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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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Title: Diagnostic agreement among experts assessing adults presenting with possible Cystic Fibrosis: need for improvement and implications for patient care.

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Abbreviations:

BMI	Body mass index
CBAVD	Congenital bilateral absence of the vas deferens
CF	Cystic Fibrosis
CFTR	Cystic Fibrosis transmembrane conductance regulator ion channel
CFTR	Cystic Fibrosis transmembrane conductance regulator gene
CFTR-RD	CFTR-related disorder
CT	Computerised tomography
FEV_1	Forced expiratory volume in 1 second
GERD	Gastroesophageal reflux disease
GI	Gastro-intestinal
ICM	Intestinal current measurement
IgE	Immunoglobulin E
MAB	Mycobacterium abscessus
MAC	Mycobacterium avium intracellulare
MRSA	Methicillin resistant Staphylococcus aureus
MSSA	Methicillin sensitive Staphylococcus aureus
NPD	Nasal potential difference
OGTT	Oral glucose tolerance test
OR	Odds ratio
PA	Pseudomonas aeruginosa
ROI	Republic of Ireland
UK	United Kingdom of Great Britain and Northern Ireland
USA	United States of America
WGS	Whole gene sequencing

Abstract: words 246

Background: Increasing awareness of milder presentations of cystic fibrosis (CF) and greater interest in non-CF bronchiectasis is 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 cystic fibrosis 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 anonymized 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 Krippendorf's *alpha* statistic.

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 years and 5-10 years vs <5 years) and location (UK/Ireland vs Canada) were associated with higher odds of recommending further testing compared to selecting a formal diagnosis (OR 2.87, p=0.022, OR 3.74; p=0.013; and OR 3.16, p=0.007, respectively). A modified standard of care was recommended in 28.7% of cases labelled as CF. 70% of respondents agreed with the statement that "*distinction between CF and CFTR-RD has become significantly more pertinent with the advent of highly effective CFTR-modulators*".

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

Background

Cystic fibrosis (CF) is among the most common life-limiting hereditary diseases in populations of European descent and is associated with multi-organ morbidity and premature mortality driven predominantly by progressive respiratory failure.[1] Mutations in the cystic fibrosis 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 >60mmol/L reflective of CFTR dysfunction *and/or* 3) identification of two recognized 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 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” (hereinafter CFTR-RD) and “cystic fibrosis”. Typically, CFTR-RD is thought of as "*a clinical entity associated with CFTR dysfunction that does not fulfil diagnostic criteria for CF"[5],* though 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 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 *Burholderia 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 mutations in *CFTR*.[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 hypothesized 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 anonymized clinical vignettes drawn from real-world adult cases referred to our CF clinic at St Paul's Hospital, Vancouver, Canada. Secondarily, 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 (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 United Kingdom (UK) and the Republic of Ireland (ROI) by representatives of CF Canada, the Cystic Fibrosis 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 anonymized, and meta-data was 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 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 minutes. Seven cases were randomly selected for inclusion and their case notes were synthesized into anonymized 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, results (and extent) of genetic analyses. Symptoms, abbreviated background histories and radiological results were available for pulmonary, sino-nasal and gastro-intestinal systems. Results of fecal 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 - further testing needed”, “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” / “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 online supplement. 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 R Studio running R V4.1.1 (the 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 (*alpha*) in the *IRR* package in R, where *alpha* 0 = perfect disagreement and 1 = perfect agreement. To examine whether the likelihood of recommending further testing was affected by location of respondent practice, we fit a generalized mixed effects logistic regression model, assessing predictors of a choice of “CF diagnosis not resolved - further testing needed” vs. all other classifications as the response variable, with responder location (Canada as reference), clinical experience (<5 years as reference) and vignette ID as fixed effects and responder ID as random effects. Models including the number of adult referrals assessed per year (with <5 as the reference) were also explored. UK and ROI responses were combined due to a) similarities in the healthcare funding models (public, no fee per service), b) the similarities in prevalence of CF, c) the small sample size for ROI (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 November 23rd 2021 and February 28th 2022, 67 responses were provided, with 55 completing classification of all 7 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 supplemental material). Four responses were excluded due to completion of only 1/7 vignette assessment in each, and 8 were excluded as only demographic information was provided (no further progression). The characteristics of the complete responders are shown in table 1.

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 & Ireland was associated with a higher proportion of cases classified as "CF diagnosis not resolved - further testing needed" compared to responses from Canada or the USA (40.3% vs 21.9 vs 17.2, p = 0.001 by χ^2 test, table 2).

In multivariate regression analyses, longer time in practice was associated with a higher odds ratio (OR) of recommending further testing compared to making a definitive diagnosis (OR 2.87, 95% CI: 1.17–7.06, p=0.022 for >10 years vs <5 years experience , and OR 3.74, 95% CI:1.32 – 10.58, p=0.013 for 5 to 10 years experience vs <5 years experience), as was a response from the UK and Ireland (OR 3.16, 95% CI: 1.37 – 7.32, p=0.007 vs Canada) (supplemental table 1). 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, and sputum positivity for *Pseudomonas aeruginosa* or *Burkholderia cepacia* complex organisms (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 *Burkholderia cepacia* complex or *Pseudomonas aeruginosa*, exocrine pancreatic insufficiency, frequent pulmonary exacerbations, and worse lung function at presentation (table 4). When gauging responder agreement with a series of

questions addressing the significance of 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 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 specialized 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 standard of care CF 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 variants (of both known and unknown clinical consequence) in the *CFTR* gene. Indeed, between 2016 and 2020, the number of individuals diagnosed with CF after the age of 40 in the US CF registry doubled 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 Cystic Fibrosis 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 in this area.

Historically, a sweat chloride threshold of >60mmol/L 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 <60mmol/L 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-recognized variants of the *CFTR* gene such as *D1152H , R117H* and *3849+10kb C→T* are associated with non-diagnostic sweat chloride levels[18-20], and yet are both pathogenic and responsive to CFTR-targeted therapies.[21]

Faced with non-diagnostic sweat chloride results and genetic panels for common CF 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 bi-allelic 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 *CFTR*, identifiable through gene sequencing or multiplex ligation-dependent probe amplification (MLPA), may account for up to 5% of all detected variants. Conversely, while 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' vs. "CF/CFTR-RD" cases in adults referred for further evaluation of an inconclusive CF workup.[28, 29] Further, 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 – need further testing*" among the diagnostic options for two reasons: a) this is a terminal 'node' in the current CFF diagnostic decision tree, and b) 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 such as 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/Ireland compared to Canada which may reflect differences in local practice or access to specialized 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, and 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 FEV_1 and BMI, age and hospitalization 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 provides a consensus of sorts, regarding the features that most concern CF clinicians, with *Burkholderia cepacia* complex and *Pseudomonas 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. 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 alpha did not improve as responses increased, and results were also similar when stratifying by responder location. Secondly, reducing cases into 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. Thirdly, we did not provide the option for open-ended comments, meaning thematic coding and further exploration of the 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 – need 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.

Interpretation

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 standardization 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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Tables

Table 1. Characteristics of responders completing the study

n				55
Location (%)				
Canada				15 (27.3)
UK & Ireland				11 (20.0)
USA				29 (52.7)
Years of clinical experience (%)				
< 5 years				10 (18.2)
5 to 10 years				11 (20.0)
> 10 years				34 (61.8)
Estimated numbers of adult referrals assessed per year (%)				
<5				19 (34.5)
5 to 10				19 (34.5)
>10				17 (30.9)
	Canada	**UK & Ireland**	**USA**	**p**
n	15	11	29	
Years of clinical experience (%)				0.21
< 5 years	4 (26.7)	3 (27.3)	3 (10.3)	
5 to 10 years	5 (33.3)	1 (9.1)	5 (17.2)	
> 10 years	6 (40.0)	7 (63.6)	21 (72.4)	
Estimated annual adult assessments (%)				0.17
<5	9 (60.0)	3 (27.3)	7 (24.1)	
>10	3 (20.0)	5 (45.5)	11 (37.9)	
5 to 10	3 (20.0)	3 (27.3)	11 (37.9)	

Table 2. Breakdown of diagnoses by a) responder locations, b) responder clinical experience, and b) choice of follow-up based on diagnosis

Based on total diagnoses made (n = 385)				
	Location			
Diagnosis	**Canada**	**UK & Ireland**	**USA**	**p**
n	105	77	203	
				0.002
CF	39 (37.1)	25 (32.5)	65 (32.0)	
CF diagnosis not resolved - needs further testing	23 (21.9)	**31 (40.3)[a]**	35 (17.2)	
CFTR-related disorder	22 (21.0)	10 (13.0)	48 (23.6)	
CF carrier	15 (14.3)	6 (7.8)	26 (12.8)	
None of the above	6 (5.7)	5 (6.5)	29 (14.3)	
	CF experience			
	<5y CF-practice	**5-10y CF-practice**	**>10y CF-practice**	**p**
n	70	77	238	
				0.163
CF	22 (31.4)	29 (37.7)	78 (32.8)	
CF diagnosis not resolved - needs further testing	10 (14.3)	21 (27.3)	58 (24.4)	
CFTR-related disorder	15 (21.4)	18 (23.4)	47 (19.7)	
CF carrier	12 (17.1)	6 (7.8)	29 (12.2)	
None of the above	11 (15.7)	3 (3.9)	26 (10.9)	
	Stratified by follow-up selected			
	No CF follow-up	**Modified CF SOC**	**CF SOC**	**p**
n	105	154	126	
				<0.001
CF	1 (1.0)	37 (24.0)	**91 (72.2)[a]**	
CF diagnosis not resolved - needs further testing	19 (18.1)	**53 (34.4)[a]**	17 (13.5)	
CFTR-related disorder	11 (10.5)	**51 (33.1)[a]**	18 (14.3)	
CF carrier	**38 (36.2)[a]**	9 (5.8)	0 (0.0)	
None of the above	**36 (34.3)[a]**	4 (2.6)	0 (0.0)	

Total diagnoses = *n* raters (55) x *n* cases (7)
Modified multi-disciplinary CF Clinic follow up (reduced frequency/monitoring/shared-care where possible)"CF SOC = CF Standard of care (quarterly review, sputum, spirometry)
[a] Significance for positive association in post-hoc testing with Bonferroni corrected p value <0.05

Table 3. Ratings of clinical feature contribution to supporting a "clinical presentation of CF" (n = 54 responses)

a) Clinical features	**Not individually supportive (%)**		**Somewhat supportive (%)**		**Strongly supportive (%)**		**Total (weighted)**
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
Vit 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	21	(38.89)	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
Vit D deficiency	37	(68.52)	15	(27.78)	2	(3.7)	28.5
b) Airway microbiology							
Burkholderia cepacia complex	2	(3.7)	14	(25.93)	**38**	**(70.37)***	135
Pseudomonas aeruginosa	1	(1.85)	23	(42.59)	**30**	**(55.56)***	124.5
Stenotrophomonas maltophilia	7	(12.96)	31	(57.41)	16	(29.63)	94.5
Mycobacterium abscessus sp.	7	(12.96)	32	(59.26)	15	(27.78)	93
Achromobacter 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
Mycobacterium avium complex	12	(22.22)	37	(68.52)	5	(9.26)	70.5
Aspergillus fumigatus sp	22	(40.74)	31	(57.41)	1	(1.85)	49.5
Streptococcus pneumoniae	48	(88.89)	6	(11.11)	0	(0)	9

*Responses with ≥50% selection as "Strongly supportive" of need for follow-up at a specialist CF centre.
ABPA: allergic bronchopulmonary aspergillus, BMI: body mass index (kg/m^2), CBAVD: congenital bilateral absence of the vas deferens, MRSA: methicillin resistant Staphylococcus aureus, MSSA: methicillin sensitive Staphylococcus aureus.
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.

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

Factor	Would not contribute		Contributes somewhat		Major determinant		Total (weighted)
Burkholderia cenocepacia 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
Pseudomonas aeruginosa 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[a]	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

[*] Response with ≥50% selection as "major determinant" of need for follow-up at a specialist CF centre.
[a] Stenotrophomonas, Achromobacter , MSSA.
ABPA: allergic bronchopulmonary aspergillus, BMI: body mass index (kg/m^2), MRSA: methicillin resistant staphylococcus aureus, MSSA: methicillin sensitive staphylococcus aureus, NTM: non tuberculous mycobacteria.
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.

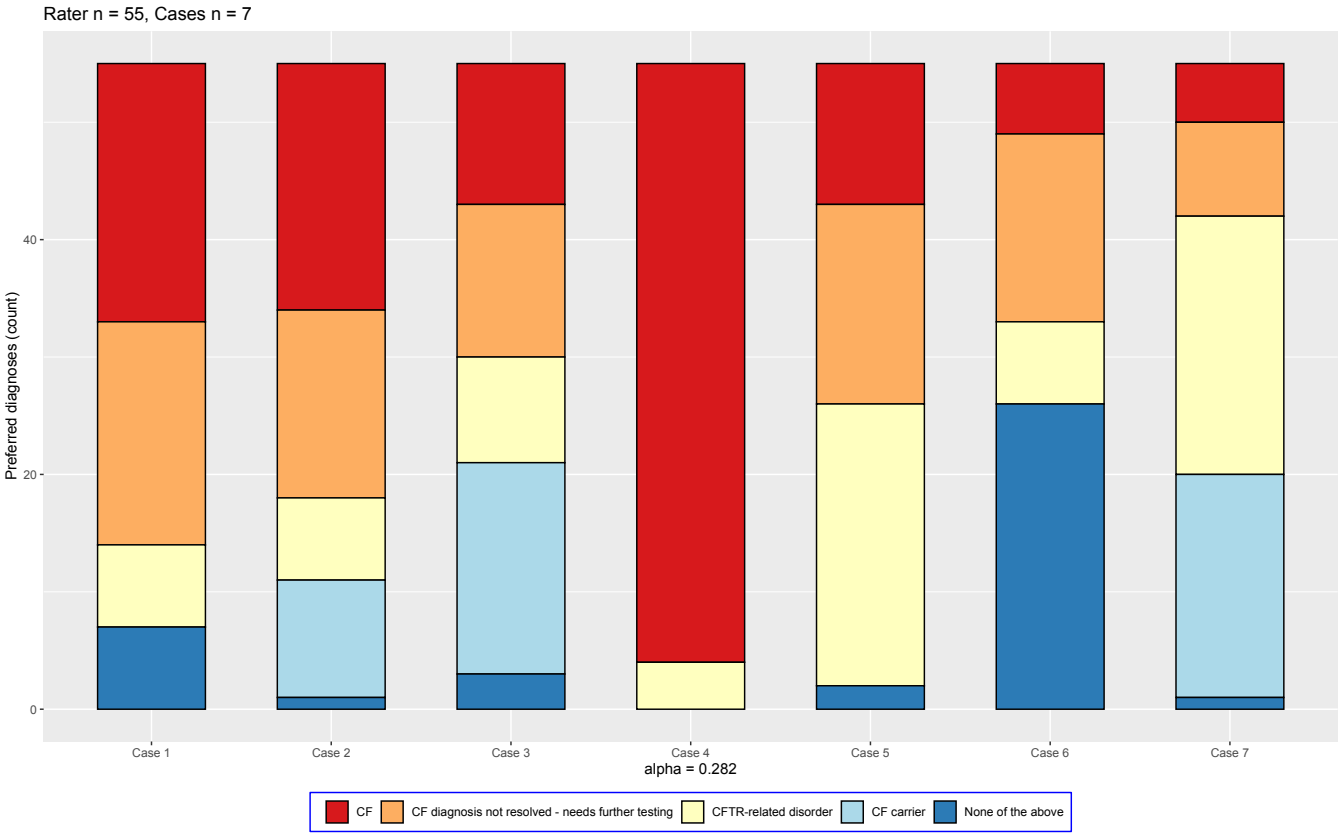
Figure legends

Figure 1. Case-specific breakdown of a) diagnoses and b) follow-up, selected by responders.

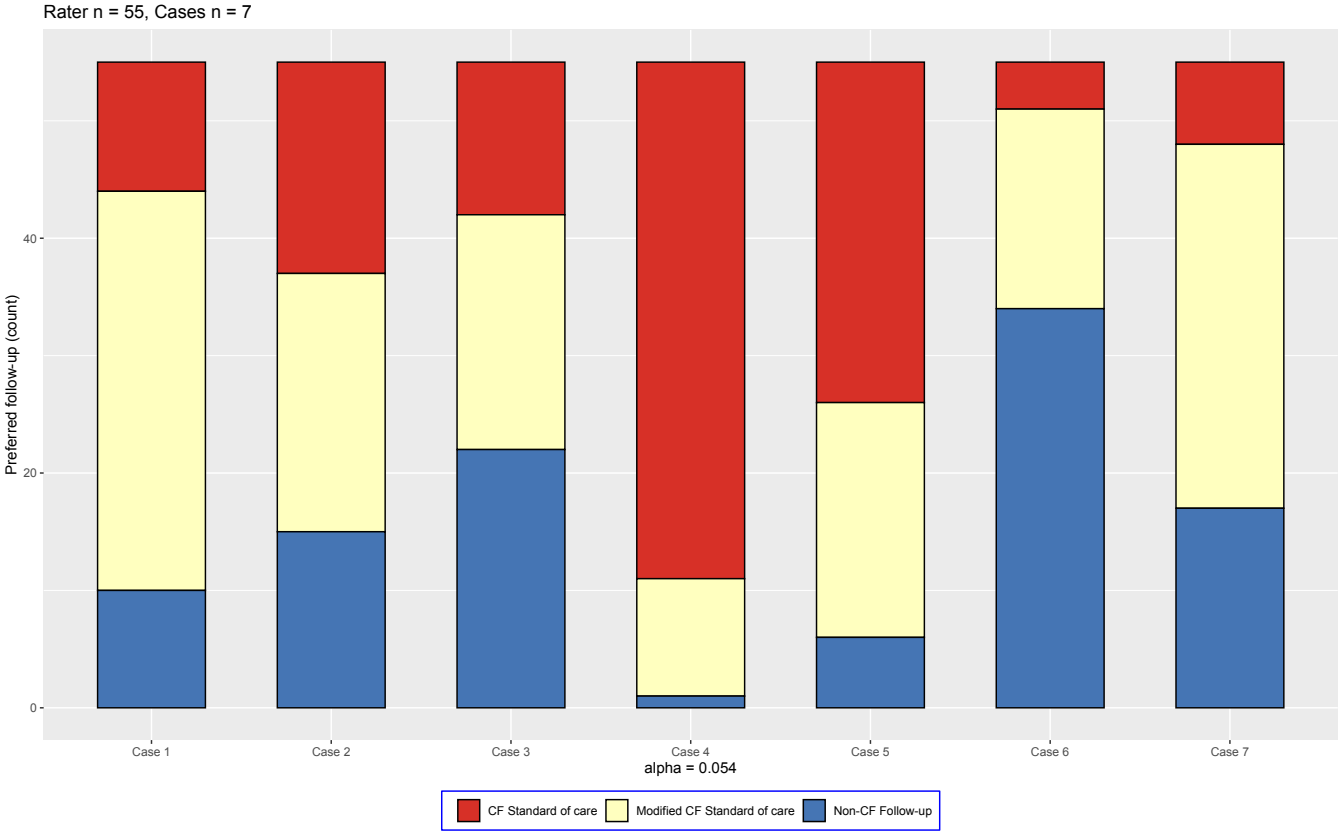
Figure 2. Alluvial plot of the follow-up selected, based on responder-selected diagnosis. 28.7% of adult CF diagnoses were assigned to modified CF standard of care follow-up (reduced frequency / monitoring / shared-care where possible). 22.5% of CFTR-RD diagnosis were assigned to full CF standard of care follow-up, while 80.9% of those recommended to require further testing were assigned to either no CF follow-up (21.3%) or modified CF follow-up (59.6%).

Figure 3. Subjective responder agreement with statements regarding implications of increased recognition and need for CFTR-RD assessments.

a)


Rater n = 55, Cases n = 7
Preferred diagnoses (count)
0
20
40
Case 1
Case 2
Case 3
Case 4
Case 5
Case 6
Case 7
alpha = 0.282
CF
CF diagnosis not resolved - needs further testing
CFTR-related disorder
CF carrier
None of the above

b)


Rater n = 55, Cases n = 7
Preferred follow-up (count)
0
20
40
Case 1
Case 2
Case 3
Case 4
Case 5
Case 6
Case 7
alpha = 0.054
CF Standard of care
Modified CF Standard of care
Non-CF Follow-up

Follow-up selection stratified by diagnosis

400
300
200
100
0

None
Carrier
CFTR-RD
Further testing
Cystic fibrosis

Non-CF follow-up
Modified CF SOC follow-up
CF SOC follow-up

Diagnosis
Follow-up

Accurate distinction between CF and CFTR-RD has become significantly more pertinent with the advent of highly effective CFTR-modulators.

Since the approval of Elexacaftor/Tezacaftor/Ivacaftor I feel more compelled to arrange Whole Gene Sequencing in individuals with clinical features of CF, sweats > 60mmol/L and a single phe508del allele.

Increased CFTR-RD identification has the potential for significant resource utilisation implications for CF centres.

The current guidelines for CF/CFTR-RD diagnosis provide a good framework for high inter-clinician agreement regarding final diagnosis and classification.

SUPPLEMENTARY DATA

Title: Diagnostic agreement among experts assessing adults presenting with possible Cystic Fibrosis: need for improvement and implications for patient care.

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Contributions: ANF conceptualized the study, designed the questionnaire, performed data analysis, and wrote the manuscript. AT contributed to case identification and selection, data collection and edited the manuscript. JG and PGW participated in study design, questionnaire proofing and manuscript editing. GS performed internal review and editing of the manuscript. AF, NGM and DGD participated in distribution, internal review, and editing of the manuscript. BSQ contributed to study and questionnaire design, manuscript editing and is the senior author.

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Supplement contents:

Response rates.

Surveys were distributed via third party collaborators (CF Canada in Canada, the CF Foundation in the USA, the ECFS – Clinical Trials Network for UK sites, and the Irish Thoracic Society in Ireland). Of these, only the US CF Foundation adopted a tracking system which allowed estimation of the number of addresses, link clicks and completion rates. Our summary metrics from the USA suggest that the survey link was issued to 399 addressees, with 29 full completions of the survey. In Canada we estimate 40-45 actively practicing adult-CF specialist clinicians, of 15 of whom provided full responses (~30-35%). In the UK, the CF trust lists 69 active adult-CF specialists across England, Wales, Scotland and Northern Ireland with 9 responses. This means estimate a response rate of approximately 13% of the UK clinicians was achieved. Finally, at the time of survey distribution, there were 9 adult-CF specialists practicing in the Republic of Ireland, with 2 providing responses (~20%). In total if we estimate a possible population of 520 respondents based on survey distribution, we estimate a response rate (67 survey accessions) representative of 12.9% of the eligible population, and a completion rate of 10.6%.

Supplementary tables

Supplemental table 1. Predictors of Recommending further testing vs making a diagnosis

	Reduced model			Expanded model		
Predictors	***Odds Ratios***	***95%CI***	***p***	***Odds Ratios***	***95%CI***	***p***
(Intercept)	0.19	0.07 – 0.55	**0.002**	0.17	0.06 – 0.50	**0.001**
Location of practice						
Canada	*Reference*			*Reference*		
UK & Ireland	3.16	1.37 – 7.32	**0.007**	2.75	1.16 – 6.53	**0.022**
USA	0.65	0.31 – 1.34	0.244	0.55	0.26 – 1.17	0.122
Experience						
<5y CF-practice	*Reference*			*Reference*		
5-10y CF-practice	3.74	1.32 – 10.58	**0.013**	3.3	1.14 – 9.54	**0.028**
>10y CF-practice	2.87	1.17 – 7.06	**0.022**	2.57	1.01 – 6.55	**0.048**
Cases						
Case 1	*Reference*			*Reference*		
Case 2	0.75	0.32 – 1.76	0.506	0.75	0.32 – 1.77	0.51
Case 3	0.54	0.22 – 1.32	0.177	0.54	0.22 – 1.33	0.18
Case 4	0	0.00 – Inf	0.991	0	0.00 – Inf	0.971
Case 5	0.83	0.36 – 1.92	0.659	0.83	0.35 – 1.94	0.663
Case 6	0.75	0.32 – 1.76	0.506	0.75	0.32 – 1.77	0.51
Case 7	0.28	0.10 – 0.75	**0.011**	0.28	0.10 – 0.75	**0.012**
<5 adults assessed annually				*Reference*		
5-10y adults assessed annually				1.83	0.84 – 3.96	0.126
>10 adults assessed annually				1.53	0.70 – 3.33	0.285
Random Effects						
σ^2	3.29			3.29		
τ_{00}	0.24 $_{\text{ResponseId}}$			0.20 $_{\text{ResponseId}}$		
ICC	0.07			0.06		
N	55 $_{\text{ResponseId}}$			55 $_{\text{ResponseId}}$		
Observations	385			385		
Marginal R^2 / Conditional R^2	0.919 / 0.924			0.923 / 0.927		

Model comparison metrics

	npar	***AIC***	***BIC***	***logLik***	***deviance***	***Chisq***	***Df***	***Pr(>Chisq)***
Reduced model	12	374.19	421.63	-175.1	350.19	39.7195	4	4.95E-08
Expanded model	14	375.78	431.13	-173.89	347.78	2.4102	2	0.2997
Model excluding Cases as fixed effects (coefficients not shown above)	8	405.91	437.54	-194.96	389.91			

Generalized mixed effects logistic regression model.
Reduced model = excludes annual referral numbers as a predictor
Expanded model = includes annual referral numbers as a predictor

CFTR – Survey document

Start of Block: Introduction

Q1.1 Thank you for taking the time to participate in this 15-minute survey. This survey is intended for clinicians practicing in **adult** CF services.

You will be presented with 7 real-world clinical vignettes and a series of follow up questions.
After, you will be asked to rate the significance of various clinical findings in the diagnostic workup of CF.
Finally, you will be asked to rate your agreement with a series of statements.

All answers will be automatically de-identified (no metadata or linked email information will be collected) prior to review by the survey team.
Study results may be submitted for publication in journals or conference abstracts.

- ○ I understand that by proceeding with this survey I consent to having my anonymized answers collected and analyzed by the study team, for possible inclusion in academic publications. (1)

End of Block: Introduction

Start of Block: Country

Q2.1 In which country do you currently practice as an adult CF specialist?

▼ Afghanistan (1) ... Zimbabwe (1357)

Q2.2 How long have you been practicing in CF clinical care?

- ○ < 5 years (1)
- ○ 5 to 10 years (2)
- ○ > 10 years (3)

Q37 On average, how many adults (CF specific diagnostic work-up starting at or after 18 years of age) do you personally assess for a possible diagnosis of Cystic Fibrosis each year?

- ○ <5 (1)
- ○ 5 to 10 (2)
- ○ >10 (3)

End of Block: Country

Start of Block: Case 1

Q3.1
CASE 1

A 65-year-old Caucasian female is referred for assessment following two successive sweat chloride levels of 80 and 72 mmol/L.

The **indication for CF testing** was a 30 year history of rhino-sinusitis and post-nasal drip (deviated septum, septoplasty in 2020, no nasal polyposis, morphologically normal sinus anatomy on CT) in conjunction with a family history of CF with 3/4 first-degree cousins reportedly passing away in childhood (approx 50 years ago). Extended CF genetics (Whole Gene Sequencing) in this patient reveal no CFTR variants.

Respiratory: No childhood issues. Reports recurrent physician-diagnosed pneumonia treated in the community in her 30s and 40s. Developed daily cough productive of clear low volume (<1 teaspoon) phlegm in her late 30s. No antibiotics were required for chest infections in the past 15 years. CT chest reveals minimal bronchiectasis isolated to the antero-medial segment of the left lower lobe. Spirometry reveals an FEV1 of 95% predicted. Sputum culture reveals methicillin sensitive *Staphylococcus aureus* (MSSA).

GI: No GI symptoms or relevant history. Morphologically normal liver and pancreas on Ultrasound. Fecal elastase normal at 320 µg/gram (assay defines "insufficiency" as <200 µg/gram). No liver disease. No history of bowel obstruction.

Other: HbA1c 5.6% (no OGTT performed), 25-OH Vit D low, Vit A/E - normal. DXA suggestive of low bone mass. No fertility issues.

Neonatal/infantile history: suggests no relevant issues.

Q3.2 Based on the available information I believe the most appropriate diagnosis is:

- ○ CF (1)
- ○ CFTR-related disorder (6)
- ○ CF diagnosis not resolved - needs further testing (3)
- ○ CF carrier (7)
- ○ None of the above (8)

Q3.3 In your opinion this individual should receive:

- ○ Follow up outside of a multi-disciplinary CF Clinic (1)
- ○ Modified multi-disciplinary CF Clinic follow up (reduced frequency/monitoring/shared-care family doctor or respirologist where possible) (2)
- ○ Full standard of care multi-disciplinary CF Clinic follow-up (quarterly review, sputum, spirometry) (3)

Q38 How easy did you find classifying this case?

	Very difficult (1)	Fairly difficult (2)	Average (3)	Fairly easy (4)	Very easy (5)
Click to write Choice 1 (1)	○	○	○	○	○

End of Block: Case 1

Start of Block: Case 2

Q4.1
CASE 2

A 58-year-old Caucasian female is referred for assessment following two successive sweat chloride measurements of 67 & 61 mmol/L.

The **indication for CF testing** was a history of ongoing GI bloating, a remote history of nasal polyposis and her child being known to have CF (phe508del homozygous). Genetic analysis (139 variants) revealed a single phe508del mutation in this patient.

Respiratory: No antibiotic requirements and no relevant lower respiratory issues until age 55, when exposure to a bleach spill at work resulted in symptoms consistent with reactive airways dysfunction syndrome. FEV1 at baseline assessment was 106% predicted on low dose ICS/LABA inhaler. Sputum culture revealed MSSA and *Mycobacterium avium* complex (MAC). CT chest demonstrated no abnormality and specifically no bronchiectasis.

ENT: Previous nasal polyposis, current IgE 112ug/L (assay ULN 515). No peripheral eosinophilia. No active symptoms or issues.

GI: > 10 years of mild-moderate abdominal bloating and cramping. GERD controlled by PPI, in the setting of a known hiatus hernia. No constipation. Fecal elastase measured 363 µg/gram (assay defines "insufficiency" as <200 µg/gram). A single pancreatic cyst was identified on CT, otherwise morphologically normal pancreatic appearance. No liver disease. No history of bowel obstruction.

Other: No history of diabetes. HbA1c 5.4% (no OGTT performed), 25-OH Vit D normal, Vit A/E normal. No fertility issues.

Neonatal/infantile history: No failure to thrive, no childhood asthma or respiratory issues. Nasal polyposis.

Q4.2 Based on the available information I believe the most appropriate diagnosis is:

- ○ CF (1)
- ○ CFTR-related disorder (3)
- ○ CF diagnosis not resolved - needs further testing (6)
- ○ CF carrier (7)
- ○ None of the above (8)

Q4.3 In your opinion this individual should receive:

- ○ Follow up outside of a multi-disciplinary CF Clinic (1)
- ○ Modified multi-disciplinary CF Clinic follow up (reduced frequency/monitoring/shared-care family doctor or respirologist where possible) (2)
- ○ Full standard of care multi-disciplinary CF Clinic follow-up (quarterly review, sputum, spirometry) (3)

Q43 How easy did you find classifying this case?

	Very difficult (1)	Fairly difficult (2)	Average (3)	Fairly easy (4)	Very easy (5)
Click to write Choice 1 (1)	○	○	○	○	○

End of Block: Case 2

Start of Block: Case 3

Q5.1
CASE 3

A 44-year-old Caucasian male is referred for assessment on the basis of three abnormal sweat chloride tests at 50, 69 and 70 mmol/L respectively.

The **indication for testing** was a 20-year history of daily severe coughing paroxysms driven by difficult to expectorate mucus plugs and post-nasal nasal discharge. CF genetics (whole gene sequencing with MLPA del/dup and intronic variant analysis) revealed a single phe508del mutation. No known family history of CF.

Respiratory: No respiratory symptoms until his early 20s, following nasal surgery to correct a sports-related defect. Subsequently, the patient developed the sensation of mucus balls/plugs dropping from his nasopharynx to his throat and great difficult clearing them. Over the subsequent ten years these symptoms increased from once weekly to 6 times daily. Now daily production of thick green plugs. No wheeze, no annual antibiotic use or exercise limitation. No hospitalizations. CT chest shows no bronchiectasis. FEV1 is 110% predicted. Sputum (and sinus) microbiology recurrently grows only normal flora.

ENT: Previous corrective septoplasty in early 20s. CT sinuses demonstrates bilateral mucus retention cysts but no features of rhino-sinusitis and normal sinus structure. No polyposis radiologically or at direct examination. The patient reports post-nasal mucus as previously described, not visualized at endoscopy.

GI: Mild esophageal dysmotility and mild GERD confirmed both symptomatically and radiologically. Occasional bloating. No constipation or history of bowel obstruction. Fecal elastase >500 µg/gram (assay defines "insufficiency" as <200). Normal pancreatic and liver morphology on abdominal ultrasound and CT.

Other: HbA1c 5.7%, normal OGTT, Vit A/D/E all normal. Bone density normal for age. Ultrasound scrotum normal (no CBAVD). Declined semen analysis. No family history. Sputum negative for eosinophilia. IgE 105 µg/L (assay normal <405 µg/L).

Neonatal/infantile history: No failure to thrive, no childhood asthma or respiratory issues.

Q5.2 Based on the available information I believe the most appropriate diagnosis is:

- ○ CF (1)
- ○ CFTR-related disorder (6)
- ○ CF diagnosis not resolved - needs further testing (3)
- ○ CF carrier (7)
- ○ None of the above (8)

Q5.3 In your opinion this individual should receive:

- ○ Follow up outside of a multi-disciplinary CF Clinic (1)
- ○ Modified multi-disciplinary CF Clinic follow up (reduced frequency/monitoring/shared-care family doctor or respirologist where possible) (2)
- ○ Full standard of care multi-disciplinary CF Clinic follow-up (quarterly review, sputum, spirometry) (3)

Q42 How easy did you find classifying this case?

	Very difficult (1)	Fairly difficult (2)	Average (3)	Fairly easy (4)	Very easy (5)
Click to write Choice 1 (1)	○	○	○	○	○

End of Block: Case 3

Start of Block: Case 4

Q6.1
CASE 4

A 56-year-old Caucasian male isreferred due to sweat chloride levels <30, 43 and 43 mmol/L

sequentially. The **indication for testing** was a diagnosis of diffuse bronchiectasis, made in the preceding 5 years. Subsequent CF genetic screening identified heterozygous phe508del/D1152H mutations (for reference from cftr2.org - "*This variant combination has varying consequences*"). No known family history of CF.

Respiratory: Mild/subtle diffuse bronchiectasis. All respiratory symptoms (cough, daily purulent sputum) came on after 50 years of age. Sputum culture identified *Psudomonas aeruginosa* (PA) and MSSA. Typically, no annual requirement for antibiotics. Spirometry demonstrates an FEV1 of 134% predicted. No symptoms of wheeze/asthma. Normal IgE.

ENT: Post nasal drip, physician-diagnosed chronic rhino-sinusitis. CT sinuses demonstrates septal deviation, opacification of the right maxillary sinus, no soft tissue abnormality. No polyposis.

GI: Pancreatic exocrine insufficiency with fecal elastase 46 µg/gram (assay defines "insufficiency" as <200 µg/gram), but no symptoms of steatorrhea. Mild GERD reported, no bloating, pain or constipation. No history of bowel obstruction. No liver disease.

Other: HbA1c 5.9%, OGTT shows impaired fasting glycaemia. Bone density normal for age. Vit D low, Vit A/E normal.

Fertility: Confirmed congenital absence of the vas deferens (CBAVD).

Neonatal/infantile history: No failure to thrive, no childhood asthma or respiratory issues.

Q6.2 Based on the available information I believe the most appropriate diagnosis is:

- ○ CF (1)
- ○ CFTR-related disorder (6)
- ○ CF diagnosis not resolved - needs further testing (3)
- ○ CF carrier (7)
- ○ None of the above (8)

Q6.3 In your opinion this individual should receive:

- ○ Follow up outside of a multi-disciplinary CF Clinic (1)
- ○ Modified multi-disciplinary CF Clinic follow up (reduced frequency/monitoring/shared-care family doctor or respirologist where possible) (2)
- ○ Full standard of care multi-disciplinary CF Clinic follow-up (quarterly review, sputum, spirometry) (3)

Q41 How easy did you find classifying this case?

	Very difficult (1)	Fairly difficult (2)	Average (3)	Fairly easy (4)	Very easy (5)
Click to write Choice 1 (1)	○	○	○	○	○

End of Block: Case 4

Start of Block: Case 5

Q7.1
CASE 5

A 61-year-old Caucasian female was referred for assessment due to sweat chloride measurements of 29 and 31 mmol/L and CF genetics (139 variants) identifying a phe508/5T allele (TG tract not provided) genotype (for reference from cftr2.org - " *This variant combination has varying consequences"*). No known family history of CF. The **indication for testing** was a known history of bronchiectasis with PA and MAC chronic infection.

Respiratory: Symptoms include daily cough and purulent sputum production with a history of frequent antibiotic requirements. CT chest demonstrates diffuse bronchiectasis, with no cavitary disease. Sputum culture is positive for PA and MAC. Baseline FEV1 is 75% predicted.

ENT: Symptoms include post-nasal drip. No polyposis, with normal CT sinus findings. Normal IgE.

GI: Symptoms are limited to mild post-prandial bloating. No history of pancreatitis. Fecal elastase >500 µg/gram (assay defines "insufficiency" as <200 µg/gram). No history of bowel obstruction. Morphologically normal liver and pancreas.

Other: HbA1c 5.3%, OGTT normal, Vit A/D/E all normal, low bone density for age. No fertility issues.

Neonatal/infantile history: No failure to thrive, no childhood asthma or respiratory issues.

Q7.2 Based on the available information I believe the most appropriate diagnosis is:

- ○ CF (1)
- ○ CFTR-related disorder (6)
- ○ CF diagnosis not resolved - needs further testing (3)
- ○ CF carrier (7)
- ○ None of the above (8)

Q7.3 In your opinion this individual should receive:

- ○ Follow up outside of a multi-disciplinary CF Clinic (1)
- ○ Modified multi-disciplinary CF Clinic follow up (reduced frequency/monitoring/shared-care family doctor or respirologist where possible) (2)
- ○ Full standard of care multi-disciplinary CF Clinic follow-up (quarterly review, sputum, spirometry) (3)

Q40 How easy did you find classifying this case?

	Very difficult (1)	Fairly difficult (2)	Average (3)	Fairly easy (4)	Very easy (5)
Click to write Choice 1 (1)	○	○	○	○	○

Page Break

Q42 Would the availability of information regarding the 5T TG tract (11 vs 12 vs 13) influence your final decision regarding diagnosis in the previous case?

- ○ Not at all (1)
- ○ Possibly (2)
- ○ Yes (3)

End of Block: Case 5

Start of Block: Case 6

Q8.1
CASE 6

An 18-year-old mixed heritage (Asian/Caucasian) patient is referred with a series of sweat chloride tests of 58, 42, 62 and 62 mmol/L. The **indication for testing** was a known history of nasal polyposis and chronic rhino-sinusitis. Genetic testing including whole gene sequencing and subsequent epithelial sodium channel (eNaC) and Carbonic Anhydrase mutation analysis reveals no CFTR/other variants. There is no family history of CF.

Respiratory: Physician-diagnosed pneumonia aged 9. Occasional throaty cough and occasional clear sputum. No recent/recurrent antibiotic requirements for lungs. Sputum culture demonstrated MSSA. CT chest reveals no bronchiectasis or other anomalies. FEV1 is 114% predicted. She reports no wheeze and no asthma symptoms. IgE (172µg/L) and Eosinophils are normal.

ENT: Symptoms include frequent episodic frontal sinus pain and congestion. Frequent "head colds" and perennial post-nasal drip. Known polyposis in childhood, medically managed with nasal corticosteroid.

No polypectomy. CT sinuses shows moderate to severe mucosal thickening throughout and stenosis of the ostiomeatal complexes. No residual polyposis.

GI: No symptoms. No constipation and no history of bowel obstruction. Fecal elastase >500 µg/gram (assay defines "insufficiency" as <200 µg/gram). Morphologically normal pancreas and liver. no liver disease. BMI 21.

Other: HbA1c 5.5%, normal OGTT. Vit D low, Vit A/E normal. Bone density low for age. No attempts to get pregnancy thus no overt fertility issues.

Neonatal/infantile history: No failure to thrive/GI issues. Nasal polyposis as stated.

Q8.2 Based on the available information I believe the most appropriate diagnosis is:

- ○ CF (1)
- ○ CFTR-related disorder (6)
- ○ CF diagnosis not resolved - needs further testing (3)
- ○ CF carrier (7)
- ○ None of the above (8)

Q8.3 In your opinion this individual should receive:

- ○ Follow up outside of a multi-disciplinary CF Clinic (1)
- ○ Modified multi-disciplinary CF Clinic follow up (reduced frequency/monitoring/shared-care family doctor or respirologist where possible) (2)
- ○ Full standard of care multi-disciplinary CF Clinic follow-up (quarterly review, sputum, spirometry) (3)

Q39 How easy did you find classifying this case?

	Very difficult (1)	Fairly difficult (2)	Average (3)	Fairly easy (4)	Very easy (5)
Click to write Choice 1 (1)	○	○	○	○	○

End of Block: Case 6

Start of Block: Case 7

Q9.1
CASE 7

A 41-year-old Caucasian female is referred having undergone sweat chloride tests demonstrating levels of 20 mmol/L and subsequently 25 mmol/L. She has a child with known homozygous phe508del CF. The **indication for testing** is a known family history of CF (in her child), along with a personal history of poorly controlled asthma.
Genetic analysis reveals heterozygous phe508del (pathogenic) / R347C (mutation of variable clinical significance) / M348K (mutation of unknown clinical significance).

Respiratory: Episodic asthma and wheeze for many years. Minimal cough between episodes. Frequent infections requiring antibiotics and the addition of prednisone. Sputum identification of MAC and MSSA. FEV1 121% predicted. CT chest reveals no bronchiectasis, and minimal tree-in-bud changes. Peripheral eosinophil count and serum IgE are normal.

ENT: The patient endorses symptoms of post-nasal drip and congestion. CT sinuses demonstrates normal morphology and normal mucosa. No polyposis.

GI: No symptoms. No GERD. No constipation or history of bowel obstruction. Fecal elastase is >500 µg/gram (assay defines "insufficiency" as <200 µg/gram). The pancreas is morphologically normal on ultrasound. There is no evidence of liver disease.

Other: HbA1c is 5.5%, OGTT is normal. Vit D is low, and Vit A/E are normal. Bone density is normal for age. There is no history of infertility or difficulty conceiving.

Q9.2 Based on the available information I believe the most appropriate diagnosis is:

- ○ CF (1)
- ○ CFTR-related disorder (6)
- ○ CF diagnosis not resolved - needs further testing (3)
- ○ CF carrier (7)
- ○ None of the above (8)

Q9.3 In your opinion this individual should receive:

- ○ Follow up outside of a multi-disciplinary CF Clinic (1)
- ○ Modified multi-disciplinary CF Clinic follow up (reduced frequency/monitoring/shared-care family doctor or respirologist where possible) (2)
- ○ Full standard of care multi-disciplinary CF Clinic follow-up (quarterly review, sputum, spirometry) (3)

Q38 How easy was this case to classify?

	Very difficult (1)	Fairly difficult (2)	Average (3)	Fairly easy (4)	Very easy (5)
Click to write Choice 1 (1)	○	○	○	○	○

End of Block: Case 7

Start of Block: Guidelines

Q10.1 The current CFF guidelines suggest that the first step in the diagnostic workup should be the presence of a "Clinical Presentation of CF"

Q10.2 In your opinion, how easy is it to define a "Clinical Presentation of CF", independently of sweat chloride result or CFTR genetics in patients presenting as adults?

- ○ Extremely difficult (1)
- ○ Relatively difficult (2)
- ○ Neither easy nor difficult (3)
- ○ Relatively easy (4)
- ○ Extremely easy (5)

Page Break

Q10.3 Please rate your opinion on the contribution each of the following has in supporting a "clinical presentation of CF" in patients presenting as adults

	Not individually supportive (1)	Somewhat supportive (2)	Strongly supportive (3)
Bronchiectasis - diffuse (1)	○	○	○
Bronchiectasis - asymmetrical (2)	○	○	○
Obstructive spirometry (3)	○	○	○
Radiographic rhinosinusitis (4)	○	○	○
Nasal polyposis (5)	○	○	○
Radiographic evidence of pancreatic fibrosis/fibrocystic change (6)	○	○	○
Constipation (7)	○	○	○
Vit D deficiency (8)	○	○	○
Vit A/E deficiency (9)	○	○	○
Osteoporosis/Osteopenia (10)	○	○	○
Infertility/Congenital Bilateral Absence of the Vas Deferens (11)	○	○	○
Aquagenic wrinkling (12)	○	○	○
ABPA diagnosis (13)	○	○	○
Liver disease/steatosis/cirrhosis (14)	○	○	○

Pancreatic insufficiency (15)	○	○	○
Daily sputum production (16)	○	○	○
Frequent need for antibiotics for chest (17)	○	○	○

Page Break

Q10.4 Please rate your opinion on the contribution each of the following airway pathogens has in supporting a "clinical presentation of CF"

	Not supportive (1)	Somewhat supportive (2)	Strongly supportive (3)
MSSA (1)	○	○	○
Pseudomonas aeruginosa (2)	○	○	○
MRSA (3)	○	○	○
Burkholderia cepacia complex organisms (6)	○	○	○
Stenotrophomonas maltophilia (7)	○	○	○
Achromobacter species (8)	○	○	○
Mycobacterium avium complex (9)	○	○	○
Mycobacterium abscessus sp. (11)	○	○	○
Streptococcus pneumoniae (13)	○	○	○
Aspergillus fumigatus sp (14)	○	○	○

End of Block: Guidelines

Start of Block: Follow up care

Q11.1 Regarding individuals meeting a diagnosis of CFTR-related disorder: Please rate the following in terms of their effect on your opinion on the need for follow up in a CF-MDT centre

	Would not contribute to decision (1)	Contributes somewhat (2)	Major determinant (3)
Younger age at presentation (1)	○	○	○
Worse lung function at presentation (2)	○	○	○
Lung function relative to age at presentation (3)	○	○	○
Frequent pulmonary exacerbations (4)	○	○	○
Nutritional status/BMI (5)	○	○	○
Pseudomonas sputum positive (6)	○	○	○
MRSA sputum positive (7)	○	○	○
Burkholderia Cenocepacia Complex sputum positive (8)	○	○	○
NTM sputum positive (9)	○	○	○
Other bacterial sputum positivity (Stenotrophomonas, Achromobacter, MSSA) (10)	○	○	○
Diagnosis of ABPA (11)	○	○	○
Confirmed diagnosis of diabetes (12)	○	○	○
Already attending a pulmonary specialist (13)	○	○	○

Recurrent pancreatitis (14)	○	○	○
Confirmed exocrine pancreatic insufficiency (15)	○	○	○

End of Block: Follow up care

Start of Block: Please rate your agreement with the following statements:

Q12.1 Accurate distinction between CF and CFTR-rd has become significantly more pertinent with the advent of highly effective CFTR-modulators.

- ○ Strongly disagree (1)
- ○ Somewhat disagree (2)
- ○ Neither agree nor disagree (3)
- ○ Somewhat agree (4)
- ○ Strongly agree (5)

Q12.2 Since the approval of Elexacaftor/Tezacaftor/Ivacaftor I feel more compelled to arrange Whole Gene Sequencing in individuals with clinical features of CF, sweats > 60mmol/L and a single phe508del allele.

- ○ Strongly disagree (1)
- ○ Somewhat disagree (2)
- ○ Neither agree nor disagree (3)
- ○ Somewhat agree (4)
- ○ Strongly agree (5)

Q12.3 Increased CFTR-rd identification has the potential for significant resource utilisation implications for CF centres.

- ○ Strongly disagree (1)
- ○ Somewhat disagree (2)
- ○ Neither agree nor disagree (3)
- ○ Somewhat agree (4)
- ○ Strongly agree (5)

Q12.4 The current guidelines for CF/CFTR-rd diagnosis provide a good framework for high inter-clinician agreement regarding final diagnosis and classification.

- ○ Strongly disagree (1)
- ○ Somewhat disagree (2)
- ○ Neither agree nor disagree (3)
- ○ Somewhat agree (4)
- ○ Strongly agree (5)

End of Block: Please rate your agreement with the following statements: