American Journal of Respiratory and Critical Care Medicine, 2026, 212(10), 2530–2541
https://doi.org/10.1093/ajrccm/aamag370
Published: July 11, 2026
Concise Clinical Review

Residual disease activity in cystic fibrosis lung disease: implications for clinical management and research

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Abstract

The advent of cystic fibrosis transmembrane conductance regulator (CFTR) modulators is fundamentally reshaping research and care for people with cystic fibrosis (CF). Despite unprecedented improvements in lung function and predicted survival, a substantial proportion of people with CF continue to exhibit residual disease activity (RDA) across multiple biological and clinical domains. Persistent abnormalities in CFTR function, mucus properties, mucociliary clearance, airway infection, inflammation, and symptom burden indicate that CFTR modulation does not fully normalize airway physiology or eliminate the pathological processes underlying CF lung disease. This review proposes RDA as a conceptual framework for identifying ongoing, potentially modifiable disease processes in people receiving CFTR modulators. Candidate measures across complementary mechanistic and clinical domains are examined, and their potential multidimensional interpretation as a means of supporting more individualized monitoring and treatment decisions is discussed. We consider the implications of RDA for clinical research by identifying key evidence gaps, outlining a stepwise pathway for its definition and validation. We further explore the potential to inform sensitive endpoint selection, enrich study populations, and guide the development of therapies targeting disease processes that persist despite CFTR modulation. As the CF population ages and disease trajectories evolve, care models and research priorities must move beyond conventional measures of disease severity alone. A better understanding and systematic evaluation of RDA may help align long-term clinical management and future trial design with the changing needs of people with CF, while ensuring that therapeutic advances translate into sustained health gains.

Keywords cystic fibrosis, residual disease activity, CFTR modulators

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Introduction

The introduction of triple-combination cystic fibrosis transmembrane conductance regulator (CFTR) modulators (CFTRm) has fundamentally impacted on the clinical trajectory of people with cystic fibrosis (pwCF), leading to marked attenuation of disease progression and a further increase in life expectancy over the coming years.[1]

Evidence from clinical trials, real-world observational studies, and registries shows significant short- to medium-term improvements in lung function, nutritional status, and patient-reported outcomes.[2-9] The clinical benefit has also been confirmed in pwCF with advanced lung disease, allowing for deferral of lung transplant in a considerable number of patients.[10] To date, the integration of real-world evidence from the French compassionate use program,[11] along with in vitro data and clinical trial results on rare variants,[11,12] has made elexacaftor/tezacaftor/ivacaftor (ETI) available to up to 95% of the European cystic fibrosis (CF) population. As a result, life expectancy is projected to move toward that of the general population.[13] This paradigm shift underscores the growing demand to characterize new clinical trajectories and to reshape prevention strategies and models of care to meet the evolving clinical needs of an aging CF population.

Multiple factors are expected to influence long-term disease trajectories in this era (Figure 1). As life expectancy increases, age-related comorbidities are likely to emerge and gain clinical relevance, contributing to residual morbidity and influencing care management needs.[14] In parallel, both age and disease severity at the time of initiation of CFTRm represent key determinants of

Received: April 11, 2026. **Accepted:** July 8, 2026
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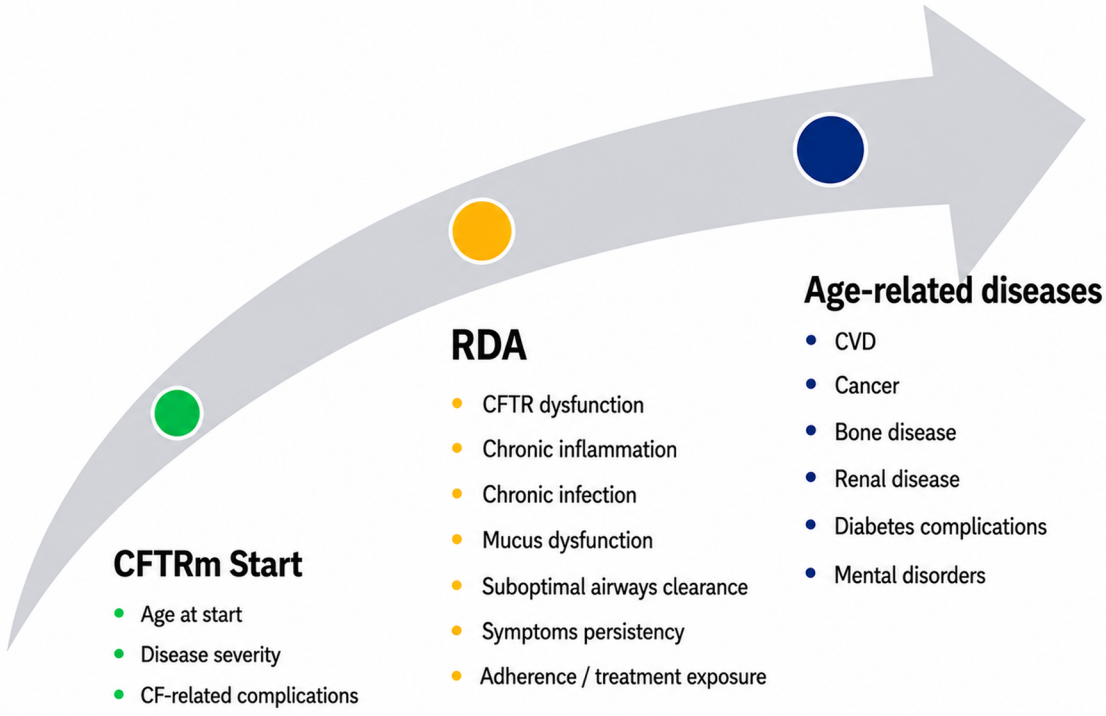


Figure 1 Factors contributing to long-term disease trajectories in the era of CFTR modulators. Abbreviations: CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; CFTRm, cystic fibrosis transmembrane conductance regulator modulators; CVD, cardiovascular disease; RDA, residual disease activity.

therapeutic response. Adults with established bronchiectasis have limited potential for structural and biological reversal compared with infants and young children who begin therapy before irreversible lung damage has occurred.[15-18]

Despite this transformative impact, a substantial proportion of pwCF may continue to exhibit persistence of pathophysiological abnormalities that can contribute to ongoing disease progression despite partial restoration of CFTR function. We propose the term "residual disease activity" (RDA) to describe this continuing and potentially modifiable pathological activity.

This review aims to explore the available evidence on persistent pathophysiological abnormalities following CFTRm and to organize these findings within a multidomain framework of RDA. A secondary aim is to examine the potential clinical relevance of this framework for patient stratification, longitudinal monitoring, and treatment optimization. This review also seeks to identify key evidence gaps, including the absence of a standardized definition of RDA, the lack of a validated assessment tool, and the limited evidence supporting RDA-guided clinical decision-making. Addressing these gaps is crucial to move beyond a purely modulator-centered view of disease control and to identify residual, potentially treatable targets that may guide individualized follow-up strategies and therapeutic interventions.

Definition of disease activity in CF

Disease activity versus disease severity

Disease activity may be defined as the current intensity of ongoing pathophysiological processes that drive disease progression and that can be potentially suppressed or partially modified by treatment.[19-21] In other fields as rheumatology, disease activity has traditionally been conceptualized as the potentially reversible inflammatory disease manifestations, in contrast to disease severity, which reflects persistent or irreversible anatomical, physiological, or functional damage accumulated over time. Given the complexity of assessing disease activity, in inflammatory disorders it is commonly assessed through validated composite tools integrating clinical manifestations, laboratory markers, and patient- and physician-reported assessments, which are measured longitudinally to guide treat-to-target decisions.[20,21]

Applied to CF, we propose that disease activity may be understood as the current intensity of residual CFTR dysfunction and its active downstream consequences that contribute to subsequent organ damage and may change in response to treatment. Inflammation is therefore a central domain of CF disease activity, but it is neither its sole determinant nor a sufficient measure of activity. Other domains of residual disease activity include residual mucus dysfunction and chronic airway infection. No validated multidimensional disease activity instrument currently exists for CF.

This concept should also be distinguished from disease severity, which reflects the overall multisystem burden of CF at a given time and is strongly influenced by cumulative, often irreversible structural and functional damage across pulmonary and extrapulmonary manifestations, including established bronchiectasis (Figure 2).

Although conceptually separate, disease activity and disease severity may coexist within the same individual: Active pathophysiological processes may persist in patients with advanced structural damage, while substantial disease severity may remain despite limited current activity. Distinguishing disease activity from disease severity is increasingly recognized across respiratory medicine,

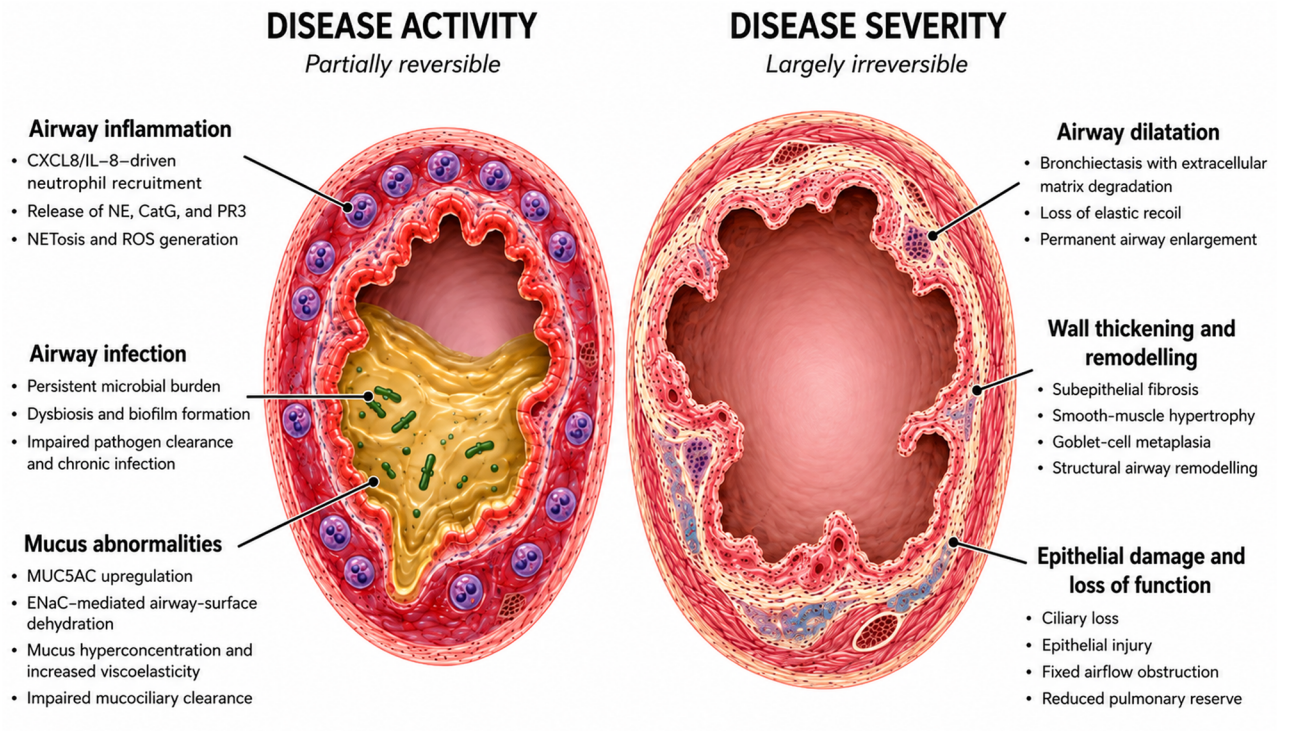


Figure 2 Distinction between disease activity and disease severity in cystic fibrosis lung disease. Disease activity reflects ongoing and partially reversible pathophysiological processes, while disease severity reflects the cumulative, largely irreversible structural and functional consequences of disease. Disease activity may occur at any level of established disease severity. Abbreviations: CatG, cathepsin G; CXCL8, C-X-C motif chemokine ligand 8; ENaC, epithelial sodium channel; IL-8, interleukin 8; NE, neutrophil elastase; NET, neutrophil extracellular trap; PR3, proteinase 3; ROS, reactive oxygen species.

including chronic obstructive pulmonary disease and bronchiectasis, where it provides a useful framework for understanding risk trajectories and informing therapeutic strategy design.[19,22]

This distinction is particularly important after initiation of CFTRm. In individuals who start treatment after structural lung disease is already established, posttreatment severity may largely reflect damage accumulated before treatment rather than continued failure to control active disease. These abnormalities may therefore persist despite effective suppression of ongoing disease activity and should not be interpreted as evidence of treatment failure. Conversely, even when CFTRm therapy is initiated early in life, it remains uncertain whether disease processes can be fully prevented. CFTR dysfunction and its downstream consequences may still emerge and could represent a distinct form of RDA occurring in the relative absence of advanced structural damage.

Although a standardized definition of RDA is still lacking in CF lung disease, a range of clinical, radiological, and biological indicators may act as surrogate markers of disease activity across different domains. These may include sputum rheology, radiological detection of mucus plugging and airway wall thickening, and airway inflammation and dysbiosis, as well as patient-reported symptom burden. Such measures have been associated with short-term clinical outcomes, including exacerbation risk and accelerated lung function decline, and may capture key mechanistic drivers of disease progression that are both measurable and potentially amenable to therapeutic intervention.[23]

Residual disease activity in CF lung disease

As CF is a multisystem disorder, RDA may also occur in extrapulmonary organs, including gastrointestinal, pancreatic, and hepatobiliary. However, the biological manifestations and relevant outcomes are likely to differ across organs and may require domain-specific definitions and validation. The present review therefore focuses primarily on RDA in CF lung disease, while recognizing the need for future work to extend and adapt this framework to extrapulmonary manifestations.

While the impact of RDA on long-term lung disease progression remains uncertain, its persistence suggests that upstream correction of CFTR dysfunction does not fully normalize airway biology. RDA in CF may therefore be conceptualized not only as a marker of ongoing pathology, but also as an obstacle to the restoration of airway homeostasis, which should remain the ultimate long-term goal of treatment.[24]

Importantly, the patterns and magnitude of RDA appear heterogeneous in pwCF, with some patients showing predominant abnormalities in specific domains but minimal involvement in others. In a recent experience of pwCF treated with ETI, changes in sweat chloride concentration (SCC), lung function, body mass index, and patient-reported respiratory symptoms showed only weak correlations with each other, indicating that restoration of CFTR function does not translate uniformly into clinical improvement across all domains of disease.[25] This framework supports the concept of RDA as a multidimensional phenomenon, where heterogeneous patterns may continue to influence long-term

outcomes even in the presence of CFTR restoration. This variability reinforces the need for domain-specific assessment and personalized management approaches.

Because markers of disease activity reflect potentially modifiable processes, their systematic identification and targeted management may help prevent further structural damage and optimize long-term outcomes in pwCF. In the following sections, we review current evidence on RDA with a focus on respiratory domains and propose measurable, clinically meaningful outcomes to inform research priorities and support personalized clinical decision-making.

Measuring residual disease activity in CF lung disease

Residual impairment of CFTR activity

CFTR activity is the primary pharmacological target of CFTRm therapy, and SCC is the most widely used surrogate marker. Registrational trials of ETI in adolescents and adults with CF demonstrated substantial reductions in SCC; nevertheless, approximately one-quarter of participants maintained values above the pathological threshold of 60 mmol/L.[5,6] Real-world cohorts and patient registry data have confirmed this heterogeneity on a larger scale. In a recent United States–based study, 79% of individuals treated with ETI achieved SCC values <60 mmol/L, whereas 21% remained above this threshold, most frequently among those with Phe508del/minimal function genotypes.[26] Even the newest generation of CFTRm do not achieve complete normalization of CFTR function. In the recent SKYLINE trials of vanzacaftor/tezacaftor/deutivacaftor (VTD), reductions in SCC appeared greater than those observed with ETI. However, 14% of individuals treated with VTD continued to have SCC values ≥60 mmol/L, compared with 23% in the ETI group. In addition, more than half of participants in both treatment arms exhibited intermediate SCC results (30-60 mmol/L), suggesting persistent incomplete physiological CFTR correction despite treatment.[3]

Residual impairment of CFTR activity may have clinically meaningful downstream implications. First, suboptimal CFTR function does not preclude disease progression over time, as illustrated by the presence of chronic inflammation and bronchiectasis in pwCF with residual function variants.[27] Zemanick and colleagues further expanded this concept by demonstrating that pwCF with intermediate SCC results after ETI experienced smaller improvements in lung function and exacerbation frequency compared to those achieving SCC <30 mmol/L.[28]

Electrophysiological assessments of CFTR function further reinforced these observations. Although nasal potential difference has been applied in relatively few studies, available data consistently indicate that ETI restores on average approximately 40% to 50% of normal CFTR activity in individuals carrying at least one Phe508del allele, with substantial variability between individuals.[29]

Taken together, these findings indicate that current CFTRm, including ETI and VTD, do not fully normalize CFTR protein function. Instead, residual CFTR dysfunction persists and may act as an upstream driver of ongoing biological activity, warranting further investigation.[29-31]

Residual impairment of mucociliary clearance

Airway mucus abnormalities remain a key treatable trait in pwCF with established bronchiectasis even after ETI initiation, and their management continues to represent a substantial component of daily treatment burden.[32] Current standards of care include mucociliary clearance techniques, mucoactive therapies, and inhaled bronchodilators, which aim to facilitate mucus mobilization and provide both therapeutic and preventive benefits in CF lung disease.[33]

Accumulating evidence from the postmodulator era indicates that mucociliary function and sputum viscoelastic properties are not fully restored. Mechanistic studies support this concept. Schaupp and colleagues showed that, despite measurable improvements in sputum rheology after 3 and 12 months of ETI therapy, significant differences persisted compared with healthy controls, indicating incomplete restoration of mucus properties.[32,34]

Evidence from the PROMISE substudy demonstrates that ETI significantly improved mucociliary clearance (MCC) in 44 patients aged 12 years and older.[35] On average, whole-lung MCC over 60 minutes increased from 14.8% at baseline to 22.8% approximately 30 days after ETI initiation. However, the individual responses varied considerably: While many patients experienced marked enhancement in MCC, others showed minimal change, and a subset even exhibited a reduction following treatment. These findings indicate that, although ETI generally enhances mucociliary transport, complete restoration is not consistently achieved across all patients; moreover, in the absence of a healthy control group, the extent to which ETI restores MCC to normal levels remains unclear.

These biological findings are consistent with clinical observations. While ETI initiation is associated with reductions in sputum volume and improved patient-reported mucociliary clearance, a proportion of individuals continue to experience daily sputum production and chronic cough, and mucus remains visible by cross-sectional imaging in many pwCF.[8,9] In a survey conducted by the German CF Association, 9% of pwCF reported persistent daily sputum production and 7% ongoing chronic cough despite ETI therapy.[36]

These data suggest that RDA related to airway mucus persists in many individuals and can be detected and quantified through clinical assessment, lung imaging, and advanced functional testing.

Functional assessments provide additional evidence of residual airway disease despite ETI. Normalization in ventilatory inhomogeneity is not universal. In a multicenter pediatric cohort, 14% of pwCF continued to exhibit abnormal lung clearance index values after 12 months of treatment.[18] Other markers of ventilation inhomogeneity and air trapping, such as Residual Volume / Total Lung Capacity ratio (RV/TLC), also remain abnormal in a subset of individuals and have been associated with attenuated FEV_1 responses, suggesting that irreversible structural changes may limit functional recovery.[37]

Imaging findings confirm these functional observations. Chronic radiological abnormalities, including established bronchiectasis and lung hyperinflation, showed limited or no improvement in studies using validated imaging scoring systems.[9,8,38] In addition, a recent multicenter French study of adolescents receiving ETI showed progression of bronchial dilatation in 7% of participants, predominantly among those with poorer baseline lung

function, indicating that structural deterioration may continue in vulnerable subgroups.[39]

Collectively, these data indicate that, although ETI provides substantial clinical benefit, it does not fully resolve mucus-related airway obstruction or its downstream consequences. Residual abnormalities in mucus properties, ventilation distribution, and air trapping may continue to contribute to ongoing disease activity, particularly in individuals with preexisting structural damage. These observations underscore the importance of continued monitoring and adjunctive therapies aimed at addressing persistent airway dysfunction in the modulator era.

Residual airway infection

Since the introduction of ETI, growing attention has focused on respiratory microbiology to determine whether and to what extent airway infection patterns change in longitudinal evaluations. Data from the PROMISE-Micro study showed that ETI is associated with a rapid reduction in sputum densities of key CF pathogens within the first month of treatment, followed by long-term stabilization over 3.5 years.[40] However, complete eradication remains uncommon. Among individuals able to provide adequate sputum samples, clearance of *Pseudomonas aeruginosa* occurred in <10% of cases and, even in patients who became culture negative, the same pathogens were often detectable by PCR months later, suggesting improved host control rather than true microbial eradication.

New infections were also observed. A subset of pwCF who were culture negative for respiratory pathogens prior to ETI developed incident airway infections during follow-up, most frequently with *Staphylococcus aureus* and *P aeruginosa* (approximately 40% and 10%, respectively). Although these events were generally transient and clinically mild, they remain potentially relevant, as they may lead to the establishment of chronic infection or contribute to ongoing airway injury. Persistent infection appears largely driven by preexisting structural lung damage and established chronic infection, with important implications for decisions regarding de-escalation or discontinuation of inhaled antibiotics.

Culture-independent microbiome analyses and longitudinal whole-genome sequencing studies provide additional insight into airway ecology dynamics in the CFTRm era. Across multiple cohorts, ETI consistently reduced total bacterial load and modestly increases microbial diversity.[41] However, these favorable shifts do not restore a healthy respiratory microbiome. Instead, persistent dysbiosis remains a defining feature after treatment initiation, with airway communities continuing to diverge substantially from those of healthy individuals.[32] This residual dysbiotic state correlates with markers of ongoing airway inflammation and has been associated with continued lung function decline, indicating that microbial ecology remains an active contributor to RDA despite CFTR modulation.[42]

At the level of individual pathogens, genomic analyses further highlight the durability of chronic infection. Whole-genome sequencing of *P aeruginosa* isolates collected before and after ETI initiation demonstrates remarkable genomic and phenotypic stability, with no consistent evidence of attenuated virulence or reversal of antimicrobial resistance.[43] These findings suggest that although ETI modifies the airway milieu, it does not exert sufficient impact to disrupt long-established pathogen populations or their adaptive strategies. Rather, ETI appears to induce a shift, but not a complete reset, of the airway microbial ecosystem, which may increasingly resemble that observed in patients with non-CF bronchiectasis.[44] A better understanding of the evolving interplay between host immunity and microbial networks in the postmodulator era will be essential to inform future microbiome-directed therapeutic strategies.

Residual airway inflammation

The persistence of pulmonary exacerbations despite CFTRm therapy reflects inflammation-related RDA. Registrational studies reported annualized exacerbation rates ranging from 0.26 to 0.42 per patient-year despite ETI or VTD therapy, events known to have a detrimental impact on prognosis.[3,5,45,46]

Real-world studies evaluating inflammatory biomarkers before and after ETI initiation showed reductions in both systemic and airway inflammation.[32,47,48] However, sputum concentrations of IL-1β, IL-6, and TNF-α, as well as the activity of free and membrane-bound neutrophil elastase (NE), declined but rarely normalized, indicating that airway inflammation persists despite effective CFTR modulation.[32,34] Similarly, single-cell transcriptomic analyses of nasal epithelial samples from children aged 6 to 11 years showed that ETI did not completely reverse proinflammatory cellular programs, indicating persistent immune activation despite CFTR correction even in younger individuals.[49] Transcriptomic analyses of CF airway epithelial cells further support this interpretation. Although neutrophil-associated inflammatory gene expression was markedly downregulated within the first months of ETI therapy in an adult CF cohort, partial reactivation of baseline inflammatory programs emerged over longer follow-up, indicating persistent inflammatory signaling that may influence airway integrity and long-term disease progression.[50] In a series of studies, NE activity and other neutrophil serine proteases, including proteinase-3 and cathepsin G, tended to decrease to levels comparable to those observed in non-CF bronchiectasis rather than healthy individuals, suggesting a shift toward a bronchiectasis-like inflammatory phenotype characterized by persistent neutrophilic activity.[32,34,48,51,52]

Although the assessment of local neutrophilic inflammation may represent an important marker of RDA in pwCF, reliable point-of-care methods for its routine evaluation are currently lacking. Biomarkers such as NE may provide a direct measurement of neutrophilic inflammation, but they remain confined to research settings and are not implemented in everyday clinical practice. Previous studies have shown that sputum purulence reflects the presence of neutrophilic airway inflammation.[53,54] The green color observed in purulent sputum is largely attributable to myeloperoxidase, an enzyme contained within the azurophilic granules of activated neutrophils. Consequently, assessment of sputum color has been proposed as a simple and accessible surrogate marker of neutrophilic inflammation. In patients with bronchiectasis, sputum purulence correlates with disease severity and clinical outcomes.[55] Therefore, it may represent a practical risk stratification tool to identify individuals at increased risk of active disease and future exacerbations.

Residual respiratory symptoms

Patient experience of disease is closely linked to the burden of symptoms. For this reason, registrational trials have consistently included patient-reported outcome measures (PROMs), most

commonly the Cystic Fibrosis Questionnaire–Revised (CFQ-R) respiratory domain, among their secondary endpoints.[3,5] Considerable heterogeneity in CFQ-R respiratory domain scores has been observed across individuals, with smaller improvements experienced in patients with specific genetic backgrounds.[2,56] Despite the increased use of PROMs in clinical trials, data specifically addressing the persistence of residual symptoms remain limited.

A nonnegligible proportion of patients continue to experience symptoms such as cough, mucus production, dyspnea, and chest tightness.[57] In the phase 3 extension study of ETI, cough remained the most frequently reported event, occurring at a rate of 31 events per 100 patient-years, followed by episodes of increased sputum production (12.7 events per 100 patient-years) and fatigue (11.3 events per 100 patient-years).[58] In a large survey of 262 pwCF in the United States (78% of whom were receiving CFTRm), the most commonly reported symptoms included lack of energy (74%), cough (73%), and shortness of breath (55%), all of which were associated with variable impacts on quality of life.[59] These observations suggest that symptom persistence represents an important clinical manifestation of RDA, potentially reflecting ongoing biological processes such as incomplete mucociliary clearance, chronic infection, or persistent inflammation.

Beyond residual symptoms, treatment burden remains a major concern for pwCF in the modulator era and has been identified by patients as a key research priority.[60] Although several studies have explored the potential for treatment simplification, surveys examining adherence patterns highlight the persistence of substantial treatment burden.[61,62]

Taken together, these findings indicate that residual symptoms and treatment burden remain important dimensions of RDA in the postmodulator era. Systematic evaluation of these domains, using appropriate assessment tools, may therefore provide valuable insight into the persistence of underlying pathophysiological processes and help guide individualized approaches and treatment optimization in the postmodulator era.

RDA in personalized clinical management in CF

Introducing the concept of RDA in CF could have important implications for clinical practice, as it offers a framework for tailoring care more closely to the needs of individual pwCF. Identifying domains of ongoing disease activity would allow clinicians to better stratify patients and personalize follow-up strategies. Regular assessment of these domains could help define patient response to therapeutic interventions and guide treatment toward those specific processes that may drive disease progression despite CFTRm.

Different profiles of RDA should not be regarded as fixed categories, but as dynamic phenotypes that may evolve under treatment exposure, adherence, and intercurrent events. A multidomain assessment could therefore help distinguish patients who may benefit from targeted treatment escalation or inflammatory endotyping from those in whom maintenance of current therapy and selective optimization may be more appropriate (Figure 3). Such an approach could also support more standardized decisions regarding treatment escalation or de-escalation. Absence of residual mucociliary clearance impairment may be useful to select the best candidates for treatment simplification, including discontinuation of mucoactive therapies.[63] On the other hand, a dynamic assessment of RDA domains may help to revise these decisions

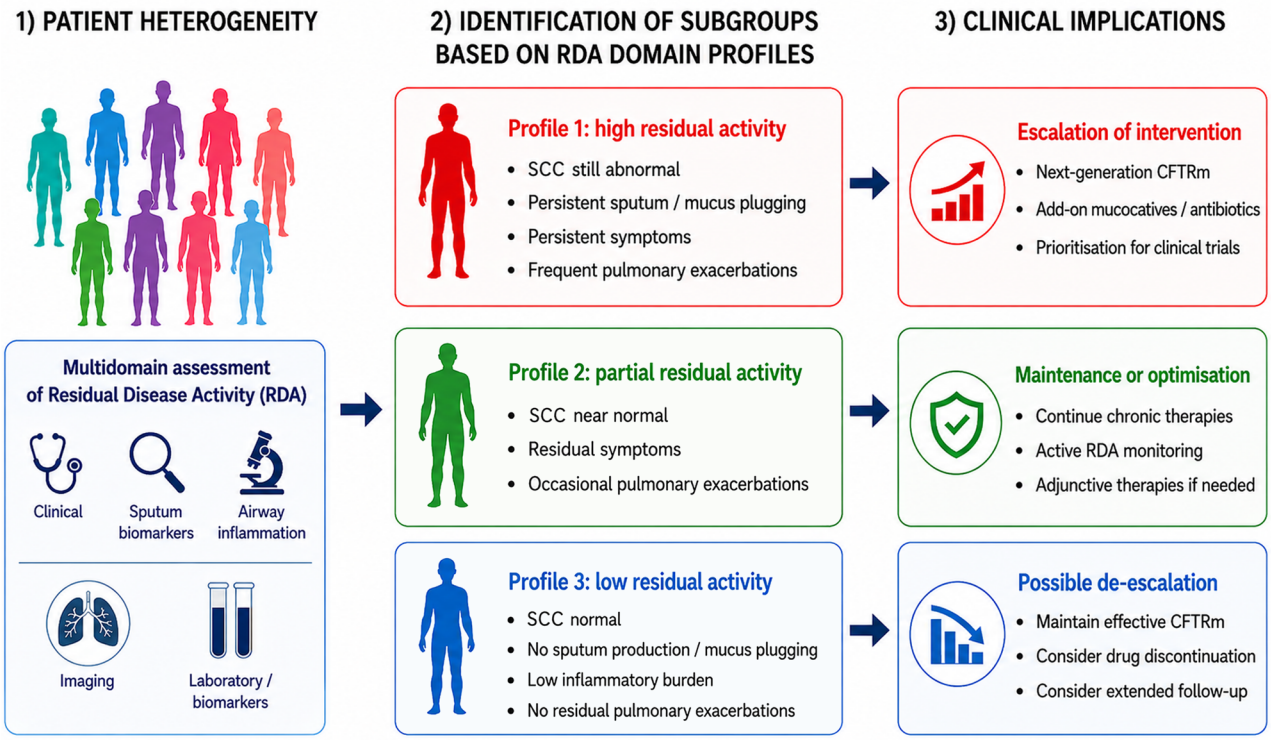


Figure 3 Residual disease activity in cystic fibrosis as a framework for therapeutic stratification and future drug development. Abbreviations: CFTRm, cystic fibrosis transmembrane conductance regulator modulators; RDA, residual disease activity; SCC, sweat chloride.

overtime. Importantly, such profiles remain illustrative and hypothesis-generating, and their clinical utility will require prospective validation before they can be used to support treatment decisions.

The availability of reliable markers of RDA could also inform how emerging therapies are evaluated and positioned within the clinical management of CF. As the pipeline of CF-targeted therapies continues to expand, better risk stratification based on measurable domains of RDA may help identify the patients most likely to benefit from novel treatments. Next-generation CFTRm or CFTR amplifier drugs aiming for full restoration of CFTR function could be prioritized for individuals showing persistent CFTR dysfunction despite current therapies.[64] We may hypothesize that in pwCF carrying predominantly neutrophilic inflammatory signatures, emerging anti-inflammatory therapies such as DPP-1 inhibitors could complement CFTR modulation and help address persistent disease activity.[65-67] However, more data are needed before any recommendation can be made.

In this way, integrating the concept of disease activity into CF care may help move the field toward a more precise and individualized approach to treatment.

RDA in clinical research: evidence gaps and future applications

The development of RDA as a clinically informative framework in CF will require a structured, stepwise research program. The initial priority should be to establish a consensus definition of RDA and its core mechanistic domains, while clearly distinguishing active and potentially modifiable processes from largely irreversible damage. This distinction is essential to avoid confusing disease activity with disease severity and to identify the processes most likely to respond to therapeutic intervention. Candidate indicators within each

Table 1 Domains of residual disease activity and proposed measurement tools.

Domain of RDA	Candidate endpoints	Strengths	Limitations	Trial readiness	Clinical readiness
CFTR activity	Sweat chloride concentration	• Directly reflects response to CFTR modulation • Standardized • Highly feasible • Familiar to regulators	• Poor representation of downstream airway RDA • Incomplete correlation with clinical outcomes	High	High
	CFTR functional assays (NPD, ICM)	• Mechanistically strong • Direct link to CFTR correction • Useful in proof-of-concept studies	• Limited availability • Technically demanding • Not scalable for multicenter trials	Low	Moderate
Mucociliary clearance	Percent predicted FEV_1	• Well-established • Widely available • Standardized • Highly feasible • Accepted by regulators	• Insensitive in mild disease • Missing early abnormalities • Ceiling effect	High	High
	Ventilatory inhomogeneity indices (LCI, RV/TLC)	• Increased sensitivity to RDA • Biologically plausible for persistent mucostasis • Validated endpoint for pediatric studies	• Limited availability across centers • More technically demanding • Longitudinal thresholds still to be defined	Moderate	High
	Sputum production/ purulence	• Simple and clinically intuitive • Relevant to patient experience	• Poor standardization • Unavailable for many patients on CFTRm • Not reflecting biological activity	Moderate	High
	Quantitative chest CT scores	• Sensitive to mucus plugging • Bridging RDA and future severity	• Radiation exposure • Higher costs • Limited reproducibility	Low	Moderate
	Chest MRI	• No ionizing radiation • Feasible in children and suitable for repeated measures • Can integrate structural and functional information • Sensitive to mucus plugging	• Longer acquisition times and relatively high cost • Not yet fully standardized • Lower spatial resolution than CT for lung • Restricted to specialized research centers	Moderate	Low
	AI-based imaging analysis	• Increased sensitivity and reproducibility • Scalable • Attractive for RDA	• Requires robust validation • Limited access • Still dependent on imaging acquisition constraints	Low	Low

(Continued)

Table 1 Continued.

Domain of RDA	Candidate endpoints	Strengths	Limitations	Trial readiness	Clinical readiness
Airway infection	Chronic infection status	• Well-established • Associated with exacerbation risk	• Binary classification • Poor sampling after CFTRm	High	High
	Quantitative microbiology	• More granularity • Measures burden, not just presence/absence	• Methodological variability • Specimen quality issues • Poorly standardized	Moderate	Moderate
	Microbiome-informed monitoring	• Detecting organisms missed by routine culture • Richer ecological and longitudinal information	• Cost • Bioinformatic complexity • Uncertain interpretation • Limited regulatory familiarity	Low	Low
Airway inflammation	Sputum neutrophil elastase	• Strong mechanistic relevance • Directly aligned with neutrophilic inflammation	• Poor standardization • Sputum collection less feasible after CFTRm	Moderate	Low
	Inflammatory cytokines (eg, IL-6, IL-8)	• Biologically informative • Useful in defining inflammatory endotypes	• Assay variability • Uncertain cut-offs • Influenced by systemic processes	Moderate	Low
	CRP and selected blood inflammatory markers	• Easy to obtain • Scalable • Inexpensive	• Nonspecific • Poorly captures localized inflammation	Moderate	Moderate
Pulmonary exacerbations	Annual exacerbation rate/time to first exacerbation/ severe exacerbations	• Well-established • Understandable to clinicians • Relevant for healthcare utilization • Accepted by regulators	• Event-driven • Less frequent after CFTRm • Sensitivity to event rates and follow-up duration • Variable thresholds	High	High
Respiratory symptoms	CFQ-R respiratory domain	• Established PROM • Relevant to patient experience	• Subjective • Possible ceiling effect	High	Moderate
	Cough, sputum, and respiratory symptom scores	• Relevant to patient experience	• Poor standardization in CF • Symptoms may dissociate from underlying biology	Moderate	Moderate
	Treatment burden PROMs	• Relevant to patient experience • Reflecting RDA in CFTRm era • Sensitive to treatment simplification strategies	• Indirect measurement of biological disease activity • Poor standardization • Vulnerable to reporting bias	Moderate	Moderate

Abbreviations: AI, artificial intelligence; CF, cystic fibrosis; CFQ-R, Cystic Fibrosis Questionnaire–Revised; CRP, C-reactive protein; CT, computed tomography; CFTR, cystic fibrosis transmembrane conductance regulator; CFTRm, cystic fibrosis transmembrane conductance regulator modulators; ICM, intestinal current measurement; LCI, lung clearance index; MRI, magnetic resonance imaging; NPD, nasal potential difference; PROM, patient-reported outcome measure; RDA, residual disease activity; RV/TLC, residual volume/total lung capacity.

domain should then be evaluated in prospective longitudinal cohorts using repeated and standardized assessments. These studies should determine their feasibility, measurement accuracy, and reproducibility, as well as association with key clinical outcomes, including clinical symptoms, pulmonary exacerbations, disease progression determined from functional decline, and PROMs.

As the direct measurement of several biological processes remains largely confined to research settings, particular emphasis should be placed on developing practical and accessible surrogate measures, including point-of-care biomarkers and imaging-based scores. The most informative and feasible indicators could subsequently be integrated into a provisional multidimensional instrument. Such an instrument would require internal and external validation in independent populations, together with the definition of clinically meaningful change and distinct RDA profiles. Such a staged process would address the principal evidence gaps currently limiting the clinical interpretation of RDA and determine whether it can evolve from a conceptual framework into a reproducible and clinically useful assessment strategy (Table 1). A similar stepwise approach has previously been adopted in systemic lupus erythematosus and rheumatoid arthritis, where multidimensional clinical and laboratory indicators were selected and validated against expert assessment and relevant outcomes to develop composite disease activity indices, such as the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and the Disease Activity Score (DAS)/DAS28.[68,69]

Once a robust RDA framework and validated assessment tool have been established, the integration into clinical trial design would represent a major research application. Conventional CF trials have frequently relied on broad eligibility criteria based

primarily on genotype, age, and lung function, together with endpoints such as percent predicted FEV_1 and pulmonary exacerbation rates. However, in the CFTRm era, these measures alone may not adequately reflect clinical heterogeneity and low event rates, and RDA-based phenotyping could support a more refined approach to patient stratification and therapy by identifying individuals with measurable abnormalities that can potentially be targeted therapeutically despite otherwise stable conventional clinical measures.[70] Markers of RDA could therefore be incorporated into eligibility criteria or enrichment strategies, allowing trials to preferentially recruit participants with a clinically relevant unmet need and a greater likelihood of responding to a targeted intervention. RDA domains may inform the selection of more sensitive and mechanism-specific endpoints, reducing reliance on measures that may show limited variability in highly treated populations.

Prospective studies should therefore determine whether incorporating RDA into research may facilitate precision trial design and accelerate the development of therapies targeting disease processes that persist despite CFTR modulation.

Author contributions

All authors made substantial contributions to conception and design, took part in drafting the article or revising it, agreed to submit to the current journal, gave final approval of the version to be published, and agree to be accountable for all aspects of the work. A.G. and G.P. contributed to study concept, data acquisition and interpretation, and review and approval of the manuscript. G.A., M.A.M., and F.B. contributed to data interpretation and review and approval of the manuscript.

Supplementary material

Supplementary material is available at *American Journal of Respiratory and Critical Care Medicine* online.

Conflicts of interest

Please see the ICMJE disclosure forms, which have been provided as supplementary material. A.G. reports grants from AstraZeneca and Insmed; consulting fees from Menarini and Vertex Pharmaceuticals; payment or honoraria for lectures from AstraZeneca, Chiesi, GSK, Guidotti, Grifols, Insmed, Menarini, Vertex Pharmaceuticals, and Zambon; and travel reimbursement received for participation in advisory board meetings or congresses for Vertex Pharmaceuticals, Insmed, Chiesi, and Neupharma. A.G. is also the Chair of the European Cystic Fibrosis Society Standards-of-Care Working Group. M.A.M. reports grants or contracts from the German Ministry of Research, Technology and Space (BMFTR), the German Research Foundation (DFG), Boehringer Ingelheim, Enterprise Therapeutics, and Vertex Pharmaceuticals with payments made to the institution; consultancy fees from Boehringer Ingelheim, Enterprise Therapeutics, Kither Biotech, Pari, Splisense, and Vertex Pharmaceuticals; payment or honoraria for lectures from Boehringer Ingelheim and Vertex Pharmaceuticals; travel reimbursement received for participation in advisory board meetings for Boehringer Ingelheim and Vertex Pharmaceuticals; and fees for participation on an advisory board from Boehringer Ingelheim, Enterprise Therapeutics, Kither Biotech, Pari, Splisense, and Vertex Pharmaceuticals. M.A.M. is an unpaid fellow of the European Respiratory Society. F.B. reports grants or contracts from AstraZeneca, Insmed, and Chiesi with payments made to the institution; consultancy fees from Menarini, OM Pharma, and Boehringer Ingelheim; payment or honoraria for lectures from AstraZeneca, Chiesi, GSK, Guidotti, Grifols, Insmed, Menarini, Novartis, OM Pharma, Pfizer, Sanofi, Vertex Pharmaceuticals, Viatris, and Zambon; travel reimbursement for participation in advisory board meetings for Novartis, Pfizer, Sanofi, Vertex Pharmaceuticals, Viatris, and Zambon; and fees for participation on an advisory board from Novartis, GSK, Pfizer, Sanofi, Vertex Pharmaceuticals, and Zambon. F.B. is an unpaid fellow of the European Respiratory Society. G.P. and G.A. report no conflicts of interest.

Funding

A.G. and F.B. have been supported by funding from Ministero della Salute Italy, Ricerca Corrente (RC2025 260/01) Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico Milano and Regione Lombardia RICERCA SULLA FIBROSI CISTICA (DRG17034 /2024 and 2025 RL_RLAOOG1_2025_9528). M.A.M. has been supported by grants from the German Federal Ministry of Research Technology and Space (82DZL009C1 and 01GL2401A) and the German Research Foundation (CRC 1449 – project 431232613 and EXC 3118/1 – project number 533770413).

Artificial intelligence disclaimer

The authors used artificial intelligence tools to rephrase selected sentences in order to avoid unnecessary repetition and to support the development and refinement of the figures. After using these tools, the authors reviewed and edited all generated content and take full responsibility for the accuracy, integrity, and content of the published article.

References

1. Mall MA, Burgel PR, Castellani C, Davies JC, Salathe M, Taylor-Cousar JL. Cystic fibrosis. *Nat Rev Dis Primers*. 2024; 10:53. https://doi.org/10.1038/s41572-024-00538-6
2. Barry PJ, Mall MA, Álvarez A, et al.; VX18-445-104 Study Group. Triple therapy for cystic fibrosis Phe508del-gating and -residual function genotypes. *N Engl J Med*. 2021;385:815-825. https://doi.org/10.1056/NEJMoa2100665
3. Keating C, Yonker LM, Vermeulen F, et al.; VX20-121-102 StudyGroup;VX20-121-103StudyGroup.Vanzacaftor-tezacaftor-deutivacaftor versus elexacaftor-tezacaftor-ivacaftor in individuals with cystic fibrosis aged 12 years and older (SKYLINE Trials VX20-121-102 and VX20-121-103): results from two randomised, active-controlled, phase 3 trials. *Lancet Respir Med*. 2025;13:256-271. https://doi.org/10.1016/S2213-2600(24)00411-9. Erratum in: Lancet Respir Med. 202513:e19. https://doi.org/10.1016/S2213-2600(25)00011-6

4. Burgel PR, Sermet-Gaudelus I, Girodon E, et al.; French Cystic Fibrosis Reference Network Study Group. The expanded French compassionate programme for elexacaftor-tezacaftor-ivacaftor use in people with cystic fibrosis without a F508del CFTR variant: a real-world study. *Lancet Respir Med*. 2024; 12:888-900. https://doi.org/10.1016/S2213-2600(24)00208-X. Erratum in: Lancet Respir Med. 202412:e70. https://doi.org/10.1016/S2213-2600(24)00333-3
5. Middleton PG, Mall MA, Dřevínek P, et al.; VX17-445-102 Study Group. Elexacaftor-tezacaftor-ivacaftor for cystic fibrosis with a single Phe508del allele. *N Engl J Med*. 2019;381:1809-1819. https://doi.org/10.1056/NEJMoa1908639
6. Heijerman HGM, McKone EF, Downey DG, et al.; VX17-445-103 Trial Group. Efficacy and safety of the elexacaftor plus tezacaftor plus ivacaftor combination regimen in people with cystic fibrosis homozygous for the F508del mutation: a double-blind, randomised, phase 3 trial. *Lancet*. 2019;394:1940-1948. https://doi.org/10.1016/S0140-6736(19)32597-8. Erratum in: Lancet. 2020;395:1694. https://doi.org/10.1016/S0140-6736(20)31021-7
7. Nichols DP, Paynter AC, Heltshe SL, et al.; PROMISE Study Group. Clinical effectiveness of elexacaftor/tezacaftor/ivacaftor in people with cystic fibrosis: a clinical trial. *Am J Respir Crit Care Med*. 2022;205:529-539. https://doi.org/10.1164/rccm.202108-1986OC
8. Graeber SY, Renz DM, Stahl M, et al. Effects of elexacaftor/tezacaftor/ivacaftor therapy on lung clearance index and magnetic resonance imaging in patients with cystic fibrosis and one or two f508del alleles. *Am J Respir Crit Care Med*. 2022;206:311-320. https://doi.org/10.1164/rccm.202201-0219OC
9. McNally P, Lester K, Stone G, et al.; RECOVER Study Group. Improvement in lung clearance index and chest computed tomography scores with elexacaftor/tezacaftor/ivacaftor treatment in people with cystic fibrosis aged 12 years and older—the RECOVER trial. *Am J Respir Crit Care Med*. 2023; 208:917-929. https://doi.org/10.1164/rccm.202308-1317OC
10. Burgel PR, Durieu I, Chiron R, et al.; French Cystic Fibrosis Reference Network Study Group. Rapid improvement after starting elexacaftor-tezacaftor-ivacaftor in patients with cystic fibrosis and advanced pulmonary disease. *Am J Respir Crit Care Med*. 2021;204:64-73. https://doi.org/10.1164/rccm.202011-4153OC
11. Burgel PR, Mall MA. Advances in cystic fibrosis: CFTR modulator triple combinations. *Eur Respir J*. 2026;67:2501783. https://doi.org/10.1183/13993003.01783-2025
12. Castellani C, Mondejar-Lopez P, Van Goor F, et al. Elexacaftor/tezacaftor/ivacaftor for cystic fibrosis and rare CFTR variants: in vitro translation to a phase 3, double-blind, randomized, placebo-controlled trial and real-world study. *Am J Respir Crit Care Med*. 2026;212:327-337. https://doi.org/10.1093/ajrccm/aamaf001
13. 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*. 2023;22:607-614. https://doi.org/10.1016/j.jcf.2023.02.004
14. Felipe Montiel A, Fernández AÁ, Amigo MC, et al. The ageing of people living with cystic fibrosis: what to expect now? *Eur Respir Rev*. 2024;33:240071. https://doi.org/10.1183/16000617.0071-2024
15. Mall MA, Brugha R, Gartner S, et al. Efficacy and safety of elexacaftor/tezacaftor/ivacaftor in children 6 through 11 years of age with cystic fibrosis heterozygous for F508del and a minimal function mutation: a phase 3b, randomized, placebo-controlled study. *Am J Respir Crit Care Med*. 2022;206:1361-1369. https://doi.org/10.1164/rccm.202202-0392OC
16. Mall MA, Wainwright CE, Legg J, et al.; VX20-445-119 Study Group. Elexacaftor/tezacaftor/ivacaftor in children aged ≥6 years with cystic fibrosis heterozygous for F508del and a minimal function mutation: results from a 96-week open-label extension study. *Eur Respir J*. 2025;66:2402435. https://doi.org/10.1183/13993003.02435-2024
17. Goralski JL, Hoppe JE, Mall MA, et al. Phase 3 open-label clinical trial of elexacaftor/tezacaftor/ivacaftor in children aged 2-5 years with cystic fibrosis and at least one F508del allele. *Am J Respir Crit Care Med*. 2023;208:59-67. https://doi.org/10.1164/rccm.202301-0084OC
18. Stahl M, Dohna M, Graeber SY, et al. Impact of elexacaftor/tezacaftor/ivacaftor therapy on lung clearance index and magnetic resonance imaging in children with cystic fibrosis and one or two F508del alleles. *Eur Respir J*. 2024;64:2400004. https://doi.org/10.1183/13993003.00004-2024
19. Singh D, Han MK, Bhatt SP, et al. Is disease stability an attainable chronic obstructive pulmonary disease treatment goal? *Am J Respir Crit Care Med*. 2025;211:452-463. https://doi.org/10.1164/rccm.202406-1254CI
20. Sammaritano LR, Askanase A, Bermas BL, et al. 2025 American College of Rheumatology (ACR) guideline for the treatment of systemic lupus erythematosus. *Arthritis Care Res (Hoboken)*. 2026;78:815-839. https://doi.org/10.1002/acr.25690
21. England BR, Tiong BK, Bergman MJ, et al. 2019 update of the American College of Rheumatology recommended rheumatoid arthritis disease activity measures. *Arthritis Care Res (Hoboken)*. 2019;71:1540-1555. https://doi.org/10.1002/acr.24042
22. Im Y, Chalmers JD, Choi H. Disease severity and activity in bronchiectasis: a paradigm shift in bronchiectasis management. *Tuberc Respir Dis (Seoul)*. 2025;88:109-119. https://doi.org/10.4046/trd.2024.0120
23. Kerem E, Viviani L, Zolin A, et al.; ECFS Patient Registry Steering Group. Factors associated with FEV1 decline in cystic fibrosis: analysis of the ECFS patient registry. *Eur Respir J*. 2014;43: 125-133. https://doi.org/10.1183/09031936.00166412
24. López-Otín C, Kroemer G. Hallmarks of health. *Cell*. 2021;184:33-63. https://doi.org/10.1016/j.cell.2020.11.034. Erratum in: Cell. 2021; 184:1929-1939. https://doi.org/10.1016/j.cell.2021.03.033
25. Alicandro G, Gramegna A, Bellino F, et al. Heterogeneity in response to elexacaftor/tezacaftor/ivacaftor in people with cystic fibrosis. *J Cyst Fibros*. 2024;23:1072-1079. https://doi.org/10.1016/j.jcf.2024.04.013
26. Zemanick ET, Emerman I, McCreary M, et al.; CHEC-SC Study Group. Heterogeneity of CFTR modulator-induced sweat chloride concentrations in people with cystic fibrosis. *J Cyst Fibros*. 2024;23:676-684. https://doi.org/10.1016/j.jcf.2024.02.001
27. Mei-Zahav M, Orenti A, Jung A, Kerem E. Variability in disease severity among cystic fibrosis patients carrying residual-function variants: data from the European Cystic

Fibrosis Society Patient Registry. *ERJ Open Res*. 2025;11:00587-02024. https://doi.org/10.1183/23120541.00587-2024
28. Zemanick ET, Ramsey B, Sands D, et al. Sweat chloride reflects CFTR function and correlates with clinical outcomes following CFTR modulator treatment. *J Cyst Fibros*. 2025;24:246-254. https://doi.org/10.1016/j.jcf.2024.12.006
29. Graeber SY, Vitzthum C, Pallenberg ST, et al. Effects of elexacaftor/tezacaftor/ivacaftor therapy on CFTR function in patients with cystic fibrosis and one or two F508del alleles. *Am J Respir Crit Care Med*. 2022;205:540-549. https://doi.org/10.1164/rccm.202110-2249OC
30. Wilschanski M, Dupuis A, Ellis L, et al. Mutations in the cystic fibrosis transmembrane regulator gene and in vivo transepithelial potentials. *Am J Respir Crit Care Med*. 2006;174:787-794. https://doi.org/10.1164/rccm.200509-1377OC
31. Hirtz S, Gonska T, Seydewitz HH, et al. CFTR Cl-channel function in native human colon correlates with the genotype and phenotype in cystic fibrosis. *Gastroenterology*. 2004;127:1085-1095. https://doi.org/10.1053/j.gastro.2004.07.006
32. Schaupp L, Addante A, Völler M, et al. Longitudinal effects of elexacaftor/tezacaftor/ivacaftor on sputum viscoelastic properties, airway infection and inflammation in patients with cystic fibrosis. *Eur Respir J*. 2023;62:2202153. https://doi.org/10.1183/13993003.02153-2022
33. Southern KW, Addy C, Bell SC, et al. Standards for the care of people with cystic fibrosis; establishing and maintaining health. *J Cyst Fibros*. 2024;23:12-28. https://doi.org/10.1016/j.jcf.2023.12.002
34. Nussstein H, Urbantat RM, Fentker K, et al. Changes in sputum viscoelastic properties and airway inflammation in primary ciliary dyskinesia are comparable to cystic fibrosis on elexacaftor/tezacaftor/ivacaftor therapy. *Eur Respir J*. 2026;67:2500616. https://doi.org/10.1183/13993003.00616-2025
35. Donaldson SH, Corcoran TE, Pilewski JM, et al. Effect of elexacaftor/tezacaftor/ivacaftor on mucus and mucociliary clearance in cystic fibrosis. *J Cyst Fibros*. 2024;23:155-160. https://doi.org/10.1016/j.jcf.2023.10.010
36. Ahting S, Vogel M, Wollschläger B, et al. Discontinuation of supportive therapies in people with cystic fibrosis treated with elexacaftor/tezacaftor/ivacaftor—a patient-reported outcomes' study. *Respir Med*. 2025;249:108464. https://doi.org/10.1016/j.rmed.2025.108464
37. Gramegna A, Alicandro G, Premuda C, et al. Relationship between lung volumes and heterogeneity in the response to elexacaftor/tezacaftor/ivacaftor in patients with cystic fibrosis and advanced lung disease. *Chest*. 2024;166:433-441. https://doi.org/10.1016/j.chest.2024.03.033
38. Cazier P, Chassagnon G, Dhote T, et al. Reversal of cylindrical bronchial dilatations in a subset of adults with cystic fibrosis treated with elexacaftor/tezacaftor/ivacaftor. *Eur Respir J*. 2024;63:2301794. https://doi.org/10.1183/13993003.01794-2023
39. Sermet-Gaudelus I, Letierce A, Berteloot L, et al.; MODUL-CF Study Group. Effect of elexacaftor-tezacaftor-ivacaftor on bronchial dilatations in adolescents with cystic fibrosis: a multicentre prospective observational study. *Lancet Respir Med*. 2026;14:38-48. https://doi.org/10.1016/S2213-2600(25)00248-6. Erratum in: Lancet Respir Med. 2026:S2213-2600(26)00079-2. https://doi.org/10.1016/S2213-2600(26)00079-2
40. Morgan SJ, Coulter E, Betts HL, et al.; PROMISE-Micro Study Group. Elexacaftor/tezacaftor/ivacaftor's effects on cystic fibrosis infections are maintained, but not increased, after 3.5 years of treatment. *J Clin Invest*. 2024;134:e184171. https://doi.org/10.1172/JCI184171
41. Milczewska J, Syunyaeva Z, Żabińska-Jaroń A, Sands D, Thee S. Changing profile of bacterial infection and microbiome in cystic fibrosis: when to use antibiotics in the era of CFTR-modulator therapy. *Eur Respir Rev*. 2024;33:240068. https://doi.org/10.1183/16000617.0068-2024
42. Frey DL, Bridson C, Dittrich S, et al. Changes in microbiome dominance are associated with declining lung function and fluctuating inflammation in people with cystic fibrosis. *Front Microbiol*. 2022;13:885822. https://doi.org/10.3389/fmicb.2022.885822
43. Ledger EL, Smith DJ, Teh JJ, et al. Impact of CFTR modulation on *Pseudomonas aeruginosa* infection in people with cystic fibrosis. *J Infect Dis*. 2024;230:e536-e547. https://doi.org/10.1093/infdis/jiae051
44. Thng KX, Tiew PY, Mac Aogáin M, et al. Sputum metagenomics in bronchiectasis reveals pan-European variation: an EMBARC-BRIDGE study. *Eur Respir J*. 2025;66:2500054. https://doi.org/10.1183/13993003.00054-2025
45. Fathima P, Pan E, Marsh J, et al. Characteristics, treatment and lung function outcomes of pulmonary exacerbations in cystic fibrosis: insights from the BEAT-CF cohort. *Eur Respir J*. 2026;67:2501349. https://doi.org/10.1183/13993003.01349-2025
46. VanDevanter DR, O'Rourke C, Konstan MW, Clancy JP, Hamblett NM. Differences in pulmonary exacerbation risks among CF subpopulations. *J Cyst Fibros*. 2026;25:204-209. https://doi.org/10.1016/j.jcf.2025.11.010
47. Halle O, Graeber SY, Kontsendorn J, et al. Reduction of systemic inflammation by elexacaftor/tezacaftor/ivacaftor correlates with lung function improvement in cystic fibrosis. *Eur Respir J*. 2025;66:2500150. https://doi.org/10.1183/13993003.00150-2025
48. Casey M, Gabillard-Lefort C, McElvaney OF, et al. Effect of elexacaftor/tezacaftor/ivacaftor on airway and systemic inflammation in cystic fibrosis. *Thorax*. 2023;78:835-839. https://doi.org/10.1136/thorax-2022-219943
49. Loske J, Völler M, Lukassen S, et al. Pharmacological improvement of cystic fibrosis transmembrane conductance regulator function rescues airway epithelial homeostasis and host defense in children with cystic fibrosis. *Am J Respir Crit Care Med*. 2024;209:1338-1350. https://doi.org/10.1164/rccm.202310-1836OC
50. Vladar EK, Gillen AE, Yadav S, et al. Transcriptomic and functional responses of the cystic fibrosis airway epithelium to CFTR modulator therapy. *JCI Insight*. 2025;10:e196018. https://doi.org/10.1172/jci.insight.196018
51. Nichols DP, Morgan SJ, Skalland M, et al.; PROMISE-Micro Study Group. Pharmacologic improvement of CFTR function rapidly decreases sputum pathogen density, but lung infections generally persist. *J Clin Invest*. 2023;133:e167957. https://doi.org/10.1172/JCI167957
52. Hisert KB, Heltshe SL, Pope C, et al. Restoring cystic fibrosis transmembrane conductance regulator function reduces airway bacteria and inflammation in people with cystic fibrosis and chronic lung infections. *Am J Respir Crit Care Med*. 2017;195:1617-1628. https://doi.org/10.1164/rccm.201609-1954OC
53. Murray MP, Pentland JL, Turnbull K, MacQuarrie S, Hill AT. Sputum colour: a useful clinical tool in non-cystic fibrosis

bronchiectasis. *Eur Respir J*. 2009;34:361-364. https://doi.org/10.1183/09031936.00163208
54. Goeminne PC, Vandooren J, Moelants EA, et al. The sputum colour chart as a predictor of lung inflammation, proteolysis and damage in non-cystic fibrosis bronchiectasis: a case-control analysis. *Respirology*. 2014;19:203-210. https://doi.org/10.1111/resp.12219
55. Aliberti S, Ringshausen FC, Dhar R, et al.; EMBARC Registry Investigators. Objective sputum colour assessment and clinical outcomes in bronchiectasis: data from the European Bronchiectasis Registry (EMBARC). *Eur Respir J*. 2024;63:2301554. https://doi.org/10.1183/13993003.01554-2023
56. Wainwright CE, Thorat T, Conner S, et al. Improvements in health-related quality of life in people with cystic fibrosis ≥6 years of age treated with vanzacaftor/tezacaftor/deutivacaftor. *J Cyst Fibros*. 2026;25:284-289. https://doi.org/10.1016/j.jcf.2025.11.014
57. Chapman N, Vekaria S, Hill K, Cavalheri V, Mulrennan S, Gucciardi DF. "An amazing transformation!" The lived experiences of elexacaftor/tezacaftor/ivacaftor in adults with cystic fibrosis. *Respiration*. 2026;105:454-469. https://doi.org/10.1159/000549098
58. Daines CL, Polineni D, Tullis E, et al.; VX17-445-105 Study Group. 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;211:1901-1914. https://doi.org/10.1164/rccm.202411-2231OC
59. Smirnova N, Lowers J, Cammarata-Mouchtouris A, Dellon EP, Fitzpatrick A, Kavalieratos D. Symptoms and quality of life in adults with cystic fibrosis: a cross-sectional analysis of the InSPIRe: CF trial. *J Cyst Fibros*. 2024;23:831-835. https://doi.org/10.1016/j.jcf.2024.03.005
60. Rowbotham NJ, Smith S, Elliott ZC, et al. A refresh of the top 10 research priorities in cystic fibrosis. *Thorax*. 2023;78:840-843. https://doi.org/10.1136/thorax-2023-220100
61. Butcher JL, Siracusa C, Grabowski H, et al. "Time out for an hour, every day, my whole life": understanding treatment burden in cystic fibrosis in the era of elexacaftor/tezacaftor/ivacaftor (ETI). *J Cyst Fibros*. 2025;24:1130-1140. https://doi.org/10.1016/j.jcf.2025.07.014
62. Hergenroeder GE, Psoter KJ, Brown CD, et al. Baseline characteristics and self-reported use of chronic daily therapies of the home reported outcomes with CFTR modulator therapy (HERO-2) cohort. *Pediatr Pulmonol*. 2025;60:e71190. https://doi.org/10.1002/ppul.71190
63. Mayer-Hamblett N, Ratjen F, Russell R, et al.; SIMPLIFY Study Group. 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;11:329-340. https://doi.org/10.1016/S2213-2600(22)00434-9
64. Graeber SY, Mall MA. The future of cystic fibrosis treatment: from disease mechanisms to novel therapeutic approaches. *Lancet*. 2023;402:1185-1198. https://doi.org/10.1016/S0140-6736(23)01608-2
65. Konstan MW, Tolle JJ, DiMango E, et al. A phase IIa, single-blind, placebo-controlled, parallel-group study to assess safety, tolerability, and pharmacokinetics/pharmacodynamics of brensocatib in adults with cystic fibrosis. *Clin Pharmacokinet*. 2025;64:1561-1574. https://doi.org/10.1007/s40262-025-01550-z
66. Chalmers JD, Shteinberg M, Mall MA, et al. Cathepsin C (dipeptidyl peptidase 1) inhibition in adults with bronchiectasis: AIRLEAF, a phase II randomised, double-blind, placebo-controlled, dose-finding study. *Eur Respir J*. 2025;65:2401551. https://doi.org/10.1183/13993003.01551-2024
67. Mall MA, Davies JC, Donaldson SH, Jain R, Chalmers JD, Shteinberg M. Neutrophil serine proteases in cystic fibrosis: role in disease pathogenesis and rationale as a therapeutic target. *Eur Respir Rev*. 2024;33:240001. https://doi.org/10.1183/16000617.0001-2024
68. Bombardier C, Gladman DD, Urowitz MB, Caron D, Chang CH. Derivation of the SLEDAI. A disease activity index for lupus patients. The Committee on Prognosis Studies in SLE. *Arthritis Rheum*. 1992;35:630-640. https://doi.org/10.1002/art.1780350606
69. van der Heijde DM, van 't Hof MA, van Riel PL, et al. Judging disease activity in clinical practice in rheumatoid arthritis: first step in the development of a disease activity score. *Ann Rheum Dis*. 1990;49:916-920. https://doi.org/10.1136/ard.49.11.916
70. Lee T, Hill K, Caudri D, et al. Pulmonary endpoints in clinical trials for children with cystic fibrosis under two years of age. *J Cyst Fibros*. 2025;24:669-683. https://doi.org/10.1016/j.jcf.2025.06.003

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American Journal of Respiratory and Critical Care Medicine 2026 212(10) 2530–2541
https://doi.org/10.1093/ajrccm/aamag370
Concise Clinical Review