Cystic Fibrosis—What's New for the Anesthesiologist?

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Disclosures

- Grants from Cystic Fibrosis Foundation, NIH, Hyperion, and FDA
- Subcontracts with PTC Corporation, N30 Corporation
- Scientific Advisory Board, Gilead Pharmaceuticals

Objectives

- Describe the changing epidemiology for patients with cystic fibrosis.
- Review the pathophysiologic changes associated with cystic fibrosis.
- Discuss the vital components of the preoperative evaluation for patients with cystic fibrosis.

Diagnosis by Clinical Triad

- Elevated Sweat Chloride
- Pancreatic Insufficiency
- Chronic Pulmonary Disease

Diagnosis by Mutation Analysis

- **F508del**
- Class 1-3 pancreatic insufficiency
- Class 4-5 pancreatic sufficiency

Diagnosis by Sweat Test

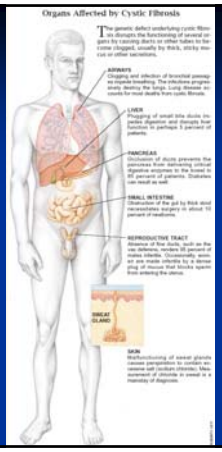
- Sweat Test
  - Pilocarpine iontophoresis
  - ≥ 60 meq/L chloride
  - Inaccurate in first month of life
- Other causes of elevated sweat chloride
  - Untreated hypothyroidism
  - Glycogen storage disease
  - Addison's disease
  - Ectodermal dysplasia

Atypical CF Diagnosis

- Often occurs in adolescence
- PMH in retrospect of CF-like symptoms
- Lung, sinus, liver, male infertility

Diagnosis by Mutation Analysis

- One identifiable mutation plus intron modifier
- Frequently Class 4-5 pancreatic sufficiency



CF pathology affects multiple exocrine Glands and tissues in the body

CF is one of the most common lethal autosomal recessive inherited disorders

Chronic obstructive pulmonary disease

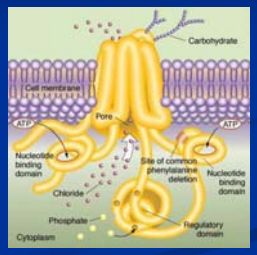
Pancreatic exocrine insufficiency

Elevated sweat electrolytes

M. Welsh and A. Smith SCIENTIFIC AMERICAN *December 1995*

Cystic Fibrosis Transmembrane Conductance Regulator (CFTR)

- Primary Function
  - Chloride Channel
- Secondary Function
  - Regulates ENaC, the sodium channel

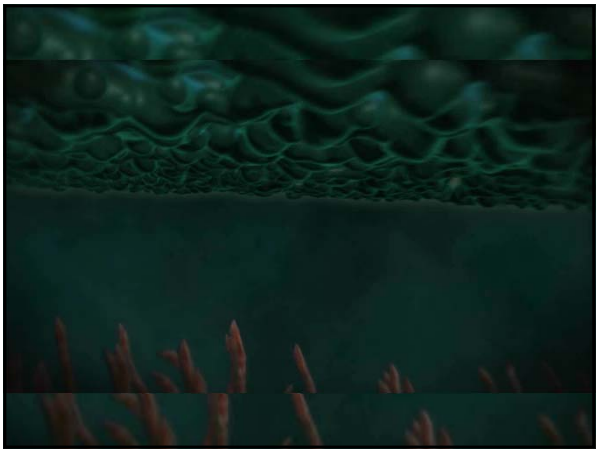


Genetics

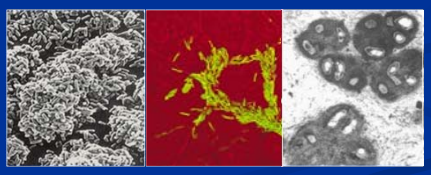
- 1:2-4000 Caucasians, carrier rate 1:28
- 1:9200 Hispanics
- 1:15,000 African Americans, carrier rate 1:60
- 1:31,000 Asians
- Gene is on chromosome 7, CFTR, most common mutation is ΔF508
- cAMP-regulated chloride channel, a nucleotide transporter, ion channel regulator

Clinical Manifestations of CF

- Respiratory
  - Chronic cough and bronchitis
  - Bronchiectasis
  - Recurrent pneumonia (staph aureus, **pseudomonas aeruginosa**)
  - Chronic sinusitis, nasal polyps
  - Hemoptysis, pneumothorax
  - Chronic airways obstruction, irreversible



Controlling Pseudomonas Aeruginosa Infection: Lessons learned from the Cystic Fibrosis Patient

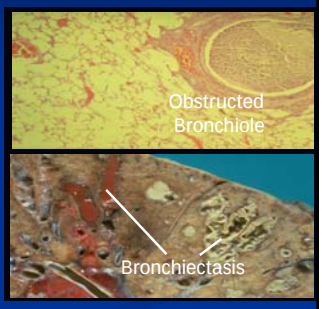


Disorders affecting the airways with similar characteristics to CF or infections with Pseudomonas Aeruginosa

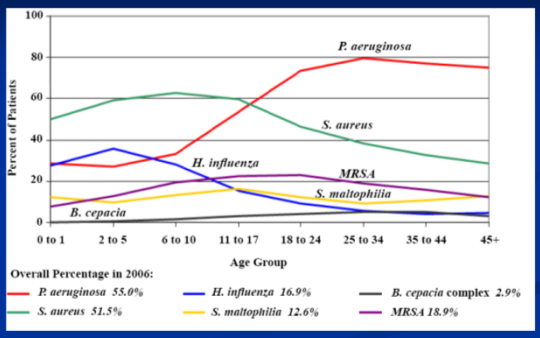
- Pan-bronchiolitis
- Chronic bronchitis
- Idiopathic bronchiectasis
- IgA, IgG, IgG subclass deficiencies
- COPD
- Patients with tracheostomy tubes

Progressive Lung Disease in Patients With Cystic Fibrosis

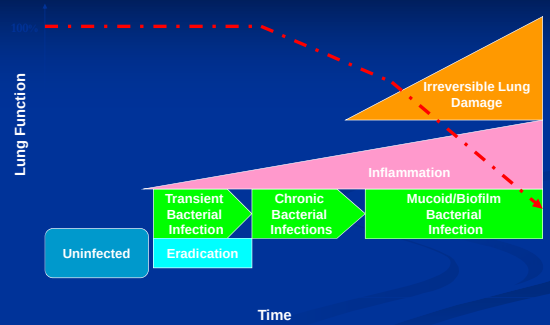
- Chronic cough
- Sputum production
- Wheezing
- Obstructive lung disease
- Persistent radiographic abnormalities
  - Hyperinflation
  - Atelectasis
  - Bronchiectasis
- Chronic infection with bacterial (and other) opportunistic pathogens



Respiratory Infections in Cystic Fibrosis Patients ?



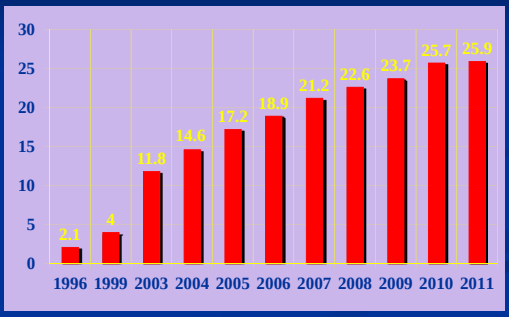
Infection With *Pseudomonas aeruginosa* and Progression of CF Lung Disease



Anti-infective Therapy for *P. aeruginosa*

Oral	Aerosolized	Parenteral	
		β-lactam Related	Aminoglycosides
Ciprofloxacin	Tobramycin	Ticarcillin	Amikacin
Levofloxacin	Colistin†	Ticarcillin-Clavulanate	Tobramycin
Trimethoprim/ sulfamethoxazole	Aztreonam lysine**	Ceftazidime	
		Piperacellin/tazobactam	
Azithromycin*	Other parenteral antibiotics	Meropenem	
		Imipenem	
		Aztreonam arginine	
		Cefepime	

Prevalence of MRSA in Cystic Fibrosis



Airway Clearance Techniques

Active Techniques
- Forced expiratory technique ("huff maneuver")
- Autogenic drainage
- Positive expiratory pressure mask
- Oral airway oscillators

Passive Techniques
- High-frequency chest wall oscillator ("vest")
- Intrapulmonary percussor ventilator

Progression of CF lung infections

- Bacterial endobronchial colonization
- Intense inflammatory reaction
- Obstructive lung disease with superimposed pulmonary exacerbations
  - Increased cough, sputum, dyspnea, declining PFTs
  - Weight loss, fatigue, rarely fever
- Intermittent courses of antibiotics
  - Oral, inhaled, intravenous
  - Airway clearance, bronchodilators, anti-inflammatories

CF Gastrointestinal Disease

- Meconium ileus, meconium peritonitis
- Small bowel atresia
- DIOS, intussusception
- Pancreatic insufficiency, malabsorption
- Hepatic cirrhosis, portal hypertension,
- Neonatal direct hyperbilirubinemia,
- gall bladder obstruction
- Rectal prolapse
- Edema, hypoalbuminemia, hypovitaminosis A,K,E

Pancreatic Disease

- Reduced volumes and bicarbonate content of pancreatic fluid
- If residual pancreatic function, prone to recurrent pancreatitis
- CF-related diabetes
  - 3% of children, 7% of age 11-17
  - 14% of adults
  - Blockage of islets leads to reduction of both insulin and glucagon, so ketacidosis is rare
  - Stresses like pregnancy, corticosteroids, pulmonary exacerbation, can trigger hyperglycemia requiring therapy

Hepatobiliary Disease

- Eosinophilic concretions in bile ducts
- High incidence of gall bladder disease, gall stones, microgallbladder
- Cirrhosis
  - 3%
  - Portal hypertension, splenomegaly, esophageal varices

Effects of General Anesthesia on Pulmonary Function and Clinical Status in Children with CF

- Common surgical procedures in CF
  - Bronchoscopy with lavage (surveillance and clinical indications), nasal polypectomy, venous access procedures
  - Additional indications: thoracoscopy,FESS, lung/liver TX, intraoperative CPT*
- Assessment of lung function key to predicting morbidity
  - 1964, 27% perioperative mortality
  - Mid 1980's, 4.5% perioperative mortality
  - Older studies used anesthetics that affected postoperative lung function
  - Australian study 2013—use of LMA, use of anesthetics with bronchodilator properties (sevofluorane, propofolon spirometry 24 hrs post procedure*

*Tannenbaum et al, Pediatric Pulmonology 42:1152–1158 (2007)
**Pandit et al, Pediatric Anesthesia 24 (2014) 164-169

Preoperative Evaluation of the Patient with Cystic Fibrosis

- Parental assessment of presence of acute illness, malaise, dyspnea, weight loss, fever, increased sputum, night cough, diabetes
- Physical Exam: presence of wheezing
- Oropharyngeal or sputum microbiology
- obstructive sleep apnea, GER
- Oxygen saturation at rest
- Capnography
- Review recent chest radiograph if available
- Review medications: corticosteroids, antibiotics

Diagnosis by CFTR Genotyping

- Greater than 1800 different mutations in CFTR
  - Common mutations in USA: F508del, G542X
  - **Mutations in China: I556V, M469V, E527N, F508del**
- Conventional commercial genotyping
  - Genzyme: 86 mutations
  - Ambry: all coding mutations
  - Many cases are either one or two unknowns at this time

Table of mutations in each class

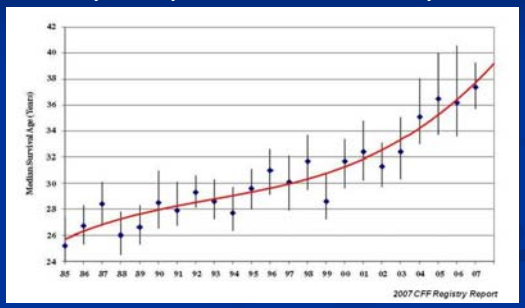
Class of mutation	Molecular Mechanism	Pancreatic status (if known)	Examples
1	No CFTR protein synthesis	PI	W1282X, G542X, R553X, 621+1G→T, 1717-1G→A, 3905insT, 394delTT
2	Abnormal CFTR processing and trafficking	PI	ΔF508, N1303K, P574H
3	Defective CFTR regulation (normal trafficking)	PI	G551D, G551S, G1349D, S1255P
4	Decreased CFTR chloride conductance	PS	R117H, R334W, R347P, P547H
5	Reduced synthesis and trafficking of normal CFTR	PS	A455E, 3849+10kbC→T, (5T)
6A	Reduced apical stability	PI	S1455X, Q1412S, 4326delTC, 4279insA
6B	Defective regulation of other ion channels	PI	G551D

Treatments for CF

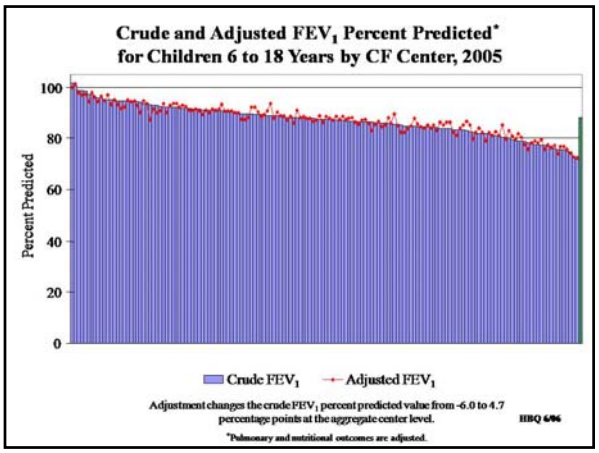
High Sweat Chloride	Dietary Salt*
Thick Airway Mucous	Chest Physiotherapy /Dnase*
Chronic Lung Infections	Antibiotics*
Inflammation	Anti-Inflammatories*
Respiratory Failure	Lung Transplant*
Pancreatic Insufficiency	Pancreatic Enzymes*
Meconium Ileus	PEG, stool softeners
Islet Cell Loss	Insulin*
Male Infertility, CBAVD	In Vitro
Biliary tract insufficiency	Bile acid salts

Median Predicted Survival Age 1985-2007

(with 95 percent confidence bounds)



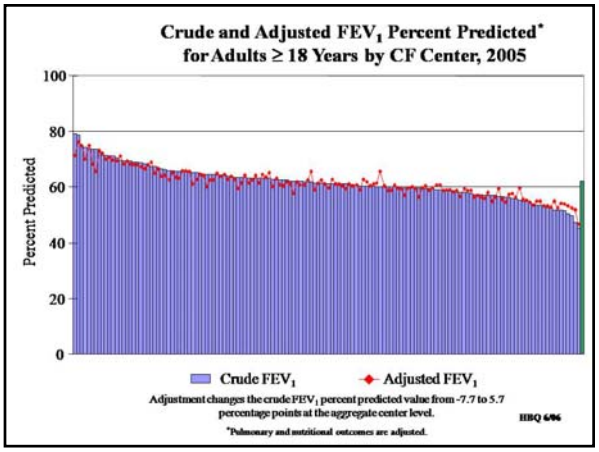
The whiskers represent the 95 percent confidence bounds for the survival estimates



2012 Center Specific Summary

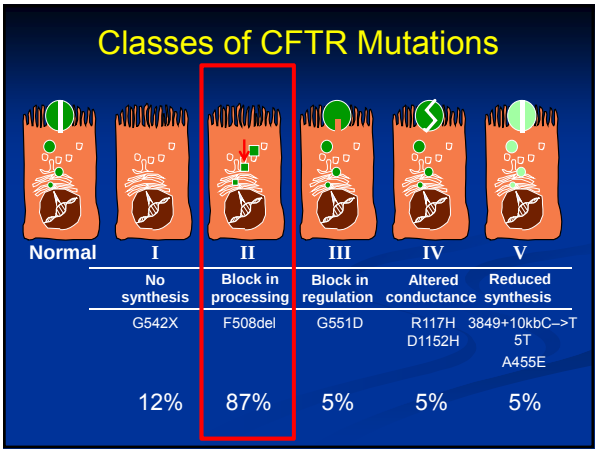
- 487 patients (pediatrics and adult)
- 12 transplanted
- FEV1 vs BMI in optimal quartile in 2012 ages 6-17

	Johns Hopkins University		Care Center Network Median	
	FEV1	BMI Percentile	FEV1	BMI Percentile
2002	92.5	37.1	88.3	40.8
2012	95.9	50.5	94.3	51.3



Advances since 2012: CFTR Modulator Therapies

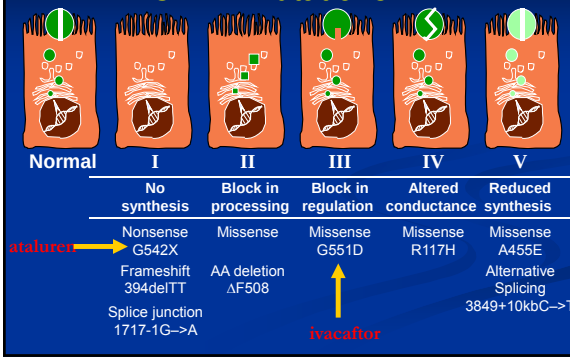
- Ivacaftor, Kalydeco®, approved by FDA 2012 for G551D CFTR a gating mutation Class III.
- Lumacaftor, a corrector of F508del trafficking defect, alone, insignificant benefit, together with invacaftor under Phase III clinical trials now.
- PTC-124, restores normal CFTR to stop codon mutants, very effective in the short term in Israel and Belgium, in Phase III multicenter clinical trial and open label extension phases



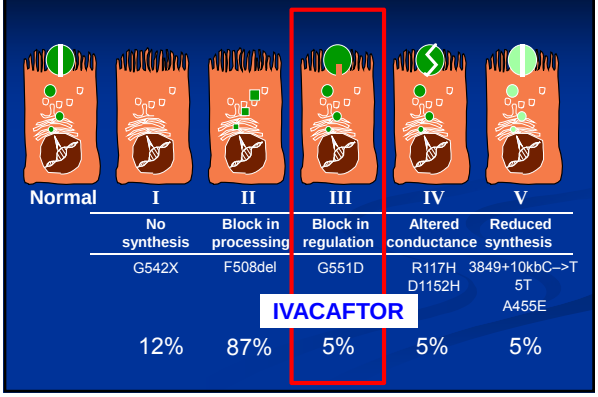
F508del

- 44% of CF patients are homozygous
- 45% of CF patients are heterozygous
- 11% of CF patients do not have ΔF508
- ΔF508 accounts for 70% of Northern European, 50% Southern European, 46% Hispanic, 30% Ashkenazi, 48% African American, < 5% Native American chromosomes

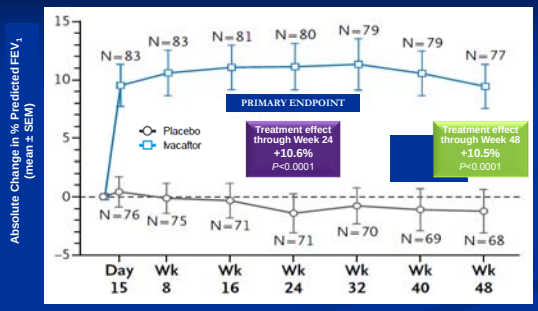
Molecular Consequences of CFTR Mutations



Classes of CFTR Mutations

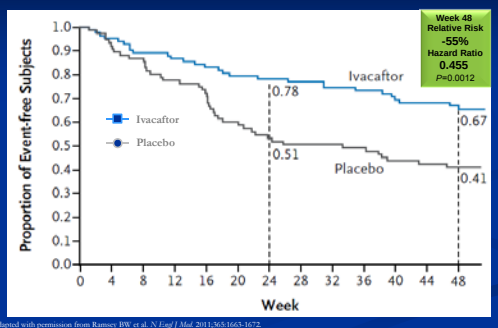


Absolute Change From Baseline Through Week 48 in % Predicted FEV_1



Adapted with permission from Ramsey BW et al. *N Engl J Med.* 2011;365:1663-1672.
Estimates are model-based. Points and 95% CI are unadjusted.
CI, confidence interval; SEM, standard error of the mean.

Time to First Pulmonary Exacerbation* Through Week 48



Adapted with permission from Ramsey BW et al. *N Engl J Med.* 2011;365:1663-1672.
Definition of pulmonary exacerbation: treatment with new or changed antibiotic therapy for ≥4 sinopulmonary signs/symptoms.

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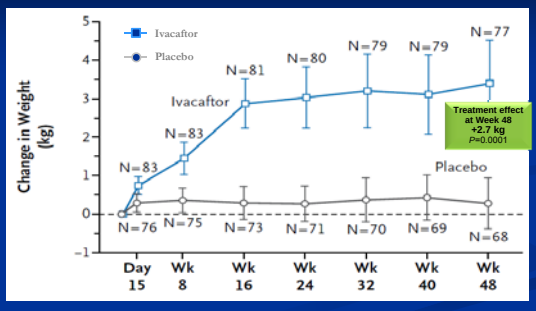
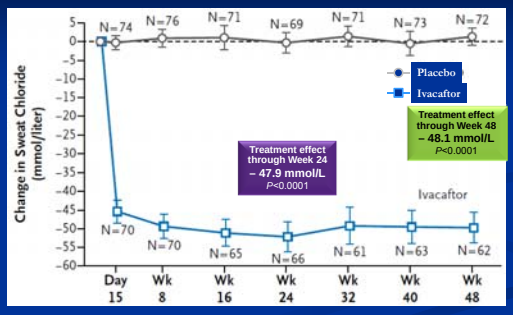
Absolute Mean Change From Baseline in Weight



Adapted with permission from Ramsey BW et al. *N Engl J Med.* 2011;365:1663-1672.
kg x 2.2 = lbs.

Change From Baseline in Sweat Chloride Levels



Adapted with permission from Ramsey BW et al. *N Engl J Med*. 2011;365:1663-1672.

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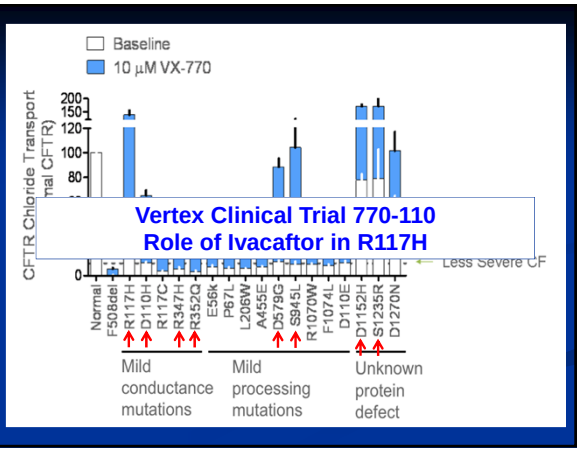
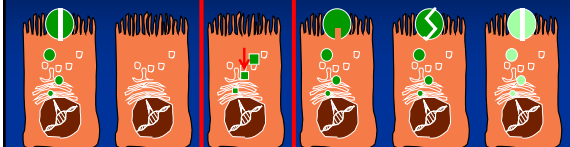
Other CFTR Gating Mutations

- 1) G551S, G178R, S549N, S549R, G790R, G1244E, S1251N, S1255P, G1349D
- 2) ~ 1% of patients
- 3) Vertex 770-111 Clinical Trial: Effect of Ivacaftor in Other Gating Mutations
  - Very little benefit, very high cost



Classes of CFTR Mutations

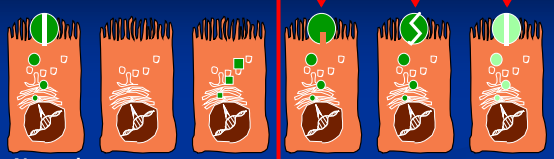


Normal	I	II	III	IV	V
	No synthesis	Block in processing	Block in regulation	Altered conductance	Reduced synthesis
	G542X	F508del	G551D	R117H D1152H	3849+10kbC–>T 5T A455E

VX-809, VX-661
N30

12% 87% 5% 5% 5%

Classes of CFTR Mutations



Normal	I	II	III	IV	V
	No synthesis	Block in processing	Block in regulation	Altered conductance	Reduced synthesis
	G542X	F508del	G551D	R117H D1152H	3849+10kbC–>T 5T A455E
12%		87%	5%	5%	5%

Table 1 – Orphan drug therapies, costs and prevalence.

Drug	Estimated Annual Cost, $	Disease	Estimated prevalence in US
Small molecules			
Kalydeco™ (Ivacaftor)	294,000*	Cystic Fibrosis, G551D-*CFTR*	1200[a]
Zavesca® (miglustat)	128,000**	Gaucher Disease Type I	4000[b]
Remodulin® (treprostinil)	120,000***	Pulmonary arterial hypertension	175,000[c]
Flolan® (epoprostenol)	100,000***	Pulmonary arterial hypertension	175,000[c]
Biologics			
Soliris® (Eculizumab)	409,500****	Paroxysymal Nocturnal Hemoglobinuria	8000 ****
Elaprase® (Idrsulfase)	375,000****	Hunter syndrome	500 ****
Naglazyme® (Galsulfase)	365,000****	Maroteaux-Lamy syndrome (Mucopolysaccharidosis VI)	50 - 300 ****
Cinryze® (C1 Esterase Inhibitor [Human])	350,000****	Hereditary Angioedema	6200[d]

Nature Rev Drug Discov. 2012 Aug 21.

Some thoughts on Costs

- Ivacaftor is not a cure, required lifelong
- Orphan Drug designation incentivized development, CFF and fundraisers enabled it as well, yet price astronomical
- Ivacaftor being studied in other conditions, even cigarette smoking, incr. potential
- Combinations with Ivacaftor likely to be equally costly for the lifetime of a patient
- Not the most expensive orphan drug, but will need additional combinations which if priced equivalently cannot be sustained.

Acknowledgements

- Cystic Fibrosis Foundation
- National Institutes of Health
- Johns Hopkins CF Centers
- Patients and Families