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Mini Review

Advances in Biomarker Discovery for Precision Diagnosis and Personalized Therapeutics in Cystic Fibrosis

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Abstract

Background: Cystic fibrosis is a complex autosomal recessive disorder caused by mutations in the CF transmembrane conductance regulator gene, leading to multisystemic dysfunction primarily affecting the lungs and pancreas. Despite advances in diagnostic and therapeutic modalities, clinical heterogeneity and variable response to CFTR modulators present ongoing challenges.

Purpose: This review synthesizes recent advances in biomarker discovery for cystic fibrosis, emphasizing the role of genetic, proteomic, metabolomic, microbiome, and immune biomarkers. It evaluates the integration of multi-omics approaches in enhancing precision diagnostics and personalized treatment strategies.

Main body: Sweat chloride testing and genetic screening remain pivotal for cystic fibrosis diagnosis but inadequately address phenotypic variability. Emerging biomarkers derived from advanced sequencing technologies, proteomic profiling, metabolomic signatures, and microbiome analyses promise improved patient stratification and real-time monitoring of therapeutic responses. Multi-omics integration, coupled with machine learning and systems biology, enables comprehensive biomarker panel development that captures disease complexity. These innovations facilitate early detection, differentiate atypical cases, predict disease progression, and optimize CFTR modulator therapies. Immune and inflammatory biomarkers provide insights into chronic infection and immune dysregulation, guiding adjunctive therapies.

Conclusion: The evolving landscape of cystic fibrosis biomarkers heralds a paradigm shift towards precision medicine, enabling tailored diagnostics and therapeutics that accommodate genetic and phenotypic diversity. Continued multi-omics research and clinical validation are critical to fully realize these biomarkers' translational potential and improve patient outcomes.

Keywords: Cystic fibrosis biomarkers, Precision medicine, CFTR modulators, Multi-omics integration, Personalized therapeutics

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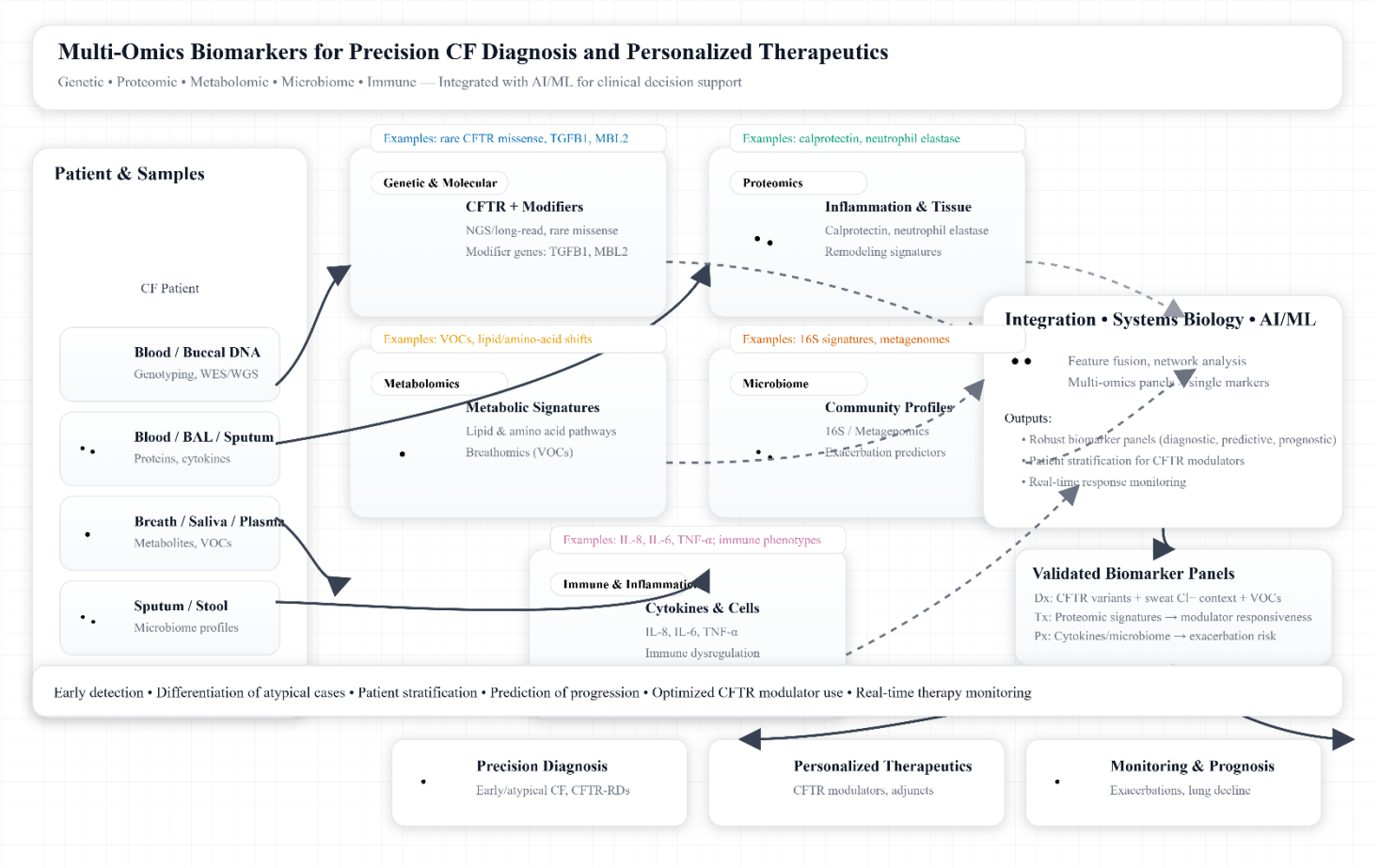

Introduction

Cystic fibrosis (CF) is a progressive autosomal recessive disorder caused primarily by mutations in the CF transmembrane conductance regulator (CFTR) gene, which encodes a chloride channel essential for epithelial fluid homeostasis. Dysfunctional CFTR leads to viscous secretions affecting multiple organs, predominantly the lungs and pancreas, culminating in chronic respiratory infections, inflammation, and organ damage. The genetic basis of CF is complex, with over 2000 CFTR variants identified, of which a subset is disease-causing. The heterogeneity in genotype-phenotype correlations and responses to therapies poses significant challenges in clinical management [1,2].

Current CF diagnosis relies heavily on sweat chloride testing and genetic screening, yet phenotypic variability and atypical presentations complicate early and precise diagnosis. Furthermore, the advent of CFTR modulators has transformed therapeutic options, but variability in treatment response remains a major hurdle. These challenges underscore the urgent need for reliable biomarkers that can guide precision medicine approaches by enabling early diagnosis, patient stratification, monitoring of treatment efficacy, and prediction of prognosis [3,4].

This mini-review aims to synthesize recent advances in biomarker discovery in CF, focusing on emerging genetic, proteomic, metabolomic, microbiome, and immune biomarkers. It also explores the integration of multi-omics approaches and their translational potential for personalized care.

Current diagnostic and therapeutic landscape in CF

The cornerstone of CF diagnosis remains the sweat chloride test, which measures elevated chloride ion concentration as a hallmark of defective CFTR. Genetic screening complements this by identifying pathogenic mutations, facilitating carrier detection and prenatal diagnosis. However, these methods have limitations, particularly in capturing phenotypic variability caused by modifier genes and environmental factors, and in atypical or mild CF cases [5, 6].

Therapeutically, CF care has evolved from symptomatic management to targeted CFTR modulators such as ivacaftor, lumacaftor, tezacaftor, and elexacaftor. These agents correct specific defects in CFTR protein processing or gating. Despite this progress, substantial heterogeneity exists in patient response due to variant-specific effects and complex disease mechanisms involving inflammation, infection, and tissue remodeling [7,

8]. The current clinical toolkit lacks robust biomarkers to stratify patients accurately, monitor therapeutic response in real-time, and predict long-term outcomes, thereby limiting the full realization of personalized medicine in CF [9, 10].

Emerging biomarkers in Cystic Fibrosis

Genetic and molecular biomarkers

Advances in next-generation sequencing (NGS), including long-read sequencing, have enhanced the detection and classification of CFTR variants, including rare missense mutations whose functional consequences are being elucidated through molecular and pharmacologic analyses. Modifier genes such as TGFB1 and MBL2 have been identified as influential in disease severity, affecting pulmonary fibrosis and immune responses, respectively. Non-CFTR genetic markers are emerging as prognostic tools, broadening the molecular landscape of CF [11, 12].

Proteomic biomarkers

Proteomic profiling of biological fluids including blood, sputum, and bronchoalveolar lavage fluid has revealed proteins associated with disease progression. Inflammatory markers like calprotectin and neutrophil elastase correlate with pulmonary exacerbations and infection status. Proteomic signatures predictive of CFTR modulator responsiveness are under investigation to optimize therapeutic regimens [13, 14].

Metabolomic biomarkers

Metabolomics has uncovered altered metabolic profiles in CF patients, with disruptions in lipid metabolism and amino acid pathways. Breathomics, analyzing volatile organic compounds (VOCs), offers a promising non-invasive diagnostic modality reflecting airway inflammation and microbial activity. Metabolic biomarkers also provide insights into nutritional status and treatment efficacy, critical in CF management [15, 16].

Microbiome-related biomarkers

The lung and gut microbiomes play integral roles in CF pathogenesis. Microbial community profiling using 16S rRNA sequencing and metagenomics has identified signatures predictive of pulmonary exacerbations and treatment outcomes. These biomarkers hold potential in guiding antibiotic stewardship and personalized interventions [17, 18].

Inflammatory and immune biomarkers

Cytokine panels measuring IL-8, IL-6, and TNF-α have emerged as markers of pulmonary inflammation. Immune cell phenotyping in blood and sputum reveals chronic infection-induced immune dysregulation. Such biomarkers provide a window into disease activity and may inform immunomodulatory therapies [19, 20].

Integration of multi-omics approaches for biomarker discovery

Combining genomics, transcriptomics, proteomics, metabolomics, and microbiomics enables a holistic understanding of CF pathophysiology as presented in Table 1. Systems biology approaches and network analyses facilitate the identification of biomarker panels rather than single markers, capturing disease complexity. Machine learning and artificial intelligence models are increasingly applied to validate biomarkers and develop predictive diagnostics, accelerating translation into clinical practice [21, 22].

Multi-omics studies in other diseases, such as prediabetes and endometrial cancer, exemplify the power of integrated approaches to uncover novel biomarkers with clinical relevance. CF research is rapidly adopting these methodologies, promising breakthroughs in precision diagnostics and therapeutics [23, 24].

Biomarker Type	Examples	Clinical Role / Utility	Current Limitations	Key References
Genetic	- CFTR variants (e.g., F508del, G551D) - Modifier genes (TGFB1, MBL2)	- Diagnosis (definitive in many cases) - Carrier and prenatal screening - Patient stratification for CFTR modulators	- Does not explain full phenotypic variability - Limited utility in atypical or mild cases	1, 3, 5, 7, 11, 12
Proteomic	- Calprotectin - Neutrophil elastase - Periostin	- Monitoring inflammation and infection - Predicting exacerbations - Assessing response to therapy	- Some markers lack specificity - Standardization needed - May require invasive sampling	13, 14, 19, 20
Metabolomic	- Lipid metabolites - Amino acid profiles - Volatile organic compounds (VOCs, breath omics)	- Non-invasive diagnosis and monitoring - Nutritional status assessment - Real-time therapy monitoring	- High inter-patient variability - Complex data interpretation - Not yet standardized	10, 15, 16
Microbiome	- 16S rRNA and metagenomics profiles of airway and gut flora	- Predicting exacerbations - Guiding antibiotic stewardship - Personalizing interventions	- Dynamic and variable over time - Requires advanced sequencing and bioinformatics	17, 18
Immune/Inflammatory	- Cytokines (IL-6, IL-8, TNF-α) - Immune cell phenotyping	- Assessing inflammation - Monitoring disease activity - Guiding immunomodulatory therapies	- Influenced by infections, comorbidities - Not all markers are CF-specific	19, 20, 21
Integrated Multi-omics	- Combined genomic, transcriptomic, proteomic, metabolomic, and microbiomic panels	- Comprehensive patient stratification - Early diagnosis of atypical/mild cases - Prognostication - Therapy selection and monitoring	- High cost - Need for robust data integration and validation - Translational gap	15, 21, 22, 23, 24

Table 1: Summary of current and emerging biomarkers in cystic fibrosis: roles, clinical utility, limitations, and key references.

Clinical applications of emerging biomarkers in CF

Precision diagnosis

Emerging biomarkers enable early and accurate diagnosis, particularly in atypical or mild CF cases where conventional tests may be inconclusive. Differentiating CF from CFTR-related disorders is critical for appropriate management and prognosis, a task increasingly supported by molecular and multi-omics biomarkers [25].

Personalized treatment strategies

Biomarkers assist in stratifying patients for CFTR modulator therapies, optimizing drug choice based on variant-specific and molecular profiles. Monitoring drug response through proteomic and metabolomic markers allows timely therapy adjustments. Biomarkers also help predict adverse reactions and long-term outcomes, enhancing patient safety and treatment efficacy [26, 27].

Prognostic and monitoring biomarkers

Biomarkers predicting disease progression and lung function decline are invaluable for patient management. Non-invasive markers for monitoring exacerbations facilitate early interventions. Additionally, biomarkers guiding nutritional and supportive care contribute to comprehensive disease management [28, 29].

Conclusions

This review concludes that the identification and integration of diverse biomarkers-genetic, proteomic, metabolomic, microbiome, and immune-are pivotal for advancing cystic fibrosis diagnosis and personalized therapy. Biomarker-driven approaches overcome the limitations of traditional diagnostic tools by capturing the disease's phenotypic and molecular heterogeneity. The incorporation of multi-omics strategies and computational analytics fosters the development of robust biomarker panels, facilitating patient stratification and dynamic treatment monitoring. These advancements promise to improve clinical outcomes by enabling tailored interventions and early detection of complications. However, challenges remain in standardizing biomarker validation, addressing inter-patient variability, and translating findings into routine

clinical practice. Future research should focus on large-scale longitudinal studies and the integration of biomarkers into clinical decision-making frameworks to fully harness their potential.

Recommendations

To accelerate the translation of biomarker discoveries into clinical practice, it is recommended to prioritize multi-center, longitudinal cohort studies that validate biomarker efficacy across diverse populations. Investment in developing standardized protocols for multi-omics data integration and machine learning models is essential to improve predictive accuracy and clinical applicability. Collaborative efforts between researchers, clinicians, and regulatory bodies should focus on establishing clear guidelines for biomarker use in diagnosis, treatment selection, and monitoring. Additionally, expanding research into the microbiome and immune dysregulation will enhance understanding of disease mechanisms and uncover novel therapeutic targets. Addressing current limitations such as sample heterogeneity and cost-effectiveness will be crucial to implement biomarker-guided precision medicine as a standard of care in cystic fibrosis.

Abbreviations

CF: Cystic Fibrosis, CFTR: Cystic Fibrosis Transmembrane Conductance Regulator, NGS: Next-Generation Sequencing, VOCs: Volatile Organic Compounds, IL: Interleukin, TNF-α: Tumor Necrosis Factor Alpha, AI: Artificial Intelligence

Declarations

Ethical approval and consent to participate

Not applicable

Clinical trial number

Not applicable

Consent for publication

Not applicable

Availability of data and materials

All data are available and sharing is available as well as publication

Code availability

No code was used in this study

Competing interests

The author hereby that they have no competing interests

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Corresponding author supplied all study materials. There was no further funding for this study.

Authors' contributions

The Corresponding author completed the study protocol and was the primary organizer of data collection and the manuscript's draft and revision process. The corresponding author wrote the article and ensured its accuracy.

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