access to rare disease medications under the Healthy China strategy (*16*). Additionally, recommendations from the Multidisciplinary Expert Seminar on Healthcare Security for Rare Diseases in China emphasize the need for basic data collection and the creation of a healthcare security model tailored to rare diseases. Proposed measures include establishing a special zone for rare disease medical care and classifying healthcare security based on treatment responsiveness (*17*).

4.2. Economic burden on patients and healthcare systems

The economic burden associated with rare dermatological diseases in China is substantial, affecting both patients and the healthcare system. A study analyzing the economic burden of 23 rare diseases in Shanghai estimated mean direct medical costs at CNY 9,588 (USD 1,521) for inpatients and CNY 1,060 (USD 168) for outpatients. Factors influencing these costs include age, disease type, complications, and payment type (*18*). High-priced orphan medicinal products (OMPs) further exacerbate the financial strain. For instance, a projected budget of CNY 179 million was required for 98 rare disease patients in Chengdu in 2019, in the absence of reimbursement policies. Under six policy scenarios, the budget ranged from CNY 32 million to CNY 156 million, with annual projections for the next three years ranging from CNY 200 million to CNY 1.303 billion (*19*).

The lack of reimbursement policies for OMPs highlights the need for optimized strategies to alleviate the financial burden on patients. Healthcare policymakers are encouraged to integrate multi-source data and consider financial affordability when designing reimbursement systems (*19*). Additionally, rare disease patients face significant challenges, including delayed diagnosis (1.4 years on average), misdiagnosis, and financial burdens. Recommendations to address these issues include legislating orphan drug acts, expanding medical insurance coverage, and protecting education and employment rights for rare disease patients (*6*).

4.3. Policy gaps and recommendations for improvement

Policy gaps in addressing rare dermatological diseases in China are evident, despite ongoing efforts to improve healthcare for rare disease patients. In 2013, China launched its first pilot project focused on 20 representative rare diseases; in concert, it also established a national network of 100 medical facilities, developed clinical guidelines, and promoted molecular testing for rare genetic disorders (*11*). While this initiative laid the groundwork for rare disease healthcare, challenges such as missed or delayed diagnosis, lack of effective drugs, and high treatment costs persist (*20*).

China utilizes a combination of top-down strategies and bottom-up interventions to address rare diseases, with the government leading policy formulation and local authorities and NGOs complementing policy gaps. This approach may serve as a model for other developing countries in improving rare disease healthcare (*21*). However, the lack of a clear definition and coding for rare diseases complicates policy implementation and economic burden calculations (*15*). Recommendations include establishing orphan drug legislation, incentive mechanisms, and reimbursement systems to improve healthcare for rare disease patients (*20*).

China's first national list of rare diseases, released in 2018, aims to improve societal awareness, diagnosis, and treatment of rare diseases. This initiative also seeks to enhance rare disease management and promote international cooperation in drug research and policymaking (*1*). To address regional disparities in policy implementation, pilot programs in qualified regions are recommended before national rollout (*15*). Furthermore, the amended Drug Administration Law of 2019 provides a legal basis for prioritizing the review and approval of new drugs for rare diseases, encouraging domestic development of such drugs (*16*).

5. The role of research and collaboration

5.1. National and international collaborative efforts

Collaboration at both the national and international level has been a cornerstone in advancing rare dermatological disease research in China. The establishment of the NRDRS in 2016 marked a significant milestone in fostering collaboration among academic institutions and research entities. Over 20 top academic institutions in China are actively participating in the NRDRS, which aims to standardize registration platforms, build genomic biobanks, and create partnerships for sharing data and collaborating in research. This system not only facilitates the collection and sharing of data but also promotes long-term research collaboration, which is essential to translating research findings into clinical applications (*9*).

Internationally, China has increasingly emphasized global cooperation in rare disease research. A national program has been implemented to promote international partnerships, enabling the exchange of knowledge, resources, and expertise. Such collaborations are critical to addressing the unique challenges posed by rare dermatological diseases, which often require specialized knowledge and resources that may not be readily available within a single country. By engaging in international networks, China can capitalize on global

advances in rare disease research while contributing its own findings to the broader scientific community (*22*).

Despite these efforts, challenges remain in aligning national and international priorities, particularly in the context of rare dermatological diseases. The relatively lower number and diversity of clinical trials in China compared to developed countries underscore the need for enhanced international collaboration to bridge these gaps (*12*). Strengthening partnerships with global research entities and patient advocacy groups could further accelerate progress in this field.

5.2. Advancing genomic and epidemiological research

Genomic and epidemiological research plays a pivotal role in understanding the etiology and prevalence of rare dermatological diseases. Since the 1980s, China has made significant strides in rare disease research, with increasing national attention in recent years (*22*). The launch of the first pilot project for rare diseases in 2013 marked a critical step forward, focusing on 20 representative rare diseases and establishing a national network of approximately 100 provincial or municipal medical facilities. This network facilitates collaboration among clinicians, researchers, and patient organizations, aiming to improve healthcare delivery and develop medical guidelines for rare diseases (*11*).

The NRDRS has further advanced genomic research by incorporating innovative informatics technologies, such as ontological and knowledge bases, to support standardization and improve rare disease diagnoses. These technologies enable the integration of genomic data with clinical information, providing a comprehensive understanding of rare dermatological diseases. Additionally, the establishment of genomic biobanks under the NRDRS framework has created a valuable resource for conducting genetic association studies, which are essential for identifying disease-causing mutations and understanding disease mechanisms (*9*).

However, challenges persist in conducting genetic association studies, particularly in handling large volumes of data and identifying small individual effects. These limitations highlight the need for advanced computational tools and collaborative efforts to overcome technical and methodological barriers. Moreover, the field of rare disease epidemiology faces challenges in coding and classification, calculating disease frequency, and conducting comprehensive studies to inform policy decisions (*23*).

China's progress in clinical trials for rare diseases also reflects the growing emphasis on research. Over the past decade, 481 clinical trials have been conducted, with the number of applications growing at an average annual rate of 28.2% from 2013 to 2022 (*24-42*) (supplementary Table S1, *https://www.irdrjournal.com/action/getSupplementalData.php?ID=265*). This growth was significantly influenced by policy support introduced in 2016, which encouraged the development of clinical trials and molecular testing for rare genetic disorders. Despite these advances, the number and diversity of clinical trials in China remain lower than in developed countries, indicating the need for further investment in genomic and epidemiological research (*12*).

5.3 The need for rare disease registries and databases

The establishment of rare disease registries and databases is critical to advancing research and improving patient outcomes. The NRDRS, launched in 2016, serves as a centralized platform for the nationwide registration of rare diseases in China. By standardizing registration platforms and incorporating genomic biobanks, the NRDRS facilitates data sharing and research collaboration among academic institutions and healthcare personnel (*9*). This system both facilitates the collection of high-quality data and it enables the development of evidence-based policies and clinical guidelines for rare dermatological diseases.

The NRDRS also uses innovative informatics technologies to enhance the accuracy and efficiency of rare disease diagnosis. These technologies include ontological frameworks and knowledge bases, which standardize data collection and improve interoperability across different research and clinical settings (*9*). Such advances are particularly important for rare dermatological diseases, where accurate diagnosis and classification are often challenging due to the limited availability of clinical and genetic data.

Despite these achievements, the need for additional rare disease registries and databases remains evident. Expanding the scope of the NRDRS to include more rare dermatological diseases and integrating it with international databases could further enhance its utility. Long-term research collaboration is also encouraged to create additional national rare disease networks, which can facilitate the translation of research findings into clinical practice (*9*).

In addition to the NRDRS, the pilot project for rare diseases launched in 2013 also emphasized the importance of establishing a rare disease patient registry and data repository (*11*). These initiatives aim to provide a comprehensive understanding of the burden of rare diseases and support the development of targeted interventions. However, challenges such as data standardization, privacy concerns, and resource allocation must be addressed to maximize the impact of these registries and databases (*23*).

6. Public awareness and education

6.1. Improving awareness among healthcare personnel

The awareness of rare dermatological diseases among

healthcare personnel in China remains critically low, posing significant challenges to early diagnosis and effective treatment. A study revealed that only 5.3% of physicians in China were moderately or well aware of rare diseases, highlighting a substantial gap in knowledge. Moreover, the majority of physicians (80.1%) reported having suspected rare diseases in their patients fewer than three times throughout their careers, underscoring the limited exposure and diagnostic experience in this domain (*8*). This lack of awareness is particularly concerning given the complexity and rarity of these conditions, which often require specialized knowledge and diagnostic acumen.

Physicians working in Grade A tertiary hospitals demonstrated a slightly better understanding of rare diseases, particularly in terms of the affordability of orphan drugs, where they were rated higher compared to their counterparts in lower-tier medical facilities (*8*). This disparity suggests that healthcare personnel in higher-tier hospitals may have greater access to resources, training, and exposure to rare disease cases, which could account for their relatively higher level of awareness. However, this localized improvement does not address the broader systemic issue of insufficient knowledge among the majority of healthcare personnel across China.

Experts in the field have emphasized the critical importance of improving rare disease awareness among physicians to facilitate early diagnosis and timely treatment. Recommendations include integrating rare disease education into medical school curricula and providing continuing medical education (CME) programs focused on rare diseases. These measures aim to equip healthcare personnel with the necessary skills and knowledge to identify and manage rare dermatological conditions effectively. Additionally, the establishment of an online "information hub" has been proposed as a practical solution to disseminate rare disease-related information among physicians (*8*). Such a platform could serve as a centralized resource for clinical guidelines, case studies, and diagnostic tools, thereby enhancing the overall competency of healthcare personnel in managing rare diseases.

6.2. Community outreach and patient advocacy

Community outreach and patient advocacy have played a pivotal role in raising public awareness of rare diseases in China. Efforts by patient organizations and spontaneous campaigns by the public have significantly contributed to heightened awareness. These initiatives have brought attention to the challenges faced by individuals with rare dermatological diseases, including missed or delayed diagnoses, the shortage of effective drugs, and the high costs of available treatments (*13*). Despite these efforts, these challenges remain substantial barriers to improving the quality of life for affected individuals.

Patient organizations have emerged as key stakeholders in advocating for the needs of individuals with rare diseases. Their campaigns often focus on educating the public, lobbying for policy changes, and providing support to patients and their families. These organizations have also been instrumental in fostering collaborations with healthcare personnel and researchers, thereby creating a more inclusive ecosystem for addressing rare diseases. However, the impact of these efforts is often limited by resource constraints and the lack of a coordinated national strategy.

The experiences of other regions, such as the US, EU, and Japan, offer valuable insights for China in addressing rare diseases. Government-funded special biomedical research programs in these regions have successfully advanced the understanding and treatment of rare diseases (*13*). These programs could serve as a reference for China to develop similar initiatives, focusing on rare dermatological conditions. By drawing on international best practices, China can enhance its community outreach and patient advocacy efforts, ultimately improving outcomes for individuals with rare diseases.

6.3. Using media and technology to raise disease awareness

Media and technology have emerged as powerful tools for raising awareness about rare diseases, including rare dermatological conditions. In 2013, China launched its first pilot project focused on 20 representative rare diseases, aiming to improve the level of prevention, diagnosis, and treatment (*11*). This initiative underscores the potential of coordinated efforts to use media and technology to disseminate information and foster collaboration among stakeholders.

A key component of the pilot project was the establishment of a national network consisting of approximately 100 provincial or municipal medical facilities. This network facilitates collaboration among clinicians in basic medical facilities, rare disease patient organizations, and other stakeholders. By building close links within this collaborative network, the project aims to enhance the dissemination of knowledge and resources related to rare diseases. Additionally, the development of medical guidelines, clinical pathways, a rare disease patient registry, and a data repository system has been prioritized to support evidence-based practices and improve patient outcomes (*11*).

Promoting molecular testing for rare genetic disorders is another key focus of the project. Advances in molecular diagnostics have the potential to revolutionize the identification and management of rare dermatological diseases, enabling more precise and timely interventions. Media campaigns and digital platforms can play a crucial role in educating both healthcare personnel and the public about the benefits of molecular testing, thereby encouraging its use.

The integration of media and technology into rare disease awareness strategies aligns with global trends in healthcare communication. Digital platforms, social media, and mobile phone apps offer innovative avenues for disseminating information, engaging stakeholders, and fostering community support. By using these tools, China can enhance its efforts to raise awareness about rare dermatological diseases, ultimately contributing to improved prevention, diagnosis, and treatment outcomes (*43-50*).

7. Conclusion

In conclusion, rare dermatological diseases in China pose challenges including fragmented data, regional disparities (*e.g.*, 60% cases in the East/North), diagnostic delays (1.4 years), and limited physician awareness (5.3%). While advances like the NRDRS (62,590 cases) and clinical trials (28.2% annual increase) have made progress, equitable policy implementation, enhanced collaboration, and patient-centered care remain critical to improving outcomes.

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**Address correspondence to:*
Peipei Song, Center for Clinical Sciences, Japan Institute for Health Security. 1-21-1, Toyama, Shinjuku-ku, Tokyo 162-8655, Japan.
E-mail: psong@jihs.go.jp

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