State-of-the-art review of lung imaging in cystic fibrosis with recommendations for pulmonologists and radiologists from the "iMAging managEment of cySTic fibROsis" (MAESTRO) consortium

Pierluigi Ciet[1,2,3], Silvia Bertolo[4], Mirco Ros[5], Rosaria Casciaro[6], Marco Cipolli[7], Stefano Colagrande [8], Stefano Costa[9], Valeria Galici[10], Andrea Gramegna[11,12], Cecilia Lanza[13], Francesca Lucca[7], Letizia Macconi[14], Fabio Majo[15], Antonella Paciaroni[16], Giuseppe Fabio Parisi [17], Francesca Rizzo[18], Ignazio Salamone[19], Teresa Santangelo[20], Luigia Scudeller [21], Luca Saba[3], Paolo Tomà [20] and Giovanni Morana [4]

[1]Radiology and Nuclear Medicine Dept, Erasmus MC, Rotterdam, The Netherlands. [2]Pediatric Pulmonology and Allergology Dept, Erasmus MC, Sophia Children's Hospital, Rotterdam, The Netherlands. [3]Depts of Radiology and Medical Science, University of Cagliari, Cagliari, Italy. [4]Radiology Dept, Ca'Foncello S. Maria Hospital, Treviso, Italy. [5]Dept of Pediatrics, Ca'Foncello S. Maria Hospital, Treviso, Italy. [6]Dept of Pediatrics, IRCCS Institute "Giannina Gaslini", Cystic Fibrosis Centre, Genoa, Italy. [7]Regional Reference Cystic Fibrosis center, University hospital of Verona, Verona, Italy. [8]Dept of Experimental and Clinical Biomedical Sciences, Radiodiagnostic Unit n. 2, University of Florence- Careggi Hospital, Florence, Italy. [9]Dept of Pediatrics, Gaetano Martino Hospital, Messina, Italy. [10]Cystic Fibrosis Centre, Dept of Paediatric Medicine, Anna Meyer Children's University Hospital, Florence, Italy. [11]Respiratory Disease and Adult Cystic Fibrosis Centre, Internal Medicine Dept, IRCCS Ca' Granda, Milan, Italy. [12]Dept of Pathophysiology and Transplantation, University of Milan, Milan, Italy. [13]Radiology Dept, University Hospital Ospedali Riuniti, Ancona, Italy. [14]Radiology Dept, Tuscany Reference Cystic Fibrosis Centre, Meyer Children's Hospital, Florence, Italy. [15]Dept of Pediatrics, IRCCS Bambino Gesù Children's Hospital, Rome, Italy. [16]Radiology Dept, "Santa Maria del Carmine" Hospital, Rovereto, Italy. [17]Pediatric Pulmonology Unit, Dept of Clinical and Experimental Medicine, University of Catania, Catania, Italy. [18]Radiology Dept, IRCCS Institute "Giannina Gaslini", Cystic Fibrosis Center, Genoa, Italy. [19]Dept of Radiology, Gaetano Martino Hospital, Messina, Italy. [20]Dept of Radiology, IRCCS Bambino Gesù Children's Hospital, Rome, Italy. [21]Clinical Epidemiology, IRCCS Azienda Ospedaliera Universitaria di Bologna, Bologna, Italy.

Corresponding author: Pierluigi Ciet (p.ciet@erasmusmc.nl)

Abstract

Objective Imaging represents an important noninvasive means to assess cystic fibrosis (CF) lung disease, which remains the main cause of morbidity and mortality in CF patients. While the development of new imaging techniques has revolutionised clinical practice, advances have posed diagnostic and monitoring challenges. The authors aim to summarise these challenges and make evidence-based recommendations regarding imaging assessment for both clinicians and radiologists.

Study design A committee of 21 experts in CF from the 10 largest specialist centres in Italy was convened, including a radiologist and a pulmonologist from each centre, with the overall aim of developing clear and actionable recommendations for lung imaging in CF. An *a priori* threshold of at least 80% of the votes was required for acceptance of each statement of recommendation.

Results After a systematic review of the relevant literature, the committee convened to evaluate 167 articles. Following five RAND conferences, consensus statements were developed by an executive subcommittee. The entire consensus committee voted and approved 28 main statements.

Conclusions There is a need for international guidelines regarding the appropriate timing and selection of imaging modality for patients with CF lung disease; timing and selection depends upon the clinical scenario, the patient's age, lung function and type of treatment. Despite its ubiquity, the use of the chest radiograph remains controversial. Both computed tomography and magnetic resonance imaging should be

routinely used to monitor CF lung disease. Future studies should focus on imaging protocol harmonisation both for computed tomography and for magnetic resonance imaging. The introduction of artificial intelligence imaging analysis may further revolutionise clinical practice by providing fast and reliable quantitative outcomes to assess disease status. To date, there is no evidence supporting the use of lung ultrasound to monitor CF lung disease.

Introduction

Cystic fibrosis (CF) is the most common fatal congenital disease in the Caucasian population with a frequency of one in 2000 to 3000 live births [1]. Lung involvement in CF is characterised by chronic bacterial infection and inflammation with acute episodes of pulmonary exacerbation resulting in progressive diffuse bronchiectasis and lung function decline [1]. Although lung disease remains the main cause of morbidity and mortality in CF patients, the last decade has seen new drug therapies and lung transplantation lead to a significant improvement in survival [2]. Data from the Cystic Fibrosis Foundation 2019 Patient Registry Annual Data Report shows that the median predicted survival for CF patients in the United States improved from 38 years for those born in 2008 (95% CI, 35–39 years) to 48.4 years (95% CI, 45.9–51.5 years) for those born in 2019 [3]. This significant improvement has been largely achieved by the introduction of prevention and yearly monitoring programmes, which aim to detect disease at an early phase and closely monitor disease progression [2].

The progression of lung disease has been routinely assessed by pulmonary function tests (PFTs) [4], although chest imaging has proved to be more sensitive than PFTs in the detection of structural lung damage [5]. In addition, chest imaging is more feasible when monitoring lung involvement in patients unable to perform PFT manoeuvres, such as neonates and infants [6].

Moving from the routine use of chest radiographs (CRs) to cross-sectional imaging, such as computed tomography (CT) and chest magnetic resonance imaging (MRI), the latter has significantly contributed to the development of patient-tailored therapy [6–13]. However, several issues related to the use of chest imaging modalities in CF remain unaddressed; for example, it is unclear precisely when, and how, to use CR, CT and MRI. For instance, while the most frequent clinical use of CT within the European Cystic Fibrosis Society Clinical Trial Network (ECFS-CTN) is a single biennial scan, other CF centres employ CT imaging annually or every 3 years [14]. This variability translates into significant radiation dose variability between CF centres [15]. Standard operating procedures concerning lung imaging across differing centres are also highly heterogeneous and rely on various factors including local expertise, accessibility to specific imaging modalities, and confidence of the referring physician in the interpretation of imaging findings [15]. To address these variations, a group of experts in CF imaging, including pulmonologists and radiologists, founded the iMAging managEment of cySTic fibROsis (MAESTRO) committee; the overall aim of the group being the development of clear and actionable recommendations for the timing and use of specific lung imaging techniques in the diagnosis and assessment of clinically stable and exacerbated CF lung disease *via* an evidence-based review of the literature.

Material and methods

A multidisciplinary panel of 13 radiologists and eight pulmonologists, all expert in paediatric and adult CF care, together with one study methodologist, were involved with the identification of clinical questions, expressed in PICOT (patient/population; intervention/indicator; compare/control; outcome; time/type of study) format. The search protocol was set up according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement [16]. Databases used were PubMed and Web of Science; in addition, the reference lists of the included articles were searched for additional articles of interest. The authors included original papers, randomised controlled trials, systematic reviews or meta-analyses, guidelines, and consensus statements; articles not written in English and case reports were excluded. The detailed search strategy is shown in Appendix 1 of the online supplementary material. The search was conducted in November 2019 and updated in June 2021; a second update occurred after first article revision in October 2021.

Relevant papers were ranked, and the level of evidence graded according to the United States Preventative Services Task Force (USPFTF) system for grading the quality of evidence and strength of recommendations. The committee then identified three representative clinical scenarios (table 1) and drafted a list of recommendations based on either evidence or expert opinion relating to the relevant clinical question. Thereafter, areas of agreement and disagreement were identified through online Delphi rounds and voted on using a nine-point Likert scale: strongly disagree (score 1), disagree (score 3), neutral (score 5), agree (score 7), and strongly agree (score 9).

TABLE 1 The three clinical scenarios		
Clinical scenario	**Type of patient**	**Statements**
First diagnosis	Asymptomatic	1.1–1.4
	Symptomatic	
Follow-up	Stable	2.1–2.18
	Declining	
	Improving (treatment with cystic fibrosis transmembrane conductance regulator modulators)	2.10 and 2.12
Pulmonary exacerbation	Diagnosis	3.1–3.6
	Monitoring treatment response	

In addition, the committee classified as "best practice" the recommendations that were felt to be underpinned by a high level of certainty despite limited evidence being available. The term "statement of fact" was used to summarise an important topic explored in the consensus when facts, rather than actions, were discussed and agreed by the committee. Furthermore, five RAND rounds were performed, to vote upon the appropriateness, or otherwise, of each technique in a given clinical scenario. According to the "RAND/UCLA (University of California at Los Angeles) Appropriateness Method', the appropriateness of timing and selection of a given imaging modality was rated on an ordinal scale of integers from one to nine grouped into three categories [17]. Integers from one to three were in the category "usually not appropriate", when the harm of undertaking a procedure or treatment outweighed its benefits; integers from four to six represented procedures that "may be appropriate"; and integers from seven to nine were in the category "usually appropriate", when the benefits of undertaking a procedure or treatment outweighed its harms or risks [17]. The final draft of recommendations and RAND results were discussed during the consensus meeting, held on 20 June 2021, to collect final agreement and vote on the strength of each recommendation.

Clinical scenarios, imaging modalities and definitions

Three clinical scenarios were defined by the committee, each of which included sub-scenarios (table 1). The first scenario (*First diagnosis)* referred to the initial imaging examination performed in patients with CF. This group usually includes either young asymptomatic infants diagnosed by screening – sweat or genetic testing – or symptomatic patients, which could be child or adult, the latter in the case of late diagnosis (which usually follows clinical manifestation).

The second scenario (*Follow-up*) included patients with CF undergoing routine (annual or biennial) clinical monitoring. In this group, a distinction was made between patients with stable, declining or improving lung function. Declining lung function was defined as the annual decrease in forced expiratory volume in 1 s (FEV$_1$ % percentage of predicted) larger than 2% and 3% in patients younger and older than 12 years of age, respectively [18–20]. Decline in FEV$_1$, based on recent UK Cystic Fibrosis Registry data, estimates ranges between 0.5 and 2.68%, with an average value of 1.5%, according to age and pancreatic status [20]. Using the lung clearance index (LCI) as a parameter, decline is defined as annual drop of 17% and 15% in CF patients younger and older than 12 years of age, respectively [21, 22]. "Improving lung function" is the sub-scenario in CF patients on treatment with new CF transmembrane conductance regulator (CFTR) modulator therapies [23]. In young children who cannot perform lung function tests, decline was defined by clinically integrated evaluation which included the presence of chronic respiratory symptoms, frequency of respiratory exacerbation and antibiotic therapy [24, 25]. The third scenario (*Pulmonary exacerbation)* referred to patients experiencing exacerbation defined as rapid decline of lung function combined with increased respiratory symptoms according to ROSENFELD *et al.* [26]. The category *Pulmonary exacerbation* involved two sub-scenarios: the initial diagnosis of pulmonary exacerbation and, secondly, follow-up of treatment response.

Recommendations refer to all modalities of thoracic imaging, namely, lung ultrasound (LUS), CR, CT and MRI. During the discussion, the authors discriminate between uncooperative and cooperative patients; an uncooperative patient is one who cannot follow breathing instructions, such as inspiratory and expiratory manoeuvres, during the examination, either because of age (*i.e.* younger than 6 years old) or level of consciousness (*i.e.* sedation). A cooperative patient is one who can follow the instructions during the examination. In this article, the term low-dose CT refers to a CT protocol which is based on the recommendations by KUO *et al.* [15] according to patient's age. The term PFT refers to standard spirometry and plethysmography assessment performed according to European Respiratory Society/American Thoracic

Society Guidelines [27]. When describing MRI techniques, a difference is made between high-resolution ultrashort echo time (UTE) sequences and conventional MRI sequences, which usually have lower spatial resolution [28].

Finally, based on the literature search, the committee provided a series of recommendations related to collaboration between the referring clinician and radiologist, the use of structured reporting in CF, and those specific to each imaging modality.

Results

Study selection

The first search identified 602 articles, of which, after removing duplicates, 288 were screened for title and abstract based on article type. The full text of 80 articles was deemed relevant to the aim of the study. A second search (June 2021) identified 75 articles, of which 66 were included in the study, resulting in a final selection of 146 articles. After the first revision of the publication (October 2021), an additional 21 articles were identified giving a total of 167 articles. The final list of articles is given in the online supplement (1E). The flowchart of the article selection is shown in figure 1.

28 recommendations are presented in table 2 (*First diagnosis*), table 3 (*Follow-up*) and table 4 (*Pulmonary exacerbation*) according to the clinical scenarios. Each table includes the USPFTF system of grading, with
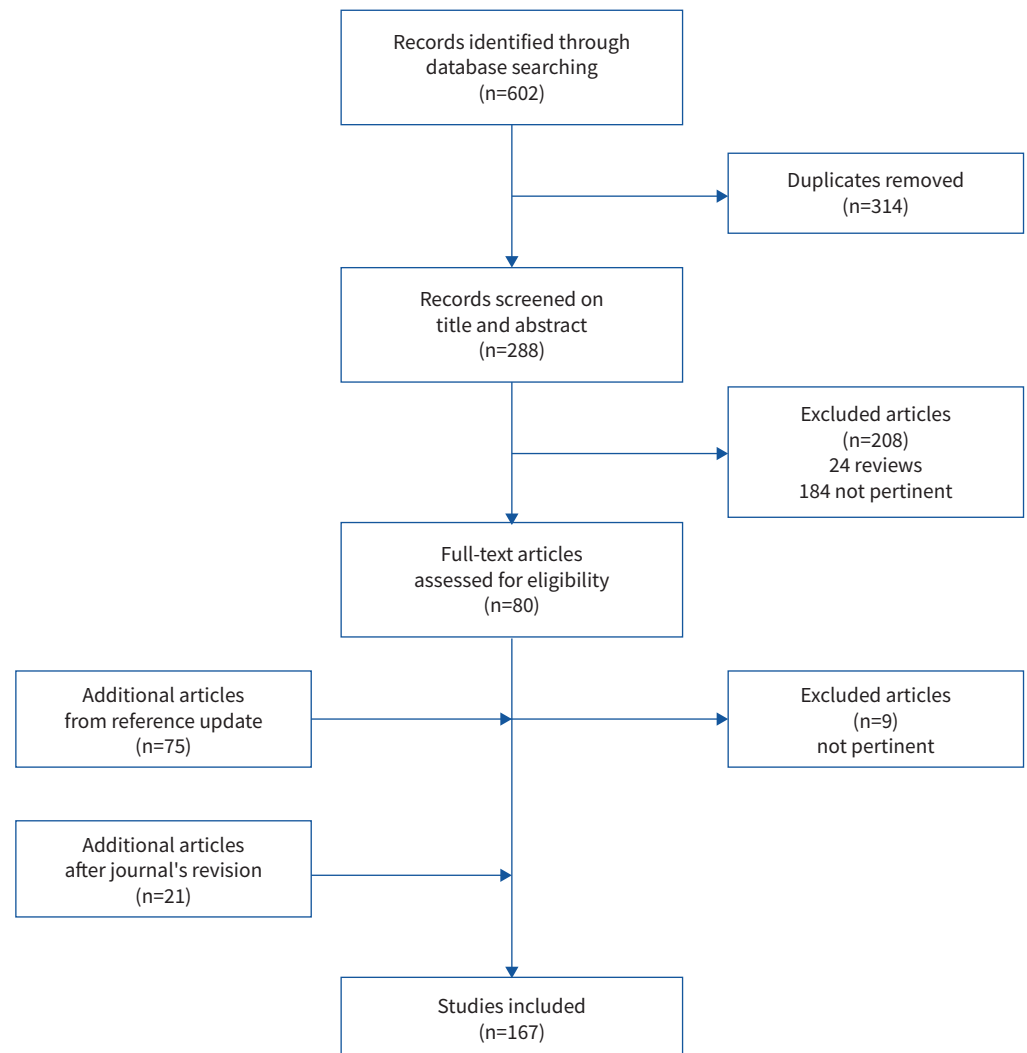

FIGURE 1 Flowchart of article selection.

TABLE 2 First diagnosis						
Statement number	Statement	Type of statement	Strength of recommendation	Quality of evidence	Type of patient	Most relevant supporting articles
1.1	In infants diagnosed *via* newborn screening, CT can be used as a sensitive tool to detect early disease, tailor treatment, and monitor disease progression both in symptomatic and asymptomatic patients.	Recommendation	Grade B	Moderate	Asymptomatic and symptomatic	[10, 13, 29, 30]
1.2	Low-dose CT is feasible both in uncooperative and cooperative patients.	Recommendation	Grade A	High	Asymptomatic and symptomatic	[31–36]
1.3	Although MRI is more feasible in cooperative patients, it can be performed in uncooperative patients with or without moderate sedation/ general anaesthesia according to the patient's age and mental status.	Recommendation	Grade B	Moderate	Asymptomatic and symptomatic	[7–9, 28, 33, 37–39]
1.4	CT dose should be as low as reasonably achievable without affecting the diagnostic quality of the image.	Recommendation	Grade A	High	Asymptomatic and symptomatic	[14, 40–44]
CT: computed tomography; MRI: magnetic resonance imaging.						

descriptions of the type of statement, strength of recommendation, quality of evidence, and type of CF patient. The last column of each table refers to the most relevant bibliography supporting the recommendation.

Recommendations relating to collaboration between the pulmonologist and radiologist, structured radiology reporting, and each imaging modality are presented in the supplementary material (Appendix 1, tables E2, E3, E4).

Discussion

The systematic literature search identified 167 relevant publications on CF imaging. Based on this review, the authors report a lack of consensus regarding imaging protocols for patients with CF, including uncertainty surrounding choice of the most appropriate imaging modality according to clinical scenario, patient's age and lung function. To bridge this gap, the authors propose 28 new recommendations by summarising and grading the quality of evidence published in the literature to date.

First diagnosis

Despite many specialist centres using CR as the imaging technique of choice in infants and preschool children, CT shows higher sensitivity in detecting early abnormalities in both symptomatic and asymptomatic CF patients [5, 10, 12, 53, 54, 60–63]. Therefore, using CR in the early post-screening phase seems to be of limited value, with CT being a more efficient way of detecting early disease and monitoring disease progression [10, 13, 29, 50]. A main limitation of CT, however, for routine imaging of preschool children, is the absence of any "CT protocol harmonisation" [15]. There is, indeed, no consensus on what dose level may be considered low and on the optimal timing of the first CT examination. State-of the art CT scanners can provide substantial dose reductions with effective radiation exposure comparable to CR [35, 158, 160]. Further dose reductions are expected by the introduction of the new photon-counting CT scanner, which could provide a dose reduction of up to 70% at no expense to image resolution [161]. Given the speed of operation, CT scanning can be performed without anaesthesia, thus avoiding cumbersome logistics and anaesthetic recovery times [32, 34, 37, 147]. Thus, CT appears to be higher-yielding and easier to perform than MRI for cross-sectional imaging in preschool patients with a new diagnosis of CF, especially when performed in uncooperative patients [32, 146–148, 162] – a group that frequently requires moderate sedation, or anaesthesia, when undergoing MRI [7, 8, 37, 146, 147].

TABLE 3 Follow-up

Statement number	Statement	Type of statement	Strength of recommendation	Quality of evidence	Type of patient	Most relevant supporting articles
2.1	Limited data are available about the use of LUS to monitor lung status or to evaluate pulmonary exacerbation. Preliminary results show good relation between LUS and CT to assess structural changes.	Recommendation	Grade I	Low	Stable and declining	[45, 46]
2.2	Use of CR scoring systems can improve sensitivity in monitoring CF lung disease. However, their routine use in clinical practice is cumbersome, due to high inter-observer variability. Fully automated CR scoring systems based on artificial intelligence algorithms may overcome this limitation increasing the sensitivity of CR in detecting disease progression.	Recommendation	Grade C	Moderate	Stable and declining	[47–52]
2.3	There is little evidence in the literature about the optimal timing of CT monitoring. There is a need for international guidelines to schedule CT surveillance in patients with CF lung disease.	Statement of fact	NA	Low	Stable	[6, 13, 29, 53–56]
2.4	Current best clinical imaging practice in several CF centres is performing CT biennially (*i.e.* 1 every 2 years).	Best practice	Grade A	Moderate	Stable	[14, 15]
2.5	State-of-the-art reviews of risk related to CT radiation exposure highlight a reasonably low risk of cumulative cancer in children using biennial low dose CT. CT protocol harmonisation between CF centres should be promoted to comply with the "as low as reasonably achievable" (ALARA) concept.	Recommendation	Grade A	High	Stable	[14, 29, 35, 36, 40–44]
2.6	CT can better detect lung disease progression than standard pulmonary function tests (*i.e.* FEV_1) both in cooperative and uncooperative patients, irrespective of disease severity.	Recommendation	Grade B	High	Stable and declining	[5, 10, 12, 53–66]
2.7	CT is complementary to lung clearance index in the detection of disease progression or improvement by clinical intervention.	Statement of fact	NA	High	Stable and declining	[67–74]
2.8	CT provides relevant information possibly capable of modifying disease trajectory, patient management and follow-up, both in uncooperative and cooperative patients.	Statement of fact	NA	Moderate	Stable and declining	[5, 10–12, 48, 75, 76]
2.9	The use of appropriate scoring systems for CT increases its sensitivity in tracking changes in symptomatic, and asymptomatic, early lung disease. Therefore, their use is recommended to standardise interpretation of CT data according to CF centre expertise and capacity.	Recommendation	Grade A	Moderate	Stable and declining	[60, 65, 77–94]
2.10	Artificial intelligence-based scoring system and segmentation tools for CF imaging allows a fully automated volumetric quantification of CF-related abnormalities over an entire lung. These novel scoring systems, when further validated, could provide a robust disease outcome in the era of effective CFTR modulator therapy.	Statement of fact	NA	Moderate	Stable, declining and improving	[60, 65, 77–94]

Continued

TABLE 3 Continued

Statement number	Statement	Type of statement	Strength of recommendation	Quality of evidence	Type of patient	Most relevant supporting articles
2.11	CT scans performed in infants and young children with symptoms is a potential clinical trial outcome measure for novel treatments in this age group.	Statement of fact	NA	Moderate	Declining	[34, 48, 53, 60, 63, 92, 95–102]
2.12	Despite improvement in clinical, lung function, and imaging outcomes in patients undertaking CFTR modulator therapy, no deviation from the usual imaging follow-up scheme should be advised, because there is no evidence in the current literature about long-term benefit of these agents.	Statement of fact	NA	Moderate	Stable, declining and improving	[35, 36, 81, 101, 103–105]
2.13	Despite conventional MRI sequences having lower sensitivity than CT in the assessment of disease extent, state-of-the-art MRI (e.g. UTE sequence) shows comparable results to CT and provides a convenient, noninvasive, and non-ionising assessment of disease progression in cooperative patients. The beneficial absence of radiation is particularly important with respect to the need for frequent follow-up examinations and the increasing life span of CF patients.	Statement of fact	NA	High	Stable and declining	[8, 9, 106–118]
2.14	MRI provides information about ventilation, inflammation, perfusion and structure (VIPS-MRI) in a single examination that is difficult to obtain with CT.	Statement of fact	Grade B	Moderate	Stable and declining	[8, 9, 33, 119–133]
2.15	MRI is a noninvasive, radiation-free endpoint to identify potentially reversible abnormalities (e.g. mucus plugging and lung hypoperfusion) in early phase clinical trials testing novel therapeutics in symptomatic, cooperative, patients with CF.	Statement of fact	Grade B	Moderate	Stable and declining	[118, 131, 134–138]
2.16	The MRI scoring system is a promising tool to predict the loss of lung function in CF patients and can serve as a clinically relevant outcome predictor for pulmonary manifestations in CF.	Statement of fact	NA	Moderate	Stable and declining	[115, 128, 139–142]
2.17	Longitudinal studies are needed to compare the sensitivity of CT and MRI in tracking disease progression.	Statement of fact	NA	Moderate	Stable and declining	[8, 116, 143]
2.18	The use of MRI in clinical practice is hampered by its higher cost than CT; the need for state-of-the-art MR systems; the occasional need for moderate sedation/general anaesthesia in uncooperative children; nonuniformity of MR protocol; as well as substantial image variability/capability between MR brands.	Statement of fact	NA	High	Stable and declining	[7, 8, 34, 37, 144–148]

CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; CR: chest radiograph; CT: computed tomography; FEV$_1$: forced expiratory volume in 1 s; LUS: lung ultrasound; MR: MRI: magnetic resonance; MRI: magnetic resonance imaging; NA: not available; UTE: ultrashort echo.

Follow-up
CR versus CT

Despite the absence of strong supporting evidence in the literature, CR remains the most frequently used imaging modality for lung disease monitoring in several specialist centres; this is due to its ready availability and low cost, and the decades-long use of this technique by CF clinicians during routine follow-up. However, the sensitivity of CR is poor, and inter-observer variability between radiologists is high, even when

TABLE 4 Pulmonary exacerbations						
Statement number	Statement	Type of statement	Strength of recommendation	Quality of evidence	Type of patient	Most relevant supporting articles
3.1	CR may not help with the detection of pulmonary exacerbation, especially in CF patients with more severe disease.	Recommendation	Grade D	Low	Diagnosis	[149]
3.2	CT can detect acute structural lung abnormalities during and after pulmonary exacerbation (e.g. increase of bronchial wall thickening and mucus plugging) in cooperative, and uncooperative, patients.	Statement of fact	NA	High	Diagnosis	[89, 95, 96, 150–156]
3.3	CT can be used to define outcome measures of pulmonary damage in clinical trials and test therapeutic interventions in patients with persistent respiratory symptoms and reduced lung function despite appropriate therapy.	Recommendation	Grade C	Low	Diagnosis and monitoring treatment response	[55, 65, 89, 95, 96, 150–154, 157]
3.4	Routine use of CT for short term follow-up during pulmonary exacerbation is not recommended due to the risk of high cumulative radiation dose. Clinicians should consider the risk/benefit ratio related to dose when prescribing CT in pulmonary exacerbation.	Recommendation	Grade D	Moderate	Monitoring treatment response	[14, 29, 35, 36, 40–44, 158]
3.5	MRI can be used as a surrogate marker for disease severity and response to treatment during short-term follow-up of symptomatic, or declining, cooperative CF patients. In uncooperative patients, the risk related to moderate sedation or anaesthesia needs to be considered.	Recommendation	Grade A	High	Diagnosis and monitoring treatment response	[118, 119, 130, 136, 159]
3.6	MRI can be used as a clinically relevant outcome predictor for pulmonary exacerbations in cooperative, declining CF patients.	Statement of fact	NA	High	Diagnosis and monitoring treatment response	[106, 116, 119, 130, 139]

CF: cystic fibrosis; CR: chest radiograph; CT: computed tomography; MRI: magnetic resonance imaging; NA: not available.

combined with adequate scoring systems [47, 48, 50]. The use of CR is frequently unable to efficiently monitor CF lung disease progression, being less sensitive than CT [48]. The MAESTRO committee believes that the frequent use of CR for follow-up of patients with CF, especially in the early phase of the disease, should be challenged. Furthermore, in view of the progressive increase in life expectancy of the CF population, the risk of radiation exposure could be minimised by an optimised use of CT, increased utilisation of MRI and improved assessment of CR. The latter could be achieved by the introduction of an artificial intelligence (AI) algorithm to increase sensitivity and limit the cumulative radiation dose at low diagnostic cost [49, 52].

Timing of imaging surveillance in the era of CFTRs

Surprisingly, the authors did not find guidelines regarding the optimal timing of imaging follow-up. The scarcity of evidence on this matter contributes to the high degree of heterogeneity within the imaging protocols among CF centres [15]. As observed above, the type and timing of imaging modality are frequently selected based on local experience and accessibility to specific radiological facilities. Current best clinical imaging practice in several CF centres within the ECFS-CTN is to perform CT biennially with a radiation dose as low as reasonably achievable (the "as low as reasonably achievable" (ALARA) concept), while avoiding sedation [163]. Despite the lack of clarity regarding the basis for this follow-up, it

seems that the risk related to CT radiation exposure within this scheme is reasonably low [14, 29, 40, 43]. To date, only one study has been conducted to assess the effect of the imaging interval on CF lung disease progression [55]. In future, however, imaging follow-up should be patient-tailored and include stratification for risk factors for disease progression, such as chronic bacterial infection, pulmonary exacerbation rate and access to new CFTR modulators. Other potential risk factors influencing disease progression could include pancreatic insufficiency, nutritional state, age at diagnosis, and therapy adherence [2, 164, 165]. Such a patient-tailored approach could further reduce the risk of radiation exposure by modifying the imaging interval according to disease status, with longer CT scan intervals in more stable CF patients. This is particularly important in the new era of CFTR modulation therapy, which has shown remarkable efficiency in terms of improvement in lung function and reduction in structural abnormalities [36, 81, 101, 166]. Although, in future, patients could benefit from shorter or longer intervals of radiological follow-up according to clinical status, it is not currently possible to make recommendations, because the long-term benefit of CFTR modulators remains unknown. The introduction of a shorter imaging surveillance methodology, either based on CT or MRI, will require in both cases a major effort in imaging protocol standardisation. While for CT this should be focus on the introduction of an ultra-low-dose CT protocol (*i.e.* radiation dose in the range of a CR), for MRI will need both international agreement on a common set of MRI sequences and development of dedicated post-processing tools for quantification of MRI findings [167]. The authors' recommendation is, therefore, to maintain routine follow-up of patients who improve under the effects of CFTR modulation; on the other hand, any significant deterioration of lung function, or clinical symptoms, should prompt further imaging investigation either with ultra-low dose CT or chest-MRI according CF centre expertise.

Integrated diagnostics – an opportunity to reduce radiation dose?

CT dose reduction may also be achieved *via* CT protocol harmonisation. Studies have shown that dose variation between specialist centres strongly contributes to a huge variability of cumulative dose, which has prompted the introduction of uniform dose-management strategies [15, 29]. Recent developments have also shown the potential for further dose reduction, up to 78%, using optimised imaging protocols, with iterative reconstruction techniques *via* the newest generation CT scanners [35, 36, 44, 158, 160, 167]. Interestingly, these optimised CT protocols have allowed the availability of diagnostic quality CT images at a dose equivalent of a CR, while demonstrating superior sensitivity to the CR and equivalent standard CT in the detection of bronchiectasis [160]. These observations invite future studies that will aim to explore the benefits of replacing CR with low-dose CT in terms of improved diagnostic yield and clinical decision making, and patient outcomes [160]. Within this context, the MAESTRO committee urges the CF research community to define international guidelines to regulate surveillance with CT in patients with CF [14, 29, 160].

Despite the risks associated with frequent imaging, CT has been shown in several studies to offer benefits over the standard PFT (*e.g.* FEV_1), given its improved sensitivity in monitoring pulmonary disease, both in cooperative and uncooperative patients, irrespective of disease severity [5, 10, 12, 60, 63, 64]. On the other hand, chest CT has shown a good correlation with LCI, especially the multiple-breath nitrogen washout technique, in defining the presence, and extent, of CF lung disease in preschool and school-aged children (although it is less sensitive in infants) [67–74, 157, 168, 169]. The LCI reflects overall ventilation inhomogeneity within the lung, even in the presence of normal spirometric volumes, and is correlated with mosaic lung attenuation on chest CT related either to gas trapping or reduced perfusion [170, 171]. These LCI/gas-trapping measurements have been utilised over the past decade in preference to FEV_1 as an early, and sensitive, tool in monitoring the progression of CF lung disease, both in terms of radiological change and clinical involvement [67, 169, 171–175]. Further integration of LCI and gas-trapping measurement with chest CT will be pivotal for a better understanding of disease progression, and as a relevant end-point in clinical intervention trials. The use of more sensitive lung function tests, such as LCI, will also help the shift towards the cross-disciplinary implementation of integrated diagnostics [176], when the use of imaging will be adjusted according to lung function and clinical status.

The rise of "machine learning" in CF chest imaging

The introduction of AI algorithms and machine-learning techniques have also found their way into CF imaging. ZUCKER *et al.* [52] have recently shown that an AI-based algorithm could be used to perform an automated Brasfield scoring of CRs and it performed similarly to a paediatric radiologist. Improvement of the diagnostic performance of CR is important in limiting the cumulative dose of CF chest imaging and reducing diagnostic uncertainty [49, 52].

AI has been also applied to CT imaging, being shown to modify disease trajectory, patient management and follow-up [10, 13, 48]. By combining the use of CT with appropriate scoring systems, or automatic segmentation tools, its sensitivity further increases, making it possible to assess early CF lung disease and

progression both in symptomatic and asymptomatic patients [11, 60, 82, 87–92, 140]. Deployment of quantitative imaging tools based on AI and machine-learning techniques can speed up the development of new CT outcome measures for novel treatments in clinical trials [53, 60, 63, 82]. Recent publications have promoted the clinical use of AI-based segmentation and scoring tools for chest CT, providing reader-independent quantitative outcomes such as: airways–artery ratio, airways tapering, and measurement of trapped air [176 55, 58, 59, 84–88, 177]. Recently, a multi-centre study involving a fully automated AI-based scoring system has proven its high diagnostic efficiency [81]. The upcoming introduction of commercially available software for thoracic imaging and, in particular, for automatic CT scoring might revolutionise clinical practice [178]. Finally, AI applications for MRI in CF are still limited, with chest CT far more advanced in terms of technique validation compared to chest MRI [119, 126, 128, 133, 135, 139, 179].

The use magnetic resonance in CF imaging

Although CT is currently the most commonly used imaging modality for monitoring disease progression, advances in MRI have taken a quantum leap and now offer improved image quality, affording a complementary/alternative imaging tool to CT [7, 8, 33]. Initial studies with conventional MRI sequencing revealed a poorer image quality compared with CT, but more recent MRI technology, such as UTE sequence, shows comparable results [107, 109, 111, 112, 114, 117, 118]. MRI therefore offers a convenient, noninvasive and nonionising means of assessing disease progression in cooperative patients. The beneficial absence of radiation is particularly important with respect to the potential need for frequent follow-up and the increasing life span of CF patients. More importantly, MRI has a unique advantage over CT, which is the ability to provide information about ventilation, inflammation, perfusion and structure in a single examination [178 7, 8, 33, 119, 129, 130, 132, 180]. For example, it has been shown that MRI can capture potentially reversible abnormalities – such as mucus plugging and lung hypoperfusion – which could be used as a new imaging outcome in early phase clinical trials and for testing novel therapeutics in symptomatic, cooperative CF patients [119, 134, 136]. Moreover, a dedicated MRI scoring system has been proven to be a clinically relevant outcome predictor for pulmonary manifestations in CF patients [115, 128, 139–141].

MRI outcomes have also shown strong correlations with lung function parameters in both early and advanced disease. Both MRI and LCI were good predictors of disease progression and response to antibiotic therapy during pulmonary exacerbation in preschool CF children [131, 134, 137]; use of MRI has also been proved to detect early subclinical disease in infants and children [128, 135, 166, 181]. MRI has also shown high sensitivity to the presence of allergic bronchopulmonary aspergillosis and might, therefore, be considered when assessing the effect of treatment on other chronic airway infections (*e.g.* *Pseudomonas aeruginosa*) [120, 121].

These results indicate that MRI may become a "one-stop-shop" for CF imaging. To date, what hampers its broader use in clinical practice is its higher cost than CT, the need for state-of-the-art MRI systems, the necessity for sedation/general anaesthesia for uncooperative patients, nonuniformity of MRI protocol, as well as large image variability/capability between MRI brands [180 7, 8, 37, 144–146, 182]. Recent development of a high performance low-field MRI system (0.55 T), capable of high-resolution lung imaging, offers new perspectives on routine MRI application, overcoming the aforementioned limitations with high-strength MRI systems (1.5–3 T) [183, 184]. Future studies should focus on MRI protocol harmonisation to foster the development of comparable image quality between CF centres and MRI vendors. Homogeneous image quality will be important to facilitate the development of dedicated post-processing tools for chest MRI and allow quantitative imaging. Recent single-centre studies have proposed new automatic tools for the detection of trapped air [135] or inflammatory changes quantification [119].

LUS

Although LUS is generally considered to be a safe bedside imaging modality, frequently used in paediatric and adult lung clinics, there is insufficient evidence to propose its use for CF lung disease monitoring [45, 46]. Further multi-centre validation studies will be needed to assess its utility in the assessment of CF lung disease.

Pulmonary exacerbations

Pulmonary exacerbations are major determinants of lung function decline and mortality in the CF population with 25–50% of patients experiencing exacerbations that do not allow them to recover their prior FEV_1 value following treatment [180]. The absence of a shared definition compromises the optimal clinical management of pulmonary exacerbation, including the use of imaging for diagnosis and follow-up [180]; this is problematic given the significant role of imaging in the clinical management of exacerbation

[79, 95, 119, 130, 136, 151, 152, 154]. The most frequently used imaging modality during exacerbation is CR, although its sensitivity and specificity are debated, especially in patients with severe disease [149]. The latter group is not only at higher risk of exacerbation, but is one where it is difficult to detect new radiographic changes in a lung substrate of diffuse parenchymal abnormality.

Within this context, CT may offer an alternative modality [79, 95, 96, 150–154, 185] where it can be used to detect acute structural lung abnormalities related to pulmonary exacerbation (*e.g.* increase in bronchial wall thickening and mucus plugging) in uncooperative and cooperative patients [79, 95, 96, 150–154, 183]. CT may also play a role in defining objective outcome measures in clinical trials of new therapies for the treatment of pulmonary exacerbation [79, 95, 96, 150–154, 185]. Despite these advantages, the challenge of cumulative radiation exposure limits its routine use for pulmonary exacerbation diagnosis and short-term follow-up. Clinicians should always consider the risk/benefit ratio related to the annual radiation dose when prescribing CT scans in these instances [14, 29, 40, 43]. A cautious approach would be to use low-dose CT only in patients with persistent respiratory symptoms and reduced lung function despite appropriate therapy.

Conversely, MRI can become a surrogate for disease severity and response to treatment for short-term follow-up of symptomatic, or declining, cooperative CF patients [119, 129, 130, 136]. Several studies have shown that MRI can track functional and morphological changes related to pulmonary exacerbation with adequate sensitivity [119, 131, 136]. The absence of radiation makes MRI an ideal solution for serial imaging during the treatment of pulmonary exacerbation, becoming a clinically relevant outcome predictor in declining cooperative patients [180]. Moreover, some authors have shown that MRI could be used to detect acute inflammatory changes related to pulmonary exacerbation, making MRI an important tool to assess treatment response [119, 129, 130]. Currently, the main limitation to the use of MRI remains the uncooperative patient, where risks related to anaesthesia need to be considered [37, 146–148].

Conclusions

The MAESTRO committee urges the establishment of international guidelines on CF imaging. These guidelines should provide clear indications regarding the timing and selection of the most appropriate imaging modality according to the clinical scenario, patient's age, lung disease severity and type of treatment (*i.e.* CFTRs). Based on this state-of-the-art review, the committee concludes that, to date, there is no concrete evidence for a role of LUS in monitoring CF lung disease. Although CR remains the most frequently used modality in CF imaging, its ability to monitor CF lung disease is controversial. Regarding CT and MRI, both techniques should be routinely and interchangeably used to monitor CF lung disease according to the patient's age, disease status and type of treatment. However, compared with MRI, CT is at a more advanced stage in terms of validation and quantitative imaging, although there is a need for CT protocol harmonisation and patient-tailored follow-up schemes to further reduce any risk relating to radiation exposure. Full implementation of MRI in CF lung imaging will require a significant effort towards MRI protocol harmonisation to enable multi-centre validation studies and image quantification. Finally, the upcoming introduction of AI-based solutions both for CR and CT might revolutionise clinical practice by providing fast and reliable quantitative outcome measures to assess disease status in patients with CF.

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