Cystic Fibrosis
Until it stands for Cure Found
Disclosure

- I do not receive funds for promoting the use of Trikafta but my bias is strongly in favor of this medication. You’ll see why, just wait and see....
A little bit about myself
Cystic Fibrosis in a nutshell

- Cystic fibrosis is a progressive, genetic disease that affects the lungs, pancreas, and other organs.
- Mutations in the cystic fibrosis transmembrane regulator (CFTR) gene.
  - CFTR protein becomes dysfunctional
- Lungs
  - Mucus clogs the airways, traps germs
  - Increased bacteria, leading to infections
  - Inflammation
  - Respiratory failure/other complications
- Pancreas
  - Buildup of mucus prevents the release of digestive enzymes
  - Lowers absorption of food and key nutrients, resulting in malnutrition and poor growth
- Liver
  - Thick mucus can block the bile duct, causing liver disease
Defective Gene

- Patients with an F508del-CFTR mutation have decreased CFTR activity at the cell surface.

\(^2\)
Genetics of CF

- People with CF have inherited two copies of the defective CF gene.
  - One copy from each parent
  - Both parents must have at least one copy of the defective gene
- 25 percent (1 in 4) the child will have CF
- 50 percent (1 in 2) the child will be a carrier but will not have CF
- 25 percent (1 in 4) the child will not be a carrier and will not have CF
- There more than 2,000 known mutations of the disease
  - 5 different classes
- The most common CFTR mutation is F508del
  - 85.4 percent of individuals have at least one copy of this variant
Newborn screening for CF

- 2010: Universal newborn screening for cystic fibrosis is instituted in all 50 states
  - Tests for 54 other disorders (genetic, endocrine, metabolic)
- Every state begins with a blood test from the baby
  - Immunoreactive trypsinogen (IRT), chemical made by the pancreas
- IRT is normally found in small levels in the body
  - With CF, IRT levels tend to be high
- IRT-DNA testing
  - Vermont does this
- Positive newborn screen, means further testing is needed for confirmed diagnosis
  - Sweat test
    - >60 mmol/L = positive for CF
    - 30-59 mmol/L = Indeterminate-needs further investigation
    - <30 mmol/L = neg for CF (usually)
The sweat test measures the amount of chloride (a component of salt) in the sweat.

- Noninvasive test

In the first part of the test, a colorless, odorless chemical (pilocarpine) and a little electrical stimulation is applied to a small area of the arm or leg to encourage the sweat glands to produce sweat.

- The sweat is then collected in a plastic coil
History and Milestones

- 1938: Dorothy Andersen, MD, publishes the first characterization of a disease mysteriously taking the lives of children
- 1955: The Cystic Fibrosis Foundation is formed
- 1989: Scientists discover the defective CFTR gene and its protein product
- 1989: F508del was discovered
- 1993: FDA approves Pulmozyme
- 1997: The FDA approves TOBI
  - First aerosolized antibiotic for CF
2010: FDA approves a new inhaled antibiotic, aztreonam for inhalation solution (Cayston®), to treat CF lung infections

2012: Kalydeco (Ivacaftor) approved for people ages 6 and older
  - Class 3 mutation G551D and other gating mutations

2015: FDA approves the lumacaftor/ivacaftor (Orkambi®)
  - Ages 12 and older who have two copies of the most common CF mutation, F508del

2018: FDA approves tezacaftor/ivacaftor (Symdeko®)
  - Ages 12 and older who have two copies of the F508del mutation
  - Later, Symdeko is approved for 26 more mutations – regardless of their other mutation
Big, big big, big milestone!

- October 2019: FDA approves the triple-combination modulator elexacaftor/tezacaftor/ivacaftor (Trikafta)
  - Ages 12 and older who have at least one copy of the F508del mutation, regardless of their other mutation
- June 2021: FDA approved the use of Trikafta
  - Ages 6 through 11 who have at least one copy of the F508del mutation
- April 2023: FDA approved the use of Trikafta
  - Ages 2 through 5 years who have at least one copy of the F508del
CFTR Modulator Timeline

- **2012**: Kalydeco approved 6+ years
- **2014**: Kalydeco approved 9 more mutations
- **2015**: Orkambi F508del/F508del 12 yrs+
- **2016**: Orkambi F508del/F508del 6-11 yrs
- **2017**: Kalydeco for 31 more mutations
- **2018**: Kalydeco 2-5 yrs
- **2019**: Trikafta 1 copy F508del 12 yrs+
- **2021**: Kalydeco 4 mos+

- **2023**: Trikafta 1 copy F508del 2 yrs+
Trikafta, the miracle drug!

- Treatment approved for approximately **90%** of patients with cystic fibrosis, many of whom had no approved therapeutic options!
- Roughly 28,000 people in the United States

Amazing!!!
What is Trikafta?

- Trikafta is a combination drug that includes three different drugs: elexacaftor, tezacaftor, and ivacaftor
  - Trikafta belongs to a class of drugs called CFTR modulators
- Elexacaftor and tezacaftor are CFTR correctors, while ivacaftor is a potentiator, keeping the CFTR open
How it works

**MECHANISM OF ACTION**

Targeting *F508del-CFTR* brings more active CFTR proteins to the cell surface.

- Patients with an *F508del-CFTR* mutation have decreased CFTR activity at the cell surface.

- Binding to a different site than tezacaftor, elexacaftor has an additive effect in improving cellular processing and trafficking of *F508del-CFTR* proteins.
Clinical Benefits

6 yo and older

- Increase in BMI
- 63% decreased in pulmonary exacerbations (12 and older)
- 10.2-14.3 % increase in FEV1
- Sweat Chloride drop of an avg. of 41.2 mmol/L
  - (avg. start 102.3 mmol/L)

All values at the end of a 24 week trial
Clinical Benefits
2-5 years old

- Increase in BMI
- Sweat Chloride drop of an avg. of 57.9 mmol/L
  - avg. start of 100.7 mmol/L

All values at the end of a 24 week trial
Based on 2022 Registry data, the mean predicted survival age of people with CF who are born between 2018 and 2022 is 56.6 years. This is an 18-year increase from 2013! Now 60% of the CF population are people over 18.
Mortality
Hospital admissions

63% lower annualized rate of pulmonary exacerbations
Individuals Treated With IV Antibiotics for a Pulmonary Exacerbation, 2007–2022

Percentage of Individuals

Year

Birth to 11 Years 12 to 17 Years 18 Years and Older
Lung transplants

>60% Drop!
Who's eligible
Vermont CF Center: Lung Function

Percent Predicted FEV1

Mean Increase of FEV1 = 17%

Functional Lung Disease Improves
Vermont CF Center: Sweat Chloride

>60 mmol/L = CF
30-59 mmol/L = indeterminate
<30 mmol/L = not CF (usually)

Mean Decrease of Sweat Chloride = 64 mmol/L
Structural Lung Disease: Can It Get Better?

- Bronchiectasis: Bronchial Dilatation
  - Chronic inflammation/infection (damage by neutrophil elastase)
  - Radiographic definition: bronchial diameter larger than the adjacent vessel
  - Impaired clearance, prone to mucous plugging
- Usually progressive in CF

Signet ring sign
Pre-Trikafta

Post-Trikafta
It’s all about a normal life
Woman’s Fertility

Number of Pregnancies in Women 14 to 45 Years With CF, 2012–2022

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Can’t put a price on life

- Average cost of Trikafta is $290,000-$311,500 PER year, with an average MONTHLY cost of $24,000-$26,000

Yes, those are right and no I did not put too many zero’s.........
Bronchiectasis can improve, even resolve!

Improved quality of life

Earlier HEMT = Years of life saved

The natural history of CF has been altered

Life changing treatments are available
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Too Late For Many
Maverick
Kade
Arel

07/05/2017
7lbs 14oz
21in long
No one understands what I'm going through.

I'm fine.

Suffocation

Anxious

Loss

Guilt

Burdensome treatments

Debt

Doom

Internal Screaming

Depression

Withdrawal

Death

Suffocation

Loneliness

Grief

No more children

Overwhelming sadness

Anger

I'm fine

No Quality of life

Helpless

Resentment

Self doubt

Seeing my child die

Speechless

Child with special needs

Short life to live

Terrified

Isolation

Hospitalizations

Shock

Anxious

Germ

Confusion

Denial

Devastation

Medications

No normal childhood
- Met with pulmonary doctors
- Met with a genetic counselor
- Met with a case manager
- Met with a nurse
- Mutations F508del/F508del
- Pancreatic Elastase - <50.0, severe pancreatic insufficiency
  - Normal >200 ug Elastase/g stool
- Sweat test - 98 mEq/L
  - Normal is <30 mEq/L
September 2017
First hospital admission
April 2018
For funsies…
Modulators

July 2019
2 years old

May 2023
5 almost 6 years old
Sweat test after Trikafta
NO MORE ENZYMES

Before Trikafta

| Patient Value |  
| ug F/g stool | Value ≤50.0 |

Interpretation

<table>
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<th>Value</th>
<th>Note</th>
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<td>Severe exocrine pancreatic insufficiency*</td>
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After Trikafta

Pancreatic Elastase,F

Normal value: >200 (Normal) mcg/g

Value 258

Pancreatic Sufficient!
Nice shiny new vest!!
A few that have pulled at the heart strings

Mayven, started on Trikafta May 2023 at 4 years old. Sweat test at birth was 100, now its 38. (x2 F508del)

Aurora, started on Trikafta June 2023 at 2 years old. Sweat test at birth was 91, now its <10. She has also become pancreatic sufficient and no longer has to take enzymes. (x2 F508del)
References

- Cystic Fibrosis Foundation
- file:///2022-Patient-Registry-Annual-Data-Report.pdf
- https://biopharma.media/triakta-kaftrio-worlds-first-triple-therapy-for-cystic-fibrosis-2535/
- https://www.triakta.com/study-information
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- https://medlineplus.gov/genetics/gene/cftr/
- https://www.cff.org/research-clinical-trials/types-cftr-mutations
Peace is the result of retraining your mind to process life as it is, rather than as you think it should be.

Wayne W. Dyer