Annals of Internal Medicine ORIGINAL RESEARCH

Survival Comparison of Patients With Cystic Fibrosis in Canada and the United States

A Population-Based Cohort Study

Anne L. Stephenson, MD, PhD; Jenna Sykes, MMath; Sanja Stanojevic, PhD; Bradley S. Quon, MD, MSc; Bruce C. Marshall, MD; Kristofer Petren, BA, BSc; Josh Ostrenga, MSc; Aliza K. Fink, DSc; Alexander Elbert, PhD; and Christopher H. Goss, MD, MSc

Background: In 2011, the median age of survival of patients with cystic fibrosis reported in the United States was 36.8 years, compared with 48.5 years in Canada. Direct comparison of survival estimates between national registries is challenging because of inherent differences in methodologies used, data processing techniques, and ascertainment bias.

Objective: To use a standardized approach to calculate cystic fibrosis survival estimates and to explore differences between Canada and the United States.

Design: Population-based study.

Setting: 42 Canadian cystic fibrosis clinics and 110 U.S. cystic fibrosis care centers.

Patients: Patients followed in the Canadian Cystic Fibrosis Registry (CCFR) and U.S. Cystic Fibrosis Foundation Patient Registry (CFFPR) between 1990 and 2013.

Measurements: Cox proportional hazards models were used to compare survival between patients followed in the CCFR (n = 5941) and those in the CFFPR (n = 45 448). Multivariable models were used to adjust for factors known to be associated with survival.

Results: Median age of survival in patients with cystic fibrosis increased in both countries between 1990 and 2013; however, in 1995 and 2005, survival in Canada increased at a faster rate than in the United States ($P < 0.001$). On the basis of contemporary data from 2009 to 2013, the median age of survival in Canada was 10 years greater than in the United States (50.9 vs. 40.6 years, respectively). The adjusted risk for death was 34% lower in Canada than the United States (hazard ratio, 0.66 [95% CI, 0.54 to 0.81]). A greater proportion of patients in Canada received transplants (10.3% vs. 6.5%, respectively [standardized difference, 13.7]). Differences in survival between U.S. and Canadian patients varied according to U.S. patients' insurance status.

Limitation: Ascertainment bias due to missing data or nonrandom loss to follow-up might affect the results.

Conclusion: Differences in cystic fibrosis survival between Canada and the United States persisted after adjustment for risk factors associated with survival, except for private-insurance status among U.S. patients. Differential access to transplantation, increased posttransplant survival, and differences in health care systems may, in part, explain the Canadian survival advantage.

Primary Funding Source: U.S. Cystic Fibrosis Foundation.

Ann Intern Med. 2017;166:537-546. doi:10.7326/M16-0858 **Annals.org**
For author affiliations, see end of text.
This article was published at Annals.org on 14 March 2017.

A comprehensive, multidisciplinary approach to medical care; early treatment of pulmonary disease; and aggressive management of malnutrition have translated into longer lives for persons with cystic fibrosis (1–3). Life expectancy depends on a patient's characteristics as well as his or her access to medical care and medications, which may vary both within and among countries (4, 5). Comparisons of national cystic fibrosis registry data have led to important discoveries in cystic fibrosis disease progression and increased our understanding of epidemiologic trends in cystic fibrosis mortality and clinical care (6–12). Recently, Goss and colleagues (7) showed that among persons aged 6 to 25 years with cystic fibrosis, pulmonary function was greater among patients in the United States than those in the United Kingdom, which was associated with differential prescribing of inhaled mucolytic therapies between the 2 countries.

In 2011, the median age of survival for patients with cystic fibrosis in the U.S. Cystic Fibrosis Foundation Patient Registry (CFFPR) annual data report was 36.8 years, whereas it was 48.5 years in the Canadian Cystic Fibrosis Registry (CCFR) report (13, 14). Directly comparing estimates of median age of survival between national registry reports is problematic because of the inherent differences in methodologies used, data processing techniques, and ascertainment bias (15, 16). We recently showed that survival estimates may be over- or underestimated depending on how data are captured and processed, as well as the proportion of missing data (15). Using a standardized approach to data processing and survival calculations would provide greater confidence in international comparisons and in the identification of factors that may contribute to the observed differences.

The objectives of this study were to determine whether using a standardized approach to data processing and survival calculations would confirm the observed difference between Canada and the United States and, if a survival gap persisted, to explore potential contributing factors. We hypothesized that differences in survival between the countries might be ex-

See also:

Editorial comment 599

Web-Only

Supplement

© 2017 American College of Physicians

Downloaded From: http://annals.org/pdfaccess.ashx?url=/data/journals/aim/936177/ by Kevin Rosteing on 04/26/2017

plained by variations in clinical characteristics of the patient populations, differential rates of transplantation, and variations between the health care systems.

METHODS

This population-based cohort study used prospectively collected data from 42 Canadian and 110 U.S. cystic fibrosis care centers from 1990 through 2013. Each center that submits data to the registry obtains patient consent for the data to be collected. This study was approved by the Research Ethics Board of St. Michael's Hospital, Toronto, Ontario, and the Institutional Review Board of Seattle Children's Hospital, Seattle, Washington.

A detailed description of both registries, as well as information on how patients are accrued and monitored within each registry, is outlined in the **Supplement** (available at Annals.org). The CCFR and CFFPR contain detailed demographic and clinical information on patients with a confirmed diagnosis of cystic fibrosis (17) receiving clinical care at accredited cystic fibrosis centers across Canada and the United States. The registries collect data on age, sex, age at diagnosis, race, symptoms at presentation, whether the patient was diagnosed through newborn screening, date of transplantation, and date and cause of death, as well as anthropometric measurements, lung function, bacteriology, cystic fibrosis–related complications, and pancreatic status.

The research team evaluated each variable in the Canadian and U.S. registries and made comparisons regarding data definitions and how data are collected to establish a unified approach to each variable. Because the CCFR records the first stable clinical measurement per person per year, we selected the first stable measurement of the year for each patient in the CFFPR to mirror data collection methods. A stable measurement was defined as one that was taken from a routine outpatient clinic visit when the patient was not being treated for a pulmonary exacerbation. Missing date of diagnosis was imputed by using date of birth plus 30 days, whereas age at diagnosis was categorized as less than 2 or 2 or more years of age (18). Genotype was classified as homozygous delta F508, heterozygous delta F508, other, or missing. Race was categorized as white, other, or missing. The FEV_1 was expressed as a percentage of the predicted values for healthy age- and sex-matched controls by using Global Lung Function Initiative reference equations (19). Body mass index (BMI) percentile was calculated for children between 2 and 19 years of age by using the Centers for Disease Control and Prevention growth charts (20). Children were then classified as underweight (BMI percentile, ≤12%), adequate weight (BMI percentile, 13% to 84%), or overweight (BMI percentile, ≥85%) (21). For persons aged 19 years and older, BMI was categorized according to World Health Organization guidelines (22) as underweight (<18.5 kg/m^2), adequate weight (18.5 to 24.9 kg/m^2), or overweight (≥25.0 kg/m^2). On the basis of the literature, respiratory bacteria may have a differential effect on survival. We categorized patients whose respiratory tract specimens grew several organisms in a given year according to the organism that carried the worst prognosis in terms of survival. This categorization allowed us to create mutually exclusive groups to avoid combining less virulent organisms with ones associated with a worse prognosis. On the basis of this hierarchical classification, patients with several types of bacteria cultured in a given year were categorized as follows: *Burkholderia cepacia* complex took precedence over any other type of infection, methicillin-resistant *Staphylococcus aureus* took precedence over *Pseudomonas aeruginosa*, and *P aeruginosa* took precedence over all remaining organisms. Cystic fibrosis–related diabetes (CFRD) was defined by the clinic according to published consensus guidelines (23). Pancreatic status was determined by patients' use of pancreatic enzyme replacement therapy; it was used as a surrogate for disease severity in the multivariable analysis, because CFTR (cystic fibrosis transmembrane conductance regulator) genotype and pancreatic status are highly correlated (24), and few patients had missing data for pancreatic enzyme replacement therapy. Previous literature suggests that most patients reported as lost to follow-up at some point during follow-up will return to the cystic fibrosis center within 2 years of nonattendance (5). Thus, patients were considered lost to follow-up if they had no death date recorded and their last reporting year was more than 2 years from the end of the study.

The single-payer universal health insurance program in Canada provides comprehensive medical care to all Canadian citizens, whereas the United States uses a multipayer approach to health care. Patients in the United States were grouped into mutually exclusive categories according to their health insurance coverage as follows: continuous Medicaid or Medicare (receiving Medicare and/or Medicaid in all 5 years), intermittent Medicaid or Medicare (receiving Medicaid and/or Medicare in at least 1 but not all 5 years), other (any other insurance besides Medicaid or Medicare—predominantly employer-provided private insurance), and none or unknown (no or unknown insurance in all 5 years).

Statistical Analyses

Demographic and clinical variables were summarized by country, with categorical variables expressed as frequency and proportion and continuous variables summarized as median and range. Differences between countries were compared by using the Mann–Whitney U test for continuous variables and the chi-square test for categorical variables. *P* values are heavily influenced by sample size; thus, the large sample sizes herein will render very small differences statistically significant. As such, the standardized difference (SD) was used to determine statistical significance. An SD greater than 10 was used to determine statistically significant differences between the countries (25).

We used period survival analysis to calculate median age of survival estimates over time. Median age of

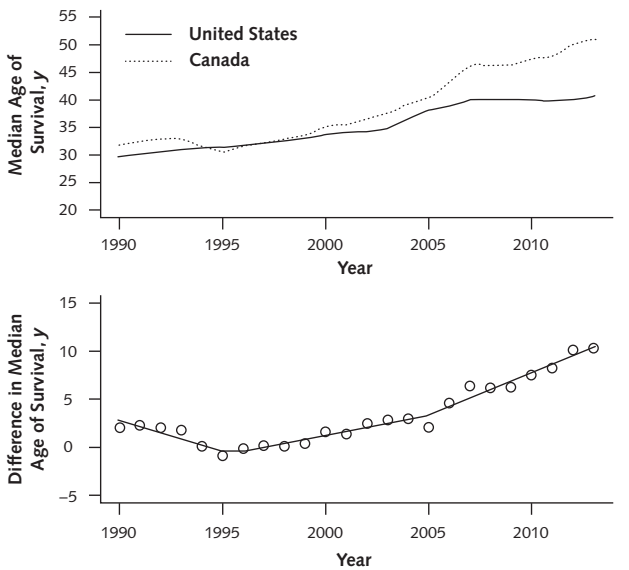
Downloaded From: http://annals.org/pdfaccess.ashx?url=/data/journals/aim/936177/ by Kevin Rosteing on 04/26/2017

survival for each year was calculated for each 5-year window beginning with the period 1986 to 1990 and ending with 2009 to 2013. Differences in median age of survival between the 2 countries over time were evaluated from 1990 to 2013 by using segmented regression analysis to determine whether significant change points emerged when the differences in median age of survival diverged (26).

We further explored differences in survival by adjusting for patient and clinical characteristics with a multivariable Cox proportional hazards model that used data from the most recent 5 years (2009 to 2013), which reflected a contemporary cohort of patients with cystic fibrosis. The multivariable Cox proportional hazards analysis was first conducted on data from all patients, including those who received transplants, and adjusted for time-independent characteristics (sex, race, age at diagnosis, and pancreatic status) and transplant status. Subsequently, we conducted additional multivariable analyses that included time-varying clinical characteristics known to be prognostic for patient survival, such as FEV_1, BMI, CFRD, and microbiology. We excluded patients younger than 6 years because lung function measurements are not reliably measured until the age of 6 years. Because clinical outcomes after transplantation, particularly FEV_1, do not represent cystic fibrosis lung disease, this analysis censored patients at the time of transplantation. Country, sex, age at diagnosis, race, genotype, pancreatic status, and insurance status were modeled as time-independent covariates. Missing lung function and BMI measurements were imputed by using multiple imputation (27) (see the **Supplement** for additional details on survival calculations and imputation methodology).

Patients with milder clinical phenotypes have longer survival; therefore, differences in the proportions of patients with milder cystic fibrosis disease in the 2 countries would bias the survival estimates. To address this potential ascertainment bias, we conducted several subgroup analyses. The multivariable Cox proportional hazards models were repeated, limiting the sample to patients with a severe clinical phenotype as defined by pancreatic status (that is, patients with pancreatic insufficiency), those with homozygous delta F508 disease, and those who received their diagnosis before the age of 2 years (17, 28). To address the differences in health care systems between the 2 countries, we further classified the U.S. patients by insurance status and compared the risk for death in these subgroups with that of Canada, which has universal health care, as a whole. The insurance status classification was used in previous studies, because Medicaid and Medicare have been associated with worse outcomes in cystic fibrosis (29, 30). Because the hierarchical approach to microbiology used in our study has not been used commonly in registry studies, we conducted a sensitivity analysis in which we classified pertinent individuals as having co-infections with several bacteria.

Figure 1. Median age of survival over time.



Top. Median survival age obtained by using a 5-year rolling window, Canada versus the United States, 1990–2013. **Bottom.** Difference in median age of survival between Canada and the United States, 1990–2013. Circles represent the point estimates for the difference.

Role of the Funding Source

This study was funded by a Cystic Fibrosis Foundation grant (STEPHE14A0). The funding source provided access to CFFPR data and contributed to the design, analysis, and interpretation of the findings as well as critical review of the manuscript.

RESULTS

Longitudinal Trends in Survival Over Time (1990 to 2013)

Between 1990 and 2013, the U.S. and Canadian cystic fibrosis registries followed 45 448 and 5941 patients, respectively, with 9654 (21.2%) and 1288 (21.7%) deaths, respectively. Demographic and clinical characteristics of these patients are listed in **Supplement Table 1** (available at Annals.org). Median age of survival in both countries increased over the study period (**Figure 1**, *top*). However, the rate of improvement in median age of survival over time between the 2 countries diverged in 1995 and 2005 (Davies test; $P < 0.001$) (**Figure 1**, *bottom*), most notably in 2005, when the improvements in the Canadian population were greater. The rate of change in survival between males and females differed by country ($P < 0.001$). Survival in Canadian males increased at a significantly faster rate than in U.S. males ($P < 0.001$) from 2005 onward, whereas no statistically significant difference was seen in survival improvement over time in Canadian versus U.S. females ($P = 0.19$). Changes in the median age at death over time and the difference in median age at death between the 2 countries are summarized in the **Supplement Figures 1** and **2** (available at Annals.org).

Downloaded From: http://annals.org/pdfaccess.ashx?url=/data/journals/aim/936177/ by Kevin Rosteing on 04/26/2017

Table 1. Characteristics of Contemporary Patients With Cystic Fibrosis in Canada and the United States, 2009–2013*

Variable	Patients, *n* (%)†		*P* Value‡	SD§
	Canada (*n* = 4662)	United States (*n* = 32 699)		
Vital status				
Censored at follow-up	4421 (94.8)	30 525 (93.4)		
Died	241 (5.2)	2174 (6.6)	<0.001	6.3
Did not receive transplant	147 (61.0)	1699 (78.2)	<0.001	38.0
Median age at death (range), *y*	31.9 (0.3–79.3)	26.9 (0.3–76.9)	<0.001	29.5
Cause of death				
Cardiorespiratory	164 (68.0)	1462 (67.2)	0.176	10.5
Other	51 (21.2)	578 (26.6)		
Unknown	26 (10.8)	134 (6.2)		
Transplantation‖				
No	4182 (89.7)	30 572 (93.5)		
Yes	480 (10.3)	2127 (6.5)	<0.001	13.7
Lost to follow-up¶				
Overall	112 (2.5)	1679 (5.5)	<0.001	14.4
Men	70 (62.5)	956 (56.9)		
Women	42 (37.5)	723 (43.1)		
After transplantation	9 (8.0)	205 (12.2)	0.24	13.7
Age at diagnosis				
Median (range), *y*	0.523 (0–71.7)	0.386 (0–81.7)	<0.001	4.7
<2 y	3108 (66.7)	23 191 (70.9)	<0.001	9.2
≥2 y	1554 (33.3)	9508 (29.1)		
Sex				
Female	2167 (46.5)	15 738 (48.1)	0.037	3.3
Male	2495 (53.5)	16 961 (51.9)		
Race				
White	4305 (92.3)	30 184 (92.3)	<0.001	0.1
Other	213 (4.6)	2515 (7.7)		
Missing	144 (3.1)	0 (0)		
Genotype				
Homozygous Δ F508	2193 (47.0)	14 272 (43.6)	<0.001	6.8
Heterozygous Δ F508	1831 (39.3)	12 517 (38.3)		2.0
Other	531 (11.4)	4427 (13.5)		6.5
Missing	107 (2.3)	1483 (4.5)		12.4
Use of pancreatic enzymes				
Pancreatic sufficient**	688 (14.8)	4585 (14.0)	0.22	1.9
Pancreatic insufficient††	3974 (85.2)	27 977 (85.6)		
Unknown	0 (0)	137 (0.4)		
Neonatal bowel obstruction				
No	3826 (82.1)	26 712 (81.7)	<0.001	9.7
Yes	660 (14.2)	5987 (18.3)		
Unknown	176 (3.8)	0 (0)		
Symptoms at diagnosis				
Asymptomatic	507 (10.9)	6507 (19.9)	<0.001	22.4
Symptomatic	3671 (78.7)	25 489 (78.0)		
Unknown	484 (10.4)	703 (2.1)		
Newborn screening				
No	4291 (92.0)	27 044 (82.7)	<0.001	34.4
Yes	291 (6.2)	5655 (17.3)		
Unknown	80 (1.7)	0 (0)		
Insurance status				
Continuous Medicaid/Medicare	0 (0)	7971 (24.4)	NA	NA
Intermittent Medicaid/Medicare use	0 (0)	10 814 (33.1)		
Other insurance	0 (0)	13 131 (40.2)		
None/unknown	0 (0)	783 (2.4)		
Canadian health care	4662 (100)	0 (0)		

Continued on following page

Downloaded From: http://annals.org/pdfaccess.ashx?url=/data/journals/aim/936177/ by Kevin Rosteing on 04/26/2017

Table 1–Continued

Variable	Patients, *n* (%)†		*P* Value‡	SD§
	Canada (*n* = 4662)	United States (*n* = 32 699)		
Cystic fibrosis-related diabetes				
Yes	1174 (25.2)	8806 (26.9)	<0.001	4.0
No	3488 (74.8)	23 893 (73.1)		
FEV_1‡‡				
Median (range), *% of predicted*	74.03 (11.9–136.7)	74.99 (6.8–148.8)	0.35	1.4
Missing	864 (18.5)	6870 (21.0)		6.2
<40% of predicted	610 (13.1)	4405 (13.5)	0.035	2.7
40–69% of predicted	1108 (23.8)	7048 (21.6)		4.2
≥70% of predicted	2080 (44.6)	14 376 (44.0)		1.8
Body mass index§§				
Underweight	449 (9.6)	2862 (8.8)	0.079	2.1
Normal weight	2527 (54.2)	16 855 (51.5)		1.7
Overweight	629 (13.5)	4597 (14.1)		3.8
Missing	1057 (22.7)	8385 (25.6)		1.0
Microbiology				
Staphylococcus aureus	3165 (70.2)	22 267 (72.6)	<0.001	5.3
Methicillin-resistant *S aureus*	416 (9.2)	11 729 (38.2)	<0.001	72.5
Pseudomonas aeruginosa	2945 (65.3)	21 006 (68.5)	<0.001	6.7
Burkholderia cepacia complex	323 (7.2)	1387 (4.5)	<0.001	11.3
Stenotrophomonas maltophilia	1316 (29.2)	8996 (29.3)	0.87	0.3
Aspergillus	1705 (37.8)	8720 (28.4)	<0.001	20.1
Atypical mycobacterium	213 (4.7)	3025 (9.9)	<0.001	19.9
Treatment‖‖				
Mucolytics¶¶				
Hypertonic saline	1141 (32.3)	15 540 (65.1)	<0.001	69.5
Dornase alfa	1604 (45.4)	20 219 (84.8)	<0.001	90.5
Other	31 (0.9)	786 (3.3)	<0.001	17.0
Inhaled antibiotics***				
TOBI (Novartis)	837 (38.3)	10 603 (68.9)	<0.001	64.4
TOBI Podhaler (Novartis)	731 (33.4)	142 (0.9)	<0.001	95.5
Tobramycin	621 (28.4)	735 (4.8)	<0.001	67.0
Colistin	436 (19.9)	2234 (14.5)	<0.001	14.4
Cayston (Gilead)	263 (12.0)	6565 (42.6)	<0.001	73.1
Azithromycin	1153 (52.7)	10 877 (70.6)	<0.001	37.4
Clinic visits†††				
Median (range), *n*	3.8 (0–33)	4.2 (0–26)	<0.001	24.9
Missing	79 (1.7)	629 (1.9)		

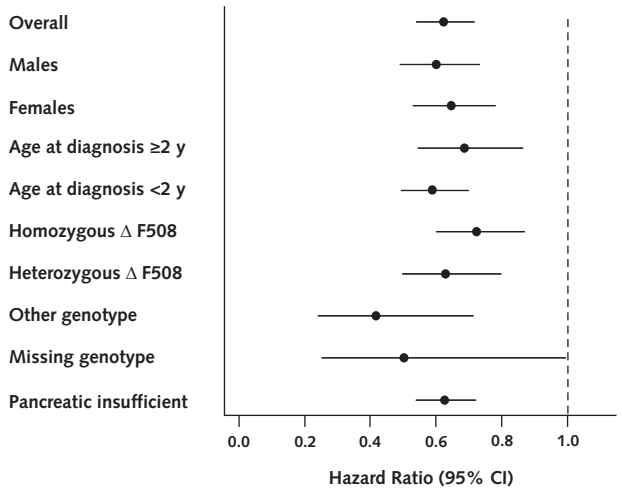
NA = not available; SD = standardized difference.
* Percentages may not sum to 100 due to rounding. All values are summarized on the basis of the last recorded measurement in the time period.
† Unless otherwise indicated.
‡ Differences between countries were compared by using the Mann–Whitney U test for continuous variables and the chi-square test for categorical variables. *P* values are heavily influenced by sample size; thus, these large sample sizes would render very small differences statistically significant. As such, the SD was used to determine statistical significance.
§ The mean difference as a percentage of the average SDs. A value >10 was generally used to determine the variables that remained sufficiently different between the 2 countries.
‖ Only the patient's first transplantation of any type was considered.
¶ Defined as patients who are alive but whose last available year of data was >2 y before the cohort end year. That is, a patient would be considered lost to follow-up if his or her last available reporting year was 2011 or earlier.
** Did not use enzymes in the most recent year.
†† Used enzymes in the most recent year.
‡‡ Calculated by using the Global Lung Function Initiative reference values using the patient's FEV_1 value from the most recent year of follow-up.
§§ Categories were defined by using the World Health Organization classification. The patient's value in the most recent year of follow-up was used.
‖‖ Because treatment data in the Canadian registry are available beginning only in 2011, these estimates are calculated for the 2011–2013 window.
¶¶ Of a total of 3530 Canadian and 23 855 U.S. patients aged >6 y with no prior transplantation.
*** Of a total of 2186 Canadian and 15 398 U.S. patients aged >6 y with no prior transplantation and infected with *P aeruginosa* at some point in the 2011–2013 window.
††† The average number per patient between 2009 and 2013.

Contemporary Cystic Fibrosis Population (2009 to 2013)

The demographic and clinical characteristics of the contemporary cystic fibrosis cohort are summarized in Table 1. A greater proportion of U.S. than Canadian patients had no symptoms at the time of diagnosis (19.9% vs. 10.9% [SD, 22.4]), which corresponds to a higher prevalence of newborn-screened patients in the United States (17.3% vs. 6.2% [SD, 34.4]). A greater proportion of Canadian than U.S. patients had transplants

Downloaded From: http://annals.org/pdfaccess.ashx?url=/data/journals/aim/936177/ by Kevin Rosteing on 04/26/2017

Figure 2. Unadjusted univariate subgroup analysis comparing the risk for death in Canada versus the United States overall and in several subgroups (2009–2013).



The hazard ratio and 95% CI for each variable are displayed. The dashed line is the null line, indicating no difference between countries.

(any organ) (10.3% vs. 6.5% [SD, 13.7]). Seventy-eight percent of all patient deaths in the United States occurred among persons who had never received a transplant, compared with 61% of the deaths in Canada (SD, 38.0). Overall, fewer Canadian patients were lost to follow-up in the registry (2.5% vs. 5.5%), and a higher proportion of U.S. than Canadian patients lost to follow-up had received transplants (12.2% vs. 8.0% [SD, 13.9]). Characteristics of the patients lost to follow-up in both countries are shown in Supplement Table 8 (available at Annals.org).

The median age of survival was 10 years higher in Canada than the United States (50.9 years [95% CI, 50.5 to 52.2 years] vs. 40.6 years [CI, 39.1 to 41.8 years]). The median age at death was 26.9 years in the United States and 31.9 years in Canada (SD, 29.5). The risk for death was consistently lower in Canada than the United States in several population subgroups (Figure 2). To account for the difference between the 2 countries in the number of patients lost to follow-up after transplantation, we recalculated median survival age, censoring patients on the date of transplant, which effectively excluded posttransplant survival time as well as deaths after transplantation in both countries. This analysis caused the survival gap between Canada and the United States to widen further (57.1 vs. 44.0 years, respectively).

Details regarding the creation of the study cohort used for the multivariable analysis are presented in Figure 3, and a summary of the demographic and clinical characteristics of the included patients is provided in Supplement Table 2 (available at Annals.org).

In the multivariable model that adjusted for patient characteristics only, the risk for death was 41% lower in Canada than the United States (hazard ratio [HR], 0.59 [CI, 0.52 to 0.68]; $P < 0.001$; $n = 37\,080$) (Table 2). In the model that adjusted for both patient characteristics and clinical factors, the risk for death was 34% lower in Canada than the United States (HR, 0.66 [CI, 0.54 to 0.81]; $P = 0.002$) (Table 3). No evidence of a statistically significant interaction was seen between country and any of the clinical factors. When U.S. patients were categorized according to their insurance status, Canadians had a 44% lower risk for death than U.S. patients receiving continuous Medicaid or Medicare ($n = 6230$; 24.3%) (HR, 0.56 [CI, 0.45 to 0.71]; $P < 0.001$), a 36% lower risk than those receiving intermittent Medicaid or Medicare ($n = 8429$; 32.9%) (HR, 0.64 [CI, 0.51 to 0.80]; $P = 0.002$), and a 77% lower risk than those with unknown or no health insurance ($n = 205$; 0.8%) (HR, 0.23 [CI, 0.14 to 0.37]; $P < 0.001$). No difference in risk for death was observed between Canadians and U.S. patients with "other" insurance ($n = 10\,754$; 42.0%), including private coverage (HR, 0.85 [CI, 0.67 to 1.07]; $P = 0.15$) (Supplement Table 3, available at Annals.org). To address potential ascertainment bias, the analyses were limited to severe patient phenotypes. Canadian patients with cystic fibrosis consistently had a statistically significantly lower risk for death in all subgroups (Supplement Tables 4 to 6, available at Annals.org). Further, results were unchanged regardless of the method used to classify patients into microbiologic categories (Supplement Table 7, available at Annals.org).

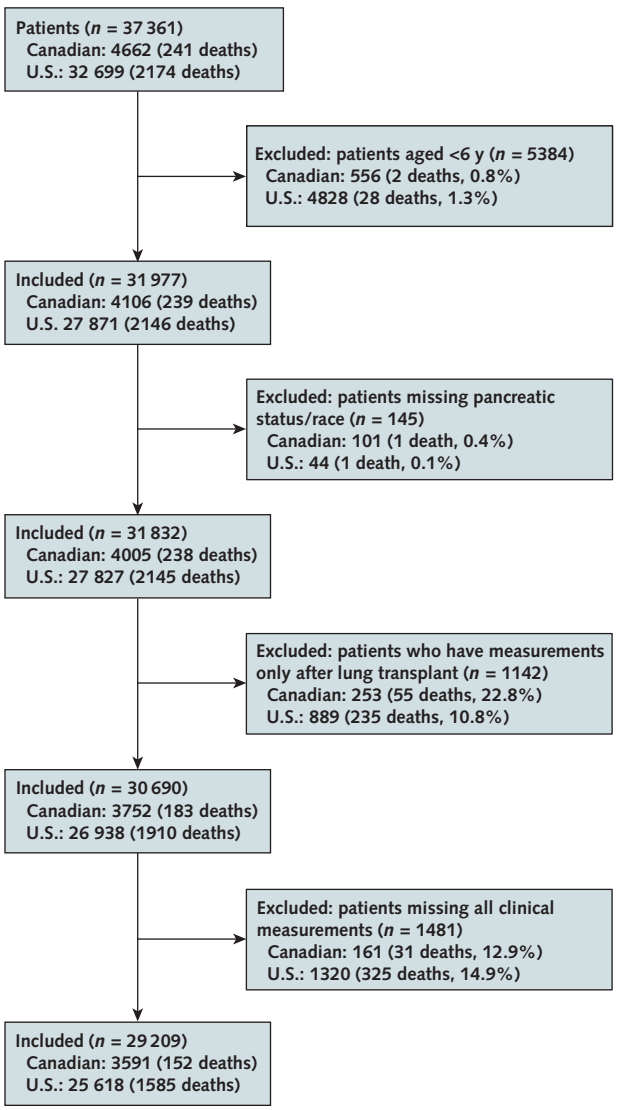
DISCUSSION

Our study confirms a significant survival gap between Canada and the United States in persons living with cystic fibrosis. In the most recent period (2009 to 2013), a 10-year survival advantage was identified for patients living in Canada, which does not seem to be attributed to methodology or data processing techniques. The risk for death was consistently lower in Canada after accounting for several patient demographic and clinical factors and persisted in patients with severe clinical phenotypes. The systematic approach used to compare data from these 2 countries demonstrates that national disease registries can be meaningfully compared and may elucidate factors associated with differences in survival. Although we cannot draw definitive causal inferences from these analyses, the observed differences raise the question of whether a disparity exists in access to therapeutic approaches or health care delivery such that hypotheses may be generated for further investigation.

Although our study was not designed specifically to evaluate the effect of transplantation on survival, few therapeutic interventions have the ability to affect survival in a short period, and several of our findings support the hypothesis that transplantation may be contributing to the observed survival gap. First, although Canada and the United States had similar proportions of patients with cystic fibrosis who had severe lung disease based on FEV_1 during the study period, more Canadian than U.S. patients received a transplant. Second, a greater proportion of deaths in the United States

Downloaded From: http://annals.org/pdfaccess.ashx?url=/data/journals/aim/936177/ by Kevin Rosteing on 04/26/2017

Figure 3. Creation of the study cohort for multivariable analysis (2009–2013).



The percentage of excluded deaths for each country was calculated by dividing the total number of excluded deaths by the total number of initial deaths in each country.

than Canada occurred in patients who had not received a transplant. Third, when we censored patients at transplantation, the median age of survival increased from 10 to 13 years, suggesting that transplantation contributes to the survival gap. Finally, we observed a significant widening of the survival gap between the countries since 2005; in May of that year, prioritization of U.S. patients with cystic fibrosis for lung transplantation changed markedly with implementation of the lung allocation score (LAS), which is not used in Canada (31).

Existing literature further supports the possible role that transplantation plays in the Canada–U.S. survival gap. For instance, median survival is longer in Canadian patients with cystic fibrosis after lung transplantation compared with data from published studies in U.S. patients with cystic fibrosis who received transplants (32, 33). Ramos and colleagues (34) showed that 35% of potentially eligible U.S. patients with cystic fibrosis were not referred for transplantation despite meeting selected criteria for lung transplant evaluation. Although the LAS used in the United States has been associated with shorter wait times and increased transplant survival (35), and the number of patients with cystic fibrosis *listed* for lung transplantation has increased since its implementation, the proportion who have *received* a transplant has decreased (36). In addition, Merlo and colleagues (35) showed that patients with cystic fibrosis who received transplants since the LAS was implemented had a higher risk for death than those who received transplants in the pre-LAS period. These studies suggest that differential access to lung transplantation and survival afterward between Canada and the United States may contribute to the survival gap, although this hypothesis requires further study.

Although transplantation may play a role, other factors likely are contributing to the survival gap, such as the substantial difference in health care delivery between Canada and the United States. In Canada, universal health care provides all persons with the opportunity to access medical services across the country; in the United States, differences in health insurance coverage affect access to medical care and costs of care and are related to socioeconomic status (SES) (30, 33). Indeed, we observed that health insurance status in the United States had a differential effect on the risk for death for persons with cystic fibrosis living in the United States compared with those in Canada. Of interest, no statistically significant difference in risk for death was seen between Canadian patients and U.S. patients with

Table 2. Risk for Death: Multivariable Model Adjusted for Patient Characteristics, 2009–2013 (*n* = 37 080)

Variable	Hazard Ratio (95% CI)	*P* Value
Country		
Canada	0.59 (0.52–0.68)	<0.001
United States	1.00 (reference)	
Race*		
White	1.00 (reference)	
Other	1.25 (1.05–1.49)	0.011
Sex		
Male	1.00 (reference)	
Female	1.29 (1.19–1.39)	<0.001
Age at diagnosis		
<2 y	1.25 (1.14–1.37)	<0.001
≥2 y	1.00 (reference)	
Pancreatic status†		
Insufficient	2.12 (1.79–2.50)	<0.001
Sufficient	1.00 (reference)	
Transplantation		
Yes	3.21 (2.89–3.56)	<0.001
No	1.00 (reference)	

* Data were missing for 144 patients.
† Data were missing for 137 patients.

Downloaded From: http://annals.org/pdfaccess.ashx?url=/data/journals/aim/936177/ by Kevin Rosteing on 04/26/2017

Table 3. Risk for Death: Multivariable Analysis Adjusted for Patient and Clinical Characteristics, 2009–2013 (n = 29 209)*

Variable	Hazard Ratio (95% CI)	*P* Value
Country		
Canada	0.66 (0.54–0.81)	0.002
United States	1.00 (reference)	
Sex		
Male	1.00 (reference)	
Female	1.40 (1.25–1.58)	<0.001
Age at diagnosis		
<2 y	1.02 (0.90–1.17)	0.70
≥2 y	1.00 (reference)	
Pancreatic status		
Insufficient	1.18 (0.93–1.49)	0.15
Sufficient	1.00 (reference)	
Body mass index		
Underweight	1.48 (1.29–1.69)	<0.001
Normal	1.00 (reference)	
Overweight	0.92 (0.74–1.15)	0.43
Cystic fibrosis–related diabetes		
Yes	1.67 (1.47–1.88)	<0.001
No	1.00 (reference)	
Percentage of predicted FEV_1	0.939 (0.935–0.943)	<0.001
Microbiology		
Burkholderia cepacia complex	1.64 (1.25–2.14)	0.002
Methicillin-resistant *Staphylococcus aureus*	1.35 (1.09–1.66)	0.011
Pseudomonas aeruginosa	1.17 (0.96–1.42)	0.11
None of these	1.00 (reference)	

* Data were limited to patients aged ≥6 y with a valid FEV_1 measurement. Reference values for percentage of predicted FEV_1 were calculated by using the Global Lung Function Initiative reference values. Patients were censored at transplantation.

other insurance (primarily private coverage). We could not draw firm conclusions on the effect of SES on the survival gap, because the Canadian registry does not capture SES data. Although all Canadians have access to health care regardless of SES, this does not imply that SES has no effect on survival in Canada, where hidden financial factors, such as costs associated with time off from work, driving long distances to be seen at a cystic fibrosis clinic, or having to relocate to a cystic fibrosis transplant center, may limit patients' ability to seek medical attention. The fact that the risk for death in the United States varied depending on the type of health insurance coverage raises the possibility that differences in the health care systems may explain part of the survival gap documented; however, further study is needed to formally evaluate this question.

Previous comparisons between Canada and the United States in the 1980s suggested that implementation of aggressive nutritional support in the early 1970s in Toronto led to increased survival there compared with Boston (6). As a result, a high-fat diet was adopted worldwide for persons with cystic fibrosis. Those born in Canada in the 1970s would have been exposed to aggressive nutritional supplementation from birth, and the effect of this early support would have reduced their risk for death in their later teenage and early adult years. As such, one would expect that U.S. survival would catch up to Canada's, because cystic fibrosis centers in the United States also implemented the high-calorie diet, albeit 5 to 10 years later.

The strengths of our study include the large sample size, the longitudinal data within both cystic fibrosis registries, the consistency of our results across several subgroups, and our unified approach to the analysis. Both registries have a high participation rate, and cystic fibrosis clinics receive financial incentives for data submission, resulting in a comprehensive national picture of the cystic fibrosis population. However, missing vital statistics may result in biased survival estimates, particularly if one country had a disproportionate number of missing events compared with the other (15). Previous literature suggested that death dates are missing in the CFFPR, particularly for patients older than 45 years, when compared with national vital statistics (37), whereas the number of deaths in the CCFR is similar to that reflected in Canadian vital statistics (5). If the U.S. data were preferentially missing deaths, this would result in an overestimation of true U.S. cystic fibrosis survival. Our data also show that more U.S. than Canadian patients were lost to follow-up, which would have the opposite effect on survival estimates (typically, a greater number of patients lost to follow-up results in an underestimation of median survival) (15). Also worth noting is that more U.S. than Canadian patients lost to follow-up had characteristics associated with a worse prognosis, such as female sex, nonwhite race, pancreatic insufficiency, and CFRD (**Supplement Table 8**). By preferentially excluding U.S. patients with a worse prognosis from the survival analysis, the survival gap may actually be wider than reported in our study. Differences between the registries regarding inclusion of patients with a mild clinical phenotype might result in a survival gap, simply because one country captures patients with mild disease and the other does not. The fact that our findings were consistent across several subgroups, including those with a severe clinical phenotype, suggests that longer survival in Canada than the United States is not the result of following patients with milder disease in the Canadian cohort. Differences in medication use may play a role in the survival gap; between 2011 and 2013, medication use was greater in the United States, but we could not examine medication use for the full study period because of the lack of medication data before 2011 in Canada. Although environmental factors, such as air pollution or climate, may affect lung health in cystic fibrosis, these data were not equally available within the registries (air pollution data have been linked only to the CFFPR). Newborn screening programs have been in place longer in the United States than Canada; however, this likely has no significant effect on the current survival estimates, because relatively few pediatric deaths occur in either country. Furthermore, having more extensive newborn

Downloaded From: http://annals.org/pdfaccess.ashx?url=/data/journals/aim/936177/ by Kevin Rosteing on 04/26/2017

screening programs in the United States would bias the results toward the null, because these patients presumably would be healthier. Regional or center-specific death rates between the countries were not examined because of the relatively few deaths within any given center, which would produce unreliable survival estimates.

In conclusion, we show a difference in survival between Canada and the United States, even after adjusting for patient characteristics and clinical factors known to be associated with survival, with the exception of private-insurance status among U.S. patients. The survival differences appear to diverge at 2 distinct time points, most notably in 2005, when the gap between the 2 countries widened. Differential access to transplantation related to the referral or donor lung allocation process; variable posttransplant survival; and differences in health care systems, including access to insurance, may, in part, explain the Canadian survival advantage. Further studies are necessary to specifically test these hypotheses.

From St. Michael's Hospital, University of Toronto, and The Hospital for Sick Children, Toronto, Ontario, Canada; University of British Columbia, Vancouver, British Columbia, Canada; Cystic Fibrosis Foundation, Bethesda, Maryland; and University of Washington Medical Center, Seattle, Washington.

Note: Dr. Stephenson had full access to all of the data in the study and takes responsibility for the integrity of the data, the accuracy of the data analysis, and the decision to submit the manuscript for publication.

Acknowledgment: The authors acknowledge the support of the U.S. Cystic Fibrosis Foundation and Cystic Fibrosis Canada, which made this study possible. They also acknowledge and thank all of the patients and families in the United States and Canada who consent to be part of their respective national cystic fibrosis patient registries, as well as the cystic fibrosis clinic staff who spend many hours inputting the data.

Grant Support: This study was funded by a Cystic Fibrosis Foundation grant (STEPHE14A0). Dr. Goss receives funding from the Cystic Fibrosis Foundation, the National Institutes of Health (grants R01HL103965, R01HL113382, R01AI101307, U M1HL119073, and P30DK089507), and the U.S. Food and Drug Administration (grant R01FD003704).

Disclosures: Dr. Stephenson reports grants from the Cystic Fibrosis Foundation during the conduct of the study and personal fees from Cystic Fibrosis Canada outside the submitted work. Ms. Sykes reports grants from the Cystic Fibrosis Foundation during the conduct of the study. Dr. Quon is supported by a Cystic Fibrosis Canada Clinician–Scientist Award, but Cystic Fibrosis Canada played no role in the study design or preparation of the manuscript. Dr. Goss reports board membership at KaloBios Pharmaceuticals and Boehringer Ingelheim; consultancy for Vertex Pharmaceuticals and Novartis; grants from Vertex Pharmaceuticals, the Cystic Fibrosis Foundation, the National Institutes of Health, and the U.S. Food and Drug Administration; speaking fees from Hoffmann–La Roche, Johns Hopkins University, the European Cystic Fibrosis Society, and Medscape; and an honorarium from Gilead Sciences. Authors not named here have disclosed no conflicts of interest. Disclosures can also be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M16-0858.

Reproducible Research Statement: *Study protocol:* Not available. *Statistical code:* Available from Dr. Stephenson (e-mail, stephensona@smh.ca). *Data set:* Available upon request from the Cystic Fibrosis Foundation and Cystic Fibrosis Canada.

Requests for Single Reprints: Anne L. Stephenson, MD, PhD, St. Michael's Hospital, 30 Bond Street, 6th Floor, Bond Wing, Toronto, Ontario M5B 1W8, Canada; e-mail: stephensona@smh.ca.

Current author addresses and author contributions are available at Annals.org.

References

1. **George PM, Banya W, Pareek N, Bilton D, Cullinan P, Hodson ME, et al.** Improved survival at low lung function in cystic fibrosis: cohort study from 1990 to 2007. BMJ. 2011;342:d1008. [PMID: 21357627] doi:10.1136/bmj.d1008
2. **Yen EH, Quinton H, Borowitz D.** Better nutritional status in early childhood is associated with improved clinical outcomes and survival in patients with cystic fibrosis. J Pediatr. 2013;162:530-535. [PMID: 23062247] doi:10.1016/j.jpeds.2012.08.040
3. **MacKenzie T, Gifford AH, Sabadosa KA, Quinton HB, Knapp EA, Goss CH, et al.** Longevity of patients with cystic fibrosis in 2000 to 2010 and beyond: survival analysis of the Cystic Fibrosis Foundation patient registry. Ann Intern Med. 2014;161:233-41. [PMID: 25133359] doi:10.7326/M13-0636
4. **Liou TG, Adler FR, Fitzsimmons SC, Cahill BC, Hibbs JR, Marshall BC.** Predictive 5-year survivorship model of cystic fibrosis. Am J Epidemiol. 2001;153:345-52. [PMID: 11207152]
5. **Corey M, Farewell V.** Determinants of mortality from cystic fibrosis in Canada, 1970-1989. Am J Epidemiol. 1996;143:1007-17. [PMID: 8629607]
6. **Corey M, McLaughlin FJ, Williams M, Levison H.** A comparison of survival, growth, and pulmonary function in patients with cystic fibrosis in Boston and Toronto. J Clin Epidemiol. 1988;41:583-91. [PMID: 3260274]
7. **Goss CH, MacNeill SJ, Quinton HB, Marshall BC, Elbert A, Knapp EA, et al.** Children and young adults with CF in the USA have better lung function compared with the UK. Thorax. 2015;70:229-36. [PMID: 25256255] doi:10.1136/thoraxjnl-2014-205718
8. **Fogarty A, Hubbard R, Britton J.** International comparison of median age at death from cystic fibrosis. Chest. 2000;117:1656-60. [PMID: 10858398]
9. **Kollberg H.** Incidence and survival curves of cystic fibrosis in Sweden. Acta Paediatr Scand. 1982;71:197-202. [PMID: 7136627]
10. **Jackson AD, Daly L, Kelleher C, Marshall BC, Quinton HB, Foley L, et al.** The application of current lifetable methods to compare cystic fibrosis median survival internationally is limited. J Cyst Fibros. 2011;10:62-5. [PMID: 20888308] doi:10.1016/j.jcf.2010.08.021
11. **McCormick J, Mehta G, Olesen HV, Viviani L, Macek M Jr, Mehta A; European Registry Working Group.** Comparative demographics of the European cystic fibrosis population: a cross-sectional database analysis. Lancet. 2010;375:1007-13. [PMID: 20304245] doi:10.1016/S0140-6736(09)62161-9
12. **Martin B, Schechter MS, Jaffe A, Cooper P, Bell SC, Ranganathan S.** Comparison of the US and Australian cystic fibrosis registries: the impact of newborn screening. Pediatrics. 2012;129:e348-55. [PMID: 22250024] doi:10.1542/peds.2011-0567

Downloaded From: http://annals.org/pdfaccess.ashx?url=/data/journals/aim/936177/ by Kevin Rosteing on 04/26/2017

13. **Cystic Fibrosis Canada.** Annual Registry Report. Toronto, ON, Canada: Cystic Fibrosis Canada; 2011.
14. **Cystic Fibrosis Foundation.** Cystic Fibrosis Foundation National Patient Registry Annual Data Report. Bethesda: Cystic Fibrosis Foundation; 2011.
15. **Sykes J, Stanojevic S, Goss CH, Quon BS, Marshall BC, Petren K, et al.** A standardized approach to estimating survival statistics for population-based cystic fibrosis registry cohorts. J Clin Epidemiol. 2016;70:206-13. [PMID: 26434789] doi:10.1016/j.jclinepi.2015.08.026
16. **McCormick J, Sims EJ, Green MW, Mehta G, Culross F, Mehta A.** Comparative analysis of Cystic Fibrosis Registry data from the UK with USA, France and Australasia. J Cyst Fibros. 2005;4:115-22. [PMID: 15978536]
17. **Farrell PM, Rosenstein BJ, White TB, Accurso FJ, Castellani C, Cutting GR, et al; Cystic Fibrosis Foundation.** Guidelines for diagnosis of cystic fibrosis in newborns through older adults: Cystic Fibrosis Foundation consensus report. J Pediatr. 2008;153:S4-S14. [PMID: 18639722] doi:10.1016/j.jpeds.2008.05.005
18. **Aaron SD, Stephenson AL, Cameron DW, Whitmore GA.** A statistical model to predict one-year risk of death in patients with cystic fibrosis. J Clin Epidemiol. 2015;68:1336-45. [PMID: 25655532] doi:10.1016/j.jclinepi.2014.12.010
19. **Stanojevic S, Wade A, Stocks J, Hankinson J, Coates AL, Pan H, et al.** Reference ranges for spirometry across all ages: a new approach. Am J Respir Crit Care Med. 2008;177:253-60. [PMID: 18006882]
20. **Kuczmarski RJ, Ogden CL, Grummer-Strawn LM, Flegal KM, Guo SS, Wei R, et al.** CDC growth charts: United States. Adv Data. 2000:1-27. [PMID: 11183293]
21. **Cole TJ, Bellizzi MC, Flegal KM, Dietz WH.** Establishing a standard definition for child overweight and obesity worldwide: international survey. BMJ. 2000;320:1240-3. [PMID: 10797032]
22. **World Health Organization.** BMI classification. 2006. Accessed at http://apps.who.int/bmi/index.jsp?introPage=intro_3.html on 26 September 2016.
23. **Moran A, Hardin D, Rodman D, Allen HF, Beall RJ, Borowitz D, et al.** Diagnosis, screening and management of cystic fibrosis related diabetes mellitus: a consensus conference report. Diabetes Res Clin Pract. 1999;45:61-73. [PMID: 10499886]
24. **Kerem E, Kerem B.** Genotype-phenotype correlations in cystic fibrosis. Pediatr Pulmonol. 1996;22:387-95. [PMID: 9016472]
25. **Normand ST, Landrum MB, Guadagnoli E, Ayanian JZ, Ryan TJ, Cleary PD, et al.** Validating recommendations for coronary angiography following acute myocardial infarction in the elderly: a matched analysis using propensity scores. J Clin Epidemiol. 2001;54:387-98. [PMID: 11297888]
26. **Muggeo VM.** Estimating regression models with unknown breakpoints. Stat Med. 2003;22:3055-71. [PMID: 12973787]
27. **van Buuren S, Groothuis-Oudshoorn K.** MICE: multivariate imputation by chained equations in R. J Stat Softw. 2011;45:1-67.
28. **Lai HJ, Cheng Y, Cho H, Kosorok MR, Farrell PM.** Association between initial disease presentation, lung disease outcomes, and survival in patients with cystic fibrosis. Am J Epidemiol. 2004;159:537-46. [PMID: 15003957]
29. **Quon BS, Psoter K, Mayer-Hamblett N, Aitken ML, Li CI, Goss CH.** Disparities in access to lung transplantation for patients with cystic fibrosis by socioeconomic status. Am J Respir Crit Care Med. 2012;186:1008-13. [PMID: 22983958] doi:10.1164/rccm.201205-0949OC
30. **Schechter MS, Shelton BJ, Margolis PA, Fitzsimmons SC.** The association of socioeconomic status with outcomes in cystic fibrosis patients in the United States. Am J Respir Crit Care Med. 2001;163:1331-7. [PMID: 11371397]
31. **Egan TM, Murray S, Bustami RT, Shearon TH, McCullough KP, Edwards LB, et al.** Development of the new lung allocation system in the United States. Am J Transplant. 2006;6:1212-27. [PMID: 16613597]
32. **Stephenson AL, Sykes J, Berthiaume Y, Singer LG, Aaron SD, Whitmore GA, et al.** Clinical and demographic factors associated with post-lung transplantation survival in individuals with cystic fibrosis. J Heart Lung Transplant. 2015;34:1139-45. [PMID: 26087666] doi:10.1016/j.healun.2015.05.003
33. **Merlo CA, Clark SC, Arnaoutakis GJ, Yonan N, Thomas D, Simon A, et al.** National healthcare delivery systems influence lung transplant outcomes for cystic fibrosis. Am J Transplant. 2015;15:1948-57. [PMID: 25809545] doi:10.1111/ajt.13226
34. **Ramos KJ, Quon BS, Psoter KJ, Lease ED, Mayer-Hamblett N, Aitken ML, et al.** Predictors of non-referral of patients with cystic fibrosis for lung transplant evaluation in the United States. J Cyst Fibros. 2016;15:196-203. [PMID: 26704622] doi:10.1016/j.jcf.2015.11.005
35. **Merlo CA, Weiss ES, Orens JB, Borja MC, Diener-West M, Conte JV, et al.** Impact of U.S. Lung Allocation Score on survival after lung transplantation. J Heart Lung Transplant. 2009;28:769-75. [PMID: 19632571] doi:10.1016/j.healun.2009.04.024
36. **Gries CJ, Mulligan MS, Edelman JD, Raghu G, Curtis JR, Goss CH.** Lung allocation score for lung transplantation: impact on disease severity and survival. Chest. 2007;132:1954-61. [PMID: 18079228]
37. **Nick JA, Chacon CS, Brayshaw SJ, Jones MC, Barboa CM, St Clair CG, et al.** Effects of gender and age at diagnosis on disease progression in long-term survivors of cystic fibrosis. Am J Respir Crit Care Med. 2010;182:614-26. [PMID: 20448091] doi:10.1164/rccm.201001-0092OC

Downloaded From: http://annals.org/pdfaccess.ashx?url=/data/journals/aim/936177/ by Kevin Rosteing on 04/26/2017

Current Author Addresses: Dr. Stephenson and Ms. Sykes: St. Michael's Hospital, 30 Bond Street, 6th Floor, Bond Wing, Toronto, Ontario M5B 1W8, Canada.
Dr. Stanojevic: Institute of Health Policy, Management and Evaluation, University of Toronto, 155 College Street, Toronto, Ontario M5T 3M6, Canada.
Dr. Quon: Centre for Heart Lung Innovation, Department of Medicine, University of British Columbia, #166–1081 Burrard Street, Vancouver, British Columbia V6Z 1Y6, Canada.
Drs. Marshall, Fink, and Elbert; Mr. Petren; and Mr. Ostrenga: Cystic Fibrosis Foundation, 6931 Arlington Road, Bethesda, MD 20814.
Dr. Goss: Division of Pulmonary and Critical Care Medicine, Department of Medicine and Pediatrics, University of Washington Medical Center, 1959 Northeast Pacific Street, Seattle, WA 98195.

Author Contributions: Conception and design: A.L. Stephenson, S. Stanojevic, B.S. Quon, B.C. Marshall, A. Fink, C.H. Goss.
Analysis and interpretation of the data: A.L. Stephenson, J. Sykes, S. Stanojevic, B.S. Quon, K. Petren, A. Fink, A. Elbert, C.H. Goss.
Drafting of the article: A.L. Stephenson, S. Stanojevic, B.S. Quon, C.H. Goss.
Critical revision for important intellectual content: A.L. Stephenson, J. Sykes, S. Stanojevic, B.S. Quon, C.H. Goss.
Final approval of the article: A.L. Stephenson, J. Sykes, S. Stanojevic, B.S. Quon, B.C. Marshall, K. Petren, J. Ostrenga, A. Fink, A. Elbert, C.H. Goss.
Statistical expertise: J. Sykes, S. Stanojevic, J. Ostrenga, C.H. Goss.
Obtaining of funding: A.L. Stephenson, S. Stanojevic, B.S. Quon, C.H. Goss.
Administrative, technical, or logistic support: A.L. Stephenson, K. Petren, A. Elbert.
Collection and assembly of data: A.L. Stephenson, J. Sykes, K. Petren, J. Ostrenga, A. Elbert.

Downloaded From: http://annals.org/pdfaccess.ashx?url=/data/journals/aim/936177/ by Kevin Rosteing on 04/26/2017