



Original Article

ECFS standards of care on CFTR-related disorders: Towards a comprehensive program for affected individuals

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ABSTRACT

After three publications defining an updated guidance on the diagnostic criteria for people with cystic fibrosis transmembrane conductance regulator (CFTR)-related disorders (pwCFTR-RDs), establishing its relationship to CFTR-dysfunction and describing the individual disorders, this fourth and last paper in the series addresses some critical challenges facing health care providers and pwCFTR-RD.

Abbreviations: AWP, aquagenic wrinkling of the palms; CAVD, congenital absence of the vas deferens; CFTR, cystic fibrosis transmembrane conductance regulator; CFTR-RD, CFTR-related disorder; CRMS/CFSPID, CFTR-related metabolic syndrome/CF Screen Positive, Inconclusive Diagnosis; DNWG, Diagnostic Network Working Group; GDPR, General Data Protection Regulation; ICD, International Classification of Diseases; IRT, immunoreactive trypsinogen; LCI, lung clearance index; NBS, newborn bloodspot screening; NSWG, Neonatal Screening Working Group; PA, *Pseudomonas aeruginosa*; pwCF, people with Cystic Fibrosis; pwCFTR-RD, people with CFTR-related disorder; SCC, sweat chloride concentration; SMA, spinal muscular atrophy; VUS, variant of unknown clinical consequences; VVCC, variant of varying clinical consequence.

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Topics included are: 1) benefits and obstacles to collect data from pwCFTR-RD are discussed, together with the opportunity to integrate them into established CF-registries; 2) the potential of infants designated CRMS/CFSPID to develop a CFTR-RD and how to communicate this information; 3) a description of the challenges in genetic counseling, with particular regard to phenotypic variability, unknown long-term evolution, CFTR testing and pregnancy termination 4) a proposal for the assessment of potential barriers to the implementation and dissemination of the produced documents to health care professionals involved in the care of pwCFTR-RD and a process to monitor the implementation of the CFTR-RD recommendations; 5) clinical trials investigating the efficacy of CFTR modulators in CFTR-RD and how endpoints and outcomes might be adapted to the heterogeneity of these disorders.

1. Introduction

In 2020, the ECFS Standards of Care Committee appointed a team from the Diagnostic Network Working Group to produce a model for the diagnosis and care of people with a CFTR-related disorder (pwCFTR-RD). Since the beginning of this undertaking, it was clear that such a large topic could not be encompassed within a single document. Four papers were planned; the first two on diagnostic criteria and CFTR dysfunction assessment have been published in the Journal of Cystic Fibrosis [1,2]. The third paper covers the individual disorders. [Paper 3 of this series: "ECFS standards of care on CFTR-related disorders: Identification and care of the disorders" Simmonds et al.]

This fourth article concludes the series and contains different aspects on CFTR-RD management for clinicians and patients and focusses on varied but important themes, such as:

- 1/ Advantages and challenges of a dedicated patient registry
- 2/ The CFTR-RD risk for infants with a CFTR-related metabolic syndrome/CF Screen Positive, Inconclusive Diagnosis (CRMS/CFSPID) designation.
- 3/ The peculiarities of genetic counseling in CFTR-RD
- 4/ Identification of barriers to disseminate, implement and monitor recommendations on CFTR-RD management
- 5/ The feasibility of clinical trials in pwCFTR-RD

2. CFTR-RD REGISTRY - ICD classification

Lutz Naehrlich, Andreas Jung, Siobhán B. Carr

2.1. Should a CFTR-RD registry be established and why?

Patient registries are powerful systems to collect uniform data on cohorts of individuals defined by a particular disease or therapy and followed over time. Depending on participation and coverage, the impact of a registry can extend from case series to a robust epidemiologic platform providing information on incidence, prevalence, burden of disease and therapy [3]. A general agreement on diagnostic criteria, as well as access to the diagnostic tools are essential cornerstones for a successful registry based on a harmonized dataset. The description of diagnostic criteria and follow-up strategies outlined in the recent CFTR-RD papers [1,2] builds the backbone for a successful CFTR-RD registry, which might fill gaps in knowledge on the long-term course and therapeutic strategies employed by health caregivers.

Nevertheless, some downsides need careful consideration as they might impede the establishment of a successful CFTR-RD registry. Urologists or andrologists, gastroenterologists, pulmonologists and clinical geneticists may have incomplete knowledge of CFTR-RD as a disease option. Professionals' awareness of CFTR-RD is critical for them to consider the diagnosis, to refer the patient to a CF center and to possibly treat them in conjunction with a CF-clinic. Without the involvement of specialists, with their knowledge of the overarching nature of CFTR-RD and a positive attitude about data capture, a registry will be supported by CF centers only. This may limit epidemiological accuracy, but could at least be a good starting point to collect data for

these patients.

2.2. Independent or included in CF registries?

An independent CFTR-RD registry would permit the development of an optimally framed dataset, but requires high start-up and running costs, including software, administration and governance structures. The diagnostic criteria for each patient may have to be reviewed over the course of the disease due to the changing interpretation of genetic results and development of novel diagnostic tools or criteria. A diagnostic shift from CFTR-RD to CF or vice versa are potential scenarios and a strong argument for a close relationship or even an integration into existing CF-registries. The complexity of performing and interpreting diagnostic tests and the possible future updates to the diagnostic criteria and categories, might risk the misclassification of patients if separate registries are implemented.

In order to cover the full spectrum of disease linked to CFTR function, and to facilitate possible changes in diagnosis, the CF Foundation registry (since 2010) and the German CF registry (since 2015), have incorporated CFTR-RD [W1,W2]. Both registries exclude CFTR-RD from the main CF analysis (e.g. the annual report) and neither have published any epidemiologic data on these conditions. The 2021 CFF annual report [4,W3] separately reports 534 pwCFTR-RD and 74 new CFTR-RD diagnoses compared to 779 new people with CF (pwCF) (personal communication Alex Elbert). The German CF registry has captured 113 pwCFTR-RD since 2015 (personal communication Lutz Naehrlich; dataset 06/Apr/2022) [W4]. The contributors of both registries are exclusively CF centers and the data collection is tailored to CF and not to the specific needs of CFTR-RD. Ideally, the registry subset for pwCFTR-RD should have parameters specific for this population, including repeat sweat test results, more phenotype specific parameters and the possibility to revert to a diagnosis of CF at some point in time.

The US and German experiences underpin the need for a framework to consider the peculiarities of CFTR-RD and the involvement not only of CF centers but also all the other specialists who may see pwCFTR-RD. Nevertheless, integration into established CF-registries seems to be the most appropriate strategy, notwithstanding the high starting and running costs and of the advantages offered by a well-established governance structure.

2.3. Quality monitoring, financial support

The success of patient registries such as the CF registries depends on a clear lead and governance model (including General Data Protection Regulation, GDPR); high commitment of contributors; high coverage and participation; harmonization of the relevant variables across the caregivers; up-to-date data collection and data management systems and completeness and quality of data provided. All these factors require substantial human and financial resources. As patient registries are not – or at least rarely – obliged by healthcare systems or health insurance, they are mainly run by committed contributors under a governance financed and coordinated by a medical society or patient organization.

2.4. How should individuals with CFTR-RD be classified using the international classification of diseases (ICD)?

A multisystem disease like CF or CFTR-RD should be coded as an overarching disease. Neither ICD10 nor ICD 11 adequately cover CFTR-RD. There is now a strong case for CFTR-RD to have its own coding in future ICD updates to improve capture of this rare disorder and aid in future research. Learned societies and patient associations may seem the best equipped to take this task. (See Section 4, Table 1A and 1B). Until then, all individual organ specific manifestations should be coded according to ICD-10 or ICD-11:

ICD-10: CBAVD: N46; Bronchiectasis: J47; Pancreatitis: K86.1 (recurrent) or K85.8 (acute); ABPA: B44.81; Primary Sclerosing Cholangitis: K83.01 2; Aquagenic Wrinkling: L99.8

ICD-11: CBAVD: GB04.0; Bronchiectasis: CA24; Pancreatitis: DC32.Y (recurrent) or DC31.Y (acute); ABPA: 1F20.1Y; Primary Sclerosing Cholangitis: DB96.2; Aquagenic Wrinkling: EK5Y.

3. CRMS/CFSPID designation: what is the risk of developing CFTR-RD?

Anne Munck, Jürg Barben, Tanja Gonska, Philip M. Farrell, Kevin W. Southern

3.1. Rationale for progression from CRMS/CFSPID to CFTR-RD

It is widely acknowledged that newborn bloodspot screening (NBS) for CF has been a successful public health intervention to facilitate early recognition of infants with CF and improve outcomes [5–7]. Some infants with a positive NBS result have less clear diagnostic certainty, and these infants are given the designation CRMS/CFSPID. The frequency and nature of the recognition of CRMS/CFSPID cases depends on the NBS approach, but all programmes will recognize CRMS/CFSPID infants who are well, but have features that may represent future risk, for example, an intermediate sweat chloride value or *CFTR* gene variants that are uncharacterized or of varying clinical consequence (VVCC).

International guidelines recommend that infants designated CRMS/CFSPID are regularly monitored for future onset of CF or CFTR-RD [7–10]. The concern is based on the presence of specific *CFTR* gene variants that are found in adults with CFTR-RD or even CF [11–16]. These *CFTR* gene variants are either VVCCs, such as D1152H, R117H (7T), 5T or variants of unknown clinical consequences (VUS), which, in many cases, are paired with a CF-causing gene variant. Signs of CFTR dysfunction may then be reflected in a sweat chloride concentration (SCC) which is higher than the concentration measured in healthy infants and carriers (<30 mmol/L) but lower than the threshold required for a CF diagnosis (≥60 mmol/L) [17]. The observation that SCC may be even low in CRMS/CFSPID due to immaturity of the sweat glands in infancy further increases the worry of missing children at risk of disease and the need for repeated clinical check-ups [18,19].

The presence of CFTR dysfunction is key for the diagnosis of CFTR-RD and links the underlying *CFTR* genotype to disease development in the affected individual. Similar CFTR dysfunction was demonstrated in a comparison between infants designated CRMS/CFSPID and CFTR-RD adults with R117H-7T showing the same mean SCC and similar percentage of isolated airway pathogens [15].

It should be acknowledged that as a cohort, people who carry a CF-causing *CFTR* gene variant have distinct physiology (higher sweat chloride and immunoreactive trypsinogen (IRT) values) compared to non-carriers [17,20,21]. Carrier status is reported as a negative NBS result (and not CRMS/CFSPID), but as a group these infants may have a small undefined risk for CFTR-RD [22,23]. This is outside the scope of this review, which is focused on CRMS/CFSPID, and further research is required to better characterize the risk for carriers.

While CRMS/CFSPID and CFTR-RD share similar genetic and functional diagnostic data, CFTR-RD is a clinical presentation, with a disease

phenotype in a CF-related organ, in contrast to CRMS/CFSPID, which is a designation for infants with no clinical features. However, there may be subtle exceptions to this – e.g. a high IRT measurement, even though often transient, may be a biomarker for pancreatic inflammation, constituting disease in a CF-related organ. Bacterial colonization may be another sign to elevate the risk for sinopulmonary CFTR-RD in CRMS/CFSPID. Early-stage interim reports of several prospective CRMS/CFSPID observational studies found *Pseudomonas aeruginosa* (PA) in throat swabs in 15–30 % of children labeled as CRMS/CFSPID, although lung function at this stage was normal [24–26]. One study reported a similar probability of finding PA in CRMS/CFSPID as in children with CF and pancreatic sufficiency [27]. While PA can also be found in healthy children, this high prevalence of PA is reason for concern, particularly since airway infection with PA is associated with progressive lung disease in CF and precedes lung function decline [28–30].

The rationale above supports monitoring of infants and children designated as CRMS/CFSPID for signs of CF or CFTR-RD, at least until robust biomarkers or future genetic risk studies allow better risk stratification [31].

3.2. Current evidence to support the rationale

The risk for infants with a CRMS/CFSPID designation of developing CFTR-RD cannot be determined with the data available so far, especially since the short duration of follow-up observations is a limiting factor. Our search identified three recent retrospective, observational studies [24,32–34], using as a reference the 2011 CFTR-RD recommendations [35].

Castaldo et al. reported a single center study in Napoli (Campania region, Italy) [24]. Among 99 infants designated with CRMS/CFSPID (born 2008–2014), eight evolved between 1 and 8 years of age to a diagnosis of CFTR-RD. Four presented with clinical features of recurrent pneumonia, two had sinonasal complications, two recurrent pancreatitis and two bronchiectasis. All were pancreatic sufficient. All had a normal SCC (<30 mmol/L) at initial and final assessment (maximal age of 11 years), except for one child with a final intermediate value of 35 mmol/L. All alleles were identified after gene sequencing, if indicated. In all cases at least one VVCC was found, including D1152H in five cases.

Terlizzi et al. reported a multicenter study from six Italian CF centers, evaluating 43 infants with a CFSPID designation carrying one D1152H *CFTR* gene variant [32]. Among them, Group A ($n = 28$) had *in trans* a CF-causing mutation and Group B ($n = 15$) an unclear variant (VVCC, VUS or non CF-causing). They were born in 2011–2018; three cases evolved to CFTR-RD (9.3 %) during a mean follow up of 40.3 months (all 3 cases from group A). They presented with clinical features of pancreatitis between the age of 7 months and 2 years. In the first year of life, isolation of PA, pancreatitis, and respiratory exacerbations were reported more commonly in Group A compared to Group B. All had initial and final normal SCC values (age range 6m–7.5 years). Another publication from the same group identified 336 infants with CRMS/CFSPID designation (born 2011–2018) and followed them for a mean duration of 40 months [34]. Four infants progressed to CFTR-RD including the three pancreatitis cases described.

These three studies demonstrate that in these younger children conversion to CFTR-RD is unusual and longer follow-up studies are required to evaluate the frequency of CFTR-RD. Newly revised criteria for the CFTR-RD definition in 2022 may affect the way these children are identified [1,2].

3.3. Communicating the risk of CFTR-RD to those with a CRMS/CFSPID designation

Counselling families and children who have a CRMS/CFSPID designation for the risk of developing CFTR-RD is complex and requires careful and consistent communication [10,36–38]. Information should be provided verbally and in other media forms (for example, written

information sheets or web resources), repeated and checked for understanding. The information may need to be updated on a regular basis as knowledge increases; for example, when clearer characterisation of a *CFTR* gene variant is published. Databases as CFTR2 [W5] and CFTR-France [W6], should be ideally re-checked by the time the patient is seen for a follow-up visit.

A major challenge for CF healthcare professionals and genetic counsellors is presentation of risk, as data are currently lacking with respect to the extent of conversion from a CRMS/CFSPID designation to CFTR-RD. For parents and children, the concept of “conversion” to a clinical phenotype is easier to appreciate than a “reclassification” (i.e., “your infant always had a CFTR-RD”). An evolution from a silent presentation to a clinical phenotype is well recognised for many other genetic conditions and understood by families [38]. It is important that families have a clear picture of what to look out for and how to communicate their concerns to an appropriate healthcare professional.

The information given as a result of having CRMS/CFSPID may facilitate an earlier diagnosis and appropriate management of CFTR-RD [10]. Therefore, particular attention should be given to the identification and interpretation of manifestations potentially evocative of CFTR-RD as described in the previous paper [Paper 3 of this series: “ECFS standards of care on *cftr*-related disorders: Identification and care of the disorders” Simmonds et al.].

Consistent information is key to supporting families. Parents have described inconsistent information and approaches from healthcare professionals as being one of the most unsettling and disturbing aspects of this situation for them [10]. Providing information in a situation that is uncertain requires great skill and time. In addition, as young people with a CRMS/CFSPID designation enter early adult life, they should have the opportunity to receive this information directly so they can understand what it means to them. For young men, this includes the issue of male infertility. The young person should be provided with written resources and other reliable information resources, as well as contact information in case of future questions. The ECFS Neonatal Screening Working Group (NSWG) has published an information leaflet for parents/carers and young adults [10]. This information should also be provided to the primary care physician, as they will be the principal point of contact for the young person as they continue their life.

In summary, this is a difficult situation for families, with significant potential for psychological harm [39,40]. Healthcare professionals need skill and time to provide clear and consistent information that families in this situation require to navigate this journey.

4. GENETIC counseling in CFTR-related disorders

Carlo Castellani, Emmanuelle Girodon, Wayne W. Grody, Karen S. Raraigh, Callum Boyd

4.1. The challenges of phenotypic variability and of unknown long-term evolution

The well-known inconsistent correlation between *CFTR* genotype and CF disease phenotype is even more pronounced when CFTR-RDs are considered. Individuals with these conditions carry at most one CF-causing variant, leaving one or two alleles occupied by VVCCs, CFTR-RD-causing variants, or non CF-causing variants. As indicated by the CFTR2 and CFTR-France databases [41,42,W5,W6], VVCCs *in trans* with a CF-causing variant are typically associated either with CF or with CFTR-RD. Non CF-causing variants may either result in no disease or lead to a CFTR-RD. Variants designated as CFTR-RD-causing by the CFTR-France dataset [42,W6] or by previous documents of this series [2] are expected to cause CFTR-RDs, but not CF, when *in trans* with a CF-causing variant.

Differences in genotype penetrance may be partially explained by undetected complex alleles, modifier genes, and non-hereditary factors. Interactome patterns of *CFTR* may play a role, where relatively modest

alterations in the level of protein function can be associated with relevant changes in cellular and clinical phenotype [43].

4.2. Does the autosomal recessive paradigm apply?

Phenotypic heterogeneity makes it hazardous to use *CFTR* genotype to predict whether someone will manifest a CFTR-RD, not only in unrelated individuals but also in siblings. Genotype alone is not sufficient to make a diagnosis [1,2]. In practice, this means that while the sibling (s) of an individual with a CFTR-RD may harbor the same *CFTR* genotype as the affected person, the diagnosis of CFTR-RD can only be appropriately applied if the sibling demonstrates clinical features of CFTR-RD. Therefore, for families with two identifiable *CFTR* variants, the recurrence risk for the CFTR-RD-causing genotype among siblings or future pregnancies remains at 25 %, consistent with autosomal recessive inheritance, but the recurrence risk for disease manifestations may be lower (or later-onset).

The most recent guidelines [1] include among CFTR-RD not only mono-organ manifestations, like CAVD or chronic pancreatitis, but also conditions involving more than one body compartment. That makes CFTR-RD more similar to CF, although in the context of milder clinical involvement and higher residual *CFTR* function. CF is a chronic disease with an individual natural history developing into progressive clinical deterioration. To a lesser degree, this is the case also for some CFTR-RDs, which can over time evolve from mono- to poly-organ or progress to a level of disease that justifies a change of the diagnosis to CF. This is more probable for *CFTR* genotypes including a CF-causing and a VCC variant than two VVCCs [2].

The limited genotype-phenotype correlation and the potential for significant clinical changes with age contribute to making genetic counseling for people with CFTR-RD very challenging. The long-term evolution from CFTR-RD to CF or from no clinical disease to CFTR-RD remains largely unpredictable.

4.3. What sort of testing, if any, should be proposed?

Genetic testing in the setting of a suspected CFTR-RD is always recommended for diagnosis. While not all individuals with CFTR-RD will have two identifiable *CFTR* variants *in trans*, many will, and detection of both variants has significant implications for provision of genetic counseling.

This allows for more accurate reproductive genetic counseling for future children of the same two carrier parents of the presenting patient but also for the adult patient couple. It permits more informative and accurate carrier testing of other relatives for their own health risks and reproductive purposes. In addition, it may aid, in some cases, to providing anticipatory guidance regarding the expected progression of disease or phenotype.

As a minimum, *CFTR* testing should include a panel of variants frequently observed in the population that matches the patient’s ancestral origin. However, given that panel testing is typically limited to CF-causing variants, it will not often identify the two variants in individuals suspected of having a CFTR-RD. Therefore, a more beneficial test is sequencing of the coding and flanking regions of *CFTR*, as well as a search for deletions, duplications and known deep intronic variants. While an even more comprehensive test is full-gene sequencing of *CFTR* that includes intronic and regulatory regions, the utility of this technology is unproven in the CFTR-RD population and may lead to significant uncertainty in variant interpretation.

In addition to *CFTR*, testing of other genes may be beneficial for some patients, particularly those with idiopathic pancreatitis, bronchiectasis, and/or CAVD [Paper 3 of this series: “ECFS standards of care on CFTR-related disorders: Identification and care of the disorders” Simmonds et al.]. There are several genetic testing laboratories that offer pancreatitis panels, which typically include *PRSS1*, *CTRC*, and *SPINK1*, among others [44]. Variation in these genes has been associated with

pancreatitis, sometimes in the setting of a heterozygous *CFTR* variant. Bronchiectasis panels may include genes associated with primary ciliary dyskinesia or other pulmonary conditions [45]. Searching for variants in *ADGRG2* may also be considered for individuals with CAVD [46]. The information provided in a genetic counseling session with respect to recurrence risk and anticipatory guidance regarding future development of symptoms is different when variants in these other genes are identified and must be tailored to an individual's specific findings.

4.4. Would cascade testing be appropriate?

Following identification of one or more *CFTR* variants in an individual with CFTR-RD, cascade testing for targeted variants in other relatives may be considered. Family members at risk of carrying one or more identified variant may elect to undergo genetic testing for reproductive purposes or to identify future personal health risks. Genetic counseling to accompany consideration of cascade testing is recommended, as the health and reproductive risks related to CFTR-RD are not straightforward.

Genetic testing and counseling for partners of individuals with a CFTR-RD is complicated and situation-dependent. If the patient harbors one CF-causing variant, genetic testing for the partner should follow the typical guidelines for testing of partners of patients with CF. As a minimum, the partner should be offered testing that includes CF-causing variants common in his/her ancestral population but it is appropriate to consider sequencing of the coding and flanking regions, as well as deletion and duplication analysis and assessment for known deep intronic variants, if the couple are looking to minimize their risk of having a child affected with CF. Careful review of reported variants is required, as it may not be beneficial to identify VUS, CFTR-RD-causing variants or VVCCs with low penetrance; only CF-causing variants or VVCC with a high penetrance for CF should be reported. If no disease-causing variants have been identified in the individual with a CFTR-RD, no specific *CFTR* genetic testing is recommended for the partner. Instead, prenatal genetic counseling (with the potential for carrier screening for other inherited conditions; e.g. spinal muscular atrophy [SMA]) that is appropriate for any couple considering pregnancy may be offered.

4.5. Ethical considerations surrounding pregnancy termination

Since Mendel's time, genetics has been a science of probabilities. Much like the Uncertainty Principle in quantum physics, we can predict likelihood of various phenotypes in populations, but not with definitive accuracy for any single patient or fetus. This is true both for CF-causing variants and even more so for the VVCCs discussed here. Furthermore, the rarer the variant, the less population data we have to go on, despite the useful *CFTR* databases cited above. Both providers and patients have come to live with this uncertainty in the practice of medical genetics over the last few decades, but the recent advent of clinical genomic technologies has dramatically expanded the number and type of such situations encountered. Moreover, the success of mutation-targeted therapies and/or gene editing in CF, SMA, sickle cell disease and other disorders further alters the prospective phenotype and natural history of these genetic conditions, and consequently the context of the prenatal genetic counseling [47].

How can reproductive couples be expected to make irreversible pregnancy decisions in the face of such uncertainty? To make matters worse, ever more restrictive abortion laws in various jurisdictions add another layer of jeopardy. Some of these laws criminalize pregnancy termination unless there is a clear, imminent threat to the life of the mother or fetus, and there are examples already of women with retained products of conception ("missed abortion") who have had to wait until their clinical symptoms became acutely dire before uterine evacuation would be performed [48]. Will medical geneticists and obstetricians be willing to take such legal risks to act on a VVCC whose clinical

consequence is nebulous at best, and not at all symptomatic *in utero*? A possible alternative is *in vitro* fertilization with preimplantation genetic testing, but there is concern that these restrictive laws could subsume that procedure as well [49].

It would seem that the only practical solution for now is to adhere to the conventions we always have in medical genetics and genetic counseling: to inform the patient and family of the clinical implications to the best of our current knowledge (with all appropriate disclaimers) and to provide them with all the available options for intervention, with facilitation for referral if needed, to a location where the intervention is available.

5. Dissemination and implementation of CFTR-RD guidance

Kevin W. Southern, Elke De Wachter, Michael D. Waller, Manu Jain, Carlo Castellani, Nick J. Simmonds, Kris De Boeck

Producing guidance documents is not enough without a careful assessment of potential barriers to their implementation, a plan to disseminate the recommendations to all the professionals involved and a process in place to monitor their implementation [50–52]. At the start of this exercise to revise the CFTR-RD guidelines, we recognized the potential barriers to dissemination and implementation of this advice [1, 2]. In part, this relates to the varied presentation of CFTR-RD and the different routes into care for pwCFTR-RD.

Since publication of the Bombieri paper [35], several manuscripts [1, 7,24,26,32,46] have highlighted the issue of implementation of these recommendations and it remains a challenge to ensure that all pwCFTR-RD have access to appropriate diagnosis and management.

One project focused on men with CAVD and highlighted that whilst the possibility of a CFTR-RD diagnosis was commonly recognized by fertility physicians and geneticists, the need to exclude a CF diagnosis was not often appreciated [53]. Another finding was the over reliance on genetic testing at the expense of sweat testing or other CFTR functional assays. This is a common theme and the second paper in this series reinforces the importance of physiological assays that quantify CFTR function [2]. To some degree, this strategy might be explained by the finding that most citations of the Bombieri paper are found in journals read by CF specialists and only 5 % in journals relevant to fertility specialists, again, a theme that challenges dissemination of knowledge for CFTR-RD.

Educating specialists outside the CF field is important, but a recent paper demonstrated that even for CF physicians looking after adult patients, there was considerable variability in the appropriate labelling of CFTR-RD and CF [54]. So, whilst CF specialists have a key role in the co-ordination of the care of pwCFTR-RD, it is clear that further education is needed for this professional body.

The publication of the four papers in this series re-examining the Bombieri criteria and guidance is a significant step in improving the care of pwCFTR-RD. However, further steps are needed to ensure the optimal dissemination of this knowledge to maximize implementation of the guidelines and improve the outlook for pwCFTR-RD.

We first identified possible barriers to dissemination and implementation of the updated recommendations (Table 1A), and secondly we developed a number of strategies (Table 1B) to address these. It is likely that a combination of different strategies will be needed in order to introduce significant changes in the diagnosis and management of pwCFTR-RD.

6. CLINICAL TRIALS and their endpoints

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Since CFTR modulators significantly improve disease severity in the majority of pwCF [55–58], it is reasonable to hypothesize that these drugs can be of benefit for pwCFTR-RD since both entities have CFTR dysfunction as the underlying defect. However, this hypothesis remains

Table 1A
Barriers to dissemination and implementation of the recommendations on CFTR-RD and strategies to address these barriers (from Table 1B).

Barriers to implementation of the CFTR-RD guidelines	Strategies to address barriers to dissemination and implementation of CFTR-RD guidance (See Table 1B)
Complexity	Strategies to address complexity
Lack of consensus on diagnostic clarity	1, 2, 3, 4, 5, 14, 16
Lack of consensus on management approach	
Imperfect correlation of CFTR- function and impact on clinical presentation	
The weight of evidence is stronger for some CFTR-RDs than for others	
Diagnostic Pathway	Strategies to address diagnostic pathway
Many diagnostic routes (CF clinic, Primary care practitioner, ENT, Fertility, Gastroenterology, Respiratory medicine)	4, 5, 6, 7, 8
Several potential management settings (CF clinic, Specialist, Primary Care)	
Lack of available diagnostic tools	1, 2, 15, 16
Unclear/misleading interpretation of genetic test results	1, 2, 3, 14, 15
Variable genotype/phenotype correlation with known pathogenic CFTR gene variants	1, 2, 3, 13, 14
Management	Strategies to address management
A variety of potential clinics for long-term management depending on the condition	4, 5, 8, 9, 10, 11, 16
Proactive approach not embraced by healthcare professionals or patients	4, 5, 6, 7, 8, 9, 10, 12, 16
Reduced access to standard therapies (if no CF diagnosis)	9, 10, 12, 13, 14, 16
Risk/benefit unclear for CF therapies (new and established)	
Lack of acceptance by the patient and/or the CF team of non-CF diagnostic label	6, 7, 8, 9, 10, 11, 12, 16
Psychological challenges, especially around uncertainty and mixed messages	6, 11, 12, 16
Social challenges, for example health and life insurance, mortgages etc.	8, 9, 10, 11, 12
Limited ability to predict or understand long-term outcomes of CFTR-RD	8, 12, 13, 14, 16

to be proven by clinical trials. Although in this section, we mainly focus on CFTR modulators, clinical trials should ideally also evaluate the effectiveness of symptomatic organ-specific CF therapies in pwCFTR-RD. There are, however, several peculiarities about clinical trials in pwCFTR-RD. The following conceptual aspects need consideration.

Table 1B
Strategies to address barriers to dissemination and implementation of revised CFTR-RD guidance.

1. Establish a clear consensus on CFTR-RD diagnostic considerations [1]
2. Establish a clear consensus on the criteria of CFTR dysfunction in CFTR-RD [2]
3. Establish a clear consensus on the diagnosis and management of the conditions characterized as CFTR-RDs ["Paper 3 of this series: "ECFS standards of care on CFTR-related disorders: Identification and care of the disorders" Simmonds et al."]
4. Involve physicians from non-CF specialties to promote dissemination of recommendations to national and international societies of their specialty
5. Target specialist groups (urology, ENT, dermatology, gastroenterology etc.) with opinion pieces and accessible resources
6. Develop multi-media resources that are accessible for CF healthcare professionals and for other specialist interest groups
7. Use social media and other resources, through stakeholder organizations, to increase awareness of CFTR-RD
8. Establish clear referral routes for a CF Specialist opinion (and care if appropriate)
9. Engage with funders to outline the importance of including this population in care pathways/clinical toolboxes
10. Develop unique ICD codes for CFTR-RD
11. Provide a framework for appropriate psychological and social support for pw CFTR-RD
12. Engage with patient groups (CF and other relevant specialist groups) and develop multi-media resources for patients and their families
13. Establish national and international registries for pwCFTR-RD
14. Establish a research strategy for pwCFTR-RD
15. Establish hubs with expertise in more advanced CFTR-functional diagnostic testing and make them known to referrers (including specialists beyond CF)
16. Develop dedicated CFTR-RD clinics where disease specific specialists work closely with CF physicians

6.1. Peculiarities

CFTR-RD is a group name for very different and often isolated disease manifestations in organs: bronchiectasis, recurrent pancreatitis, primary sclerosing cholangitis, CAVD and possibly other diseases like allergic bronchopulmonary aspergillosis, chronic/recurrent rhinosinusitis, aquagenic wrinkling of the palms (AWP) [1, 2, Paper 3 of this series: "ECFS standards of care on CFTR-related disorders: Identification and care of the disorders" Simmonds et al.]. Isolated CAVD is at present considered irreversible unless maybe at a very young age [59], and it is unlikely that CFTR modulators will improve it. Hence, it will be excluded from this section discussion.

The definition of CFTR-RD is not as clear-cut as that of CF, therefore it may be more complex to define inclusion and exclusion criteria in clinical trials. In any case, the presence of a CFTR-RD clinical entity plus proof of reduced CFTR function (a combination of abnormalities in sweat test, nasal PD or presence of 2 CFTR-RD associated variants as defined in papers 1 and 2 in this series) must be demonstrated [1,2].

We can anticipate that disease manifestations and severity may vary extensively between people included in a trial focused on CFTR-RD. Indeed, in CFTR-RD, CFTR function may vary from approximately 10 % to 50 % of normal, which is a much wider range than that seen in pancreatic insufficient pwCF (0 to 5% of normal function) [2] in whom we have the highest clinical trials experience. In CFTR-RD isolated bronchiectasis FEV₁ ranges can be used to categorize patients as mild or severe, but this may or may not be useful in other CFTR-RDs.

The duration of the active treatment necessary to reach the trial clinical endpoint may differ between the various diseases, e.g. it could be longer for patients with recurrent pancreatitis that may have fewer episodes per year compared to episodes of pulmonary exacerbations in isolated bronchiectasis.

Current CFTR modulators have very different mechanisms of action (potentiators, correctors type 1 and type 2) and compounds under development may have other mechanisms of action (amplifiers, stabilizers) [60]. Hence it should be evaluated which modulators or their combination may benefit pwCFTR-RD most.

Finally, logistic peculiarities, like the high cost and non-ubiquitous availability of CFTR modulators, need to be considered. The current relative rarity of people diagnosed with CFTR-RD leads to few patients per clinical center, which will complicate patient recruitment as well as standardization of outcome measures and equipment across participating sites.

6.2. Questions to be answered, endpoints, outcomes

The questions to be answered in clinical trials are whether treatment with CFTR modulators improves symptoms, decreases disease burden and/or slows down disease progression. In specific CFTR-RDs additional

outcomes need to be considered (eg. diminished risk of malignancy or death in patients with sclerosing cholangitis).

In consideration of some of the difficulties listed above, it is important to evaluate whether *in vitro* individual prescreening of efficacy would be possible. PwCFTR-RD have residual CFTR function, and the *in vitro* forskolin induced swelling assay in for example intestinal organoids has a limited sensitivity in the high range of CFTR function because the organoids are already relatively swollen before adding modulators [61]. It should be explored whether pwCFTR-RD isolated bronchiectasis display CFTR dysfunction in their intestinal organoids and, if so, whether the preswollen organoids still respond to modulators. It needs also to be assessed whether organoids derived from nasal cells would be more useful in this context. Reprogrammed nasal cells can be used, but the sensitivity to assess gain-of-function by modulators in the high range of CFTR function is also not fully known [62].

The logistical challenges inherent to these clinical studies make it unlikely that the classical randomized double-blind placebo controlled parallel or cross-over trials will quickly move the field of CFTR-RD forward. Moreover, because of the complexity of determining the sample size needed and of the scarcity of eligible patients. Hence, different trial options might be considered (Table 2). An alternative design could be a basket trial [63] grouping different CFTR-RDs. Whereas the primary endpoint might be a measure of CFTR function recovery, this will not be considered sufficient evidence by health care authorities or payers. Presumably, demonstration of patient benefit, e.g. by extending life or by improvement in a surrogate clinical outcome will be required for such novel and expensive treatment. A better proof of real life benefit could be derived from $N = 1$ trials [64] in a comparable and predefined format for all CFTR-RDs and with repeated on/off drug episodes. Advantages are that patients have the possibility of starting such a trial whenever a diagnosis of CFTR-RD is made and that costs would be lower compared to a classical randomized controlled trial. Disadvantages are the difference between CFTR-RDs in terms of outcome measures other than CFTR function, of duration of on/off periods, and of a possible carry-over effect after an active phase (Table 2).

It is critical to identify objective outcomes for the different disorders. Both those with expertise in CF and those with expertise outside of CF should be involved in the effort of identifying outcome measures for clinical trials.

Suggestions for clinical / surrogate outcomes in trials on specific disorders may be:

- Bronchiectasis: FEV₁ or lung clearance index (LCI). Pulmonary exacerbations or lung imaging would be more difficult in $N = 1$ trials
- Pancreatitis: frequency of episodes of pancreatitis and time to recurrence are a meaningful endpoint but may require long off/on drug periods in $N = 1$ trials in some patients
- Primary sclerosing cholangitis: MRI imaging or elastography (fibroscan), however, clinical relevance may be insufficiently proven
- Rhinosinusitis: symptom scores like SNOT-20, olfactory and gustatory tests [65], nasal flow measurements [66] and imaging (CT or MRI sinuses)
- AWP: occurrence of the symptom will be an easy endpoint to monitor in a $N = 1$ trial, but standardized tests are not yet available [Paper 3 of this series: "ECFS standards of care on CFTR-related disorders: Identification and care of the disorders" Simmonds et al.]

6.3. Sustainability

At present CFTR-RDs are insufficiently captured by CF registries of most countries (or not captured at all). However, CFTR-RD registries could play a crucial role of facilitating CFTR-RD clinical trials by better describing the natural course of different CFTR-RDs, collecting data on significant endpoints, and identifying eligible patients. (See section 2. CFTR-RD REGISTRY - ICD CLASSIFICATION)

The cost and sustainability of CFTR-RD trials is challenging given the

Table 2
Clinical trial options for CFTR-RD

Trial design	Basket trial	$N = 1$ trials	Double-Blind Placebo Controlled trials
Patient population	Gather all pwCFTR-RDs in one trial as the underlying defect is the same (reduced CFTR function)	Patient is his/her own control	Separate trials for CFTR-RDs to focus on disease characteristics and specific outcome parameters
PRO	Only one trial needed when grouping by basic defect	Straightforward design, intraindividual changes can be evaluated	Large experience with classical design; high acceptance by authorities and payers
CON	Clinical symptoms differ extensively – because of different disease entities, challenge to evaluate clinical outcomes	Requires adapted statistics, aggregating $N = 1$ trial data not straightforward	Costly study, elaborate design, long duration until research question is answered
Endpoint(s)	Improvement of CFTR function in functional assays	Individual response of CFTR function as well as clinical endpoints, individual “real-life” benefit	Focus on clinical endpoints of specific CFTR-RD; assessment of “real-life” benefits in whole patient group
PRO	Objective measure as endpoint	Objective measure combined with subjective benefits	Primary focus on clinical benefits
CON	Unclear how this translates into individual benefit	Duration of observed time-period might be too short to detect benefit	Costly study, elaborate design, long study duration needed
Number of patients needed	↑↑	↑	↑↑↑
PRO	Moderate number needed, recruitment manageable, moderate costs	Low number needed, easy recruitment	Clear scientific answer after performance of trial
CON	Some questions might be left unanswered	Many questions might be left unanswered	High cost, recruitment and organization difficult
Acceptance by authorities	?	?	+
PRO	Innovative, adapted trial design to current needs	Innovative, adapted trial design to current needs	Classical trial design, accepted by authorities
CON	Discussions with authorities needed; might slow down process	Discussions with authorities needed; might slow down process	High cost, trial duration and interest of patients uncertain
Duration of trial	Short	Moderate	Long
PRO	Improvement in CFTR functional assay likely preceeds clinical improvements	Both functional and clinical improvements	Classical trial design, accepted by authorities
CON	Unclear how it translates into clinical benefit; no long-term safety data	Carry-over effect after an intervention	Placebo group might need benefit via an open label extension trial
Motivation of	Estimated as moderate	Likely high	Estimated as low

(continued on next page)

Table 2 (continued)

Trial design	Basket trial	N = 1 trials	Double-Blind Placebo Controlled trials
pwCFTR-RDs			
PRO	Short trial	Short trial with intraindividual effects detected –moderate duration expected for assessment of effect in sequential subjects	Classical study design with answer provided at study end
CON	Clinical benefits might not be detected	Duration of needed intervention unclear, might risk not detecting clinical benefit	Long duration and placebo group unattractive
Individual pre- screening in vitro	Probably feasible	Feasible	Not feasible
PRO	Reduction of pwCFTR-RD needed for trial	Correlation to individual clinical outcome possible, obtaining information about ex-vivo and in-vivo correlation	Correlation to clinical outcome possible, maybe feasible for some CFTR-RDs
CON	Correlation to clinical outcome not possible	Complex to organize for all eligible patients	High cost and complex organization

high drug price, the complexity of the disorders and the need to complete them within a reasonable time. It might be reasonable to start with CFTR-RD isolated bronchiectasis, as this has the advantage of being similar to standard CF trials and outcome measures, and thus might provide the best guarantee for a first successful experience to build on.

Other factors possibly affecting sustainability include:

- Patients’ needs and opinions and their desire to remain motivated and understand/accept long term follow-up, especially for some CFTR-RDs where treatment is unlikely to bring an immediate symptomatic benefit.
- The lack of competition between pharmaceutical companies, as currently the market is being dominated by one.
- Discussions with health care authorities and health care technology specialists about which trial designs and endpoints could eventually lead to drug reimbursement, also taking into account the drug cost and the different severity of the various CFTR-RDs.

7. Summary

In this final paper, we have reflected on the interaction between CFTR-RD and the clinical world. The challenge of managing a varied group of conditions in a co-ordinated and systematic manner is considered, and how we address the potential barriers to implementing this guidance. We have considered the risk for infants with an unclear NBS test and how this and other genetic factors should be communicated to families. Finally we have outlined the importance of establishing robust registries to improve quality of care, better characterise the conditions and facilitate research to improve the lives of people with CFTR-RD.

8. WEB references (date last accessed 18th Sep 2023)

- W1. CFF patient’s registry: <https://www.cff.org/medical-professionals/patient-registry>
- W2. German Cystic Fibrosis Registry: <https://www.muko.info/englis>

- ch-version/registry
- W3. CFF annual report 2021: <https://www.cff.org/sites/default/files/2021-11/Patient-Registry-Annual-Data-Report.pdf>
- W4. German CF Registry annual report 2021: https://www.muko.info/fileadmin/user_upload/was_wir_tun/register/berichtsbaende/annual_report_2021.pdf
- W5. CFTR2 database: <https://cftr2.org>
- W6. CFTR-France database: <https://cftr.iurc.montp.inserm.fr/cftr>

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Castellani C, De Boeck K, De Wachter E, Sermet-Gaudelus I, Simmonds NJ, Southern KW, ECFS Diagnostic Network Working Group. ECFS standards of care on CFTR-related disorders: updated diagnostic criteria. *J Cyst Fibros* 2022;21(6): 908–21. <https://doi.org/10.1016/j.jcf.2022.09.011>. Epub 2022 Oct 8. PMID: 36220763.

[2] Sermet-Gaudelus I, Girodon E, Vermeulen F, Solomon GM, Melotti P, Graeber SY, et al. ECFS standards of care on CFTR-related disorders: diagnostic criteria of CFTR dysfunction. *J Cyst Fibros* 2022;21(6):922–36. <https://doi.org/10.1016/j.jcf.2022.09.005>. NovEpub 2022 Oct 5. PMID: 36207272.

[3] Zolin A, Bossi A, Cirilli N, Kashirskaya N, Padoan R. Cystic fibrosis mortality in childhood. Data from European cystic fibrosis society patient registry. *Int J Environ Res Public Health* 2018;15(9):2020. <https://doi.org/10.3390/ijerph15092020>. Sep 15PMID: 30223583; PMCID: PMC6163251.

[4] Cystic Fibrosis Foundation Patient Registry; 2021 Annual data report Bethesda, Maryland ©2022 Cystic Fibrosis Foundation.

[5] Scotet V, Gutierrez H, Farrell PM. Newborn screening for CF across the globe—where is it worthwhile? *Int J Neonatal Screen* 2020;6:18. <https://doi.org/10.3390/ijns6010018>.

[6] De Boeck K. Cystic fibrosis in the year 2020: a disease with a new face. *Acta Paediatr* 2020;109:893–9. <https://doi.org/10.1111/apa.15155>.

[7] Bell SC, Mall MA, Gutierrez H, Macek M, Madge S, Davies JC, et al. The future of cystic fibrosis care: a global perspective. *Lancet Respir Med* 2020;8:65–124. [https://doi.org/10.1016/S2213-2600\(19\)30337-6](https://doi.org/10.1016/S2213-2600(19)30337-6).

[8] Borowitz D, Robinson KA, Rosenfeld M, Davis SD, Sabadosa KA, Spear SL, et al. Cystic Fibrosis Foundation evidence-based guidelines for management of infants

- with cystic fibrosis. *J Pediatr* 2009;155:S73–93. <https://doi.org/10.1016/j.jpeds.2009.09.001>.
- [9] Munck A, Mayell SJ, Winters V, Shawcross A, Derichs N, Parad R, et al. Cystic Fibrosis Screen Positive, Inconclusive Diagnosis (CFSPID): a new designation and management recommendations for infants with an inconclusive diagnosis following newborn screening. *J Cyst Fibros* 2015;14:706–13. <https://doi.org/10.1016/j.jcf.2015.01.001>.
 - [10] Barben J, Castellani C, Munck A, Davies JC, de Winter-de Groot KM, Gartner S, et al. Updated guidance on the management of children with cystic fibrosis transmembrane conductance regulator-related metabolic syndrome/cystic fibrosis screen positive, inconclusive diagnosis (CRMS/CFSPID). *J Cyst Fibros* 2021;20:810–9. <https://doi.org/10.1016/j.jcf.2020.11.006>.
 - [11] Gonska T, Choi P, Stephenson A, Ellis L, Martin S, Solomon S, et al. Role of cystic fibrosis transmembrane conductance regulator in patients with chronic sinopulmonary disease. *Chest* 2012;142:996–1004. <https://doi.org/10.1378/chest.11-2543>.
 - [12] Ooi CY, Durie PR. Cystic fibrosis transmembrane conductance regulator (CFTR) gene mutations in pancreatitis. *J Cyst Fibros* 2012;11:355–62. <https://doi.org/10.1016/j.jcf.2012.05.001>.
 - [13] Wilschanski M, Dupuis A, Ellis L, Jarvi K, Zielenski J, Tullis E, et al. Mutations in the cystic fibrosis transmembrane regulator gene and in vivo transepithelial potentials. *Am J Respir Crit Care Med* 2006;174:787–94. <https://doi.org/10.1164/rccm.200509-1377OC>.
 - [14] Bishop MD, Freedman SD, Zielenski J, Ahmed N, Dupuis A, Martin S, et al. The cystic fibrosis transmembrane conductance regulator gene and ion channel function in patients with idiopathic pancreatitis. *Hum Genet* 2005;118:372–81. <https://doi.org/10.1007/s00439-005-0059-z>.
 - [15] Keenan K, Dupuis A, Griffin K, Castellani C, Tullis E, Gonska T. Phenotypic spectrum of patients with cystic fibrosis and cystic fibrosis-related disease carrying p.Arg117His. *J Cyst Fibros* 2019;18:265–70. <https://doi.org/10.1016/j.jcf.2018.09.002>.
 - [16] Salinas DB, Sosnay PR, Azen C, Young S, Raraigh KS, Keens TG, et al. Benign and deleterious cystic fibrosis transmembrane conductance regulator mutations identified by sequencing in positive cystic fibrosis newborn screen children from California. *PLoS ONE* 2016;11:e0155624. <https://doi.org/10.1371/journal.pone.0155624>.
 - [17] Farrell PM, Kosik RE. Sweat chloride concentrations in infants homozygous or heterozygous for F508 cystic fibrosis. *Pediatrics* 1996;97(4):524–8. AprPMID: 8632940.
 - [18] Ooi CY, Castellani C, Keenan K, Avolio J, Volpi S, Boland M, et al. Inconclusive diagnosis of cystic fibrosis after newborn screening. *Pediatrics* 2015;135:e1377–85. <https://doi.org/10.1542/peds.2014-2081>.
 - [19] Quinton PM. Cystic fibrosis: lessons from the sweat gland. *Physiology* 2007;22:212–25. <https://doi.org/10.1152/physiol.00041.2006>.
 - [20] Laroche D, Travert G. Abnormal frequency of delta F508 mutation in neonatal transient hypertrypsinemia. *Lancet* 1991;337:55. [https://doi.org/10.1016/0140-6736\(91\)93377-1](https://doi.org/10.1016/0140-6736(91)93377-1).
 - [21] Castellani C, Picci L, Scarpa M, Dechecchi MC, Zanolla L, Assael BM, et al. Cystic fibrosis carriers have higher neonatal immunoreactive trypsinogen values than non-carriers. *Am J Med Genet A* 2005;135:142–4. <https://doi.org/10.1002/ajmg.a.30470>.
 - [22] Miller AC, Comellas AP, Hornick DB, Stoltz DA, Cavanaugh JE, Gerke AK, et al. Cystic fibrosis carriers are at increased risk for a wide range of cystic fibrosis-related conditions. *Proc Natl Acad Sci U S A* 2020;117:1621–7. <https://doi.org/10.1073/pnas.1914912117>.
 - [23] Farrell PM, Langfelder-Schwind E, Farrell MH. Challenging the dogma of the healthy heterozygote: implications for newborn screening policies and practices. *Mol Genet Metab* 2021;134:8–19. <https://doi.org/10.1016/j.ymgme.2021.08.008>.
 - [24] Castaldo A, Cimbalo C, Castaldo RJ, D'Antonio M, Scorza M, Salvadori L, et al. Cystic fibrosis-screening positive inconclusive diagnosis: newborn screening and long-term follow-up permits to early identify patients with CFTR-related disorders. *Diagnostics* 2020;10:570. <https://doi.org/10.3390/diagnostics10080570>.
 - [25] Munck A, Bourmaud A, Bellon G, Picq P, Farrell PM, DPAM Study Group. Phenotype of children with inconclusive cystic fibrosis diagnosis after newborn screening. *Pediatr Pulmonol* 2020;55:918–28. <https://doi.org/10.1002/ppul.24634>.
 - [26] Salinas DB, Sosnay PR, Azen C, Young S, Raraigh KS, Keens TG, et al. Benign outcome among positive cystic fibrosis newborn screen children with non-CF-causing variants. *J Cyst Fibros* 2015;14:714–9. <https://doi.org/10.1016/j.jcf.2015.03.006>.
 - [27] Gonska T, Keenan K, Au J, Dupuis A, Chilvers MA, Burgess C, et al. Outcomes of cystic fibrosis screening-positive infants with inconclusive diagnosis at school age. *Pediatrics* 2021;148:e2021051740. <https://doi.org/10.1542/peds.2021-051740>.
 - [28] Gascon Casaredi I, Shaw M, Waters V, Seeto R, Blanchard AC, Ratjen F. Impact of antibiotic eradication therapy of *Pseudomonas aeruginosa* on long term lung function in cystic fibrosis. *J Cyst Fibros* 2023;22:98–102. <https://doi.org/10.1016/j.jcf.2022.08.007>.
 - [29] Earnest A, Salimi F, Wainwright CE, Bell SC, Ruseckaite R, Ranger T, et al. Lung function over the life course of paediatric and adult patients with cystic fibrosis from a large multi-centre registry. *Sci Rep* 2020;10:17421. <https://doi.org/10.1038/s41598-020-74502-1>.
 - [30] Keating C, Poor AD, Liu X, Chiuhan C, Backenroth D, Zhang Y, et al. Reduced survival in adult cystic fibrosis despite attenuated lung function decline. *J Cyst Fibros* 2017;16:78–84. <https://doi.org/10.1016/j.jcf.2016.07.012>.
 - [31] Collaco JM, Raraigh KS, Betz J, M Atalar Aksit, n Blau, Brown J, et al. Accurate assignment of disease liability to genetic variants using only population data. *Genet Med* 2022;24:87–99. <https://doi.org/10.1016/j.gim.2021.08.012>.
 - [32] Terlizzi V, Padoan R, Claut L, Colombo C, Fabrizio B, Lucarelli M, et al. CRMS/CFSPID subjects carrying D1152H CFTR variant: can the second variant be a predictor of disease development? *Diagnostics (Basel)* 2020;10:1080. <https://doi.org/10.3390/diagnostics10121080>.
 - [33] Terlizzi V, Claut L, Colombo C, Tosco A, Castaldo A, Fabrizio B, et al. Outcomes of early repeat sweat testing in infants with cystic fibrosis transmembrane conductance regulator-related metabolic syndrome/CF screen-positive, inconclusive diagnosis. *Pediatr Pulmonol* 2021;56:3785–91. <https://doi.org/10.1002/ppul.25683>.
 - [34] Barben J, Claut L, Tosco A, Colombo C, Raia V, Fabrizio B, et al. A survey of the prevalence, management and outcome of infants with an inconclusive diagnosis following newborn bloodspot screening for cystic fibrosis (CRMS/CFSPID) in six Italian centres. *J Cyst Fibros* 2021;20:828–34. <https://doi.org/10.1016/j.jcf.2021.03.015>.
 - [35] Bombieri C, Claustres M, De Boeck K, Derichs N, Dodge J, Girodon E, et al. Recommendations for the classification of diseases as CFTR-related disorders. *J Cyst Fibros* 2011;10(Suppl 2):S86–102. [https://doi.org/10.1016/S1569-1993\(11\)60014-3](https://doi.org/10.1016/S1569-1993(11)60014-3).
 - [36] Barben J, Chudleigh J. Processing Newborn Bloodspot Screening Results for CF. *Int J Neonatal Screen* 2020;6:25. <https://doi.org/10.3390/ijns6020025>. eCollection 2020 Jun.
 - [37] Chudleigh J, Ren CL, Barben J, Southern KW. International approaches for delivery of positive newborn bloodspot screening results for CF. *J Cyst Fibros* 2019;18:614–21. <https://doi.org/10.1016/j.jcf.2019.04.004>.
 - [38] Chudleigh J, Chinnery H, Bonham JR, Olander E, Moody L, Simpson A, et al. Qualitative exploration of health professionals' experiences of communicating positive newborn bloodspot screening results for nine conditions in England. *BMJ Open* 2020;10:e037081. <https://doi.org/10.1136/bmjopen-2020-037081>.
 - [39] Johnson F, Southern KW, Ulph F. Psychological Impact on Parents of an Inconclusive Diagnosis Following Newborn Bloodspot Screening for Cystic Fibrosis: a Qualitative Study. *Int J Neonatal Screen* 2019;5:23. <https://doi.org/10.3390/ijns5020023>. eCollection 2019 Jun.
 - [40] Perobelli S, Zanolla L, Tamanini A, Rizzotti P, Maurice Assael B, Castellani C. Inconclusive cystic fibrosis neonatal screening results: long-term psychosocial effects on parents. *Acta Paediatr* 2009;98:1927–34. <https://doi.org/10.1111/j.1651-2227.2009.01485.x>.
 - [41] Sosnay PR, Siklosi KR, Van Goor F, Kaniecki K, Yu H, Sharma N, et al. Defining the disease liability of variants in the cystic fibrosis transmembrane conductance regulator gene. *Nat Genet* 2013;45(10):1160–7. <https://doi.org/10.1038/ng.2745>. Epub 2013 Aug 25. PMID: 23974870; PMCID: PMC3874936.
 - [42] Claustres M, Thèze C, des Georges M, Baux D, Girodon E, Bienvenu T, et al. CFTR-France, a national relational patient database for sharing genetic and phenotypic data associated with rare CFTR variants. *Hum Mutat* 2017;38(10). <https://doi.org/10.1002/humu.23276>. 12970-1315Epub 2017 Jun 28. PMID: 28603918.
 - [43] McCague AF, Raraigh KS, Pellicore MJ, Davis-Marcisak EF, Evans TA, Han ST, et al. Correlating cystic fibrosis transmembrane conductance regulator function with clinical features to inform precision treatment of cystic fibrosis. *Am J Respir Crit Care Med* 2019;199:1116–26. <https://doi.org/10.1164/rccm.201901-0145OC>.
 - [44] Masson E, Zou WB, Génin E, Cooper DN, Le Gac G, Fichou Y, et al. Expanding ACMG variant classification guidelines into a general framework. *Hum Genomics* 2022;16(1):31. <https://doi.org/10.1186/s40246-022-00407-x>. Aug 16PMID: 35974416; PMCID: PMC9380380.
 - [45] Guan WJ, Li JC, Liu F, Zhou J, Liu YP, Ling C, et al. Next-generation sequencing for identifying genetic mutations in adults with bronchiectasis. *J Thorac Dis* 2018;10(5):2618–30. <https://doi.org/10.21037/jtd.2018.04.134>. MayPMID: 29997923; PMCID: PMC6006054.
 - [46] Bieth E, Hamdi SM, Mieuisset R. Genetics of the congenital absence of the vas deferens. *Hum Genet* 2021;140:59–76. <https://doi.org/10.1007/s00439-020-02122-w>.
 - [47] Massie J, Castellani C, Grody WW. Carrier screening for cystic fibrosis in the new era of medications that restore CFTR function. *Lancet* 2014;383(9920):923–5. [https://doi.org/10.1016/S0140-6736\(13\)61092-2](https://doi.org/10.1016/S0140-6736(13)61092-2). Epub 2013 Aug 30. PMID: 23992917.
 - [48] MacDonald A, Gershengorn HB, Ashana DC. The challenge of emergency abortion care following the dobbs ruling. *JAMA* 2022;328(17):1691–2. <https://doi.org/10.1001/jama.2022.17197>. PMID: 36318126.
 - [49] Feinberg EC, Kawwass JF, Cedars MI. Roe v wade and the threat to fertility care. *Obstet Gynecol* 2022;140(4):557–9. <https://doi.org/10.1097/AOG.0000000000004928>. Epub 2022 Jul 20. PMID: 35861359.
 - [50] Castellani C, Duff AJA, Bell SC, Heijerman HGM, Munck A, Ratjen F, et al. ECFS best practice guidelines: the 2018 revision. *J Cyst Fibros* 2018;17(2):153–78. <https://doi.org/10.1016/j.jcf.2018.02.006>. Epub 2018 Mar 3. PMID: 29506920.
 - [51] Madge S, Bell SC, Burgel PR, De Rijcke K, Blasi F, Elborn JS. ERS/ECFS task force: the provision of care for adults with cystic fibrosis in Europe. Limitations to providing adult cystic fibrosis care in Europe: results of a care centre survey. *J Cyst Fibros* 2017;16(1):85–8. <https://doi.org/10.1016/j.jcf.2016.07.001>. Epub 2016 Jul 26.
 - [52] Walicka-Serzysko K, Peckova M, Noordhoek JJ, Sands D, Drevinek P. Insights into the cystic fibrosis care in Eastern Europe: results of survey. *J Cyst Fibros* 2018;17(4):475–7. <https://doi.org/10.1016/j.jcf.2018.04.003>. Epub 2018 Apr 19. PMID: 29681443.

- [53] Destoop M, Daelemans S, Peeters L, De Wachter E. Do fertility clinics use the current recommendations to exclude CF in men with congenital bilateral absence of the vas deferens? A pilot study. *J Cyst Fibros* 2021. 20S2: S153 - abst 319.
- [54] Franciosi AN, Tanzler A, Goodwin J, Wilcox PG, Solomon GM, Faro A, et al. Diagnostic agreement among experts assessing adults presenting with possible cystic fibrosis: need for improvement and implications for patient care. *ERJ Open Res* 2022;8(4):00227–2022. <https://doi.org/10.1183/23120541.00227-2022>. PMID: 36655218; PMCID: PMC9835972.
- [55] Ramsey BW, Davies J, McElvaney NG, Tullis E, Bell SC, Dřevínek P, et al. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. *N Engl J Med* 2011;365:1663–72. <https://doi.org/10.1056/NEJMoa1105185>.
- [56] De Boeck K, Munck A, Walker S, Faro A, Hiatt P, Gilmartin G, et al. Efficacy and safety of ivacaftor in patients with cystic fibrosis and a non-G551D gating mutation. *J Cyst Fibros* 2014;13:674–80. <https://doi.org/10.1016/j.jcf.2014.09.005>.
- [57] Heijerman HGM, McKone EF, Downey DG, Van Braeckel E, Rowe SM, Tullis E, et al. Efficacy and safety of the elxacaftor plus tezacaftor plus ivacaftor combination regimen in people with cystic fibrosis homozygous for the F508del mutation: a double-blind, randomised, phase 3 trial. *Lancet* 2019;394:1940–8. [https://doi.org/10.1016/S0140-6736\(19\)32597-8](https://doi.org/10.1016/S0140-6736(19)32597-8).
- [58] Middleton PG, Mall MA, Dřevínek P, Lands LC, McKone EF, Polineni D, et al. Elxacaftor-tezacaftor-ivacaftor for cystic fibrosis with a single Phe508del Allele. *N Engl J Med* 2019;381:1809–19. <https://doi.org/10.1056/NEJMoa1908639>.
- [59] Bieniek JM, Lapin CD, Jarvi KA. Genetics of CFTR and male infertility. *Transl Androl Urol* 2021;10:1391–400. <https://doi.org/10.21037/tau.2020.04.05>.
- [60] Cuyx S, De Boeck K. Treating the underlying cystic fibrosis transmembrane conductance regulator defect in patients with cystic fibrosis. *Semin Respir Crit Care Med* 2019;40:762–74. <https://doi.org/10.1055/s-0039-1696664>.
- [61] van Mourik P, Beekman JM, van der Ent CK. Intestinal organoids to model cystic fibrosis. *Eur Respir J* 2019;54(1):1802379. <https://doi.org/10.1183/13993003.02379-2018>. Jul 4PMID: 31023844.
- [62] Park JK, Shrivastava A, Zhang C, Pollok BA, Finkbeiner WE, Gibb ER. Functional profiling of CFTR-directed therapeutics using pediatric patient-derived nasal epithelial cell models. *Front Pediatr* 2020;8:536. <https://doi.org/10.3389/fped.2020.00536>.
- [63] Lu CC, Li XN, Broglio K, Bycott P, Jiang Q, Li X, et al. Practical considerations and recommendations for master protocol framework: basket, umbrella and platform trials. *Ther Innov Regul Sci* 2021;55(6):1145–54. <https://doi.org/10.1007/s43441-021-00315-7>. Epub 2021 Jun 23. PMID: 34160785; PMCID: PMC8220876.
- [64] Schork NJ. Personalized medicine: time for one-person trials. *Nature* 2015;520(7549):609–11. <https://doi.org/10.1038/520609a>. PMID: 25925459.
- [65] Lindig J, Steger C, Beiersdorf N, Michl R, Beck JF, Hummel T, et al. Smell in cystic fibrosis. *Eur Arch Otorhinolaryngol* 2013;270(3):915–21. <https://doi.org/10.1007/s00405-012-2124-2>. Epub 2012 Aug 14. PMID: 22890694.
- [66] Ottaviano G, Fokkens WJ. Measurements of nasal airflow and patency: a critical review with emphasis on the use of peak nasal inspiratory flow in daily practice. *Allergy* 2016;71:162–74. <https://doi.org/10.1111/all.12778>.