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Longevity of Patients With Cystic Fibrosis in 2000 to 2010 and Beyond: Survival Analysis of the Cystic Fibrosis Foundation Patient Registry

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Abstract

Background—Advances in treatments for cystic fibrosis (CF) continue to extend survival. An updated estimate of survival is needed for better prognostication and to anticipate evolving adult care needs.

Objective—To characterize trends in CF survival between 2000 and 2010 and to project survival for children born and diagnosed with the disease in 2010.

Design—Registry-based study.

Setting—110 Cystic Fibrosis Foundation–accredited care centers in the United States.

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Patients—All patients represented in the Cystic Fibrosis Foundation Patient Registry (CFFPR) between 2000 and 2010.

Measurements—Survival was modeled with respect to age, age at diagnosis, gender, race or ethnicity, F508del mutation status, and symptoms at diagnosis.

Results—Between 2000 and 2010, the number of patients in the CFFPR increased from 21 000 to 26 000, median age increased from 14.3 to 16.7 years, and adjusted mortality decreased by 1.8% per year (95% CI, 0.5% to 2.7%). Males had a 19% (CI, 13% to 24%) lower adjusted risk for death than females. Median survival of children born and diagnosed with CF in 2010 is projected to be 37 years (CI, 35 to 39 years) for females and 40 years (CI, 39 to 42 years) for males if mortality remains at 2010 levels and more than 50 years if mortality continues to decrease at the rate observed between 2000 and 2010.

Limitations—The CFFPR does not include all patients with CF in the United States, and loss to follow-up and missing data were observed. Additional analyses to address these limitations suggest that the survival projections are conservative.

Conclusion—Children born and diagnosed with CF in the United States in 2010 are expected to live longer than those born earlier. This has important implications for prognostic discussions and suggests that the health care system should anticipate greater numbers of adults with CF.

Primary Funding Source—Cystic Fibrosis Foundation.

Cystic fibrosis (CF) is a heritable, life-shortening disease in which dysfunction of the CF transmembrane conductance regulator (CFTR) epithelial chloride channel dehydrates secretions in the airways, the pancreatic ducts, and elsewhere in the body, causing progressive organ damage (1). In 1966, the Cystic Fibrosis Foundation Patient Registry (CFFPR) was established to track the natural history of the disease, the effect of treatments, and patient health status and to design clinical trials. Registry data have been used to describe survival in CF and the role of specific clinical features in outcomes (2–5). Approximately 30 000 persons in the United States have CF (2), and slightly more than 26 000 living persons were represented in the CFFPR in 2010.

In the earliest years of the CFFPR, persons with CF did not live to attend elementary school (6). By 2010, almost half of the patients in the registry were aged 18 years or older (6, 7). Advances in pulmonary and nutritional therapies continue to extend the life span of patients with CF. Daily regimens include airway clearance therapy; inhaled mucoactive agents and antibiotics; and a high-calorie, high-fat diet (8, 9). Early identification and management of CF-related diabetes (CFRD) has also been emphasized as a standard of care (10). In addition, universal newborn screening for CF, which has been linked to overall improved health by enabling earlier initiation of treatment (11), was instituted in all 50 states by 2009. Of persons diagnosed in 2010, 57.5% were diagnosed by newborn screening compared with only 8.0% of those diagnosed in 2000 (12).

As new therapies emerge and patients with CF live longer, estimating survival is essential to providing an accurate prognosis to parents of newly diagnosed infants. Understandably, parents of children diagnosed with the disease want to provide the best possible care for their child and seek to understand what their child's future will hold (13). Because adults

with CF are increasingly apt to pursue life-defining activities, such as marriage, parenthood, higher education, and employment (7, 14), parents may also need to reassess their supportive roles, such as during the period of transition from pediatric to adult care (15).

Updated survival estimates will also inform the medical needs of an expanding population of adults with CF (16, 17). Decades of exposure to aminoglycosides are likely to result in increased vestibular (18) and renal dysfunction (19) in the older CF patient population. The prevalence of microvascular complications from CFRD (microalbuminuria, peripheral neuropathy, and retinopathy) increases with the duration of CFRD and should therefore inform screening efforts in older adults (20). Clinicians must also remain vigilant for depression and anxiety (21) among aging patients with CF. Additional unanticipated complications may emerge as the CF patient population continues to age.

Recent evaluations of survival in the United Kingdom suggest that children diagnosed with CF since 2000 can anticipate a median survival greater than 50 years (22). Our objective in this study was to characterize survival in the United States between 2000 and 2010 in order to project survival for children born and diagnosed with CF in 2010 and thereby improve the clarity of prognostic dialogue and inform adult care needs.

Methods

The CFFPR is an institutional review board–approved observational study at 110 Cystic Fibrosis Foundation–accredited care centers, encompassing more than 260 adult, pediatric, and affiliate programs. Data on patients with CF who have provided consent are collected through a secure Web-based portal. Findings on clinical presentation (such as respiratory symptoms, failure to thrive, and positive newborn screening result confirmed as CF); age at diagnosis; and encounter-based measures of nutritional status, pulmonary function, respiratory cultures, prescribed therapies, and CF-related complications are collected.

Our analyses used data from patients in the CFFPR between 1 January 2000 and 31 December 2010 with a confirmed diagnosis of CF based on genotype and phenotype (including sweat chloride, pulmonary function, pancreatic status, and respiratory microbiology) (23). We sought to describe survival between 2000 and 2010, with analysis of mortality according to age, age at diagnosis, gender, race or ethnicity, F508del mutation status, and calendar year, and to project survival of children born and diagnosed with CF in 2010.

Statistical Analysis

We assessed trends in mortality between 2000 and 2010 by using multivariable Cox proportional hazards models. Calendar year was included as a time-dependent covariate, both as a continuous variable to estimate the rate of change over the decade and as a categorical indicator variable to estimate the rate relative to the year 2000. The time scale in the Cox proportional hazards models was age, with left truncation at entry into the registry or the year 2000, whichever occurred later. We adjusted for gender, race or ethnicity, F508del mutation status, presence of symptoms at diagnosis, and age at diagnosis (24, 25) because these patient characteristics are known at diagnosis (time-independent), are not

modifiable by clinical care, and have been shown to be important predictors of survival in CF (24, 25). Therefore, these factors will be most relevant to clinicians who are providing information on prognosis to parents of children with the disease. We adjusted for F508del mutation status because it is an important predictor of survival (26) and its distribution in the CFFPR decreased during the study period. Furthermore, the F508del mutation accounts for approximately 70% of abnormal CFTR alleles, and approximately half of persons with CF are homozygous for this mutation (27).

We estimated absolute annual mortality as a function of age, gender, and F508del mutation status for the period from 2000 to 2010 by smoothing age-specific rates with a triangular kernel with a radius of 5 years. Further details on the Cox proportional hazards models, the smoothed estimate of mortality, and subgroup analyses can be found in **Appendix 1** (available at www.annals.org).

We projected survival of children born and diagnosed with CF in 2010 because most future diagnoses will be made early in life due to universal newborn screening. Diagnoses made beyond infancy will probably be in persons with residual CFTR function and a milder phenotype. We present overall results and those stratified by gender and F508del mutation status using the mortality hazards estimated with data from 2000 to 2010 (additional information is provided in **Appendix 2**, available at www.annals.org). We derived projections assuming that mortality does not change from the rate observed in 2010, mortality decreases at the same rate observed between 2000 and 2010 (1.8%), and mortality decreases at half the rate observed between 2000 and 2010 (0.9%).

Institutional review board approval to conduct these analyses was obtained from the Dartmouth Committee for the Protection of Human Subjects. We used R, version 2.15.1, for the analyses, specifically the libraries “survival” and “quantreg.”

Role of the Funding Source

This project was funded by the Cystic Fibrosis Foundation. The funding source had no role in the design, conduct, or analysis of the study but provided access to the CFFPR data and contributed to the interpretation of the findings and the manuscript.

Results

Table 1 shows characteristics of all 34 547 unique patients in the CFFPR from 2000 to 2010. Of these, we excluded patients with missing genotype data (11.9%) and those with missing data on gender, age at diagnosis, or age at entry into the registry (0.4%) from further analyses. Fewer than 4000 individuals (approximately 2.0% per year) were lost to follow-up, with no death date recorded. Between 2000 and 2010, the median age of the cohort increased from 14.3 to 16.7 years and the proportion of patients aged 18 years or older increased from 39% to 48%. Among newly diagnosed patients (that is, those with incident disease), the median age at diagnosis decreased from 6 months in 2000 to 1 month in 2010. The proportion of persons in the CFFPR who were homozygous for the F508del mutation decreased from 51% to 48%. Forty-two percent of patients entering the CFFPR in 2000 were homozygous for the F508del mutation compared with 36% of those entering in 2010.

Mortality rate ratios from 2000 to 2010 with respect to calendar year, age at diagnosis, presentation at diagnosis, race or ethnicity, gender, and F508del mutation status are shown in **Table 2**. Mortality decreased with increasing age at diagnosis; for example, patients diagnosed between ages 5 and 9 years had a 21% (95% CI, 9% to 31%) lower adjusted risk for death than those diagnosed before age 1 year. Males had a 19% (CI, 13% to 24%) lower adjusted risk for death than females. Compared with patients who were homozygous for the F508del mutation, those with 1 copy of the mutation and those with no copies had a 14% (CI, 7% to 20%) and 25% (CI, 15% to 34%) lower adjusted risk for death, respectively. As reported in **Table 2**, the adjusted hazard ratio for the 10-year change in calendar year (2000 to 2010) was 0.83 (CI, 0.75 to 0.93), which equates to a 17% reduction in mortality for the decade or a 1.8% reduction per year (CI, 0.5% to 2.7%). Further detail about the decrease in CF mortality by year between 2000 and 2010 is shown in **Figure 1**, which presents mortality hazard ratios with 2000 as the referent year and adjusted for age, presentation at diagnosis, age at diagnosis, gender, race or ethnicity, and F508del mutation status. The improvement in survival did not vary among patient subgroups (details are provided in **Appendix 1** and the **Appendix Figure**, available at www.annals.org). Sensitivity analyses reported in **Appendix 3** (available at www.annals.org) were conducted to address the effect of loss to follow-up among transplant recipients, exclusion of patients with missing genotype data from the model, variation in survival among care centers, and exclusion of age at entry into the registry from the model. These analyses derived estimates of the rate of improvement that were approximately double the estimate we report in **Table 2**.

Figure 2 shows the dependence of annual mortality on age and F508del mutation status for females (top panels) and males (bottom panels). Annual mortality is less than 0.5% until age 10 years, when it begins to increase steeply before plateauing at 3% to 4% per year in females and 2% to 3% in males at age 25 years, depending on mutation status.

Survival projections based on CF mortality during 2000 to 2010 were developed for children born and diagnosed in 2010. This cohort included 66% of all CF diagnoses in 2010. **Figure 3** shows projected survival overall, by gender, and by F508del mutation status, with 3 distinct projections of mortality. When age-specific mortality was assumed to remain at 2010 levels indefinitely, the median survival of children born and diagnosed with CF in 2010 was 39 years (CI, 38 to 40 years) overall (37 years [CI, 35 to 39 years] in females and 40 years [CI, 39 to 42 years] in males). When mortality was assumed to decrease at the rate observed between 2000 and 2010, the median survival was projected to be 56 years (CI, 54 to 58 years) overall (54 years [CI, 50 to 58 years] in females and 58 years [CI, 55 to 60 years] in males). When mortality was assumed to decrease at half the rate observed between 2000 and 2010, the median survival was projected to be 45 years (CI, 44 to 46 years) overall (43 years [CI, 41 to 44 years] in females and 47 years [CI, 45 to 49 years] in males). Further details are shown in **Table 3**.

Discussion

Our analyses show that CF survival improved from 2000 to 2010 at a rate of 1.8% per year (CI, 0.5% to 2.7%) and that the projected median survival of children born and diagnosed with the disease in 2010 is 39 years (CI, 38 to 40 years) if the mortality rate does not change

and 56 years (CI, 54 to 58 years) if the mortality rate continues to decrease at the rate observed between 2000 and 2010. Additional sensitivity analyses and recent advances in CF care (such as the adoption of universal newborn screening and the availability of new therapeutics) suggest that these projections are conservative. We also show a persistent disparity in mortality favoring males.

Our findings are consistent with those of an analysis of the U.K. CF Registry (22) by Dodge and colleagues that used data up to 2003 and calculated a life expectancy of 37 years for females and 43 years for males born in 2003. They presented hazard ratios indicating an improvement in survival between 1970 and 2003 but did not incorporate F508del mutation status, age at diagnosis, or any other variables besides gender into their analysis (22). Elborn and associates (28) used data from the United Kingdom to show substantial gains in median survival (5 years in 1960 vs. 19 years in 1970). Using data up to 1986 and assuming a rate of improvement of nearly 5% per year (more than double our most optimistic projection), they projected median survival of 40 years for children born in 1990. Our results are based on a larger cohort than that used in either of these studies. Unlike previous reports, our analysis is restricted to a period in which newborn screening became widespread and we account for the role of F508del mutation status, gender, race or ethnicity, age at diagnosis, and asymptomatic presentation at diagnosis.

We used a semiparametric survival prediction model, which has fewer assumptions than the parametric approach taken by Jackson and coworkers with an Irish cohort of patients with CF (29). They argued that their parametric approach is preferable when the follow-up period is short and the data set is small. However, the CFFPR data set we used was large and contained up to 10 years of follow-up on patients of all ages. Of note, we showed that the 2 assumptions of our semiparametric approach were valid (the mortality rate changes linearly [on the log scale] with respect to year, and the annual rate of change does not depend on the age of patients with CF). Thus, we believe that our approach was the most appropriate for the CFFPR data set.

The increased mortality risk that we observed among adolescents is poorly understood. Schluchter and colleagues (30) determined that the maximum correlation between lung function and survival occurs around age 15 to 20 years, which suggests that mortality is primarily respiratory in origin. Others have shown that airway colonization by *Pseudomonas aeruginosa* (31) or methicillin-resistant *Staphylococcus aureus* (5) independently increases the risk for death in CF, and these organisms become more prevalent during adolescence (3). Declines in nutritional status (32) and treatment adherence (33) may also contribute to the increased mortality risk among adolescents. Although we cannot explain the spike in mortality during adolescence, this highly vulnerable period warrants further research and the attention of the clinical community.

As in previous studies, we identified a survival advantage for males compared with females (34, 35), a phenomenon referred to as the “gender gap” (34). The reasons for this are not well-understood. Treatment adherence does not seem to be lower in women (36). In a recent analysis of U.K. CF Registry data collected between 2007 and 2009, Fogarty and associates (37) suggested that serum creatinine (a marker of lean muscle mass) and other

anthropometric features may explain the CF gender gap. An alternative explanation is the effect of hormones on the respiratory system. Coakley and coworkers (38) discovered that high levels of 17β-estradiol, the major circulating estrogen in women, reduce calcium-activated chloride secretion by airway epithelial cells in vitro. Zeitlin (39) has reviewed how this phenomenon could adversely influence sputum rheology in females with CF during the menstrual cycle. Although the underlying pathophysiology is not completely understood, our finding of a persistent gender gap in mortality warrants awareness by patients with CF, their families, and clinicians.

With longer life expectancy, patients with CF are at greater risk for comorbid conditions that may influence mortality and affect health-related quality of life. Isolated reports have emphasized that chronic renal insufficiency (40), hypertriglyceridemia (41), and colon cancer (42) affect adults with CF at higher rates than those without it. Roughly 30% of older adults with CF have depression, which has negative consequences for health-related quality of life regardless of lung function (43). The prevalence of these diagnoses is likely to increase in an aging CF patient population. Clinicians must be aware of these and other potential comorbid conditions.

Increasing the lifespan and treatment options comes with costs, both in expenditures and in indirect costs to the patient, such as increased treatment burden (44). Comparative effectiveness research is currently under way to better understand the effect of therapies and to evaluate the need for additive therapies with disease progression (45). Patient engagement initiatives may help patients with CF and their families address challenges in managing treatments (46). Clinicians and their patients must work together to address knowledge gaps, create solutions to challenges, and seek resources to ensure best care.

With the growing number of adults with CF, clinical care programs are challenged to provide high-quality and efficient care in addition to coordinating with other subspecialists to address comorbid conditions. Despite efforts to keep pace with the increase in numbers of patients and complexity of care, including training opportunities for pulmonary and critical care physicians with adult care–focused and topic-focused (such as CFRD) quality improvement collaboratives, many adult care institutions do not fully appreciate the multidisciplinary needs of patients with CF and often do not perceive a strong business case for the development and ongoing support of an adult CF care program (47–49).

Our study has several important limitations. First, these projections apply to patients diagnosed within the first year of life. Most patients diagnosed after that time would be expected to be pancreatic-sufficient, with a better prognosis than those diagnosed in the first year. Second, patients with CF must be treated at Cystic Fibrosis Foundation–accredited care centers and provide consent to be included in the CFFPR. Most patients with CF in the United States are included in the CFFPR; however, they may not be fully representative of the entire U.S. CF patient population. Nonetheless, the trends in survival are informative. Third, the improving survival of patients with CF may relate in part to the diagnosis of more patients with a milder phenotype and better survival (50). These patients may have been diagnosed less frequently in the past before the widespread availability of genotype analysis. For example, the proportion of newly diagnosed patients who are homozygous for the

F508del mutation decreased from 42% to 36% between 2000 and 2010. However, we adjusted for changes in the distribution of F508del mutation status in our analyses. Fourth, about 2% of patients with CF in the CFFPR are lost to follow-up each year, and the rate is 7% among patients who have had a transplant. Thus, the study sample could have been biased. To address this issue, we made several assumptions for this missing population by using varying survival rates; these sensitivity analyses had minimal effect on our results (**Appendix 3**). Fifth, we encountered a substantial minority of patients with missing genotype data. We excluded these patients from our primary analyses because we anticipate that missing genotype data will become less common as therapies are targeted to specific mutations. When we used multiple imputation to include these patients, the adjusted rate of improvement in survival was considerably higher (2.8% per year, which corresponds to a 32% improvement over the decade [CI, 24% to 38%]) (more detail is provided in **Appendix 3**). Finally, clinical care delivered at individual care centers is likely to be correlated within centers and associated with survival; however, adjustment for these effects did not affect the results (**Appendix 3**). Collectively, these sensitivity analyses support our findings and suggest that our survival projections are conservative.

The median survival estimates observed between 2000 and 2010 are driven by patients with CF born in the 1970s and 1980s. We do not yet have data on median survival for those born in the 1990s and 2000s to evaluate whether their survival is similar to that of their predecessors. Given the implementation of newborn screening and the addition of several new pulmonary therapies, including the recent approval of the first therapy aimed at the basic defect of CF, the assumptions underlying our projections may be too conservative.

In conclusion, patients with CF born and diagnosed in 2010 can expect to live for almost 40 years if there are no further improvements in clinical care and survival and into their 50s if current rates of improvement continue. This has important prognostic implications for patients with CF, their families, and clinicians. It also suggests continued growth in the adult CF population, which will require further attention to developing and sustaining adult care capacity and expertise for this challenging multisystem disease.

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Appendix 1: Additional Information on the Assessment of Survival Between 2000 and 2010

Cox Proportional Hazards Models

We used Cox proportional hazards models to assess trends in survival between 2000 and 2010. Because data are left-truncated with respect to age (that is, patients become *at risk* when they are diagnosed with CF) and calendar year is a time-dependent covariate with respect to age, the entry–exit implementation of the Cox proportional hazards model was used (51). In this approach, each patient was represented by 1 record for each calendar year of follow-up, with the entry time defined as the age at the beginning of the year or entry into

the registry (whichever was larger) and exit time defined as the age at the end of the year or death (whichever was smaller). Patients still alive at last follow-up or the end of the study period were defined as censored. Age at entry into the registry was a significant predictor of mortality ($P = 0.003$), even after adjustment for age at diagnosis and the other characteristics in the model. Some patients diagnosed with CF are not referred to an accredited care center and entered into the registry until challenging clinical issues arise. When we adjusted for age at entry, our estimate of the rate of improvement per calendar year between 2000 and 2010 increased from 1.8% (CI, 0.5% to 2.7%) to 2.7% (CI, 0.8% to 4.0%).

We assessed the proportional hazards assumption by testing whether Schoenfeld residuals were correlated with the time scale (age). We also assessed the log-linearity assumption underlying the hazard ratio estimate for a unit change in calendar year by testing the significance of a quadratic term for calendar year. In both cases, the data supported the validity of the model assumptions.

Smoothed Estimate of Annual Mortality (Triangular Kernel)

For each gender and genotype subgroup, we estimated annual mortality by age using a weighted moving average with a triangular kernel with a radius of 5 years (52). For example, the estimate of annual mortality for patients aged 20 years was equal to:

$$\sum_{i=-5}^{5}\left(5-|i|d\,(20+i)\,/\sum_{i=-5}^{5}\,(5-|i|n\,(20+i)\right.$$

where $d(x)$ is the number of deaths among patients of age x and $n(x)$ is the number of patients of age x. These smoothed age-specific mortality rates were converted to annual mortality by using the transformation [1 – exp(–mortality rate)]. Confidence bounds were derived on the log scale and back-transformed.

Variation in Survival by Subgroups

To examine whether trends in mortality vary among patient subgroups, we report the trends in a forest plot by gender, race or ethnicity, F508del mutation status, age, age at diagnosis, and presentation at diagnosis (**Appendix Figure**). The rate of improvement was similar across gender, F508del mutation status, age at diagnosis, and symptoms at diagnosis. In patients younger than 10 years, mortality increased at a rate of 1.2% per year (CI, −5.9% to 3.7%) between 2000 and 2010, but this did not differ significantly from the rate in the other age groups ($P > 0.10$). We assessed the significance of the interaction between calendar year and age group in the Cox model using a Wald test.

Appendix 2: Survival Projections

The projected survival function was calculated by the formula:

$$S\,(A)=\prod_{0}^{A}\,[1-HR^{a}\,dCH\,(a)$$

where A is age, *HR* refers to the adjusted hazard ratio for a 1-year increment in calendar year (entered as 0 for the conservative projection [no improvement after 2010], 0.982 for the optimistic projection [1.8% rate of improvement per year], and 0.991 for the half-optimistic projection [0.9% rate of improvement per year]), *CH* is the Breslow estimator of the baseline cumulative hazard from the Cox model in which years since 2010 (the baseline value) was entered as the covariate, and *dCH(a)* is the differential of *CH* with respect to age. This method was carried out using all data to get the overall estimator, data from female registry patients to get projected survival for females, and so on according to the patient subgroup being analyzed.

Table 3 displays the data used for **Figure 3** and shows projected survival overall, by gender, and by F508del mutation status, with 3 distinct projections of mortality. In addition to the information shown in **Figure 3**, the table contains projected median survival for the 6 combinations of gender and F508del mutation status.

Appendix 3: Sensitivity Analysis

Loss to Follow-up Among Transplant Recipients

Data from the CFFPR indicated that the rate of loss to follow-up is greater among patients who received an organ transplant than among those who did not (7% vs. 2%). Because the CFFPR is based within CF care centers, posttransplant patients will be lost to follow-up if they elect to receive their ongoing care at the transplant center rather than returning to the CF care center. This is relevant to our study because the mortality rate of transplant patients is probably higher than among nontransplant patients of the same age. To address this potential limitation, we conducted a sensitivity analysis to consider the effect of shorter follow-up of transplant patients within the registry. We simulated an additional year of data for the 548 transplant patients who were lost to follow-up, assuming a mortality rate that was 2, 3, or 5 times as high as that among patients of similar age and genotype. We observed that the adjusted mortality hazard ratio for a year was 0.982 (CI, 0.973 to 0.995) under all 3 scenarios, which is the same as the hazard ratio reported in **Table 2**. Thus, our projections of median survival for a child born and diagnosed in 2010 were not affected.

Missing Genotype Data

Patients with missing genotype data were excluded from the primary analysis because we anticipate that missing genotype data will be less common in this era of therapies targeting specific mutations. The **Appendix Table** shows a comparison of the characteristics of patients in the CFFPR who had complete genotype data and those with missing data. It shows that patients with missing genotype data were older and more likely to have had a transplant, so it is not surprising that they were 1.9 times (CI, 1.3 to 2.7 times) more likely to have died (adjusted $P < 0.001$) than those who were not missing genotype data. In analyses in which we included all patients and did not adjust for genotype, the estimate of the improvement in survival was 4.0% (CI, 3.0% to 4.8%) per year, or 33% (CI, 25% to 40%) over the decade. We conclude that the 1.8% (CI, 0.5% to 2.7%) improvement in survival per year (17% improvement over the decade [CI, 7% to 25%]) reported in **Table 2** is probably

conservative. Assuming continued improvement at this higher rate, we calculated a projected median survival of 73 years (CI, 68 to 78 years) for females and 74 years (CI, 71 to 77 years) for males. Projections based on half this rate of improvement yielded a median survival of 49 years (CI, 45 to 55 years) for females and 53 years (CI, 50 to 56 years) for males.

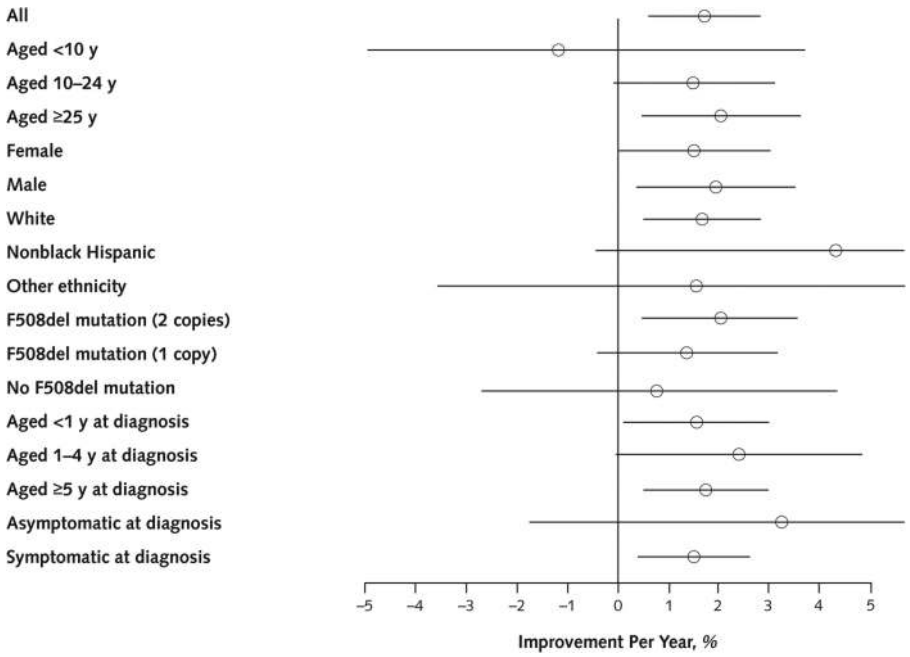
Additional sensitivity analyses were done to assess the effect of including patients with missing genotype data (11.9%) by making various assumptions about the missing data. The estimate of the improvement in survival over the decade was 30% (CI, 23% to 36%), or 3.5% per year, if we assumed that all patients with missing genotype information had no copies of the F508del mutation. If we assumed that all patients with missing genotype data had 2 copies of the mutation, the estimated improvement per year was 33% (CI, 26% to 39%). When we randomly imputed mutation status according to its marginal distribution in patients with genotype data between 2000 and 2010, the estimate of improvement over the decade was 32% (CI, 24% to 38%). These estimates are nearly double the estimate of the rate of improvement reported in **Table 2**, again suggesting that our survival projections are conservative.

Variation in Survival Among Centers During 2000 to 2010

Analyses of the CFFPR data have indicated that the level of adherence to care guidelines and utilization of various nutritional and pulmonary treatments differ depending on the CF care center. Therefore, when calculating the hazard ratios of trends in mortality, we considered the role of the center where the patient was receiving most of their care. The center effect was significantly ($P < 0.001$) associated with survival when we used either a fixed or random effect (γ frailty) (53, 54); however, we report results without this adjustment because inclusion of the center effect had no substantive effect on any of the hazard ratios we report. For example, the estimate of the annual reduction in mortality was the same (1.8% [CI, 0.5% to 2.7%]). Thus, our projections of median survival for a child born and diagnosed in 2010 were not affected.

Age at Entry Into the Registry

When we estimated the annual rate of improvement after adjusting for age at entry into the registry in addition to age, age at diagnosis, gender, race or ethnicity, and genotype, we found a rate of improvement of 2.7% per year (CI, 1.5% to 3.9%). Projections based on this higher rate yield a median survival of 71 years (CI, 66 to 76 years) for females and 72 years (CI, 69 to 75 years) for males. Projections based on half of this rate yield a median survival of 46 years (CI, 42 to 50 years) for females and 52 years (CI, 49 to 55 years) for males. We speculate that patients who entered the registry later in life were less likely to have had regular contact with CF centers, thus limiting their access to treatments that increase longevity.



Appendix Figure.

Rate of reduction in mortality per year, by patient characteristics, calculated by using hazard ratios from a Cox proportional hazards model and adjusted for age, gender, F508del mutation status, and age and presentation at diagnosis.

Appendix Table

Characteristics of Patients With and Without Missing Genotype Data in the Cystic Fibrosis Foundation Patient Registry

Variable	Patients With Complete Genotype Data				Patients Missing Genotype Data			
	2000	2005	2010	2000–2010	2000	2005	2010	2000–2010
Patients, *n*	19 265	20 938	24 125	31 311	2975	2211	2173	4236
Deaths, *n*	270	280	357	3404	151	78	50	998
Median age (IQR), *y*	14.1 (7.6–22.2)	15.3 (8.3–23.7)	16.7 (8.8–26.1)	NA	19 (12.9–27.3)	20.2 (14.0–28.2)	22.1 (13.1–31.1)	NA
Age, *n (%)*								
0–9 y	6584 (34.2)	6500 (31.0)	6936 (28.8)	NA	457 (15.4)	333 (15.1)	434 (20.0)	NA
10–17 y	5655 (29.4)	5860 (28.0)	8071 (25.2)	NA	915 (30.8)	562 (25.4)	352 (16.2)	NA
18–29 y	4447 (23.1)	5459 (26.1)	6758 (28.0)	NA	1029 (34.6)	840 (38.0)	778 (35.8)	NA
30–39 y	1723 (8.9)	1860 (8.9)	2373 (9.8)	NA	396 (13.3)	313 (14.2)	360 (16.6)	NA
≥40 y	856 (4.4)	1259 (6.0)	1987 (8.2)	NA	178 (6.0)	163 (7.4)	249 (11.5)	NA
Median age at diagnosis among patients with incident disease* (IQR), *y*	0.5 (0.1–2.6)	0.4 (0.0–4.6)	0.1 (0.0–4.2)	0.5 (0.1–3.2)	0.6 (0.2–2.8)	0.5 (0.2–2.5)	0.5 (0.2–3.2)	0.6 (0.2–3.5)
Female, *n (%)*	10 116 (52.5)	10 816 (51.7)	12 395 (51.4)	16 197 (51.7)	1660 (55.8)	1236 (55.9)	1205 (55.5)	2378 (56.1)
Race/ethnicity, *n (%)*								
Non-Hispanic white	17 377 (90.2)	18 688 (89.3)	21 241 (88.0)	27 484 (87.8)	2695 (90.6)	1968 (89.0)	1900 (87.4)	3738 (88.2)
Nonblack Hispanic	1020 (5.3)	1259 (6.0)	1603 (6.6)	2102 (6.7)	136 (4.6)	124 (5.6)	141 (6.5)	261 (6.2)
Other	868 (4.5)	991 (4.7)	1281 (5.3)	1725 (5.5)	144 (4.8)	119 (5.4)	132 (6.1)	237 (5.6)
Ever received lung transplant, *n (%)*	394 (2.0)	548 (2.6)	836 (3.5)	1055 (2.8)	238 (8.0)	151 (6.8)	165 (7.6)	1931 (7.4)
Patients with incident disease* who were asymptomatic at diagnosis, *n (%)*	133 (14.3)	235 (26.7)	462 (57.7)	3222 (28.8)	3 (6.1)	7 (14.6)	45 (51.7)	155 (22.0)

IQR = interquartile range; NA = not applicable.

* For the purpose of these analyses, patients were considered to have incident disease the year they were diagnosed.

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Context

Cystic fibrosis (CF) is a life-shortening disease, but care has improved. An updated assessment of survival is important for patients and their families and to plan for the health care needs of an increasing number of patients with CF living to adulthood.

Contribution

The survival of patients with CF enrolled in a national registry increased between 2000 and 2010. Conservative estimates assuming no further improvements suggest that median survival of a patient born and diagnosed in 2010 would be about 39 years.

Implication

The prognosis of patients with CF has improved, and more of these patients can be expected to need adult care.

—The Editors

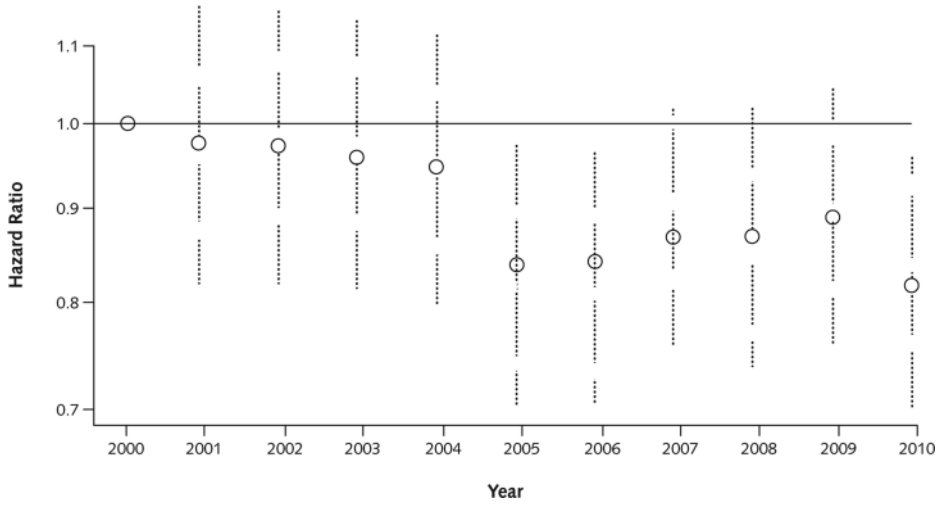

Figure 1.

Mortality from 2001 to 2010 relative to 2000.

The graph depicts changes in mortality between 2000 and 2010 using mortality hazard ratios (estimated using a Cox proportional hazards model) with 2000 as the referent year and adjusted for age (the time scale), age at diagnosis, race/ethnicity, presentation at diagnosis, gender, and F508del mutation status. The rate of decrease in mortality was 1.8% per year (95% CI, 0.7% to 2.8%).

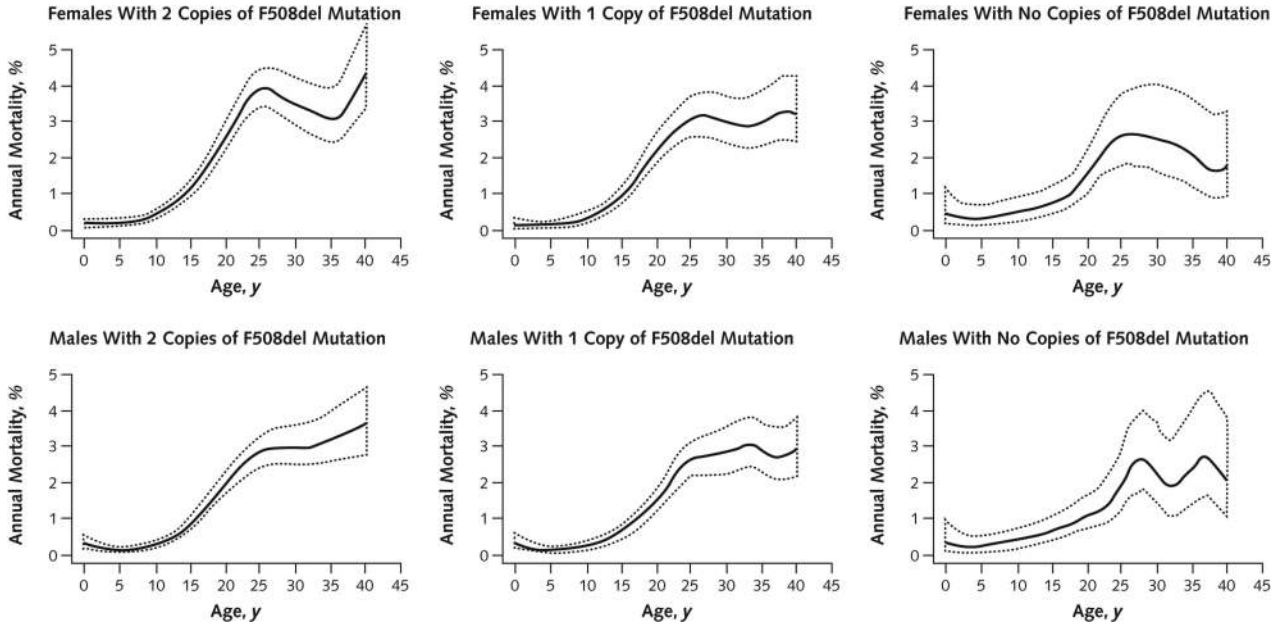

Figure 2.

Annual mortality and 95% CIs, by age, gender, and F508del mutation status, estimated by using a triangular kernel with a radius of 5 y.

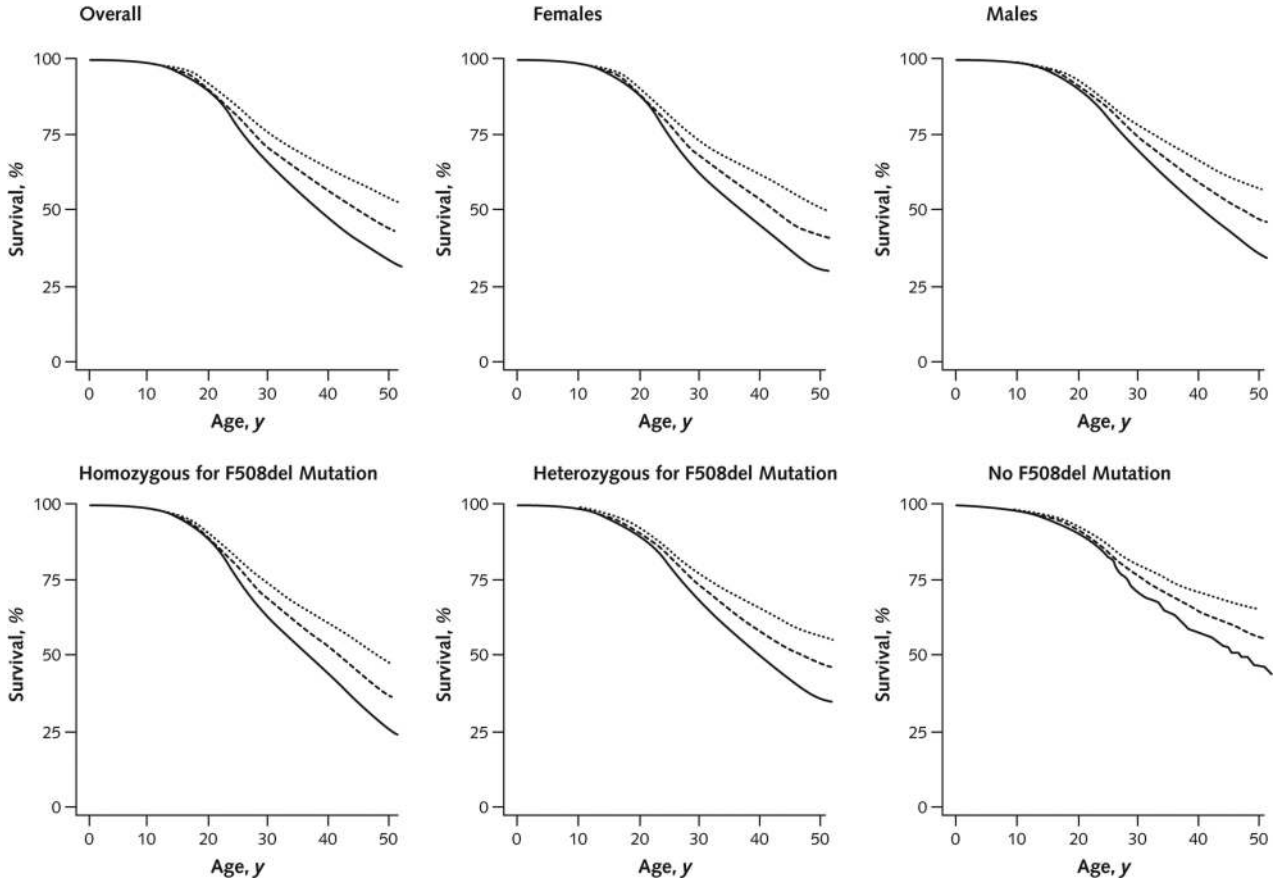

Figure 3.

Projected survival curves for children born and diagnosed with cystic fibrosis in 2010, overall and by gender and genotype.

The most optimistic projection (*dotted line*) assumes that mortality will continue to decrease indefinitely at the rate observed between 2000 and 2010 (1.8% per year). The solid line represents survival if mortality does not decrease further (i.e., stays at 2010 levels). The other projection (*dashed line*) assumes that mortality decreases at half the rate seen from 2000 to 2010 (0.9% per year). Further details are provided in **Table 3**.

Table 1

Characteristics of Patients in the Cystic Fibrosis Foundation Patient Registry

Characteristic	2000	2005	2010	2000–2010
Patients, *n*	22 240	23 149	26 298	34 547
Deaths, *n*	421	358	407	4402
Median age (IQR), *y*	14.3 (7.7–22.5)	15.3 (8.1–23.7)	16.7 (8.5–26.1)	NA
Age, *n (%)*				
0–9 y	7041 (31.8)	6833 (29.5)	7370 (28.0)	NA
10–17 y	7041 (29.5)	6422 (27.7)	6423 (24.4)	NA
18–29 y	6570 (24.6)	6299 (27.2)	7536 (28.7)	NA
30–39 y	2119 (9.5)	2173 (9.4)	2733 (10.4)	NA
≥40 y	1034 (4.6)	1422 (6.1)	2236 (8.5)	NA
Female, *n (%)*	10 464 (47.1)	11 097 (47.9)	12 698 (48.3)	16 972 (47.7)
Median age at diagnosis among patients with incident disease* (IQR), *y*	0.5 (0.2–2.6)	0.5 (0.0–4.9)	0.1 (0.0–6.2)	0.5 (0.1–3.2)
Race/ethnicity, *n (%)*				
Non-Hispanic white	20 072 (90.3)	20 656 (89.2)	23 141 (88.0)	31 222 (87.8)
Nonblack Hispanic	1156 (5.2)	1383 (6.0)	1744 (6.6)	2363 (6.6)
Other	1012 (4.6)	1110 (4.8)	1413 (5.4)	1962 (5.5)
F508del mutation, *n (%)*				
2 copies	9820 (51.0)	10 480 (50.1)	11 484 (47.6)	14 525 (46.4)
1 copy	7279 (37.8)	7952 (38.0)	9531 (39.5)	12 309 (39.3)
0 copies	2166 (11.2)	2506 (12.0)	3110 (12.9)	4477 (14.3)
Unknown	2975 (13.4)	2211 (9.6)	2173 (8.3)	4236 (11.9)
Ever received lung transplant, *n (%)*	632 (2.8)	699 (3.0)	1001 (3.5)	1106 (3.2)
Patients with incident disease* who were asymptomatic at diagnosis, *n (%)*	136 (13.9)	242 (26.0)	507 (57.1)	3222 (28.8)

IQR = interquartile range; NA = not applicable.

*For the purpose of these analyses, patients were considered to have incident disease the year they were diagnosed.

Table 2

Mortality Rate Ratios Observed in the Cystic Fibrosis Foundation Patient Registry From 2000 to 2010

Variable	Person-Years	Hazard Ratio (95% CI)	Adjusted Hazard Ratio* (95% CI)
Age at diagnosis			
<1 y	163 947	1.00	1.00
1–4 y	53 798	0.84 (0.78–0.91)	0.81 (0.74–0.89)
5–9 y	17 722	0.77 (0.68–0.86)	0.79 (0.69–0.91)
10–25 y	17 892	0.57 (0.51–0.64)	0.57 (0.50–0.65)
≥25 y	8056	0.39 (0.32–0.46)	0.38 (0.31–0.47)
Symptomatic at diagnosis			
Yes	232 563	1.00	1.00
No	29 285	0.71 (0.62–0.82)	0.65 (0.55–0.76)
Gender			
Female	125 354	1.00	1.00
Male	136 503	0.85 (0.80–0.90)	0.81 (0.76–0.87)
Race/ethnicity			
Non-Hispanic white	233 584	1.00	1.00
Nonblack Hispanic	15 471	1.42 (1.24–1.63)	1.61 (1.37–1.87)
Other	12 802	1.09 (0.94–1.26)	1.31 (1.10–1.55)
F508del mutation			
2 copies	116 648	1.00	1.00
1 copy	90 713	0.82 (0.76–0.88)	0.86 (0.80–0.93)
0 copies	28 563	0.69 (0.61–0.77)	0.75 (0.66–0.85)
Calendar year	–	0.965 (0.956–0.974)	0.982† (0.972–0.993)
10-y change	–	0.70 (0.64–0.77)	0.83‡ (0.75–0.93)

*Adjusted for age at diagnosis, presentation at diagnosis, gender, race/ethnicity, and F508del mutation status.

†1.8% improvement in survival/y during 2000 to 2010.

‡Cumulative 17% adjusted reduction in mortality during the decade, which can be derived from the calendar year mortality rate ratio of 0.982 (i.e., 1.8% improvement in survival/y) as follows: $(0.982)^{10} = 0.83$.

Table 3

Projections of Median Survival of Children Born and Diagnosed With Cystic Fibrosis in 2010 Under 3 Scenarios of Rate of Improvement in Survival*

Group	Median Survival (95% CI), *y*		
	No Further Improvement	Half the Rate of Improvement Observed From 2000 to 2010†	Same Rate of Improvement Observed From 2000 to 2010‡
Overall	39 (38–40)	45 (44–46)	56 (54–58)
2 copies of F508del mutation	37 (35–39)	43 (41–44)	54 (50–58)
1 copy of F508del mutation	40 (39–42)	47 (45–49)	58 (55–60)
No F508del mutation	46 (41–53)	55 (51–63)	67 (64–73)
Females	37 (35–39)	43 (41–44)	54 (50–58)
2 copies of F508del mutation	35 (33–38)	40 (38–42)	45 (44–49)
1 copy of F508del mutation	38 (36–41)	45 (43–47)	60 (54–66)
No F508del mutation	44 (38–57)	54 (47–64)	66 (60–73)
Males	40 (39–42)	47 (45–49)	58 (55–60)
2 copies of F508del mutation	39 (37–41)	44 (42–46)	53 (49–57)
1 copy of F508del mutation	42 (39–45)	50 (46–53)	60 (56–63)
No F508del mutation	49 (40–70)	56 (52–73)	67 (62–90)

*Data were used for Figure 3.

†0.9%/y.

‡1.8%/y.