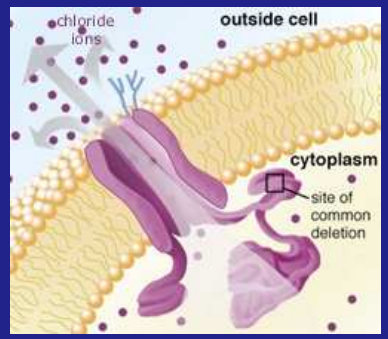
AGGIORNAMENTI IN TEMA DI FIBROSI CISTICA



Laura Claut
Carla Colombo

Centro Regionale di Riferimento per la Fibrosi cistica
Milano

La scoperta della fibrosi cistica

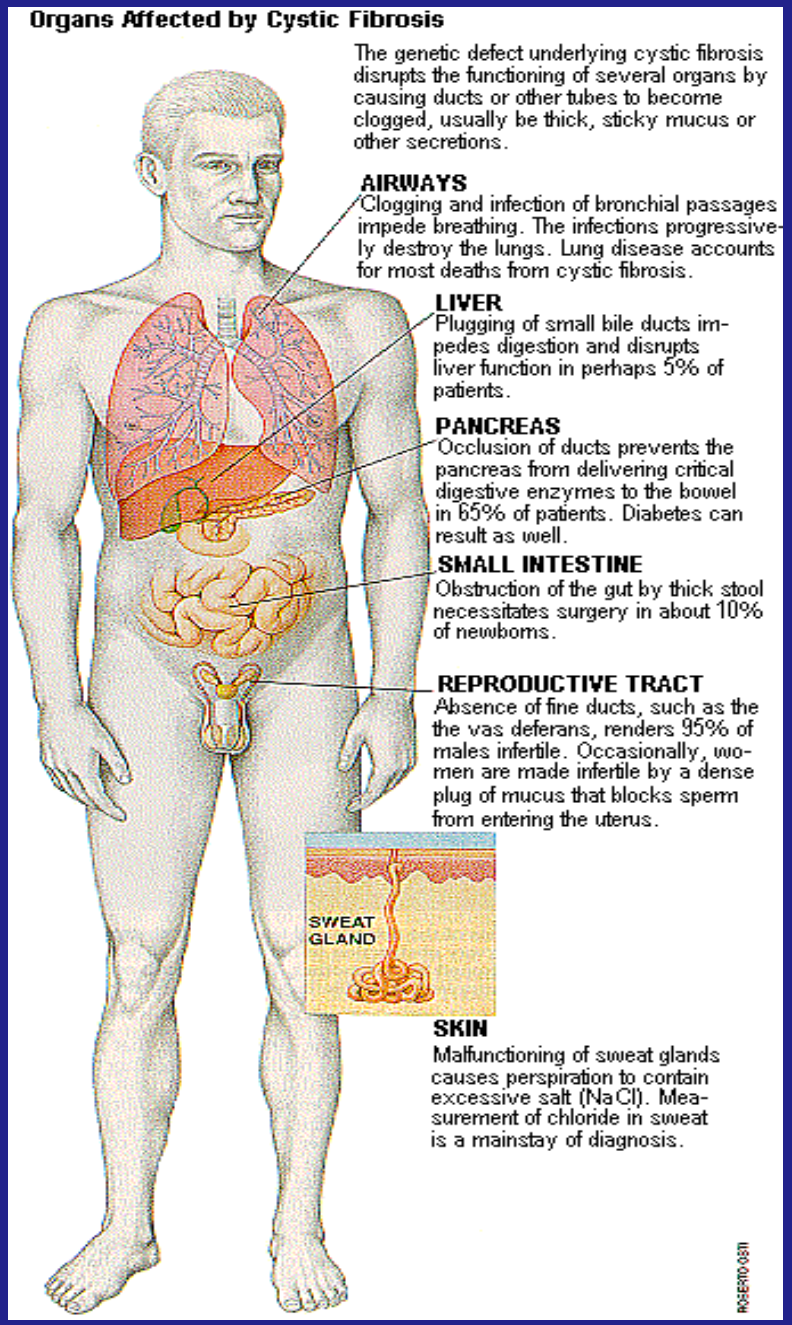
Andersen, D. H. (1938)
Cystic Fibrosis of the Pancreas and its relation to Celiac Disease:
a Clinical and Pathological Study.
American J Diseases of Children **56**: 344.

Dorothy Andersen, M.D.

FIBROSI CISTICA

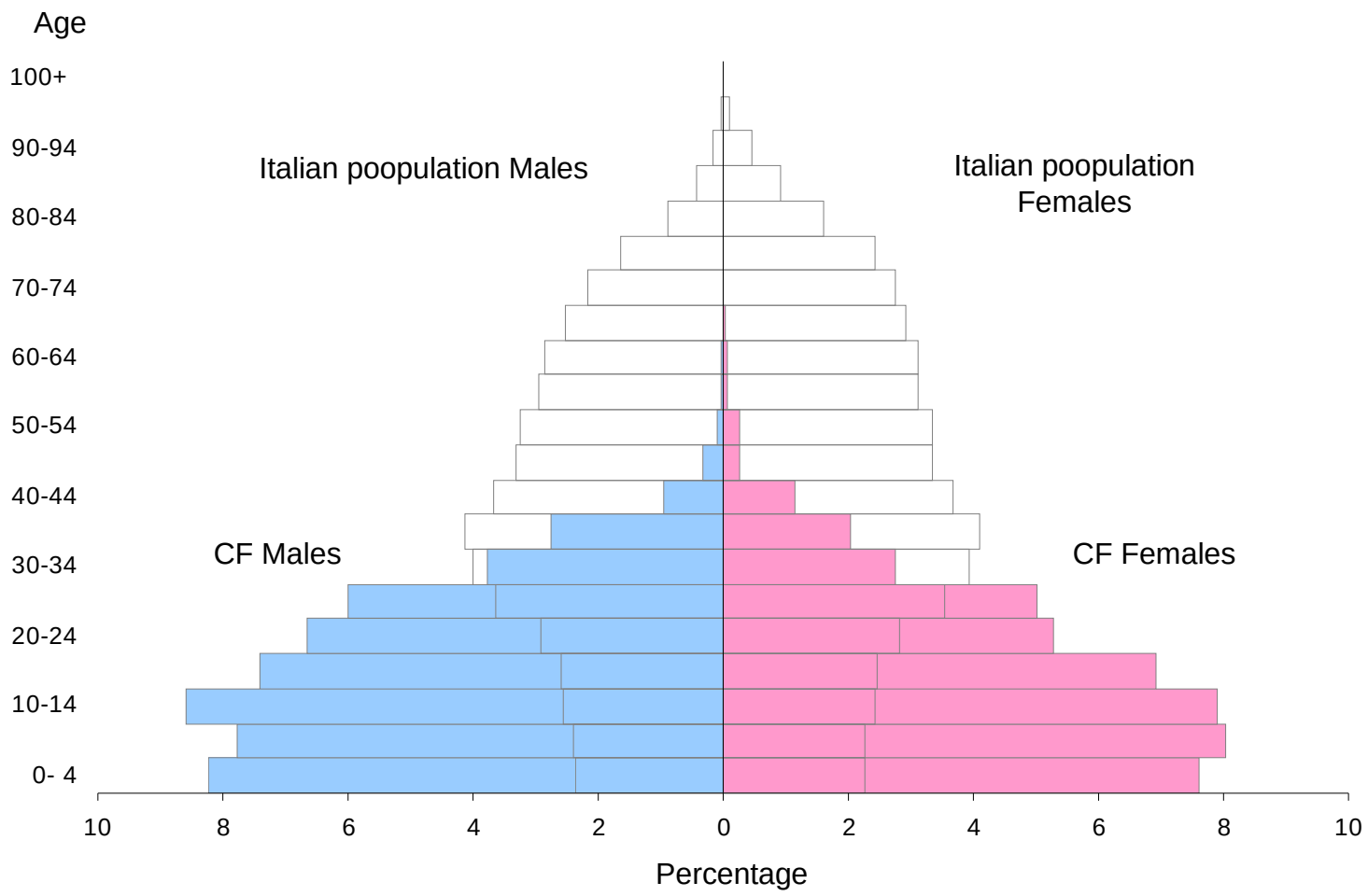
- Malattia genetica a trasmissione autosomica recessiva caratterizzata essenzialmente da turbe delle funzioni di trasporto ionico degli epiteli, cui conseguono anomalie della secrezione esocrina di vari apparati
- È la più comune nella popolazione caucasica
- Incidenza in Italia 4456 nati vivi (1:2500)

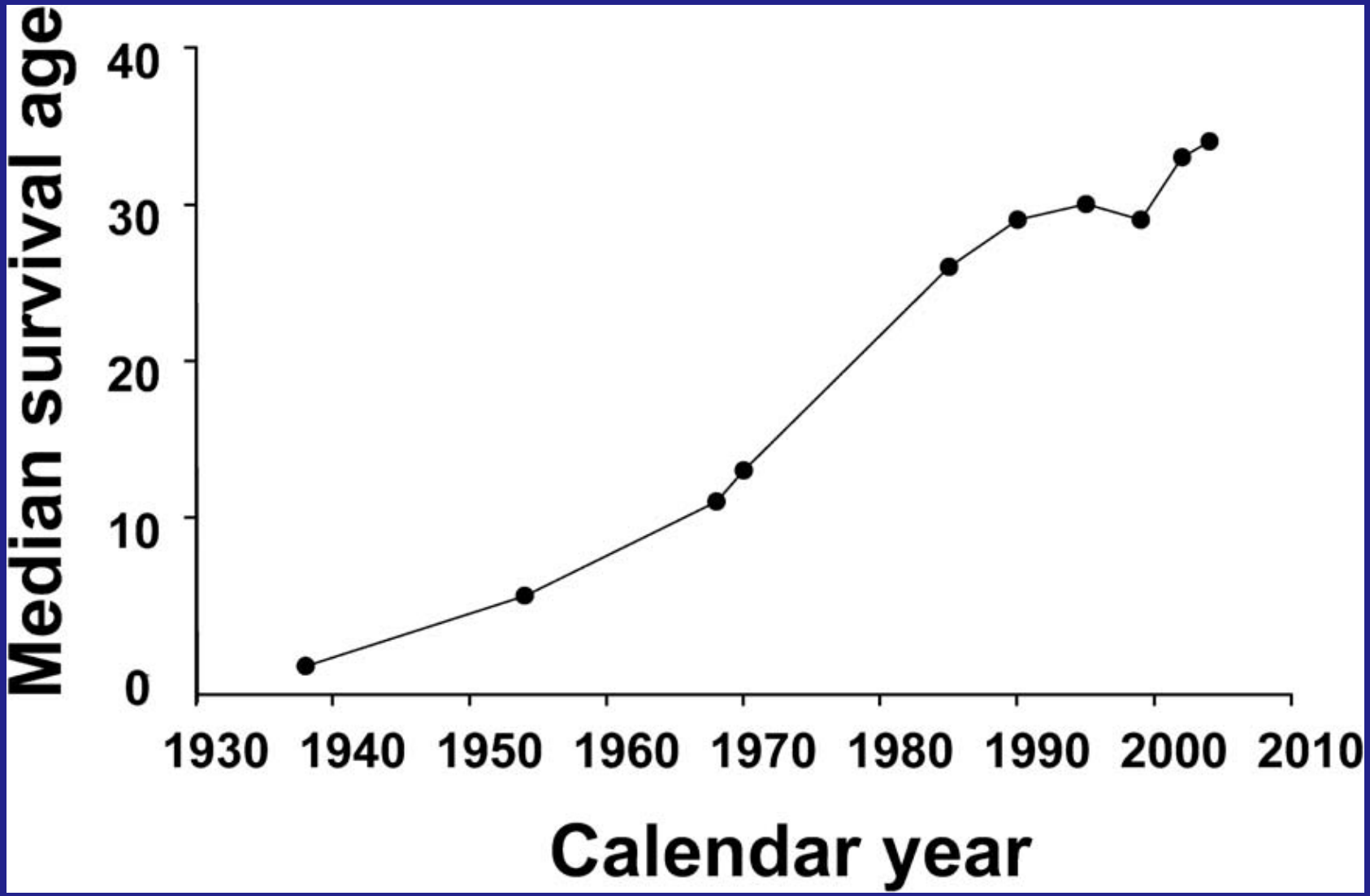
- E' caratterizzata da una notevole eterogeneità clinica per l'interessamento di molti organi (ghiandole salivari e sudoripare,vie aeree, pancreas,fegato, intestino, dotti deferenti)
- la compromissione polmonare è presente in più del 90% dei pazienti ed è la principale causa di morbilità e mortalità



Registro Italiano Fibrosi Cistica

DISTRIBUZIONE DELL' ETA' DEI PAZIENTI E DELLA POPOLAZIONE ITALIANA

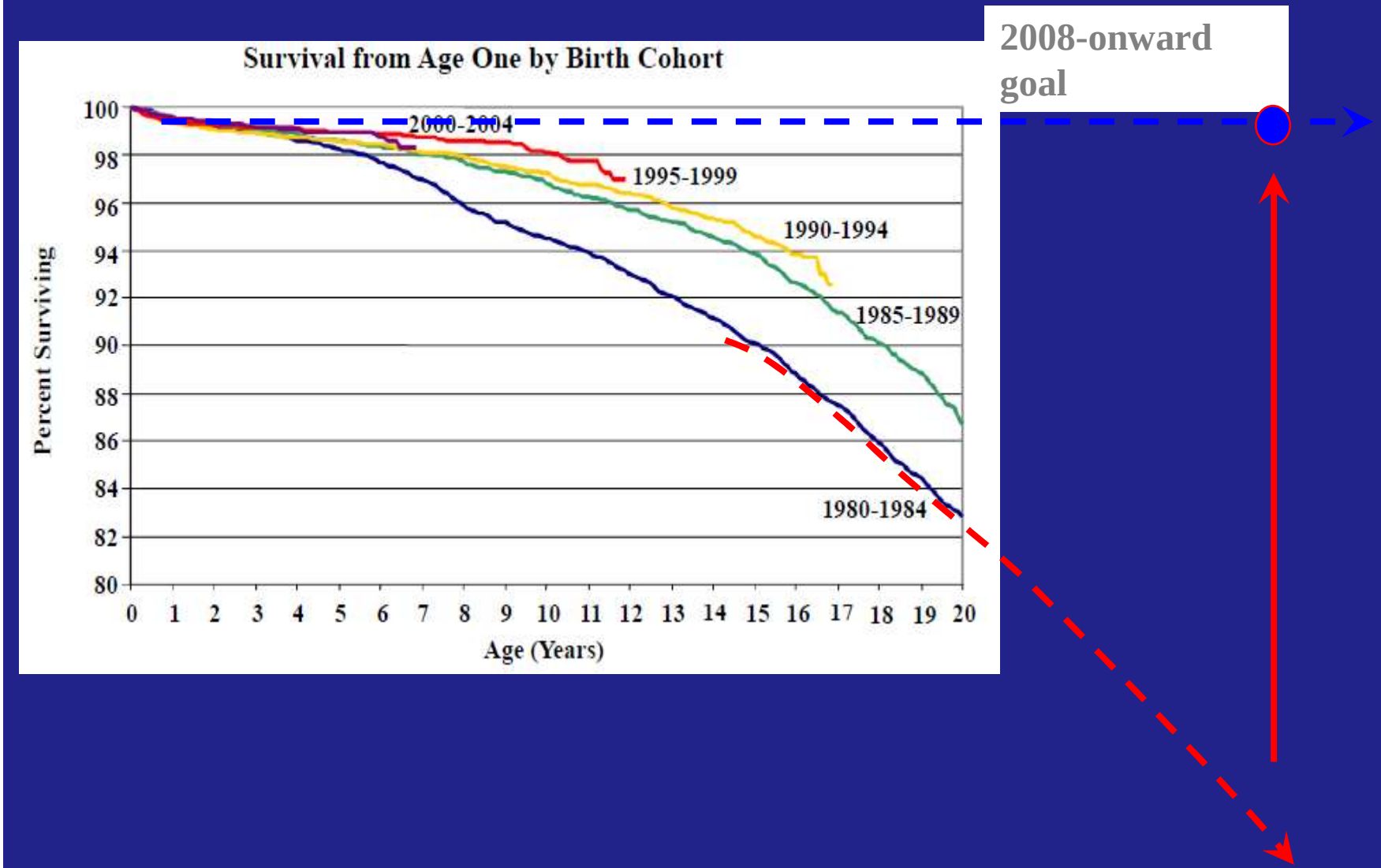




Median survival age for patients with CF at various times since the first description of CF. Data before 1970 are gleaned from then current literature. Data since 1985 are from CF Foundation Data Registry and represent projections of median survival age for a child born in that year with CF.

Davis PB, 2006

Curve di sopravvivenza per coorti selezionate alla nascita

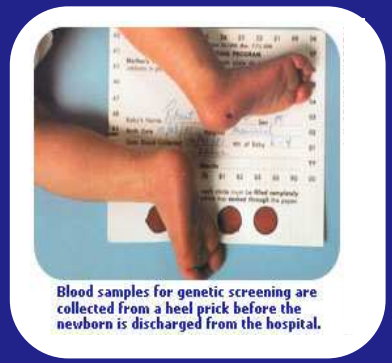


CFF Patient Registry, 2006 Annual data Report

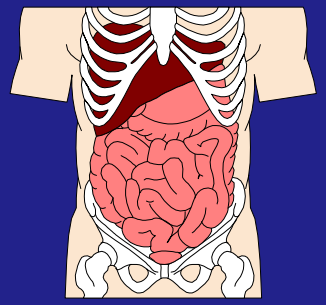
Motivo di diagnosi

CRRFC Milano

sintomi
41.4%



screening neonatale
42.6%



Ileo da meconio
10.3%

storia familiare
3.6%

Forme atipiche di fibrosi cistica (CFTR-related deseases)

- Screening positivo (ipertripsinemia)
- Test del sudore borderline o negativo
- Genetica : mutazione severa/mild
- Forme pauci o spesso monosintomatiche
- Assenza di sintomi alla diagnosi

- Futuro…..?

- **54/63** pts underwent newborn screening:
  - 48 patients had positive IRT
  - 6 patients had negative IRT

- In **37** pts diagnosis was made by means of NBS (mean age at diagnosis 0.24yrs):
  - 70.3% no symptoms
  - 27% respiratory symptoms
  - 2.7% GI symptoms

- **26** pts had CF fenotype or a history of CF in a sibling (mean age at diagnosis 6yrs):
  - 15.4% no symptoms
  - 65.4% respiratory symptoms
  - 11.5% GI symptoms
  - 7.7% dehydration

FIBROSI CISTICA

MALATTIA AD ELEVATO IMPATTO SOCIALE

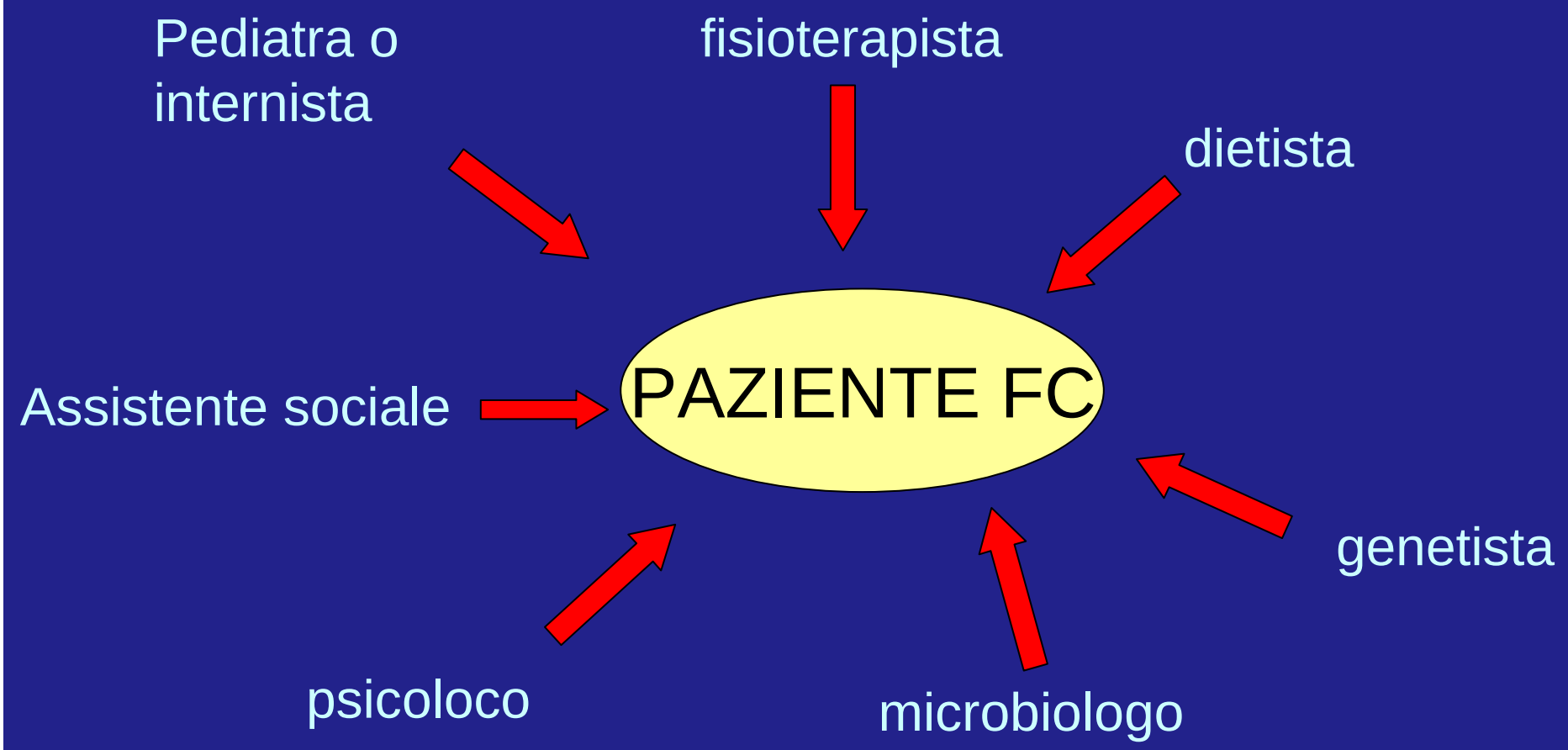
Implicazioni

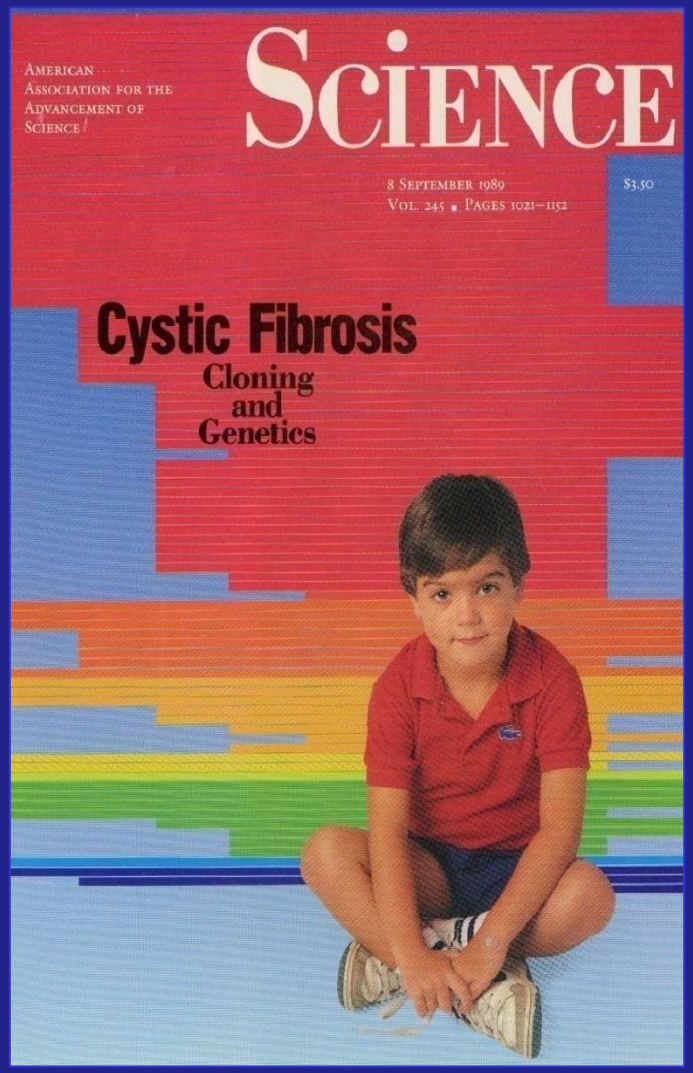
GENETICHE	→	Prevenzione
CLINICHE	→	Terapia
	→	Riabilitazione
PSICO-SOCIALI	→	Supporto psicologico sociale
SCIENTIFICHE	→	Ricerca
ORGANIZZATIVE	→	Servizi

↓

CENTRI REGIONALI FC

I CENTRI PER LA CURA DELLA FIBROSI CISTICA





1989

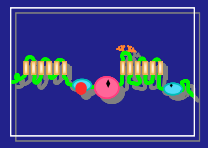
- Knowledge about the pathophysiology of CF has progressively increased after the discovery of the gene

- CF has evolved into a **model** demonstrating how a better understanding of the underlying defect can lead to novel therapeutic approaches

The CF Pathogenesis Cascade

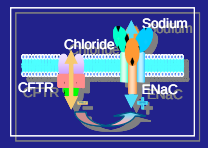
Defective CF Gene

Deficient CFTR Protein

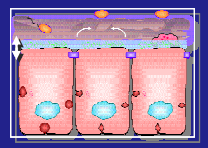


Act here to rescue the basic CF defect and block the cascade!

Abnormal Chloride Permeability
Altered Ionic Transport



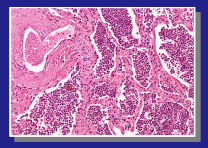
Decreased Water in ASL Abnormal Mucus Composition



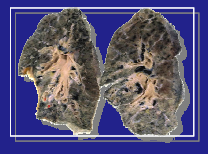
Bronchial Obstruction

Bacterial Infections

Inflammation



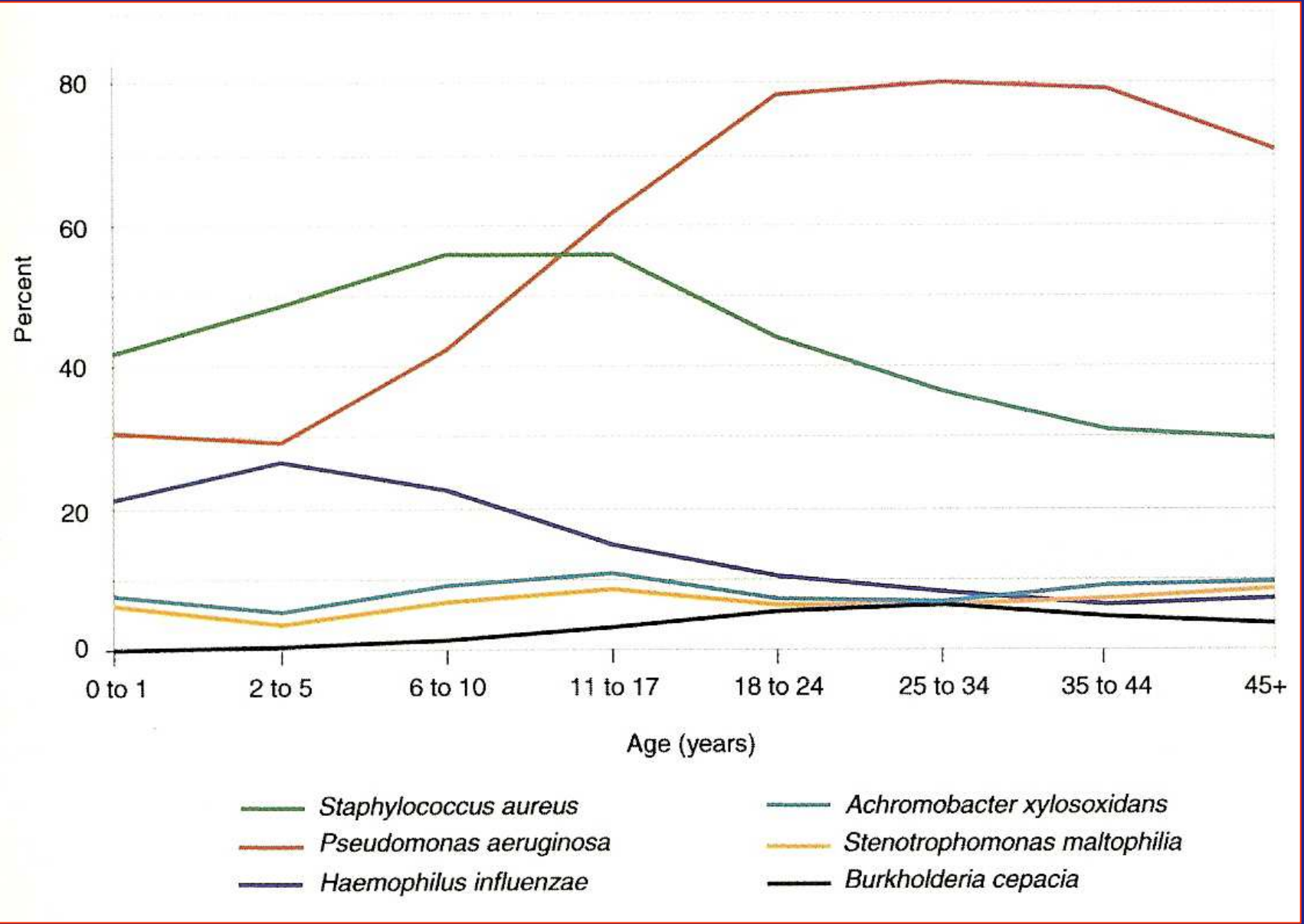
Bronchiectasis + Lung Insufficiency



Most current therapies in CF!

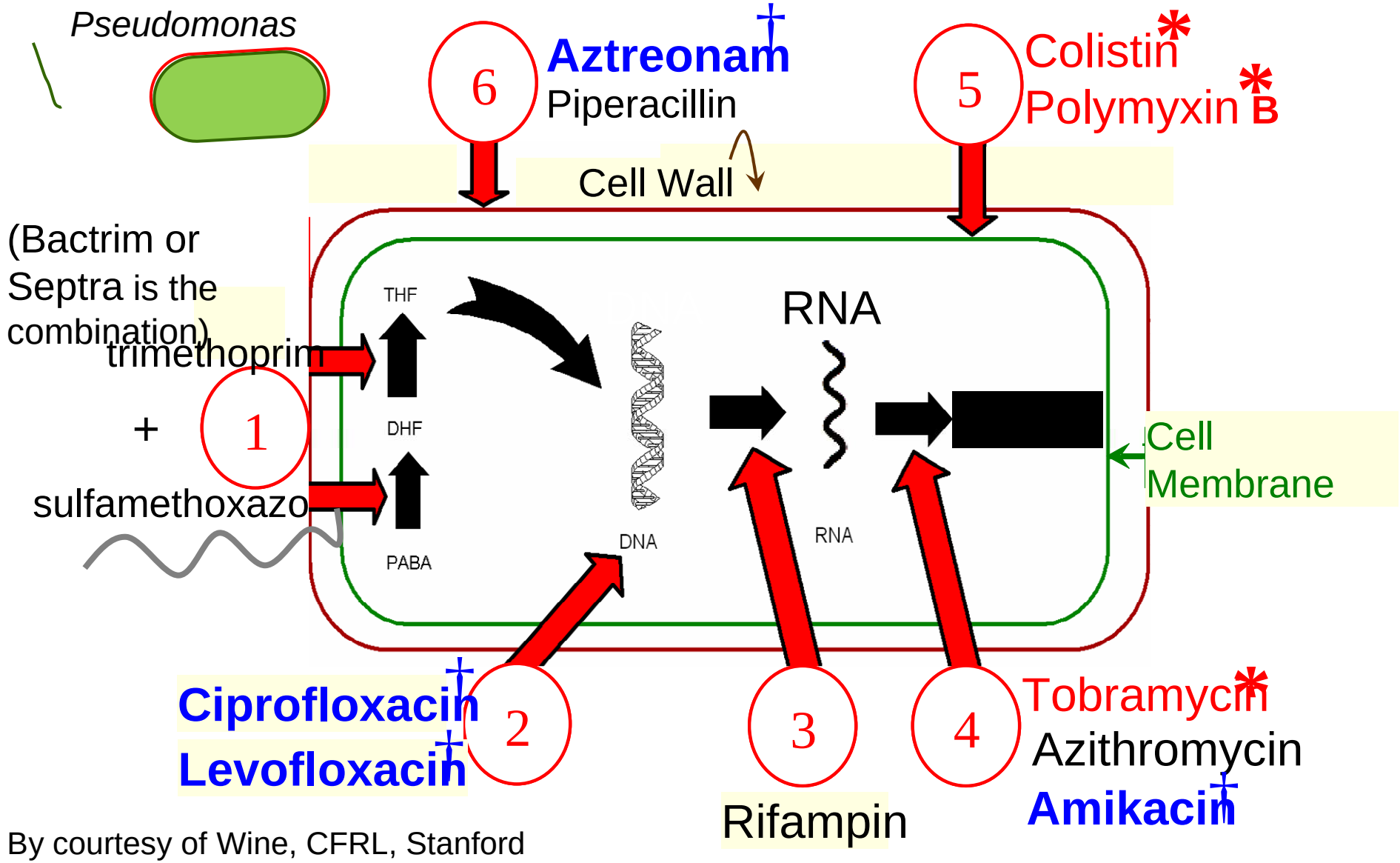
Amaral & Kunzelmann (2007) *Trends Pharmacol Sci* **28**: 334-341

EVOLUZIONE DELLA PATOLOGIA RESPIRATORIA IN FC


80
60
40
20
0
Percent
0 to 1
2 to 5
6 to 10
11 to 17
18 to 24
25 to 34
35 to 44
45+
Age (years)
Staphylococcus aureus
Pseudomonas aeruginosa
Haemophilus influenzae
Achromobacter xylosoxidans
Stenotrophomonas maltophilia
Burkholderia cepacia

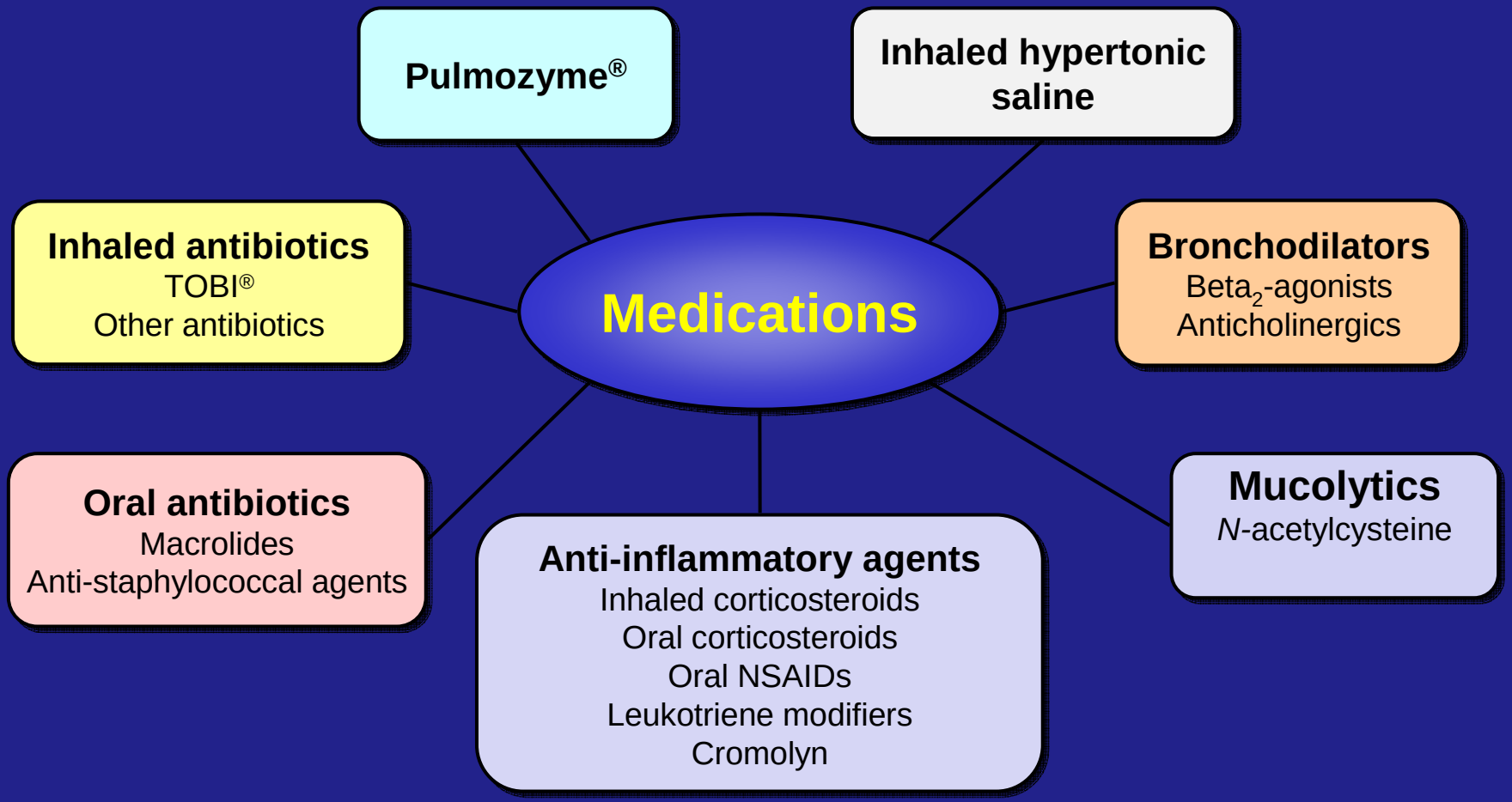
ANTIBIOTIC TARGETS

Aerosols: * Available
† In development



By courtesy of Wine, CFRL, Stanford

CFF Guidelines: Medications for Maintenance of Pulmonary Function



NSAIDS=nonsteroidal anti-inflammatory drugs.
TOBI® is a registered trademark of Novartis Pharmaceuticals Corporation.
Adapted from Flume PA et al. *Am J Respir Crit Care Med.* 2007;176:957-969.

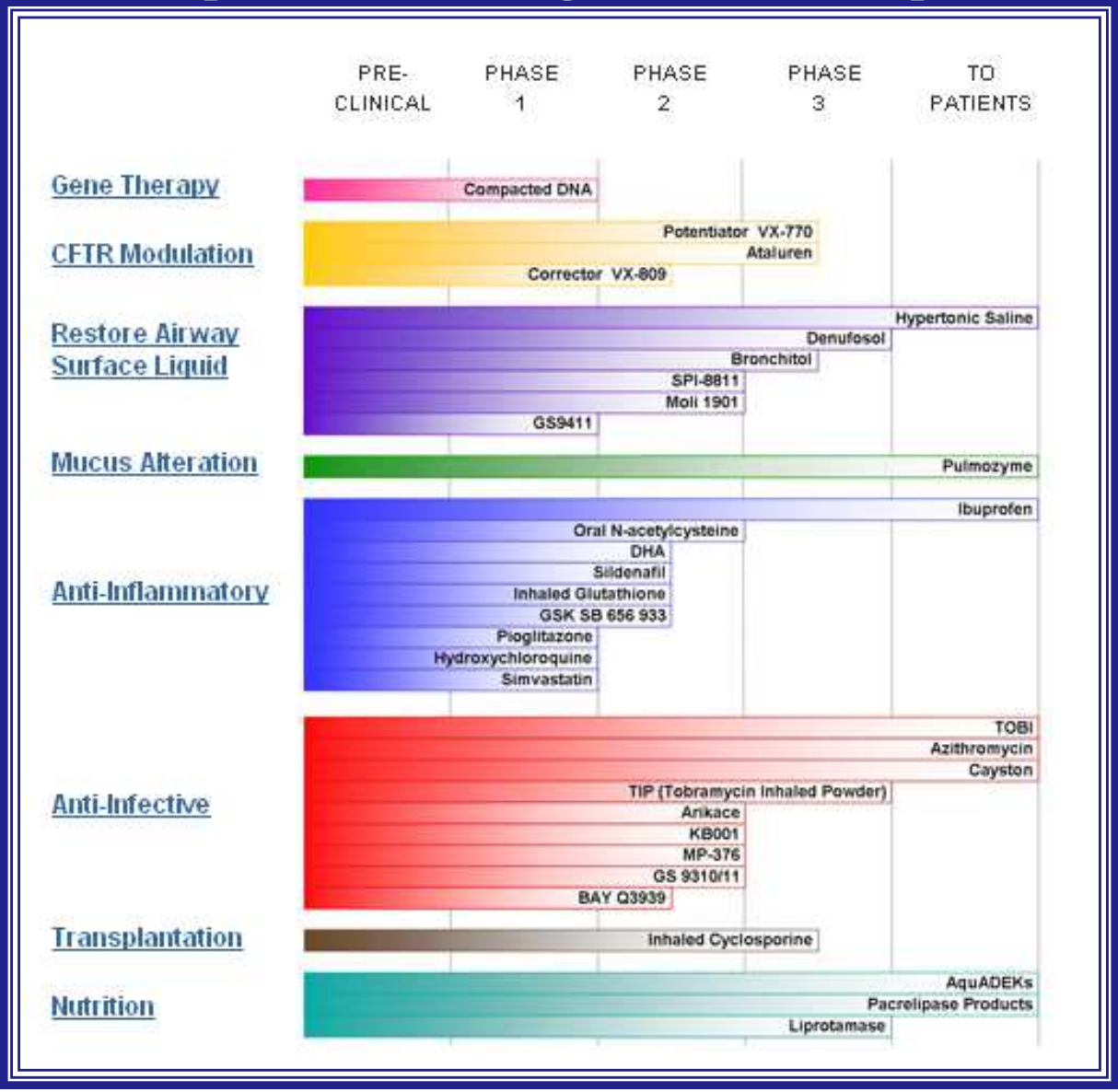
Nuove terapie

Compound	Company	Stage of development	Mechanism of action
Bronchitol (mannitol)	Pharmaxis	Phase III trial ongoing	Osmotic agent
Lancovutide (Moli1901)	Lantibio	Phase II trial completed, results pending	Alternative chloride channel activator
Denufosol	Inspire Pharmaceuticals	First Phase III trial completed Second Phase III trial ongoing	P2Y receptor agonist, ion channel regulator
VX-809	Vertex Pharmaceuticals	Phase IIa trial completed	CFTR corrector
VX-770	Vertex Pharmaceuticals	Phase III trials ongoing	CFTR potentiator
Ataluren (PTC124)	PTC Therapeutics	Phase III trials ongoing	Suppressor of premature stop codons
GS-9411	Gilead	Phase I trial	Sodium channel blocker

Grasemann H, Ratjen F, 2010

Potential CF therapies that are currently in development

http://www.cff.org/treatments/Pipeline



La prospettiva del trapianto…

Special Considerations for Patients With Cystic Fibrosis Undergoing Lung Transplantation*

Denis Hadjiliadis, MD, MHS, FCCP

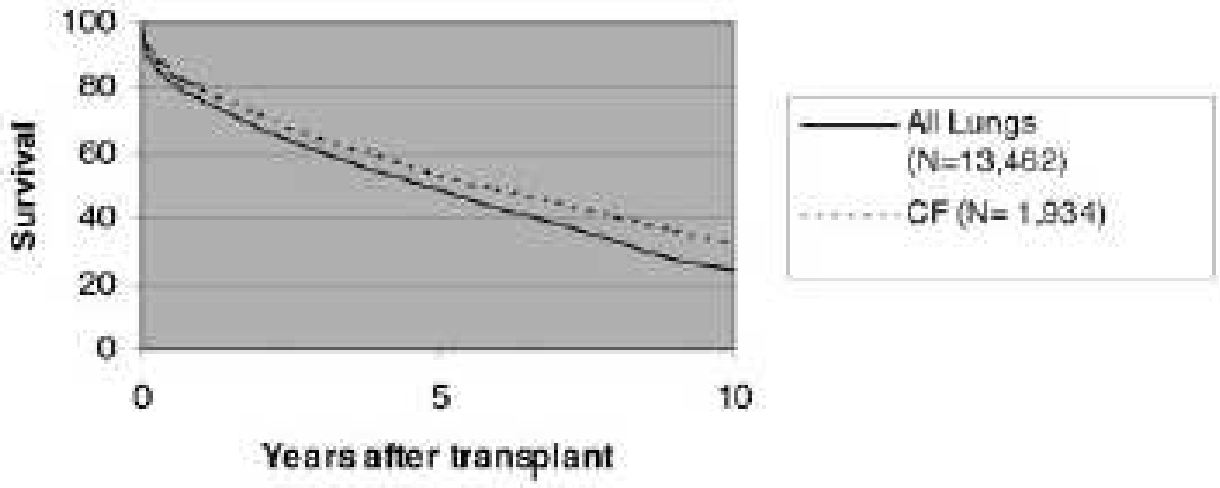


FIGURE 1. Survival of lung transplant recipients with CF compared with that of other lung transplant recipients.

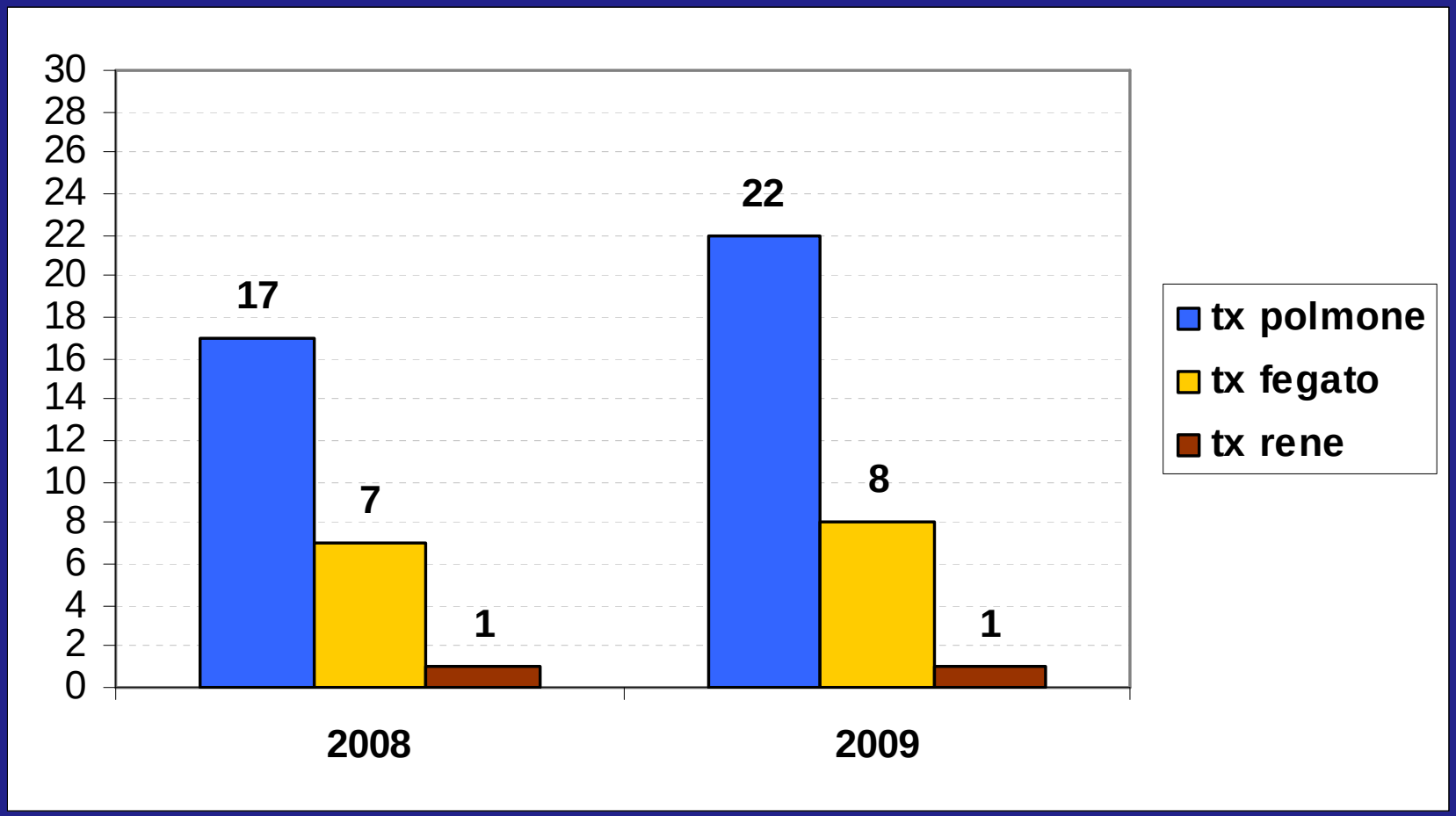
CHEST / 131 / 4 / APRIL, 2007

Lung Tx

Criticità della FC

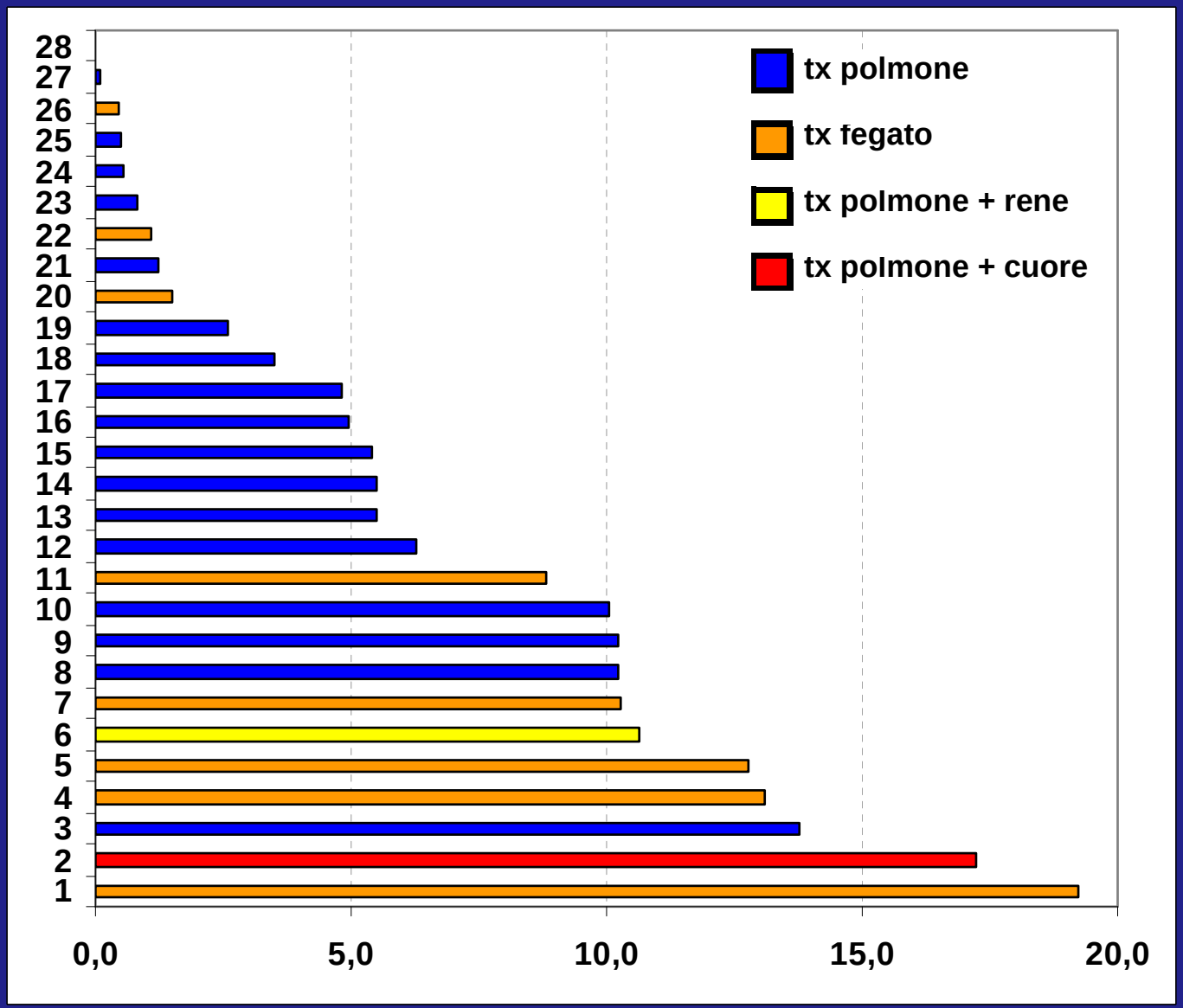
1. Reflusso gastroesofageo
2. Germi multiresistenti (*Burkholderia*)
3. Micobatteri non tubercolari
4. *Aspergillus fumigatus*

CASISTICA
CRR FIBROSI CISTICA MILANO



Report CRRFC Milano 2009

CASISTICA
CRR FIBROSI CISTICA MILANO



Report CRRFC
Milano 2009

FC… il futuro