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# Cystic fibrosis in China: addressing the cycle of underdiagnosis and treatment inaccessibility

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Cystic fibrosis (CF) is substantially underdiagnosed in China, and access to targeted therapy remains limited. Cystic fibrosis transmembrane conductance regulator (CFTR) modulator therapy has dramatically improved survival internationally, yet none has been approved or entered clinical trials in China. A circular problem contributes to this situation: CF is not included in newborn screening programmes because it has historically been considered extremely rare in East Asian populations. Yet, fewer than 300 patients have been genetically confirmed, in part due to limited diagnostic infrastructure. Epidemiological data based on carrier frequency suggest the true affected population exceeds 17,000 individuals. Patients who receive a molecular diagnosis face additional challenges, including a CFTR variant spectrum that differs from Western populations without established theratyping pathways, and the absence of regulatory submissions for CFTR modulators. Here, we discuss three potential approaches: expanding diagnostic capacity through standardised sweat chloride testing and clinician education, building theratyping infrastructure via patient-derived organoid biobanks, and applying existing rare disease regulatory pathways to facilitate drug approval.

**Keywords** cystic fibrosis; CFTR modulators; China; underdiagnosis; health equity

Elexacaftor/tezacaftor/ivacaftor (ETI) has transformed cystic fibrosis (CF) from a fatal childhood disease into a manageable chronic condition, with projected median survival exceeding 70 years for patients homozygous for F508del in high-income countries [1]. However, ETI is not yet available in many countries outside North America and Europe, in part because its annual cost exceeds USD 300,000 [2]. Some countries, including Brazil and Argentina, have secured access through price negotiations or judicial rulings. To date, no cystic fibrosis transmembrane conductance regulator (CFTR) modulator has been approved, marketed, or entered clinical trials in China.

The problem in China is not limited to drug pricing. CF remains underdiagnosed due to a circular problem. CF is not currently included in newborn screening programmes in China, likely because the disease has historically been considered extremely rare in Chinese populations [3,4]. Standardised sweat chloride testing, the diagnostic gold standard, is available at only a limited number of tertiary centres [4]. Most frontline physicians have limited exposure to CF given its perceived rarity, and CF is seldom considered in the differential diagnosis of chronic respiratory symptoms at primary and secondary care levels [3,4]. As a result, fewer than 300 genetically confirmed Chinese CF patients have been reported in the literature [3]. The pace of diagnosis has accelerated markedly as clinical awareness has grown: only 34 Chinese CF cases were reported over the 40 years from 1974 to 2014, yet this number rose to over 200 by 2022 following the establishment of a dedicated referral pathway [3]. The small number of identified patients has not yet generated

sufficient market incentive for manufacturers to pursue regulatory approval, and the absence of approved therapy in turn reduces impetus to expand diagnostic capacity.

Epidemiological data support a much larger affected population. A targeted genetic screening study of 33,894 Chinese newborns identified a cumulative CFTR pathogenic allele frequency of 0.35%, corresponding to a carrier rate of approximately 1 in 143 [5]. Under Hardy–Weinberg equilibrium, this allele frequency ($q = 0.0035$) predicts a disease incidence of $q^2 \approx 1$ in 81,810 live births. Applied to China's population of approximately 1.4 billion, this yields an estimated 17,000 affected individuals nationwide [5]. This figure does not account for reduced survival among undiagnosed patients, but likely underestimates cumulative incidence because the sequencing panel could not detect large CFTR deletions or duplications [3,5]. A separate gnomAD-based analysis estimated CF incidence at 0.2–1 per 100,000 births in East Asian populations [6], which is broadly consistent with the above estimate. The 2023 Chinese Expert Consensus independently estimated that the cumulative number of CF patients in China likely exceeds 20,000 [4], further supporting these projections. Many undiagnosed patients are presumably managed as recurrent pneumonia or bronchiectasis of unknown cause without disease-modifying therapy.

> CF in China faces a circular problem where low diagnostic rates reduce perceived disease burden, which in turn reduces incentive for regulatory submissions and treatment access.

Among patients who do achieve a molecular diagnosis, access to ETI faces three specific challenges. First, the CFTR variant spectrum in Chinese patients differs substantially from that of European populations. Several variants that are relatively common in Chinese CF cohorts are not included in current ETI indications and have not undergone theratyping [3]. Patient-derived organoid assays, the standard method for expanding modulator eligibility to rare variants, have not been established in mainland China, so there is currently no pathway for Chinese patients to demonstrate drug responsiveness. Second, no regulatory submission for CFTR modulators has been filed with China's National Medical Products Administration (NMPA) to date, nor have voluntary licensing agreements been established that would permit generic manufacture for the Chinese market [2]. Third, as no CFTR modulator is approved in China, the question of reimbursement has not yet arisen; however, the annual cost of ETI would represent a substantial financial burden for most families without public coverage.

> Addressing this requires concurrent efforts in expanding diagnostic infrastructure, establishing theratyping capacity for Chinese-prevalent CFTR variants, and applying existing rare disease regulatory pathways to facilitate drug approval.

Several measures could help address this situation. Expanding diagnostic capacity is a priority: this includes standardising sweat chloride testing at additional tertiary centres, incorporating CF into the differential diagnosis of unexplained bronchiectasis through clinician education programmes, and establishing a national CF patient registry to quantify disease burden. The 2023 Chinese Expert Consensus provides a framework for these efforts [4]. Equally important is building theratyping infrastructure. Establishing organoid biobanks from Chinese CF patients would enable functional assessment of population-specific CFTR variants and generate preclinical data to support regulatory applications. On the regulatory front, CF is already listed on China's First National List of Rare Diseases. *CFTR* modulators could be eligible for NMPA priority review, subject to the applicable criteria and application procedures. The inclusion of ETI in the 2025 WHO Model List of Essential Medicines provides further support for efforts to improve access in China [7]. Advocacy for regulatory submission or voluntary licensing through the Medicines Patent Pool may help address this barrier [2].

The precedent of spinal muscular atrophy in China illustrates how rapidly the landscape can change for a rare disease once key conditions are met. Nusinersen was approved by NMPA in 2019 through the priority review pathway, and by 2021 it was included in the National Reimbursement Drug List following price negotiation, with the price per injection reduced from approximately Renminbi (RMB) 700,000 to RMB 33,000 [8]. This was made possible by several factors: a clearly defined patient population identified through genetic testing, robust international efficacy data, and active advocacy by patient organisations and clinicians. CF could follow a similar trajectory if the diagnostic gap is addressed and clinical data from Chinese patients become available.

CF also shares common challenges with other rare diseases that have achieved improved access in China, including Gaucher disease and Pompe disease. However, CF is distinct in that the primary barrier is not treatment cost alone. For Gaucher and Pompe diseases, local reimbursement mechanisms have improved treatment access [8], although affordability remains a challenge. For CF, the fundamental problem is identifying patients in the first place. Unlike lysosomal storage disorders, which typically present with recognisable clinical phenotypes leading to enzymatic or genetic diagnosis, CF in Chinese patients often manifests predominantly as chronic respiratory disease and is misattributed to more common conditions [3]. This difference highlights the importance of CF-specific awareness campaigns and diagnostic algorithms tailored to the Chinese clinical context.

Potential barriers to implementation include the small number of confirmed diagnoses reducing perceived market size, limited clinical familiarity with CF among specialists outside major referral centres, and the absence of Chinese-specific efficacy data. Nevertheless, CF in China is substantially underdiagnosed, and affected patients currently have no access to CFTR modulators. Expanding diagnostic infrastructure, building theratyping capacity, and pursuing regulatory pathways are needed to improve outcomes for Chinese CF patients.

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