



# The Aging Patient with Cystic Fibrosis

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## Abstract

Cystic fibrosis (CF) is an inherited condition that leads to multiorgan dysfunction, especially in the respiratory, gastrointestinal, and reproductive tracts, with associated conditions including persistent pulmonary infection, liver disease, pancreatic insufficiency, and infertility. Historically, people with CF (pwCF) suffered a shortened lifespan due to complications of the condition, namely respiratory. The emphasis on center-based, multidisciplinary care and the widespread introduction of cystic fibrosis transmembrane conductance regulator (CFTR) modulator therapy has resulted in pwCF living longer and healthier lives. Now they may encounter some of the health and social issues associated with growing older, which previously were not a typical experience for this population. In this article, we review relevant health issues for the aging CF population, including complications that arise from the condition itself, issues encountered due to treatment, and general conditions associated with aging that may manifest earlier or differently in pwCF. We discuss the recommendations for screening and treatment of relevant conditions, and considerations for the integration of healthcare professionals across disciplines into the care of this population.

## Key Points

People with cystic fibrosis are living longer with an ever-growing number entering the geriatric age group.

The implementation of center-based care and the widespread use of CFTR modulators has contributed to the increased life expectancy, necessitating a renewed focus on diseases traditionally associated with aging and not experienced by this patient population.

Recommendations for screening for chronic conditions, such as diabetes and bone disease, among others, differ in this population, and there are additional considerations for drug–drug interactions related to CFTR modulators and other chronic CF-related therapies.

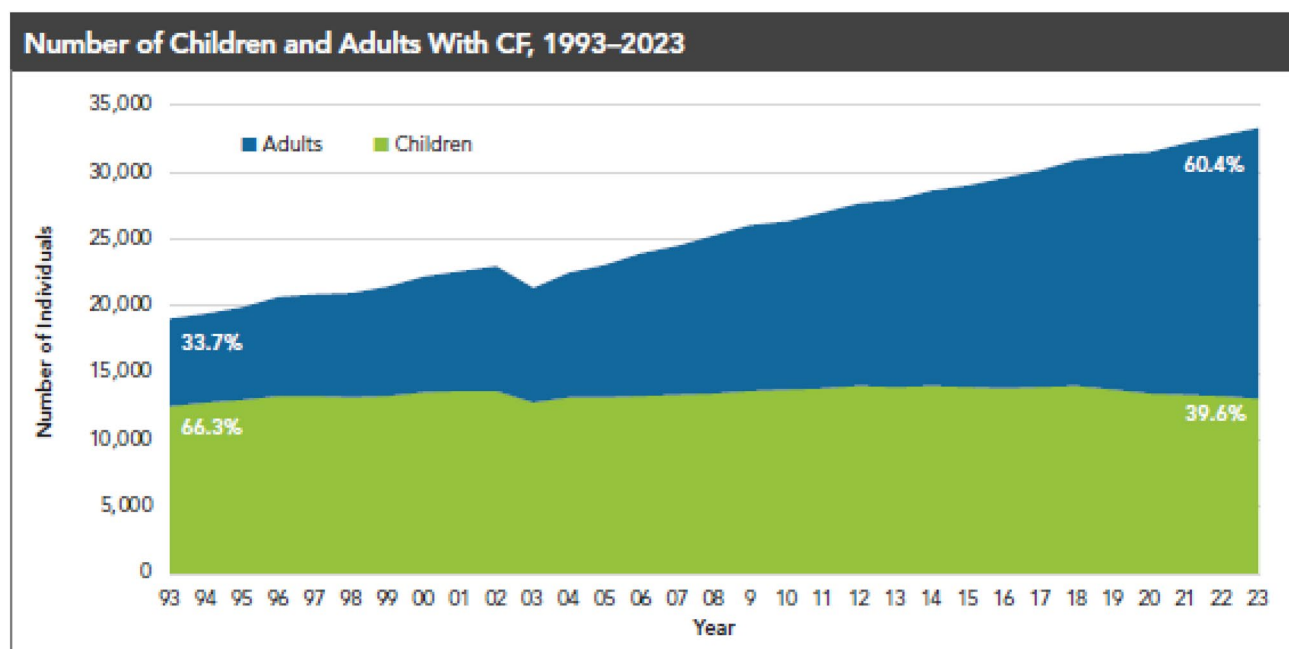
## 1 Introduction

Cystic fibrosis (CF) is an inherited autosomal recessive condition with an estimated population of nearly 40,000 children and adults living with CF in the USA and more than 160,000 people with CF (pwCF) worldwide [1]. CF is caused by defects in the cystic fibrosis transmembrane conductance regulator (CFTR) protein, an epithelial surface channel that governs chloride and bicarbonate conductance in various organs, including the sweat glands and the respiratory, gastrointestinal, and reproductive tracts. Dysfunction or absence of the CFTR channel leads to a range of adverse health consequences, including bronchiectasis with persistent pulmonary infection, pancreatic insufficiency, liver disease, and infertility, among others [2]. These contribute to considerable comorbidities requiring chronic medications and therapies, as well as frequent hospitalizations to address acute CF-related complications. Historically, CF was also associated with early mortality (Fig. 1), which improved incrementally with center-based specialty care and medications approved to treat the consequences of CF complications.

In addition to the advent of center-based care, the development of CFTR modulators, small molecules that address the basic defect in CF by increasing the quantity and function of CFTR protein at the cell surface [3], has led to remarkable improvements in the health of pwCF. There are

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**Fig. 1** The adult CF population is growing. The number of children (< 18 years) and adults ( $\geq$  18 years) reported in the Cystic Fibrosis Foundation Patient Registry (1). The pediatric population has

remained fairly stable over time with patients transitioning into adulthood at a rate similar to new diagnoses at birth, but the adult population has grown steadily and is predicted to continue

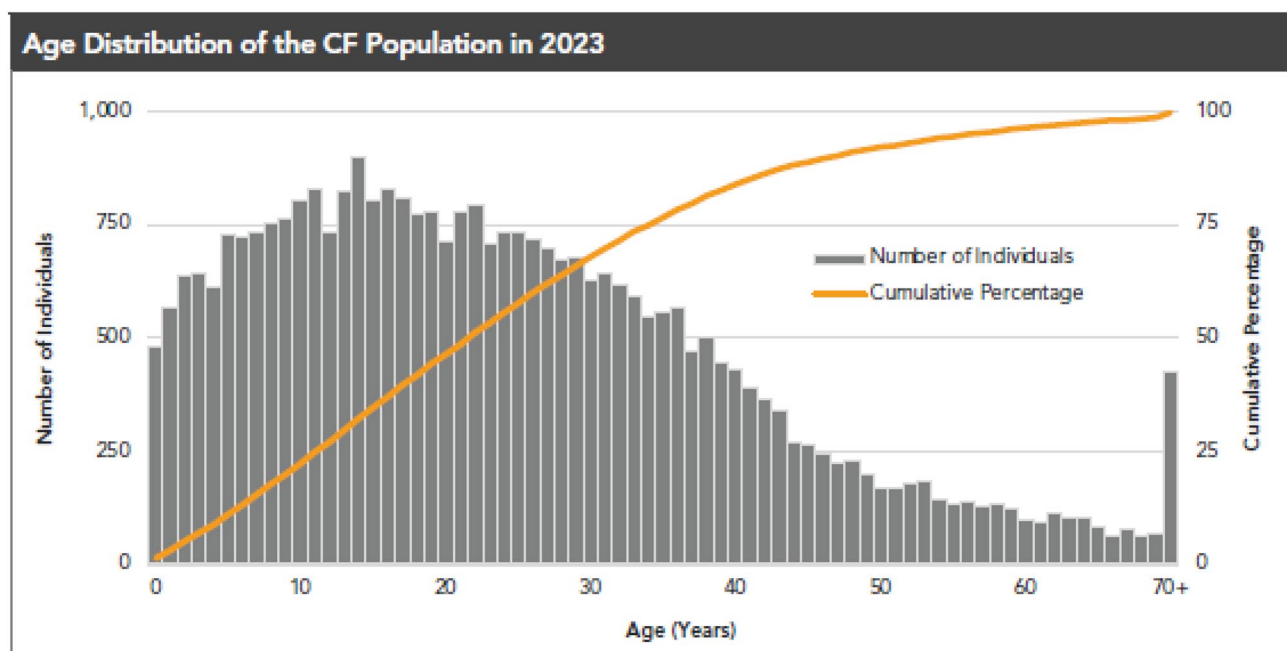
fewer symptoms (e.g., cough and sputum production), fewer events that lead to hospitalization, and a marked increase in the predicted survival of pwCF [4–6]. The result has been an increase in the number of adults with CF, reaching parity with the pediatric population in ~2014. Adults now represent a majority of the CF population (Fig. 1). In addition, there is an increasing number of pwCF reaching into later adult years (Fig. 2) with ~ 25% of pwCF over the age of 40 years [7]. These observations suggest a need for healthcare providers to have greater knowledge of CF and its complications to best address this aging population.

What follows is a summary of relevant healthcare conditions for an aging CF population. Some of these are known sequelae of CF, others are related to the consequences of CF treatments, and there are issues relevant to all adults (not just those with CF) but not previously a common experience or expectation for pwCF. Finally, we will comment on how care can be best provided for the adult with CF, addressing the roles of the CF center as well as primary care providers or consultants who may encounter pwCF.

## 2 CF-Related Complications

### 2.1 Bronchiectasis and Persistent Airway Infection

The natural history of pulmonary disease in pwCF starts with the defect in CFTR activity, resulting in a reduction of airway surface liquid and impaired mucociliary clearance. This leads to retention of phlegm in the airways and creates a vulnerable environment for chronic bacterial infection. The ensuing inflammatory response is exaggerated, leading to a greater amount of phlegm in the airways, causing obstruction and injury, leading to the development of bronchiectasis. Typical daily symptoms include cough with sputum production; there are also periods of worsening with increased pulmonary and systemic symptoms and reduced lung function, deemed pulmonary exacerbations [8]. The result is a progressive loss of lung function and reduced survival. Typical therapies to manage airways disease include regular use of airway clearance therapies [9] and aerosolized treatments



**Fig. 2** People with CF are living longer and age distribution is changing. The Cystic Fibrosis Patient Registry shows that people with CF (pwCF) are living longer and the predicted survival has increased

considerably. Approximately 25% of pwCF are > 35 years of age, with many living into their 60s (1)

including hypertonic saline, dornase alfa, and antibiotics. These symptomatic therapies addressed the symptoms associated with the downstream consequences of reduced CFTR activity.

The introduction of CFTR modulators, which unlike the symptomatic therapies address the underlying defect, have led to better clearance of airway phlegm, fewer symptoms, improved lung function, and fewer pulmonary exacerbations for many pwCF [4, 5]. The bronchiectasis does not reverse, nor does the persistence of infection, although the burden of infection is significantly lessened such that some patients may no longer grow a pathogen in their respiratory cultures. However, many patients will continue to suffer pulmonary exacerbations. CFTR modulators may not be effective for some because of unresponsive mutations, often in people from minority groups [10, 11], or because of adverse reactions to the medications [12]. Thus, there is a heterogeneous population of pwCF in terms of their eligibility for CFTR modulators as well as their tolerance of them.

Some pwCF will have improvement in symptoms and lung function in response to CFTR modulators such that it is hard to appreciate the benefit of other CF-approved aerosolized therapies. Short-term trials have demonstrated no apparent adverse response to stopping these therapies [13], but there remain pwCF who will continue to benefit from them. Those pwCF with advanced lung disease and

those who cannot use the CFTR modulators may still benefit from their chronic therapies.

Although registry data suggest that infection rates decreased with increasing age and there are fewer hospitalizations in older populations (age > 60 years) [7], we must be cautious with our interpretation of these data. Because CF patients generally had an earlier mortality, only those pwCF with milder manifestations of disease would survive into older years. Now that many pwCF are benefiting from CFTR modulators, we will see many more patients living into later decades, but it is not yet known whether they will have similar outcomes to those with inherently milder disease. For example, imaging of adult patients with a good clinical response to CFTR modulators demonstrate persistent bronchiectasis (Supplementary Fig. 1); it remains to be seen what happens to pwCF who are started on CFTR modulators early in life, potentially delaying the development of bronchiectasis and slowing the development of more severe impairment.

## 2.2 Pancreatic Insufficiency

Most pwCF have pancreatic insufficiency and will need supplemental digestive enzymes. Although this status has been shown to change in pediatric subjects in response to CFTR modulators, this does not seem to be the case in adult pwCF, and they will continue to need enzyme replacement to properly digest their food. However, the CFTR modulators

may normalize the pH in the gastrointestinal tract, making the digestive enzymes more effective, perhaps contributing to the development of obesity seen in pwCF [14]. This could alter symptoms in response to this change in the intestinal milieu, but the dose of enzymes should not be decreased as a response; these are typically titrated to the size and content of the meals to assure sufficient enzymes to digest the food [15].

Abdominal discomfort is a common symptom reported by pwCF. There can be many etiologies (e.g., cholecystitis, pancreatitis) but the most common is fecal obstruction of the colon (also known as constipation). An abdominal x-ray is most helpful in these cases with evidence of a significant amount of stool without signs of complete bowel obstruction (i.e., air–fluid levels). The recommended approach consists of osmotic laxatives to clear the bowels, increased hydration, and consideration for a maintenance bowel regimen [16].

### 2.3 Cystic-Fibrosis-Related Diabetes (CFRD)

CFRD is a common complication of CF, affecting up to 20% of teenagers and half of adults over the age of 50 years [17]. Although the pathogenesis of CFRD is complex and not fully understood, it is largely driven by insulin insufficiency through progressive damage to pancreatic tissue, including insulin-producing beta cells. However, there is no direct correlation between the degree of pancreatic fibrosis and development or severity of diabetes, suggesting alternative mechanisms such as a direct influence of CFTR on beta cells and a contribution of insulin resistance [18, 19]. Risk factors for developing CFRD include severe genotype, exocrine pancreatic insufficiency, liver disease, systemic corticosteroid use, and nocturnal continuous enteral feedings [17, 18]. CFRD is associated with increased mortality and greater decline in lung function over time, as well as the development of microvascular complications [20].

Typical diabetes features such as polyuria, polydipsia, and ketoacidosis are rare, thus screening is important to detect disease. The recommended screening for CFRD is a 2-h oral glucose tolerance test (OGTT), with guidance for interpretation outlined in guidelines [20]. Alternative diagnostic recommendations exist for CFRD diagnosis during acute illness and for patients on continuous enteral feeding [20]. Hemoglobin A1c is thought to underestimate the degree of hyperglycemia in CFRD, and thus is not recommended as a single test for screening. Continuous glucose monitoring has been proposed as an alternative screening tool for CFRD, however, to date there are no specific guidelines for its use in screening or treatment monitoring [21].

Management of CFRD is similar to Type 1 DM and includes insulin as the therapy of choice [20]. To date, oral agents used for type 2 diabetes have not proven efficacious

for CFRD, but there may be a role for glucagon-like peptide (GLP) agonists or dipeptidyl peptidase-4 inhibitors [17, 22–24]. Microvascular complications, including retinopathy, neuropathy, and nephropathy, are seen in CFRD, albeit at lower rates than in type 1 or 2 DM [25]; annual screening with eye exam, foot exam, and urine albumin excretion is recommended beginning 5 years after the diagnosis, or if the time of diagnosis is not known, when fasting hyperglycemia is documented [18]. The CF Foundation has recommended inclusion of an endocrinologist as an essential partner to a CF center [26].

### 2.4 Cystic-Fibrosis-Related Bone Disease

Bone disease is another common extrapulmonary complication of CF. Prior to the development of CFTR modulators, the prevalence of osteoporosis in young adults was 23.5%, and the prevalence of osteopenia was 38% [27]. Annualized losses in bone mineral density in young adults with CF are similar to postmenopausal women [28]. Rates of low bone density and fragility fractures are even higher in patients awaiting lung transplantation, and if severe, can preclude eligibility for transplant [29]. With an aging CF population we expect complications from bone disease to become a more prominent issue, although the impact of CFTR modulators is unclear.

The pathogenesis of CF bone disease is multifactorial. It arises from an interplay of factors, including the inability to achieve peak bone mass in early adulthood, impaired fat-soluble vitamin absorption, and delayed puberty. Medication use, including glucocorticoids and proton pump inhibitors, may also play a role, along with the impact of recurrent infections, chronic inflammation, and comorbid disease states, including liver disease and diabetes. CFTR may also directly impact bone homeostasis and remodeling [28, 30].

The recommended screening for CF-related bone disease is dual-energy x-ray absorptiometry (DXA) for all adults (age 18 years and older) and especially if undernourished, with poor lung function (i.e.,  $FEV_1 < 50\%$  predicted), glucocorticoids  $> 5$  mg/day for  $> 90$  days/year, or history of fracture. For interpretation in adults 18–30 years, *T*- and *Z*-scores are equivalent, whereas *T*-scores should be used for those 30 years or older [28]. The World Health Organization (WHO) classification for osteopenia (*T*-score less than  $-1$  and greater than  $-2.5$  SD) and osteoporosis (*T* score less than or equal to  $-2.5$  SD) are also used in CF-related bone disease [31]. Treatment recommendations as well as the frequency of repeat DXA are determined by *T*- and *Z*-scores (see Table 1) [28]. The treatment of CF-related bone disease is controversial. Guidelines recommend treatment of osteoporosis with bisphosphonates, which act by reducing bone resorption and may be given orally or intravenously (IV) [32]. In a 2023 Cochrane review, bisphosphonates were

shown to increase bone mineral density at the lumbar spine and hip in adults. The impact of highly effective modulator therapy on the natural history of bone disease is not yet known, however, several ongoing observational studies are seeking to evaluate this question.

## 2.5 Nutrition and Obesity

In previous decades, pwCF were generally undernourished because of their pancreatic insufficiency as well as increased caloric usage given their underlying lung disease, persistent infection, and excess inflammation. Attention to nutritional health had been a priority and pwCF increased their weight and body mass index (BMI), and this is likely a major contributor to improved survival over time. It is well established that lung health is associated with nutritional status [33, 34] and the CFF established guidance for a target BMI for male (23 kg/m<sup>2</sup>) and female individuals (22 kg/m<sup>2</sup>) in response to these observations [35].

Over the last two decades there has been a reduction in the number of pwCF categorized as undernourished (i.e., BMI < 18 kg/m<sup>2</sup>); however, an analysis of the CF Registry showed a steady increase in the proportion of pwCF who meet the criteria for overweight and obese [14, 36]. Factors associated with obesity included milder CFTR mutations, pancreatic sufficiency, milder lung impairment, and the use of CFTR modulators [14, 36]. At the time of that analysis, relatively fewer pwCF were prescribed CFTR modulators; now that most pwCF are taking CFTR modulators, there is even greater interest on the impact this will have on the prevalence of obesity in this population. Proposed mechanisms of weight gain related to CFTR modulators include reduced resting energy expenditure, improved nutrient absorption, and increased caloric intake [37] on a background of generally poor diet quality, which includes high saturated fat and low fiber intake [38]. Long-term (1 year) of exposure to modulators, particularly elexacaftor/tezacaftor/ivacaftor (ETI), has been associated with increased rates of metabolic syndrome, defined by abnormalities in fasting glucose, HDL cholesterol, triglycerides, waist circumference, and hypertension [39].

Pharmacologic therapies, including GLP-1 receptor agonists, have been increasingly prescribed for weight management in the general population [40], and there is interest in the effectiveness and safety of these medications in pwCF. One small study of pwCF treated with GLP-1 agonists showed associations with weight loss, as well as improved glycemic control in the subset of patients with CFRD [41]. Larger studies are needed to confirm this finding. Overweight and obesity are epidemic in the USA, with an estimated prevalence of 75% in adults in the general population [42]. Overnutrition is a problem in both pwCF and the general population that is projected to increase over

time [42], with associated complications including type 2 diabetes, cardiovascular disease, hypertension, obstructive sleep apnea, and certain types of cancer [43].

## 2.6 Liver Disease

Liver disease affects up to 40% of pwCF with a broad array of manifestations. CFTR is present along the apical surface of cholangiocytes in bile ducts and plays a role in bile acid production and homeostasis. CFTR dysfunction leads to biliary stasis and fibrosis, with subsequent cirrhosis and portal hypertension [44]. Not all liver disease in pwCF stems from CFTR dysfunction; other contributing factors include medication toxicity, nutritional deficiencies, pancreatic dysfunction, recurrent infections, and hepatic congestion [44]. Excessive alcohol use has also been identified in the adult population [45]. The majority of cases of serious liver disease with cirrhosis and portal hypertension manifest before the age of 18 years, and 75% of liver transplants in pwCF are in children [46]. However, since pwCF are living longer and may be experiencing more conditions associated with metabolic dysfunction, as detailed above, there is the potential for increased incidence of liver disease later in life.

Liver disease in cystic fibrosis has been broadly defined as CF hepatobiliary disease (CFHBI), with advanced CF liver disease (aCFLD) representing a subset with more severe disease (Table 2). For all adults, annual screening for CFHBI with labs (including total bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, gamma-glutamyltransferase, and platelet count) and physical examination to evaluate for hepatosplenomegaly are recommended [47]. Adults should have a baseline abdominal ultrasound (US) to assess the liver and spleen [47]. Hepatic steatosis is a common finding in pwCF, but is not hypothesized to be directly related to CFTR dysfunction; other factors including nutritional factors as well as obesity have been implicated [44]. Liver elastography is useful to detect early fibrosis and is recommended annually in all adults with identified CFHBI [47]. There are no specific treatments for CFHBI. Ursodeoxycholic acid (UDCA) is a bile acid that has been used in cholestatic liver conditions, including CF-related liver disease. Given conflicting data regarding its efficacy, and no robust evidence that it prevents aCFLD, routine use is not recommended in pwCF [47, 48].

Hepatotoxicity is common adverse effect of CFTR modulators, and monitoring of liver function tests is recommended at baseline, every month for the first 6 months of therapy, and periodically thereafter [49]. There is a box warning for drug-induced liver injury and liver failure for both elexacaftor/tezacaftor/ivacaftor (ETI, or Trikafta) and the new, once-daily modulator vanzacaftor/tezacaftor/deutivacaftor (Alyftrek). Modulators can be safe to use in

CFHBI and even after liver transplantation, but should be used cautiously in patients with aCFLD, particularly in the setting of decompensated or advanced disease; these patients should be managed in close conjunction with a hepatologist and a pharmacist [47, 49].

### 3 Complications Associated with Treatment of CF

#### 3.1 Consequences of Medications

PwCF are likely to have been treated with aminoglycosides throughout their lives. *Pseudomonas aeruginosa* is one of the most common pathogens overall, and especially in adults or those with more advanced lung impairment. Current strategies to address *P. aeruginosa* include eradication at first identification in respiratory cultures and suppression of the bacteria in those with chronic infection [50, 51]. Aerosolized tobramycin has been commonly used for both of these circumstances, either as a limited duration (for eradication) or continuous therapy (for suppression). In addition, pwCF are subject to intermittent events of clinical worsening called pulmonary exacerbations; these are often manifest as increased cough and sputum production, loss of weight, increased fatigue, and a reduction in pulmonary function [8, 52]. Oftentimes these are treated with systemic antibiotics, which may also include aminoglycosides such as tobramycin. Intravenous or inhaled amikacin may be used as part of treatment of nontuberculous mycobacterial infection, which affects approximately 12–25% of pwCF [53].

The most common toxicities of aminoglycosides include nephrotoxicity and ototoxicity, including cochleotoxicity and vestibulotoxicity [54, 55]. These can occur acutely or could be a result of the cumulative effect of many courses of antibiotics. Symptoms of ototoxicity may include tinnitus, sensorineural hearing loss, or vertigo/balance issues, which can be permanent [55]. Therapeutic drug monitoring is recommended for systemic aminoglycoside use [56] but acute effects on hearing can be detected even with careful dose monitoring [57]. The prevalence of hearing loss in the CF population varies widely in registry data and studies, but is likely underappreciated and associated with cumulative exposure [58–60].

Given the potential to receive ototoxic medications, including aminoglycosides, macrolides, and glycopeptides such as vancomycin, the CF Foundation recommends a baseline hearing study for all adults and children with CF, and annual monitoring in pwCF who continue to receive ototoxic medications [55]. Careful medication reconciliation can help minimize the use of other potential ototoxic medications, including nonsteroidal

antiinflammatory drugs (NSAIDs) and diuretics, when possible, especially if intravenous aminoglycosides are being used [61].

The majority of eligible pwCF take CFTR modulators, including elexacaftor/tezacaftor/ivacaftor (Trikafta), tezacaftor/ivacaftor (Symdeko), and lumacaftor/ivacaftor (Orkambi). Of these, Trikafta is the most commonly prescribed [58]. Pharmacologic interactions are possible between the CFTR modulators and other agents that are metabolized in the liver by cytochrome P450 family of enzymes; additional interactions are possible through effects on drug transport proteins [62]. Recent comprehensive reviews on drug–drug interactions with modulators are available [62, 63], and a pharmacist should be engaged when starting new medications on pwCF.

#### 3.2 Complications Related to Vascular Access

PwCF who are treated with systemic antibiotics for pulmonary exacerbations may have vascular access, including peripherally inserted central catheters (PICCs), placed to make home intravenous therapy easier. Many pwCF will have had multiple devices placed over their lifetime or may have a totally implantable venous access device (TIVAD), e.g. a port, placed for recurrent use [64]. Complications of PICC lines include insertion site pain, thrombosis, and infection. Historically, larger diameter and multi-lumen PICCs were associated with higher complication rates, including deep venous thrombosis (DVT) [65]. Prolonged pain after insertion and catheter obstruction were also common, affecting up to 20% of patients [66]. Patient-associated risk factors for complications have been identified, including poor nutritional status and multiple line placements [64]. A recent prospective, observational study showed that placement of single lumen, smaller diameter (e.g.,  $\leq 4.5$  French) PICCs under ultrasound guidance has low rates of vascular and infectious complications in pwCF [67].

The reduction in pulmonary exacerbations attributed to CFTR modulators should reduce the need for indwelling catheters, and removal of TIVADs should be considered to avoid potential long-term complications. It is also important to have knowledge of catheter usage, as this may inform evaluation of unusual symptoms (e.g., edema in an extremity) or planning for a surgical procedure.

### 4 Issues that pwCF May Get to Experience that are More Typical of Adulthood

Since most, if not all, children with CF will age into adulthood, there should be planning on how to live a long life, much as for any other child. Transitions from

adolescence, young adulthood, and older adulthood have long been discussed in the CF literature and attention is placed on assisting families with preparing their child with CF for eventual independence. Although much of this has focused on the health care issues as they move into an adult clinic, there is also discussion about relationships, as well as greater emphasis on sexual issues, education, and career planning, among others.

#### 4.1 Reproductive Health and Parenthood

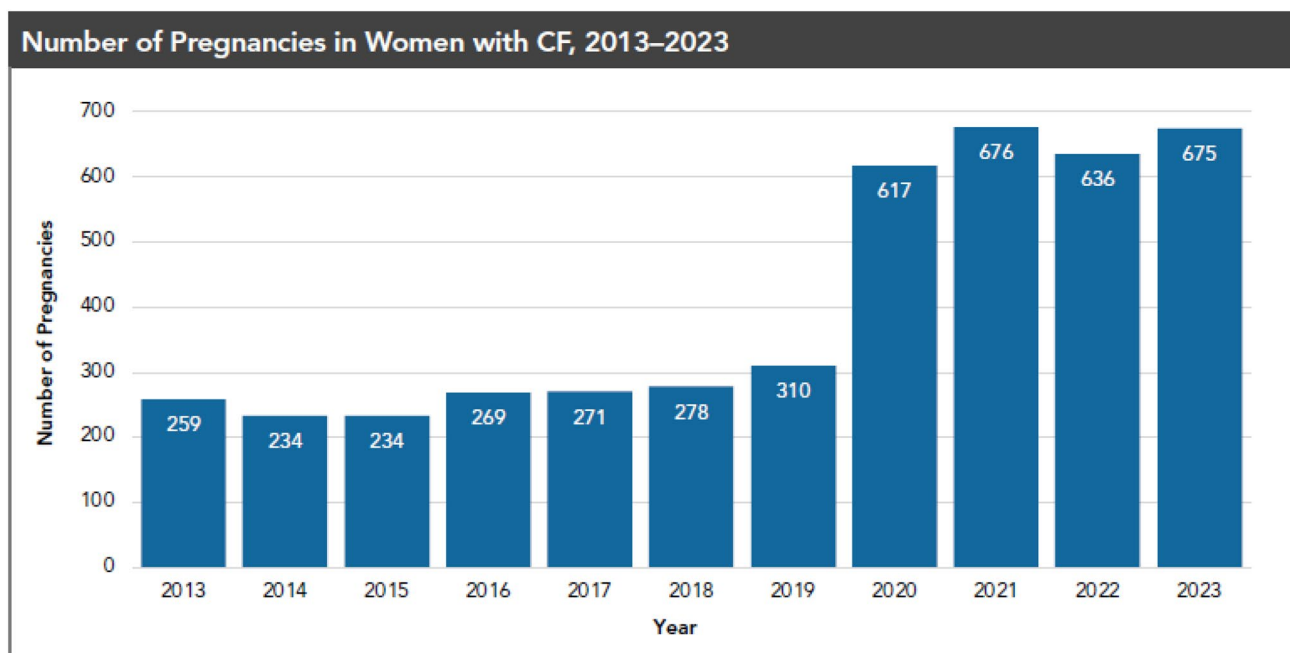
Almost all male and many female individuals with cystic fibrosis experience infertility. Historically, the presence of subfertility in female individuals with CF has been estimated to be around 35%, which is higher than the rate of 5–15% in the general population [68]. Dysfunction of CFTR in the female reproductive tract causes dehydrated cervical mucus, as well as an altered intrauterine milieu that may be inhospitable for fertilization. In addition, nutritional deficiencies and chronic inflammation may contribute to anovulation [69]. Since the introduction of modulators in 2019, there has been a significant increase in pregnancy rates in female individuals with CF (Fig. 3). Overall, studies do not demonstrate a significant impact of pregnancy on maternal health with regard to survival, decline in lung function, or rates of pulmonary exacerbations [70]. The Maternal and Fetal Outcomes in the Era of Modulators (MAYFLOWERS) study is an ongoing multicenter observational trial that is examining the impact of pregnancy in CF in the era of widespread

modulator use [71]. Gestational diabetes is common and management is similar to women without CF [70]. Female individuals with CF should be counseled about the possibility for pregnancy and options for contraception.

There remain uncertainties regarding pregnancy in CF as most female pwCF who become pregnant will also be on some medications. Some of these drugs are known to be safe (e.g., beta-lactams, dornase), while others are likely to be safe (e.g., macrolides), and there is limited guidance on medications during pregnancy [72]. There is a growing experience of CFTR modulators during pregnancy that suggests they are likely to be safe, balancing the risk of stopping these medications with the potential risk for continuance [73].

Most male individuals with cystic fibrosis are infertile because of congenital bilateral absence of the vas deferens, leading to a lack of sperm in the ejaculate fluid. Diagnosis can be confirmed with both semen analysis showing azoospermia, as well as with physical examination and scrotal ultrasound. Male individuals with CF produce normal sperm and can father biological children with assisted reproductive technology, which includes sperm retrieval through testicular or epididymal aspiration/biopsy and subsequent intrauterine insemination or in vitro fertilization [74].

While some pwCF may choose to pursue pregnancy, other options for family building exist and can be explored. These options include adoption, step-parenthood, foster care, and surrogacy [75].



**Fig. 3** Rising numbers of pregnancies in women with CF. The reported pregnancies in the CF Foundation Patient Registry (1) showed a marked increase following the introduction of elexacaftor/tezacaftor/ivacaftor

## 4.2 Menopause

Menopause is defined as the cessation of menstrual periods for 12 consecutive months, with an average age of onset of 51 years in the general population [76]. A total of 80–90% of women will experience symptoms with menopause, including vasomotor symptoms such as night sweats and hot flashes, cognitive and mood changes, and urogenital issues. Menopause also influences long-term health with impacts on bone loss, the development of cardiovascular disease, and cognitive function [76]. There are few data on menopause in female individuals with CF, although one study found a median age of onset of menopause to be earlier (48.5 years) than in the general population. A significant proportion of female individuals reported worsening of CF-related symptoms during and after menopause [77].

Medications used to treat menopausal symptoms include hormone-replacement therapy (HRT), including both estrogen and progesterone therapy, selective-serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), gabapentin, and fezolinetant. HRT is recommended for women younger than 60 years or who are within 10 years of menopause with no contraindications. Special considerations that may preclude safe HRT use in women with CF include history of venous thromboembolic disease or liver disease. Caution is recommended for the CFTR modulator lumacaftor-ivacaftor, which can reduce efficacy of HRT and interact with SSRIs.

## 4.3 Cancer Screening

As the life expectancy of pwCF increases, we anticipate increased rates of cancer in this population, particularly among older patients. Registry data have signaled an increased number of multiple types of cancer in pwCF, including gastrointestinal, renal, thyroid, testicular, and lymphoma [78, 79]. Of these, digestive tract cancers, particularly colorectal cancer, have been of the highest concern, and screening guidelines for pwCF differ from the general population.

An elevated risk of gastrointestinal tract cancer in pwCF has been well established [80]. Proposed mechanisms behind this include CFTR dysfunction in the GI tract leading to impaired epithelial homeostasis, nutritional factors including high fat diet, and gut dysbiosis [81]. Rates are also higher in patients with more severe genotypes and following solid organ transplant [82]. The median age of onset of colorectal cancer in pwCF is 20–30 years younger than in the general population [81, 83]. Therefore, the CF Colorectal Cancer Screening Consensus guidelines recommend screening colonoscopy beginning at age 40 years, with rescreening every 5 years assuming negative examinations [81]. If adenomas are discovered, the next colonoscopy should occur

in 3 years. In pwCF who have undergone an organ transplant, colonoscopy is recommended starting at age 30 years and within 2 years of transplant. To date, there is insufficient evidence to support less invasive modes of screening, including fecal immunochemical tests (FIT) or computed tomography (CT) colonography [81]. The median colorectal cancer screening rate among the eligible CF population hovers around 30%, highlighting the need for increased awareness and implementation of this recommendation [58].

Retrospective studies have suggested an increased risk of human papilloma virus (HPV)-related dysplasia and high rates of abnormal pap smears in women with CF [84]. Patients who have undergone lung transplantation are at even higher risk for cervical dysplasia and cervical cancer [85]. In one study, transplantation was associated with 4.5-fold higher risk of HPV; non-transplanted women had higher rates of abnormal cervical cytology, but similar rates of high-risk HPV compared with the general population [86]. These data highlight the importance of cervical cancer screening and HPV vaccination in the CF population.

Increased rates of testicular cancer have been seen in registry studies and is more common in severe genotypes. There are currently no specific guidelines for screening for testicular cancer in the CF population, however, providers should be aware of this association [87].

## 4.4 Cardiovascular Disease and Dyslipidemia

Historically, cardiovascular disease has not been a significant comorbidity in pwCF. This has been attributed to low prevalence cardiovascular risk factors in this population (e.g., hypertension, overweight and obesity, and tobacco use). In addition, the earlier mortality perhaps prevented pwCF from living long enough to develop cardiovascular disease. However, the observation regarding obesity prevalence noted above has generated greater concern about complications related to dyslipidemia and cardiovascular disease.

A multinational, retrospective cohort study found that pwCF have a higher risk of major adverse cardiac events (MACE), including myocardial infarction, left-sided heart failure, and atrial fibrillation, compared with a matched, non-CF population. Additionally, the risk of MACE in people with CF was on par with other inflammatory conditions that portend a higher risk for cardiovascular disease, including human immunodeficiency virus (HIV), systemic lupus erythematosus, and rheumatoid arthritis. MACE were associated with diabetes and hypertension, as well as disease-specific risk factors including lung function and intravenous antibiotic use. This study included data from the years 2016–2020, and thus does not reflect the full impact of CFTR modulator therapy [88]. Providers should be cognizant of the potential for cardiovascular disease in

pwCF, however, there are no specific screening or treatment recommendations in this population.

CFTR is present in vascular smooth muscle cells and endothelial cells, however, its physiological role is not fully understood. Lower rates of hypertension in the CF population have been attributed to salt losses from CFTR dysfunction [89]. The prevalence of hypertension is 2–11% in adults with CF, which is lower than the general population rates in the UK and USA, which range from 25 to 48% [88, 90]. This prevalence may change with widespread use of modulators, which can increase blood pressure. In one case series of 79 patients who were started on modulator therapy with elexacaftor-tezacaftor-ivacaftor (ETI), 4 developed hypertension requiring antihypertensive therapy. Patients who developed hypertension had preexisting metabolic conditions, including CFRD and liver disease [91]. Treatment for hypertension in CF should follow standard age-based guidelines and targets.

Abnormal lipid metabolism is another evolving topic in the care of pwCF. Historically, hypertriglyceridemia was more common in pwCF compared with the general population, possibly related to nutrient malabsorption or chronic inflammation; conversely, cholesterol and LDL levels were lower in pwCF [92]. These metabolic parameters may be impacted by treatment with modulators, which has implications for other related health conditions. In one study, treatment with ETI increased total, HDL, and LDL cholesterol in patients with CFRD [93]. Another study showed that overweight and obese pwCF had higher total and LDL cholesterol levels compared with normal/underweight pwCF [36].

Screening for lipid disorders with an annual lipid profile is strongly recommended in all men age 35 years or older and in women age 45 years or older with risk factors for coronary heart disease (CHD) [94]. Earlier screening in men age 20–35 years and women age 20–45 years with other risk factors for CHD is also recommended [94]. An annual lipid profile is recommended for patients with CF-related diabetes and pancreatic exocrine sufficiency or if any of the following risk factors are present: obesity, family history of CHD, or immunosuppressive therapy following transplantation [20]. Treatment of dyslipidemia should follow standard guidelines [95], however drug–drug interactions, particularly with regards to potential hepatotoxicity, should be considerations in the CF population.

#### **4.5 Planning for Work, Financial Independence, and Retirement**

PwCF are living not only longer but overall healthier lives and should be encouraged to develop educational and vocational goals. Currently, many adults are pursuing bachelor's or other advanced degrees [58], and

a significant proportion of pwCF have part-time or full-time jobs [96]. In many individuals, the diagnosis of CF affects career choice [97], and most are engaged in non-manual occupations, including clerical, professional, or managerial positions [96]. PwCF may face unique barriers impacting their ability to work, including the need for time off due to illness [97]. The CF Foundation provides guidance related to workplace accommodations and benefits [98], and social workers are available as a core part of the CF team to offer guidance [2]. Projected increases in survival owing to modulator therapy are substantial [6], and more pwCF will enter the retirement years. Appropriate financial planning should be promoted in younger people with CF, and guidance provided to older pwCF who may not have anticipated needing a pension or retirement savings [99].

### **5 The CF Care Model**

The benefit of the CFTR modulators has changed the health of pwCF dramatically, such that now many are looking to reduce the frequency of office visits and some of their treatments. There is recent guidance on how this should impact the CF center care team and how the team provides care [26]. The CF center remains essential, but primary care providers (PCPs) should be engaged as key partners in the delivery of care. This will require increased communication between pwCF, their families, the CF center and the PCP so that all will know who should be contacted for different health questions and to assure that complications could be detected early to allow for appropriate intervention.

The role of the pharmacist as a member of the core CF team has been made clear [100], but this role should be highlighted given the potential for the additional comorbidities described here and the potential for drug–drug interactions.

It is also critical to recognize that not all pwCF are benefiting from the CFTR modulators. Some do not have CFTR mutations that are responsive to the modulators and others are not able to tolerate the medications due to adverse effects. We should anticipate even greater heterogeneity in the health status of our patients, and although CF-related complications are common, they may manifest differently in patients, thus an individualized care plan is needed for all.

## 6 Conclusions

PwCF are experiencing longer and healthier lives due to modulator therapy and standardized, center-based care. Despite this, complications do occur, which may be related to the underlying disease, the treatments, or just by virtue of people living longer. There remains heterogeneity in this population with regard to the severity of lung disease and the presence of CF-related comorbidities. Metabolic complications, including weight gain, hypertension, and lipid disorders, which have historically been of low concern in this population, may become more prominent over time. The model of care is evolving in response to the changing health of our patients, and that should include greater partnership with PCPs.

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