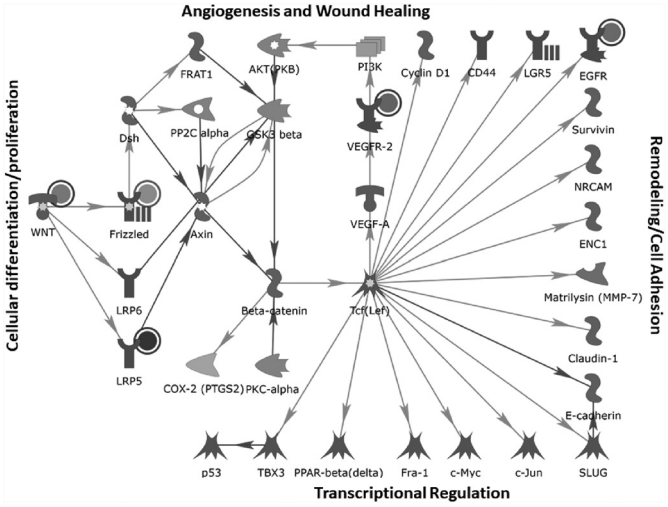

Figure 1. Pathway analysis comparing plasma protein expression before ivacaftor initiation of lung function nonresponders and responders. MetaCoreby Clarivate, version 21.3 build 70400, pathway analysis software was used to analyze protein expression differences in individuals with cystic fibrosis (CF) before initiation of CF transmembrane conductance regulator modulation therapy using a standard stringent cutoff. Lung function responders had an increase in percentage predicted forced expiratory volume in 1 second of more than 5% 6 months after drug initiation. These analyses revealed wound healing, proliferation, and structural remodeling.

Conclusions: Before initiation of ivacaftor, there are protein differences between patients with lung function response sustained at 6 months and those without a change in lung function at 6 months. Pathway analysis reveals that these differences are associated with wound healing and cell migration, suggesting that differences in structural remodeling and inflammation before therapy initiation may affect lung function response and diminish the full benefit of therapy. By 6 months, pathway differences in nitrogenous compound metabolic processes suggest that differences in the processing of ivacaftor, an aromatic nitrogen-containing compound, may decrease the benefit of high-efficacy modulation of CFTR.

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QuestionCF 2022: Updating the top 10 research priorities for clinical research in cystic fibrosis

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Background: The top 10 research priorities for clinical research in cystic fibrosis (CF) were identified in 2017 through a James Lind Alliance Priority-Setting Partnership, engaging the patient and clinical communities [1]. Funders have adopted these priorities, leading to at least £23 million of funding in the United Kingdom alone. Much has changed in CF over the past 5 years, so we are undertaking a global update to identify priorities in post-modulator times.

Methods: Led by a multinational steering group representative of the patient and clinical communities, we have developed a new methodology. An initial questionnaire administered in January and February 2022 identified which of the 2017 priorities were still relevant and identified new questions to add. The questionnaire was available online in several languages and was promoted through our "QuestionCF" social media channels, plus professional, charity, and patient group partners. The new suggestions were checked and grouped, and umbrella questions were formed where possible. A second ranking survey administered in May and June 2022 asked individuals to select their personal top 10, and an online workshop involving representatives of the patient and clinical communities will agree on the updated top 10 priorities in summer 2022.

Results: We had 1,608 responses to the first survey from 1,370 individual respondents. Of these, 74% were from lay people (people with CF and their families and friends) and 26% from health care professionals and researchers in CF. The median age of people with CF answering (or with answers on their behalf) was 27 (range 0–79). Sixty-five percent of respondents with CF were on modulator therapies, with 14% not yet eligible. We had responses from 29 countries, including North America, Europe, New Zealand, Australia, Africa, and the Middle East. We had 971 question suggestions. We will present the results of the next stage and final updated top 10 priorities for clinical research in CF at the North American Cystic Fibrosis Conference.

Conclusions: Ours is the first James Lind Alliance Priority-Setting Partnership in any medical or disease condition are to update its priorities. We are working with the global community to keep CF research relevant and focused on the needs of people with CF.

Acknowledgements: This work was supported by the Cystic Fibrosis Trust and a Research England, Participatory Research grant.

Reference

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How frequently should the lung clearance index be measured in children with cystic fibrosis?

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Background: The lung clearance index (LCI) can identify individuals with cystic fibrosis (CF) at risk of subsequent lung function decline [1]. Some CF centers have implemented LCI measurements as part of a routine annual assessment, but it is unclear what the optimal monitoring frequency is and whether more-frequent LCI measurements (e.g., every 3 or 6 months) would increase detection of otherwise clinically stable individuals with deteriorating lung function.

Methods: In a prospective longitudinal study, 98 school-aged children with CF were followed, and LCI was measured every 3 months for 2 years. Study visits were categorized as clinically stable (respiratory symptoms judged to be representative of a participant's baseline) or as acute respiratory event visits (increased respiratory symptoms). The baseline LCI for each study visit to calculate a relative change was defined as an LCI measurement from a stable visit 3, 6, or 12 months before. A significant change was defined as an LCI increase of 10%, a threshold than can identify clinically meaningful changes in LCI [2]. We used generalized estimating equation models for linear outcomes to determine whether different testing intervals affected the magnitude of LCI change between stable visits and binary outcomes to determine the proportion of visits associated with a 10% or greater worsening in LCI.

Results: On average, LCI changes between stable visits were similar when a 3- (0.22%, 95% CI, −1.2–1.6%; reference group), 6- (0.45%, 95% CI, −0.1–2.0%; $p = 0.85$), or 12-month (1.44%, 95% CI, −0.13–3.0%; $p = 0.33$) baseline was used to calculate changes. On an individual level, a similar proportion of stable visits were associated with a 10% or greater increase in LCI when different baseline LCI values were used to calculate changes (3-month

baseline [reference group], n = 259, 13.2%, 95% CI, 8.8–17.7%; 6-month baseline, n = 204, 16.5%, 95% CI, 11.1–21.9%, $p = 0.31$; 12-month baseline, n = 171, 19.8%, 95% CI, 14.0–25.6%, $p = 0.05$), but significantly more acute respiratory event visits (including treated and untreated events) qualified as a 10% or greater worsening in LCI when the baseline was defined as a stable visit 6 months before (n = 109, 44.0%, 95% CI, 34.2–53.8%, $p = 0.008$) or 12 (n = 94, 42.8%, 95% CI, 32.3–53.1%, $p = 0.02$), compared with the reference group of 3 months before (n = 140, 28.7%, 95% CI, 20.7–36.7%).
Conclusions: More frequent LCI testing in clinically stable children does not result in greater detection of significant LCI changes than annual monitoring, although if LCI is being used to define worsening of lung function with acute respiratory events, shorter intervals between tests increase the precision of classifying events with worsened lung function.
Acknowledgements: Funding for the study was obtained from Cystic Fibrosis Foundation RATJEN16A0, Cystic Fibrosis Canada Grant 3187, and the Cystic Fibrosis Foundation Therapeutics Development Network National Resource Center (Center for Pediatric Lung Function).

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Elexacaftor/tezacaftor/ivacaftor treatment in pediatric cystic fibrosis lung disease reduces ventilation heterogeneity measured using hyperpolarized ^{129}xenon multiple-breath washout magnetic resonance imaging

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Background: Sensitive tools to monitor changes in early cystic fibrosis (CF) lung disease in children are needed to assess the efficacy of elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA). The lung clearance index (LCI), measured according to multiple-breath washout (MBW), can show treatment effects in pediatric CF [1] but is limited to whole-lung averages of ventilation, thereby missing regional information. Hyperpolarized ^{129}xenon magnetic resonance imaging (Xe-MRI) conducted in a MBW fashion (MBW Xe-MRI) yields maps of fractional ventilation (FV), a measure of percentage gas clearance per breath. The coefficient of variation derived from FV (CoV_{FV}) maps can be used to assess spatial ventilation heterogeneity [2]. By regionally quantifying gas replacement and ventilation heterogeneity, MBW Xe-MRI can potentially provide information about treatment response different from information from LCI. This work assesses the ability of MBW Xe-MRI to capture changes in CF lung disease in children treated with elexacaftor/tezacaftor/ivacaftor.
Methods: Seven children (median age 17, range 14–17.5) underwent two visits each (baseline, 1 month) at which nitrogen MBW and MBW Xe-MRI

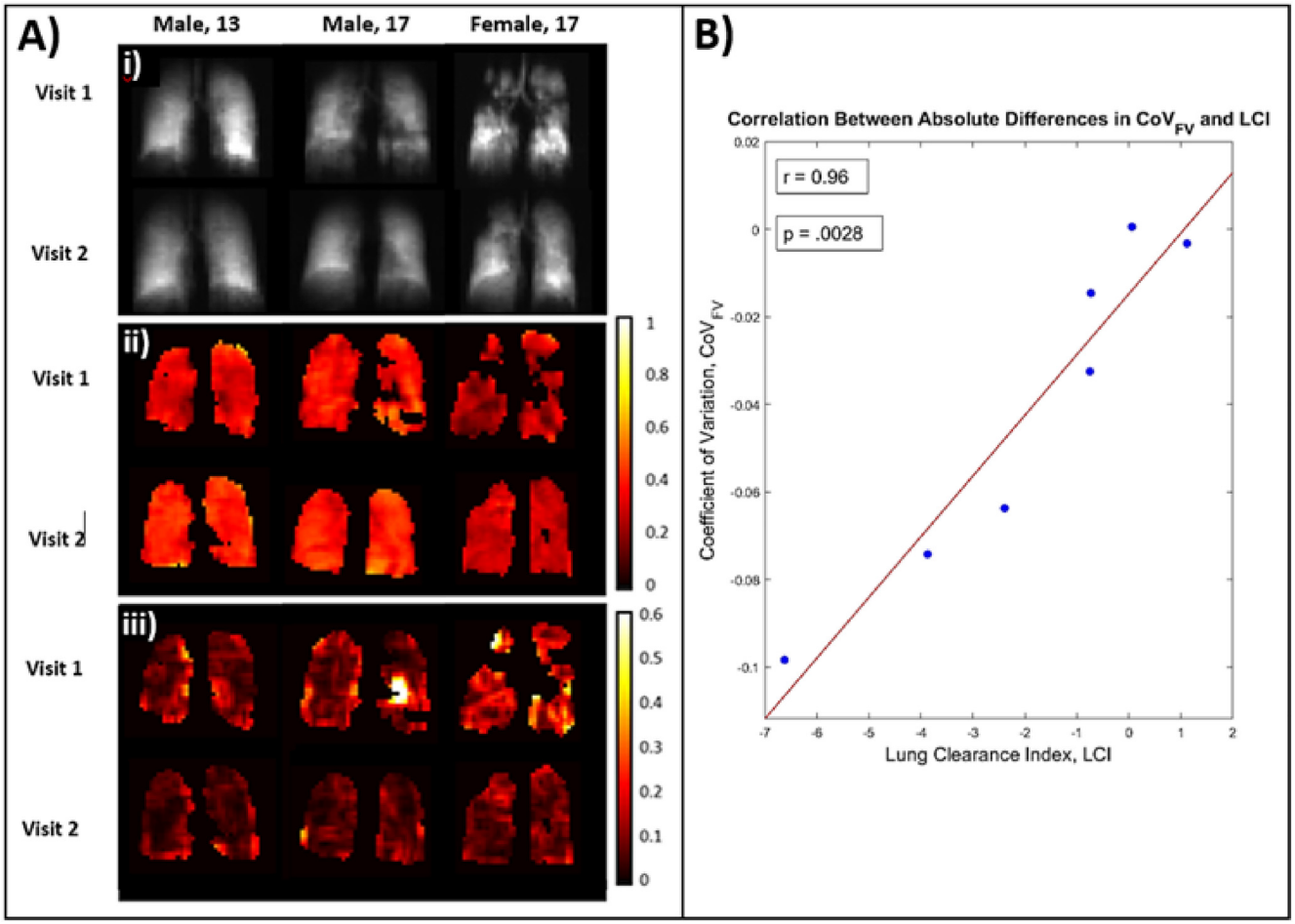

Figure 1 (abstract 177): Sample images and correlation: A) Three sample subject results from visit 1 (baseline) to visit 2 (1 month), with i) signal intensity images from first washout breath, ii) fractional ventilation (FV) maps, and iii) coefficient of variation FV (CoV_{FV}) maps. B) Correlation between absolute differences in CoV_{FV} and lung clearance index (LCI) values before and after treatment