available through commercial sources. For difficult cases, complete *CFTR* exonic sequencing together with analysis of splice junctions and key regulatory elements can be obtained. Sweat electrolytes following pilocarpine iontophoresis comprise an invaluable diagnostic measurement, with levels of chloride markedly elevated in CF compared to non-CF individuals. The sweat test result is highly specific and served as the mainstay of diagnosis for many decades prior to availability of *CFTR* genotyping. Notably, hyperviscosity of eccrine sweat is not a clinical feature of the disease. Sweat ducts function to reabsorb chloride from a primary sweat secretion produced by the glandular coil. Malfunction of CFTR leads to diminished chloride uptake from the ductular lumen, and sweat emerges on the skin with markedly elevated levels of chloride. For the unusual situation in which both *CFTR* genotype and sweat electrolytes are inconclusive, in vivo measurement of ion transport across the nasal airways can serve as a specific test for CF and is used by a number of referral centers. For example, elevated (sodium-dependent) transepithelial charge separation across airway epithelial tissue and failure of isoproterenol-dependent chloride secretion (via CFTR) represent bioelectric findings highly specific for the disease. Measurements of CFTR activity in excised rectal mucosal biopsies can also be obtained.

COMPLEXITY OF A CF PHENOTYPE

CF classically presents in childhood with chronic productive cough, malabsorption including steatorrhea, and failure to thrive. The disease is most common among whites (~1 in 3300 live births) and much less frequent among African-American (~1 in 15,000) or Asian populations (~1 in 33,000). Several "severe" defects that impair CFTR activity (including F508del, G551D, and truncation alleles) are predictive of pancreatic insufficiency, which is clinically evident in 80–90% of individuals with CF. These few specific genotype-phenotype correlations notwithstanding, genotype is, in general, a poor predictor of overall respiratory prognosis.

A spectrum of CFTR-related diseases with features resembling classic CF has been well described. In addition to multiorgan involvement, forme frustes, such as isolated congenital bilateral absence of the vas deferens or pancreatitis (without other organ system findings), are strongly associated with *CFTR* mutations in at least one allele. Although CF is a classic monogenic disease, the importance of non-*CFTR* gene modifiers and proteins that regulate ion flux, inflammatory pathways, and airway remodeling has been increasingly appreciated as influencing clinical course. For example, the magnitude of transepithelial sodium reabsorption in CF airways, which helps control periciliary fluid depth and composition, is strongly influenced by CFTR and represents a molecular target for disease intervention.

THERAPEUTICS DIRECTED TOWARD CF SEQUELAE

Standard care for outpatients with CF is intensive, with regimens that include exogenous pancreatic enzymes taken with meals, nutritional supplementation, anti-inflammatory medication, bronchodilators, and chronic or periodic administration of oral or aerosolized antibiotics (e.g., as maintenance therapy for patients with *P. aeruginosa*). Recombinant DNAse aerosols (degraded DNA strands that contribute to mucus viscosity) and nebulized hypertonic saline (serves to augment PCL depth, activate mucociliary clearance, and mobilize inspissated airway secretions) are administered routinely. Chest physiotherapy several times each day is a standard means to promote clearance of airway mucus. Among older individuals with CF, malabsorption, chronic inflammation, and endocrine abnormalities can lead to poor bone mineralization, requiring treatment with vitamin D, calcium, and other measures. The time, complexity, and expense of home care are considerable and take a significant toll on patients and their families.

Severe respiratory exacerbation is commonly managed by hospital admission for frequent chest physiotherapy and parenteral antibiotics directed against serious (and often multiply resistant) bacterial pathogens. Aggressive intervention in this setting can restore a large component of lung function, but ongoing and cumulative loss of pulmonary reserve reflects the natural history of the disease. Poor prognostic indicators such as sputum culture containing *B. cepacia*, mucoid *P. aeruginosa*, or atypical mycobacteria are rigorously monitored in the CF patient population. An increasing incidence of methicillin-resistant *S. aureus* has also been observed, although the clinical significance of this finding has not been fully elucidated. Typical inpatient antibiotic coverage includes combination drug therapy with an aminoglycoside and β-lactam for up to 14 days. Maximal improvement in lung function is often achieved by 8–10 days in this setting. Many families elect parenteral antibiotic treatment at home, and additional studies are needed to evaluate specific drug combinations, duration of therapy, and home versus inpatient management. Other CF respiratory sequelae that may require hospitalization include hemoptysis and pneumothorax. Hypersensitivity to *Aspergillus* (allergic bronchopulmonary aspergillosis) occurs in approximately 5% of individuals with the disease and should be suspected in the absence of a response to conventional treatment.

Lung transplantation remains a viable therapeutic option in the setting of end-stage CF pulmonary failure, with 5-year postoperative survival rates on the order of 50–60%. Determining the optimal timing for surgery presents a substantial challenge, particularly because overall prognosis for individuals with severe lung disease is sometimes difficult to predict, and mortality associated with transplantation is significant (1-year survival rates of approximately 80%). Forced expiratory volume in 1 s (FEV_1) measurements less than 30% predicted, together with an assortment of other clinical features, are often used as thresholds for entry onto transplantation lists, although waiting periods for healthy donor lungs can be quite protracted. Based on clinical outcome and limited access to healthy donor lungs, many CF patients and their families do not pursue this option.

CFTR MODULATION

Potentiation of Mutant CFTR Gating A massive effort directed toward high-throughput drug analysis of large compound libraries (containing millions of individual agents) has identified novel and promising approaches to CF therapy. The approved compound ivacaftor, for example, robustly potentiates CFTR channel opening and stimulates ion transport. Ivacaftor overcomes the G551D CFTR gating defect, and individuals carrying this mutation exhibit dramatic improvement in lung function, weight gain, and other clinical parameters after only a few weeks of oral therapy. Remarkably, sweat chloride values are significantly improved with this treatment in patients with G551D CFTR. No clinical intervention of any sort has previously been shown to normalize the CF sweat chloride abnormality. Long-term studies of the drug in patients with G551D CFTR are ongoing. Ivacaftor has been viewed as the harbinger of a new era for CF therapeutics directed at treating the most fundamental causes of the disease.

Correction of the F508del Processing Abnormality Advancement of new drugs that address specific CFTR defects in protein folding and maturation has been bolstered by clinical studies of F508del rescue in combination with ivacaftor. So-called "corrector" molecules (as distinct from CFTR gating "potentiators" such as ivacaftor) discovered through compound library screening are suitable for promoting cell surface localization of the F508del protein. Significant improvement in pulmonary function of F508del homozygous individuals has been achieved with potentiator/corrector combination therapy in early clinical trials, and several candidate molecules are under evaluation.

Personalized Molecular Therapies The advent of modulators with robust clinical impact has engendered new optimism regarding care of patients with CF. It is clear that future interventions will be tailored to specific genotypic abnormalities. Drug screening campaigns and other research programs have identified agents capable of suppressing CFTR nonsense alleles, augmenting potentiator activity, and promoting F508del correction. Efforts to apply these compounds in a fashion that will benefit CF subjects carrying a single copy of F508del (i.e., with a distinct or unusual *CFTR* mutation on the second allele) comprise an essential priority for the future. Progress in CF drug discovery is emblematic of what might be accomplished in other refractory genetic diseases using an approach grounded in molecular mechanism and unbiased compound library screening.