Cystic Fibrosis:
A Multi-Disciplinary Review

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History of CF Diagnosis and Treatment

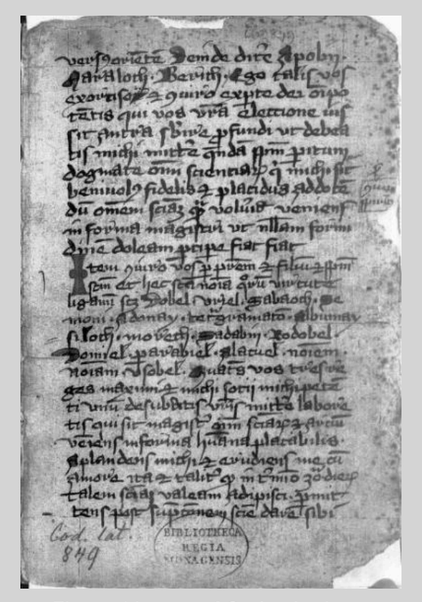


Figure 1 Image of Codex Latinus Monacensis 849

The "Codex Latinus Monacensis 849 (Clm 849)[5] was the first written account of CF dating to the 15th century. The German text was written in Latin, on bewitchment, and necromancy[5]. It describes that if a salty taste was observed by licking the nose of an infant, then they were 'bewitched,' and would most likely die soon[5, 6]. In a sense this was a very rudimentary 'sweat test' for CF.

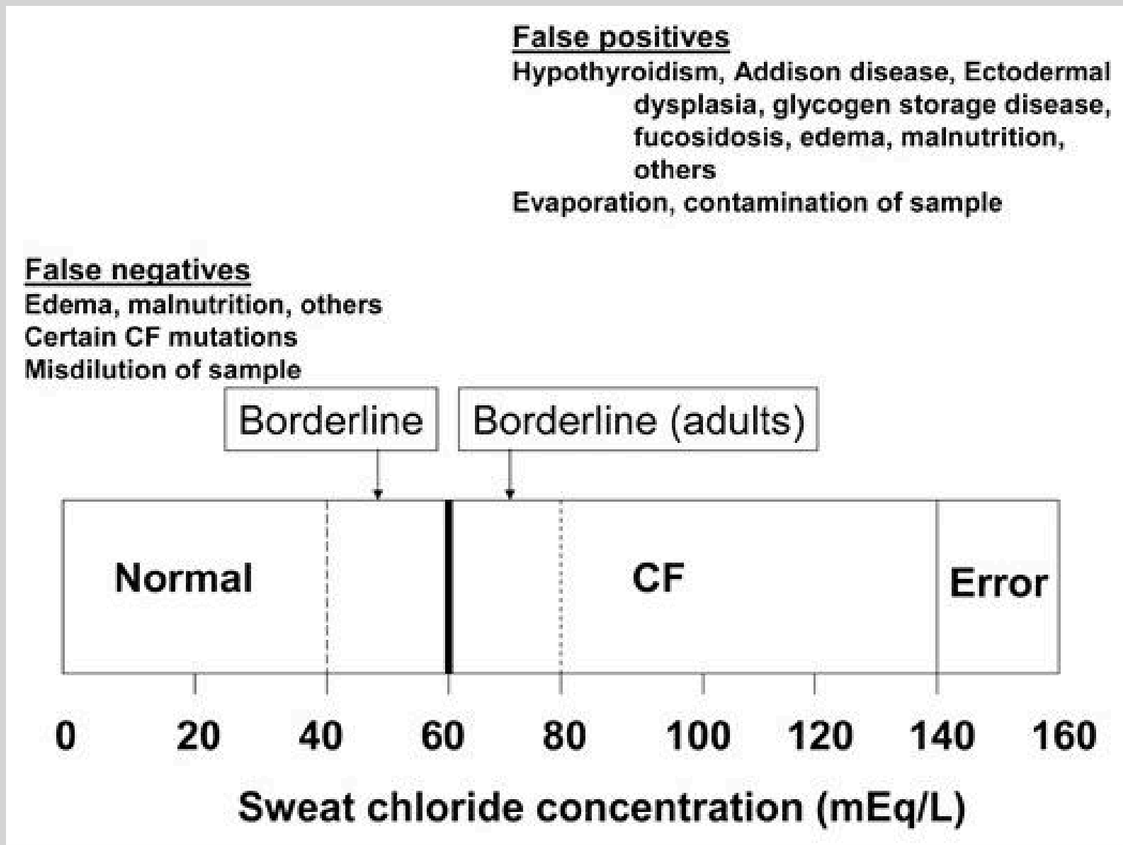

False positives
Hypothyroidism, Addison disease, Ectodermal dysplasia, glycogen storage disease, fucosidosis, edema, malnutrition, others
Evaporation, contamination of sample
False negatives
Edema, malnutrition, others
Certain CF mutations
Misdilution of sample
Borderline
Borderline (adults)
Normal
CF
Error
0
20
40
60
80
100
120
140
160
Sweat chloride concentration (mEq/L)

Figure 2 Sweat chloride concentrations related to cystic fibrosis (CF) diagnosis. Revised and reprinted by permission from Davis PB. Cystic fibrosis. Pediatr Rev 2001;22:257–264.

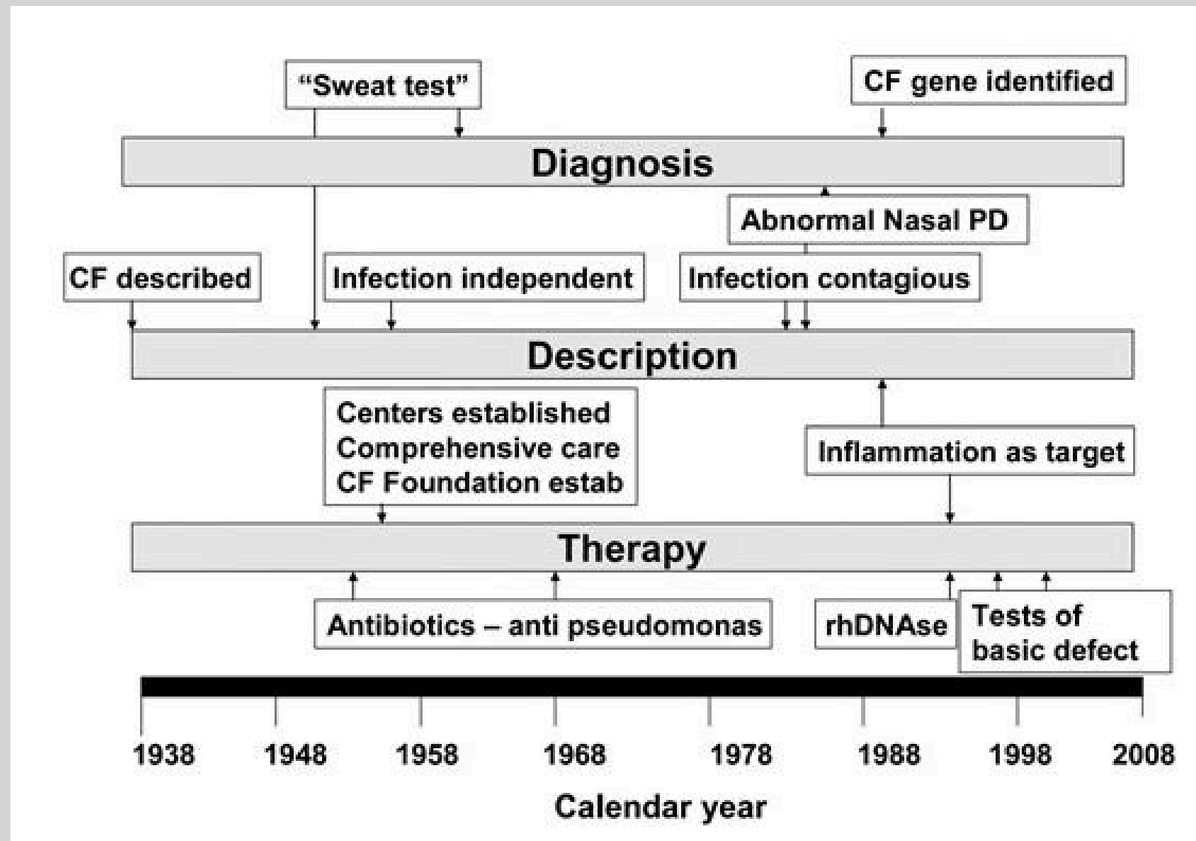

"Sweat test"
CF gene identified
Diagnosis
Abnormal Nasal PD
CF described
Infection independent
Infection contagious
Description
Centers established
Comprehensive care
CF Foundation estab
Inflammation as target
Therapy
Antibiotics – anti pseudomonas
rhDNAse
Tests of basic defect
1938
1948
1958
1968
1978
1988
1998
2008
Calendar year

Figure 3 Discoveries relevant to diagnosis, clinical description, and therapy of CF. PD = potential difference.

- In 1938 the autopsy studies of malnourished children, allowed for the proper distinction of CF from celiac disease[7].
- In New York during a heat wave in 1948, a pediatrician, Paul di Sant'Agnese, discovered that children who presented with heat exauhstion also had an elevated chance of having CF[7]. This discovery lead to the development of the sweat test, which uses chloride concentration in the sweat to diagnose CF[7].
- In 1989, the discovery of the CFTR gene using cells from the sweat gland prompted a surge of research activity in the area, prompting advancements such as the direct identification of CFTR gene mutations to diagnose CF[7].
- In 1955 the Cystic Fibrosis Foundation was created with the goal of improving the quality of life for CF patients, as well as promoting research into treating the disease[7].
- In 1980, Matthews and colleagues observed that some patients with CF have very low IgG levels, and surprisingly, rather than being vulnerable to bacterial infection, they were remarkably healthy, prompting a new pillar of therapy to emerge, treatment of inflammation[7].
- The mean life expectancy of someone with CF in the late 1930s was only around 6 months, and now children born between 2019 and 2023 have a life expectancy of 61 years[2, 7].

Evolutionary History of CF

- ΔF508 is the most common CF causing CFTR mutation among North American and European populations, accounting for 70-90% of CF mutations in these populations[3].
- A haplotype study from 1994 revealed that this ΔF508 mutation, which accounts for the majority of CF cases worldwide, arose roughly 52 000 years ago from a single DNA polymerase slippage event[3].
- The study used ΔF508 microsatelite haplotypes and found that the 23-31-11 haplotype was common among most ΔF508 carriers, making it likely to have been possessed by the individual who experienced the original DNA polymerase slippage event[3].
- They estimated the time it took for the 23-31-13 to experience a slippage event, and become 17-31-13, and then 17-32-13. This then allowed them to estimate the year of the original slippage event[3].

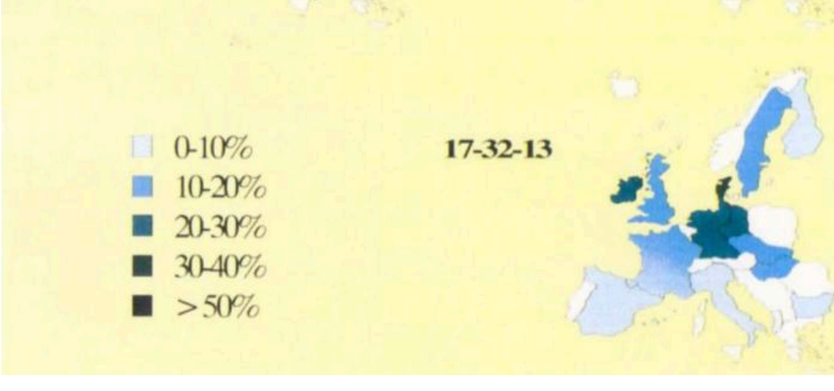

23-31-13
17-31-13
17-32-13
0-10%
10-20%
20-30%
30-40%
>50%

Figure 4 Frequency distribution of common dF508 haplotypes 23-31-13, 17-31-13 and 17-32-13 in Europe. The populations not analysed are shown in white.

Even now this founder effect affects the treatment and diagnosis of CF patients worldwide. Even though certain populations are at elevated risk (North Americans and Europeans), areas of the world which have low rates of CF, struggle in properly diagnosing and treating CF due to a lack of infrastructure, resources, and experience dealing with the disease[9].

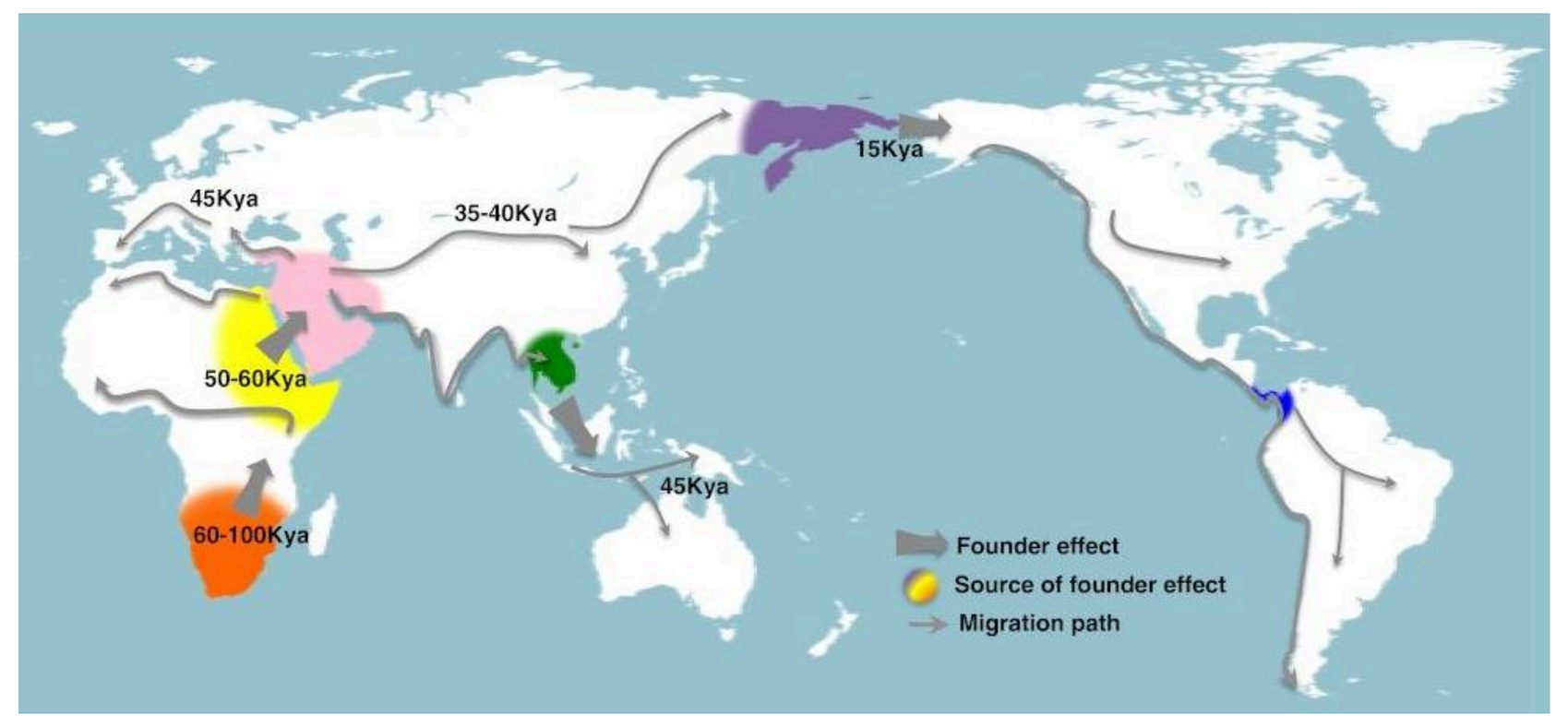

45Kya
35-40Kya
15Kya
50-60Kya
60-100Kya
45Kya
Founder effect
Source of founder effect
Migration path

Figure 5 Ancient dispersal patterns of modern humans during the past 100,000 y. This map highlights demic events that began with a source population in southern Africa 60 to 100 kya and conclude with the settlement of South America approximately 12 to 14 kya. Wide arrows indicate major founder events during the demographic expansion into different continental regions. Colored arcs indicate the putative source for each of these founder events. Thin arrows indicate potential migration paths. Many additional migrations occurred during the Holocene.

Another estimate from the same study based on germline mutation rates, estimated that the ΔF508 mutation occurred 173 000 years ago[3]. This estimate precedes the expansion of modern humans out of Sub-Saharan Africa, and therefore is unlikely, as there are large differences in ΔF508 frequency among the different continents of the world[3, 4].

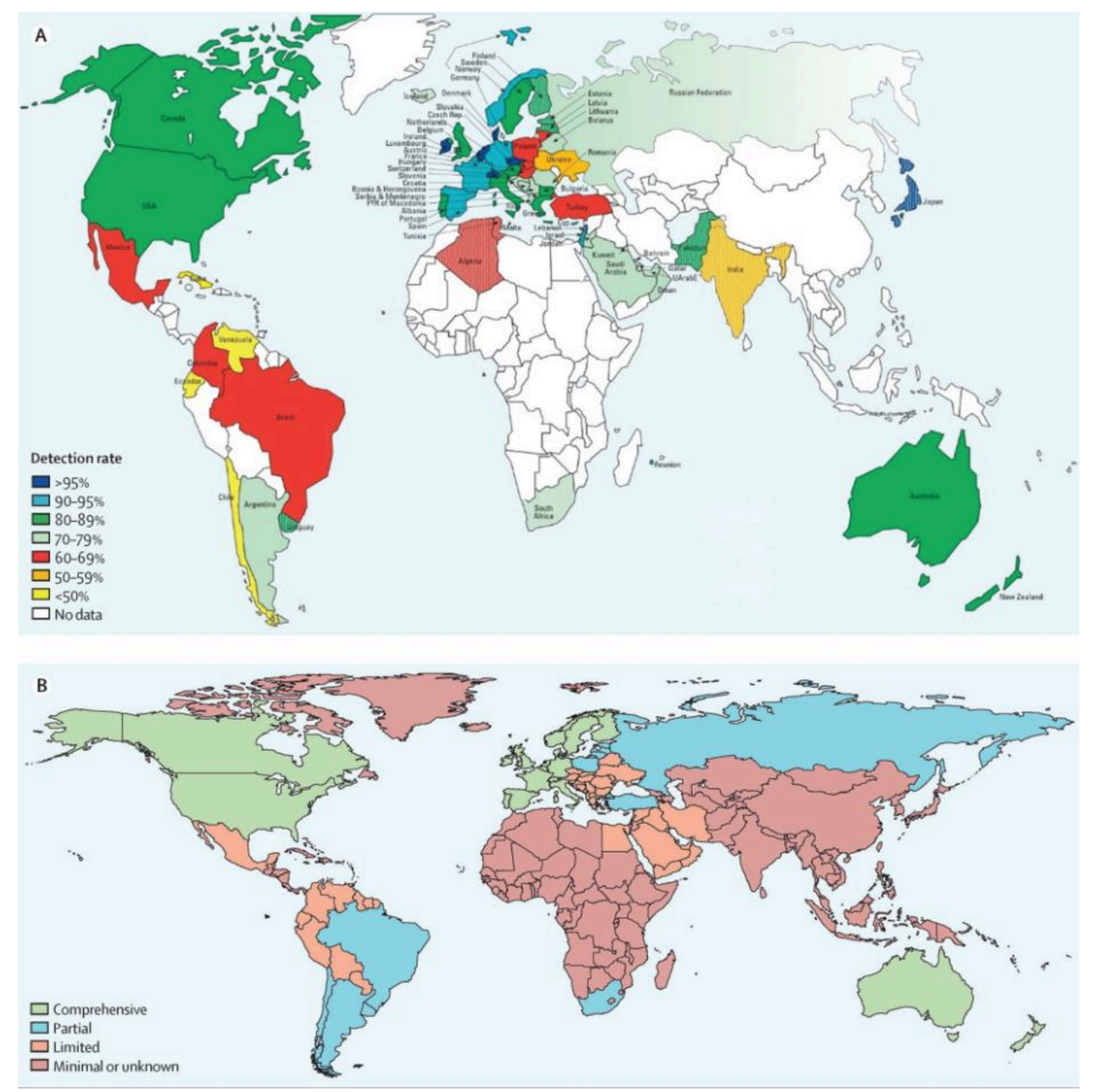

A
Detection rate
>95%
90-95%
80-89%
70-79%
60-69%
50-59%
<50%
No data
B
Comprehensive
Partial
Limited
Minimal or unknown

Figure 6 Global genetic epidemiology and standards of care for cystic fibrosis (A) The detection rate of cystic fibrosis-causing CFTR mutations. The names of several regions have since been updated as follows: Bosnia and Herzegovina, Cyprus, Czech Republic, Kuwait, Montenegro, North Macedonia, Russia, Serbia, and United Arab Emirates. (B) Global standards of care for cystic fibrosis defined according to factors such as resources, training, coverage, outcomes, access, and data management. Comprehensive=all factors present. Partial=at least half of these factors present. Limited=more than one factor present. Minimal or unknown=one or no factors present.

Pathophysiology

- Cystic fibrosis (CF) is a chronic disease caused by a rare, and heritable mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene 1. - The CFTR channel specializes in transporting chloride and bicarbonate, and when it is deformed, or otherwise ineffective in CF cases, mucus hydration and clearance is impaired, and pH balance in exocrine ducts is altered[9, 10].
- While in a nutshell, loss of CFTR protein function is the root cause of CF, there are six different classes of mutation (variants) that can cause CF through varying mechanisms such as alteration to RNA transcription, protein trafficking, channel function, and protein stability[10].
- CF has wide reaching systematic effects within the human body, including chronic pulmonary infection and inflammation, pancreatic insufficiency, male infertility, obstruction of exocrine glands in various organs, steatorrhea, poor growth, gastrointestinal malignancy, pulmonary hypertension, hearing impairment, and much more[9, 10].
- Even though classically CF is recessive, new research has found even carriers of only one CFTR mutation might have subtle, but very real symptoms as well[14, 15]. One study found that out of 59 CF related conditions, carriers were at a significantly (p < 0.005) higher risk for 57 of these conditions compared to controls[14]. - Carriers may confer an evolutionary advantage; however as one study found that carriers of the CFTR mutation were less susceptible to diarrhea, potentially indicating a resistance to cholera symptoms[13].

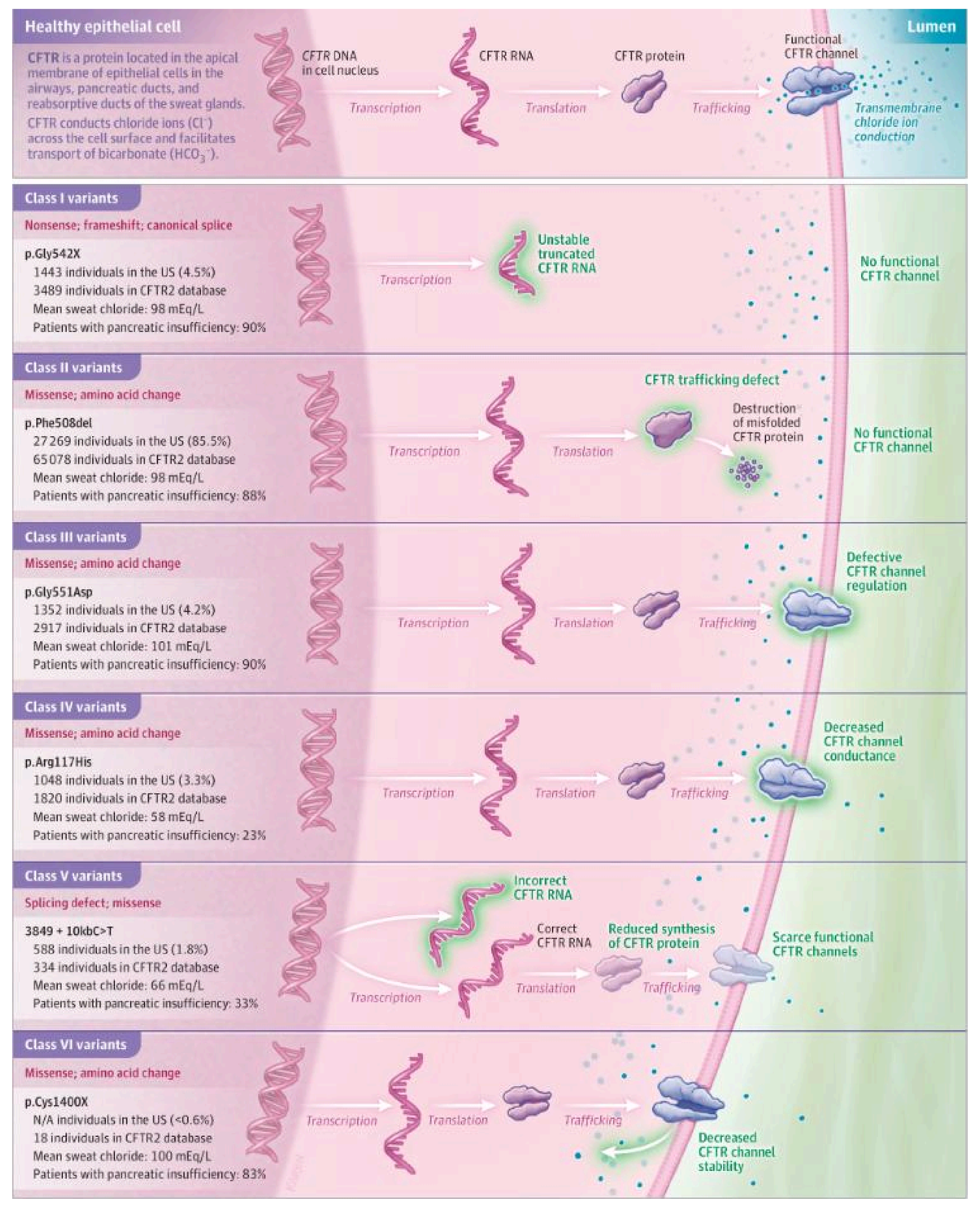
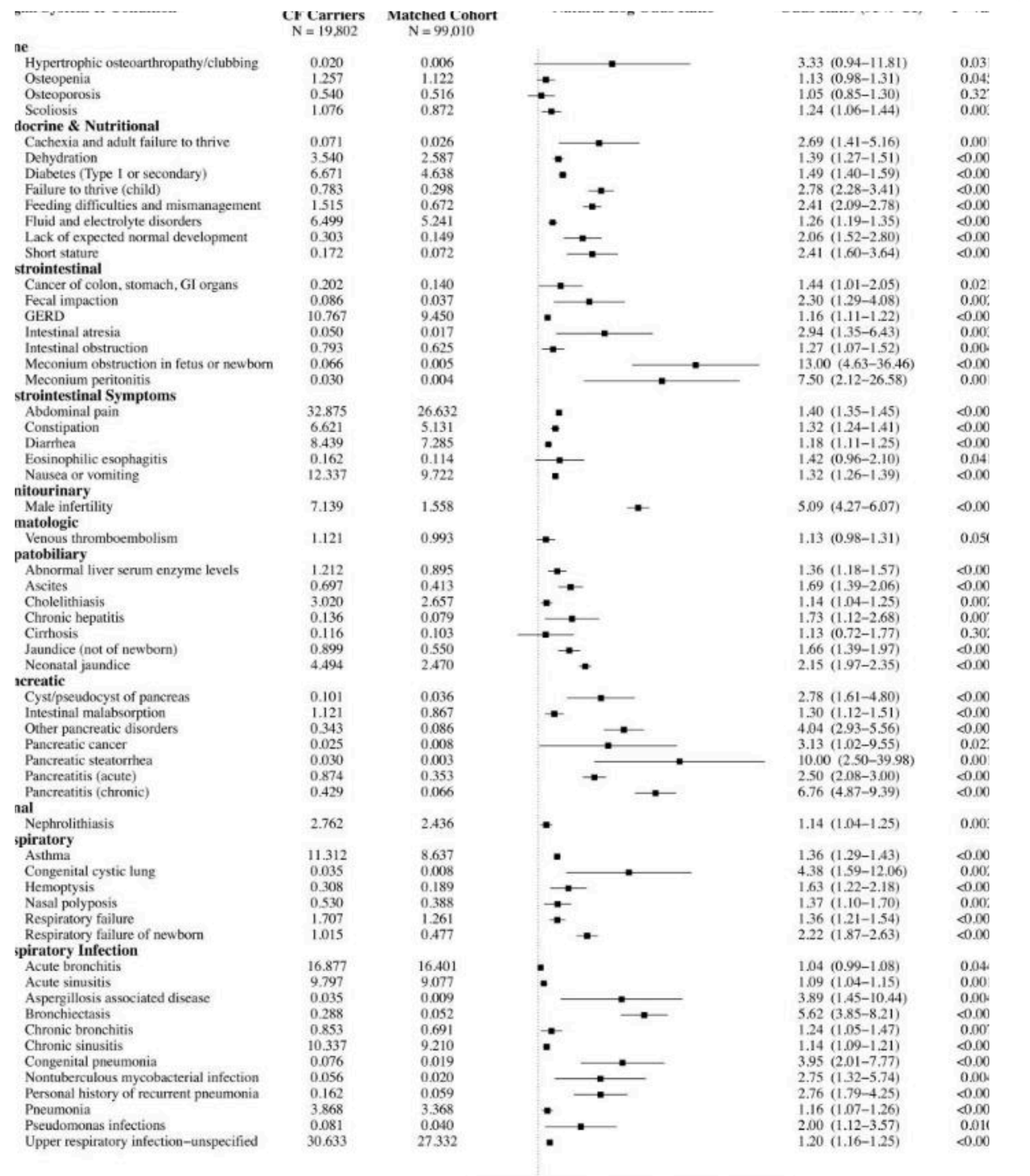

Healthy epithelial cell
Lumen
CFTR is a protein located in the apical membrane of epithelial cells in the airways, pancreatic ducts, and reabsorptive ducts of the sweat glands.
CFTR conducts chloride ions (Cl⁻) across the cell surface and facilitates transport of bicarbonate (HCO₃⁻).
CFTR DNA in cell nucleus
CFTR RNA
CFTR protein
Functional CFTR channel
Transcription
Translation
Trafficking
Transmembrane chloride ion conduction
Class I variants
Nonsense; frameshift; canonical splice
p.Gly542X
1443 individuals in the US (4.5%)
3489 individuals in CFTR2 database
Mean sweat chloride: 98 mEq/L
Patients with pancreatic insufficiency: 90%
Unstable truncated CFTR RNA
No functional CFTR channel
Class II variants
Missense; amino acid change
p.Phe508del
27 269 individuals in the US (85.5%)
65 078 individuals in CFTR2 database
Mean sweat chloride: 98 mEq/L
Patients with pancreatic insufficiency: 88%
CFTR trafficking defect
Destruction of misfolded CFTR protein
No functional CFTR channel
Class III variants
Missense; amino acid change
p.Gly551Asp
1352 individuals in the US (4.2%)
2917 individuals in CFTR2 database
Mean sweat chloride: 101 mEq/L
Patients with pancreatic insufficiency: 90%
Defective CFTR channel regulation
Class IV variants
Missense; amino acid change
p.Arg117His
1048 individuals in the US (3.3%)
1820 individuals in CFTR2 database
Mean sweat chloride: 58 mEq/L
Patients with pancreatic insufficiency: 23%
Decreased CFTR channel conductance
Class V variants
Splicing defect; missense
3849 + 10kbC>T
588 individuals in the US (1.8%)
334 individuals in CFTR2 database
Mean sweat chloride: 66 mEq/L
Patients with pancreatic insufficiency: 33%
Incorrect CFTR RNA
Correct CFTR RNA
Reduced synthesis of CFTR protein
Scarce functional CFTR channels
Class VI variants
Missense; amino acid change
p.Cys1400X
N/A individuals in the US (<0.6%)
18 individuals in CFTR2 database
Mean sweat chloride: 100 mEq/L
Patients with pancreatic insufficiency: 83%
Decreased CFTR channel stability

Figure 7 Cystic fibrosis transmembrane conductance regulator (CFTR) variants can be generally classified in 6 mechanistic classes based on how they alter CFTR RNA transcription, protein trafficking, channel function, and stability. Reported prevalence, and clinical features (sweat chloride, pancreatic insufficiency) are summarized for exemplar variants per class. The CFTR2 database provides information on all the CFTR variants and updates it as information becomes available.



	CF Carriers N = 19,802	Matched Cohort N = 99,010		
ne				
Hypertrophic osteoarthropathy/clubbing	0.020	0.006	3.33 (0.94–11.81)	0.03
Osteopenia	1.257	1.122	1.13 (0.98–1.31)	0.04
Osteoporosis	0.540	0.516	1.05 (0.85–1.30)	0.32
Scoliosis	1.076	0.872	1.24 (1.06–1.44)	0.00
docrine & Nutritional				
Cachexia and adult failure to thrive	0.071	0.026	2.69 (1.41–5.16)	0.00
Dehydration	3.540	2.587	1.39 (1.27–1.51)	<0.00
Diabetes (Type 1 or secondary)	6.671	4.638	1.49 (1.40–1.59)	<0.00
Failure to thrive (child)	0.783	0.298	2.78 (2.28–3.41)	<0.00
Feeding difficulties and mismanagement	1.515	0.672	2.41 (2.09–2.78)	<0.00
Fluid and electrolyte disorders	6.499	5.241	1.26 (1.19–1.35)	<0.00
Lack of expected normal development	0.303	0.149	2.06 (1.52–2.80)	<0.00
Short stature	0.172	0.072	2.41 (1.60–3.64)	<0.00
strointestinal				
Cancer of colon, stomach, GI organs	0.202	0.140	1.44 (1.01–2.05)	0.02
Fecal impaction	0.086	0.037	2.30 (1.29–4.08)	0.00
GERD	10.767	9.450	1.16 (1.11–1.22)	<0.00
Intestinal atresia	0.050	0.017	2.94 (1.35–6.43)	0.00
Intestinal obstruction	0.793	0.625	1.27 (1.07–1.52)	0.00
Meconium obstruction in fetus or newborn	0.066	0.005	13.00 (4.63–36.46)	<0.00
Meconium peritonitis	0.030	0.004	7.50 (2.12–26.58)	0.00
strointestinal Symptoms				
Abdominal pain	32.875	26.632	1.40 (1.35–1.45)	<0.00
Constipation	6.621	5.131	1.32 (1.24–1.41)	<0.00
Diarrhea	8.439	7.285	1.18 (1.11–1.25)	<0.00
Eosinophilic esophagitis	0.162	0.114	1.42 (0.96–2.10)	0.04
Nausea or vomiting	12.337	9.722	1.32 (1.26–1.39)	<0.00
nitourinary				
Male infertility	7.139	1.558	5.09 (4.27–6.07)	<0.00
matologic				
Venous thromboembolism	1.121	0.993	1.13 (0.98–1.31)	0.05
patobiliary				
Abnormal liver serum enzyme levels	1.212	0.895	1.36 (1.18–1.57)	<0.00
Ascites	0.697	0.413	1.69 (1.39–2.06)	<0.00
Cholelithiasis	3.020	2.657	1.14 (1.04–1.25)	0.00
Chronic hepatitis	0.136	0.079	1.73 (1.12–2.68)	0.00
Cirrhosis	0.116	0.103	1.13 (0.72–1.77)	0.30
Jaundice (not of newborn)	0.899	0.550	1.66 (1.39–1.97)	<0.00
Neonatal jaundice	4.494	2.470	2.15 (1.97–2.35)	<0.00
ncreatic				
Cyst/pseudocyst of pancreas	0.101	0.036	2.78 (1.61–4.80)	<0.00
Intestinal malabsorption	1.121	0.867	1.30 (1.12–1.51)	<0.00
Other pancreatic disorders	0.343	0.086	4.04 (2.93–5.56)	<0.00
Pancreatic cancer	0.025	0.008	3.13 (1.02–9.55)	0.02
Pancreatic steatorrhea	0.030	0.003	10.00 (2.50–39.98)	0.00
Pancreatitis (acute)	0.874	0.353	2.50 (2.08–3.00)	<0.00
Pancreatitis (chronic)	0.429	0.066	6.76 (4.87–9.39)	<0.00
nal				
Nephrolithiasis	2.762	2.436	1.14 (1.04–1.25)	0.00
spiratory				
Asthma	11.312	8.637	1.36 (1.29–1.43)	<0.00
Congenital cystic lung	0.035	0.008	4.38 (1.59–12.06)	0.00
Hemoptysis	0.308	0.189	1.63 (1.22–2.18)	<0.00
Nasal polyposis	0.530	0.388	1.37 (1.10–1.70)	0.00
Respiratory failure	1.707	1.261	1.36 (1.21–1.54)	<0.00
Respiratory failure of newborn	1.015	0.477	2.22 (1.87–2.63)	<0.00
spiratory Infection				
Acute bronchitis	16.877	16.401	1.04 (0.99–1.08)	0.04
Acute sinusitis	9.797	9.077	1.09 (1.04–1.15)	0.00
Aspergillosis associated disease	0.035	0.009	3.89 (1.45–10.44)	0.00
Bronchiectasis	0.288	0.052	5.62 (3.85–8.21)	<0.00
Chronic bronchitis	0.853	0.691	1.24 (1.05–1.47)	0.00
Chronic sinusitis	10.337	9.210	1.14 (1.09–1.21)	<0.00
Congenital pneumonia	0.076	0.019	3.95 (2.01–7.77)	<0.00
Nontuberculous mycobacterial infection	0.056	0.020	2.75 (1.32–5.74)	0.00
Personal history of recurrent pneumonia	0.162	0.059	2.76 (1.79–4.25)	<0.00
Pneumonia	3.868	3.368	1.16 (1.07–1.26)	<0.00
Pseudomonas infections	0.081	0.040	2.00 (1.12–3.57)	0.01
Upper respiratory infection–unspecified	30.633	27.332	1.20 (1.16–1.25)	<0.00

Figure 8 CF carriers are at greater risk for a wide range of CF-related conditions. For each CF-related health condition, the figure compares the prevalence between CF carriers and matched controls in terms of percent prevalence, OR and associated 95% CI, and P value for a test of the hypothesis that prevalence is greater among CF carriers. In addition, each natural log OR and its associated 95% CI are graphically depicted. The prevalence of CF-related conditions was greater in CF carriers compared with matched controls for all 59 conditions. The natural log OR for carriers was significantly greater than that for controls (P < 0.05) for 57 of the 59 conditions.

- Even though classically CF is recessive, new research has found even carriers of only one CFTR mutation might have subtle, but very real symptoms as well[14, 15]. One study found that out of 59 CF related conditions, carriers were at a significantly (p < 0.005) higher risk for 57 of these conditions compared to controls[14].
- Carriers may confer an evolutionary advantage; however as one study found that carriers of the CFTR mutation were less susceptible to diarrhea, potentially indicating a resistance to cholera symptoms[13].

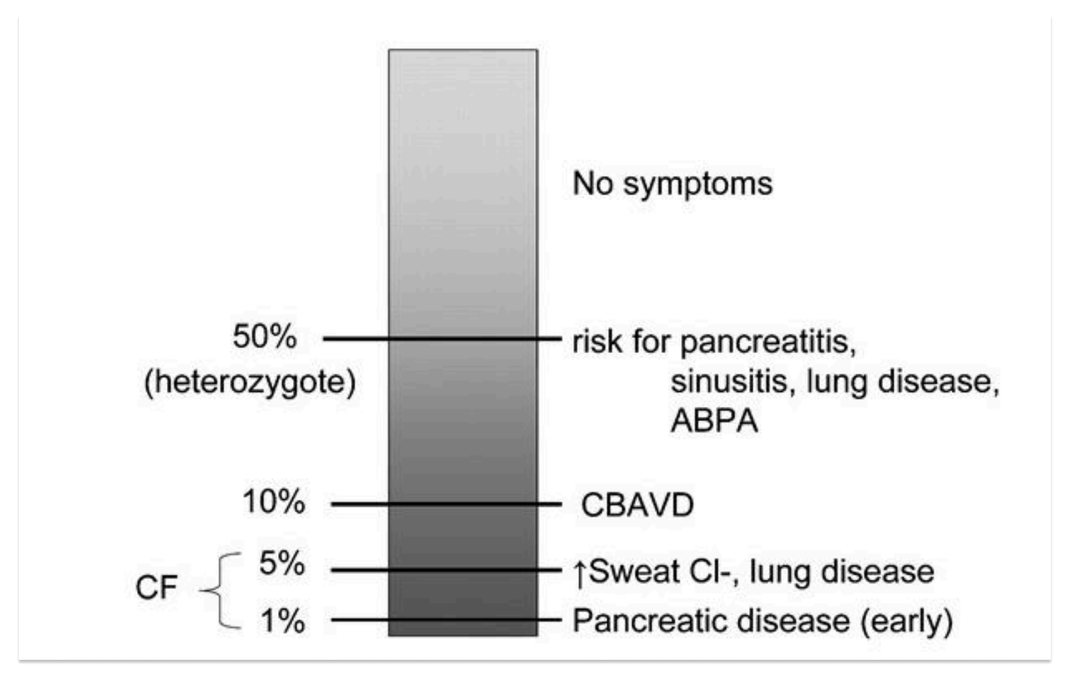

No symptoms
50% (heterozygote)
risk for pancreatitis, sinusitis, lung disease, ABPA
10%
CBAVD
CF
5%
↑Sweat Cl-, lung disease
1%
Pancreatic disease (early)

Figure 9 CF transmembrane conductance regulator (CFTR) activity related to clinical manifestations. ABPA = allergic bronchopulmonary aspergillosis, CBAVD = congenital bilateral absence of the vas deferens. Revised and reprinted by permission from Davis PB. Cystic fibrosis. Pediatr Rev 2001;22:257–264.

Treatments

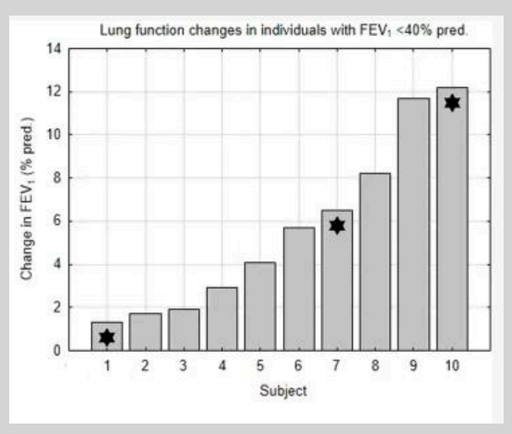


Figure 10 Changes in lung function in subgroups of the study population over 24 weeks. FEV1 = forced expiratory volume in 1 s. Dark gray bars = subjects with FEV1 <40% pred. Asterisks = subjects with pathogens at risk of more rapid FEV1 decline.

CFTR modulators encompass a range of pharmaceuticals which share a common design feature of treating the root causes of CF. Different CFTR modulators have been designed to treat different CF variants, such as ivacaftor which is a CFTR potentiator, allowing CFTR proteins to stay on the cell surface, or elexacaftor and tezacaftor which are correctors that help guide CFTR proteins to the surface. The three of these drugs have been researched as a combination therapy for CF, and have shown promising results[8].

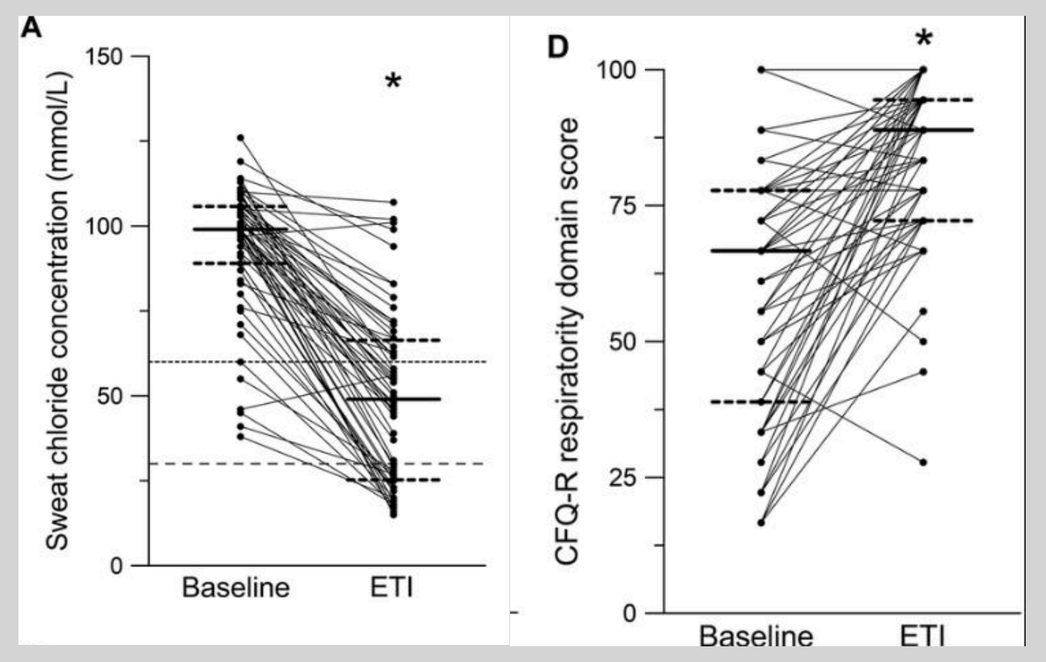


Figure 12 Effects of elexacaftor/tezacaftor/ivacaftor (ETI) on sweat chloride concentration, percent predicted forced expiratory volume in one second (FEV1% predicted), and Cystic Fibrosis Questionnaire-Revised (CFQ-R) -respiratory domain. (A–D) Paired measurements of sweat chloride concentration (A), and CFQ-R respiratory domain score in patients with CF and at least one F508del mutation at baseline and after initiation of ETI therapy. Solid lines represent the group median and dashed lines represent 25th and 75th percentile. *p < 0.001 compared with baseline.

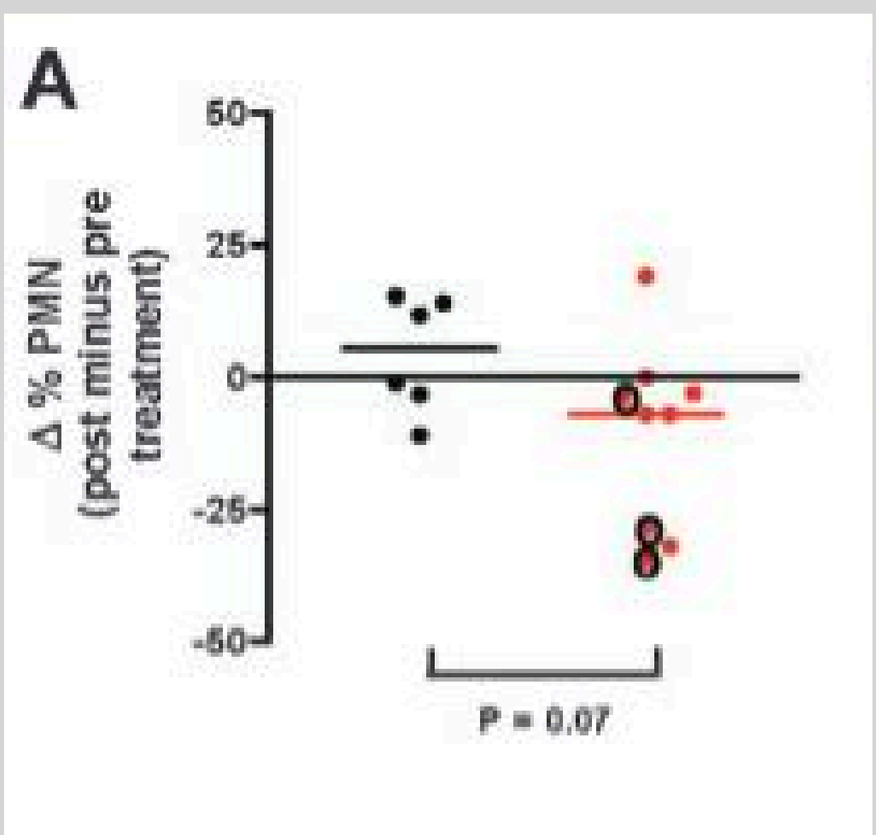


Figure 11 Effect of treatment on "worst" lobe BALF inflammationfor Inhaled Group (inhaled tobramycin; black symbols) andSystemic Group (i.v. antibiotics; red symbols) in PA-positivechildren with CF. Lines indicate medians. Circled data points inGroup 2 indicate subjects treated with an alternative "systemic"treatment (oral ciprofloxacin and inhaled TOBI) due to lack ofi.v. access. Intergroup comparison was by Mann–Whitney U-test(1-tailed). A: D%PMN (primary study endpoint).

A major barrier to current CF life expectancy is chronic pulmonary infection by Pseudomonas aeruginosa, and the inhalation of aerosolized antibiotics, allows for more direct delivery of medication to the surface of the lungs, that helps to bypass the Pseudomonas aeruginosa biofilms, and when used in combination with systemic drugs delivered by IV or orally, it produces lower levels of inflammation than when taken in isolation[11, 19].

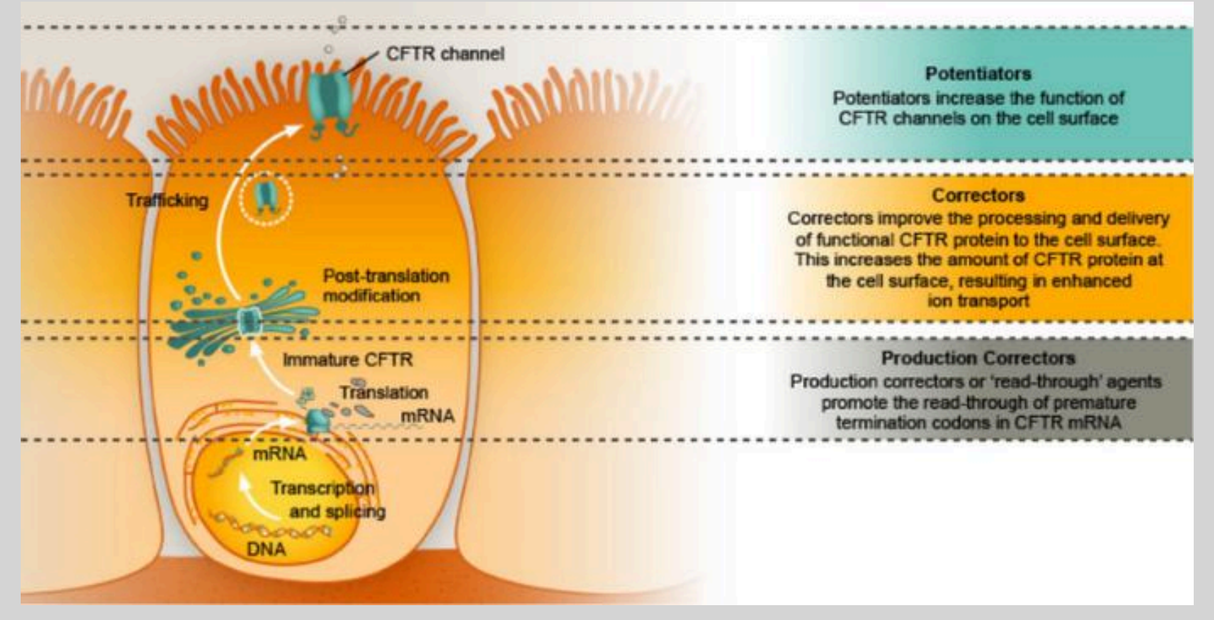

CFTR channel
Trafficking
Post-translation modification
Immature CFTR
Translation
mRNA
mRNA
Transcription and splicing
DNA
Potentiators
Potentiators increase the function of CFTR channels on the cell surface
Correctors
Correctors improve the processing and delivery of functional CFTR protein to the cell surface. This increases the amount of CFTR protein at the cell surface, resulting in enhanced ion transport
Production Correctors
Production correctors or 'read-through' agents promote the read-through of premature termination codons in CFTR mRNA

Figure 13 Site and mechanism of action of different CFTR modulator drugs.

Microbiology of the CF Lung

- Mutation of the CFTR gene also produces a weakening of the immune system such that shortly after birth, individuals with CF are almost guaranteed to have their lungs colonized by malign bacterial species[12].
- Frequently, the first lung infections a CF patient encounters are caused by either Staphylococcus aureus or Haemophilus influenzae, however, as the individual ages, it becomes increasingly likely that their lungs are dominated by Pseudomonas aeruginosa infection[12].

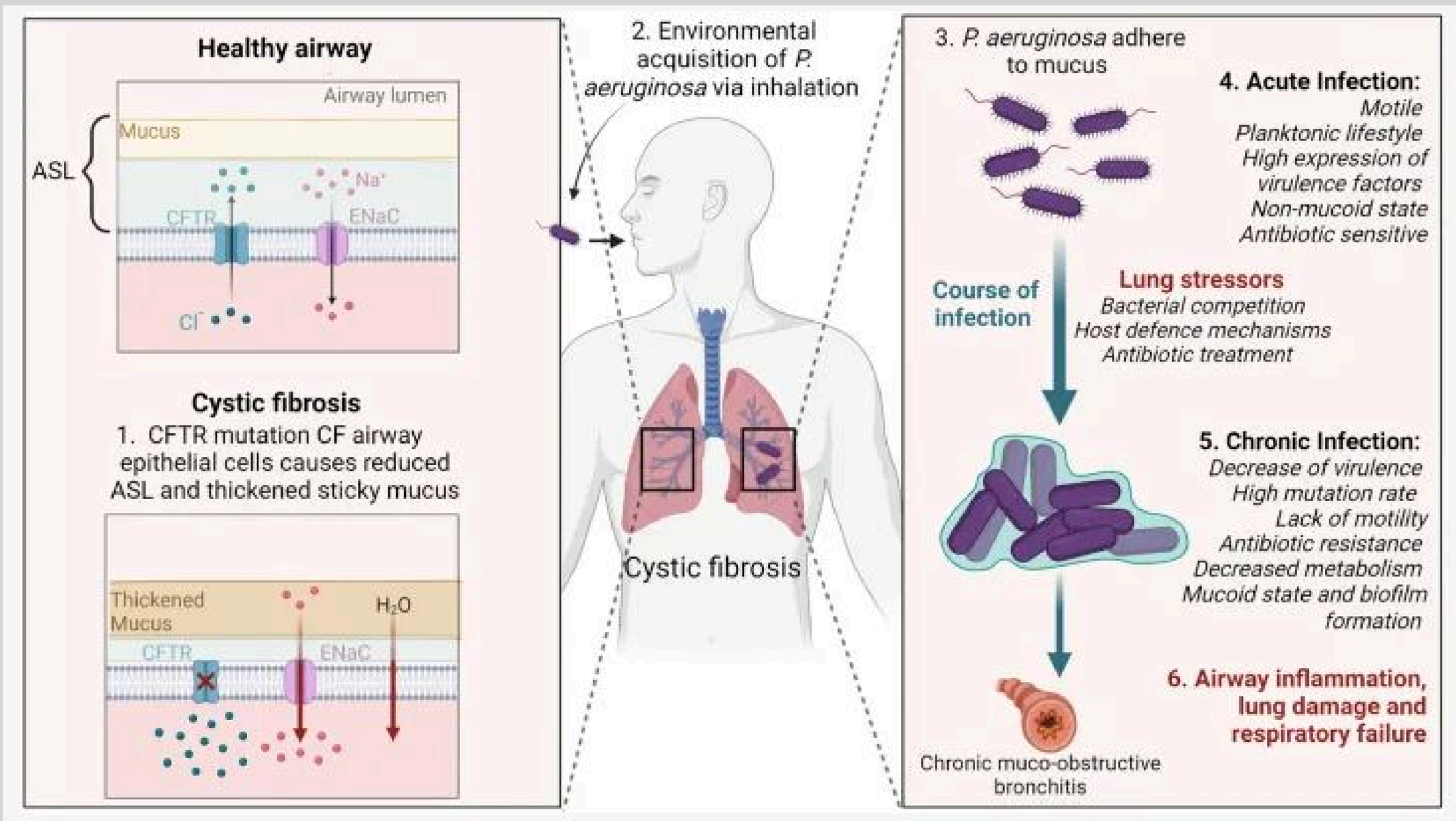

Healthy airway
Airway lumen
ASL
Mucus
CFTR
Na⁺
ENaC
Cl⁻
Cystic fibrosis
1. CFTR mutation CF airway epithelial cells causes reduced ASL and thickened sticky mucus
Thickened Mucus
H₂O
CFTR
ENaC
2. Environmental acquisition of P. aeruginosa via inhalation
Cystic fibrosis
3. P. aeruginosa adhere to mucus
4. Acute Infection:
Motile
Planktonic lifestyle
High expression of virulence factors
Non-mucoid state
Antibiotic sensitive
Course of infection
Lung stressors
Bacterial competition
Host defence mechanisms
Antibiotic treatment
5. Chronic Infection:
Decrease of virulence
High mutation rate
Lack of motility
Antibiotic resistance
Decreased metabolism
Mucoid state and biofilm formation
6. Airway inflammation, lung damage and respiratory failure
Chronic muco-obstructive bronchitis

Figure 14 Schematic illustrating Pseudomonas aeruginosa infection and adaptation to cystic fibrosis (CF) lungs. Chronic lung infections result in airway inflammation, lung tissue damage and eventually respiratory failure. CFTR; cystic fibrosis transmembrane conductance regulator, ENaC; epithelial sodium channel, ASL; airway surface liquid.

- Pseudomonas aeruginosa, is a Gram-negative rod shaped bacteria that is extremely prevalent in the environment[12]. Healthy individuals frequently come in contact with Pseudomonas aeruginosa, and while it can sometimes cause opportunistic infection, in individuals with compromised immune systems, it can cause devastating chronic infection by evading treatments[12, 13].
- Pseudomonas aeruginosa infection has been found to directly cause bronchiectasis and end-stage lung disease, with over 80% of adult aged individuals with CF facing lung failure due to Pseudomonas aeruginosa infection at some point in their lives[12, 13]. A genome wide association study in CF -patients found that beyond CFTR mutation, there are two genetic loci, rs62369766 (chr5p12; p=1.98×10−8) and rs927553 (chr13q12.12; p=1.91×10−8), that have a direct association with the age of Pseudomonas aeruginosa infection onset in CF patients[13].
- Even variant class of the CFTR mutation has an effect on the age of onset, and how severe Pseudomonas aeruginosa infection is due to variations in the mechanism which causes CF[12].

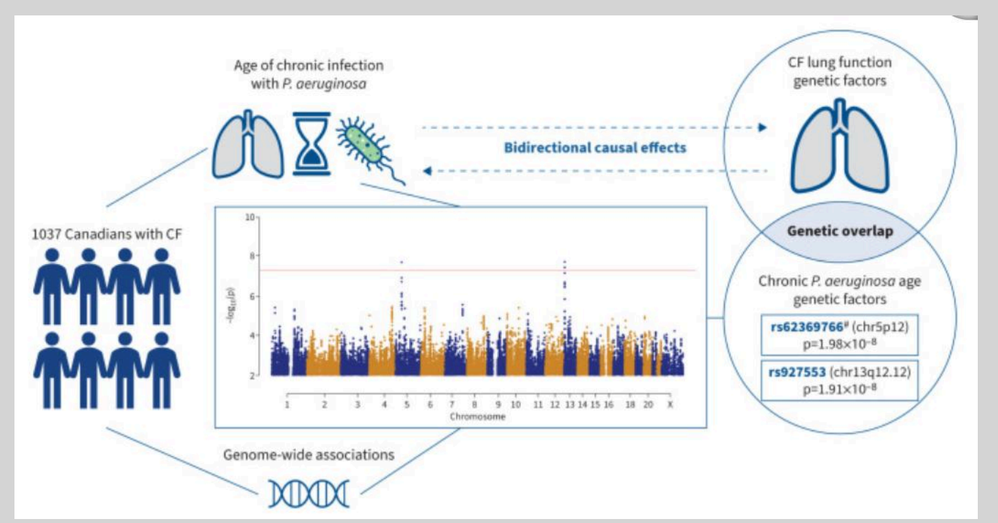

Age of chronic infection with P. aeruginosa
CF lung function genetic factors
Bidirectional causal effects
1037 Canadians with CF
Genetic overlap
Chronic P. aeruginosa age genetic factors
rs62369766ᵃ (chr5p12) p=1.98×10⁻⁸
rs927553 (chr13q12.12) p=1.91×10⁻⁸
Chromosome
Genome-wide associations

Figure 15 In a genome-wide association study (GWAS) of 1037 Canadians with cystic fibrosis (CF), two novel loci found linked to chronic Pseudomonas aeruginosa infection age. Evidence found of a shared polygenic component and a potential causal relationship between chronic P. aeruginosa infection and lung disease. #: the rs62369766 locus was validated using an independent French cohort (n=501).

Psychosocial Challenges of an Aging Population and Conclusions

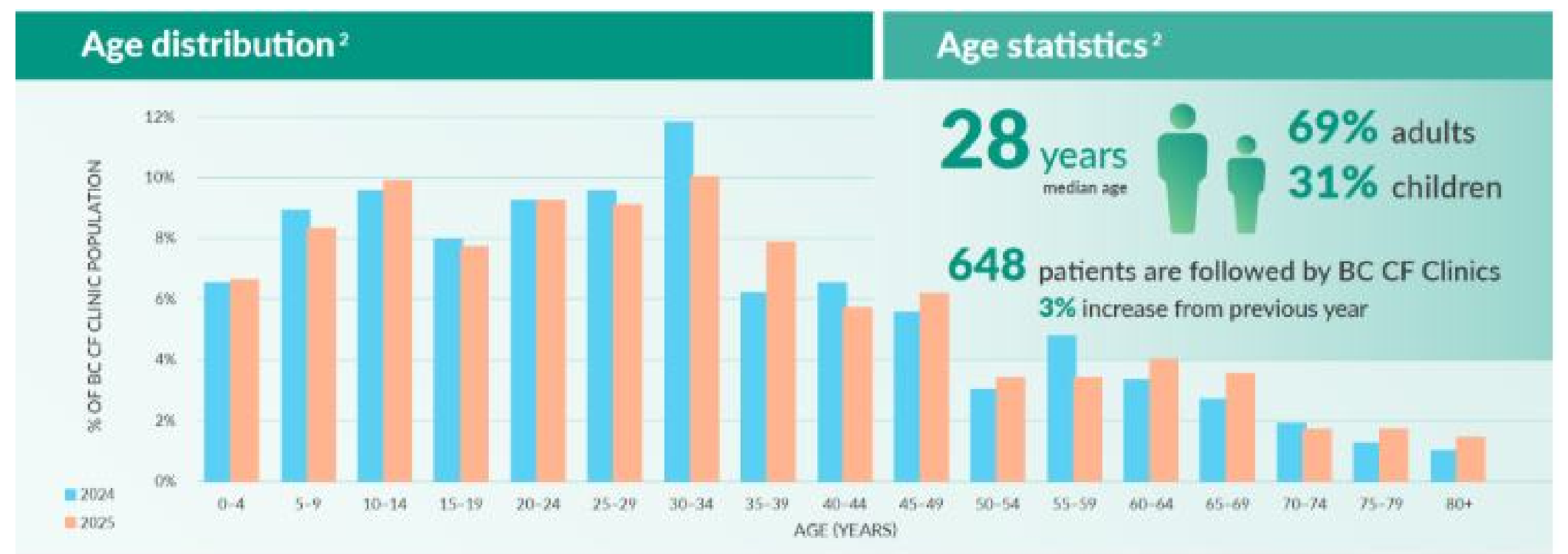


Figure 16 Age distribution of CF patients in Canada in 2024 Vs. 2025

- Treatments and diagnoses for CF are constantly improving, and as such, the life expectancy is improving each year[2, 7].
- Increased life expectancy means that the psychosocial impacts of CF are constantly evolving as new problems emerge due to an aging population and changing demographics.
- A screening of 50 CF patients, and 50 parents of those patients, revealed that a high percentage of both patients and parents of CF affected individuals scored high on anxiety and depression tests[16]. [72% mild; 28% moderate] for patients on anxiety tests, [67% mild; 33% moderate] for patients on depressions tests, [39% mild; 36% moderate; 25% severe] for parents on anxiety tests, and [60% mild; 27% moderate; 13% severe] for parents on depression tests[16].
- Further studies have confirmed that anxiety and depression symptoms are worse in caregivers compared to children with CF, indicating that psychosocial interventions or treatments should be designed to target caregivers as well as individuals with the disease[1].
- It is unclear how these statistics may shift as the CF population ages and becomes less dependant on caregivers.
- Lower socioeconomic status has been associated with worsened pulmonary health, and poorer nutritional levels compared to those in the population with higher socioeconomic status, and under the view of intersectionality, the stacking effects of CF, low socioeconomic status, and increased risk of mental health diagnoses might create devastating symptoms[17, 18].

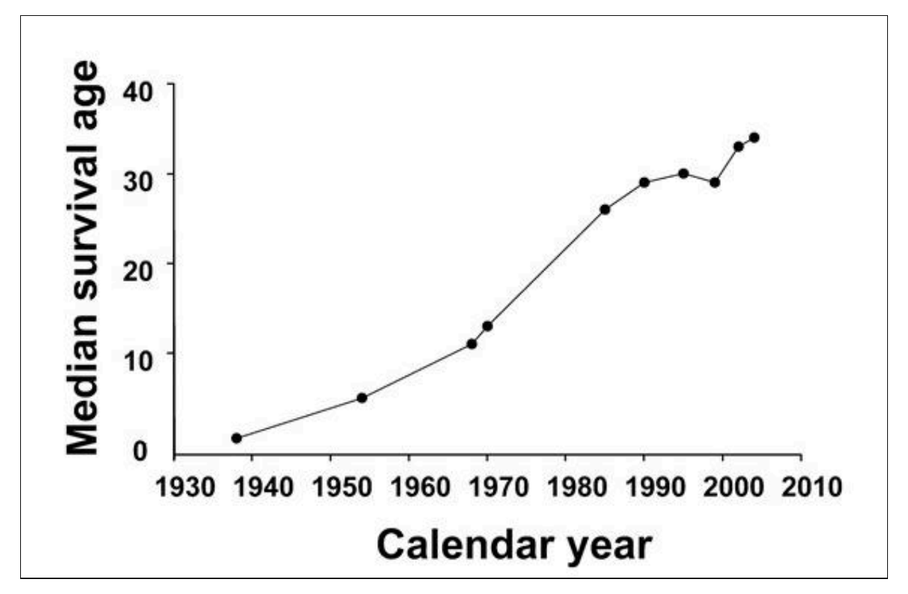


Figure 17 Median survival age for patients with CF at various times since the first description of CF. Data before 1970 are gleaned from then-current literature. Data since 1985 are from CF Foundation Data Registry and represent projections of median survival age for a child born in that year with CF.

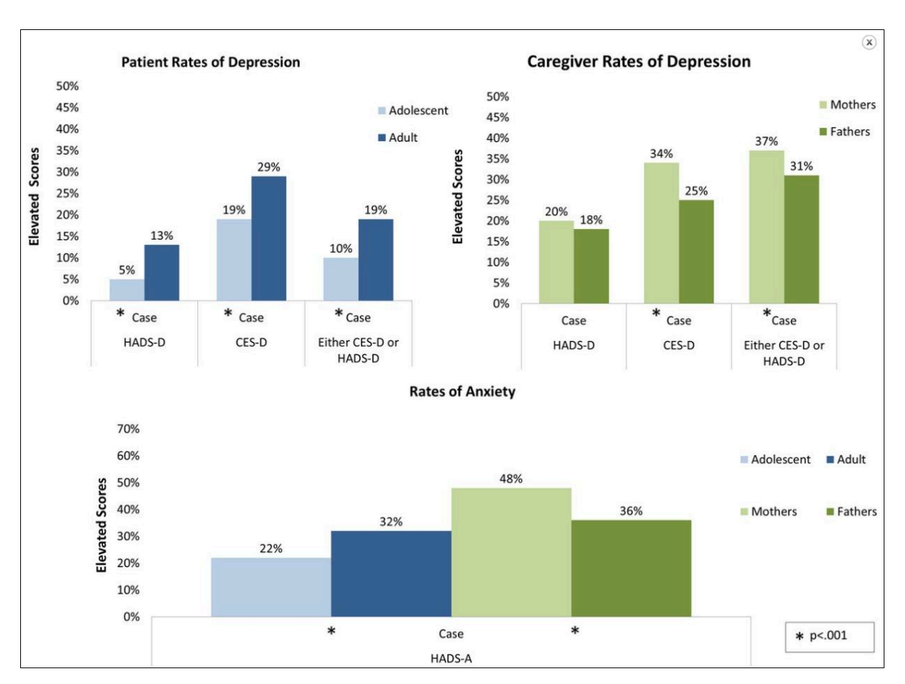


Figure 18 Rates of depression and anxiety by respondent to the International Depression Epidemiological Study on (Hospital Anxiety and Depression Scale; HADS & Center for Epidemiologic Studies-Depression Scale; CES-D)

Conclusion

In conclusion, CF is a multifaceted disease that requires the careful management of chronic pulmonary infections, organ insufficiencies, and mental health diagnoses. In our modern world CF is evolving in numerous ways, whether it be the understanding of CF carrier symptomology, the acknowledgement of global disparities in treatment and diagnosis, or the aging demographic of the CF population. All of these points present their own unique opportunities to combat CF, by pharmaceutical treatment, improved policy and healthcare infrastructure, or treatment of mental disorders.

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