PRIMEVIEW

CYSTIC FIBROSIS

nature REVIEWS DISEASE PRIMERS

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Cystic fibrosis is a disorder caused by mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene, which encodes a transmembrane chloride and bicarbonate ion channel on the apical surface of glandular epithelial cells throughout the body. Although CFTR dysfunction affects many organs, lung disease is responsible for the vast majority of morbidity and mortality.

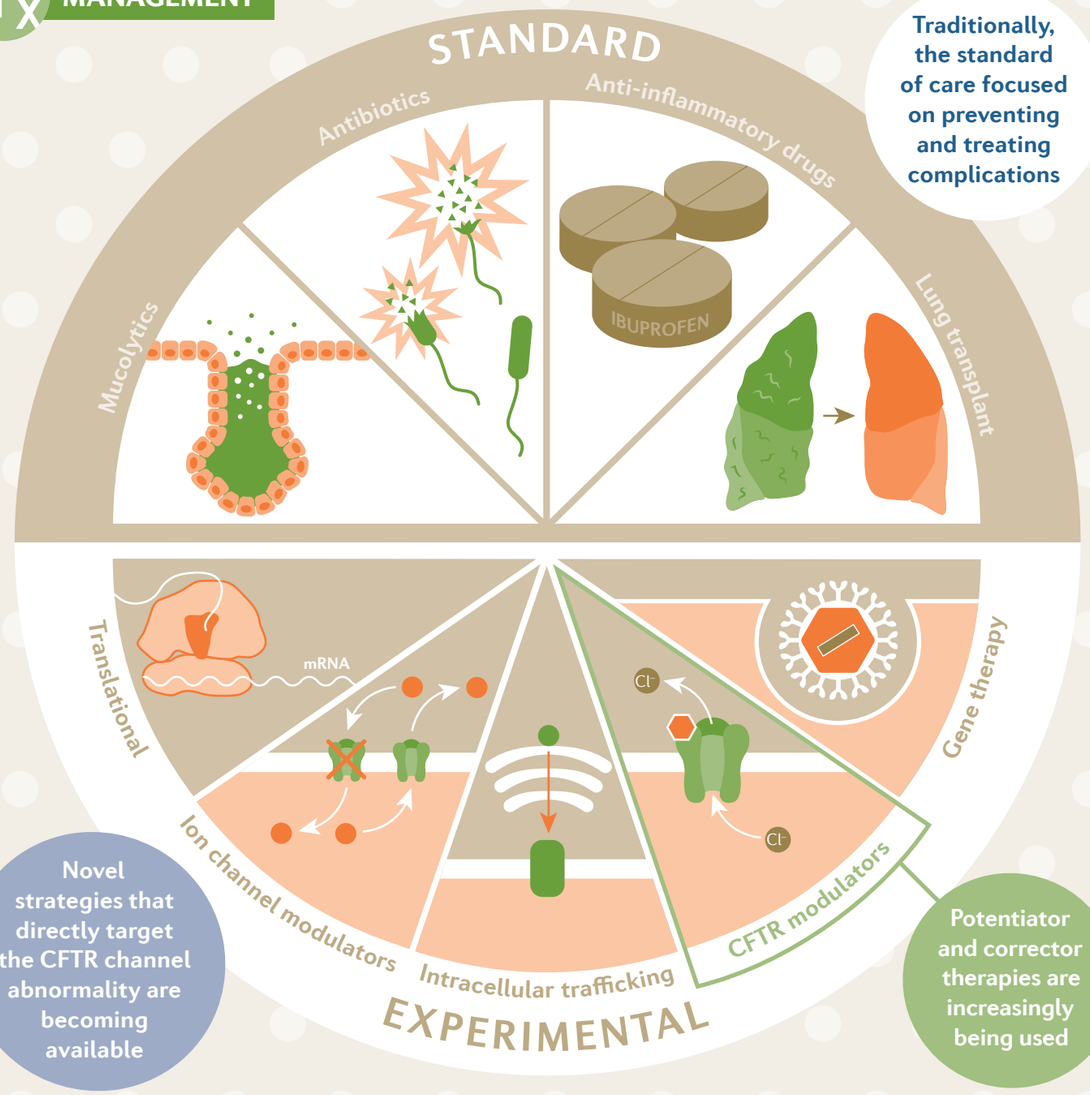
SCREENING

Cystic fibrosis is increasingly being diagnosed earlier in life because of the introduction of newborn screening in past 20 years. In 2010, over half of the patients with cystic fibrosis in the United States were diagnosed shortly after birth. Newborn screening offers the ability to manage lung health before symptoms develop.

DIAGNOSIS

Screen-positive newborns can be diagnosed by a sweat test; individuals with cystic fibrosis have more chloride in their sweat than unaffected individuals. Identifying lung disease relies on lung function measurements, imaging and bronchalveolar lavage, which is used to detect infection and inflammation. Genetic testing is an important part of modern diagnostics, because mutation-specific therapy is an increasing reality.

MANAGEMENT



Traditionally, the standard of care focused on preventing and treating complications

Novel strategies that directly target the CFTR channel abnormality are becoming available

Potentiator and corrector therapies are increasingly being used

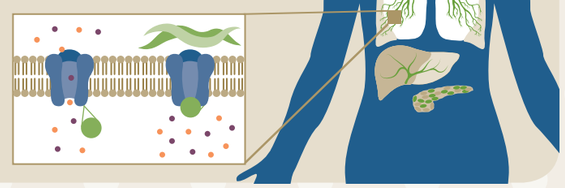
OUTLOOK

Many modifier genes might be active in cystic fibrosis, influencing intracellular pathways or other ion channels. Understanding these functions might help to predict the variability in responses to genotype-specific treatments, and to design better treatments. Indeed, finding therapeutic strategies for the aspects of the disease beyond CFTR dysfunction will be important to maintain lung health in patients with cystic fibrosis.

MECHANISMS

CFTR mutations cause various molecular defects, including no production of functional protein, absent or diminished protein processing, defective ion gating or decreased ion conductance. In the lungs, CFTR dysfunction results in mucus accumulation that obstructs the airway lumen and diminishes mucociliary clearance. The lack of bicarbonate secretion leads to an acidic pH of the airway surface liquid in cystic fibrosis, which might contribute to defective bacterial killing — predisposing patients to infection.

In extrapulmonary organs (for example, the pancreas and liver), ductular obstruction is also observed



QUALITY OF LIFE

Cystic fibrosis is a multisystem disease that affects many organs, but over the past 20 years health outcomes and lifespan have improved dramatically with the introduction of long-term therapies. However, treatment complexity and perceived burden are concerns among patients, and might affect adherence to treatment. Modern trials now routinely use reliable and valid instruments to assess quality-of-life domains in cystic fibrosis.

The presence of one *CFTR* allele that is at least partially active can vastly improve clinical outcome

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