Cystic fibrosis in the post-modulator era

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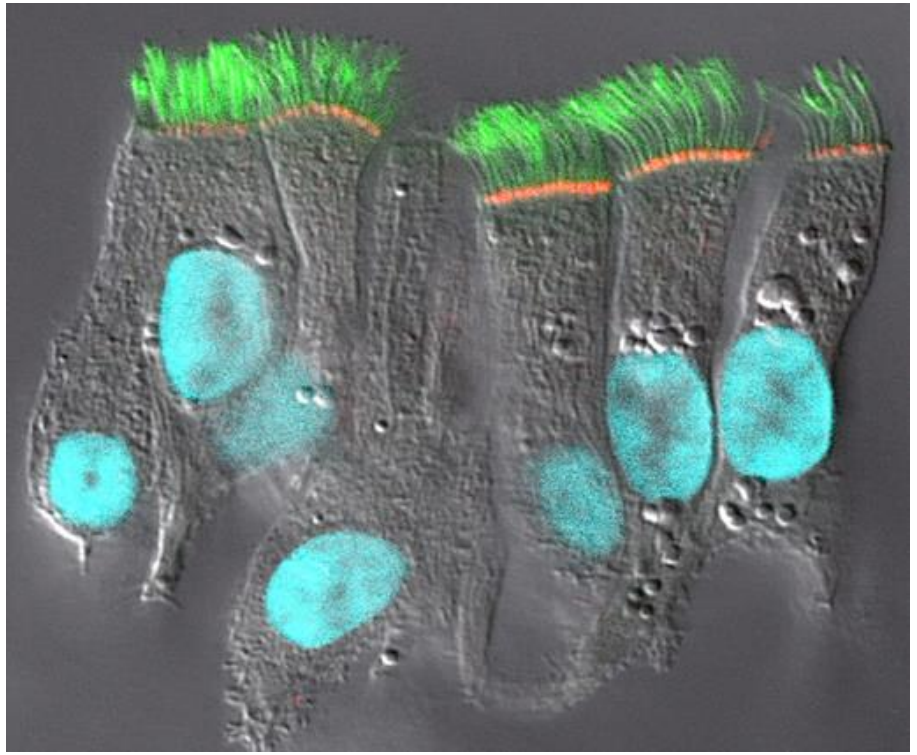
- Diagnosing CF in adults
- CFTR modulators
- Common emergency presentations
- The future



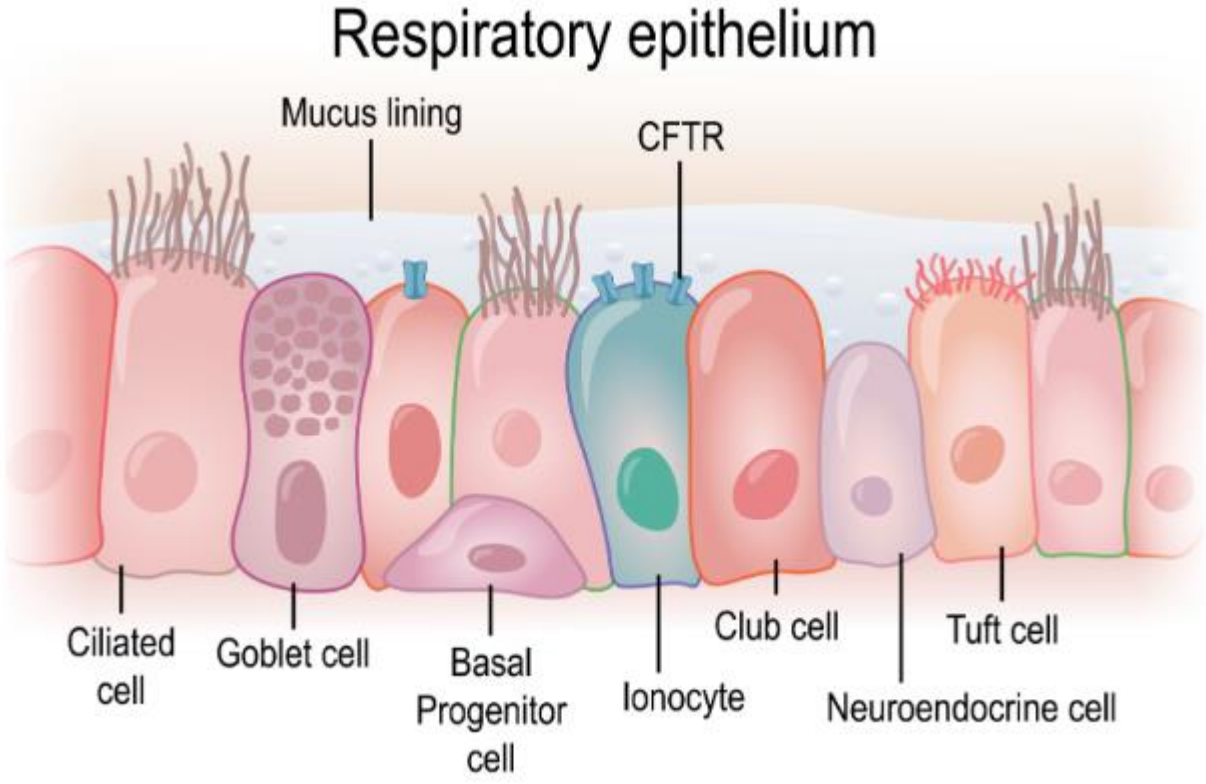
I have no COI to declare

Kreda et al, (2005) Mol Biol Cell 16,2154

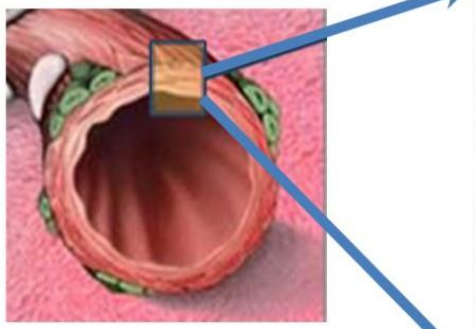
What is CFTR?

CFTR

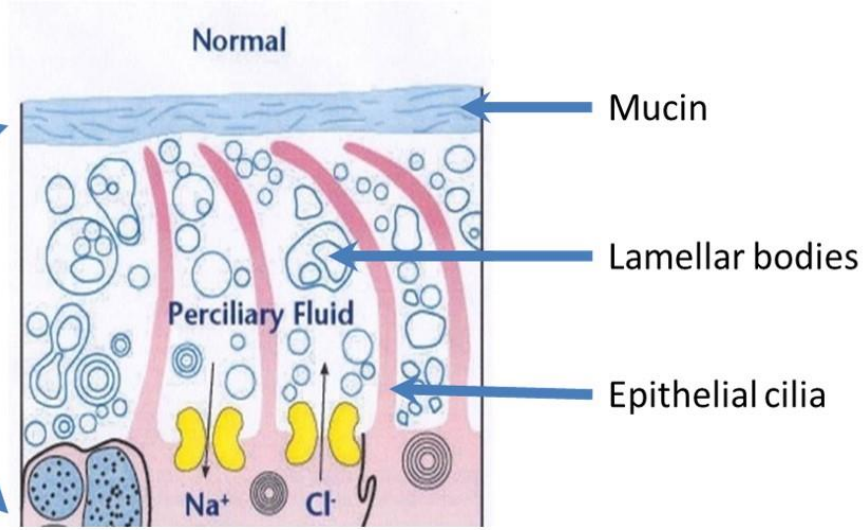
- ATP-binding cassette (ABC) transporter
- Anion channel
- Active transport of Cl- and HCO_3- across epithelial cell membranes
- Apical surfaces of multiple exocrine organs

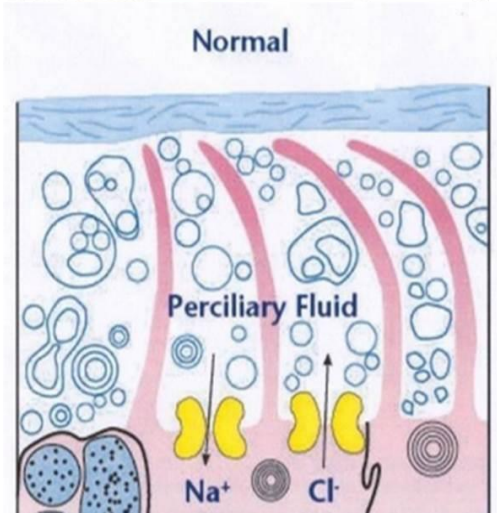


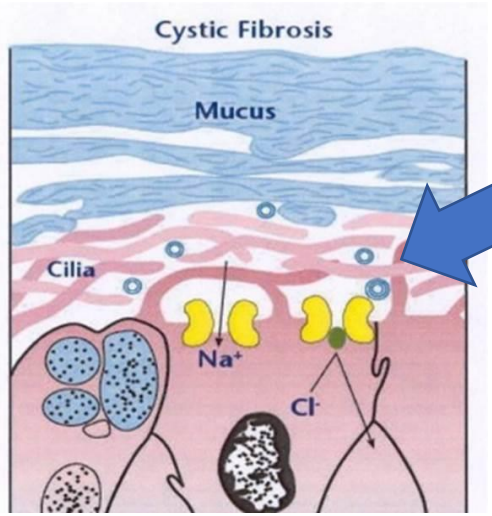
CFTR function



Airway cross section







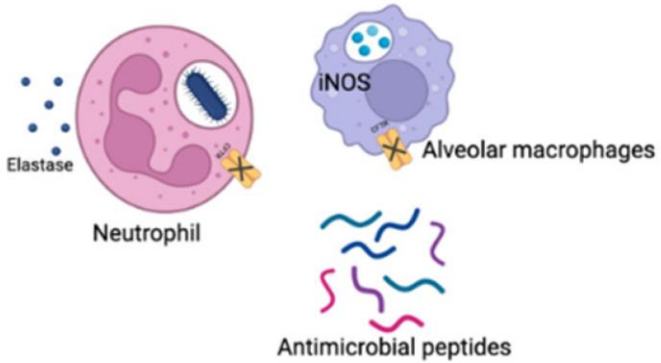
- Salt and fluid regulation in mucous membranes
- pH regulation

No chloride or bicarbonate released into the cilia via CFTR therefore, no water either

CF Airway

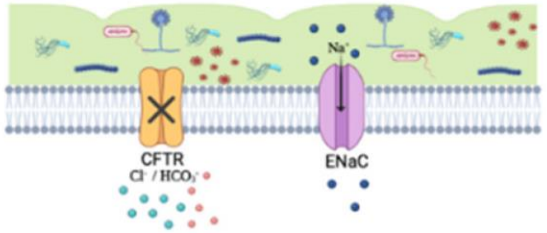
↓mucociliary transport

Dysregulated innate immune response



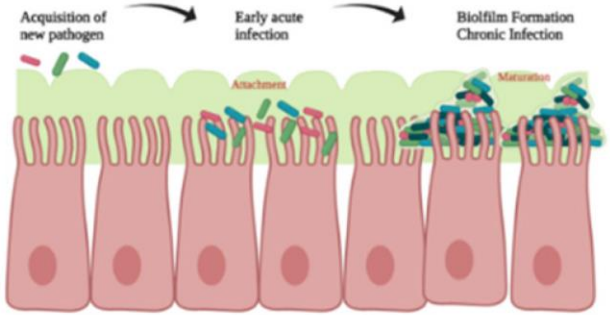
- Impaired phagocytosis
- Changes in neutrophil degranulation
- Increase polarisation to M1 phenotype
- Cleaved, denatured and ineffective AMPs

Abnormal airway microenvironment



- Dehydration and acidification of airway surface liquid
- Production of thick sticky mucus
- Reduced clearance of trapped microorganisms

Biofilm Formation



- Acquisition of new pathogens
- Initial aggregation and adherence to epithelium
- Reduced killing by impaired immune defences
- Adaption to the available nutritional and environmental conditions
- Maturation of bacterial aggregates to polymeric biofilm
- Chronic pulmonary infection

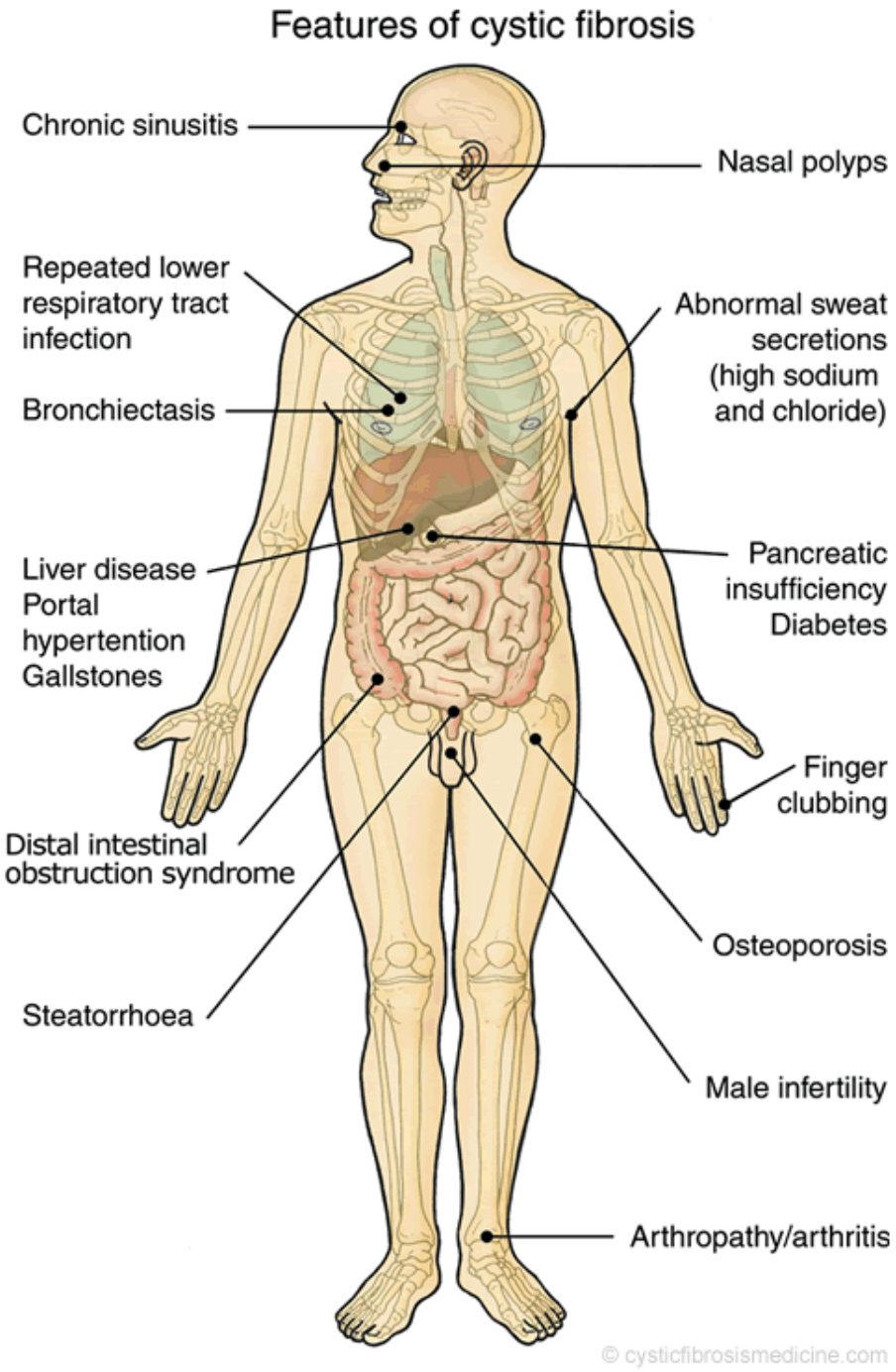
Harvey, C. et al. The Effect of CFTR Modulators on Airway Infection in Cystic Fibrosis. *Int. J. Mol. Sci.* **2022**, *23*, 3513

CF patients in the UK

- >11,000
- 56% adults
- Autosomal recessive
- CFTR mutations in 1 in 25 of the Caucasian population
- 2000+ mutations within CFTR >380 know to be pathogenic
- 53% homozygous for delF508
- Approx 85% heterozygous or homozygous for delF508

Consequences of abnormal epithelial cell function due to abnormal CFTR..

85% diagnosed by new born screening (positive heel prick test for trypsinogen)



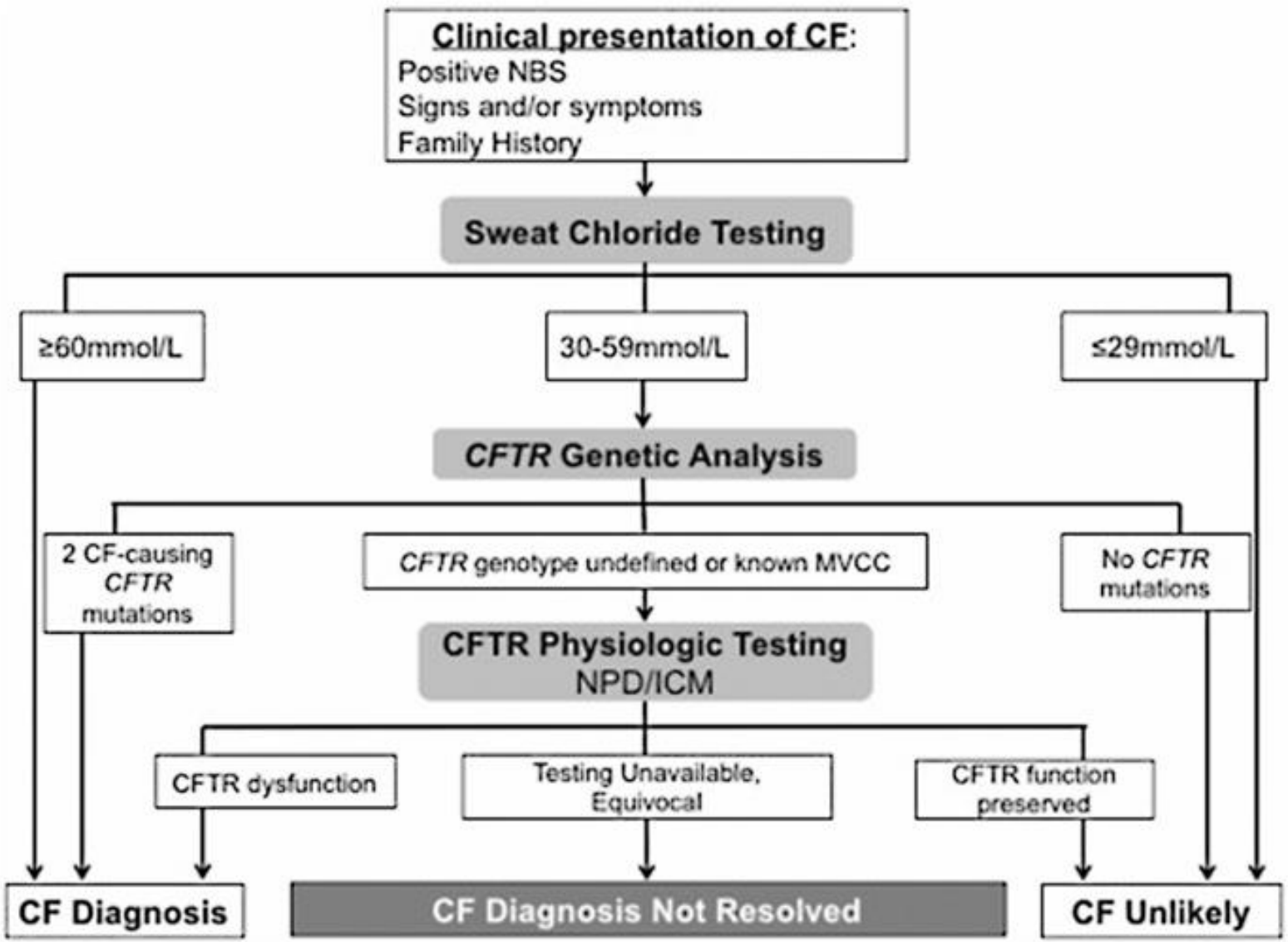
So does your patient have CF?

NBS Newborn screening

NPD Nasal Potential Difference

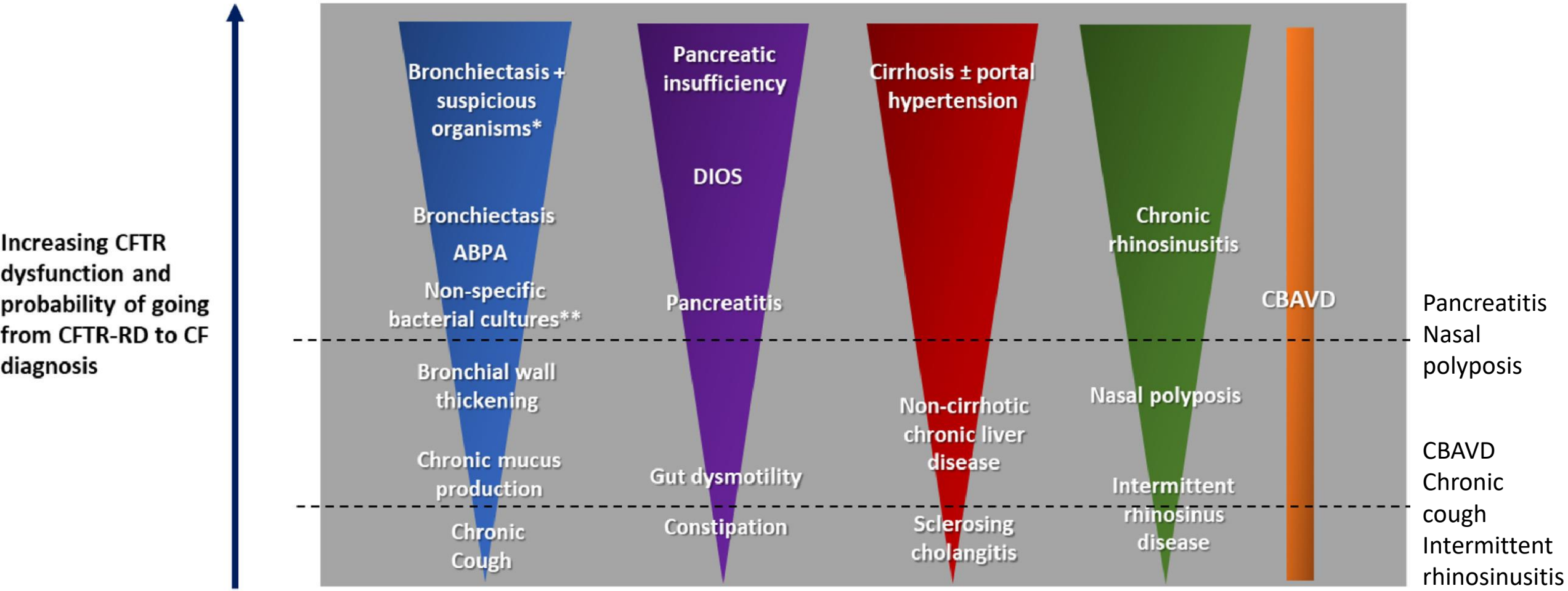
ICM Intestinal Current Measurement

MVCC Mutation of Variable Clinical Consequence



Farrell PM, White TB, Ren CL, et al. Diagnosis of cystic fibrosis: consensusguidelinesfromthecystic fibrosisfoundation.JPediatr 2017;181S:S4–S15, 15.e1

Clinical features associated with CF and CFTR-RD and the relationship with CFTR dysfunction



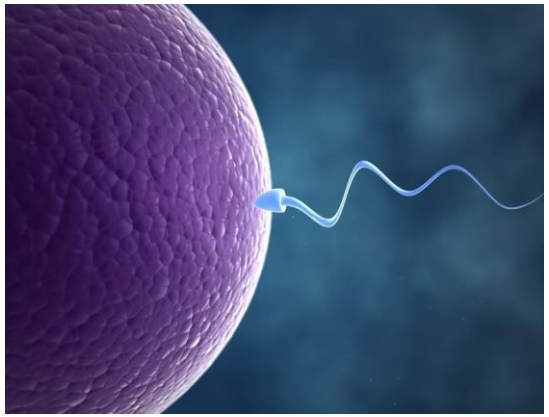
*Suspicious organisms from respiratory tract – e.g. *Pseudomonas aeruginosa*, *Burkholderia cepacia* complex, *Mycobacterium abscessus*

**Non-specific organisms from respiratory tract –

Castellani C et al., ECFS standards of care on CFTR-related disorders: Updated diagnostic criteria. JCF 21 (2022) 908-921.

How do adults present with CF?

- 15% diagnosed late (~1000 patients in the UK)
- 30-50 new adult cases per year in the UK



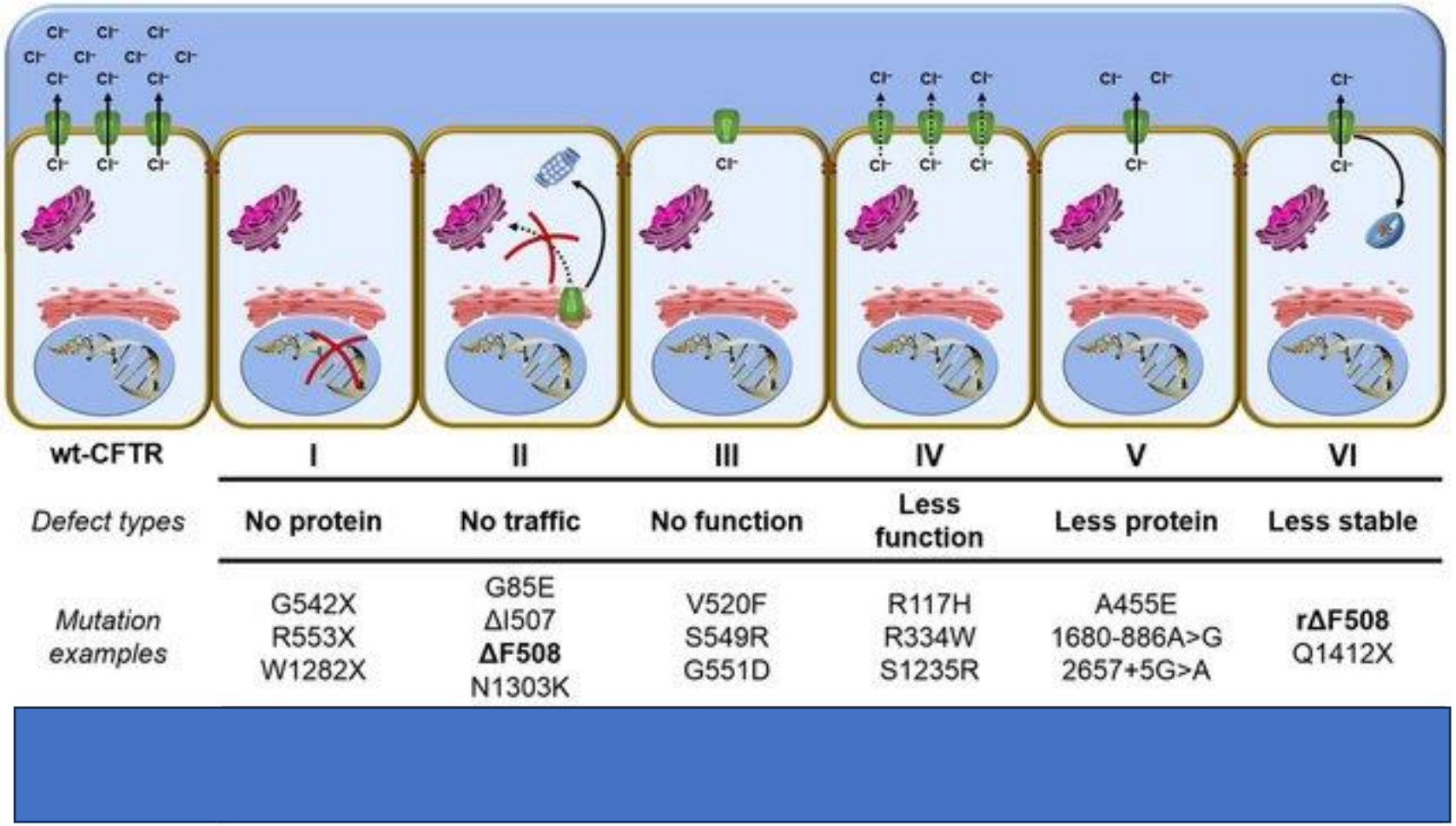
- >50% of those cases have bronchiectasis and recurrent infections
- 7% infertility (?)
- 6% GI symptoms (e.g. recurrent pancreatitis)
- 5% nasal polyposis
- 23% genetic diagnosis (reason for sending test could be infertility etc…)

UK CF Registry Report, 2021

Classification of CFTR mutations

I – III: minimal function mutation

IV – VI: residual function mutation



Lopes-Pacheco M (2016) Front. Pharmacol. 7:275.

Classification of CFTR mutations

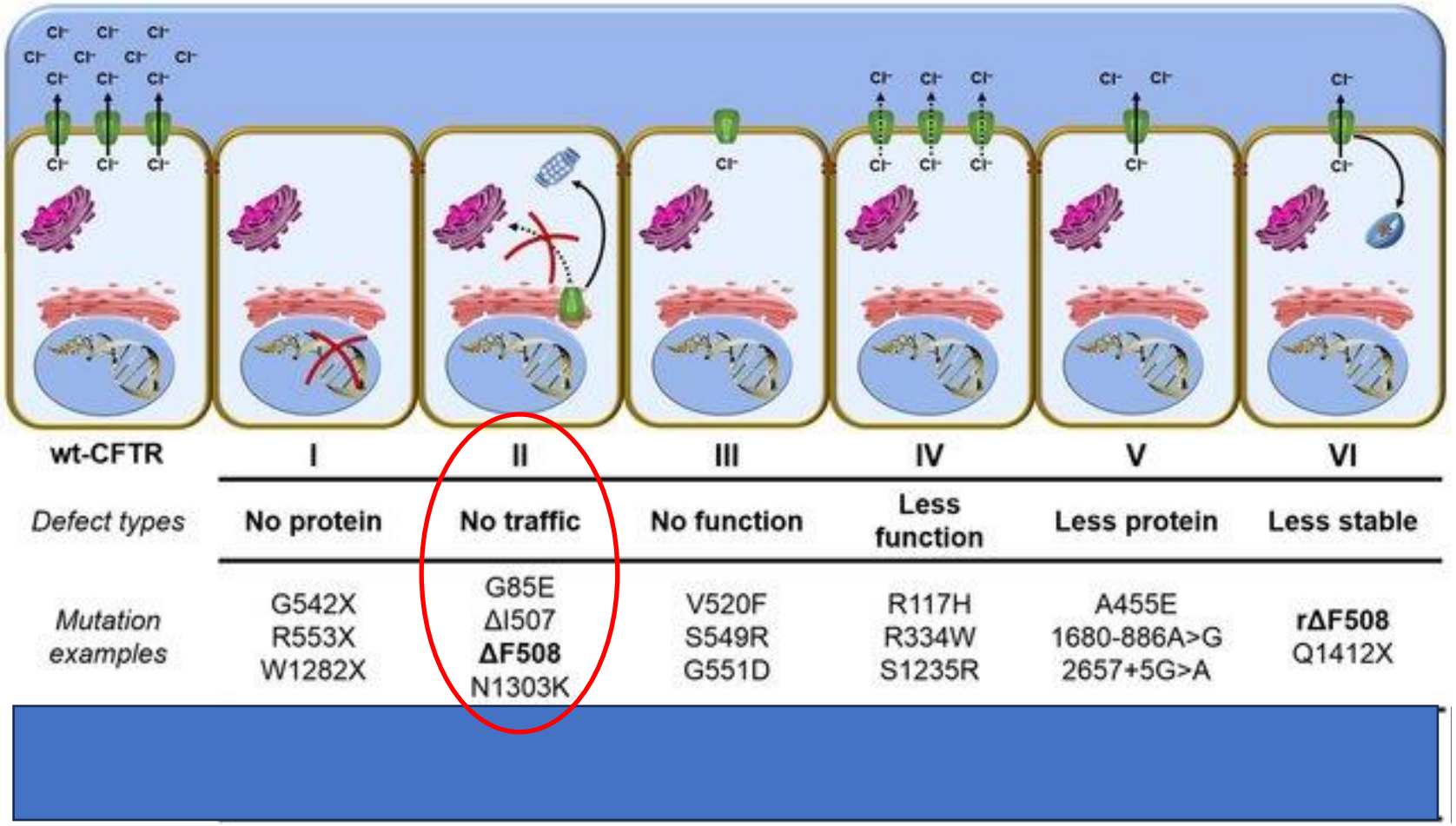
In the UK,

Del F508 homozygous 53%

DelF508 heterozygous 32%

III – VI mutations 4%

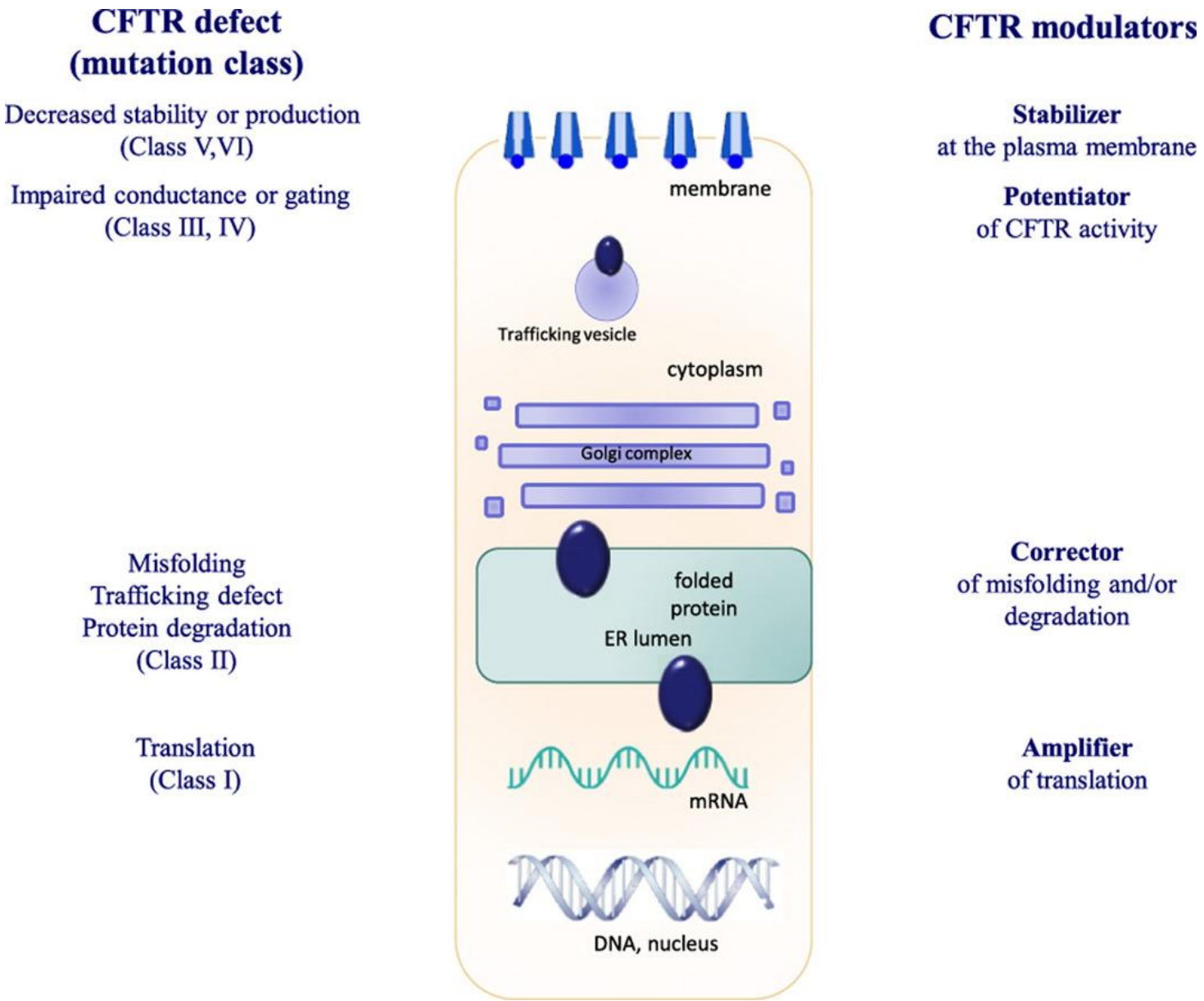
Other mutations or not identified 11%



Lopes-Pacheco M (2016) Front. Pharmacol. 7:275.

A revolution in CF care - CFTR modulators..

a class of drugs that act by improving production, intracellular processing, and/or function of the defective CFTR protein.



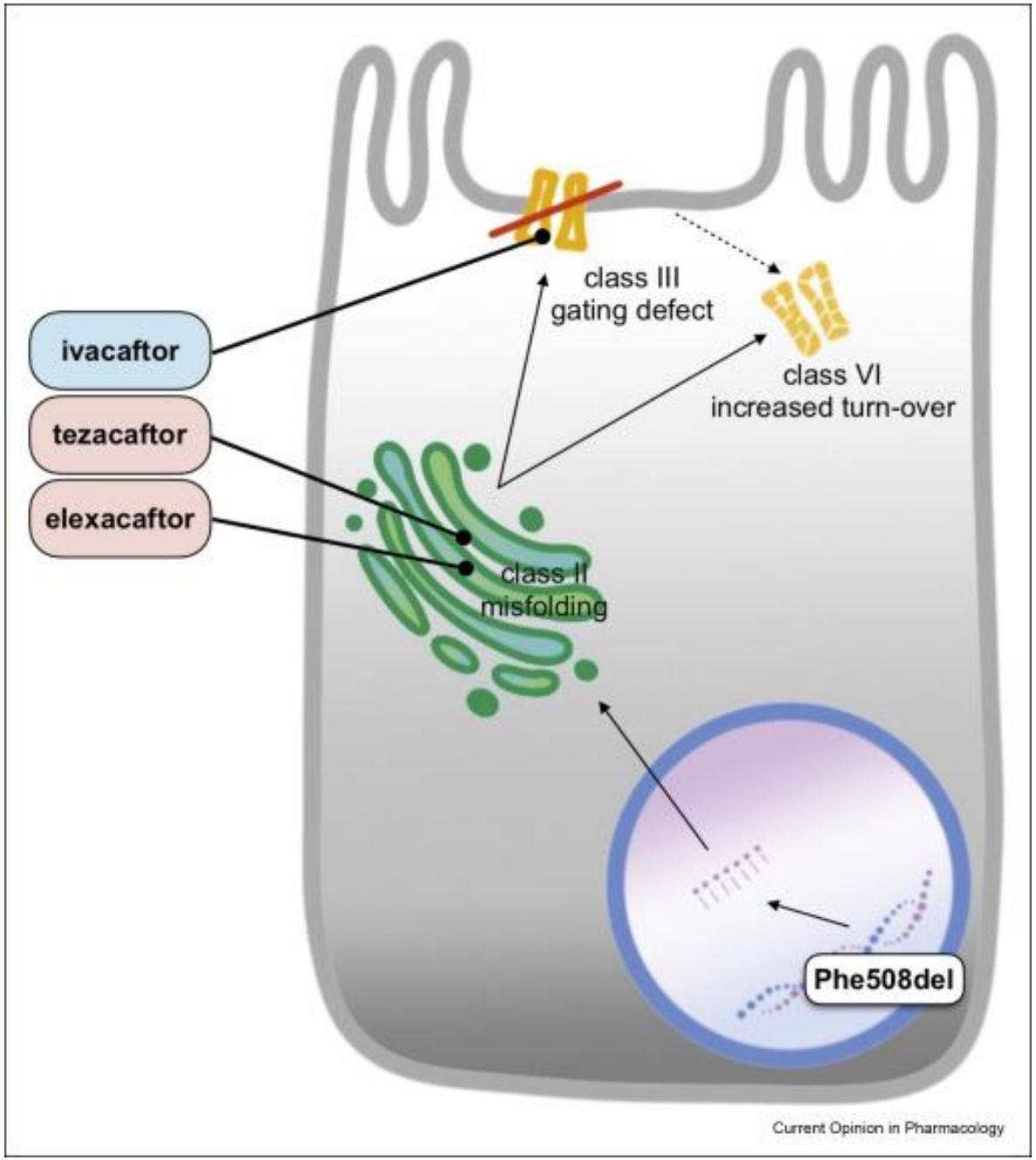
Bardin E. et al., ERJ Med Chem. (2021) 213, 113195.

Kaftrio (ETI)

Elexacaftor

Tezacaftor

Ivacaftor



Modulator results: Triple therapy (Kaftrio)

Versus placebo	Kaftrio (2 studies; 510 pts)
FEV_1 improvement over 24 weeks	14% ↑
Nutritional changes BMI kg/m2	1.5 ↑
Sweat chloride mmol/mol	43↓
QOL (SGRQ)	19.4 ↑

Middleton P.G., et al., N. Engl. J. Med. 2019;381:1809–1819.

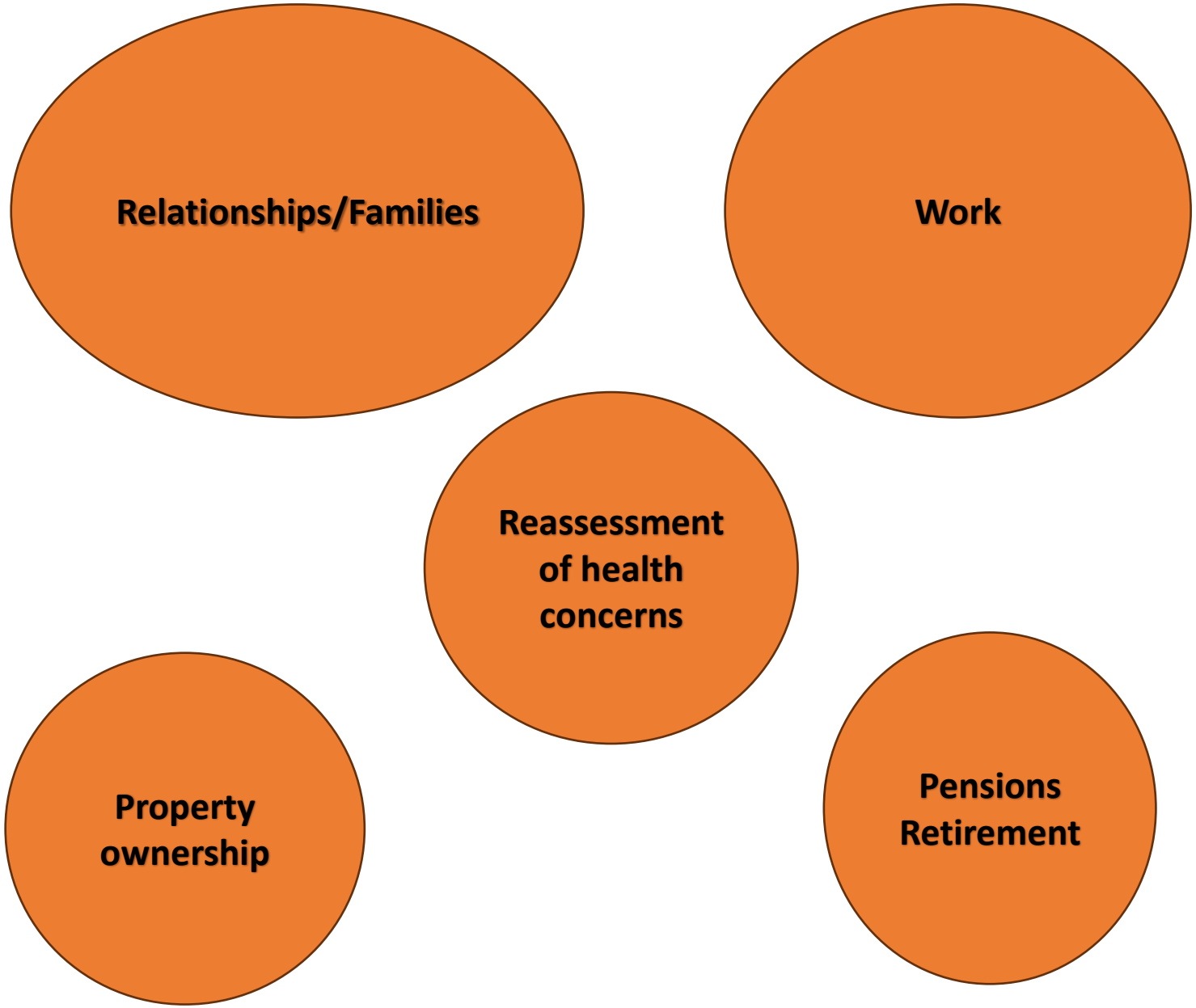
Heijerman H.G.M., et al., Lancet. 2019;394:1940–1948

Adult outcome data pre and post modulators in England and Wales

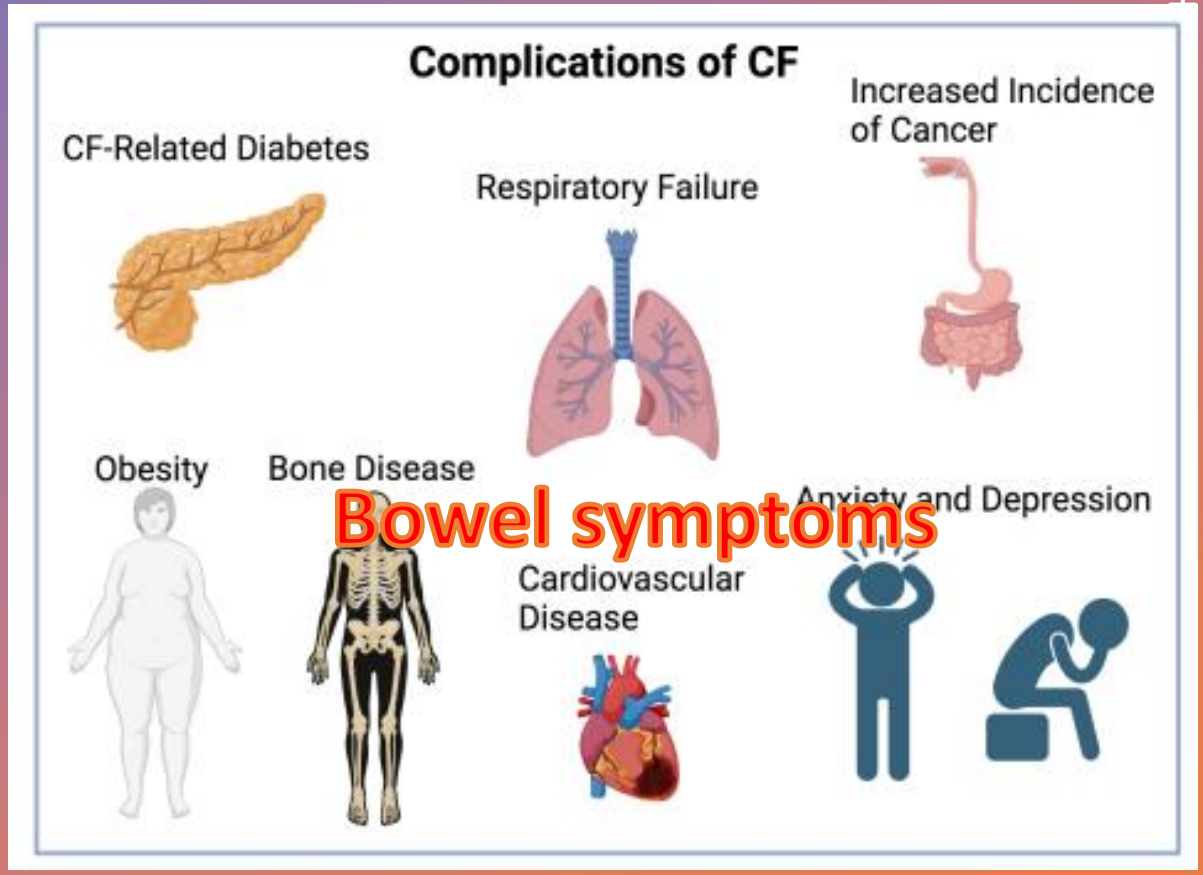
	2012	2022
Median survival (yrs)	43.5	56.1
Median age of death (yrs)	27	33
Median BMI	22	24.2
Median % predicted FEV1	65	75.5
% with chronic pseudomonas	56	16.7 (???)

CF Trust Registry data 2012 and 2022, cftrust.org.uk

The future:


Relationships/Families
Work
Reassessment of health concerns
Property ownership
Pensions Retirement

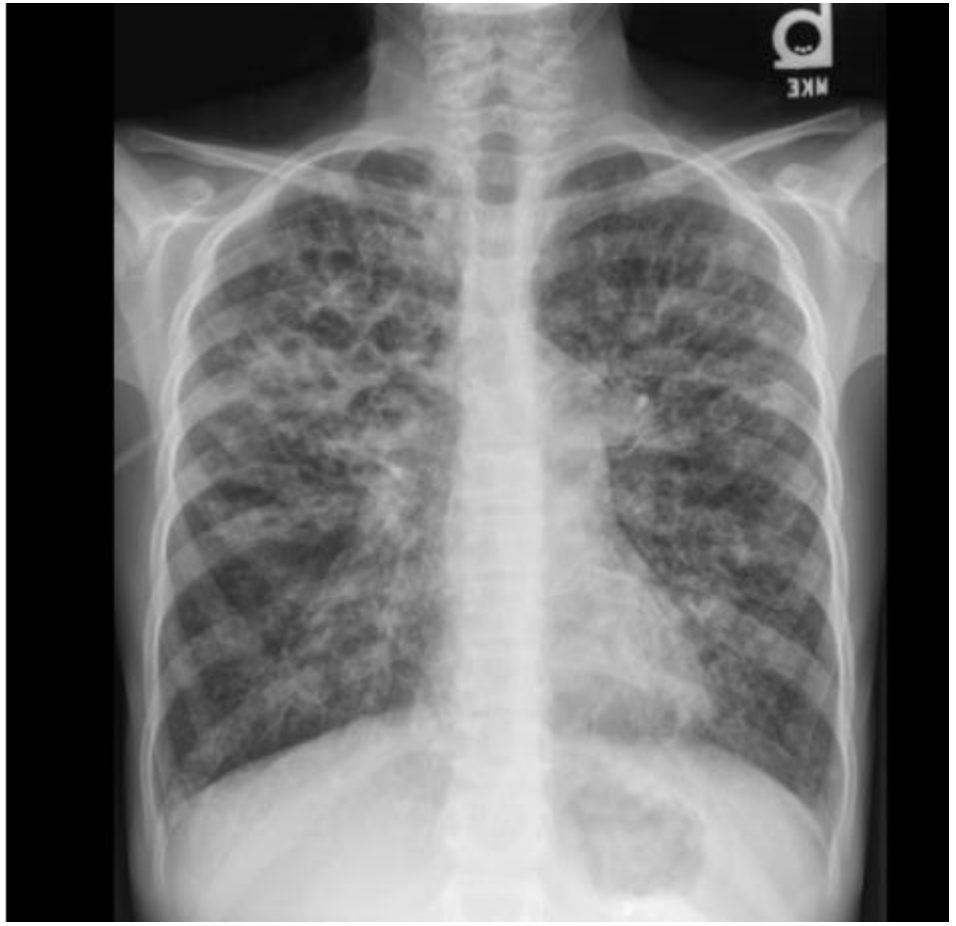
The future:


Complications of CF
CF-Related Diabetes
Respiratory Failure
Increased Incidence of Cancer
Obesity
Bone Disease
Bowel symptoms
Anxiety and Depression
Cardiovascular Disease

Where are you likely to come across these patients?

CF adults presenting to ED: Bronchiectasis exacerbation..

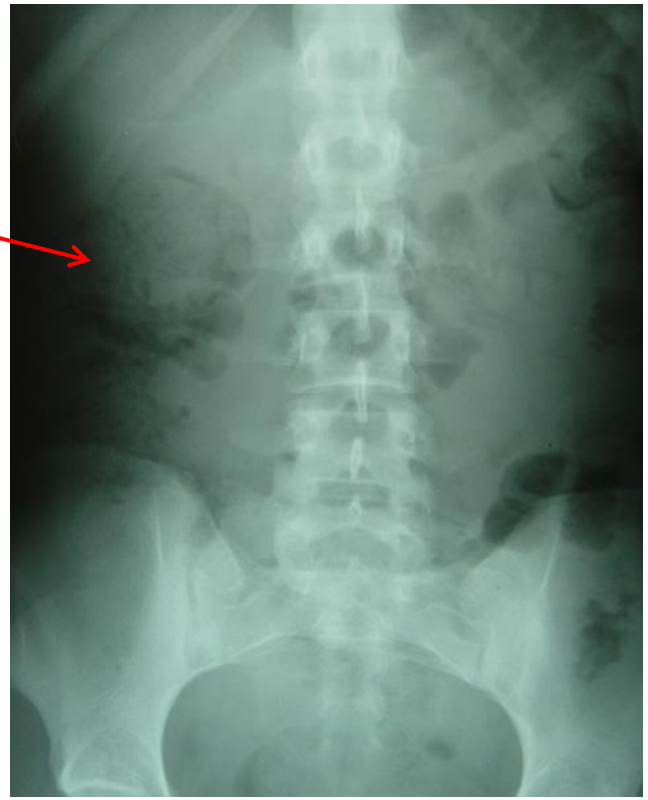
- Previous sputum cultures
- 2X anti-pseudomonal antibiotics (Ceftazidine 2g tds and Tobramycin 10mg/kg od), 14 days; use Colistin 2MU tds if vestibular disease/renal impairment
- Hydrate (often need IV fluids), send sputum, restart/escalate mucolytics (DNase/HTS/Mannitol), salt tablets NaCl 600mg MR tds
- Control BMs
- Chest physio bd



Common cause of presentation to ED: Distal Intestinal Obstruction Syndrome (DIOS)

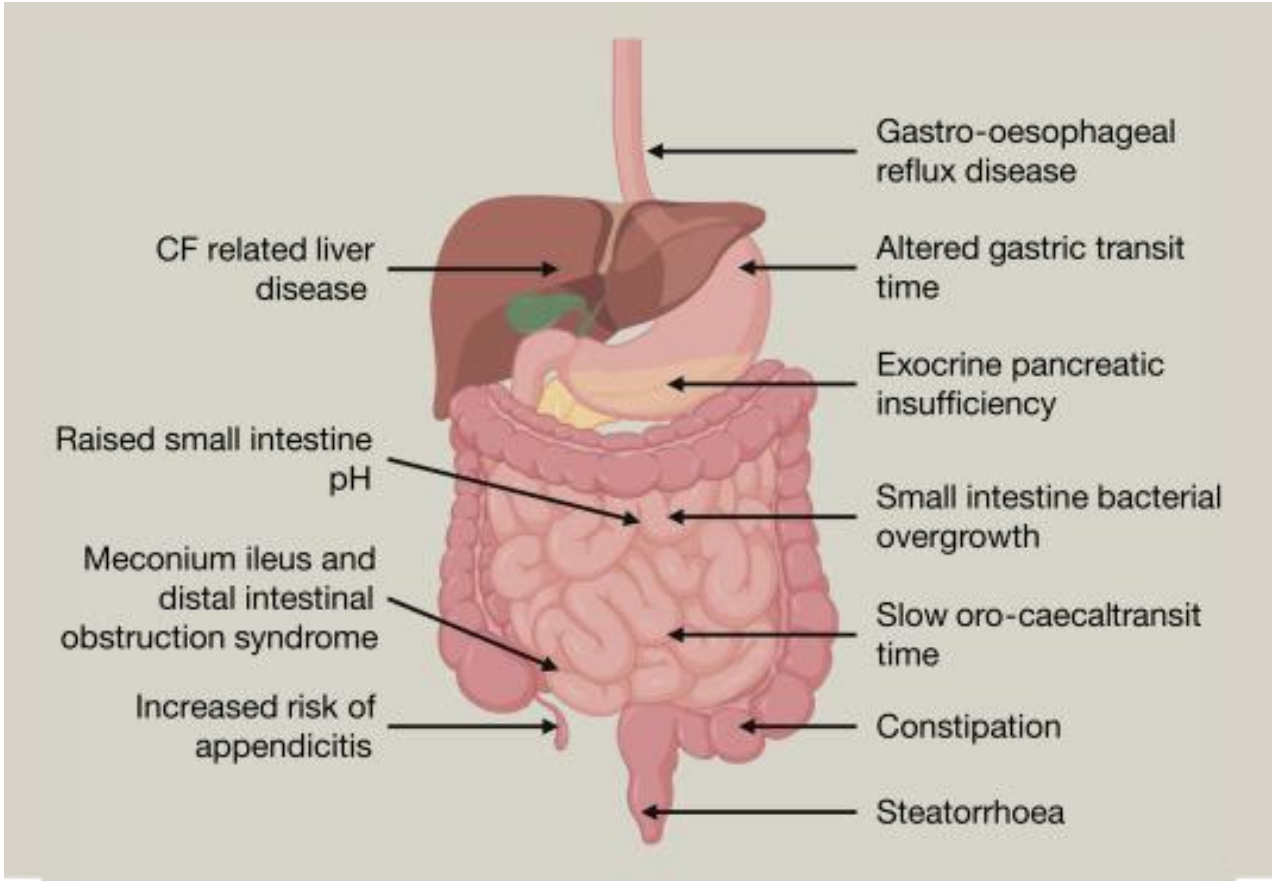
- a complete or incomplete intestinal obstruction with a faecal mass in the small bowel
- 27% > 30 years
- May have little change in bowel frequency
- Differentials include appendicitis or intussusception

- Rx: Rehydrate, Osmotic agents – Macrogol, Gastrografin 100mls in 400mls (can give as a high enema)



CF and bowel symptoms:

- 85% pancreatic insufficient
- Acidic secretions, inflamed mucosa, slow gut transit time
- 65% have significant daily symptoms



CF-related Diabetes

- Affects 50% of the adult CF population
- Worsens prognosis
- Nearly 40% of children with CF age 0–5 years have abnormal glucose tolerance,

- Risk factors: PI, other modifier genes, steroids

- Characterised by;
- insulin deficiency
- variable insulin resistance
- no ketoacidosis

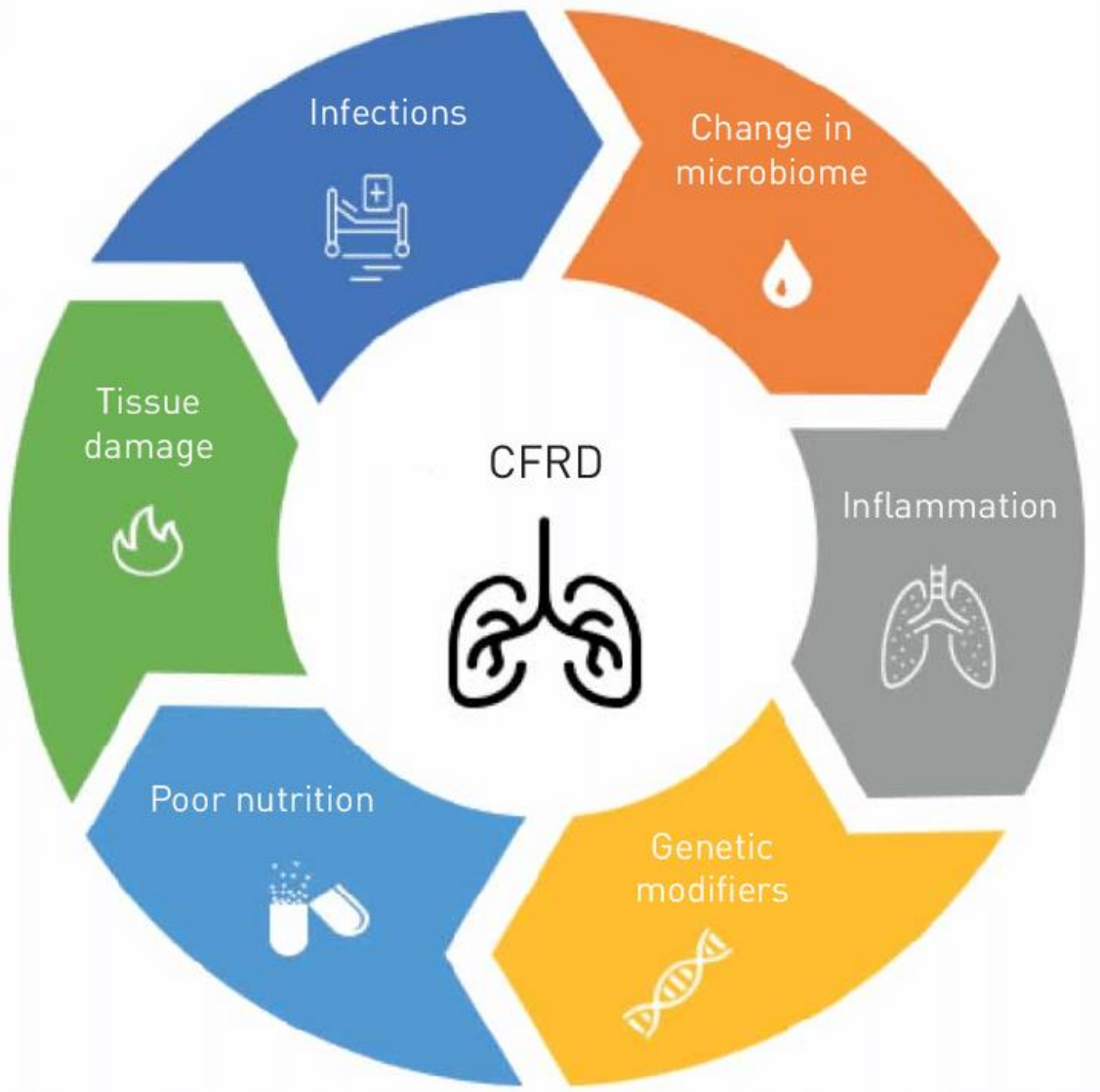
Blackman SM et al. Genetic modifiers of cystic fibrosis-related diabetes. Diabetes 62, 3627–35 (2013). Cystic fibrosis-related diabetes: current trends in prevalence, incidence, and mortality. Moran A et al. Diabetes Care. 2009 Sep; 32(9):1626-31
Abnormal Glucose Tolerance in Infants and Young Children with Cystic Fibrosis Yaling Yi, et al. Am J Respir Crit Care Med. 2016 Oct 15; 194(8): 974–980
Connor Lewis et al. Diabetes-related Mortality in Adults with Cystic Fibrosis. Role of Genotype and Sex Am J Respir Crit Care Med. 2015 Jan 15; 191(2): 194–200.

CFRD causes…

- Microvascular complications
- Fewer macrovascular effects evident yet
- Autonomic dysfunction/delayed gastric emptying is a feature

- Psychological morbidity +++

- BUT….islet cells relatively preserved…



Female infertility → full CF obstetric clinics!

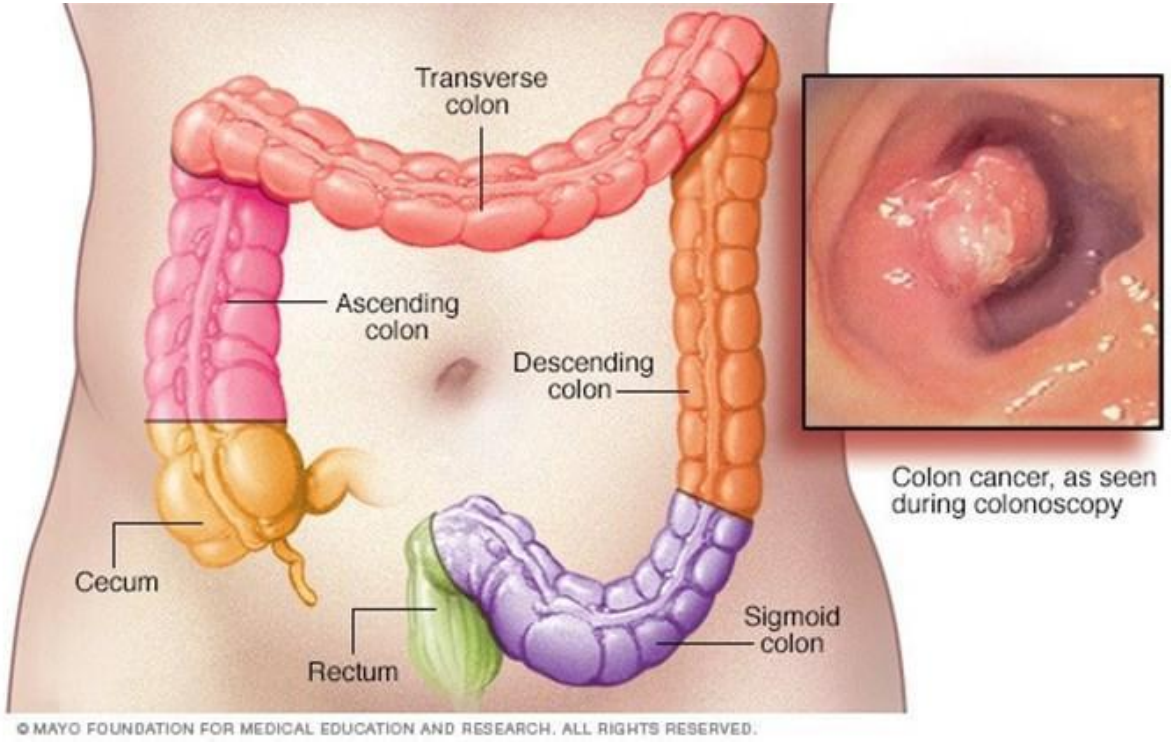
KAFTRIO

- Ovulation – affected by low weight and general health
- Uterine cervical mucous – very thick
- Uterine environment is usually bicarbonate rich to allow sperm to fertilize egg. CF is a bicarbonate deficient environment
- CFTR modulators improve fertility – 39 pregnancies in 200 women since 2020!
- Most develop diabetes

Ahmad, A et al. *Curr Opin Obstet Gynecol.* 2013; 25(3): 167-72.
Rutherford, AJ *J R Soc Med.* 2007; 100 (Suppl. 47): 29-34.

Cancer risk: CFTR in the gut

- Highest to lowest density of CFTR in small bowel from top to bottom.
- Most CFTR in caecum, reducing in density more distally.
- CFTR localizes to the intestinal crypt stem cell compartment – does influencing stem cell function cause the increased cancer risk?

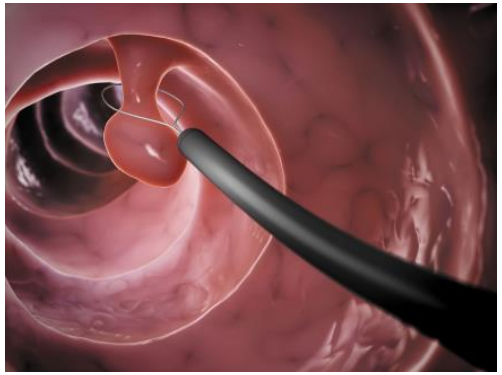


Colorectal Cancer

- CFTR-/- knockout mice

- Prospective studies in humans:
- 49% have adenomatous polyps from 40 yrs
- 25% have advanced adenomatous polyps

- Colorectal screening via colonoscopy:
- UK guidelines now recommend for pwCF ≥40yrs every 5 years
- Transplant pwCF ≥30 years



Maisonneuve, P.; Marshall, B.C.; Knapp, E.A.; Lowenfels, A.B. Cancer risk in cystic fibrosis: A 20-year nationwide study from the United States. J. Natl. Cancer Inst. 2013, 105, 122–129
Hadjiliadis D et al. Cystic Fibrosis Colorectal Cancer Screening Task Force. Cystic Fibrosis Colorectal Cancer Screening Consensus Recommendations. Gastroenterology. 2018 Feb;154(3):736-745.e14.

Iatrogenic comorbidities

- Iatrogenic complications – hearing loss, kidney damage
- Vascuports for poor veins
- multiple antibiotic allergies
- PEG and/or NG overnight feeding

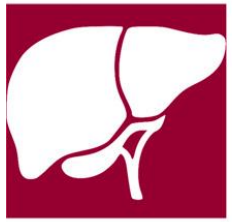
CFTR modulator effects in adult pwCF

↑↑ QOL, some reported anxiety

↓rhinosinusitis symptoms (SNOT 22)

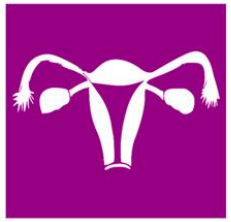
↑ FEV1, ↓↓ exacerbations (63%)

Reversal of hepatic steatosis; registry data



PI and CFRD already present

↑growth and nutrition, ↑BMI, ↓ DIOS ↓ faecal calprotectin and CFAbd-score



Cervical mucous barrier removed; Pregnancies +++ on Kaftrio!

?↓ development of osteoporosis, if relates to catabolism

Adapted from Valentine Sergeev et al. Ann Am Thorac Soc Vol 17, No 2, pp 147–154, Feb 2020

In summary..

- CFTR Modulators really are life changing
- Patients still present with bronchiectasis exacerbations and challenging bugs
- Chronic bowel symptoms, diabetes and multi-organ dysfunction are increasing
- Older patients face other complications e.g. colon cancer

Thank you!