# Guidance and standard operating procedures for functional exercise testing in cystic fibrosis

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**Functional exercise testing in cystic fibrosis (CF) lacks rigorous global standardisation in both choice of test and test conduct. Guidance is provided from the European CF Society Exercise Working Group to inform and harmonise global practice.** https://bit.ly/3PhSe4O

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## Abstract

Regular exercise testing is recommended for all people with cystic fibrosis (PwCF). A range of validated tests, which integrate both strength and aerobic function, are available and increasingly being used. Together, these tests offer the ability for comprehensive exercise evaluation. Extensive research and expert consensus over recent years has enabled the adaptation and standardisation of a range of exercise tests to aid the understanding of the pathophysiology related to exercise limitation in PwCF and has led to the development of novel exercise tests which may be applied to PwCF. This article provides expert, opinion-based clinical practice guidance, along with test instructions, for a selection of commonly used valid tests which have documented clinimetric properties for PwCF. Importantly, this document also highlights previously used tests that are no longer suggested for PwCF and areas where research is mandated. This collaboration, on behalf of the European Cystic Fibrosis Society Exercise Working Group, represents expert consensus by a multidisciplinary panel of physiotherapists, exercise scientists and clinicians and aims to improve global standardisation of functional exercise testing of PwCF. In short, the standardised use of a small selection of tests performed to a high standard is advocated.

## Stakeholder involvement in the development of these recommendations

A representative group from the European Cystic Fibrosis Society Exercise Working Group (ECFS-EWG), including members from the Physiotherapy Special Interest Group (PhySIG), comprised the writing group for this review, which aimed to develop guidance and standard operating procedures for an agreed selection of exercise tests that allow for the comprehensive functional evaluation of people with cystic fibrosis (PwCF). To facilitate test selection and, more specifically, a hierarchy of the most-used and best-validated exercise tests for PwCF, an international panel (n=64; 81.3% Europe), comprising physicians (5%), exercise scientists (14%), physiotherapists (78%), physiotherapy assistants and fitness instructors (3%), were also consulted *via* an online survey that aimed to obtain a snapshot of current practice compared to the evidence base. The survey was distributed to members of the ECFS PhySIG and

ECFS-EWG and responses are presented in the online supplementary material. From this, a proposed list of appropriate functional exercise tests for use in different subgroups of PwCF was developed, alongside guidance and standard operating procedures for running and reporting the selected functional exercise tests. Recommendation statements developed within this article were then presented to members of the wider ECFS-EWG at the January 2023 bi-annual meeting, with agreement/disagreement obtained. Further stakeholder feedback on the test instructions and reporting templates was provided by physiotherapy experts from CF Physio.com Inc. (https://cfphysio.com/).

## Introduction

National and international consensus documents recommend that standardised exercise testing is undertaken as part of routine assessment for all people with cysticfibrosis (PwCF) aged >10 years [1–3], with some suggesting that exercise testing should form part of the cystic fibrosis (CF) annual review [2, 3]. Exercise testing provides unique insight into cardiorespiratory health – information that cannot be assessed with static measures of resting lung function (*e.g.* spirometry, multiple breath washout or chest imaging). With the implementation of effective CF transmembrane conductance regulator (CFTR) modulator therapy, the clinical course for many PwCF is dramatically changing. These individuals still, however, are likely to require close lifelong follow-up and careful monitoring of their health status. As such, appropriately evaluating the physical (and physiological) function of all PwCF has perhaps never been as important as now.

Exercise testing allows for the assessment of an individual's functional abilities and the physiological mechanisms underpinning them. Exercise testing has a key role in identifying exercise-related adverse events (*e.g.* hypoxaemia or arrhythmias [4]), assessing interval changes in clinical status, predicting mortality [5], planning individualised exercise counselling and can be empowering and motivating to the individual with CF.

Focus to date has been on establishing standardised practice for cardiopulmonary exercise testing (CPET) – a fully integrated, objective assessment of the efficiency and performance of the cardiovascular, respiratory and musculoskeletal systems. CPET remains the first-choice test of aerobic exercise performance for PwCF, offering understanding of fitness levels and exercise-limiting factors, whilst opening up avenues for exercise counselling and the derivation of individualised training programmes [1]. Furthermore, several CPET-derived outcome measures have high prognostic utility [5–7]. The most recent European consensus statement on exercise testing in CF, endorsed by the European Respiratory Society (ERS) [1], recommends CPET as the test of choice for routine monitoring and assessment of exercise-related symptoms for PwCF. However, other standardised tests can be useful to assess aerobic fitness, integrated exercise performance or muscle strength – all of which are important considerations in PwCF.

Although the use of CPET is increasing in some countries [8, 9], CPET is not the only test of aerobic fitness and remains unavailable in many clinics for reasons of testing time, space, cost, expertise or clinician availability [10–14], as well as patient preference and certain pathogens prohibiting analysis of ventilatory parameters. Indeed, a recent UK-based survey [8] demonstrated that whilst exercise testing has increased from 54% of centres using some form of exercise testing in 2010 [10] to 94% in 2021, only 48% of these currently use CPET, despite considerable investment in the guidance for this (*e.g.* [1, 15, 16]). Given that over half of clinics are using exercise tests other than CPET, in line with findings in other countries (*e.g.* [9]), it is a priority for guidance to be in place to assist test choice (who and when to use a test for) and ensure standardisation of test conduct and outcome reporting (how to use a test). Understanding the clinimetric properties of each test and test limitations must also be central to such expert consensus guidance. Exercise testing is also about more than aerobic fitness; peripheral muscle strength and functional performance are also important, for example when determining individualised exercise training programmes for PwCF or evaluating changes over time.

## What are clinimetric properties and why do they matter?

"Clinimetrics" is a methodological discipline focused on the quality of measurements within medicine [17, 18]. It is essential to have measurement instruments that make it possible to detect clinically relevant improvements that are truly due to a change in clinical status or therapeutic interventions [19]. The quality of an outcome measurement instrument can be assessed by evaluating its measurement or "clinimetric" properties. In the context of exercise testing, the validity of a test (how accurately does a test measure what it is supposed to – ideally compared to a gold standard), reliability/reproducibility (the error of a test/measurement) and responsiveness (the ability of the test to detect change over time) are important. Understanding the clinimetric properties of exercise tests is important to ensure the quality of measurement and help inform selection.

Challenges lie in both improving the quality of measurement instruments and how people perform the measurements, as well as assessing their suitability for use in clinical practice [19]. It is intended that this ECFS-EWG guidance document will aid the improvement of both the global selection and the performance of appropriate functional exercise testing for PwCF. This work is intended to act as a companion to the 2015 statement on exercise testing in CF [1], which predominantly focused on CPET. Whilst clinimetric properties are not fully available for all exercise tests [20], best clinical practice is defined, including test instructions and templates for test reporting, for selected functional exercise tests for PwCF.

## CPET for PwCF

As recommended in the 2015 statement on exercise testing in CF [1], measurement of peak pulmonary oxygen uptake ($V'_{O_2peak}$) by CPET remains the gold standard method for evaluating aerobic fitness. CPET offers comprehensive assessment of ventilatory, circulatory and metabolic parameters at various exercise intensities and is the sole test to provide a thorough evaluation of any exercise limitations and potential risks. Since the 2015 statement [1], the clinical applicability and importance of CPET for people with chronic respiratory disease has been strengthened and further documents are now available for test conduct [15, 16] and reporting [14]. It is accepted that CPET testing protocols for individuals with respiratory disease, including PwCF, may include linear ramp or stepwise minute-by-minute incremental exercise testing protocols, with preference for cycle ergometer over treadmill testing in PwCF [1, 15]. To improve standardisation and comparability of CPET data between studies, peak exercise data are ideally reported as 30 s averages of the interval with the highest 10–15 s oxygen uptake values taken to represent $V'_{O_2peak}$.

The known prognostic importance of CPET for PwCF [6, 7, 21] is further cemented by long-term, international follow-up data from 433 PwCF [5], demonstrating that, in addition to lung function (forced expiratory volume in 1 s ($FEV_1$)), several key predictors of mortality are derived from CPET (*e.g.* $V'_{O_2peak}$, peak power output ($W_{peak}$) and the ventilatory equivalents for oxygen and carbon dioxide) – strengthening the clinical applicability and prognostic utility of this exercise testing method. There is, however, also a greater awareness of the need for standardisation of CPET in respiratory disease, in order to reduce variability in test conduct and reporting between centres [15, 22]. For example, criteria for acceptance of maximal exercise tests are outlined in the ERS exercise testing task force statement [15], along with guidance for the CPET reporting structure.

The range of reference values available to those reporting CPET has also increased, enhancing interpretation of CPET data [23–25], though it is pertinent to note the limitations of reference data and the interpretation problems which may arise if reference values are applied incorrectly [26]. Finally, some centres have advocated for an additional phase of CPET testing, known as supramaximal ($S_{max}$) verification testing, to test the validity of acquired "maximal" CPET data [27–30]. However, at present, $S_{max}$ remains a research tool in CF.

## Exercise testing without gas exchange measures

In situations where CPET is unable to be performed (*e.g.* due to lack of time, staff, equipment or infection control considerations), $W_{peak}$ testing using a cycle ergometer (ramp or minute-by-minute stages; see online supplementary material) is recommended as a testing option. $W_{peak}$ is associated with key prognostic outcome measures in PwCF [5] and such testing also enables additional physiological measures to be collected (*e.g.* heart rate (HR) and oxygen saturation ($S_{pO_2}$)) alongside perceptual measures of exertion and dyspnoea [1]. Whilst a stand-alone treadmill test can also be performed instead of CPET, this modality of testing does not provide a measure of power output, and the minimal clinically important difference (MCID) for treadmill testing outcomes (speed and gradient) and association with clinical outcomes are less clear than for cycle ergometry. For these reasons, cycle ergometer $W_{peak}$ testing should be preferentially considered in such situations.

## Suggested functional exercise tests considered suitable for PwCF

The value of alternative exercise tests *(i.e.* not CPET; rather field and localised peripheral muscle function tests) for PwCF should not be discounted. Such tests have been performed in settings where time, space, equipment and cost are barriers to CPET, but a complementary role (*e.g.* more frequent interval assessment and provision of complementary information) to CPET should also be an indication for such tests.

It is also of note that $V'_{O_2peak}$ is hard to improve and is not the most sensitive marker when looking at physical fitness improvements following exercise training programmes and, at times, alternative tests may be more appropriate. Importantly, alternative exercise tests should not be considered as simply a cheap "replacement" for CPET. The utility of and information provided by some of these tests are different from

those from CPET, *e.g.* the 1-min sit-to-stand (1-min STS) test integrates both aerobic and strength measurements and can be useful in measuring interval improvement following a training intervention.

Field-based exercise tests, including shuttle and step tests, can be used to measure aerobic fitness in PwCF (see [31] for a contemporary review), whilst the 1-min STS test is a measure of functional exercise performance. These tests are portable and low cost, but offer limited information regarding the cause(s) of exercise intolerance when compared with CPET. Where only a single exercise test is possible, teams should focus on prioritising a test of aerobic fitness where possible, with the 1-min STS test reserved for guiding exercise prescription or interim functional assessments in those with more severe lung disease or deconditioning [32, 33], or during periods of telerehabilitation [34] and exercise training. However, as outlined earlier, where time allows, a combination of a test of aerobic fitness alongside integrated tests of functional performance and peripheral muscle function is desirable. For each of the selected tests, test instructions and templates for test reporting (online supplementary material), a summary of their respective clinimetric properties (table 1), as well as a decision-making algorithm (figures 1 and 2) have been provided.

In this section, an update is provided on those tests for which sufficient data on clinimetric properties (*e.g.* validity, reliability and responsiveness to change) are available, alongside test instructions and templates for test reporting, to facilitate global standardisation. A recent clinical trial of CFTR modulator therapy [35] highlighted the need to ensure strict standardisation and calibration methods are always followed to minimise measurement variability for CPET. The same strict standardisation procedures (highlighted in this article) should be applied to alternative tests of function, irrespective of their complexity, particularly as a recent UK-based survey [8] reported that 93% of centres using exercise testing are performing "field tests" either as their first-choice exercise test or additional to CPET.

## Tests of aerobic capacity for PwCF

### *6-minute walk test (6MWT)*

The 6MWT is a functional exercise test that requires a person to walk up and down a 30-m corridor, covering as much distance as possible in 6 min. Across Europe, the 6MWT remains one of the most commonly used exercise tests within clinical practice (see table S3); however, it is grossly submaximal for most PwCF unless they have severe lung disease. Although it is still applied in young people with mild and moderate disease, with questionable usefulness [36], contemporary survey data suggests that it is preferentially used in adults with moderate-to-severe lung disease (see table S3).

Recent data in adults with severe respiratory disease suggests that the 6MWT is sensitive to change following CFTR modulator treatment [37, 38], suggesting potential utility for this group of PwCF. The utility of the 6MWT should now be restricted solely to those with advanced CF lung disease or as part of lung transplant assessment [39]. For PwCF with an $FEV_1$ <40% predicted, an annual 6MWT has been recommended, to assess the need for supplemental oxygen (note: quality of pulse oximeter signal is crucial) as well as transplant referral need; with a 6-min walk distance (6MWD) <400 m suggestive of transplant referral, irrespective of $FEV_1$ [39]. Of note, this cut-off was established more than 20 years ago in a cohort of 145 individuals with six different chronic respiratory diseases including 41 PwCF [40]. More recent data from a French cohort of PwCF (n=286, median $FEV_1$ 45% pred) found that a cut-off value of <475 m predicted death or lung transplant [41]. Since these thresholds were generated prior to highly effective CFTR modulator treatments, it is necessary to properly re-evaluate the prognostic value of 6MWD in a prospective study.

For those undertaking the test, technical standards have previously been published by the ERS/American Thoracic Society (ATS) [42] and practical test instructions and templates for PwCF have been provided in the online supplementary material. There is a learning effect and variability associated with this test and two tests should be undertaken on the first occasion, with the 6MWD used to guide decision making [43–45]. These two tests can be performed on the same day; however, there must be an interval of ⩾30 min between tests and measures of HR and $S_{pO_2}$ must have returned to baseline prior to the second test [42].

Given the volitional nature and absence of gas analysis, symptom scores and HR percentage predicted scores should be considered to gauge effort. Clinimetric properties and limitations for this test are available in table 1 and should be considered when determining if it is appropriate for a given indication (figure 1). Importantly, most of the studies investigating clinimetric properties of the 6MWT in CF were conducted decades ago [33, 46–48] and urgently need updating.

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**TABLE 1** Summary of the clinimetric properties, target population and limitations of field-based functional exercise tests

| Exercise test | Measures | Validity | Reliability | Responsiveness | Target population | Strengths and limitations |
|---|---|---|---|---|---|---|
| **Cycle ergometry ($W_{peak}$)** | Peak power, continuous $S_{pO_2}$, HR, breathlessness, leg effort, recovery | Predictor of prognosis [2, 3] (death, lung transplant)<br>Positive (weak) correlation with HRQoL scales [4] | Reliable when familiarised with the test [5, 6] | Responsive to high physical activity and exercise training [7, 8] | Children (⩾5 years) and adults covering the entire spectrum of lung disease severity | Not much space required<br>Ability to test PwCF with CF-related pathogens<br>Prognostic value of similar magnitude as $V'_{O_2peak}$<br>Test can be done with supplemental oxygen<br>Continuous monitoring of ECG and $S_{pO_2}$ |
| **6MWT [9]** | Distance, continuous $S_{pO_2}$ [9], HR, breathlessness, leg effort, recovery | Able to discriminate between PwCF and healthy controls<br>Lower exercise response compared to other field tests<br>Moderate evidence for construct and content validity in adults and children with CF [10–12] | Reliable once learning effects are ruled out<br>Test–retest reliability when two tests undertaken [13–19] | Most responsive in people with more severe lung disease; minimal clinically important difference: 33 m [10] | Lung transplant assessment<br>People with advanced lung disease, including those prescribed some modulator medication<br>Interim functional assessments in people with advanced lung disease or in those who are deconditioned [10, 20–23] | Volitional, not externally paced, constant workload<br>Test can be done with supplemental oxygen<br>Substantially less information about the cause of exercise intolerance compared to laboratory-based exercise tests<br>Insufficient cardiorespiratory response and ceiling effect in children with normal lung function and fit adults with CF [22, 24–26]<br>Requires 30 m floor<br>Risk of transmission of pathogens while exercising on the hospital floor |
| **MST-15 [27]** | Level, HR, breathlessness, leg effort, recovery | Comparable $V'_{O_2peak}$, MSTD, HR and breathlessness compared to CPET (treadmill) [28]<br>Moderate evidence for criterion, construct and content [25, 29, 30] | Reliable<br>Inconclusive data on learning effect [9, 31, 32]<br>Test–retest reliability [25, 33–35] | Responsive to hospital and home-based exercise therapy [25, 34, 36–38]; minimal clinically importance difference in children and adolescents with CF: 97 m [34] | Interim functional assessments (MST-25) [10]<br>People with moderate and advanced lung disease | Requires space (⩾15 m)<br>In people with mild lung disease, 40% would complete all 15 levels of the MST [39]<br>It is very challenging to conduct the test with supplemental oxygen<br>Infection control guidelines may preclude conducting the test in certain individuals in the hospital setting |

Continued

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**TABLE 1** Continued

| Exercise test | Measures | Validity | Reliability | Responsiveness | Target population | Strengths and limitations |
|---|---|---|---|---|---|---|
| **MST-25 [40]** | Level, HR, breathlessness, leg effort, recovery | Strong correlation between MSTD and $V'_{O_2peak}$ in children with CF [35, 40] | Reliable<br>Test–retest reliability [10] | Responsiveness unclear [39] | Physically fit people with mild-to-moderate lung disease | Requires space (⩾15 m)<br>Few published studies reported on the 25-level version of the MST<br>It is very challenging to conduct the test with supplemental oxygen<br>Infection control guidelines may preclude conducting the test in certain individuals in the hospital setting |
| **1-min STS** | Repetitions, HR, breathlessness, leg effort, STS power index | Moderate-to-strong correlations with $V'_{O_2peak}$ and $W_{peak}$ in adults [41, 42]<br>Moderate correlations with quadriceps muscle strength in adults with CF [43]<br>Moderate correlations with 6MWT distance in children with CF [13]<br>No correlation between 1-min STS and quadriceps strength and maximal mouth pressures in children [13] | Substantial learning effect (*i.e.* 18% improvement between first and second test) in adults with CF and children with CF (*i.e.* 3.1 (95% CI 1.3–4.9) repetitions) [13]<br>Reliable once learning effects are ruled out [41] | Responsive to exercise-based pulmonary rehabilitation; estimated minimal important difference: five repetitions [42] | People with moderate-to-severe lung disease and lung transplant candidates<br>Interim functional assessments [41–44] | Limited space requirements<br>Test can be done with supplemental oxygen<br>Continuous $S_{pO_2}$ measurement complicated due to motion artifacts<br>Minimal evidence for use in children |
| **Quadriceps muscle strength** | Maximal voluntary strength | Able to discriminate between PwCF and healthy controls<br>Correlation between quadriceps strength and 6MWT distance [45] | Reliable once learning effects are ruled out (less than 5 min) [46] | Responsive to strength training (*e.g.* [47]) | Interim functional assessments | Requires specific material (chairs with strain gauges)<br>No accepted normative reference values for use in CF |
| **Handgrip strength** | Maximal voluntary strength | Able to discriminate between PwCF and healthy controls although generally less affected than other muscle groups<br>Correlation between handgrip strength and $FEV_1$ [45] | No specific assessment in PwCF | Responsive to high-intensity interval training (*e.g.* [48]) | Interim functional assessments | Easy to conduct, no specific training required<br>Preserved handgrip strength may mask reduced quadriceps strength |

1-min STS: 1-min sit-to-stand; 6MWT: 6-min walk test; CF: cystic fibrosis; CPET: cardiopulmonary exercise test; $FEV_1$: forced expiratory volume in 1 s; HR: heart rate; HRQoL: health-related quality of life; MST: modified shuttle test; MST-15: modified shuttle test 15-level; MST-25: modified shuttle test 25-level; MSTD: modified shuttle test distance; PwCF: people with cystic fibrosis; $S_{pO_2}$: oxygen saturation; STS: sit-to-stand; $V'_{O_2peak}$: peak oxygen uptake; $W_{peak}$: peak work rate.

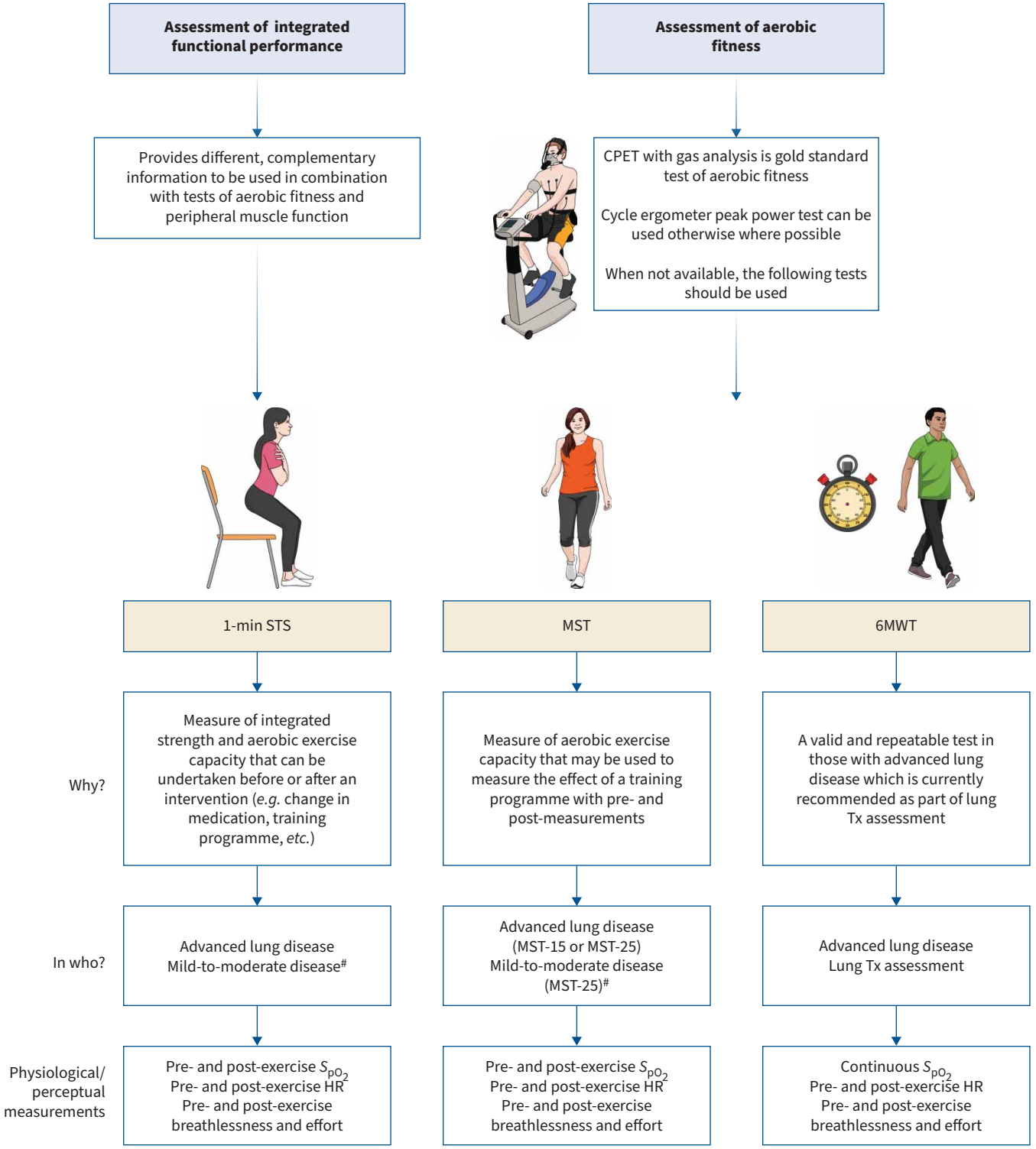


**FIGURE 1** Overview of functional tests of exercise performance (1-min sit-to-stand test (1-min STS)) and tests of aerobic fitness selected for use in people with cystic fibrosis. 6MWT: 6-min walk test; CPET: cardiopulmonary exercise testing; HR: heart rate; MST: modified shuttle test; MST-15: modified shuttle test 15 level; MST-25: modified shuttle test 25 level; $S_{pO_2}$: oxygen saturation; Tx: transplant. #: Ceiling effect is possible.

*Key message (6MWT)*

The 6MWT is preferably used in people with advanced CF lung disease or as part of lung transplant assessment.

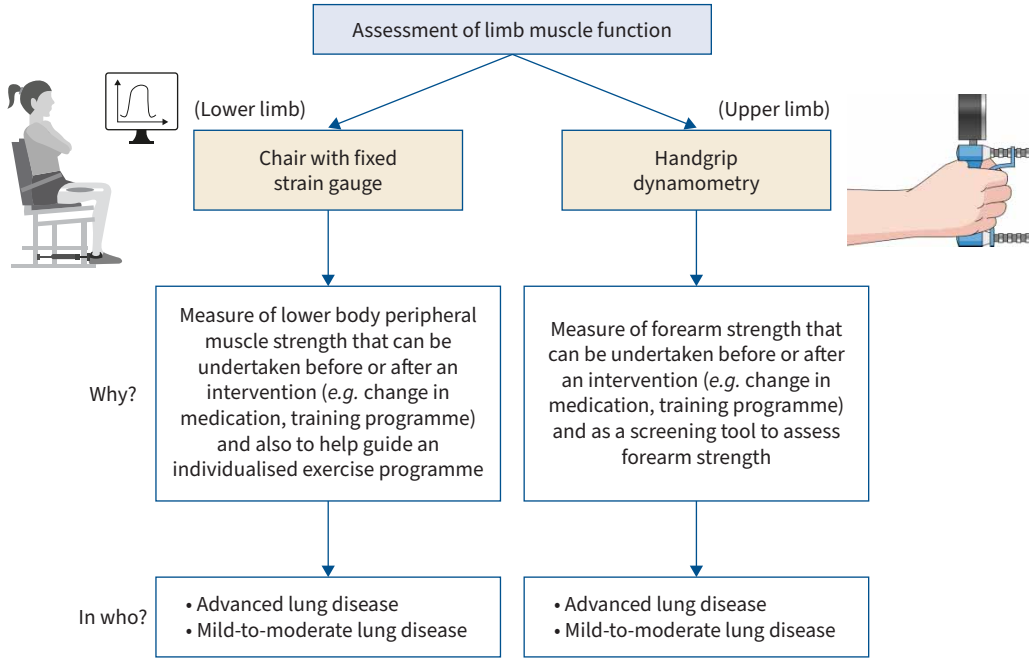


**FIGURE 2** Overview of limb muscle function tests of peripheral muscle function selected for use in people with cystic fibrosis.

### *Shuttle tests*

Certain tests (*e.g.* 25-level modified shuttle test (MST-25) [49]) are incremental, externally paced and have the potential to measure maximal exercise in PwCF; these tests would be better field tests than the 6MWT, especially in those with mild and moderate lung disease [36].

The incremental shuttle walk test [50] was originally composed of 12 levels each lasting 1 min and was modified to allow participants to run – the modified shuttle test (MST). The test involves running back and forth (shuttling) over a measured course, completing each leg of the test before a beep (or bleep) sounds. As the speed of the test increases, the participant is taken to levels close to exhaustion, with this (along with HR and $S_{pO_2}$ measures) offering some utility in evaluating their maximal exercise capacity [51]. The principal MST outcome (distance achieved on the test or shuttle level) is correlated ($r$=0.79) with $V'_{O_2peak}$ [52]; although the MST lacks precise measurement of whether effort was maximal and/or which physiological factor(s) limit the individual.

There are 20 m [51, 53] and 10 m shuttle tests available, with the 10 m MST available as 15-level (MST-15) [54–58] and 25-level (MST-25) [49] tests. The test is completed when the participant states that they are unable to continue or fails to make the course marker on two consecutive beeps. This standardised, externally paced 10 m shuttle walk test was developed originally for adults with COPD [50] and later adapted for PwCF, by allowing participants to run and increasing the number of levels to 15 with a maximum speed of 10.2 km·h$^{-1}$[54]. The modified shuttle walk test has been reported to have excellent test–retest repeatability for measures of distance covered, maximal HR, Borg score and $S_{pO_2}$ [56]. Despite these adaptations, the 15-level test remains submaximal for some adults with CF who exceed the 15th level [49] and will likely have ceiling effects in many younger PwCF. As such, the MST-25 may be the shuttle test of choice, with good test–retest repeatability and a potential to be maximal for all [59]; although at present this has only been published in abstract form [49]. Although research is urgently needed to provide further clinimetric properties of this test in PwCF, recent survey data supports the current use of this test in clinical practice across both adult and paediatric cohorts (tables S2 and S3). When considering these tests in children, it is important to use age-appropriate subjective measures of perceived effort and breathlessness (as outlined below).

Standardisation of test conduct enables test results to be transferable across differing clinical settings, in both adults and children, demonstrating a correlation with other parameters such as HR, muscle strength and lung function [51, 52, 54, 60–62]. Excellent test–retest reliability and an MCID of ~97 m was recently

reported for the MST-15 in children and adolescents with CF and well-preserved lung function [58] and the MST-25 has recently been shown to be a valid and reliable field test for the assessment of aerobic fitness in children with CF that can be used to assess fitness and prescribe exercise training when CPET is not available [59]. The MCID for the MST-25 is not known for younger and/or fitter PwCF and information concerning neither the MST-15 nor MST-25 is known for PwCF on modulators. The benefits of highly effective CFTR modulators may also improve exercise capacity and completion of the MST-25 may be seen in more PwCF. Reference equations for MST predictions for children [51, 52, 63], adolescents [52, 63] and adults [64] with CF can be found in the test instructions (online supplementary material).

Finally, the caveat that shuttle tests, if used to estimate maximal exercise capacity, lack the precision of CPET, must be recognised. Furthermore, due to motion artifacts, pulse oximetry readings may be compromised and no valid information may be available in a reasonable number of PwCF. Infection control issues may also preclude shuttle testing, especially in people with multi-drug resistant strains, and the 20 m version is impractical in most clinic settings.

*Key message (shuttle tests)*

The MST offers a standardised incremental load protocol that is maximal in some PwCF. Although there is a body of evidence supporting the 20 m version, this is impractical in most clinic settings. The MST-25 can be considered for use in all PwCF, particularly those who are fitter and for whom the MST-15 would elicit submaximal responses at test completion, due to ceiling effects. However, further research is needed to characterise the clinimetric properties of this test.

## Tests that are no longer suggested for use in PwCF

While other exercise tests are available, some have no clinical utility for PwCF. For example, the 3-min step test is a volitional, nonexternally paced test that is grossly submaximal for all except those with severe lung disease [17]. There is a lack of known measurement properties along with improved well-being in PwCF, each of which mean that this test no longer has a place in clinical practice.

## Integrated tests of aerobic capacity and muscle strength for PwCF

### *1-min STS test*

Sit-to-stand (STS) tests are frequently applied in chronic respiratory diseases, including CF. Different versions of STS tests are now available, of which the 1-min STS test is the most frequently studied in respiratory disease and for which good data on clinimetric properties are available [44, 65]. Unlike the tests discussed thus far, which are focused on primarily measuring aerobic fitness, the 1-min STS test measures various components of functional capacity, including muscle strength, muscular endurance, coordination skills and postural control. The 1-min STS test appears to be a promising test for PwCF due to its short duration, portability and good correlations with the outcome measures from maximal tests of exercise capacity.

The 1-min STS test is a valid, reliable and responsive submaximal exercise test for PwCF [66–69] and simply measures the maximum number of times that a person can stand up and sit down on a chair in 1 min. Like all exercise tests, it depends on participant effort – perhaps more so in this test which is self-paced rather than externally paced. In adults with CF, 1-min STS repetitions show moderate-to-strong correlations with $V'_{O_2peak}$ and $W_{peak}$ [66, 67], key prognostic markers in PwCF [5], as well as moderate-to-strong correlations with quadriceps muscle strength [66–68, 70]. The test may be used as a screening test for oxygen desaturation [66, 68], although it is less sensitive than exhaustive CPET [68], and to follow muscle weakness in PwCF [70]. Similar to other nonlaboratory "field" tests (*e.g.* the 6MWT), there is a clear learning effect for the 1-min STS test [44, 67, 71] that can even exceed the estimated minimal important difference of five repetitions in adults with CF [67]. Consequently, at least one practice 1-min STS test must be performed in naïve individuals to ensure a valid measurement of functional capacity. Currently, it is not clear how much recovery time is needed to recover after a 1-min STS test before a second test may be conducted without compromising performance. Based on data from the Wingate test (a 30 s cycling test of anaerobic power), 10 min has been suggested as suitable recovery time for healthy children and 20–30 min in more severe disease [1] and at least 15 min "between-test" recovery has been used in research studies involving the 1-min STS test (e.g. [67]), which is in line with ERS/ATS technical standards for other field tests [42]. At present, we suggest that if two tests are performed on the same day, ~30 min would allow for sufficient recovery.

*Key message (1-min STS test)*

The 1-min STS test offers a safe and feasible integrated test of both aerobic and muscle performance, making it a desirable functional test that may complement aerobic testing. Two tests should always be

completed in naïve individuals given a known learning effect. It should be noted that this test is measuring integrated exercise performance rather than assessing maximal exercise capacity.

Whilst some indirect assessment of muscle strength is provided by the 1-min STS test, more detailed strength assessments or direct measures of peripheral muscle strength may be required; for example, when developing or assessing a strength training programme.

### Tests of localised peripheral muscle function for PwCF

Physical activity and exercise training should be part of the routine management of all PwCF [72], with structured exercise training being a combination of both aerobic and resistance exercise [73]. It is therefore important that there are modalities of exercise testing to allow measurement of both of these components of fitness (aerobic fitness and muscle strength/function) over time.

Strength tests, including handgrip and knee extension, can be quick and easy to administer, although such testing has to date been underused in PwCF, particularly within clinical practice (see online supplementary material) and as an end-point in clinical trials, despite skeletal muscle dysfunction being common [74], even in those with mild lung disease.

While respiratory muscle function is often preserved in CF [75], limb muscles can be more severely affected, including increased fatigability, reduced endurance and strength; the latter being a common feature in both children and adults with CF [74] and associated with poor clinical outcomes [76]. Assessing changes in muscle strength may become important in the increasingly overweight population of PwCF, whereby high body mass index may mask depletion of functional fat-free mass even in mild CF [77]. Limb muscle weakness and understanding changes in muscle strength and body composition may have a role in understanding responses to CFTR modulator therapy.

Limb muscle strength can be measured using dynamic or isometric measurements targeting the upper or lower limbs. Most studies have focused on lower-limb muscles (*i.e.* knee extensors), as they are particularly vulnerable to change in PwCF (*e.g.* steroid use and/or pro-inflammatory state) and directly influence the performance of various locomotor activities [74]. Equipment, space and expertise available will play a key part in determining the most appropriate test of muscle function in PwCF. Dynamic measurements (*e.g.* isokinetic contractions) require expensive computerised dynamometry that will likely not be accessible in most CF clinics. With other procedures, such as isotonic strength (*e.g.* one- or five-repetition maximum testing using gym-based resistance machines [78]), the clinimetric properties are unknown for PwCF.

At present, chairs with fixed strain gauges offer a relatively inexpensive and valid alternative procedure to computerised dynamometry in chronic respiratory disease to measure quadriceps muscle strength [79] and have high test–retest reliability in adults with CF [80]. Fixed strain gauges can also be used to capture muscle strength independent of an individual's motivation and effort (*e.g.* muscle twitch following magnetic nerve stimulation in the resting muscle), which may be useful in situations where increased symptoms may interfere with the validity of volitional strength procedures (*e.g.* during hospitalisation for an exacerbation [81]). When used with real-time visual feedback, fixed strain gauges can also be useful to assess local muscle endurance and fatigability [82]. However, it should be noted that although normative reference values for knee extensor strength exist for both children and adults [83, 84], there are currently no widely accepted equations for use in CF.

Handgrip strength is a measure of muscle strength or, more specifically, the maximum force/tension that an individual can generate using their forearm muscles and a dynamometer device. Handgrip strength tests are logistically very easy to perform and often also used as an indicator of nutritional status. Measuring handgrip strength may offer a simple alternative global indicator of muscle strength and has been used in both adults and children with CF (*e.g.* [58, 85–92]). It is, however, important to note that upper-limb strength is generally less affected than lower-limb strength in PwCF [93] and thus normal handgrip strength does not necessarily imply preserved quadriceps strength. Handgrip strength offers a very simple and inexpensive functional assessment for PwCF and should be considered rather than conducting no assessment of peripheral muscle strength; however, future work needs to evaluate its clinical usefulness in CF. While several reference values are available, it is important to consider their potential dependence on the device used to measure handgrip strength (*e.g.* [94]).

Some practitioners are now starting to incorporate tests of muscle function within clinical evaluations (see the online supplementary material). It should be noted that limited information exists on the clinimetric properties of measures of muscle function [43]. Research is urgently needed to obtain more information

regarding the clinimetric properties of the range of available tests of peripheral muscle function, especially for some specific outcomes currently restricted to research settings (*e.g.* muscle endurance and fatigability [95]), to inform which tests should be incorporated into clinical practice and their value. Given this need to establish standard procedures for measurements and equations to predict normal values across the age and disease severity spectrum of CF, detailed test instructions have been provided in the online supplementary material to initiate this process.

### *Key message (peripheral muscle testing)*

Research is urgently needed to inform the choice and clinical usefulness of muscle function tests. Chairs with fixed strain gauges offer a relatively inexpensive, valid alternative to computerised dynamometry for the measurement of quadriceps strength. Handgrip dynamometry offers a simple and inexpensive assessment of distal muscle strength, but reduced handgrip strength should not be considered as a surrogate of reduced strength of proximal muscle groups. Peripheral muscle testing can be considered complementary to tests of aerobic fitness and functional performance.

## Standardising subjective assessments during exercise testing in PwCF

A variety of adult and paediatric numerical and pictorial scales exist to evaluate subjective ratings of exertion and dyspnoea during exercise testing; however, a lack of standardisation is common. Suggestions are herein provided to assist in the standardisation of these two key measures. Exertional dyspnoea, defined as a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity, is an important exercise-limiting symptom in PwCF [96]. There is growing awareness of the clinical importance of dyspnoea, which may be assessed using a range of self-report visual scales. A pictorial scale for people with respiratory disease that is being increasingly used in CF is the Dalhousie pictorial scale [97–99].

The Dalhousie scale consists of a sequence of seven pictures, depicting three dyspnoea constructs, namely chest tightness, throat closure and breathing effort, plus an additional pictorial scale depicting leg effort [97]. This scale has been reported to accurately track dyspnoea and perceived exertion and to strongly correlate with ventilation and work intensity in both children and adults with and without respiratory disease [98–100], including CF [96]. Indeed, the pictorial nature of this scale ensures that it is applicable across the age range, including in children in whom the use of descriptions and/or numbers to delineate dyspnoea and exertion are generally less reliable. It is pertinent to note, however, that irrespective of the scale selected, they are inherently reliant on the ability of an individual to be able to arrange and understand items in a sequence according to prescribed criteria, which typically develops around 7 years of age [101]; ratings of dyspnoea and exertion are therefore discouraged in children <7 years of age.

### *Key message (subjective assessments of exercise intensity)*

Standardised measures of perceived effort and dyspnoea (breathlessness) should accompany all exercise tests, whether they are CPET or more functional tests. The Dalhousie scale as the most suitable for universal use in PwCF for its correlation with measures of ventilation and work intensity on CPET including in PwCF. Subjective assessments are not considered suitable for those aged <7 years.

## Which field test for who?

As outlined above, numerous different functional exercise tests exist that are suitable for use with PwCF in routine clinical practice. The choice of test depends on test indication and clinical characteristics of the individual (*e.g.* age, lung disease severity and comorbidities). Importantly, there is no "one-fits-all" approach when performing exercise testing in PwCF. The first and most important step, however, is to define the reason for testing (test indication) and what you plan to do with the test information – as this will directly influence what exercise testing data is needed.

Test indications include:

1) General assessment of functional exercise capacity and muscle function
2) Screening for exercise-induced oxygen desaturation
3) Assessment for lung transplantation
4) Evaluation of therapeutic interventions
5) Assessment of baseline exercise performance prior to implementation of physical promotion and/or an exercise training programme.

Although CPET is the gold-standard test for certain indications, it is not the test for all situations. It is important to acknowledge that functional tests, in comparison to CPET, are limited in their ability to clearly

identify different cause(s) of exercise limitation and exercise-induced risks (*e.g.* cardiac arrhythmias [4]) and may be less suitable for providing accurate aerobic exercise recommendations (*i.e.* using target HR based on the lactate threshold or oxygen saturation "safe zones"). Importantly, different tests serve different purposes and the choice of test should, wherever possible, be guided by its rationale rather than the testing equipment available – with functional tests complementing CPET. Field tests may be used as a screening tool for exercise-induced desaturation and not to confirm or exclude exercise-induced hypoxaemia. If the indication of the test is to assess hypoxaemia, cycle ergometry has the lowest rate of artefacts and is best applied; however, it should be noted that, when measuring at the fingertip, actions such as gripping the handlebars tightly and exercise-induced reduction of peripheral blood flow can impact signal quality. As such, measurement at the forehead or earlobe may be preferable to reduce signal artefacts [102–104].

Figures 1 and 2 provide a simplified decision-making flowchart to facilitate the choice of exercise test to be applied in the clinical setting for functional tests (figure 1) and those assessing peripheral muscle function (figure 2). Of note, $FEV_1$ alone is not a strong predictor of exercise capacity and some individuals with advanced lung disease can still have an exercise capacity close to normal. Nevertheless, a broad distinction of tests based on lung disease severity may help select the right test for an individual, allowing the clinical question to be answered appropriately. It is important to remember that, where possible, assessments of functional capacity (*e.g.* aerobic fitness) as well as more localised assessments of peripheral muscle strength are desirable.

Functional capacity tests (with the exception of the 20 m shuttle run and the MST-25) are submaximal for physically fit individuals, due to low cardiorespiratory demands and potential ceiling effects. Consequently, tests like the 6MWT are more useful for people with advanced CF lung disease and lung transplant candidates with more significant peripheral muscle dysfunction and ventilatory limitation. Post-transplant, when PwCF are typically limited by deconditioning and effects of medication rather than respiratory function, it is important to select a test based on what is intended to be measured.

Another clinically relevant aspect during exercise testing in clinical settings is infection prevention in regard to risk of transmission of pathogens (*e.g.* *Pseudomonas aeruginosa*, *Burkholderia cepacia* and *Mycobacterium abscessus*), with centres using disposable flow heads for CPET or undertaking $W_{peak}$ tests without breath-by-breath gas measures or other tests (*e.g.* the 1-min STS test and MST) in patients colonised with these organisms. Furthermore, exercise testing is an aerosol-generating procedure and required pre-test severe acute respiratory syndrome coronavirus 2 screening in recent times in most institutions. Resource use is also an important consideration in the clinical environment but, where feasible, should be secondary to test indication.

In addition to considering indications for testing, it is important to consider whether there are any contraindications (see table 2). Primary CF contraindications to testing would include pneumothorax, haemoptysis, musculoskeletal injury, pulmonary exacerbation and/or an inability to co-operate with the testing procedure. A more detailed set of contraindications related to cardiac and other pathologies, unchanged from the 2015 statement in CF [1] other than the additional considerations of pulmonary exacerbation and transmissible infections, is available in table 2. Further lists are also provided in previous CPET [15] and field testing [42] statements published by the ERS.

## Exercise testing in PwCF who have access to highly effective CFTR modulator therapy

CF has entered a time of change with widespread availability of highly effective CFTR modulator therapy. In Western Europe, PwCF aged ⩾6 years with at least one copy of the F508del mutation are eligible for the triple combination therapy elexacaftor–tezacaftor–ivacaftor (ETI).

ETI improved $FEV_1$ by 10–14% in clinical trials, with concomitant improvements in weight and quality of life [105, 106]. It is postulated that improved CFTR function in lung and gut confers these benefits, with CFTR expression in muscle and bone also likely to increase. PwCF on ETI may, thus, be physiologically advantaged with improvements in ventilatory capacity, skeletal muscle mass and mitochondrial density hypothesised [107]. Indeed, a recent case report [108] demonstrated improved exercise capacity following only 6 weeks of treatment, with improvements greatest in the presence of more severe CF lung disease and lower aerobic fitness at baseline.

There is a unique opportunity to understand the "before" and "after" of exercise physiology in those on ETI and future therapies. Careful consideration needs to be given to the best exercise testing measurements for such studies (CPET, tests of muscle function), as well as avoiding pitfalls encountered by others (*e.g.*

**TABLE 2** Contraindications to exercise testing in people with cystic fibrosis

| Absolute | Relative |
|---|---|
| **Pulmonary disease** | |
| Pulmonary arterial obstructive disease | Significant pulmonary hypertension |
| Uncontrolled asthma | Pulmonary exacerbation |
| Pulmonary oedema | |
| Massive haemoptysis | |
| Large pneumothorax | |
| **Cardiac disease** | |
| Acute or unstable coronary heart disease | Left main coronary stenosis |
| Symptomatic and/or haemodynamic uncontrolled dysrhythmias | Moderate stenotic valvular heart disease |
| Acute or chronic cardiac inflammatory or infectious disease | Tachyarrhythmias or bradyarrythmias |
| Symptomatic severe aortic stenosis | High-degree arterioventricular block |
| Uncontrolled heart failure | Hypertrophic cardiomyopathy |
| **Vascular disease** | |
| Thrombosis of lower extremities | Severe untreated arterial hypertension at rest (>200 mmHg systolic blood pressure; >120 mmHg diastolic blood pressure) |
| Suspected dissecting aneurysm | |
| **Other** | |
| Acute noncardiopulmonary disorder that my affect exercise performance or be aggravated by exercise (*i.e.* infection, renal failure, thyrotoxicosis) | Advanced or complicated pregnancy |
| Mental impairment leading to inability to cooperate with procedures | Electrolyte abnormalities |
| Transmissible infections (*e.g.* SARS-Cov-2) | Orthopaedic impairment that compromises exercise performance |

Contraindications adapted from those presented by Hebestreit *et al.* [1] in the 2015 statement on exercise testing in cystic fibrosis. SARS-Cov-2: severe acute respiratory syndrome coronavirus 2.

ensuring standardisation of equipment, correcting measures for lean body mass and accounting for baseline fitness) [35].

## Future perspectives

There is clear evidence that exercise testing in all PwCF is of real benefit, not only for monitoring disease progression and the response to interventions, but perhaps more importantly in tailoring appropriate and individualised exercise programmes. Although the frequency of exercise testing in PwCF is steadily increasing across the globe, many clinical teams predominantly use tests other than CPET and lack standardisation (*e.g.* [8]). A contemporary update of the existing evidence and up-to-date best practical guidance has been provided in the hope of improving global standardisation.

As an increasing number of PwCF transition onto CF modulator therapy and CF survival continues to rise, it is suggested that a standardised, combined approach to exercise testing, using assessments of both aerobic fitness and muscle function is utilised. This represents an important next step in advancing the understanding of how the pathophysiology of CF, ageing and new treatments truly impact physical function, as well as moving closer to the goal of individualised exercise prescription and personalised medicine that incorporates the needs and wishes of PwCF.

Prospective (multicentre) studies are urgently needed to further understand the clinimetric properties of functional tests, in addition to clinical utility (*e.g.* prognostic value) using standardised, globally endorsed protocols. Such an exercise would be aided by using the standard operating procedures provided in this review. Improving the standardisation of exercise test selection, conduct and reporting will enable appropriate selection of additional outcomes that can contribute to CF registries and ensure that high-quality data is subsequently entered into them, thereby facilitating large registry-based studies.

The clinimetric properties of new tests being developed specifically for PwCF, such as the Alfred step test – A-Step [109] which is already being used in some clinics (see table S2), must also be established. Enhanced global practice will not only enable correct data interpretation and better care for PwCF, but also large-scale data acquisition, to understand the fitness of PwCF across the spectrum of disease and with varied treatment access; an approach already demonstrated as an impactful and cost-efficient use of time by authors of this consensus (*e.g.* [5, 110]). This will help us understand interactions between new considerations in CF (CF-related diabetes, overweight/obesity) and strength and fitness, as well as the future role of physiotherapy and exercise.

**Points for clinical practice**

- Functional exercise testing in CF lacks rigorous global standardisation in both choice of test and test conduct. This article provides expert, opinion-based clinical practice guidance from the European CF Society Exercise Working Group.
- Test indications may include establishing aerobic fitness, measuring integrated exercise performance and/or assessing muscle strength.

**Tests of aerobic fitness**

- CPET is the gold standard test recommended for the evaluation of aerobic exercise performance in PwCF.
- If a metabolic cart is not available or assessment of pulmonary gas exchange and ventilation is not possible due to pathogens, teams should consider undertaking a cycle-ergometer peak power ($W_{peak}$) test, with measures of heart rate, oxygen saturation, perceived exertion and breathlessness.
- The 6MWT is preferable for use in people with advanced CF lung disease or as part of lung transplant assessment.
- The MST-25 can be considered for the assessment of aerobic fitness when CPET is not available. This test is suggested for use in all PwCF, particularly those who are fitter and for whom the MST-15 would elicit submaximal responses at test completion, due to ceiling effects. Other shuttle tests available with 20 m tracks tests are often not practical.

**Integrated tests of functional performance and tests of peripheral muscle strength**

- The 1-min STS test offers a safe, feasible functional performance test. It should be noted that this test is measuring integrated exercise performance rather than assessing maximal exercise capacity and can offer additional complementary information to an aerobic exercise test.
- Peripheral muscle testing allows the determination of skeletal muscle strength. Research is urgently needed to inform the choice and clinical usefulness of these tests. Current available tests are outlined in this article.

## Summary and considerations

This review has outlined test properties for a range of functional exercise tests that can be undertaken for PwCF. The available evidence has been reviewed and a selection of tests is provided, along with test instructions and test report templates for how to perform and report exercise tests for PwCF, including flowcharts to assist with decision-making on test selection. This consensus aims to foster a culture of global standardisation within clinical practice, as well as enabling the development of large, multinational datasets for multicentre scientific analyses. Increasing standardised test provision will also aid the functional evaluation of changes in exercise performance for PwCF in the era of highly effective CFTR modulator therapy.

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