

The definition of rare disease in China and its prospects

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SUMMARY The latest definition of rare disease in China was released on September 11, 2021 at the third multidisciplinary expert seminar on the definition of rare diseases/orphan drugs in China. A rare disease is defined as a condition satisfying at least one of the following three criteria: an incidence among newborns of less than 1/10,000, a prevalence of less than 1/10,000, and an affected population of less than 140,000. Before this new definition, rare diseases were defined by different agencies with different parameters in China. The 2021 definition is a milestone, it could further spur the development of rare diseases beyond *China's First List of Rare Disease* in May 2018. This definition also provides a reference for the total number of rare diseases in China.

Keywords Rare disease, definition, China, incidence, prevalence, *China's First List of Rare Disease*

The latest definition of rare diseases in China was released on September 11, 2021, as suggested at the third multidisciplinary expert seminar on the definition of rare diseases/orphan drugs in China. A rare disease is defined as a condition with an incidence of less than 1/10,000 among newborns, a prevalence of less than 1/10,000, or an affected population of less than 140,000 (1). The definition refers to the number of patients with a given rare disease since it is difficult to determine the incidence and prevalence of some rare diseases and emerging diseases is difficult. The number 140,000 was calculated based on the China's total population of 1.4 billion multiplied by a prevalence of 1/10,000 (1).

A number of years before the new definition was issued, the National Health Commission, the Ministry of Science and Technology, the Ministry of Industry and Information Technology, the National Medical Products Administration, and the National Administration of Traditional Chinese Medicine issued *China's First List of Rare Disease* in May 2018. This marks China as the world's first country to use a list to classify rare diseases (2).

In 2010, the Medical Genetics Branch of Chinese Medical Association suggested that a rare disease be defined as one with a prevalence of less than 1 in 500,000 or a neonatal incidence of less than 1 in 10,000. From the point of view of orphan drugs, 300,000 - 500,000 patients was suggested as the threshold for a rare disease (3). In 1980s, rare diseases were termed rare and uncommon diseases by Chinese scholars Gui Lin and Chenglin Wang. Wang suggested that the term rare

and uncommon disease is a relative concept. From the perspective of dialectics, rare is related to uncommon, and uncommon is related to common diseases (4). Rare and uncommon diseases were recorded as a medical record index as early as in 1990 in China (5).

According to the definition of rare diseases that was updated in 2021, 12 rare diseases should be removed from the first list of rare diseases, including cardiac ion channelopathies, Charcot-Marie-Tooth Disease, congenital scoliosis, coronary artery ectasia, familial Mediterranean fever, Marfan syndrome, myotonic dystrophy, non-syndromic deafness, Noonan syndrome, primary hereditary dystonia, progressive muscular dystrophy, and retinitis pigmentosa (1). As the registration of patients with rare diseases and the epidemiological study of those diseases advance, the population of patients with hemophilia and idiopathic pulmonary arterial hypertension has grown larger than most of the patients with rare diseases on the list (6-8). Hence, revision of the *China's First List of Rare Disease* should be considered in accordance with the new 2021 definition of rare diseases and epidemiological data. The national rare disease list and the definition of rare diseases will co-exist and complement each other for some time in China due to a lack of epidemiological data for most rare diseases.

The incidence of rare diseases in newborns is used as a criterion in China but not in other countries. Approximately 80% of rare diseases are genetic diseases caused by specific pathogenic genes. Data from newborns is useful in tallying the number of patients

with rare diseases and helps with clinical diagnosis and treatment in a disease's early stage. Since some rare diseases occur in children (*e.g.*, pediatric lupus nephritis and children's interstitial lung disease), others occur in both children and adulthood (*e.g.*, central hypoventilation syndrome), and others occur only in adulthood (*e.g.*, Huntington-chorea and Gaucher-disease), there will be some discrepancies in incidence/prevalence between a disease's actual rate and its rate according to the definition.

The Chinese population has aged and the birthrate has declined, so the definition of rare diseases should be a dynamic concept. Some influencing factors, environmental factors, and models should be considered when tallying rare diseases. Modeling is one of the main criteria for evaluation of rare diseases, and especially for those lacking a nationwide registry and epidemiological data.

There is no standard definition of rare diseases, it is affected by many factors, such as medical status, the level of social security, social and economic development, and human cognition of disease. The criteria for defining rare diseases differ in various countries or regions, including the total population affected, prevalence, and the severity of the disease (9-11). The definition of rare diseases is a key factor to determining the number of rare diseases. The terminology used to define rare diseases is another essential aspect of rare diseases figures that China should take into account. Whether rare infectious diseases, trauma, cancer, or other conditions that are caused by environmental factors, such as PM2.5 pollutants, should be included or excluded as rare diseases will definitely affect the total number of rare diseases. For example, hepatitis E infection would be classified as a rare disease due to its low prevalence (12), but hepatitis B, C, and D would not under current definition of rare diseases in China. The definition of rare diseases will help China to expand research on rare diseases, raise the level of medical technology, and meet the healthcare needs of society as a whole. The new 2021 definition of rare diseases represents just the tip of the rare disease iceberg.

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