Don’t Sweat It: The Evolution of Nutrition in CF Care

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NO CONFLICTS OF INTEREST TO DISCLOSE

Objectives

- Understand CFTR protein dysfunction and how it causes cystic fibrosis
- Discuss the traditional nutrition therapies and recommendations for cystic fibrosis
- Review the trending nutrition related topics and new recommendations in the era of highly effective modulator therapies (HEMT) for cystic fibrosis

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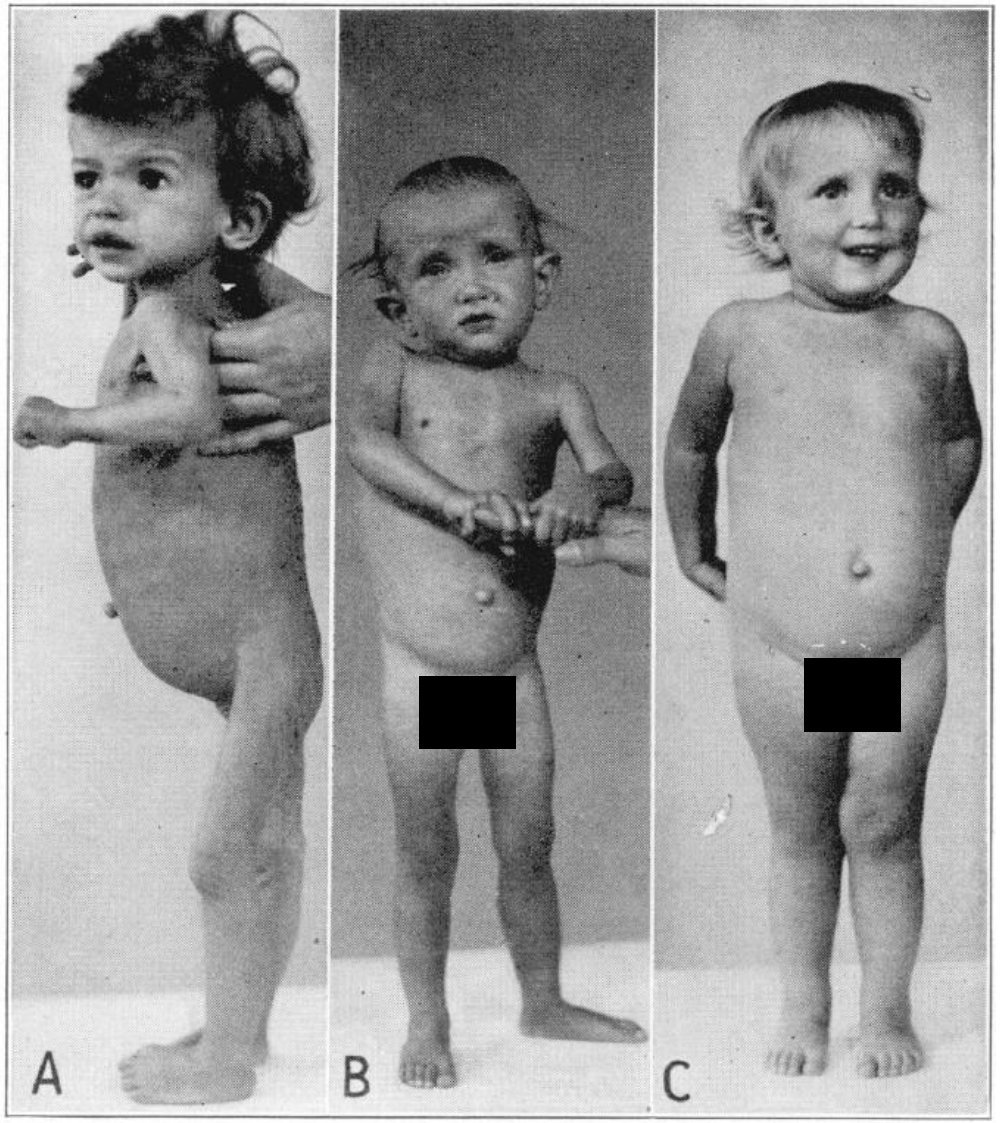
History of CF



- "Woe to the child who tastes salty from a kiss on the brow, for he is hexed and soon will die" – Medieval European folk saying ~1400 AD
- First described by Dr. Dorothy H. Anderson on May 5th, 1938
- Traditionally defined as the most common life-threatening inherited disorder of children in Caucasian populations
- Children usually died within their first year of life

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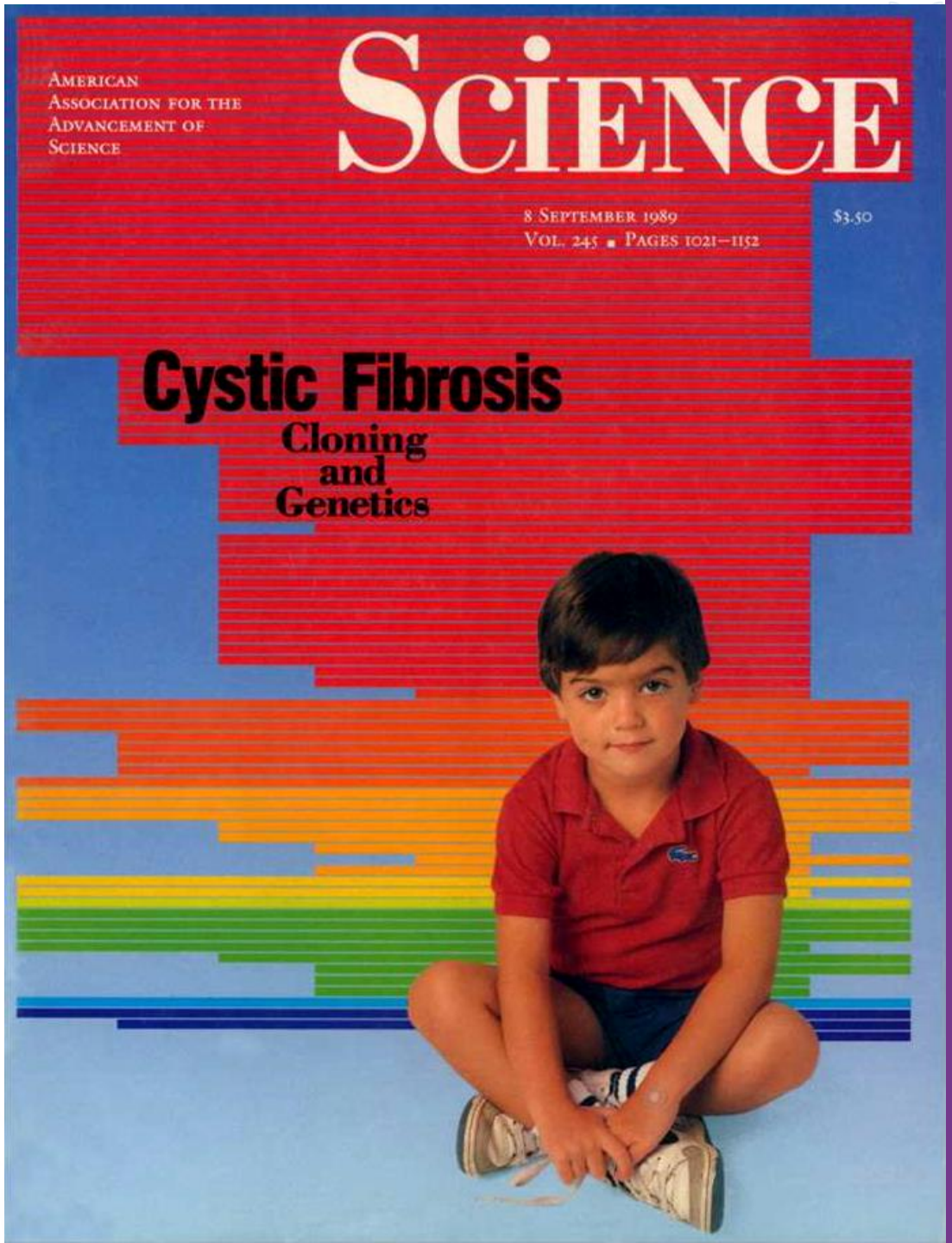
Discovery of the Gene

- Discovery of the gene published in 1989
- Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) protein
- Chloride ion channel in all exocrine cells
- Autosomal recessive inheritance
- Mutations may cause partial or total loss of function

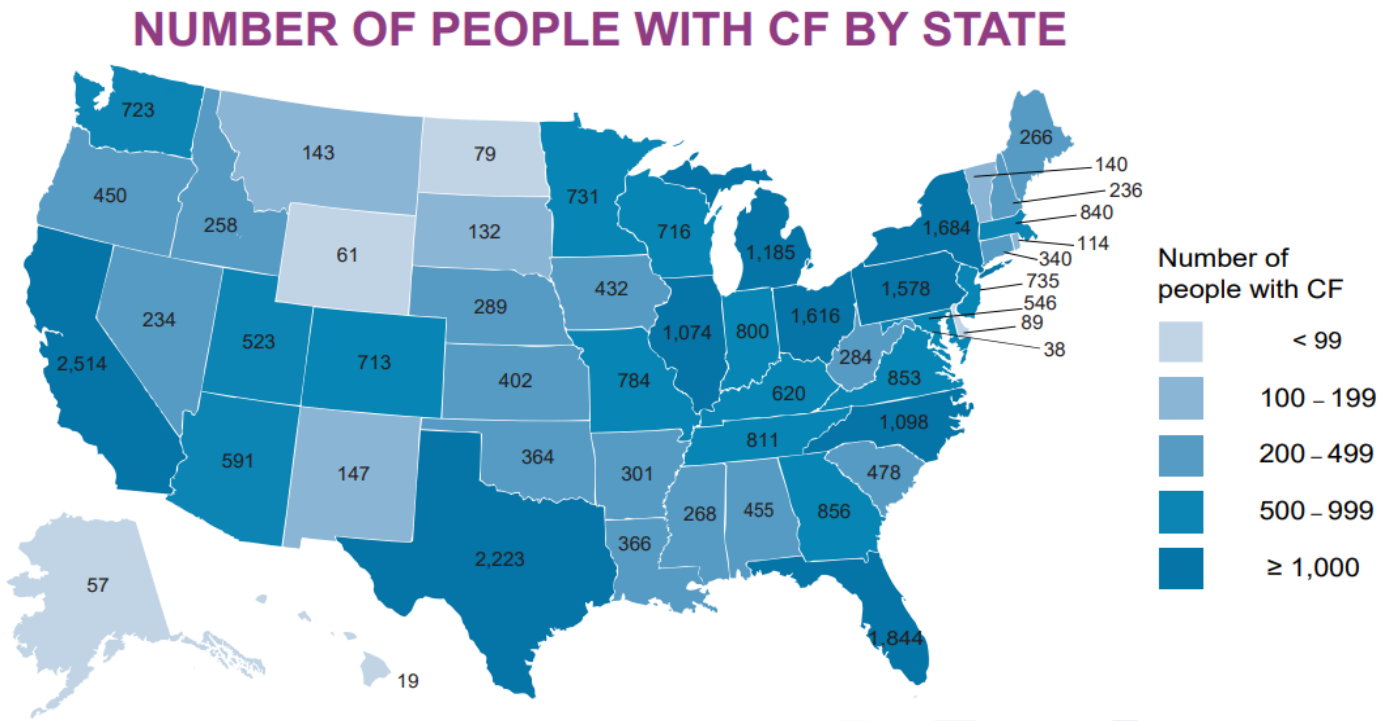


Incidence of CF

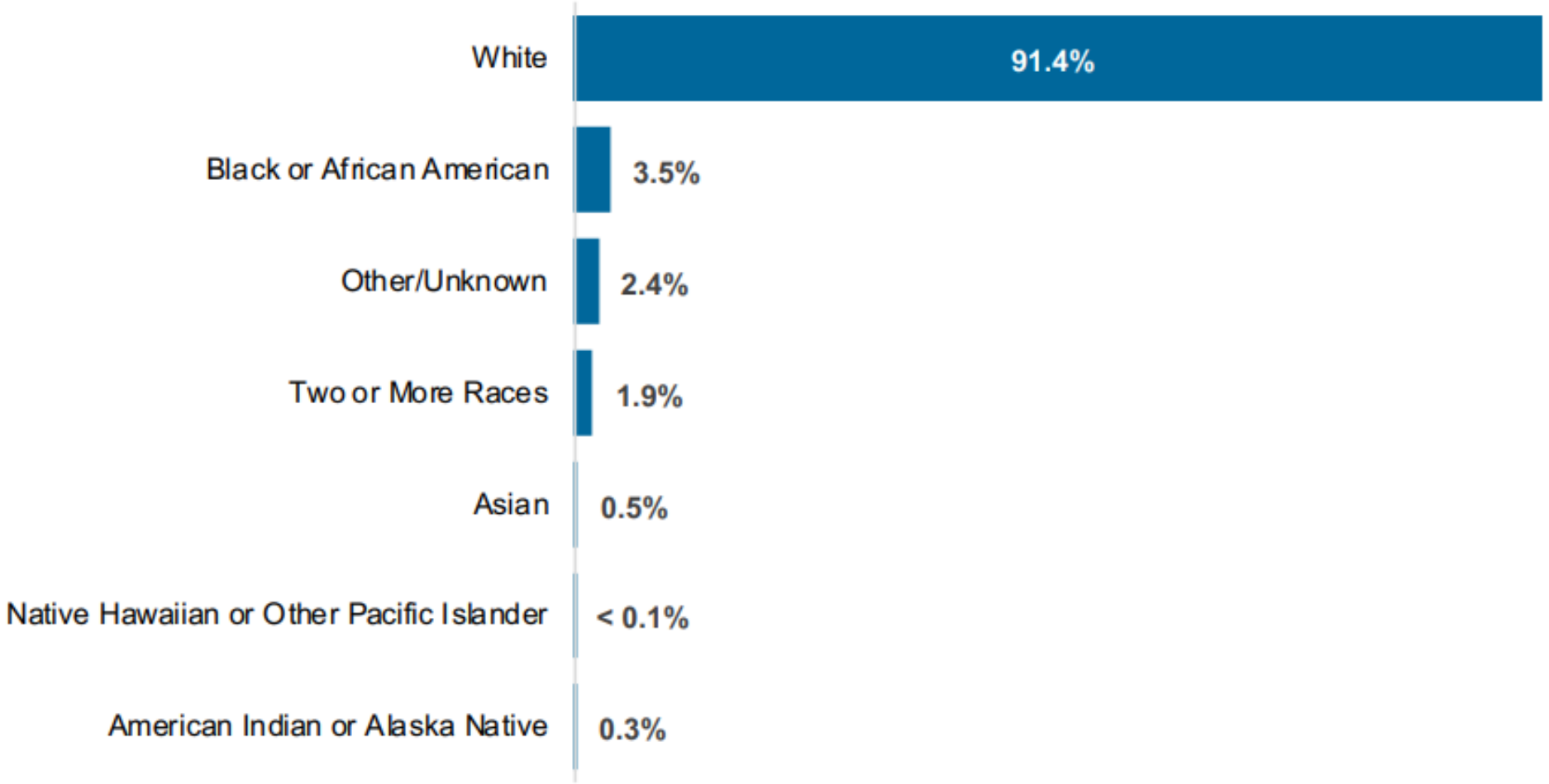
- 40,000 people with CF (PwCF) living in U.S.
- 105,000 PwCF worldwide

- Traditionally, has been estimated at 1/2500 live births in a populations of European descent

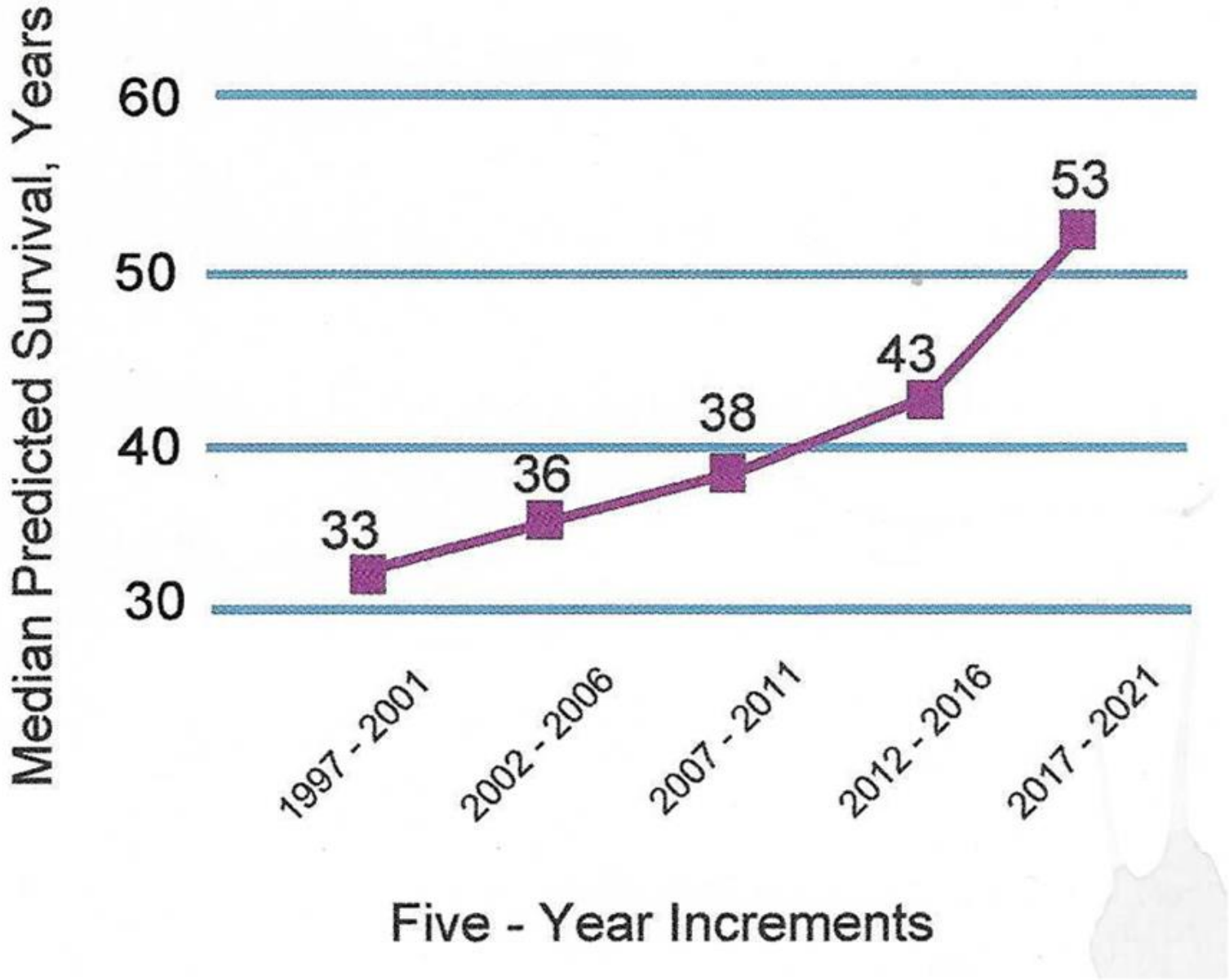
- More recent data suggests between 1/3000 and 1/6000



Race Distribution of the CF Population in 2021



Median Age of Survival



2021 Cystic Fibrosis Foundation Patient Registry Annual Data Report

Diagnosis

Diagnosing CF is a multi-step process:

- Newborn Screening
  - Immunoreactive trypsinogen level (IRT)
- Genetic testing
  - 2 CFTR mutations – positive
  - May or may not be disease causing
- Sweat test
- Fecal elastase test
- Clinical evaluation at a CF Foundation accredited CF care center

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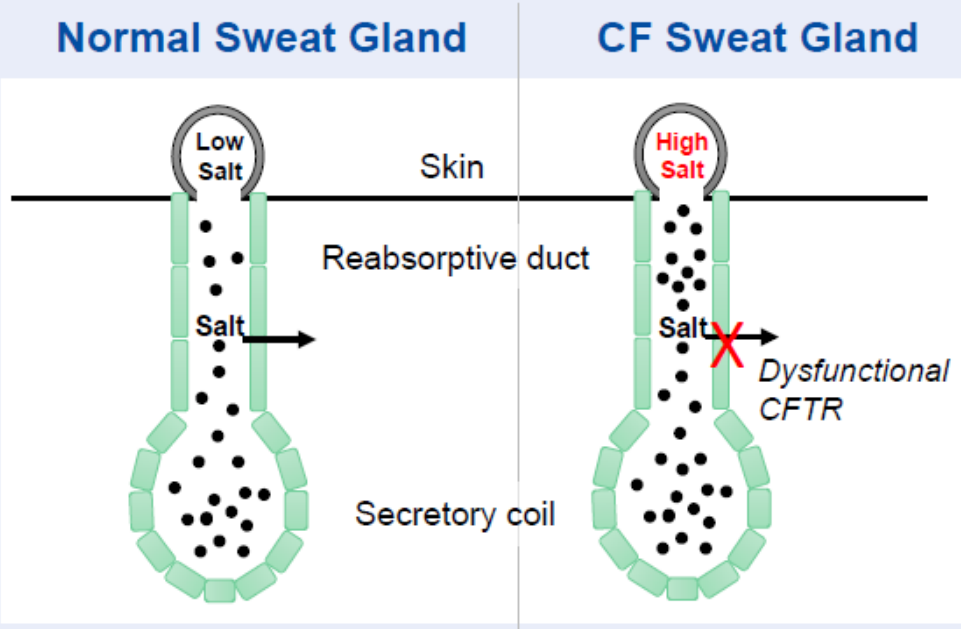
Sweat Test

Sweat Chloride Guidelines in the Diagnosis of CF[1]	
Sweat Chloride Level (mmol/L)	Relation to CF
<30	**CF unlikely**
30 to 59	**Warrants further diagnostic tests**
≥60	**Consistent with CF**

The sweat gland is a tube-shaped structure in the skin, and has a secretory coil and a reabsorptive duct[2]



Normal sweat contains water and salt (sodium chloride). As fluid passes through the reabsorptive duct, salt is absorbed back into the body. The remaining fluid is emitted onto the skin as sweat.

In CF, the CFTR channel is unable to reabsorb chloride back into the body, resulting in sweat with a high chloride concentration.

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Fecal Elastase Test

Fecal elastase test is a diagnostic test for exocrine pancreatic function. The elastase enzyme (EL1) remains intact during its intestinal transition and its concentration reflects the secretory capacity of the pancreas with 100% sensitivity.

Age: All ages	**Range: (mcg/g)**
Normal:	>200
Moderate to slight exocrine pancreatic insufficiency:	100 to 200
Severe exocrine pancreatic insufficiency:	<100

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Symptoms of CF

People with CF can have a variety of symptoms, including:

Very salty-tasting skin

Persistent coughing, at times with phlegm

Frequent lung infections including pneumonia or bronchitis

Wheezing or shortness of breath

Poor growth or weight gain despite a good appetite/intake

Frequent greasy, bulky stools or difficulty with bowel movements

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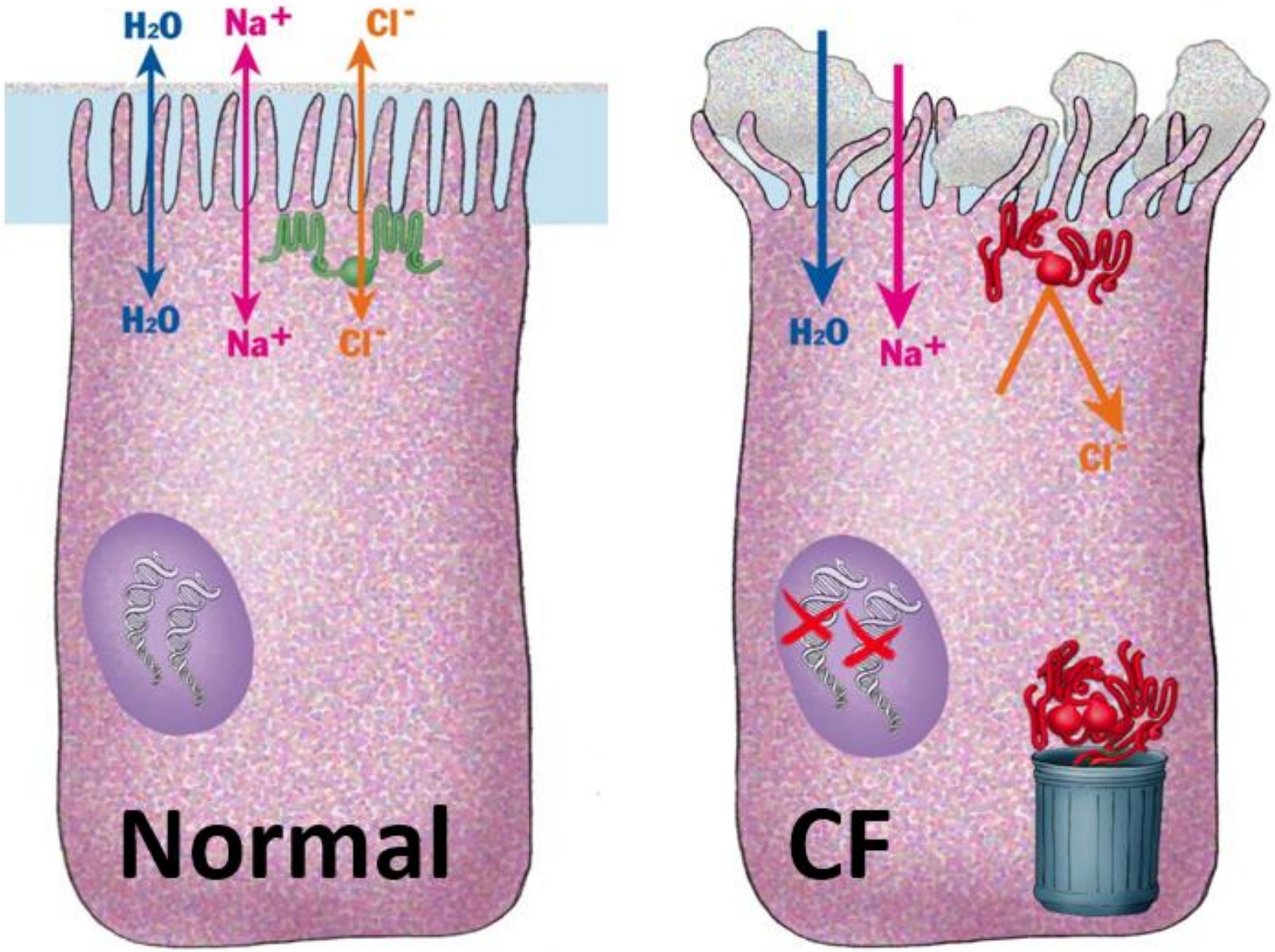
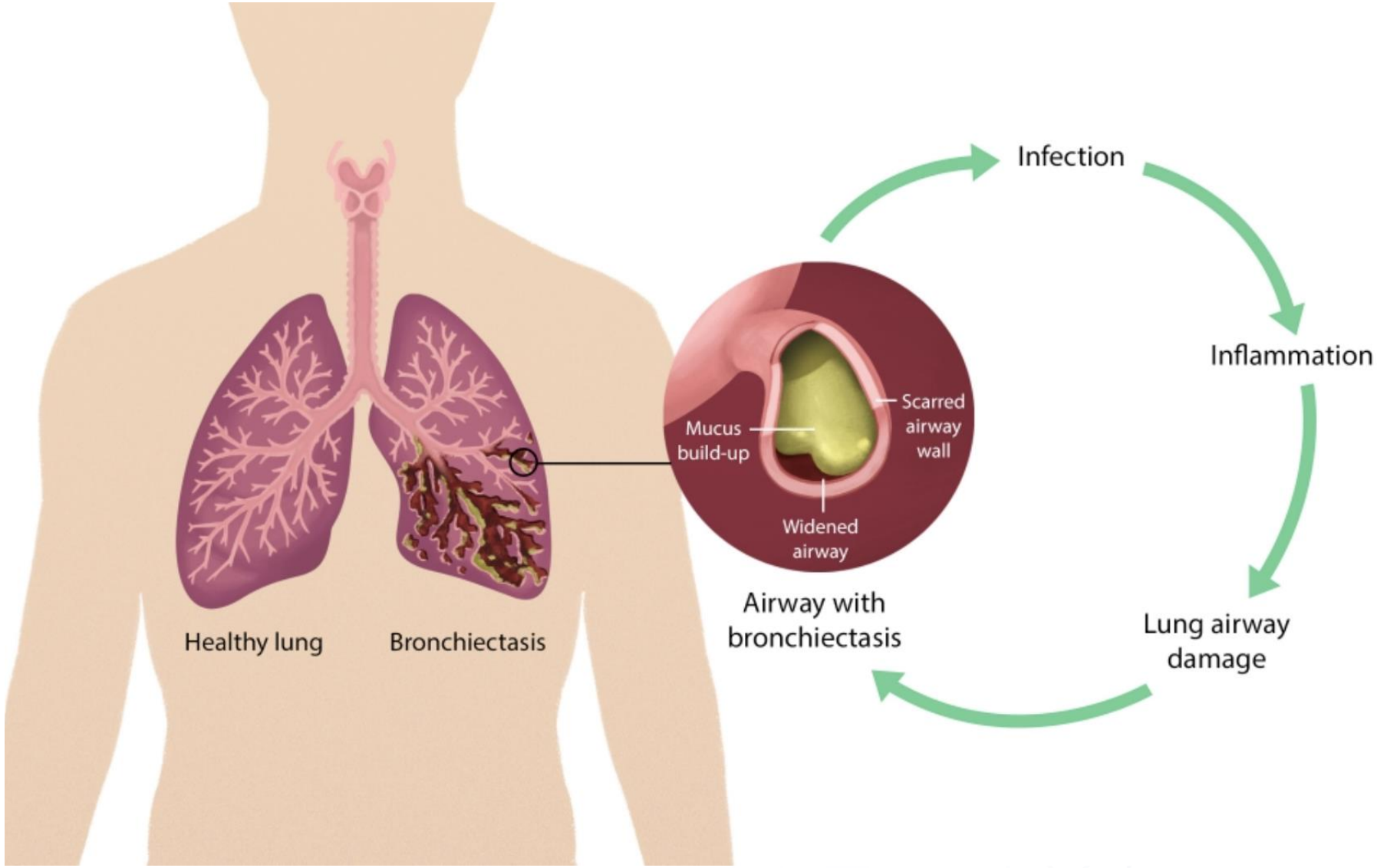
CFTR Protein

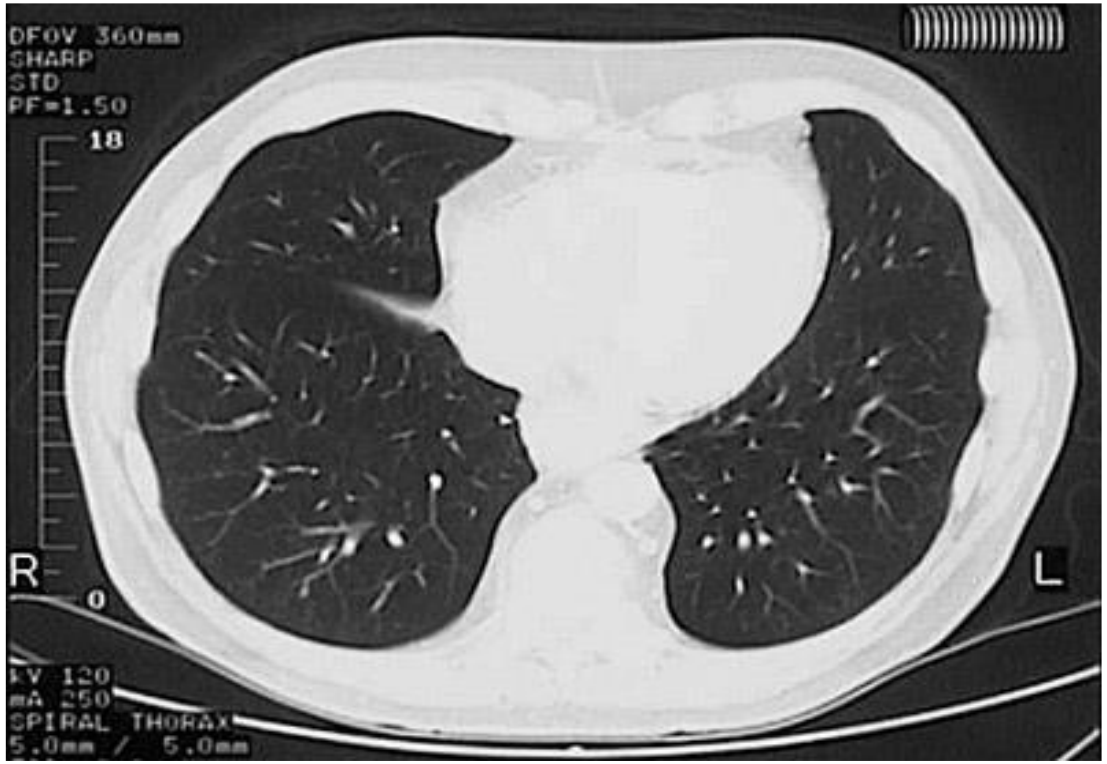


CF Lung Disease

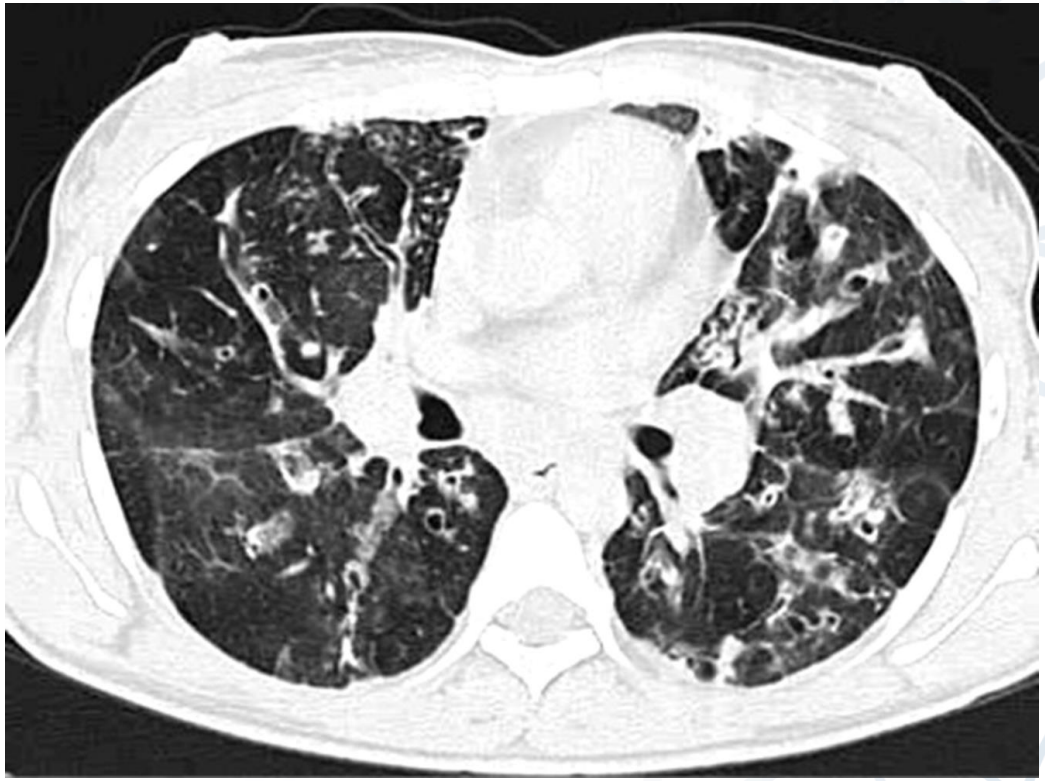


CF Lung Disease

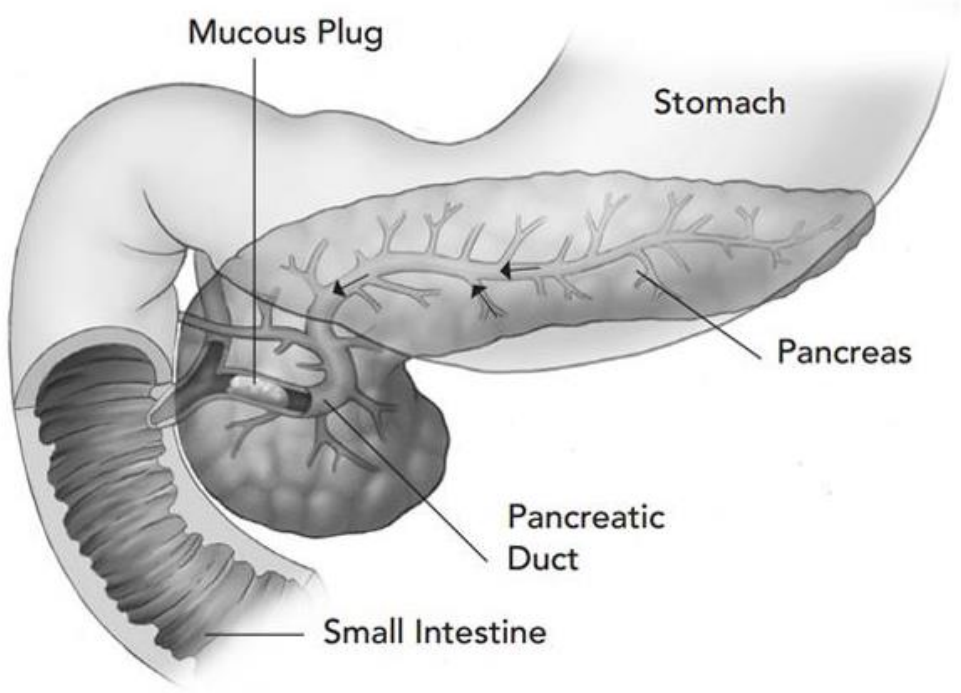
Normal Chest CT



CF Bronchiectasis



The CF Pancreas



Digestive enzymes from the pancreas are blocked and do not make it into the small intestine.

- 85-90% of PwCF have pancreatic insufficiency
- Thickened mucus blocks the pancreatic duct and prevents digestive enzymes from reaching the intestine
- Altered gut pH due to decreased secretion of bicarbonate

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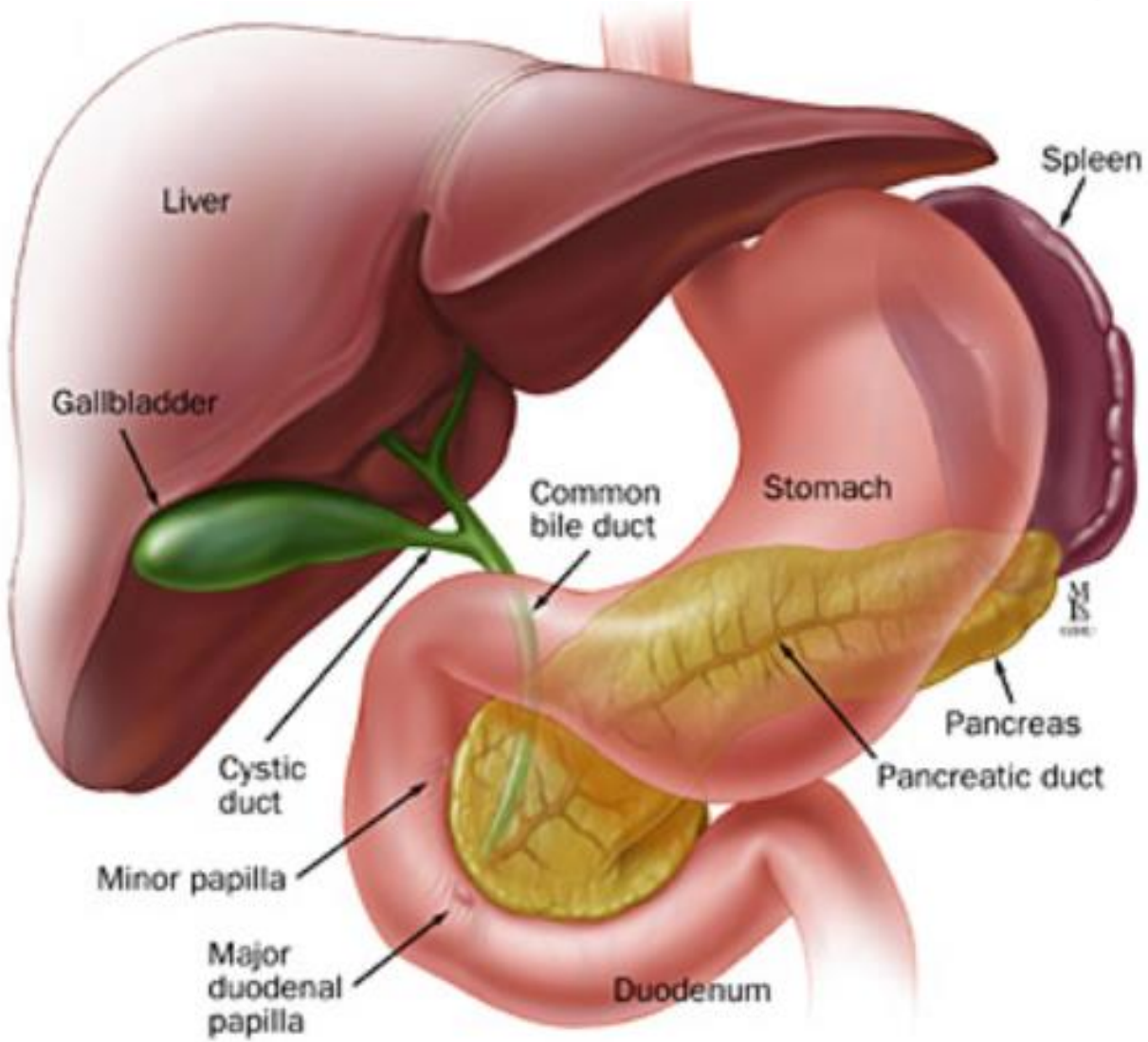
The CF Gut

Liver:

- Thickened biliary secretions cause cirrhosis
- CF related Liver Disease is present variably in 5%-15% of CF patients
- Severe cases may require a liver transplant

Intestinal tract:

- Thick secretions cause build up of stool leading to constipation and gut inflammation
- Distal Intestinal Obstruction Syndrome (DIOS) is a severe complication of CF constipation



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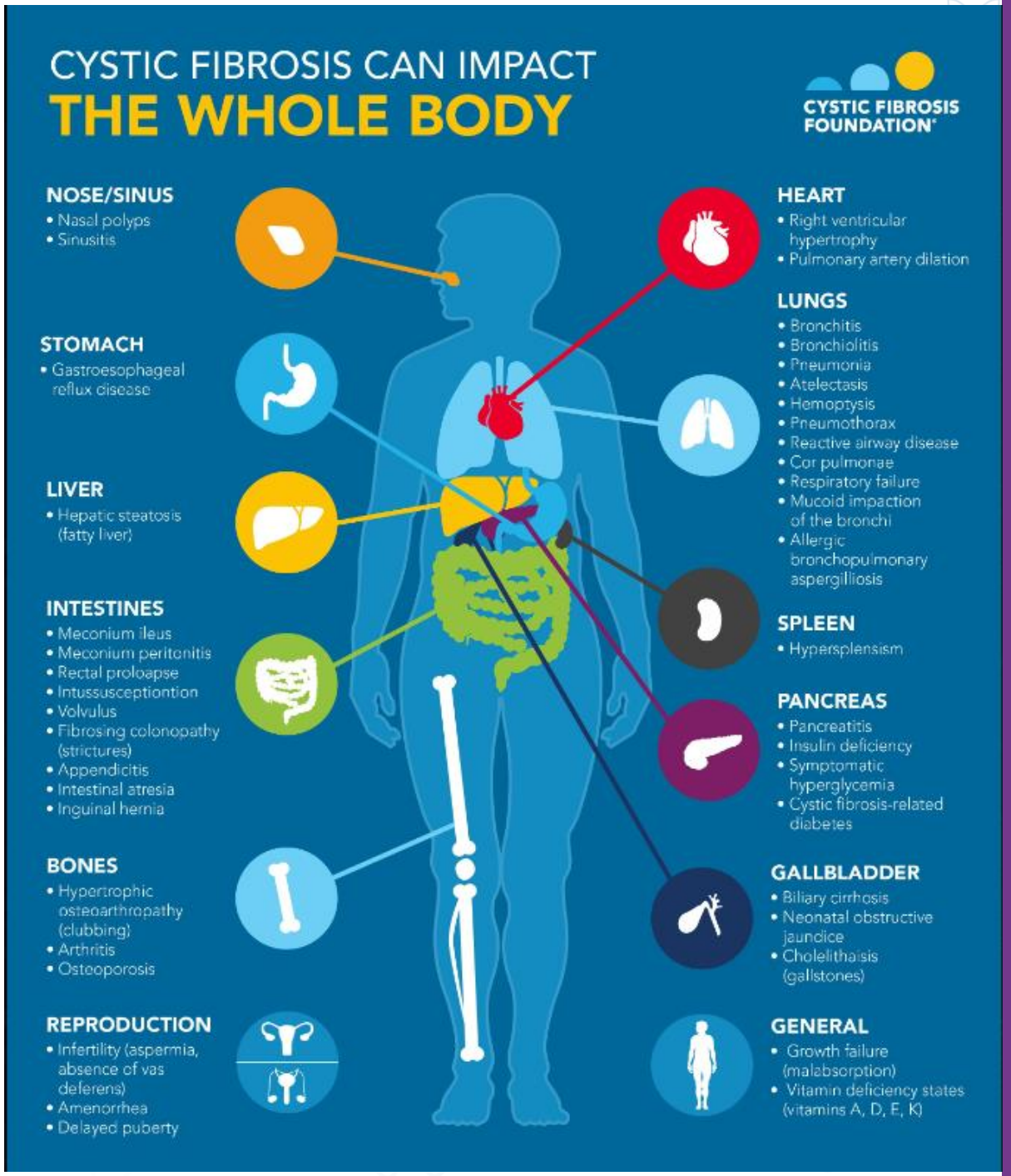
Other Complications

- Meconium ileus (newborn)
- Chronic pancreatitis
- Hepatic steatosis
- CF related diabetes
- Osteopenia/Osteoporosis
- Sinusitis
- Infertility



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Nutrition Goals for CF

Achieve optimal weight gain and linear growth velocities for age

The CF Foundation recommends:

- Weight/length $\geq$ 50%ile (CDC), >70%ile (WHO)
- BMI/age $\geq$ 50%ile and $\leq$ 85%ile
- BMI $\geq$ 22 kg/m^2 for adult women
- BMI $\geq$ 23 kg/m^2 for adult men

Research has shown best long-term maintenance of lung function (FEV1) with these BMI goals

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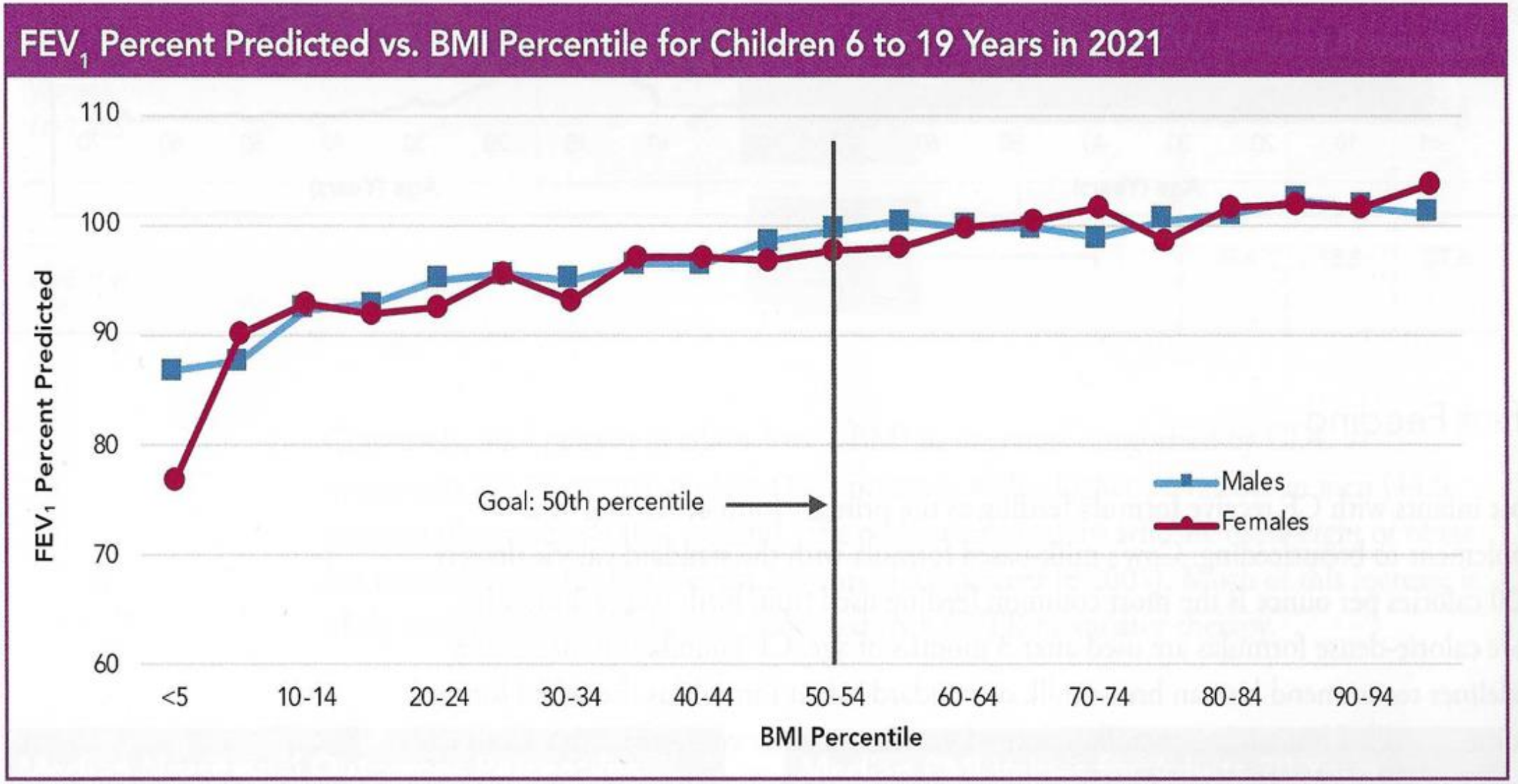
BMI/FEV1 Relationship



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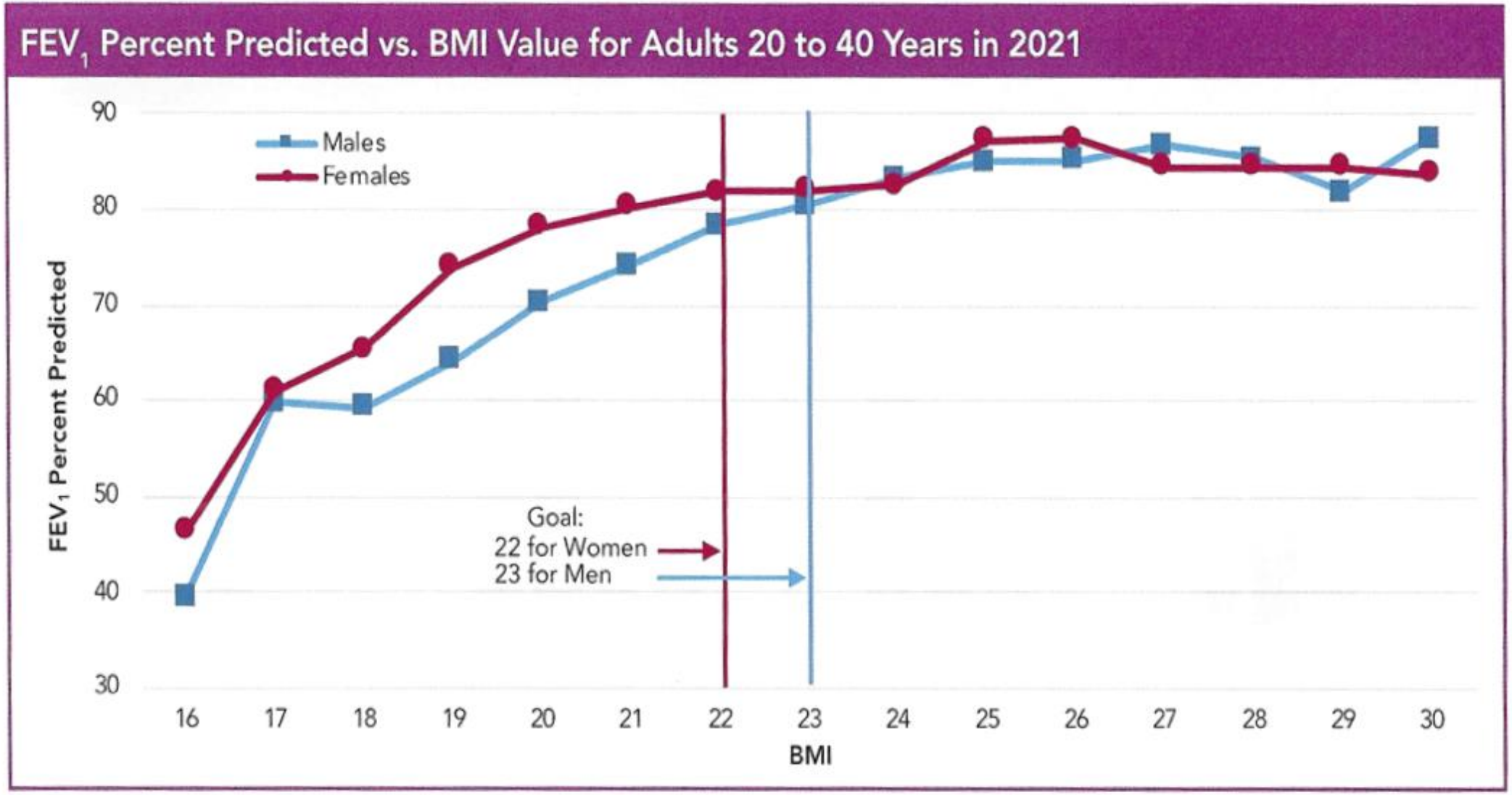
BMI/FEVI Relationship



2021 Cystic Fibrosis Foundation Patient Registry Annual Data Report

Nutrition Assessment

- Research has shown that estimated nutrient needs for children with CF are 110-200% higher than the normal, healthy population

Energy needs:

- Pancreatic insufficiency: 110-130+ kcal/kg (infants) or DRI x 1.5-2.0 (3yrs+)
- Pancreatic sufficiency: 90-110+ kcal/kg (infants) or DRI x 1.2-1.5 (3yrs+)

Protein needs:

- Infant – 2 yrs: 2-3 gm/kg
- > 2 yrs: 1.5 gm/kg

Fluid needs:

- Fluid maintenance - Holliday Segar Method

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Annual Nutrition Labs

- Fat soluble vitamins
  - A, D, E, K
    - Retinol, 25OH D, Alpha-tocopherol, and PT
- Minerals
  - Iron panel, zinc
- Screening for CF related Diabetes (10yrs+)
  - Oral Glucose Tolerance Test, 2 hr result
    - Normal <140 mg/dl
    - Impaired Glucose Tolerance: 140-199 mg/dl
    - CFRD: ≥ 200 mg/dl
  - HgbA1c

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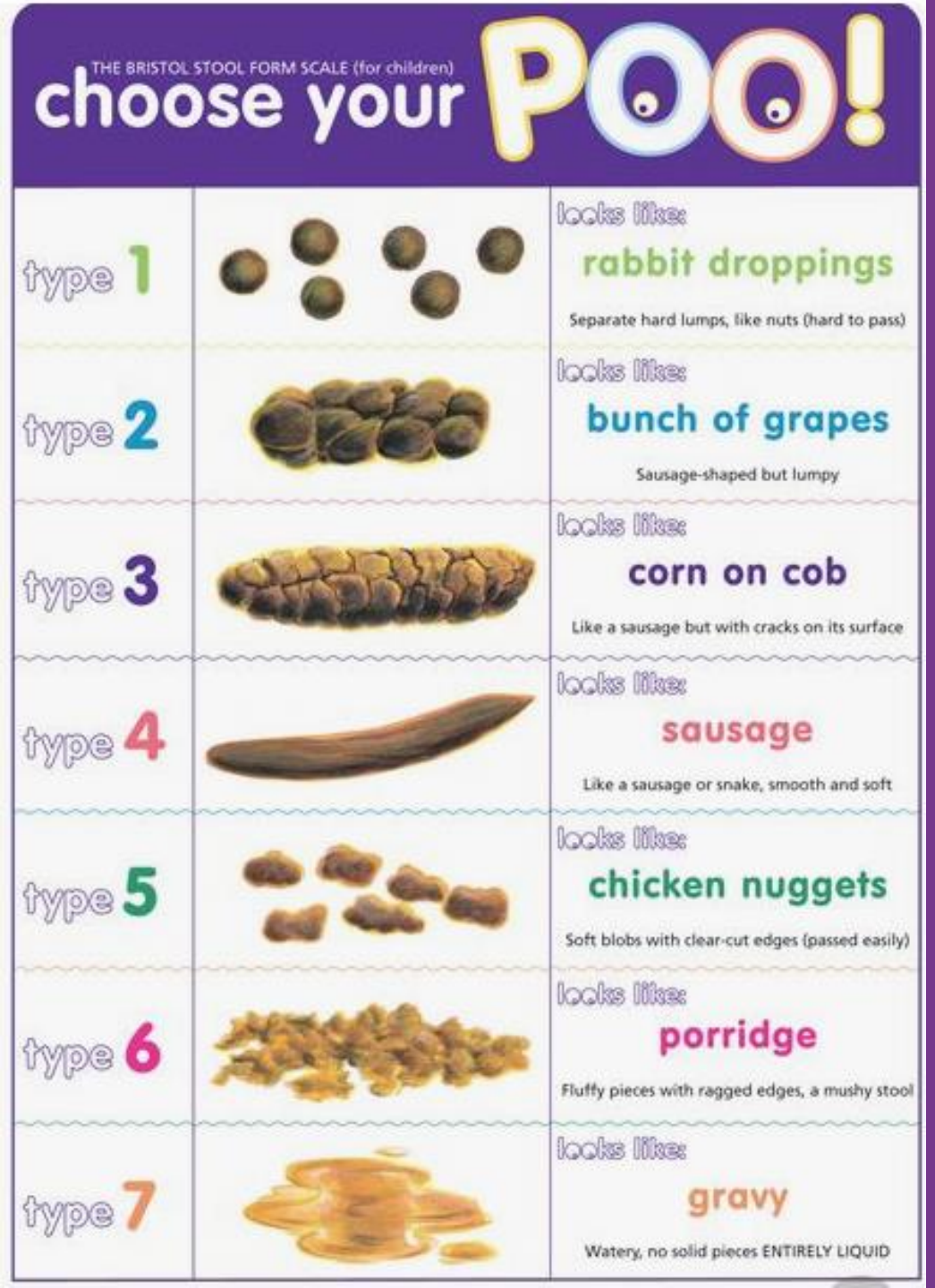
Stool/GI Assessment

- Frequency
- Consistency (loose vs. solid)
- Volume
- Buoyancy
- Color
- Presence of grease
- Smell
- Presence of bloating/gas



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Traditional CF Diet

- In order to treat high energy needs, often complicated by a component of malabsorption of nutrients:
  - High calorie
  - High protein
  - High/unrestricted salt
  - High fiber
  - Fats are also unrestricted

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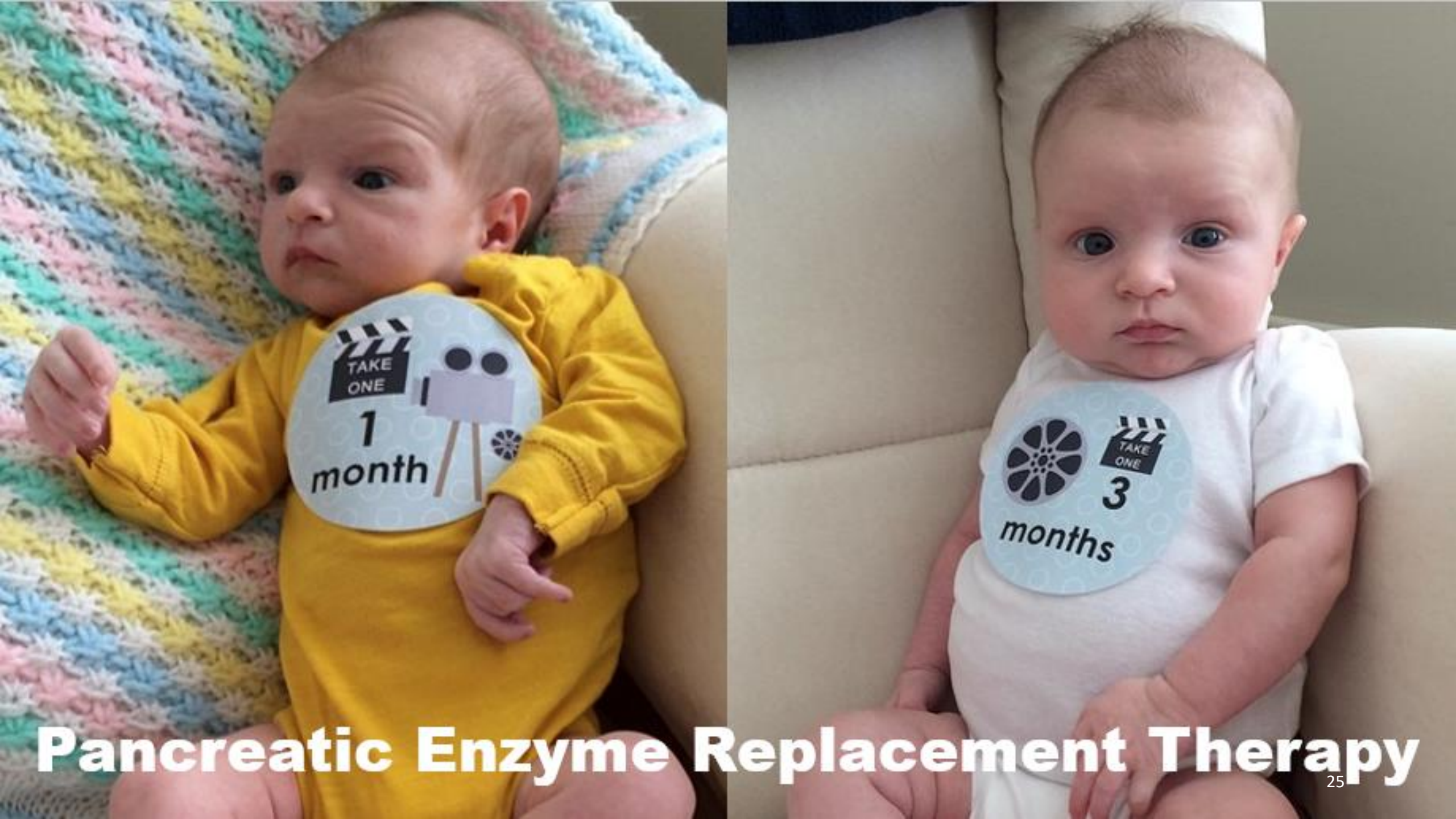
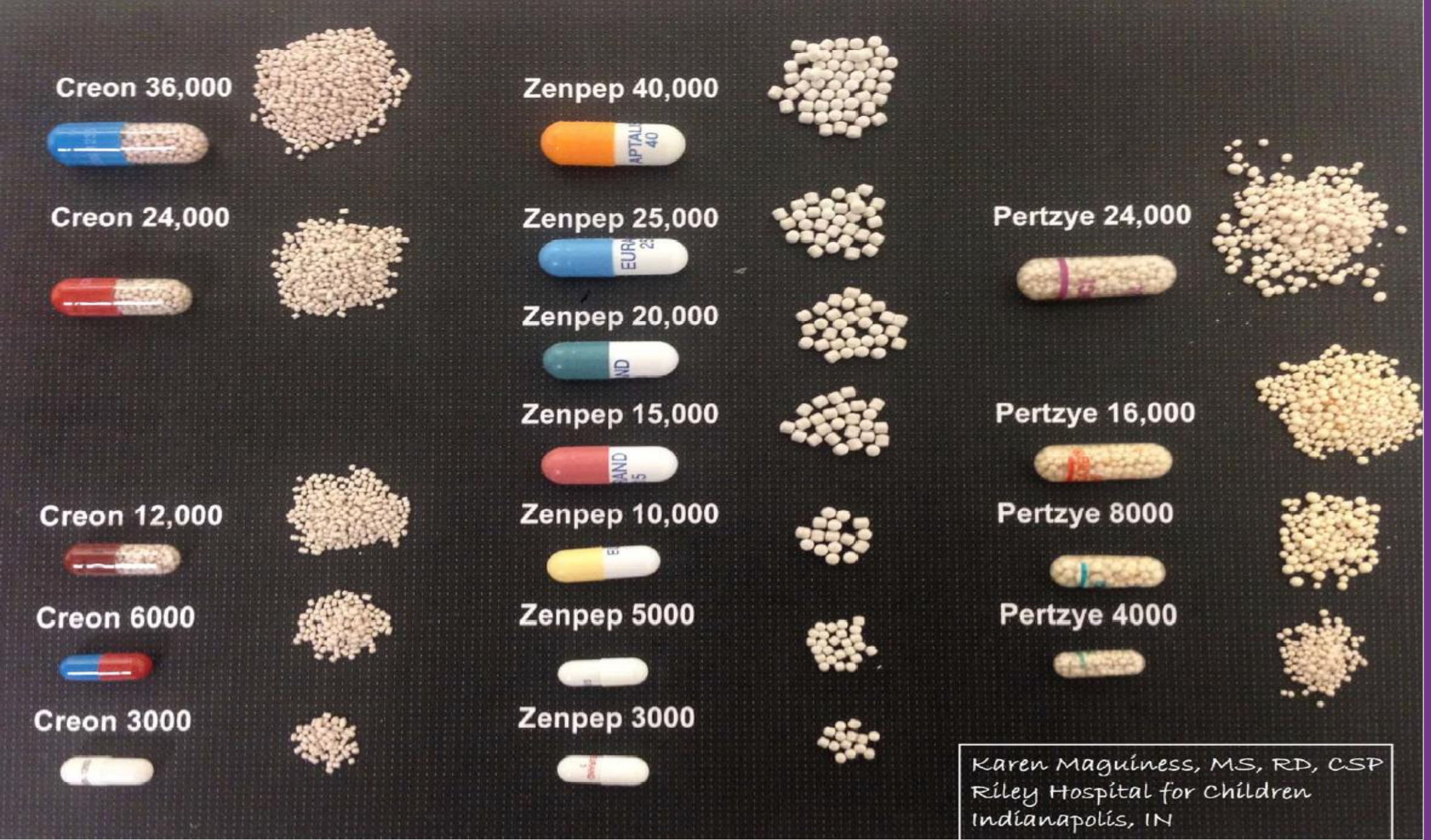


Pancreatic Enzyme Replacement Therapy

Pancreatic enzyme replacement therapy (PERT)

- Capsules filled with enzyme “beads” containing lipase, amylase and protease must be taken with every fat and protein containing meal/snack/drink
- Infants are provided the enzyme “beads” in apple sauce before each bottle
- RD assesses for adequacy of dose at every visit (s/s of fat malabsorption)


Creon 36,000
Creon 24,000
Creon 12,000
Creon 6000
Creon 3000
Zenpep 40,000
Zenpep 25,000
Zenpep 20,000
Zenpep 15,000
Zenpep 10,000
Zenpep 5000
Zenpep 3000
Pertzye 24,000
Pertzye 16,000
Pertzye 8000
Pertzye 4000
Karen Maguiness, MS, RD, CSP
Riley Hospital for Children
Indianapolis, IN

PERT Calculations

- Enzyme dosing guidelines:
  - Meal dosing: 500-2500 units lipase/kg meal
  - Maximum daily dose: 10,000 units lipase/kg/day

- Example:
  - 22 kg patient who is having s/s of malabsorption
  - Creon 12,000, 3 capsules with meals, 1 capsule with snacks
  - 12,000 units lipase x 3 = 36,000 units lipase
  - 36,000 units / 22kg = 1636 units lipase/kg/meal

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PERT Calculations

- Determine maximum dose per day for the 22 kg patient receiving Creon 12,000
  - 10,000 units lipase/kg/day max
  - 10,000 units lipase x 22 kg = 220,000 units lipase
  - 220,000 units / 12,000 units = ~18 capsules per day

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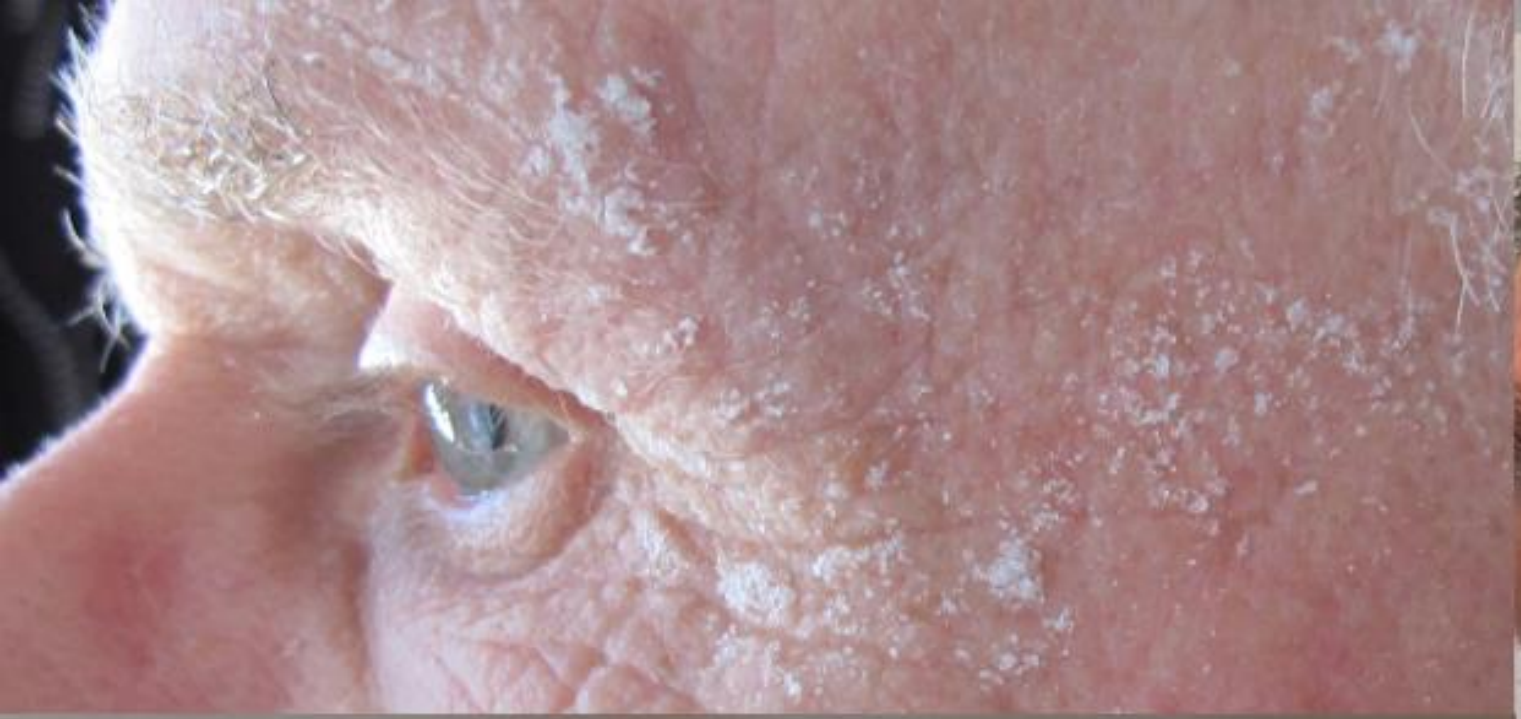

Salt Supplementation

- Infants
  - 0-6 months: 1/8 tsp added to breast milk or formula daily
    - Advised to measure out at beginning of day and added to feeds throughout the day
  - 6-12 months: ¼ tsp added to formula or pureed foods daily

- Toddlers, Children and Adolescents
  - No salt restriction
  - Salty snacks
  - Added salt to meals
  - 12 oz Gatorade or powerade + 1/8 tsp extra salt

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Fat soluble vitamin supplementation

- Vitamins A, D, E and K are frequently low due fat malabsorption

- CF specific vitamins provide larger amounts of these vitamins and/or in a water miscible form

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Vitamins

- MVW Complete Formulation
  - Liquid, tablet chewable, gummy, soft gel and mini soft gel
- DEKAs Plus*
  - Liquid, chewable, soft gel
- GenADEK*
  - Liquid, chewable, soft gel

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Bone Health

- Causes and risk factors of low bone density
  - Malabsorption
  - Low body weight
  - Lack of exercise
  - Low vitamin D/calcium intake
  - Chronic infection
  - Long term steroid use

- Recommendations
  - Baseline DEXA scan at 10 yrs
  - Screening every 1-2 yrs thereafter pending results
  - Diet education – Vitamin D and calcium
  - Supplements
  - Weight bearing exercise
  - Referral to Endocrine for Bisphosphonate Therapy

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CF Related Diabetes

- CFRD is found in 35% of adults aged 20-29 and 43% for those over 30 years old
- CFRD is unique and has features of both Type 1 and Type 2 diabetes
  - Like type 1:
    - they have insulin deficiency related to scarring of the pancreas
    - can be treated only with insulin but they never have elevated ketone levels
  - Like type 2:
    - insulin resistance related to inflammation, increased cortisol levels and chronic use of steroids.
  - Weight loss will not improve condition
  - Will not cause macro vascular complications (heart disease, hypertension) but can cause microvascular complications (↓ kidney function, diabetic retinopathy) if untreated

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RELiZORB Cartridge

- Lipase containing cartridge hydrolyzes fat in formula during administration

- Potential Benefits:
  - Improved weight gain and growth, improvement in BMI/age
  - Improved tolerance of GT feeds
  - Improved adherence

Figure 1. RELiZORB Cartridge

The iLipase is retained within the RELiZORB cartridge by two filters as enteral formula flows through RELiZORB, and is not ingested by the patient.

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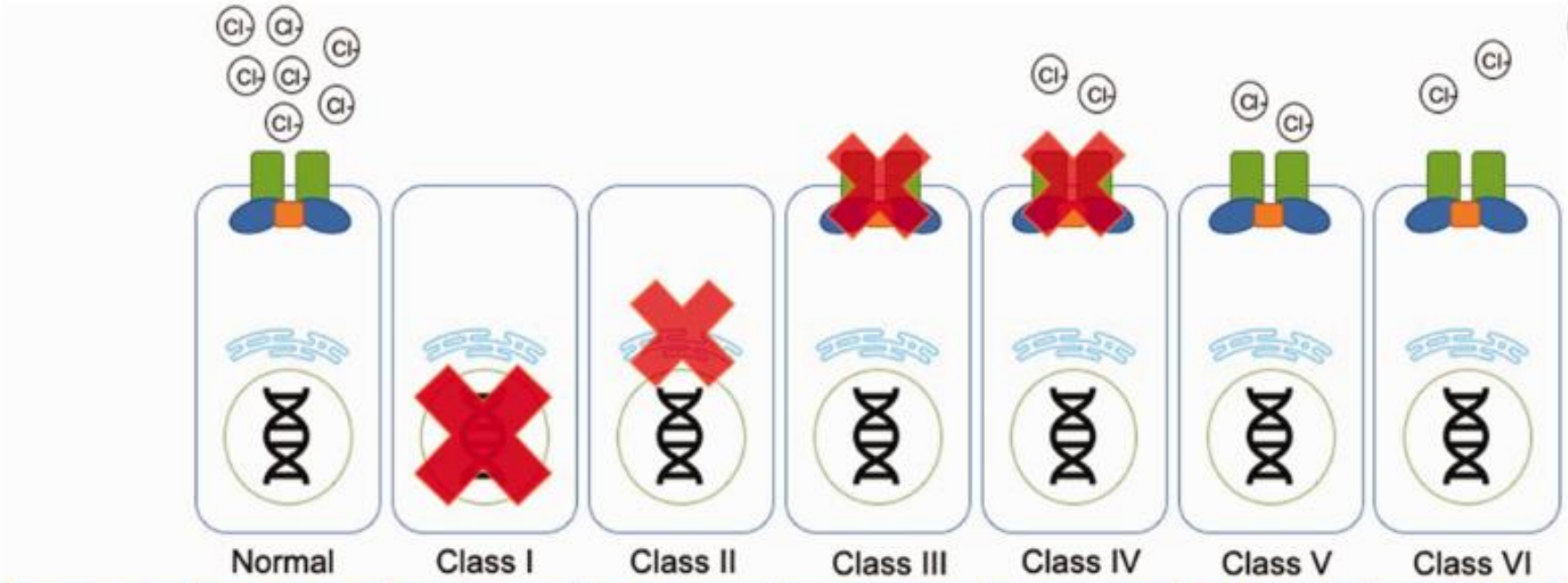
Emerging Topics in the era of HEMT

- Overweight/Obesity and related comorbidities
- Cardiovascular effects, hypertension and decreasing sodium needs
- Altered Vitamin Levels with HEMT
- Pancreatic insufficiency → sufficiency



Description	CFTR is formed, reaches cell surface and functions properly, allowing transfer of ions and water.	No functional CFTR is formed	CFTR is misfolded, preventing it from reaching the cell surface	CFTR protein is formed and is transported to the cell surface but does not function	The opening in the CFTR protein ion channel is faulty	CFTR is created in insufficient quantities	Diminished CFTR stability, thus decreased quantity of functional CFTR
Mutation Examples		G542X W1282X R553X	F508del N1303K I507del	G551D S549N V520F	R117H D1152H R347P	3272-26A→G, 3849+10 kg C→T	120del123, rPhe580del

Figure 1. CF mutation classes. Adapted from Cystic Fibrosis Foundation 2017 Patient Registry Annual Data Report.9

CFTR, cystic fibrosis transmembrane conductance regulator.

CFTR Modulator Therapies

- 2012 – ivacaftor (Kalydeco®) approved by FDA for treatment of those carrying at least one G551D mutation
  - Significant improvements in sweat chloride level, nasal potential difference and lung function with a median increase of 8.7 point in FEV1 percent predicted

- 2015 – lumacaftor/ivacaftor (Orkambi®) combination approved by FDA for treatment of those who were homozygous for the F508del mutations (most common mutation)

- 2018 – elexacaftor/ivacaftor (Symdeko®) combination approved by FDA for those homozygous for F508del or who have one other mutation that would respond to its treatment (153 mutations)

- 2019 – elexacaftor/tezacaftor/ivacaftor (Trikafta™ or ETI) triple combination therapy approved for the treatment of those carrying one F508del mutation
  - Improvement in predicted FEV1 up to 14 points, improvement in BMI, significant improvements in sweat chloride concentration, pulmonary exacerbations and quality of life

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Overweight/Obesity

- Consumption of high fat/high sugar foods starting early in life
- According to 2019 CFF Patient Registry data, 23% of PwCF had an overweight/obese BMI, compared to 40% from 2021 data
- Highly effective modulator therapies likely:
  - ↓ energy expenditure from work of breathing
  - ↑ taste/smell, enhances appetite
  - optimizes intestinal pH and absorption [6]
  - ↑ fat mass [7]

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Obesity related Comorbidities

- Prevalence of overweight and obesity are increasing, along with associated comorbidities
- Overnutrition in CF associated with OSA [8]
- Median blood cholesterol levels and systemic hypertension are higher in those who are overweight with CF [9]
- Higher visceral adiposity, correlated with sugar consumption and higher fasting BG
- Increased insulin resistance may be more likely in those PwCF who are overweight [9]

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Cardiovascular Effects of HEMT

- Essential hypertension not historically a common comorbidity for pwCF
- Sweat tests can normalize on treatment with HEMT
- 7.2% of adult pwCF had a diagnosis of hypertension in 2021 according to CFF Patient Registry data
- Modest increases in systolic and diastolic BP noted in clinical trials for ETI[9]
- Reduced salt losses along with the legacy high salt diet in PwCF, may contribute to the modest increases in blood pressures

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Altered Fat Soluble Vitamin Levels

- Increased levels of Retinol and Alpha-tocopherol
- Vitamin D levels appear unaffected
- Unclear etiology
  - Increased absorption vs. metabolization in liver?
- Vitamins formulated for those taking HEMT

Pancreatic Function

- Pancreatic insufficiency was thought to be a lifelong condition
- Emerging data suggest that there is the potential for return of pancreatic function in some children taking HEMT (<5yrs) [10]
  - Continued monitoring of fecal elastase warranted as return of exocrine function may take several years [10]
- Ability to discontinue PERT observed in older pwCF, but may be able to titrate down dosage
- HEMT has been shown to reduce random blood glucose and hemoglobin A1C in pwCF
- In children with CFRD, one study demonstrated improved glycemic control after initiation of HEMT with some children able to reduce or discontinue insulin [11]

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Conclusions [5]

- Nutrition care should be individualized using clinical data and goals of pwCF
  - BMI does not account for body composition or genetic predisposition to metabolic derangements
  - Vitamin levels should be monitored, and supplementation adjusted as appropriate
- Increased awareness of potential cardiovascular complications associated with the traditional high fat/high calorie CF diet
  - Lipid screening should follow guidelines in the general population
- Lack of data to make specific recommendations for salt intake in pwCF who have or are at risk for hypertension
  - Regular monitoring of blood pressure
- Fecal elastase should be monitored if a change in pancreatic status is suspected
- Undernutrition is still a concern for those 10-15% who do not qualify for a modulator therapy

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Questions???