The Changing Epidemiology of Cystic Fibrosis

The Implications for Adult Care

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Cystic fibrosis (CF) is a genetic disease in which mutations in the gene encoding for the CF transmembrane conductance regulator protein result in a multisystem disease dominated by digestive and respiratory manifestations. In the mid-20th century, CF caused death within the first years of life. Over the past decades, advances in disease management, which includes systematic neonatal screening, multidisciplinary symptomatic CF care, lung transplantation and, more recently, highly effective CF transmembrane conductance regulator modulators, have transformed the prognosis of people with CF markedly. In most countries with well-established CF care, adults now outnumber children, and life expectancy is expected to increase further, narrowing the survival gap with the general population. However, marked differences in the prognosis of CF exist not only among high-, low-, and middle-income countries but also among high-income countries, based on the presence and quality of a specialized CF care provision network. Current evidence suggests that differences in patient clinical status and survival could be attributable not only to intrinsic disease severity but also to disparities in access to high-quality specialized care. Because CF is generally a progressive disease, adults with CF often show increased pulmonary severity and complications and increased occurrence of comorbidities, which highlights the need for specialized adult CF centers. This article seeks to describe the evolution of CF demography over the past decades, predict future trends, and anticipate the future provision of adult CF care. CHEST 2022; ■(■):■-■

KEY WORDS: cystic fibrosis; cystic fibrosis transmembrane conductance regulator; lung transplantation; registry

Cystic fibrosis (CF) is a rare genetic disease that was identified initially in White populations. It was first described in the 1930s as a disease that caused death within the first few months of life, either because of malnutrition and pancreatic insufficiency and/or because of respiratory failure that resulted from lung infections.[1-3] Over the past 80 years, the life expectancy of people with CF (pwCF) has increased dramatically thanks to the development of specialized CF centers and therapeutic advances. The availability of pancreatic enzyme replacement therapy allowed a high fat-high

ABBREVIATIONS: CF = cystic fibrosis; CFFPR = Cystic Fibrosis Foundation patient registry; CFTR = cystic fibrosis transmembrane conductance regulator; ECFSPR = European Cystic Fibrosis Society patient registry; LMIC = low- and middle-income countries; pwCF = people with cystic fibrosis

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calorie diet, which resulted in improved nutritional status. Development of airway clearance techniques and chest physiotherapy, along with the use of systemic and inhaled antibiotics, improved lung function. Lung transplantation, which has become widely available in many countries over the past 30 years, has provided further opportunity to increase longevity in pwCF.[4] More recently, the highly effective CF transmembrane conductance regulator (CFTR) modulators have the potential to further reduce the survival gap between pwCF and the general population. Although only a small number of pwCF were eligible for CFTR modulators 10 years ago,[5] > 85% of pwCF have become eligible to receive highly effective CFTR modulators in the past 2 years.[6,7] This article seeks to (1) describe the past and current epidemiologic condition and demography of CF and (2) anticipate the future of adult CF care provision, with a focus on the specificities of adult care, because most pwCF are or will become adults.

The Changing Epidemiology of CF

The Increasing Number of pwCF in the World

The exact number of pwCF worldwide is unknown. Available data mostly derive from national registries, which exist in many countries but to varying degrees of comprehensiveness.[8] The two largest registries in the world are the European Cystic Fibrosis Patient Registry (ECFSPR), which, in 2019, contained data from > 50,000 pwCF across 38 European and neighboring countries, and the United States Cystic Fibrosis Foundation Patient Registry (USCFFPR) which, in 2020, included 30,000 patients, totaling 80,000 pwCF. A recent review suggested that there were at least 100,000 pwCF worldwide.[9] In comparison, the 2012 USCFFPR report estimated the total worldwide CF population at 70,000 pwCF.[10] Because the incidence of CF, which lies between 1:2,500 and 1:6,000 in European countries,[11] has not increased over the past decades, the increase in prevalence is attributable to two major factors: improved life expectancy, especially in countries with well-established CF care provision, and increased CF awareness in countries in which the disease was not reported previously. Better coverage (ie, reporting of cases from an increasing number of CF centers) in established national registries also accounts for some of the observed increase in prevalence. Systematic newborn screening programs have been implemented in multiple countries[12]; it allows for a diagnosis of CF earlier in life, which results in earlier therapeutic intervention and improvement in short- and long-term health outcomes.

In countries with well-established CF care, where national registry data are quite comprehensive (> 90 % of pwCF are accounted for) and has been available for many years, the increase in numbers of pwCF can be estimated to a high degree of precision. For example, the USCFFPR counted 27,000 pwCF in 2012 and 31,411 in 2020 (+4,411 pwCF; +16% over 8 years) and the French CF registry captured 5,792 pwCF in 2010 and 7,280 pwCF in 2019 (+1,084 pwCF; +26% over 9 years). Figure 1 shows the evolution of the number of pwCF in France between 1992 and 2020.

For many years, data regarding CF epidemiologic condition were limited to North America, Western Europe, and Australia-New Zealand. Over the past 10 years, it has become obvious that CF is also prevalent in other areas of the world, including Eastern Europe,[13] Latin America,[14] the Middle East, North Africa,[15] and South Africa.[16] The ECFSPR reported data from 22 countries in 2010 and from 38 countries in 2019; these 16 new countries accounted for 6,274 pwCF in 2019, 12% of all pwCF in the ECFSPR.[17] Because registry coverage often is not complete in the countries that began collecting data for the ECFSPR only recently, these numbers are underestimated. The Brazilian CF registry counted approximately 5,500 pwCF in 2018[18]; the South African registry reported > 500 pwCF in 2020[19]; and Turkey reported > 1,600 pwCF in 2019.[20]

Emerging registry data from countries in which only scarce data were previously available are essential and should be encouraged. Very limited data currently are available in other areas such as India,[21] Iran,[22] Eastern Asia, and Sub-Saharan Africa, where it remains unclear whether the incidence and prevalence of CF are low or whether the limited awareness of CF and limited health care system capacity to support CF diagnosis are responsible for the lack of data. Nonetheless, the overall number of pwCF is undeniably increasing and should continue to do so in future years as the prognosis and awareness of CF keep improving.

The Increasing Number of Adults With CF

For many years, CF was primarily a pediatric disease, and children with CF outnumbered adults by a wide margin. In the early 1990s, the proportion of adults in the CF population was only 32% in the United States[10] and 20% in France.[23] The remarkable upward curve in the number of adults over the past 2 decades is primarily attributable to increased life expectancy in children,[24] most of whom now live beyond the age of 18 years, and in adults. Better awareness of the possibility of achieving

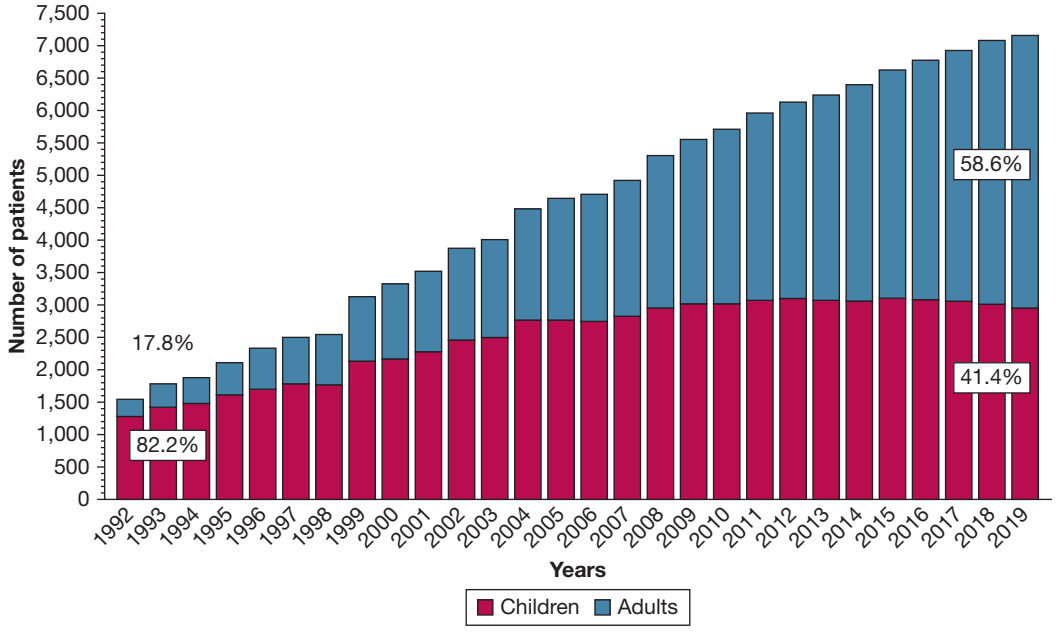

Figure 1 – *Evolution of the number of children and adults with cystic fibrosis in France from 1992 to 2019. The French Cystic Fibrosis Registry was established in 1992. At that time, only a limited numbers of centers in France contributed to the annual data; the number of people with cystic fibrosis that was captured within the Registry was approximately 1,500; adults represented < 20%. The registry coverage progressively improved, and coverage became > 90% by 2005. At that time, the registry contained approximately 4,500 people with cystic fibrosis; adults represented approximately 45% of this number. In 2019, the overall number of people with cystic fibrosis increased up to 7,000 people with cystic fibrosis (+55% compared with 2005); adults representing close to 60% of the people with cystic fibrosis (+200% compared with 2005). (From the French CF Registry; Annual Data Report 2019; Vaincre la Mucoviscidose. With permission.)*

a diagnosis of CF in adults with clinical manifestations (eg, bronchiectasis) also contributed to the increase in the number of adults with CF.[25] In the United States, for example, adults represented 39% of pwCF in 2000, 48% in 2010, and 57% in 2020; the proportion of those patients > 40 years old increased from 4.6% to 8.5% from 2000 to 2010,[26] and the predicted median survival improved from 35.3 years to 50 years from 2005 to 2020.[27] Comparable trends have been observed in countries where CF care is well-established (Fig 1), because mortality rates in children under the age of 18 years are now negligible in these countries.[24] As predicted some years ago with the use of data from the ECFSPR,[28] the number of pwCF has increased steadily over the past 10 years, with the adult population now representing 50% and 60% of pwCF in most countries with well-established CF care (Fig 2, Table 1). A recent study that analyzed data from 2005 to 2015 in France further found that large subgroups of adults with CF had very low 10-year mortality rates, which suggests that they will continue ageing.[29] Remarkably, these figures reflect a trend that began before the release of highly effective CFTR modulators, to which the great majority of pwCF are now eligible,[6,7] and which will likely further extend survival in the CF population.[30-32] Thus, the increase in the numbers of adults with CF is likely to continue in future years.

Variability in Prognosis Among Countries

Multinational registry comparisons reveal major differences among high-income countries with well-established CF care and low- and middle-income countries (LMICs) in which CF care provision is less well developed and where a smaller proportion of pwCF reach adult age. More than 10 years ago, McCormick et al[33] used ECFSPR data from 2003 to 2007 to show that the proportion of adults (≥18 years) with CF was 44% in European Union countries, whereas it was only 25% in non-European Union countries. This difference, which was ascribed to differences in resource allocation for CF care, persists today.[34] As shown in Figure 2, the proportion of adults with CF is related closely to health expenditure per capita, which can be used as a proxy indicator for the quality of CF care. In LMICs with comprehensive registry data, the number of adults remains markedly lower than the number of children. We speculate that the demographic profile is comparable in LMICs with registry coverage < 80% or without registries.

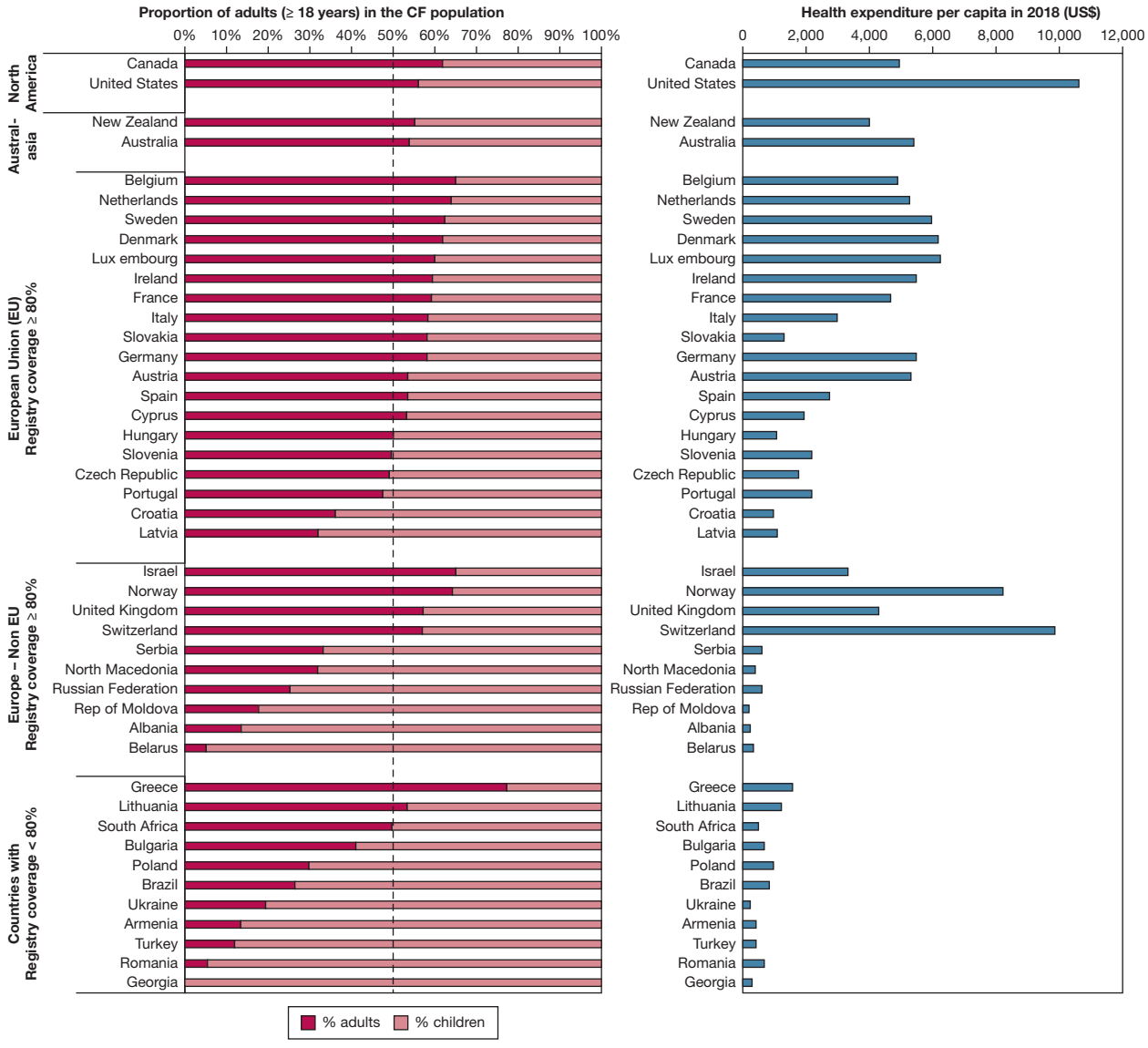

Figure 2 – *A and B, Comparison of the proportion of A, adults vs children and B, health expenditure per capita in individual countries. This Figure was constructed with data on the proportion of adults and children with cystic fibrosis that were obtained from the European Cystic Fibrosis Society patient registry 2019 for European countries and neighboring countries*[17] *and from the following national registries: Australia 2019*[78]*; Brazil 2018*[18]*; Canada 2020*[79]*; New Zealand 2017*[80]*; South Africa 2019-2020,*[19] *and the United States Cystic Fibrosis Foundation Patient Registry 2020.*[27] *Data on health expenditure per capita in 2018 were obtained from the World Bank.*[81] *Countries with national registries coverage of ≥ 80% of people with cystic fibrosis were grouped by geographic origin: North America, Australasia, and Europe. European countries were further grouped according to their participation to the European Union. Countries in which national registry coverage is ≤ 80%, people with cystic fibrosis were considered as one group, regardless of geographic origin. The data show that countries with high levels of health expenditure per capita, which is a surrogate marker for the quality of the cystic fibrosis health care system, have generally ≥ 50% adults; in countries with lower health expenditure per capita (especially when < $2,000 US), the percentage of adults is markedly lower (10% to 40%) and/or the national registries have a coverage of ≤ 80%, which questions the validity of the reported percentage of adults.*

Heterogeneity in median survival has also been described among high-income countries with well-organized CF care provision. For example, life expectancy was 10 years higher in Canada than in the United States (50.9 vs 40.6 years, respectively) in 2013,[35] and the difference persisted after adjustment for most risk factors that are associated with clinical severity.[35] Recent data suggest that the difference could have been associated partly with disparities in access to lung transplantation[36] and to worse clinical outcomes after lung transplantation in the United States than in Canada.[37] Recent international comparisons of patient outcomes with the use of contemporary data revealed that life expectancy in France exceeded 65 years and was on average 10 years higher than in Australia, Canada, and New Zealand.[38] This could be associated with the

development of an emergency lung transplantation program in France over the past 15 years, which has reduced the risk of death without transplantation dramatically, while maintaining posttransplantation survival rates like those of Canada.[39]

Although the prognosis of pwCF is better in high-income countries than in LMICs, economic markers (eg, gross domestic product and health expenditure per capita) do not fully capture the quality of CF care. Factors related to health care financing (single payer vs private insurance), access to lung transplantation and CFTR modulators, and distance from CF and lung transplantation centers likely play major roles in the observed differences among high-income countries.

Estimating Future Trends in CF Demography

Forecasting future trends in CF demography can help inform policymakers of the urgency of adapting health care provision to the needs of an increasing CF population with a growing number of adults. An estimate of population growth and of the proportion of adults vs children can be derived from the annual percentage of patients who enter and exit CF registries over multiple years. This strategy was applied in 2015 with the use of data from countries that reported longitudinal data in the ECFSPR. The results of this latter study predicted a 75% increase in the number of adults with CF from 2010 to 2025 in selected European countries.[28] Comparing this forecast with current data confirmed that the methods used can evaluate demographic trends accurately over a relatively short period of time.[40,41] However, the model that was used assumed that no major therapeutic changes would occur. The advent of highly effective CFTR modulators, to which a growing number of pwCF are eligible, will likely lead to further improvements in prognosis.[30-32] The predicted rise in the number of adults with CF in future is therefore most likely underestimated in the forecast. Other statistical methods such as microsimulation, which can include the potential effect of novel therapies, may help calculate estimates of future demographic trends.[42]

Challenges for Adult Care

The Specificity of Adult CF Centers

Disease progression in CF occurs gradually over multiple years, and the complexity of care increases as patients grow older.[43] Pulmonary manifestations such as hemoptysis,[44] pneumothorax[45] and advanced lung disease and respiratory failure[46] and nonpulmonary complications such as diabetes mellitus and osteoporosis are more prevalent in adults.[47] Depression, anxiety, and other psychologic issues are highly prevalent in pwCF, and their prevalence is increased in adults.[48] Consequences of the cumulative use of systemic aminoglycosides for the treatment of pulmonary exacerbations include chronic kidney disease[49] and hearing loss.[50] Emerging complications (eg, cardiovascular disease[51] and cancer[52]) have been described in older patients; colon cancer screening is now recommended in pwCF older than 40 years,[53] and pregnancy[54] and fertility issues in men[55] and women[56] usually are addressed in adulthood. Further, the combination of ageing with the recent availability of highly effective CFTR modulators for a large number of patients will likely result in changes in the spectrum of comorbidities: for example, increasing concerns with excessive weight gain[57] and systemic hypertension[58] have been described in patients who were treated with CFTR modulators; dyslipidemia is also being described increasingly.[59] The ageing of the CF population will also result in increased prevalence of age-related diseases that are observed in the general population. For example, the prevalence of systemic hypertension in the United States increased with age, from 7.5% among adults aged 18 to 39 years to 33.2% among those aged 40 to 59 years, and 63.1% among those aged $>$ 60 years.[60] Similarly, data from the US National Cancer Institute indicates that the incidence rates for cancer overall climb steadily as age increases, from fewer than 25 cases per 100,000 people in age groups under age 20 to approximately 350 per 100,000 people among those patients aged 45 to 49 years and further increases in older age groups.[61] Adult CF centers therefore should have access to specialists from a wide range of disciplines, which include respiratory medicine, radiology, hepatology, nephrology, diabetes mellitus, metabolic bone disease, assisted reproduction, and lung transplantation.[43]

Increasing the Number and Capacity of Adult CF Centers

The increasing number of adults creates a growing need for organized and specialized care provision in CF centers that have developed expertise in the management of adult pwCF.[43] The predicted 75% increase in the number of adults in Europe from 2010 to 2025 was calculated with the use of data from 16 countries within the ECFSPR, which accounted for 13,000 adults in 2010,and in which the total number of adults is expected to rise to 24,000 by 2025.[28] If a CF

adult center follows an average of 250 pwCF, the number of centers required for the care of these pwCF would be 52 in 2010 and 96 centers in 2025, nearly twice as many. A study in the United Kingdom forecasted an increase by 28% in adults with CF from 2017 to 2030, which concurs with the conclusion that there is an urgent requirement to review adult CF health care provision.[62]

Opening new adult centers is necessary in areas where there is a clear need to meet demographic changes and/or adequate geographic coverage. Increasing the number of pwCF per center is another possibility, but it comes with organizational challenges as well. Although large adult CF centers, with > 500 pwCF existing in several countries, most adult CF centers care for 50 to 250 pwCF and will need to adapt their physical/architectural and staffing capacity to the size of the patient population.[43] In countries with less well-developed CF care provision (eg, in Eastern Europe[13,63] or in Brazil[64]), in which the number of adults is still relatively low, deficiencies in adult care management have been reported, and access to specialized care will have to adjust to meet the predicted demographic trends.

Future Adult CF Centers: The Challenge of Multiple Groups of Adult pwCF With Different Needs Coexisting

The phenotypic heterogeneity of the adult CF population implies that different subpopulations have different needs and poses a major challenge. Many CF centers have experience with the diversity of clinical manifestations and severity, which range from mild symptoms caused by CFTR-related disease to slower disease progression caused by residual function *CFTR* genotypes that are associated with moderate pulmonary disease and/or with advanced pulmonary disease that occurs later in life[65,66] and patients with classic CF that leads to advanced pulmonary disease in the first decades of life. These differences in phenotypes are expected to increase in future years, depending on the timing of exposure to multidisciplinary CF care, CFTR modulators, and lung transplantation.

Early exposure to symptomatic multidisciplinary care is known to be responsible for the dramatic increase in life expectancy because almost all children reach adult age in countries with well-established CF care provision. It has also resulted in significant improvement in clinical features in the adult population. For example, as Fig 3 shows, the proportion of pwCF in the United States with normal lung function at age 18 years increased from < 20% to approximately 50% from 1989 to 2019. A similar trend has been observed in many countries with well-organized CF care provision and illustrates the progress made in CF management, which for many adults is now associated with a very low 10-year risk of death and/or lung transplantation.[29]

With up to 85% of pwCF eligible for current CFTR modulator therapy, those patients with mild-to-moderate respiratory impairment will see rapid improvement in lung function, as illustrated in the change seen from 2019 to 2020 (Fig 3), which is concomitant to the release of elexacaftor-tezacaftor-ivacaftor. Over time, other clinical benefits for patients with mild-to-moderate respiratory disease will also likely include fewer daily symptoms, decreased frequency of respiratory exacerbations, and improved nutritional status.[6,7,67] CFTR modulators are now administered to children earlier in life[68] who will be in better condition when transitioning to adult care. The current model of

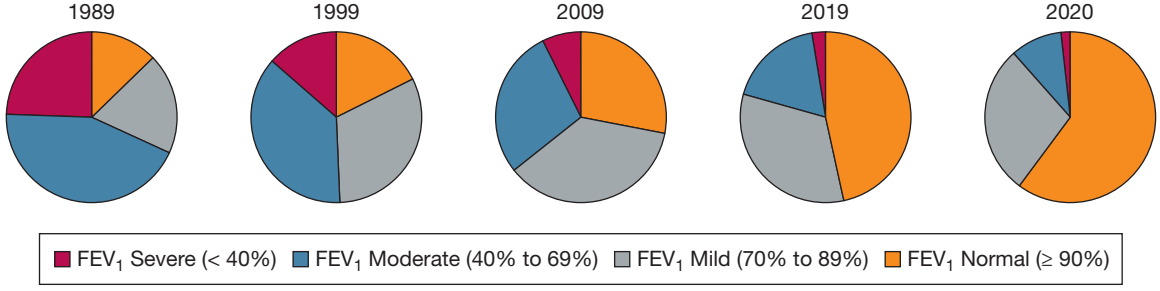

Figure 3 – *Median FEV_1 percent predicted in 18-year-old patients from 1989 to 2020 in the United States. The proportion of people with cystic fibrosis aged 18 years who are in the normal/mild lung disease category ($FEV_1 \geq 70\%$ predicted) has increased from 33.8% in 1989 to 78.3% in 2019. Of note, the proportion of people with cystic fibrosis in the normal/mild lung disease category increased to 87.4 percent in 2020, which reflects the effect of elexacaftor-tezacaftor-ivacaftor commercialization in 2020. The proportion in the severe lung disease category ($FEV_1 < 40\%$ predicted) has decreased from 24.0% in 1988 to 2.6% in 2019 and 1.8% in 2020. (From the Cystic Fibrosis Foundation Patient Registry 2019 and 2020. Bethesda, Maryland. ©2020 and ©2021. Cystic Fibrosis Foundation. With permission.)*

TABLE 1] Numbers of Adults and Children With Cystic Fibrosis That Were Obtained From National Registries

	Adults		Children		Cystic Fibrosis Population	
Geographic Origin	No.	%	No.	%	Total No.	%
North America						
Canada	2,693	62	1,651	38	4,344	> 95
United States	17,471	56	13,728	44	31,199	> 95
Australasia						
New Zealand	277	55	224	45	501	> 95
Australia	1,854	54	1,592	46	3,446	> 95
European Union countries[a]						
Belgium	881	65	473	35	1,354	> 90
Netherlands	973	64	554	36	1,527	95
Sweden	438	62	264	38	702	95
Denmark	324	62	200	38	524	99
Luxembourg	24	60	16	40	40	> 95
Ireland	750	60	508	40	1,258	90
France	3,959	59	2,731	41	6,690	90
Italy	3,258	58	2,325	42	5,583	95
Slovakia	187	58	134	42	321	> 90
Germany	3,737	58	2,697	42	6,434	80
Austria	445	54	383	46	828	> 90
Spain	1,292	54	1,112	46	2,404	80
Cyprus	16	53	14	47	30	> 80
Hungary	261	50	259	50	520	90
Slovenia	56	50	57	50	113	> 95
Czech Republic	316	49	327	51	643	99
Portugal	173	48	191	52	364	> 95
Croatia	52	36	92	64	144	> 95
Latvia	15	32	32	68	47	> 90
Non-European Union countries[a]						
Israel	381	65	204	35	585	> 95
Norway	204	64	114	36	318	90
United Kingdom	6,026	57	4,515	43	10,541	99
Switzerland	568	57	427	43	995	> 95
Serbia	67	33	134	67	201	> 90
North Macedonia	45	32	96	68	141	> 90
Russian Federation	855	25	2,526	75	3,381	> 95
Republic of Moldova	10	18	47	82	57	> 90
Albania	18	14	115	86	133	80
Belarus	8	5	147	95	155	90
Countries with < 80% cystic fibrosis population coverage						
Greece	346	77	101	23	447	> 70
Lithuania	16	53	14	47	30	52
South Africa	236	50	289	50		…
Bulgaria	80	41	114	59	194	> 70
Poland	368	30	863	70	1,231	> 60

(Continued)

TABLE 1] *(Continued)*

Geographic Origin	Adults		Children		Cystic Fibrosis Population	
	No.	%	No.	%	Total No.	%
Brazil	856	26	2,375	74	3,231	…
Ukraine	41	20	169	80	210	23
Armenia	4	13	26	87	30	> 70
Turkey	240	12	1,752	88	1,992	> 60
Romania	13	5	229	95	242	50
Georgia	0	0	79	100	79	50

Data used for designing this table were obtained from the European Cystic Fibrosis Society patient registry 2019[17] and from the following national registries: Australia 2019[78]; Brazil 2018[18]; Canada 2020[79]; New Zealand 2017[80]; South Africa 2019-2020,[19] and the US Cystic Fibrosis Foundation patient registry 2020.[27]

[a]European Cystic Fibrosis Society patient registry with ≥ 80% cystic fibrosis population coverage.

CF care may need to adapt to less symptomatic patients who will likely be reluctant to come to the hospital on a quarterly basis. Nevertheless, careful monitoring of these patients remains mandatory to monitor potential long-term adverse effects of CFTR modulators (eg, excessive weight gain and metabolic syndrome[69]) and to evaluate disease progression in patients with fewer respiratory symptoms and limited ability to produce sputum at each visit.

The situation may be different for adult pwCF who initiated highly effective CFTR modulators when they already had advanced CF disease. Current evidence suggests that rapid improvement in symptoms, lung function, nutritional status, and pulmonary exacerbations occurs after the initiation of elexacaftor-tezacaftor-ivacaftor therapy in these patients.[30,70] The benefit has also been shown to be sustained over 1 year and to safely delay lung transplantation in most patients.[31] The benefit of CFTR modulators on lung function decline remains a matter of debate. A recent modeling study with the use of the UK Cystic Fibrosis Registry data suggested that ivacaftor could reduce FEV_1 decline.[71] However, a single center observational study of 35 patients with a Gly551Asp mutation that was treated with ivacaftor, a highly effective CFTR modulator in these patients, suggests that, despite an initial increase in lung function after treatment initiation, lung function decline remains unchanged over 5 years.[72] Close monitoring of patients with advanced pulmonary disease in whom rapid clinical improvement was observed after the initiation of CFTR modulators is warranted to examine the likelihood of clinical deterioration occurring over time to the extent that lung transplantation may again be required. Because lung transplantation is predicted to be deferred by several years, these patients may have a higher burden of comorbidities (eg, complications of diabetes mellitus and diseases associated with ageing, such as cardiovascular diseases and cancer), which will require higher levels of health care.

Importantly, current CFTR modulators are available for pwCF with only selected CFTR genotypes. Although in the White population approximately 85% of pwCF have genotypes eligible for CFTR modulators, pwCF of minority race and ethnicity more often have genotypes that are not eligible for CFTR modulators.[73] Therefore, in countries with mixed ethnicity, a larger number of pwCF may have not be eligible to CFTR modulators, even where the health authority has agreed to cover the associated costs. Further access remains a major challenge in LMICs, where the health care system cannot absorb the costs.[74]

Patients with advanced lung disease and uncontrolled respiratory failure, despite optimal medical management, can benefit from lung transplantation[75]; CF is one of the most common indications for lung transplantation worldwide.[76] It is important to maintain access to lung transplantation for pwCF whose disease course has reached terminal respiratory failure. Because the outcomes of lung transplantation have improved over the past 3 decades, the number of adult patients living with a lung transplant has increased in many countries. Although CF registries do not always collect data systematically on posttransplantation pwCF, transplant recipients are known to represent 10% to 20% of adult pwCF in countries with easy access to transplantation.[17] The care of pwCF after lung transplantation that requires specific expertise, including for the management of extrapulmonary complications (eg, diabetes mellitus, osteoporosis, sinus diseases, nutrition), may be provided either in CF centers or in specialized transplantation centers. Very little data are currently available on the use of highly effective CFTR

modulators in CF transplant recipients because of the uncertainty regarding potentially dangerous interactions with immunosuppressants and questions regarding the effectiveness of CFTR modulators in these patients. Access to specialized transplantation expertise is still required and should include the option of retransplantation in case of graft rejection.[77]

Conclusion

Therapeutic advances and multidisciplinary disease management have resulted in major improvements in the prognosis and life expectancy of pwCF, transforming a disease in which most patients used to die within the first years of life to one in which most patients now reach adult age and are expected to experience prolonged survival and grow old with CF. This has resulted in an important increase of the number of adults living with CF, although the proportion of pwCF who reach adult age remains highly heterogeneous among countries because of differences in access to specialized CF care provision. The heterogeneity in patient needs has increased and will keep increasing because of heterogeneity in intrinsic disease severity and access to care, including eligibility to CFTR modulators and lung transplantation. Novel challenges are likely to emerge over the next few years and will require adjustments to match an ever-increasing number of adults with CF and changes in patient phenotypic presentation.

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