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BRIEF REPORT

CFTR genotype analysis of Asians in international registries highlights disparities in the diagnosis and treatment of Asian patients with cystic fibrosis

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ABSTRACT

Purpose: Cystic fibrosis (CF) is not well-characterized in Asians, potentially resulting in delayed diagnosis and poor prognosis. We characterized CF in Asian subgroups to address these disparities.

Methods: De-identified ethnicity and *CFTR* variant data were obtained from the United States, United Kingdom, and Canadian CF registries. We measured the prevalence of CF, *CFTR* variant allele frequencies, effectiveness of screening panels, and eligibility for modulator therapies.

Results: The prevalence of CF was 1 in 74,982 people (Canada) to 1 in 13,340 people (United Kingdom) for South Asians and 1 in 256,541 (Canada) to 1 in 52,563 (United Kingdom) for other Asians, suggesting 26,000 to 146,000 patients with CF in South Asia. p.(F508del) variant was markedly less frequent in Asians than in non-Hispanic Whites. Splicing and nonsense variants occurred at high allelic frequencies in Asians, resulting in 41% to 49% of South Asians and 21% to 39% of other Asians being ineligible for CFTR modulator therapies. Hologic/EU2v1 panels failed to identify 37% to 47% of South Asian and 23% to 46% of other Asian patients with CF.

Conclusions: Among Asians, CF appears to be more common in South Asians. A significant CF population may exist in South Asia. *CFTR* variants in South and other Asians markedly differ from non-Hispanic Whites causing inequities in newborn screening, diagnosis, and treatment. New strategies are necessary to mitigate these health care disparities.

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Introduction

Cystic fibrosis (CF) is a fatal autosomal recessive genetic disorder caused by variations in the *CFTR* gene. Although untreated CF is fatal in childhood, therapeutic advances have improved the median predicted survival up to 50 years in the United States.[1] However, timely detection and access to therapeutic interventions are vital for patient survival.

CF is most characterized in the non-Hispanic White (White hereafter) population in which 1 in 2500 newborns

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have CF.[2] Although CF affects other races, its true prevalence is unclear. Furthermore, CF causing variants differ between races.[3] For example, the p.(F508del) (c.1521_1523delCTT) variant affects approximately 90% of White patients with CF but it affects only approximately 30% to 40% of Asian patients.[4-9] Furthermore, non-White patients with CF are missed while screening using genetic panel testing for pathogenic variants common in Whites.[10] In addition to diagnosis, knowledge of CF causing variants is important because highly effective modulator therapies that restore CFTR activity are variant specific. Significantly, the recent modulator therapy, elexacaftor/tezacaftor/ivacaftor (ETI), is beneficial for 90% of White patients because it is approved for cases with at least a copy of the p.(F508del) variant.[1] However, significantly more non-White patients lack access to modulator therapies owing to their *CFTR* genotype.[11]

Asians form approximately 60% of the world's population and are also the fastest growing racial group in North America and Europe. Asians are genetically diverse with strong founder effects within and across different regions in Asia.[12] Consistent with such observations, there is an approximately 10-fold difference in the reported prevalence of CF ranging from 1 in 350,000 people in Japan[13] to 1 in 9,000 to 40,000 in South Asia.[2] Previous studies characterizing CF causing variants in Asian patients using panels designed for White population have reported large proportions of patients with unknown variants.[4-9] Schrijver et al[14] reported allele frequencies of pathogenic variants present in American patients with CF of all races, including Asians. However, it is unclear whether this data set is representative of *CFTR* variants observed in Asians from different parts of Asia.

Because the health care systems in the United States, United Kingdom, and Canada have advanced molecular diagnostic tools to diagnose CF, we reasoned that their registries may enable us to estimate the prevalence of CF and the allele frequencies of CF causing variants in Asians. Although we attempted to disaggregate patients from different parts of Asia, it was only possible to disaggregate South Asian patients from patients originating from the rest of Asia. Our results suggest that among Asians, CF is more common in South Asians and indicate significant disparities in the diagnosis and treatment of CF in all Asians.

Materials and Methods

Institutional Review Board approval and demographic analysis of patients with CF at Stanford

Stanford Research Repository contains clinical and demographic data from patients treated in the Stanford Health Care System since 2000. Data access was approved by the Institutional Review Board (#56965). Asians were identified through self-reporting and manual identification by investigators.

Acquisition of patient data from registries

De-identified patient data were obtained from the registries maintained by the Cystic Fibrosis Canada (2011-2018), the UK Cystic Fibrosis Trust (2009-2019), and the Cystic Fibrosis Foundation (United States) (2010-2018). Only patients with confirmed CF were included and patients with conditions such as CFTR related metabolic syndrome were excluded. South Asian patients are classified separately in the Canadian and UK registries but patients from other parts of Asia are not disaggregated. Asians are not disaggregated in the US registry. Patients belonging to 2 or more races were excluded from analysis for all 3 data sets.

Prevalence estimates for CF in Asians

The prevalence of CF in South and other Asians were calculated by dividing the number of patients with CF in the registry by the number of people of that ethnicity reported in the census of Canada (2016) and the United Kingdom (2011 Census and 2019 community update).[15]

Results

Registries indicate more patients with CF of South Asian origin

Using the Stanford Research Repository database, we identified 24 Asian patients with CF at our center. Of these, 79% (19/24) were South Asian and 21% (5/24) were other Asian. To confirm if South Asians are more likely to be affected by CF, we examined the data from the UK and Canadian CF registries that disaggregate Asian subgroups. Of the patients in the UK registry, 3.3% (356/10,655) were Asian. Among them, 88% (314/356) were South Asian and 12% (42/356) were other Asian. In the Canadian CF registry, 0.9% (41/4344) of patients with CF were Asian, of which 68% (28/41) were South Asian and 32% (13/41) were other Asians. Using the disaggregated census data (Supplemental Tables 1 and 2), we estimated the prevalence of CF in South Asians to range from 1 in 13,340 (United Kingdom) to 1 in 74,982 (Canada). In contrast, only 1 in 52,563 (United Kingdom) to 1 in 256,541 (Canada) other Asians have CF (Figure 1A). Thus, all data sets indicate that South Asians are more likely to be affected by CF than other Asians.

Asians patients with CF are affected by a variety of pathogenic variants

Next, we evaluated the CF causing variants in South Asians and other Asians with CF. In the aggregated US registry,

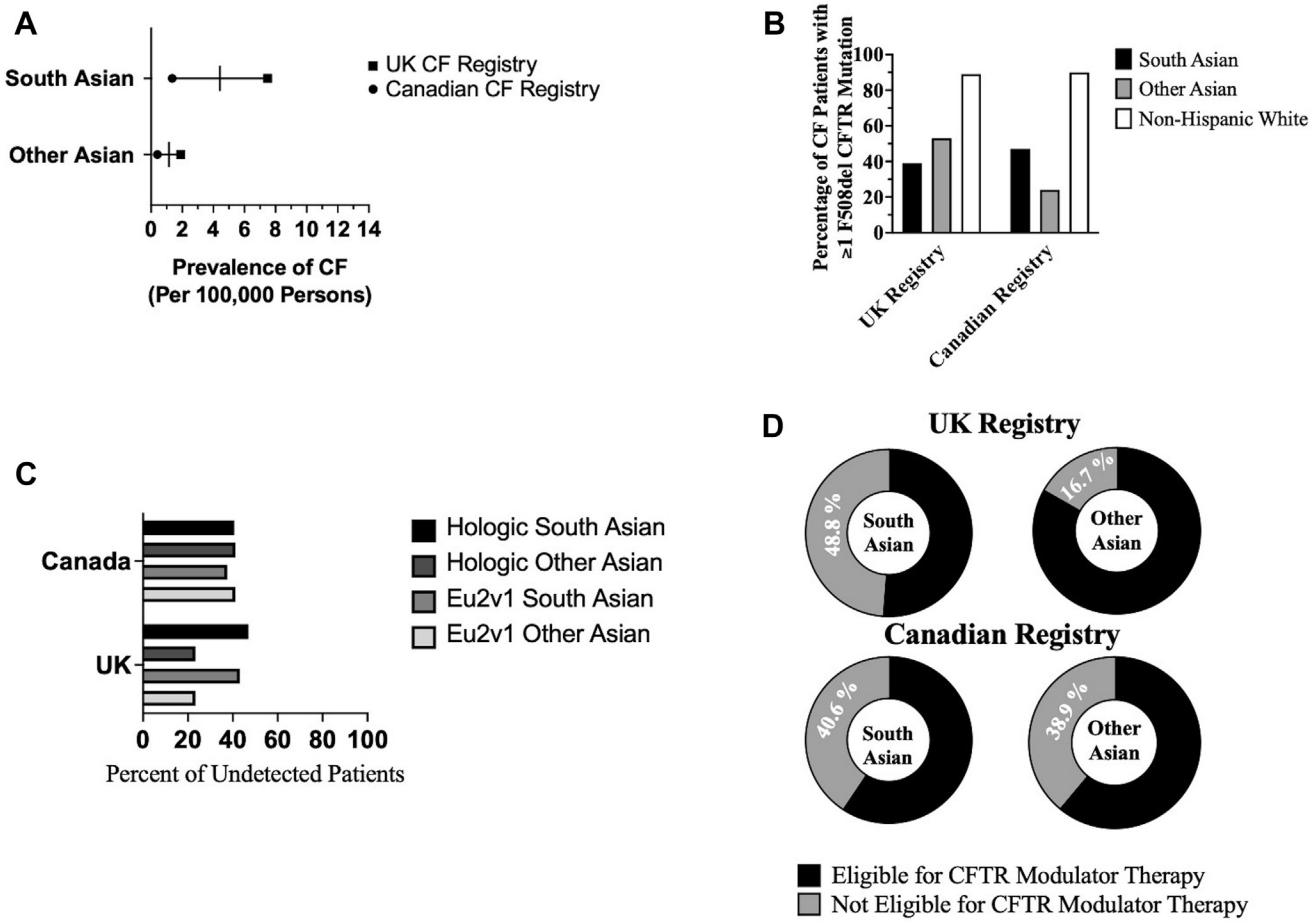

Figure 1 Diverse *CFTR* variants cause challenges in diagnosis and treatment of Asian patients with CF. A. The prevalence of CF in South Asians ranged from 1.33 per 100,000 (1 patient with CF/74,982 people) to 7.50 per 100,000 people (1 patient with CF/13,340 people) in the Canadian and UK data sets, respectively. The prevalence of CF in other Asians ranged from 0.4 cases per 100,000 people (1 patient with CF/256,541 people) to 1.90 cases per 100,000 people (1 patient with CF/52,563 people). B. A significantly lower fraction of South Asian (39%-47%) and other Asian (27%-53%) patients with CF have at least 1 allele with the p.(F508del) variant compared with Whites (89%-90%) in both the UK and Canadian registries. C. In total, 40.7% to 47.0% of South Asian patients and 23.3% to 41.2% of other Asian patients have no CF causal alleles that can be detected using the Hologic InPlex *CFTR* variant panel commonly used in the United States, which tests for 44 different variants. In total, 37.5% to 43.0% of South Asians and 23.3% to 41.2% of other Asian patients have no CF causal alleles that can be detected using EU2v1 *CFTR* variant panel that is commonly used in the United Kingdom and Europe. D. In total, 40.6% to 48.8% of South Asian patients with CF and 16.7% to 38.9% of other Asian patients are affected by 2 pathogenic variants that are not responsive to highly effective modulator therapies including elexacaftor/tezacaftor/ivacaftor or ivacaftor alone.

only 55% of Asian patients had at least 1 copy of the p.(F508del) variant (Supplemental Table 3). Among the disaggregated patients at our CF Center, only 47% of the South Asian and 40% of other Asian patients had at least 1 allele with the p.(F508del) variant.

In the UK and Canadian CF registries, 39.0% and 46.9%, respectively, of South Asian patients with CF and 53.3% and 23.5%, respectively, of other Asians had at least 1 copy of the p.(F508del) variant (Figure 1B). Significantly, unknown variants rank within the 3 most frequent entries in both the UK and Canadian data sets (Table 1, Supplemental Table 4). Supplemental Table 5 lists variants using different nomenclature systems including Human Genome Variation Society nomenclature.

Pathogenic variants frequently affecting Asian patients with CF are absent from screening panels

CF is commonly included in many newborn screening programs globally but with varying genotyping criteria. We assessed the Hologic CF InPlex and Elucigene CFEU2v1 kit with 50 variants (EU2v1) panels used widely in the United States and United Kingdom, respectively.[14] Of the 10 most frequent pathogenic variants affecting South Asians, 6 are not present in the Hologic CF InPlex panel. In the UK and Canadian registries, 47.0% and 40.7% of South Asian patients and 23.3% and 41.2% of other Asian patients, respectively, have 2 variants not present in this panel and are more likely to be missed in screening programs (Figure 1C).

Table 1 Pathogenic variants reported in South Asians and other Asians treated in the United Kingdom and Canada between 2011 and 2019

c. HGVS (Legacy Name[a])	p. HGVS	Number of Alleles	Allele Frequency	c. HGVS (Legacy Name[a])	p. HGVS	Number of Alleles	Allele Frequency
South Asian							
UK				Canada			
c.1521_1523delCTT	p.(F508del)	189	0.309	c.1521_1523delCTT	p.(F508del)	23	0.359
c.3718-2477C>T (3849+10kbC>T)		37	0.0603	c.653T>A	p.(L218X)	9	0.141
c.1705T>G	p.(Y569D)	33	0.0537	c.3718-2477C>T (3849+10kbC>T)		4	0.0625
c.653T>A	p.(L218X)	31	0.0505	c.1393-1G>A (1525-1G>A)		4	0.0625
c.1393-1G>A (1525-1G>A)		21	0.0342	c.1705T>G	p.(Y569D)	2	0.0313
c.292C>T	p.(Q98X)	18	0.0293	c. (273+1_274-1)_ (1584+1_1585-1)del (EXON4-10deletion)		2	0.0313
c.2125C>T	p.(R709X)	20	0.0326	c.3909C>G	p.(N1303K)	2	0.0313
c.1367T>C	p.(V456A)	19	0.0309	c.1040G>A	p.(R347H)	2	0.0313
c.1029delC	p.(C343X)	17	0.0277	c.1518C>G	p.(I506M)	2	0.0313
c.1646G>A	p.(S549N)	16	0.0261	c.1646G>A	p.(S549N)	1	0.0156
c.3472C>T	p.(R1158X)	13	0.0212	c.223C>T	p.(R75X)	1	0.0156
c.(273+1_274-1)_ (1584+1_1585-1)del (EXON4-10deletion)		12	0.0147	c.1367T>C	p.(V456A)	1	0.0156
c.3484C>T	p.(R1162X)	10	0.0163	c.3484C>T	p.(R1162X)	1	0.0156
c.2052dupA (2184insA)	p.(Q685T fs X4)	10	0.0163	c.1210-6T>A		1	0.0156
c.1175T>G	p.(V392G)	6	0.0098	c.3490_3491insT (3622insT)	p.(K1165X)	1	0.0156
c.2657+5G>A (2789+5G>A)		5	0.0081	Nucleotide change not reported	p.(R553P)	1	0.0156
c.489+2T>C (621+2T>C)		5	0.0081	c.1210-33_1210-6GT[12]T[4] (5T;TG12)		1	0.0156
c.2T>C	p.(M1T)	5	0.0081	c.164+1G>T (296+1G>T)		1	0.0156
c.1210-12T[5] (5T)		4	0.0065	Unknown		5	0.0781
c.595C>T	p.(H199Y)	4	0.0065				
c.1505T>C	p.(I502T)	4	0.0065				
c.709C>G	p.(Q237E)	4	0.0065				
Variants with frequency <0.005 (Supplemental Table 4)		69	0.11				
Unknown		53	0.0863				
Incomplete annotation		9	0.0147				
Other Asian							
c.1521_1523delCTT	c.p.(F508del)	26	0.441	c.1521_1523delCTT	**c.**p.(F508del)	6	0.171
c.1646G>A	p.(S549N)	4	0.0678	c.1646G>A	p.(S549N)	4	0.114
c.3484C>T	p.(R1162X)	3	0.0508	c.254G>A	p.(G85E)	4	0.114
c.1652G>A	p.(G551D)	2	0.0339	c.1393-1G>A (1525-1G>A)		2	0.0571
c.1393-1G>A (1525-1G>A)		2	0.0339	c.3718-2477C>T (3849+10kbC>T)		2	0.0571
c.3718-2477C>T (3849+10kbC>T)		2	0.0339	Nucleotide change not reported (exon 15 deletion)		2	0.0571
Nucleotide change not reported	Large deletion[b]	2	0.0339	c.488A>T	p.(K163M)	2	0.0571
c.292C>T	p.(Q98X)	2	0.0339	c.2909G>A	p.(G970D)	1	0.0286
c.164+12T>C (296+12T>C)		2	0.0339	c.2551C>T	p.(R851X)	1	0.0286
c.2909G>A	p.(G970D)	2	0.0339	Nucleotide change not reported (exon 4-8 deletion)		1	0.0286
c.1367T>C	p.(V456A)	2	0.0339	c.1703T>A	p.(L568X)	1	0.0286
c.1666A>G	p.(I556V)	1	0.0169	c.1798A>G	p.(R600G)	1	0.0286

(continued)

Table 1 Continued

c. HGVS (Legacy Name[a])	p. HGVS	Number of Alleles	Allele Frequency	c. HGVS (Legacy Name[a])	p. HGVS	Number of Alleles	Allele Frequency
c.1585-1G>A (1717-1G>A)		1	0.0169	c.489+2T>C (621+2T>C)		1	0.0286
c.413_415dup	p.(Leu138dup)	1	0.0169	c.1766+5G>T (1898+5G>T)		1	0.0286
c.2657+5G>A (2789+5G>A)		1	0.0169	Unknown		2	0.0571
c.1766+5G>T (1898+5G>T)		1	0.0169	Incomplete annotation		3	0.0857
c.2052dupA (2184insA)	p.(Q685T fsX4)	1	0.0169				
c.709C>G	p.(Q237E)	1	0.0169				
c.2125C>T	p.(R709X)	1	0.0169				
Unknown		1	0.0169				
Incomplete annotation		1	0.0169				

The transcript reference for the listed variants is NM_000492.4 and the protein reference is NP_000483.3. Incomplete annotation represents variants that were determined to be incorrect.

cDNA, complementary DNA; *CFTR2*, Clinical and Functional Translation of CFTR; *HGVS*, Human Genome Variation Society.

[a]cDNA legacy names have been included for cDNA variants that don't have a corresponding amino acid variant name (eg, splicing variants). For variants resulting in a change in protein sequence, the HGVS compliant single letter amino acid correspond to legacy names. Some variants have multiple legacy names. Supplemental Table 5 crossreferences legacy names, 1 letter, and 3 letter amino acid names more comprehensively.

[b]Variants were crossreferenced with CFTR2 and ClinVar to ascertain correctness. HGVS compliant description of some variants (eg, IVS17BTA) could not be determined. There are previous publications describing some of these variants. Hence, these variants were included as is from the registry and need further verification/characterization. Large deletions and whole exon deletions were also reported as is from the registry.

In the EU2v1 panel, 43% and 37.5 % of South Asian and 23.3% and 41.2 % of other Asian patients in the UK and Canadian data sets, respectively, will be missed (Figure 1C).

The addition of the 5 most frequent pathogenic variants seen in South Asians in the Hologic panel and EU2v1 panels, p.(Y569D) (c.1705T>G), p.(L218X) (c.653T>A), 1525-1G->A (c.1393-1G>A), p.(Q98X) (c.292C>T), p.R709X (c.2125C>T), reduces the percentage of South Asian patients missed using the Hologic and EU2v1 panels from 41% to 47% to 22% to 27% and from 37.5% to 43% to 19% to 23%, respectively (Supplemental Figure 1). For the other Asian cohorts, the modified Hologic and EU2v1 panels both reduce the percentage of missed patients from 23% to 41% to 13.3% to 35%.

More Asian patients are affected by pathogenic variants that are not responsive to modulator therapies

ETI or ivacaftor alone is used to treat patients with CF with at least 1 copy of the p.(F508del) variant and certain other variants. Given the lower prevalence of the p.(F508del) variant in the Asian population, we evaluated the percentage of patients with 2 identified causal alleles containing premature stop, frameshift, canonical splicing, nonresponsive missense, and large rearrangement variants that are not responsive to ETI or ivacaftor alone based on US Food and Drug Administration guidelines. We observed that 40.6% and 48.8% of South Asian patients in the United Kingdom and Canada, respectively, were not eligible for treatment using either ETI or ivacaftor alone (Figure 1D). Among other Asians, 16.7% and 38.9 % of patients in the United Kingdom and Canada, respectively, were ineligible for treatment (Figure 1D).

Discussion

Consistent with previous studies, all disaggregated data sets show a higher prevalence of CF in South Asians than in other Asians.[2,16] Although the pathogenicity of variants can be uncertain, we have not re-evaluated the basis on which these patients were clinically diagnosed with CF. Benign variants account for <5% of all data sets except other Asians in Canada in whom benign variants account for 11% (4/35) of alleles.

Our results further confirm previous reports that the p.(F508del) variant only affects 30% to 35% of South Asian and other Asian patients.[4,6] Our study characterizes the allele frequencies of other pathogenic variants in South Asians. The most common variants are known CF causing variants identified in the Clinical and Functional Translation of CFTR database (www.cftr2.org). The 6 most frequent CF causing variants in South Asians are the same in both the Canadian and UK registries but with different allele frequencies. The most widely recognized among these is 3849+10kbC >T (c.3718-2477C>T), which accounts for 4% to 6% of alleles compared with 0.8% of alleles in the Clinical and Functional Translation of CFTR database. P.(Y569D), 1525-1G→A (c.1393-1G>A), and p.(L218X) each account for >5% of alleles even though these had been reported as rare in early studies.[17,18] These variants are also present in the US registry data set but with lower allele frequencies. The difference is probably because the US data set is not disaggregated. Finally, the high percentage of unknown alleles can be attributed to either the use of panels tailored for Whites or the need for advanced sequencing techniques to identify complex rearrangements in the *CFTR* locus.

There is less agreement between the 2 data sets in the other Asian category but p.(F508del) is still the most common variant. It is likely that the ethnic compositions of other Asians in these data sets are different. Pathogenic variants reported to

be common in Chinese and Japanese patients such as p.(Q98R) (c.293A>G) and p.(G970D) (c.2909G>A) were not observed at high frequencies possibly because of undersampling or missed patients.[19] Moreover, the US data set reports a common pathogenic variant, p.(R334W) (c.1000C>T), not observed in other data sets indicating a group of Asians unique to the United States.

Our study validates reports that current newborn screening panels are less effective in identifying CF in ethnic minorities.[10] We showed that adding common South Asian variants into existing panels improves the detection of South Asian patients from approximately 50% to 60% to 70% to 80%. Although we did not evaluate the effectiveness of these panels in identifying Asian individuals heterozygous for CF causing variants and prenatal screening, other studies have shown the reduced effectiveness of current panels for these applications.[20] Thus, improved screening panels may also affect genetic counseling and prenatal screening outcomes.

Finally, we show that up to 47% of South Asians are affected by 2 variants that are not known to be responsive to modulators compared with 20% to 30% of Hispanics, African Americans, and <10% of White patients with CF.[11] This nonresponsiveness to modulators is driven more by premature stop, frameshift, splicing, and large rearrangement variants, which account for >20% of alleles in the Asian population with CF as opposed to frameshift and nonresponsive missense variants. It is widely perceived that alternative approaches to restore CFTR function such as gene therapies are relevant for only 10% of patients with CF. Our data indicate that new therapies may be critical for a much larger number of non-White patients with CF globally. Given the estimated prevalence of CF in approximately 1 in 13,000 to 1 in 75,000 South Asians, South Asia alone could have approximately 26,000– to 146,000 patients with CF compared with approximately 30,000 patients in the United States. Finally, we may be still underestimating the true impact of CF in Asians owing to the high mortality associated with untreated CF.[2]

Conclusion

Our study shows that CF affects South Asians at a higher frequency than generally appreciated. Furthermore, both South Asians and other Asians show a significantly lower frequency of the p.(F508del) variant and are affected by diverse variants that are less common in Whites. This results in disparities in newborn screening, diagnosis, and treatment of Asian patients with CF.

Data Availability

Data are available upon written approval from the UK Cystic Fibrosis Trust, Cystic Fibrosis Canada, and the US Cystic Fibrosis Foundation. Authors may contact Z.M.S (zsellers@stanford.edu) or S.V. (sriram.vaidyanathan@nationwidechildrens.org).

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Author Information

Conceptualization: S.V., Z.M.S.; Formal Analysis: S.V., A.M.T., L.B., M.R., Y.Y., Z.M.S.; Writing: S.V., A.M.T., L.B., M.R., Y.Y., Z.M.S.

Ethics Declaration

Data access to the Stanford Research Repository (STARR) was approved by the Institutional Review Board (#56965). Health information from consenting patients was obtained from clinical centers by Cystic Fibrosis Canada, UK Cystic Fibrosis Trust and the Cystic Fibrosis Foundation in compliance with the relevant national and local laws. Data was requested from the Cystic Fibrosis Canada (https://www.cysticfibrosis.ca/our-programs/cf-registry/requesting-canadian-cf-registry-data), UK Cystic Fibrosis Trust (https://www.cysticfibrosis.org.uk/the-work-we-do/uk-cf-registry/apply-for-data-from-the-uk-cf-registry), and the Cystic Fibrosis Foundation (https://www.cff.org/researchers/patient-registry-data-requests) as instructed. Patient privacy was a major consideration in the review of our applications. To ensure privacy, data was de-identified by Cystic Fibrosis Canada, UK Cystic Fibrosis Trust, and the Cystic Fibrosis Foundation before their release for our use.

Conflict of Interest

The authors declare no conflicts of interest.

Additional Information

The online version of this article (https://doi.org/10.1016/j.gim.2022.06.009) contains supplementary material, which is available to authorized users.

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