AAVBC

AMERICAN ACADEMY OF VALUE BASED CARE

Cystic Fibrosis

Quick Reference Guide

2026

Table of Contents

1 CLINICAL SNAPSHOT

Definition: **Cystic fibrosis** (**CF**) is an autosomal recessive multisystem disease caused by **mutations in the cystic fibrosis transmembrane conductance regulator** (**CFTR**) **gene**, which encodes a chloride channel expressed in epithelial cells of the lungs, pancreas, gastrointestinal tract, hepatobiliary system, reproductive tract, and sweat glands.[1] Dysfunctional CFTR produces thick, viscous secretions that **obstruct airways**, **impair mucociliary clearance**, and drive: chronic infection, bronchiectasis, and progressive end-organ damage; pulmonary disease remains the **leading cause of morbidity and mortality**.[1] Highly effective **CFTR modulator therapy**, elexacaftor/tezacaftor/ivacaftor (ETI, Trikafta) for patients ≥2 years with at least one responsive CFTR variant (including **F508del**, which accounts for **~85% of US alleles**), has **transformed the disease**, improving percent-predicted FEV1 (ppFEV1) by approximately **10–14 points** in pivotal trials and lowering the hazard of death by **66%** (HR 0.34; 95% CI 0.28–0.41) in a 25,103-patient registry cohort.[2,3] CF is now a disease PCPs increasingly encounter in adults and older adults.[4,5]

ICD-10 Codes:[6]

The primary code is **E84** (cystic fibrosis), subdivided by organ manifestation: **E84.0** (with pulmonary manifestations), **E84.11** (meconium ileus), **E84.19** (with other intestinal manifestations), **E84.8** (with other manifestations), and **E84.9** (unspecified). CF requires combination coding: code the specific **E84.x** subtype documented, then add secondary codes for infectious organisms: **B96.5** (*Pseudomonas aeruginosa*), **B95.8** (*Staphylococcus aureus*); for complications such as bronchiectasis (**J47.0/J47.1/J47.9**), spontaneous pneumothorax (**J93.83/J93.9**), and hemoptysis (**R04.2**). The single most common coding error is defaulting to **E84.9** (unspecified), which is flagged by payers and fails to capture true acuity; **E84.9** is appropriate only at initial diagnostic workup before manifestations are characterized.[6] Comorbidities are coded separately; CF-related diabetes (CFRD) is **E13.x** (other specified diabetes), NOT **E11** (type 2).[6,7]

Prevalence and Burden: CF affects approximately **40,000 individuals** in the United States, with roughly 1,000 new diagnoses annually.[1] The demographic has shifted dramatically: median predicted survival rose from **36.3 years** (95% CI 35.1–37.9) **in 2006** to **53.1 years** (95% CI 51.6–54.7) **in 2021**, and microsimulation modeling projects a median survival of 71.6 years for F508del-homozygous patients treated with ETI, rising to 82.5 years when ETI is started between ages 12–17.[8,9] Adults now form **the majority of the CF population**, and those aged 40 and older are the fastest-growing cohort, with a meaningful number **living into their 60s**, **70s, and beyond**.[1,10] A critical caveat for the Medicare population: **no patients aged 65+ were included in ETI clinical trials**, and no CF guideline specifically addresses the geriatric population; **all 65+ recommendations are extrapolated** from general adult CF data and expert consensus.[10]

HCC/RAF V28 Mapping

ICD-10 CODE(S)[6]	HCC CATEGORY (V28)[11]	RAF (CNA)*[12]	DOCUMENTATION REQUIREMENT
E84.0 (CF with pulmonary manifestations)	**HCC 277** Cystic Fibrosis	0.998	**Most clinically complete code for CF patients** with lung disease; document chronic cough, bronchiectasis, recurrent pneumonia, *Pseudomonas* colonization, and FEV_1 values; add **B96.5** for *Pseudomonas*

ICD-10 CODE(S)[6]	HCC CATEGORY (V28)[11]	RAF (CNA)*[12]	DOCUMENTATION REQUIREMENT
E84.11 (meconium ileus in CF)	**HCC 277** Cystic Fibrosis	0.998	**Historical/pediatric diagnosis**; rare in new geriatric presentations but **documents lifelong disease history**
E84.19 (CF with other intestinal manifestations)	**HCC 277** Cystic Fibrosis	0.998	Document steatorrhea, DIOS, pancreatic insufficiency, malabsorption; **add K56.49** for DIOS when present
E84.8 (CF with other manifestations)	**HCC 277** Cystic Fibrosis	0.998	**Corresponds to**: hepatobiliary disease, male infertility, and other non-pulmonary/non-GI involvement; **CFRD** must be coded separately as **E13.x**
E84.9 (CF, unspecified)	**HCC 277** Cystic Fibrosis	0.998	**AVOID**: undercodes complexity; use **ONLY** at initial workup **before** manifestations are characterized; **replace with specific E84.x** once organ involvement is documented
E13.9 (CFRD, uncomplicated)	**HCC 38** Diabetes with Glycemic/ Unspecified/No Complications	0.166	Code **CFRD as E13.x** (other specified diabetes), **NOT E11** (type 2); **E13.9** is the default for **uncomplicated CFRD**; insulin is the only guideline-recommended therapy[13]
E13.0x-E13.5x (CFRD with complications)	**HCC 36** Diabetes with Severe Acute Complications	0.166	**Specify complication**: **E13.2x** (kidney), **E13.3x** (ophthalmic), **E13.4x** (neurological), **E13.5x** (circulatory), **E13.1x** (ketoacidosis)
B96.5 (*P. aeruginosa*)	**No HCC**	—	**Secondary code**, **pair with E84.0**; document chronic vs. intermittent colonization and culture results
B95.61/B95.62 (*S. aureus* MSSA/ MRSA)	**No HCC**	—	**Secondary code, pair with E84.0**; use B95.62 for MRSA. Document susceptibility and chronic carriage vs. acute infection
A31.0 (Pulmonary NTM infection)	**No HCC**	—	**Secondary code, pair with E84.0**; document species, AFB cultures, and CT findings. Rising prevalence in aging CF patients

ICD-10 CODE(S)[6]	HCC CATEGORY (V28)[11]	RAF (CNA)*[12]	DOCUMENTATION REQUIREMENT

ABBREVIATIONS: ICD-10 = International Classification of Diseases, 10th Revision; HCC = Hierarchical Condition Category; CMS-HCC V28 = Centers for Medicare & Medicaid Services Hierarchical Condition Category Model V28; RAF = Risk Adjustment Factor; CNA = Community Non-Dual Eligible, Aged segment; CF = cystic fibrosis; FEV_1 = forced expiratory volume in 1 second; DIOS = distal intestinal obstruction syndrome; GI = gastrointestinal; CFRD = cystic fibrosis–related diabetes; MSSA = methicillin-susceptible Staphylococcus aureus; MRSA = methicillin-resistant Staphylococcus aureus; NTM = nontuberculous mycobacteria; AFB = acid-fast bacilli; CT = computed tomography
*RAF values represent the Community Non-Dual Eligible Aged (CNA) coefficient from the 2026 CMS-HCC model;[12] values vary across patient populations based on eligibility and care setting

RAF values represent the Community Non-Dual Eligible Aged (CNA) coefficient from the 2026 CMS-HCC model; values vary across patient populations based on eligibility and care setting

Risk-Adjusted Care Resources per Patient/Year[11,12]

Risk-adjusted care resource allocation — MA base rate ($10,402.34) × RAF coefficient

CYSTIC FIBROSIS	CYSTIC FIBROSIS-RELATED DIABETES
$10.4K	**~$12.1K**
HCC 277 · RAF 0.998	HCC 277 + HCC 36/38 · combined RAF 1.164

RAF values represent the Community Non-Dual Eligible Aged (CNA) coefficient from the 2026 CMS-HCC model; values vary across patient populations based on eligibility and care setting

AAVBC PERSPECTIVE

***From the AAVBC's perspective**, value-based care in cystic fibrosis requires that primary care **recognize multisystem symptom clustering** — upper-lobe bronchiectasis paired with chronic sinusitis, recurrent pancreatitis, or male infertility — as potential **atypical late-onset CF**, even in older adults with **no newborn-screen history**.[14,15] A negative newborn screen **does not exclude CF**: false-negative rates reach 9.2% in Black infants, and standard panels miss 13–28% of minority cases.[16] Clinical suspicion should prompt **sweat chloride testing** and **comprehensive CFTR sequencing**, not reliance on NBS status.*

***Two distinct aging CF populations now exist**: long-term survivors developing age-related comorbidities atop established disease, and newly diagnosed late-onset patients previously mislabeled with "recurrent bronchitis" or "idiopathic pancreatitis." **For both**, PCPs must own preventive care: **colonoscopy at age 40**, **CFRD screening via OGTT**, **cardiovascular/metabolic monitoring**, and **bone health**;[17,18] all while co-managing CFTR modulator therapy (**ETI**) safety and drug interactions with the **CF center**. The **SIMPLIFY trial** supports de-escalation of hypertonic saline or dornase alfa in **stable ETI-treated patients**, reducing treatment burden; this treatment decision **must be made in collaboration** with the accredited CF care team.[19]*

2 RECOGNITION AND DIAGNOSIS

Cystic fibrosis is included on the federal **Recommended Uniform Screening Panel**, and universal newborn screening (NBS) for CF has been implemented in **all 50 US states and the District of Columbia since 2010**.[1,20,21] Most programs use **immunoreactive trypsinogen** (**IRT**) followed by **CFTR variant panel testing**; some states now include third-tier CFTR sequencing to improve equity across ancestral groups.[16,20] The CFF published updated NBS consensus guidelines in 2025 recommending **screening for all CF-causing CFTR2 variants** and use of a floating IRT cutoff.[16] NBS **does not replace** confirmatory sweat chloride testing, and approximately 20% of infants with inconclusive initial results **will later meet CF diagnostic criteria**.[1] **There is currently no population-wide adult screening program for CF**; adult diagnosis relies on **clinical suspicion** in patients presenting with compatible symptoms (chronic sinopulmonary disease, bronchiectasis, male infertility, pancreatitis).[1]

Medicare Part B-Covered Diagnostic and Surveillance Tests (Adult and Geriatric CF)

TEST	FREQUENCY	CPT/ HCPCS	CLINICAL INDICATION
Sweat chloride test (collection + analysis)	**Once at diagnostic evaluation**; repeat if intermediate[13]	89230/ 82435	**Gold-standard confirmatory test**: Cl^- ≥60 mmol/L diagnostic, 30–59 intermediate, <30 CF unlikely[1]
CFTR genetic testing/ sequencing	**Once for diagnosis**; expand panel if standard negative[13]	81220–81224	Two disease-causing variants confirm diagnosis;[13] consider screening **all CFTR2 variants**[1]
Spirometry (FEV_1, FVC)	**At minimum twice annually in pwCF ≥6 years old**;[22] more often during exacerbation	94010/ 94060	**FEV_1 40%** predicted triggers **advanced-lung-disease evaluation**; insensitive for early disease in modulator era[23]
OGTT: CFRD screening	**Annually** from age 10[18]	82947/ 82950	HbA1c alone is insufficient (spuriously low in CF); ADA 2026 permits **A1C ≥5.5%** as first-step screen with **confirmatory OGTT for 5.5–6.4%**[18]
DXA bone density	**Baseline then q2–5 yr**[1]	77080	**CF patients qualify** due to chronic inflammation, vitamin malabsorption, and steroid exposure[24]

TEST	FREQUENCY	CPT/ HCPCS	CLINICAL INDICATION
Colonoscopy: high-risk CRC screening†	Begin **age 40** (age 30 post-transplant); **q5y** normal, **q3y** if adenomas	G0105	CF is a recognized **increased-risk CRC category** (SIR 6.2);[17] CF-specific intensive bowel prep required[25]
Liver function tests (ALT, AST, GGT, alk phos, bilirubin, platelets)	**Annually** at clinical stability	80076	CFF 2024 recommends **annual labs from diagnosis**;[26] calculate ≥1 fibrosis index (APRI, FIB-4) annually
Renal function (eGFR; consider cystatin C)‡	**Annually**; more often with IV antibiotic courses	82565/ 82610	**Cystatin C–based eGFR more accurate in CF** given reduced muscle mass[27]
Chest CT	**At diagnosis**/ complication evaluation	71250/ 71260	**Bronchiectasis assessment**; upper-lobe cylindrical bronchiectasis is a classic late-onset CF imaging clue[28]
Annual Wellness Visit§	**Annually**	G0438/ G0439	**Document all CF manifestations**; **reconcile medications**; ACP (99497/99498) billable with no copay

ABBREVIATIONS: CPT/HCPCS = Current Procedural Terminology/Healthcare Common Procedure Coding System; CF = cystic fibrosis; CFTR = cystic fibrosis transmembrane conductance regulator; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; pwCF = people with cystic fibrosis; OGTT = oral glucose tolerance test; CFRD = cystic fibrosis–related diabetes; HbA1c = hemoglobin A1c; ADA = American Diabetes Association; DXA = dual-energy X-ray absorptiometry; CRC = colorectal cancer; SIR = standardized incidence ratio; ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyl transferase; CFF = Cystic Fibrosis Foundation; APRI = AST-to-platelet ratio index; FIB-4 = Fibrosis-4 Index; eGFR = estimated glomerular filtration rate; IV = intravenous; CT = computed tomography; AWV = Annual Wellness Visit; ACP = advance care planning; FIT = fecal immunochemical test; BUN = blood urea nitrogen; GFR = glomerular filtration rate

† CFF Colorectal Cancer Screening Consensus (2018): CF is a colon cancer syndrome; standard bowel prep is inadequate — CF-specific intensive prep is required. FIT has not been validated in CF

‡ GeneReviews recommends annual serum electrolytes, BUN, and creatinine for all CF patients. Cystatin C provides superior GFR estimation in CF due to low muscle mass confounding creatinine-based equations

§ ACP is covered with no patient copay when performed during the AWV; 99497 covers the first 30 minutes, 99498 each additional 30 minutes

Subtle and Atypical Signs in Older Adults

SIGN/SYMPTOM[13,14,29]	CLINICAL SIGNIFICANCE[18,22,30–33]
Upper-lobe cylindrical bronchiectasis without clear etiology	**Classic late-onset CF imaging clue**; prompt sweat chloride and CFTR testing **even with negative newborn screen**
Recurrent "bronchitis," chronic sinusitis, or nasal polyps	**Mild/late-onset CF** masquerades as isolated airway disease; clustering suggests multisystem CF rather than separate diagnoses

SIGN/SYMPTOM[13,14,29]	CLINICAL SIGNIFICANCE[18,22,30–33]
Idiopathic recurrent pancreatitis	Pancreatic-sufficient atypical CF can present as **recurrent pancreatitis**; consider CFTR-related disease in unexplained cases
Obstructive azoospermia/male infertility	Congenital bilateral **absence of the vas deferens** is a common adult CF presentation rarely linked to CF during fertility workup
Unexplained weight loss, fatigue, or dyspnea in known CF	Red flag, **not normal aging**; often signals pulmonary exacerbation, new CFRD, or emerging malignancy; low threshold for CF-center contact
New or increasing hemoptysis	Decades of airway remodeling place older CF patients at **highest lifetime risk for massive hemoptysis**; any new hemoptysis warrants urgent pulmonology contact
Recurrent pulmonary infection with S. aureus or NTM	Older CF patients have **higher *S. aureus* and NTM rates than the *Pseudomonas*-dominant younger pattern**; new NTM on culture needs ID/ pulmonology input
Polyuria/polydipsia or unexplained hyperglycemia in CF	**CFRD affects ~50% of adults** and rises with age; do **not** default to type 2 diabetes → Confirm with OGTT and **treat with insulin**
Persistent constipation or partial bowel obstruction	**DIOS risk is higher** in older adults due to age-related dysmotility layered on CF mucous viscosity; distinguish from simple constipation

ABBREVIATIONS: CF = cystic fibrosis; CFTR = cystic fibrosis transmembrane conductance regulator; CFRD = cystic fibrosis–related diabetes; NTM = nontuberculous mycobacteria; ID = infectious disease; OGTT = oral glucose tolerance test; DIOS = distal intestinal obstruction syndrome

Geriatric Risk Factors

FACTOR	RISK SIGNAL	NOTES
Colorectal cancer (all CF adults)	**SIR 6.2** (95% CI 4.2–9.0) non-transplant[17,33]	CF is a formally recognized **colon-cancer-risk syndrome**;[17,33] colonoscopy begins at **age 40** with CF-specific prep[25]
Colorectal cancer (post-transplant)	**~20-30x** general population[17,33]	Immunosuppression **intensifies risk**; screening begins at **age 30** post-transplant[17,25]

FACTOR	RISK SIGNAL	NOTES
Small bowel cancer	**SIR ~20x** general population[33]	Part of the broader **CF GI-cancer signal** (esophageal, gastric, biliary);[33] low threshold for unexplained GI symptoms
CF-related diabetes (CFRD)	**~50% of CF adults**;[1] rises ~10% per decade after age 10	Female sex, severe mutation class, liver disease, low FEV_1, and pancreatic insufficiency **raise risk**;[1] annual **OGTT screening**[18]
Chronic kidney disease	**RR 2.1** vs. non-CF;[34,35] onset ~20 years earlier	**Insulin-dependent CFRD ≥5 years**: HR **4.56** for ≥40% eGFR decline; each IV-antibiotic course **HR 1.13**[34–36]
Cardiovascular disease (modulator era)	**CVD RR 2.9** vs. non-CF;[37,38] ~20 years earlier	**ETI raises total cholesterol and LDL**;*[37] high-fat/high-salt CF diet now **poses CV risk**; manage statin–modulator interactions
Accelerated osteoporosis	Markedly elevated **fracture risk**[37]	Driven by **chronic inflammation**, vitamin D malabsorption, steroid exposure; DXA q2–5 y with CF-specific thresholds[1,22]
Depression/anxiety	**2–3x** higher than community samples[39]	**Screen annually** with PHQ-9/GAD-7
Adult-onset/ atypical CF profile	73% **pancreatic sufficient**; 84% **compound heterozygous**[14,15]	**Single-organ presentation common**; [14,15,22] **do not require** classic malabsorption to suspect CF

ABBREVIATIONS: SIR = standardized incidence ratio; CI = confidence interval; CF = cystic fibrosis; GI = gastrointestinal; CFRD = cystic fibrosis–related diabetes; FEV_1 = forced expiratory volume in 1 second; OGTT = oral glucose tolerance test; RR = rate ratio; eGFR = estimated glomerular filtration rate; HR = hazard ratio; IV = intravenous; CVD = cardiovascular disease; ETI = elexacaftor/tezacaftor/ivacaftor; LDL = low-density lipoprotein; CV = cardiovascular; DXA = dual-energy X-ray absorptiometry; PHQ-9 = Patient Health Questionnaire-9; GAD-7 = Generalized Anxiety Disorder-7

Diagnostic Criteria and Severity Classification

TEST/SYSTEM	DIAGNOSTIC CRITERION	NOTES
Sweat chloride test (gold standard)	**≥60** mmol/L diagnostic; **30–59** mmol/L intermediate; **<30** mmol/L CF unlikely[1,15]	Adult/late-onset diagnosis often shows lower values (mean 75±26 mmol/L vs. 100±19 in childhood);[15] intermediate results require genetic and clinical correlation

TEST/SYSTEM	DIAGNOSTIC CRITERION	NOTES
CFTR genetic testing	**Two disease-causing CFTR variants confirm diagnosis**[16,40]	Standard 23–40 mutation panels **miss many variants**; CFF 2025 recommends screening **all CFTR2-database variants**, especially in non-White patients[16]
Nasal potential difference testing	Adjunct when sweat testing and mutation analysis are **inconclusive**[29]	Reserved for **diagnostically ambiguous cases**; performed at specialized CF centers[29]
Diagnostic framework	Clinical features **OR** positive newborn screen, **PLUS** evidence of CFTR dysfunction[13,16]	A negative newborn screen **does not satisfy or exclude the framework in a symptomatic adult** → pursue confirmatory testing
CFF Advanced CF Lung Disease (ACFLD) criteria	**FEV1 <40% predicted when stable**, **OR** transplant referral, **OR** ICU respiratory failure, hypercarbia (PaCO2 >50), resting daytime O2, PA systolic >50, NYHA IV, or 6MWT <400 m[23]	Identifies patients needing **intensified care**, **transplant evaluation**, and **palliative-care integration**[23]
CFF lung transplant referral threshold	**Refer no later than** stable FEV1 <30% predicted (~10% annual mortality at this level)[41]	**Additional markers**: 6MWT <400 m, BMI <18 kg/m^2, >2 IV-treated exacerbations/ year, massive hemoptysis, pneumothorax[23]
CFRD diagnosis	**OGTT-confirmed** (HbA1c alone insufficient); ADA 2026 two-step A1C ≥5.5% → OGTT[18]	**Insulin is the only guideline-recommended treatment**;[18] complication screening begins 5 years after diagnosis

ABBREVIATIONS: CF = cystic fibrosis; CFTR = cystic fibrosis transmembrane conductance regulator; CFF = Cystic Fibrosis Foundation; ACFLD = advanced cystic fibrosis lung disease; FEV_1 = forced expiratory volume in 1 second; ICU = intensive care unit; $PaCO_2$ = partial pressure of carbon dioxide; PA = pulmonary artery; NYHA = New York Heart Association; 6MWT = 6-minute walk test; BMI = body mass index; IV = intravenous; CFRD = cystic fibrosis–related diabetes; OGTT = oral glucose tolerance test; HbA1c = hemoglobin A1c; ADA = American Diabetes Association

Clues to Dig Deeper

CLINICAL CLUE	WHY IT MATTERS	NEXT DIAGNOSTIC STEP
Upper-lobe bronchiectasis without clear etiology in adult ≥60	Late-onset atypical CF classically **localizes to the upper lobes**; easily mislabeled idiopathic bronchiectasis[10]	**Sweat chloride test**; comprehensive CFTR sequencing; refer to adult CF center[13,16]
Chronic sinusitis with nasal polyps + airway disease	Sinonasal disease clustering with lung symptoms suggests **multisystem CFTR-related disease**[10,15]	**Sweat chloride**; CFTR genetic testing; sinus CT if not already imaged[10,13]

CLINICAL CLUE	WHY IT MATTERS	NEXT DIAGNOSTIC STEP
Idiopathic recurrent pancreatitis	**Pancreatic-sufficient CF** can present as **recurrent pancreatitis** even with normal absorption[15]	**CFTR variant testing**; sweat chloride; GI/CF-center referral[13,15]
Male infertility/obstructive azoospermia	**CBAVD** is a frequent **isolated adult CF presentation** missed in fertility workup[15]	**CFTR testing**; sweat chloride
Unexplained weight loss or fatigue in established CF	Red flag for exacerbation, new CFRD, or malignancy = **not normal aging**[18,29]	**Spirometry vs. baseline**; **OGTT**; review CRC screening status; CF-center contact[18,29]
New glucose abnormality in a CF patient	**CFRD is frequently miscoded and mistreated** as type 2 diabetes[13,18]	**Confirm with OGTT** (not HbA1c alone); endocrinology referral for insulin initiation; code E13.x[18]
New medication added to a patient on ETI	**ETI is a CYP3A4 substrate with 86 identified drug-drug interactions**;*[42,43] a new drug can cause toxicity or therapeutic failure	Pharmacist-led interaction review **before prescribing**; check statins, warfarin, azoles, immunosuppressants[42,43]

ABBREVIATIONS: CF = cystic fibrosis; CFTR = cystic fibrosis transmembrane conductance regulator; CT = computed tomography; GI = gastrointestinal; CBAVD = congenital bilateral absence of the vas deferens; CFRD = cystic fibrosis–related diabetes; OGTT = oral glucose tolerance test; CRC = colorectal cancer; HbA1c = hemoglobin A1c; ETI = elexacaftor/tezacaftor/ivacaftor; CYP3A4 = cytochrome P450 3A4
***Consult FDA labels for the most up-to-date dosage information, contraindications, and drug-drug interactions**

Common Oversights

OVERSIGHT/SHORTCUT	WHY IT MATTERS — WHAT TO DO INSTEAD
Ruling out CF because the newborn screen was negative	**9.2% false-negative** in Black infants; panels miss **13–28%** of minority CF[13,16]
Treating recurrent bronchitis, sinusitis, or pancreatitis as isolated problems	Multisystem clustering = atypical CF pattern; **single-organ presentation** common in late-diagnosed adults[13]
Screening CFRD with HbA1c alone	**HbA1c spuriously low in CF**; **OGTT** is required screening tool[18]
Deferring all preventive care to the CF center	**PCP owns** colonoscopy, CV/metabolic screening, DXA, mental health
Starting colonoscopy at 45 with standard bowel prep	CF colonoscopy at **age 40** (**30 post-transplant**);[17] CF-specific intensive prep required[25]

OVERSIGHT/SHORTCUT	WHY IT MATTERS — WHAT TO DO INSTEAD
Assuming modulator-treated patients are 'cured' or disease-free	**Chronic infection persists**;[22,44] ~10% non-responsive variants; FEV_1 can decline after 2–5 years
Attributing weight loss, fatigue, or dyspnea to normal aging	Red flags for exacerbation, CFRD, or malignancy in CF[1,13]
Prescribing a new drug to an ETI patient without pharmacist review	86 drug-drug interactions documented*[42,43]
Independently de-escalating CF-specific therapy	**SIMPLIFY** supports de-escalation only with CF care team collaboration[19]

ABBREVIATIONS: CF = cystic fibrosis; CFRD = cystic fibrosis–related diabetes; HbA1c = hemoglobin A1c; OGTT = oral glucose tolerance test; PCP = primary care provider; CV = cardiovascular; DXA = dual-energy X-ray absorptiometry; FEV_1 = forced expiratory volume in 1 second; ETI = elexacaftor/tezacaftor/ivacaftor; SIMPLIFY = randomized trial of therapy de-escalation in ETI-stable patients
***Consult FDA labels for the most up-to-date dosage information, contraindications, and drug-drug interactions**

Key Differentials in Elderly

PRESENTATION	DIFFERENTIAL	KEY TESTS
Upper-lobe bronchiectasis in adult ≥60	**Atypical late-onset CF**; non-CF bronchiectasis; ABPA; NTM lung disease; prior tuberculosis; **alpha-1 antitrypsin deficiency**[45]	**Sweat chloride**;[15,22] CFTR sequencing; sputum culture/AFB; serum IgE; alpha-1 antitrypsin level[45]
Chronic sinusitis with nasal polyp	**Atypical CF**; chronic rhinosinusitis; aspirin-exacerbated respiratory disease; primary ciliary dyskinesia[15]	**Sweat chloride**; CFTR testing; sinus CT; ciliary studies if indicated[13,15]
New diabetes in a CF patient	**CFRD**; type 2 diabetes; steroid-induced hyperglycemia; pancreatogenic diabetes[18]	**OGTT** (not HbA1c alone);[18] code **E13.x**; endocrinology referral for insulin
Recurrent pancreatitis	**CFTR-related pancreatitis**;[13,15] gallstone disease; alcohol/ hypertriglyceridemia; autoimmune pancreatitis	**CFTR variant testing**; sweat chloride; lipid panel; imaging[13,15]
Declining renal function in CF	**CF-related kidney disease**;[27,34,35] aminoglycoside nephrotoxicity; diabetic nephropathy (CFRD); age-related decline	eGFR (**cystatin C–based**);[27] urinalysis; review IV-antibiotic and modulator exposure
New cardiovascular/ metabolic findings on ETI	**Modulator-associated** dyslipidemia/ obesity/hypertension; primary metabolic syndrome; secondary causes*[22]	**Lipid panel**; BP monitoring; weight/BMI tracking; statin–modulator interaction review[22]

PRESENTATION	DIFFERENTIAL	KEY TESTS

ABBREVIATIONS: CF = cystic fibrosis; CFTR = cystic fibrosis transmembrane conductance regulator; ABPA = allergic bronchopulmonary aspergillosis; NTM = non-tuberculous mycobacteria; AFB = acid-fast bacilli; IgE = immunoglobulin E; CT = computed tomography; CFRD = cystic fibrosis–related diabetes; OGTT = oral glucose tolerance test; HbA1c = hemoglobin A1c; CRC = colorectal cancer; eGFR = estimated glomerular filtration rate; IV = intravenous; ETI = elexacaftor/tezacaftor/ivacaftor; BP = blood pressure; BMI = body mass index
***Consult FDA labels for the most up-to-date dosage information, contraindications, and drug-drug interactions**

Comorbidity Screening

CONDITION	PREVALENCE/ASSOCIATION	SCREENING APPROACH
CF-related diabetes (E13.x)	**~50% of adult CF patients**; rises ~10% per decade after age 10; often misdiagnosed as type 2[1,14,18]	**Annual OGTT** from age 10 (HbA1c insufficient); code **E13.x not E11**; insulin is first-line; microvascular screening 5 y after diagnosis[18,22]
Colorectal cancer (Z12.11)	**SIR 6.2** vs. general population;[17] up to 50% have adenomatous polyps at screening[25]	Colonoscopy at **age 40** (**30 post-transplant**);[17] q5y normal, q3y adenomas; CF-specific intensive bowel prep[25]
Chronic kidney disease (N18.x)	RR 2.1 vs. non-CF;[35] onset **~20 y earlier**; insulin-dependent CFRD strongest predictor	Annual eGFR (**cystatin C–based preferred**);[34] more often with IV-antibiotic courses; nephrology if progressive
Cardiovascular/metabolic disease (I10, E78.x)	CVD RR 2.9 vs. non-CF;[1] **ETI raises total cholesterol and LDL**; emerging obesity/HTN[37]	**Lipid panel**; BP monitoring; weight/BMI; reassess high-fat CF diet; manage statin–ETI interactions
Osteoporosis (M81.0)	**Accelerated bone loss**;[22] postmenopausal women at **highest compounding risk**	**DXA baseline then q2–5 y**; calcium + vitamin D; bisphosphonate when indicated; **fall prevention**
Hepatobiliary disease (E84.8 + K74.x)	Ranges from steatosis to cirrhosis;[26] **modulator hepatotoxicity adds risk**	**Annual LFTs**; elastography if involvement; HCC surveillance in cirrhosis; pharmacist review q6 mo
Depression/anxiety (F32.x, F41.x)	**2–3x higher** than community;[39] symptoms misattributed to aging	**Annual PHQ-9 and GAD-7**; PHQ-9 ≥10 prompts evaluation; treat to improve adherence

CONDITION	PREVALENCE/ASSOCIATION	SCREENING APPROACH
DIOS (K56.49)	**Higher baseline risk** in older adults from gut-motility changes + CF mucus[32]	**Distinguish from simple constipation**; bowel regimen; CF-center input for recurrent episodes
Polypharmacy/modulator interactions (Z79.899)	ETI has **86 identified drug-drug interactions**;* risk amplified by geriatric polypharmacy	Pharmacist-led reconciliation **at every visit** and every new prescription; deprescribing review

ABBREVIATIONS: CF = cystic fibrosis; CFRD = cystic fibrosis–related diabetes; OGTT = oral glucose tolerance test; HbA1c = hemoglobin A1c; SIR = standardized incidence ratio; RR = rate ratio; eGFR = estimated glomerular filtration rate; IV = intravenous; CVD = cardiovascular disease; ETI = elexacaftor/tezacaftor/ivacaftor; LDL = low-density lipoprotein; HTN = hypertension; BP = blood pressure; BMI = body mass index; DXA = dual-energy X-ray absorptiometry; LFT = liver function test; HCC = hepatocellular carcinoma; PHQ-9 = Patient Health Questionnaire-9; GAD-7 = Generalized Anxiety Disorder-7; DIOS = distal intestinal obstruction syndrome
***Consult FDA labels for the most up-to-date dosage information, contraindications, and drug-drug interactions**

⚠ RED FLAG — EMERGENCY/ACTIVATE CRISIS RESPONSE

These emergency conditions require **same-day ED transfer and immediate notification of the accredited CF center:**

- **Massive hemoptysis** (>240 mL in 24 hours or hemodynamically significant bleeding)[22]
  - → **Emergent bronchial artery embolization or surgical consultation**; volume resuscitation; position bleeding lung dependent
  - × Hemoptysis is the **leading cause of non-transplant CF death** in adults; delay in embolization increases mortality
- **Tension or large spontaneous pneumothorax with respiratory distress** (E84.0 + J93.83)
  - → **Emergent chest tube placement**; thoracic surgery consultation; notify transplant team if listed[41]
  - × Recurrence rate **exceeds 50% in CF**; pneumothorax is a relative contraindication to future transplant at some centers[41]
- **Acute respiratory failure with hypoxemia (SpO_2 <88%) or hypercarbia ($PaCO_2$ >50 mmHg)**
  - → **ICU-level care**; NIV if appropriate; culture-directed IV antibiotics; contact CF center for co-management
  - × Acute-on-chronic respiratory failure in CF carries **high short-term mortality**; early escalation is critical
- **Severe DIOS with complete bowel obstruction, peritonitis, or hemodynamic instability**[1]
  - → **Surgical consultation**; IV hydration and Gastrografin via NG if no perforation; emergent laparotomy if peritonitis
  - × Complete DIOS mimics surgical abdomen; CF-experienced surgical input **prevents unnecessary resection**

⚠ RED FLAG — URGENT (24-72 HOURS)

Expedited workup required = **do not** refer to routine follow-up:

- **Acute pulmonary exacerbation with FEV_1 decline >10% from baseline, fever, or increased sputum**[13]
  - → **Sputum culture**; prompt IV-antibiotic initiation (culture-directed); intensified airway clearance
  - × Delayed treatment of exacerbations accelerates **irreversible lung function loss**
- **Suspected modulator-induced liver injury** (ALT/AST >5× ULN, or >3× ULN with bilirubin >2× ULN)
  - → **Hold ETI immediately**; contact CF center/hepatology; serial LFTs; do not rechallenge without specialist guidance
  - × ETI hepatotoxicity is dose-dependent and **reversible if caught early**; continuation risks fulminant injury
- **Stable FEV_1 approaching <40% predicted**
  - → **Expedited CF-center referral for transplant workup**; integrate palliative care; evaluate markers of shortened survival
  - × ~10% annual mortality at FEV_1 <30%; transplant evaluation takes months: **late referral narrows the window**[41]
- **New CFRD diagnosis or uncontrolled hyperglycemia**[13,18,22]
  - → **Endocrinology referral for insulin initiation**; code **E13.x** (not E11); begin microvascular screening at 5 years
  - × Untreated CFRD accelerates lung function decline and increases mortality; **metformin is not recommended**[18]
- **Unexplained weight loss or failure to maintain weight in established CF**
  - → **Active workup**: spirometry vs. baseline, OGTT, colonoscopy status; low threshold for CF-center contact
  - × **Do not attribute to aging** → weight loss in CF signals exacerbation, CFRD, or malignancy until proven otherwise

3 MEAT DOCUMENTATION ESSENTIALS

Cystic fibrosis documentation translates **multisystem complexity** into a record that supports **continuity, quality measurement, and coordinated care**. The most common gaps are defaulting to **E84.9** (unspecified) instead of coding the specific organ manifestation, miscoding CF-related diabetes as **E11** (type 2) rather than **E13.x**, omitting required secondary codes for organisms and complications, and failing to capture the expanding comorbidity burden (colorectal cancer risk, CKD, cardiovascular/metabolic disease, osteoporosis, depression) that now **applies to**

the aging CF patient. Each gap obscures the patient's real clinical picture and impedes shared decision-making with the accredited CF care team, pulmonology, endocrinology, and GI colleagues. The MEAT framework below ties each element into **appropriate clinical action**:

*A 67-year-old male presents to his PCP for an annual wellness visit with a **2-year history of recurrent "bronchitis,"** chronic sinusitis with nasal polyps, and one episode of **idiopathic pancreatitis**. He reports **lifelong subfertility**. PMH: hypertension (amlodipine), borderline dyslipidemia. Chest CT (ordered for persistent cough) shows upper-lobe cylindrical bronchiectasis. Newborn screening status unknown (born before universal NBS). Functional status: independent in all ADLs.*

MONITOR: "Smoking status: never. Weight: stable at 82 kg. Functional status: independent ADLs. Respiratory: **recurrent lower-respiratory infections** and chronic sinusitis with nasal polyps over 2 years; upper-lobe cylindrical bronchiectasis on chest CT. GI: one prior episode of **idiopathic pancreatitis**. Reproductive: **lifelong subfertility** (possible CBAVD). Spirometry: **FEV_1 78%** predicted. BP 138/84 on amlodipine. Fasting glucose 104 mg/dL. No prior CF testing; newborn screening status unknown."

EVALUATE: "Sweat chloride testing ordered given constellation of upper-lobe bronchiectasis, sinonasal disease, pancreatitis, and infertility → **atypical late-onset CF suspected** despite no known newborn-screen history. Sweat chloride result (date): 68 mmol/L (diagnostic, ≥60 threshold). Comprehensive CFTR sequencing (date): F508del plus residual-function variant identified (compound heterozygous) = consistent with **pancreatic-sufficient atypical CF**. OGTT ordered to screen for CFRD given fasting glucose 104 mg/dL. OGTT result (date): 2-hour glucose 215 mg/dL (diagnostic for CFRD, ≥200 threshold)."

ASSESS: "Cystic fibrosis with pulmonary manifestations confirmed (**E84.0**): chronic cough, upper-lobe bronchiectasis (**J47.9**). CF-related diabetes, OGTT-confirmed (**E13.65**) = **NOT type 2**; code **E13.x**, **not E11**. Obstructive azoospermia (**N46.023**). Essential hypertension (**I10**). Mixed hyperlipidemia (**E78.2**). PHQ-9 screened: [score]. No ACFLD criteria met (FEV_1 78%)."

TREAT: "**Referred to accredited adult CF center** for CFTR-modulator evaluation (**ETI appropriate** given F508del allele) and multidisciplinary management. Colonoscopy initiated now (age >40, CF increased-risk designation per NCCN with CF-specific intensive bowel prep); endocrinology referral for insulin initiation for newly diagnosed CFRD; DXA and lipid panel ordered. Pharmacist-led drug-interaction review completed **before any new prescription**: amlodipine and any statin interact with ETI; rosuvastatin or pravastatin selected over simvastatin/lovastatin. Patient counseled on high-fat dosing requirement for ETI **balanced against cardiovascular risk**. CF-center co-management plan documented. ACP documented (CPT 99497): surrogate named, code status discussed. Shared decision-making documented; patient agrees to CF-center referral and modulator evaluation."

Clinical Documentation Elements

- **Code the specific organ manifestation**: **E84.0** (pulmonary), **E84.19** (intestinal), **E84.8** (other), or **E84.11** (meconium ileus history) = reserve **E84.9** (unspecified) for **initial workup only**; it is flagged by payers and undercodes acuity[6]
- **Use combination coding**: add secondary codes for organisms (**B96.5** *Pseudomonas*, **B95.8** *S. aureus*), bronchiectasis (**J47.x**), pneumothorax (**J93.83/J93.9**), and hemoptysis (**R04.2**) when documented[6]
- **Code CF-related diabetes as E13.x** (other specified diabetes), **NOT E11** (type 2);[6,18] document insulin use and annual OGTT screening → **insulin is the only guideline-recommended therapy**[18]

- **Document and code the aging-CF comorbidity burden separately**: CKD (**N18.x**), cardiovascular disease (**I25.x**), metabolic syndrome/dyslipidemia (**E78.x**), osteoporosis (**M81.0**), hepatobiliary disease (**K74.x**), and depression/anxiety (**F32.x/F41.x**)[6]
- **Document the CFTR genotype, modulator therapy, and modulator status**; inform patient that **ETI does not cure CF** and that chronic infection/airway-clearance needs can persist[15,22]
- **Document disease severity** using FEV1/ppFEV[1] and, when relevant, **ACFLD criteria** (FEV1 <40%) and transplant referral thresholds (FEV1 <30%)[23,41]
- **Document CF-specific preventive care ownership**: colonoscopy date and CF-specific prep, DXA result, lipid panel, mental-health screen, and OGTT
- **Document the pharmacist-led drug-interaction review** for any CFTR-modulator patient on polypharmacy, and advance care planning discussions for older adults[46]

Reframing Common Documentation Shortcuts

INSTEAD OF...	DOCUMENT…*[13,18,29]
'Cystic fibrosis'/'CF, unspecified'	'Cystic fibrosis with **pulmonary manifestations** (**E84.0**): chronic cough, upper-lobe bronchiectasis (**J47.9**), chronic *Pseudomonas* colonization (**B96.5**); FEV1 78% predicted'
'Diabetes' in a CF patient	'Cystic fibrosis–related diabetes (**E13.x**), **OGTT-confirmed**, on insulin; **NOT** type 2 → code **E13.x**, not **E11**'
'Bronchiectasis, idiopathic'	'Upper-lobe cylindrical bronchiectasis = **atypical late-onset cystic fibrosi**s confirmed by sweat chloride 68 mmol/L and CFTR sequencing (**E84.0**)'
'On Trikafta'	'Elexacaftor/tezacaftor/ivacaftor (**ETI**) per CF center; taken with fat-containing food; **pharmacist-led CYP3A4 interaction review completed**; LFTs and renal function monitored'
'CF, stable'	'CF, FEV1 78% predicted, **ACFLD criteria not met**; ETI-treated with persistent chronic airway infection = not disease-free; airway clearance continues'
'Frail elderly CF patient'	'Functional status documented; treatment burden assessed; de-escalation candidacy discussed with CF care team per **SIMPLIFY criteria**; IPOS screening completed'

INSTEAD OF...	DOCUMENT…*[13,18,29]
'Colon cancer screening deferred to CF center'	'Colonoscopy at age 40 per CF increased-risk designation (NCCN v2.2026) with CF-specific intensive bowel prep; **PCP-initiated and tracked**'
'Osteoporosis, age-related'	'Osteoporosis (**M81.0**): **CF-accelerated bone loss** from chronic inflammation and fat-soluble vitamin malabsorption; DXA T-score documented; on calcium/vitamin D'
'Renal function stable'	'eGFR (**cystatin C–based**) monitored annually; CF-related CKD risk from cumulative IV aminoglycoside exposure and insulin-dependent CFRD documented'
'Atypical CF, late onset'	'Late-onset atypical cystic fibrosis (**E84.0/E84.8**): **compound heterozygous F508del + residual-function variant**; pancreatic sufficient; single-organ-predominant phenotype'

ABBREVIATIONS: CF = cystic fibrosis; FEV_1 = forced expiratory volume in 1 second; CFRD = cystic fibrosis–related diabetes; OGTT = oral glucose tolerance test; CFTR = cystic fibrosis transmembrane conductance regulator; ETI = elexacaftor/tezacaftor/ivacaftor; CYP3A4 = cytochrome P450 3A4; LFT = liver function test; ACFLD = advanced cystic fibrosis lung disease; SIMPLIFY = randomized trial of therapy de-escalation in ETI-stable patients; IPOS = Integrated Palliative Care Outcome Scale; NCCN = National Comprehensive Cancer Network; PCP = primary care provider; DXA = dual-energy X-ray absorptiometry; eGFR = estimated glomerular filtration rate; CKD = chronic kidney disease; IV = intravenous
***Consult FDA labels for the most up-to-date dosage information, contraindications, and drug-drug interactions**

4 TREATMENT AND REFERRAL QUICK GUIDE

CF treatment is built on **CFTR modulator therapy**, layered chronic symptomatic therapies, exacerbation management, and specialist/transplant referral for advanced disease.[22,23,41] **Chronic suppressive inhaled antibiotics** are a cornerstone of CF lung care: the Cystic Fibrosis Foundation strongly recommends inhaled tobramycin (300 mg nebulized twice daily, 28 days on/28 days off) for patients ≥6 years with persistent *Pseudomonas aeruginosa* and moderate-to-severe lung disease (**Grade A**), and recommends it for mild disease to reduce exacerbations (**Grade B**).[47] Inhaled aztreonam and colistin are guideline-supported alternatives.[47]

In the modulator era, the PCP's highest-value contributions shift toward **preventive and comorbidity care**: suspecting atypical late-onset CF, ensuring confirmatory testing, owning colorectal cancer and CFRD screening, managing cardiovascular/metabolic/bone health, and co-monitoring modulator safety and drug interactions. **De-escalation of burdensome therapy** is appropriate for stable modulator-treated patients but **only in collaboration with the accredited CF care team**, never independently.[19,22] Decisions are made on functional status and goals of care, **not** chronologic age.

Therapy and Referral Triggers

TRIGGER[13,23,29]	ACTION[17,29,41]
Upper-lobe bronchiectasis, chronic sinusitis/ polyps, recurrent pancreatitis, or male infertility in an adult	Order **sweat chloride test** and **CFTR sequencing**; refer to accredited adult CF center; do **not** rely on a negative newborn screen
Sweat chloride ≥60 mmol/L or two disease-causing CFTR variants	**Confirm CF diagnosis**; code specific **E84.x** manifestation; refer to CF center for modulator evaluation
At least one F508del allele	CFTR-modulator candidate → **ETI per CF center**; take with fat-containing food
New medication in a patient on ETI	Pharmacist-led drug-interaction review **before prescribing**; avoid simvastatin/lovastatin; rifampin contraindicated
CF patient ≥40 years without colonoscopy	**Initiate colonoscopy now with CF-specific intensive bowel prep** (age 30 if post-transplant); PCP responsibility
Glucose abnormality or annual CFRD screen due	**Order OGTT** (HbA1c alone insufficient); if positive, endocrinology referral for insulin; code **E13.x**
FEV_1 declining toward <40% predicted	**Trigger ACFLD evaluation**; intensify care; integrate palliative care; evaluate for markers of shortened survival
Stable FEV_1 <30% predicted	**Refer for lung transplant evaluation** (~10% annual mortality at this threshold)
Stable modulator-treated patient with high treatment burden	**Discuss therapy de-escalation** (hypertonic saline, dornase alfa) **WITH** the CF care team per **SIMPLIFY**: do **not** de-escalate independently
New NTM or persistent resistant organism on sputum culture	Infectious disease/pulmonology input **before treatment decisions**; document organism with secondary code
Unexplained weight loss, fatigue, or dyspnea in established CF	**Active workup** (spirometry vs. baseline, OGTT, CRC status); low threshold for CF-center contact; do **not** attribute to aging
Advanced disease or limited life expectancy	**Annual IPOS screening**; proactive advance care planning; consider hospice when goals align

TRIGGER[13,23,29]	ACTION[17,29,41]

ABBREVIATIONS: CFTR = cystic fibrosis transmembrane conductance regulator; CF = cystic fibrosis; ETI = elexacaftor/tezacaftor/ivacaftor; PCP = primary care provider; CFRD = cystic fibrosis–related diabetes; OGTT = oral glucose tolerance test; HbA1c = hemoglobin A1c; FEV_1 = forced expiratory volume in 1 second; ACFLD = advanced cystic fibrosis lung disease; SIMPLIFY = randomized trial of therapy de-escalation in ETI-stable patients; NTM = non-tuberculous mycobacteria; CRC = colorectal cancer; IPOS = Integrated Palliative Care Outcome Scale

CLINICAL PEARL — NEBULIZED TOBRAMYCIN - VALUE-BASED HOME THERAPY

Inhaled tobramycin delivers high airway drug concentrations while largely **avoiding the nephrotoxicity and ototoxicity** of IV aminoglycosides: a crossover trial showed equivalent FEV_1 improvement but significantly less renal tubular injury with nebulized versus IV tobramycin, and **longer time to next hospitalization**.[48] In the landmark 520-patient RCT, inhaled tobramycin **reduced hospitalizations by 26%** and parenteral antibiotic use from 16.5% to 6.2% versus placebo.[49] Because patients self-administer at home with a jet nebulizer, **this therapy avoids**: inpatient admission, IV access complications, and the cumulative systemic toxicity of repeated IV aminoglycoside courses; nebulized tobramycin is therefore a **high-value strategy** that shifts infection suppression from hospital to home.

CFF-Aligned Treatment Escalation Pathway

STEP/SETTING	PREFERRED REGIMEN(S)*	KEY PCP NOTES
Step 1: CFTR modulator (≥1 F508del allele)	**Elexacaftor/tezacaftor/ivacaftor** (**ETI**, Trikafta): 200 mg ELX + 100 mg TEZ + 150 mg IVA AM, then 150 mg IVA PM; **take with fat-containing food**[1]	**ppFEV₁ +14.3 points in pivotal trial**;[3] 192-week extension showed no FEV_1 loss over 4 years;[50] registry data: 72% lower death rate, 85% lower transplant rate vs. pre-ETI era;[51] no patients ≥65 in trials = **extrapolate with caution**
Step 1 (alternate): gating/splice variants	**Ivacaftor** (Kalydeco) 150 mg every 12 hours	For non-F508del patients with **ivacaftor-responsive variants**; same CYP3A4 interaction profile as ETI*
Step 2: Chronic symptomatic therapies	**Dornase alfa 2.5 mg** inhaled daily; **hypertonic saline** 7%, 4 mL inhaled daily; inhaled tobramycin 300 mg BID (28-day cycles) for chronic *Pseudomonas*; azithromycin 250–500 mg three times weekly*	Maintain **airway clearance and reduce infection burden**; long-term azithromycin risks **macrolide resistance** and **QT prolongation**[1]

STEP/SETTING	PREFERRED REGIMEN(S)*	KEY PCP NOTES
Step 2 (de-escalation): modulator era	**Consider stopping hypertonic saline or dornase alfa** in ETI-stable patients (**SIMPLIFY**: non-inferior)[19]	Reduces treatment burden; **MUST** be done with CF care team[1]
Step 3: Pulmonary exacerbation	Culture-directed IV antibiotics; **10 days non-inferior to 14** in early responders (**STOP2**); [52] intensified airway clearance and nutritional support	IV aminoglycosides carry **ototoxic/ nephrotoxic risk amplified in older adults** → monitor renal function
Step 4: Specialist/ interventional referral	**Lung transplant** (stable FEV_1 <30%);[41] hepatology (advanced liver disease); endocrinology (CFRD, insulin); GI/oncology (colonoscopy age 40)	Advanced age is **not** an absolute transplant contraindication;[41] refer earlier as FEV_1 trends toward 40%; CF transplant volumes declined **~80%** since ETI approval[53]
CFRD management	**Insulin** (only guideline-recommended therapy);[18,32] oral hypoglycemics **not recommended** outside trials	Code **E13.x not E11**; annual OGTT; microvascular complication screening 5 years after diagnosis[32]
Frailty/high treatment burden in older adults	Functional and goals-of-care assessment; **reduce non-essential treatment burden** with CF team; integrate palliative care[46,54]	Decisions on functional status and patient goals, not chronologic age[46,54]

ABBREVIATIONS: CFTR = cystic fibrosis transmembrane conductance regulator; ETI = elexacaftor/tezacaftor/ivacaftor; ELX = elexacaftor; TEZ = tezacaftor; IVA = ivacaftor; $ppFEV_1$ = percent-predicted forced expiratory volume in 1 second; FEV_1 = forced expiratory volume in 1 second; CYP3A4 = cytochrome P450 3A4; BID = twice daily; CF = cystic fibrosis; SIMPLIFY = randomized trial of therapy de-escalation in ETI-stable patients; IV = intravenous; GI = gastrointestinal; CFRD = cystic fibrosis–related diabetes; OGTT = oral glucose tolerance test

***Consult FDA labels for the most up-to-date dosage information, contraindications, and drug-drug interactions**

CLINICAL PEARL — MODULATORS TRANSFORM CF BUT DO NOT CURE IT

A CFTR modulator **transforms CF but does not cure it**. ETI lowers the hazard of death by 66% (HR 0.34; 95% CI 0.28–0.41), and real-world registry data in 16,116 ETI-treated patients showed **pulmonary exacerbations fell 79%** and hospitalizations 74% over 2 years;[44,51] the longest extension study to date held FEV1 stable over 4 years — yet **~10% of patients carry variants no modulator addresses**, chronic airway infection persists, and FEV1 can **resume decline** after 2–5 years with poor adherence or established structural disease.[50] **Do not assume a modulator-treated patient is asymptomatic or disease-free**. The complementary truth: as patients age, the highest-value work moves **upstream to the PCP**: suspecting atypical late-onset CF, owning preventive and comorbidity care, and coordinating with the CF center.

Non-Pharmacologic Care and Supportive Interventions

INTERVENTION[22,46,54]	TARGET/ RECOMMENDATION[17,19,55]	NOTES[29,39,56]
Airway clearance therapy	**High-frequency chest wall oscillation vests**, positive expiratory pressure devices; daily	**Adapt for frailty or arthritis**; physical therapy consult for individualized approach
Therapy de-escalation (with CF team)	Consider **stopping hypertonic saline or dornase alfa** in ETI-stable patients per SIMPLIFY	**Reduces 2–4 hours/day treatment burden**; only with CF team collaboration
CF-specific dietary counseling (modulator era)	Balance ETI's high-fat dosing requirement against **emerging cardiovascular/metabolic risk**	Older patients may need **dietary transition**; CF dietitian referral recommended
Colorectal cancer screening	**Colonoscopy at age 40** (30 post-transplant); q5y normal, q3y if adenomas	**CF-specific intensive bowel prep required**; PCP-owned
Bone health	**Calcium + vitamin D**; DXA q2–5 years; bisphosphonate if indicated	Postmenopausal women at highest compounding risk; **fall prevention essential**
CFRD screening and glucose monitoring	**Annual OGTT from age 10**; home glucose monitoring for diagnosed patients	Post-meal glucose more revealing than fasting; insulin is first-line
Mental health screening	**Annual PHQ-9 and GAD-7 from age 12**; treat to improve adherence and outcomes	Depression/anxiety **2–3x** community rates; symptoms often misattributed to aging

INTERVENTION[22,46,54]	TARGET/ RECOMMENDATION[17,19,55]	NOTES[29,39,56]
Pharmacist-led medication review	**Every 6 months** on modulators; at every new prescription	ETI has extensive drug-drug interactions;*** deprescribing review reduces polypharmacy harm**
Exercise/physical activity	**150–300 min/week moderate-intensity aerobic**; 2 days/week resistance training	Supports FEV_1, bone health, glycemic control, and quality of life; **adapt for disease severity**
Home spirometry and self-monitoring	**Teach recognition of >10% FEV_1 decline**, sputum change, weight loss as care-team triggers	Empowers early exacerbation detection between visits
Early palliative care integration	**Primary palliative care from diagnosis**; annual IPOS screening from age 12	**ACP should be proactive**; specialist palliative care when considering/declining transplant

ABBREVIATIONS: ETI = elexacaftor/tezacaftor/ivacaftor; SIMPLIFY = randomized trial of therapy de-escalation in ETI-stable patients; CF = cystic fibrosis; PCP = primary care provider; DXA = dual-energy X-ray absorptiometry; CFRD = cystic fibrosis–related diabetes; OGTT = oral glucose tolerance test; PHQ-9 = Patient Health Questionnaire-9; GAD-7 = Generalized Anxiety Disorder-7; FEV_1 = forced expiratory volume in 1 second; IPOS = Integrated Palliative Care Outcome Scale; ACP = advance care planning
***Consult FDA labels for the most up-to-date dosage information, contraindications, and drug-drug interactions**

Medication Safety and Key Interactions

DRUG/CLASS*	INTERACTION/TOXICITY*[42,57]	CLINICAL ACTION[22,43,58]
Azole antifungals (itraconazole, posaconazole, voriconazole) + ETI	Strong CYP3A4 inhibitors; itraconazole increases ivacaftor AUC **up to 15.6-fold**	**ETI dose reduction** per FDA label (twice-weekly dosing); monitor LFTs closely
Strong CYP3A4 inducers (rifampin, carbamazepine, phenytoin, St. John's Wort) + ETI	Reduce ETI exposure by up to 89% → may render modulator non-therapeutic	**Concomitant use not recommended**; choose alternative agents; consult CF pharmacist
Statins (simvastatin, lovastatin) + ETI	CYP3A4/OATP inhibition **raises statin levels** (atorvastatin AUC ↑3.27-fold) → **myopathy risk**	**Avoid simvastatin/lovastatin**; rosuvastatin has weakest interaction (AUC ↑1.83-fold); pharmacist review
Warfarin + ETI	CYP2C9 inhibition increases anticoagulant effect → **bleeding risk**	Increase INR monitoring frequency after ETI initiation or dose change

DRUG/CLASS*	INTERACTION/TOXICITY*[42,57]	CLINICAL ACTION[22,43,58]
Immunosuppressants (cyclosporine, tacrolimus, sirolimus) + ETI	CYP3A4 inhibition raises immunosuppressant exposure = **critical post-transplant**	Therapeutic drug monitoring mandatory; **transplant pharmacist involvement required**
Calcium channel blockers (amlodipine) + ETI	Elevated plasma levels → **enhanced hypotensive effect**	**Monitor BP when initiating ETI**; adjust antihypertensive dose as needed
Long-term azithromycin	**QT prolongation risk** when combined with other QT-prolonging agents	Baseline ECG in older adults; **avoid combining with other QT-prolonging drugs**
IV aminoglycosides (tobramycin)	**Nephrotoxicity** (AKI in ~20% of courses) and **ototoxicity** (93% cochleotoxicity in one study); **cumulative renal injury**	Mandatory renal monitoring; cystatin C–based eGFR; **minimize cumulative exposure**; nebulized, once-daily dosing preferred (self-administer option)
Trikafta (ETI): hepatic/ renal cautions	Boxed warning: drug-induced liver injury and liver failure; **contraindicated in severe hepatic impairment** (Child-Pugh C)	**Baseline + periodic LFTs**; hold for ALT/AST >5× ULN or >3× ULN with bilirubin >2× ULN; caution if eGFR 30
Proton pump inhibitors	**No major ETI interaction**; may mask DIOS or drug-related GI symptoms	Document indication; reassess annually for continued need

ABBREVIATIONS: CYP3A4 = cytochrome P450 3A4; ETI = elexacaftor/tezacaftor/ivacaftor; AUC = area under the curve; LFT = liver function test; CF = cystic fibrosis; OATP = organic anion transporting polypeptide; CYP2C9 = cytochrome P450 2C9; INR = international normalized ratio; BP = blood pressure; ECG = electrocardiogram; QT = QT interval; IV = intravenous; AKI = acute kidney injury; eGFR = estimated glomerular filtration rate; ULN = upper limit of normal; DIOS = distal intestinal obstruction syndrome; GI = gastrointestinal; FDA = Food and Drug Administration
***Consult FDA labels for the most up-to-date dosage information, contraindications, and drug-drug interactions**

When to Refer

CRITERION[22,23]	SPECIALIST[41,54]	URGENCY[23]
Massive hemoptysis (>240 mL/24 h or hemodynamically significant)	Emergency department/pulmonology; bronchial artery embolization	**Emergent**
Tension or large spontaneous pneumothorax with respiratory distress	Emergency department/thoracic surgery	**Emergent**
Acute respiratory failure (SpO_2 88%) or hypercarbia ($PaCO_2$ 50 mmHg)	Emergency department/pulmonology	**Emergent**

CRITERION[22,23]	SPECIALIST[41,54]	URGENCY[23]
Severe DIOS with complete obstruction or peritonitis	Emergency department/surgery	**Emergent**
Suspected modulator-induced liver injury (ALT/AST 5x ULN)*	CF center/hepatology (hold ETI)	**Urgent** (same/next day)
Acute pulmonary exacerbation with FEV_1 decline 10% from personal best	CF center/pulmonology	**Urgent** (same/next day)
New-onset hemoptysis (240 mL)	Pulmonology	**Urgent** (within days)
Stable FEV_1 30% predicted	Lung transplant program	**Urgent** (within weeks)
FEV_1 trending toward 40% predicted (ACFLD criteria)	CF center/palliative care integration	**Expedited**
New CFRD or uncontrolled hyperglycemia	Endocrinology (insulin initiation)	**Expedited**
CF patient ≥40 without colonoscopy	GI/endoscopy (CF-specific intensive prep)	**Routine** (initiate promptly)
New NTM or persistent resistant organism	Infectious disease/pulmonology	**Routine** to expedited
Suspected atypical late-onset CF (sweat chloride borderline or positive, single-organ presentation)	Accredited adult CF center	**Routine** (after confirmatory testing)
Advanced disease/limited life expectancy	Palliative care; hospice when goals align	**When goals align**

ABBREVIATIONS: SpO_2 = peripheral oxygen saturation; $PaCO_2$ = partial pressure of carbon dioxide; DIOS = distal intestinal obstruction syndrome; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal; CF = cystic fibrosis; ETI = elexacaftor/tezacaftor/ivacaftor; FEV_1 = forced expiratory volume in 1 second; ACFLD = advanced cystic fibrosis lung disease; CFRD = cystic fibrosis–related diabetes; GI = gastroenterology; NTM = non-tuberculous mycobacteria

***Consult FDA labels for the most up-to-date dosage information, contraindications, and drug-drug interactions**

Monitoring and Follow-Up Intervals

PARAMETER	FREQUENCY[22,30,54]	THRESHOLD/MONITORING[18,23,55]
Spirometry (FEV_1, FVC)	**Minimum twice yearly per CFF**; more frequently during exacerbation, therapy changes, or new pathogen identification	**FEV_1 decline >10%** from personal best triggers evaluation; **FEV_1 40%** meets ACFLD criteria; **FEV_1 30%** (adults) or **50%** with rapid decline triggers **transplant referral**
Liver function tests	**Annually** (AST, ALT, GGT, alk phos, bilirubin, albumin); **every 6 months** with hepatobiliary involvement or on ETI	**Hold ETI** if ALT/AST >5x ULN or >3x ULN with bilirubin >2× ULN;* ultrasound with Doppler and elastography if persistent elevation >6 months
Renal function (eGFR; cystatin C)	**Annually minimum** (electrolytes, BUN, creatinine); more often with IV-antibiotic courses	**eGFR decline ≥40%** from baseline; **eGFR <30** prompts ETI dose review; cystatin C–based eGFR preferred (creatinine confounded by low muscle mass); each IV course HR 1.13
HbA1c monitoring	**Quarterly** once CFRD diagnosed; **annually** as part of CFRD screening if OGTT not feasible (two-step strategy)	**A1C ≥6.5%** consistent with CFRD diagnosis; A1C 5.5–6.4% → **OGTT within 3 months**; A1C 5.5% has ~98% NPV and can defer OGTT; A1C 6.5% does not rule out CFRD → **do not use A1C alone** to exclude the diagnosis
Glycemic monitoring during acute illness	Fasting and 2-h postprandial glucose for first 48 h of any pulmonary exacerbation requiring IV antibiotics or systemic glucocorticoids	**FPG ≥126 mg/dL** or 2-h postprandial **≥200 mg/dL persisting >48 h** = diagnostic of CFRD; confirm by certified laboratory if detected by SMBG
CFRD screening (OGTT)	**Annually from age 10**; A1C ≥5.5% → OGTT within 3 months; A1C ≥6.5% consistent with CFRD diagnosis	**OGTT-confirmed diagnosis** → endocrinology for insulin initiation; microvascular complication screening begins 5 years after diagnosis
Bone density (DXA)	**Baseline in adolescence** if risk factors present; then **every 2–5 years**; sooner with fracture, steroids, or CFRD	T-score **≤−2.0** or Z-score **≤−2.0** triggers bisphosphonate consideration; T-score **≤−1.5** if on systemic glucocorticoids or awaiting transplant
Colorectal cancer (colonoscopy)	**Begin age 40** (**age 30 post-transplant** or within 2 years of transplantation); **every 5 years** if normal, **every 3 years** if adenomas	**CF-specific intensive bowel prep required**; standard prep is inadequate

PARAMETER	FREQUENCY[22,30,54]	THRESHOLD/MONITORING[18,23,55]
Mental health (PHQ-9, GAD-7)	**Annually** for all patients ≥12 years	**PHQ-9 ≥10** prompts clinical evaluation and treatment planning; rates 2–3x community samples; untreated depression worsens adherence and exacerbations
IPOS palliative care screening	**Annually** and at disease milestones (changes in disease severity, functional decline, hospitalization, transplant consideration)	**Any unmet need** triggers care-team discussion; ACP conversations recommended for all individuals meeting ACFLD criteria; SPC consultation when considering or declining transplant
Pharmacist medication review	**Every 6 months** on modulators; at every new prescription	ETI is a CYP3A4 substrate and OATP1B1/1B3 inhibitor;*** flag interactions** with statins, azoles, warfarin, immunosuppressants, digoxin, and hormonal contraceptives

ABBREVIATIONS: FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; CFF = Cystic Fibrosis Foundation; ACFLD = advanced cystic fibrosis lung disease; AST = aspartate aminotransferase; ALT = alanine aminotransferase; GGT = gamma-glutamyl transferase; ETI = elexacaftor/tezacaftor/ivacaftor; ULN = upper limit of normal; eGFR = estimated glomerular filtration rate; BUN = blood urea nitrogen; IV = intravenous; HR = hazard ratio; CFRD = cystic fibrosis–related diabetes; OGTT = oral glucose tolerance test; DXA = dual-energy X-ray absorptiometry; CF = cystic fibrosis; PHQ-9 = Patient Health Questionnaire-9; GAD-7 = Generalized Anxiety Disorder-7; IPOS = Integrated Palliative Care Outcome Scale; ACP = advance care planning; SPC = specialist palliative care; CYP3A4 = cytochrome P450 3A4; OATP1B1/1B3 = organic anion transporting polypeptide 1B1/1B3
***Consult FDA labels for the most up-to-date dosage information, contraindications, and drug-drug interactions**

CLINICAL PEARL — WHY HBA1C ALONE IS INSUFFICIENT FOR CFRD SCREENING

CFRD is characterized by **postprandial hyperglycemia** that **precedes fasting hyperglycemia**: the earliest glycemic abnormality is post-meal glucose excursions that **HbA1c cannot reliably detect**.[59] HbA1c is often **spuriously low in CF due to**: increased red blood cell turnover, chronic inflammation, and malnutrition → a "**normal**" HbA1c can **mask clinically significant dysglycemia**.[30] In one study, mean HbA1c was **not significantly different** between patients with normal glucose tolerance and those with impaired glucose tolerance or impaired fasting glucose ($p = 0.250$).[60] The **ADA/CFF joint guidelines** explicitly **recommend against** using HbA1c as a standalone screening test (**ADA-B**; **USPSTF-D**), instead endorsing the 2-hour 75-g OGTT annually from age 10 as the preferred screen.[18,59] When OGTT is not feasible (adherence remains poor at only 30–40% of adults) the ADA 2026 Standards of Care now endorse a **two-step alternative**: HbA1c ≥5.5% triggers OGTT within 3 months, while HbA1c <5.5% (NPV ~98%) can reasonably defer OGTT.[18] Once CFRD is diagnosed, HbA1c **shifts from a screening tool to a quarterly treatment target** (<7% for most patients), and insulin remains the **only guideline-recommended therapy**.[30]

Comorbidity Management — Primary Care Role

COMORBIDITY	APPROACH[17,26,30]	CAUTION[39,56]
CF-related diabetes (E13.x)	**Insulin** (only guideline-recommended therapy); annual OGTT from age 10; microvascular screening 5 years after diagnosis	Do **NOT** code as **E11** or treat with oral agents; HbA1c alone is **insufficient for screening** = may be spuriously low in CF
Colorectal cancer risk	**Colonoscopy at age 40** (age **30 post-transplant**) with CF-specific intensive prep; PCP-owned	Standard bowel prep is **inadequate**; do not defer screening to the CF center
Chronic kidney disease (N18.x)	Annual eGFR (cystatin C–based preferred); nephrology referral if progressive	Cumulative IV aminoglycosides and insulin-dependent CFRD ≥5 years **accelerate decline**; avoid nephrotoxins
Cardiovascular/ metabolic (I10, E78.x)	Lipid panel, BP monitoring, weight/BMI; **reassess high-fat CF diet** in modulator era	Manage statin–ETI CYP3A4 interaction;* ETI raises total cholesterol and LDL;* new-onset hypertension reported post-ETI
Osteoporosis (M81.0)	Calcium + vitamin D; DXA q2–5 years; **bisphosphonate if indicated**	**Accelerated CF bone** loss from chronic inflammation, malabsorption, and steroids; **fall prevention essential**
Hepatobiliary disease (E84.8 + K74.x)	**Annual LFTs** (AST, ALT, GGT, alk phos, bilirubin, platelets); **elastography** if hepatobiliary involvement identified	**Modulator hepatotoxicity adds risk**; pharmacist review at least every 6 months
Depression/anxiety	Annual PHQ-9/GAD-7 **from age 12**; treat with pharmacotherapy or psychotherapy	Untreated mood disorder **worsens adherence and exacerbations**
Polypharmacy	Pharmacist reconciliation **every visit**; deprescribing review	ETI is a CYP3A4 substrate and OATP1B1/1B3 inhibitor;* **flag interactions** with statins, azoles, warfarin, immunosuppressants, and digoxin
Frailty/treatment burden	Functional assessment; **de-escalate non-essential therapy** with CF team; exercise adaptation	Recurrent infection and lifelong nutritional stress **accelerate frailty**; base decisions on function, **not age**

COMORBIDITY	APPROACH[17,26,30]	CAUTION[39,56]

ABBREVIATIONS: OGTT = oral glucose tolerance test; PCP = primary care provider; CF = cystic fibrosis; eGFR = estimated glomerular filtration rate; CFRD = cystic fibrosis–related diabetes; IV = intravenous; BP = blood pressure; BMI = body mass index; ETI = elexacaftor/tezacaftor/ivacaftor; CYP3A4 = cytochrome P450 3A4; LDL = low-density lipoprotein; DXA = dual-energy X-ray absorptiometry; LFT = liver function test; AST = aspartate aminotransferase; ALT = alanine aminotransferase; GGT = gamma-glutamyl transferase; PHQ-9 = Patient Health Questionnaire-9; GAD-7 = Generalized Anxiety Disorder-7; OATP1B1/1B3 = organic anion transporting polypeptide 1B1/1B3.
***Consult FDA labels for the most up-to-date dosage information, contraindications, and drug-drug interactions**

Cost-Smart Options

BRAND (EST. COST)*[61]	GENERIC/ ALTERNATIVE (EST. COST)*[62]	EST. SAVINGS	COST-SMART TIP
Trikafta (elexacaftor/ tezacaftor/ ivacaftor; ETI) (~$272,000–$312,000/yr wholesale acquisition cost)	No generic available (single-source brand)	Patient assistance variable	Manufacturer copay assistance for eligible patients; confirm formulary tier and prior authorization; **do not interrupt or adjust without CF-center input**;[22] mean total cost of care **increases ~3-fold** after initiation but hospitalizations **decrease ~62%** and ED visits **~43%**[61]
Pulmozyme (dornase alfa) (~$2,700/12 weeks; ~$11,700/yr)	No generic available; candidate for discontinuation in **ETI-stable patients** per **SIMPLIFY**[19]	**~$11,700/yr if safely stopped**	**SIMPLIFY** showed **discontinuation noninferior** to continuation for ppFEV₁ (difference 0.35%; 95% CI −0.45 to 1.14);[19] discontinue **only with CF team** in patients with ppFEV₁ >70%
Hypertonic saline 7% (~$880/yr)	**Generic available**; candidate for discontinuation in ETI-stable patients per SIMPLIFY	**~$880/yr** if safely stopped	**SIMPLIFY** showed **discontinuation noninferior** (difference −0.32%; 95% CI −1.25 to 0.60);[19] **discontinue only with CF team**; caution if ppFEV₁ 60–70%
TOBI (tobramycin inhalation solution) (~$4,000–$6,000/28-day cycle brand)	**Generic tobramycin inhalation solution available** (56 ampules/28-day supply)	Significant	**Use generic when appropriate**; 28 days on/28 days off cycling; reserve for documented chronic *Pseudomonas aeruginosa*

BRAND (EST. COST)*[61]	GENERIC/ ALTERNATIVE (EST. COST)*[62]	EST. SAVINGS	COST-SMART TIP
Brand insulin (variable by formulation)	**Biosimilar**/follow-on insulins available; human insulins **~$25/ vial** at select retailers	Significant; Medicare caps at **$35/month** per insulin	**Insulin is first-line for CFRD** (not metformin);[18,22] Medicare IRA cap reduced out-of-pocket spending ~21% overall and >51% for highest-cost beneficiaries; use cost-effective formulations
Brand statins (e.g., Lipitor ~$330/mo, Crestor ~$245/mo)	**Generic** atorvastatin (**~$15/mo**), pravastatin (**~$10/ mo**), rosuvastatin (**~$15/mo**)	**~$200–$300/mo**	**Avoid simvastatin and lovastatin with ETI**;* rosuvastatin has weakest ETI interaction (AUC ratio 1.83); **all available as generics**

ABBREVIATIONS: ETI = elexacaftor/tezacaftor/ivacaftor; CF = cystic fibrosis; ED = emergency department; $ppFEV_1$ = percent-predicted forced expiratory volume in 1 second; CI = confidence interval; SIMPLIFY = randomized trial of therapy de-escalation in ETI-stable patients; AUC = area under the curve; CFRD = cystic fibrosis–related diabetes; IRA = Inflation Reduction Act

***Consult FDA labels for the most up-to-date dosage information, contraindications, and drug-drug interactions**

Patient Education and Adherence

CF patient education is distinguished by the **complexity of a multisystem disease requiring lifelong daily therapie**s, the modulator era's paradox of dramatically improved lung function without cure, strict high-fat dosing requirements that **now conflict with emerging cardiovascular risk**, and the need for every prescriber to be aware of **CYP3A4-mediated drug interactions** that can cause serious harm.[1,14,22]

DOCUMENTATION — PATIENT EDUCATION

Document the following education topics, the patient and caregiver(s) present, materials provided, and patient understanding (**teach-back method**):

- **Diagnosis in plain language**: Document that the patient **understands their CFTR genotype** (e.g., F508del homozygous, F508del/residual-function compound heterozygous), **which organs are affected**, and that atypical or late-onset CF is real disease requiring the **same multisystem surveillance** as classic CF[32]
- **Treatment plan and modulator expectations**: Document modalities discussed (CFTR modulator regimen, airway clearance, inhaled therapies, pancreatic enzymes); clarify that **ETI does not cure CF** = chronic infection, airway-clearance needs, and multisystem screening **persist on modulator therapy**; document which therapies may be safely reduced only in coordination with the CF care team[22]
- **High-fat dosing requirement**: Document counseling that ETI m**ust be taken with fat-containing food** for adequate absorption; counsel that the traditional high-fat, high-salt CF diet **now poses cardiovascular risk** in the modulator era → dietary guidance should balance ETI bioavailability against emerging dyslipidemia and hypertension risk*[3,63]
- **What to report between visits**: >10% FEV_1 decline from baseline; change in sputum volume, color, or consistency; unintentional weight loss; hemoptysis; new polyuria, polydipsia, or unexplained fatigue (glucose symptoms); new medication started by any provider[22,32]
- **CF-specific screening schedule**: Document counseling on **colonoscopy at age 40** (age 30 post-transplant) with CF-specific intensive bowel preparation; annual OGTT for CFRD screening; DXA every 2–5 years for osteoporosis; annual PHQ-9/GAD-7 for depression and anxiety[22,23,25]
- **Drug-interaction counseling**: Document counseling that the patient **must inform every prescriber** (including urgent care, dental, and pharmacy) **about modulator therapy**; ETI interacts with statins, azole antifungals, warfarin, immunosuppressants, and hormonal contraceptives via CYP3A4 and OATP pathways*
- **Advance care planning**: Surrogate designation, code status, goals of care; CPT 99497/99498 billable during AWV with no patient copay; CFF recommends routine ACP conversations for all patients meeting ACFLD criteria, emphasizing that ACP and aggressive treatment (including transplant pursuit) are not mutually exclusive[23,46]
- **Caregiver assessment**: Document caregiver present, their understanding of modulator dosing, airway-clearance schedule, and screening timeline, and burden screening; **refer to social work if strain identified**[22]

***Consult FDA labels for the most up-to-date dosage information, contraindications, and drug-drug interactions**

Quality Metrics Tie-In

No CF-specific HEDIS or MIPS measures are currently active in MY2026, but CF intersects multiple quality measurement domains **simultaneously**: depression screening (PHQ-9/GAD-7), medication safety (high-risk medications, medication reconciliation), care transitions (post-hospitalization follow-up), and goals-of-care documentation (advance care planning). **The disease's combination of** polypharmacy (CFTR modulators, inhaled therapies, pancreatic enzymes, fat-soluble vitamins, insulin, antibiotics), CYP3A4-mediated drug interactions, immunosuppression-driven hospitalizations (in transplant recipients), and high psychological distress means that **cross-cutting national measures apply across the entire care trajectory** and can anchor quality reporting for any PCP managing a CF patient in a value-based program.

MEASURE	STANDARD	APPLICABILITY TO CF
HEDIS COA: Care for Older Adults- Medication Review	**Denominator**: MA enrollees ≥66, continuously enrolled **Numerator**: 4 sub-measures documented annually: (**1**) functional status assessment, (**2**) medication review, (**3**) pain assessment, (**4**) advance care planning; **Exclusions**: hospice, ESRD	**CF polypharmacy** (ETI, inhaled therapies, enzymes, insulin, antibiotics) creates **high interaction risk**; reconcile CYP3A4/OATP substrates and nephrotoxic drugs **at every review**
HEDIS COA: Care for Older Adults- Functional Status Assessment	**Denominator**: enrollees ≥66 **Numerator**: functional status assessment documented annually **Exclusions**: hospice, ESRD	**FEV_1/ppFEV$_1$ trend** satisfies this sub-measure; track trajectory toward **ACFLD** (40%) and transplant (30%) thresholds[23]
HEDIS TRC: Transitions of Care	**Denominator**: enrollees ≥18 with inpatient discharge **Numerator**: 4 sub-measures within 30 days: **(1)** notification of inpatient admission, **(2)** receipt of discharge information, **(3)** patient engagement after discharge, **(4)** medication reconciliation post-discharge; **Exclusions**: hospice	**Frequent hospitalizations** for pulmonary exacerbations and IV antibiotics;[1] post-discharge medication reconciliation critical given **ETI drug interactions and renal dosing***

MEASURE	STANDARD	APPLICABILITY TO CF
HEDIS DMS-E: Utilization of the PHQ-9 to Monitor Depression Symptoms for Adolescents and Adults	**Denominator**: enrollees ≥12 with diagnosis of major depression or dysthymia **AND** elevated PHQ-9 ≥10 **Numerator**: follow-up PHQ-9 documented within 4–8 months of index elevated score; **Exclusions**: hospice	Depression/anxiety **2–3x community rates**;[32] CFF recommends annual PHQ-9/ GAD-7 screening from age 12[22]
HEDIS ACP: Advance Care Planning	**Denominator**: enrollees ≥66 **Numerator**: advance care plan or surrogate decision-maker documented, **OR** documentation that ACP was discussed but patient declined **Exclusions**: hospice	CFF recommends **ACP for all patients meeting ACFLD criteria**;[22,23] billable as 99497/99498 during AWV with no copay
HEDIS PCR: Plan All-Cause Readmission	**Denominator**: enrollees ≥18 with acute inpatient discharge **Numerator**: unplanned readmission within 30 days (lower is better) **Exclusions**: planned readmissions, hospice, psychiatric	Exacerbations, pneumothorax, and nephrotoxic antibiotic–related AKI **drive readmissions**; 7-day PCP follow-up with medication reconciliation reduces risk
HEDIS COL-E: Colorectal Cancer Screening	**Denominator**: enrollees 45–75, continuously enrolled **Numerator**: age-appropriate CRC screening completed (colonoscopy within 10 y, FIT within 1 y, mt-sDNA/mt-sRNA within 3 y, flexible sigmoidoscopy within 5 y); **Exclusions**: CRC diagnosis, total colectomy, hospice	**Colonoscopy at age 40** (not 45); age **30 post-transplant**; CF-specific prep required; NCCN lists CF as increased-risk category[25]
HEDIS CBP: Controlling High Blood Pressure	**Denominator**: enrollees 18–85 with diagnosed hypertension **Numerator**: most recent BP 140/90 mmHg during measurement year **Exclusions**: ESRD, pregnancy, hospice, nonacute inpatient admission	ETI raises BP via **salt preservation**;*[64] new-onset hypertension reported post-ETI; monitor and code **I10**

MEASURE	STANDARD	APPLICABILITY TO CF
HEDIS HBD: Diabetes Care-HbA1c Control	**Denominator**: enrollees 18–75 with diabetes diagnosis, continuously enrolled **Numerator**: most recent HbA1c at goal per measure year **Exclusions**: hospice, ESRD	Code CFRD as **E13.x** (not E11); HbA1c alone insufficient →annual OGTT remains recommended screening[18]
HEDIS SPC: Statin Therapy for Patients with Cardiovascular Disease	**Denominator**: enrollees ≥21 with clinical ASCVD **Numerator**: received statin therapy during measurement year **Exclusions**: hospice, ESRD, pregnancy, adverse reaction/ allergy to statin, active liver disease, rhabdomyolysis	**ETI increases atorvastatin AUC 3.27-fold**;* rosuvastatin has weakest interaction (1.83-fold); pharmacist DDI review **before prescribing**

ABBREVIATIONS: MA = Medicare Advantage; ETI = elexacaftor/tezacaftor/ivacaftor; CYP3A4 = cytochrome P450 3A4; OATP = organic anion transporting polypeptide; ESRD = end-stage renal disease; FEV_1 = forced expiratory volume in 1 second; $ppFEV_1$ = percent-predicted forced expiratory volume in 1 second; ACFLD = advanced cystic fibrosis lung disease; IV = intravenous; CF = cystic fibrosis; PHQ-9 = Patient Health Questionnaire-9; GAD-7 = Generalized Anxiety Disorder-7; CFF = Cystic Fibrosis Foundation; ACP = advance care planning; AWV = Annual Wellness Visit; PCP = primary care provider; AKI = acute kidney injury; CRC = colorectal cancer; FIT = fecal immunochemical test; mt-sDNA/mt-sRNA = multi-target stool DNA/multi-target stool RNA; NCCN = National Comprehensive Cancer Network; BP = blood pressure; CFRD = cystic fibrosis–related diabetes; OGTT = oral glucose tolerance test; ASCVD = atherosclerotic cardiovascular disease; AUC = area under the curve; DDI = drug-drug interaction; SDoH = social determinants of health; HEDIS = Healthcare Effectiveness Data and Information Set

***Consult FDA labels for the most up-to-date dosage information, contraindications, and drug-drug interactions**

QUALITY OUTCOME

Active primary care co-management of CF produces measurably better outcomes than passive oversight. This means **suspecting atypical late-onset CF** and pursuing confirmatory sweat chloride and CFTR testing. It means **coding the specific organ manifestation** rather than defaulting to E84.9, and coding CFRD as **E13.x with insulin** documentation. It means **facilitating colorectal cancer screening at age 40**, managing cardiovascular, metabolic, and bone health longitudinally, and routing every new prescription through a **pharmacist drug-interaction review**. **The result**: accurate diagnosis, complete risk-adjusted documentation, and the right preventive care at the right time, with **far fewer missed comorbidities** than passive co-management produces.

5 CODING REMINDERS AND CASE EXAMPLES

Coding Specificity

- **Specific E84.x Manifestation:** Every CF encounter note should specify the **documented organ manifestation**: **E84.0** (pulmonary), **E84.11** (meconium ileus), **E84.19** (intestinal), **E84.8** (other, including hepatobiliary); **E84.9** (unspecified) **is the highest audit-risk code in CF** because the supporting documentation almost always contains organ-specific information; auditors will downgrade= reserve **E84.9 only during initial diagnostic workup** before organ involvement is characterized
- **Combination Coding; Secondary Codes:** CF rarely presents as a single-system disease → add organism codes for chronic respiratory pathogens (**B96.5** *Pseudomonas*, **B95.8** *S. aureus*, **B44.0/B44.1** *Aspergillus*), bronchiectasis with specificity (**J47.0** with lower respiratory infection, **J47.1** with hemorrhage, **J47.9** uncomplicated), pneumothorax (**J93.83** CF-related, **J93.9** unspecified), and hemoptysis (**R04.2**). Each secondary code carries **independent clinical significance**, affects treatment decisions, and creates the auditable trail linking CF to its downstream complications[1]
- **CF-Related Diabetes (CFRD):** Code as **E13.x** (other specified diabetes), **NOT E11** (type 2). **CFRD has a distinct pathophysiology** (progressive beta-cell loss with preserved insulin sensitivity) and requires insulin, **not metformin**, as first-line therapy.[18] Document insulin regimen, most recent OGTT date and 2-hour glucose result, and annual screening schedule. **Miscoding as E11 drives the wrong treatment algorithm** and creates an inaccurate clinical record[11,12]
- **Chronic Kidney Disease (CKD):** Code stage-specific **N18.x**; **HCC 326** (Stage 5, CNA RAF 0.815) and **HCC 327** (Stage 4, CNA RAF 0.514) carry significant weight → unstaged CKD forfeits HCC mapping entirely. Document eGFR with method; **cystatin C–based eGFR is more accurate in CF patients** due to low muscle mass confounding creatinine-based estimates.[36] Note that insulin-dependent CFRD ≥5 years confers **HR 4.56 for ≥40% eGFR decline**;[35] each IV-antibiotic course adds HR 1.13 → document **cumulative antibiotic exposure** as a CKD risk modifier
- **Osteoporosis and Hepatobiliary Disease:** Osteoporosis (**M81.0**) with DXA date and T-score; document fracture history and risk factors (chronic inflammation, vitamin D malabsorption, steroid exposure, inactivity, impaired glucose metabolism). CF hepatobiliary disease maps under **E84.8** → also code **liver disease specifically** (**K74.x** cirrhosis/fibrosis, **K73.x** chronic hepatitis). Dual coding captures both the CF attribution and the hepatic severity for accurate risk stratification

- **Disease Severity:** Document FEV_1 and $ppFEV_1$ **at every encounter** with trend from prior values.[23] Note advanced cystic fibrosis lung disease (ACFLD) criteria when FEV_1 <40% predicted, and **transplant evaluation threshold** when FEV_1 <30% predicted.[41] Severity documentation drives referral timing, treatment intensity decisions, and supports the clinical rationale for CF-center co-management structure
- **CFTR Genotype and Modulator Status:**[1] Document **full genotype** (e.g., F508del/F508del homozygous, F508del/residual-function compound heterozygous), **modulator regimen** with start date and dose, and that **ETI does not cure CF**; chronic infection, airway-clearance needs, and multisystem surveillance **persist on modulator therapy**.[1] Genotype determines **modulator eligibility** and creates the auditable treatment-rationale trail for prior authorization and ongoing therapy justification
- **Atypical and Late-Onset Diagnosis:** Document **confirmatory sweat chloride value** with date and CFTR **full-gene sequencing results**. A negative newborn screen **does not exclude CF**; NBS panels **miss 9.2%** of Black infants and **13–28%** of minority CF cases.[65] Late-diagnosed adults are frequently **pancreatic sufficient** (73%) and compound heterozygous (84%);[66] **single-organ presentation is common**. Do not require classic malabsorption to assign **E84.x** when sweat chloride and genotype are confirmatory
- **Drug-Interaction Review**: Document the **pharmacist-led CYP3A4 interaction review** for any modulator patient, especially those on polypharmacy.[58] ETI is a strong CYP3A4 substrate; flag **interactions with statins** (use non-CYP3A4 options such as rosuvastatin or pravastatin), a**zole antifungals**, **warfarin**, **immunosuppressants** (tacrolimus, cyclosporine), and **hormonal contraceptives**. Document review date, pharmacist sign-off, and any dose adjustments at every encounter and with every new prescription
- **Active vs. Resolved Status**: Always use **E84.x** for cystic fibrosis → **disease is lifelong**. CF is never reclassified as personal history; **there is no Z85-equivalent transition**

Annual Clinical Review and Confirmation

- **Annual review**: Active cystic fibrosis (**E84.x**) requires **annual MEAT documentation**;[6] organ manifestations, modulator status, CFTR genotype, FEV_1 with trend, and comorbidity burden (CFRD, CKD, cardiovascular/metabolic disease, osteoporosis, hepatobiliary disease, mental health) **updated each encounter**
- **Visit modality**: Face-to-face **or** synchronous audio-video telehealth qualifies when it supports meaningful clinical evaluation; chart updates **without an encounter do not satisfy MEAT**
- **Clinical context**: Under **CMS-HCC V28**, **E84.x** cystic fibrosis maps to **HCC 277** (CNA RAF **0.998**);[11,12] **CF-related diabetes** (**E13.x**) maps to **HCC 36/38** (CNA RAF **0.166**) and must be coded E13.x, not E11; CKD maps to **HCC 326/327** (CNA RAF **0.815/0.514**) when staged; confirm reporting period and CNA segment against **current CMS tables**

- **Avoid rollover**: Do **not** copy forward last year's CF note **without:** updating organ manifestations, current modulator therapy and response, FEV_1/severity, CFRD status and regimen, CKD stage, preventive care intervals (colonoscopy, OGTT, DXA, PHQ-9/GAD-7), and pharmacist drug-interaction review

EHR Workflow Tips

- **[EHR TIP — Smartphrase]** Build a **.cfcare dot phrase** that auto-populates ICD-10 with organ-specific CF manifestation (**E84.0/E84.11/E84.19/E84.8/E84.9**), bronchiectasis with laterality (**J47.x**), chronic pathogen (**B96.5** *Pseudomonas*, **B44.x** *Aspergillus*), CFRD status and regimen (**E13.x**, OGTT date/result), CFTR genotype, current modulator with start date, most recent FEV_1 with trend, and **active comorbidities**. Eliminates **unspecified E84.9 coding** and supports MEAT documentation in a single paste
- **[EHR TIP — Best Practice] Problem list hygiene**: maintain the problem list entry at **full specificity** (e.g., "Cystic fibrosis with pulmonary manifestations (**E84.0**), chronic *Pseudomonas* (**B96.5**); CFRD (**E13.10**) on insulin; FEV_1 78%; ETI-treated"). Code **each comorbidity individually**: CKD with stage (**N18.x**), osteoporosis (**M81.0**) with DXA date, obstructive azoospermia (**N46.023**), depression (**F32.x/F33.x**), hepatobiliary disease (**K74.x**). Include CFTR genotype and modulator eligibility to support HCC mapping
- **[EHR TIP — Workflow] Status line protocol**: place a structured status field at the top of **every CF encounter note**: e.g., "ETI-treated | FEV_1 78% (stable) | Chronic Pseudomonas | CFRD on insulin | Not ACFLD" **versus** "Advanced lung disease | Transplant referral pending | Listed [date] | LAS [score]." Update at **every visit**. This single line orients any covering provider, supports care transitions, and documents disease trajectory for risk-adjustment continuity
- **[EHR TIP — Alert]** Worklist filter "**CF Active**" = surfaces patients with a**ny E84.x on the problem list without a CF-center or PCP visit in the past 6 months**. Second filter: "**CF Preventive Care Due**" = patients with **E84.x** missing any of the following within specified intervals: colonoscopy (age ≥40 or age ≥30 post-transplant, q5 yr with CF-specific prep), OGTT (annual, age ≥10), DXA (q2–5 yr), PHQ-9/GAD-7 (annual), lipid panel (annual on ETI), LFTs (per modulator monitoring schedule), pharmacist drug-interaction review (annual or with any new prescription). Identifies active patients with **overdue preventive care** and closes the screening gap
- **[EHR TIP — Order Set]** Three sets, auto-attached when **E84.x is on the problem list**: (**1**) "CF Preventive Care" → OGTT, DXA, lipid panel, PHQ-9/GAD-7, eGFR/UA, LFTs, pharmacist review. (**2**) "CF Colonoscopy" → CF-specific high-volume prep, **age-triggered at 40** (or **30 post-transplant**), repeat per findings. (**3**) "CF New Diagnosis Workup" → sweat chloride, CFTR sequencing, sputum culture with fungal, spirometry, OGTT, DXA, lipid panel, LFTs, eGFR, CF center referral

Brief Case Examples

SUCCESS: COMPREHENSIVE DOCUMENTATION

SCENARIO

A 67-year-old male; annual wellness visit; 2-year history of **recurrent bronchitis**, chronic sinusitis with nasal polyps, one episode of **idiopathic pancreatitis**, **lifelong subfertility**; chest CT shows upper-lobe cylindrical bronchiectasis; newborn-screen status unknown.

Documentation: "Upper-lobe bronchiectasis + sinonasal disease + pancreatitis + infertility: **atypical late-onset CF suspected despite no NBS history**. Sweat chloride 68 mmol/L (diagnostic); **CFTR sequencing**: F508del + residual-function variant. Cystic fibrosis with pulmonary manifestations (**E84.0**), bronchiectasis (**J47.9**); obstructive azoospermia (**N46.023**). OGTT 2-h glucose 215 → **CF-related diabetes** (**E13.x**), started on insulin. Referred to accredited adult CF center for **ETI evaluation** (F508del eligible). PCP-owned preventive care: **colonoscopy initiated with CF-specific prep**; endocrinology for insulin titration; DXA and lipid panel ordered. Pharmacist review completed before adjusting amlodipine and selecting a non-CYP3A4 statin. **Advance care planning** and CF-center co-management documented."

Outcome: E84.0 supported with **sweat chloride confirmation** and **CFTR genotyping**;[6] CFRD coded as **E13.x** with insulin initiated per CFF/ADA guidelines;[13,18,22] colonoscopy, DXA, and lipid panel ordered per CF-specific preventive protocols.[17,24,25,33] Pharmacist drug-interaction review completed **before prescribing** (ETI is a CYP3A4 substrate). **Every MEAT element present**: diagnostic confirmation with sweat chloride and genotype, organ-specific coding, treatment rationale, preventive care plan with intervals, CF-center co-management structure documented.

PITFALL: INSUFFICIENT DOCUMENTATION

Documentation as written: "72-year-old female with cystic fibrosis. Diabetes: started metformin. E84.9 and E11.9 on problem list. Follow with CF center."

Consequence: E84.9 (unspecified) **undercodes acuity** and is payer-flagged despite documented bronchiectasis and chronic *Pseudomonas*. **CFRD miscoded as E11** (type 2) and treated with metformin instead of insulin (the guideline-recommended therapy).[18,30] Preventive care (colonoscopy, DXA) entirely deferred to the CF center with no PCP-owned action items.

RAF Impact: Active CF maps to **HCC 277** (CNA RAF 0.998) = correctly mapped via **E84.0** but **at risk if E84.9 is challenged**.[6] Miscoding CFRD as **E11** drives the wrong treatment algorithm and inaccurate clinical record; **unstaged CKD forfeits HCC 326/327 mapping**.

Fix: "Cystic fibrosis with pulmonary manifestations (**E84.0**), bronchiectasis (**J47.9**), chronic *Pseudomonas* (**B96.5**). CF-related diabetes (**E13.x**) → **switch metformin to insulin**; annual OGTT. PCP to initiate **age-appropriate colonoscopy with CF-specific prep** and DXA. Pharmacist drug-interaction review before any new prescription." Coding after fix: **E84.0** (→ **HCC 277**) with organ-specific manifestations, **E13.x** with insulin, and preventive care plan with intervals = **specificity preserved**.

REFERENCES

1.Grasemann Hartmut, Ratjen Felix. Cystic Fibrosis. *N Engl J Med*. 2023;389(18):1693-1707. doi:10.1056/NEJMra2216474

2.Nichols DP, Paynter AC, Heltshe SL, et al. Clinical Effectiveness of Elexacaftor/Tezacaftor/Ivacaftor in People with Cystic Fibrosis: A Clinical Trial. *Am J Respir Crit Care Med*. 2022;205(5):529-539. doi:10.1164/rccm.202108-1986OC

3.Middleton Peter G., Mall Marcus A., Dřevínek Pavel, et al. Elexacaftor–Tezacaftor–Ivacaftor for Cystic Fibrosis with a Single Phe508del Allele. *N Engl J Med*. 2019;381(19):1809-1819. doi:10.1056/NEJMoa1908639

4.Arya R, Sharpe I, Cheng SY, et al. Elevated Rates and Earlier Onset of Nonpulmonary Comorbidities in Adults with Cystic Fibrosis: A Population-based Study. *Ann Am Thorac Soc*. 2025;22(12):1874-1880. doi:10.1513/AnnalsATS.202502-170OC

5.Sullivan LJ, Mingora CM, Flume PA. The Aging Patient with Cystic Fibrosis. *Drugs Aging*. 2025;42(6):513-525. doi:10.1007/s40266-025-01207-3

6.Centers for Medicare & Medicaid Services (CMS), National Center for Health Statistics (NCHS), American Hospital Association (AHA), American Health Information Management Association (AHIMA). *ICD-10-CM Official Guidelines for Coding and Reporting, FY 2026*. U.S. Department of Health and Human Services; 2025. https://www.cms.gov/medicare/coding-billing/icd-10-codes

7.American Diabetes Association Professional Practice Committee. 2. Diagnosis and Classification of Diabetes: Standards of Care in Diabetes—2024. *Diabetes Care*. 2023;47(Supplement_1):S20-S42. doi:10.2337/dc24-S002

8.Lopez A, Daly C, Vega-Hernandez G, MacGregor G, Rubin JL. Elexacaftor/tezacaftor/ivacaftor projected survival and long-term health outcomes in people with cystic fibrosis homozygous for F508del. *J Cyst Fibros Off J Eur Cyst Fibros Soc*. 2023;22(4):607-614. doi:10.1016/j.jcf.2023.02.004

9.McBennett KA, Davis PB, Konstan MW. Increasing life expectancy in cystic fibrosis: Advances and challenges. *Pediatr Pulmonol*. 2022;57 Suppl 1(Suppl 1):S5-S12. doi:10.1002/ppul.25733

10.Frost FJ, Peckham DG, Felton IC, et al. Managing an ageing cystic fibrosis population: challenges and priorities. *Eur Respir Rev Off J Eur Respir Soc*. 2025;34(176). doi:10.1183/16000617.0261-2024

11.Centers for Medicare & Medicaid Services. *2026 Final ICD-10-CM Mappings (CMS-HCC V28)*. U.S. Department of Health and Human Services; 2025. https://www.cms.gov/medicare/health-plans/medicareadvtgspecratestats/risk-adjustors/2026-model-software

12.Centers for Medicare & Medicaid Services. *CMS-HCC Model Relative Factor Tables (Community, Non-Dual, Aged)*. 2024. https://www.cms.gov/files/document/revised-cms-hcc-model-relative-factor-tablespdf

13.Farrell PM, White TB, Ren CL, et al. Diagnosis of Cystic Fibrosis: Consensus Guidelines from the Cystic Fibrosis Foundation. *J Pediatr*. 2017;181:S4-S15.e. doi:10.1016/j.jpeds.2016.09.064

14.Boyle MP. Adult Cystic Fibrosis. *JAMA*. 2007;298(15):1787-1793. doi:10.1001/jama.298.15.1787

15.Gilljam M, Ellis L, Corey M, Zielenski J, Durie P, Tullis DE. Clinical manifestations of cystic fibrosis among patients with diagnosis in adulthood. *Chest*. 2004;126(4):1215-1224. doi:10.1378/chest.126.4.1215

16.McGarry ME, Raraigh KS, Farrell P, et al. Cystic Fibrosis Newborn Screening: A Systematic Review-Driven Consensus Guideline from the United States Cystic Fibrosis Foundation. *Int J Neonatal Screen*. 2025;11(2). doi:10.3390/ijns11020024

17.Cystic Fibrosis Colorectal Cancer Screening Task Force, Hadjiliadis D, Khoruts A, et al. Cystic Fibrosis Colorectal Cancer Screening Consensus Recommendations. *Gastroenterology*. 2018;154(3):736-745.e. doi:10.1053/j.gastro.2017.12.012

18.American Diabetes Association Professional Practice Committee for Diabetes*. 2. Diagnosis and Classification of Diabetes: Standards of Care in Diabetes—2026. *Diabetes Care*. 2025;49(Supplement_1):S27-S49. doi:10.2337/dc26-S002

19.Mayer-Hamblett N, Ratjen F, Russell R, et al. Discontinuation versus continuation of hypertonic saline or dornase alfa in modulator treated people with cystic fibrosis (SIMPLIFY): results from two parallel, multicentre, open-label, randomised, controlled, non-inferiority trials. *Lancet Respir Med*. 2023;11(4):329-340. doi:10.1016/S2213-2600(22)00434-9

20.McGarry ME, Ren CL, Wu R, Farrell PM, McColley SA. Detection of disease-causing CFTR variants in state newborn screening programs. *Pediatr Pulmonol*. 2023;58(2):465-474. doi:10.1002/ppul.26209

21.Rosenfeld M, Ostrenga J, Cromwell EA, et al. Real-world Associations of US Cystic Fibrosis Newborn Screening Programs With Nutritional and Pulmonary Outcomes. *JAMA Pediatr*. 2022;176(10):990-999. doi:10.1001/jamapediatrics.2022.2674

22.CFF Care Model Committee, Goetz DM, Brown RF, et al. Cystic fibrosis foundation position paper: Redefining the CF care model. *J Cyst Fibros*. 2024;23(6):1055-1065. doi:10.1016/j.jcf.2024.08.007

23.Kapnadak SG, Dimango E, Hadjiliadis D, et al. Cystic Fibrosis Foundation consensus guidelines for the care of individuals with advanced cystic fibrosis lung disease. *J Cyst Fibros Off J Eur Cyst Fibros Soc*. 2020;19(3):344-354. doi:10.1016/j.jcf.2020.02.015

24.Aris RM, Merkel PA, Bachrach LK, et al. Guide to bone health and disease in cystic fibrosis. *J Clin Endocrinol Metab*. 2005;90(3):1888-1896. doi:10.1210/jc.2004-1629

25.National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Colorectal Cancer Screening (Version 1.2026). April 8, 2026. https://www.nccn.org/professionals/physician_gls/pdf/colorectal_screening.pdf

26.Sellers ZM, Assis DN, Paranjape SM, et al. Cystic fibrosis screening, evaluation, and management of hepatobiliary disease consensus recommendations. *Hepatol Baltim Md*. 2024;79(5):1220-1238. doi:10.1097/HEP.0000000000000646

27.Beringer PM, Hidayat L, Heed A, et al. GFR estimates using cystatin C are superior to serum creatinine in adult patients with cystic fibrosis. *J Cyst Fibros*. 2009;8(1):. doi:10.1016/j.jcf.2008.07.004

28.Sheahan KP, Glynn D, Joyce S, Maher MM, Boland F, O'Connor OJ. Best Practices: Imaging Strategies for Reduced-Dose Chest CT in the Management of Cystic Fibrosis-Related Lung Disease. *AJR Am J Roentgenol*. 2021;217(2):304-313. doi:10.2214/AJR.19.22694

29.Ong T, Ramsey BW. Cystic Fibrosis: A Review. *JAMA*. 2023;329(21):1859-1871. doi:10.1001/jama.2023.8120

30.Moran A, Brunzell C, Cohen RC, et al. Clinical care guidelines for cystic fibrosis-related diabetes: a position statement of the American Diabetes Association and a clinical practice guideline of the Cystic Fibrosis Foundation, endorsed by the Pediatric Endocrine Society. *Diabetes Care*. 2010;33(12): 2697-2708. doi:10.2337/dc10-1768

31.Floto RA, Olivier KN, Saiman L, et al. US Cystic Fibrosis Foundation and European Cystic Fibrosis Society consensus recommendations for the management of non-tuberculous mycobacteria in individuals with cystic fibrosis. *Thorax*. 2016;71 Suppl 1(Suppl 1):i. doi:10.1136/thoraxjnl-2015-207360

32.Shteinberg M, Haq IJ, Polineni D, Davies JC. Cystic fibrosis. *Lancet Lond Engl*. 2021;397(10290): 2195-2211. doi:10.1016/S0140-6736(20)32542-3

33.Abraham JM, Taylor CJ. Cystic Fibrosis & disorders of the large intestine: DIOS, constipation, and colorectal cancer. *J Cyst Fibros Off J Eur Cyst Fibros Soc*. 2017; Suppl 2:S40-S49. doi:10.1016/j.jcf.2017.06.013

34.Rachel M, Galiniak S, Biesiadecki M, Gala-Błądzińska A. Renal Function in Patients with Cystic Fibrosis: A Single-Center Study. *Int J Environ Res Public Health*. 2022;19(9). doi:10.3390/ijerph19095454

35.Quon BS, Mayer-Hamblett N, Aitken ML, Smyth AR, Goss CH. Risk factors for chronic kidney disease in adults with cystic fibrosis. *Am J Respir Crit Care Med*. 2011;184(10):1147-1152. doi:10.1164/rccm.201105-0932OC

36.Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group, Stevens PE, Ahmed SB, et al. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int*. 2024;105(4):S117-S314. doi:10.1016/j.kint.2023.10.018

37.O'Donnell JEM, Hastings LA, Briody JN, et al. SHIFTing goals in cystic fibrosis—managing extrapulmonary disease in the era of CFTR modulator therapy; Proceedings of the International Shaping Initiatives and Future Trends (SHIFT) Symposium. *Pediatr Pulmonol*. 2024;59(6):1661-1676. doi:10.1002/ppul.26970

38.Despotes KA, Ceppe AS, Donaldson SH. Alterations in lipids after initiation of highly effective modulators in people with cystic fibrosis. *J Cyst Fibros Off J Eur Cyst Fibros Soc*. 2023;22(6): 1024-1026. doi:10.1016/j.jcf.2023.10.002

39.Quittner AL, Abbott J, Georgiopoulos AM, et al. International Committee on Mental Health in Cystic Fibrosis: Cystic Fibrosis Foundation and European Cystic Fibrosis Society consensus statements for screening and treating depression and anxiety. *Thorax*. 2016;71(1):26-34. doi:10.1136/thoraxjnl-2015-207488

40.Deignan JL, Gregg AR, Grody WW, et al. Updated recommendations for CFTR carrier screening: A position statement of the American College of Medical Genetics and Genomics (ACMG). *Genet Med Off J Am Coll Med Genet*. 2023;25(8):100867. doi:10.1016/j.gim.2023.100867

41.Ramos KJ, Smith PJ, McKone EF, et al. Lung transplant referral for individuals with cystic fibrosis: Cystic Fibrosis Foundation consensus guidelines. *J Cyst Fibros Off J Eur Cyst Fibros Soc*. 2019;18(3):321-333. doi:10.1016/j.jcf.2019.03.002

42.Hong E, Shi A, Beringer P. Drug-drug interactions involving CFTR modulators: a review of the evidence and clinical implications. *Expert Opin Drug Metab Toxicol*. 2023;19(4):203-216. doi:10.1080/17425255.2023.2220960

43.Hong E, Chung PS, Rao AP, Beringer PM. Evaluation of Complex Drug Interactions Between Elexacaftor-Tezacaftor-Ivacaftor and Statins Using Physiologically Based Pharmacokinetic Modeling. *Pharmaceutics*. 2025;17(3). doi:10.3390/pharmaceutics17030318

44.Kurgansky KE, Collaco JM, Ng DK, Lesko CR. Effectiveness of Cystic Fibrosis Transmembrane Conductance Regulator Modulator Therapy on Risk of Death for Individuals With Cystic Fibrosis. *Chest*. Published online May 8, 2026:S0012-3692(26)00614-8. doi:10.1016/j.chest.2026.04.041

45.Sandhaus R, Turino G, Brantly M. The Diagnosis and Management of Alpha-1 Antitrypsin Deficiency in the Adult. *Chronic Obstr Pulm Dis*. 2016;3(3):668-682. doi:10.15326/jcopdf.3.3.2015.0182

46.Todd SH, Sonntag EA, Buchanan ML, et al. Development of an Advance Care Planning Protocol in a Cystic Fibrosis Outpatient Clinic. *J Palliat Med*. 2021;24(9):1383-1386. doi:10.1089/jpm.2021.0186

47.Mogayzel PJJ, Naureckas ET, Robinson KA, et al. Cystic fibrosis pulmonary guidelines. Chronic medications for maintenance of lung health. *Am J Respir Crit Care Med*. 2013;187(7):680-689. doi:10.1164/rccm.201207-1160oe

48.Al-Aloul M, Nazareth D, Walshaw M. Nebulized tobramycin in the treatment of adult CF pulmonary exacerbations. *J Aerosol Med Pulm Drug Deliv*. 2014;27(4):299-305. doi:10.1089/jamp.2013.1055

49.Ramsey BW, Pepe MS, Quan JM, et al. Intermittent administration of inhaled tobramycin in patients with cystic fibrosis. Cystic Fibrosis Inhaled Tobramycin Study Group. *N Engl J Med*. 1999;340(1):. doi:10.1056/NEJM199901073400104

50.Daines CL, Polineni D, Tullis E, et al. Long-Term Safety and Efficacy of Elexacaftor/Tezacaftor/Ivacaftor in Adults and Adolescents with Cystic Fibrosis and at Least One F508del Allele: A Phase 3 Open-Label Extension Study. *Am J Respir Crit Care Med*. 2025;211(10):1901-1914. doi:10.1164/rccm.202411-2231OC

51.Bower JK, Volkova N, Ahluwalia N, et al. Real-world safety and effectiveness of elexacaftor/tezacaftor/ivacaftor in people with cystic fibrosis: Interim results of a long-term registry-based study. *J Cyst Fibros Off J Eur Cyst Fibros Soc*. 2023;22(4):730-737. doi:10.1016/j.jcf.2023.03.002

52.Goss CH, Heltshe SL, West NE, et al. A Randomized Clinical Trial of Antimicrobial Duration for Cystic Fibrosis Pulmonary Exacerbation Treatment. *Am J Respir Crit Care Med*. 2021;204(11):1295-1305. doi:10.1164/rccm.202102-0461OC

53.Merlo C, Geiger JM, Wang Z, Lyden GR, Schladt DP, McGarry L. Impact of availability of a highly effective cystic fibrosis treatment (elexacaftor/tezacaftor/ivacaftor) on lung transplant waitlist and lung transplantation trends in the US. *Respir Med*. 2025;245:108171. doi:10.1016/j.rmed.2025.108171

54.Kavalieratos D, Georgiopoulos AM, Dhingra L, et al. Models of Palliative Care Delivery for Individuals with Cystic Fibrosis: Cystic Fibrosis Foundation Evidence-Informed Consensus Guidelines. *J Palliat Med*. 2021;24(1):. doi:10.1089/jpm.2020.0311

55.Savant A, Lyman B, Bojanowski C, Upadia J. Cystic Fibrosis. In: Adam MP, Bick S, Mirzaa GM, eds. *GeneReviews® [Internet]*. Last Revision: August 8, 2024. University of Washington, Seattle; 2001. Accessed August 8, 2024. https://www.ncbi.nlm.nih.gov/books/NBK1250/

56.Leonard A, Bailey J, Bruce A, et al. Nutritional considerations for a new era: A CF foundation position paper. *J Cyst Fibros*. 2023;22(5):788-795. doi:10.1016/j.jcf.2023.05.010

57.Ochs MA, Dillman NO, Caverly LJ, Chaffee VD. Aminoglycoside dosing and monitoring for Pseudomonas aeruginosa during acute pulmonary exacerbations in cystic fibrosis. *Pediatr Pulmonol*. 2021;56(12):3634-3643. doi:10.1002/ppul.25441

58.Grant JJ, McDade EJ, Zobell JT, Young DC. The indispensable role of pharmacy services and medication therapy management in cystic fibrosis. *Pediatr Pulmonol*. 2022;57(S1):S17-S39. doi:10.1002/ppul.25613

59.Alves C, Della-Manna T, Albuquerque CTM. Cystic fibrosis-related diabetes: an update on pathophysiology, diagnosis, and treatment. *J Pediatr Endocrinol Metab JPEM*. 2020;33(7):835-843. doi:10.1515/jpem-2019-0484

60.Darukhanavala A, Van Dessel F, Ho J, Hansen M, Kremer T, Alfego D. Use of hemoglobin A1c to identify dysglycemia in cystic fibrosis. *PloS One*. 2021;16(4):e0250036. doi:10.1371/journal.pone.0250036

61.Marshall LZ, Espinosa R, Starner CI, Gleason PP. Real-world outcomes and direct care cost before and after elexacaftor/tezacaftor/ivacaftor initiation in commercially insured members with cystic fibrosis. *J Manag Care Spec Pharm*. 2023;29(6):599-606. doi:10.18553/jmcp.2023.29.6.599

62.U.S. Food and Drug Administration. *Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book)*. 46th ed. U.S. Food and Drug Administration; 2026. https://www.fda.gov/drugs/drug-approvals-and-databases/approved-drug-products-therapeutic-equivalence-evaluations-orange-book

63.Barry Peter J., Mall Marcus A., Álvarez Antonio, et al. Triple Therapy for Cystic Fibrosis Phe508del–Gating and –Residual Function Genotypes. *N Engl J Med*. 2021;385(9):815-825. doi:10.1056/NEJMoa2100665

64.Gramegna A, De Petro C, Leonardi G, et al. Onset of systemic arterial hypertension after initiation of elexacaftor/tezacaftor/ivacaftor in adults with cystic fibrosis: A case series. *J Cyst Fibros Off J Eur Cyst Fibros Soc*. 2022;21(5):885-887. doi:10.1016/j.jcf.2022.04.010

65.Madden K, Mueller R, Brown C, Valverde KD, Langfelder-Schwind E. Facilitators and Barriers to Increasing Equity in Cystic Fibrosis Newborn Screening Algorithms. *Pediatr Pulmonol*. 2025;60(1):e27449. doi:10.1002/ppul.27449

66.Kristidis P, Bozon D, Corey M, et al. Genetic determination of exocrine pancreatic function in cystic fibrosis. *Am J Hum Genet*. 1992;50(6):1178-1184.

Medical Disclaimer

The information provided by the American Academy of Value-Based Care (AAVBC) in this document, including but not limited to coding guidance, and related content, is intended for educational and informational purposes only. This content is designed to assist healthcare providers, organizations, and professionals in understanding and applying Value-Based Care principles, practices, and regulatory compliance standards.

AAVBC does not provide legal, clinical, or medical advice. The content presented should not be interpreted or relied upon as specific legal, medical, clinical, or professional guidance. While efforts are made to ensure the accuracy and currency of the information provided, AAVBC does not guarantee that the materials presented are complete, comprehensive, or without error.

Providers and healthcare professionals must independently evaluate all content and guidance presented herein in the context of applicable laws, regulations, clinical guidelines, payer policies,

patient-specific conditions, and contraindications. Any treatments, procedures, diagnostic approaches, medications, or strategies discussed are illustrative and should not be directly applied without a thorough and independent review of current, evidence-based clinical resources, and regulatory requirements.

For coding, documentation, utilization management, quality measures (including STAR ratings), and compliance matters, users are responsible for consulting official guidelines issued by regulatory bodies, including but not limited to the Centers for Medicare and Medicaid Services (CMS), the American Medical Association (AMA), relevant state agencies, and other authoritative entities.

AAVBC expressly disclaims liability for any loss, claim, or damages arising directly or indirectly from the use or reliance on information provided in this document. Users should consult their organization's legal counsel, compliance officer, or qualified professional advisor for advice specific to their situation. By accessing and using this document, you agree to AAVBC's terms and acknowledge that the use of the content is at your own risk and discretion.