Managing the Endocrine Complications of Cystic Fibrosis: A UMass Subspecialty Collaboration

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Disclosure

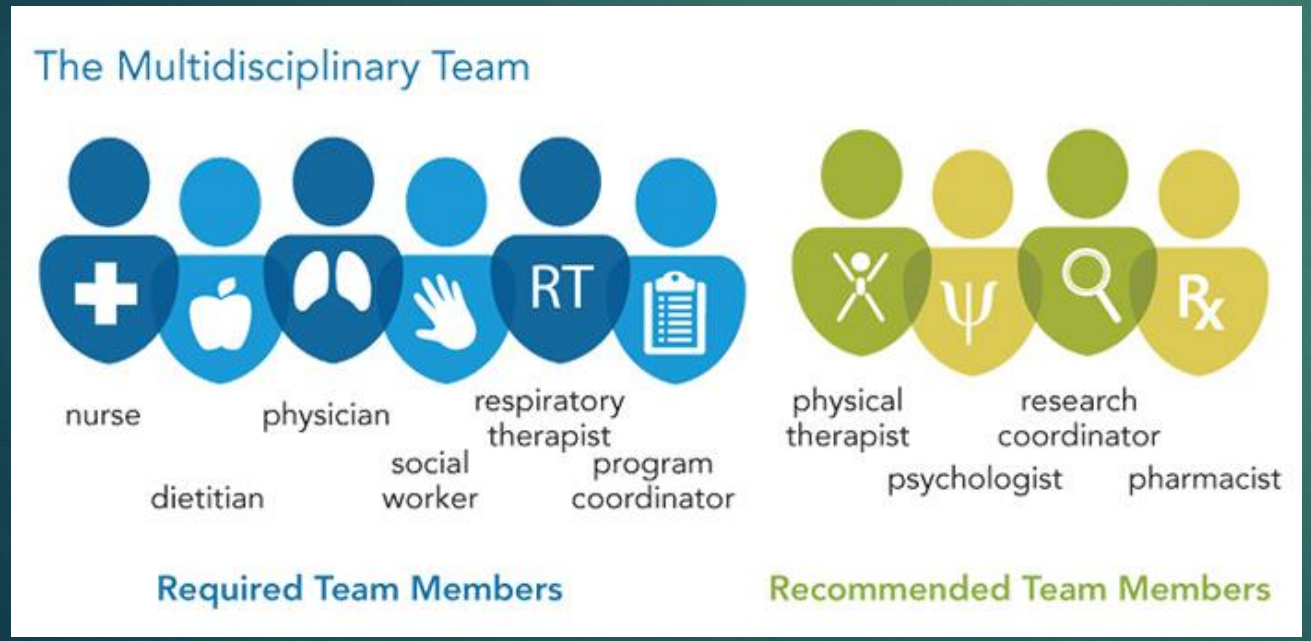
I have no actual or potential conflict of interest in relation to this program/presentation.

Objectives

- Learn about the Umass pediatric endocrinology/cystic fibrosis collaboration to improve patient care
- Review the most common endocrine complications of cystic fibrosis
- Understand screening and management guidelines for endocrine disorders in the pediatric patient with cystic fibrosis

www.cff.org

"The CF care team approach means that health care professionals work together in partnership with you to provide comprehensive and high quality care for you or your child."



- **Other Physician Specialists**
- Additional members of your CF care team may include physician specialists. These health care professionals are also referred to as subspecialists and have extensive training and practice in a particular field of medicine or surgery.
- Physician specialists who may be involved with CF care include:
- **Otolaryngologist**
- An otolaryngologist (or "ENT" for ear, nose and throat doctor) is a doctor who has special training in the diagnosis and treatment of disorders that affect the nose and sinuses. The same basic defect that affects the lining of the lungs can also affect the lining of the nose and sinuses in people with CF.
- **Gastroenterologist**
- A gastroenterologist is a doctor who has special training in the diagnosis and treatment of diseases of the digestive system. This includes problems with the esophagus, stomach, intestines and liver.
- **Endocrinologist**
- **An endocrinologist is a doctor with special training in the diagnosis and treatment of CFRD and other hormonal diseases, including problems with thyroid hormone and growth hormone.**

EnVision CF: Emerging Leaders in CF Endocrinology Program

- Funded by the Cystic Fibrosis Foundation
- **Goal: support a training program that would expand the availability of CF-endocrinology experts throughout the country and develop the next generation of leaders in pediatric and adult CF endocrinology**
- **Round 2**
- 9/1/19 - 8/31/22
- Based off of successful DIGEST program for gastroenterologists
- Requires all mentors (senior endocrinologists) and mentees (junior endocrinologists) to have a multidisciplinary clinic
- Sixteen EnVision Emerging Leaders were selected, 8 pediatric endocrinologists, 8 adult endocrinologists
- ~ 8 CF/endo clinics 8 years ago → > 25 clinics today

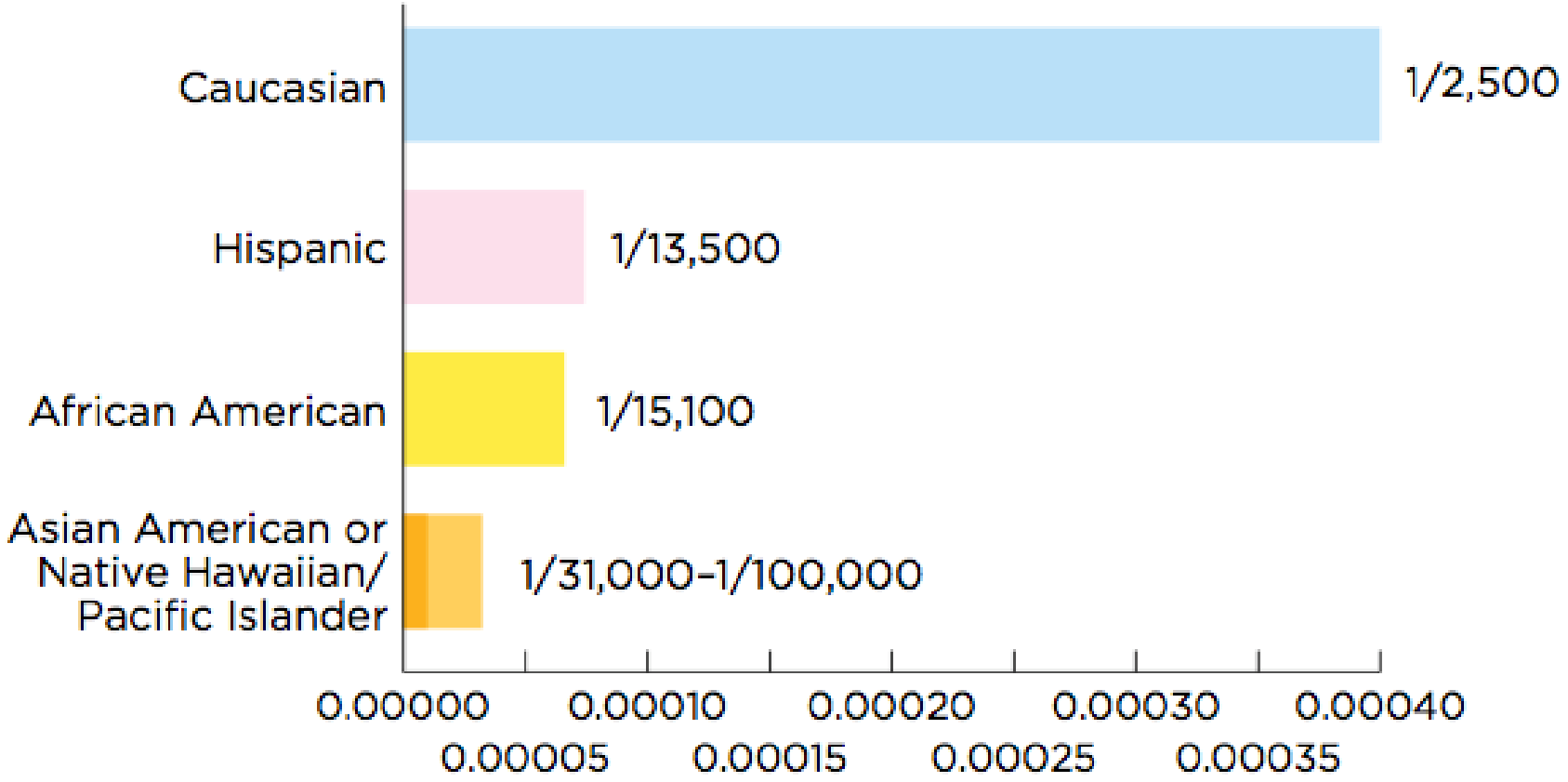
Benefits of a Subspecialty Collaboration

- Limits medical visits and exposure to hospital and clinics
- Relieves burden of time and money for the patient
- Reduces mental and physical stress of multiple subspecialty visits
- Cost effective
- Better health outcomes
- Improved screening for endocrine disorders that may have been overlooked
- Improved communication between providers
- Increases patient confidence in overall care

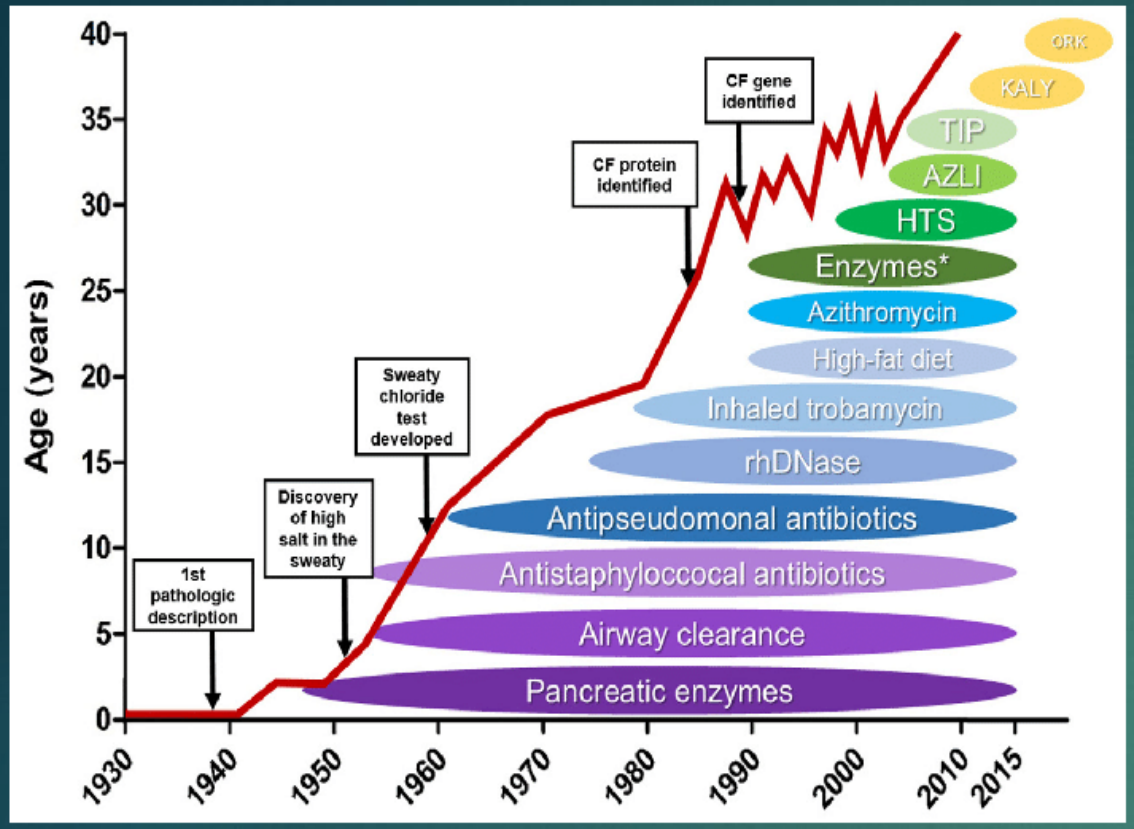
UMass Cystic Fibrosis Program

- UMass Pediatric CF Clinic: ~ 125 patients
- Prior referrals to pediatric endocrinology/year: ~ 5 patients
- UMass Family Night

Figure 1: Estimated Cystic Fibrosis Prevalence Rates by Race and Ethnicity

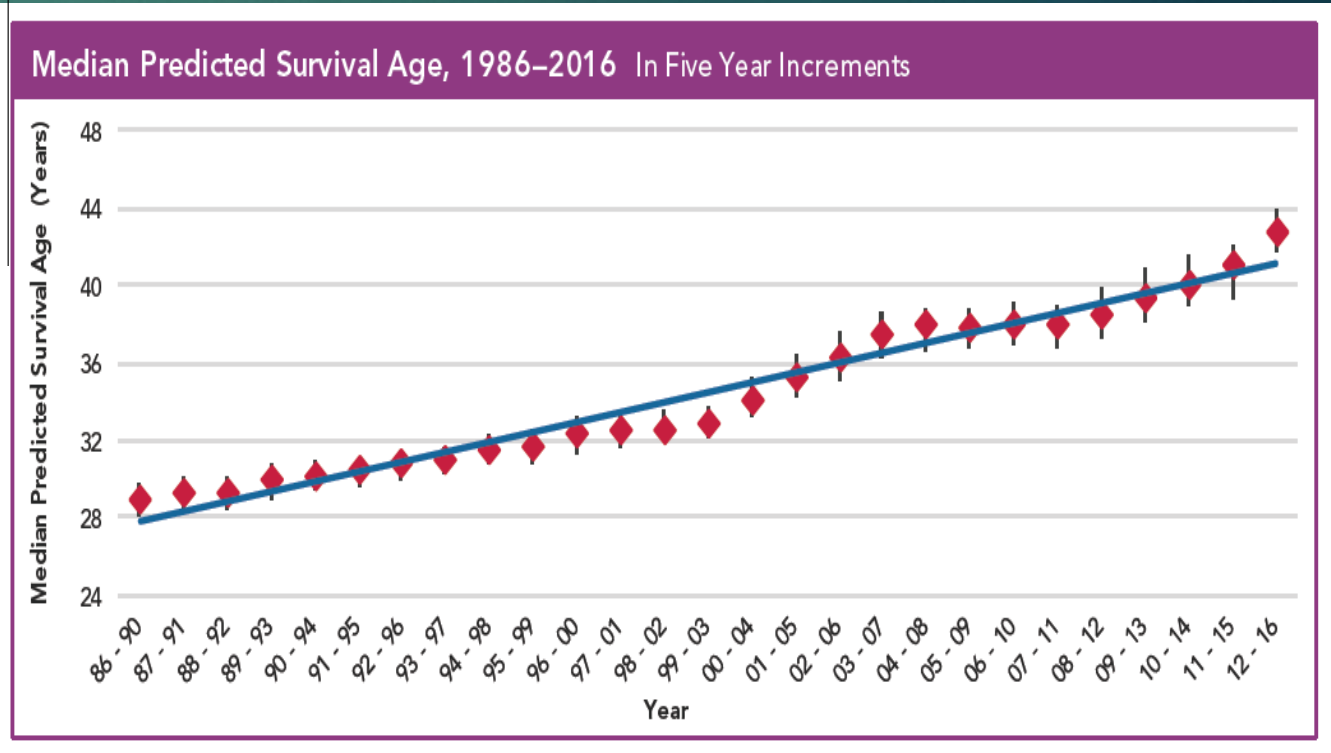


Source: CDC. Cystic Fibrosis Clinical Validity. September 10, 2007



Estimated 70,000 individuals with CF in NA and Europe (60% <18 years)

Median life expectancy is now 47 years (increased from age 2 years in past 6 decades)

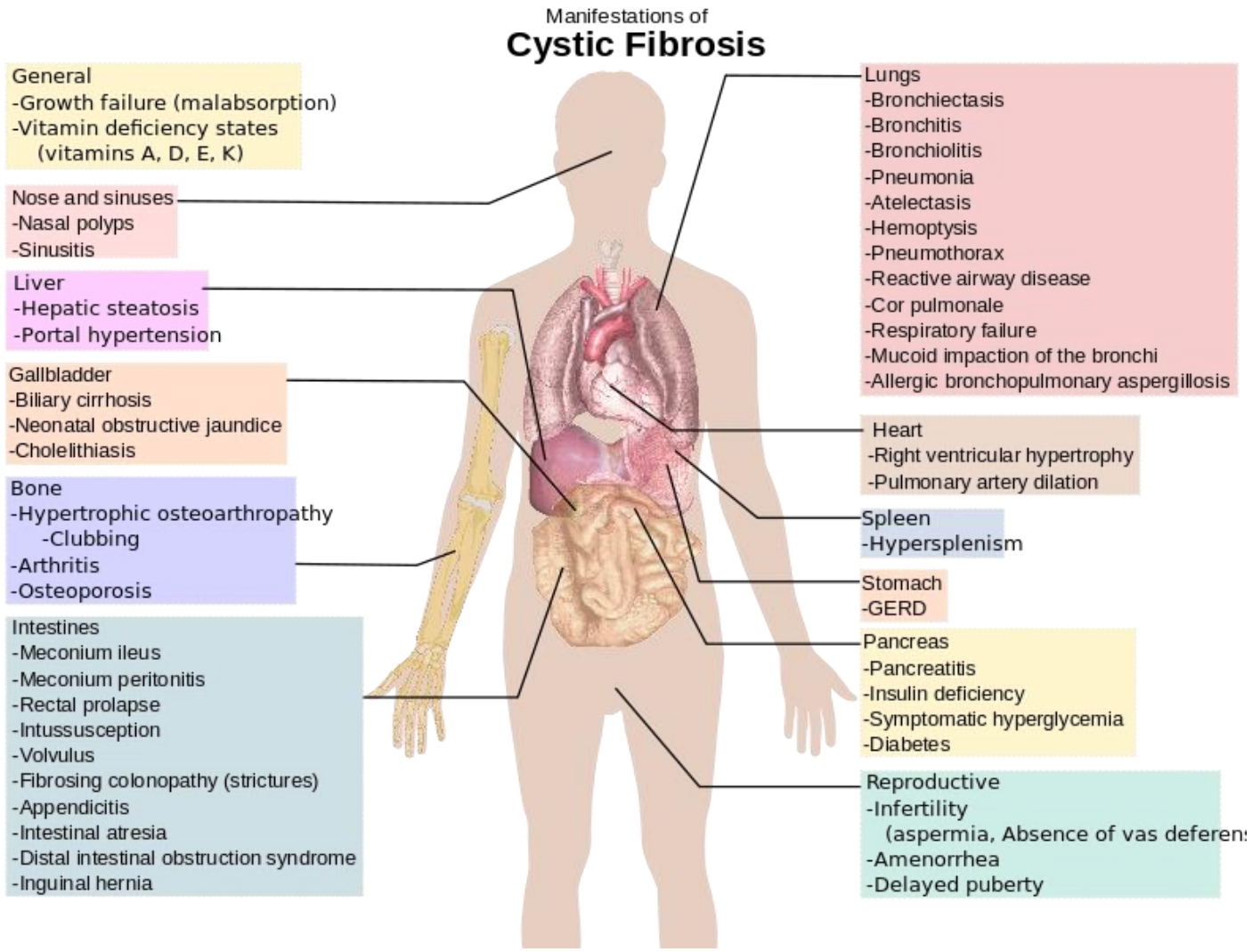


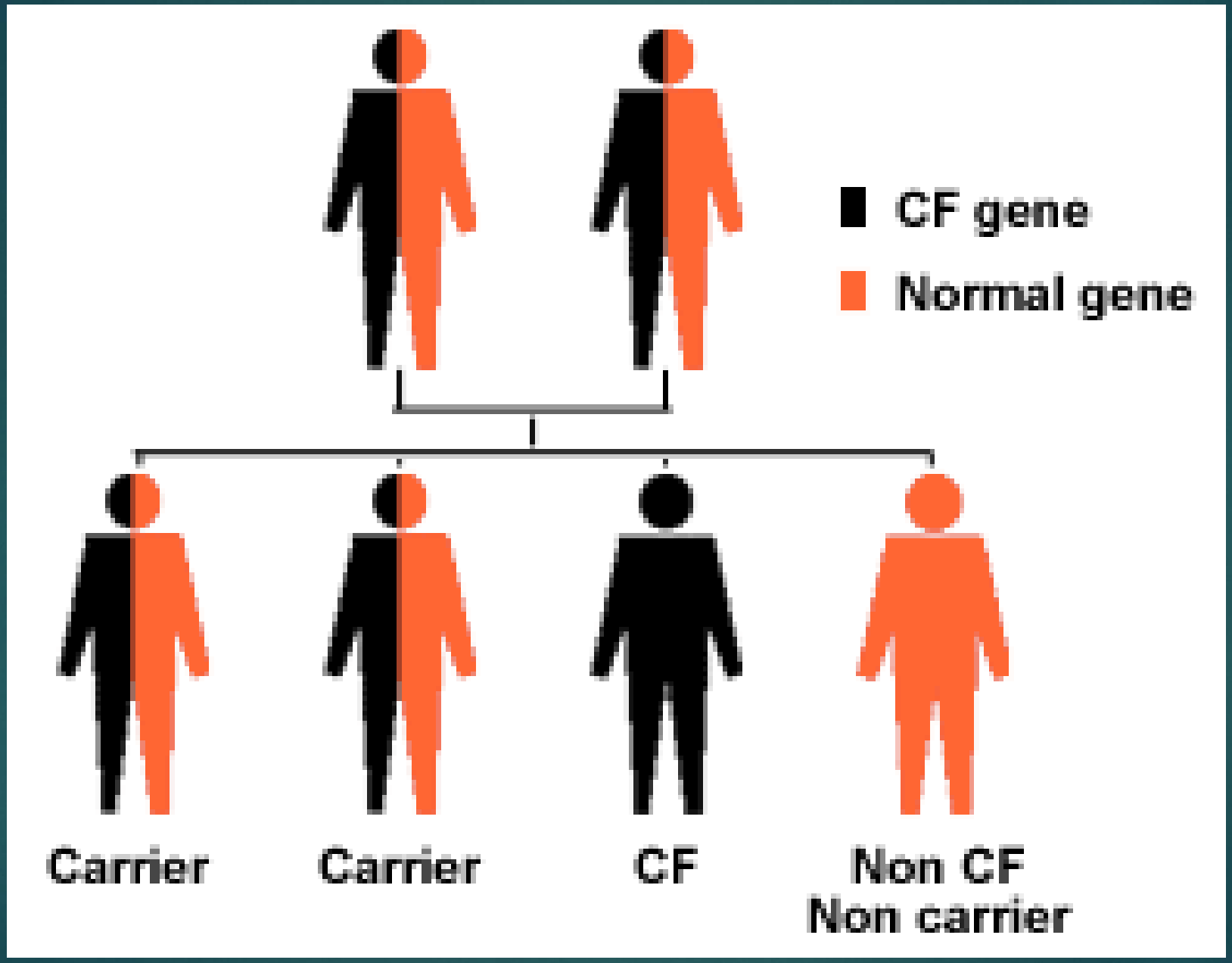
- Meconium ileus
- Pancreatic insufficiency
- Lung infection
- Lung structural changes

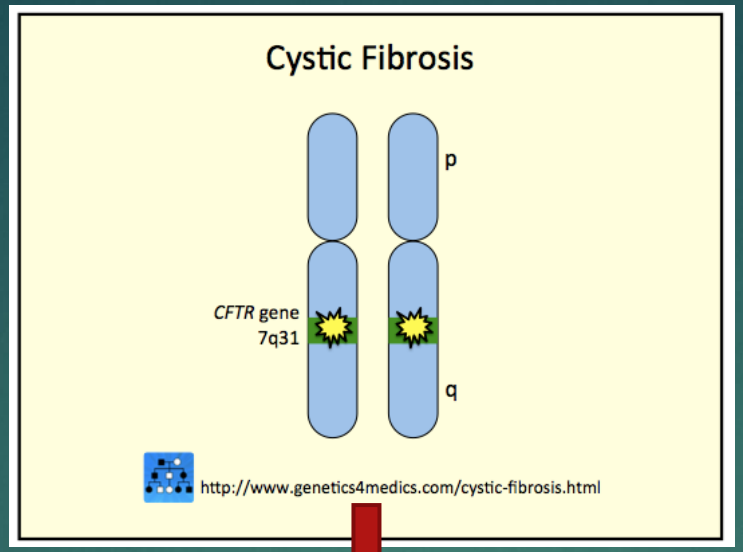
- Increased lung structural changes
- Nasal polyposis
- CFRD
- CF liver disease
- GERD
- Depression and Anxiety

- Chronic lung infection
- Distal intestinal obstructive syndrome
- Severe lung disease
- Increased risk of CFRD
- Increased risk of GERD
- Bone Disease
- Increased risk of liver disease
- Infertility
- Increased Depression and Anxiety

CF: Not Just a Pulmonary Disease




CF gene
Normal gene
Carrier
Carrier
CF
Non CF
Non carrier



CFTR gene mutation

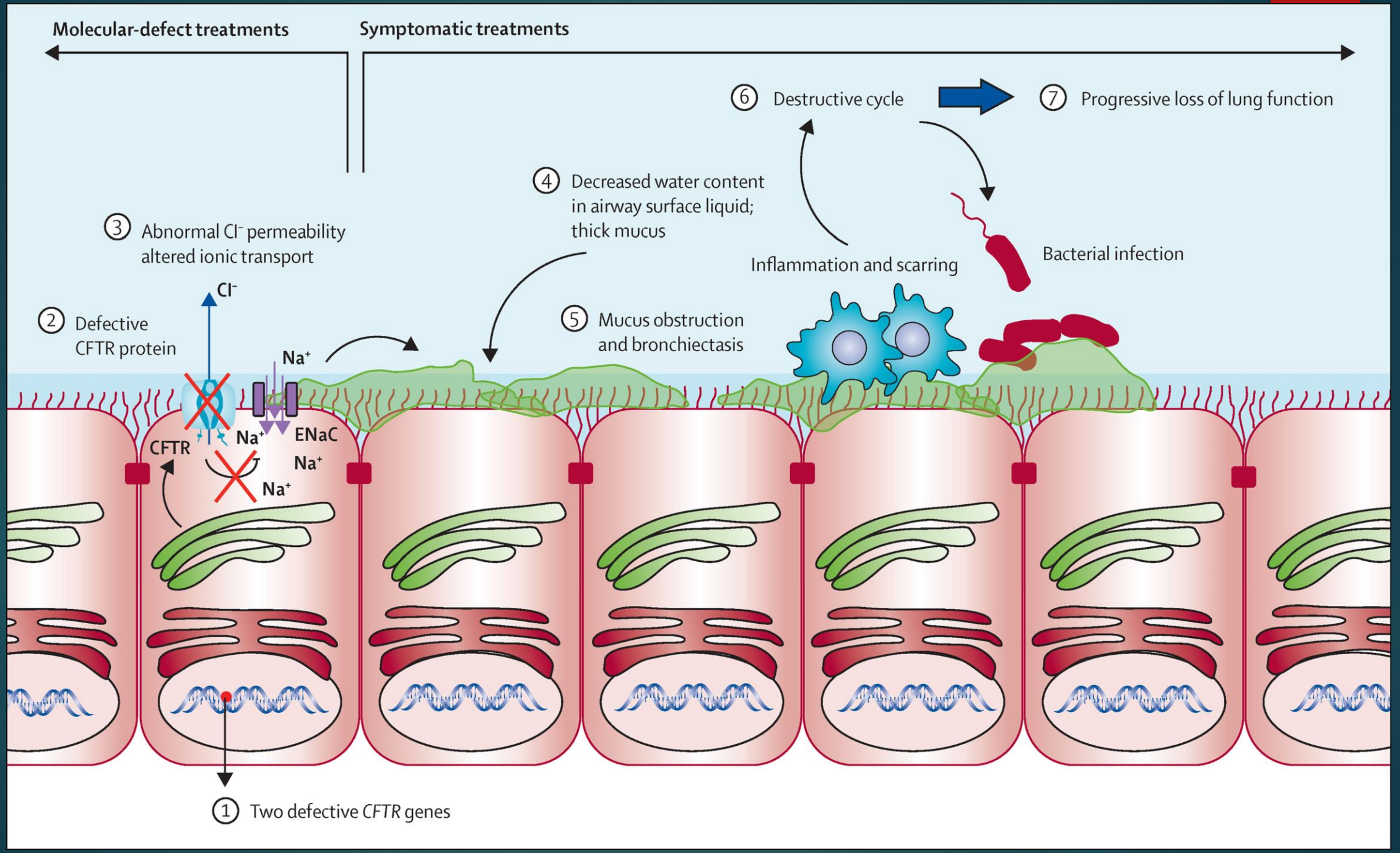
Reduced quantity and/or function of CFTR protein

Defective ion transport

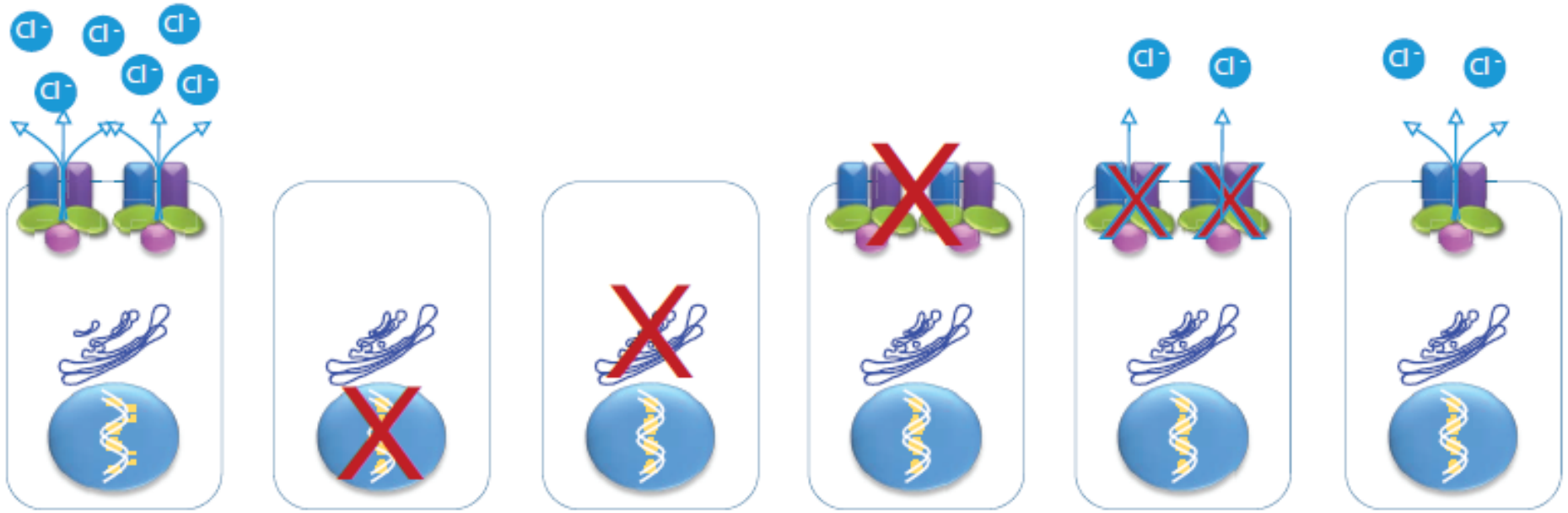
Fluid and electrolyte imbalance

Lung disease

Extrapulmonary manifestations


Molecular-defect treatments
Symptomatic treatments
1 Two defective CFTR genes
2 Defective CFTR protein
3 Abnormal Cl⁻ permeability altered ionic transport
4 Decreased water content in airway surface liquid; thick mucus
5 Mucus obstruction and bronchiectasis
6 Destructive cycle
7 Progressive loss of lung function
Inflammation and scarring
Bacterial infection
Cl⁻
Na⁺
CFTR
ENaC

Classification of CFTR Mutations



	Normal	Class I	Class II	Class III	Class IV	Class V
DESCRIPTION	CFTR is created, reaches cell surface and functions properly, allowing transfer of chloride and water.	No functional CFTR created.	CFTR protein is created, but misfolded, keeping it from reaching the cell surface.	CFTR protein is created and reaches cell surface, but the gate does not function properly.	The opening in the CFTR protein ion channel is faulty.	CFTR is created in insufficient quantities.
EXAMPLES		G542X W1282X R553X	F508del N1303K I507del	G551D S549N V520F R117H	R117H D1152H R347P	3849+10kbC->T 2789+5G->A A455E

CF: Endocrine Concerns

- Growth
- Puberty/Hypogonadism
- Cystic Fibrosis Bone Disease (CFBD)
- Cystic Fibrosis Related Diabetes (CFRD)

CF: Growth

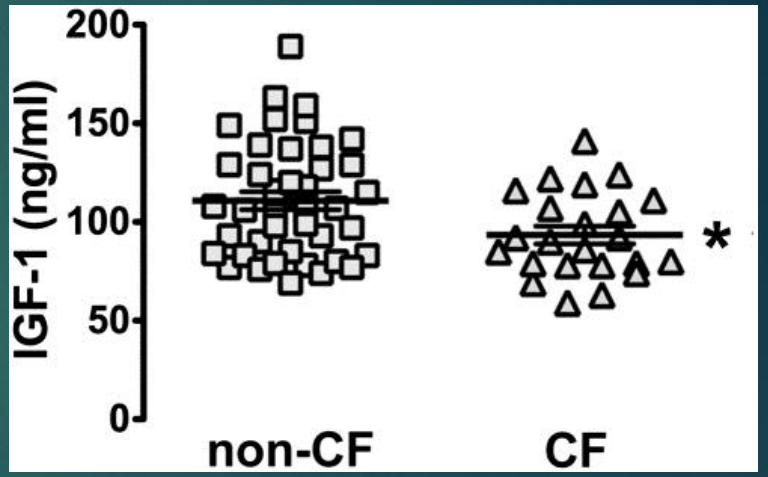
- Poor growth affects at least 20% of children with CF
- Height of adults with CF averages 2-3 inches shorter than that of age-matched peers
- Lower peak height velocity
- May lead to additional poor outcomes

Reduced Birth Weight in CF: An Early Disadvantage

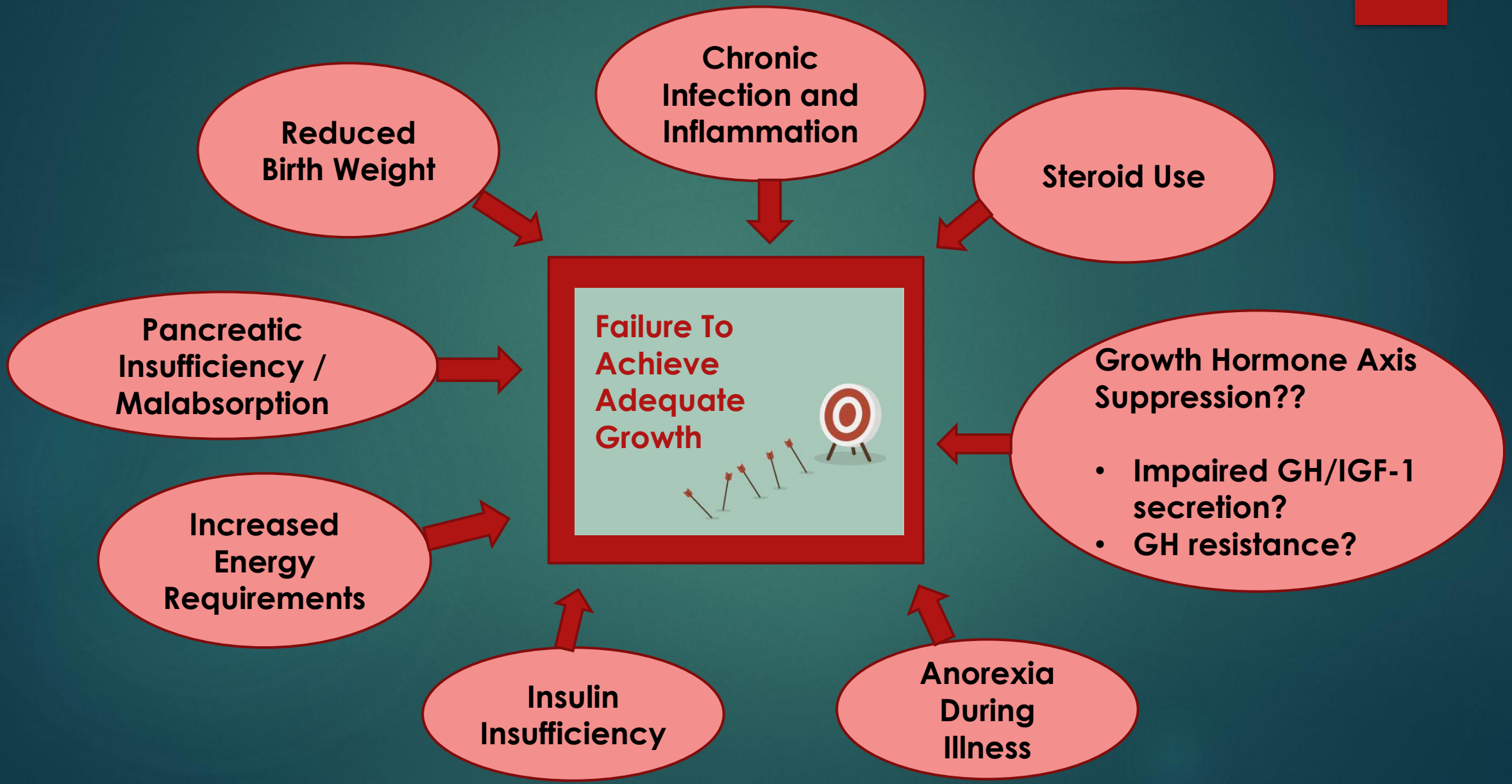
- **Gestational and Neonatal Characteristics of Children with Cystic Fibrosis: A Cohort Study**. Filippo Festini RN, BA, BSN and Giovanni Taccetti MD et al. The Journal of Pediatrics. September 2005.
  - Retrospective cohort study: CF babies born in Tuscany, Italy, from 1991 to 2002 (n = 70) compared to population of non-CF-affected children born in the same period (n = 290,059)
  - Mean BW of newborns with CF was 246.2 g lower than the mean BW of the non-CF neonatal population (*P* = .0003)
- **Perspectives of longitudinal growth in cystic fibrosis from birth to adult age.** Haeusler G et al. Eur J Pediatr. March 1994.
  - longitudinal growth in 139 patients with CF investigated from birth until 19 years
  - Birth:
    - weight: -0.83 +/- 0.13 SDS in girls, -0.44 +/- 0.13 SDS in boys
    - length: 0.55 +/- 0.13 SDS in girls, -0.39 +/- 0.14 SDS in boys
- **Cystic fibrosis: a cause of reduced birth weight?** Andreas Mueller et al. European Journal of Pediatrics. 1999
  - 86 full term CF patients born between 1981 and 1996 at the Children's' Hospital of the University of Leipzig, were compared to a randomly selected group of 320 full term healthy infants born in the same period
  - The CF group showed lower birth weights than the control group ($P < 0.01$). The difference was more pronounced in girls (2963 g vs 3351 g in controls) than in boys (3140 g vs 3442 g in controls)

Reduced Birth Weight in CF: Possible Etiologies

- Pancreatic Insufficiency:
  - Pancreatic insufficiency, growth, and nutrition in infants identified by newborn screening as having cystic fibrosis M. N. Bronstein, PhD. J PEDIATR 1992
  - Up to 60% may have pancreatic insufficiency at birth (92% by 1 year)
  - Reduced intrauterine and enteral nutrition
- Reduced Growth Hormone/IGF-1
  - Pigs and humans with cystic fibrosis have reduced insulin-like growth factor 1 (IGF1) levels at birth. Rogan MP et al. Proc Natl Acad Sci U S A. Nov 23 2010
  - IGF1 levels in human newborns with CF (*n* = 23) were lower than in non-CF newborns (*n* = 41); *P = 0.016.
- Placental insufficiency:
  - CFTR protein expressed on the maternal part of the placenta has been demonstrated
  - Evidence from case studies suggests that this protein, if changed, alters placental ionic exchange → reduction of fetal nutrition?



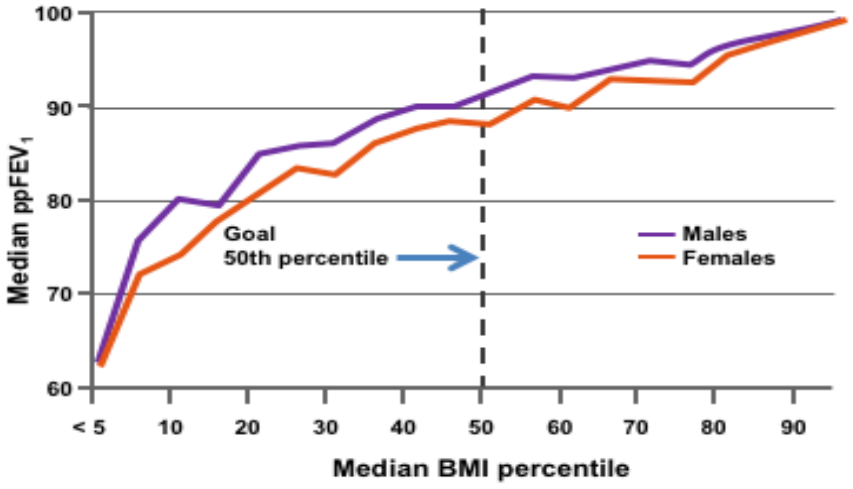
CF: Causes of Growth Failure



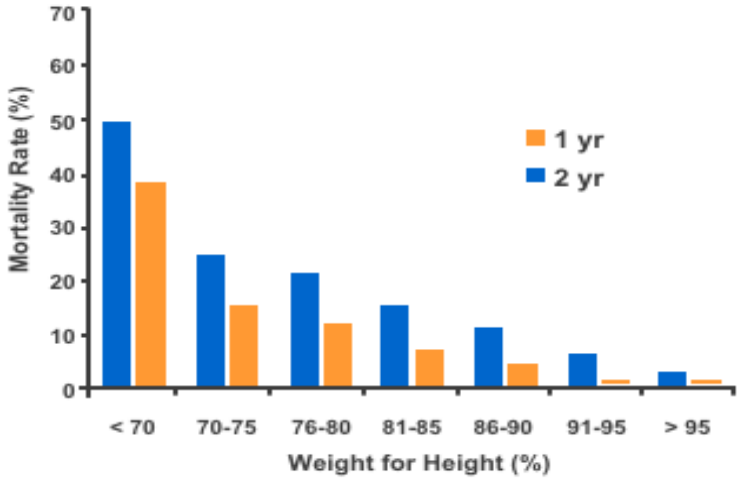
Poor Growth in CF Associated with Decreased Pulmonary Function and Increased Mortality

Growth and Nutritional Status Associated With Pulmonary Function and Survival in Patients With CF

Higher BMI is associated with better FEV_1 in children with CF[1] aged 6-19 years old



Greater weight-for-height is associated with improved survival in CF[2]



CF Growth Failure: Additional Outcomes of Low GH/IGF-1

- Reduced nutrition
- Reduced lean body mass
- Decreased bone mineral density
- Increased hospitalization rate

Growth Hormone Treatment?

Study	Study Summary	Improved with GH	No Significant Change
Effect of growth hormone on exercise tolerance in children with cystic fibrosis. Hütler M et al. Med Sci Sports Exerc. April 2002.	10 prepubertal children randomly assigned to control group or treatment group for 6 months, and then assigned to other group for the next 6 months	**Height** **Total Body mass** **Lean Body mass** **VO(2peak)** **Peak ventilation** **Peak oxygen pulse**	
Prospective randomized treatment with recombinant human growth hormone in cystic fibrosis. Schibler A et al. Arch Dis Child. December 2003.	20 CF patients(10-23 years) randomized to age and sex matched treatment and control groups. Treatment group received daily subcutaneous injections of 1 IU/kg/wk rGH for 12 months.	**Lean Body Mass**	**Weight** **Pulmonary Function**
A multicenter, randomized, double-blind, placebo-controlled trial to evaluate the metabolic and respiratory effects of growth hormone in children with cystic fibrosis. Schnabel D et al. Pediatrics. June 2007.	63 CF patients randomly assigned for 24 weeks to 1 of 3 treatment arms: growth hormone dosage of 0.11 IU/kg body weight per day, growth hormone dosage of 0.21 IU/kg body weight per day, or placebo.	**Height** **Growth Velocity** **Growth Factors**	**Weight** **FEV1**
A multi-center controlled trial of growth hormone treatment in children with cystic fibrosis. Stalvey MS et al. Pediatr Pulmonol. March 2012	Multicenter, open-label, controlled clinical trial in 68 prepubertal CF children, randomized to GH treatment or no treatment for 12 months, followed by a 6-month observation	**Height** **Weight** **Lean Body Mass** **Forced Vital Capacity** **FEV 1**	**Exercise Tolerance** **Glucose Tolerance**
Growth hormone treatment enhances nutrition and growth in children with cystic fibrosis receiving enteral nutrition. Hardin DS et al. J Pediatr. March 2005	18 prepubertal children were randomly assigned to receive no GH for 1 year, followed by 1 year of GH. Nine were randomly assigned to receive 1 year of GH followed by a second year of GH.	**Height** **Weight** **Bone Mineral Content** **Lean Tissue Mass** **Hospitalizations** **Forced Vital Capacity** **FEV1**	
Growth Hormone Treatment Improves Growth and Clinical Status in Prepubertal Children with Cystic Fibrosis: Results of a Multicenter Randomized Controlled Trial. Hardin DS et al. The Journal of Clinical Endocrinology & Metabolism. December 2006.	61 prepubertal CF subjects (≤25th percentile for height and weight) were randomized into two groups: daily rhGH treatment or no treatment groups for 1 yr. In yr 2, treatments were crossed over.	**Height** **Weight** **Lean Mass** **Bone Mineral Content** **Hospitalizations** **Q of Life**	**Forced Vital Capacity** **FEV1** **Caloric Intake** **Glucose Tolerance**

CF: Puberty

- Increased risk of delayed puberty with homozygous delta F508 mutation, poor nutritional status, abnormal OGTT results, and diminished lung function
- Possible etiologies:
  - raised resting energy expenditure
  - ovarian dysfunction
- Females: Mean age of menarche 14.4-14.6 years (normal 12.9 years). 52% have menstrual irregularities
- Males: 25-30% males have hypogonadism/low testosterone
- Outcomes of delayed or insufficient puberty:
  - Decreased bone mineral density; osteopenia
  - Decreased muscle mass
  - Growth Failure
  - Severe Emotional Distress
- Treatment: Screen/provide optimal estrogen and testosterone replacement

CF: Fertility

Fertility in CF

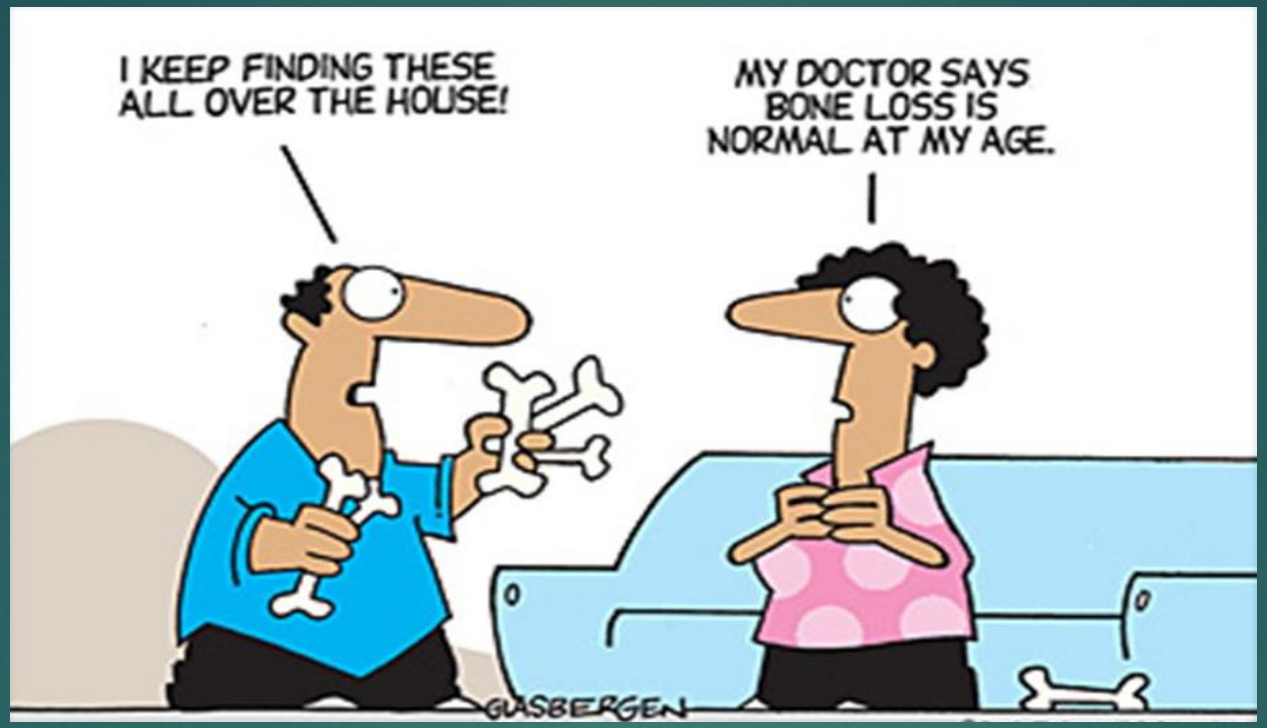
Male ♂

- 98% of men with CF are infertile[1]
  - Predominantly due to obstructive azoospermia caused by congenital bilateral absence of vas deferens (CBAVD)[1,2]
  - Some infertility seen regardless of obstruction[1]
    - Role of CFTR in transporting HCO_3^- associated with sperm motility[1]
    - *CFTR* mutations may also influence spermatogenesis due to fluid and electrolyte modifications in the epididymis[1]

Female ♀

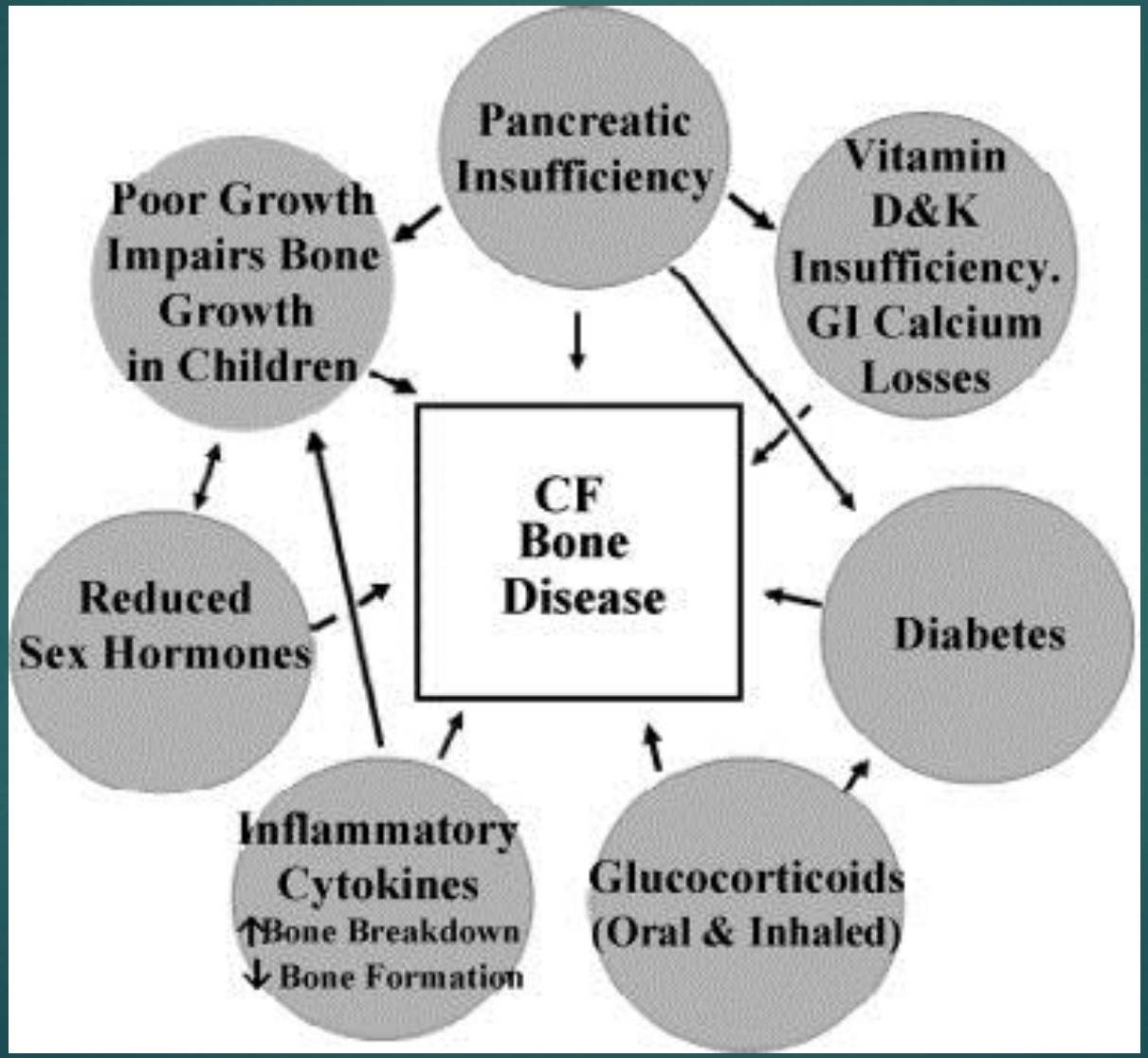
- Up to 50% of women with CF are able to conceive a child[1]
- Typically normal anatomy[1]
- Ovulation disturbances and delayed menarche (multifactorial)[1]
- Large amounts of CFTR in the cervix[1]
  - Most common abnormality is thick, dehydrated cervical mucus[1]
    - Impairs cervical penetration by sperm[1]
- Alterations of uterine HCO_3^- concentrations can result in failure of sperm capacitation and fertilization[1]

Cystic Fibrosis Bone Disease: CFBD



- First described in 1979
- Decreased BMD and bone quality regardless of steroid use (50-75% of adults)
- Increased risk of osteoporosis (23.5%), osteopenia (38%), vertebral fractures (14%), and non-vertebral fractures (20%)
- Risk increases with increasing age, hypogonadism, disease severity and malnutrition

Pathogenesis of CFBD



Abnormal Histomorphometry

- Decreased osteoblastic numbers and activity
- Increased osteoclastic numbers

→ Net increase in resorptive surfaces →

Sex Steroid Deficiency

- Delayed puberty
- Early hypogonadism

→ Inadequate bone accrual →

Pancreatic Insufficiency

- Exocrine insufficiency
- Endocrine insufficiency

→

- Malabsorption of vitamin D, vitamin K and calcium
- Diabetes

→

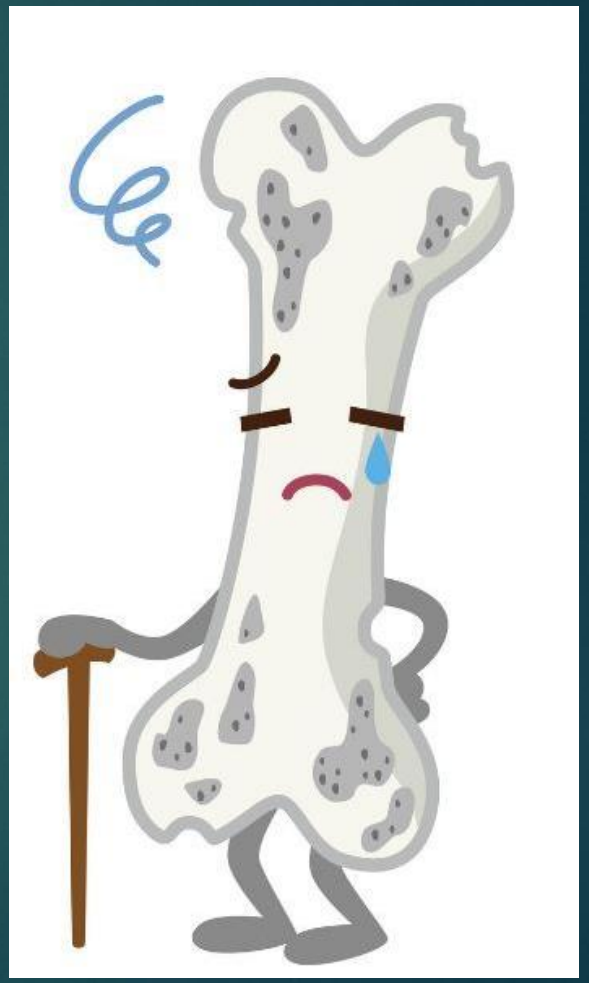
Chronic Infection

- Inflammatory cytokines increase
- Use of glucocorticoids
- Physical inactivity

→

- Cytokines
- Glucocorticoids
- Decreased weight bearing activity

→



CFBD

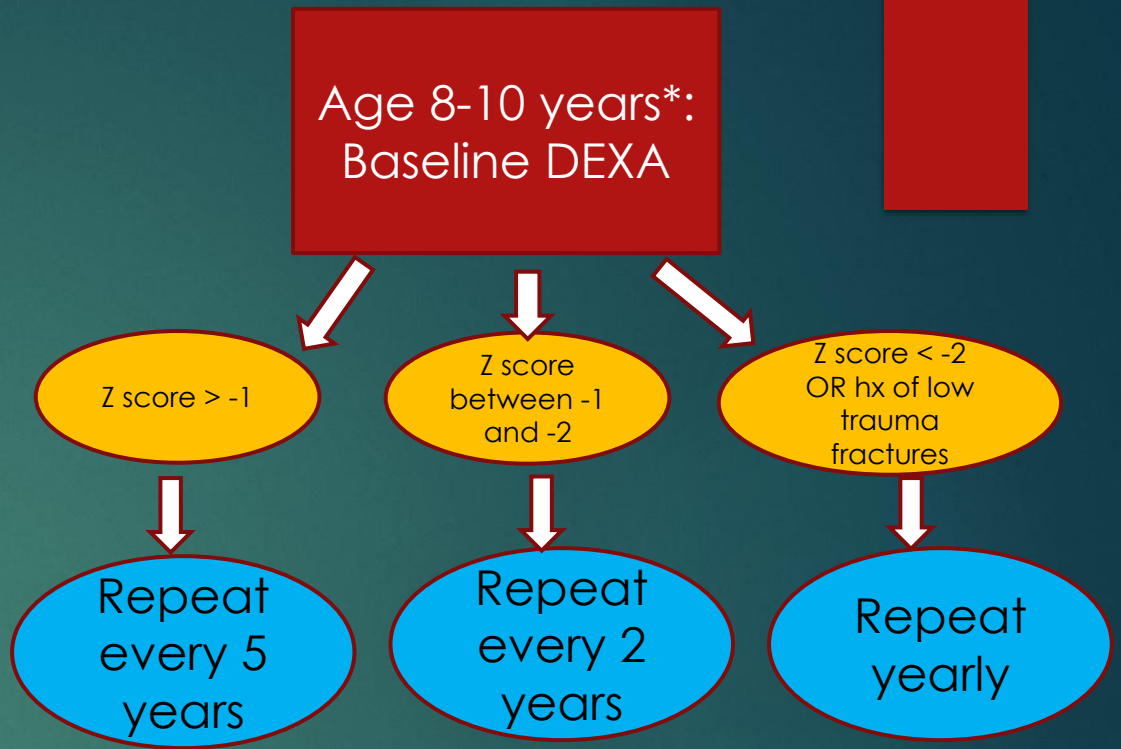
- Vitamin D
  - 30-60 ng/ml is optimal range
  - Severe deficiency (< 10 ng/ml) noted in 5-10%
  - Studies show adults with CF absorb 50% less oral vitamin than controls
  - Possible altered 25-hydroxylase activity due to biliary disease
  - Possible degradation of 25OHD due to increased oxidant and P450 activity
  - Reduced sunlight exposure and fat mass
- Vitamin K
  - Vitamin K insufficiency in 40%
  - K→ γ -carboxylated osteocalcin → binding of calcium ion of hydroxyapatite molecule

CFBD

- Pain
- Debilitation
- Chest Wall Deformities → Decreased Lung Function (lung volume and capacity)
- Inhibited cough → Decreased airway clearance
- Increased risk of fractures
- Worsening kyphosis
- Possible lung transplant exclusion

CFBD: Assessment

- Nutrition Assessment:
  - Height, weight and BMI measurements/percentiles every visit
  - CF nutritionist should annually assess dietary energy and protein intake
  - Annual screening for levels of vitamin 25 OHD, calcium, phosphorus, PTH and vitamin K
- Endocrine Evaluation:
  - Growth velocity determined every visit
  - Biannual evaluation of pubertal development
  - Full endocrine workup if there is a concern
  - Monitor for Cystic fibrosis related diabetes
- Imaging
  - DEXA
    - Use Z score unless postmenopausal or male >50 (T score)
    - Total Body < 20 years; L spine and hip > 20 years
    - Short stature: Adjust BMD for height < 20 years or < 1 SD normal
  - Lateral CXR for vertebral fractures



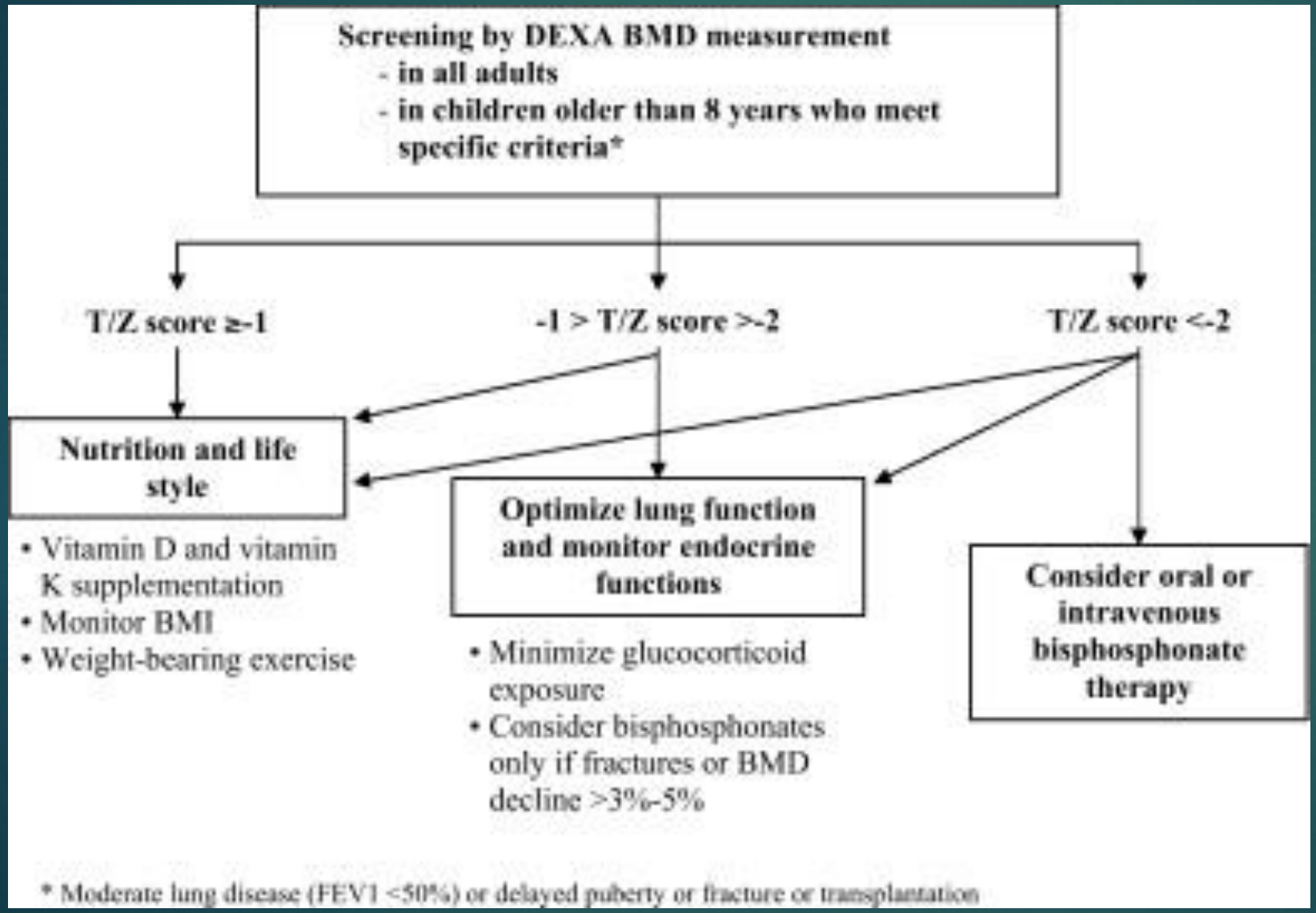
	CF related low BMD	Osteoporosis
<20 years	Z score < -2	Z score < -2 AND Significant low trauma fracture
>20 years	Z score < -2	Z score < -2 AND Significant low trauma fracture
Postmenopausal women and Men > 50 years	Z score < -2	T score < -2.5 AND/OR Significant low trauma fracture

CFBD: prevention

- Nutrition
  - Maintain normal BMI (> 50th percentile)
  - Vitamin D, Vitamin K and Calcium supplementation
- Endocrine
  - Provide growth hormone if needed
  - Provide sex hormone replacement if needed
- Other
  - Limit pulmonary exacerbations and glucocorticoid use
  - Encourage weight bearing exercises

	Infants	childhood	adolescent	Adult	>50 years
D (IU)	1000 - 2000	1000 - 5000	1000 - 5000	1000 - 5000	1000 - 5000
K (mg)	0.5 - 2	1 - 10	1 - 10	1 - 10	1 - 10
Ca (mg)	210 - 270	500-800	1300	1000	1200

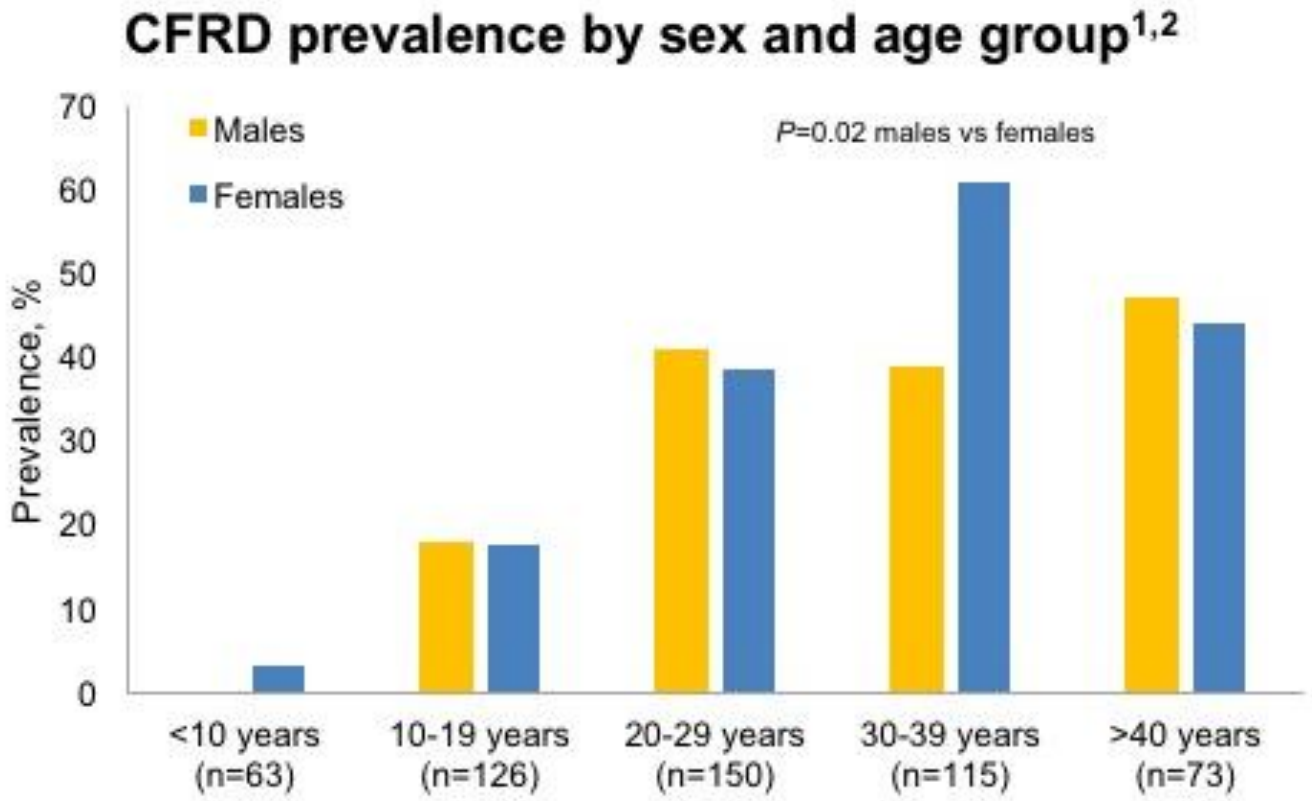
CFBD: Treatment



- Growth hormone/sex hormone replacement
- Bisphosphonates in children
  - Z score < -2 + hx of low trauma fracture
  - Z score < -2 + waiting or undergone solid organ transplantation
  - Z score < -2 + systemic continuous glucocorticoids

Cystic Fibrosis Related Diabetes: CFRD

Prevalence of CFRD Increases With Age

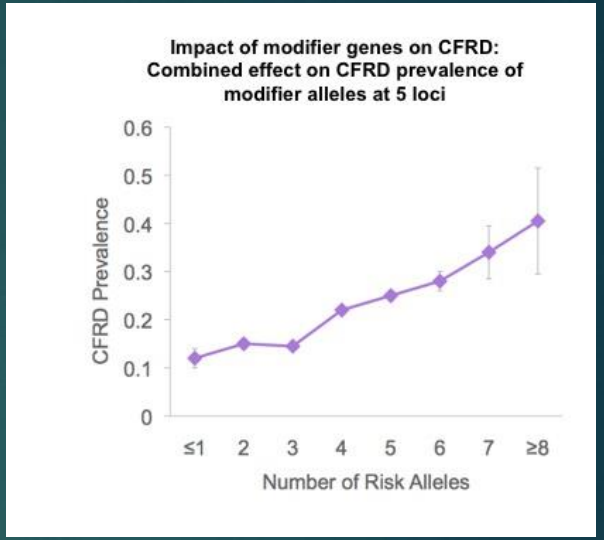


CFRD Vs. Type I/II

	Type 1 diabetes	Type 2 diabetes	CFRD
Onset	Acute	Insidious	Insidious
Peak age of onset	Children & adolescents	Adults	18-24years
Antibody+	Yes	No	Probably No
Insulin secretion	Eventually absent	Decreased	Severely decreased but not absent
Insulin sensitivity	Somewhat decreased	Severely decreased	Somewhat decreased
Treatment	Insulin	Diet, oral medication, insulin	Insulin
Microvascular Complications	Yes	Yes	Yes but less
Macrovascular Complications	Yes	Yes	No
Cause of death	Cardiovascular disease Nephropathy	Cardiovascular disease	Pulmonary disease

CFRD

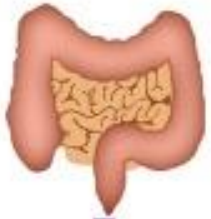
- Clinical Symptoms:
  - Failure to gain weight/weight loss
  - Poor growth velocity
  - Delayed puberty
  - Unexplained decline in pulmonary function
  - Late signs → polyuria, polydipsia
  - Often clinically silent
- Risk Factors:
  - Older Age
  - Pancreatic Exocrine insufficiency (up to 5 x higher risk with some genotypes)
  - Delta 508 homozygous genotype
  - Female Gender
  - Family History of DM-2
  - Liver Disease



Genes with modifications (SNPs) associated with CFRD

Gene	Potential Mechanism
SLC26A9	Anion transporter that interacts with CFTR and may modify CF phenotype
TCF7L2	Known susceptibility for type 2 diabetes
CDKAL1	
CDKN2A/B	
IGF2BP2	

Glucose Concentrations Are Tightly Regulated in Healthy Individuals



Nutrient absorption (carbohydrates, protein, fat)

↑ Blood glucose[1]

Incretin secretion (GLP-1, GIP)[3]

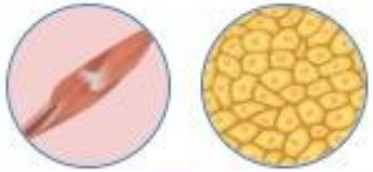
- Incretins increase pancreatic insulin secretion[1]
- "Incretin effect" may account for ~70% of total insulin secretion[2]

Pancreas

↑ Insulin secretion[1] → Suppression of protein, carbohydrate, fat catabolism[1]

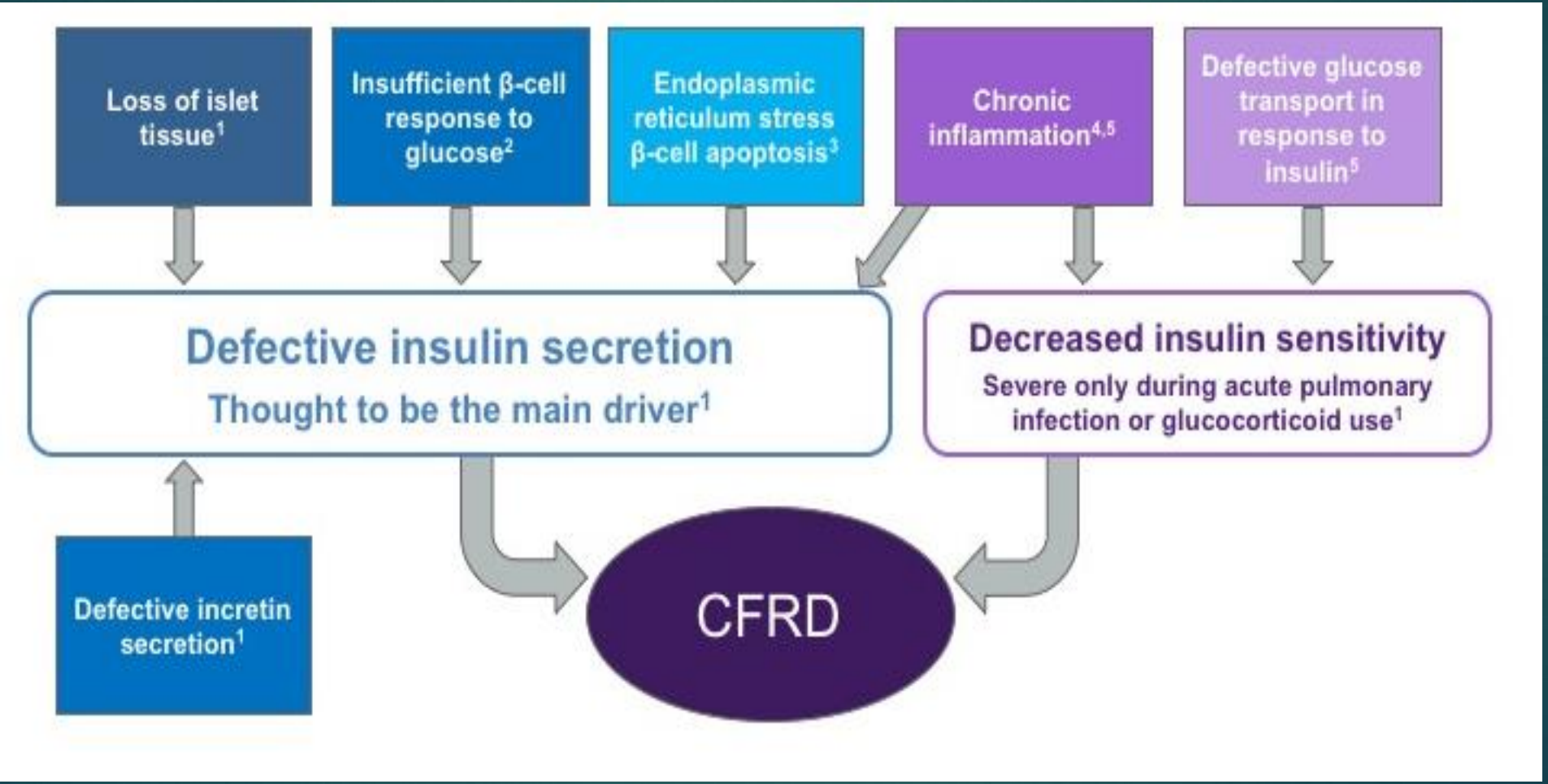
↑ Glucose storage[1]

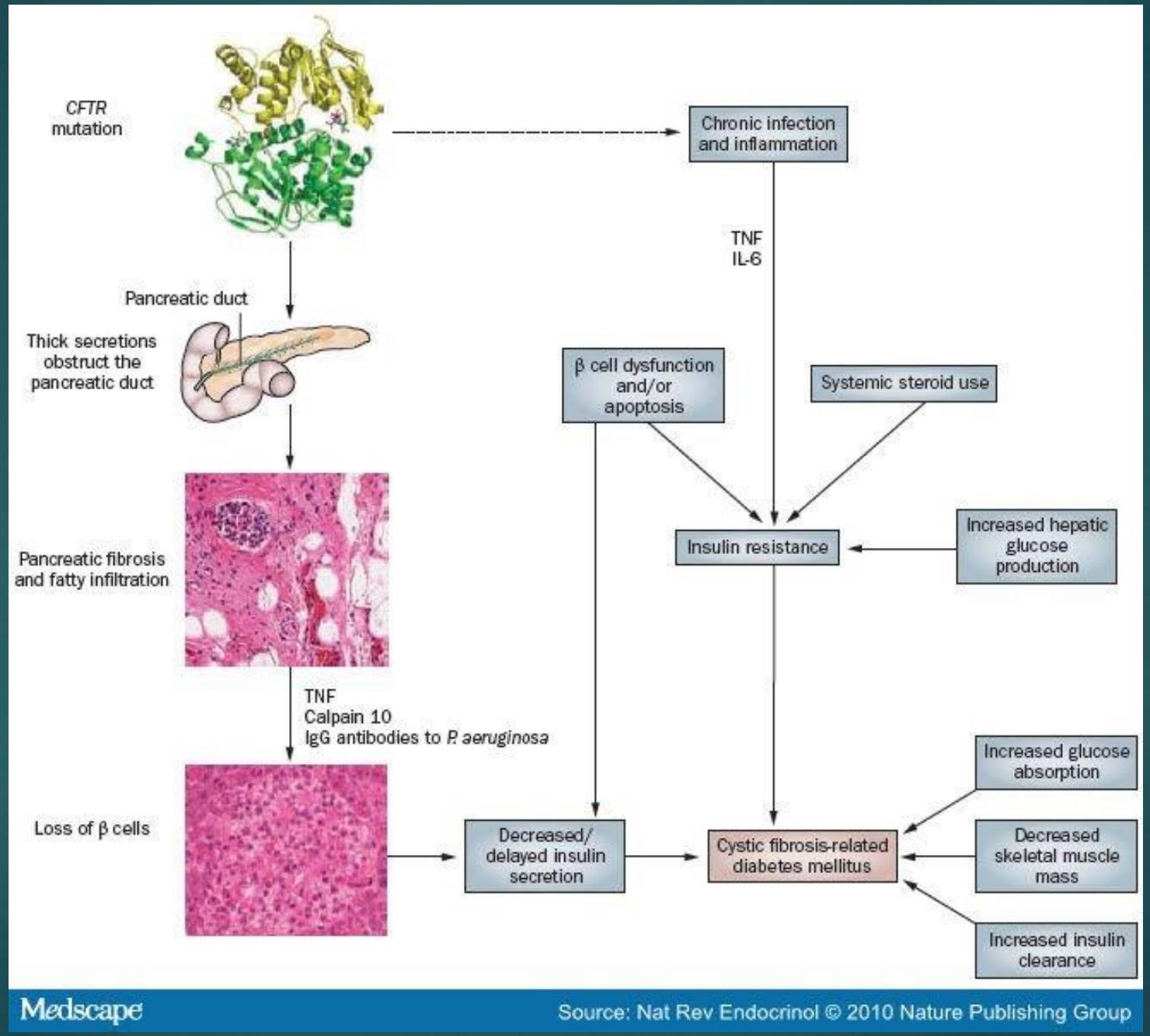
↑ Glucose uptake in muscle and fat[1]



→ Blood glucose normalization[3]

Pathophysiology




CFTR mutation
Chronic infection and inflammation
TNF
IL-6
Pancreatic duct
Thick secretions obstruct the pancreatic duct
β cell dysfunction and/or apoptosis
Systemic steroid use
Pancreatic fibrosis and fatty infiltration
Insulin resistance
Increased hepatic glucose production
TNF
Calpain 10
IgG antibodies to P. aeruginosa
Increased glucose absorption
Loss of β cells
Decreased/ delayed insulin secretion
Cystic fibrosis-related diabetes mellitus
Decreased skeletal muscle mass
Increased insulin clearance
Medscape
Source: Nat Rev Endocrinol © 2010 Nature Publishing Group

CFRD: Does Amyloidosis Play a Role?

Diabetes Mellitus in Cystic Fibrosis Is Characterized by Islet Amyloidosis*

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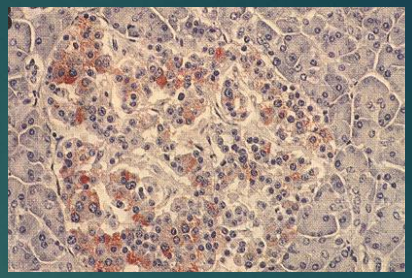
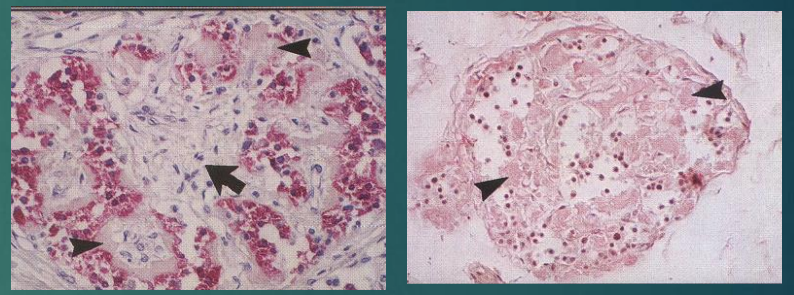


Healthy Beta Cell



CFRD

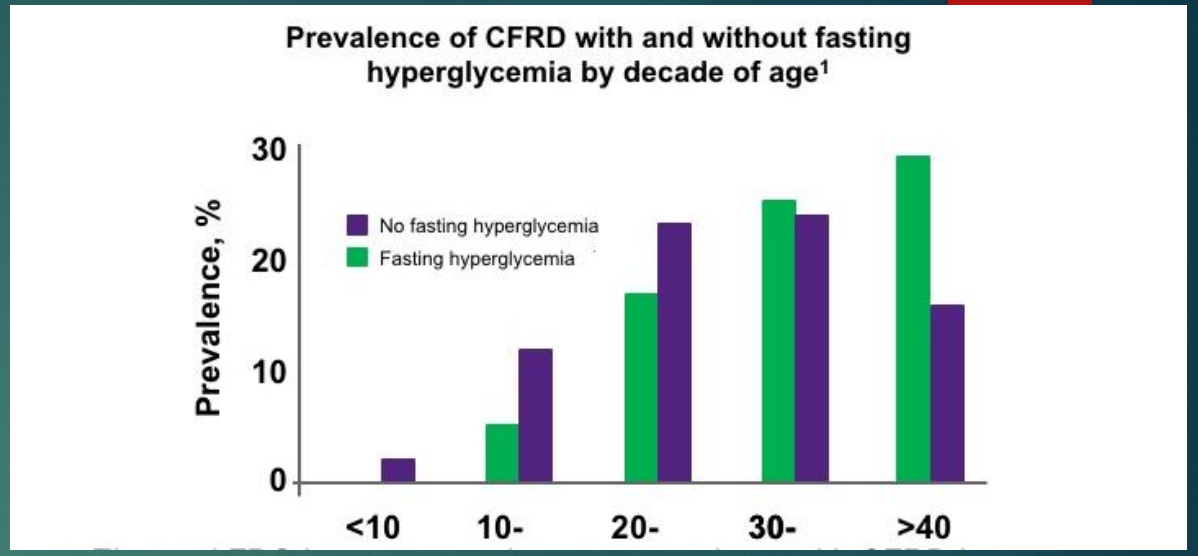
TABLE 2. Light microscopy islet morphology

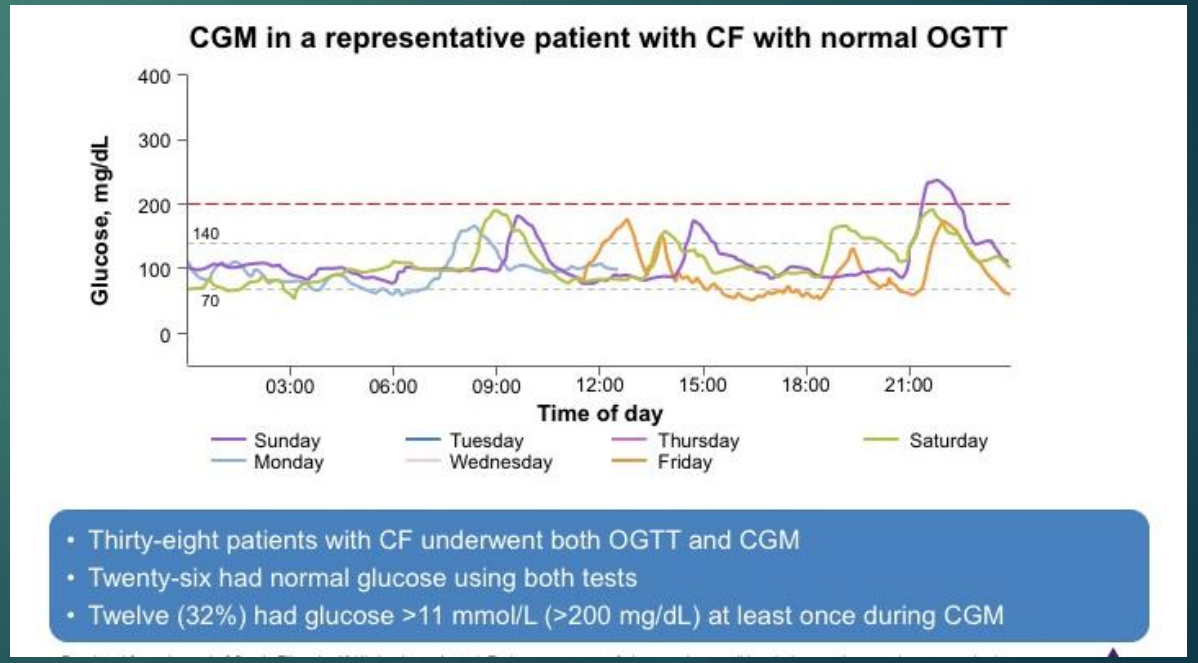
	No.	Age (yr)	Glyco (%)	Mean islet area ($\times 10^4$ μm^2)	% Cases with islet amyloid	% Islet area amyloid[a]	% Islet area insulin staining
Controls	9	65 ± 10[b]		6.2 ± 0.6	0		30 ± 3[b]
CF-ND	13	26 ± 3	5.9 ± 0.3	5.6 ± 0.9	0		17 ± 2
CF-BD	12	18 ± 2	6.1 ± 0.3	5.2 ± 0.1	16.7	7.1 ± 1.3	15 ± 2
CF-D	16	27 ± 2	7.9 ± 0.4	6.3 ± 1.0	69	11.1 ± 1.0	12 ± 2

[a] Islets positive for amyloid only.
[b] $P < 0.01$, controls *vs.* all CF cases.

CFRD: Screening

- Hemoglobin A1C: poor sensitivity
  - Low correlation with glucose tolerance
  - Low PPV
  - Spuriously low due to inflammation causing increased RBC turnover
- Also not used:
  - Fructosamine
  - Urine glucose
  - Random glucose
  - CGM (intermittent high BG non-diagnostic)
  - Fasting plasma glucose (will miss ½ of CFRD)
  - Self monitoring with glucometer (up to 20% variability from true BG)

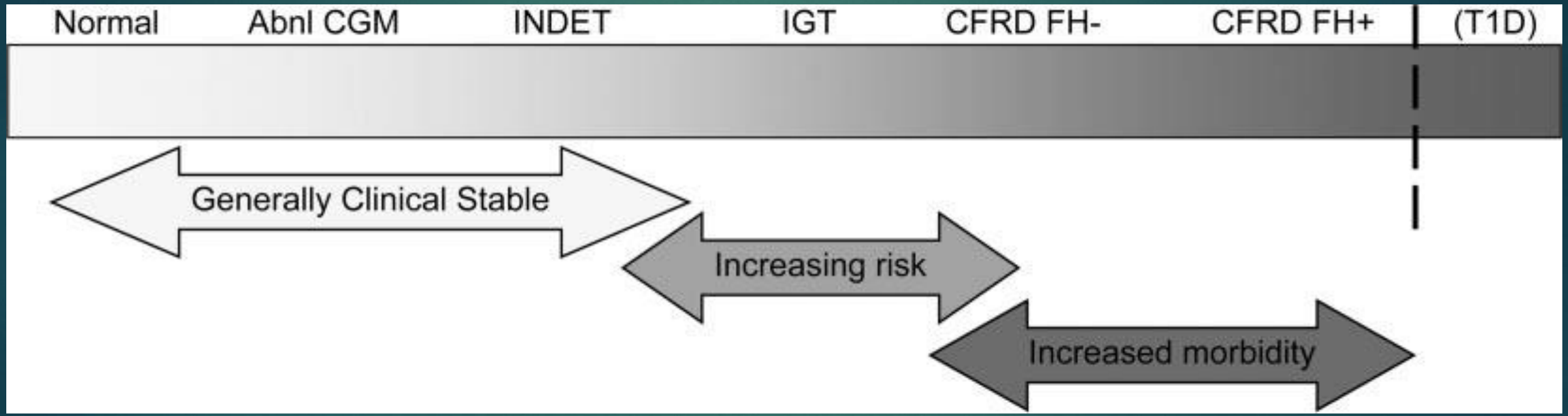




CFRD: 2 Hour OGTT

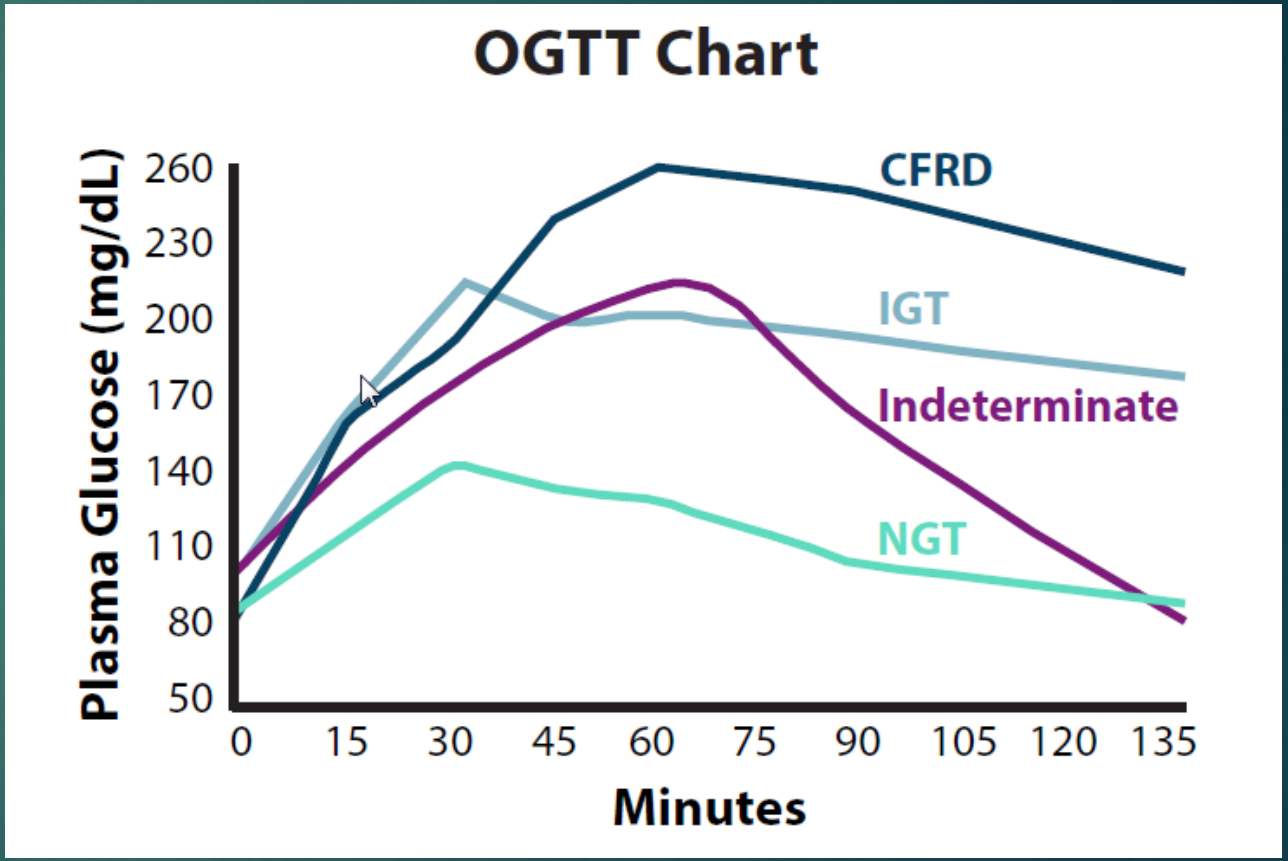
- Annual 2 hour OGTT beginning latest by 10 years of age
- Done fasting, usually in AM
- Identifies patients in need of insulin
- Correlates with clinically important CF outcomes such as lung function, microvascular complications and mortality
- Confirmed through second OGTT on another day
- Period of stable baseline health (6 weeks since last exacerbation)

CFRD: Spectrum of Glucose Tolerance



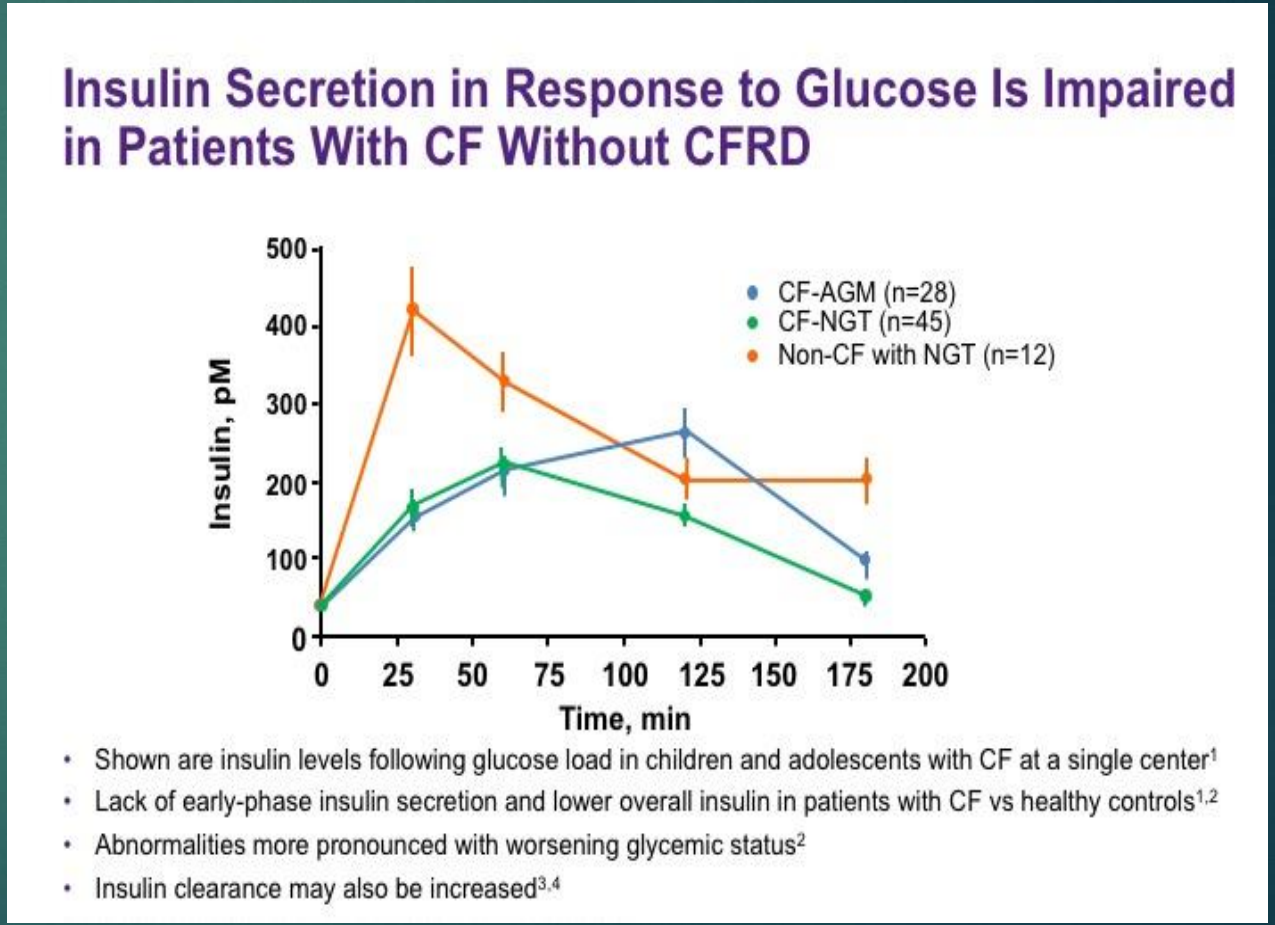
CFRD: Diagnostic Criteria

	0 hour mg/dl	1 hour mg/dl	2 hour mg/dl
NGT	<100		<140
IGT	100-125		140-199
INDET	<100	≥200	<140
CFRD	≥126		≥200



Screening: INDET

- Impaired fasting glucose and indeterminant glycemia are common
- 28% abnormal glucose tolerance age 3-5 and 33% by age 6-9.
- Delay and blunting of first phase insulin response
- OGTT should always contain 1 hour intermediate value
- INDET and IFG strongly associated with decline in lung function and nutritional status
- Associated with early onset CFRD in prepubescent CF patients
- Early studies suggest treatment of INDET improves lung function and BMI



CFRD: Management

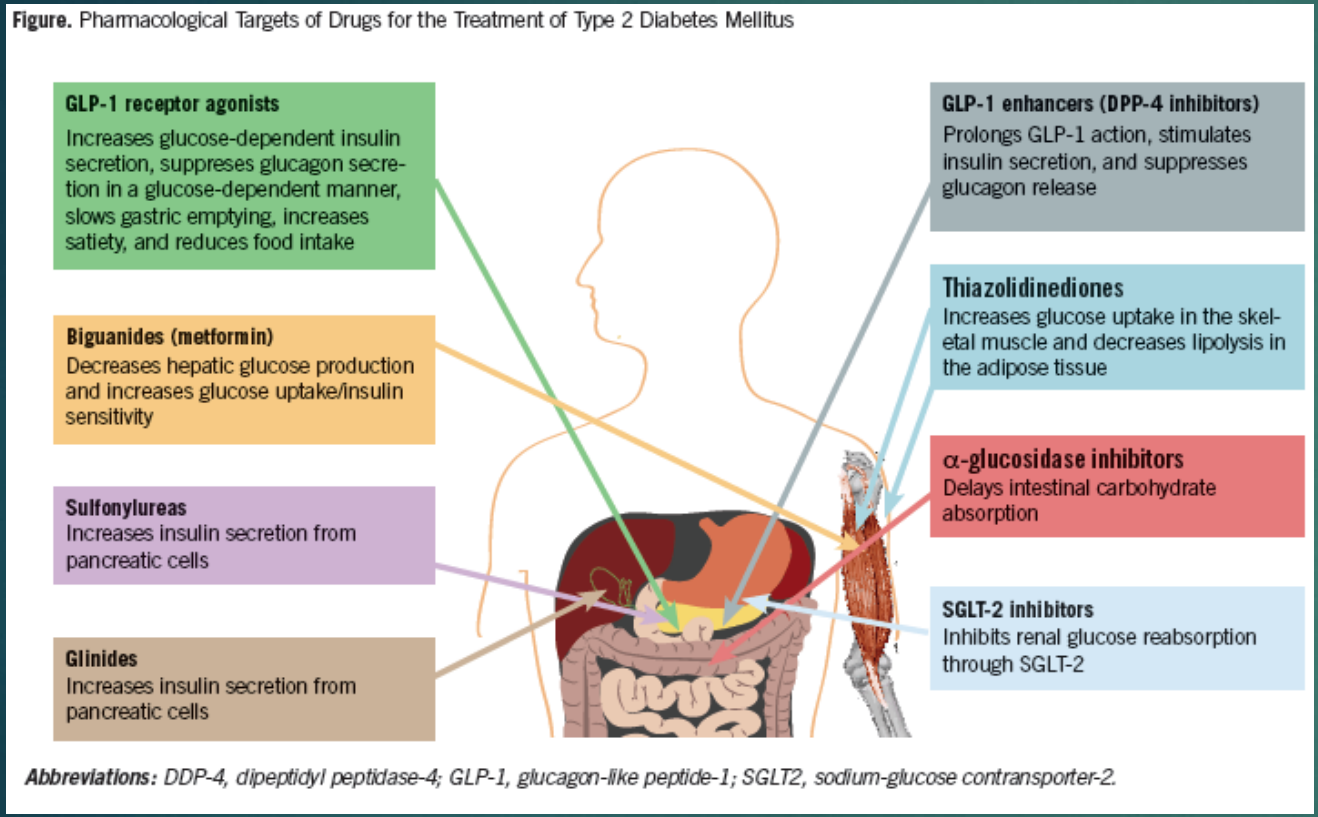
- Insulin is the treatment of choice[1]
- Oral diabetes agents are not recommended[1]
- Patients with CFRD receiving insulin should perform blood glucose monitoring ≥3 times daily[1]
  - HbA1c quarterly to guide insulin therapy decisions
- Treatment goals are to maintain glucose levels in accordance with ADA guidelines for diabetes (postprandial: <180 mg/dL [10.0 mmol/L] for adults and adolescents, <200 mg/dL [11.1 mmol/L] for children)[1,2]
- Adherence to CFF nutritional guidelines and moderate aerobic exercise are recommended[1]

CFRD: Management

- Insulin therapy: basal/bolus through injection or pump
  - Self monitoring minimum 4 times per day
  - Instructions for hypoglycemia management
  - Quarterly A1C for measurement of glycemic control
  - CGM

	Fasting and pre-meal, mg/dL	2–3 h post-prandial, mg/dL	Bedtime, mg/dL
Adults	**70–130**	**<180**	**90–150**
Adolescents	**90–130**	**<180**	**90–150**
School-age children	**90–180**	**<200**	**100–180**
Children <6 years	**100–180**	**<200**	**110–200**
Pregnant women	**≤95**	**≤120**	**60–99**

CFRD: Management with Oral Agents?



- CFRD characterized by reduced or delayed insulin secretion and mostly normal insulin sensitivity
- Insulin secretagogues: Repaglinide failed to demonstrate improving lung function or BMI
- Sulphonylureas: Glipizide demonstrated a good early response but a poor response in overt CFRD. May bind/inhibit CFTR
- Insulin sensitizing: metformin or thiozoladinediones ineffective due to normal insulin sensitivity
- Alpha glucosidase inhibitors: Not recommended due to CF nutritional requirements
- GLP-1 agonists and DPP4 inhibitors: under investigation

CFRD: Nutrition Management

	Type 1/type 2 diabetes	CFRD
Calories	• Calculated for maintenance, growth or reduction diets	• 120–150% RDA
		• Calories never restricted
Carbohydrate	• Individualized	• Total intake unrestricted
Fat	• Individualized	• High fat intake (35–40% of total calories)
	• <10% calorie intake from saturated fats	
	• Dietary cholesterol intake <300 mg/day	
Protein	• Protein reduction in presence of diabetic nephropathy (0.8 g/kg)	• Protein reduction may not be appropriate
Sodium	• Salt restriction to reduce macrovascular complications (<2400 mg/day)	• High sodium diet essential (>4000 mg/day)

CFRD: Morbidity

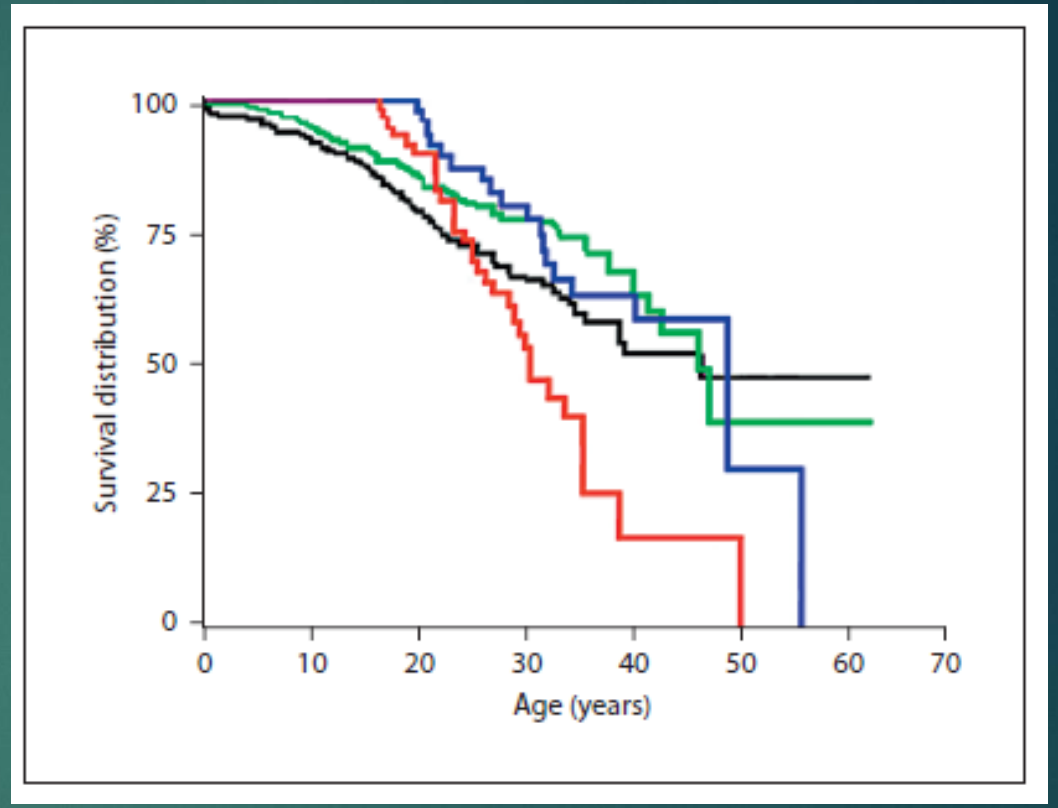
- Worsening lung disease and nutritional status (up to 2-6 yr before diagnosis)
- Increased microvascular complications
  - *Microvascular Complications in Cystic Fibrosis Related Diabetes*. Schwarzenberg SJ et al. Diabetes Care. 2007.
    - 39 patients with CFRD + FH
    - 14% microalbuminuria, 16 % retinopathy, 55% neuropathy, 50% gastropathy

Complications of CFRD in 2016 (n=6,204)

	All (n)	All (%)	Age < 18 (%)	Age ≥ 18 (%)
Retinopathy	46	0.7	0.2	0.8
Microalbuminuria	111	1.8	0.2	2.1
Chronic renal insufficiency	213	3.4	<0.1	4.0
Chronic renal failure requiring dialysis	24	0.4	<0.1	0.5
Peripheral neuropathy	67	1.1	0.1	1.2
Any episodes of severe hypoglycemia	295	4.8	3.4	5.0

CFRD: Mortality

- Increased mortality
  - *Diabetes Mellitus Associated with Cystic Fibrosis*. Finkelstein et al. J. of Pediatrics. 1988.
    - 448 patients with CF followed for 10 years
    - 25% with CFRD alive at age 30 years; 60% without CFRD alive at age 30 years
- Women: significantly lower survival with CFRD



CF Men - CFRD (49.5)
CF Men + CFRD (47.4)

CF Women - CFRD (47)
CF Women + CFRD (30.7)

In Summary…

- Cystic Fibrosis can lead to multiple endocrine disorders
- A collaboration between subspecialties allows for careful monitoring of growth, puberty, bone disease and CFRD
- It is expected that advances in CF therapies and longer lifespans will increase prevalence of endocrine disorders
- Early identification and treatment of endocrine disorders improves morbidity and mortality in the CF patient

Thank you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℞
"The top doesn't come off. It's preventative medicine."