REVIEW

WILEY

Current situation and prospect for the diagnosis and treatment of pediatric critical rare diseases in China

Yingchao Liu | Suyun Qian

Pediatric Intensive Care Unit, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, China

Correspondence
Suyun Qian, Pediatric Intensive Care Unit, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing 100045, China.
Email: syqian2020@163.com

Funding source
National Key Clinical Specialty Construction Project, Grant/Award Number: 2021-451; Beijing Major Epidemic Prevention and Control Key Specialty Outstanding Project, Grant/Award Number: 2021-135

Received: 28 December 2023
Accepted: 16 January 2024

ABSTRACT
The onset of critical rare diseases (RDs) in children is rapid and dangerous, accompanied by a high mortality rate, which brings a heavy burden to both families and society. Multiple malformations, neuromuscular diseases, metabolic diseases, and heart diseases are the most common types of RDs in children of China, often manifesting with multiple organ dysfunction. At present, the diagnosis and treatment of critical RDs in children face challenges such as prolonged diagnosis time, a high misdiagnosis rate, limited treatment modalities, and a significant disease burden. However, with the progress in genetic testing technology, the establishment of multidisciplinary diagnosis and treatment platforms, and the implementation of relevant RD policies in China, children with critical RDs will received enhanced medical services, experience improved prognoses, and reintegrate into social life.

KEYWORDS
Children, Critical, Current situation, Prospect, Rare diseases

INTRODUCTION

Contrary to common diseases, rare diseases (RDs) refer to a large category of diseases with a relatively low prevalence rate. Countries/organizations have different definitions of RDs given their distinct national conditions.[1–6] Although the number of patients with RDs seems rare, it is not rare because of the diversity of diseases. Orphadata, which extracts data sets from Orphanet, revealed that there are more than 10 000 known RDs worldwide (https://www.orphadata.com/), accounting for approximately 10% of human diseases, and the number of individuals with RDs is approximately 473 million.[7,8] In China, more than 20 million individuals are estimated to be affected by various RDs. The estimated prevalence rate of RDs has been increasing, with an average annual growth rate of 19.46%.[9]

RDs have received relatively insufficient attention because of their particularity. However, with the continuous improvement of economic levels and social development, social awareness of RDs has been increasing. In May 2010, the concept of RDs in China was first defined during the Expert Seminar on the Definition of RDs in China.[5] Over the following 10 years, China has successively released key initiatives such as the First Batch of RDs,[6] the Diagnosis and Treatment Guideline for RDs (2019 Edition),[10] and the

DOI: 10.1002/ped4.12419

Second Batch of RDs[11] and established a national cooperative network for the diagnosis and treatment of RDs. Thus, the diagnosis and treatment system for RDs is gradually improving. This article mainly discusses the characteristics and current status of the diagnosis and treatment of pediatric critical RDs and explores its prospect in the future, in the hope to provide valuable reference for the management of pediatric critical RDs in China.

CHARACTERISTICS OF PEDIATRIC CRITICAL RDs

Approximately 80% of RDs have a genetic origin, contributing to a high incidence of these diseases in children. According to the First Batch of RDs, among 121 RDs, pediatrics is the leading department for 49 diseases.[6] Shi et al.[12] analyzed the status of 121 RDs on the basis of more than 15 million hospitalized cases in China and found that the age group of 0–14 years accounted for 28.6% of all cases. These studies indicated the importance of children in the group of patients with RDs in China.

Children with RDs often present with an acute onset and a critical condition. They are often directly admitted to the neonatal intensive care unit/pediatric intensive care unit (PICU) for treatment because of sudden cardiac arrest, shock, respiratory failure, status epilepticus, and changes in their state of consciousness.[13,14] The most common critical RDs in children are multiple malformations, neuromuscular diseases, metabolic diseases, and cardiac diseases.[15,16] Children with neuromuscular disease primarily manifest muscular hypotonia, status epilepticus, ventilator dependence with inability to be weaned, general developmental delay, motor delay, and so on. Children with metabolic diseases usually start with a metabolic crisis, which may present as hypoglycemia, metabolic acidosis, diabetes ketoacidosis, hyperammonemia, or other abnormalities of specific indicators. Children with rare heart-related diseases often experience cardiac arrest, dilated cardiomyopathy, pulmonary artery stenosis, or arrhythmia. Children with multiple malformations may present simultaneous multiple system abnormalities. A study from the Beijing Children's Hospital has shown that phenotypes can guide the diagnosis of RDs.[15] In the PICU, patients with the phenotype of metabolism/homeostasis disorder, growth delay, or ocular anomalies demonstrated a significantly higher diagnosis yield than those without these phenotypes.

Children with critical RDs often have concurrent multiple organ dysfunction. Sanford et al.[13] reported that more than 50% of children with critical RDs need to consult more than five experts from relevant disciplines after admission. Liu et al.[15] found that 83.7% of critically ill children with RDs need to receive antibiotic treatment after hospitalization, 79.0% need to receive mechanical ventilation, and almost 50% need endotracheal intubation.

Children with critical RDs not only experience prolonged hospitalization time and a high readmission rate, but also a high mortality rate.[17,18] Stevenson and Carey[19] reported that malformations and genetic disorders accounted for 63.9% of newborn deaths, 51% of infant deaths, and 34.4% of children over 1-year old deaths. Huang[20] reported that, from 2005 to 2014, 21.37% of children died of congenital malformations in the PICU of the Children's Hospital of Chongqing Medical University of China. Congenital malformations ranked first among all causes of death. Therefore, strengthening clinicians' understanding of RDs in children, especially infants, can facilitate early diagnosis and treatment. This will improve survival rates, enhance prognoses, reduce the financial burden of families and society, and, finally, improve the quality of population.

DIAGNOSIS AND TREATMENT STATUS OF CRITICAL RDs IN CHILDREN

Long diagnosis time and high misdiagnosis rate

Timely diagnosis is a great challenge for individuals with RDs. A study has shown that up to 50% of children with RDs have never been diagnosed.[21] A cross-sectional study on the misdiagnosis of RDs in China, involving 2040 patients with RDs, showed that the diagnosis time was 2.26 $\pm$ 4.81 years, and more than two thirds of patients with RDs were misdiagnosed.[22] Delayed diagnosis would delay the start of targeted treatment, leading to serious, irreversible, and life-threatening consequences. In the process of seeking diagnosis, patients often visit many hospitals for multiple examinations and receive various incorrect diagnoses. Such activity can lead to ineffective and even harmful treatments, resulting in physical and mental burdens to patients and their families.

The misdiagnosis may be affected by various factors. First, as the name implies, RDs are rare or even never have been observed in clinical practice. Most doctors lack relevant medical knowledge and the ability to correctly identify RDs in time.[23,24] Second, most RDs, especially genetic ones, exhibit genetic and phenotypic heterogeneity, and some present with atypical early clinical manifestations. Thus, doctors are often unable to make accurate diagnoses promptly. Additionally, at present, most RDs are diagnosed mainly through gene detection, which is expensive, and not all hospitals have the testing conditions. Therefore, these factors collectively contribute to a difficult situation characterized by a high misdiagnosis and missed diagnosis rate, prolonged diagnostic turnaround time, and even incorrect treatment of patients with RDs.

Limited treatment

Due to the low incidence rate and wide variety of RDs, the research and development of drugs for RDs are difficult and costly. He et al.[25] reported that less than 10% of RDs had approved treatment drugs or approaches, such as enzyme replacement therapy (e.g., agalsidase α/β) for Fabry disease, gene therapy (e.g., nusinersen) for treating spinal muscular atrophy, targeted treatment (e.g., burosumab) for X-linked hypophosphatemic rickets, as well as diet therapy and surgical treatment. In addition, achieving early prevention and early treatment is crucial for most children with RDs. This involves evaluating the affected system and initiating regular disease monitoring after diagnosis to improve symptoms and ensure long-term survival.

Heavy economic burden of disease

A study in the United States showed that 16% of all pediatric hospitalization expenses in South Carolina (28% for infants) and 28% of all pediatric hospitalization expenses in California (51% for infants) were related to birth defects and genetic diseases.[26] Given the low incidence of RDs and the high cost of drug research and development, the medical cost of patients with RDs is expensive. According to EvaluatePharma's Orphan Drug Report 2018, the mean cost per patient per year was 4.8 times greater for orphan drugs than for nonorphan drugs.[27] For example, Fabry disease is an X-linked lysosomal storage disorder caused by mutations in the *GLA* gene, resulting in deficient α-galactosidase A activity. This enzyme deficiency leads to the accumulation of metabolic substrates in the kidneys, nerves, heart, skin, and other organs, resulting in multiorgan damage.[28] Agalsidase α is the specific drug for Fabry disease. The recommended dose for children is 0.2 $mg \cdot kg^{-1}$ once every other week, and the annual treatment cost is approximately 161 200 RMB (if the weight is 35 kg). Another drug, agalsidase β, is recommended for children at a dose of 1 $mg \cdot kg^{-1}$ once every other week, with an annual treatment cost of approximately 884 000 RMB (if the weight is 35 kg). Moreover, children with critical RDs may also need comprehensive treatment, such as respiratory support and renal replacement therapy, leading to higher medical costs. However, the national medical security system for RDs in China is not yet sound, and patients with RDs and their families still bear a heavy burden of the disease.

PROSPECTS OF CRITICAL RDs IN CHILDREN

Early diagnosis and treatment of children with critical RDs has become feasible with the development of genetic testing technology

According to the Orphanet database, approximately 80% of RDs are caused by genetic factors.[29] With the rapid development of gene detection technology and the intensive research on medical genetics, the diagnosis yield of RDs has greatly improved. In particular, the advent of whole exome sequencing (WES) provides a new strategy for diagnosing genetic disorders. Numerous studies have shown that WES has a unique value in the diagnosis of critical genetic RDs in children. Through WES, 25.6%–52.5% of critically ill children suspected of having genetic RDs can be definitively diagnosed. This not only changes the clinical management of diagnosed patients but also reduces mortality and hospitalization costs.[15,16,30–33] However, for critically ill children with RDs in the intensive care unit, early diagnosis and early treatment can be achieved only if the WES test results are obtained as soon as possible, thereby reducing mortality and unnecessary examinations and minimizing the anxiety of the children's families. In recent years, several research teams have committed to rapid WES for the diagnosis of critical genetic diseases in children. Wang et al.[34] from the Children's Hospital of Fudan University, Shanghai, China, performed rapid trio-WES on 33 critically ill children from the neonatal intensive care unit/PICU. The median turnaround time was 24 h, significantly shorter than that of regular trio-WES detection, and 23 patients got a definite diagnosis. In addition, the development of the new nanopore sequencing technology and artificial intelligence is conducive to improving the efficiency and accuracy of diagnosing RDs.[35–37] However, clinicians should determine under what circumstance to use which type of WES and collaborate with geneticists to explain in detail to families the implications, risks, and limitations of WES results. This is essential to avoid overusing WES, which could impose an unnecessary financial burden on patients.

A comprehensive diagnosis and treatment platform for children with critical RDs has been established using a multidisciplinary team

Most of the rare critical diseases in children involve multiple organs or systems, leading to diverse symptoms and complex phenotype. The symptoms and signs of each child with RDs often involve multiple clinical subspecialties. A multidisciplinary team (MDT) refers to the consultation and discussion involving more than two disciplines for a single patient. The MDT focuses on the difficult problems in disease diagnosis and treatment and finally formulates a reasonable and executable clinical diagnosis and treatment plan. It aims to provide patients with reasonable, effective, and convenient medical services to the greatest extent.[38] In 2021, a tertiary children's hospital in Shanghai launched a 1-year MDT screening project for pediatric Fabry disease.[39] The screening team, comprising a nephrologist, neurologist, rheumatologist, cardiologist, gastroenterologist, dermatologist, ophthalmologist, neonatologist, psychologist, otologist, pathologist, and geneticist,

was formed throughout the hospital to screen children with high-risk profiles of Fabry disease, such as an episodic crisis of burning in the hands or feet, unexplained chronic kidney disease, unexplained hypertrophic myocardiopathy, or heart failure. Thirty-five children with high-risk profiles were referred for screening, with a diagnosis rate of 14.3% (5/35). Prior to this screening, no case of Fabry disease had been diagnosed in the hospital. The MDT at Beijing Children's Hospital has also played an important role in the diagnosis and treatment of difficult RDs. Established more than 2 years ago, the MDT has attended to 237 patients, of which 50% we definitely diagnosed and timely treated after consultation, which led to an improved prognosis for these patients.

MDT cannot only improve the rate of diagnosing RDs but also the development of individualized treatment or family management strategies for children with identified RDs. The relevant specialist clinicians would make diagnosis and treatment plans, including drug treatment, surgical correction, stem cell transplantation, and gene therapy. The nutritionist would develop a special diet recipe. Geneticists could also provide the families with fertility guidance. The psychological state of children with RDs and their families should also be given attention. Psychological counseling provided by social workers may help relieve their nervous and anxious mental states. With the involvement of MDT, some hospitals in China have built a one-stop, comprehensive diagnosis and treatment platform for children with RDs, thus improving the prognosis of patients.

The future of children with critical RDs is promising because of policy support

In recent years, the Chinese government has continuously improved the policy support system for RDs. Since 1999, a number of incentive policies for RD drugs have been issued to promote the research and development of innovative drugs for RDs and to require regulators to hasten the approval process on the premise of ensuring the safety and effectiveness of drugs. Notably, a total of 207 drugs included in China's first and second list of RDs have been available within the Chinese market, effectively addressing 88 different RDs.[40,41] With the release of the implementation plan of *Hainan Boao Lecheng International Medical Tourism Pilot Zone*, this strategy supports top medical domestic institutions to establish clinical trial institutions, perform multicenter clinical trials, and even conditionally allow individuals to take imported drugs with reasonable doses out of the pilot zone for use. These measures not only effectively solve the dilemma of patients with RDs at this stage but also pave the way for China to develop orphan drugs by itself. At the same time, the gap with developed countries, such as European countries and the United States, should also be recognized. Further acceleration of independent drug research and development is needed to bring hope for the treatment of more children with RDs.

In terms of medical resources, the diagnosis of RDs is related to the level of hospitals and the education level of doctors. A survey on the diagnosis and treatment of RDs among clinicians in Tangshan, Hebei Province, showed that the probability of clinicians in tertiary hospitals treating patients with RDs was approximately 2.5 times that of secondary hospitals. With enhanced educational level, technical titles, and years of medical practice, the probability of clinicians treating patients with RDs increased by 67.8%, 19.0%, and 14.9%, respectively.[42] Another survey has shown that 25% of patients with RDs need to go to another region to be diagnosed.[43] These results show that the balanced development of medical resources is particularly important to improve the ability to diagnose and treat RDs. In 2019, the National Health Commission of the People's Republic of China issued the Notice of the General Office of the National Health Commission on the Establishment of a National Collaborative Network for the Diagnosis and Treatment of RDs, which arranged for the diagnosis and treatment of RDs at the national level.[44] With the increasing number of specialized children's hospitals and pediatricians, the establishment and improvement of genetic diagnosis and treatment systems, the development of national and regional medical center network, and the systematic advancement of RD pediatrician training, high-quality pediatric medical resources will continue to expand to meet the diagnosis and treatment needs of patients with RDs in different regions.

In terms of medical insurance, the number of drugs for RDs that can be covered by the national medical insurance has been increasing in China. Recently, 97 drugs included in China's first and second list of RDs have been encompassed within the medical insurance framework and earmarked for RD treatment, contributing to coverage for 52 RDs.[40,41] From the state to the local level, medical guarantees for patients with RDs are provided through various schemes, such as serious disease insurance, medical assistance, special financial services, commercial insurance, and charity assistance, and gradually integrated into the 2030 Healthy China process.[45]

In conclusion, children constitute a significant group of RDs, with a high proportion experiencing critical illnesses. Some challenges persist in the diagnosis and treatment of RDs in China. Nevertheless, with the development of genomics, the continuous improvement of national policies on RD drug research and development, medical security, professional training of RD clinicians, and the development of pediatric critical care medicine, more and more children with critical RDs will be cured, and their future is promising.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

REFERENCES

1. Public law 107-280-Nov.6, 2022. Rare Disease Act 2002. Accessed December 1, 2023. https://www.congress.gov/107/plaws/publ280/PLAW-107publ280.pdf
2. Official Journal of the European Communities. Regulation (EC) No. 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products. Accessed December 1, 2023. https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32000R0141
3. Song P, Gao J, Inagaki Y, Kokudo N, Tang W. Rare diseases, orphan drugs, and their regulation in Asia: current status and future perspectives. *Intractable Rare Dis Res.* 2012;1:3-9. DOI: 10.5582/irdr.2012.v1.1.3
4. The Ministry of Health and Welfare of Taiwan. Rare Disease Control and Orphan Drug Act. Accessed December 1, 2023. http://law.moj.gov.tw/LawClass/LawAll.aspx?PCode=L0030003
5. Li D, Wang L, Xu X. The revision of the definition of rare diseases in China from the perspective of clinical epidemiology (in Chinese). *J Clin Pediatr.* 2021;39:561-564. DOI: 10.3969/j.issn.1000-3606.2021.08.001
6. National Health Commission of the People's Republic of China. Notice on publishing the first batch of rare diseases. Accessed December 1, 2023. http://www.nhc.gov.cn/yzygj/s7659/201806/393a9a37f39c4b458d6e830f40a4bb99.shtml
7. Ferreira CR. The burden of rare diseases. *Am J Med Genet A.* 2019;179:885-892. DOI: 10.1002/ajmg.a.61124
8. Smedley D, Smith KR, Martin A, Thomas EA, McDonagh EM, Cipriani V, et al. 100,000 Genomes pilot on rare-disease diagnosis in health care – preliminary repor. *N Engl J Med.* 2021;385:1868-1880. DOI: 10.1056/NEJMoa2035790
9. Hsu JC, Wu HC, Feng WC, Chou CH, Lai EC, Lu CY. Disease and economic burden for rare diseases in Taiwan: a longitudinal study using Taiwan's National Health Insurance Research Database. *PLoS One.* 2018;13:e0204206. DOI: 10.1371/journal.pone.0204206
10. National Health Commission of the People's Republic of China. Notice of the General Office of the National Health Commission on Issuing the Guidelines for Diagnosis and Treatment of Rare Diseases (2019 Edition). Accessed January 19, 2024. http://www.nhc.gov.cn/yzygj/s7659/201902/61d06b4916c348e0810ce1fceb844333.shtml
11. National Health Commission of the People's Republic of China. Notice on publishing the second batch of rare diseases. Accessed January 19, 2024. http://www.nhc.gov.cn/yzygj/s7659/202309/19941f5eb0994615b34273bc27bf360d.shtml
12. Shi XM, Liu H, Wang L, Wang ZX, Dong CY, Wang YF, et al. Study on the current situation of China's First List of Rare Diseases based on 15 million hospitalizations (in Chinese). *Natl Med J China.* 2018;98:3274-3278. DOI: 10.3760/cma.j.issn.0376-2491.2018.40.012
13. Sanford EF, Clark MM, Farnaes L, Williams MR, Perry JC, Ingulli EG, et al. Rapid whole genome sequencing has clinical utility in children in the PICU. *Pediatr Crit Care Med.* 2019;20:1007-1020. DOI: 10.1097/PCC.0000000000002056
14. Śmigiel R, Biela M, Szmyd K, Błoch M, Szmida E, Skiba P, et al. Rapid whole-exome sequencing as a diagnostic tool in a neonatal/pediatric intensive care unit. *J Clin Med.* 2020;9:2220. DOI: 10.3390/jcm9072220
15. Liu Y, Hao C, Li K, Hu X, Gao H, Zeng J, et al. Clinical application of whole exome sequencing for monogenic disorders in PICU of China. *Front Genet.* 2021;12:677699. DOI: 10.3389/fgene.2021.677699
16. Wu ET, Hwu WL, Chien YH, Hsu C, Chen TF, Chen NQ, et al. Critical trio exome benefits in-time decision-making for pediatric patients with severe illnesses. *Pediatr Crit Care Med.* 2019;20:1021-1026. DOI: 10.1097/PCC.0000000000002068
17. FitzPatrick DR, Skeoch CH, Tolmie JL. Genetic aspects of admissions to a paediatric intensive care unit. *Arch Dis Child.* 1991;66:639-641. DOI: 10.1136/adc.66.5.639
18. Hall JG, Powers EK, Mcllvaine RT, Ean VH. The frequency and financial burden of genetic disease in a pediatric hospital. *Am J Med Genet.* 1978;1:417-436. DOI: 10.1002/ajmg.1320010405
19. Stevenson DA, Carey JC. Contribution of malformations and genetic disorders to mortality in a children's hospital. *Am J Med Genet A.* 2004;126A:393-397. DOI: 10.1002/ajmg.a.20409
20. Huang M. *Analysis of 917 Dead Cases in Intensive Care Unit (in Chinese)*. Master Dissertation. Chongqing Medical University; 2017.
21. Shashi V, McConkie-Rosell A, Rosell B, Schoch K, Vellore K, McDonald M, et al. The utility of the traditional medical genetics diagnostic evaluation in the context of next-generation sequencing for undiagnosed genetic disorders. *Genet Med.* 2014;16:176-182. DOI: 10.1038/gim.2013.99
22. Dong D, Chung RY, Chan R, Gong S, Xu RH. Why is misdiagnosis more likely among some people with rare diseases than others? Insights from a population-based cross-sectional study in China. *Orphanet J Rare Dis.* 2020;15:307. DOI: 10.1186/s13023-020-01587-2
23. Tang L, Zhang J, Zhao B, Ai X, Wang ZY, Se R, et al. Current situation and consideration of drug development for rare diseases (in Chinese). *Chin J Clin Pharmacol.* 2021;37:3295-3299. DOI: 10.13699/j.cnki.1001-6821.2021.23.022
24. Shafie AA, Supian A, Ahmad Hassali MA, Ngu LH, Thong MK, Ayob H, et al. Rare disease in Malaysia: challenges and solutions. *PLoS ONE.* 2020;15:e0230850. DOI: 10.1371/journal.pone.0230850
25. He S, Gao SQ, He XY, Liu P, Jin Y, Li XY, et al. Advances in rare diaseases in China (2020-2021) (in Chinese). *Med J Peking Union Med Coll Hosp.* 2022;13:39-45. DOI: 10.12290/xhyxzz.2021-0248
26. Yoon PW, Olney RS, Khoury MJ, Sappenfield WM, Chavez GF, Taylor D. Contribution of birth defects and genetic diseases to pediatric hospitalizations. A population-based study. *Arch Pediatr Adolesc Med.* 1997;151:1096-1103. DOI: 10.1001/archpedi.1997.02170480026004

27. Evaluate. EvaluatePharma's Orphan Drug Report 2018. Accessed December 1, 2023. https://www.evaluate.com/sites/default/files/media/download-files/OD18.pdf
28. Chinese Fabry Disease Expert Panel. Expert consensus for diagnosis and treatment of Fabry diasease in China (2021) (in Chinese). *Chin J Intern Med.* 2021;60:321-330. DOI: 10.3760/cma.j.cn112138-20201218-01028
29. Nguengang Wakap S, Lambert DM, Olry A, Rodwell C, Gueydan C, Lanneau V, et al. Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database. *Eur J Hum Genet.* 2020;28:165-173. DOI: 10.1038/s41431-019-0508-0
30. Meng L, Pammi M, Saronwala A, Magoulas P, Ghazi AR, Vetrini F, et al. Use of Exome Sequencing for Infants in intensive care units: ascertainment of severe single-gene disorders and effect on medical management. *JAMA Pediatr.* 2017;171:e173438. DOI: 10.1001/jamapediatrics.2017.3438
31. French CE, Delon I, Dolling H, Sanchis-Juan A, Shamardina O, Mégy K, et al. Whole genome sequencing reveals that genetic conditions are frequent in intensively ill children. *Intensive Care Med.* 2019;45:627-636. DOI: 10.1007/s00134-019-05552-x
32. Kingsmore SF, Cakici JA, Clark MM, Gaughran M, Feddock M, Batalov S, et al. A randomized, controlled trial of the analytic and diagnostic performance of singleton and trio, rapid genome and exome sequencing in ill infants. *Am J Hum Genet.* 2019;105:719-733. DOI: 10.1016/j.ajhg.2019.08.009
33. Lunke S, Eggers S, Wilson M, Patel C, Barnett CP, Pinner J, et al. Feasibility of ultra-rapid exome sequencing in critically ill infants and children with suspected monogenic conditions in the australian public health care system. *JAMA.* 2020;323:2503-2511. DOI: 10.1001/jama.2020.7671
34. Wang H, Qian Y, Lu Y, Qin Q, Lu G, Cheng G, et al. Clinical utility of 24-h rapid trio-exome sequencing for critically ill infants. *NPJ Genom Med.* 2020;5:20. DOI: 10.1038/s41525-020-0129-0
35. Birgmeier J, Haeussler M, Deisseroth CA, Steinberg EH, Jagadeesh KA, Ratner AJ, et al. AMELIE speeds Mendelian diagnosis by matching patient phenotype and genotype to primary literature. *Sci Transl Med.* 2020;12:eaau9113. DOI: 10.1126/scitranslmed.aau9113
36. Gorzynski JE, Goenka SD, Shafin K, Jensen TD, Fisk DG, Grove ME, et al. Ultrarapid nanopore genome sequencing in a critical care setting. *N Engl J Med.* 2022;386:700-702. DOI: 10.1056/NEJMc2112090
37. Gurovich Y, Hanani Y, Bar O, Nadav G, Fleischer N, Gelbman D, et al. Identifying facial phenotypes of genetic disorders using deep learning. *Nat Med.* 2019;25:60-64. DOI: 10.1038/s41591-018-0279-0
38. Song H, Ma S. Application and thinking of MDT in diagnosis and treatment of difficult and rare diseases in children (in Chinese). *China Med News.* 2020;35:9. DOI: 10.3760/cma.j.issn.1000-8039.2020.22.109
39. Shen Q, Liu J, Chen J, Zhou S, Wang Y, Yu L, et al. Multidisciplinary approach to screening and management of children with Fabry disease: practice at a Tertiary Children's Hospital in China. *Orphanet J Rare Dis.* 2021;16:509. DOI: 10.1186/s13023-021-02136-1
40. Liu Q, Liu X, Wang S, Shang J, Tang Y, Zhang B. Research of accessibility of rare disease drugs based on the *China's First List of Rare Disease* (in Chinese). *Med J Peking Union Med Coll Hosp.* 2023;14:1208-1216. DOI: 10.12290/xhyxzz.2023-0163
41. Li KC, Zhao K, Zheng JY, Yang YQ, Li LK. Current status of drug development and implementation for diseases included in *the Second Catalog of Rare Disease* (in Chinese). *J Rare Dis.* 2023;2:596-601. DOI: 10.12376/j.issn.2097-0501.2023.04.015
42. Shang Y, Chang JH, Song H. Analysis on influencing factors of clinicians' diagnosis and treatment behavior of rare disease in Tangshan (in Chinese). *Med Soc.* 2021;34:57-61. DOI: 10.13723/j.yxysh.2021.08.012
43. Kole A, Faurisson F. Rare diseases social epidemiology: analysis of inequalities. *Adv Exp Med Biol.* 2010;686:223-250. DOI: 10.1007/978-90-481-9485-8_14
44. National Health Commission of the People's Republic of China. Notice of the General Office of the National Health Commission on the Establishment of a National Collaborative Network for the Diagnosis and Treatment of Rare Diseases. Accessed January 19, 2024. http://www.nhc.gov.cn/yzygj/s7659/201902/3a8228589bf94e6d9356008763387cc4.shtml
45. Liu W, Zhang BL, Huang JY. Management of rare diseases in children: status quo, progress and prospects (in Chinese). *J Rare Dis.* 2022;1:20-27. DOI: 10.12376/j.issn.2097-0501.2022.01.004

How to cite this article: Liu Y, Qian S. Current situation and prospect for the diagnosis and treatment of pediatric critical rare diseases in China. *Pediatr Investig*. 2024;8:66–71. https://doi.org/10.1002/ped4.12419