What we are learning from cystic fibrosis modulators

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Disclosure

- I have no conflicts of interest

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Objectives

By the end of this talk, you should be able to:

1. Interpret individual *CFTR* variants using laboratory report and the CFTR2 website

2. Summarize the types of CFTR modulator therapies and kinds of variants they target

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Agenda

- Part 1: CF basics
  - (brief) Review CFTR, CF, and ‘CFTR-opathies’
  - CFTR2 website, terminology, and uses

- Part 2: Treatment
  - CFTR modulators, terminology, and indications for use
  - Where we are headed with treatment

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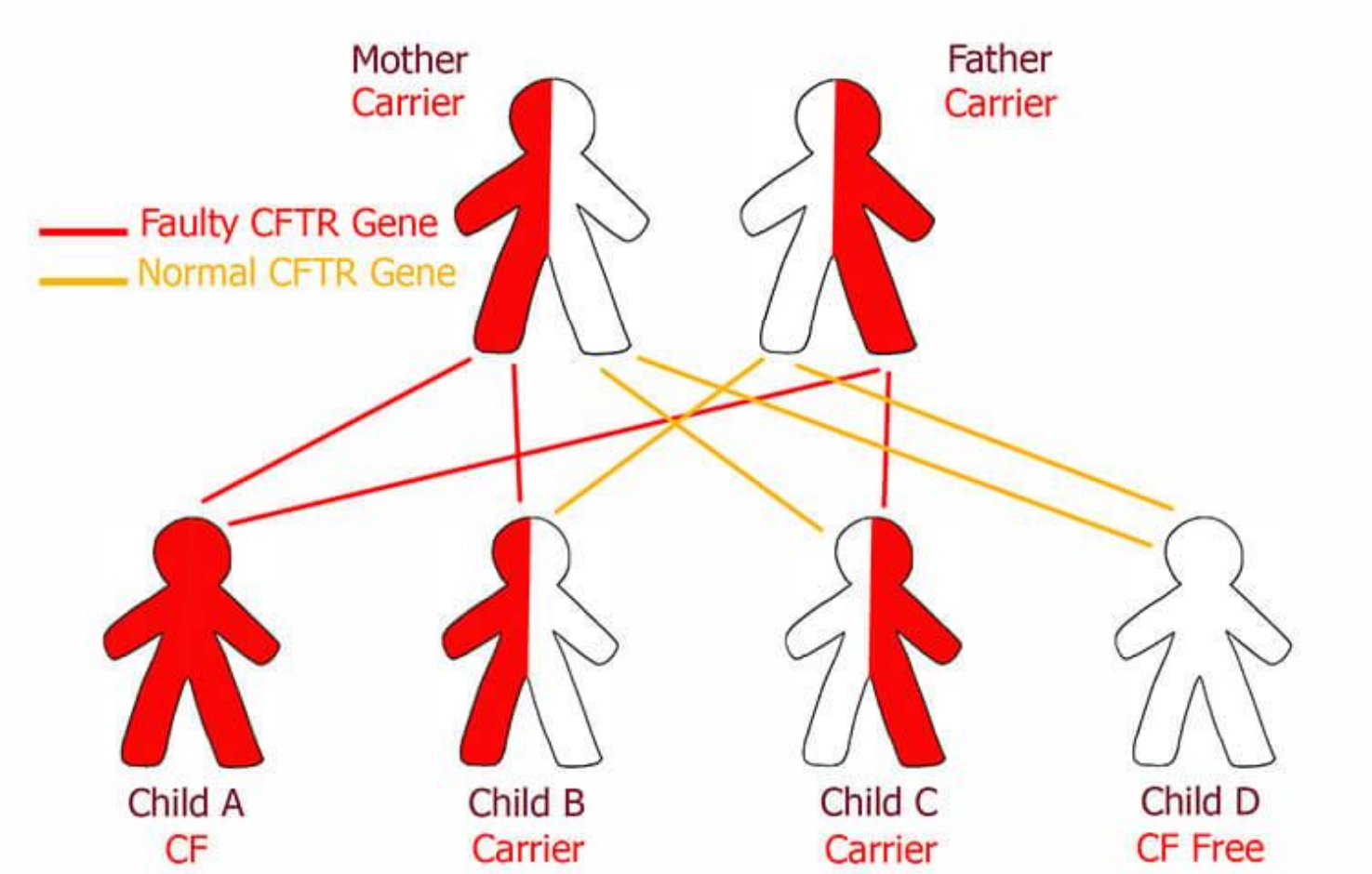
Part 1: CF basics



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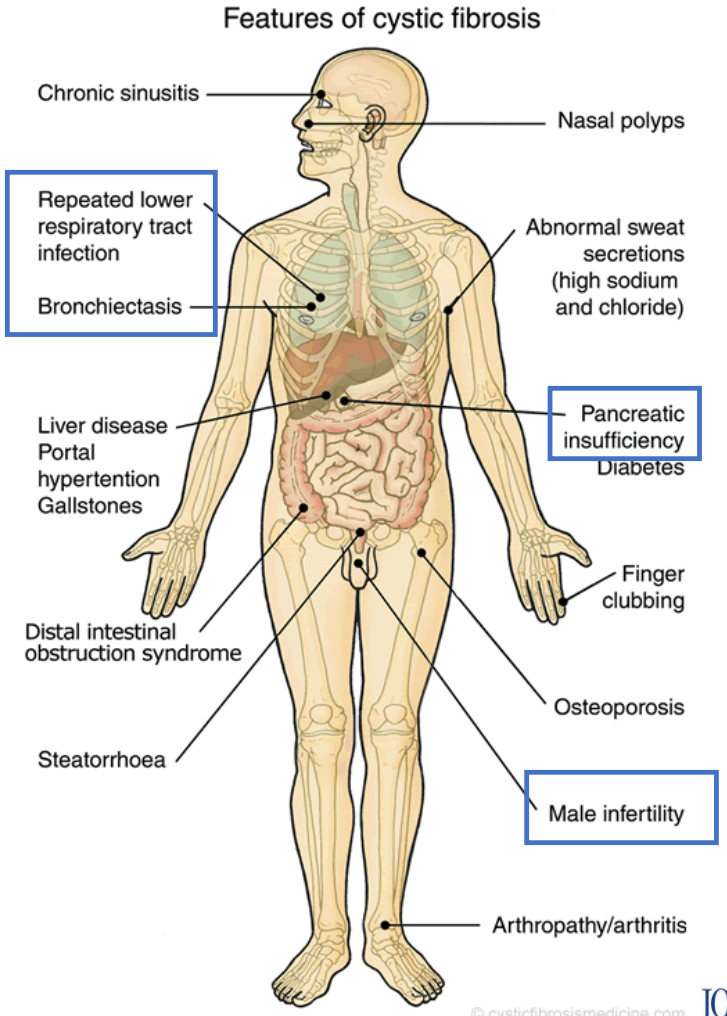
http://www.cfbuzz.org/about-cystic-fibrosis/what-is-cf/

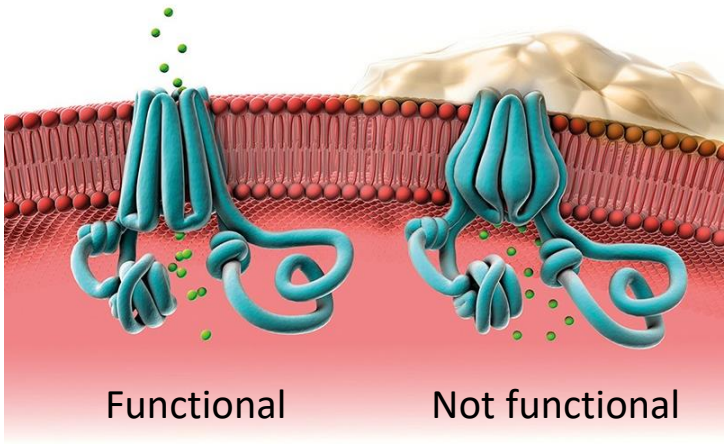
Reminders about CF and CFTR

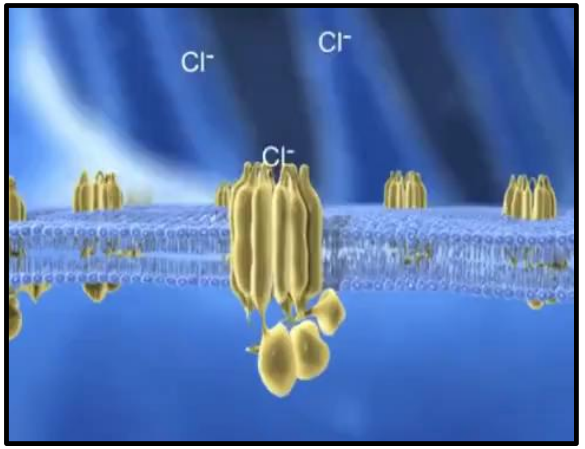
- Multi-organ disease
- Main morbidity/mortality risk: progressive obstructive lung disease
- ‘Classic’ onset is in infancy or childhood, but the spectrum of CFTR-related conditions has expanded greatly
- Predicted survival for individuals with CF born 2015-2019 is now 46 years



Reminders about CF and CFTR

- CFTR is an ion channel for Cl^- and HCO^3
  - Resides at the surface of epithelial cells
- The protein must be:
  - Produced
  - Folded/trafficked
  - Functional
- >2,000 variants within *CFTR* have been reported in LSDBs
  - only ~25% have been definitively interpreted as CF-causing or otherwise
  - Variants may have varying functional impacts





Normal (left) and abnormal CFTR proteins. Credit: Gunilla Elam/SPL. In Plackett B, Nature 2020, 583(7818):S17.

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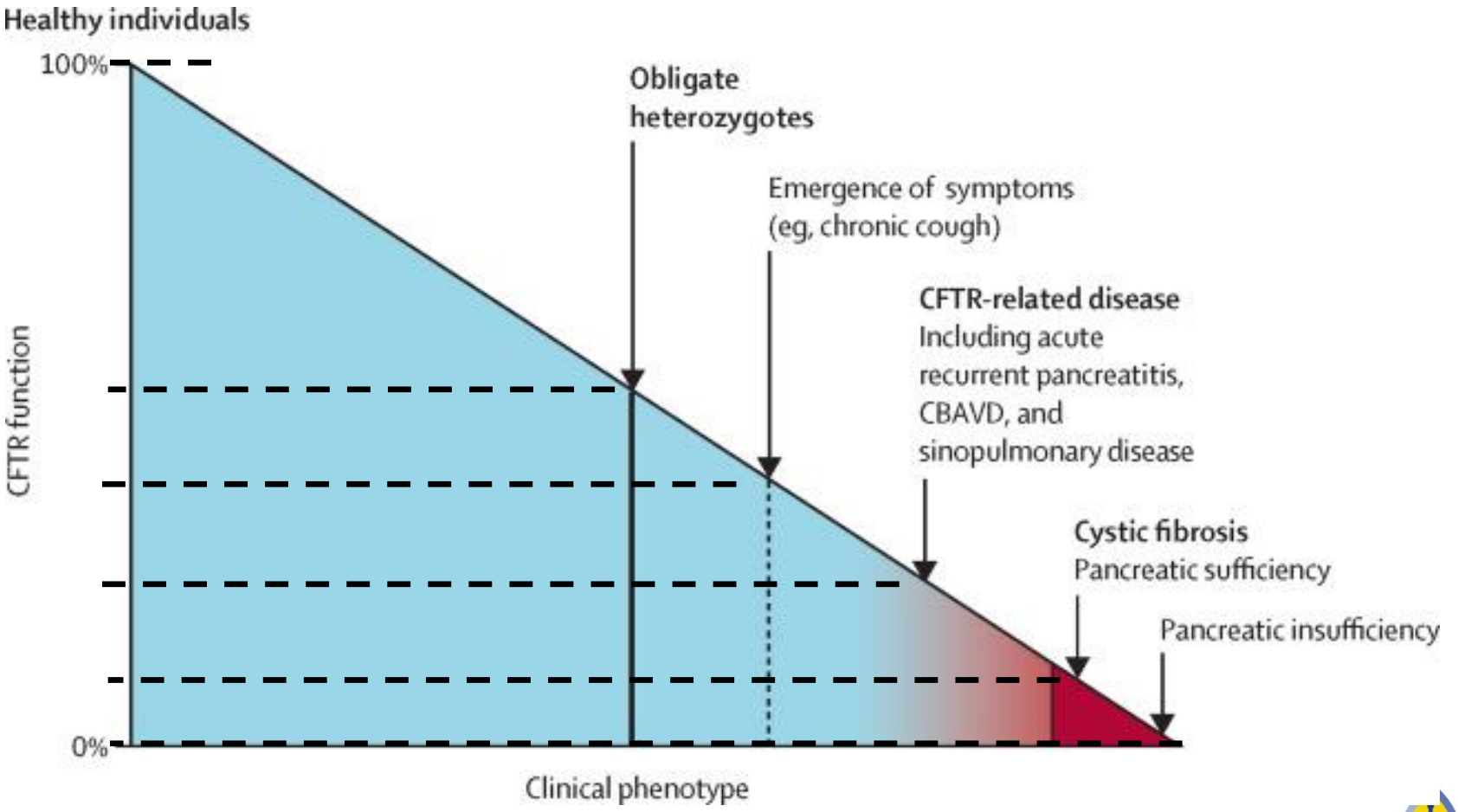
Function-phenotype correlations



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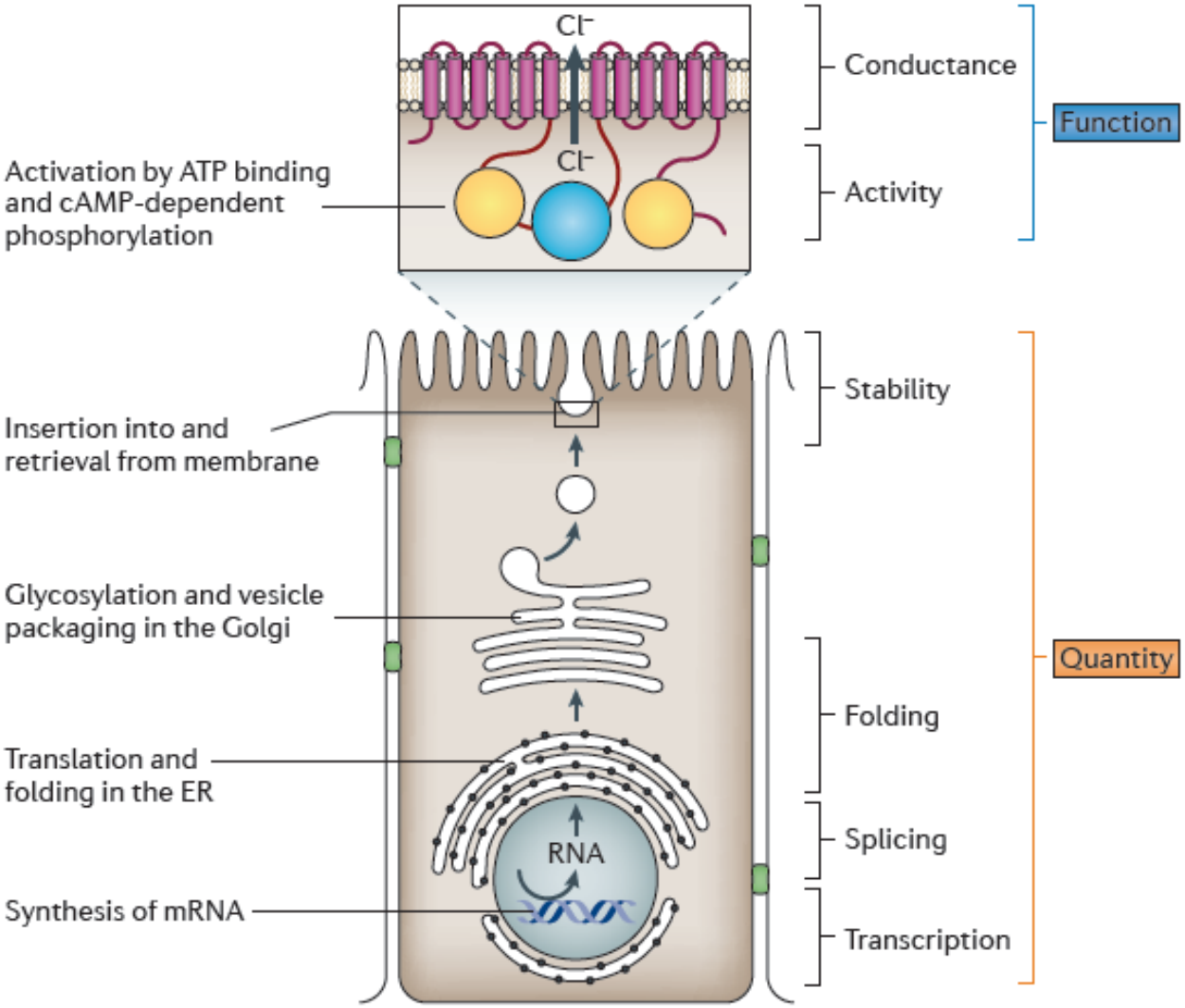
The stages to get to functional CFTR



Cutting GR, Nat Reviews Genet, 2015

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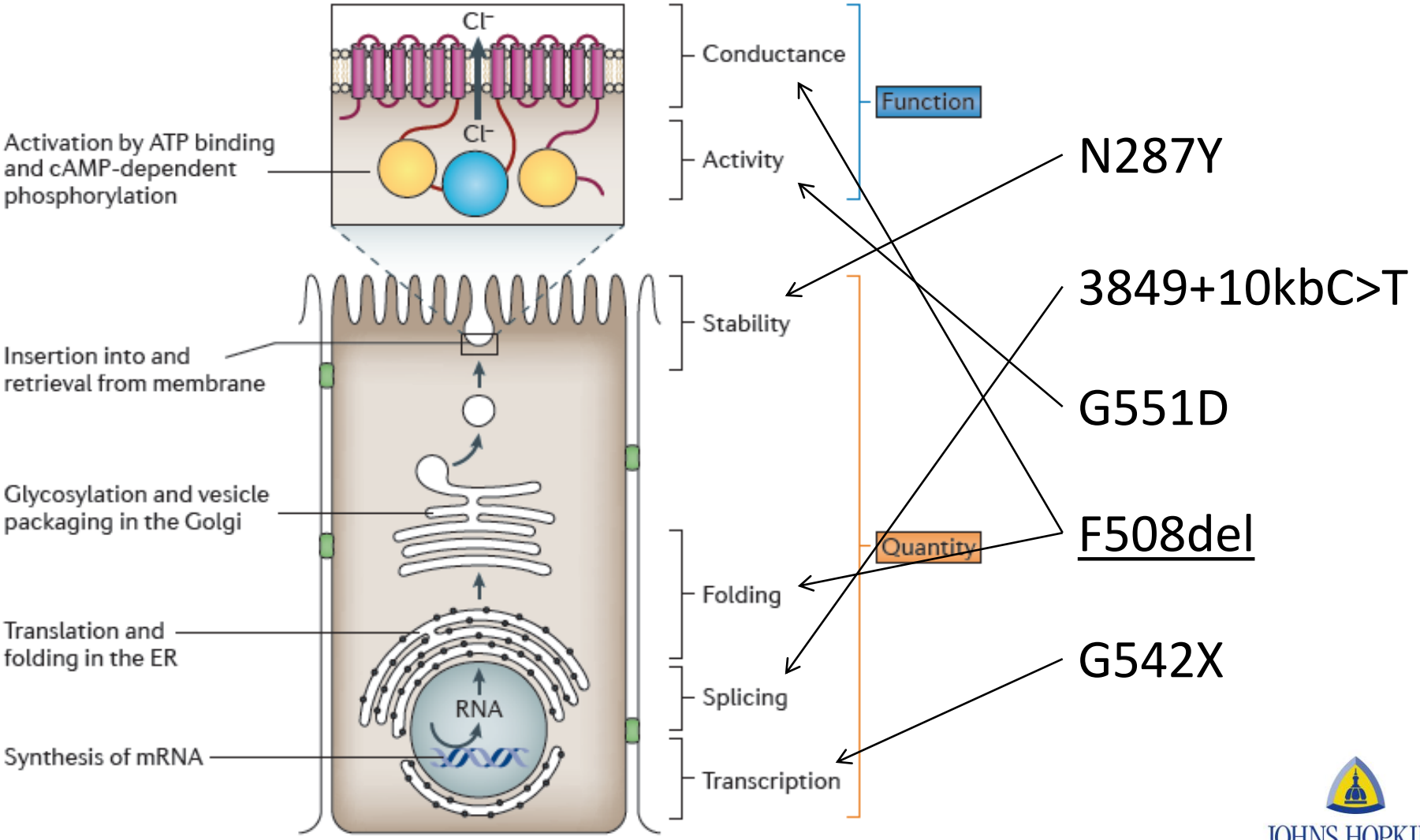
The stages to get to functional CFTR



Cutting GR, Nat Reviews Genet, 2015

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The CFTR2 project

- CFTR2: Clinical and Function TRanslation of CFTR
- A global initiative to bridge the gap between our ability to detect CFTR variation and interpret what it means for an individual

https://cftr2.org

CFTR2 Clinical and Functional Translation of CFTR

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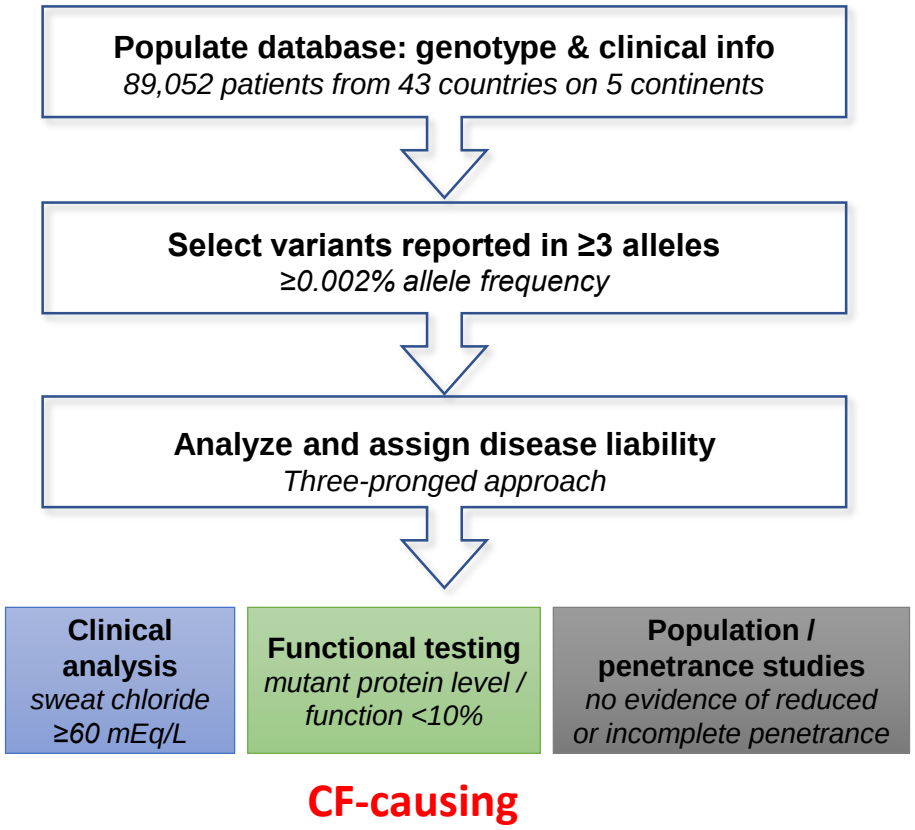
CFTR2 goals and process

Goals:

- Analyze *CFTR* variants reported in **individuals with CF** from across the globe
- Determine and assign **disease liability** to *CFTR* variants
- Provide complete and expert-reviewed **variant interpretations** to researchers, care providers, patients, and families



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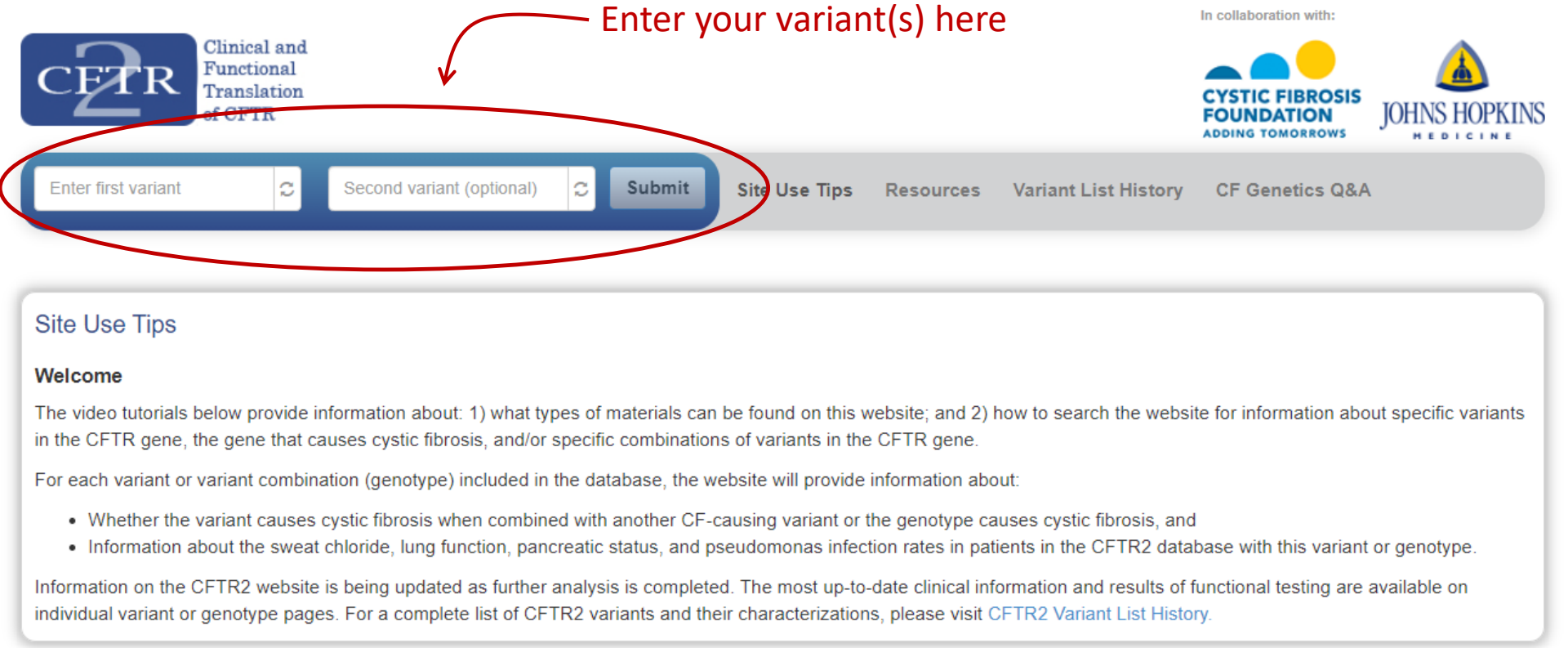
https://cftr2.org



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Results for F508del

Variant F508del can be referred to as F508del, p.Phe508del, c.1521_1523delCTT, or c.1521_1523del or 1653delCTT,

- The drug combination of elexacaftor and tezacaftor and ivacaftor (Trikafta), the drug combination of ivacaftor and lumacaftor (Orkambi), and the drug combination of ivacaftor and tezacaftor (Symdeko or Symkevi) has been approved in some countries for certain individuals with this variant. Please contact your physician to discuss whether any of these drug combinations is appropriate for you.

The information shown below is for a single variant. To search for a variant combination, enter your first variant in the search box above and then start typing in the "Second variant (optional)" search box. If you do not find your second variant listed or don't know what it is, you can select a group of variants to search.

Summary Information | Clinical Information | Functional Testing | Population Analysis | Additional Information

The variant F508del is seen in 65,046 patients in our worldwide database. This variant is expected to result in CF.

The diagnosis of any individual patient with CF should be made based upon clinical parameters. The content of this website should not be used as a substitute for clinical judgement.

History of Changes in the Variant Information

This variant page was last updated 04/10/2012. If a change in the variant final determination was made at that time, that information will appear in the table below.

Variant	Variant final determination	Date	Comment
F508del	CF-causing	04/10/2012	original call

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Results for F508del and G551D

Variant F508del can be referred to as F508del, p.Phe508del, c.1521_1523delCTT, or c.1521_1523del or 1653delCTT,

- The drug combination of elexacaftor and tezacaftor and ivacaftor (Trikafta), the drug combination of ivacaftor and lumacaftor (Orkambi), and the drug combination of ivacaftor and tezacaftor (Symdeko or Symkevi) has been approved in some countries for certain individuals with this variant. Please contact your physician to discuss whether any of these drug combinations is appropriate for you.

Variant G551D can be referred to as G551D, p.Gly551Asp, c.1652G>A, or ,

- The drug ivacaftor (Kalydeco) has been approved in some countries for individuals with this variant. Please contact your physician to discuss whether ivacaftor (Kalydeco) is appropriate for you.

Summary Information | Clinical Information | Functional Testing | Population Analysis | Additional Information

The combination of F508del and G551D is seen in 2,064 patients in our worldwide database. This genotype is expected to result in CF. Patients with this genotype are expected to be pancreatic insufficient.

The diagnosis of any individual patient with CF should be made based upon clinical parameters. The content of this website should not be used as a substitute for clinical judgement.

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Variant	Variant final determination	Date	Comment
F508del	CF-causing	04/10/2012	original call
G551D	CF-causing	04/10/2012	original call

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CFTR2 variant interpretations

- **CF-causing**
  - When in *trans* with CF-causing variant, expected to result in CF
- **Non CF-causing**
  - When in *trans* with CF-causing variant, not expected to result in CF
- **Varying clinical consequences (VCC)**
  - When in *trans* with CF-causing variant, may result in CF in some people but not in others
    - Those not meeting criteria for CF diagnosis may have CFTR-related disorder or mild CF symptoms
- **Unknown (Indeterminate)**
  - After evaluation, we cannot determine disease liability of variant or genotype
    - There may be multiple reasons for this!

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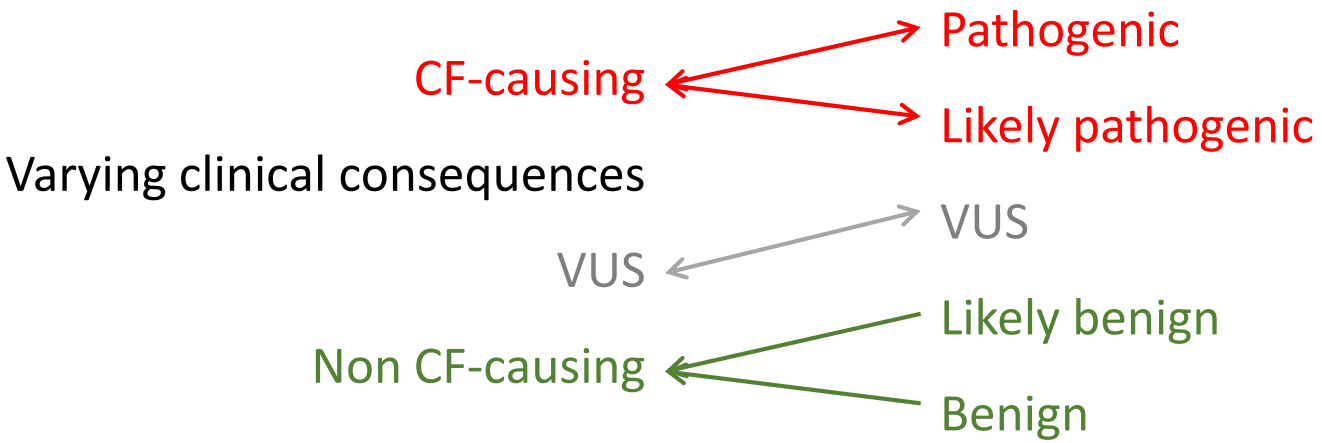
Correlation between CFTR2 and ACMG interpretations



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Correlation between CFTR2 and ACMG interpretations

Varying clinical consequences

- **No good equivalent within ACMG annotations**
- Not VUS, because significance *IS* known
- Usually reduced penetrance and/or variable expressivity

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When interpreting an ACMG P/LP classification…

- …it is important to define: ***pathogenic for what?***
- A non CF-causing variant should not cause CF, but it may be pathogenic for CBAVD
- A variant of varying clinical consequences may not always cause CF, but may be pathogenic for a CFTR-related disorder (ie pancreatitis)
- You MUST pay attention to the fine print in the lab report!

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Part 2: Treatment

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https://www.nm.org/healthbeat/patient-stories/what-does-my-doctor-do

Clinical terms to know

https://cff.org

- **Sweat chloride**
  - Concentration of chloride in a person's sweat
    - Normal: <30 mmol/L
    - Intermediate / grey zone: 30-59 mmol/L
    - CF diagnostic: ≥60 mmol/L
      - Average for F508del homozygote / classic CF: ~102 mmol/L

- **FEV1% predicted**
  - Forced expiratory volume in 1 second
  - Reported as a % of the predicted FEV1 without CF of the same age, height, and sex
    - The most common way to track a person's lung function decline over time
    - Normal is usually >85%, transplant often considered <30%
  - Usually the 'primary outcome measure' in clinical trials evaluating CF treatments

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Modulator terms to know

- **CFTR modulator**
  - Molecular therapy that acts to improve production, intracellular processing, and/or function of the defective CFTR protein
  - Treats 'underlying cause' of CF rather than symptoms

- **Potentiator**
  - A drug that helps the 'gate' of CFTR open longer and more effectively so that chloride transport is improved
    - Requires that CFTR be normally folded and located in the cell membrane
    - ivacaftor

- **Corrector**
  - A drug that aids in the folding and stabilization of the CFTR protein so that it can more effectively be trafficked to its destination in the cell membrane
    - Lumacaftor, tezacaftor, elexacaftor

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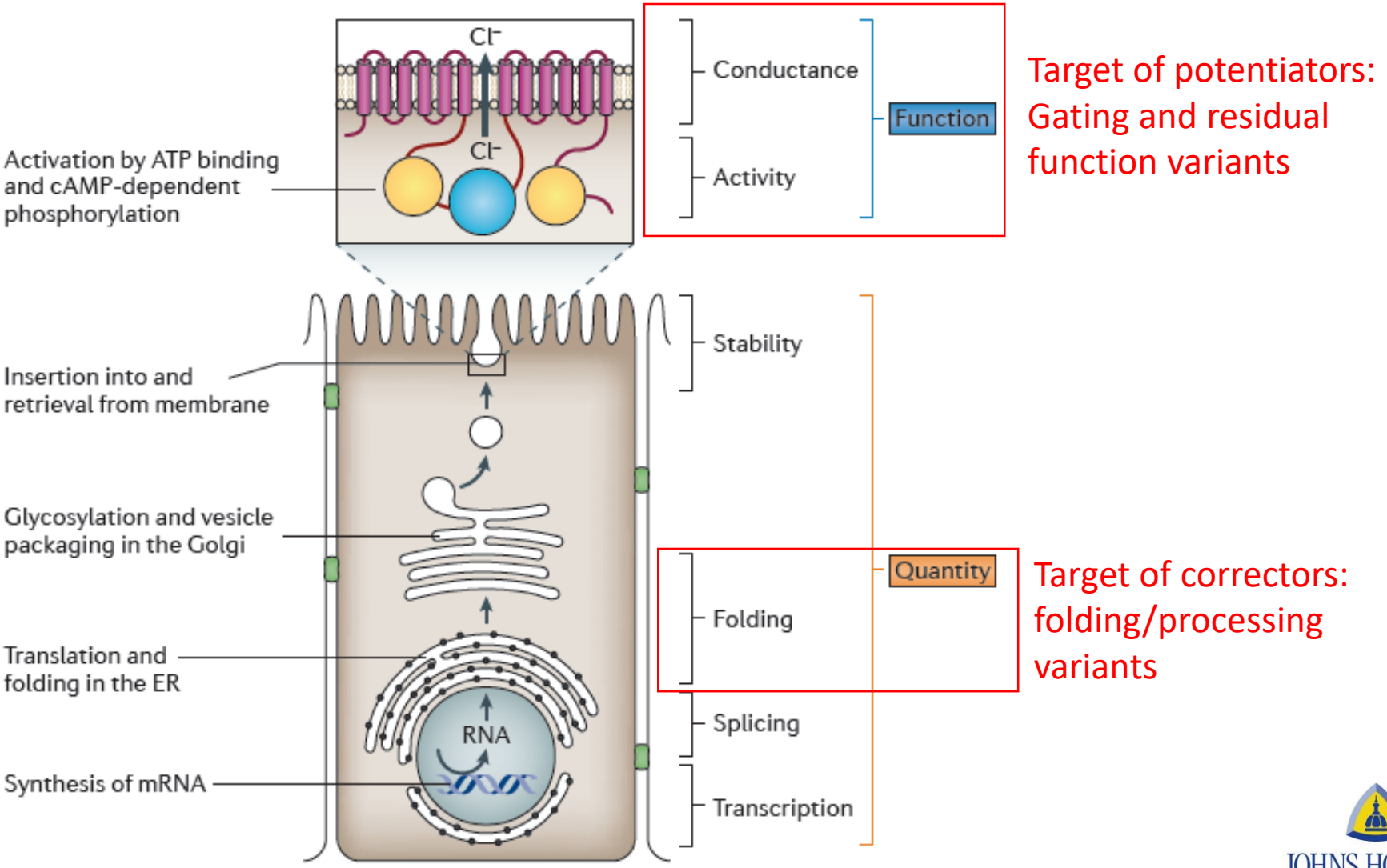
The stages to get to functional CFTR



Target of potentiators: Gating and residual function variants

Target of correctors: folding/processing variants

Cutting GR, Nat Reviews Genet, 2015

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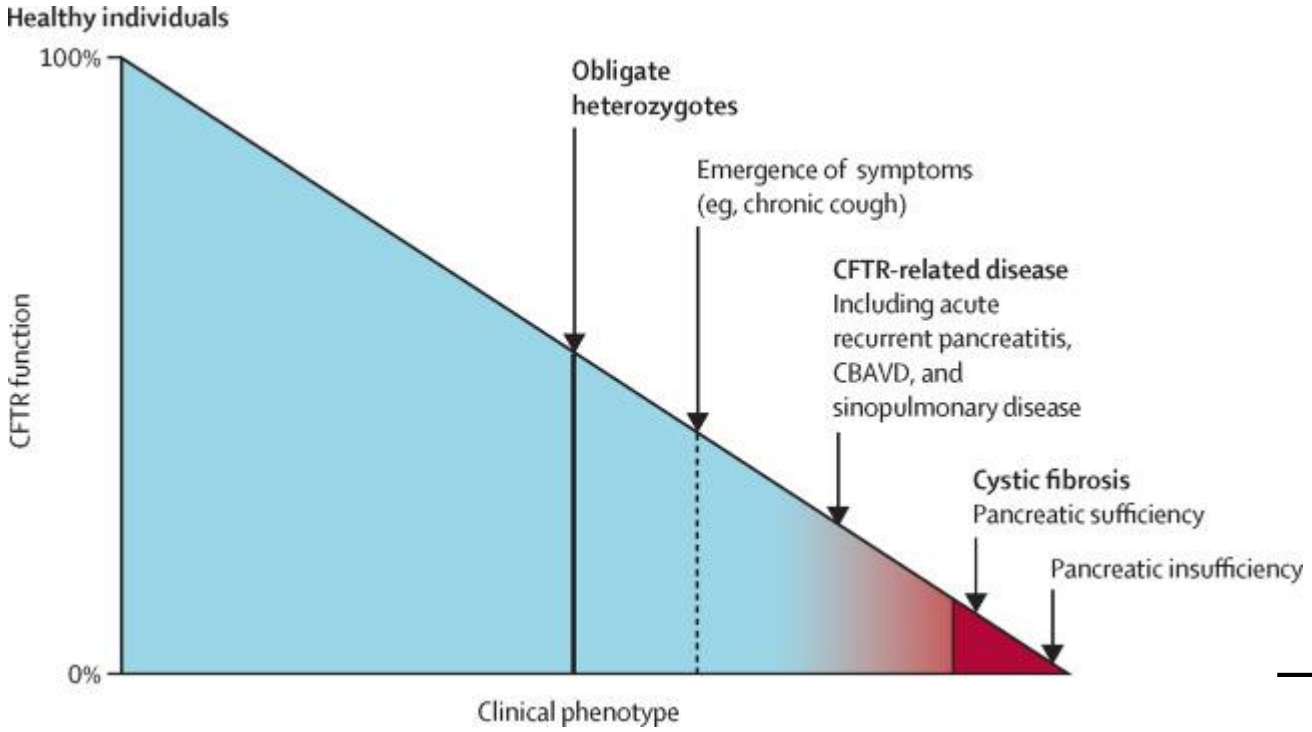
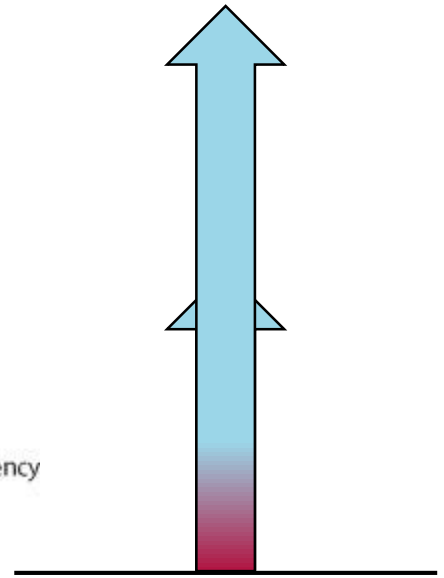
The goal of CFTR modulators

Restore CFTR function





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Modulator logistics

- Oral medications taken daily (pills)
- Currently prescribed *in addition* to other CF therapies
  - Clinical trials are ongoing to evaluate the stoppage of some regular treatments
- Medications are generally well-tolerated, but side effects can occur
- We are going on ~10 years of data for ivacaftor; starting to have opportunity to evaluate long-term use

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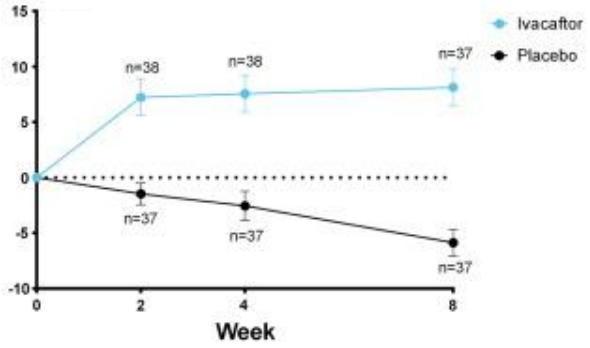
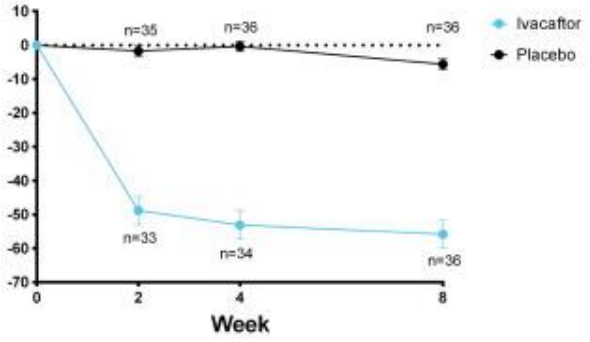
Modulator outcomes

- In general, modulators have the following effects:
  - **Sustained higher FEV1**
    - Reduced rate of lung function decline
  - **Sustained lower sweat chloride**
    - May drop into the normal range





Exacerbation frequency

Hospital admissions

IV use frequency

Breathlessness, coughing

(potential) lower rate of CF-related diabetes

BMI

Quality of life (better sleep!)

(predicted) survival

Exercise tolerance

Mental health

De Boeck K, et al., *JCF*, 2014
Efficacy and safety of ivacaftor in patients with CF and a non-G551D gating mutation

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CFTR Modulators: cost and eligibility

Brand name	Generic	Type	Cost per year	Genotype target
	**Ivacaftor**	**Potentiator**	**$311k**	**G551D, other gating and residual function variants**
	Ivacaftor + lumacaftor	Potentiator + corrector	$272k	F508del homozygotes
	Ivacaftor + tezacaftor	Potentiator + corrector	$292k	F508del homozygotes, residual function variants
	**Ivacaftor + tezacaftor + elexacaftor**	**Potentiator + corrector + corrector**	**$311k**	**F508del homozygotes and heterozygotes (~90% of CF population)**

*label expansion in late 2020 now makes 183 total CFTR variants eligible for treatment; see https://www.vertextreatments.com/homepage

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CFTR Modulators: cost and eligibility

Brand name	Generic	Type	Cost per year	Genotype target
kalydeco (ivacaftor) tablets 150 mg oral granules 25•50•75 mg	**Ivacaftor**	**Potentiator**	**$311k**	**G551D, other gating and residual function variants***
ORKAMBI (lumacaftor/ivacaftor)	**Ivacaftor + lumacaftor**	**Potentiator + corrector**	**$272k**	**F508del homozygotes**
symdeko (tezacaftor/ivacaftor and ivacaftor) 100/150 mg and 150 mg tablets 50/75 mg and 75 mg tablets	**Ivacaftor + tezacaftor**	**Potentiator + corrector**	**$292k**	**F508del homozygotes, residual function variants***
trikafta (elexacaftor/tezacaftor/ivacaftor and ivacaftor) 100 mg/50 mg/75 mg and 150 mg tablets	**Ivacaftor + tezacaftor + elexacaftor**	**Potentiator + corrector + corrector**	**$311k**	**F508del homozygotes and heterozygotes* (~90% of CF population)**

‘Highly effective’ modulators

*label expansion in late 2020 now makes 183 total CFTR variants eligible for treatment; see https://www.vertextreatments.com/homepage

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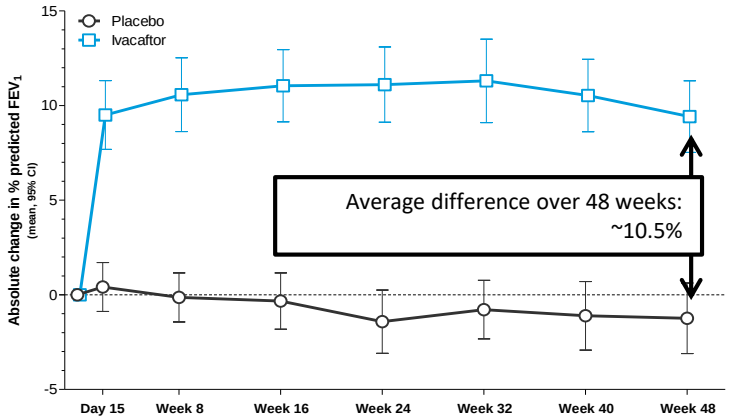
Ivacaftor

- Genotype: at least one copy of:
  - ~4-7% of CF population
- Age: 4 months and older
- Expected outcomes:
  - +11% FEV_1, -55 mmol/L



Ramsey, et al., NEJM, 2011

Gating Mutations

G178R	G1244E	S549R
G551D	G1349D	S1251N
G551S	S549N	S1255P

Residual Function Mutations

A455E	E193K	R117C
A1067T	F1052V	R347H
D110E	F1074L	R352Q
D110H	G1069R	R1070Q
D579G	K1060T	R1070W
D1152H	L206W	S945L
D1270N	P67L	S977F
E56K	R74W	

Splice Mutations

711+3A→G	3272-26A→G	E831X
2789+5G→A	3849+10kbC→T	

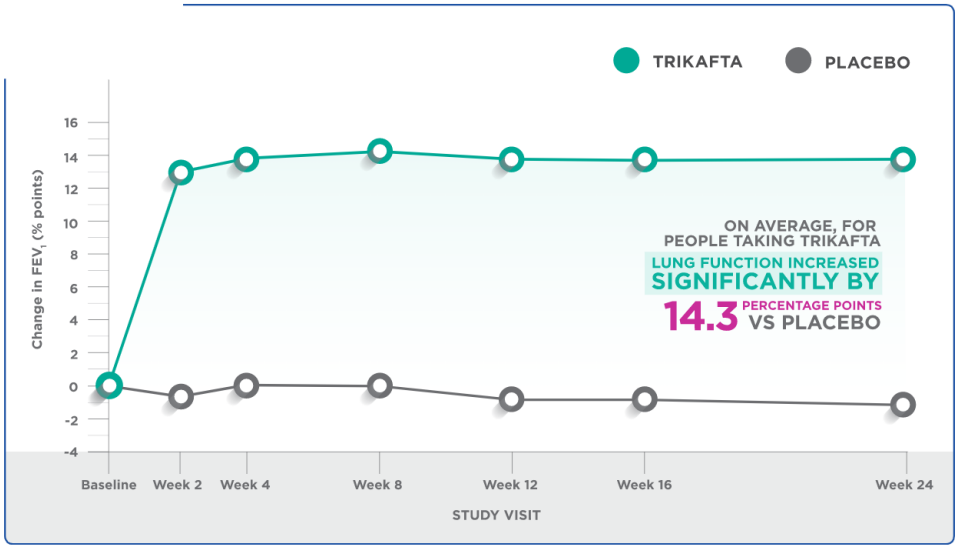
Conduction Mutation

R117H

ETI

(elexacaftor + tezacaftor + ivacaftor)

- Genotype: at least one copy of F508del or 170+ other variants
  - ~90% of CF population
- Age: 6 and older
- Expected outcome: +14% FEV_1, -41.8 mmol/L
- Side effects:
  - Liver abnormalities (severe in some)
  - Headache
  - Emotional distress / mental health issues (severe in some)



http://trikafta.com

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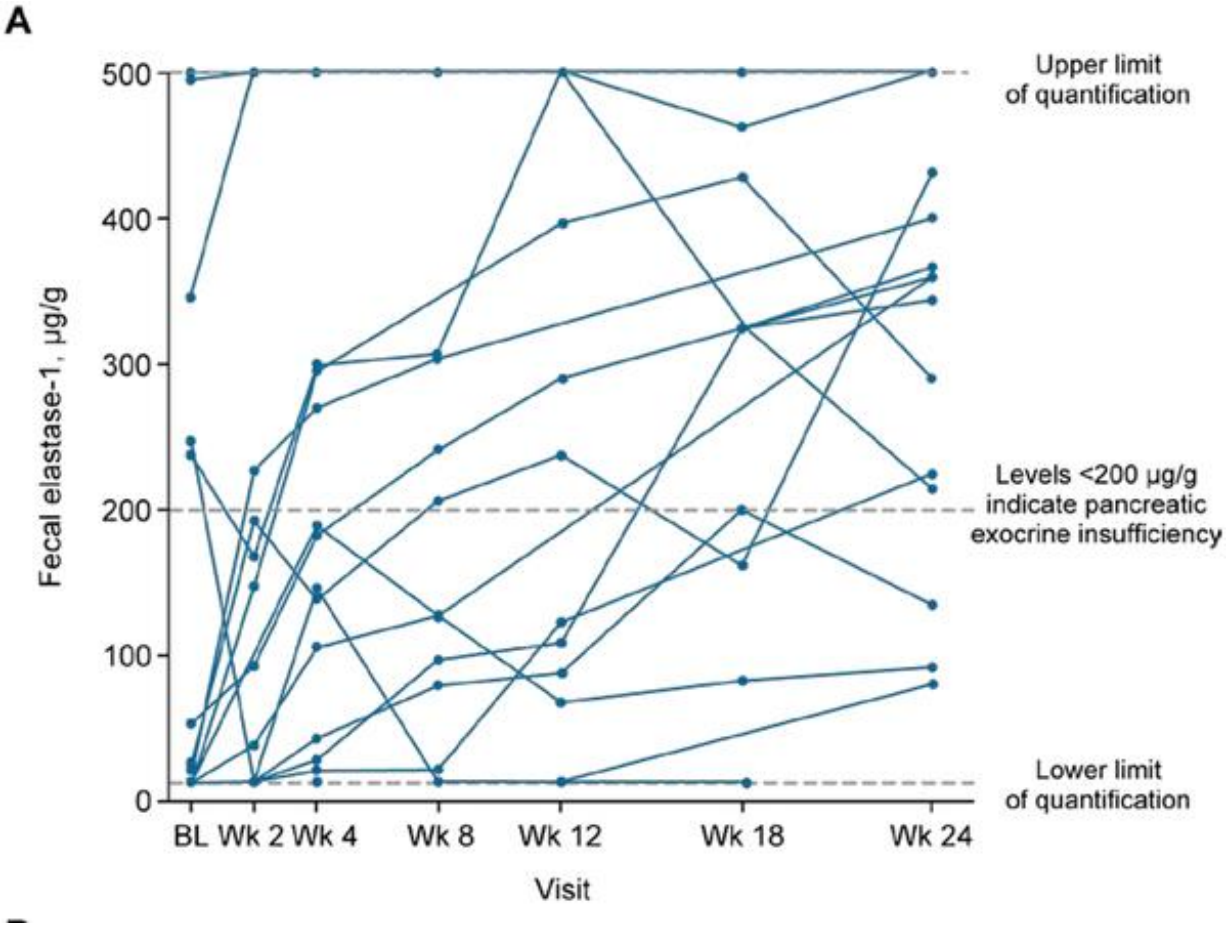
A pleasantly surprising outcome



Use of ivacaftor in children ages 12 months to <24 months demonstrated increase in fecal elastase levels

Rosenfeld, et al, *Lancet* 2018

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Real-world experience

- Many patients have outcomes similar to those seen in clinical trials
  - May be slight decrease in effectiveness with more heterogeneous population on drug

- Some discontinuation due to adverse events:
  - Hypertension (Sergeev, et al., Can J Respir Crit Care Sleep Med, 2020)
  - GI pain or symptoms (Burgel, et al., AJRCCM, 2020)
  - Pulmonary exacerbation (many studies)
  - Mental health, neurocognitive, neuropsychiatric events (Dagenais, et al., J Clin Med, 2021)

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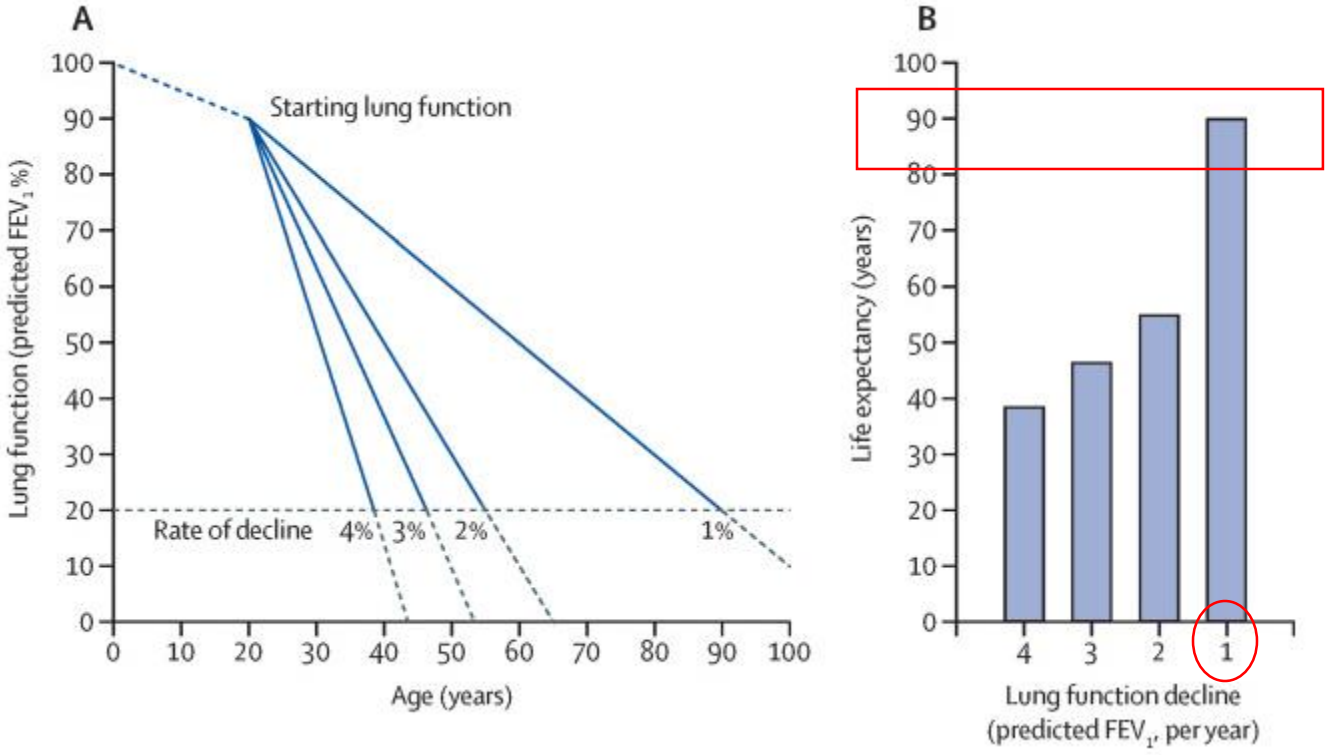
How does this change long-term outlook?



Rowe SM, Lancet Respir Med, 2017

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How does this change long-term outlook?

There is so much promise out there. This promise exists not just for me, but for thousands of us. For adults like me who were already blessed with the gift of reaching mid-life, this means that now we might have to think about heretofore foreign concepts like *menopause* and *retirement plans*.

- Elaine K. Malik, adult with CF (from the CF Community Blog)

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Modulator use in pregnancy may affect newborn screening results

Journal of Cystic Fibrosis 20 (2021) 835–836

Contents lists available at ScienceDirect

Journal of Cystic Fibrosis

journal homepage: www.elsevier.com/locate/jcf

Case report

Normal pancreatic function and false-negative CF newborn screen in a child born to a mother taking *CFTR* modulator therapy during pregnancy

Christopher N. Fortner[a,*], Julie M. Seguin[a], Denise M. Kay[b]

[a] *SUNY Upstate Medical University, Syracuse NY*
[b] *Wadsworth Center, New York State Department of Health, Albany NY*

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Modulator use in pregnancy may affect newborn screening results

- CF-affected mother with modulator-eligible genotype started ETI soon after its approval
  - Became pregnant within 6 weeks, after previously being unable to conceive prior to ETI initiation
  - Husband known to carry F508del

- 20 week U/S – concern for possible echogenic bowel
  - Repeat U/S at 32 weeks – normal

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Modulator use in pregnancy may affect newborn screening results

- Baby underwent routine NBS in New York State
  - Normal IRT level
- Mother's CF center requested CFTR genotyping on DOL 3
  - F508del in homozygosity = CF-affected
- Infant evaluation:
  - >90%th percentile for length and weight
  - Normal fecal elastase (>500 µg/g)
  - Sweat chloride at 5 weeks: 60 and 67 mmol/L

	IRT	Sweat chloride	Fecal elastase
Infant value	37 ng/mL	60 mmol/L 67 mmol/L	>500 µg/g
Median (range) for pancreatic insufficient CF	140-160 ng/mL (60 to >300 ng/mL)	~100 mmol/L	10 µg/g*

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*Cade, et al., 2000, *Pediatr Pulmonol*; sample not limited to newborns

The next dilemma

- The CF-affected baby is not eligible for CFTR modulator treatment based on age
  - LUM/IVA could be started at age 2
  - ETI could be started at age 6

- At the time of publication, baby was breastfed
  - CFTR modulators do appear in breastmilk, albeit at low levels

- Is there any way to consider bridge therapy?
  - Might this save her pancreas?

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The next-next dilemma/question

- What about prophylactic treatment with modulators during fetal development even if Mom is not CF-affected?
- Would bridge therapy be available?
- Would a prenatal diagnosis be required?
- At what stage in pregnancy is modulator treatment helpful for the fetus?

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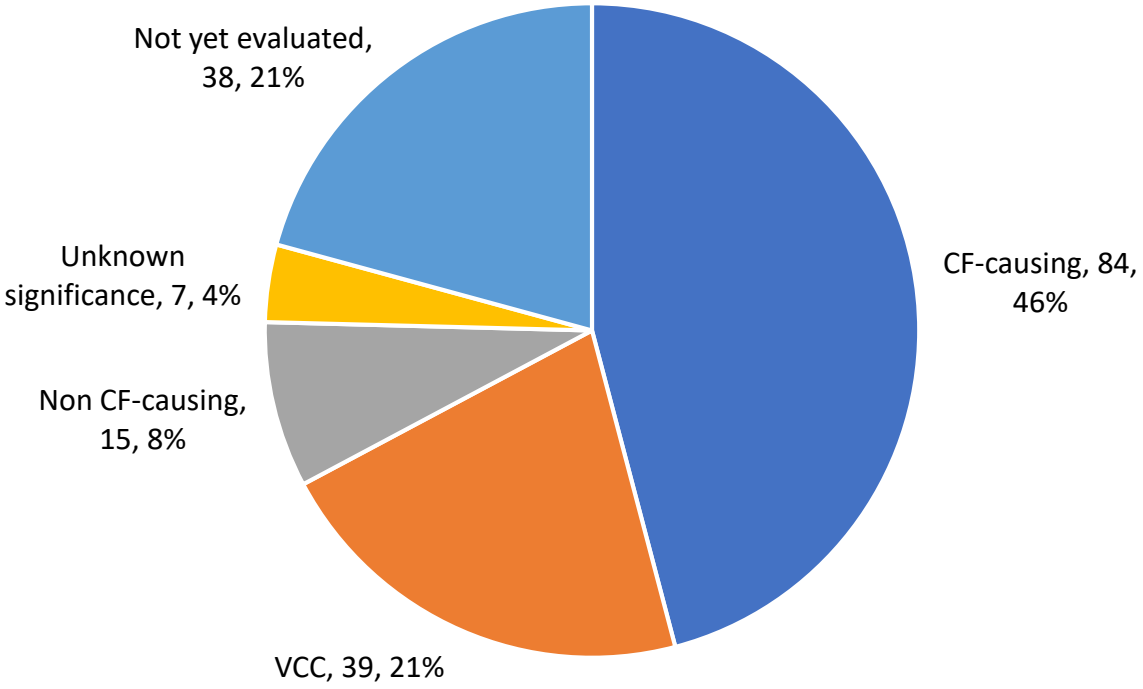
A word of caution about modulators

- Modulators are approved to treat 183 unique CFTR variants…

  …but not all of those variants are known to cause CF



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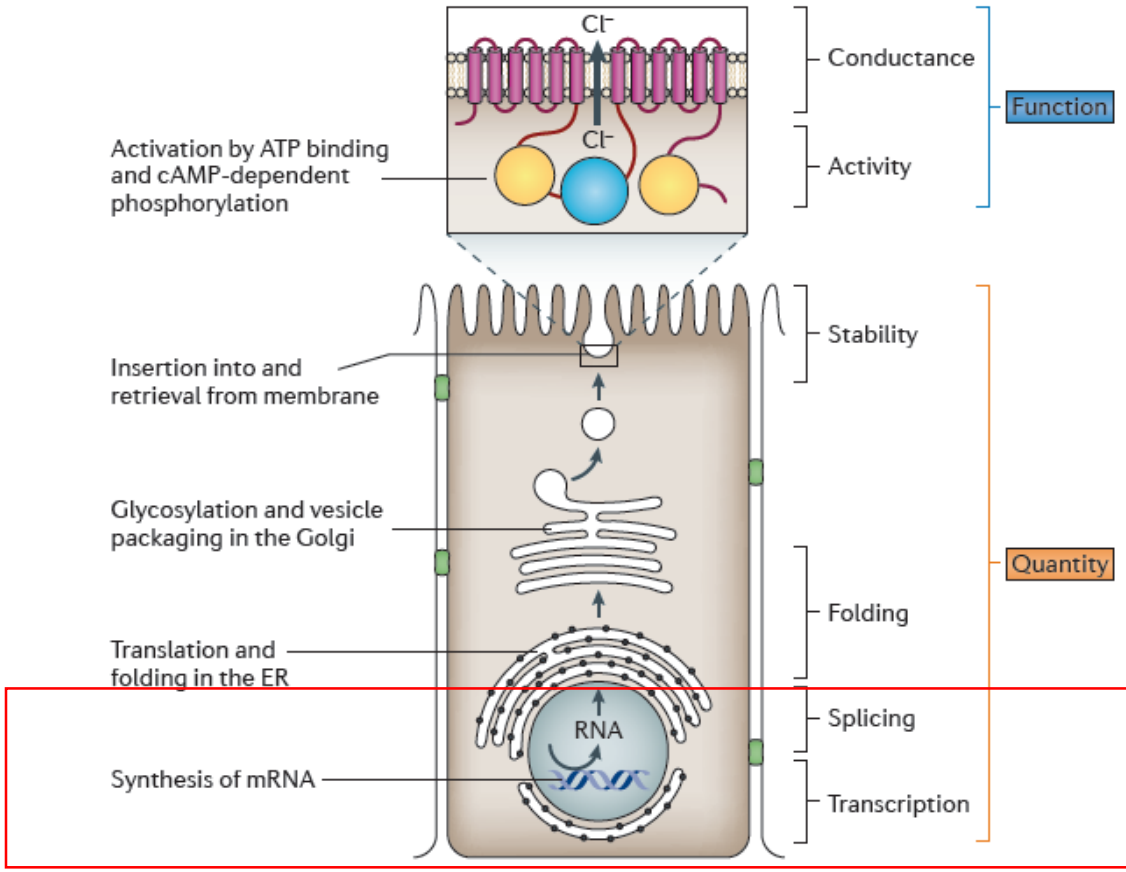
What can CFTR modulators NOT treat?

- Genotypes/variants resulting in no protein



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What about patients ineligible for modulators?

- Ineligible due to un-treatable genotype:
  - Variants that don't make protein (nonsense, frameshift, exon del/dup, canonical splice)
  - A variety of other therapies are under development:
    - Readthrough agents
    - NMD suppressors
    - RNA/DNA editing
    - Gene replacement

- Ineligible due to rare genotype:
  - Consider n=1 studies, ex vivo studies, or trial of modulators
  - *This population is more likely to be non-White*

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Take-home points

- Interpretation and understanding of CFTR variants helps with risk assessment, anticipatory guidance, and identification of possible treatments

- CFTR modulators treat the underlying cause of CF, and are likely to significantly change outcomes in the future
  - Better lung function = significantly longer lifespan
  - Better quality of life

- >90% of the CF population has an available modulator by genotype
  - Age restrictions, but these may lower over time

- *Therefore, counseling for a CF carrier couple or newly-diagnosed family must be tailored to the specific expected genotype*

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What are we learning?

- We are reminded of all the ways that non-functional CFTR can affect the body
  - By seeing what improves when we fix it!
- We may need to rethink our approach to nutritional advice
- We need more focus on aging with CF and planning for previously-unthinkable milestones
- Correction of a molecular defect resulting in systemic improvement is possible

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Thank you!

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