

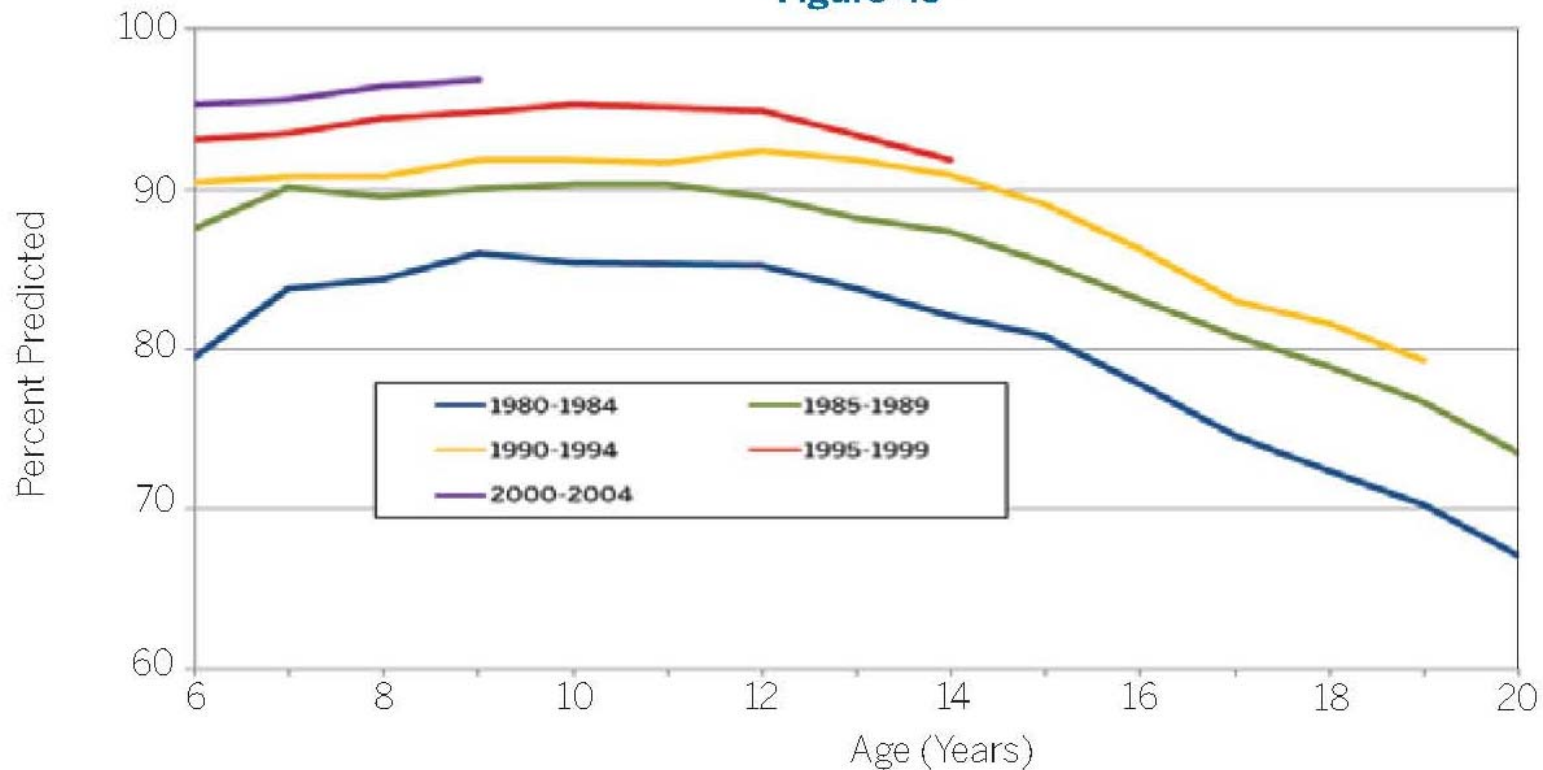
New Cystic Fibrosis Therapies

Marci Sontag, PhD

Cystic Fibrosis

- Genetic condition – 1/3,500 births; 35,000 individuals in US
- Progressive lung disease

Median FEV₁ Percent Predicted vs. Age by Birth Cohort
Figure 49



FEV₁ is steadily improving and stays above 90 percent predicted into adolescence.

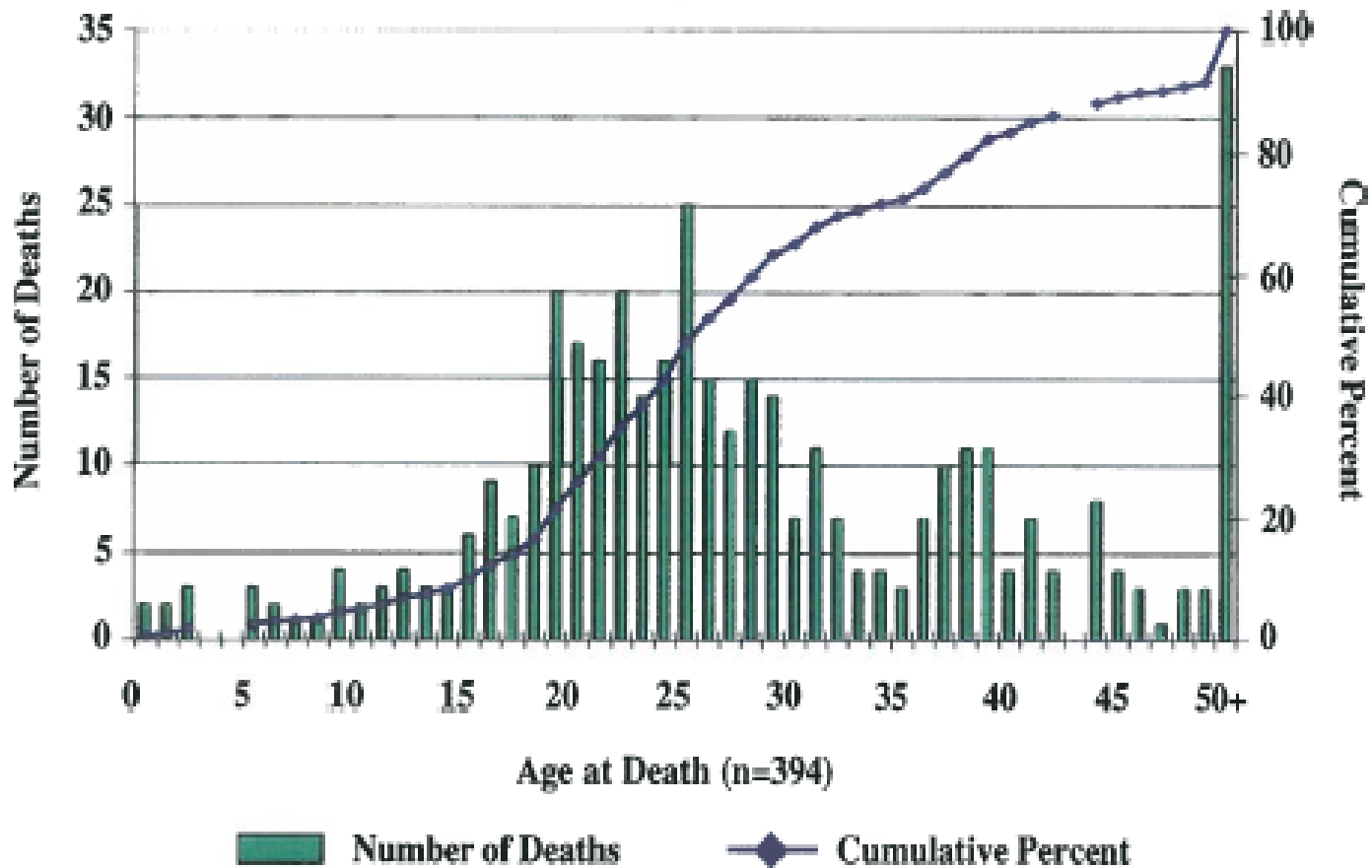
Cystic Fibrosis: Survival

- Median Predicted Survival – 37 years
- Median Age at Death – 26 years

Patient Registry, Cystic Fibrosis Foundation, Bethesda MD

Age at Death, 2007

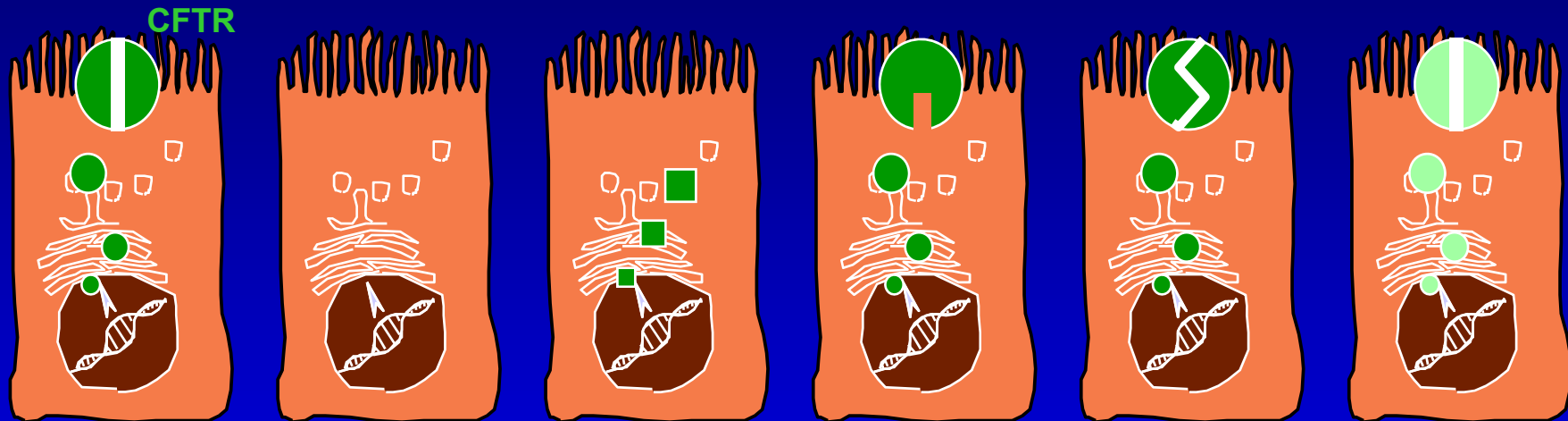
Figure 8



CFTR

- CF gene encodes for the cystic fibrosis transmembrane conductance regulator (CFTR) protein
 - CFTR functions as an ion channel and controls the movement of salt and water into and out of cells
 - Mutations in the CF gene impairs this movement, critically altering host defense in the lung

Molecular Consequences of CFTR Mutations



Normal

I

II

III

IV

V

**No
synthesis**

**Block in
processing**

**Block in
regulation**

**Altered
conductance**

**Reduced
synthesis**

Nonsense
G542X

AA deletion
 Δ F508

Missense
G551D

Missense
R117H

Missense
A455E

Frameshift
394delTT

Alternative
splicing
3849+10kbC→T

Splice junction
1717-1G→A

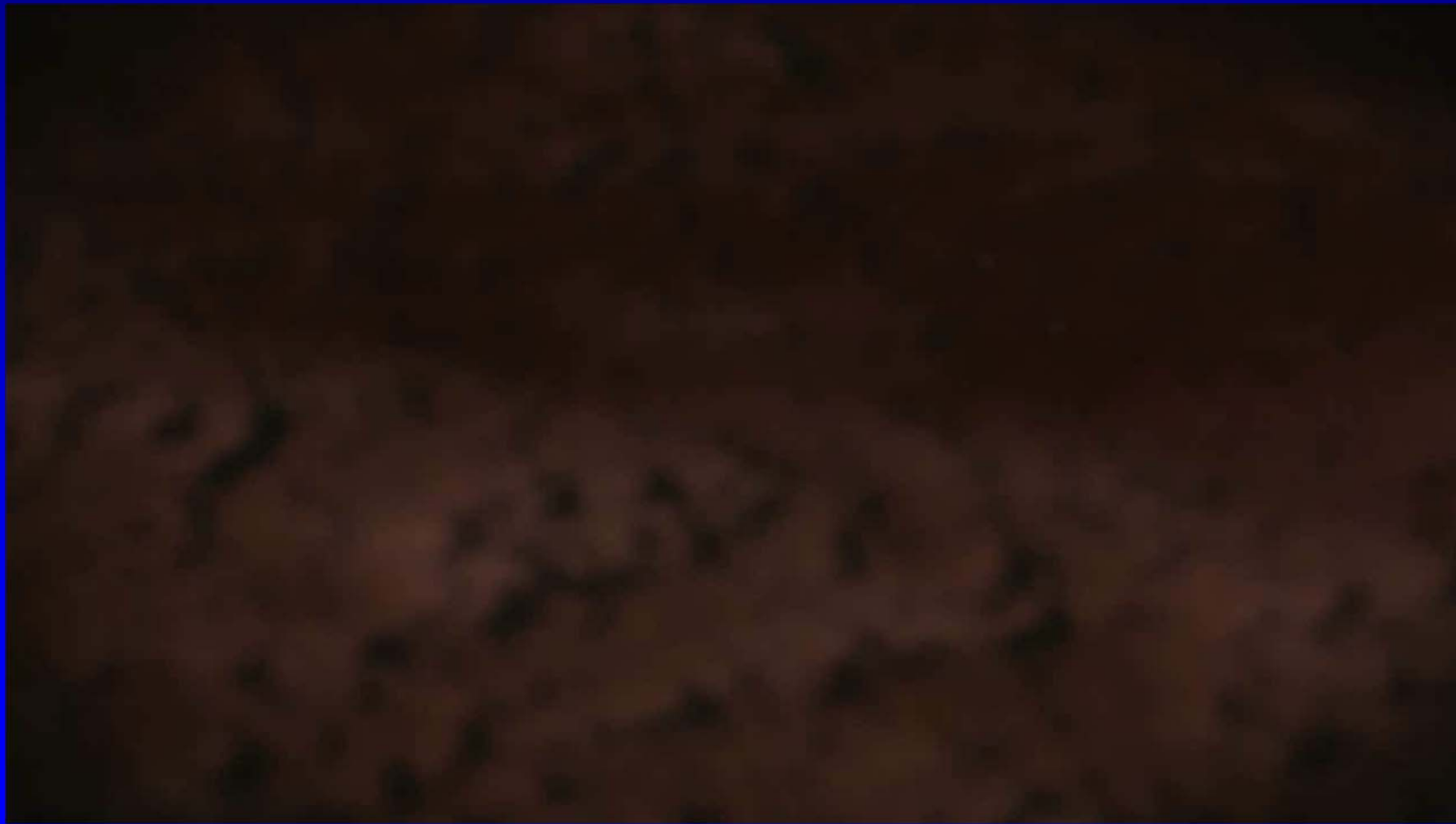
Cystic Fibrosis Mutation Database (Tsui, Zielenski)
<http://www.genet.sickkids.on.ca/cftr/>

Healthy Cell



Animation courtesy of the U.S. Cystic Fibrosis Foundation

Cell with CF



Animation courtesy of the U.S. Cystic Fibrosis Foundation



Clinical and Functional Translation of CFTR



Quick Links

- Home
- Start Here to Search
- How to Use This Website
- Links
- FAQs
- Glossary
- CFTR2 Contributors
- CFTR2 Team

Tools

- Take CFTR2 Survey
- CFTR2 Progress Report

Site Settings

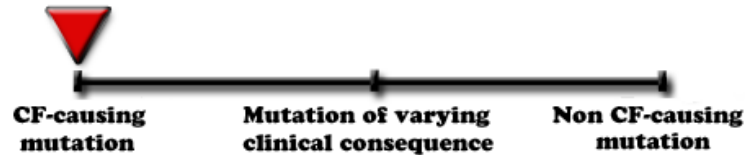
Scientific/medical view



The CFTR2 project is partially supported by Grant Number 5R37DK044003 from the National Institute of Digestive, [Diabetes](#) and Kidney Diseases of the National Institutes of Health, by funding from the US [Cystic Fibrosis](#) Foundation, and by an unrestricted [educational grant](#) from Sequenom to the US Cystic Fibrosis Foundation.

This is the scientific / medical view. Click to switch to the general user view.

Summary: 663delT is seen in 9 patients in our worldwide CF database. Based on the combination of clinical and functional evaluation, this is a mutation that **would cause CF**. Based on the patients we have reviewed we would expect this mutation would be associated with *pancreatic insufficient* [CF](#).



The information displayed below shows how we came to this decision.

- Clinical Characteristics
- Mutation Characteristics
- Functional Testing
- Literature Review
- Population Screening
- Bioinformatics Assessment

This mutation entry was last updated on: 3/5/2012

[Contact Us](#) [Privacy Policy](#) [Legal Terms & Conditions](#)

Permitted use available to clinicians, patients, and family members for clinical, research, and educational uses only. All other rights reserved.
 © Copyright 2011 US CF Foundation, Johns Hopkins University, The Hospital for Sick Children.

http://cftr2.org/mutation.php?view=scientific&mutation_id=128

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

NOVEMBER 3, 2011

VOL. 365 NO. 18

A CFTR Potentiator in Patients with Cystic Fibrosis and the G551D Mutation

Bonnie W. Ramsey, M.D., Jane Davies, M.D., M.B., Ch.B., N. Gerard McElvaney, M.D., Elizabeth Tullis, M.D., Scott C. Bell, M.B., B.S., M.D., Pavel Dřevínek, M.D., Matthias Griese, M.D., Edward F. McKone, M.D., Claire E. Wainwright, M.D., M.B., B.S., Michael W. Konstan, M.D., Richard Moss, M.D., Felix Ratjen, M.D., Ph.D., Isabelle Sermet-Gaudelus, M.D., Ph.D., Steven M. Rowe, M.D., M.S.P.H., Qunming Dong, Ph.D., Sally Rodriguez, M.S., Karl Yen, M.D., Claudia Ordoñez, M.D., and J. Stuart Elborn, M.D., for the VX08-770-102 Study Group*

ABSTRACT

BACKGROUND

Increasing the activity of defective cystic fibrosis transmembrane conductance regulator (CFTR) protein is a potential treatment for cystic fibrosis.

METHODS

We conducted a randomized, double-blind, placebo-controlled trial to evaluate ivacaftor (VX-770), a CFTR potentiator, in subjects 12 years of age or older with cystic fibrosis and at least one G551D-CFTR mutation. Subjects were randomly assigned to receive 150 mg of ivacaftor every 12 hours (84 subjects, of whom 83 received at least one dose) or placebo (83, of whom 78 received at least one dose) for 48 weeks. The primary end point was the estimated mean change from baseline through week 24 in the percent of predicted forced expiratory volume in 1 second (FEV₁).

RESULTS

The change from baseline through week 24 in the percent of predicted FEV₁ was greater

From Seattle Children's Hospital and University of Washington School of Medicine, Seattle (B.W.R.); Respiratory Biomedical Research Unit, Royal Brompton and Harefield National Health Service Foundation Trust, London (J.D.); Royal College of Surgeons in Ireland, Beaumont Hospital (N.G.M.), and St. Vincent's University Hospital (E.F.M., C.E.W.) — both in Dublin, Ireland; St. Michael's Hospital, University of Toronto (E.T.), and Department of Pediatrics, Hospital for Sick Children (F.R.) — both in Toronto; Department of Thoracic Medicine, Prince Charles Hospital (S.C.B.), and Queensland Children's Medical Research Institute, University of Queensland (S.C.B., C.E.W.) — both in Brisbane, Australia; Department of

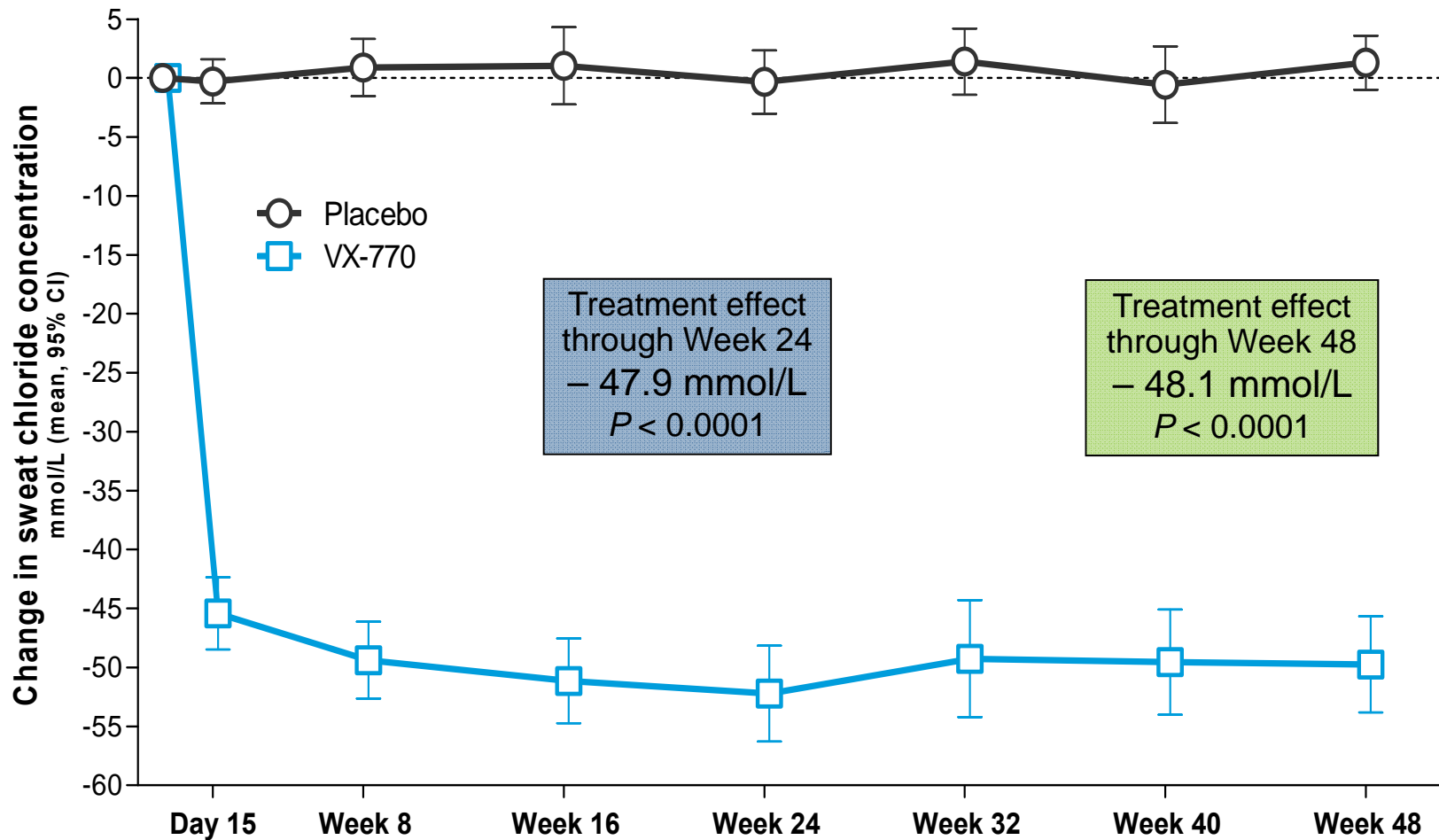
Potentiator

- Some CFTR proteins makes it to the cell surface but do not allow chloride to pass through properly – Gating Mutations
- Potentiators bind to the CFTR located at the cell surface and allows chloride to move out of the cell.



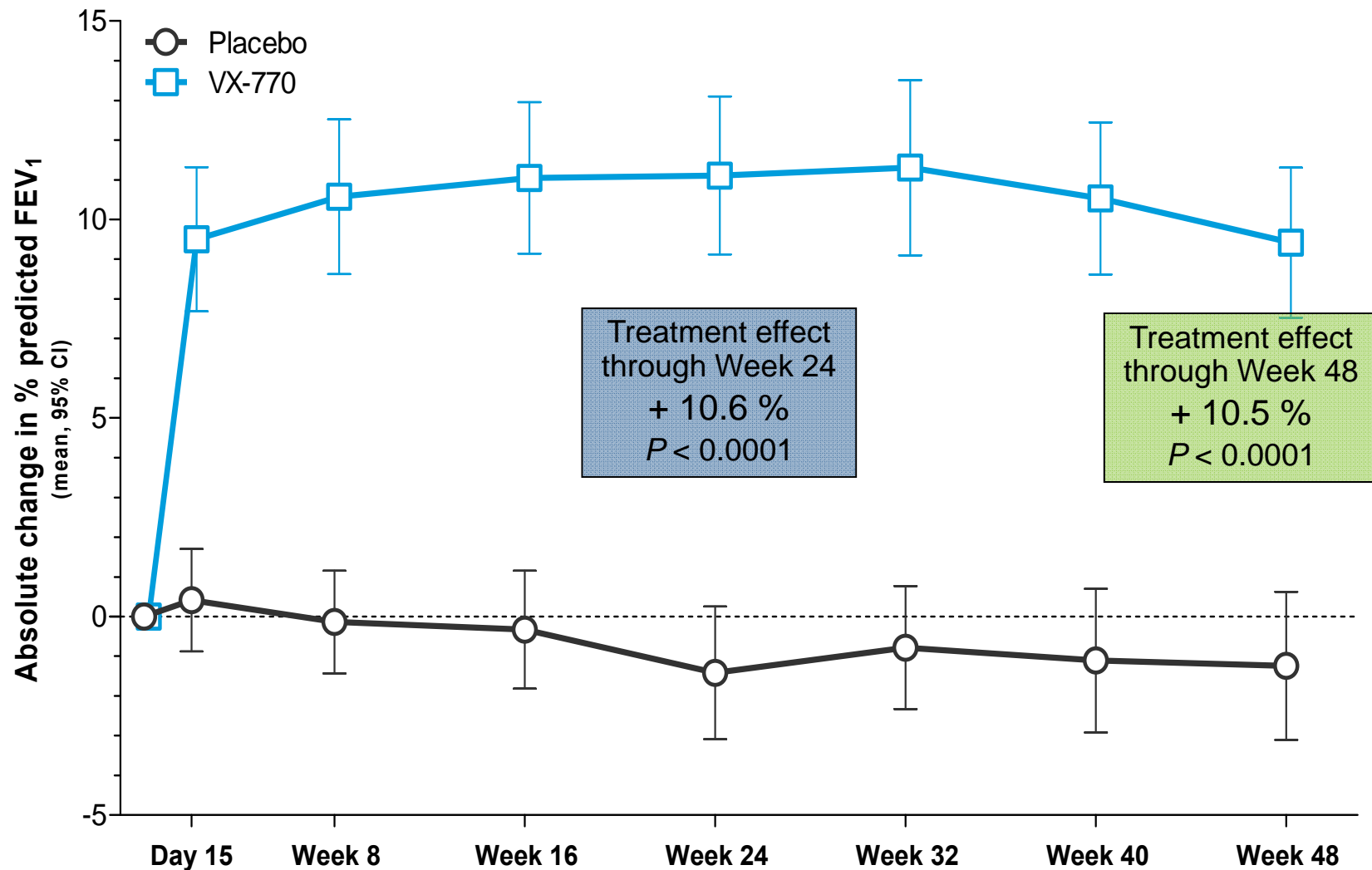
Animation courtesy of the U.S. Cystic Fibrosis Foundation

Change from Baseline in Sweat Chloride



Phase 3 Trial (Ramsey et al, NEJM, 2011)

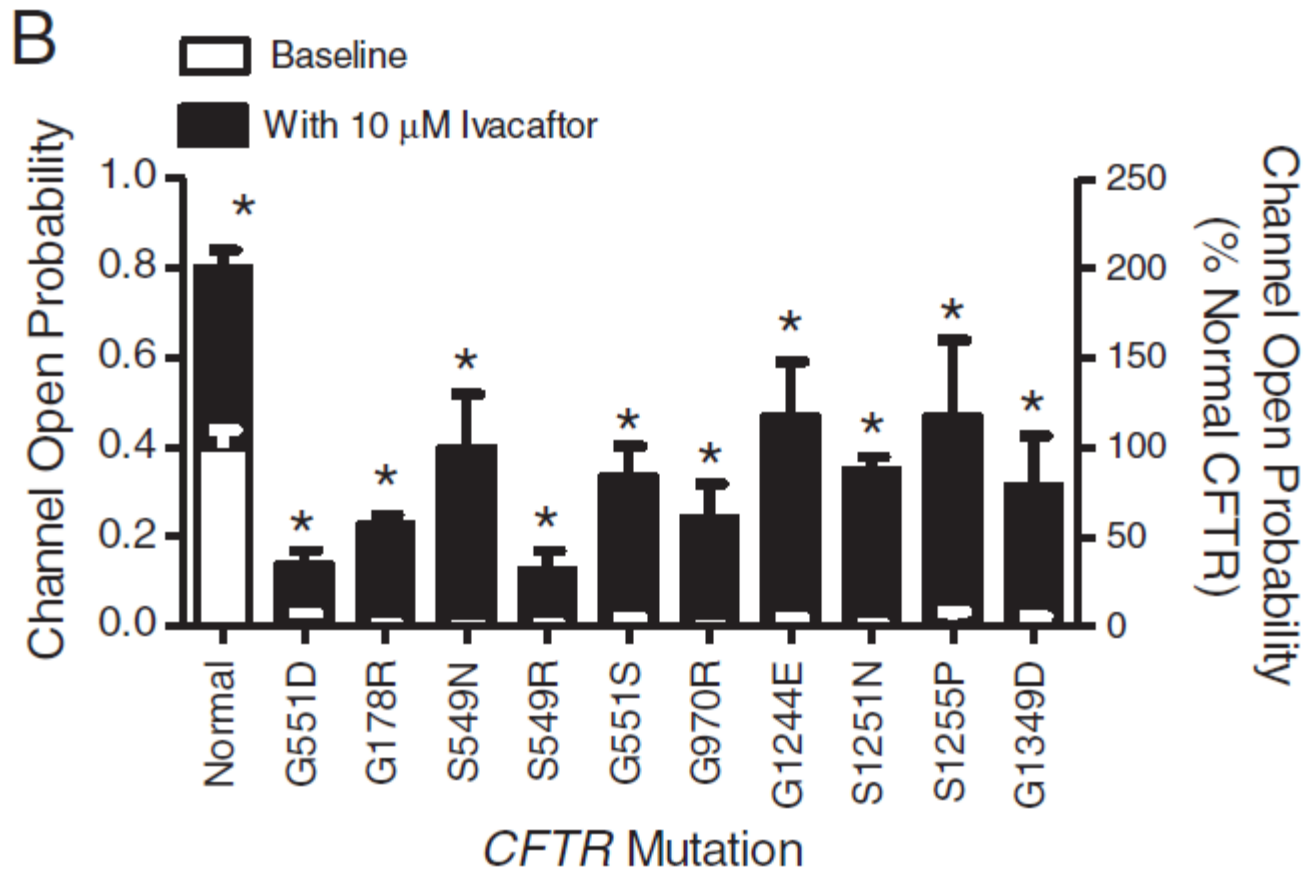
Absolute Change in FEV₁ % Predicted



Phase 3 Trial (Ramsey et al, NEJM,

Slide courtesy of F. Accurso

Ivacaftor Potentiation in Gating Mutations



(Yu et al., 2012)

Ivacaftor (FDA approval 1/31/2012)

- **First in Class (CFTR Modulators)**
- **No animal studies except toxicity**
- **CFTR Mutations**
 - **Only G551D (4%)... for now**
 - **Ultimately, 20% CFTR 2 program**
- **Treat “cellular phenotype” not by targeting biochemical abnormality (Swinney et al 2011)**
- **Molecular Mechanism of Action is incompletely understood**
- **Infection not considered as an outcome measure**
- **Currently approximately 1,000 patients under treatment**

Corrector

- Normal CFTR proteins make their way to the cell surface and transport chloride ions. in most people with CF, the CFTR protein never makes it to the cell membrane
- Correctors - drug that binds to the CFTR protein, allowing the protein to reach the cell surface.

Corrector



Modern Healthcare

THE ONLY HEALTHCARE BUSINESS NEWS WEEKLY

JANUARY 28, 2013

\$5.50

STICKER SHOCK

Insurers, providers push back on high-priced specialty drugs

Page 6

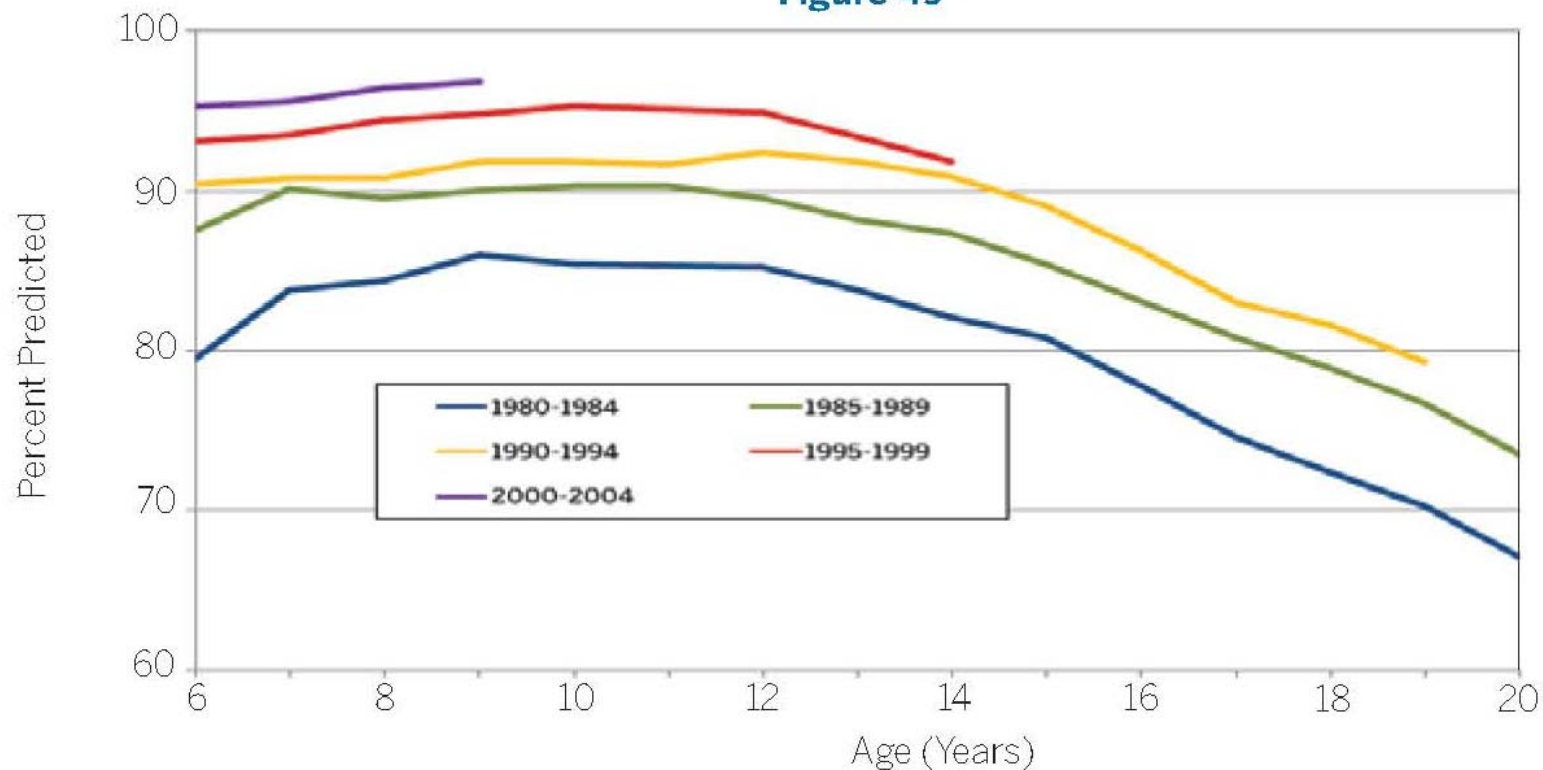


Ivacaftor Cost – Rare Disease Drug Development

- **\$294,000 per year.**
- **Comparable to some other drugs**
- **Resources for families**
 - **CFF patient assistance**
 - **Vertex patient assistance fund**
 - **No insurance – no cost to family**
 - **Insurance – help with copay**
 - **CFF legal assistance**

New Cystic Fibrosis Therapies May Change the Trajectory

Median FEV₁ Percent Predicted vs. Age by Birth Cohort
Figure 49



FEV₁ is steadily improving and stays above 90 percent predicted into adolescence.

Conclusion

- Ivacaftor is changing the course of cystic fibrosis in a portion of CF patients
- Other compounds are being tested that are targeted at more common mutations (F508) that may cover >90% of CF patients
- Early introduction of potentiators and correctors following newborn screening may prevent early lung disease and could make CF a chronic disease controlled by a pill

Acknowledgments

- Frank Accurso MD
- Cystic Fibrosis Foundation
- Patients and Families in the Cystic Fibrosis Community
- Vertex Pharmaceuticals Inc.