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Diagnostic agreement among experts assessing adults presenting with possible cystic fibrosis: need for improvement and implications for patient care

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Shareable abstract (@ERSpublications)

Adult presentations of possible CF present a major diagnostic challenge and agreement on diagnosis is unsatisfactory. This is an area in need of significant improvement, and has potential consequences for patient experience and access to specialised care. <https://bit.ly/3PhpnKc>

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Abstract

Background Increasing awareness of milder presentations of cystic fibrosis (CF) and greater interest in non-CF bronchiectasis are likely to lead to more CF screening by respiratory clinicians. As a result, adults who may not strictly fulfil CF diagnostic criteria yet display evidence of abnormal CF transmembrane conductance regulator (CFTR) function are being identified. The degree of agreement on diagnosis and care needs in these cases between CF clinicians remains unknown, and has implications for patient care, including access to CFTR modulator therapies.

Methods We surveyed adult CF physicians in Canada, the USA, the UK and Ireland, and presented them with anonymised vignettes of adult patients referred for assessment of possible CF. Diagnostic inter-rater agreement over diagnosis, ease of classifying cases and appropriate follow-up was assessed using Krippendorff's reliability coefficient (α).

Results Agreement over diagnosis ($\alpha=0.282$), ease of classification ($\alpha=-0.01$) and recommended follow-up ($\alpha=0.054$) was weak. Clinician experience (>10 and 5–10 years versus <5 years) and location (UK and Ireland versus Canada) were associated with higher odds of recommending further testing compared with selecting a formal diagnosis (respectively, OR 2.87; $p=0.022$, OR 3.74; $p=0.013$ and OR 3.16; $p=0.007$). A modified standard of care was recommended in 28.7% of cases labelled as CF. 70% of respondents agreed with the statement that “Accurate distinction between CF and CFTR-related disorder has become significantly more pertinent with the advent of highly effective CFTR modulators”.

Conclusions Our results demonstrate low diagnostic concordance among CF specialists assessing cases of possible adult CF and highlight an area in need of improvement.

Introduction

Cystic fibrosis (CF) is among the most common life-limiting hereditary diseases in populations of European descent, and is associated with multiorgan morbidity and premature mortality driven predominantly by progressive respiratory failure [1]. Mutations in the CF transmembrane conductance regulator (CFTR) gene can lead to dysfunction and/or deficiency of the CFTR protein channel. While making a diagnosis of CF might appear to be a straightforward task, usually requiring 1) a clinical presentation in keeping with CF and 2) two measured sweat chloride levels $>60 \text{ mmol}\cdot\text{L}^{-1}$ reflective of



CFTR dysfunction and/or 3) identification of two recognised disease-causing variants by genetic analysis [2, 3], increased awareness of delayed presentations of CF, and consequently greater testing, has led to a growing number of individuals presenting in later life with varying and often milder phenotypes [4].

Adult presentations of possible CF can represent a complex diagnostic challenge for clinicians. Frequently, the criteria for a diagnosis of CF are not strictly met, with sweat chloride measurements often found to be in the indeterminate range of 30–59 mmol·L⁻¹ reflective of residual CFTR function and mutations of varying clinical consequence. These issues have led to the emergence of a spectrum of diagnostic labels in adults, ranging from “CF carrier” to “CFTR-related disorder” (CFTR-RD) and “CF”. Typically, CFTR-RD is thought of as “a clinical entity associated with CFTR dysfunction that does not fulfil diagnostic criteria for CF” [5], although recent guidelines imply that physiological evidence of CFTR dysfunction using alternative CFTR functional assays can be used to qualify a diagnosis of CF even in the absence of meeting other diagnostic criteria [2]. Regardless, until recently the distinction between CFTR-RD and CF was somewhat academic. However, with the emergence of transformative CFTR modulator therapies [6–8], accurate diagnostic classification carries greater significance, given that in certain cases access to these therapies may be dependent on an established diagnosis of CF.

Underpinning all these considerations lies the challenge of defining a “clinical presentation of CF”, which becomes a somewhat subjective task when assessing individuals presenting in late adulthood with milder phenotypes. While bronchiectasis, rhinosinusitis, chronic airway infection with certain pathogens such as *Pseudomonas aeruginosa* and *Burkholderia cepacia* complex, and pancreatic insufficiency are the classic manifestations of CF, they are not individually specific to the condition. Conversely, congenital absence of the vas deferens (CBAVD) is strongly associated with *CFTR* mutations [9, 10]. Defining a clinical presentation of CF in adult patients referred for assessment is therefore a complex task, likely to be open to significant variation in clinician interpretation and biases, and consequently a widely variable patient experience.

We hypothesised that in adult referred cases, diagnostic classification could vary significantly between adult CF specialists. We performed an exploratory study to measure inter-clinician diagnostic concordance when presented with seven anonymised clinical vignettes drawn from real-world adult cases referred to our CF clinic at St Paul’s Hospital (Vancouver, BC, Canada). Secondly, we sought to examine the concordance for 1) the most appropriate follow-up schedule, 2) the ease of classifying each case and 3) the relative importance given by respondents to various clinical features, when considering a diagnostic label for adults presenting with phenotypes in the CF spectrum.

Methods

This study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki. Ethical approval was granted by the University of British Columbia (Vancouver, BC, Canada; REB H21–03325).

We designed a digital questionnaire using Qualtrics XM (Qualtrics, Provo, UT, USA). Questionnaires were distributed to adult CF specialists in Canada, the USA, the UK and the Republic of Ireland by representatives of CF Canada, the US CF Foundation, the European CF Society Clinical Trials Network and the Irish Thoracic Society, respectively. Consent to participation was a mandatory field in the title page. All responses were anonymised and metadata were not captured. Respondent location, years practicing in CF care and estimated annual number of adult referrals assessed per year were recorded.

We identified 20 cases of adult referrals (age >18 years at index sweat chloride or genetic testing for CF) assessed in our clinic in the past 3 years. To improve completion rates, vignette numbers were then reduced to achieve an estimated survey completion time of 15 min. Seven cases were randomly selected for inclusion and their case notes were synthesised into anonymised clinical vignettes. All respondents assessed the same seven vignettes, which included: age at index CF testing (first sweat chloride or genetic testing), indication for testing, sweat chloride levels and results (and extent) of genetic analyses. Symptoms, abbreviated background histories and radiological results were available for pulmonary, sino-nasal and gastrointestinal systems. Results of faecal elastase and pulmonary microbiology analyses were included for all cases, as were brief targeted family histories and selected relevant medical history.

Respondents were asked to select the most appropriate diagnosis from the clinical vignettes, selecting from “CF”, “CF diagnosis not resolved – needs further testing”, “CFTR-related disorder”, “CF carrier” and “None of the above”. Respondents were then asked to select the most appropriate follow-up for the case in question: “Follow-up outside of a multi-disciplinary CF Clinic”, “Modified multi-disciplinary CF Clinic

follow-up (reduced frequency/monitoring/shared-care where possible)”and “Full standard of care multi-disciplinary CF Clinic follow-up (quarterly review, sputum, spirometry)”.

Finally, respondents were asked to rate the subjective ease of classifying each case (5-point net promoter score: very hard=1 point, very easy=5 points). In the subsequent exploratory section, respondents were presented with a list of clinical findings (e.g. “bronchiectasis – diffuse”, “nasal polyposis”) and asked to rate the significance of each finding in contributing to a “clinical presentation of CF” (3-point net promoter score: “Not individually supportive”, “Somewhat supportive” and “Strongly supportive”). The order of presentation of the clinical feature options was randomised for each respondent. In the final section, responders were asked to rate their agreement with a series of statements pertaining to the topic of classification of CFTR-related disorders and CF. The full survey and case vignettes are available in the supplementary material. Responses were defined as per the standard definitions set out by the American Association for Public Opinion Research [11].

Statistical analysis

Statistical analysis was performed in RStudio (RStudio, Boston, MA, USA) running R version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria). Overall inter-clinician concordance on diagnosis, ease of diagnosis and appropriate follow-up was assessed using Krippendorff’s reliability coefficient (α) in the IRR package in R, where $\alpha=0$ indicates perfect disagreement, $\alpha=1$ indicates perfect agreement and $\alpha<0$ indicates agreement lower than expected by chance. To examine whether the likelihood of recommending further testing was affected by location of respondent practice, we fit a generalised mixed effects logistic regression model, assessing predictors of a choice of “CF diagnosis not resolved – needs further testing” versus all other classifications as the response variable, with responder location (Canada as reference), clinical experience (<5 years as reference) and vignette identifier as fixed effects and responder identifier as random effects. Models including the number of adult referrals assessed per year (with <5 as the reference) were also explored. UK and Ireland responses were combined due to 1) similarities in the healthcare funding models (public, no fee per service), 2) similarities in prevalence of CF and 3) small sample size for Ireland (n=2). In the exploratory analysis of the relative importance of clinical features when considering a clinical presentation of CF, the provided options were ranked by cumulative score where “Not individually supportive”, “Somewhat supportive” and “Strongly supportive” were assigned 0, 1.5 and 3 points, respectively. All other data were summarised in descriptive form.

Results

In total, between 23 November 2021 and 28 February 2022, 67 responses were provided, with 55 responders completing classification of all seven cases (82.1% completion rate), equating to 385 individual case reviews. 54 responders then completed all subsequent exploratory questions (80.1%). Due to the third-party distribution of the study questionnaire, accurate response rates could not be calculated; however, based on an estimation of 520 eligible respondents, response rate approximated 13% (further information in the supplementary material). Four responses were excluded due to completion of only one out of seven vignette assessments in each and eight were excluded as only demographic information was provided (no further progression). The characteristics of the complete responders are shown in table 1.

	Total	Location			p-value
		Canada	UK and Ireland	USA	
Location	55 (100.0)	15 (27.3)	11 (20.0)	29 (52.7)	
Years of clinical experience					0.21
<5 years	10 (18.2)	4 (26.7)	3 (27.3)	3 (10.3)	
5–10 years	11 (20.0)	5 (33.3)	1 (9.1)	5 (17.2)	
>10 years	34 (61.8)	6 (40.0)	7 (63.6)	21 (72.4)	
Estimated annual adult assessments (n)					0.17
<5	19 (34.5)	9 (60.0)	3 (27.3)	7 (24.1)	
5–10	19 (34.5)	3 (20.0)	5 (45.5)	11 (37.9)	
>10	17 (30.9)	3 (20.0)	3 (27.3)	11 (37.9)	

Data are presented as n (%), unless otherwise stated.

The overall inter-rater agreement for diagnosis was weak ($\alpha=0.282$) (figure 1a), and very weak for subjective ease of classification ($\alpha=-0.01$) and recommended follow-up ($\alpha=0.054$) (figure 1b). In six of the seven cases a minimum of four of the five possible options were chosen, with all available options selected in three cases. In univariate analyses, a response from the UK and Ireland was associated with a higher proportion of cases classified as “CF diagnosis not resolved – needs further testing” compared with responses from Canada or the USA (40.3% versus 21.9% versus 17.2%; $p=0.001$ by Chi-squared test) (table 2).

In multivariate regression analyses, longer time in practice was associated with a higher odds ratio of recommending further testing compared with making a definitive diagnosis (OR 2.87, 95% CI 1.17–7.06; $p=0.022$ for >10 versus <5 years experience and OR 3.74, 95% CI 1.32–10.58; $p=0.013$ for 5–10 versus

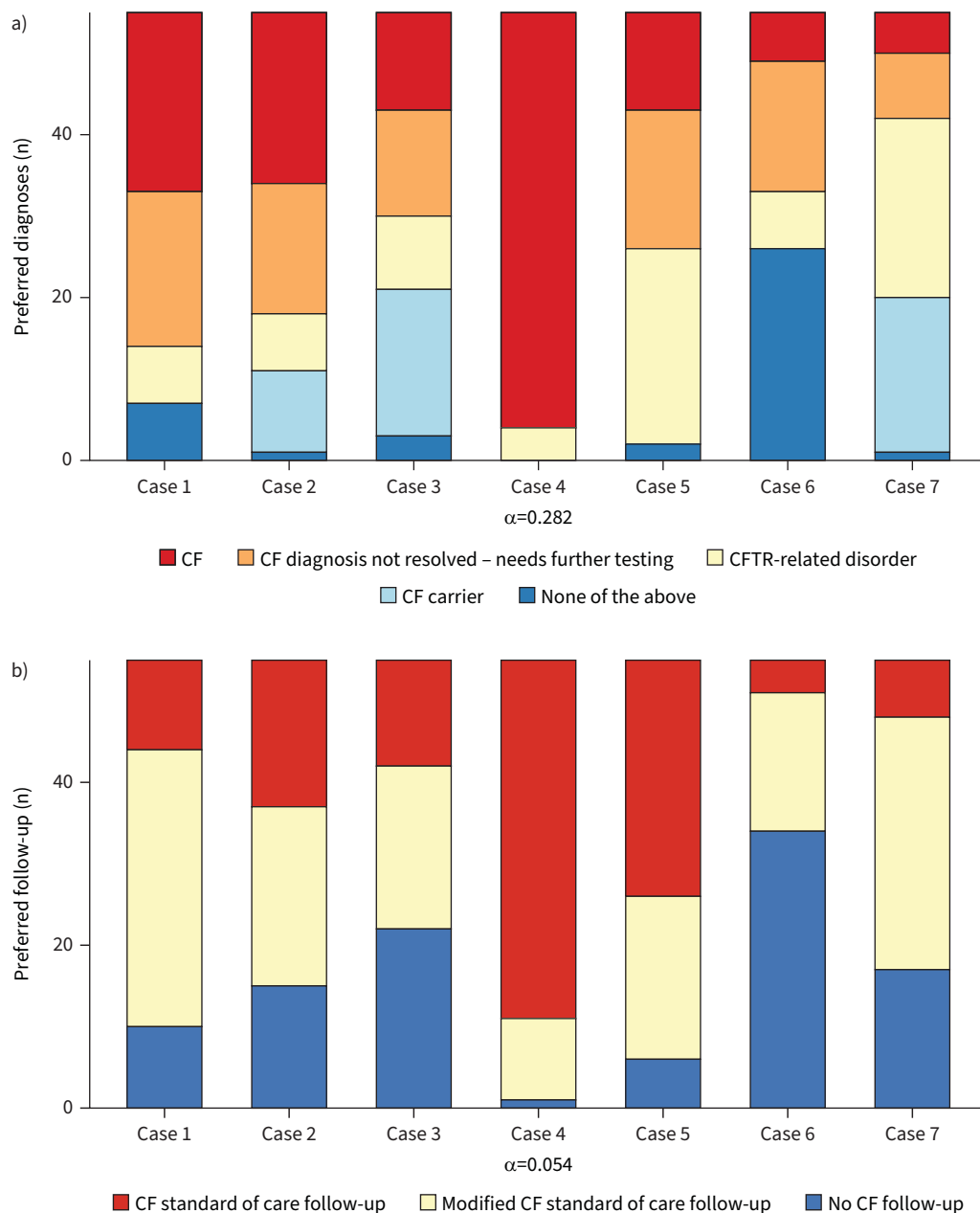


FIGURE 1 Case-specific breakdown of a) diagnoses and b) follow-up, selected by responders. Total diagnoses=number of raters (55)×number of cases (7)=385. CF: cystic fibrosis; CFTR: CF transmembrane conductance regulator.

TABLE 2 Breakdown of diagnoses by responder locations, responder clinical experience and choice of follow-up based on diagnosis[#]

Diagnoses	Location			p-value	CF practice experience			p-value	Stratified by follow-up selected			p-value
	Canada	UK and Ireland	USA		<5 years	5–10 years	>10 years		No CF follow-up	Modified CF SOC	CF SOC	
Diagnoses	105	77	203		70	77	238		105	154	126	
Diagnosis				0.002				0.163				<0.001
CF	39 (37.1)	25 (32.5)	65 (32.0)		22 (31.4)	29 (37.7)	78 (32.8)		1 (1.0)	37 (24.0)	91 (72.2)*	
CF diagnosis not resolved – needs further testing	23 (21.9)	31 (40.3)*	35 (17.2)		10 (14.3)	21 (27.3)	58 (24.4)		19 (18.1)	53 (34.4)*	17 (13.5)	
CFTR-related disorder	22 (21.0)	10 (13.0)	48 (23.6)		15 (21.4)	18 (23.4)	47 (19.7)		11 (10.5)	51 (33.1)*	18 (14.3)	
CF carrier	15 (14.3)	6 (7.8)	26 (12.8)		12 (17.1)	6 (7.8)	29 (12.2)		38 (36.2)*	9 (5.8)	0 (0.0)	
None of the above	6 (5.7)	5 (6.5)	29 (14.3)		11 (15.7)	3 (3.9)	26 (10.9)		36 (34.3)*	4 (2.6)	0 (0.0)	

Data are presented as n or n (%), unless otherwise stated. CF: cystic fibrosis; SOC: standard of care; CFTR: CF transmembrane conductance regulator. [#]: total diagnoses=number of raters (55)×number of cases (7)=385. *: significance for positive association in *post hoc* testing with Bonferroni corrected p-value <0.05.

<5 years experience), as was a response from the UK and Ireland (OR 3.16, 95% CI 1.37–7.32; p=0.007 *versus* Canada) (supplementary table S1). Interestingly, 29% of cases classified as CF were assigned to modified CF follow-up, as opposed to standard of care (figure 2).

When assessing the relative importance given to various clinical features in supporting a “clinical presentation of CF” only five features received >50% endorsement as “Strongly supportive”: pancreatic insufficiency, infertility/CBAVD, diffuse bronchiectasis, sputum positivity for *B. cepacia* complex and sputum positivity for *P. aeruginosa* (table 3). When then asked to rate factors which influence a decision of the need for follow-up at a CF specialist centre, five factors received >50% endorsement as a “Major determinant”: sputum positivity for *B. cepacia* complex, exocrine pancreatic insufficiency, frequent pulmonary exacerbations, sputum positivity for *P. aeruginosa* and worse lung function at presentation (table 4). When gauging responder agreement with a series of questions addressing the significance of

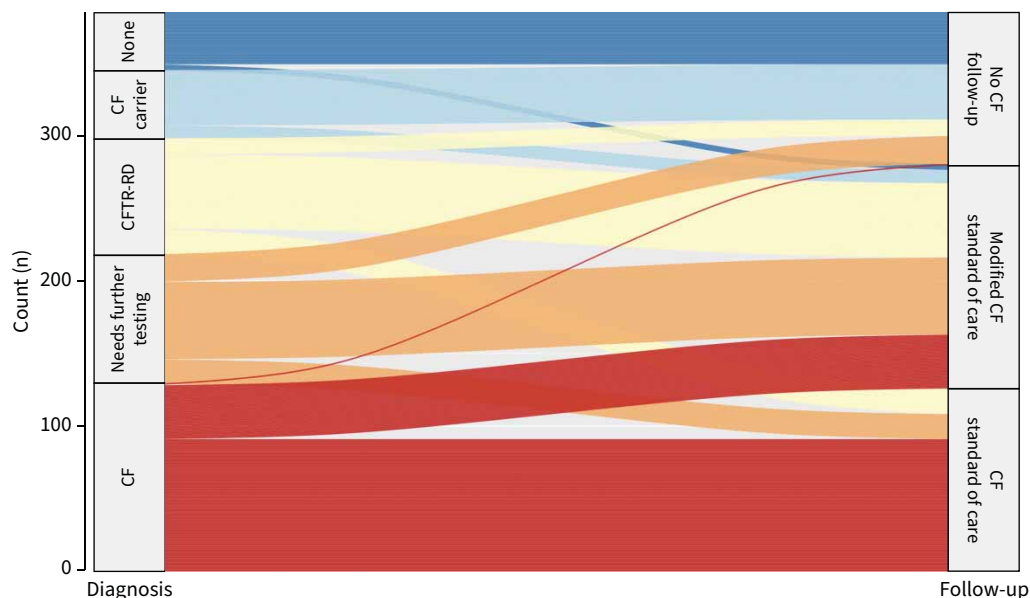


FIGURE 2 Alluvial plot of the follow-up selection based on responder-selected diagnosis. 28.7% of adult cystic fibrosis (CF) diagnoses were assigned to modified CF standard of care follow-up. 22.5% of CF transmembrane conductance regulator-related disorder (CFTR-RD) diagnosis were assigned to full CF standard of care follow-up, while 80.9% of those recommended to need further testing were assigned to either no CF follow-up (21.3%) or modified CF follow-up (59.6%).

TABLE 3 Ratings of clinical feature contribution to supporting a “clinical presentation of CF” (n=54 responses)

	Not individually supportive	Somewhat supportive	Strongly supportive	Total (weighted)
Clinical features				
Pancreatic insufficiency	0 (0)	13 (24.07)	41 (75.93) [#]	142.5
Infertility/CBAVD	0 (0)	13 (24.07)	41 (75.93) [#]	142.5
Bronchiectasis – diffuse	1 (1.85)	22 (40.74)	31 (57.41) [#]	126
Radiographic pancreatic fibrosis	1 (1.85)	33 (61.11)	20 (37.04)	109.5
Daily sputum production	6 (11.11)	38 (70.37)	10 (18.52)	87
Aquagenic wrinkling	16 (29.63)	24 (44.44)	14 (25.93)	78
Frequent need for antibiotics for chest	10 (18.52)	36 (66.67)	8 (14.81)	78
Vitamin A/E deficiency	10 (18.52)	38 (70.37)	6 (11.11)	75
Nasal polyposis	14 (25.93)	32 (59.26)	8 (14.81)	72
ABPA diagnosis	13 (24.07)	38 (70.37)	3 (5.56)	66
Bronchiectasis – asymmetrical	19 (35.19)	27 (50)	8 (14.81)	64.5
Radiographic rhinosinusitis	15 (27.78)	36 (66.67)	3 (5.56)	63
Liver disease/steatosis/cirrhosis		29 (53.7)	4 (7.41)	55.5
Obstructive spirometry	20 (37.04)	32 (59.26)	2 (3.7)	54
Osteoporosis/osteopenia	32 (59.26)	20 (37.04)	2 (3.7)	36
Constipation	37 (68.52)	14 (25.93)	3 (5.56)	30
Vitamin D deficiency	37 (68.52)	15 (27.78)	2 (3.7)	28.5
Airway microbiology				
<i>Burkholderia cepacia</i> complex	2 (3.7)	14 (25.93)	38 (70.37) [#]	135
<i>Pseudomonas aeruginosa</i>		23 (42.59)	30 (55.56) [#]	124.5
<i>Stenotrophomonas maltophilia</i>	7 (12.96)	31 (57.41)	16 (29.63)	94.5
<i>Mycobacterium abscessus</i> sp.	7 (12.96)	32 (59.26)	15 (27.78)	93
<i>Achromobacter</i> species	9 (16.67)	30 (55.56)	15 (27.78)	90
MRSA	12 (22.22)	33 (61.11)	9 (16.67)	76.5
MSSA	12 (22.22)	36 (66.67)	6 (11.11)	72
<i>Mycobacterium avium</i> complex	12 (22.22)	37 (68.52)	5 (9.26)	70.5
<i>Aspergillus fumigatus</i> sp.	22 (40.74)	31 (57.41)	1 (1.85)	49.5
<i>Streptococcus pneumoniae</i>	48 (88.89)	6 (11.11)	0 (0)	9

Data are presented as n (%), unless otherwise stated. Total score calculated on a basis of 0, 1.5 and 3 points allocated for each count of “Not supportive”, “Somewhat supportive” and “Strongly supportive”, respectively. CF: cystic fibrosis; CBAVD: congenital bilateral absence of the vas deferens; ABPA: allergic bronchopulmonary aspergillosis; MRSA: methicillin-resistant *Staphylococcus aureus*; MSSA: methicillin-sensitive *S. aureus*. [#]: responses with ≥50% selection as “Strongly supportive” of need for follow-up at a specialist CF centre.

TABLE 4 Ratings of factors influencing responder decision on individual need for follow-up at a cystic fibrosis (CF) specialist centre (n=54 responses)

	Would not contribute	Contributes somewhat	Major determinant	Total (weighted)
<i>Burkholderia cenocepacia</i> complex sputum positive	2 (3.7)	13 (24.07)	39 (72.22) [#]	136.5
Confirmed exocrine pancreatic insufficiency	1 (1.85)	15 (27.78)	38 (70.37) [#]	136.5
Frequent pulmonary exacerbations	3 (5.56)	14 (25.93)	37 (68.52) [#]	132
<i>Pseudomonas aeruginosa</i> sputum positive	4 (7.41)	19 (35.19)	31 (57.41) [#]	121.5
Worse lung function at presentation	5 (9.26)	19 (35.19)	30 (55.56) [#]	118.5
Recurrent pancreatitis	3 (5.56)	28 (51.85)	23 (42.59)	111
Nutritional status/BMI	5 (9.26)	29 (53.7)	20 (37.04)	103.5
NTM sputum positive	7 (12.96)	26 (48.15)	21 (38.89)	102
Lung function relative to age at presentation	10 (18.52)	25 (46.3)	19 (35.19)	94.5
MRSA sputum positive	11 (20.37)	26 (48.15)	17 (31.48)	90
Other bacterial sputum positivity [¶]	10 (18.52)	29 (53.7)	15 (27.78)	88.5
Younger age at presentation	12 (22.22)	29 (53.7)	13 (24.07)	82.5
Diagnosis of ABPA	11 (20.37)	33 (61.11)	10 (18.52)	79.5
Confirmed diagnosis of diabetes	17 (31.48)	28 (51.85)	9 (16.67)	69
Already attending a pulmonary specialist	23 (42.59)	27 (50)	4 (7.41)	52.5

Data are presented as n (%), unless otherwise stated. Total score calculated on a basis of 0, 1.5 and 3 points allocated for each count of “Would not contribute”, “Contributes somewhat” and “Major determinant”, respectively. BMI: body mass index; NTM: nontuberculous mycobacteria; MRSA: methicillin-resistant *Staphylococcus aureus*; ABPA: allergic bronchopulmonary aspergillosis. [#]: response with ≥50% selection as “Major determinant” of need for follow-up at a specialist CF centre; [¶]: *Stenotrophomonas*, *Achromobacter* and methicillin-sensitive *S. aureus*.

increased detection of CFTR-RD and improving discrimination between CF and CFTR-RD, 70% agreed that “accurate distinction ... was significantly more pertinent” given the emergence of CFTR modulators, while 76% agreed that increasing CFTR-RD identification could have significant resource implications for CF centres. There was equipoise regarding the statement “The current guidelines for CF/CFTR-RD diagnosis provide a good framework for high inter-clinician agreement regarding final diagnosis and classification” (figure 3).

Discussion

We present the results of an exploratory assessment of inter-clinician diagnostic agreement when rating possible adult presentations of CF. Our results suggest that expert adult CF clinicians demonstrate weak agreement over diagnostic classification in these cases, as well as weak agreement over the subjective ease of classifying each case and the most appropriate follow-up. Whether these findings are accounted for by individual biases/experience, resource constraints (including differential access to specialised testing) or perceived thresholds of benefit warrants further clarification. Our exploratory results suggest that factors such as clinician experience or location of practice may influence some decisions in this area. Whether the effect of responder location is related to differences in healthcare funding models or access to advanced physiological testing is worthy of further exploration. Regardless, significant variability in diagnosis and follow-up could be a major issue for these patients, based largely on the chance effect of which clinician is tasked with assessing their case. Interestingly, nearly one-third of cases determined to meet a diagnosis of CF were not then assigned to CF standard of care follow-up by the same assessor, perhaps suggesting that for milder adult-diagnosed cases, some CF specialists may feel there is room for flexibility in the optimal delivery of clinical care.

With the growing calls to address the knowledge and service gaps for non-CF bronchiectasis [12, 13], it is likely that systematic assessment of people with bronchiectasis will result in increased screening for CF, leading to greater identification of patients with sweat chloride abnormalities and/or *CFTR* variants (of both known and unknown clinical consequence). Indeed, between 2016 and 2020, the number of individuals diagnosed with CF after the age of 40 years in the CF Foundation Patient Registry doubled

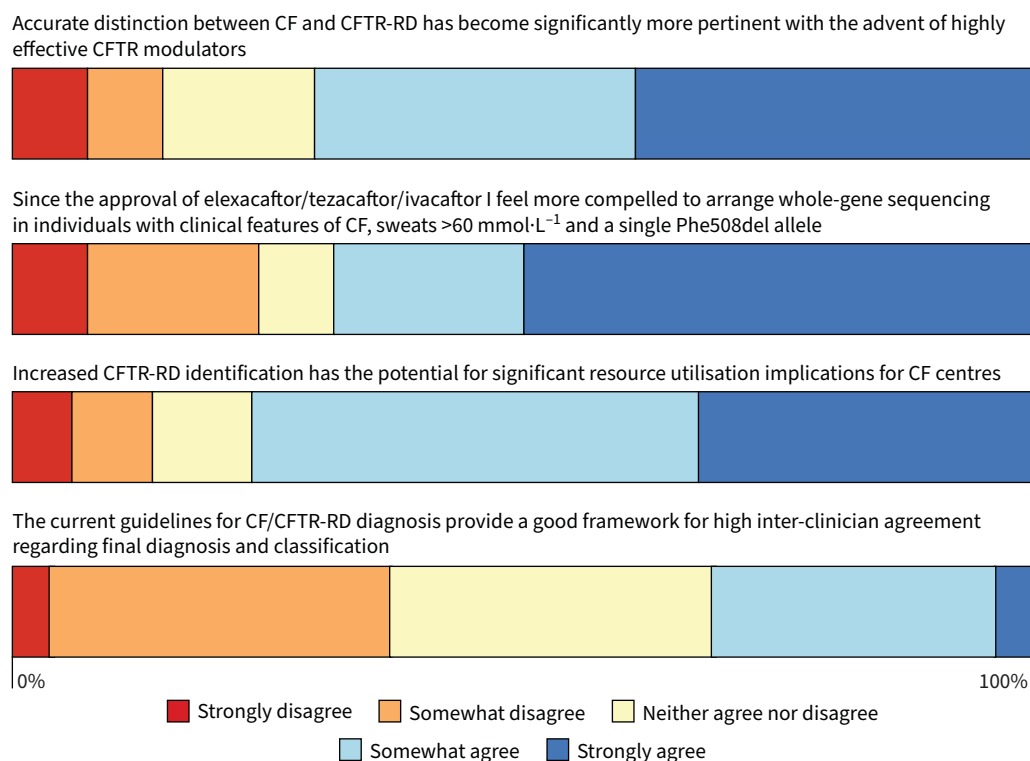


FIGURE 3 Subjective responder agreement with statements regarding implications of increased recognition and need for cystic fibrosis transmembrane conductance regulator-related disorder (CFTR-RD) assessments. CF: cystic fibrosis.

from approximately 500 to 1000, while the number diagnosed in the first year of life increased by only 20% [14, 15]. How exactly these patients should then best be served is clearly an area in need of greater consensus. With this very challenge in mind, the European CF Society has recently established a diagnostic working group to develop more robust guidelines in this area, the recommendations of which will hopefully add clarity and consensus.

Historically, a sweat chloride threshold of $>60 \text{ mmol}\cdot\text{L}^{-1}$ for diagnosing CF has served its purpose well in terms of achieving a high diagnostic specificity, with this cut-off being associated with CFTR function $<1\%$ of the mean for healthy controls [16]. Conversely, whether such a threshold can be assumed to have a high sensitivity for CF is debatable as factors other than CFTR function can influence the clinical phenotype, including epigenetics, genetic modifiers, age and environmental factors [17]. As such, the clinical presentation of patients classified as having CFTR-RD based on two sweat chlorides $<60 \text{ mmol}\cdot\text{L}^{-1}$ can be more severe than patients meeting diagnostic criteria for CF. To assess sensitivity and specificity, one must start with a clear definition of what a “positive” and “negative” case represents, and as highlighted by our data, there is suboptimal consensus among experts as to what represents a “positive” case of CF in cases where sweat chlorides are indeterminate or borderline. Indeed, various well-recognised *CFTR* variants such as D1152H, R117H and 3849+10 kb C→T are associated with nondiagnostic sweat chloride levels [18–20], yet are both pathogenic and responsive to CFTR-targeted therapies [21].

Faced with nondiagnostic sweat chloride results and genetic panels for common *CFTR* variants, clinicians have the option of considering further genetic analyses to aid in more accurate classification. Recent evidence suggest that full-gene sequencing of *CFTR* reveals biallelic disease-causing variants in 98.1% of individuals, increasing the yield from 95.8% in the same cohort before based on pre-sequencing analyses [22]. Furthermore, some intronic mutations, not commonly detectable through standard *CFTR* genetic panels [23], may be responsive to CFTR modulators [24, 25]. This raises the prospect that some cases of CF, which could benefit from novel therapies, might go undetected without advancing to full-gene sequencing. Moreover, deletion and duplications in the *CFTR* gene, identifiable through gene sequencing or multiplex ligation-dependent probe amplification, may account for up to 5% of all detected variants. Conversely, although price is decreasing, full-gene sequencing remains costly and many of the less common mutations identified may ultimately not be targetable by currently available modulator therapies. Therefore, their identification may help to clarify the diagnosis and possibly inform suitability for future therapies, but may not result in changes in immediate management. Moreover, unique mutations or mutations of unknown clinical significance are frequently detected in milder cases [22] and in the absence of supportive clinical evidence can put clinicians in a difficult situation when trying to convey the significance of the results to patients.

While gene sequencing seeks to find evidence for the genetic basis for CFTR dysfunction, advanced physiological testing provides an opportunity to demonstrate evidence of CFTR dysfunction *in vivo* or *ex vivo*. Nasal potential difference (NPD) [26, 27] and intestinal current measurement (ICM) improve classification of “normal” versus “CF/CFTR-RD” cases in adults referred for further evaluation of an inconclusive CF workup [28, 29]. Furthermore, studies demonstrate that parameters from sweat chloride analysis and NPD can be combined, leading to improved discrimination between controls, carriers and CF, in cases where the two tests were discordant at the outset [30]. However, whether these approaches can distinguish between CF and CFTR-RD, or indeed at what point the severity of the associated phenotype makes a distinction between the two redundant in practice, is unclear. Although CFTR modulator therapies may now offer a credible therapeutic option for some of these patients regardless of their diagnostic label, it remains unclear as to what extent patients will benefit given their older age at diagnosis and generally milder clinical presentation.

Compounding the challenge of harmonising diagnostic practices, advanced diagnostic methodologies are only available at validated reference centres since specialised materials and significant expertise are required to achieve technical standards, meaning they are not readily available to most clinicians. We chose to include the classification “CF diagnosis not resolved – needs further testing” among the diagnostic options for two reasons: 1) this is a terminal “node” in the current CF Foundation diagnostic decision tree and 2) the decision to proceed to further testing in such cases is not inconsequential, resulting in costs incurred for either gene sequencing, NPD, ICM or other functional CFTR assays, *e.g.* nasal epithelial cell-derived spheroid testing or rectal organoid morphology analysis [31, 32]. Exploring the proportion of respondents who feel further testing is warranted in cases such as these is informative and helps gauge the appetite for this approach among practicing clinicians. Indeed, in our study, 23.1% of case assessments resulted in a recommendation to advance to further testing, and the proportion of respondents choosing this

option was higher in the UK and Ireland compared with Canada, which may reflect differences in local practice or access to specialised testing. Nevertheless, these tests are not always readily available and even when they are the cost-benefit ratio of pursuing them likely becomes a judgement call, as perhaps highlighted by the fact that so many respondents were happy to apply a diagnostic label without feeling the need to recommend further testing. Further exploration of the variability of access to further testing and the associated impact on diagnostic practice would be welcome. As the number of adults referred for CF assessment increases, development of novel easily applicable tests and improving access should be an area of focus.

Aside from the challenge of deciding on the appropriateness of further testing, clinicians are tasked with determining whether the clinical history is consistent with a diagnosis of CF. It is likely that it is this task specifically which might drive the greatest variability in the final diagnostic label applied. Fundamentally, CF is thought of as a life-limiting disease, the severity of which broadly correlates with sweat chloride and genotype [17, 33]. However, outcomes such as death or lung transplantation are best predicted by more granular clinical factors, with lower forced expiratory volume in 1 s, body mass index, age and hospitalisation frequency repeatedly demonstrated to be the primary predictors of mortality in CF [34, 35]. How then should one rank concern over negative outcomes in adult cases such as those presented in our survey, many of whom present with abnormal sweat chloride, but reassuringly normal spirometry, many decades into their life? Our data provide a consensus of sorts, regarding the features that most concern CF clinicians, with *B. cepacia* complex and *P. aeruginosa* sputum positivity, exocrine pancreatic insufficiency, frequent pulmonary exacerbations, and worse lung function at presentation all strongly endorsed as major determinants of the need for ongoing CF specialist care.

Our study has several limitations which should be considered when interpreting the results. First, the survey response rates were low and clustering of responses from a smaller number of centres cannot be ruled out. Consequently, generalisability of these results needs to be confirmed in larger studies. Nonetheless, the poor agreement demonstrated is cause for concern regardless of whether it represents practice within or between selected centres, or indeed in the wider international clinician body. Furthermore, throughout interim analyses α did not improve as responses increased and results were also similar when stratifying by responder location. Second, reducing cases to succinct vignettes removes many subtle but contributory cues and details that can determine the clinical assessment of a patient. Consequently, our study provides a proof of concept but is not wholly equivalent to measuring agreement between clinicians had all assessed the same patients in person. Third, we did not provide the option for open-ended comments, meaning thematic coding and further exploration of responder rationale was not possible. Specifically, we did not explore the ease of access to advanced physiological and genetic testing for each responder, a factor which may well influence the choice of “CF diagnosis not resolved – needs further testing” as the appropriate diagnostic label and which could have further reduced the statistical inter-responder agreement. Finally, the spectrum of the cases was limited in scope as they did not include clinical presentations with CBAVD or recurrent pancreatitis, which are highly relevant to the wider medical community and can similarly pose diagnostic challenges for CF clinicians.

Conclusions

Adult presentations of possible CF represent a major challenge, and agreement on diagnosis and recommended follow-up is variable even among CF specialists. Our data provide insights into an area in need of better consensus and standardisation, with potential consequences for patient experience and equitable access to care. Given our findings, concrete plans to address these issues and achieve greater consensus should be a priority.

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