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Unmet needs in cystic fibrosis: the next steps in improving outcomes

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Abstract

Introduction: Cystic fibrosis (CF) outcomes and survival have improved over the last century primarily due to advancements in antibiotics, nutritional and pulmonary therapies. Reviewed here are the significant unmet needs that exist for individuals with CF.

Areas Covered: With the recent development of medications that address the underlying defect in the CF protein, there is hope that there will be continued improvement in CF outcomes. However, there remains a need to prevent or stop progression of CF related complications, as the CF protein is important to several body systems. As end stage lung disease is the primary cause of mortality in CF, a need exists for advancements in pulmonary therapies to reduce time burden, identification of best practices for the treatment of pulmonary exacerbations, further development of anti-infective and anti-inflammatory therapies, and appropriately-timed referral for lung transplantation at end stage lung disease. Extra-pulmonary complications are increasingly recognized and better understanding of such problems as CF related liver disease is needed.

Expert Commentary: While CFTR modulators are available for the majority of CF patients, there remains a need for effective therapies to address infection, inflammation, irreversible lung disease, and extrapulmonary complications of CF.

Keywords

Cystic fibrosis; Unmet needs; Ivacaftor; Lumacaftor; Tezacaftor; Pulmonary Exacerbations; Lung Transplant; Inflammation; Pancreatic Insufficiency; Cystic Fibrosis Related Liver Disease

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Declaration of interest

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1. Background

Cystic fibrosis (CF) is the most common autosomal recessive genetic disorder affecting Caucasians, affecting ~70,000 worldwide[1]. CF is characterized by chronic airways infection with repeated pulmonary exacerbations (PE_x), which lead to decreased survival, decline in lung function, and decreased quality of life[2–13]. Respiratory failure secondary to end stage lung disease is the most common cause of death[14]. CF is also associated with a variety of other complications including chronic sinusitis, pancreatic insufficiency, distal intestinal obstruction syndrome (DIOS), CF-related liver disease and biliary cirrhosis, CF-related diabetes, osteopenia/osteoporosis, renal dysfunction, infertility, and anxiety and depression[14]. While median survival in the 1950s was approximately 5 years of age[15], median survival age of those born in 2016 is now predicted to be 47.7 years of age[1]. The improvement in survival has been attributed to center care and advancements in airway clearance, nutrition, and antibiotic therapy for chronic infection[14]. Even though survival has considerably improved, it remains well below that of normal life expectancy, and CF patients continue to live with considerable morbidity. Current therapies address the consequence of the disease (antibiotics, pancreatic enzymes, mucolytics), but there is not a cure for the underlying cause of the disease for everyone with CF. There is a need for further advancements in therapies in CF, and here is described the more pressing unmet needs perceived for the care of individuals with CF (Table 1).

2. Treatment of the underlying cause of cystic fibrosis

The discovery of the CF gene led to great expectations that the condition would soon be cured by replacement with a normal gene. Although that dream has not yet been realized, several medications and therapies have been developed specifically for the treatment of complications of CF; only recently are medications available that address the basic underlying cause, while remaining shy of a cure. The CF gene mutation results in impaired activity of the cystic fibrosis transmembrane conductance regulator (CFTR), either by reduced quantity of protein or impaired function of the protein (or both)[14,16] (Figure 1). Therapies developed to treat patients with CF have been directed at the downstream consequences of the basic defect. Dornase alfa works to alter the properties of the airways mucus with the intent to reduce the obstruction[17]. Inhaled antibiotics suppress the chronic infection in the airways[18,19]. Even digestive enzymes are merely replacing those lost to the patient because of obstruction of the pancreatic ducts[14].

Recent approval of ivacaftor, lumacaftor, and tezacaftor represent an advance in treatment that targets the basic underlying problem in CF – a lack of functioning CFTR present in the cell membrane. Ivacaftor, a potentiator, increases the probability that the CFTR channel will be open, allowing improved function for those mutations that result in impairment of the gating or channel conductivity. This proved highly effective in studies of patients with gating mutations [20](e.g. G551D) and has since had its indication expanded to include other mutations[21].

In order for ivacaftor to be effective there must be CFTR present in the cell membrane. The most common mutation, F508del, is not responsive to ivacaftor alone[22], as the defect

results in impaired folding and trafficking of the protein to the cell surface. The available correctors, lumacaftor and tezacaftor, stabilize the trafficking process, allowing for more protein to be folded and transported[23], and when combined with ivacaftor to increase channel function, these drugs have proven effective in improving lung function and reducing pulmonary exacerbations in patients who are homozygous for F508del[24,25]. However, they have not been sufficient to achieve a clinical benefit in patients who are heterozygous (i.e. one copy) of F508del, but tezacaftor/ivacaftor has shown clinical benefit in individuals heterozygous for F508del who also have a residual function mutation, which has expanded the number of mutations approved for a CFTR modulator[26].

Although these new drugs have been effective, there remain major gaps in this approach to treatment. First, these drugs are intended for specific mutations, and will not be effective for all patients. For example, ivacaftor is indicated for 38 mutations[21], accounting for up to 15% of the CF population. Lumacaftor and tezacaftor, each in combination with ivacaftor, are approved for homozygous F508del, accounting for approximately 50% of patients[24,25]. A combination of correctors, again with ivacaftor, has demonstrated even greater CFTR activity in Phase II studies for patients with F508del suggesting there could be a meaningful clinical benefit for heterozygous subjects[27] and Phase III studies are planned.

Should this approach be successful, this would allow some form of CFTR modulation for up to 90% of patients, meaning there are still patients lacking this option, such as those with a premature stop codon in which the mutation results in an early termination code and a truncated, non-functioning protein. The approach to address this would require a “read-through” of the false termination code, allowing complete translation of the protein. This does not guarantee normal protein and correction or potentiation may still be needed.

Mutation-agnostic approaches to CFTR correction are also in development. Strategies have included amplification of protein translation resulting in greater amount of protein that could be corrected[28,29], editing of mRNA such that normal protein could be produced[30], and even editing of the gene[31], an alternative method of gene therapy whereas previous attempts have been to simply replace the gene. While much of this work remains in preclinical development, some have entered into human trials (clinicaltrials.gov NCT03258424, NCT02532764).

In addition, these novel therapies are developed through studies of adult patients, but it would be crucial to introduce such therapy into patients much earlier in the hopes of preventing the consequences of disease. Ivacaftor has been approved for patients as young as 2 years, lumacaftor-ivacaftor has been approved down to age 6 years, and tezacaftor-ivacaftor approved for as young as 12 years. This demonstrates that there is still work to do to demonstrate that these therapies are safe and effective in the very young, perhaps one day considering in utero use of CFTR modulators to prevent sequelae of CF such as pancreatic insufficiency or absence of the vas deferens.

3. Pulmonary Therapies

The development of CFTR modulators has improved outcomes for some, yet they do not repair existing lung disease (i.e. bronchiectasis) that is irreversible and thus other chronic therapies remain necessary. These include airway clearance therapies, mucolytics, and inhaled antibiotics. Dornase alfa and hypertonic saline are nebulized medications, as are most antibiotics, although some may be delivered through a dry-powder mechanism[17–19,32–35]. Airway clearance techniques to further mucociliary clearance include manual percussion, vest, acapella valve, and active cycle of breathing, among others[36]. All of these therapies, while effective, are time consuming, often taking 2–3 hours per day to perform, and they come with additional impediments. Medications may have to be refrigerated before use, mixed before inhaling, and/or taken via a nebulizer that requires electricity and is not easily portable. The equipment should be meticulously cleaned to avoid bacterial contamination. Worse adherence to CF pulmonary medications is associated with increased hospitalizations[37]. Thus, there is a need for therapies that are much more efficient and effective, so as to reduce the burden of care. More efficient nebulizers and development of dry powder formulations that reduce the treatment time and increase portability should improve adherence to therapies but development of new models of therapeutic drug delivery should continue. Reduced treatment burden could potentially improve adherence, which could ultimately result in improved outcomes in CF.

4. Treatment of infection

Chronic infection of the airways is a common consequence with infection occurring early in life and persisting despite antibiotic therapy[38]. Typical pathogens include *Staphylococcus aureus* (including methicillin-resistant *staphylococcus aureus* (MRSA)), *Pseudomonas aeruginosa*, and *Haemophilus influenza*[1], but there are many others. Recent knowledge of the microbiome has taught us that the infection is much more complex than revealed by standard culture methodologies[39]. Recognition of the association of *P aeruginosa* with worse outcomes[40] has driven the current treatment strategies of suppression of chronic infection with aerosolized antibiotics and antibiotic therapy at the finding of first infection to attempt eradication; prophylaxis to prevent *Pseudomonas* infection has not been an adopted practice[41]. Since these practices have become the standard of care to address *Pseudomonas*, it is reasonable to question whether similar strategies should be used for other pathogens. There is evidence that the acquisition and persistence of MRSA may also be associated with worse outcomes[42,43] and eradication and suppressive therapies are currently being tested[44].

Inhaled antibiotics have been the typical approach to suppression of chronic infection and eradication of new infection. Approved products are repurposed intravenous antibiotics formulated for airways delivery, and there remains off-label use of intravenous antibiotics (e.g. ceftazidime, colistin, and vancomycin). Concerns for an attenuation of the response to treatment cry for a need for additional therapies but new antibiotics have not been forthcoming, leading to additional reformulation of existing antibiotics for the airways (e.g. levofloxacin[45,46]) or the development of novel approaches to treating infection. Current studies are investigating a role for gallium ([clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02354859) NCT02354859) and nitric oxide

(clinicaltrials.gov NCT02498535). *Pseudomonas* needs iron to build and support its bacterial colonies. The rationale for gallium is that it can mimic iron, and *Pseudomonas* will incorporate gallium as if it were iron. However, gallium cannot be used by *Pseudomonas*, so it effectively leaves *Pseudomonas* without its food source, and decreases the pathogenicity[47]. There may be a role for airway-based iron chelation to reduce *Pseudomonas* biofilm, based on preclinical observations[48,49]. Nitric oxide at greater concentrations is toxic to pathogens, and although it is also toxic to humans at this concentration because of accumulation of methemoglobin, strategies of repeated dosing with sufficient intervals to allow for resolution of the methemoglobinemia are currently under investigation[50,51].

Microbiological surveillance of the CF patient has led to the discovery of emerging pathogens[1], which may have virulent properties. Previously there had been an emergence of *Burkholderia* species, highly resistant and associated with severe comorbidities[52–54]. This led to a change in treatment practices with greater attention to infection control, and although this pathogen still exists in some patients it has not become epidemic. More recently there has been greater attention paid to nonbacterial species such as mycobacteria and fungi. The criteria used to define mycobacterial lung disease include symptoms consistent with infection (e.g. cough, sputum production, weight loss), radiographic changes consistent with infection (e.g. bronchiectasis, nodules), and the presence of mycobacteria in respiratory cultures [55]. Unfortunately, most CF patients display these attributes irrespective of mycobacterial infection, so more discriminating strategies are needed to identify patients whose health is being actually being undermined by these pathogens. Additional clinical features have been proposed (e.g. those patients not responding to treatment, loss of lung function over time)[56], but further clarification of best practices to identify when mycobacteria should be treated is needed. There are published guidelines on the regarding NTM in CF patients[57] and ongoing studies attempting to define which patients need to be treated (PREDICT, NCT02073409) and how well one treatment approach fares (PATIENCE, NCT02419989). A further discussion of the treatment of mycobacterial lung disease is beyond the scope of this discussion but better therapies is clearly an unmet need[58]. Fungi have long been identified in the CF airways, predominately *Candida* and *Aspergillus* species, but for the most part have been deemed to be mere innocent bystanders. Yet there are findings that challenge this notion for *Aspergillus*. There is an increased prevalence of allergic bronchopulmonary aspergillosis (ABPA) but there is growing evidence that *Aspergillus*, even in the absence of ABPA, may be associated with clinical worsening in some patients[59]. In addition, there are other fungi that are increasingly recognized as problematic[60] including *Scedosporium* and *Trichosporon*. There is a need to identify which pathogens are causing problems and how best to treat them; treatment of fungal infections has been particularly challenging for the CF patient.

Finally, once there is clarification of which pathogens should be treated, the next step should be to define best practices on how to detect them. Surveillance with cultures of respiratory specimens has become an increasingly common practice, but it is not clear which methods should be used and how often testing should be performed, and there is clearly a variance in practice among and within centers. Although treatment of bacteria based on the results of susceptibility testing is considered critical in the general understanding of infection, in the

complex infection of the CF airways there is discordance between antibacterial susceptibility testing and clinical outcomes[41]. That is, susceptibility testing does not predict response to treatment very well; it is not uncommon for patients to respond to antibiotics to which pathogens are resistant. Therefore, there needs to be an understanding on which microbiologic information is needed to best guide treatment of CF patients.

5. Treatment of inflammation

The inflammatory response to infection is excessive in the CF airways, and it is believed that it is the inflammation that causes the progressive injury to the airways leading to bronchiectasis and loss of lung function. Currently there are limited therapies that specifically address inflammation. Although there is an attempt to reduce inflammation by suppression of infection and clearance of airway phlegm, there remains a need for more effective anti-inflammatory methods. Prior studies of corticosteroids demonstrated mild clinical benefit to the airways but the adverse effects of steroids on growth and glucose control limit their utility and they are not recommended as a routine therapy[62]. Chronic ibuprofen use has been associated with slower rate of decline in FEV₁ in individuals with CF[63], and recently was shown to be associated with improved survival in children with CF[64] but the uptake of this therapy by CF clinicians has been poor[1]. This may be because of perceived adverse effects associated with chronic use of ibuprofen relative to the potential benefit[65], so additional work is needed to understand its role in routine care. Chronic macrolide therapy has been suggested to work as an anti-inflammatory agent, and there is evidence of anti-inflammatory effects in vitro[66]; however, these are also antibiotics and the specific mechanism of action in the CF airways has not yet been elucidated.

The common approach to addressing inflammation is to try to prevent its occurrence. This has not yet proven effective in CF, and there have been examples of increased risk of infection-related adverse events[67]. The clear need here is a product that sufficiently, but not completely, suppresses the inflammation.

A key challenge of the study of anti-inflammatory therapies for CF is to define the meaningful clinical endpoint. It is essential to identify an easily measured inflammatory mediator that is responsive to a therapy [68], and several biomarkers have shown promise in CF drug development in sputum (neutrophil elastase, myeloperoxidase, calprotectin) and blood (C reactive protein, calprotectin, serum amyloid A)[69]. This must then correlate with a clinical outcome that would allow for eventual approval. It is unlikely that suppression of inflammation will provide an immediate lung function improvement[64] and monitoring of loss of lung function requires many patients and longer studies. Reduction of pulmonary exacerbations would certainly be relevant, but there is not yet agreement in a reliable definition of such events. Finally, studying such changes in younger, healthier patients will require identification of surrogate markers as they are likely to have even fewer events.

6. Pulmonary Exacerbations

Individuals with CF suffer from repeated PEx, which is generally described as worsening respiratory symptoms that are typically treated with antibiotics [11]. PEx are associated with

loss of lung function (forced expiratory volume over one second [FEV₁]), decreased survival, and worsened quality of life[2–13]. Analyses of patient registries have suggested that 25–35% of individuals do not recover baseline FEV₁ after treatment for a PEx[2,12,13,70,71], resulting in permanent lung function loss, however, the reality may be even worse based on recent reports. An observational study of PEx found that when comparing to pulmonary function values recorded in the patient registry, the lung function at the initiation of treatment for a PEx was the best in the previous 6 months in 20% of subjects[11]. Post hoc analysis of data from a Phase III study showed that >50% of patients who suffered a PEx did not recover to their baseline lung function as measured in the previous 30 days, and there was no better recovery when treated with a CFTR modulator[72]. Given the strength of evidence of the deleterious outcomes after a PEx despite treatment, there is a need to improve upon techniques in prevention and detection of PEx, as well as enhance therapeutic strategies for treatment. Prevention requires a better recognition of chronic treatment opportunities and improved patient adherence, while the latter means a need exists to identify PEx earlier and treat more effectively. There were more than 17,000 PEx treated with intravenous (IV) antibiotics recorded in the CF Foundation Patient Registry in 2014[73], but despite these events being so common, treatment practices vary widely as there is a lack of sufficient evidence to support guidelines for best practices[1,10,74–77].

Since the publication of the CF Pulmonary Guidelines on the treatment of PEx[78], there has been movement in an effort to establish best practices for the myriad of treatment decisions made in the management of the patient with a PEx. The *Standardized Treatment of Pulmonary Exacerbations (STOP)* program first conducted an observational study (clinicaltrials.gov NCT02109822) of 220 individuals hospitalized for treatment of a PEx with IV antibiotics. This study was necessary for the development of interventional trials and sought to describe clinical characteristics of patients with PEx, evaluate physician treatment practices, establish the feasibility of future clinical trials, and, most importantly, identify clinical endpoints (i.e. what to measure and when) to be used in future trials[11,12,79]. Consistent with prior reports, only 39% fully recovered lost lung function, and only 65% recovered at least 90% of lost lung function [11,12]. Most importantly the study was informative in defining potential clinical endpoints and the parameters needed to power future trials[79].

There are a number of questions regarding PEx treatment in need of robust clinical data including antibiotic selection (number, route of delivery), optimal duration of antibiotics, location of treatment, among others[78]. *STOP-2* (clinicaltrials.gov NCT02781610) is the first randomized clinical trial of treatment of PEx and randomizes individuals to different durations of IV antibiotics (10, 14, or 21 days), based on their initial response to IV antibiotics. The trial is currently enrolling, and the results of this trial should change clinical treatment and shape future clinical trials of PEx in order to establish best practices.

7. Conduct of clinical research

The last decade has been a robust period for development of CF specific therapies. The understanding of the pathophysiology has led to many novel therapies ripe for clinical

investigation. The challenge for this rapidly evolving space is how best to study new medications. There are trials competing for patient enrollment, having similar inclusion criteria, yet there is a limited population available for study. Inclusion criteria commonly used for trials often exclude a large number of patients because they are too healthy or too sick. In addition, with improved center-driven care, patients' lung function may be at their best with little room for further improvement, meaning traditional clinical endpoints (e.g. increase in FEV₁) may no longer be appropriate for a clinical trial. This means evaluation of other relevant clinical endpoints that can demonstrate efficacy while maintaining feasibility for the trial is needed (i.e. not excessive duration or numbers of subjects)[80].

Clinical research is not merely about developing new medications, but also defining best practices of how best to use existing and new therapies. The notion of personalized medicine is easily understood when looking at medications developed for specific mutations, but it is also about determining which of the available therapies are most effective for the individual patient, including therapies generally recommended in guidelines. Although investigation of best use of therapies is not as exciting as developing new medications, they are important and may require novel comparative effectiveness studies. Funding for such studies will have to come from federal and foundation sources.

8. Lung Transplantation

Despite the advancements in CF care and survival, many patients will progress to end-stage lung disease when lung transplantation should be considered. Lung transplant survival has improved for individuals with CF over the last 2 decades, with a mean survival post-transplant of 8.9 years[81], but still much shorter than that of other solid organ transplants. Complications following lung transplantation include acute and chronic rejection, infection, and adverse effects of immunosuppressive medications, all presenting opportunities for improved post-transplant outcomes.

A recent analysis of registry data demonstrated a survival advantage for Canadians compared to the US, partially due to a greater proportion of Canadian CF patients undergoing lung transplantation compared to the US[82], suggesting earlier referral of patients for consideration for transplant may be beneficial. Approximately one-third of patients with advanced stage lung disease were not referred for lung transplant evaluation, despite their FEV₁ being consistently <30% predicted for the previous 2 years[83]. CF lung transplant recipients with a greater lung allocation score (LAS) at time of transplant, indicating more severe disease, were associated with worse survival in the first year after transplant[84]. Factors associated with greater risk of death include a need for supplemental oxygen requirement and frequent PEx in individuals whose FEV₁ is <30% predicted, and these should trigger prompt referral for lung transplant evaluation[81].

Disparities in health systems and insurance status, especially US public health insurance, are also implicated in worse outcomes following lung transplant[82,85]. The CF Foundation has identified a need for greater standardization and implementation of best practices to improve transplant outcomes and has established the CF Lung Transplant Transition Leadership and Learning Collaborative (LLC), in collaboration with the Dartmouth Institute, Microsystem

Academy. This LLC aims to improve the recognition of patients appropriate for lung transplant evaluation and the transition of patients into the lung transplant process. Given these initiatives, lung transplant outcomes and in particular, survival, might improve from where it stands today.

9. Nutrition and gastrointestinal complications

Most patients have pancreatic insufficiency, and are prescribed replacement digestive enzymes. Although nutritional measures have also been improving over time, this does not mean that nutritional questions are resolved. The CFTR modulators are associated with improved nutritional outcomes, presumably because of greater effectiveness of digestive enzymes and absorption[86]. However, most patients are not likely to recover lost pancreatic exocrine function and will be reliant upon supplemental enzymes for life. Existing products are derived from porcine pancreas and these have been in abundant supply. Yet, there could be vulnerabilities as demonstrated by the Mad Cow experience[87]. Should a highly virulent pathogen adversely affect the supply of porcine products, this could prove devastating to the CF population. Other sources of digestive enzymes, such as derived from plants, are being investigated[88].

Perhaps the most frustrating gastrointestinal complication is distal intestinal obstruction syndrome (DIOS). Whereas constipation can be addressed with enemas and laxatives, DIOS results in obstruction in a site not easily reached and which is poorly responsive to laxatives. There is little evidence on how to prevent or treat this complication[89]. Although there is hope that CFTR modulators may reduce the occurrence of this complication, this remains to be seen.

10. Liver disease

Liver involvement in CF is common, with elevated liver enzymes occurring in 20–30% by age 20 years old, and hepatic steatosis found on liver biopsy in 23–75% of individuals[90]. CF related liver disease (CFRLD) occurs secondary to dysfunctional CFTR on the apical side of biliary epithelium, causing dehydration of biliary ducts leading to plugging and fibrosis. The major impact of liver disease on CF outcomes is the development of multi-lobar cirrhosis (7% incidence), which progresses to portal hypertension. Unfortunately, most of the signs of advanced liver disease are subtle in CF and are often not present until end-stage liver disease has occurred and is irreversible. Interestingly, liver enzymes can be normal in CF patients even in the setting of cirrhosis[90]. Therefore, there is a need to establish best practices for screening and detecting early liver disease in CF. Ultrasound is used to evaluate for increased echogenicity or nodularity of the liver, however, the prognostic value needs to be validated in a large clinical study. Newer methods of imaging are being explored such as shear wave elastography (SWE), which measures liver stiffness, and is currently being evaluated in a clinical trial in a collaboration with the NIH (NCT01144507) and CF Foundation. Several biomarkers have the potential to advance screening and detection sensitivity, but need further evaluation[90]. Furthermore, once first signs occur of CFRLD, there are few tools to prevent acceleration of the disease, and few guidelines in terms of what to do once liver disease is diagnosed. There is a need for

clinically effective treatment once CFRLD has been diagnosed. The role of ursodeoxycholic acid (UDCA) in CFRLD has not been established[90], as there is a lack of robust clinical data to determine whether UDCA is effective for preventing the progression of CFRLD. CFTR modulators may help to prevent or slow CFRLD progression, but that has not been thoroughly studied. Other bile acid analogues are being considered, but all proposed treatments have yet to be evaluated in multi-center clinical trials[90].

11. Conclusions

Incredible advancements in CF care and survival has been made over the past 7 decades, which are largely due to the development in nutritional and pulmonary therapies. In the last 5 years, CFTR modulators have become available to help correct the underlying mechanism of CF disease, but fail to cover every class of mutation. Reviewed here are a portion of questions yet to be addressed in the care of CF patients and there are many more. Further work is needed to address other extra-pulmonary complications such as sinus disease, CF-related diabetes, osteopenia/osteoporosis, and anxiety/depression which are becoming more common as individuals with CF are living longer[1]. Additionally, studies are needed related to complications from aminoglycosides (nephrotoxicity and ototoxicity) and catheter related issues (thrombus). Until a cure is found for every individual with CF, advancements in therapeutics are needed to prevent the progression of CF related disease. As individuals with CF are living longer, more therapies are needed to treat the vast complications of CF.

12. Expert Commentary

While CF has had great improvements over the last several decades, it is still a disease with multiple complications and no cure currently exists. There is enthusiasm over the advancements in CFTR modulators and the field is moving rapidly with development of new medications likely available in the near future. While there may be safe and more effective CFTR modulators available for a large fraction (~90%) of CF patients, there remain many for which the current therapies would not work, and the CF community is committed to solving that gap. The assumption is that more effective modulators, resulting in greater (perhaps even supra-normal) CFTR activity will result in even greater improvement in lung function. However there must be a ceiling effect in which no further increases of FEV₁ are possible. It is not yet known how we will recognize we have reached the ceiling. It is also assumed that use of such therapy in younger patients will prevent the development of the known complications of CF (e.g. bronchiectasis and chronic airways infection), but it cannot be known if these sequelae will be prevented or merely delayed (which is still a major benefit), and treatment of our patients who have established disease will not resolve those problems. Therefore it is likely that patients will still need and benefit from medications and therapies that address airways obstruction, infection and inflammation. Novel approaches to these target areas will be needed

CFTR modulators are likely to impact the extra-pulmonary manifestations of CF as well, such as improved sinus disease, CF related diabetes, and CFRLD, and potentially affect the airways microbiome such that certain infections may be less common (e.g. NTM). It will be important to monitor these effects over time

We cannot ignore the burden of therapies, despite their benefit, as they are time-consuming and costly. Highly effective therapies will not be so if patients do not use them, so development of more efficient and effective therapies for CF patients is essential. As new products are developed they will be made available at considerable expense and will be needed over a lifetime. Health care systems will need to determine how best to integrate them into the chronic care of our patients. These are exciting times for the CF community as the investment in research has finally come to the realization of considerable benefits.

13. Five-year Review

There has been rapid development of therapies, notably CFTR modulators, in the last few years, and multiple trials ongoing and planned for even greater expansion of medications and their indications (e.g. younger patients). It is highly likely that within the next 5 years there will be some form of modulator therapy available for at least 90% of CF patients. Yet there remains the need for other types of therapies (e.g. anti-infectives and anti-inflammatories). Their development is somewhat hampered by the challenge of recruitment of subjects into trials given the number of studies ongoing and planned. The STOP program will have laid the foundation for studies identifying best practices for the treatment of pulmonary exacerbations and there should be a greater consistency of care in this area.

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Abbreviations

CF	cystic fibrosis
PE_x	pulmonary exacerbations
DIOS	distal intestinal obstruction syndrome
CFTR	cystic fibrosis transmembrane conductance regulator
MRSA	methicillin-resistant <i>staphylococcus aureus</i>
ABPA	allergic bronchopulmonary aspergillosis
FEV₁	forced expiratory volume over one second
IV	intravenous

CFRLD	cystic fibrosis related liver disease
UDCA	ursodeoxycholic acid

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Reference annotations

* Of interest

** Of considerable interest

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The latest expert review of the pathophysiology, epidemiology, treatment and management of complications, and future directions in CF

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Key issues

- Survival in CF has increased dramatically over the last half century and mean predicted survival is currently ~47 years old.
- CFTR modulators have been developed and have substantially improved the ability to correct the underlying defect for some CF mutations, yet further advancements in these therapies are needed.
- Even with effective CFTR modulators medical therapies aimed at preventing further disease progression are still required.
- Further advancements in pulmonary treatment is needed: reduction in burden of time-consuming medications, guidelines for treatment of pulmonary exacerbations, and development of effective anti-infective and anti-inflammatory treatments.
- Chronic infection of the airways persists despite eradication and suppressive antibiotic therapies for *Pseudomonas*; there is a need to know if this strategy is appropriate for other bacteria commonly found in CF airways.
- Development of best practices of identification and treatment of emergent pathogens (e.g. non-tuberculous mycobacteria and fungi) are needed.
- While it is known that chronic inflammation is excessive in CF airways, there are limited therapeutic options to address and lessen the inflammatory response.
- Best practices for referral for lung transplantation and detection of liver disease is needed, and outcomes for both need to be improved.

Figure 1. Classes of CFTR modulators. (Abbreviation: cystic fibrosis transmembrane conductance regulator (CFTR)). Reprinted from The Lancet Respiratory Medicine, Vol 1, Michael P Boyle and Kris De Boeck, A new era in the treatment of cystic fibrosis: correction of the underlying CFTR defect, 158–163., Copyright (2013), with permission from Elsevier.

Table 1:

Abbreviated list of unmet needs.

Topic	Unmet need
CFTR modulation	Need a CFTR modulator for all patients (not necessarily all mutations) Greater potency of activity Available for younger patients
Infection	More therapies that target <i>Pseudomonas</i> (e.g. new antibiotics, non-antibiotics) Should eradication of newly identified bacteria be attempted (e.g. MRSA)? Should suppression of chronic infection for other bacteria be a goal of therapy (e.g. MRSA)? Should new emerging pathogens be treated (e.g. NTM, fungi)? What is the role for bacterial susceptibility testing?
Inflammation	Effective anti-inflammatory medications Is there a role for ibuprofen?
Pulmonary exacerbations	When should intervention occur? What are the best approaches to treatment to optimize effect while minimizing cost and toxicity?
Lung transplantation	When is appropriate time for referral? Prevention of bronchiolitis obliterans
Nutrition	Alternative to porcine digestive enzymes
Gastrointestinal	How to prevent and treat DIOS?
Liver	How to diagnose and treat liver disease?
Clinical research	Defining meaningful clinical endpoints for future therapeutic development

Abbreviations: cystic fibrosis transmembrane conductance regulator (CFTR), methicillin-resistant *staphylococcus aureus* (MRSA), non-tuberculous mycobacteria (NTM), distal intestinal obstruction syndrome (DIOS)