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Cystic Fibrosis Care in South Africa: Facing the Challenge of Diversity and Inequality

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ABSTRACT

Low-and-middle-income countries (LMIC) like South Africa (SA) were left behind with advancements in cystic fibrosis (CF) care that followed re-imbursement agreements in high-income countries of CF transmembrane regulator protein modulators (CFTRm) for the treatment of CF. A combination of global monopoly, patent protection by international trade agreements and delays in regulatory approvals are factors keeping these transformative drugs out of reach for many LMIC due to their high cost. Unequal and delayed access to CFTRm is amplifying existing disparities in CF care and outcomes worldwide, including SA where currently only 200 (50%) of the 400 eligible people have access to CFTRm. However, the SA experience demonstrated how health professionals, legal experts and global CF community activists can collaborate to mobilize local and international resources to advocate for affordable and equal access to CFTRm In this paper we describe the journey followed in SA to overcome some of these inequalities and challenges and highlight the current and future impact on CF care in SA that may have much in common with other LMIC.

1 | Introduction

South Africa's (SA) history and society are shaped by centuries of immigration and colonization of the diverse indigenous African populations who remain the demographic majority in modern SA. South Africa's history is also marked by inequality in wealth and racial disparity, which was enforced through the Apartheid government rule which ended with the first democratic elections in 1994. The legacy of SA's divisive history remains entrenched today with stark inequalities in socioeconomic and health care delivery which cut across all sectors, including diagnosis and treatment of rare diseases such as cystic fibrosis (CF). Although SA is classified by the World Bank as an upper-middle income country, significant inequity in standards of CF care exist which have negative impact on CF outcomes [1]. Newborn screening is not practised in SA and access to basic diagnostic tests and treatment is restricted to the major cities and divided between public and private health care sectors. The first epidemiological description of CF in SA was published in 1978 by Super who established a registry of 299 White patients with CF, of which 179 were alive at the time [2]. CF has been documented in SA as early as 1959 as well as first reporting of CF in indigenous Black Africans as early as 1960's [3–5]. In the pre-modulator era, standards of CF care in SA were generally aligned with international norms, supported by a network of multidisciplinary public and private CF clinics, locally adapted treatment

guidelines and an active CF community organization [6]. However, like most other low- and middle-income countries (LMIC) across the world, SA was left behind by the rapid advancements in CF care with the discovery and licensing of CF transmembrane regulator protein modulators (CFTRm), further amplifying existing disparities in CF care both nationally and internationally. In this paper we describe the journey followed in SA to overcome some of these inequalities and challenges and highlight the current and future impact on CF care in SA that may have much in common with other LMIC.

1.1 | The Current Status of CF in South Africa

According to the current South African CF Registry (SACFR), first established in 2018, 505 people were documented as living with CF in December 2023, with a median age of 17.3 years (Table 1) [7]. While this represents a modest increase from the median age of 15.5 years, in 2018, it remains substantially lower than corresponding figures reported in 2023 for Canada (25.8 years), United States (22.5 years) and Europe (20.3 years) [8–10]. Consequently, SA, like other middle-income countries, demonstrated a higher proportion of children living with CF (53%) compared to Canada (35%), US (39.6%) and Europe (44.5%) [8–10].

Significant genetic diversity is observed in SA and dependent on ancestry; F508del is the most prevalent CFTR variant (64%) in SA and more common in White/European and mixed ancestry groups, while 3120 + 1 G > A (class 1) is the most common variant in people with Black African ancestry [7]. This genetic heterogeneity results in an overall reduced eligibility for CFTRm therapy (85%) in SA, comparable to Brazil (79.5%) but lower than that of most Northern Hemisphere countries (range 94%−100%) [11, 12]. Importantly, stark disparity in eligibility for CFTRm are drawn along racial lines, where currently most Black Africans with CF in SA are not eligible for CFTRm due to genotype.

The incidence of new CF diagnoses remained constant at on average 15 cases per annum (3% of the total registry), reflecting persistent health care challenges, including the absence of newborn screening programs and limited diagnostic infrastructure within under-resourced public health care facilities, particularly those in rural regions. This diagnostic disparity is evident by the finding that 58% of registered patients, in 2023, reported accessing private health care services and despite being the majority demographic group in SA, Black Africans remain significantly underrepresented with only 58 (11.5%) currently reported in the SACFR [7, 13]. The estimated live birth incidence of CF in SA varies according to ancestry: 1: 3000 (White/European); 1: 10,000 (Mixed ancestry) and 1: 13,000 in Black Africans [14]. Although these estimates have not been updated with modern approaches, it highlights the high probability that CF is underdiagnosed in SA, especially in Mixed and Black African ancestry populations. With almost one million live births reported annually in SA, projections are that there could be an estimated 62 Black African infants born with CF each year in SA, many more than the recorded annual diagnosis rate of less than ten. Although speculative, clinical experience and some evidence in SA point toward high CF-related infant mortality before and without diagnosis as the most likely explanation for the observed discrepancy in estimated and observed CF cases in SA [15]. Similar and alarming infant mortality has been reported from southern India in one center, where 7% of all under 6-month age mortality in a pediatric intensive care was postmortem genetically confirmed to be CF-related [16].

The clinical burden of CF disease in SA is substantial, with 49% of patients demonstrating forced expiratory volume in 1 s percent predicted (FEV1pp) values below 80%, of which 9% have severe

TABLE 1 | South African cystic fibrosis patient registry summary data 2018−2023.

		2018 *N* = 482	2019 *N* = 515	2020 *N* = 525	2021 *N* = 523	2022 *N* = 522	2023 *N* = 505
Children (<18 years)	Number (%)	276 (57.3%)	295 (57.3%)	291 (55.4%)	277 (53.0%)	269 (51.5%)	267 (52.9%)
Age (years) on 31 december	Median (IQR)	15.5 (8.3, 26.2)	15.7 (8.3, 26.1)	16.7 (9.1, 27.0)	17.2 (9.8, 27.3)	17.3 (10.3, 28.0)	17.3 (10.6, 27.8)
Males	Number (%)	231 (47.9%)	247 (48.0%)	252 (48.0%)	254 (48.6%)	254 (48.7%)	250 (49.5%)
New diagnosis	Number (%)	33 (6.8%)	32 (6.2%)	11 (2.1%)	10 (1.9%)	15 (2.9%)	15 (3.0%)
Age of new diagnosis (months)	Median (IQR)	8.4 (4.0, 81.8)	35.8 (5.9, 173.8)	7.6 (0.6, 162.1)	5.0 (0.7, 7.0)	5.9 (0.7, 132.0)	4.8 (3.0, 41.1)
F508del homozygous	Number (%)	229 (47.5%)	237 (46.0%)	245 (46.7%)	241 (46.1%)	236 (45.2%)	232 (45.9%)
F508del heterozygous	Number (%)	151 (31.3%)	174 (33.8%)	175 (33.3%)	171 (32.7%)	178 (34.1%)	167 (33.0%)
Eligible for CFTR modulatory therapy	Number (%)	427 (88.6%)	454 (88.2%)	460 (87.6%)	460 (82.2%)	450 (86.2%)	430 (85.1%)
Eligible and receiving CFTR modulator therapy	Number (%)	1 (0.2%)	2 (0.4%)	4 (0.9%)	5 (1.0%)	49 (10.8%)	77 (17.9%)
Lung transplants	Number (%)	3 (0.6%)	2 (0.4%)	2 (0.4%)	1 (0.2%)	3 (0.6%)	2 (0.4%)
Liver transplants	Number (%)	0	0	0	0	0	0
Deaths	Number (%)	3 (0.6%)	5 (1.0%)	5 (1.0%)	17 (3.3%)	17 (3.3%)	7 (1.4%)

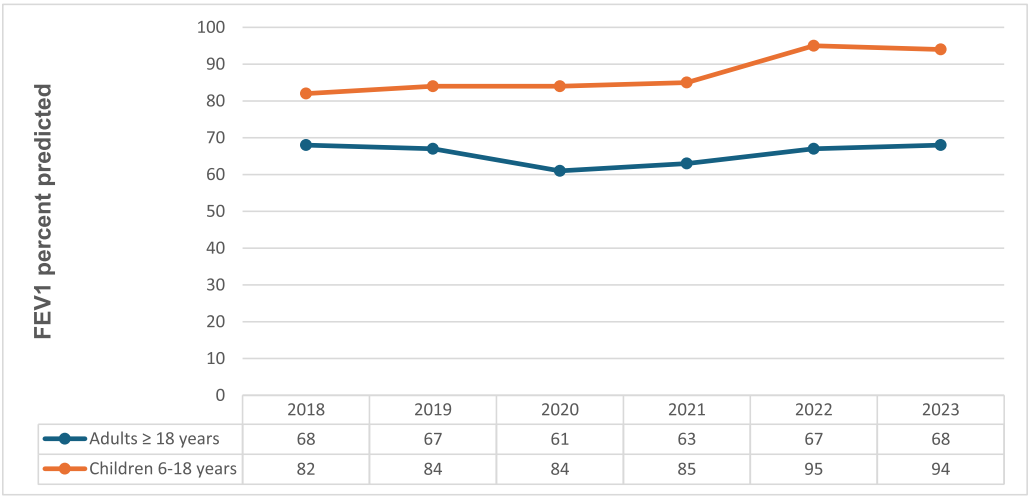

FIGURE 1 | Median FEV1% predicted for adults and children, included in the registry in 2023, who have never had a lung transplant, 2018–2023 [7]. Adults and Children are categorized by the corresponding age each year. [Color figure can be viewed at wileyonlinelibrary.com]

lung function impairment (FEV1pp < 40) [7]. This burden was lower in those with access to private health care with FEV1pp > 80% (53%) more frequently seen compared to those who receive care exclusively in the public health sector (38.5%) [7].

Nutritional status indicators reveal concerning trends, with children (<18 years) presenting a median body mass index (BMI) *z*-score of −0.31, while adults demonstrated a median BMI of 21.70 [6]. Notably, nutritional outcomes have been shown to correlate with socio-economic status, as patients dependent exclusively on public health care services have a higher prevalence of malnutrition [17]. Before the introduction of CFTRm, lung function and nutrition outcomes in SA were significantly lower across all age groups compared to a matched cohort in Canada, a high-income country [18].

The annual mortality rate in 2023 (1.4%) surpassed both European (0.5%) and Canadian (0.8%) figures, with a notably younger median age of death in South Africa (21.0 years) compared to US (36.9 years) Canada (41.2 years) [7–9].

In 2023, 77 (17.9% of eligible individuals) were receiving CFTRm therapy, which may explain the slight overall improved FEV1pp in both adults and children documented in the SACFR report (Figure 1) [7]. Estimates in 2025 are that about half ($n = 200$) of all eligible people in SA are now accessing CFTRm (personal correspondence), the majority White and all in the higher income bracket that can afford private health insurance. The wealth and health gap between public and private health care in SA has been significantly accelerated by the inequity in access to CFTR modulators due to their high cost. Disparities in CF care experienced within SA across socioeconomic classes and race groups reflect a similar concerning global trend, especially relating to access to transformative CFTR modulators.

1.2 | How Drug Patent Laws are Perpetuating Disparities in CF Care

Before April 2024, eligible people with CF in SA were unable to access CFTRm developed by Vertex Pharmaceuticals. This was due, in part, to Vertex having registered several patents, which provided it with a statutory monopoly that prevented any other pharmaceutical company from manufacturing or distributing supplying more affordable generic equivalents. A bioequivalent generic of elexacaftor/tezacaftor/ivacaftor (ETI) was in fact available at the time in Argentina at 20% of the cost of ETI distributed by Vertex.

South Africa is a member of the World Trade Organization (WTO) and its membership requires accession to the Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS) which "establishes the minimum standards of (intellectual property rights) protection to be provided by each WTO Member" [19]. These rights are not absolute, however, and the WTO claims that it aims to apply TRIPS to achieve optimal results for public health, although it acknowledges "the difficult task of balancing the interest of providing incentives for research and development of new drugs with the interest of making these drugs as widely accessible as possible to patients needing them." The TRIPS Agreement "recognizes the right of members to take various kinds of measures to qualify or limit IPRs, including for public health purposes" [20].

South Africa has yet to achieve a fair and equitable balance between the protection of intellectual property rights and the human right to access life-saving medicines. Access in this context implies the release of medicines in sufficient quantities to satisfy demand, at affordable prices. Where the patent holder fails to provide access to its medicine, it can be said to be abusing its patent. The Patents Act provides a remedy for patent abuse in the form of the grant of a compulsory licence where the patent holder is shown to be abusing its patent. A compulsory licence is an involuntary contract between a willing buyer and an unwilling seller imposed and enforced by the state [21]. This incursion into territory of the registered monopoly permits a third party to exploit the patented invention against the payment of a royalty to the patentee.

Despite patent abuse not being comprehensively defined in SA law, a South African living with CF challenged the failure by Vertex to supply CFTRm to the SA market (let alone at a fair

price) by instituting a claim for a compulsory licence [22]. This individual faced many difficulties of litigating, exacerbated by the fact that she was an individual bringing a claim against a large company with deep pockets. She challenged the inequity of Vertex's registration of multiple patents over CFTRm while it seemed to have no intention of bringing CFTRm to South Africa. Adding to her struggle was the fact that no compulsory licence has ever been granted by SA courts, and the Patents Act fails to limit intellectual property rights, expressly, on the grounds of the human right of access to medicines.

The challenge to Vertex's patents was premised on Vertex's failure to introduce a patented medicine coupled with restrictions on importing and distribution of competitor products, constituting patent abuse. A broad approach to the abuse claims utilized provisions of the Patents Act, the Bill of Rights under the Constitution, the Competition Act and various statutes aimed at ensuring access to medicines at a reasonable cost. Vertex opposed the application and filed several opposing affidavits.

Meanwhile, the landmark case attracted unprecedented attention in local and international media, largely due to the tremendous efforts of Just Treatment, an activist organization based in the United Kingdom, which had been instrumental in the introduction of CFTRm in that country, despite the high price demanded by Vertex [23]. There can be little doubt that this publicity campaign had an effect and facilitated a partial resolution to the problem facing South Africans with CF and eventual out-of-court settlement that led to market access through a unique treatment access program in April 2024 for approximately half of eligible SA with good health insurance. The challenge continues, however, to provide access to the less fortunate other half who do not have health insurance and rely on the resource-poor public health care services in SA where no agreement for reimbursement of ETI has been achieved.

1.3 | Parallel Access Solutions to CFTR Modulators in South Africa: Argentina to the Rescue!

Before ETI became available to South Africans with health insurance through the access program in 2024, some people with CF faced a difficult choice: undertake arduous journeys to another country to secure generic ETI or succumb to CF' devastating progression. A grassroots CF community-led effort emerged as a lifeline when it was apparent that Vertex had no intention to seek regulatory approval for ETI in SA, nor allow the distribution of a generic version of ETI by lifting patent restrictions on their product. The lack of access compelled a small number of SA to travel to Argentina to personally collect and pay out-of-pocket for generic ETI, marketed as Trixacar by Gador Pharmaceuticals.

Argentina does not recognize Vertex's patents, permitting the legal local manufacture and sale of the generic formulation at a fraction of the US list price. While Vertex's ETI cost upwards of $300,000 per year, Trixacar was available for approximately $60,000 per year—still a significant sum, but one that some families could manage by pooling resources, depleting savings, selling assets or turning to crowdfunding to afford the substantial expenses associated with travel and medication. Many depended heavily on one insurance company that reimbursed a limited annual benefit of approximately $20,000 for the Argentinian product, underscoring the financial strain placed on affected households [24, 25]. While personally retrieving the medication circumvented patent barriers, the legal and logistical hurdles associated with international travel, customs clearance, and medication transport placed considerable burdens on patients and families already coping with the daily challenges of CF.

To further reduce costs, most people procuring the Argentinian product were forced to adopt a modulator-sparing strategy employing clarithromycin, a strong cytochrome P450 3A (CYP3A) inhibitor that delays hepatic metabolism of ETI components [26]. Under medical supervision, ETI dosing was reduced to twice-weekly alongside daily clarithromycin, prolonging the effective duration of each dose and allowing medication packs to last significantly longer, thereby reducing monthly expenses. Although this off-label approach was pharmacokinetically rational, it had not been evaluated in controlled clinical trials, and long-term safety data remained limited [26].

Between December 2021 and March 2024, an observational study documented the real-world outcomes of 70 people with CF in SA treated with either standard daily or modulator-sparing regimens of Trixacar [27]. Improvements in pulmonary function, BMI, and sweat chloride concentration comparable to the originator product were observed across both dosing strategies of Trixacar, with no significant differences in efficacy or safety between the dosing strategies (Table 2, Figure 2) [27]. Adverse events reported were generally mild and infrequent, and no hepatotoxicity necessitating ETI dose adjustment was observed. Limitations of the study included lack of randomization, retrospective design, and lack of therapeutic drug monitoring, which was unavailable locally. Despite these limitations, the findings provided evidence that dose reduction strategies combined with CYP3A inhibition offered a feasible interim solution to improve access in resource-limited settings.

This experience underscores the glaring inequity in global CF care. While CFTRm are widely accessible in high-income settings, many LMICs experienced similar delays and barriers to access CFTRm due to prohibitive costs and restrictive patent protections. To date, Vertex has not engaged in voluntary licensing agreements for any of its CFTRm, perpetuating global barriers to access. The Argentine pipeline, while a testament to patient resilience, underscored the systemic barriers faced by the most vulnerable. Until equitable access is achieved, parallel importation and dose-sparing strategies will remain critical, though suboptimal, measures to bridge the treatment gap. The global CF community—including governments, regulators, and industry—must urgently pursue sustainable solutions balancing innovation incentives with the fundamental right to health.

1.4 | Inequity of CF Care in South Africa: Lessons for Global Health

The unequal access to lifesaving CFTRm in SA has forced health professionals and the CF community to confront this

TABLE 2 | Dosing of generic elexacaftor/tezacaftor/ivacaftor (gETI) and clarithromycin boosting according to age and weight as modulator-sparing strategy [27].

Dose	Age and weight	Number of gETI (100 mg/37.5 mg/75 mg) and gIVA (150 mg) tablets per dose	Clarithromycin dose	Number of gETI and gIVA) tablets needed per month
100%	<12 years; <30 kg	gETI 1 morning gIVA ½ evening	None	28 gETI 14 gIVA
	≥12 years; ≥30 kg	gETI 2 morning gIVA 1 evening	None	56 gETI 28 gIVA
50%	<12 years; <30 kg	gETI one morning (Monday, Wednesday, Friday) gIVA ½ morning (Tuesday, Thursday, Saturday)	125 mg BD	12 gETI 6 gIVA
	≥12 years; ≥30 kg	gETI 2 morning (Monday, Wednesday, Friday) gIVA 1 morning (Tuesday, Thursday, Saturday)	250 mg BD	24 gETI 12 gIVA
25%	<12 years; <30 kg	gETI 1 morning (Monday and Thursday) No gIVA	250 mg BD	8 gETI 0 gIVA
	≥12 years; ≥30 kg	gETI 2 morning (Monday and Thursday) No gIVA	500 mg BD	16 gETI 0 gIVA

Abbreviations: BD, twice daily dosing; gIVA, generic ivacaftor; gETI, generic elexacaftor/tezacaftor/ivacaftor.

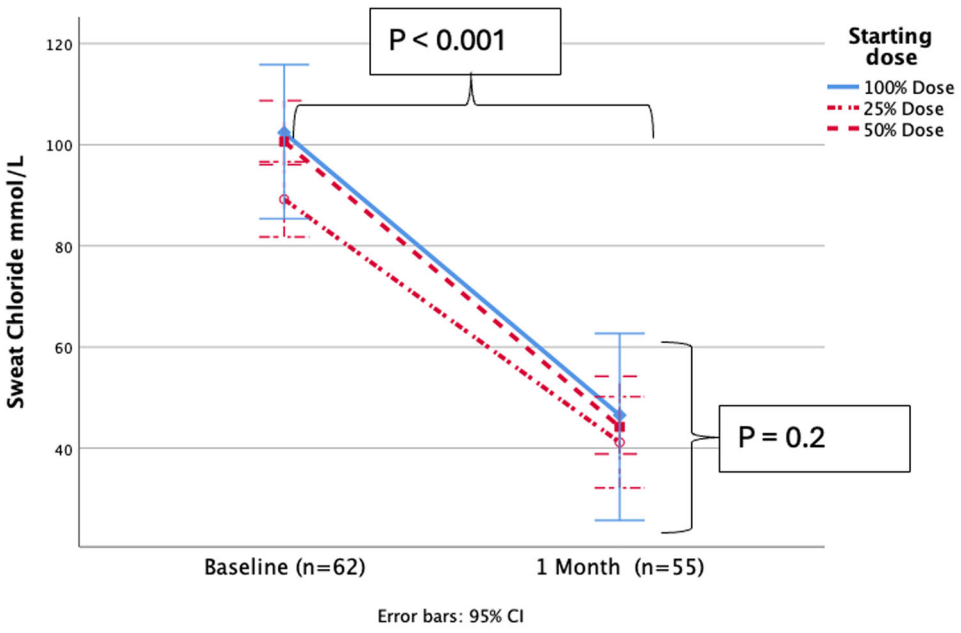

FIGURE 2 | Sweat chloride change in people starting generic elexacaftor/tezacaftor/ivacaftor with and without clarithromycin-boosted, modulator sparing doses [27]. [Color figure can be viewed at wileyonlinelibrary.com]

unjust reality in their daily lives and practice. This uncomfortable reality raises many ethical and moral dilemmas. The 2030 Agenda for Sustainable Development advocates for universal health care equity, yet despite improvements in response to advocacy efforts, access to CFTRm in SA remains limited to those with eligible genotypes (excluding most Black Africans) and those with comprehensive health insurance, who can afford these life-saving drugs. This is exacerbating existing health care disparities between rich and poor within the country and globally, violating the ethical principles of autonomy, justice and beneficence and challenging the right to health of individuals with CF, which is enshrined in the SA Constitution [28].

As demonstrated through the SA experience, addressing inequalities requires a combined approach employing legal challenges to existing patent laws, as well as innovative drug and community-led social justice initiatives. Ultimately, equitable global access to expensive new drug therapies for rare diseases such as CF will become increasingly relevant and

troubling as health technology in the field of new gene-based therapies rapidly advances, mostly in high-income countries. Solutions aimed at accelerating affordable access to new therapies will require leveraging of existing strategies such as the issuing of voluntary licenses for production and distribution of generics, pooled medicines patent agreements and inclusion of life-saving transformative therapies in the World Health Organization Essential Drug List [29, 30].

2 | Conclusion

South Africa′s journey and struggle with equitable access to CFTRm has exposed deep systemic inequalities in CF care both regionally and globally. At the same time, experience and partial success in SA has provided some pathway of how health professionals and global CF communities can collaborate to mobilize international resources to advocate for affordable and equal access to new drug therapies for rare diseases Inequalities in access to CFTRm are driven by global market forces and international trade agreements that prioritize protection of drug patent rights over patient lives. Cost-effective health care for the majority needs to be balanced against the moral and social obligation to provide effective, lifesaving and life-changing treatment for people living with rare diseases such as CF, without compromising broader public health care priorities.

Author Contributions

Marco Zampoli: conceptualization; writing – original draft; visualization; writing – review and editing; project administration. **Cathy Baird:** writing – original draft; visualization; writing – review and editing. **Brenda Morrow:** writing – original draft; visualization; writing – review and editing. **Janine Verstraete:** writing – original draft; writing – review and editing; visualization. **Greg Calligaro:** writing – original draft; visualization; writing – review and editing. **Mark Seale:** writing – original draft; writing – review and editing; visualization.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The authors have nothing to report.

References

1. “The World Bank Income and Region,” accessed 13 July 2025, https://datatopics.worldbank.org/world-development-indicators/the-world-by-income-and-region.html.

2. M. Super, “Cystic Fibrosis in Southern Africa. Including the Preparation of a Register of Carriers and Potential Carriers,” *South African Medical Journal = Suid-Afrikaanse Tydskrif Vir Geneeskunde* 54, no. 1 (1978): 18–21.

3. S. S. Grove, “Fibrocystic Disease of the Pancreas in the Bantu,” *South African Journal of Laboratory and Clinical Medicine. Suid-Afrikaanse Tydskrif Vir Laboratorium-En Kliniekwerk* 5, no. 2 (1959): 113–119.

4. L. Macdougall, “Fibrocystic Disease of the Pancreas in African Children,” *Lancet* 280, no. 7252 (1962): 409–410.

5. S. E. Levin, H. Blumberg, R. Zamit, A. Schmaman, and L. Wagstaff, “Mucoviscidosis (Cystic Fibrosis of the Pancreas) in Bantu Twin Neonates,” *South African Medical Journal = Suid-Afrikaanse Tydskrif Vir Geneeskunde* 41, no. 19 (1967): 482–485.

6. *The South African Cystic Fibrosis Consensus Guidelines*, 5th Edition, accessed 20 September 2020, http://www.sacfa.org.za/wp-content/uploads/2017_09_14_CF_Consensus_Guidelines_2017.pdf.

7. M. Zampoli, J. Verstraete, M. Frauendorf, et al., “South African Cystic Fibrosis Patient Registry Report 2023,” 2024, https://sacfa.org.za.

8. The Canadian Cystic Fibrosis Registry, “Annual Data Report,” 2023, www.cysticfibrosis.ca.

9. Cystic Fibrosis Foundation Patient Registry, “Annual Data Report 2023, Bethesda, Maryland,” ©2023 Cystic Fibrosis Foundation, 2023, https://www.cff.org/medical-professionals/patient-registry.

10. A. Zolin, A. Adamoli, and E. Bakkeheim, “ECFSPR Annual Report 2023,” 2025, https://www.ecfs.eu/projects/ecfs-patient-registry/annual-reports.

11. L. V. R. F. da Silva Filho, M. Zampoli, M. Cohen-Cymberknoh, and S. K. Kabra, “Cystic Fibrosis In Low and Middle-Income Countries (Lmic): A View From Four Different Regions of the World,” *Paediatric Respiratory Reviews* 38 (2021): 37–44.

12. “Brazilian Cystic Fibrosis Registry (REBRAFC),” 2021, www.gbefc.org.br′.

13. “Stats SA Press Release,” accessed 13 July 2025, https://www.statssa.gov.za/?p=16716#:~:text=Black%20Africans%20remain%20the%20dominant,Educational%20enrolment%20and%20attainment.

14. C. Padoa, A. Goldman, T. Jenkins, and M. Ramsay, “Cystic Fibrosis Carrier Frequencies In Populations of African Origin,” *Journal of Medical Genetics* 36, no. 1 (1999): 41–44.

15. M. Zampoli, R. Kassanjee, J. Verstraete, A. Westwood, H. J. Zar, and B. M. Morrow, “Trends in Cystic Fibrosis Survival over 40 Years in South Africa: an Observational Cohort Study,” *Pediatric Pulmonology* 57, no. 4 (2022): 908–918.

16. S. Varkki and E. J. GJames, “Is Cystic Fibrosis Contributing Significantly to Infant Mortality Rate in India?,” *Childhood* 2 (2022): 4.

17. M. Zampoli, J. Verstraete, M. Frauendorf, et al., “Cystic Fibrosis In South Africa: Spectrum of Disease and Determinants of Outcome,” *ERJ Open Research* 7, no. 3 (2021): 856–2020.

18. M. Zampoli, J. Sykes, J. Verstraete, et al., “Global Disparities in Cystic Fibrosis Outcomes Prior to CFTR Modulators: A CF Registries Cohort Study in South Africa and Canada,” *Journal of Cystic Fibrosis* 23, no. 2 (2024): 334–340.

19. “The Marrakesh Agreement Establishing the World Trade Organisation Which Came Into Force on 1 January 1995,” accessed 25 July 2025, https://www.wto.org/english/docs_e/legal_e/marag_e.htm.

20. “World Trade Organization TRIPS Agreement Overview,” accessed 19 July 2025, https://www.wto.org/english/tratop_e/trips_e/intel2_e.htm.

21. G. Julian-Arnold, “International Compulsory Licensing: The Rationales and the Reality,” *Idea* 33 (1992): 349.

22. S. N. R. Robbins, “Miracle Cystic Fibrosis Drug Kept Out of Reach in Developing Countries,” New York Times 7, accessed 7 February 2023, https://www.nytimes.com/2023/02/07/health/cystic-fibrosis-drug-trikafta.html?smid=url-share.

23. “Just Treatment,” accessed 19 July 2025, https://justtreatment.org/global-access-to-cf-drugs.

24. Juta Medical Brief, “Discovery Battles for Affordable Cystic Fibrosis Drug. 15 March 2023,” accessed 15 June 2025, https://www.medicalbrief.co.za/discovery-battles-for-affordable-cystic-fibrosis-drug/.

25. Médecins Sans Frontiè, “TAC and MSF Intervene in a Case for a Lifesaving Cystic Fibrosis Drug Priced at Over R5 Million,” 10 May 2023, accessed 15 June 2025, https://www.msf.org.za/news-and-resources/press-release/tac-and-msf-intervene-case-lifesaving-cystic-fibrosis-drug-priced.

26. E. Hong, M. Zampoli, and P. M. Beringer, “Pharmacokinetic Enhancement of Elexacaftor/Tezacaftor/Ivacaftor for Cystic Fibrosis: A Cost Reduction Strategy to Address Global Disparities in Access,” *Clinical Pharmacology and Therapeutics* 115, no. 6 (2024): 1204–1207.

27. M. Zampoli, J. Verstraete, C. Baird, et al., “Real-World Outcomes of Generic Elexacaftor/Tezacaftor/Ivacaftor (gETI) in South Africans (SA) with CF Using Standard Versus Clarithromycin-Boosted Geti, Modulator-Sparing Strategies to Reduce Cost,” *Journal of Cystic Fibrosis* 24, no. 2 (2025): 284–289.

28. T. L. Beauchamp and J. F. Childress, *Principles of Biomedical Ethics* (Oxford University Press, 2001). 5th ed.

29. K. C. Shadlen, “Accelerating Pooled Licensing of Medicines to Enhance Global Production and Equitable Access,” *Lancet* 400, no. 10352 (2022): 632–634.

30. E. Costa, H. A. van den Ham, and H. G. Leufkens, “Challenges and Opportunities of Adding CFTR Modulators for Cystic Fibrosis to the WHO Essential Medicines List,” *Journal of Cystic Fibrosis*. Published On-Line 5 July 2025, https://doi.org/10.1016/j.jcf.2025.06.006.