**Title:** Time to get serious about the detection and monitoring of early lung disease in cystic fibrosis

**Proceedings of the international SHIFT Meeting: Shaping imaging and functional testing for early detection of lung disease in Cystic Fibrosis at the Australasian Cystic Fibrosis Conference 2019.**

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**Abstract**

Structural and functional defects within the lungs of children with cystic fibrosis (CF) are detectable soon after birth and progress throughout preschool years often without overt clinical signs or symptoms. By school age most children have structural changes such as bronchiectasis or gas trapping/hypoperfusion and lung function abnormalities that persist into later life. Despite improved survival, gains in $FEV_1$ achieved across successive birth cohorts during childhood have plateaued, and rates of $FEV_1$ decline in adolescence and adulthood have not slowed. This suggests that interventions aimed at preventing lung disease should be targeted to mild disease and commence in early life. Spirometry-based classifications of "normal" ($FEV_1$ ≥90% predicted) and "mild lung disease" ($FEV_1$ 70-89% predicted) are inappropriate given the failure of spirometry to detect significant structural or functional abnormalities shown by more sensitive imaging and lung function techniques. The state and readiness of two imaging (CT and MRI) and two functional tools (Multiple Breath washout and Oscillometry) for the detection and monitoring of early lung disease in children and adults with CF are discussed in this article.

Prospective research programs and technological advances in these techniques mean that well-designed interventional trials in early lung disease, particularly in young children and infants are possible. Age appropriate, randomised controlled trials (RCTs) are critical to determine the safety, efficacy and best use of new therapies in young children. Regulatory bodies continue to approve medications in young children based on safety data alone and extrapolation of efficacy results from older age groups. Harnessing the complementary information from structural and functional tools, with measures of inflammation and infection, will significantly advance our understanding of early CF lung disease pathophysiology and responses to therapy. Defining clinical utility for these novel techniques will require effective collaboration across multiple disciplines to address important remaining research questions. Future impact on existing management burden for CF patients and their family must be considered, assessed and minimised.

To address the possible role of these techniques in early lung disease, a meeting of international leaders and experts in the field was convened in August 2019, attended by representatives across the range of disciplines involved in modern CF care. This

document summarises the proceedings, key priorities and important research questions highlighted.

## 1. Introduction

In Cystic Fibrosis (CF), onset and progression of lung disease in early life is now well-documented[1]. Structural and functional defects, which act as surrogate markers of early lung disease, are detectable soon after birth[2,3]. These defects progress through preschool years, frequently in a "clinically silent" fashion without symptoms or abnormalities on chest X-ray and spirometry. By school age, 60-80% have bronchiectasis and/or gas trapping/hypoperfusion[4-6] and lung function abnormalities[7,8] that persist into later life. Despite advances in CF care, incremental improvement in lung function over successive birth cohorts has plateaued in childhood (Figure 1). The rate of decline in adolescence and adulthood remains unchanged. These observations suggest that lung disease is established by early school age, and to improve long-term survival in the newborn screening (NBS) era, interventions must focus on preventing lung disease progression and target early lung disease[9].

Preventing lung disease in CF requires the development of effective, evidence-based interventions. This is dependent on the ability to detect and measure early, potentially reversible changes, and a thorough understanding of the pathophysiology driving disease progression. The work of several research programs (including AREST CF[2], London CFC[10], ACFBAL[5], SHIELD CF[11], TRACK-CF[12]) have characterised early lung disease and provided a framework for well-designed mechanistic and intervention studies in infants and preschool children. Therapeutic trials using novel and sensitive endpoints developed by these programs have already been conducted in older cohorts[13,14] and preschool children and infants[15-18]. Multiple Breath Washout (MBW)[2,6,8,19-23], chest computed tomography (CT)[2,6,8,24] and Magnetic Resonance Imaging (MRI)[12,25] can detect early functional and structural abnormalities in children and adults despite normal $FEV_1$ values and in the absence of other clinical features of CF disease.

Reducing current treatment burden for patients and families is a priority for the CF community[26]. Incorporating novel, more sensitive approaches to monitoring and measuring outcomes for people with CF, while minimizing the associated burdens for patients, families and the health care teams, is a major challenge.

In recognition of these issues a meeting of experts was convened in August 2019, Perth, Western Australia, attended by representatives from paediatric and adult multidisciplinary research and clinical teams. The program was independently designed and coordinated by the senior authorship group (PDR, SMS, CEW). Vertex Pharmaceuticals sponsored the meeting.

The meeting aimed to:

- Describe current state-of-the-art approaches to early lung disease detection,
- Discuss practicality, utility and limitations of these surrogate techniques
- Discuss priorities for future collaborative research
- Describe challenges and opportunities for integration of these novel techniques into clinical practice.

Key priorities and important unresolved questions are summarised in Tables 1 and 2.

Referenced articles were chosen by authors to broadly represent the evidence base around novel techniques in the detection of CF lung disease. This did not include a standardised literature search. All included studies were deemed to be high quality based on the expertise of the author team. ~~The literature searches (key word search criteria using the National Library of Medicine, PubMed®) focused on studies of subjects with "normal' or "mild disease", as currently defined.~~ Several forerunner studies for these techniques also contained subjects with greater disease severity. Effort was made to include all known institutes/groups with published data in peer-reviewed journals, using these techniques within the field of CF. Descriptions of novel techniques include feasibility and practicability, sensitivity to detect early lung disease and correlates with other measures, standardisation and regulatory approvals, and use in research studies and clinical trials to date.

## 2. Current status of Lung Function techniques

Spirometry remains the main functional measure used in clinics and clinical trials in people with CF to detect change and assess progress. However, it is now well recognised that spirometry is not sufficiently sensitive to detect early or mild lung disease, and shows only weak correlations with structural lung damage[27], inflammation[28], and variable associations with airway infection[29]. Despite the universal

use of spirometry, the minimum clinically important difference (MCID) remains unknown. A revised definition based on sensitive surrogates of early lung disease is needed to expedite the use of novel techniques as end-points in future intervention studies[30].

The Raised Volume Rapid Thoracoabdominal Compression (RVRTC) technique can detect abnormalities in infancy and has guidelines for technical standards[31]. Unfortunately, a lack of suitable reference range data for commercial equipment, and problematic availability of commercial equipment and sedation limits its research and clinical utility[32,33]. For this reason. RVRTC was not discussed at the meeting.

### 2.1 Multiple Breath Washout (MBW)

MBW is a tidal breathing-based technique with high feasibility across infancy to adulthood[34]. MBW detects ventilation inhomogeneity (or unevenness of gas mixing), most commonly reported as lung clearance index (LCI)[8,19,35].

LCI becomes abnormal (increases) with disease onset prior to changes in spirometry indices[7,8,22], and correlates strongly with structural disease on CT[2,27]. The prognostic utility of pre-school LCI to predict future abnormal spirometry and structural lung disease has been published by the London CFC[36,37]. LCI appears more sensitive than spirometry as an indicator of acute lung function decline with respiratory events in pre-school[38] and school-aged children[39], and has highlighted that many do not recover to baseline values.

Consensus guidelines and technical standards have been published for pre-school (and older) children[40,41], and validated commercial equipment is now available[42,43] including both FDA and CE approved options. Between-subject variability has been defined in CF across several paediatric studies[21,44-46].

The sensitivity of LCI to detect improvements with interventions (e.g. hypertonic saline, HTS[47,48] and dornase alfa[49]) in pre-school and school-aged children with established disease, led to its endorsement as a primary outcome measure for clinical trials[50]. Successful integration into large international clinical trials in pre-school[16] and school-age[15] children utilised a central over-reading centre framework governing training, certification and data quality control[51]. Improved LCI trajectories have been demonstrated in infants and pre-schoolers with early lung disease treated with HTS[16,17].

Greater LCI improvements have been achieved with CFTR modulators[52]. Challenges associated with MBW include total testing time (up to 60 minutes in pre-schoolers at initial visits), additional staff training in technical aspects, and feasibility of infant testing (i.e. sedation). MCID for LCI remains unclear: increase/decrease in LCI of 15% is considered significant[44,46], but whether this is clinically relevant is uncertain[53].

### 2.2. Oscillometry

Oscillometry is another tidal breathing technique, which measures airway impedance of the respiratory system. It is relatively quick and feasible across all ages[54].

Technical standards were published in 2003[55] and recently updated[56]. Commercial equipment is widely available, has FDA and CE approval, and a Global Lungs Initiative (GLI) task force is currently collating robust reference ranges.

The interest in oscillometry in early CF lung disease is based on its demonstrated utility in paediatric and adult asthma, correlating with disease control[57,58], and response to treatment[59]. Differences between health and CF in pre-school subjects have been reported[60], however, oscillometry did not correlate with neutrophil elastase activity, pathogenic infection or structural lung abnormalities[61]. Studies are underway in CF to assess the value of more sophisticated measures that are more sensitive to changes in wheeze/asthma detection and control, including day-to-day variability[62] and within-breath fluctuations[63].

## 3. Current status of Imaging techniques

### 3.1 Computed Tomography

CT is the current gold standard for demonstrating CF-related structural lung disease, characterised through indices such as bronchial wall thickening, bronchiectasis and gas trapping. CT scan abnormalities correlate with markers of lung inflammation[3,64], infection[65] and with LCI[2,27].

CT and MBW have similar sensitivities to detect early lung impairment[2,6]. Early structural changes on CT predict later structural disease. Mucus plugging and gas trapping at age 5-6 years predicts subsequent lung function trajectory for up to 10 years, a far longer-term predictive ability than early spirometry[66]. Atelectasis predicts later bronchiectasis[64]. There is some evidence that radiological signs of bronchiectasis

do not invariably persist in young children with CF[65]. In addition, whether structural changes such as airway dilatation reflect disease-related changes or age-dependent differences in airway wall compliance remains unclear. Future intervention studies will be important to define thresholds for reversibility/improvement in structural disease indices, and improve our understanding of what these changes represent in this setting.

~~Indices of bronchiectasis extent likely reflect permanent changes whilst those of bronchial wall thickening and gas trapping may reflect earlier, potentially reversible disease. Future intervention studies will be important to determine whether this assumption is correct and define structural thresholds for reversibility.~~

Since chest CT abnormalities in infants with CF were first detected[67], standardised protocols using ultra-low dose radiation and sensitive scoring systems for mild disease have been implemented within multicentre clinical trials. Notably, CT detected beneficial effects of CFTR modulator therapy among adults with mild and more severe lung disease[68,69] (Figure 2), as well as children with "normal/mild" lung disease[70].

Several challenges have been successfully navigated to develop CT as a primary outcome measure in early lung disease intervention studies[71]. The limitations of historical CT scoring systems are well recognised[72]. Research-based scoring systems have evolved. Initial binary scores for structural disease (e.g. bronchiectasis yes/no in Brody-II)[73] were shown to be insensitive in the setting of early, mild disease[10]. More sensitive analyses have been developed (e.g. Perth-Rotterdam Annotated Grid Morphometric Analysis for CF – PRAGMA[74]), which differentiate severity grades across individuals, and detect progression over time in early lung disease[75]. CT protocols have been standardised across multiple sites internationally[76] and across different scanners. Central over-reading centre facilities and water phantoms providing standardised density readings have been developed[18]. At the time of writing, objective CF-specific CT scoring systems[74,77] are at varying stages of automation and do not have FDA or CE approval. Spirometer-directed CT enhances image quality[78] and standardises lung volume to improve longitudinal comparison.

Challenges remain around CT use in disease detection, particularly in preschool children and infants. While free-breathing scans are available, they may underestimate airway abnormalities, and pressure-controlled scans involve anaesthesia and the associated burdens. Reliability of CT scoring (using the Brody-II Score) in infants has been questioned and until there are validated CT scoring systems for infants it is

essential that steps are taken to minimise observer-bias and optimise intra-observer agreement[10,72]. Ongoing international multicentre studies using CT PRAGMA scores will provide further insight into CT as a primary outcome measure[18,79].

### 3.2 Magnetic Resonance Imaging

Proton MRI using clinical MRI scanners (1.5T) is attractive not only as a radiation-free technique, but also through the ability to derive both structural information and regional ventilation/perfusion homogeneity: so-called morpho-functional MRI[80]. MRI is feasible across a broad age range but requires sedation in infants and pre-schoolers and is time consuming. Awake-MRI is being explored.

Despite lower resolution, detection of early lung disease is achievable and comparable across sites[81,82]. Morpho-functional CF-MRI scoring systems have been developed[83]. In contrast to CT, structural changes of bronchiectasis/airway wall thickening are categorised together as differentiation is challenging. Gas trapping is identifiable and mucus plugging easier to differentiate than in CT due to its high T2 signal[84]. In a cohort of children and young people (range 0.2-21.1 years) who were almost exclusively non-newborn-screened[12], structural disease was prevalent and reported from the first year of life, with abnormalities increasing with age[12]. Treatment of pulmonary exacerbation led to reduction in airway wall thickening, mucus plugging and consolidation (Figure 3)[81]. MRI correlates strongly with LCI [12].

Hyperpolarised gas MRI permits visualisation and assessment of global and regional ventilation distribution, and outcomes correlate with MBW ventilation inhomogeneity[85]. Ventilation defect percentage (VDP) appears to be the most promising functional MRI index[86].

The role of MRI endpoints in intervention trials is emerging. Between-site stability, acceptable intra-subject variability[87], and ability to detect disease progression over time[25] has been demonstrated. Studies have shown detectable responses to antibiotic therapy[12,81,86] and CFTR modulators[88]. MRI standardisation was achieved across multiple sites[89] in the PRESIS Study[17]. In that study, LCI trajectory improved but MRI score (based on indices of lung structure only) did not. This suggests that some treatments may improve function without improving structural changes and emphasises the value of measuring multiple outcomes in future intervention studies.

MRI imaging does present several challenges[90]. Low proton density of air results in reduced signal-to-noise ratio, whilst numerous air-tissue interfaces create greater magnetic heterogeneity and faster signal decay (or loss). Magnitude of this effect increases at higher field strength (i.e. 3T). Additionally, this low signal target moves throughout image detection (both lung and cardiac), with higher respiratory rates and heart rates encountered at younger ages. Cost of hyperpolarised gases (e.g. polarisers and access to physicists) is significant. Oxygen-enhanced proton MRI techniques have been recently developed[91,92].

## 4. Future Directions

### 4.1 Combining sensitive tools to gain insights into CF pathophysiology

Combining techniques aids interpretation of changes observed with specific techniques/indices and may provide further insight into the pathophysiological mechanisms behind early CF lung disease. This may enable targeted approaches to prevent disease progression.

LCI reflects gas mixing in the volume of lung in direct communication with the mouth. The potential for a bidirectional LCI response is well recognised in more severe disease[34,93]. Imaging may provide the topographical information to explain this (e.g. illustrating areas of recruited lung with impaired gas mixing in response to an intervention). Raised MRI morphology/perfusion/global scores in the setting of normal LCI[12,25] (Figure 4), or longitudinal worsening of gas trapping on CT despite improvements in LCI[94] all reflect combined use in early disease. Several specialised MRI techniques exist[95,96] and the challenge for researchers is to utilise them effectively in future studies, combining/allocating resources based on varying regional expertise, cost and access issues, to advance CF understanding in early disease detection.

Understanding the evolution of, and relationships between, inflammation, infection and structural lung disease is critical to efforts to develop effective treatment strategies. Longitudinal research programs have shown that combining several of these techniques with assessments of inflammation and infection is both feasible and

informative. Strong correlations existed between early structural change, neutrophil elastase[3] and neutrophil exocytosis[97]; early airway inflammation at age 5 years was associated with bronchiectasis in adolescence[64,98]. The roles of specific airway organisms in structural disease onset and progression remain unclear[75,99]. Future studies should address optimal study design for longitudinal monitoring of infection[100], and insights gained from animal models of CF[101-105] should also be considered.

### 4.2 Anticipated hardware and software advances

Hardware and software advances should optimise early disease detection, enable consistent and reliable scoring, and reduce labour intensity. This may help reduce associated costs whilst generating an improved signal for use in intervention trials and future clinical practice.

Future MBW device design should reduce equipment-related dead space volume, e.g. via main stream gas analysers[106] and optimise performance at lower flow rates. This will aid testing in infancy where age-specific technical standards are still awaited, and testing remains challenging because of the need for sedation (beyond early infancy) and lengthy testing time. Advances in MBW quality control[51,107] hold promise for future automation of scoring. Prototypes of commercial devices for infant oscillometry measurement[108] show promise. Advances in commercial software should soon allow intra-breath assessments of tidal-volume dependent variation in respiratory resistance and reactance[63].

Advances are occurring at a rapid pace for all of the techniques discussed within this document, and particularly in the imaging domain. Advances in CT technology will improve image quality and speed of data acquisition, and aid further radiation dose reduction (whilst maintaining required image quality for analysis). Standardisation to address impact of differences in hardware and software between centres will remain critical for future multicentre trials. CT is further ahead in this regard. Improvements in MRI scanner technology will provide better gradient fields (higher signal contrast, less artefact), whilst novel MRI research sequences include ultra-short echo times, minimise signal decay and enhance detection of smaller size anomalies (e.g. mucus

plugging[109]). Phase-resolved functional lung MRI provides dynamic regional ventilation and perfusion mapping without IV contrast. In younger age groups it enables free-breathing data acquisition and a shorter examination time (≈10mins)[110]. Paediatric CF data using these techniques are emerging[111,112]. Increased MRI field strength (e.g. 3T scanners), driven by advances in neuroimaging, are problematic for lung imaging, which operates best at lower field strength, and must be addressed by either maintaining a market for 1.5T scanners or adapting acquisition/analysis to this ≥3T setting.

Software advances will facilitate automated analysis and better correction for confounding factors (e.g. spatially corrected density approaches to adjust for anterior-posterior distribution of lung density improving gas trapping detection). Artificial intelligence has shown significant progress in imaging-recognition tasks in recent years[113]. MRI VDP is likely to evolve into more sophisticated indices for quantitative assessment, improving its sensitivity and utility.

### 4.3 Interpretation of radiation risk

Concerns about radiation limit the use of surveillance CT in research studies and CF clinical care, and risks must be interpreted in the correct context. Detection of parenchymal pathology is felt to be less important than airways in CF, enabling lower dose protocols and radiation reduction. Estimated exposure of annual surveillance scans from some centres is low: ≈2mSv by age 6 which is less than the average annual background radiation exposure across USA cities (3.1 mSv/year)[114]. Recent modelling data based on biennial CT scan until age 50 found the risk to be 0.2%, lower than the 0.7% from background radiation[115]. CF survival may reach 60+ years, so future research needs to balance the apparently low risk of radiation exposure from a chest CT with clinical utility and subsequent action[116,117].

### 4.4 Opportunities with data registries

CF registries offer a unique opportunity to learn from the increasing research and clinical use of these techniques. Global CF registries now capture data on almost 100,000 individuals with CF and have provided valuable insight into CF epidemiology, pathogenesis and prognosis (e.g. US[118], Canada[119], UK[120] and Australia[121]). These

large-scale platforms could collate results of newer techniques such as LCI, CT and MRI chest imaging from clinical experience. Integration of outcome markers using these novel techniques into data registries will be aided by standardisation of timepoints for assessment and treatment protocols. This could allow investigations into effects of interventions compared with defined control groups[122]. Data sharing of existing and future research studies on open-access platforms, such as Project Data Sphere used in cancer trials, could have numerous benefits for CF if established[123]. Making control data freely available has the potential to reduce placebo group numbers, a particular challenge for studies performed in young age groups, and those using techniques with ionising radiation.

### 4.5 Multicentre collaboration

Multicentre collaboration, including different age ranges and techniques, is vital to ensure future research studies are appropriately designed to address the key questions remaining for early disease detection and monitoring (Table 2). Observational studies that characterise natural disease progression[21] and adequately powered intervention studies[16] that demonstrate disease reversal, or prevention of progression, will be important. Collectively these studies will determine the optimal age and stage of disease for intervention. Comparisons of novel techniques with existing clinical monitoring tools and age-appropriate quality of life measures[124] is required.

## 5 Incorporating new techniques into clinical practice

### 5.1 Are these tests ready for clinical use?

Pre-requisites for clinical utility include widespread availability, feasibility, repeatability and sensitivity, using standardised protocols and equipment. Many of the tests discussed above satisfy several of these fundamental criteria. Questions remain, however, regarding optimal choice, frequency and timing at different clinical stages, and how to interpret results to guide clinical management.

Clinical experience with LCI is emerging[20,125], as well as the challenges faced when incorporating into busy clinics and younger pre-school age groups[126]. The optimal age to start and frequency for MBW monitoring has not been defined, and younger age-groups such as pre-schoolers present specific challenges[126]. Use of LCI at annual

review in young children or those with normal $FEV_{1,}$ has begun to appear in management recommendations[127-129]. Before clinical use can be universally recommended, further studies are needed to define clinically meaningful change in acute and chronic CF care (particularly exacerbations), ways to reduce testing time, and guidance around the use of LCI in clinical disease surveillance.

CF clinical care already uses CT: 75% "used CT scans regularly" in a recent questionnaire survey across 25 participating CF centres in Europe and Australia[117]. Whilst recent studies have illustrated the utility of CT in clinical decision making[116,117] and initiating management changes[117], whether regular CT surveillance improves health outcomes is unclear. Before routine CT surveillance can be recommended, clinical guidelines are required to address optimal timing and frequency of surveillance. Biennially has been recommended by some authors[130].

MRI and oscillometry are still not sufficiently validated for integration into routine CF clinical care. MRI is resource intensive, expensive and widescale use across clinics might not be feasible despite the lack of ionising radiation. Protocols enabling free-breathing data acquisition and a shorter examination time may address concerns regarding need for sedation in younger children. Oscillometry is less expensive and more feasible within busy clinics than MBW, but what the data tells us about CF disease and progression is uncertain.

### 5.2 Organisational challenges

Implementing novel surveillance techniques into clinical practice will be largely governed by the size of the clinic population (influencing frequency and timing of measures). Physical and staff resources available to accommodate procedures (including training and education) are important factors. Implementation is contingent on robust partnerships with radiology, anaesthetists, respiratory scientists, health care professionals, patients and families. Prior engagement with stakeholders, including local regulatory bodies, is recommended to navigate financial, technological and logistic issues. CF infection control requirements are a primary consideration in the use of technical equipment and associated clinical areas. Time constraints placed around

testing may detrimentally affect feasibility[126,131] as well as need for general anaesthesia or sedation.

## 6 Impact on patients and families

The impact these measures have on perceptions of health, burden of care[26] and the psychosocial implications of disease detection must be addressed. Positive attitudes from parents towards infants recruited at NBS[132] and high adherence rates reported in recent infant[17] and preschool[16] intervention studies are encouraging. The generalisability of intervention trial settings to clinical practice is uncertain. Parental expectations of clinical benefit associated with enhanced surveillance techniques[132,133] and available therapies require careful management[134]. Discussion of limitations, roles and expectations of these techniques to avoid therapeutic misconceptions is important. Parental uncertainty about novel techniques, and anxiety related to perceived risks and safety[132,134], particularly around sedation for CT or MRI, highlight the importance of well-designed information resources and the role of CF psychosocial teams. They ensure patients and/or families are prepared and supported. Impacts on child and parent emotional well-being should be anticipated[133,134]. Policies that prevent and manage procedural distress should be incorporated into trials and clinical practice[135-137]. Routine screening of mental health and assessment of coping skills in caregivers (and children) from diagnosis[138], with interventions that promote psychological adjustment and effective coping are suggested[137,139].

## 7 Conclusions

The prevention of early lung disease is a priority for researchers, clinicians, CF patients and their families[30]. We currently possess tools and expertise that may be used to assess early lung disease progression. Future work must better define how and when to incorporate different testing modalities, the parameters to use, and the frequency of testing for clinical use and research outcomes. We must advocate for properly designed, rigorously conducted, interventional studies in mild disease, especially in young children, and advise against regulatory submissions of safety data or extrapolated efficacy data from older age groups only. Trials in young subjects with CF and early lung disease in general are poorly served by current regulatory endpoints, which should instead be based on the techniques described in this manuscript. Advances in

understanding around the evolution of early CF lung disease present an exciting opportunity to prevent structural damage and slow the ongoing decline in lung function that we have failed to prevent to date. Intensification of monitoring in this setting is justified if the correct balance is achieved between burden, gaining useful clinical information and creating opportunity to intervene and improve outcomes. In an era of wider access to highly effective CFTR modulator therapies, the ability to detect the evolution of early disease and its response to intervention will be of increasing importance.

## Figure Legends

**Figure 1.** Changes in median $FEV_1$ percent predicted by age across successive birth cohorts. No further increase was achieved in comparing the last two birth cohorts and to date no improvement has been achieved in the subsequent rate of decline, suggesting that the foundations of lung disease are established at an earlier age. CF Foundation registry data. (2017 report)[140].

**Figure 2.** CT images from a CF adult, before (left) and after (right) ivacaftor treatment. There was a reduction in the degree of peribronchial wall thickening and foci of mucous plugging in the left and right lower lobes, and resolution of right middle lobe medial segmental consolidation and collapse. Reprinted with permission from the publisher of Ronan NJ et al. CORK Study in Cystic Fibrosis: Sustained Improvements in Ultra-Low-Dose Chest CT Scores After CFTR Modulation with Ivacaftor. Chest. 2018;153(2):395-403. Licence number 4895361424485.

**Figure 3.** MRI images before (left) and 1-month after (right) intravenous antibiotic treatment for pulmonary exacerbation in a 6-year-old child with CF. Improvements were observed in airway wall thickening (white arrows), mucus plugging (white arrowheads), consolidation (black arrows) and perfusion abnormalities (black arrowheads). Reprinted with permission of the American Thoracic Society. Wielputz MO et al. Magnetic resonance imaging detects changes in structure and perfusion, and response to therapy in early cystic fibrosis lung disease. Am J Respir Crit Care Med 2014;189:956–965. The American Journal of Respiratory and Critical Care Medicine is an official journal of the American Thoracic Society.

**Figure 4.** MRI imaging from four different CF children tested at two time points (1.3-2 years apart) using hyperpolarised gas ventilation MRI (helium-3 ventilation MRI) and MBW. Patients were clinically stable at both time points and had normal spirometry values. Localised ventilatory defects increased in size from baseline to visit 2 (white arrows). The values for Ventilatory defect percentage (VDP), and for LCI, assessed by MBW, at the time of each scan are shown alongside each image. Increases in VDP were accompanied by increases in LCI for subjects A and B, but not C and D.
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Smith L et al. 2018 Longitudinal Assessment of Children with Mild Cystic Fibrosis Using Hyperpolarized Gas Lung Magnetic Resonance Imaging and Lung Clearance Index. Am J Respir Crit Care Med;197(3):397-400. The American Journal of Respiratory and Critical Care Medicine is an official journal of the American Thoracic Society. Readers are encouraged to read the entire article for the correct context at [https://www.atsjournals.org/doi/pdf/10.1164/rccm.201705-0894LE]. The authors, editors, and The American Thoracic Society are not responsible for errors or omissions in adaptations.

## Tables

**Table 1:** Summary of key priorities from the meeting

| Priorities |
|---|
| **1. Amend current categorisation of early lung disease**<br>Significant functional and structural lung disease can be detected with more sensitive techniques. "Normal" and "mild lung disease" categories, defined as $FEV_1$ ≥90 and 70-89 percent predicted~~, respectively,~~ are inappropriate~~.~~ ~~given the significant functional and structural lung disease that may be present, detectable with the more sensitive techniques described.~~ Future classification and approaches must address this by~~,~~ utilising outcomes from the techniques described in this manuscript. |
| **2. Optimal detection of early lung disease to aid effective intervention ~~is a research and clinical priority~~**<br>Targeting "effective (treatments) in delaying or preventing the progression of lung disease in early life" is a leading ~~(ranked 4th of 10)~~ research priority for people with CF and healthcare providers ~~globally~~[26]. ~~Despite advances in CF management, there has been N~~no ~~change in the~~Our failure to change long-term rate of $FEV_1$ decline suggest~~sing foundations of~~ lung disease is~~are~~ established by early school age. Future research studies should address this concern to best inform future clinical practice. |
| **3. Use the tools~~s described~~ in well-designed intervention studies targeting early CF lung disease**<br>~~The~~ These techniques ~~described within this document are available and~~ offer ~~exciting~~ potential to detect and better understand the ~~the~~ complex ~~complex~~ relationships driving early lung disease ~~evolution~~. ~~Results pertain to~~~~They provide the information for the essential~~They enable clinical trials that we must perform to describe, intervene and prevent progressive lung disease. We must ~~are now in a position to~~ advocate for, and conduct, well-designed intervention trials in early lung disease across all age ranges, especially young children and infants. |
| 4. **Be aware, a~~ware of, a~~ssess, and actively try to minimise ~~the~~ impact on overall burden of care/treatment**<br>Reducing CF management burden ~~wa~~is ~~the~~a *top* research priority[26]. ~~We have a responsibility to~~ U~~u~~nderstand the experiences of patients/~~young children and~~ caregivers as we push for optimised early disease detection ~~and subsequent intervention~~ and ~~ensure~~ acceptability among the clinic population~~. Reducing CF management burden was the *top* research priority identified by the global~~ |

~~CF patient and healthcare community~~[26]. Optimal timing~~/ and~~ frequency of early surveillance ~~monitoring~~ is ~~not~~ unclear and a balance ~~must be achieved~~ between gaining ~~necessary~~ information ~~to inform clinical decisions~~ whilst minimising impact on patients~~the child~~ and families~~y~~ is necessary. ~~Opportunities across CF management to offset this increased testing burden must be considered.~~

5. **Design ~~research~~ studies with ~~combinations of~~ these tests to maximise the pathophysiological insight gained**

Effective early disease detection ~~and intervention~~ will not be possible with one single test~~ – there is no single silver bullet~~. Future work must harness technological advances, ensure collaboration across different~~ce~~ sites~~/ and~~ disciplines, and prioritise studies combining these techniques to answer key ~~research~~ questions. The complementary nature of ~~the~~ tools ~~discussed~~ should be used ~~harnessed~~ to better understand the underlying CF pathophysiology ~~of CF and the different patterns of pathophysiology encountered~~. ~~Each technique has intrinsic limits and we have to think very hard as to how we combine them and get the most out of them.~~

6. **Accurate understanding of the risk of radiation with surveillance CT is critical ~~when assessing its role in early lung disease detection~~**

Radiation c~~C~~oncerns ~~about radiation~~ are limiting ~~use of surveillance~~ CT use in research studies and CF ~~CF~~ clinical care. Radiation risks need~~s~~ to be accurately portrayed to ensure rational decisions and recommendations can be made and ~~that~~ radiation fears do not hamper integration into surveillance programs. The clinical and research benefits of CT should not be ignored ~~in discussions regarding radiation risk~~, nor should ~~discussion regarding~~ the risk cloud interpretation ~~or scrutiny~~ of research data.

7. **Integration of data ~~using these techniques~~ into CF Registries and data sharing open-access platforms ~~offer exciting opportunities top aid integration into clinical care~~**

Standardisation of timepoints for assessment and treatment protocols will increase the i~~I~~nsight ~~gained~~ from real-world experience and large-scale monitoring using these techniques through integration into global CF registries ~~can be optimised by standardisation of timepoints for assessment and treatment protocols~~. Data sharing of existing and future ~~research~~ studies on open-access platforms (including raw/control data) mean potential ~~could have numerous benefits for this field, including making control data freely available and potentially~~ reduc~~t~~ioning in~~the~~ numbers of placebo subjects~~. that have to be exposed to placebo medications in the future~~.

8. **Simplify the terminology associated with these techniques**

There is a need to simplify the language used to describe outcomes with these techniques to make terminology more straightforward for health care professionals to understand.

| |
|---|
| **9. Defining minimal clinically important difference ~~for these techniques is a research priority~~**<br>Understanding what constitutes the smallest meaningful change (outside of natural variability) for each technique (i.e. the minimal clinically important difference, MCID) remains poorly understood. Research studies must incorporate clinically relevant outcomes to aid this. |
| **10. Optimise future progress through multidisciplinary collaboration**<br>Regular meetings to establish and maintain collaborative networks targeting advances in early disease detection in CF are essential to achieve effective integration into clinical care. |

**Table 2:** Focused Questions or Challenges for the future of these techniques; research and clinical (Priorities for future collaborative research)

| | **Top 5 Research Questions or Challenges** |
|---|---|
| **1** | What is the pathophysiology of early lung disease? |
| **2** | What features are the best predictors of lung disease progression or the best outcomes for assessing response to treatment? |
| **3** | What is the optimal combination of techniques and outcomes to use in the setting of different research questions? |
| **4** | What is the minimal clinically important difference for the techniques and outcomes discussed? |
| **5** | Standardisation of techniques including minimising the impact of differing hardware and software across sites for multicentre studies. |
| | **Top 5 Clinical Questions or Challenges** |
| **1** | How to use these measures across different clinical scenarios i.e. long-term disease tracking vs. short-term changes and response to interventions. |
| **2** | What do the results mean clinically for individual patients? E.g. implications of gas trapping, or change in LCI etc. What do the results mean in terms of predicting disease progression, and as markers of acute deterioration or response to intervention? |
| **3** | What is the impact of these novel techniques on families and patients in both research and clinical settings? How can we best minimise impact and support patient and families? |
| **4** | How to overcome organisational challenges to deliver effective early disease surveillance. |
| **5** | How to make these techniques and their outcomes more user-friendly (simplify terminology, less expensive, less time consuming, less sedation etc). |

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