Addressing Reduced Laboratory-Based Pulmonary Function Testing During a Pandemic

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To reduce the spread of the severe acute respiratory syndrome coronavirus 2, many pulmonary function testing (PFT) laboratories have been closed or have significantly reduced their testing capacity. Because these mitigation strategies may be necessary for the next 6 to 18 months to prevent recurrent peaks in disease prevalence, fewer objective measurements of lung function will alter the diagnosis and care of patients with chronic respiratory diseases. PFT, which includes spirometry, lung volume, and diffusion capacity measurement, is essential to the diagnosis and management of patients with asthma, COPD, and other chronic lung conditions. Both traditional and innovative alternatives to conventional testing must now be explored. These may include peak expiratory flow devices, electronic portable spirometers, portable exhaled nitric oxide measurement, airwave oscillometry devices, and novel digital health tools such as smartphone microphone spirometers and mobile health technologies along with integration of machine learning approaches. The adoption of some novel approaches may not merely replace but could improve existing management strategies and alter common diagnostic paradigms. With these options comes important technical, privacy, ethical, financial, and medicolegal barriers that must be addressed. However, the coronavirus disease 19 pandemic also presents a unique opportunity to augment conventional testing by including innovative and emerging approaches to measuring lung function remotely in patients with respiratory disease. The benefits of such an approach have the potential to enhance respiratory care and empower patient self-management well beyond the current global pandemic.

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As of June 23, 2020, there are > 9.1 million confirmed cases of coronavirus disease 19 (COVID-19) globally, and many countries have implemented broad and extraordinary public health strategies in hopes of flattening the curve.[1] One important consequence of these strategies has been the widespread suspension of nonurgent health-care services, such as nonurgent outpatient in-person consultations and routine diagnostic testing. This has resulted in the full or partial closure of most pulmonary function testing (PFT) laboratories, in keeping with guidance provided by the American Thoracic Society. This guidance is founded primarily on concerns that the testing performed in these laboratories, which includes spirometry, lung volume, and diffusion capacity measurement, presents a higher risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) transmission compared with other diagnostic tests, given the potential for aerosol formation and coughing during the testing of patients with lung disease.[2] Although these and other societal measures have resulted in some success in slowing the spread of SARS-CoV-2, modeling at both local and national levels has suggested that current policies will likely need to be maintained for as long as 18 months to prevent a deadly rebound.[3,4] For PFT laboratories, this implies continued closure vs limited reopening with strict previsit viral testing, personal protective equipment use, and cleaning protocols—either scenario leading to a significant reduction in testing capacity compared with historical norms. Although the provisional diagnosis and management of chronic respiratory diseases with limited access to objective measures of lung function may be feasible in the short term, sustained reductions in testing will almost certainly lead to suboptimal care for many. Furthermore, the inability to diagnose new conditions objectively, for example occupational asthma, may worsen long-term outcomes.[5] As such, it is important to address this issue as soon as possible. With the decrease in in-person consultations, virtual and digital technologies may play an important role going forward,[6] but it is vital to consider the technical, administrative, ethical, and financial implications that will arise as newer technologies replace, complement, or augment conventional PFT.

Role of Pulmonary Function Measurement in the Care of Chronic Respiratory Diseases

PFT is essential to the care of respiratory disorders. It is used to diagnose lung disease, monitor disease course and the effect of therapeutic interventions, determine perioperative risk, and assess prognosis.[7] Reduced access to PFT over the next 6 to 18 months would affect the nearly one-half a billion children and adults worldwide who live with asthma and COPD, the two most common chronic respiratory conditions, and those who will be under- and overdiagnosed during that time period because of reduced testing.[8] In both children and adults with asthma, respiratory symptoms correlate poorly with lung function measurements and cannot be used to infer underlying pulmonary function and pathophysiology.[9,10] The results of PFT have also been shown to change physicians' treatment plans in as many as 48% of patients with asthma,[11] and are a strong independent predictor of exacerbation risk.[9] With COPD, PFT is critical for diagnosis, for assessing the impact of pharmacologic and nonpharmacologic interventions, and for prognosis because deteriorating function is associated with increased exacerbations, hospitalization, and risk of death.[12] PFT is equally vital in preventing misdiagnosis of asthma and COPD, which can result in the unnecessary, potentially harmful, and costly use of respiratory medications in patients who will not benefit from them.[13-15] As many as one-third of patients receiving antiasthma therapy in Canada are found not to have the disease when objective measures of lung function are used diagnostically.[13] The overdiagnosis and misdiagnosis of COPD may be even worse, with estimates of overdiagnosis in primary care ranging from 31% to 60%.[14] Objective measurement of lung function has also been shown to reduce the problem of sex bias in COPD.[16]

Beyond asthma and COPD, many other chronic respiratory conditions rely on the objective measurements of lung function to guide diagnosis, management, and prognostication. Guideline-based care of patients with cystic fibrosis, interstitial lung disease, and pulmonary hypertension, for example, depends on regular access to PFT results.[17-20] Access to reliable pulmonary function data is particularly critical for lung transplant patients when weekly monitoring with spirometry is the criterion standard care during the first 3 months posttransplant when the risk of acute graft rejection is highest.[21] Although some respiratory subspecialists have already provided guidance as to how care should be adjusted while deferring nonessential PFT,[22] it is not yet clear how long this new paradigm of care will be effective in avoiding negative health outcomes, especially as increasing numbers of patients have their testing postponed.

Potential Alternatives to Laboratory-Based PFT

To prevent undue harm to both patients and technicians in communities with high prevalence of COVID-19, many health-care facilities have restricted laboratory-based PFT to essential cases where results will influence immediate treatment decisions.[2] However, this has the secondary effect of further limiting the information available to physicians who must already manage patients without physical examinations because many have now moved almost exclusively to virtual care for outpatient visits.[23] Without this information, management decisions are being made based on history alone. This may be adequate for routine follow-up of some patients with stable respiratory disease but is challenging for new patients and follow-up patients whose clinical status has changed. Although PFT laboratories may gradually open as COVID-19 numbers plateau and begin to decrease, infection control requirements will likely still reduce testing capacity for a long time. Similar concerns around infection control and testing capacity will also adversely affect traditional alternatives to in-laboratory testing such as office-based spirometry because current international recommendations do not distinguish between health-care settings when assessing the risks of aerosol-generating procedures, and even the use of spirometer filters does not eliminate the need for enhanced infection control measures.[2,24,25] Alternatives to laboratory- and office-based PFT may be sought in existing approaches and innovative technologies.

Peak Expiratory Flow Measurement

Home measurement of peak expiratory flow (PEF) using an inexpensive portable handheld device is already a guideline-recommended option to facilitate patient self-management in asthma and in the diagnosis of occupational asthma, but its role is less well defined in COPD.[9,12,26] Many studies have investigated the potential for PEF to be used as a surrogate for PFT in the diagnosis and management of patients with asthma and COPD, but the results have been mixed. Some research has shown that PEF, in combination with other tools such as validated patient questionnaires, can be used to help diagnose COPD when spirometry is not easily available,[27-30] and may be helpful in COPD prognostication independent of spirometry.[31] However, other work in both diseases has shown that agreement between PEF (a purely effort-dependent measure) and spirometry can be highly variable, and may lead to

inappropriate clinical decision-making if relied on exclusively, particularly in children and in cases with either very mild or severe airway obstruction.[32-35] Additionally, studies in children with asthma have shown that self-recorded peak flow is often inaccurate and adherence levels low, and similar concerns may extend to adults.[36] Therefore, although PEF may continue to be used by patients with asthma already familiar with its measurement and tracking, it is unlikely to suffice as a long-term replacement for PFT across chronic respiratory diseases. Given the potential for aerosol generation during the forced exhalation maneuver required for PEF measurement, patients using this technique to monitor their respiratory status at home should also be counseled on measures to avoid infecting other members of their household while using their flowmeter.

Portable Electronic Spirometers

A more sophisticated alternative to PEF measurement is the use of portable spirometers. As a home-based measurement, it minimizes the exposure risk of forceful expiratory measurements and cough in the laboratory or office setting. Many of these devices are now commercially available and in addition to providing more accurate objective measurements of lung function compared with PEF, most are now also designed to pair with and download results onto personal mobile devices or computers, facilitating transmission to and monitoring by health-care professionals.[37] Electronic portable spirometers have been studied and found to be comparable with conventional laboratory spirometry in several chronic respiratory conditions, such as asthma and COPD, cystic fibrosis, idiopathic pulmonary fibrosis, and post-lung and hematopoietic stem cell transplant monitoring.[37-43] Indeed, the ability of patients to monitor spirometry weekly, more frequently than is feasible using laboratory-based measurements, offers advantages in some settings where early detection of problems is important—pulmonary fibrosis monitoring and lung transplant surveillance are two established examples.[39,40]

Limitations of these devices include cost, which can range from $99 to > $1,000, lack of feedback on quality of the breathing maneuvers in many devices, variable reporting of accuracy levels (although some devices claim to meet American Thoracic Society standards for spirometry and include Global Lung Function Initiative reference equations), and the need to validate results against reference standards when starting them for new patients.[37] Additionally, most of these devices are only

able to provide spirometry readings, and cannot aid in lung volume or diffusion capacity measurement. Given these limitations, physicians considering electronic portable spirometers must select the most appropriate devices available locally, ideally balancing price, accuracy, and features that support correct and safe usage. With the correct device-patient match, portable spirometers may present a valuable in-home alternative to PFT for monitoring patients with known chronic lung conditions, augmenting virtual care with important physiological data. Their use could also offload the testing demand on PFT laboratories and outpatient clinics, allowing them to focus their limited capacity on new diagnoses and more urgent testing. As with flowmeter use, patients using portable spirometers at home should be counseled on measures to avoid potentially infecting other members of their household.

Exhaled Nitric Oxide

The fraction of exhaled nitric oxide (FENO) has been studied extensively in asthma, but also in other respiratory diseases, as a noninvasive biomarker that can supplement or potentially replace conventional spirometry in diagnosis and management decisions.[44-47] Unlike spirometry, measurement of FENO does not require forceful expiratory maneuvers and is not prone to trigger cough.[48] FENO may be particularly useful in identifying asthma characterized by type 2 airway inflammation,[49] and may help guide treatment initiation decisions in these patients.[44,50] Guidelines do not currently recommend using FENO alone in either the diagnosis or ongoing management of asthma across different phenotypes.[9] However, increased use of the technology could see revision of these paradigms. At present, laboratory-based measurements are used to diagnose asthma by demonstrating evidence of variable airflow obstruction. Such an approach is fraught with difficulty because patients with mild asthma seldom demonstrate bronchodilator responsiveness at times of randomly scheduled laboratory visits. In fact, operating characteristics of exhaled nitric oxide measurement for asthma diagnosis were clearly superior to those of spirometry with bronchodilator testing in a recent review.[51] Moreover, traditional challenge studies are not only cumbersome to carry out, but also produce variable responses in different subpopulations of patients with asthma and depending on the challenge used.[52] Arguably, recognizing and managing airways inflammation is a more important treatment decision in asthma than the decision to use albuterol for symptoms, and exhaled nitric oxide has been suggested as a

predictor of inhaled corticosteroid responsiveness is patients with asthma or asthma-like symptoms.[50]

Institutions familiar with FENO testing may therefore consider using this technology as a potentially safer (ie, less likely to generate aerosols) method in inpatient and outpatient settings for diagnosing and following patients with asthma characterized by type 2 airway inflammation. Portable handheld devices that can measure FENO are also available, and could be a useful remote monitoring option in patients with eosinophilic asthma in the future; however, strategies to ensure appropriate technique and quality standards will be required. However, the high cost of portable devices, requirement for patient coaching, and lack of validation for FENO in different asthma phenotypes and across other chronic respiratory diseases mean it is unlikely to provide an adequate long-term substitute for PFT.[53]

Airwave Oscillometry

Oscillometry is emerging as an alternative form of PFT that offers some advantages over conventional PFT.[54] It has been shown to be more sensitive than spirometry in early diagnosis of COPD,[55,56] and to correlate better with respiratory symptoms and asthma control,[57,58] and in identifying spirometrically silent episodes of biopsy-proven acute graft rejection after lung transplant.[59] However, there is a dearth of normal reference values for oscillometry because of its relative infancy when compared with conventional PFT; however, this is anticipated to improve with recent publications of technical and interpretation guidelines.[60,61] Because oscillometry is conducted under normal tidal breathing and does not require forced expiratory efforts, it may also have infection control advantages over spirometry, being less likely to generate aerosol and minimizing potential SARS-CoV-2 transmission. Furthermore, oscillometry can be easily conducted in the very young, older adults, and those with physical or cognitive impairment. Oscillometry may also be a useful end point in methacholine or other challenge studies, obviating the need for forceful maneuvers (although challenge-induced cough remains a potential hazard).[62] Finally, remote home monitoring with portable oscillometry is available and likely to provide more reliable readings than portable spirometry because coaching, a crucial component for quality control in spirometry, is not needed for oscillometry.[63] One barrier to the broader use of oscillometry is the high cost of the limited portable

devices available (eg, Tremoflo device [Thorasys]); however, some of this may be recouped over time given the increased volume of testing permitted by oscillometry, and staff training is considerably simpler than with traditional spirometry.[60,64-66]

Novel Digital Health Alternatives

A growing body of literature is exploring the potential to turn existing mobile devices and smartphones into portable electronic spirometers using their built in microphones, supplemented with machine learning techniques.[67,68] Pilot studies of these smartphone spirometers in healthy subjects and patients with asthma and COPD have demonstrated reasonable levels of agreement between resulting values and traditional spirometry, particularly with the FEV_1/FVC ratio.[69-73] Although rigorous clinical evaluation and validation of these innovative approaches against laboratory-based PFT has not been done, and they cannot be considered a current alternative during the COVID-19 crisis, their low cost and capacity for broad dissemination and digital integration offer considerable promise.

Mobile health (mHealth) self-monitoring technology is another digital health option that is not a direct substitute for formal PFT but may contribute to improved management outcomes if implemented during the COVID-19 pandemic. In asthma care, mHealth applications supporting patient self-management through education, medication reminders, symptom monitoring, and action plan provision have been shown to improve asthma control, medication and action plan adherence, and quality of life.[74,75] Similar mHealth interventions for COPD have been associated with decreased hospitalization risk.[76] Importantly, many mHealth self-monitoring technologies are able to facilitate the transmission of clinical data to health-care professionals, which could enhance the virtual and remote patient monitoring and management currently taking place.[77] These types of mHealth solutions may be leveraged in patients with established respiratory diagnoses and relationships with mHealth-savvy health-care professionals, but are likely less useful in new patient assessments or cases of diagnostic uncertainty. Additionally, it is important to note that mHealth in asthma and COPD is an emerging research field, and long-term studies of clinical effectiveness are still lacking.[74,75]

Another innovative approach to enhance remote and virtual monitoring is the use of machine learning algorithms with telemonitoring data. In COPD for example, machine learning techniques have been combined with sociodemographic, clinical, and physiological telemonitoring data to predict acute exacerbations of COPD with high sensitivity and specificity.[78-80] As these technologies mature, they may become particularly useful in centers with established telemonitoring programs in helping physicians to identify which patients are at higher risk of clinical deterioration, allowing triaging of limited PFT resources. However, as with all applications of machine learning with health-care data, interpreting clinical applicability, generalizability, and the potential for algorithmic bias must be carefully addressed.[81]

An Opportunity to Improve on the Traditional Use of PFT

Our present concern is to maintain the usual management standards of patients with chronic respiratory disease until conventional lung function laboratories are able to reopen. However, as new technology is developed and validated, we may find our management strategies improved. Convenience is one obvious advantage of remote patient-measured pulmonary function options. Patients, especially those living in underserved areas, may be spared the need for frequent office visits and laboratory-based studies if equally useful measurements can be generated at home. More frequently monitored lung function at home or in the workplace also offers obvious advantages in the management of difficult asthma, for example. The benefits of weekly home spirometry for monitoring patients with interstitial lung disease, posttransplant patients, and those with cystic fibrosis have already been demonstrated and seems likely to replace at least some of the quarterly clinic visits now used.[37,39,40,42] Additionally, many of the nonremote options reviewed such as in-laboratory FENO and airwave oscillometry currently offer a lower-risk alternative to PFT in the short-term because they are less likely to generate aerosols, but they may also prove to be viable longer-term alternatives as more research is dedicated to their validation across respiratory conditions. One important question that remains with the proposed use of alternative and/or portable PFT technologies is what criteria would warrant confirmation with in-laboratory testing. Although some options such as FENO have established cutoffs, interpretation guidelines for other options such as airwave oscillometry have only recently been published and have yet to be incorporated into computer-based interpretation algorithms.[60,61]

TABLE 1] Summary of Evidence for PFT Alternatives During a Pandemic

Conventional PFT Alternatives	Potential Uses	Limitations
Peak expiratory flow measurement	Use in asthma[9]: • Diagnosis of variable expiratory airflow limitation (diurnal variation, response to therapy, variation between visits) • Diagnosis of occupational asthma and work-exacerbated asthma • Short- and long-term self-monitoring (ie, use in asthma action plans) Use in COPD[28-33]: • Diagnosis, in combination with validated patient questionnaires • Prognostication	Results less reliable in children and in patients with very mild or severe airways obstruction; may also be adherence issues, particularly in children but also in adults
Portable electronic spirometers	Remote follow-up in patients diagnosed with[37-43]: • Asthma • COPD • Cystic fibrosis • Idiopathic pulmonary fibrosis • Post-lung and hematopoietic stem cell transplant	Cost, lack of technique feedback, variable accuracy, not suitable for new diagnosis of respiratory conditions—right device-patient match is crucial
F$_{ENO}$ measurement (portable or in-laboratory)	Use in asthma[9,44,50]: • Can be used to support the diagnosis of and the decision to start inhaled corticosteroids in patients with suspected asthma • May help differentiate between asthma and COPD in nonsmokers	Cost of portable devices, lack of validation in all asthma phenotypes and other chronic respiratory diseases
Airwave oscillometry (portable and in-laboratory)	Use in asthma[57,62,63]: • Assess ICS responsiveness • Remote self-monitoring • Assess bronchodilator challenge response Use in COPD[55,56]: • Identify patients with small airways inflammation • Earlier diagnosis in patients with respiratory symptoms Use in lung transplant[59]: • Earlier noninvasive detection of acute cellular rejection after lung transplant	Normal reference values lacking, more outcomes evidence needed to validate for long-term use in chronic respiratory diseases
Smartphone spirometers	Use in asthma and COPD[69-73]: • Pilot studies including patients with COPD and asthma have demonstrated low mean error between smartphone and conventional spirometry results	Larger validation studies are lacking, accuracy of results is uncertain
mHealth self-management interventions	Use in asthma[74,75]: • Associated with improvement in asthma control and quality of life Use in COPD[76,77]: • Associated with decreased hospitalization risk	Limited utility in new diagnosis, requires high digital health literacy
Telemonitoring with machine learning	Use in COPD[78-80]: • Can help predict early COPD exacerbations	Requires existing telemonitoring program, must be locally validated

F$_{ENO}$ = fraction of exhaled nitric oxide; ICS = inhaled corticosteroid; mHealth = mobile health; PFT = pulmonary function testing.

Physicians will have to be mindful of emerging evidence when using any PFT alternative and incorporate other sources of clinical information into their decision-making. However, any signals of deterioration from the options suggested could equally prove useful in the triaging of limited in-laboratory PFT resources. See Table 1 for a summary of reviewed alternatives and their limitations.

Challenges to Shifting the Paradigm of PFT

Although the COVID-19 pandemic presents an opportunity to study and explore the potential alternatives to conventional PFT in managing the care of patients with chronic respiratory diseases, these alternatives are not without their own unique challenges. Integrating many of the proposed remote alternatives into existing care workflows and electronic health records that are already struggling to cope with the massive shift to virtual care would be challenging. Privacy and equity issues would need to be carefully addressed, particularly when dealing with interventions that interact with patients' personal digital devices and when considering the costs of various alternatives. Technical support for both patients and health-care workers may be needed with new technologies and devices. Remuneration systems would need to be adjusted to recognize the technical and professional components involved in the introduction of new and advancing technologies, and to compensate for potential loses in hospital revenue associated with decreased laboratory testing. This is already occurring to some extent because the US administration has enacted several regulatory changes to support expanded remuneration for remote patient monitoring and telehealth services.[82] Finally, the use of novel technologic solutions may herald unanticipated or new medicolegal implications which will require consideration.[67]

Conclusions

In the face of serious limitations to the availability of conventional laboratory and office-based PFT that are likely to persist for at least the next 6 to 18 months, respiratory physicians, researchers, and administrators must begin to consider how alternatives to conventional PFT could be integrated into the care of patients with chronic respiratory diseases to provide the best possible quality of care. Although no current individual alternative is sufficient to replace conventional testing in all patients, many of the options reviewed may provide acceptable and actionable physiological information to improve clinical management. Examples include the use of portable electronic spirometry and mHealth self-monitoring technologies in patients with asthma and COPD, and portable oscillometry for monitoring patients after lung transplant. The COVID-19 pandemic provides a unique opportunity for the respiratory community to implement existing alternatives to PFT and to engage in the rigorous clinical evaluation of new digital solutions and systems that may enhance the management of those with respiratory diseases, while being mindful of the importance of privacy and autonomy to the patients.

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