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ORIGINAL RESEARCH

Comparison of Reporting Quality in National Cystic Fibrosis Patient Registries: Implications for Identifying Use of Novel CFTR Modulators

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ABSTRACT

***Introduction*:** Advances in development of cystic fibrosis transmembrane conductance regulator modulator (CFTRm) therapies mean that now people who are heterozygous (instead of having to be homozygous) for the common F508del variant can benefit from these therapies. Recent economic estimates suggest only approximately 15% of the global population have CFTRm access, yet it is unknown how prevalence of F508del and economic factors may affect this availability.

***Methods*:** Data related to prevalence of cystic fibrosis (CF), CFTRm usage, and prevalence of F508del in 10 countries were extracted from publicly accessible registry reports from 2021. National gross domestic product (GDP) was obtained via open access World Bank data. Descriptive statistics and correlation coefficients assessed relationships.

***Results*:** Notable discrepancies were noted in the equity of availability of data between national registries—only four countries reported number of patients eligible for CFTRm. Registry data represented 70,694 patients, with 42,858 found to be using CFTRm (60.6%). Prevalence of CFTRm usage ranged from 1.8% to 76.7% and prevalence of F508del ranged from 35.2% to 94.4%. The correlation between prevalence of CFTRm usage and F508del is positive ($r=0.56$, $p=0.10$), and the correlation between CFTRm usage and GDP (per capita) was also positive, and significant ($r=0.72$, $p=0.02$).

***Conclusion*:** Both F508del prevalence and GDP are associated with variable CFTRm usage rates, although a predominant reason is unclear as a result of poor consistency in registry reporting. Urgent action is needed to create uniform reporting of registry data and increase

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availability of novel CFTRm therapies to the global CF population.

Keywords: Modulator therapy; Registry; Genotype; Respiratory disease; Ivacaftor; Lumacaftor; Tezacaftor; Elexacaftor

Key Summary Points

Cystic fibrosis transmembrane conductance regulator modulator (CFTRm) therapies are of high importance for management of cystic fibrosis (CF).

Disparities in access are present, with genotype eligibility and financial ability both playing a part in this access.

Some nations have better access to CFTRm than others, despite similar finances and genotype distribution.

National CF registries can help identify usage statistics, but this will be dependent on eligibility data, which is not recorded in all registries at present and therefore this uniformity is needed.

INTRODUCTION

Cystic fibrosis (CF) is an autosomal recessive condition that predominantly affects the lungs and digestive tract via an accumulation of mucus, which results in progressive cycles of lung infection and inflammation. This results in progressive declines in lung function and a reduced life expectancy [1]. Currently, over 2000 distinct variants code for CF [2], although of these, 159 variants account for 96% of CF alleles [3]. The F508del variant (deletion of phenylalanine at the 508th codon) is the most common in populations of European descent, whereby, for example, more than 95% of white patients in the UK are at least heterozygous for the variant [4].

In recent years, the introduction of highly effective cystic fibrosis transmembrane conductance regulator modulator (CFTRm) therapies has markedly changed the nature of care for CF. These medications target the underlying defects in protein channels that manifest in CF [5], and have been shown to improve lung function, quality of life and decrease exacerbations [6]. The most recent of these medications, elexacaftor-tezacaftor-ivacaftor (ETI; branded as Kaftrio® and Trikafta® in Europe and the USA respectively), has been shown to also improve lung function, quality of life and decrease exacerbations in patients who are heterozygous for F508del (alongside a minimal function variant) [7]. Therefore, patients with CF with this variant (amongst other variants, although F508del is most prevalent) can now gain great benefit from CFTR modulator therapy, given how the drugs target the underlying protein defects which are rooted in their genotype [8].

These advances in CFTRm therapies have led to clinicians, patients, advocacy groups and academics to collectively look towards a CFTR modulated clinical environment, in how best to manage CF whilst using CFTRm [9]. However, recent estimates suggest that less than 15% of patients worldwide have access to CFTRm therapies, via combinations of underdiagnosis, lack of reimbursement agreements between national governments and pharmaceutical companies, and ineligible genotypes [10, 11].

To aid clinicians and researchers in CF management, nationalised registries [12, 13] can help identify cohorts of patients with certain genotypes that may benefit from CFTRm treatment, and to note how many patients are receiving each CFTRm treatment. Data within these registries are frequently used for research and quality improvement purposes [14], although given the recent introduction of CFTRm, it is unclear how these are being reported on national and international levels. Equity in reporting standards ensures similarities (and differences) in CFTRm usage and the factors contributing towards such access, such as genotype and finances, are fully understood.

Therefore, the aim of this study was to retrospectively quantify using publicly available registry data (a) quality and consistency of

reporting of the prevalence of CFTRm and the predominant F508del genotype, and (b) the associations between prevalence of the F508del genotype, gross domestic product, and the number of patients using CFTRm therapy.

METHODS

Registry data were attempted to be sourced from 21 countries—the 15 countries in Europe with the highest prevalence of CF as per the 2020 European CF Registry [15], alongside the USA, Canada, Australia, New Zealand, South Africa and Brazil—all nations with established registries [10, 16]. Searches and data extraction were undertaken in June 2023. No ethics approval was required for this analysis as it was a secondary analysis of publicly available data.

Data were eventually obtained from 10 national registries, for whom information from 2021 was publicly available, allowing a level of international comparison: Australia [17], Canada [18], Czechia [19], France [20], Germany [21], Ireland [22], the Netherlands [23], Turkey [24], the UK [25], and the USA [26]. Full registry reports were available for eight countries, one infographic (the Netherlands) and one summary document (Czechia). Reports for 2021 data were published between December 2021 and February 2023. Of the excluded 11 countries, several only had data available for 2020 (Italy, Russia, Brazil, South Africa) or earlier (Belgium, Sweden, Spain = 2019; New Zealand = 2017). Publicly accessible registry reports could not be found for others (Austria, Poland, Switzerland).

Population statistics were extracted from each registry where possible. To identify common data available, a customised reporting tool was developed, whereby data from each registry was classified as 'provided', 'could be calculated', or 'not available'. A total of 26 data categories were identified (e.g. total number of patients, number on each CFTRm, number of patients with F508del), and each national registry graded on how (un) available the data were. A full breakdown of variables and scoring is provided in the Supplementary Material.

Data extracted from each registry (where possible) included (1) prevalence of CF; (2) number of patients eligible for CFTRm (i.e. including those eligible by genotype and age); (3) numbers actually receiving CFTRm; (4) number of patients receiving each CFTRm therapy; and (5) prevalence of the F508del variant.

For each registry, 'eligibility' was defined by each national registry, and not by authors, with data extracted solely where it is explicitly provided by each registry. Furthermore, data pertaining to each country's gross domestic product (GDP) was obtained from open access data via the World Bank [27] and reported in US dollars ($USD), as a marker of economic welfare.

Analyses were undertaken as either Pearson's correlations or Spearman's correlations, dependent upon normal distribution of data. Simple linear regressions established association between prevalence of CFTRm usage, and F508del prevalence and GDP. As all analyses use existing, publicly available information, no ethics approval was required.

RESULTS

In retrieving data from registries, only five variables (of 26) were either fully available or could be calculated from provided data, from all registries: total number of patients, total number patients on CFTRm, proportion of patients on CFTRm, total number of patients with F508del, and proportion of patients with F508del. The majority of data was either available or could be calculated from eight registries; the Netherlands and Czechia had limited availability of data, missing 81% and 69% of data respectively. Top performing nations included Germany and the USA, missing 0% and 8% of data respectively. A summary of availability of data is provided in Fig. 1 and a full breakdown in the Supplementary Material.

Numbers included within registries ranged from 679 (Czechia) to 32,100 (USA), covering a total of 70,694 patients. The number of patients eligible for CFTRm is reported in our registries, with absolute numbers given in three registries (USA, Germany, Czechia), and the percentage

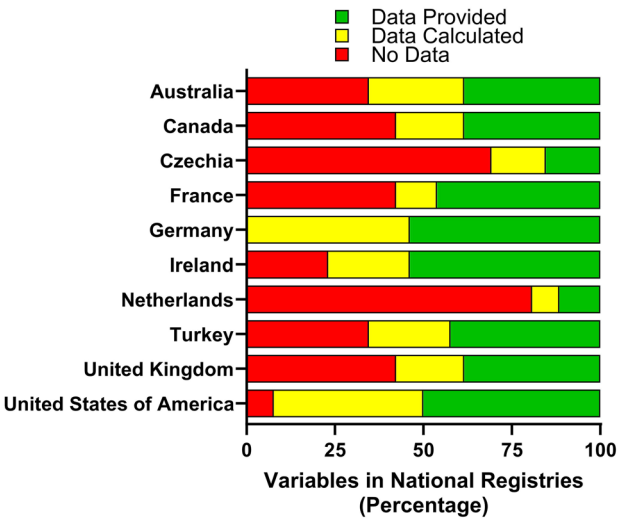

Fig. 1 Summary of availability of data from each national registry. Data provided as a percentage of how many variables (out of possible 26) had data either (a) provided, (b) could be calculated from provided data, or (c) unavailable, or non-calculable. Nations listed alphabetically. Full breakdown of derivation of results provided within Supplementary Material

eligible in a further registry (Ireland). Within these four registries, the percentage of patients eligible for CFTRm ranged from 66.7% to 94.8% (Table 1).

All registries reported the number of patients actually receiving CFTRm, which ranged from 35 (Turkey) to 22,327 (USA); a proportion that ranged from 1.8% (Turkey) to 76.7% (Ireland; Table 1). A total of 42,858 people were receiving such medication, and when considered against the total number of patients (70,694), this reflects a total prevalence of 60.6%. Not all registries provided a breakdown of each CFTRm received, but where this was done, the majority of patients were receiving ETI, ranging from 24 to 19,263 (30,918 reported patients in total) as shown in Table 1. All registries reported the prevalence of F508del, ranging from 35.2% (Turkey) to 91.7% (Ireland), as shown in Table 2.

The prevalence of patients receiving CFTRm therapies was positively correlated with F508del prevalence, but not statistically significant ($r=0.56$, $p=0.1$). When Turkish registry data is excluded from the correlation (because of outlying data in terms of low F508del prevalence and low CFTRm usage), this correlation remained stable; positive but not significant ($r=0.55$, $p=0.12$; Fig. 2). When we only focused on prevalence of F508del and use of ETI, eight countries had data to report (Czechia and the Netherlands did not), with non-significant correlation coefficients to report when data from Turkey (as an outlier) is included ($r=0.23$, $p=0.58$) and excluded ($r=-0.07$, $p=0.88$; Fig. 3).

National GDP ranged from $\$2.9\times10^{11}$ USD (Czechia) to $\$2.5\times10^{13}$ USD (USA), and GDP per capita ranged from \$9661 USD (Turkey) to \$100,172 USD (Ireland). When correlated against CFTRm usage, only GDP per capita was significantly correlated ($r=0.72$, $p=0.02$) as shown in Fig. 4. Finally, the relationship between CFTRm usage and GDP when data from Turkey is excluded (as a result of outlier status) is non-significant as shown in the Supplementary Material.

DISCUSSION

These data indicate that national registries are highly variable in their reporting of fundamental statistics and data—an issue that impacts upon interpretation of factors that results in access to CFTRm. As a result of the paucity of data, the underlying argument of whether

Table 1 Prevalence of patients with CF and patients using CFTRm therapy from 2021 registry data

Country	Total patients with CF (*n*)	Total patients with CF eligible for CFTRm (*n*, %)	Number of patients using specific CFTRm therapy (*n*)					Percentage of eligible patients using CFTRm therapy (%)	Percentage of all patients with CF using CFTRm therapy (%)
			IVA	IVA/LUM	IVA/TEZ	IVA/TEZ/ELX	Total		
USA	32,100	25,497 (79.4)	1412	1089	563	19,263	22,327	87.6	69.6
UK	10,908	–	606	942	515	5321	7384	–	67.7
Germany	6776	4954 (73.1)	190	512	160	3170	4032	81.4	59.5
France	7513	–	190	717	174	2196	3277	–	43.6
Australia	3616	–	289	722	629	356	1996	–	55.2
Canada	4338	–	133	213	165	944	1455	–	33.5
Netherlands	1601	–	–	–	–	–	1010	–	63.1
Ireland	1315	1247 (94.8)	–	–	–	–	1009	80.9	76.7
Czechia	679	453 (66.7)	–	–	–	–	333	73.5	49.0
Turkey	1948	–	3	2	6	24	35	–	1.8
Total	70,694	32,151*	2823*	4197*	2212*	30,918*	42,858	–	–

Table listed from highest number of total number receiving CFTRm (USA) to lowest (Turkey)

CF cystic fibrosis, *CFTRm* cystic fibrosis transmembrane conductance regulator modulator therapy, *IVA* ivacaftor, *LUM* lumacaftor, *TEZ* tezacaftor, *ELX* elexacaftor

*Totals reflect sums of provided numbers, not true totals (i.e. missing data excluded from sum value)

For further details on which countries provided data, and which required data to be calculated, please see Supplementary Material

genotype, or financial ability, is the main limiting factor towards CFTRm is unclear and requires examination.

Within this analysis, it is shown that all registry reports include the number of people with CF and a way to calculate the prevalence of CFTRm usage. However, not all include a breakdown of which CFTRm therapies are used (Fig. 1, Supplementary Material), and most importantly, data pertaining to patient eligibility (and therefore also eligible, but not receiving CFTRm) is lacking in many registries. Only four countries—Czechia, Germany, Ireland, USA—provided data on eligibility.

This paucity of this clinically pertinent data is concerning, as the reasons behind patients not receiving CFTRm must be explored and addressed in order to increase global access. Two broad arguments could initially be proposed as limits to full access—genotype and finances. The availability of data from national registries can impact upon the interpretation of each of these. For example, data in Table 1 reflects a disparity in patients eligible for CFTRm vs. total patients receiving CFTRm (e.g. 87.6% vs. 69.6% in the USA). However, in the UK, it is stated that 67.7% of all patients are receiving CFTRm, although it is unclear what this number is as a percentage of eligible patients, and therefore whether the UK is "good" or "bad" at providing access, for example. It is also unclear how many have been commenced but subsequently stopped therapy (e.g. as a result of side effects).

These data show that CFTRm usage varies highly amongst countries, even amongst those with a high prevalence of F508del (>80%), with the total prevalence of those taking CFTRm being approximately 60%, corroborating

Table 2 Prevalence of F508del variant in each national registry

Country	% F508del/F508del	% F508del/other	% F508del total
Ireland	54.4	37.3	91.7
Australia	47.0	43.0	90.0
Netherlands	55.0	34.9	89.9
UK	47.7	41.3	89.1
Canada	45.7	41.1	86.8
Germany	46.6	39.5	86.1
Czechia	44.3	41.7	86.0
USA	44.1	41.4	85.5
France	40.8	42.3	83.1
Turkey	10.3	24.9	35.2
Mean	*43.6*	*38.7*	*82.3*

Countries listed by largest to smallest total F508del prevalence. Totals may not always reflect addition of homozygous and heterozygous data as a result of rounding in registries. F508del, deletion of phenylalanine at 508th codon [common CFTR variant]. NB. Prevalence of F508del will only be amongst those patients genotyped (mean = 98.5% patients are genotyped). For further details on which countries provided data, and which required data to be calculated, please see Supplementary Material

existing data that suggests CFTRm access is variable [10]. For people with CF, possessing the F508del will fundamentally increase eligibility for CFTRm therapy, as shown by the associations between prevalence of the F508del variant and CFTRm usage in Fig. 2, and prevalence of F508del and usage of ETI (for whom those with F508del is most appropriate) as shown in Fig. 3. From these data we can propose that some countries 'outperform' others when the ratio between these two prevalence rates is examined. For example, France has a lower prevalence of F508del than Canada (83.1% vs. 86.8%) yet has a higher number of patients on CFTRm (43.6% vs. 33.5%), indicating a higher CFTRm/F508del ratio (0.52 vs. 0.39). This index (and adaptations thereof, accounting for different CFTRm therapies) could be utilised as a way of comparing access to therapies across countries when F508del prevalence varies, although this remains a highly complex healthcare issue. It must be acknowledged that many patients without F508del will still be able to access CFTRm (and ETI), and thus this ratio would only provide an approximation, until full data on eligibility is published in registries.

This interpretation is heavily reliant on the F508del variant, and data from the 2020 European CF Registry indicates that 80.7% of patients across the continent have at least one F508del allele [15]. However, national frequencies of being at least heterozygous for F508del vary, from less than 20% (e.g. Georgia, Armenia) to over 90% (e.g. Albania, Denmark, Croatia) [15], this latter data supporting the existing notion of the "missing 10%" [4] in relation to CFTRm access. This assumption is rooted in the existence of F508del, and therefore this 'missing' proportion is likely far higher in populations who are not of European descent, supported by recent predictions that indicate that a high number of people in the global south likely have undiagnosed CF [10]. Therefore, given the link between ethnicity and F508del prevalence [28, 29], it is highly likely that many patients around the world will unfortunately be wholly ineligible for current CFTRm based upon genotype alone, and therefore urgent action is required to rectify this [30]. This furthers calls for including CFTRm 'eligibility' within registries, as reporting genotype data on its own does not clearly indicate whether patients will be able to have these medications.

Finally, this analysis has also identified a significant association between usage of CFTRm and GDP (Fig. 4), indicating that even amongst 'high-income' countries (as per the World Bank), there is notable discrepancy in how many patients are receiving these therapies. These inequalities may exacerbate the lack of access to CFTRm on the basis of genotype, and therefore, financial reimbursement for CFTRm must also be considered when considering determinants of CFTRm usage, as well as type of national health care system (universal coverage, out-of-pocket etc.). However, without clear reporting of 'eligibility' data in registries, these financial arguments remain assumptions.

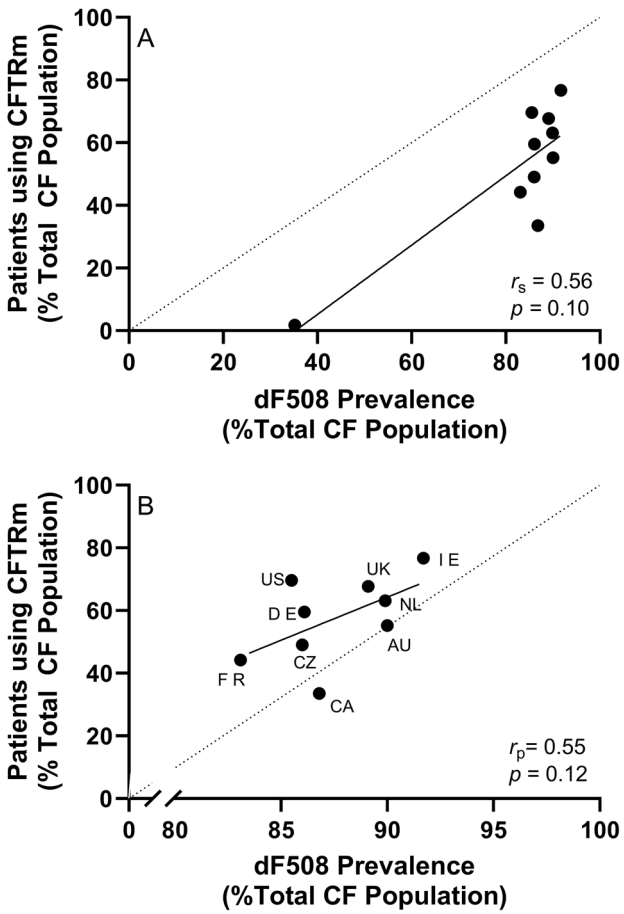

Fig. 2 The relationship between prevalence of F508del genotype and patients using CFTRm therapy, from different countries using 2021 registry data. **a** Data from all analysed countries. Sole outlier in plot **a** represent data from Turkey. **b** Data from all countries, excluding Turkey. *AU* Australia, *CA* Canada, *CZ* Czechia, *DE* Germany, *FR* France, *IE* Ireland, *NL* the Netherlands, *UK* United Kingdom, *US* United States of America. *CFTRm* cystic fibrosis transmembrane conductance regulator modulator therapy, *F508del* deletion of phenylalanine at 508th codon [common CFTR variant]. *r* value provided via Pearsons (r_p) or Spearmans (r_s) correlation coefficient. Solid line indicates line of best fit between variables. Dashed line indicates line of identity

There are strengths to report in these analyses, primarily how data from the same year (2021) is taken from summaries to facilitate comparisons, particularly as IVA/TEZ/ELX was licensed for use in most analysed countries in 2020 [31, 32]. This, combined with the volume of data obtained from these summaries (>70,000 patients represented), and the fact many registries include the overwhelming majority of people with CF from within their respective nations (the UK report, for example, includes over 99% of people with CF in their registry) enhances the strong international patterns provided within. Given that estimates published in 2022 approximated that approximately 160,000 people worldwide have CF [10], the inclusion of registry data that represents approximately 70,000 people worldwide (ca. 44% global total) mean that this analysis very likely reflects overall global patterns and thus is representative of the global CF population.

It is also acknowledged this analysis has limitations, whereby this data is obtained directly from published registry summaries instead of the registries themselves. Moreover, whilst a

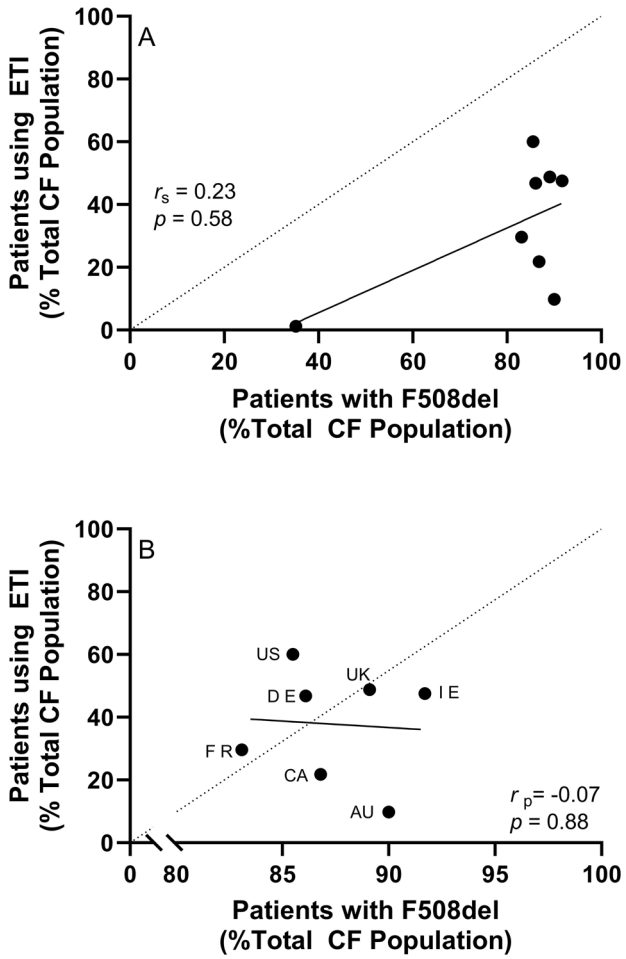

Fig. 3 Relationship between number of patients using elexacaftor-tezacaftor-ivacaftor (ETI) and number of people with F508del variant. **a** Data from all analysed countries. Sole outlier in plot **a** represent data from Turkey. **b** Data from seven countries, excluding Turkey. *AU* Australia, *CA* Canada, *DE* Germany, *FR* France, *IE* Ireland, *UK* United Kingdom, *US* United States of America. *ETI* elexacaftor-tezacaftor-ivacaftor, *F508del* deletion of phenylalanine at 508th codon [common CFTR variant]. Solid line indicates line of best fit between variables. Dashed line indicates line of identity. *r* value provided via Pearsons (r_p) or Spearmans (r_s) correlation coefficient. Solid line indicates line of best fit between variables. Dashed line indicates line of identity

uniform date of 2021 can be seen as an advantage, it can also be interpreted as dated, although updated registries for 2022 are not available for the majority of countries at the time of publication. Data from the European CF Registry does include some data on eligibility, and provides definitions for such eligibility [33] (unlike many national registries) which is a promising development, although direct comparisons against other non-European registries remain lacking. Moreover, rapidly changing access agreements for CFTRm therapies in individual countries over the intervening time period means that the number of patients receiving CFTRm is likely higher, and therefore replication of this analysis in future years will be warranted.

Finally, it must also be acknowledged that a key argument within this study surrounds prevalence of F508del, and the impact upon CFTRm eligibility. However, some patients will possess the F508del variant, yet not take the appropriate CFTRm. This may be due to age restrictions, as well as adverse effects [34],

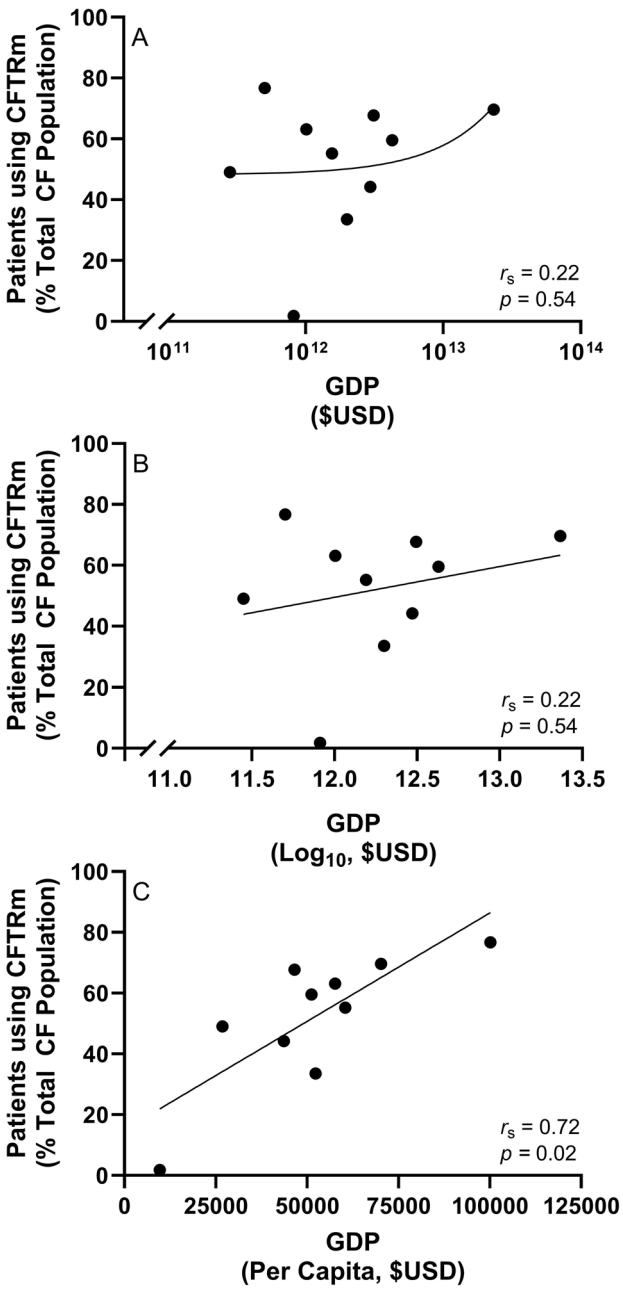

Fig. 4 Relationship between national gross domestic product and prevalence of patients using CFTR therapy. **a** Relationship between national GDP and prevalence of CFTRm usage. x-axis provided on logarithmic scale. **b** Relationship between national GDP (log-transformed) and prevalence of CFTRm usage. x-axis provided on linear scale. **c** Relationship between national GDP (per capita) and prevalence of CFTRm usage. x-axis provided on linear scale. *CFTRm* cystic fibrosis transmembrane conductance regulator modulator therapy, *GDP* gross domestic product, *USD* US dollar. *r* value provided via Pearsons (r_p) or Spearmans (r_s) correlation coefficient

including mental health [35]. This disparity in turn increases the validity of the requirement to include 'eligibility' data (and explicit definitions of such eligibility) in all registries, and not solely rely on genotype data as a proxy. Including data on why patients are not taking CFTRm (genotype, reactions, adherence etc.) should also be included within national registries to enhance understating of long-term CFTRm usage, and increase the number of patients taking the appropriate medication for them.

CONCLUSIONS

This analysis has shown that variable agreement in the reporting of national registry data and therefore presence of F508del can explain some variance in CFTRm usage, but that finances also play a part in CFTRm access in high-income countries. Further action is needed to improve uniformity of reporting in national registries—in particular in relation to eligibility—but also in improving access for all patients globally, tackling both genotype eligibility and financial ability.

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Author Contribution. Owen W Tomlinson: conceptualisation, data extraction and analysis, writing, reviewing, accountability for final publication. Philip Mitchelmore: writing, reviewing, accountability for final publication. Craig A Williams: writing, reviewing, accountability for final publication.

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Data Availability. All data are presented within the manuscript and supplementary material.

Declarations

Conflict of Interest. Owen W Tomlinson reports conference fees from Chiesi Ltd., and speaker fees from Vertex Pharmaceuticals. Philip Mitchelmore reports no conflicts of interest. Craig A Williams reports no conflicts of interest.

Ethical Approval. No ethical approval was required for this study, as it is a secondary analysis of publicly available data. References to the included databases are included within the reference list.

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