

# Innovative measures to combat rare diseases in China: The national rare diseases registry system, larger-scale clinical cohort studies, and studies in combination with precision medicine research

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## Summary

China is facing the great challenge of treating the world's largest rare disease population, an estimated 16 million patients with rare diseases. One effort offering promise has been a pilot national project that was launched in 2013 and that focused on 20 representative rare diseases. Another government-supported special research program on rare diseases – the "Rare Diseases Clinical Cohort Study" – was launched in December 2016. According to the plan for this research project, the unified National Rare Diseases Registry System of China will be established as of 2020, and a large-scale cohort study will be conducted from 2016 to 2020. The project plans to develop 109 technical standards, to establish and improve 2 national databases of rare diseases – a multi-center clinical database and a biological sample library, and to conduct studies on more than 50,000 registered cases of 50 different rare diseases. More importantly, this study will be combined with the concept of precision medicine. Chinese population-specific basic information on rare diseases, clinical information, and genomic information will be integrated to create a comprehensive predictive model with a follow-up database system and a model to evaluate prognosis. This will provide the evidence for accurate classification, diagnosis, treatment, and estimation of prognosis for rare diseases in China. Numerous challenges including data standardization, protecting patient privacy, big data processing, and interpretation of genetic information still need to be overcome, but research prospects offer great promise.

**Keywords:** Rare diseases, registry system, precision medicine, big data, predictive model, diagnosis and treatment

## 1. Introduction

Rare diseases are a major public health issue and a challenge to medical care (1). The World Health Organization (WHO) defines a disease as a rare disease when its incidence ranges approximately from 0.65-1‰ in the entire population. In different countries, standards for classification as a rare disease vary based

on specific legislation, such as that in the United States of America (USA), Japan, Australia, the European Union (EU), and South Korea (2,3). In China, a rare disease has yet to be officially defined due to a lag in legislation. A consensus on the definition of a rare disease is emerging in accordance with the Expert Seminar on the Definition of Rare Diseases in China that was held in 2010. The Seminar proposed that a disease be classified as a rare disease if it is prevalent in fewer than 1/500,000 or it has a neonatal morbidity of fewer than 1/10,000 (4). Although each specific disease affects a limited number of patients because of its rarity, the total number of patients with rare diseases represents a striking proportion of the total population because there are estimated 5,000-7,000 distinct rare diseases worldwide (5). There are an estimated 16 million patients with rare diseases in China (6).

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Government-supported special research programs and information platforms are a key measure to combat rare diseases. These programs should be implemented and these platforms should be established to promote the development of rare diseases research and to improve the quality of care for patients with those diseases (7,8). Many countries and regions around the world have developed national strategies regarding rare diseases research. For example, the Office of Rare Diseases Research (ORDR) was established in the USA in 1993 within the National Institutes of Health (NIH) to coordinate and support rare disease research, explore opportunities to research rare diseases, and provide information on rare diseases. In the EU, the Rare Disease Task Force (RDTF) was established in 2004 within the European Commission Public Health Directorate to provide evidence to support policymaking, provide medical services, and provide community support for rare diseases and orphan drugs through coordination among member states. In Japan, measures to combat rare diseases have been part of the Japanese national health system for decades (9,10). Within this national framework, multifaceted research on rare diseases, including epidemiological studies, basic research, clinical research, and applied research, has been conducted. As of 2014, epidemiological data have been collected on 925,646 patients with rare diseases. As of 2015, 98 standardized guides for diagnosis (75.38%) and 72 standardized guides for treatment (55.38%) of 130 rare diseases have been issued. In addition, 121 hospitals have been certified as centers for treatment of rare diseases and 1,456 hospitals have been certified as hospitals collaborating in the treatment of rare diseases (8).

China is facing the great challenge of treating the world's largest rare disease population. However, China has a weak overall capacity for clinical diagnosis and treatment due to the long-standing lack of investment in rare diseases research and imbalances in research resources. To deal with these circumstances, China launched a pilot national project in 2013 that focused on 20 representative rare diseases to promote improved levels of care for rare diseases. To implement this project, a national collaborate network involving more than 100 provincial and municipal medical centers was established by the China Rare Diseases Prevention and Treatment Alliance (11).

On December 2016, another government-supported special research program on rare diseases – the "Rare Diseases Clinical Cohort Study" – was launched in China (12). In combination with precision medicine research, this study will establish the unified National Rare Diseases Registry System of China as of 2020 and it will conduct a large-scale cohort study to provide the evidence for accurate classification, diagnosis, treatment, and estimation of prognosis for rare diseases in China.

## **2. The unified national rare diseases registry system of China and larger-scale clinical cohort studies**

The characteristics of rare diseases have not been fully investigated until now because few patients were affected and those that were affected were widely scattered. The accumulation of knowledge of rare diseases takes time, so the development of scientific research and technology to diagnose and treat those diseases lags behind that of other more common diseases. Registering cases of rare diseases can effectively solve this problem. Scattered rare disease resources are collected together for clinicians and researchers to better conduct research and treat rare diseases, and this can also greatly promote the development of orphan drugs by pharmaceutical companies.

In addition, current studies on clinical manifestations in patients with rare diseases are often based on a large number of case reports, but the system to conduct such studies is poorly structured and inconsistent. Obtaining reliable epidemiological data is extremely difficult. Large cohort studies and case registration are one of the best solutions to the aforementioned problems. Several large cohort studies of rare diseases have been conducted and registries of rare diseases have been established around the world (13-16). These efforts provide a vital platform for the development of rare diseases, the evaluation of adverse reactions and the effectiveness of interventions, the compilation of basic epidemiological data and health economic parameters, the development of drug targets, and the provision of clinical trial support. These efforts effectively improve the level of diagnosis and treatment of rare diseases and the development of scientific research.

In China, the "Rare Diseases Clinical Cohort Study" is a joint program implemented by the Peking Union Medical College Hospital and the country's 19 major rare disease research facilities. According to the plan for this research project, the unified National Rare Diseases Registry System of China will be established as of 2020, and a large-scale cohort study will be conducted from 2016 to 2020. The project plans to develop 109 technical standards, to establish and improve 2 national databases of rare diseases – a multi-center clinical database and a biological sample library, and to conduct studies on more than 50,000 registered cases of 50 different rare diseases (17). On the basis of that large-scale cohort study, the natural course of disease can be ascertained, prognosis can be estimated, treatment response can be determined, and costs can be assessed. This will greatly provide an important scientific basis for the promotion of rare diseases research and policies related to rare diseases.

The "Rare Diseases Clinical Cohort Study" will be conducted based on the existing rare diseases collaboration network and it will continue to register cases, establish cohorts, and follow-up on the course

of clinical diagnosis and treatment services. Four categories of diseases have been initially selected: rare diseases of the heart, lungs and kidneys, rare diseases of the endocrine and metabolic systems and the blood, rare diseases of the skeleton and skin, and rare diseases in children (12).

### 3. Rare diseases research in combination with precision medicine

Eighty percent of rare diseases have identified genetic origins, 50% of rare diseases affect children, and 30% of patients with rare diseases die before the age of 5 (18). The delay in diagnosis is a huge challenge to overcome. A survey of 18,000 individuals found that 25% of patients waited for 5-30 years before being correctly diagnosed and 40% of patients were diagnosed incorrectly before being diagnosed correctly (19).

With current advances in technology, the diagnosis of rare diseases depends more on the combination of clinical and omics information and the classification of diseases with a consistent clinical phenotype. Precision medicine is a medical model that takes into account the individual differences in genetics, environment, and lifestyle in order to achieve the most effective individualized diagnosis and treatment of diseases (20). The main breakthrough lies in the collection of large amounts of clinical data and proteomic data, extraction and standardization of phenotypic data, data compilation and phenotypic data grouping, the depth of data analysis, and the integration of corresponding life sciences data.

Rare diseases research has been plagued by a small sample size, scattered patients, a lack of follow-up, a lack of data, and other factors. Precision medicine will provide support for rare diseases research. In combination with innovative methods of diagnosing clinical phenotypes and groups, early diagnosis of and intervention in some rare diseases can be achieved to improve prognosis. In addition, the use of the core concept of precision medicine and the full examination of the genome, affected groups, microbial environments, living habits, and other forms of information (21) will help enhance the level of individual treatment for patients with rare diseases.

In China, the "Rare Diseases Clinical Cohort Study" will be combined with the concept of precision medicine. Based on the clinical cohort study data and use of the sample database, information on clinical diagnosis and treatment will be integrated to fully analyze the correlation between clinical phenotypes and genotype. The study will use individual information to create a comprehensive predictive model with a follow-up database system and a model to evaluate prognosis (12). This will provide the evidence for accurate classification, diagnosis, treatment, and estimation of prognosis for rare diseases in China.

In research on rare diseases of the heart and lungs, gene mutations will be detected and that information will be integrated with clinical information from patients in order to create a digital model of clinical phenotypes and a model to evaluate genotype. In research on rare diseases of the endocrine and metabolic systems, the genetic and molecular characteristics of those diseases will be analyzed. The generation sequencing technology and functional test platforms for genomics will be used to identify new pathogenic genes. In research on rare diseases of the blood, the genome of biological samples will be analyzed, and the diagnosis and treatment (including molecular typing) will be standardized along with molecular diagnosis of rare diseases in children and prenatal diagnosis to facilitate prenatal diagnosis and guidance during pregnancy (17).

### 4. Challenges to the promotion of rare diseases research in China

Compared to other countries, China has vast research resources and the largest rare disease population. However, most of the current studies on rare diseases in China are conducted by researchers at single or multiple centers. Research resources are scattered, research capacity is weak, and information is seldom exchanged or shared, so resource advantages do not translate into scientific advantages. With the launch of the "Rare Diseases Clinical Cohort Study," a unified National Rare Diseases Registry System should be established. However, many challenges need to be overcome in order to establish a unified national registry system.

*Data standardization* The establishment of a unified registry system first requires the development of unified standards, and especially data transmission standards, terminology and ontology, and research protocols (22). The level of diagnosis and treatment at domestic hospitals in China varies more widely than that in other countries, resulting in substantial problems with inconsistent, non-standard diagnosis and treatment. Therefore, the establishment and maintenance of standards for registry systems is a major challenge.

*Protection of patient privacy* Data on rare diseases involves safeguarding patient privacy. However, standards for patient privacy protection are lacking in China, leading to ethical problems with rare diseases research. Independent research facilities need to accurately record patient information, so protecting patient privacy is a major issue (23). The security of network platforms needs to be enhanced and personal data needs to be protected to study rare diseases in China.

*Big data processing* Large-scale cohort studies will yield large amounts of various types of data that need to be processed with scalable, high-throughput systems (24). Once data are collected, medical informatics tools need to be used for further precise analysis. Therefore,

research on rare diseases requires medical knowledge as well as technical assistance from medical informatics. The processing of big data from large-scale cohort studies is a challenge that needs to be overcome.

*Interpretation of genetic information* With a decline in the cost of generation sequencing technology and analysis, the gene sequencing technology are being widely used in genetic disease research and clinical testing. In the genetic diagnosis of disease, clinicians are generally concerned about the problem of what type of genetic testing is suitable for patients with a given clinical phenotype. In addition, the results of genetic testing will directly guide clinical treatment for patients with rare diseases. However, many organizations are detecting genes, and currently there are no uniform protocols and standards for sequencing and analysis. When clinicians receive the results of sequencing, how they should judge the quality of those results and how they should interpret the genetic information depicted by those results is also a challenge.

In light of the challenges mentioned, relevant solutions have put forward in a report on the "Rare Diseases Clinical Cohort Study" (25) and those solutions have been interpreted by representative experts (17). Solutions include: *i*) establishing 109 technical standards to ensure the accuracy of data; *ii*) formulation of a strategy for safe data storage by separating keys and encrypted data; *iii*) developing software for a network platform to register rare diseases to provide advanced data storage and a computing architecture; and *iv*) promoting the training of medical personnel and medical informaticians. However, compared to the proposed research plan, the effect of its implementation is more worthy of attention and expectations.

## 5. Conclusion

Efforts related to rare diseases research that offer promise are government-supported special research programs and information platforms in China. These programs are being implemented and these platforms are being established to promote the development of rare diseases research and to improve the quality of care for patients with those diseases. According to the plan for the "Rare Diseases Clinical Cohort Study" launched in 2016, the unified National Rare Diseases Registry System of China will be established as of 2020. In combination with precision medicine research, the large-scale cohort study will collect and analyze Chinese population-specific information on rare diseases. This will provide the evidence for accurate classification, diagnosis, treatment, and estimation of prognosis for rare diseases in China.

China is facing the great challenge of treating the world's largest rare disease population. More government-supported special research programs should be implemented and information platforms should be

established in China to promote the development of rare disease research and to effectively improve the level of diagnosis and treatment for patients with rare diseases.

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