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Original Article

ECFS standards of care on CFTR-related disorders: Identification and care of the disorders

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Aquagenic wrinkling
Aquagenic palmoplantar keratoderma

ABSTRACT

This is the third paper in the series providing updated information and recommendations for people with cystic fibrosis transmembrane conductance regulator (CFTR)-related disorder (CFTR-RD). This paper covers the individual disorders, including the established conditions - congenital absence of the vas deferens (CAVD), diffuse bronchiectasis and chronic or acute recurrent pancreatitis - and also other conditions which might be considered a CFTR-RD, including allergic bronchopulmonary aspergillosis, chronic rhinosinusitis, primary sclerosing cholangitis and aquagenic wrinkling. The CFTR functional and genetic evidence in support of the condition being a CFTR-RD are discussed and guidance for reaching the diagnosis, including alternative conditions to consider and management recommendations, is provided. Gaps in our knowledge, particularly of the emerging conditions, and future areas of research, including the role of CFTR modulators, are highlighted.

The European Cystic Fibrosis Society (ECFS) and its Standards of Care Committee and Diagnostic Network Working Group have launched a project to update recommendations on the diagnosis and management of cystic fibrosis transmembrance conductance regulator (CFTR)-related disorders (CFTR-RD). Two of the four planned documents addressing the general considerations of the definition and management of CFTR-RD have been published in the *Journal of Cystic Fibrosis* [1,2]. This third paper of the series examines in more depth the characteristics of the well established disorders that are either occasionally or commonly related to CFTR dysfunction - these are congenital absence of the vas deferens (CAVD), disseminated bronchiectasis and chronic or acute recurrent pancreatitis. Conditions which might be considered a CFTR-RD, but where the mechanistic link with CFTR dysfunction is less well established, are also discussed, including allergic bronchopulmonary aspergillosis (ABPA), chronic rhinosinusitis, primary sclerosing cholangitis and aquagenic wrinkling. An important objective of this work is to not only provide guidance to CF teams, but also, importantly, to raise awareness and provide guidance to specialists outside of the CF field who are likely to encounter these conditions (e.g. experts in fertility, respiratory medicine, gastroenterology, otorhinolaryngology, dermatology, etc.).

For each disorder an overview of the clinical and pathological features is included, along with alternative aetiologies to be considered and ruled out. The key principle is that it is expected that the more common causes of each condition are excluded first by the specialist in their field, then referral to a CF service, for sweat testing and genetic analysis, should be made, so that 1) CF is excluded, and 2) CFTR-RD is confirmed (or excluded). The timing and extent of genetic analysis may vary in some situations, so further discussion is provided in each section, as is the role of further CFTR functional testing, such as nasal potential difference (PD) and intestinal current measurement (ICM). A more detailed overview of the CFTR-RD diagnostic pathway and biomarkers is provided in the first two papers of the series [1,2], although the key CFTR criteria are summarised below (Table 1).

1. Congenital absence of the vas deferens

1.1. *Veerle Vloeberghs, Dilip Nazareth, Nicholas J. Simmonds*

The vas deferens (VD) is a tubular structure that connects the epididymis to the ejaculatory duct. The proximal part is palpable in the scrotum and the distal part passes through the inguinal canal and retroperitoneally into the pelvis ending in the ampulla. An absent VD can be associated with anomalies of the seminal vesicles (SV) in the form of agenesis or hypoplasia, absence of the corpus or tail of the epididymis and/or absence of the vas ampulla.

Congenital absence of the VD (CAVD) has different clinical manifestations: it can be bilateral (CBAVD) or unilateral (CUAVD), with further classification dependent on the partial or complete absence of the VD. CAVD is reported in 0.1 % of males and in up to 2 % of infertile males; it is almost universal in men with an unequivocal diagnosis of CF [3]. CUAVD is probably underestimated as conception is still possible due to normal function of the contralateral vas deferens [4]; however, a prevalence of around 1 % in males is often reported [3]. In azoospermic males, the prevalence of CBAVD is 6–12 % [5,6].

1.2. *Diagnosis of absent vas deferens*

The diagnosis of CAVD can be made (1) during systematic work-up of CF or CFTR-RD (in symptomatic patients), (2) in healthy infertile males with obstructive azoospermia, and (3) in fertile men with CUAVD discovered as an incidental finding during inguinal hernia surgery or vasectomy [7]. Incidental identification aside, the diagnosis of CAVD is based on clinical examination and semen analysis. The VD is considered absent if there is no firm, tubular structure in continuation of the epididymis that can be followed to the external inguinal canal [3]. Unfortunately, diagnosis by clinical examination is easy to miss [8]; it is often easier to be confident that the VD is present rather than absent. Only the intrascrotal part of the VD can be palpated, and sometimes a misleading structure (e.g. the fibrotic cord) can be palpated. To overcome these limitations, recent guidelines include imaging in the work-up [7–13]. By scrotal and transrectal ultrasound (TRUS), the VD, including its pelvic tract, can be evaluated, along with the SV and vas

Table 1
Key diagnostic criteria for CFTR-RD after CF has been excluded [1].

In vivo or *ex vivo* CFTR dysfunction in the CFTR-RD range in at least 2 different CFTR functional tests (sweat test, nasal potential difference (PD) measurements, intestinal current measurements (ICM))
OR
One *CFTR* variant and evidence of in vivo or *ex vivo* dysfunction in at least two functional tests
OR
Two *CFTR* variants shown to reduce CFTR function, with at most one CF-causing variant

ampulla [8,9,12,13]. Magnetic resonance imaging (MRI) can be helpful, but it is not yet established in clinical practice [14].

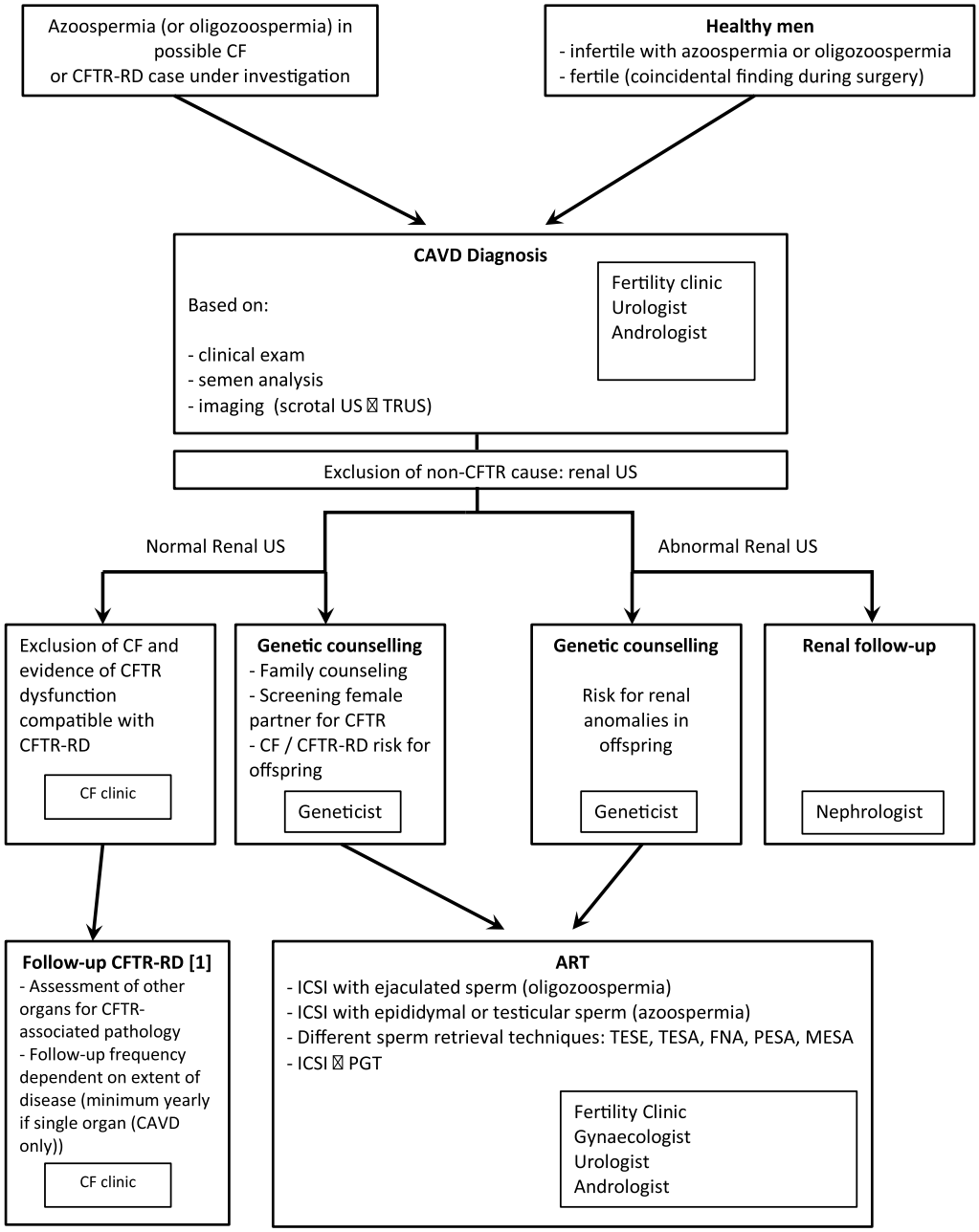
If CBAVD is associated with bilateral absence of the SV, semen analysis typically shows a low volume (<1 ml), low pH (<7.0) and low level of seminal plasma biochemical markers [7].

1.3. Diagnostic criteria for CFTR-RD CAVD

The most common route to diagnosis is a male presenting to a fertility specialist (andrologist/urologist) with azoospermia or oligozoospermia on semen analysis. The specialist determines the underlying pathology and anatomical abnormality, rules out other causes and considers the likelihood of CFTR dysfunction (Fig. 1). Genetic causes other than *CFTR* may need consideration, such as mutations in the *ADGRG2* gene [15]. In the absence of alternative aetiologies, the patient should be referred to a CF clinic (or a clinic with a specialist interest in CFTR-RD) for further evaluation to 1) exclude CF, 2) determine if CFTR-RD is the cause, and 3) to investigate for evidence of CFTR dysfunction in other organs [1].

Occasionally, CAVD will be diagnosed directly by the CF clinic, e.g. when a male is undergoing investigations for CF or CFTR-RD due to other symptoms. In this situation, semen analysis is recommended first (usually performed via fertility or urology services), followed by imaging (looking for the presence of the VD), as physical examination expertise of the VD in the CF center setting may be limited.

Individuals with CUAVD exhibit a higher frequency of *CFTR* variants



CF: Cystic Fibrosis, CFTR-RD: CFTR-related disease, CAVD: congenital absence vas deferens, US: ultrasound, TRUS: transrectal ultrasound, CFTR: cystic fibrosis transmembrane conductance regulator, ART: assisted reproductive technologies, ICSI: intracytoplasmic sperm injection, TESE: testicular sperm extraction, TESA: testicular sperm aspiration, FNA: fine needle aspiration, PESA: percutaneous epididymal sperm aspiration, MESA: microsurgical sperm aspiration

Fig. 1. Recommended diagnostic and management pathway for congenital absence of the vas deferens (CAVD).

than healthy men. At least one *CFTR* variant is found in 46 % of CUAVD males, with *5T, R117H* and *F508del* being the most common variants [16]. While *5T* is a relatively frequent variant [17], in combination with (TG)12 or (TG)13 repeats in *CFTR* intron 9, it may increase CAVD severity (e.g. increase the risk of partial to complete obstruction/absence of the VD) [18]. These individuals should be worked up in a similar fashion to those with CBAVD.

1.4. Alternative causes of CAVD

Two different mechanisms have been suggested to be responsible for CAVD. The first one is atrophy-based where dysfunction of the seminal duct epithelium disrupts the intraluminal fluid homeostasis, leading to thick secretions and involution of the VD. Alternatively, CAVD might be the result of VD agenesis during the embryonic development of the Wolfian duct [7].

Renal abnormalities (25 %), often in the form of ipsilateral renal agenesis, may be detected during CAVD assessment [19]. CUAVD is more frequently associated with unilateral renal absence than CBAVD - 39 % and 19 %, respectively [11]. Men carrying *CFTR* mutations are unlikely to have renal agenesis [20].

1.5. Recommendation for follow-up and treatment of CFTR-RD CAVD

Isolated CFTR-RD CAVD is not usually considered a progressive (or reversible) condition, but individuals should be made aware that over time other CFTR-related manifestations might develop. As it is unreasonable to expect an andrologist to follow-up a patient with CFTR-RD long-term, annual follow-up in a CF clinic or a clinic specific for CFTR-RD is recommended, as the lifetime risk of developing other CFTR-related complications is currently unknown. Alternatively, if follow-up is not wanted/feasible, the person with CAVD and their family physician should be made aware of the clinical features to look out for which would trigger a referral back to the CF center for further evaluation [1].

2. Disseminated bronchiectasis

2.1. Peter Middleton, James Chalmers, Damian Downey, Jerry Nick, Kris De Boeck

Bronchiectasis is characterised by abnormal dilatation of the large and medium airways, often also involving the small airways [21]. Affected airways become inflamed, thick walled and irregularly dilated, resulting in airflow obstruction and impaired clearance of secretions. Bronchiectasis can present as a focal process in one airway due to partial or complete obstruction of the airway (e.g. tumour, inhaled foreign body) or following severe pneumonia. More commonly, bronchiectasis is a generalised disease involving many airways in different lobes, causing recurrent lower respiratory tract infections, chronic cough and sputum production.

2.2. Diagnosis of bronchiectasis

Bronchiectasis is defined as an increase in the size of an airway relative to the accompanying pulmonary artery, generally measured on High Resolution Computerized Tomography (HRCT). Since airway size increases with increasing lung volume, the level of inspiration should be standardized during HRCT. The Bronchus to Artery Ratio (BAR) increases with age, with an upper limit of normal in young children of around 0.76, increasing up to 1.0 in adults [22,23].

The possibility of bronchiectasis should be considered in people with chronic “wet” cough with or without expectoration. A new diagnosis of bronchiectasis should prompt a thorough investigation in a specialist service to find the underlying cause [24,25].

2.3. Diagnostic criteria for CFTR-RD bronchiectasis

The diagnosis of CFTR-RD should be considered for people with bronchiectasis, especially in the absence of other causes (see below), when there is evidence of CFTR protein dysfunction but the diagnostic criteria for CF are not fulfilled, as outlined in the first paper of this CFTR-RD series [1]. In settings where CFTR functional tests, such as intestinal current measurement (ICM) or nasal potential difference (PD), are not available, it may be helpful to first search for *CFTR* variants by genetic testing before referring the patient [1]. This is especially important in people with bronchiectasis and intermediate sweat test results. Historical sweat tests reported narratively as ‘normal’ or ‘borderline’ should be repeated.

An association between *CFTR* variants and bronchiectasis has long been reported. Uncontrolled, observational studies have reported at least one *CFTR* variant in up to 50 % of people with bronchiectasis, with a high incidence of the *5T* splicing variant of the poly T tract [26–28]. In one study, two sequence variants were found in up to 20 % of cases, though segregation analysis was not always performed to ensure the variants were inherited *in trans*. Other studies, however, have not shown an association [29]. A population-based investigation examined more than 100,000 carriers of the *F508del* variant, showing that carriers had an odds ratio of 1.31 (95 % confidence interval (CI) 1.16–1.48) for chronic bronchitis and a hazard ratio of 1.88 (95 % CI 1.03–3.45) for bronchiectasis [30].

The involvement of CFTR dysfunction in bronchiectasis associated with other systemic diseases raises further considerations. An extensive genetic, clinical and physiological examination of 26 people with rheumatoid arthritis and bronchiectasis reported that seven had sequence variants in *CFTR*, including four with *F508del* [31]. Of the remaining 19 individuals, seven had sweat chloride values $\geq$60 mmol/L. Only two of 25 sweat tests demonstrated chloride values in the normal range ($<$30 mmol/L). Importantly, 20 of the 26 individuals had childhood onset bronchiectasis often predating the onset of rheumatoid arthritis by decades, highlighting the difficulty of assigning causation at an individual point in time [31]. Similarly for people with a diagnosis of bronchiectasis due to ABPA, an increased incidence of *CFTR* variants has been reported (discussed later in this paper) [32]. These data indicate that in certain circumstances it may be appropriate to revisit an assigned diagnosis (such as rheumatoid arthritis-associated bronchiectasis or ABPA) to determine if these individuals now fulfil the updated diagnostic criteria for CFTR-RD [1].

2.4. Alternative causes of disseminated bronchiectasis

In addition to ABPA and rheumatoid arthritis, disseminated bronchiectasis can be associated with other underlying conditions, including a variety of immune deficiencies, primary ciliary dyskinesia (PCD), autoimmune diseases, inflammatory bowel disease and other connective tissue disorders. Significant infections may also result in bronchiectasis, termed “post-infectious,” with the remaining cases termed “idiopathic,” although there is emerging evidence that *CFTR* variants (without CF or CFTR-RD) may alter this risk [33]. Despite an exhaustive evaluation, a specific aetiology may not be identified in up to half of cases [24,25].

A detailed medical history should focus on the age of onset of symptoms, in particular neonatal respiratory distress and early childhood respiratory infections, weight loss, hearing problems, infertility, presence of nasal polyps or chronic ear infections and gastrointestinal symptoms, including gastro-oesophageal reflux, and a family history [24]. Routine testing should include differential blood count, serum immunoglobulins and testing for ABPA (see below for more details on ABPA testing)[24]. Depending on history, findings on physical examination and HRCT, other tests may be indicated.

The distribution of bronchiectasis on HRCT can point towards a specific aetiology, with upper lobe predominant disease found in CF and lower and middle lobe predominant disease in PCD and immune

deficiencies, in some but not all studies [34–36]. Other aspects may point towards a diagnosis of CF, including airway infections with *Staphylococcus aureus, Pseudomonas aeruginosa, Burkholderia* spp. and non-tuberculous mycobacteria (e.g. *Mycobacterium abscessus* and *M. avium*). Extrapulmonary manifestations may also increase the suspicion for CF, including male infertility, pancreatitis and/or exocrine pancreatic insufficiency, bowel disease, chronic sinusitis and/or nasal polyposis and skin changes (such as a salt crust following exercise or aquagenic wrinkling).

The diagnostic tests for CF and CFTR-RD have already been outlined above, but the assessment for other CFTR-related organ pathology may also be indicated (e.g. pancreatic function and semen analysis). More specialised measures of CFTR function such as ICM and nasal PD is recommended in people with intermediate results on sweat testing and *CFTR* analysis. Adults presenting with bronchiectasis and characteristic involvement in at least one other organ may have CF and severe lung disease may already be present at the time of diagnosis [37,38].

The "PICADAR" (PrImary Ciliary Dyskinesia Rule) scoring system for PCD may assist in the assessment of people with chronic sputum production in childhood [39]. A combination of nasal nitric oxide testing, ciliary structure/function testing (by electron microscopy and high speed video microscopy) and genetics should be considered to investigate for PCD [40].

Testing of autoantibodies to screen for connective tissue or autoimmune disease, is indicated in the presence of suggestive findings towards these pathologies on history and physical examination. The diagnosis of post-infectious bronchiectasis is typically reserved for those with severe lung infections earlier in life and is rare in individuals with access to standard medical care.

2.5. Recommendations for follow-up and treatment of CFTR-RD bronchiectasis

The European Respiratory Society (ERS) and British Thoracic Society (BTS) published guidelines for the treatment and follow up of adults with non-CF bronchiectasis with separate standards of care for CF [24,25]. The first paper in this series provides an overview of the general recommendations for the follow-up of people with CFTR-RD but, in the absence of specific guidelines for people with CFTR-RD bronchiectasis, the ERS/BTS guidelines can be considered, recognising that many recommendations lack a strong evidence-base. Individualised treatment based on clinical acumen should achieve symptom control, improve quality of life and prevent pulmonary exacerbations. This is likely best achieved in specialist centres, ideally attached to CF centres, including clinics specific for CFTR-RD.

The recent BTS guidelines suggest a follow-up frequency appropriate to the patients' disease severity with at least an annual specialist review during clinical stability for assessment of symptoms, exacerbation frequency and presence of comorbidities, as well as for measurements of body mass index, dyspnoea score, pulse oximetry, sputum bacteriology culture and lung function [25]. Review by a specialist respiratory physiotherapist is recommended and airway clearance techniques should be initiated for chronic productive cough or difficulty with sputum expectoration. Subjects with impaired exercise capacity should participate in a pulmonary rehabilitation programme and take regular exercise.

When standard airway clearance techniques do not control symptoms, mucoactive treatment such as hypertonic saline should be considered. Although recombinant human DNAse is contraindicated in non-CF bronchiectasis overall, given the beneficial effects in people with CF, use may be evaluated on a case-by-case basis in those with CFTR-RD. Long acting bronchodilators and inhaled corticosteroids, are useful in subjects with concomitant asthma or COPD but are not generally recommended for use in people with bronchiectasis [24].

Antibiotic eradication treatment should be offered to patients with a new sputum isolation of *P.aeruginosa*, but is not generally recommended for other pathogens [24]. Long-term antibiotic treatment is indicated in patients who experience three or more exacerbations per year, since both macrolides and inhaled antibiotics have been proven effective to reduce exacerbation frequency in randomized controlled trials of people with bronchiectasis [25].

Pulmonary exacerbations should be treated with oral/inhaled/intravenous antibiotics as per the CF and non-CF treatment guidelines [24,25,41,42]. Currently CFTR modulators are not approved outside of the CF diagnosis, although as CFTR dysfunction is present in CFTR-RD bronchiectasis, it seems highly plausible that benefit will be derived for many, although further research is required.

In summary, individuals with CFTR-RD bronchiectasis should be counselled appropriately about their condition, explaining that our understanding of *CFTR* and its relationship to bronchiectasis has evolved, with discussion about why the distinction between CF and CFTR-RD has been made (see paper 1 of this series for advantages/disadvantages) [1]. Until evidence specific for subjects with bronchiectasis due to CFTR-RD emerges, individualised treatment should be based on the guidelines for both CF and non-CF bronchiectasis, taking into account both disease severity and other factors pertinent to that individual.

3. Chronic or acute recurrent pancreatitis

3.1. Frank Bodewes, Michael Wilschanski, Isabelle Scheers, Chee Y. (Keith) Ooi, Isabelle Sermet-Gaudelus

Acute pancreatitis (AP) is characterised by acute inflammation of the pancreas and is associated with typical symptoms suggestive of pancreatic origin (e.g. severe abdominal pain, nausea and vomiting) and elevated serum amylase or lipase $\geq$3 times the upper limit of normal and/or imaging findings (e.g. ultrasound) compatible with acute pancreatitis. Acute recurrent pancreatitis (ARP) is characterized by recurrent episodes of inflammation of the pancreas. The diagnosis requires at least two episodes of acute pancreatitis with complete resolution of pain and normalization of amylase and lipase between episodes. Chronic pancreatitis (CP) is a progressive and irreversible inflammation of the pancreas defined by at least one of the following three criteria: 1) abdominal pain of pancreatic origin with imaging findings of chronic pancreatitis (e.g., calcification); 2) evidence of exocrine pancreatic insufficiency with imaging findings of CP; and, 3) endocrine pancreatic insufficiency with imaging findings of CP. All types of pancreatitis can be caused by known or unknown underlying conditions (see below). CP can lead to permanent loss of function of the pancreas and requires lifelong follow up and management.

CFTR plays a crucial role in the physiological functioning of the pancreas. Defects in CFTR lead to impaired bicarbonate secretion, disrupting the normal balance of pancreatic secretions and contributing to the development of pancreatitis and other pancreatic diseases. Diagnostic criteria for CFTR-RD pancreatitis rely on (1) excluding other aetiologies and (2) confirming the criteria for CFTR-RD [1].

3.2. Diagnosis of pancreatitis

In addition to measuring serum amylase and lipase levels, the initial workup for ARP typically includes full liver enzymes, calcium, fasting triglycerides, coeliac antibodies (e.g. anti-TTG [tissue transglutaminase]) and IgG4, pancreatic imaging (e.g. Magnetic Resonance Cholangiopancreatography, MRCP), sweat chloride analysis and genetic testing [43,44]. Apart from *CFTR*, there are other genes associated with an increased risk of developing pancreatitis, including variants in *PRSS1, SPINK1, CTRC, TRPV6* and *CPA1*, amongst others [45–47]; these risk factors may be present even among those who carry 1–2 *CFTR* variants. Additional testing to consider include serum amino acids and urine organic acids (for the inherited conditions methylmalonic academia and propionic academia) and stool for parasites/fungi as these

are all rare but important causes of pancreatitis

Anatomical anomalies, specifically pancreas divisum, are associated with ARP in 5–20 % of cases. In ARP and CP, MRCP is the preferred imaging technique for the assessment of the pancreas. Endoscopic cholangiopancreatography (ERCP) is usually reserved for therapeutic purposes.

3.3. Alternative causes of pancreatitis

The causes of AP, ARP and CP are diverse – internationally recognised 'checklists' of the causes include TIGAR-O (Toxic-metabolic, Idiopathic, Genetic, Autoimmune, Recurrent and severe acute pancreatitis and Obstructive) checklist for adults, and INSPPIRE (International Study Group of Pediatric Pancreatitis: In Search for a Cure) checklist for children [43,44,48]. The evaluation should thus include a history of possible past attacks, medications taken, exposure to toxins, a family history of pancreatitis, diabetes, alcohol, and gallbladder disease. Primary aetiologies of pancreatitis should be carefully investigated, including toxic or metabolic causes (e.g. alcohol, tabacco, hypercalcemia, hyperlipidemia, medications), autoimmune factors, and obstructive causes [43,49]. Some of these may only be risk factors, which increase the likelihood of developing pancreatitis but do not directly cause it. Risk factors for pancreatitis include genetics, lifestyle, and environmental.

3.4. Diagnostic criteria for CFTR-RD pancreatitis

As outlined above, pancreatitis is widely recognized as a multifactorial disease, resulting from the combined impact of multiple insults, including genetic variants and anatomical factors, like a pancreas divisum [43,48]. All of these need to be considered. Patients at risk of pancreatitis usually have normal exocrine pancreatic function, and one of the *CFTR* variants in these pancreatic sufficient patients is usually associated with residual function.

To determine if a patient has AP, ARP, or CP associated with *CFTR* protein dysfunction, it is important to assess for *CFTR* variants and protein function [1,2]. Next-Generation Sequencing for pancreatitis gene variants should be performed in all patients with otherwise unexplained ARP or CP, including the *CFTR* polyT variants. If *CFTR* variants are identified, their relevance should be assessed by evaluating CFTR function primarily via a sweat test, but other functional tests such as nasal PD and ICM may be required. It is important to note that a normal sweat chloride (<30 mmol/L) does not rule out the diagnosis of CF in all cases (even though it is considered standard care for ARP and CP). The order of genetic testing and CFTR function testing, particularly sweat testing, can differ depending on the individual situation and circumstances (Table 2).

CFTR dysfunction can affect chloride and bicarbonate transport. Several reports have suggested that specific *CFTR* variants (e.g. *R74Q, R75Q, R170H, L967S, R1162L, L997F, D1152H, S1235R, D1270N* and *R117H*) can lead to impaired bicarbonate secretion and result in various disease states, including pancreatitis [50,51]. Some *CFTR* variants that alter bicarbonate but not chloride transport have been associated with a normal sweat test [50], which reinforces the need to always perform genetic testing in this clinical context. Indeed, the current definition of CFTR-RD only includes CFTR functional tests (sweat test, nasal PD, ICM) related to chloride transport. Therefore, these functional tests may not detect a bicarbonate transport defect, and genetic testing is mandatory in this clinical situation to differentiate pancreatitis in CFTR-RD from CF and CFTR carriers (Table 2).

3.5. Recommendations for follow-up and treatment of CFTR-RD pancreatitis

The management and treatment of pancreatitis in general is applicable to this population and is beyond the scope of this article. The issues specific to CFTR function are summarised in Table 2. The impact of CFTR modulators on pancreatic function and related complications have been reported [52,53]. In people with CF, ivacaftor has been shown to improve symptoms and reduce inflammation in CF pancreatitis [54], and CFTR modulators have been linked to a decrease in hospitalizations due to acute pancreatitis [55]. Conversely, it has also been suggested that CFTR modulators may increase the incidence of pancreatitis in exocrine pancreatic insufficiency [56]. Currently, classifying pancreatitis as CFTR-RD does not impact standard disease treatment, as CFTR modulators are not approved beyond the strict diagnosis of CF. Since the CFTR-RD classification for pancreatitis provides a mechanistic link between *CFTR* mutations and CFTR protein-related chloride (or bicarbonate) transport in individual patients, CFTR modulators might in the future be considered as potential treatment option for CFTR-RD-associated pancreatitis. Further research is needed to establish the effects of CFTR modulators, determine eligibility, optimal dosage and treatment duration, across the full spectrum of CFTR function, so that an accurate assessment of risk/benefit can be determined.

Table 2
Pancreatitis and CFTR: a summary of the different clinical scenarios and recommendations.

	Acute recurrent (>1 episode) and chronic pancreatitis			
Diagnosis	**Cystic fibrosis with pancreatitis**	**Pancreatitis in CFTR-RD**	**Pancreatitis in CFTR carriers**	**Pancreatitis with no CFTR variants**
Key diagnostic tests	Exclude common causes of pancreatitis Newborn screening *CFTR* genetic testing* Sweat test	Exclude common causes of pancreatitis *CFTR* genetic testing* Sweat test Nasal PD ICM	Exclude common causes of pancreatitis *CFTR* genetic testing* Sweat test Consider Nasal PD Consider ICM	Exclude common causes of pancreatitis *CFTR* genetic testing* (no variants detected)
Key CFTR-related management principles	Patient diagnosed with CF developing pancreatitis or CF patients with pancreatitis as the primary presentation should be treated as a CF patient for ongoing care and management. Refer to CF specialist center. Potentially eligible for CFTR modulator therapy.	Diagnose CFTR-RD according to the ECFS CFTR-RD diagnostic guidelines. Refer to CF specialist center. Theoretically might be eligible for CFTR modulator therapy in the future.	When a single *CFTR* mutation is detected, it is necessary to exclude CFTR-RD (and CF). Refer to CF specialist center. Theoretically might be eligible for CFTR modulator therapy in the future.	CFTR does not play a role in either causing or increasing the risk of pancreatitis.

When the diagnosis is unclear, consider testing for a panel of genes associated with pancreatitis (see text).
Abbreviations: CFTR=cystic fibrosis transmembrane conductance regulator; PD=potential difference; ICM=intestinal current measurement; ECFS=European CF Society. *Extended CFTR analysis should be performed if first-line targeted assessment is inconclusive.

4. Chronic Rhinosinusitis

4.1. Jochen G. Mainz, Assen Koitschev, Daniel Peckham, Donald Vandevanter, Kevin W Southern

Chronic rhinosinusitis (CRS) is a common condition with a number of underlying causes affecting children and adults. It is a characteristic feature of CF, especially in adults, and is a significant cause of morbidity in this population [57]. Nasal polyposis, occasionally extensive, is also a feature of CF. In contrast, aside from medication toxicity (e.g. aminoglycosides, azithromycin) of the vestibulocochlear system secondary to treatment of CF airway bacterial pathogens, the ear does not appear to be affected by CFTR dysfunction. An increased prevalence of chronic rhinosinusitis has also been reported in carriers of *CFTR* variants [58, 59].

Rhinosinusitis is inflammation of the mucosa of the nasal and paranasal cavities characterised by two or more symptoms, one of which should be either:

- nasal blockage / obstruction / congestion
  or
- nasal discharge (anterior and/or posterior nasal drip)

Other symptoms can include facial pain/pressure and/or reduction or loss of smell as a second diagnostic symptom according to the European Position Paper on Rhinosinusitis and Nasal Polyps 2020 [60].

For a CRS diagnosis, the above mentioned symptoms should persist for more than 12 weeks. The extent of CRS can be confirmed either by endoscopic examination, and/or CT or MRI imaging of the sinuses [61]. Typical endoscopic findings include nasal polyps and/or mucopurulent discharge and/or oedema/mucosal obstruction, primarily from the middle meatus. Pathological changes observed on CT/MRI are most frequent within the ostiomeatal complex and maxillary sinus.

4.2. Can CRS be considered a CFTR-RD?

Given that CRS is a hallmark of CF, that virtually all adults with CF have some sinonasal abnormalities by imaging, and that the presence of nasal polyps in preschool children are highly predictive of CF, it seems reasonable to assume that the upper airway is sensitive to CFTR dysfunction and that CRS is a candidate condition for CFTR-RD [61–65]. The resolution of CRS symptoms among those treated with CFTR modulators supports the rationale that CFTR dysfunction is causative [65–67]. A study of family members related to people with CF found an increased prevalence of CRS, supporting the assertion that mildly reduced CFTR function may be associated with CRS, even among obligate CF carriers [68]. A case-control study comparing people with CRS to age matched controls found an increased prevalence of CF-causing *CFTR* variants, again supporting the hypothesis that for some people with CRS, the underlying cause may be CFTR dysfunction and that the condition represents a CFTR-RD [68].

4.3. CFTR-RD CRS diagnostic criteria and recommendations for follow-up and treatment

To fulfil the diagnostic criteria for CFTR-RD, alternative causes of CRS and a diagnosis of CF should both be excluded [1].

4.4. Alternative causes of CRS

CRS is frequently associated with inhaled allergens [60]. Allergic secretions are usually serous and often combined with endoscopic findings of pale swollen mucosa and associated with other allergic manifestations e.g. conjunctivitis. The histological appearances of allergy-associated nasal polyps is a predominant eosinophilic inflammatory infiltrate, which typically responds well to topical corticosteriod therapy.

CRS is a hallmark of PCD, which is associated with impaired mucociliary clearance due to ciliary dysfunction. The pattern of PCD airway bacterial colonization is similar to that of CF or CFTR-RD, although *P. aeruginosa* is detected less frequently. PCD is also associated with situs inversus and troublesome chronic otitis media, which can lead to difficulty in hearing and speech delay [69].

4.5. Excluding a diagnosis of CF

CF should be excluded in individuals with severe CRS, with or without nasal polyps, refractory to anti-allergic therapies, especially when associated with purulent secretions and isolation of CF-typical bacterial pathogens from the airways, such as *P.aeruginosa*. As CRS is relatively common, sweat testing first is recommended. Only if refractory disease persists, despite repeated sinonasal surgery and/or the sweat test is not normal (<30 mmol/L), should more extensive testing (including genetic analysis) be performed, following ECFS CFTR-RD diagnostic guidelines [1]. Furthermore, in pre-schoolers, the presence of nasal polyps (not hyperplastic adenoids, which may be erroneously termed 'polyps') should prompt CFTR investigations. In some cases, more extensive electrophysiological testing may be appropriate (e.g. ICM or nasal PD, although it should be noted that significant nasal inflammation can affect the quality of nasal PD measurements) [70]. Genetic testing may identify variants associated with CFTR-RD or carriers of *CFTR* variants. A negative genetic test does not exclude CFTR-RD, but makes it less likely, especially if other potential CRS causes are identified [1,2]. With some evidence of CFTR dysfunction and/or identification of *CFTR* variants, in the absence of another cause of CRS, a diagnosis of CFTR-RD seems appropriate.

4.6. Recommendations for follow-up and treatment of CFTR-RD CRS

A history of nasal blockage, snoring and mouth-breathing is indicative of CRS, together with purulent secretions visible by rhinoscopy and often also by oral inspection, e.g. on the dorsal pharygeal wall from postnasal drip. If questioned or assessed by methods such as "Sniffin sticks," impaired smelling, reduced taste and appetite, may be detected [71]. Monitoring of progress should include direct visualisation of the nasal cavity with nasendoscopy and imaging. In absence of a nasendoscope, the examination can be performed by an otoscope usually available to physicians in routine practice.

In patients with CRS refractory to conservative therapies, sinonasal imaging should be performed, ideally by MRI to monitor progress and need for surgical intervention. Sinus radiographs are of low diagnostic value and are associated with radiation exposure (which is not associated with MRI), so should be avoided. Low-dose CT scans can be performed on an individual basis, especially before scheduled surgery. Diagnostic nasal lavage [72], such as by nasal pasage rinsing with 10mls of isotonic saline or nasal swabs [73], facilitates detection of CF-typical bacteria (e.g. *P.aeruginosa*) in the sinonasal space, which has been identified as a reservoir and a site of first colonization of the "united airway" system. However *P.aeruginosa* may also be isolated in other diseases, such as PCD, with similar clones being identified in both the lungs and paranasal sinuses [74].

CRS is actively treated in CF with topical nasal therapies and surgical intevention. The extent of treatment depends on the impact of the condition on the quality of life of people with CF (and also likely CFTR-RD). The management of CF-related CRS depends on a good working partnership between CF and ENT teams [75]. A similar active ethos is appropriate for patients with CFTR-RD. A systematic review of therapies for CF-related CRS identified clear evidence to support the use of nasal douches with saline, endoscopic sinus surgery and CFTR modulators [76]. Evidence for topical corticosteroids and antibiotics was less robust but these interventions should be considered [76,77]. Importantly, inhalation with conventional aerosols and even nasal lavages do not

sufficiently reach the paranasal sinuses, but this can be achieved with pulsating aerosols [78]. This is particularly important if attempting to eradicate pathogens from the paranasal sinuses. Small studies have demonstrated some effectiveness of mucolytics and antibiotics, but there is a lack of large trials in this field [79–81].

Conservative therapies for upper airway blockage by polyps and/or swollen mucosa include topical nasal steroids as first-line long term therapy, even if sufficiently powered studies have not yet been performed in CF [82]. For relieving the airways from mucopurulent secretions and crusts, therapeutic nasal lavages are performed with 250mls of isotonic or slightly hypertonic saline.

Surgery is required if conservative therapeutic measures are unsuccessful. However, relapses are frequent, as the underlying defect remains. CFTR modulators for people with CF and significant CRS have been shown to reduce sinonasal inflammation, as well as improvements in imaging and endoscopy findings [65,66,83,84]. On rare occasions, CFTR modulators are also prescribed for non-pulmonary indications, including sinus disease, in people with CF after lung transplantation [85]. Further studies are needed to characterise the relative risk/benefit of such treatment in this group. All of the aforementioned treatment strategies should also be relevant to CFTR-RD, although specific evidence is lacking. Importantly, there is currently no evidence to support the use of modulators in CFTR-RD CRS, but as these agents become generic and more accessible, a role may emerge.

5. Allergic bronchopulmonary aspergillosis

5.1. Carsten Schwarz, Patience Eschenhagen, Michael Waller

Allergic bronchopulmonary aspergillosis (ABPA) is an immunoallergic disease triggered by inhalation of *Aspergillus* spp. spores in susceptible and genetically predisposed individuals, such as people with asthma or CF [86,87]. It is characterised by a T-helper-2 cellular response and humoral response resulting in the production of polyclonal IgE as well as Aspergillus-specific IgE, IgG and IgA antibodies. The clinical presentation is usually an acute or subacute clinical deterioration with cough, wheeze, exercise intolerance, exercise-induced asthma, decline in pulmonary function, and increased sputum. The CF community relies mainly on the consensus criteria issued by the Cystic Fibrosis Foundation in 2003 (Table 3) [88].

5.2. Can ABPA be considered a CFTR-RD?

The actual prevalence of ABPA in CF is difficult to establish because of the substantial overlap with classical CF respiratory disease. Retrospective data from epidemiological studies report a range of 2–14 % [89,90]. Pathophysiological mechanistic links between ABPA and CFTR deficiency are described in the literature. In one systematic review and meta-analysis a possible pathogenetic link between *CFTR* variants and ABPA was shown as the odds of encountering *CFTR* variants was higher in ABPA compared with the control group (odds ratio (OR) 10.39; 95 % CI, 4.35–24.79) or the asthma population (OR 5.53; 1.62–18.82) [32]. In an ABPA patient cohort [91], *F508del* was identified more often than in the general population and another study reported a significantly higher frequency of *CFTR* heterozygotes among ABPA patients (28.5 %) compared to control asthmatic patients (4.6 %; $p = 0.01$) and individuals seeking genetic counseling ($p < 0.001$) [92]. A further study found the frequency of *F508del* to be higher in patients with ABPA than in 53 Caucasian patients with chronic bronchitis ($p < 0.0003$) and the general population ($p < 0.003$) [93].

A link between CFTR and ABPA is also supported by evidence from animal models. The *Aspergillus fumigatus* extract sensitisation of *CFTR*-Null mice has been reported to affect eicosanoid pathway gene expression with distinct regulation of *PLA2G4C, PLA2G2D* and *ALOX15* genes, thus impacting ABPA and CF [94]. *CFTR*-Null mice also showed a significanly elevated response in IgE to Aspergillus sensitisation as well as a shift from IL-5 to IL-4 responses compared to controls [95]. Furthermore, gene therapy with rAAV5Delta-264CFTR attenuated the hyper-IgE response in a reproducible CF mouse model of ABPA, with systemic effects also evident in the cytokine response of stimulated splenocytes [96]. These data substantiate a correlation between CFTR dysfunction and ABPA and suggest an aetiological role of CFTR in a subset of ABPA patients. In these individuals ABPA may be considered a CFTR-RD.

5.3. CFTR-RD ABPA diagnostic criteria and recommendations for follow-up and treatment

Before reaching a diagnosis of CFTR-RD, alternative conditions associated with ABPA, including CF itself, should be excluded. Other associated conditions include asthma, COPD and non-CF bronchiectasis [2,97-101]. After excluding these conditions, evidence of CFTR dysfunction should be sought by sweat testing and genetic analysis (follwed by nasal PD and/or ICM, if indicated), as per the CFTR-RD diagnostic guidelines [1,2]. As the exclusion of CF and the interpretation of the diagnostic tests may prove challenging, the diagnosis of CFTR-RD ABPA should be made in a CF center [1]. As for the other CFTR-RD conditions, the ideal follow-up should take place in a CF clinic or specialist CFTR-RD clinic, where the possible involvement of other organs and evolution of the clinical condition are appropriately monitored [1]. As treatment of ABPA can be challenging, particularly when CFTR impairment is present, close collaboration with specialists in fungal disease is recommended.

6. Primary sclerosing cholangitis

6.1. Michael Wilschanski, Frank Bodewes, Dominique Debray, Isabelle Sermet-Gaudelus

Primary sclerosing cholangitis (PSC) is a progressive inflammatory and scarring disease of the large bile ducts that may lead to ductal obstruction, cholestasis, cholangitis, biliary fibrosis, and cirrhosis. The diagnosis is based on radiographic features. The cholangiographic features on MRCP or ERCP are specific and include the characteristic "beading" appearance of dilatation and stricturing involving the intrahepatic and/or extrahepatic biliary tree. PSC is histologically characterized by progressive periductal fibrosis with luminal stenosis or obliteration, along with the formation of a fibrous core, and dilatation (cholangiectasis). PSC is a rare disease, with a frequency of 0.6 per 100,000 patients/year and a bimodal peak at 15 and 35 years of age. It is the most common hepatobiliary disease associated with inflammatory bowel disease, particularly ulcerative colitis. Many patients are asymptomatic, and the diagnosis is suggested by routine liver tests. 10–15 % of adult patients present with anorexia, weight loss, pruritus,

Table 3
ABPA definition in CF [88]. These criteria are also likely applicable to CFTR-RD.

- a (sub-)acute clinical deterioration not attributable to another aetiology
- total serum IgE >1000 IU/mL in steroid-free patients
- positive immediate cutaneous hypersensitivity to Aspergillus antigens (Ags) or elevated *A.fumigatus*-specific IgE levels
- precipitating or IgG antibodies against *A.fumigatus* in serum
- and new radiological abnormalities, which have not cleared with physiotherapy and antibiotic treatment.

jaundice, and right upper abdominal quadrant pain.

6.2. Can PSC be considered a CFTR-RD?

The similar cholangiographic characteristics of CF and PSC have prompted investigations on the role of CFTR dysfunction in the development of PSC [102,103]. Genetic analysis of *CFTR* variants in children and adults with PSC has yielded controversial results. An increased frequency of *CFTR* pathogenic variant heterozygosity has been reported, but this was not significantly different to the rate observed in the control adult population in other studies [104–109]. Functional analysis showed in a minority of patients a decrease of CFTR function to the level of 30 to 65 % wild type [106,107,109]. Of the approximately 100 patients studied so far, a subgroup of 20 would be considered to have CFTR-RD on the basis of current diagnostic criteria [106,107,109]. These observations raise the question of whether a decrease in CFTR function can contribute to the development of PSC, and whether CFTR modulators would be of potential benefit. Larger studies involving patients with PSC tested for CFTR dysfunction are warranted to investigate this hypothesis.

6.3. Diagnostic criteria and recommendations for follow-up and treatment

Other causes of sclerosing cholangitis should be excluded before investigations for CFTR-RD are considered (Table 4). PSC is rare in adults and children, and its aetiology remains mostly unknown. Particularly in children, there is an association of PSC with autoimmune sclerosing cholangitis, characterized by the presence of autoantibodies (ANA, SMA, LKM1) and histological features of sclerosing cholangitis with other autoimmune features. Other secondary causes of sclerosing cholangitis are listed in Table 4.

Based on the available evidence, if no other cause of sclerosing cholangitis is identified, *CFTR* genetic testing is recommended. This should be followed by sweat testing and further electrophysiological testing (nasal PD and/or ICM), if indicated [1]. As per updated guidelines, if CFTR-RD is confirmed, then follow-up in a CF or specialist CFTR-RD centre is advised, in collaboration with a specialist gastroenterology team [1]. There is no known treatment for PSC. Ursodeoxycholic acid may improve liver tests but has no impact on outcome [110]. Portal hypertension may develop with progressive disease. PSC is associated with hepatobiliary malignancies, particularly cholangiocarcinoma. Liver transplantation is at present the only treatment.

Table 4
Causes of sclerosing cholangitis to be considered before investigations for CFTR-RD are initiated.

Pediatric age group [110]	Adult age group [111]
Neonatal sclerosing cholangitis	Cryptosporidiosis, microsporidiosis
PFIC 3 / MDR 3 deficiency	Ruptured hydatid (parasite)
Ischemic injury (ITBL)	Recurrent pyogenic cholangitis/Oriental cholangitis
Bacterial cholangitis	CMV infection
Portal biliopathy	Primary immunodeficiency syndromes
Surgical complications	Secondary immunodeficiency (AIDS)
Cystic fibrosis	Critical illness disease
AIDS-related cholangiopathy	Hepatic allograft
Retroperitoneal fibrosis	Hepatic artery thrombosis/stenosis/ ligation
Langerhans cell histiocytosis	Chemotherapy
Primary immunodeficiency	Ig4 associated SC
Secondary immunodeficiency	Eosinophilic cholangitis
IgG4-associated cholangitis	Mast-cell cholangiopathy
Eosinophilic Cholangitis	Choledochal varices (cavernous formation)
Sickle cell disease	Choledocholithiasis
Histiocytosis X	Iatrogenic stricture
CMV infection	Malignant infiltration/Cholangiocarcinoma
Cryptosporidium infection	Langerhans histiocytosis
	Caustic or alcohol instillation into bile duct, eg, treatment of hepatic hydatid cyst

Abbreviations: CMV=cytomegalovirus; ITBL=ischaemic type bilary lesions; AIDS=acquired immunodeficiency syndrome.

7. Aquagenic wrinkling of the palms

7.1. Elke De Wachter, Emmanuelle Girodon, Caroline Raynal, Geoffroy Hickman, Emmanuelle Bourrat

Aquagenic wrinkling of the palms (AWP), also named aquagenic palmoplantar (pseudo) keratoderma (APPK), is a rare skin disease characterized by transient wrinkling, oedema and whitish papules mostly on the palms, with pruritus, burning and pain appearing within five minutes of water immersion [112,113]. It resolves rapidly after drying. The diagnosis is made by immersion of both hands in tap water for five minutes followed by clinical examination of the palms [112,114,115]. No standardized test is available and differences occur in the literature on water temperature (range: 15–40 °C), immersion time (5–15 min) and scoring systems [114–118]. Histopathological features include thickness of the stratum corneum, however, a biopsy is not needed for the diagnosis [119].

7.2. Can AWP be considered a CFTR-RD?

AWP has been reported in up to 84 % of patients with CF [115,120], as well as 8 % of obligate CF carriers [116]. The improvement of AWP in response to CFTR modulator therapy in CF patients underlines the relationship between dysfunctional CFTR and AWP [121,122]. Only one large study, involving 112 French patients presenting with isolated AWP, has assessed the frequency of pathogenic *CFTR* variants [123]. A significant excess of *CFTR* variant carriers (33 %) was found, compared to the healthy control group (~3 %). Moreover, 6.3 % of patients carried two *CFTR* variants, making CFTR-RD a possibility in these patients and thus strengthening the argument that AWP can be considered a CFTR-RD.

7.3. CFTR-RD AWP diagnostic criteria and recommendations for follow-up and treatment

CF should be excluded in individuals presenting with AWP, particularly if symptoms in other systems co-exist, regardless of their severity [121,124]. If the CF diagnostic criteria are not satisfied then CFTR-RD could still be the diagnosis so further testing should be considered, particularly if the symptoms are painful and unresponsive to standard treatment (see below). Previous studies have not confirmed a relationship between sweat chloride concentration and the severity of AWP and data on other functional tests in AWP (e.g. nasal PD and ICM) are not available [115,118]. Therefore, it is recommended that genetic analysis is the first diagnostic test, particularly as AWP is frequently found in individuals without any CFTR involvement. When a single *CFTR* variant is found, further assessment is recommended. The genotypes that have been reported in AWP are the same as those found in the other conditions associated with CFTR-RD.

7.4. Alternative causes of AWP and how to exclude them

Other conditions associated with AWP include marasmus, nephrotic syndrome, cardiac abnormalities and drug reactions [114,117,125-127]. Genetic causes, other than *CFTR,* have been indentified, including heterozygosity for variants in the *Aquaporin 5* (*AQP5*) gene in 3 % of 198 French patients with isolated AWP [128]. *AQP5* variants have been described in autosomal-dominant diffuse Non-Epidermolytic

Palmoplantar Keratoderma of Bothnian type, which is a permanent condition of wrinkling, worsened by water immersion [129]. Heterozygosity for *CFTR* and *AQP5* variants could increase the risk of AWP, as previously suggested [130]. The inclusion of *CFTR* and *AQP5* genes in the genetic exploration of AWP is thus worth considering.

7.5. Recommendations for follow-up and treatment of CFTR-RD AWP

Patients presenting with AWP and at least one *CFTR* variant, should be referred to a CF center for sweat testing and a complete clinical evaluation with appropriate follow-up [1]. Referral for genetic counselling is recommended.

Usually specific treatment is not needed. If AWP interferes with daily life, local topical aluminium hydroxide should be considered for first line treatment. Botulinum toxin injection has been described as an alternative treatment in some cases [131].

8. Conclusions

This is the third paper of the ECFS CFTR-RD project, covering the individual disorders, including their clinical features, route to diagnosis, alternative causes and key elements to their management. By undertaking this process, it became clear early on, that the evidence underpinning each disorder, is highly variable. This was not only the situation for the 'established' disorders (i.e. CAVD, bronchiectasis and pancreatitis) but particularly for the 'emerging' pathologies. Although this was not unexpected, it presented challenges reaching definitive conclusions for some conditions, which explains the variable presentation of the information and recommendations. Table 5 summarises the paper, providing an overview for the reader, with areas of uncertainty highlighted. Notwithstanding this, the paper provides an important up-to-date overview of the conditions associated with CFTR dysfunction and, importantly, extends into new areas, explaining the principles of their diagnosis based on *CFTR* genetics and electrophysiological testing, and the exclusion of other (often more common) causes. However, as each condition has its own unique set of clinical, practical and cost challenges, it is acknowledged that unified recommendations across all of them is not realistic at the current time, although with greater recognition of CFTR-RD across the specialities from this programme, we hope this can be achieved in the future. It is clear, that gaps in our knowledge remain, including an accurate estimate of the prevalence of each condition, the precise level of CFTR dysfunction and why some organs are affected more than others. Producing evidence showing that the accurate diagnosis of these conditions leads to a change in treatment and long-term outcomes, and the specific role of CFTR modulators, is an area in urgent need of further research. This, along with the role of registries, genetic counselling and effective dissemination of CFTR-RD knowledge beyond the CF community, are the topics in the next and final paper of this project.

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Table 5
Summary of the disorders considered a CFTR-RD and key diagnostic, genetic and clinical features.

	CAVD	Diffuse Bronchiectasis	Chronic or acute recurrent pancreatitis	Chronic rhinosinusitis	ABPA	Primary Sclerosing Cholangitis	Aquagenic wrinkling of the palms
Diagnostic confirmation*	Semen analysis Clinical examination Imaging (US)	High resolution thoracic CT	Serum amylase/ lipase MRCP	Clinical examination Nasendoscopy CT ±MRI	Aspergillus serology (total IgE, specific IgE, IgG) ±skin prick tests	MRCP ERCP	Clinical examination Biopsy – not usually required
Main alternative diagnoses/ causes to consider**	Renal pathology	Immunological, Autoimmune, Post infective	Gallstones, Alcohol, Toxic/ metabolic causes	Allergic	Asthma	Autoimmune	Marasmus, nephrotic syndrome, cardiac abnormalities, drug reactions
Other genes implicated	*ADGRG2*	PCD genes *ENaC*	*SPINK1* *PRSS1* *CTRC* *TRPV6* *CPA1*		*PLA2G4, PLA2G2D* *ALOX15*		*AQP5*
Uncertainties and research questions	The role of MRI. The extent of disease – bilateral/ unilateral disease or partial obstruction. The role of CFTR modulators and disease reversal.	The role of other non-CFTR genes. The effectiveness of CF-specific treatment, e.g. dornase alpha and CFTR modulators.	The impact of non-CFTR genes. The role of CFTR modulators.	The accuracy of nasal PD in CRS. The role of CFTR modulators.	The role of CFTR modulators.	The mechanistic significance of CFTR function.	The mechanistic significance of CFTR function. The true prevalence in the general population, CF and other CFTR-RDs.

Key: *the principal modalities/tests for reaching the diagnosis of the individual condition; **not exhaustive (see the main text for a more complete list); US=ultrasound; CT=computed tomography; ERCP=endoscopic retrograde cholangiopancreatography; MRCP=magnetic resonance cholangiopancreatography; MRI=magnetic resonance imaging; PD=potential difference.

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