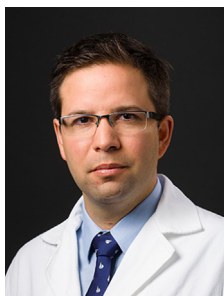


## Preface

# Cystic Fibrosis in the Era of Highly Effective CFTR Modulators



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Editors

Cystic fibrosis (CF) was described as a clinical entity more than eighty years ago.<sup>1–3</sup> With the development of comprehensive care centers and therapies directed at the signs and symptoms of the disease, survival improved.<sup>4</sup> What once was a disease only of children has become a chronic disease of adults for whom the median predicted survival is fifty years of age.<sup>5,6</sup> As the natural history of CF has evolved, so has the recognition of previously underdiagnosed populations of people with CF, contributing to its rising prevalence around the world.<sup>7–10</sup>

We are in the midst of a new era in CF care ushered in by the advent of cystic fibrosis transmembrane conductance regulator (CFTR) modulators, small molecules that significantly restore CFTR protein function. People with CF are experiencing marked rapid and sustained improvements in lung function, nutritional state, and quality of life.<sup>11–13</sup> With the approval of the first triple-modulator combination, elexacaftor/tezacaftor/ivacaftor, for people with CF with at least one copy of the most common CF mutations in those of European ancestry, *Phe508del* (*F508del*), approximately 90% of the CF population is now eligible for highly effective modulator therapy

(HEMT) and its associated transformational health benefits.<sup>13</sup>

Since the previous CF-focused issue of *Clinics in Chest Medicine*,<sup>14</sup> there have been broad advances in our understanding of the immunopathogenesis of CF and the remarkable impact of modulators on immune cell function, inflammation, and repair mechanisms.<sup>15–17</sup> Indeed, the CFTR correction afforded by HEMT is increasingly recognized as a modifying factor in the microbiome and airway inflammatory response of people with CF.<sup>18–22</sup>

Advances have also emerged in animal models, cell-based assays, and approaches to measure and titrate functional responses to modulators in human tissues and cells.<sup>23–26</sup> Emerging tools, such as novel pulmonary function measures, pulmonary imaging, patient-reported outcomes, and new molecular biomarkers, will become increasingly important in understanding CF pathogenesis and treatment response.<sup>27–34</sup>

Apart from the well-documented impact of HEMT on lung function and nutritional outcomes, HEMT promises to have extensive effects in multiple areas of clinical care. Emerging reports of effects range from changes in airway microbial

communities with associated opportunities for developing novel antimicrobial therapies, evolving knowledge regarding the surveillance and management of long-term endocrine and gastrointestinal complications, and new opportunities in family planning and reproductive health.<sup>35–41</sup>

HEMT has had a transformative effect on the lives of many people with CF. However, some questions remain to be answered. For example, there are ongoing efforts to develop safe and effective readthrough agents and the next generation of modulators and immunomodulatory drugs for those ineligible for or intolerant of currently approved HEMT. Ultimately, gene replacement or editing will be necessary to cure CF.<sup>42–47</sup> We speculate that one day we will be able to turn back the clock on the development of clinical disease through very early intervention; such intervention is currently being investigated in animal models of CF and in trials of HEMT administration in infants and toddlers.<sup>48,49</sup> Finally, although we anticipate that recent advances will result in a smaller proportion of people with CF requiring lung transplantation or end-of-life care,<sup>50</sup> the CF community remains committed to optimizing care for each individual with CF.

In this issue of *Clinics in Chest Medicine*, we take stock of the gains enabled by the development of HEMT and consider the remaining challenges to assessing and improving the quantity and quality of life for all people with CF. As the clinical course and management of CF evolve in this new therapeutic era, we look forward to a promising and bright future in which CF-related morbidity is rare, health is maintained, and CF finally becomes a curable disease.

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