Colorado School of Public Health

New Cystic Fibrosis Therapies

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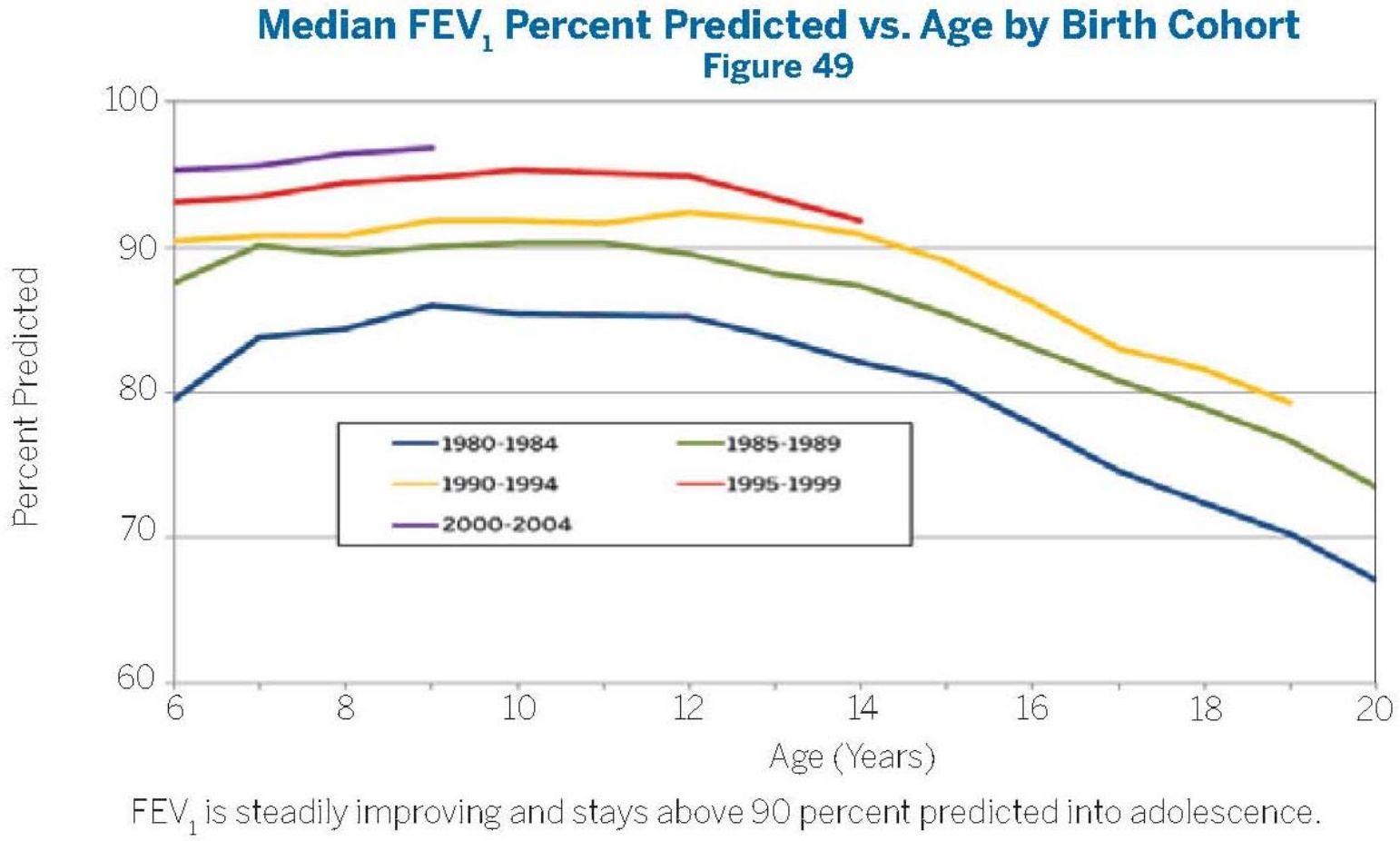
Cystic Fibrosis

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

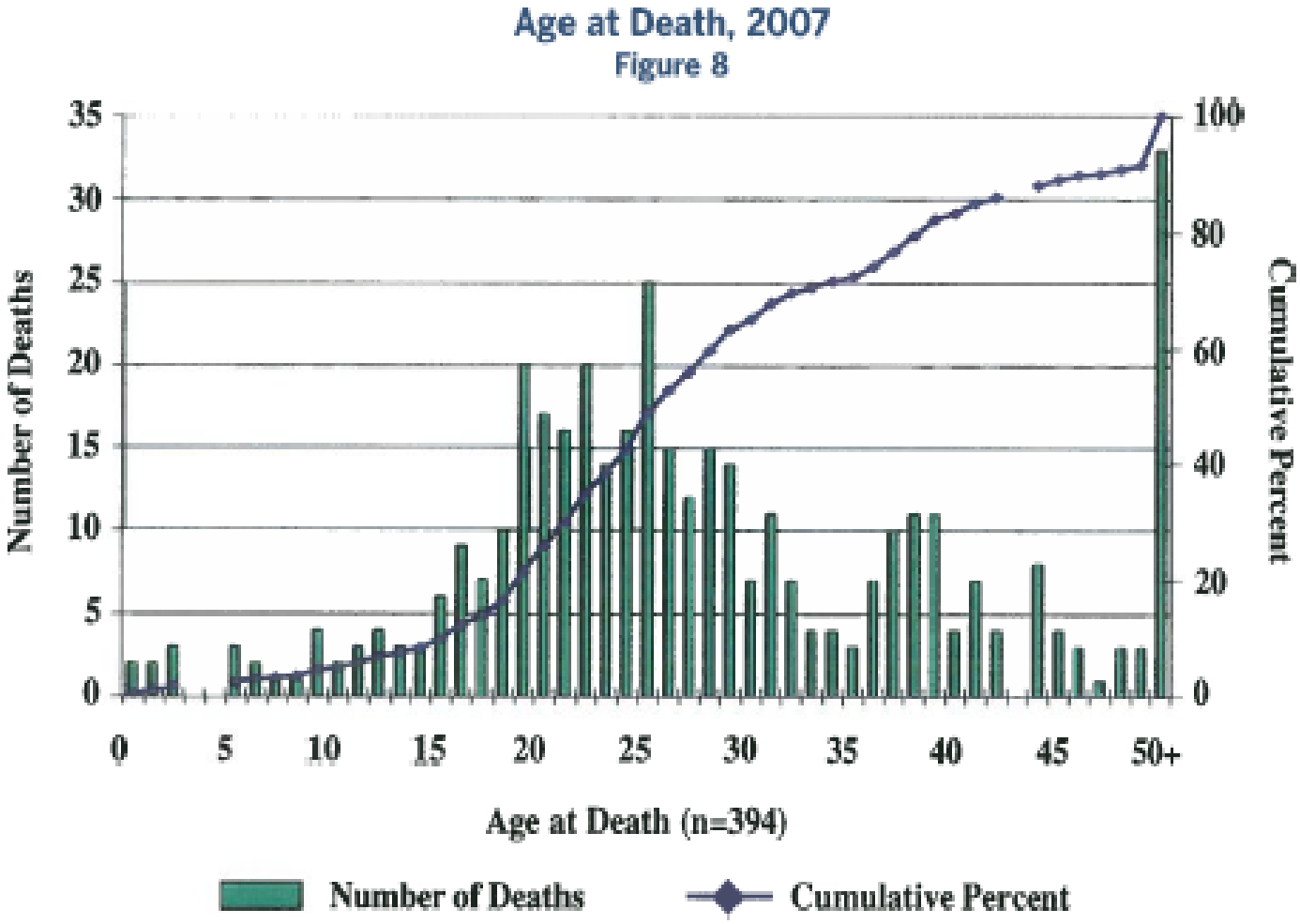


Patient Registry, Cystic Fibrosis Foundation, Bethesda MD

Cystic Fibrosis: Survival

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

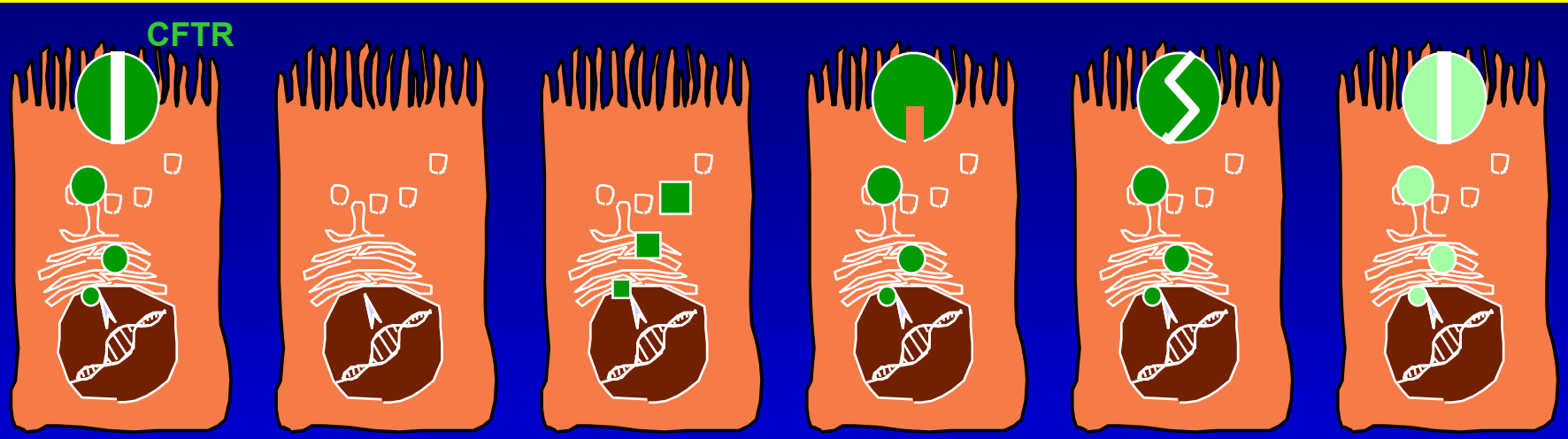
Patient Registry, Cystic Fibrosis Foundation, Bethesda MD



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

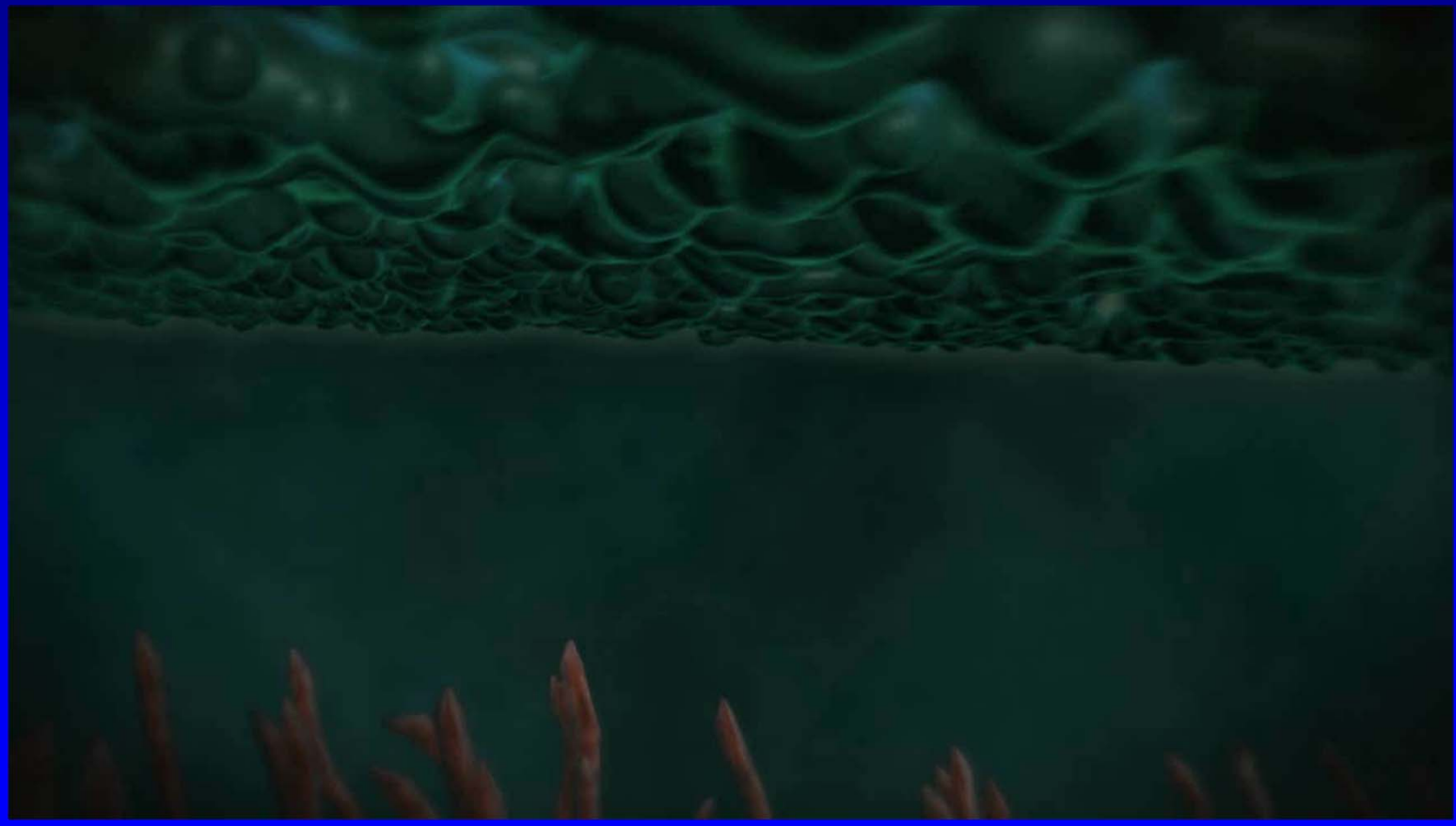
Molecular Consequences of CFTR Mutations



Normal	I	II	III	IV	V
	No synthesis	Block in processing	Block in regulation	Altered conductance	Reduced synthesis
	Nonsense G542X	AA deletion ΔF508	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

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

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

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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 (FEV_1).

RESULTS

The change from baseline through week 24 in the percent of predicted FEV_1 was greater

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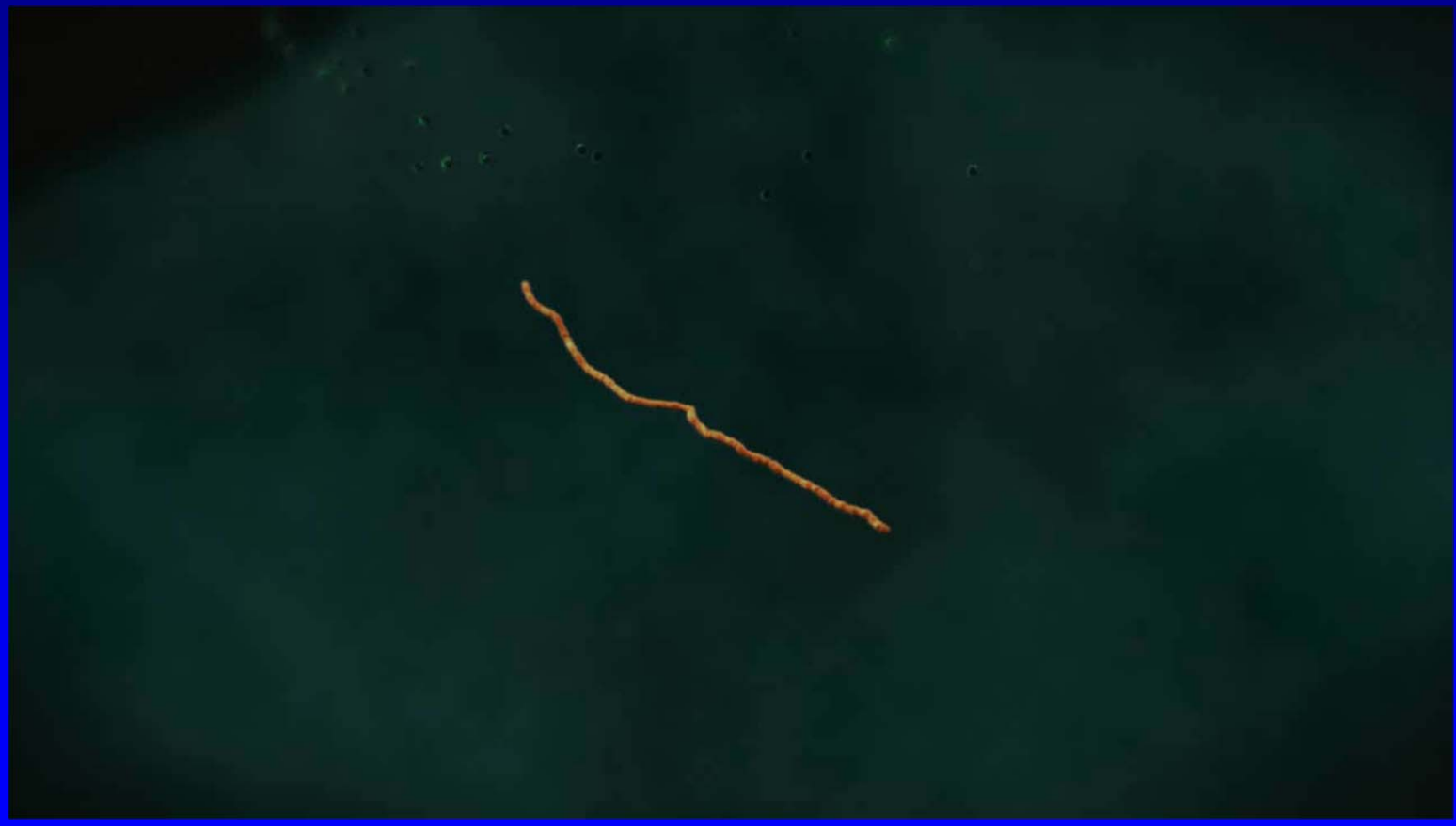
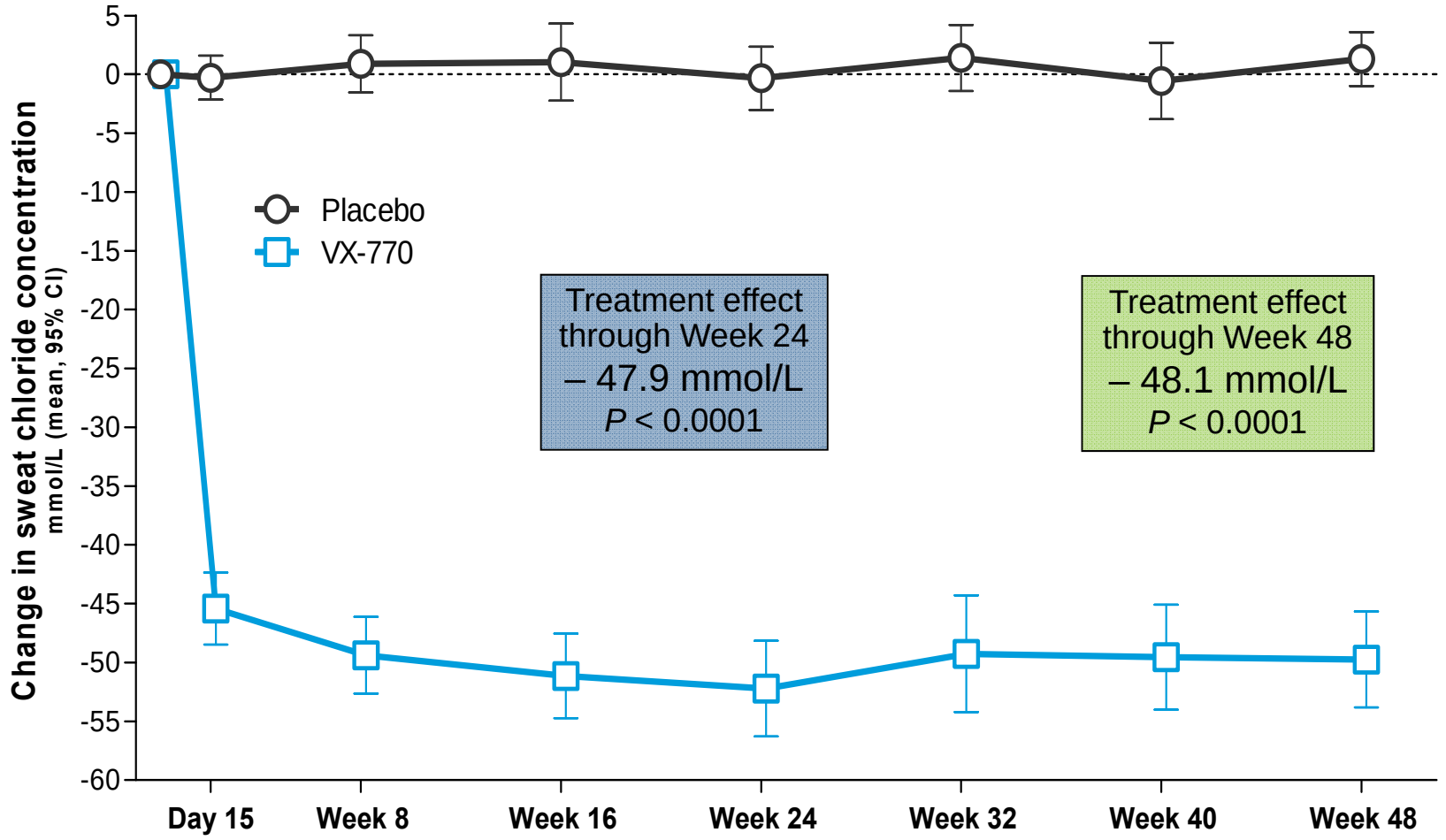
Potentiator

- 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

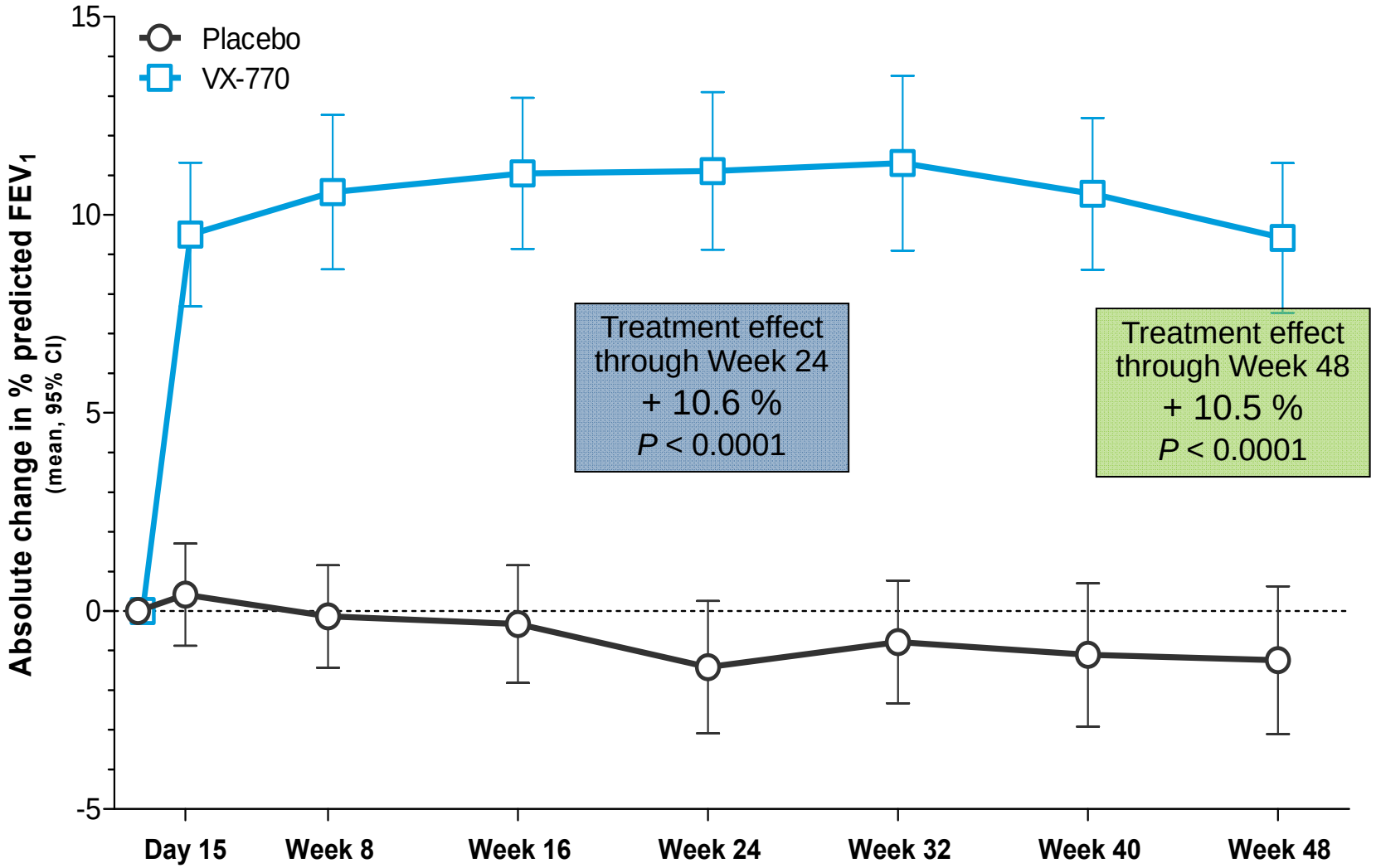
Change from Baseline in Sweat Chloride



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

Slide courtesy of F. Accurso

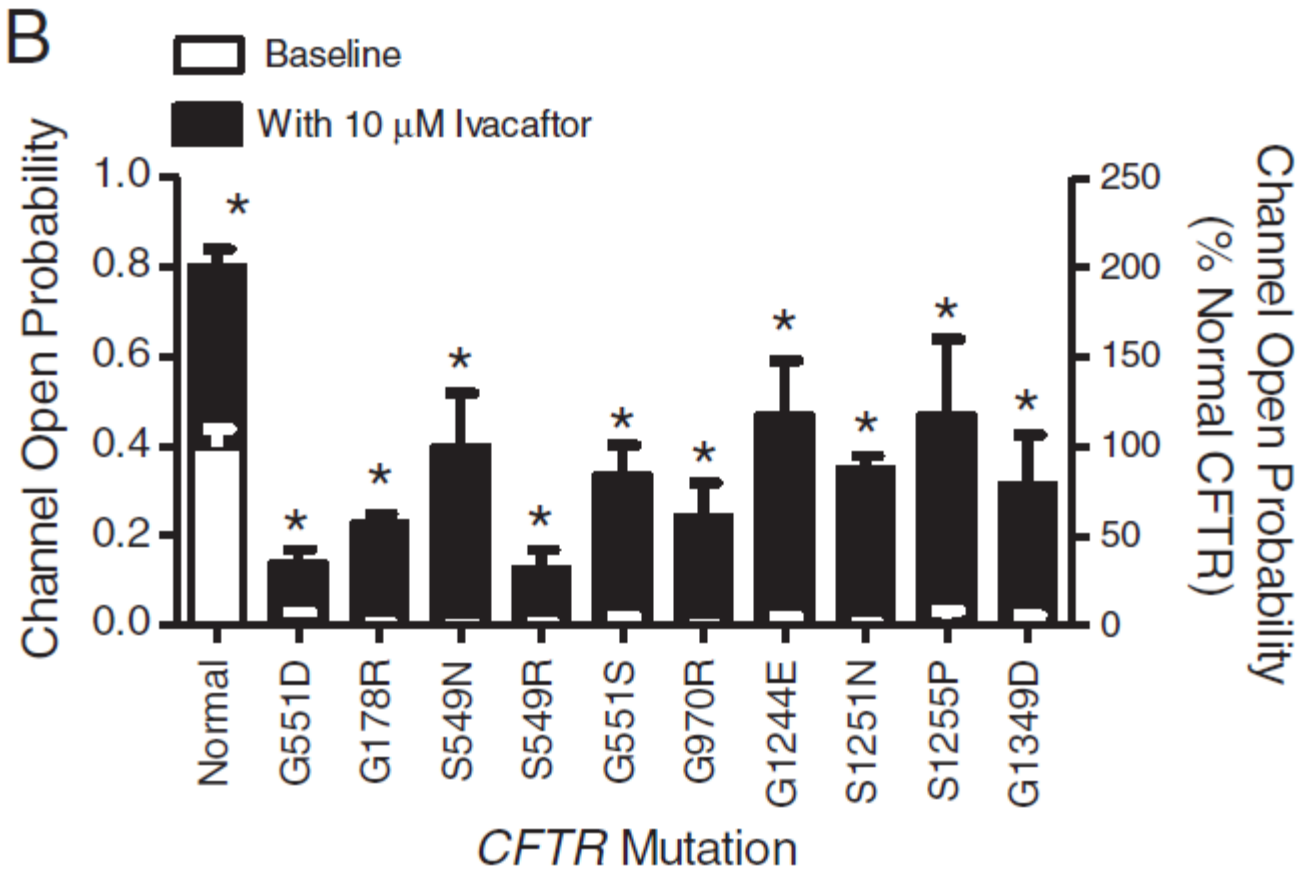
Absolute Change in FEV_1 % Predicted



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

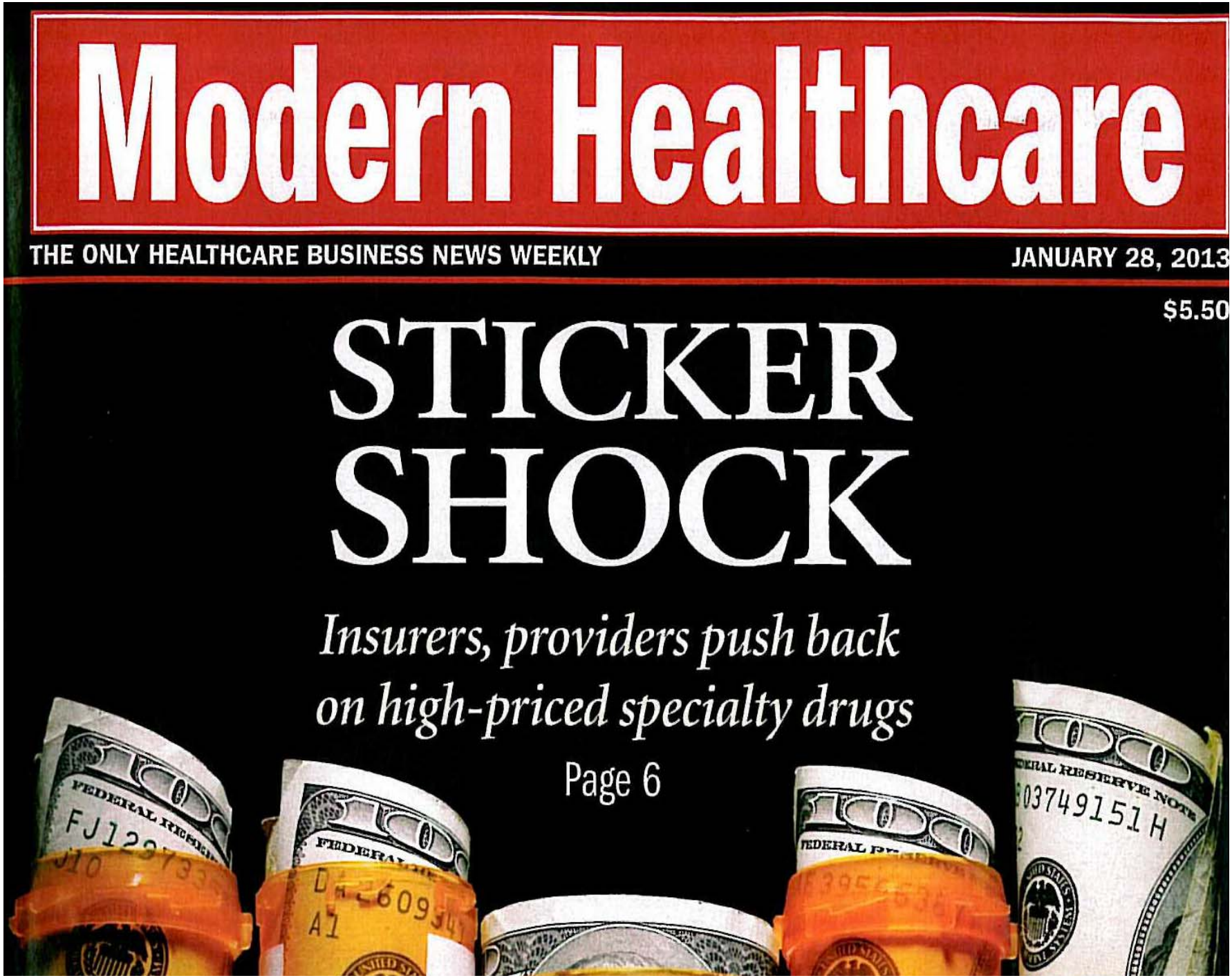
Slide courtesy of F. Accurso

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.

Animation courtesy of the U.S. Cystic Fibrosis Foundation

Corrector


Modern Healthcare
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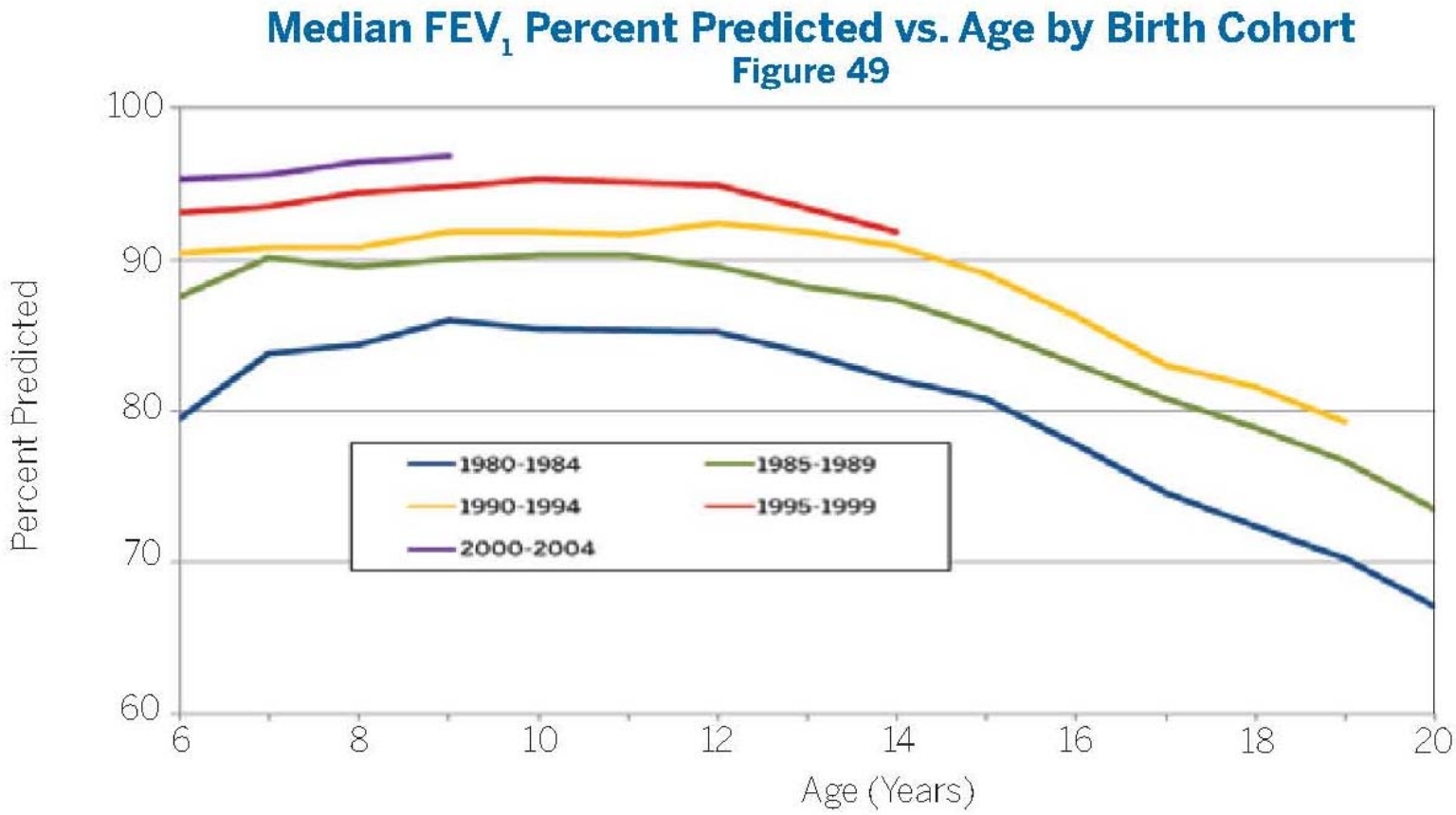
STICKER SHOCK
Insurers, providers push back on high-priced specialty drugs
Page 6

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



FEV_1 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

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- Cystic Fibrosis Foundation
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