ONLINE DATA SUPPLEMENT

Children and young adults with CF in the US have better lung function compared to the UK

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Data Merging

The study employed a retrospective cohort design using data provided at baseline, annual follow-up records, and medical encounters according to the structure of the US Cystic Fibrosis Foundation (CFF) Patient Registry and the UK CF Trust Patient Registry. Data from the two patient registries were entered into two web-based electronic data capture systems (PortCF). Though the data fields are nearly identical, there were some key differences in the collection of data between the two registries. The US CFF Patient Registry collects data at all clinical encounters throughout the year and documents whether the subjects were stable or having a pulmonary exacerbation. The UK CF Trust Registry collects data on an annual basis when subjects are well. Preliminary analyses showed that there was a clear seasonality to the UK registry encounter dates with a higher proportion of encounters entered in the final quarter of the year compared to the US which had patient encounters evenly spread throughout the calendar year. During the merge of the data, the US CFF Patient Registry data were annualized to mirror the UK Trust CF Registry ensuring that for both Registries, only data when the subjects were clinically stable were included.

Both data sets included CF demographics: age of diagnosis, year of diagnosis, age, gender, race/ethnicity, as well as clinical data: pulmonary function, height, weight, body mass index (BMI), CF-related diabetes and pancreatic insufficiency (defined by the use of pancreatic enzymes) and CF transmembrane conductance regulator (CFTR) genotype (F508del, ΔF508 status). Genotype was coded as F508del homozygous, heterozygous, non- F508del and non-genotyped. A number of outcome measures were re-coded within the US CFF Patient Registry to reflect an annualized value of parameters selected for the comparisons between countries. Sputum microbiology (*Pseudomonas aeruginosa*, *Staphylococcus aureus*, MRSA, *Burkholderia cepacia* complex, and others) in the UK are coded annually as negative, positive (≥ 2 sputum samples positive in one year) and intermittent (positive culture not fulfilling definition of

"positive"). Thus, the US clinical encounter data were re-coded to reflect these definitions. The specific chronic nebulized antibiotics used differs significantly between countries. To compare the two countries, we combined all of the chronic nebulized antimicrobial agents and defined the use of inhaled antimicrobial agents as "any nebulized antibiotic."

Because seasonality of clinical encounter could potentially confound our comparison of lung function between the countries, we then employed a matching algorithm to select only one care episode from each subject in the US registry matched on month of calendar year to the UK patients to ensure a similar temporal distribution of the clinical data (Figure E1a and E1b). This algorithm allowed selection of US encounters that almost ideally matched (perfectly matching all months except November and December were error was <0.05% - off just by 1 encounter) monthly distribution of UK encounters thus limiting potential seasonal bias (Figure E1a and E1b). Overall, records of 24,835 of the US patients were selected for comparison with 7,937 records of the UK CF patients (Figure E2). There were no exclusions based on age.

Primary and Secondary Outcomes

The clinical sites involved in the respective registries employ ATS/ERS guidelines for the conduct of spirometry but no formal evaluation is done to ensure compliance with these guidelines.[1, 2] Data were explored to ensure that non-physiologic values were excluded (e.g., FEV_1 > FVC). Absolute values of lung function including forced vital capacity (FVC) as well as FVC % predicted were also analyzed. Age was handled as a categorical variable grouped by 4 age increments (<12 years, 12-18 years, 18-24 years, ≥24 years). Non-physiologic values of weight, height and spirometry were assumed to be missing data. Race was classified as White, Black, Asian and Other (a category that included Hispanic ethnicity and subjects who selected more than one race); each category was made mutually exclusive.

Statistical Methods

Categorical data were presented as frequencies and proportions; continuous data as either means and standard deviations, or medians and inter-quartile ranges (IQR). Chi-square test, Student's t-test (assuming unequal variances) and the Wilcoxon rank-sum test were used to make group comparisons where appropriate. Where data were not normally distributed, differences between the groups were presented as the median difference between values sampled from two groups.

Post-hoc Treatment Intensity Assessment

Because not all the treatments or dosing interval were available in both data sets, we added major treatments to create a simple additive index of level 2 therapies adapted from Sawicki et al. for a total of 6 different therapies.[3] The following medications were available in both registries: hypertonic saline, tobramycin solution, rhDNase, macrolides, colistin, other aminoglycosides.[3] Patients could be treated to up to 6 therapies at one time generating a value from 1 to 6 depending on the number of therapies given to each patient. Given the distribution of the treatment intensity index we combined those patients receiving 4 or more of these therapies (4, 5 and 6) into a single category in order to have 5 levels (0, 1, 2, 3,and 4+) reflecting, roughly, quintiles. When stratified by children and adults there were clear differences between the UK and US.

Completeness of the Data

The following table summarizes the completeness of the data from each cohort and in the combined cohort based on key variables used in the analysis. As can be seen in the table, BMI outcomes were complete for over 95% of patients and lung function for over 92% in both countries. This demonstrates the limited impact of missing data on the analyses that we have conducted.

Variable	Criteria	USA	UK	Total

FEV_1 % predicted (Wang and Hankinson)	Caucasians aged 6 years and older	16,963/18,077 = 93.8%	5,904/6,398 = 92.3%	22,867/24,475 = 93.4%
FVC % predicted (Wang and Hankinson)	Caucasians aged 6 years and older	17,609/18,077 = 97.4%	5,897/6,398 = 92.2%	23,506/24,475 = 96.0%
BMI percentile	Children aged 2-17 years	12,047/12,119 = 99.4%	3,450/3,583 = 96.3%	15,497/15,702 = 98.7%
BMI	Adults aged 18 years and older	10,952/11,058 = 99.0%	3,803/3,965 = 95.9%	14,755/15,023 = 98.2%

Additional Tables Referenced in the Text:

Table E1: Comparisons of lung function and BMI between UK and US data.

Results are presented as means (SD), medians (IQR) or n(%). *[n]* refers to the number of non-missing observations for each given variable in each country/subgroup

	USA		UK		US-UK Difference (95% CI) *	p-value
N	24,835		7,933			
Number of centers providing data in 2010	237		132			
	[n]		*[n]*			
BMI value median (IQR) for age 18 and older						
Male						
18-21 years	*1481*	21.0 (19.2-23.1)	*493*	20.8 (19.0-23.1)	0.20 (-0.20,0.50)	0.316
22-25 years	*1159*	21.8 (19.6-23.9)	*434*	21.9 (20.2-23.8)	-0.20 (-0.60, 0.10)	0.1700
26-29 years	*889*	22.0 (19.9-24.8)	*343*	22.4 (20.2-24.7)	-0.20 (-0.60, 0.20)	0.385
30-33 years	*610*	23.0 (20.8-25.5)	*252*	23.2 (21.2-25.3)	-0.20 (-0.70, 0.30)	0.445
34-37 years	*446*	23.4 (21.1-25.7)	*170*	23.6 (21.9-25.8)	-0.20 (-0.80, 0.40)	0.511
38-41 years	*388*	24.0 (21.5-26.2)	*155*	23.6 (21.9-25.9)	0.10 (-0.60, 0.70)	0.773
42-45 years	*284*	24.4 (21.7-26.9)	*94*	23.4 (21.8-26.3)	0.50 (-0.30, 1.40)	0.205
46-49 years	*213*	24.2 (22.6-26.5)	*79*	24.6 (22.3-27.0)	-0.30 (-1.20, 0.60)	0.515
50+ years	*320*	24.5 (22.5-26.7)	*81*	24.1 (22.4-26.7)	0.10 (-0.70, 0.90)	0.752
Female						
18-21 years	*1313*	20.8 (19.1-22.7)	*435*	20.4 (18.8-22.4)	0.40 (0.10, 0.60)	0.022
22-25 years	*1055*	20.7 (19.1-22.9)	*354*	21.0 (19.3-23.0)	-0.20 (-0.50, 0.20)	0.325
26-29 years	*774*	21.1 (19.5-23.0)	*276*	21.5 (19.5-23.6)	-0.30 (-0.70, 0.10)	0.200
30-33 years	*557*	21.8 (19.9-24.1)	*197*	21.8 (20.0-24.0)	0 (-0.50, 0.50)	1.000
34-37 years	*390*	21.6 (19.8-24.0)	*122*	22.0 (20.8-24.8)	-0.70 (-1.30, 0)	0.038
38-41 years	*331*	22.2 (20.2-25.0)	*110*	22.3 (20.2-24.3)	0.20 (-0.50, 0.90)	0.600
42-45 years	*238*	22.2 (20.3-24.8)	*85*	23.6 (21.0-26.3)	-1.10 (-2.00, -0.20)	0.024
46-49 years	*170*	22.0 (19.9-25.8)	*50*	22.3 (21.1-26.1)	-0.90 (-1.90, 0.20)	0.161
50+ years	*334*	23.1 (20.7-26.9)	*73*	23.4 (20.6-26.4)	0 (-1.20, 1.10)	0.949
BMI percentile (patients aged 2 to 17 years);						

mean (SD)						
Male						
2-5 years	*1,359*	58.75 (26.75)	*447*	60.20 (29.24)	-1.45 (-4.51, 1.62)	0.354
6-9 years	*1,525*	55.39 (25.79)	*368*	52.31 (27.34)	3.09 (-0.0003, 6.17)	0.050
10-13 years	*1,599*	48.08 (27.57)	*482*	45.19 (28.47)	2.89 (0.004, 5.77)	0.050
14-17 years	*1,614*	42.02 (28.22)	*464*	38.88 (27.66)	3.14 (0.27, 6.01)	0.032
Female						
2-5 years	*1,296*	55.59 (27.20)	*414*	58.26 (27.65)	-2.68 (-5.73, 0.38)	0.086
6-9 years	*1,635*	51.68 (25.98)	*403*	49.33 (27.76)	2.35 (-0.64, 5.34)	0.124
10-13 years	*1,536*	46.55 (27.88)	*423*	47.29 (27.53)	-0.73 (-3.71, 2.24)	0.628
14-17 years	*1,483*	48.69 (26.34)	*449*	47.70 (26.90)	1.00 (-1.84, 3.82)	0.492
All						
2-5 years	*2,655*	57.21 (27.01)	*861*	59.27 (28.49)	-2.06 (-4.23, 0.10)	0.0620
6-9 years	*3,160*	53.47 (25.95)	*771*	50.75 (27.58)	2.72 (0.57, 4.87)	0.013
10-13 years	*3,135*	47.33 (27.73)	*905*	46.17 (28.04)	1.16 (-0.91, 3.23)	0.272
14-17 years	*3,097*	45.21 (27.54)	*913*	43.22 (27.63)	2.00 (-0.04, 4.04)	0.055
FEV1 % predicted (Caucasian patients age 6 years and older); mean (SD)						
Overall	16,963	75.72 (26.49)	*5904*	70.23 (24.45)	5.49 (4.75, 6.23)	<0.001
6-9 years	2,518	95.79 (18.47)	*624*	89.54 (15.99)	6.25 (4.80, 7.70)	<0.001
10-13 years	2,627	91.63 (19.92)	*793*	84.71 (19.58)	6.92 (5.36, 8.48)	<0.001
14-17 years	2,618	83.48 (22.31)	*843*	78.23 (20.13)	5.25 (3.64, 6.85)	<0.001
18-21 years	2,391	71.46 (24.36)	*878*	66.14 (22.97)	5.33 (3.52, 7.13)	<0.001
22-25 years	1,900	65.55 (24.20)	*749*	62.93 (23.06)	2.62 (0.64, 4.60)	0.010
26-29 years	1,429	61.15 (24.19)	*590*	59.63 (22.97)	1.53 (-0.71, 3.77)	0.181
30-33 years	969	60.92 (22.66)	*442*	62.23 (23.66)	-1.31 (-3.94, 1.32)	0.329
34-37 years	706	58.09 (23.07)	*280*	59.78 (23.90)	-1.68 (-4.97, 1.60)	0.314
38-41 years	556	58.67 (22.81)	*252*	58.04 (23.34)	0.63 (-2.83, 4.09)	0.722
42-45 years	421	55.17 (22.84)	*175*	56.45 (24.62)	-1.28 (-5.55, 2.98)	0.554
46-49 years	311	53.29 (22.81)	*128*	57.38 (24.32)	-4.09 (-9.04, 0.85)	0.104
50+ years	517	55.43 (22.93)	*150*	60.90 (24.74)	-5.47 (-9.92, -1.03)	0.016
<12 years	3,787	95.06 (18.59)	*1011*	87.76 (17.68)	7.30 (6.06, 8.54)	<0.001
12 to <18 years	3,976	85.63 (22.02)	*1249*	80.29 (20.11)	5.34 (4.03, 6.65)	<0.001
18 to <24 years	3,403	69.89 (24.33)	*1258*	65.19 (22.95)	4.70 (3.19, 6.21)	<0.001
≥24	5,797	59.70 (23.66)	*2386*	60.19 (23.66)	-0.48 (-1.61, 0.64)	0.401
FVC % predicted (Caucasian patients age 6 years and older); mean (SD)						
Overall	*17,609*	86.38 (22.16)	*5897*	83.20 (20.62)	3.18 (2.56, 3.80)	<0.001
6-9 years	*2,515*	100.17 (16.89)	*622*	96.38 (14.67)	3.79 (2.46, 5.12)	<0.001
10-13 years	*2,627*	98.03 (17.16)	*793*	93.36 (17.17)	4.68 (3.31, 6.04)	<0.001
14-17 years	*2,640*	93.73 (19.64)	*841*	89.76 (17.67)	3.97 (2.56, 5.38)	<0.001

18-21 years	*2,426*	83.25 (21.37)	*878*	80.03 (20.19)	3.22 (1.64, 4.81)	<0.001
22-25 years	*1,970*	79.23 (21.47)	*749*	77.76 (20.40)	1.47 (-0.27, 3.21)	0.098
26-29 years	*1,510*	76.61 (21.54)	*590*	76.05 (20.78)	0.56 (-1.44, 2.56)	0.584
30-33 years	*1,056*	76.94 (20.07)	*442*	78.29 (20.12)	-1.34 (-3.58, 0.89)	0.239
34-37 years	*773*	74.94 (20.04)	*279*	75.73 (20.69)	0.79 (-3.61, 2.02)	0.581
38-41 years	*660*	75.10 (19.77)	*252*	75.27 (21.16)	-0.17 (-3.20, 2.85)	0.911
42-45 years	*485*	71.35 (19.77)	*173*	73.01 (19.52)	-1.65 (-5.07, 1.76)	0.341
46-49 years	*350*	70.76 (20.23)	*128*	72.80 (19.28)	-2.03 (-6.01, 1.95)	0.315
50+ years	*597*	70.83 (19.94)	*150*	74.36 (19.91)	-3.53 (-7.11, 0.05)	0.054
<12 years	*3,781*	99.71 (16.72)	*1009*	94.82 (16.01)	4.88 (3.76, 6.01)	<0.001
12 to <18 years	*4,001*	94.95 (19.13)	*1247*	91.25 (17.46)	3.70 (2.57, 4.84)	<0.001
18 to <24 years	*3,465*	82.15 (21.41)	*1258*	79.35 (20.27)	2.80 (1.47, 4.13)	<0.001
≥24	*6,362*	75.37 (20.76)	*2383*	76.11 (20.45)	-0.74 (-1.70, 0.23)	0.135
Pancreatic enzyme use; n(%)	*24,835*	21542 (86.7%)	*7543*	6,646 (88.1)	1.4% (0.5%, 2.2%)	0.002

* Where medians are used, differences between the groups are presented as the median difference between values sampled from two groups. This difference is not strictly equal to the difference between the two medians.

Table E2: Analysis restricted to F508del homozygote patients

	USA		**UK**		**USA-UK Difference (95% CI) ***	**p-value**
N	10,957		3,973			
	[n]		*[n]*			
BMI value (patients aged 2 years and older); median (IQR)						
Male						
18-21 years	*671*	20.8 (19.1, 22.8)	*257*	20.9 (19.0, 23.3)	-0.20 (-0.60, 0.20)	0.367
22-25 years	*527*	21.6 (19.5, 23.8)	*238*	21.8 (20.1, 23.6)	-0.10 (-0.60, 0.30)	0.526
26-29 years	*447*	21.6 (19.7, 24.4)	*168*	22.4 (20.1, 24.5)	-0.50 (-1.00, 0.10)	0.135
30-33 years	*283*	22.8 (20.5, 25.1)	*137*	23.0 (20.6, 25.1)	-0.20 (-0.90, 0.40)	0.507
34-37 years	*186*	23.3 (21.0, 25.5)	*73*	22.6 (20.8, 24.8)	0.60 (-0.30, 1.40)	0.193
38-41 years	*145*	23.7 (21.4, 25.8)	*59*	23.4 (21.5, 25.3)	0.20 (-0.80, 1.10)	0.729
42-45 years	*106*	24.0 (21.2, 25.6)	*30*	22.7 (20.9, 26.1)	0.50 (-0.90, 1.90)	0.442
46-49 years	*71*	24.0 (22.9, 26.2)	*31*	22.9 (21.2, 25.3)	1.10 (-0.20, 2.30)	0.091
50+ years	*68*	24.4 (21.7, 26.2)	*16*	23.2 (22.1, 26.3)	0.40 (-1.30, 2.00)	0.616
Female						
18-21 years	*611*	20.6 (18.9, 22.2)	*226*	20.4 (18.9, 22.0)	0.10 (-0.20, 0.50)	0.488
22-25 years	*481*	20.6 (18.9, 22.9)	*186*	20.9 (19.2, 22.9)	-0.20 (-0.70, 0.20)	0.321
26-29 years	*352*	20.9 (19.4, 22.7)	*131*	21.3 (19.3, 23.3)	-0.20 (-0.80, 0.40)	0.515
30-33 years	*227*	21.1 (19.6, 23.3)	*83*	21.4 (19.6, 23.3)	-0.10(-0.80, 0.60)	0.828
34-37 years	*162*	20.9 (19.3, 22.9)	*49*	21.7 (20.2, 23.2)	-0.70 (-1.50, 0.10)	0.108
38-41 years	*125*	21.9 (20.2, 24.1)	*43*	22.3 (19.5, 24.3)	-0.10 (-1.20, 1.10)	0.913
42-45 years	*66*	21.9 (20.0, 24.4)	*31*	22.7 (20.7, 25.8)	-0.70 (-2.30, 0.80)	0.305
46-49 years	*38*	21.7 (19.7, 23.8)	*17*	23.8 (21.7, 26.4)	-2.20 (-4.00, -0.30)	0.026
50+ years	*46*	21.4 (19.9, 23.7)	*11*	22.2 (21.5, 25.6)	-1.00 (-2.50, 0.60)	0.262
BMI percentile (patients aged 2 to 17 years); mean (SD)						
Male						
2-5 years	*577*	58.42 (25.87)	*244*	59.50 (28.11)	-1.08 (-5.20, 3.05)	0.608

6-9 years	*748*	54.37 (25.40)	*214*	52.36 (26.72)	2.01 (-2.02, 6.04)	0.327
10-13 years	*759*	46.41 (26.83)	*265*	43.04 (27.01)	3.38 (-0.40, 7.16)	0.080
14-17 years	*729*	39.77 (27.16)	*265*	37.32 (27.25)	2.45 (-1.39, 6.29)	0.211
Female						
2-5 years	*570*	55.78 (26.26)	*196*	59.18 (26.57)	-3.40 (-7.71, 0.92)	0.122
6-9 years	*771*	49.97 (25.63)	*211*	48.59 (27.01)	1.37 (-2.71, 5.46)	0.509
10-13 years	*713*	45.28 (27.64)	*212*	48.06 (26.71)	-2.78 (-6.92, 1.37)	0.189
14-17 years	*694*	47.48 (25.80)	*225*	45.61 (26.39)	1.87 (-2.09, 5.83)	0.354
All						
2-5 years	*1,147*	57.11 (26.08)	*440*	59.36 (27.40)	-2.25 (-5.22, 0.73)	0.139
6-9 years	*1,519*	52.14 (25.60)	*425*	50.49 (26.90)	1.65 (-1.22, 4.52)	0.260
10-13 years	*1,472*	45.86 (27.22)	*477*	45.27 (26.96)	0.60 (-2.20, 3.39)	0.675
14-17 years	*1,423*	43.53 (26.78)	*490*	41.13 (27.15)	2.40 (-0.38, 5.18)	0.090
FEV1 % predicted (patients age 6 years and older); mean (SD)						
6-9 years	*1,318*	95.12 (18.97)	*354*	89.36 (15.70)	5.76 (3.82, 7.69)	<0.001
10-13 years	*1,330*	90.78 (20.40)	*430*	83.23 (16.61)	7.56 (5.40, 9.71)	<0.001
14-17 years	*1,313*	82.72 (22.77)	*458*	76.88 (20.03)	5.84 (3.62, 8.05)	<0.001
18-21 years	*1,160*	69.86 (24.36)	*467*	65.40 (22.60)	4.46 (1.97, 6.95)	0.001
22-25 years	*904*	64.02 (23.98)	*415*	62.27 (22.69)	1.74 (-0.95, 4.43)	0.204
26-29 years	*718*	59.91 (23.99)	*291*	57.03 (22.18)	2.88 (-0.22, 5.98)	0.069
30-33 years	*432*	59.03 (21.66)	*220*	58.78 (22.85)	0.26 (-3.40, 3.92)	0.889
34-37 years	*304*	55.60 (21.39)	*120*	54.85 (23.43)	0.75 (-4.11, 5.61)	0.761
38-41 years	*209*	56.44 (21.18)	*97*	55.27 (22.75)	1.17 (-4.23, 6.57)	0.669
42-45 years	*131*	51.37 (21.69)	*62*	53.12 (23.52)	-1.75 (-8.76, 5.26)	0.622
46-49 years	*91*	47.80 (18.20)	*47*	57.42 (25.39)	-9.62 (-17.93, -1.31)	0.024
50+ years	*77*	50.34 (19.81)	*26*	59.21 (27.97)	-8.87 (-20.93, 3.19)	0.144
<12 years	*1,980*	94.20 (19.19)	*570*	87.22 (17.75)	6.98 (5.30, 8.67)	<0.001
12 to <18 years	*1,981*	84.91 (22.44)	*672*	78.75 (19.88)	6.16 (4.36, 7.96)	<0.001
18 to <24 years	*1,650*	68.42 (24.18)	*683*	64.42 (22.52)	4.00 (1.95, 6.06)	<0.001
≥24	*2,376*	58.16 (22.97)	*1062*	57.81 (23.16)	0.35 (-1.32, 2.03)	0.677

* Where medians are used, differences between the groups are presented as the median difference between values sampled from two groups. This difference is not strictly equal to the difference between the two medians.

Table E3. Treatment differences stratified by lung function impairment and age

Note the differences in treatment rates in the USA compared to the UK generally are larger in children than adults over most stata of lung function.

Hypertonic saline

	USA	UK	USA-UK Difference (95% CI)	p-value
FEV_1<40%				
<18 years	113 (62.4)	20 (29.0)	33.4 (20.6, 46.3)	<0.001
≥18 years	1,150 (62.3)	158 (21.2)	41.2 (37.5, 44.8)	<0.001
FEV_1≥40% and <70%				

<18 years	668 (64.4)	72 (17.4)	47.0 (42.3, 51.7)	<0.001
≥18 years	2,057 (60.0)	251 (17.1)	42.9 (40.4, 45.5)	<0.001
FEV_1≥70% and <90%				
<18 years	1,127 (54.6)	103 (12.1)	42.5 (39.5, 45.6)	<0.001
≥18 years	1,175 (50.4)	91 (9.9)	40.5 (37.7, 43.3)	<0.001
FEV_1≥90%				
<18 years	1979 (45.6)	61 (6.8)	38.9 (36.7, 41.1)	<0.001
≥18 years	575 (40.4)	34 (7.3)	33.1 (29.6, 36.6)	<0.001

Any nebulized antibiotics

	USA	**UK**	**USA-UK Difference (95% CI)**	**p-value**
FEV_1<40%				
<18 years	166 (91.7)	51 (73.9)	17.8 (6.7, 28.9)	<0.001
≥18 years	1,531 (83.0)	543 (72.8)	10.2 (6.6, 13.8)	<0.001
FEV_1≥40% and <70%				
<18 years	818 (78.8)	298 (71.8)	7.0 (2.0, 12.0)	0.004
≥18 years	2,520 (73.5)	984 (67.0)	6.5 (3.7, 9.3)	<0.001
FEV_1≥70% and <90%				
<18 years	1,236 (59.9)	476 (55.8)	4.1 (0.1, 8.0)	0.042
≥18 years	1,424 (61.1)	519 (56.6)	4.5 (0.7, 8.3)	0.018
FEV_1≥90%				
<18 years	1,795 (41.4)	378 (41.8)	-0.4 (-4.0, 3.1)	0.809
≥18 years	638 (44.9)	180 (38.8)	6.1 (0.9, 11.2)	0.022

rhDNase

	USA	**UK**	**USA-UK Difference (95% CI)**	**p-value**
FEV_1<40%				
<18 years	177 (97.8)	49 (71.0)	26.8 (15.9, 37.7)	<0.001
≥18 years	1,611 (87.3)	529 (70.9)	16.4 (12.8, 20.0)	<0.001
FEV_1≥40% and <70%				
<18 years	960 (92.5)	281 (67.7)	24.8 (20.0, 29.6)	<0.001
≥18 years	2,799 (81.7)	846 (57.6)	24.0 (21.2, 26.9)	<0.001
FEV_1≥70% and <90%				
<18 years	1,861 (90.2)	423 (49.6)	40.6 (37.0, 44.2)	<0.001
≥18 years	1,760 (75.5)	391 (42.6)	32.9 (29.3, 36.5)	<0.001
FEV_1≥90%				
<18 years	3,599 (83.0)	303 (33.5)	49.4 (46.2, 52.7)	<0.001
≥18 years	956 (67.2)	105 (22.6)	44.6 (40.1, 49.1)	<0.001

Macrolides

	USA	**UK**	**USA-UK Difference (95% CI)**	**p-value**
FEV_1<40%				
<18 years	134 (74.0)	48 (69.6)	4.5 (-8.1, 17.1)	0.478
≥18 years	1,466 (79.5)	584 (78.3)	1.1 (-2.4, 4.6)	0.506

FEV_1≥40% and <70%				
<18 years	664 (64.0)	224 (54.0)	10.0 (4.4, 15.6)	<0.001
≥18 years	2,478 (72.3)	997 (67.9)	4.4 (1.6, 7.2)	0.002
FEV_1≥70% and <90%				
<18 years	969 (47.0)	272 (31.9)	15.1 (11.3, 18.9)	<0.001
≥18 years	1,418 (60.9)	478 (52.1)	8.7 (4.9, 12.5)	<0.001
FEV_1≥90%				
<18 years	1,668 (38.5)	222 (24.6)	13.9 (10.7, 17.1)	<0.001
≥18 years	694 (48.8)	150 (32.3)	16.5 (11.5, 21.5)	<0.001

Table E4. Stratified analyses of FEV_1 (% predicted among Caucasian patients) between countries and treatment intensity (TIS)

Regardless of the age and TIS level, FEV_1% predicted was higher in the US compared to the UK, suggesting a lower threshold to add therapies in the US. This phenomenon was more marked in the children and young adults compared to older adults.

	USA		**UK**		**USA-UK Difference (95% CI)**	**p-value**
	[n]	**Mean FEV_1(SD)**	*[n]*	**Mean FEV_1(SD)**		
By age category and TIS category*						
< 12 years						
TIS = 0 (no rx)	*241*	100.63 (14.79)	*345*	92.70 (14.01)	7.94 (5.54, 10.33)	<0.001
TIS = 1 (1 rx)	*976*	98.72 (16.24)	*276*	90.25 (16.41)	8.47 (6.28, 10.66)	<0.001
TIS = 2 (2 rx)	*1,096*	96.39 (17.27)	*215*	84.54 (18.09)	11.85 (9.22, 14.49)	<0.001
TIS = 3 (3 rx)	*876*	92.49 (19.73)	*112*	79.35 (20.66)	13.15 (9.07, 17.22)	<0.001
TIS = 4 (4+ rx)	*512*	85.75 (21.64)	*56*	73.98 (20.74)	11.78 (5.93, 17.63)	<0.001
12-18 years						
TIS = 0 (no rx)	*159*	99.60 (16.99)	*218*	91.66 (15.66)	7.94 (4.57, 11.32)	<0.001
TIS = 1 (1 rx)	*586*	94.57 (17.12)	*324*	83.53 (18.51)	11.04 (8.59, 13.49)	<0.001
TIS = 2 (2 rx)	*993*	90.68 (19.09)	*334*	80.25 (18.13)	10.43 (8.15, 12.71)	<0.001
TIS = 3 (3 rx)	*1,111*	83.81 (21.72)	*252*	72.64 (20.70)	11.17 (8.30, 14.04)	<0.001
TIS = 4 (4+ rx)	*1,071*	75.29 (23.30)	*109*	65.16 (21.20)	10.13 (5.87, 14.38)	<0.001
18-24 years						
TIS = 0 (no rx)	*157*	90.68 (19.20)	*160*	81.70 (19.96)	8.98 (4.66, 13.31)	<0.001
TIS = 1 (1 rx)	*407*	83.16 (20.76)	*233*	73.02 (21.99)	10.14 (6.66, 13.62)	<0.001
TIS = 2 (2 rx)	*669*	73.81 (22.79)	*331*	63.99 (21.64)	9.82 (6.92, 12.73)	<0.001
TIS = 3 (3 rx)	*980*	68.84 (23.19)	*354*	59.61 (21.71)	9.23 (6.54, 11.92)	<0.001
TIS = 4 (4+ rx)	*1,146*	60.10 (23.13)	*161*	51.92 (19.17)	8.18 (4.91, 11.45)	<0.001
≥24 years						
TIS = 0 (no rx)	*346*	80.34 (21.20)	*390*	79.07 (22.39)	1.26 (-1.89, 4.42)	0.432
TIS = 1 (1 rx)	*720*	68.04 (24.04)	*496*	63.85 (21.82)	4.19 (1.58, 6.79)	0.002
TIS = 2 (2 rx)	*1,208*	61.27 (23.11)	*580*	57.92 (22.42)	3.35 (1.11, 5.60)	0.004
TIS = 3 (3 rx)	*1,668*	57.07 (22.40)	*587*	52.31 (20.48)	4.76 (2.78, 6.74)	<0.001
TIS = 4 (4+ rx)	*1,723*	52.22 (21.17)	*303*	49.19 (19.96)	3.03 (0.56, 5.50)	0.016

*patients age 6 years and older

Table E5: Center-level treatment rates evaluating rates for nebulized antibiotics, rhDNase, hypertonic saline and macrolides

Treatment	USA	UK	p-value
rhDNase			
Median	80.6%	36.1%	<0.001
Minimum	16.3%	0	
25th percentile	71.0%	22.7%	
75th percentile	87.0%	49.8%	
Maximum	100%	100%	
Hypertonic saline			
Median	43.7%	5.3%	<0.001
Minimum	0	0	
25th percentile	28.3%	0	
75th percentile	60.0%	16.6%	
Maximum	100%	50.0%	
Macrolides			
Median	47.6%	28.0%	<0.001
Minimum	0	0	
25th percentile	33.0%	14.3%	
75th percentile	66.4%	50.0%	
Maximum	100%	100%	
Nebulised antibiotics			
Median	56.0%	50.0%	<0.001
Minimum	0	0	
25th percentile	45.9%	36.1%	
75th percentile	66.4%	59.5%	
Maximum	100%	100%	

Table E6. Regression models restricted to homozygote F508del

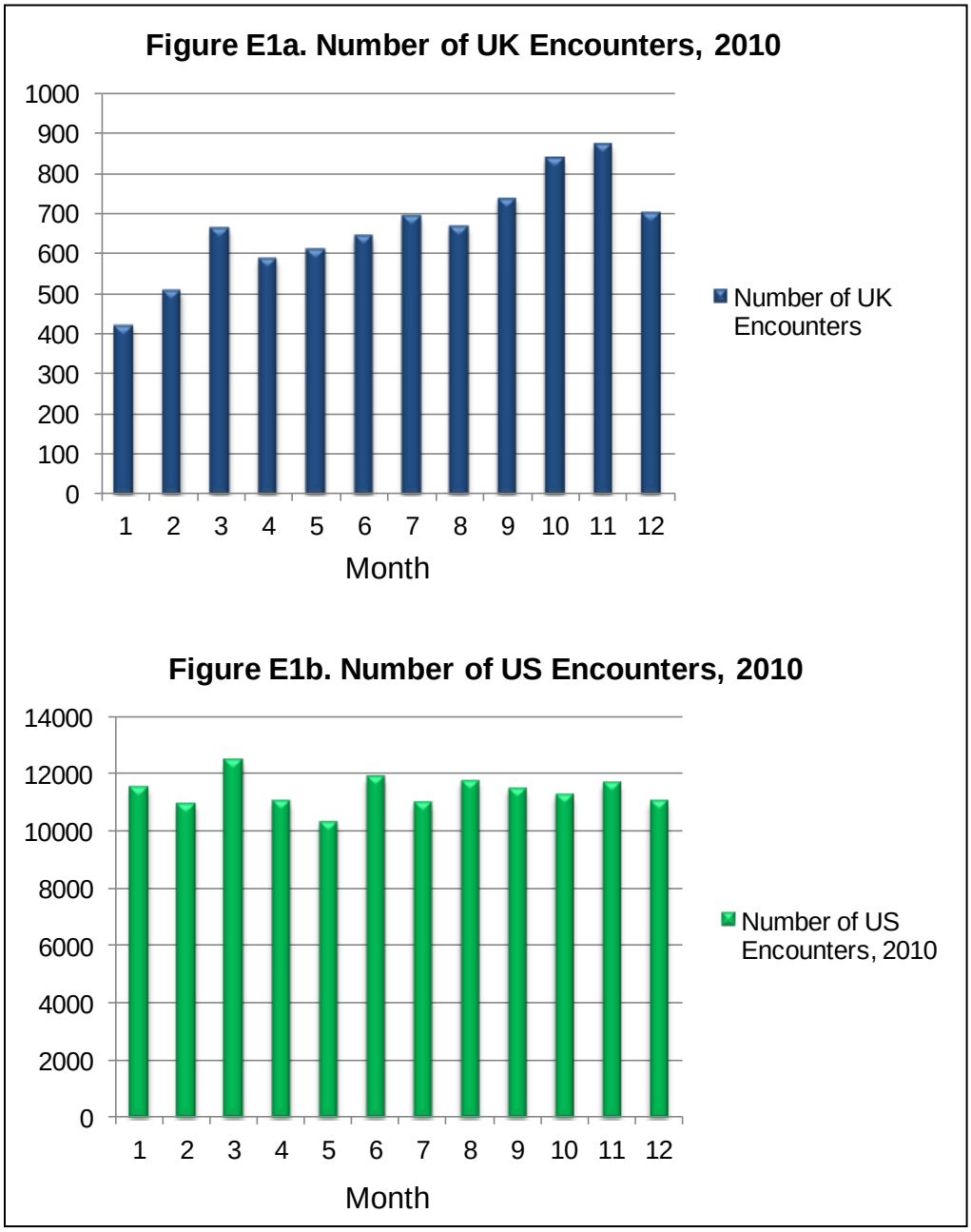
Regression models	US-UK effect (95% CI)
Model 1: Adjusting for age, gender, age at diagnosis and pancreatic enzyme use	3.75 (2.83, 4.68)
Model 2: Adding microbiology to Model 1	4.61 (3.63, 5.59)
Model 3: Model 1 with adjustment for height	3.81 (2.89, 4.74)
Model 4: Model 1 with adjustment for height and microbiology	4.66 (3.69, 5.64)

Table E7. Analysis of FEV_1 (liters) adjusted for height, age and gender within the model (restricted to Caucasians).

The US-UK differences in FEV1 are not an artifact of reference equations or reference populations.

Age strata and Models		US-UK effect (95% CI)
Children aged 6 to 17 years		
	Model 1: Adjusting for age, gender, age at diagnosis, mutation, height and pancreatic enzyme use	0.150 (0.126, 0.175)
	Model 2: Adding microbiology to Model 1	0.173 (0.147, 0.200)
Adults 18 years and older		
	Model 1: Adjusting for age, gender, age at diagnosis, mutation, height and pancreatic enzyme use	0.044 (0.010, 0.078)
	Model 2: Adding microbiology to Model 1	0.082 (0.048, 0117)

Additional Figures Referenced in the Text:



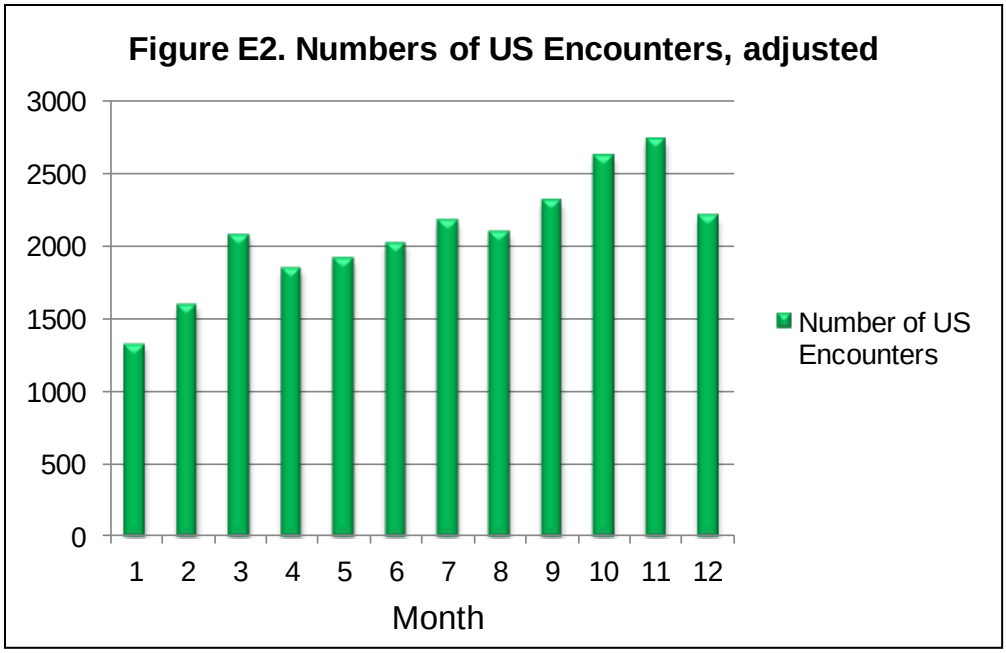
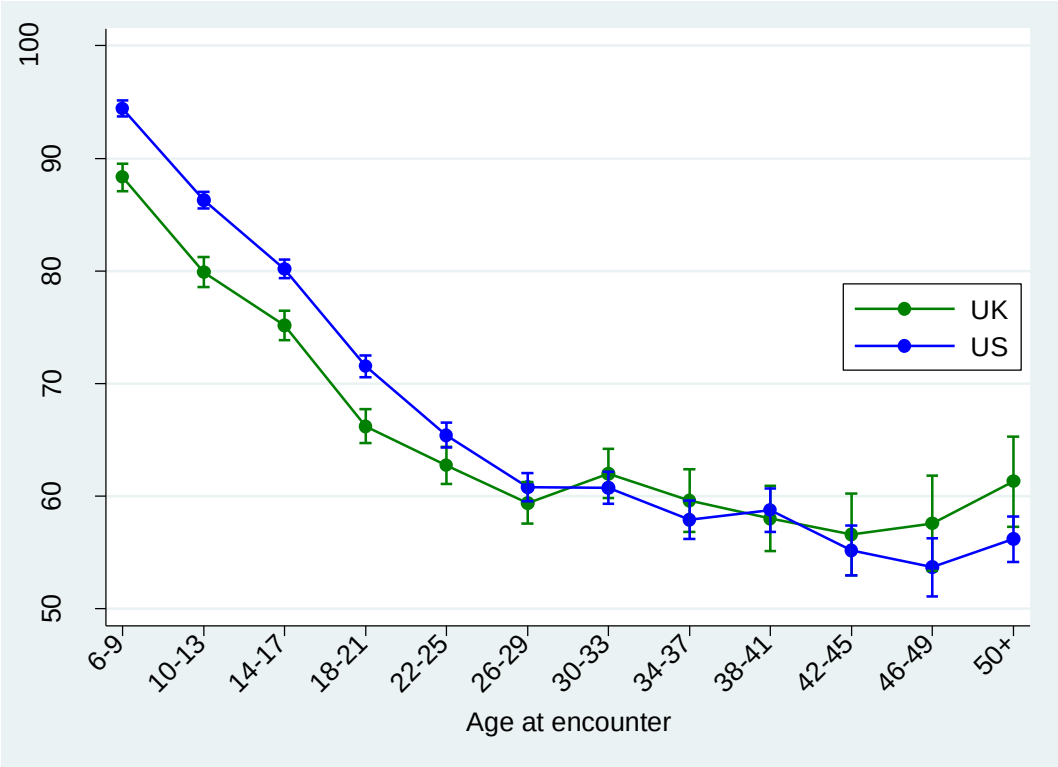


Figure E3: FEV_1 % predicted calculated using Global Lungs Initiative reference equations by age at clinical encounter and year



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