Forum LIFC
22-24 Novembre 2019

Genetica e destino: un rapporto immutabile?

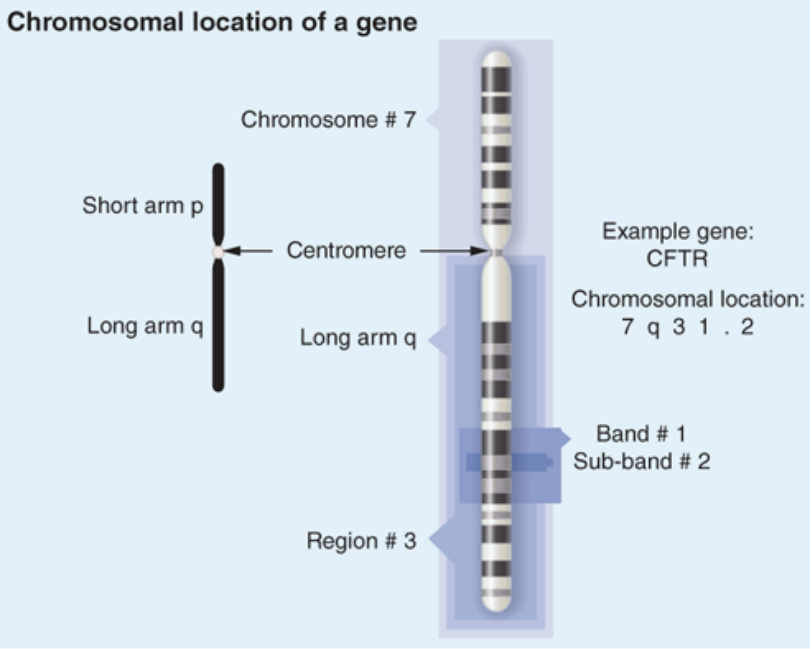
Carlo Castellani
Centro Fibrosi Cistica
Istituto Giannina Gaslini, Genoa

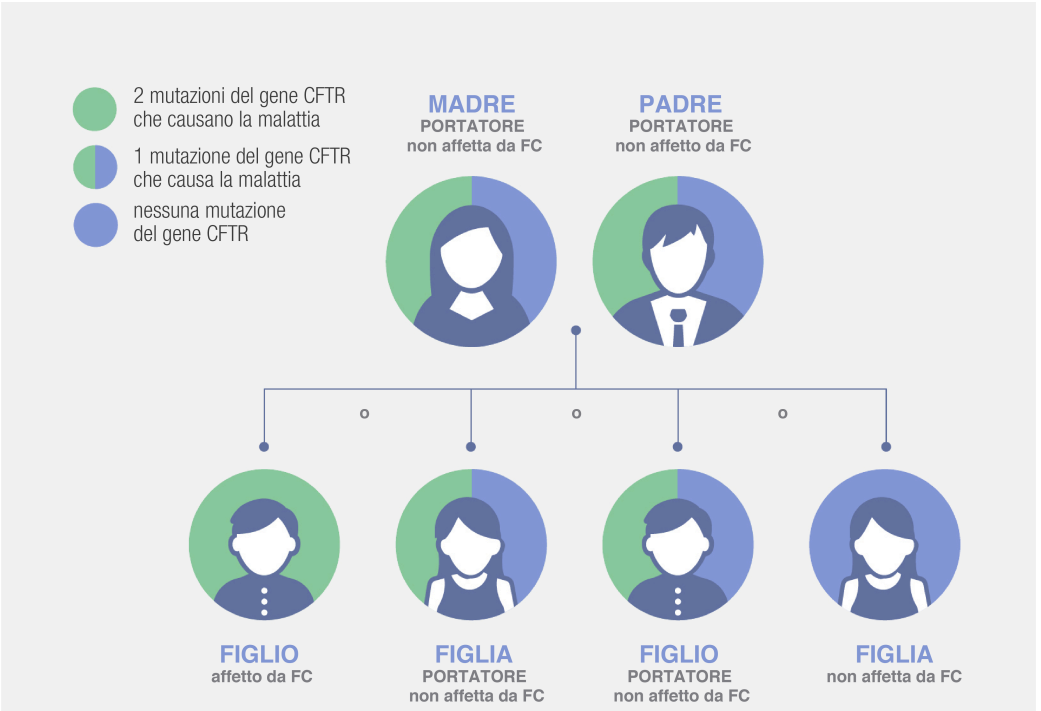
BAROUKH M. ASSAEL

IL GENE DEL DIAVOLO

Le malattie genetiche, le loro metafore,
il sogno e la paura di eliminarle

Bollati Boringhieri



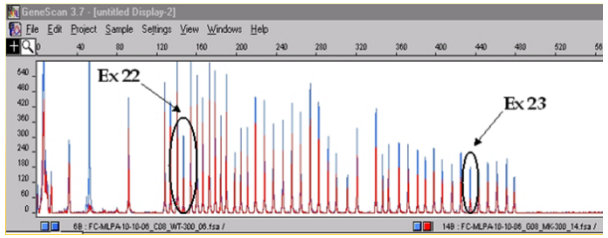


Elaborato da NH Gentics Home reference Handbook: Help me to understand Genetics, 2011 [1]

Mutazioni CFTR

Fase di scoperta

Fase tecnica

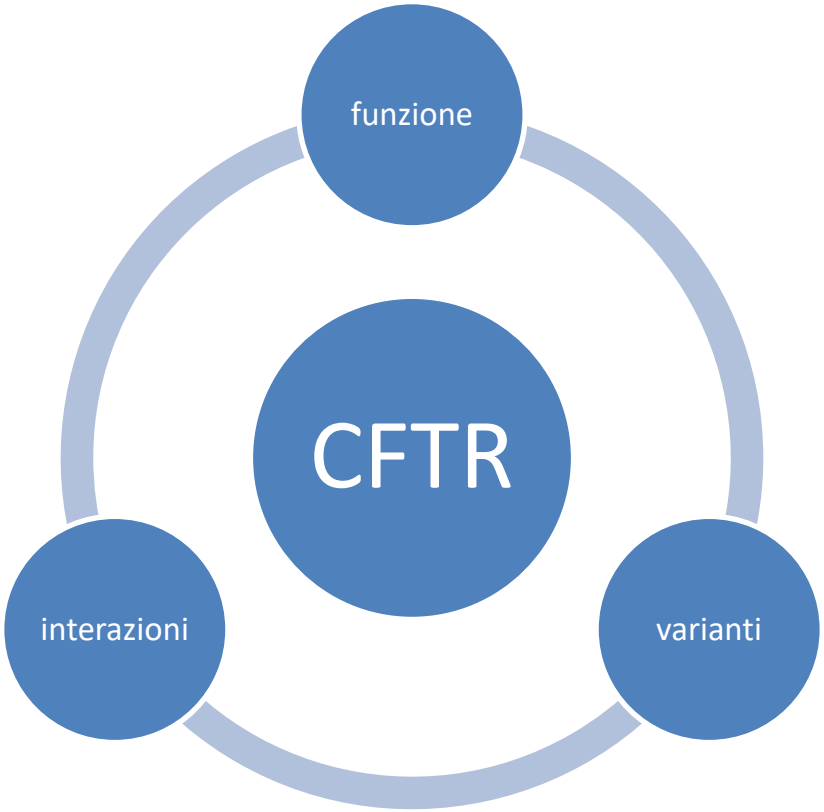


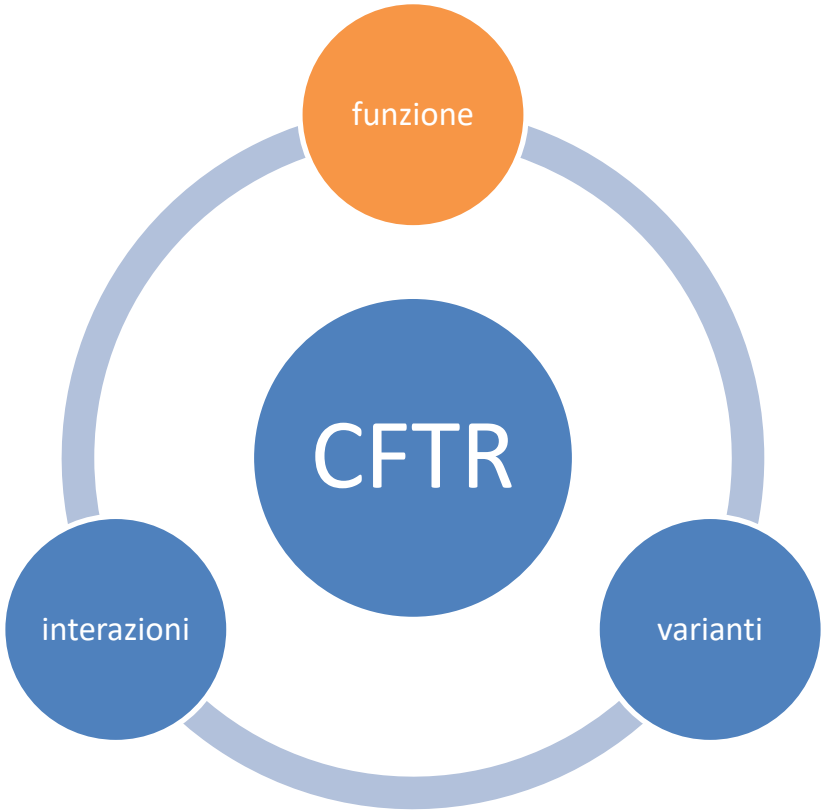
Fase interpretativa

Strumento diagnostico

Strumento predittivo

Strumento di sviluppo terapeutico


funzione
CFTR
interazioni
varianti


funzione
CFTR
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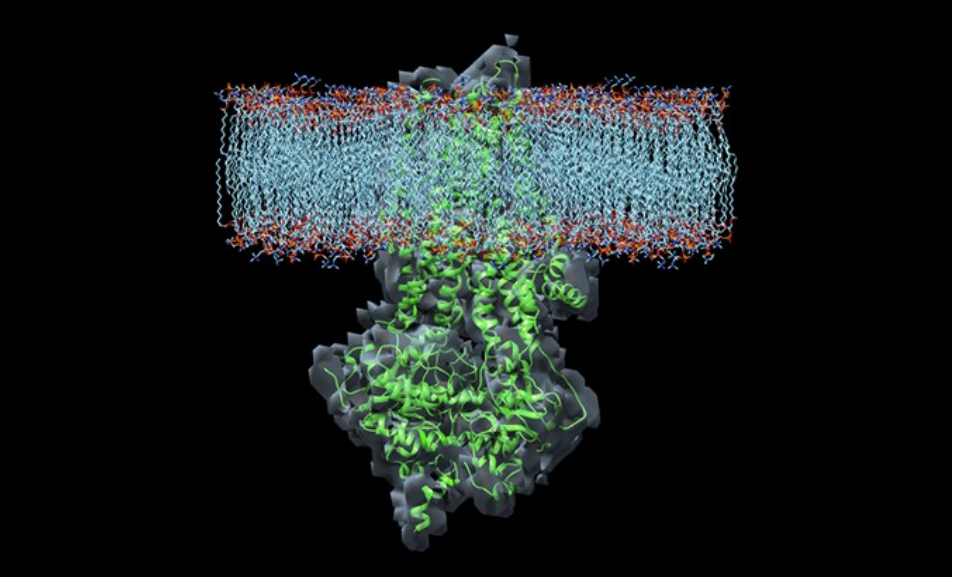
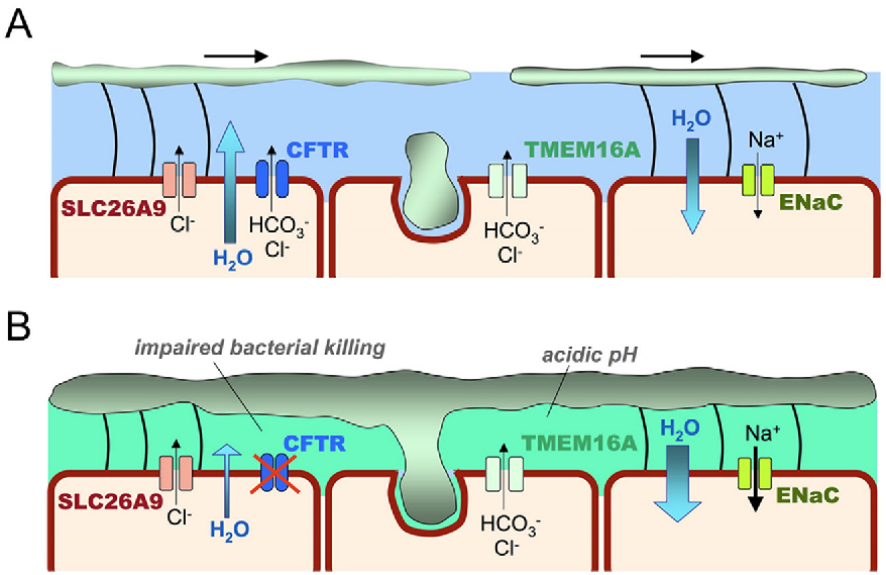
varianti

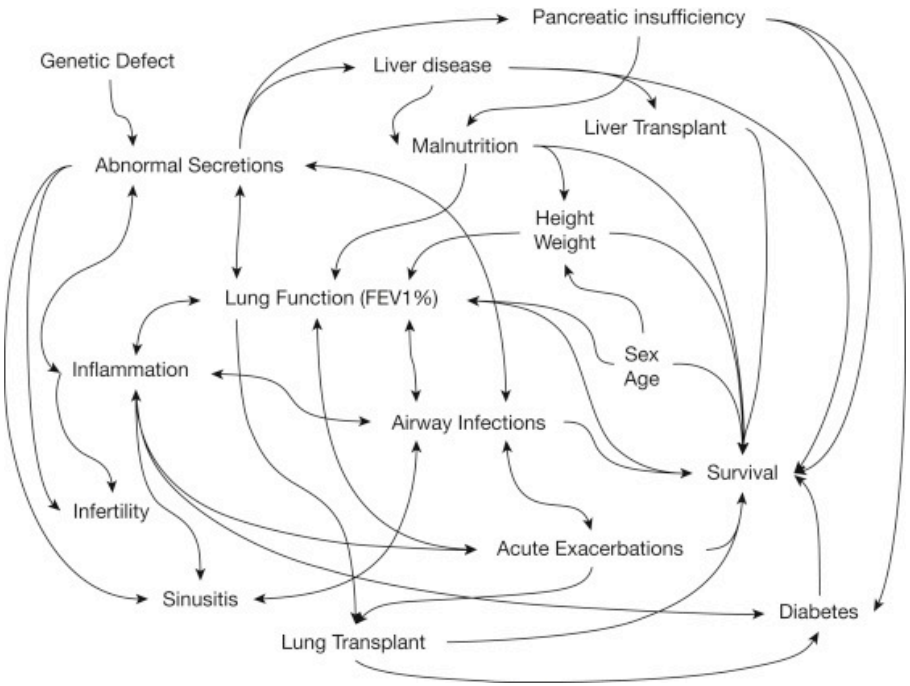


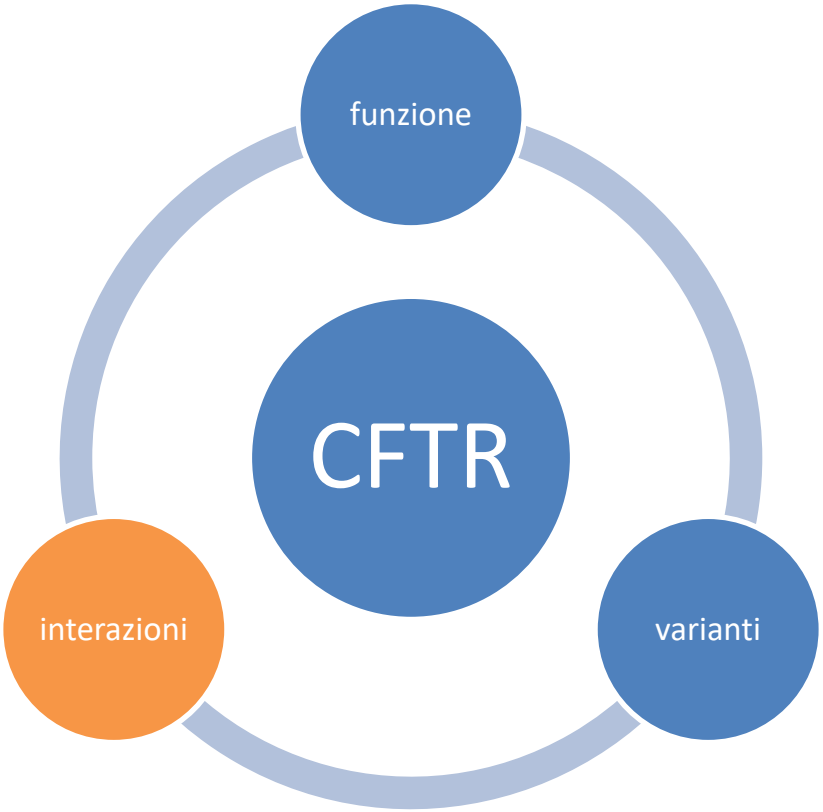
[Cystic fibrosis -- From basic science to clinical benefit: A review series.]

Hartl D, **Amaral** M.

J **Cyst Fibros**. 2015 Jul;14(4):415-6.

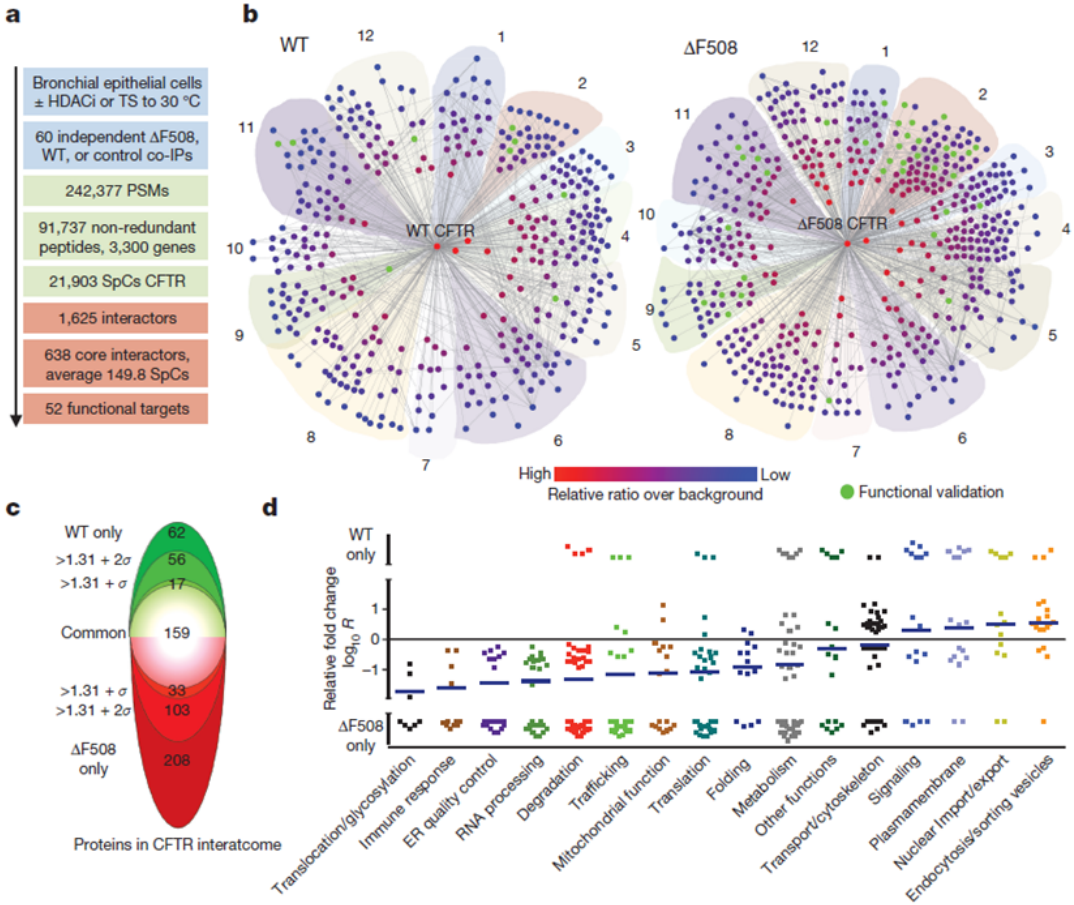





funzione
CFTR
interazioni
varianti

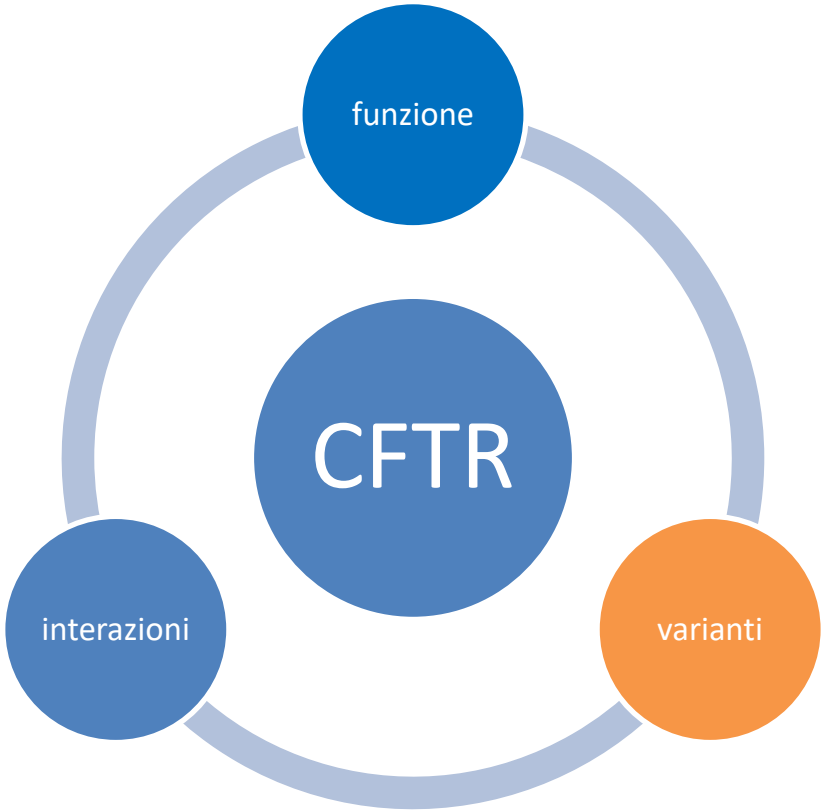
CFTR FUNCTIONAL LANDSCAPE

CFTR operates in a dynamic network of interactor proteins



WT and ΔF508 CFTR interactome in bronchial epithelial cells

doi:10.1038/nature15729


funzione
CFTR
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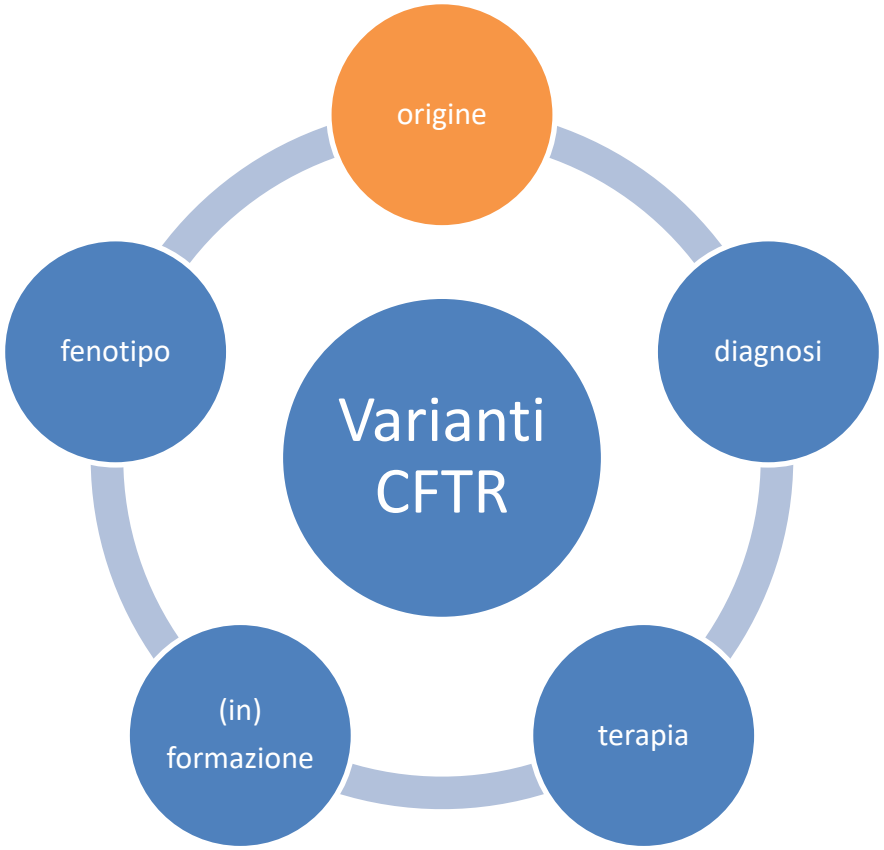
varianti


origine
diagnosi
terapia
(in)
formazione
fenotipo
Varianti
CFTR

European Journal of Human Genetics
https://doi.org/10.1038/s41431-018-0234-z

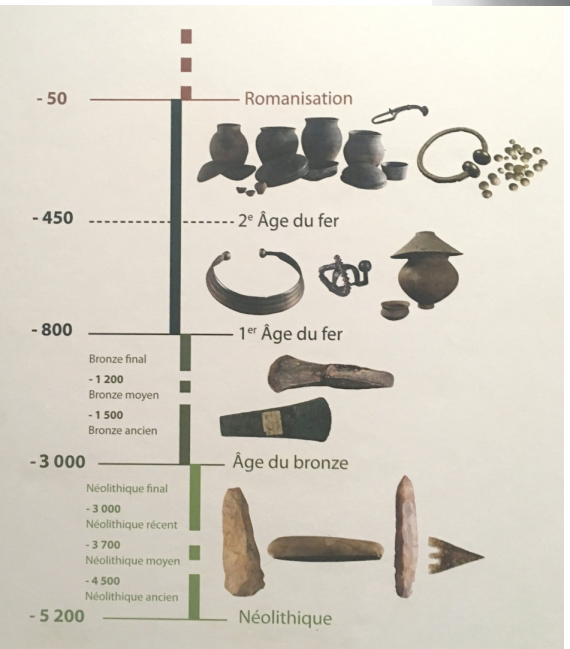
ESHG

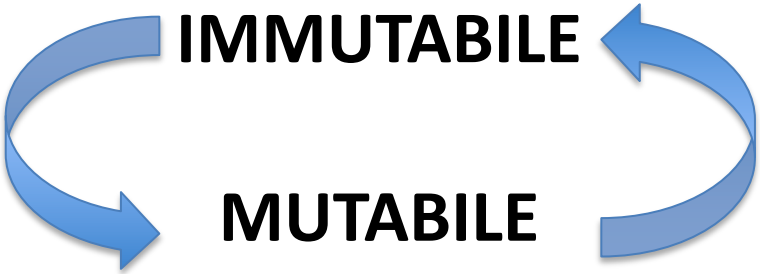
ARTICLE

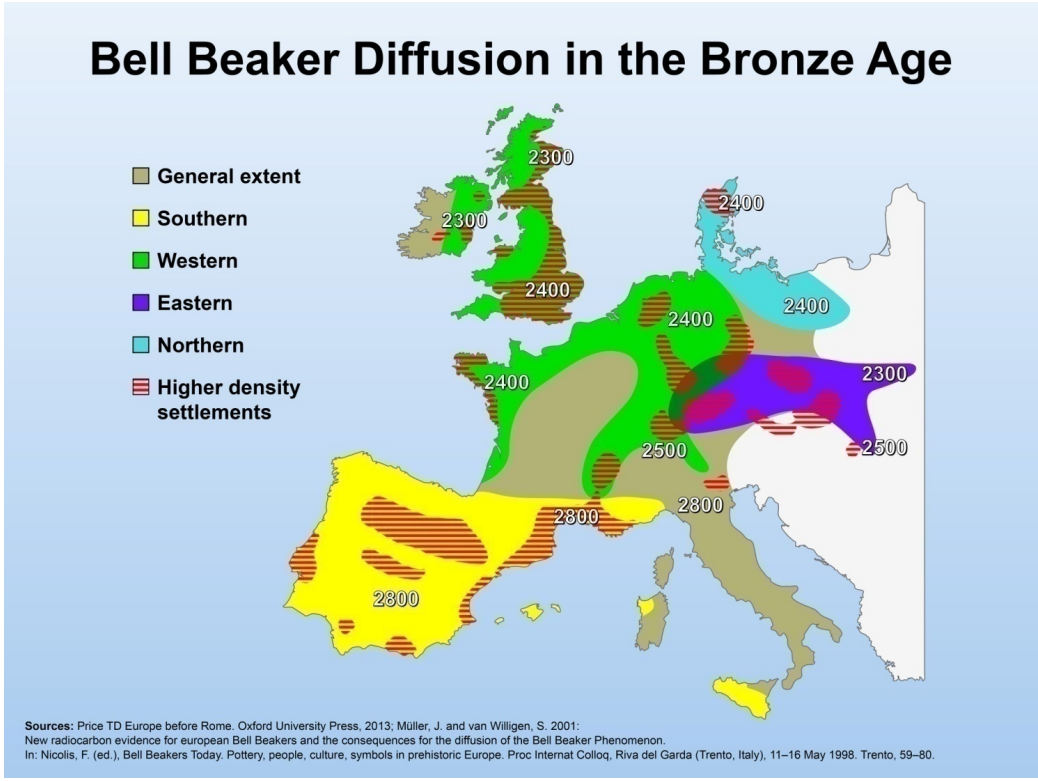
Estimating the age of p.(Phe508del) with family studies of geographically distinct European populations and the early spread of cystic fibrosis

Philip Farrell[1] · Claude Férec[2,3] · Milan Macek[4] · Thomas Frischer[5] · Sabine Renner[5] · Katharina Riss[5] · David Barton[6,7] · Teresa Repetto[8] · Maria Tzetis[9] · Karine Giteau[3] · Morten Duno[10] · Melissa Rogers[6] · Hara Levy[11] · Mourad Sahbatou[12] · Yann Fichou[2] · Cédric Le Maréchal[2,3] · Emmanuelle Génin[2]

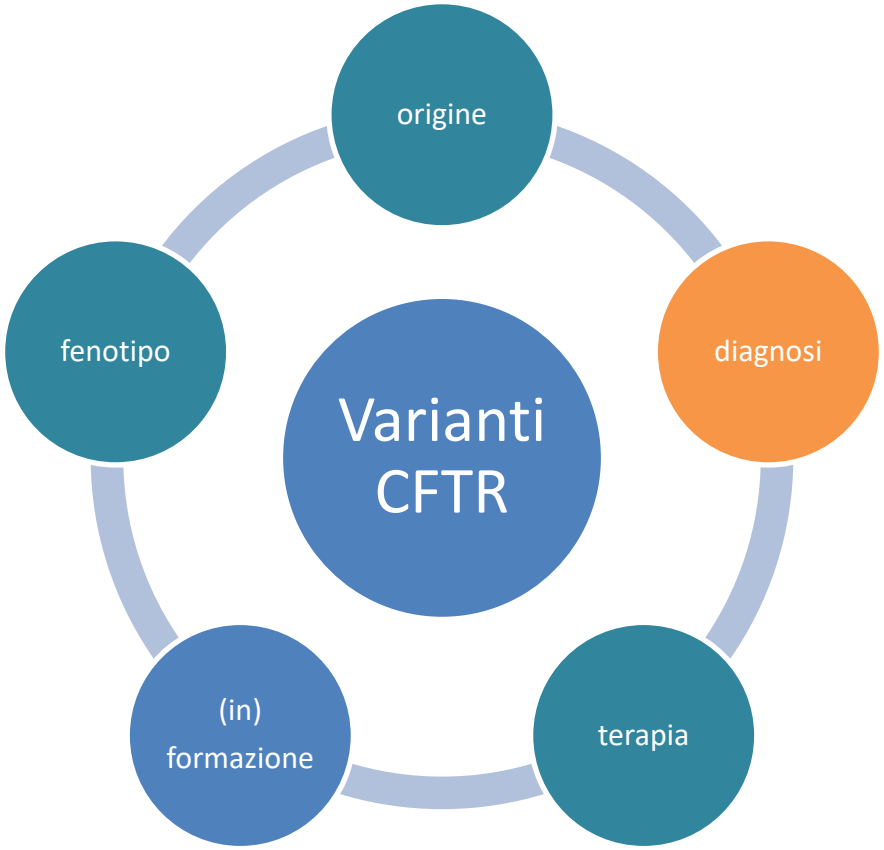
Received: 1 May 2018 / Revised: 10 July 2018 / Accepted: 19 July 2018



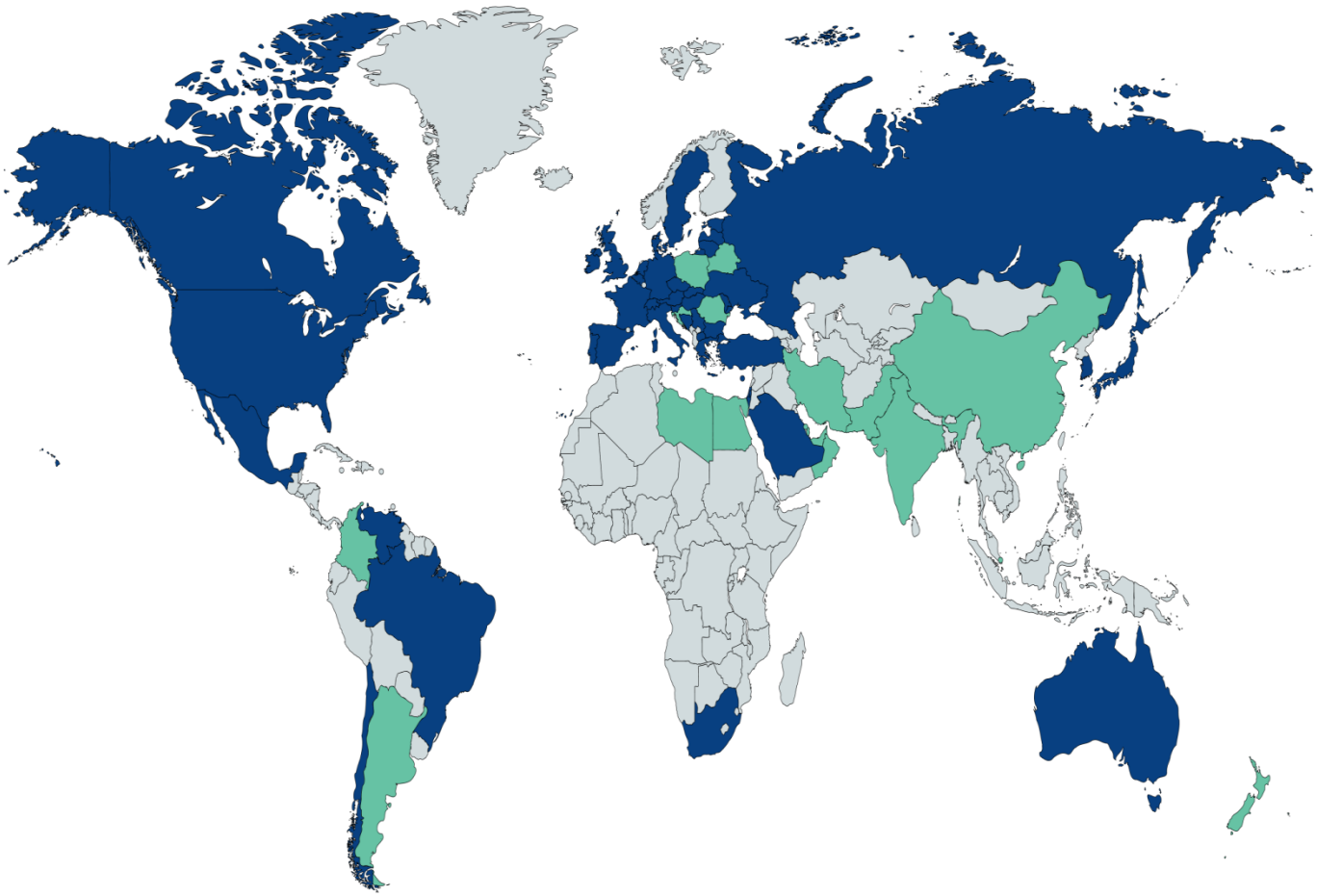




Courtesy Phil Farrell / modified


origine
diagnosi
terapia
(in)
formazione
fenotipo
Varianti
CFTR

CFTR2 worldwide collection



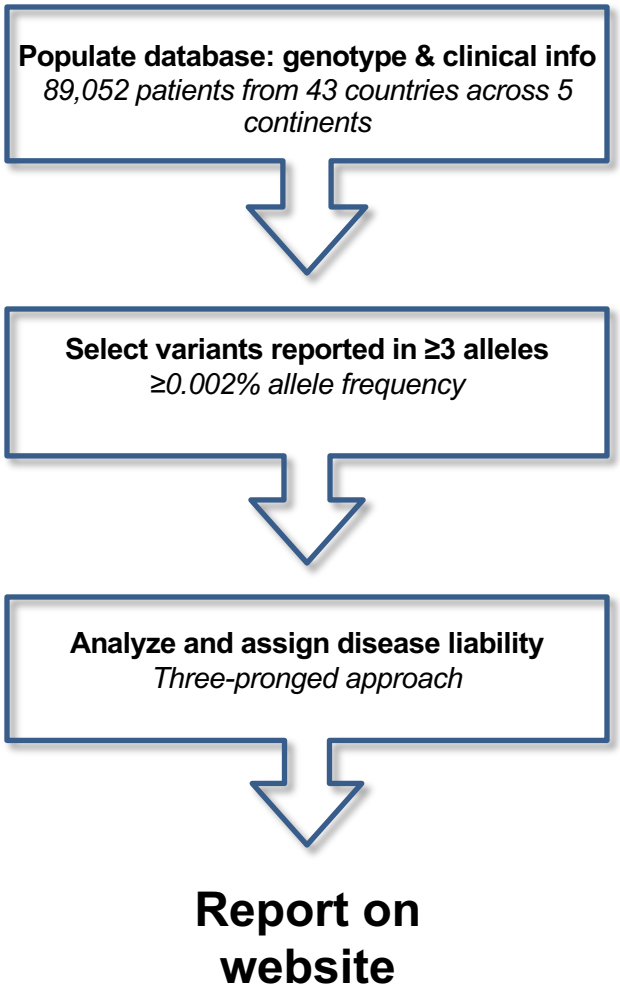
Countries with patients represented in CFTR2

Countries interested in future contributions to CFTR2

Map created with mapchart.net ©

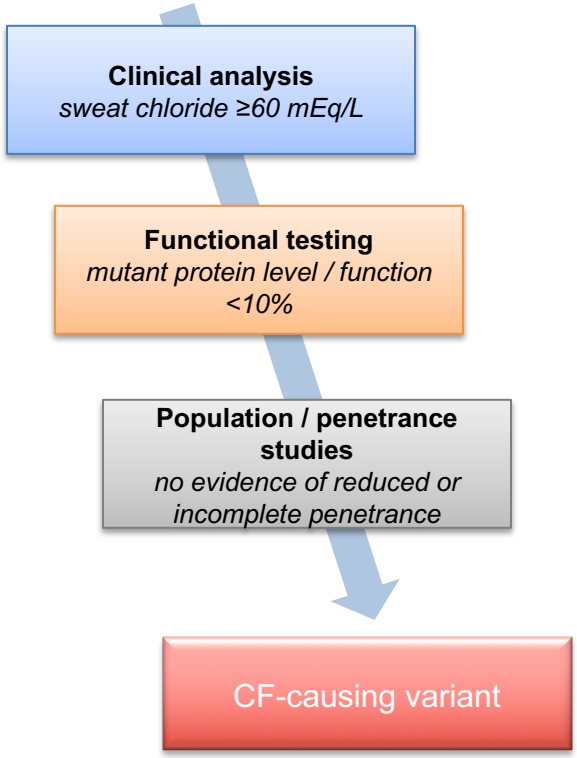
Source: CFTR2 team

CFTR2 variant annotation process



Three-pronged approach:

criteria for CF-causing annotation indicated



Sosnay P, et al., *Nat Genet* 2013

Source: CFTR2 team

Results for N1303K

Variant N1303K can be referred to as N1303K, p.Asn1303Lys, c.3909C>G, or ,

The information shown below is for a single variant. To search for a variant combination, enter your first variant in the search box above and then start typing in the "Second variant (optional)" search box. If you do not find your second variant listed or don't know what it is, you can select a group of variants to search.

Summary Information | Clinical Information | Functional Testing | Population Analysis | Additional Information

The variant N1303K is seen in 2,142 patients in our worldwide database. This variant is expected to result in CF.

The diagnosis of any individual patient with CF should be made based upon clinical parameters. The content of this website should not be used as a substitute for clinical judgement.

THE JOURNAL OF PEDIATRICS • www.jpeds.com SUPPLEMENT

Applying Cystic Fibrosis Transmembrane Conductance Regulator Genetics and CFTR2 Data to Facilitate Diagnoses

Patrick R. Sosnay, MD[1], Danieli B. Salinas, MD[2], Terry B. White, PhD[3], Clement L. Ren, MD[4], Philip M. Farrell, MD, PhD[5], Karen S. Raraigh, MGC[6], Emmanuelle Girodon, MD[7], and Carlo Castellani, MD[8]

DETECTION RATE **75%** → 100 AFFECTED

- TWO MUTATIONS DETECTED **56.25**
- ONE MUTATION DETECTED **37.25**
- NO MUTATION DETECTED **6.25**

DETECTION RATE **85%** → 100 AFFECTED

- TWO MUTATIONS DETECTED **72.25**
- ONE MUTATION DETECTED **25.25**
- NO MUTATION DETECTED **2.25**

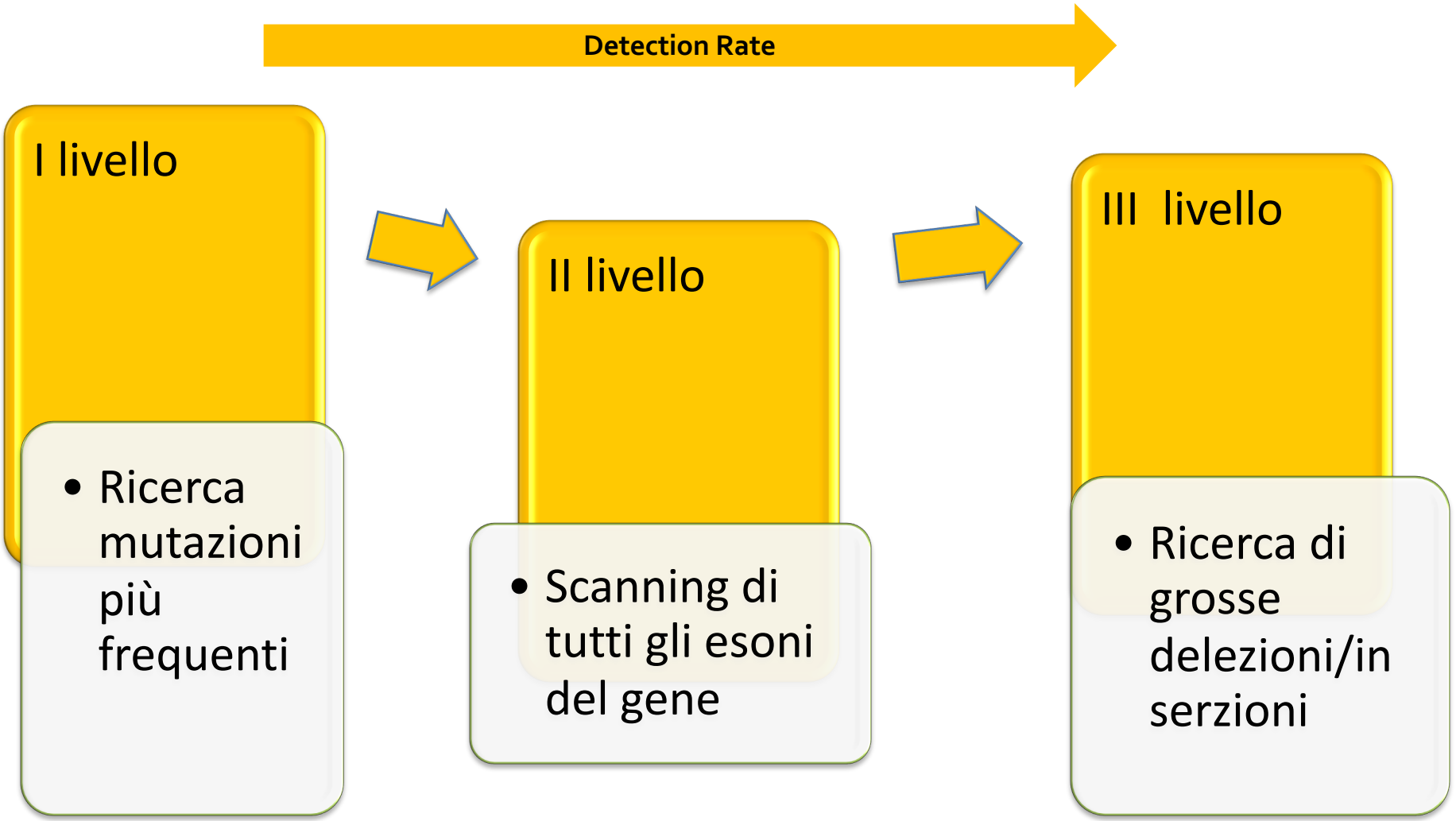
DETECTION RATE **90%** → 100 AFFECTED

- TWO MUTATIONS DETECTED **81.00**
- ONE MUTATION DETECTED **18.00**
- NO MUTATION DETECTED **1.00**

DETECTION RATE **95%** → 100 AFFECTED

- TWO MUTATIONS DETECTED **90.25**
- ONE MUTATION DETECTED **9.5**
- NO MUTATION DETECTED **0.25**

A Che Livello Proporre il Test FC

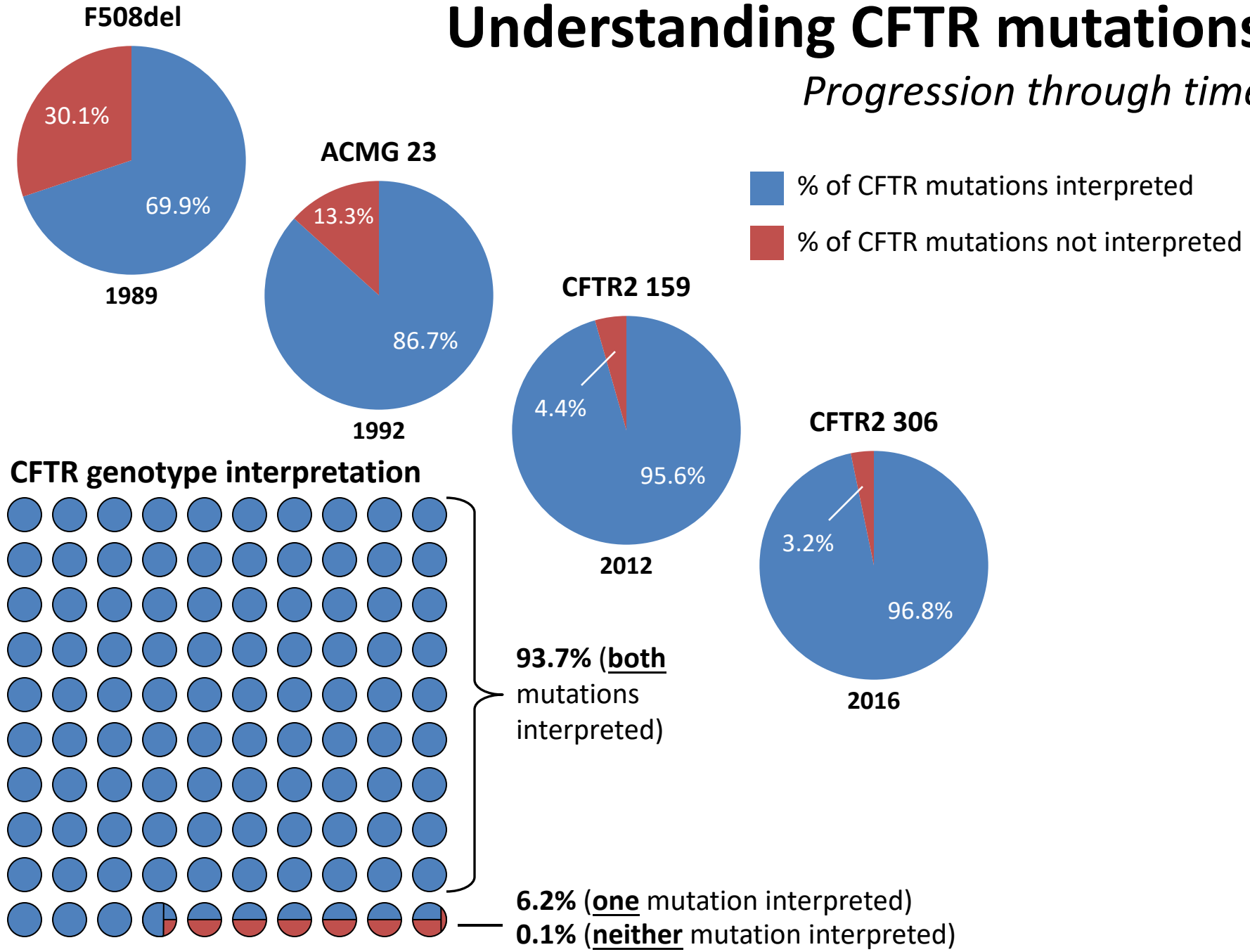


TEST DEL PORTATORE

INQUADRAMENTO DIAGNOSTICO

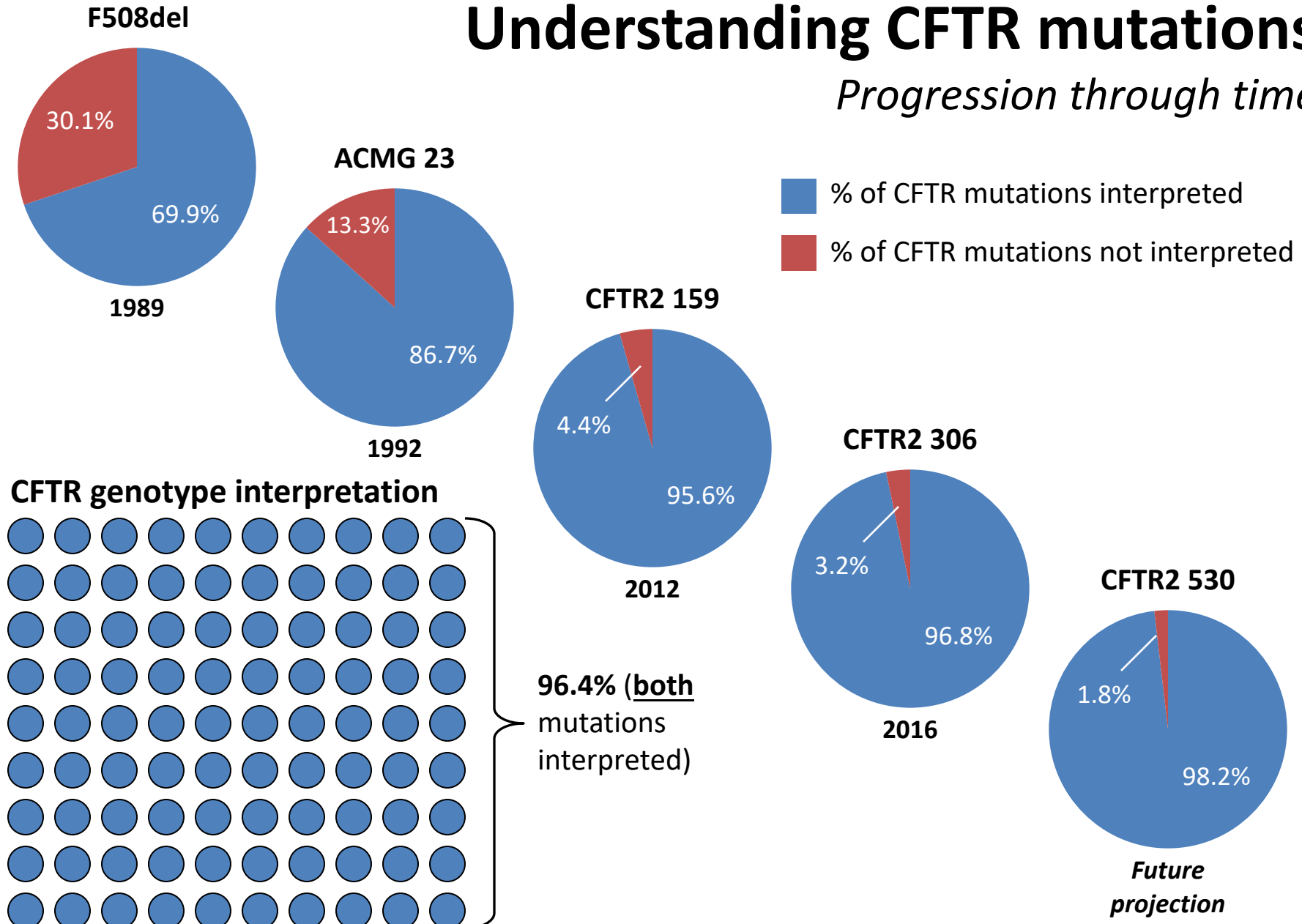
Understanding CFTR mutations

Progression through time



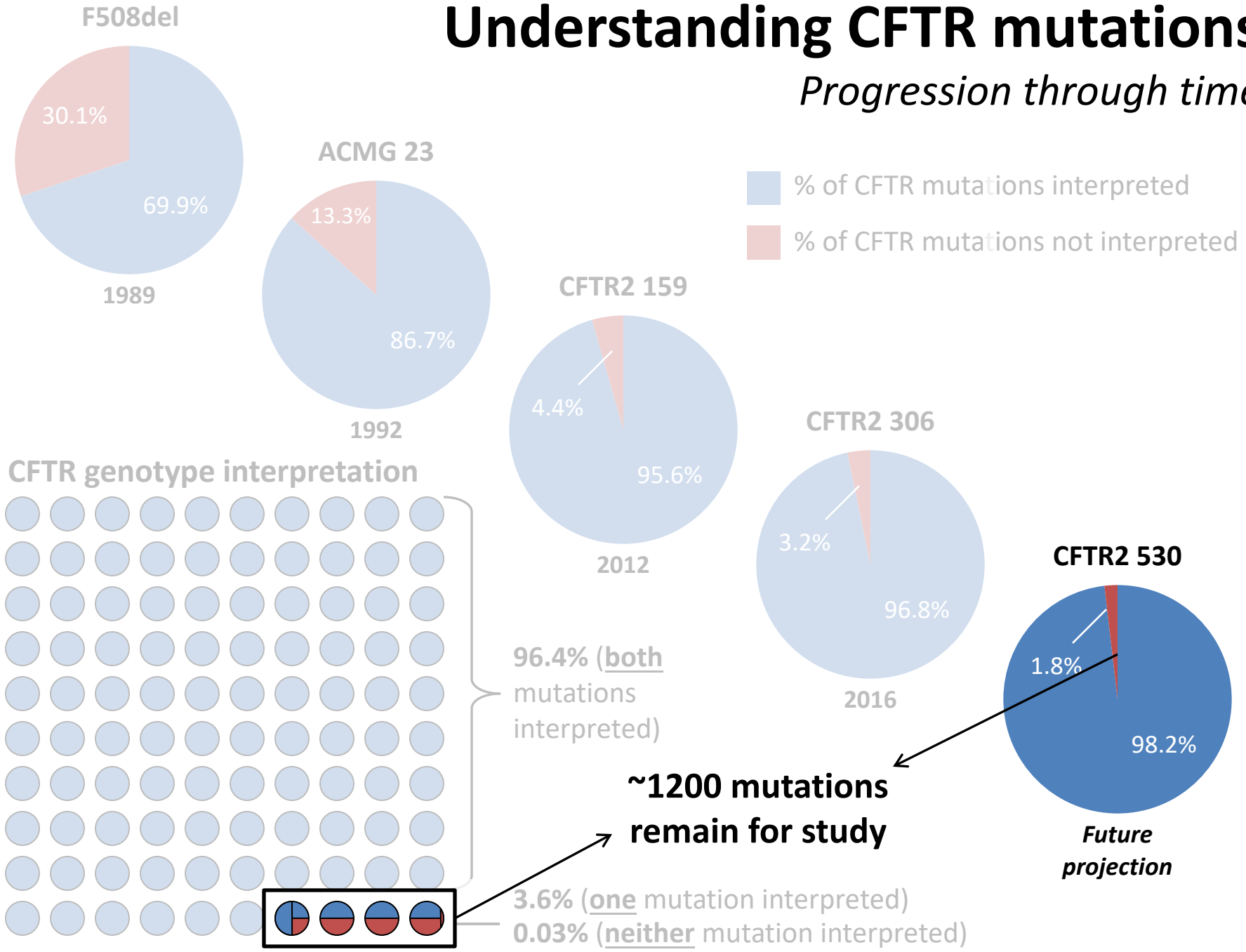
Understanding CFTR mutations

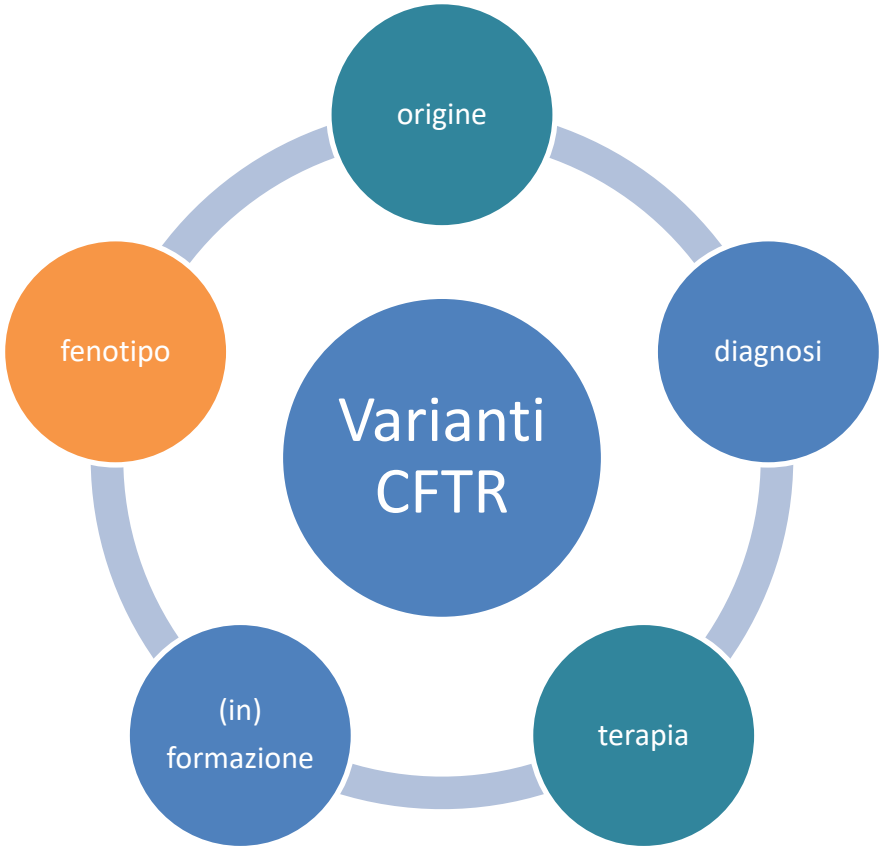
Progression through time



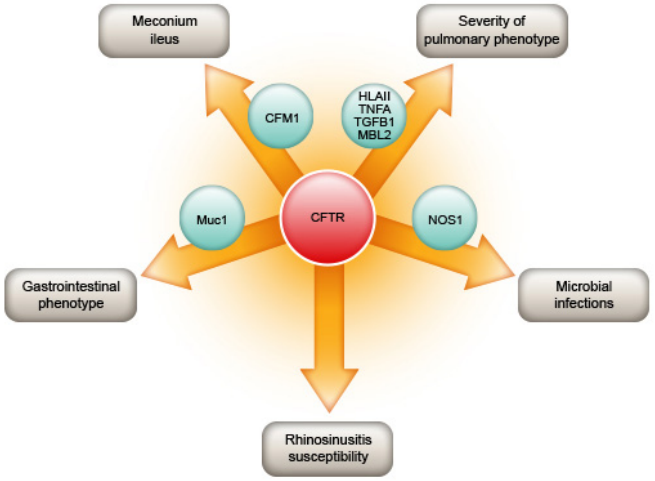
Understanding CFTR mutations

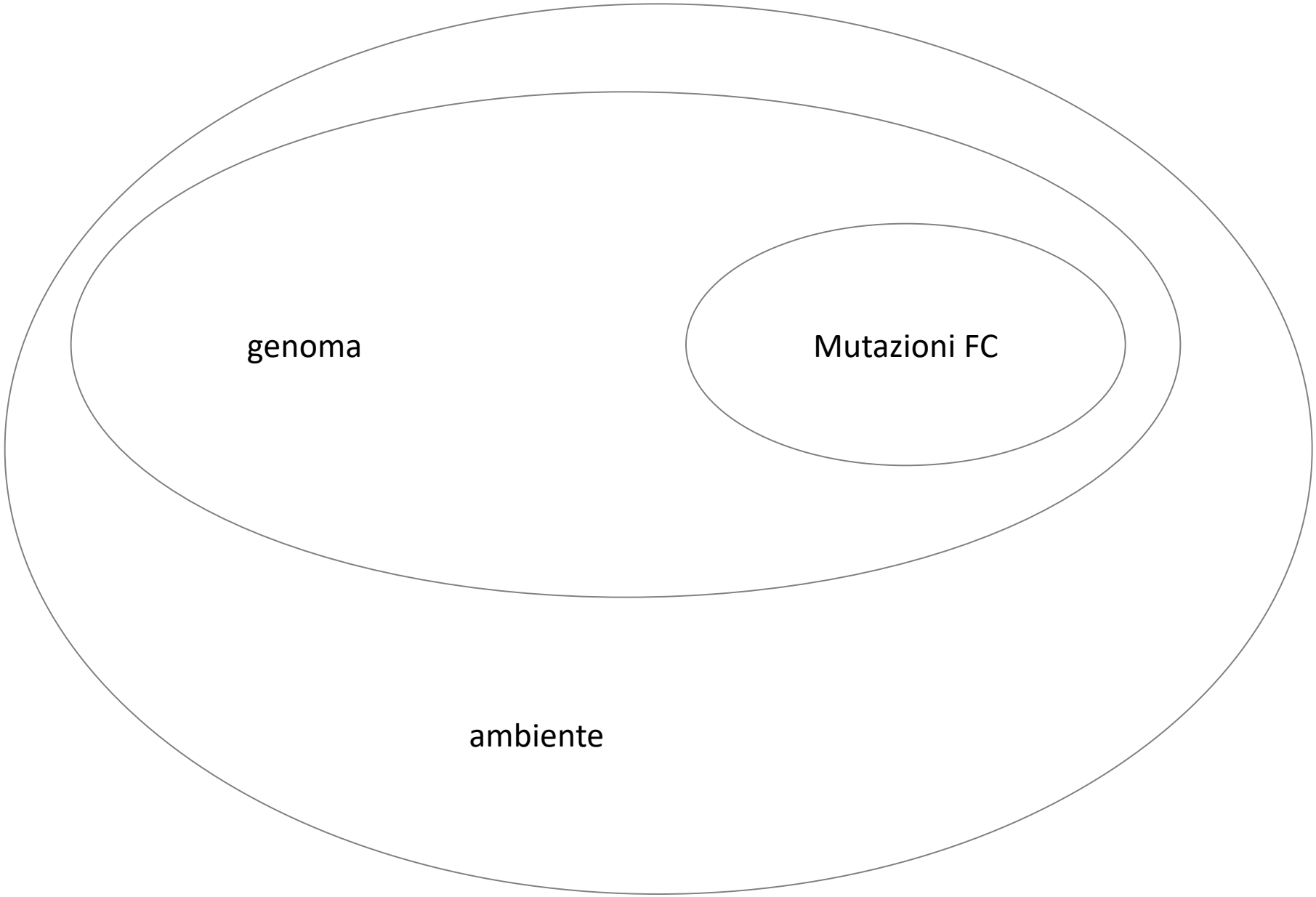
Progression through time

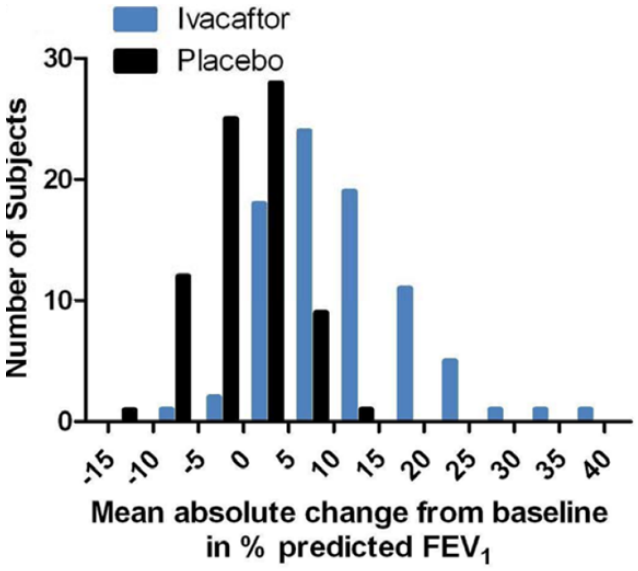



origine
diagnosi
terapia
(in)
formazione
fenotipo
Varianti
CFTR

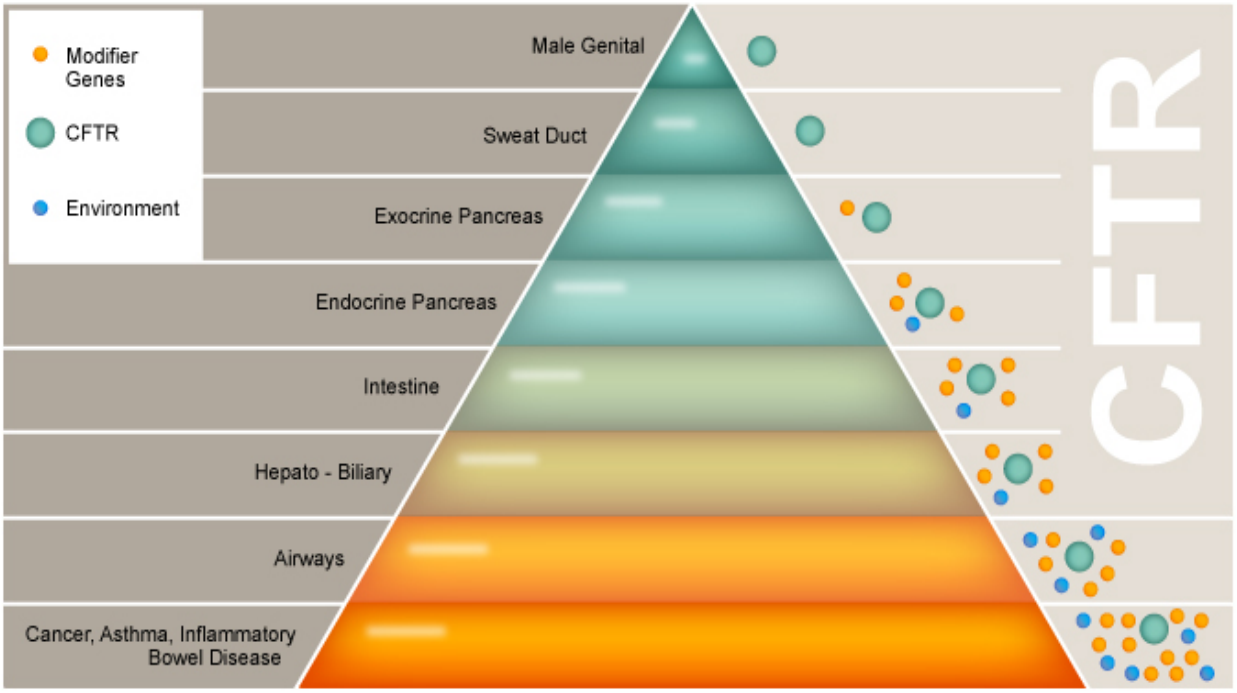
geni modificatori



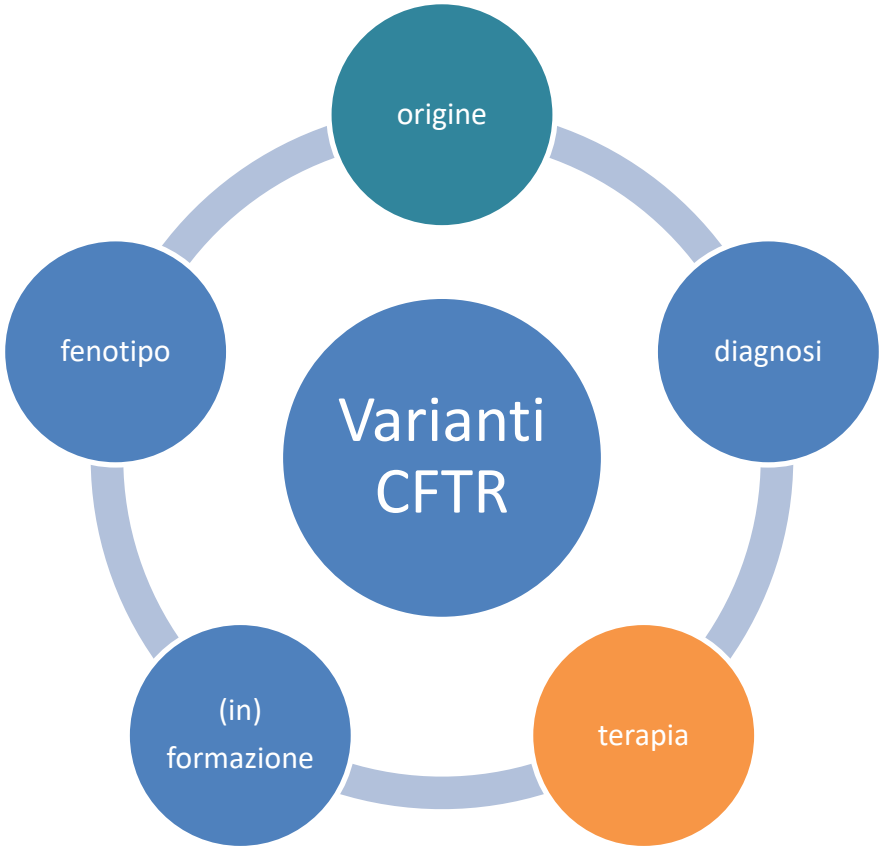

genoma
Mutazioni FC
ambiente

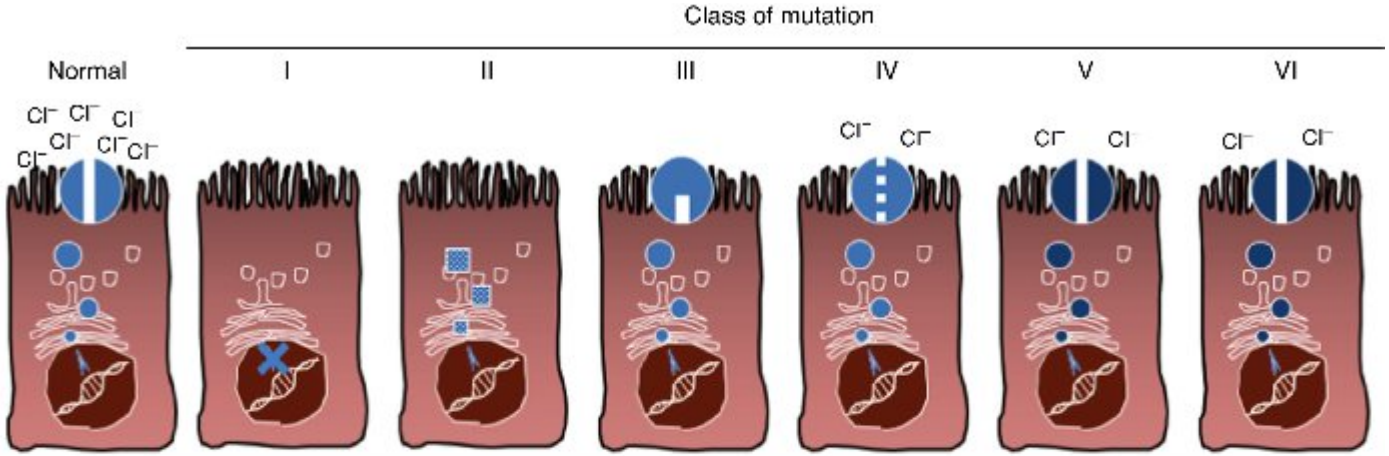


N Engl J Med 2011; 365:1663-1672



Courtesy Milan Macek Jr

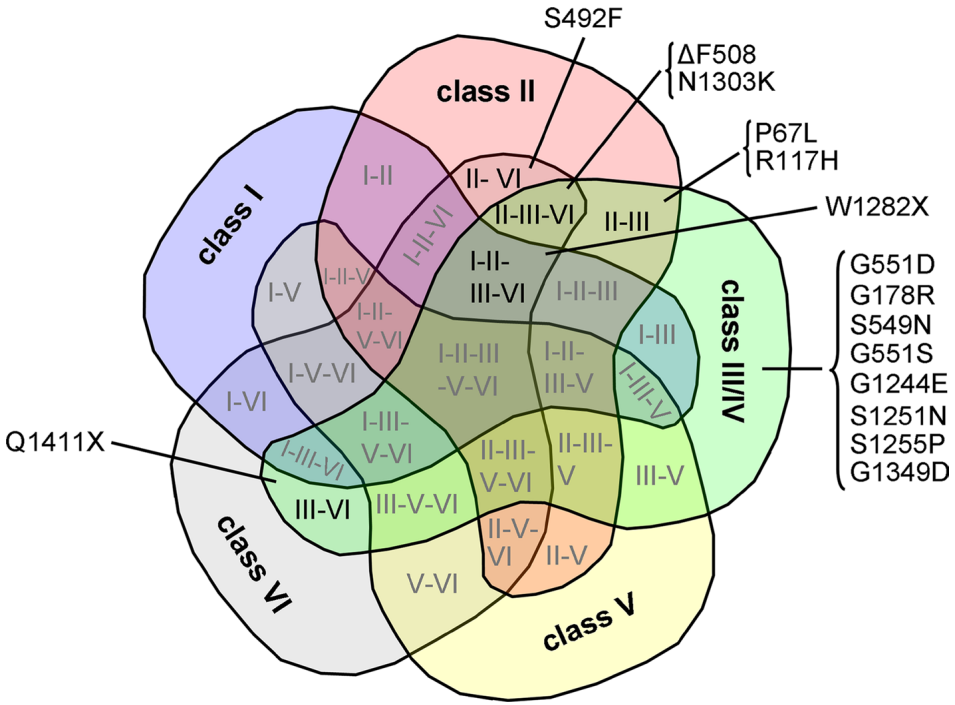

origine
diagnosi
terapia
(in)
formazione
fenotipo
Varianti
CFTR



Molecular defect	No synthesis	Block in processing	Block in regulation	Reduced conductance	Reduced synthesis	Reduced half-life
Functional abnormality	Protein is not synthesized	Folding defect	Channel opening defect	Ion transport defect	Decreased protein synthesis	Decreased half-life of the protein
Main mutations	Gly542X Trp128X Arg553X 621+1G→T	Phe508del Asn1303Lys Ile507del Arg560Thr	Gly551Asp Gly178Arg Gly551Ser Ser549Asn	Arg117His Arg347Pro Arg117Cys Arg334Trp	3849+10kbC→T 2789+5G→A 3120+1G→A 5T	4326delTC Gln1412X 4279insA

MUTATION CLASSES

31 possible classes of mutations, including the original classes I, II, III/IV, V, and VI, as well as their 26 combinations

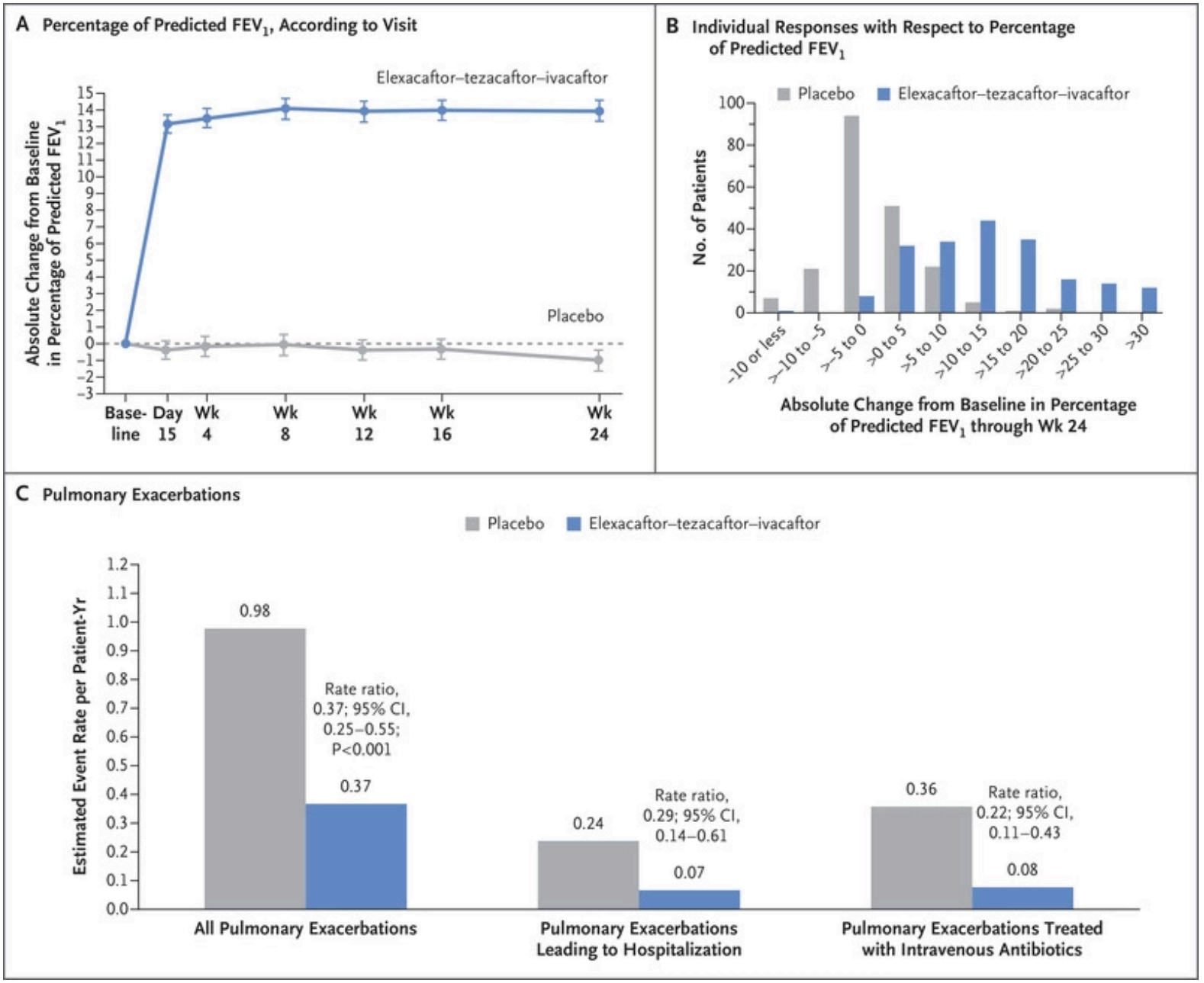


DOI:10.1091/mbc.E14-04-0935

THE 'THERATYPE'

concept where a given variant can be classified according to a particular response to existing therapeutics and/or 'small molecule' drug-like compounds currently in development >> suggests drug combinations for treatment of different patient populations

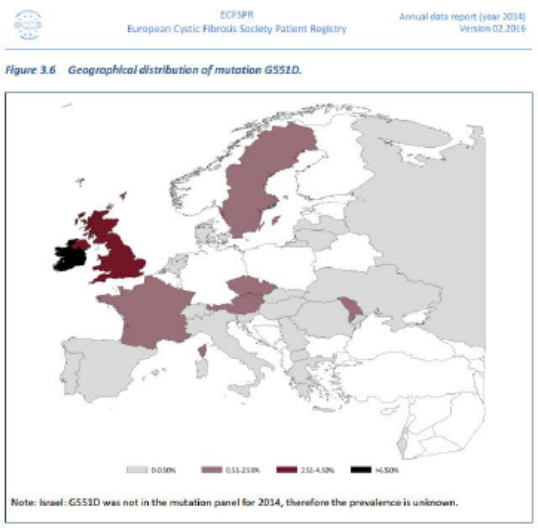
Journal of Cystic Fibrosis 14 (2015) 687–699

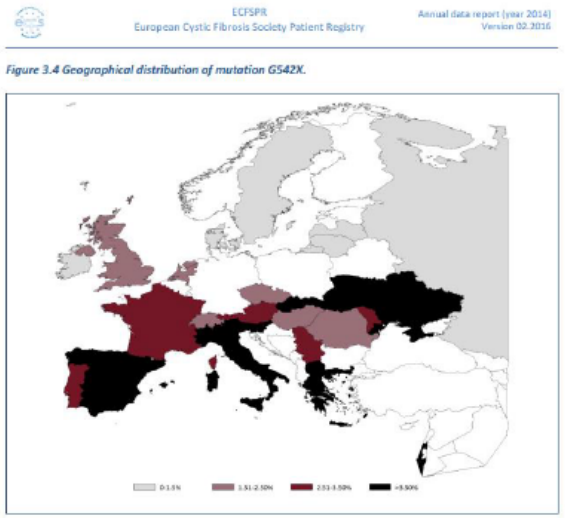


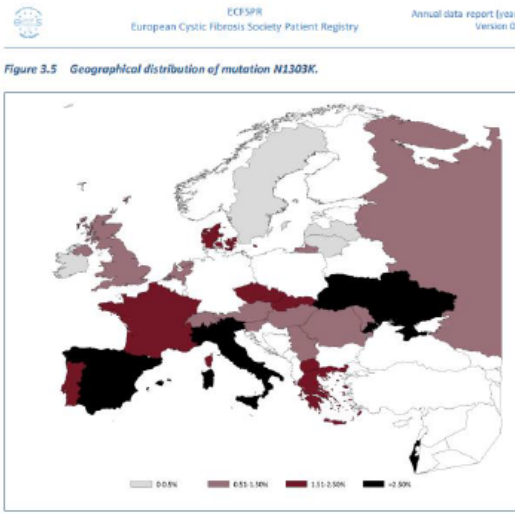
DOI: 10.1056/NEJMoa1908639

A large segment of the CF population stil awaits an etiological cure

need to include robust estimates of available patient populations naïve to CFTR modulators as well as those already receiving these therapies to maximise the worldwide population of individuals with CF available for inclusion in studies

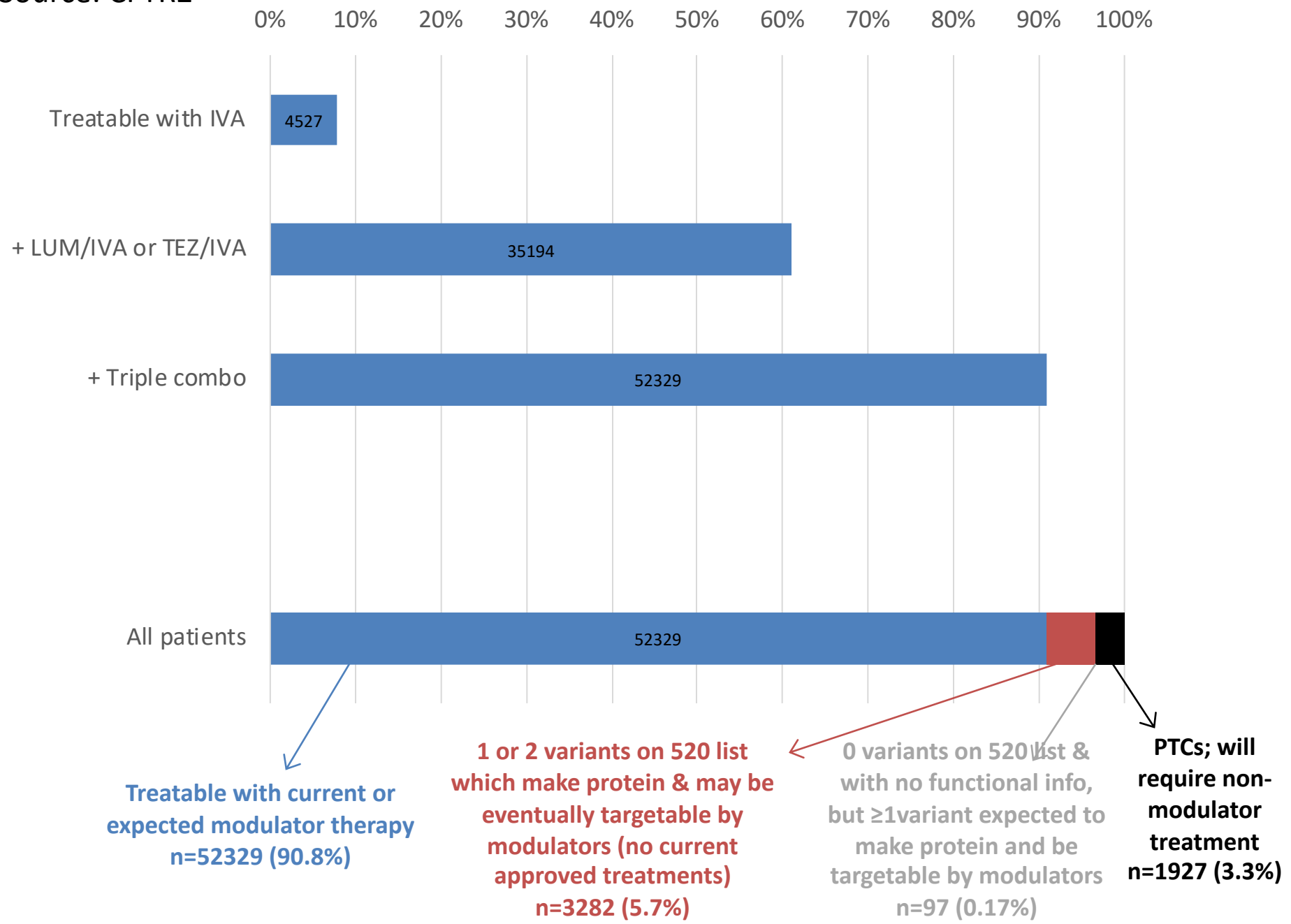






rare CFTR genotype populations are too small for traditional randomised studies, and thus alternative approaches must be discussed to enable individuals with rare mutations comparable access to safe and effective therapies

Source: CFTR2

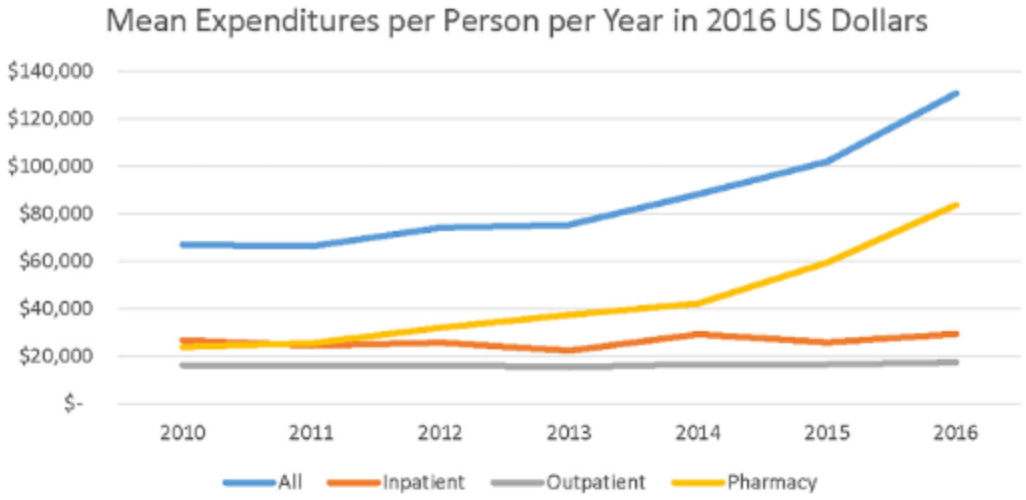


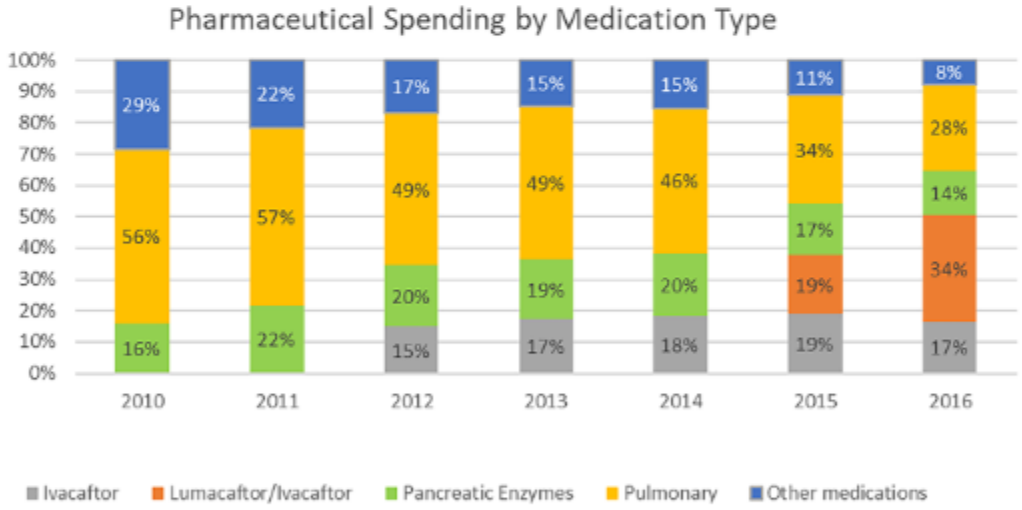
Received: 27 April 2018 | Accepted: 5 September 2018
DOI: 10.1002/ppul.24178

WILEY

Healthcare expenditures for privately insured US patients with cystic fibrosis, 2010-2016

Scott D. Grosse PhD[1] | Thuy Quynh N. Do PhD, MPH[1] | Michelle Vu PharmD, MPH[2] | Lisa B. Feng DrPH[3] | Jay G. Berry MD, MPH[4,5] | Gregory S. Sawicki MD, MPH[5,6]



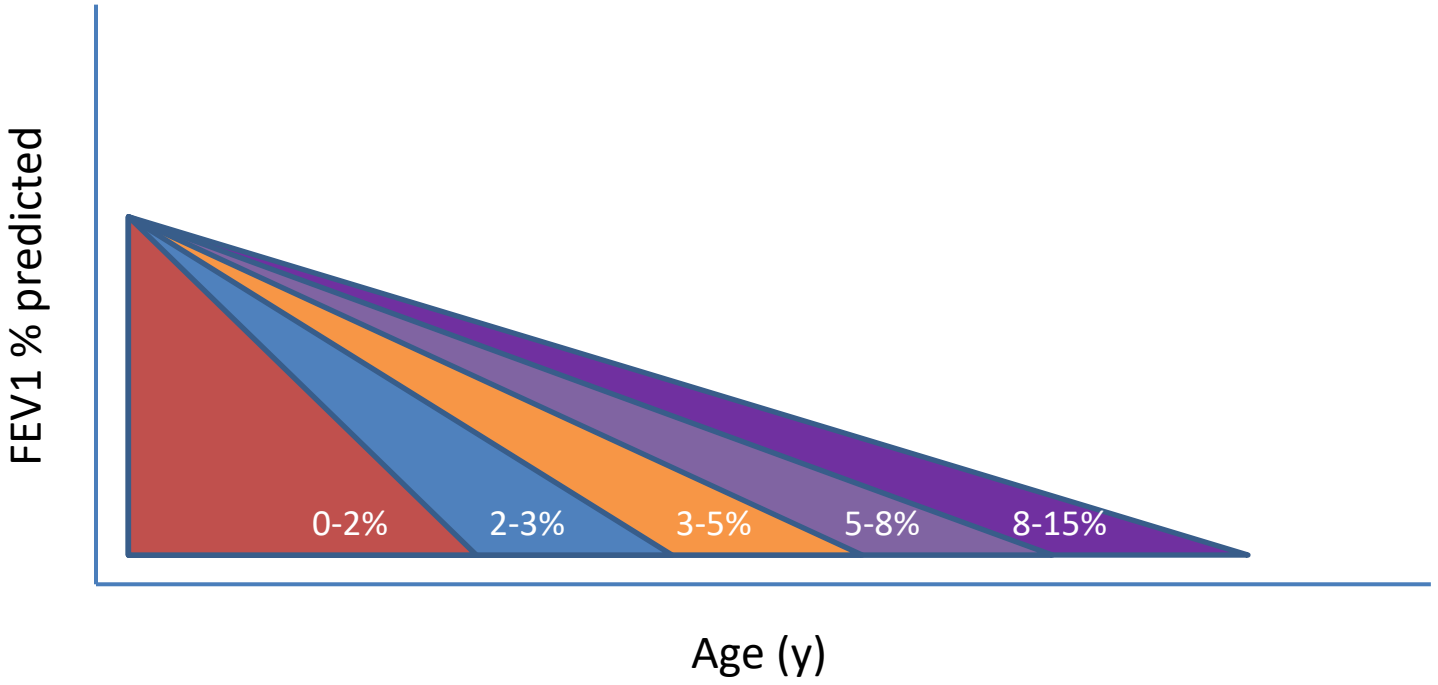


The Lancet Respiratory Medicine Commission

The future of cystic fibrosis care: a global perspective

Scott C Bell, Marcus A Mall, Hector Gutierrez, Milan Macek, Susan Madge, Jane C Davies, Pierre-Régis Burgel, Elizabeth Tullis, Claudio Castaños, Carlo Castellani, Catherine A Byrnes, Fiona Cathcart, Sanjay H Chotirmall, Rebecca Cosgriff, Irmgard Eichler, Isabelle Fajac, Christopher H Goss, Pavel Drevinek, Philip M Farrell, Anna M Gravelle, Trudy Havermans, Nicole Mayer-Hamblett, Nataliya Kashirskaya, Eitan Kerem, Joseph L Mathew, Edward F McKone, Lutz Naehrlich, Samya Z Nasr, Gabriela R Oates, Ciaran O'Neill, Ulrike Pypops, Karen S Raraigh, Steven M Rowe, Kevin W Southern, Sheila Sivam, Anne L Stephenson, Marco Zampoli, Felix Ratjen**

Source: CFTR2 team



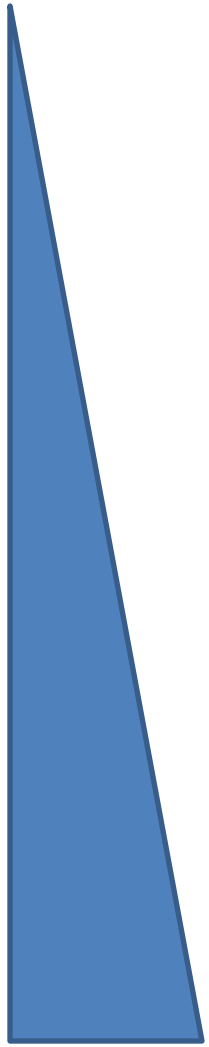
Source: CFTR2 team

Correlating Cystic Fibrosis Transmembrane Conductance Regulator Function with Clinical Features to Inform Precision Treatment of Cystic Fibrosis

Allison F. McCague[1,*], Karen S. Raraigh[1,*], Matthew J. Pellicore[1], Emily F. Davis-Marcisak[1], Taylor A. Evans[1], Sangwoo T. Han[1], Zhongzhou Lu[1], Anya T. Joynt[1], Neeraj Sharma[1], Carlo Castellani[2], Joseph M. Collaco[3], Mary Corey[4], Michelle H. Lewis[5], Chris M. Penland[6], Johanna M. Rommens[7], Anne L. Stephenson[8], Patrick R. Sosnay[9], and Garry R. Cutting[1]

CFTR function

MODULATOR



CF

CFTR-RELATED BRONCHIECTASIS

NON CF BRONCHIECTASIS

Lancet Respir Med 201
3: 684–9

Repeated nebulisation of non-viral *CFTR* gene therapy in patients with cystic fibrosis: a randomised, double-blind, placebo-controlled, phase 2b trial

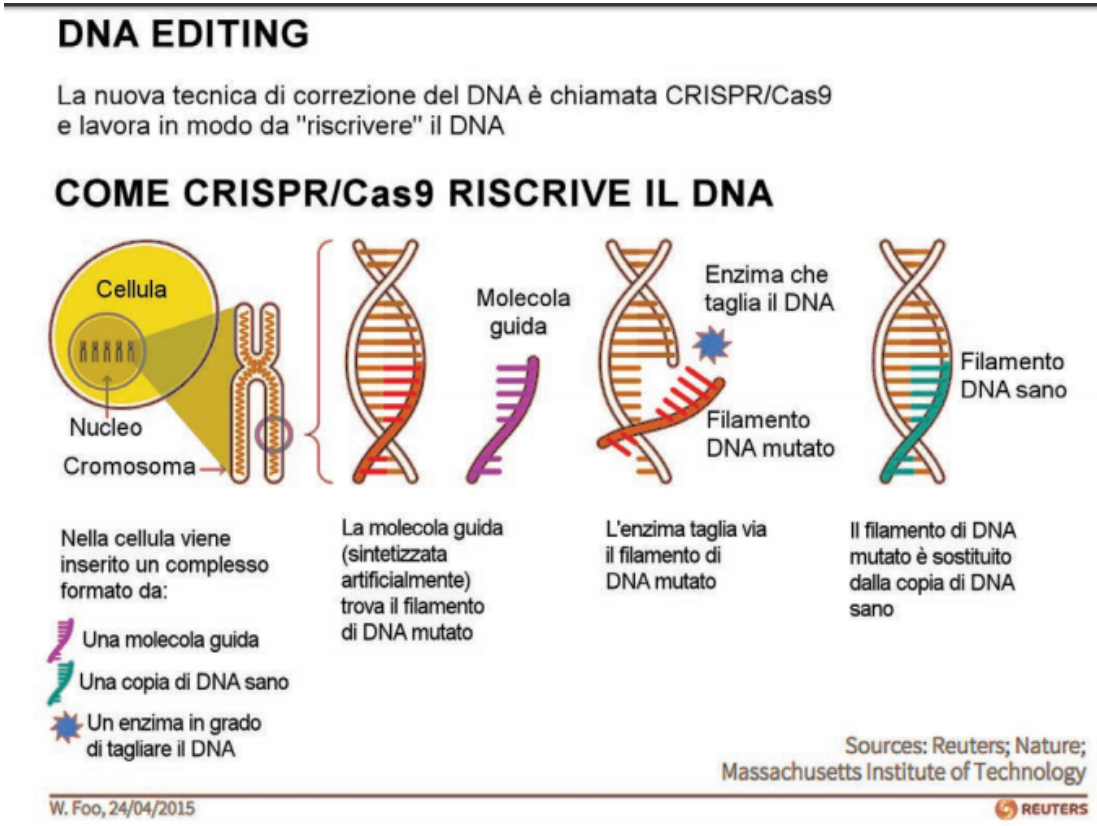
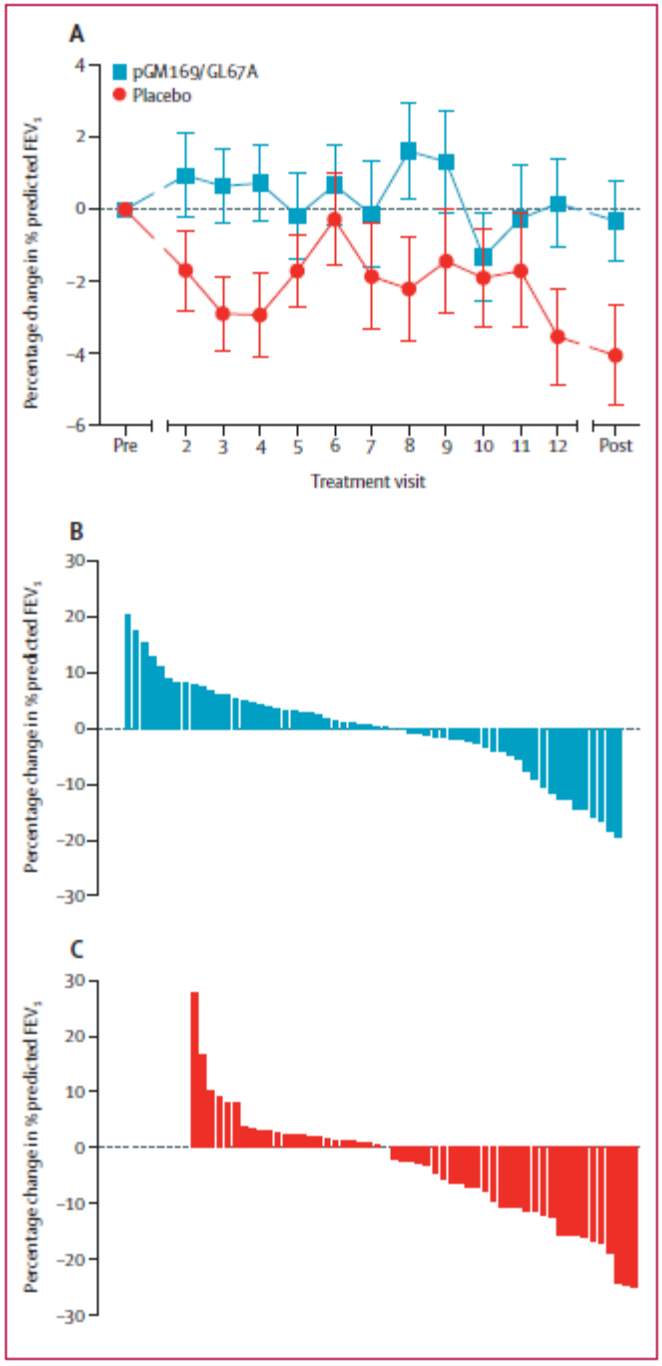


Figura 2. Come funziona il "Genome-editing" con la tecnica CRISPR/Cas9. (Inserimento redazionale)



per i pazienti

Posso partecipare?

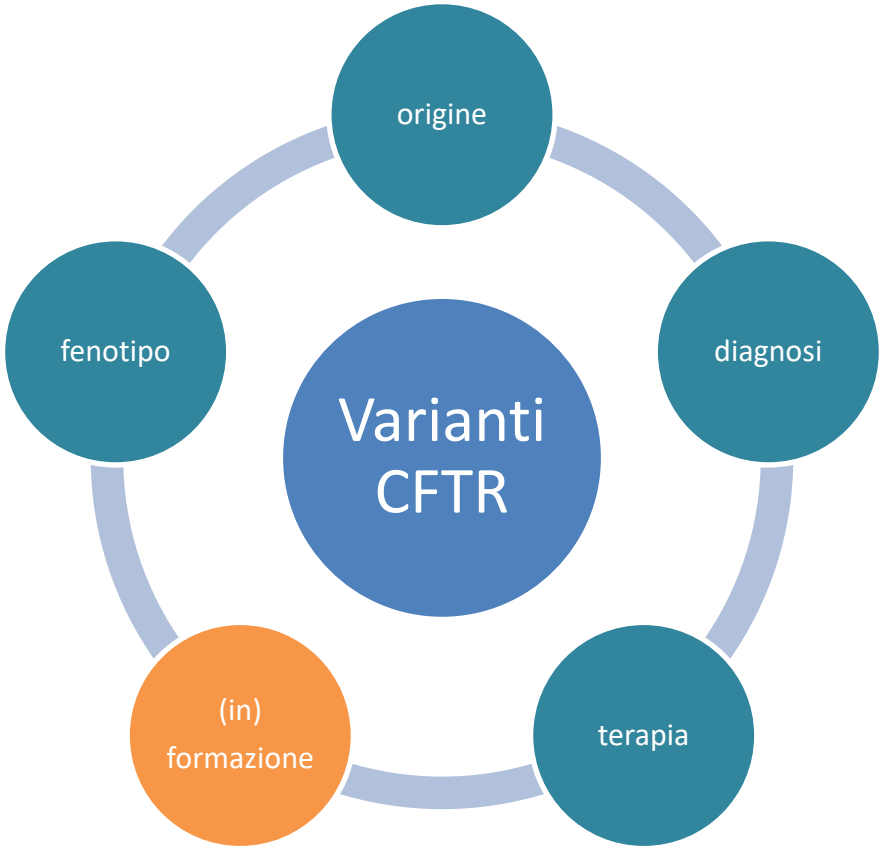
È possibile partecipare a questo progetto europeo quando si è 16 anni di età o più anziani * al giorno della firma del consenso informato per l'assunzione di biopsia. Bisogna avere una diagnosi confermata di CF e un profilo genetico raro (vedi sotto: **è il mio profilo genetica rara?**). È inoltre necessario essere in grado di fare una visita a uno degli ospedali partecipanti per raccogliere biopsie rettali per rendere il vostro organoidi unici. Inoltre, se si verrà selezionata per una sperimentazione clinica è necessario visitare questo ospedale probabilmente per 6-8 volte.

* 18 anni o più anziani in alcuni paesi a causa delle leggi nazionali

È il mio profilo genetico raro?

Solo i pazienti con rari genotipi possono partecipare al progetto HIT-CF Europa. È **Non si può** partecipare se si dispone di:

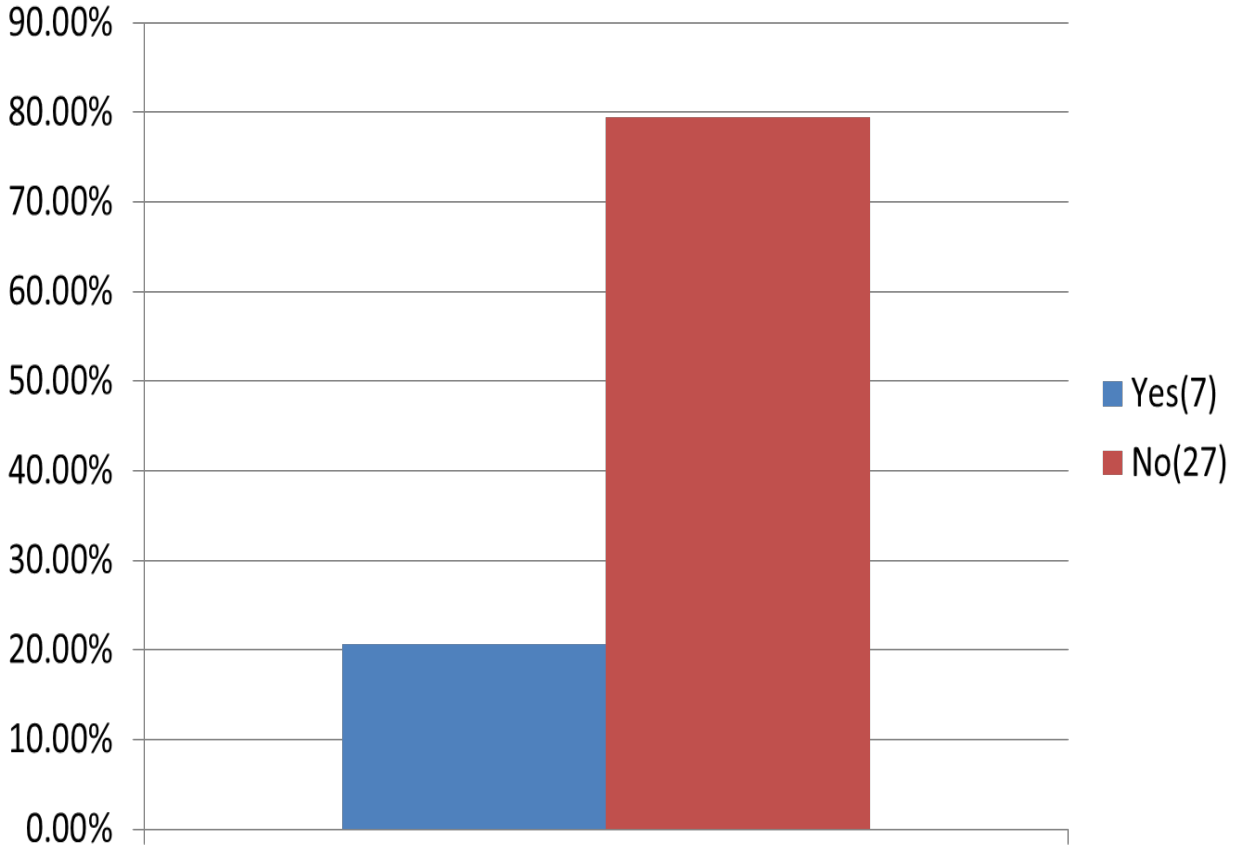
- *uno* dei seguenti mutazioni: F508del, G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, R117H, mutazioni A455E, 3849 10kbC> T, o
- una combinazione di qualsiasi *due* delle seguenti mutazioni: G542X, 1717-1G> A, 621 + 1G> T, 3120 + 1G> A 1898 + 1G-> A, CFTRdele2,3 e


origine
diagnosi
terapia
(in)
formazione
fenotipo
Varianti
CFTR

Filtra per:

- **Tutti** (3666)
- Complicanze e associazioni morbose (272)
- Decorso clinico e sintomi (143)
- Diagnosi FC, screening neonatale e forme atipiche (992)
- Genetica e mutazioni CFTR (946)
- Intestino, pancreas, fegato (251)
- Infezione, infiammazione, batteri (525)
- Nutrizione (112)
- Ricerca (575)
- Riproduzione (568)
- Terapie correnti e strategie terapeutiche (546)
- Varie (393)
- Vivere con FC (347)

Nel corso delle tua sedute di consulenza genetica su fibrosi cistica dai informazioni aggiornate sull'attesa di vita per un bambino che nasca oggi con la malattia?



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