era for CF therapeutics directed at treating the most fundamental causes of this disease.

Correction of the F508del Processing Abnormality Lumacaftor and tezacaftor, two U.S. Food and Drug Administration (FDA)–approved "corrector" molecules that repair CFTR misfolding (as distinct from CFTR gating "potentiators" such as ivacaftor), partially overcome defective F508del CFTR biogenesis. The drugs promote cell surface localization of F508del CFTR. Formulations of lumacaftor or tezacaftor (together with ivacaftor to augment channel opening) typically confer modest improvement in pulmonary function among individuals homozygous for F508del (~45% of the U.S. CF population). Elexacaftor, a next-generation corrector that operates through a different mechanism of action, is FDA-approved in combination with tezacaftor and ivacaftor for patients with CF encoding at least one F508del variant (irrespective of the other *CFTR* mutations), as well as for a series of less common CFTR defects. This triple combination therapy (TCT) may, therefore, benefit >90% of individuals with the disease. Marked enhancement of forced expiratory volume in 1 s (FEV_1), fewer respiratory exacerbations, improved quality of life, and diminished sweat chloride have all been demonstrated in patients following TCT, leading to designation as "highly effective modulator treatments" (HEMTs). For example, among patients carrying one F508del together with a *CFTR* minimal function variant, FEV_1 (% predicted) was improved by ~14% over a 4- to 24-week treatment period. Monitoring liver function of patients started on TCTs and attention to pharmacologic interactions, including effects mediated by CYP3A, are required. (**See Video 291-2A,B**).

Personalized Molecular Therapies The advent of CFTR modulators with robust clinical impact has engendered new optimism regarding care of patients with CF. Based on the large number of disease-causing *CFTR* mutations, together with the ability to group these into molecular categories (Fig. 291-2), CF has been deemed a condition ideally suited for personalized (i.e., mechanistically tailored) drug treatment. That being said, many CFTR variants