FIBROSI CISTICA

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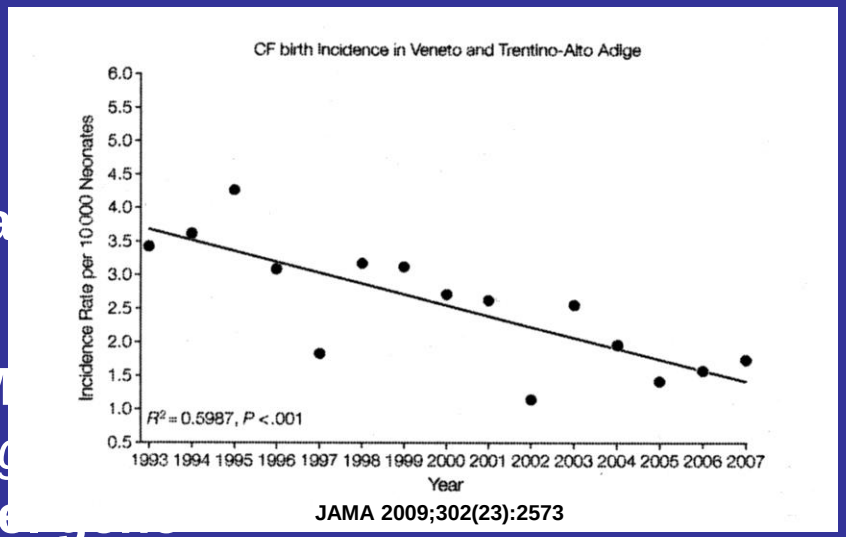
Fibrosi Cistica:
" La malattia del bacio salato"

Già le mamme romane, 2000 anni fa, riconoscevano il bambino malato per il sapore di mare nel baciargli la fronte. In tal modo, la saggezza popolare aveva già anticipato quanto l'osservazione medica avrebbe poi scoperto negli anni '50 e la ricerca scientifica non ancora completamente chiarito indicando nella concentrazione di sali nel sudore, il **metodo di diagnosi** per la Fibrosi Cistica. È proprio questa caratteristica del sudore particolarmente salato, avvertito dalle madri quando baciavano i bambini affetti, che farà chiamare la Fibrosi Cistica **"la malattia del bacio salato"**

La Fibrosi Cistica

- **Più comune MALATTIA GENETICA potenzialmente LETALE della razza Caucasica**
- **Trasmissione AUTOSOMICA RECESSIVA**
- **Incidenza in ITALIA di circa 1/4176 nascite (nati/anno 120- 130). Attualmente si registrano in Italia 6182 pazienti in vita (RIFC)**
- **ETA' mediana alla MORTE di 57.2**
- **Frequenza di PORTATORI di circa**
- **Determinata dal MALFUNZIONAM**
  (*Cistic Fibrosis Transmembrane Reg*
  la presenza di DUE MUTAZIONI ne



JAMA 2009;302(23):2573

FIBROSI CISTICA IN 3 MINUTI

- *Malattia **grave***
- *La più **frequente** delle genetiche gravi*
- ***Poco** o niente affatto **visibile***
- *Accorcia sensibilmente la vita*
- *Necessità di **cure quotidiane***
- *Cure per allungare la vita, **non per guarire***
- ***Qualità di vita discreta***
- *Fase **terminale** molto **critica***

FIBROSI CISTICA CLASSICA – Fenotipo

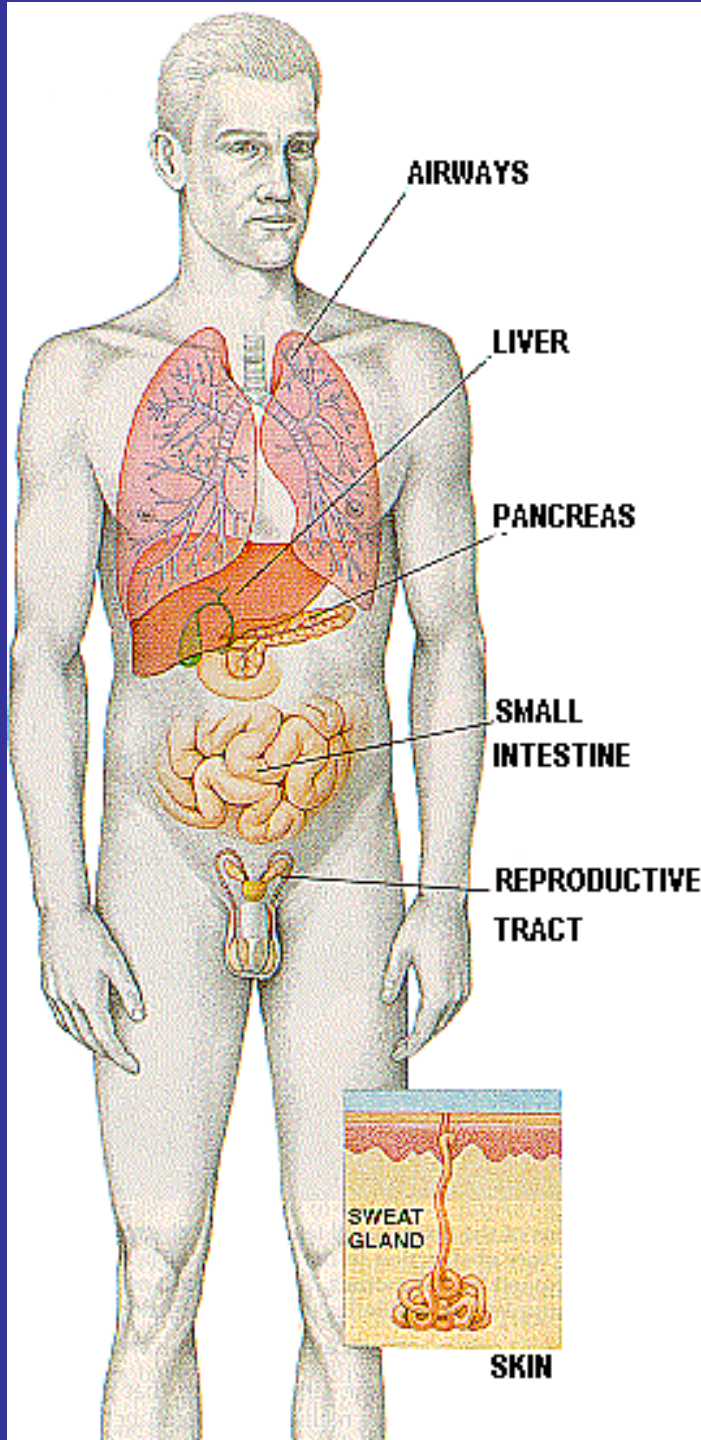
1. Vie aeree: ostruzione e infezione, causa della maggior parte dei decessi

2. Pancreas: occlusione dotti ed enzimi digestivi insufficienti nell'85% dei pazienti

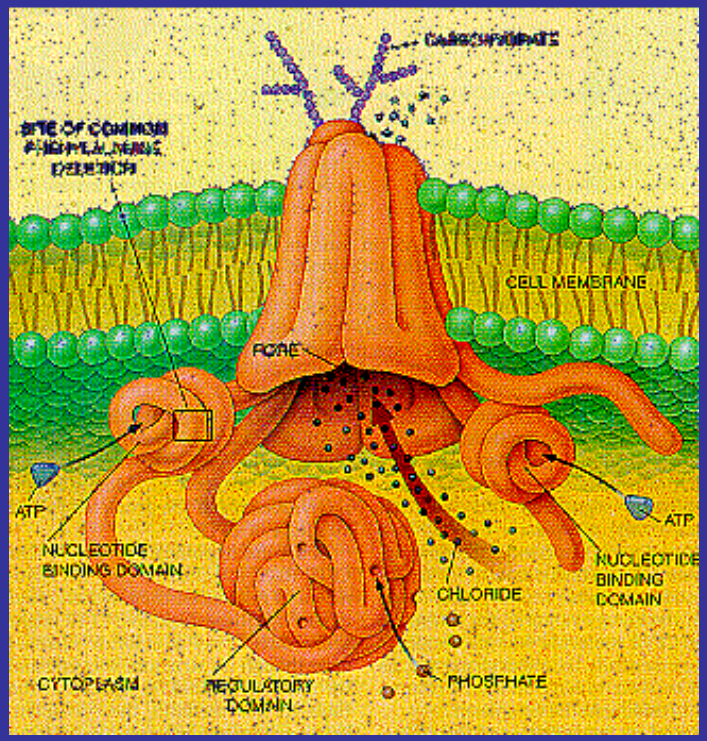
3. Intestino non riceve abbastanza enzimi digestivi specifici per i grassi provocando denutrizione ed eccesso di grassi nelle feci (steatorrea).
Occlusione fecale nel 10% dei neonati (ileo da meconio)

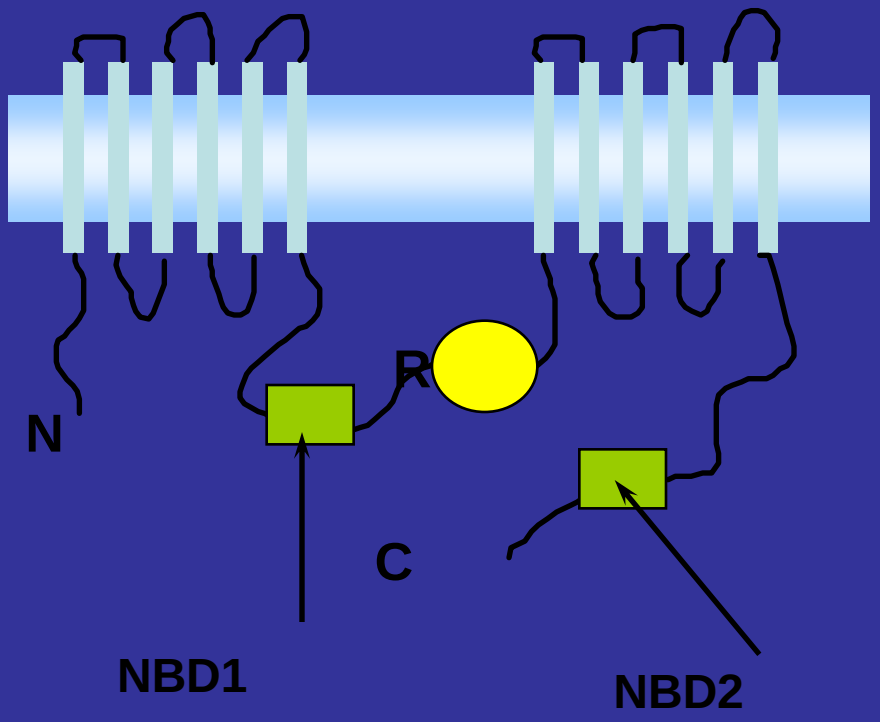
4. Apparato riproduttivo: nel 95% dei maschi assenza congenita dei dotti deferenti.
Nelle donne possibile tappo mucoso uterino

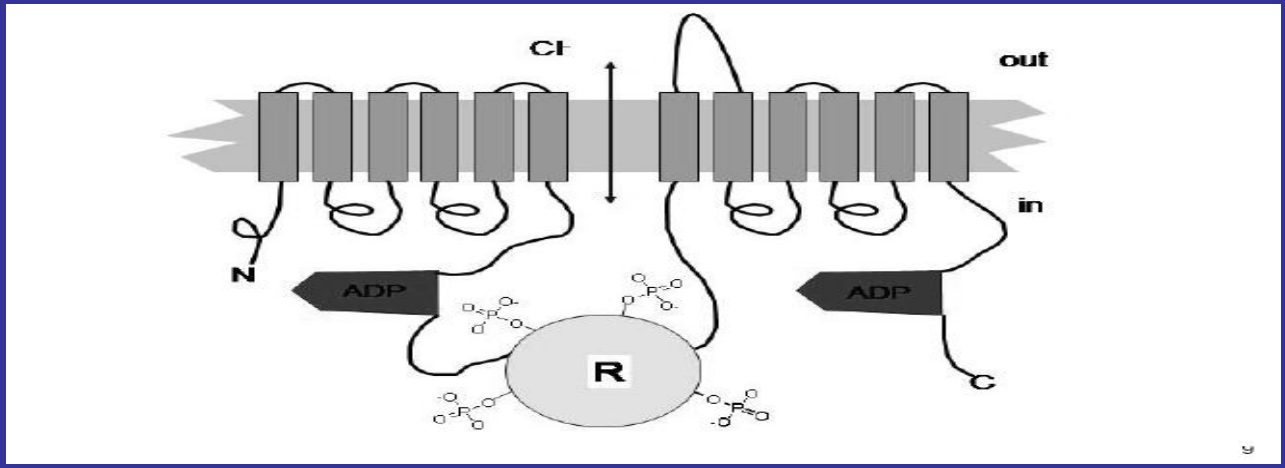
5. Ghiandola sudoripara:eccesso di cloro nel sudore,test diagnostico fondamentale



Regolazione di CFTR

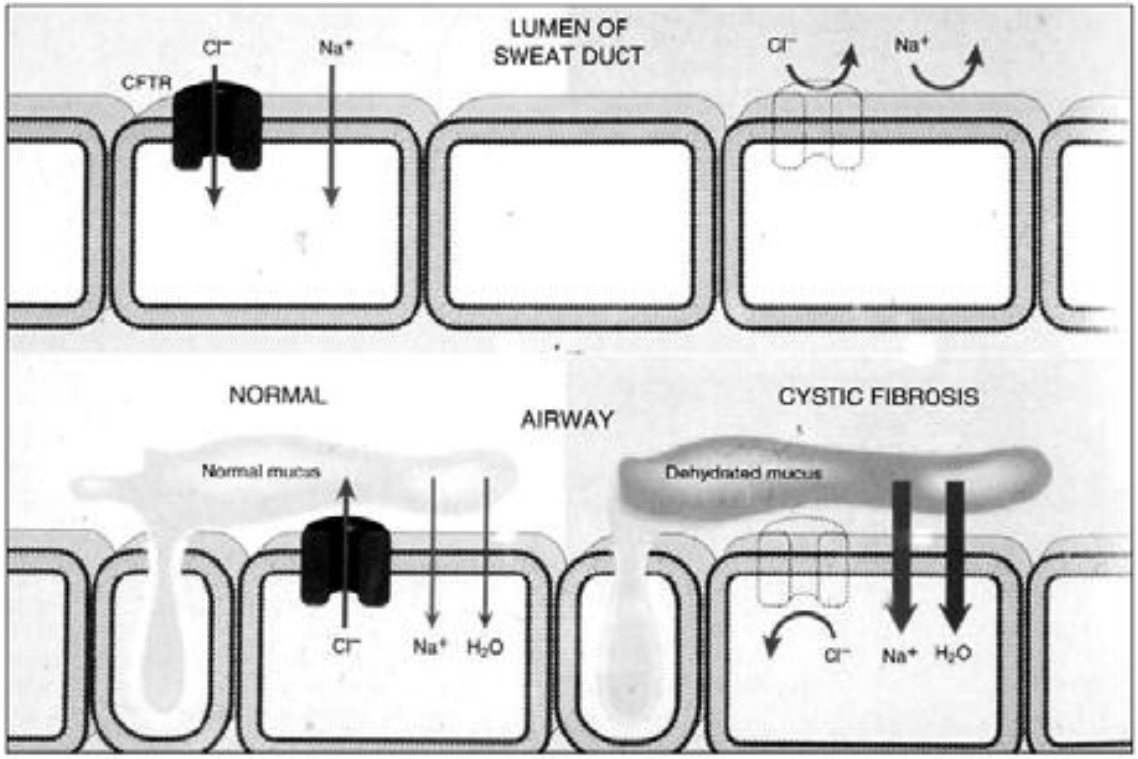






Funzione della proteina

La principale funzione è il trasporto di Cl^-. La direzione del trasporto dipende dalla specifica funzione del tessuto.



Ghiandole sudoripare

N: Cl^- va dal lume al citoplasma

FC: difetto assorbimento Cl^- e Na^+. Aumentata concentrazione di sale nel sudore.

Epitelio respiratorio

N: Cl^- va dall'interno all'esterno della cellula

FC: difetto secrezione Cl^- ed eccesso assorbimento Na^+ e di H_2O. Disidratazione ed ispessimento del muco sulla superficie dell'epitelio.

The CF Pathogenesis Cascade

Defective CF Gene

Deficient CFTR Protein

Abnormal Chloride Permeability
Altered Ionic Transport

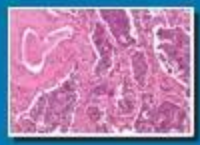
Act here to rescue the basic CF defect and block the cascade!

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

TEST DEL SUDORE

Test normale
< 30 mEq/L cloro

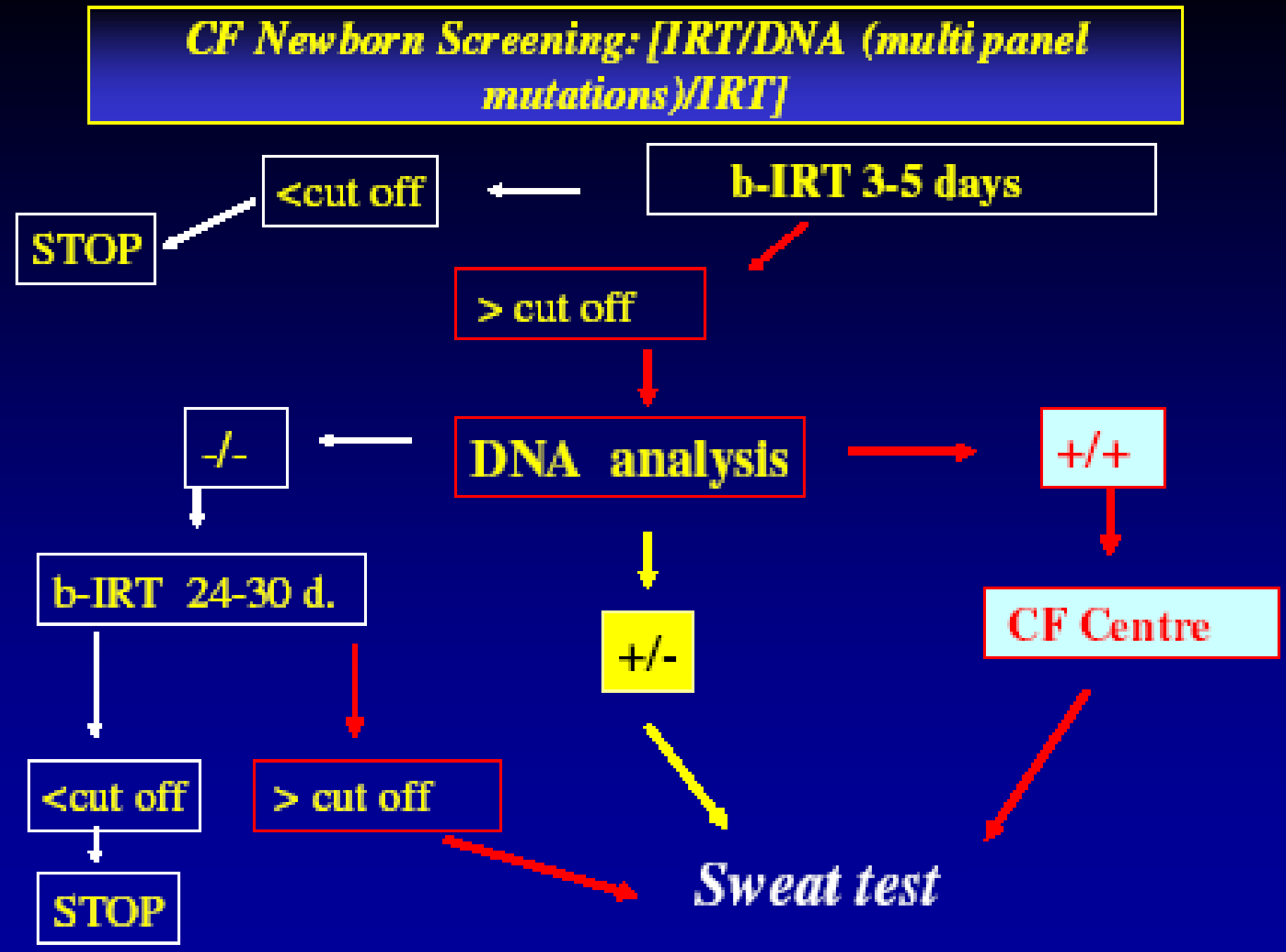
Test borderline
> 30 mEq/L cloro

Test patologico
>60 mEq/L cloro

STIMOLAZIONE con **PILOCARPINA**

RACCOLTA del SUDORE

DOSAGGIO del **CLORO:**
Clorurimetro


CF Newborn Screening: [IRT/DNA (multi panel mutations)/IRT]
b-IRT 3-5 days
<cut off
STOP
> cut off
DNA analysis
-/-
+/+
b-IRT 24-30 d.
+/-
CF Centre
<cut off
> cut off
STOP
Sweat test

CRITERI DIAGNOSTICI

THE DIAGNOSIS OF CYSTIC FIBROSIS: CONSENSUS STATEMENT

one or more characteristic phenotypic features
and/or
history of CF in a sibling
and/or
positive newborn screening test

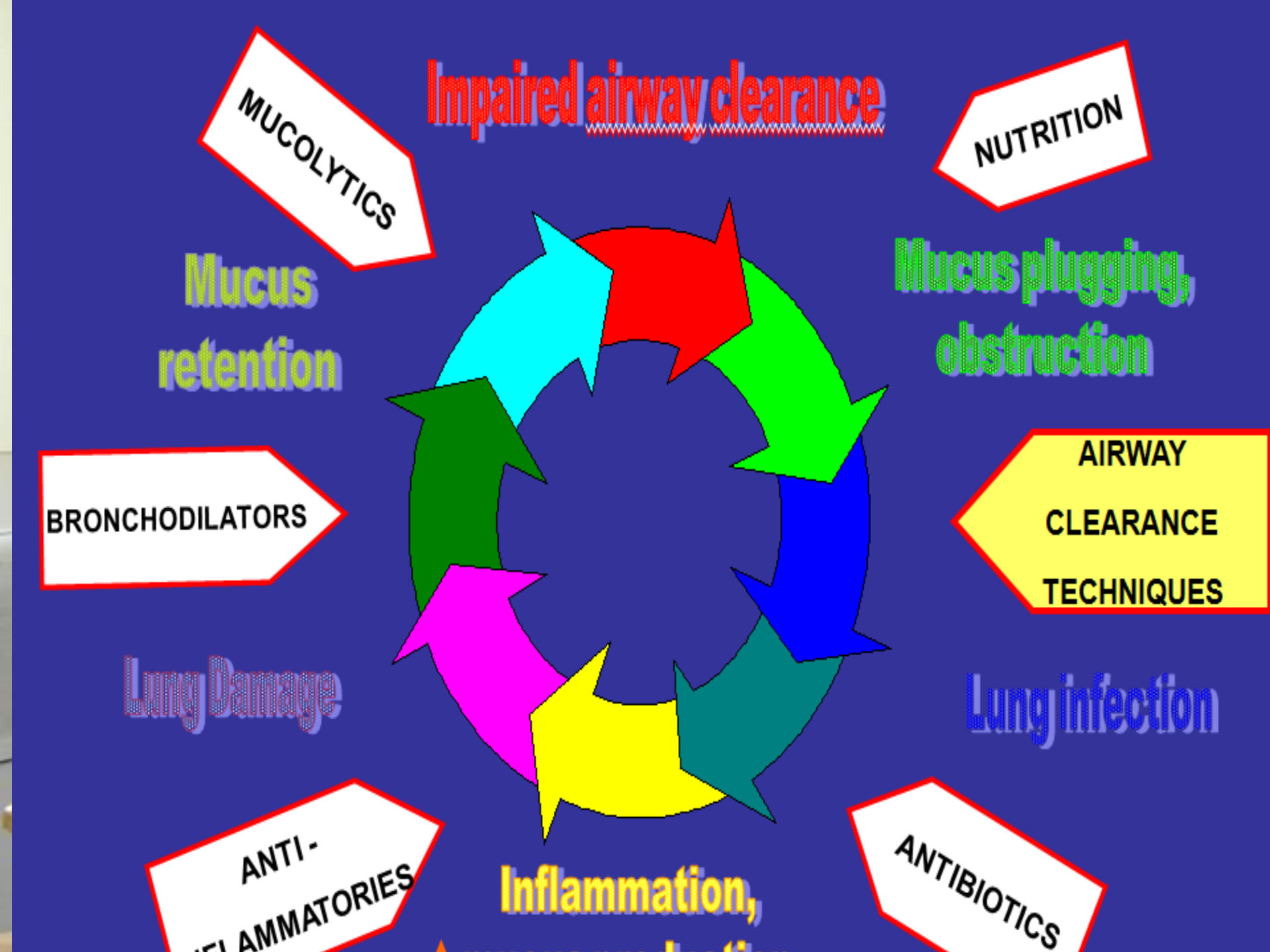
+

elevated sweat chloride concentrations
and/or
identification of two CF-causing mutations
and/or
demonstration of characteristic abnormalities in ion transport across the nasal epithelium

=

CF

Rosenstein BJ et al. J. Pediatr 1998; 132: 589-95


Impaired airway clearance
MUCOLYTICS
NUTRITION
Mucus retention
Mucus plugging, obstruction
BRONCHODILATORS
AIRWAY CLEARANCE TECHNIQUES
Lung Damage
Lung infection
ANTI - INFLAMMATORIES
Inflammation,
ANTIBIOTICS

TEST DEL SUDORE

Test normale
< 30 mEq/L cloro

Test borderline
> 30 mEq/L cloro

Test patologico
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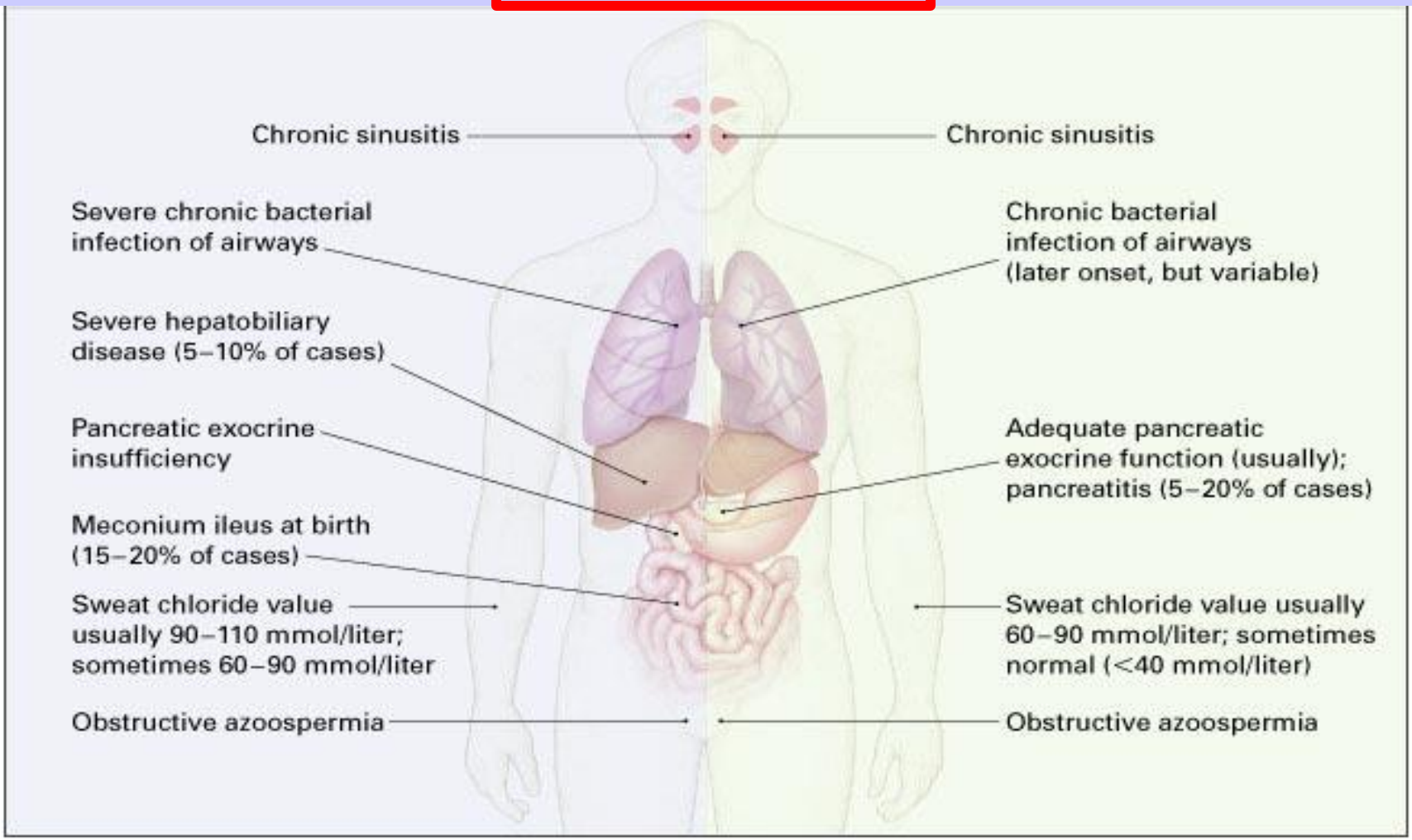
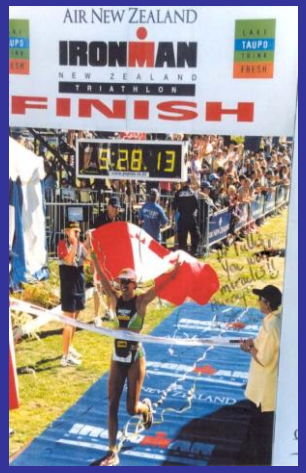


Spectrum of Cystic Fibrosis



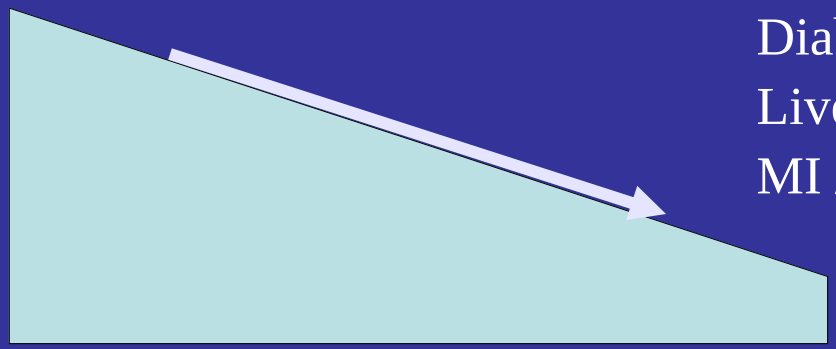
CBAVD: **C**ongenital **B**ilateral **A**bsence of the **V**as **D**eferens

CFSPID: **CF S**creening **P**ositive **I**nconclusive **D**iagnosis

CRMS: **C**FTR **R**elated **M**etabolic **S**yndrome

CFTR-RD: **CFTR**-**R**elated **D**isorder

PS
Less severe lung disease
Male infertility
Pancreatitis

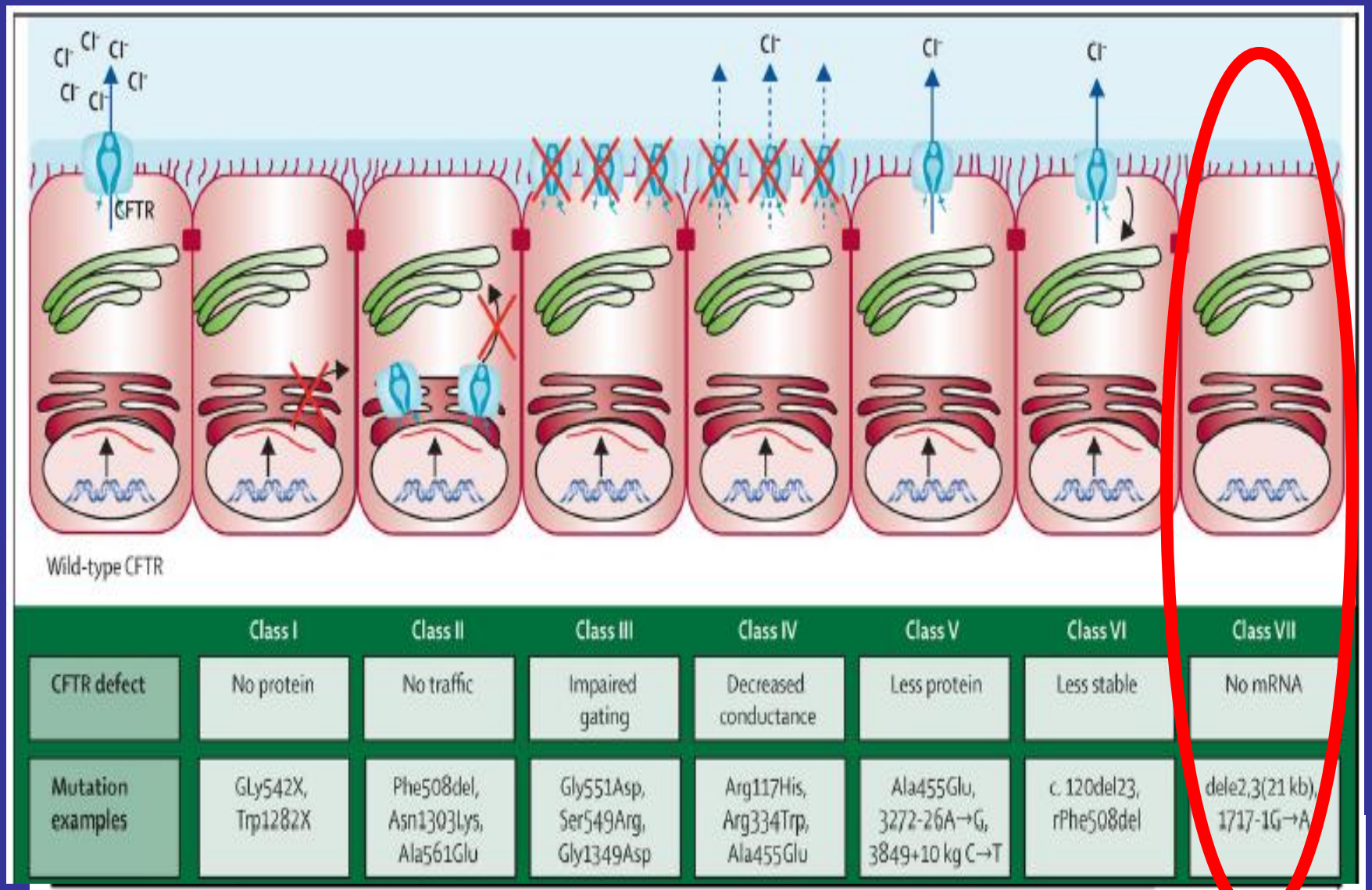


PI
Severe lung disease
Diabetes
Liver disease
MI / DIOS

CFTR Mutations and the Phenotypic Continuum

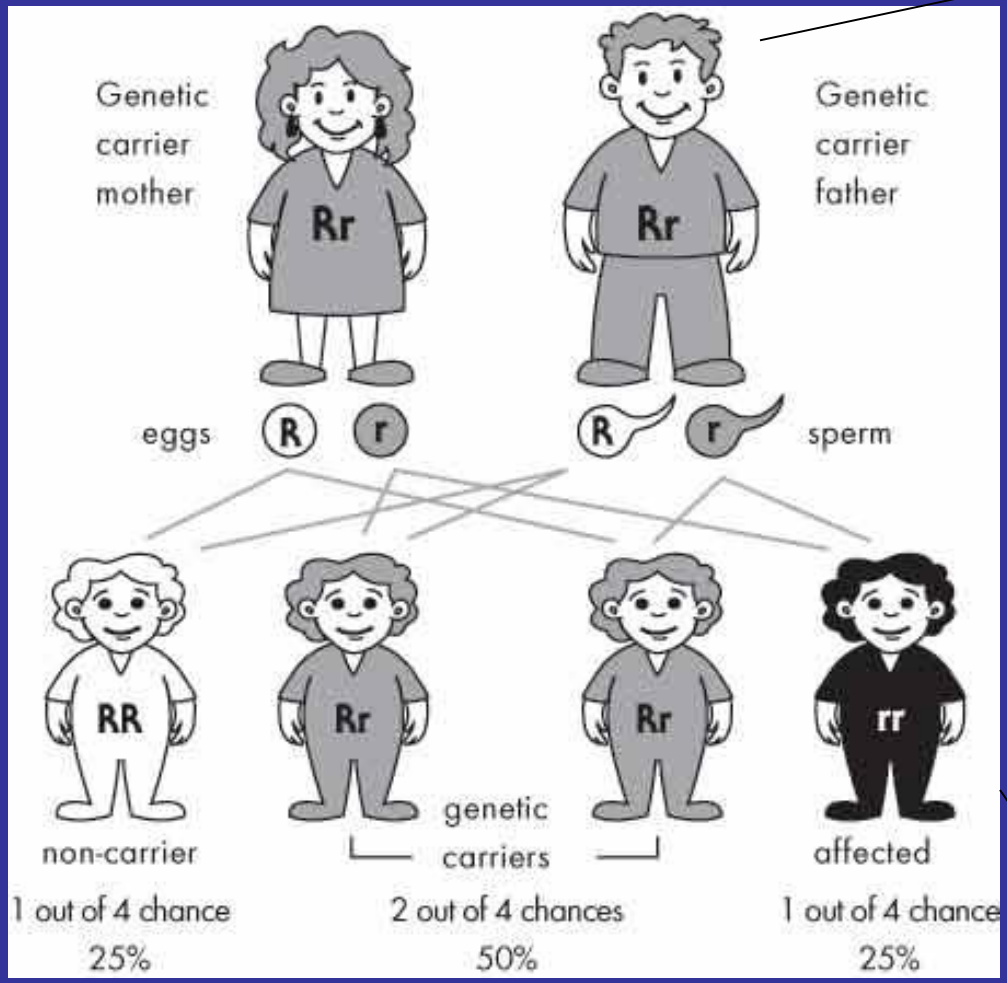
Cystic Fibrosis	CFTR-related disorders

2124 mutazioni note: 6 classi funzionali



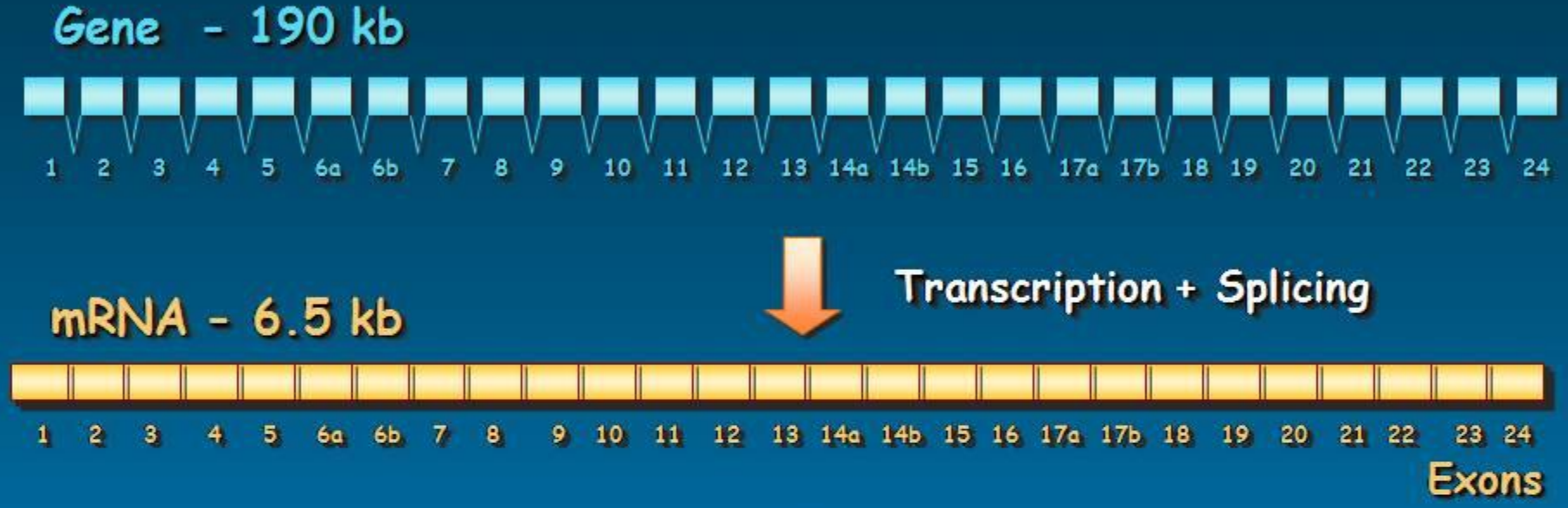
	Class I	Class II	Class III	Class IV	Class V	Class VI	Class VII
CFTR defect	No protein	No traffic	Impaired gating	Decreased conductance	Less protein	Less stable	No mRNA
Mutation examples	GLy542X, Trp1282X	Phe508del, Asn1303Lys, Ala561Glu	Gly551Asp, Ser549Arg, Gly1349Asp	Arg117His, Arg334Trp, Ala455Glu	Ala455Glu, 3272-26A→G, 3849+10 kg C→T	c. 120del23, rPhe508del	dele2,3(21 kb), 1717-1G→A

1/25-30



1/3000-3500

CFTR: from Gene to Protein



QUANTI SONO I PORTATORI SANI DEL GENE DELLA FIBROSI CISTICA NEL MONDO

MUTAZIONE	NOME cDNA	NOME PROTEINA	CLASSE DI MUTAZIONE	2022	
				n.	%
F508del	c.1521_1523delCTT	p.Phe508del	2	5375	44,23
N1303K	c.3909C>G	p.Asn1303Lys	2	653	5,37
G542X	c.1624G>T	p.Gly542X	1	560	4,61
2789+5G>A	c.2657+5G>A		5	348	2,86
D1152H	c.3454G>C	p.Asp1152His	4	252	2,07
5T;TG12	c.[1210-12[5];1210-34TG[12]]			240	1,97
W1282X	c.3846G>A	p.Trp1282X	1	232	1,91
2183AA->G	c.2051_2052delAAinsG	p.Lys684SerfsX38	1	223	1,84
1717-1G->A	c.1585-1G>A		1	185	1,52
3849+10kbC->T	c.3718-2477C>T		5	169	1,39
R553X	c.1657C>T	p.Arg1162X	1	142	1,17
R1162X	c.3484C>T	p.Arg553X	1	140	1,15
G85E	c.254G>A	p.Gly85Glu		137	1,13
L1077P	c.3230T>C	p.Leu1077Pro	2	100	0,82
G1244E	c.3731G>A	p.Gly1244Glu	3	90	0,74
R347P	c.1040G>C	p.Arg347Pro	4	88	0,72
4382delA	c.4251delA	p.Glu1418ArgfsX14	6	87	0,72
P5L	c.14C>T	p.Pro5Leu	2	79	0,65
R1066H	c.3197G>A	p.Arg1066His	2	69	0,57
T338I	c.1013C>T	p.Thr338Ile	4	67	0,55
L997F**	c.2991G>C	p.Leu997Phe		62	0,51
4016insT	c.3884_3885insT	p.Ser1297PhefsX5	1	61.	0,50
unknown				175	1,44

Dati estrapolati dal RIFC 2022

Mutation with allelic frequency ≥0.5% (No. 6,076; allels 12,152). Year 2022.

VENETO

Mutazione	%
DF508	44.84
R1162X	9.00
2183AA->G	7.96
1717-1G->A	3.83
N1303K	3.54
711+5G->A	2.65
2789+5G->A	2.51
G542X	2.36
R553X	1.77
G85E	1.62
Q552X	1.47
DI507	1.18
3132delTG	0.59
3849+10kbC->T	0.44
621+1G->T	0.44
Altro*	2.36
UN	**13.40**
Totale	100.00

SARDEGNA

Mutazione	%
DF508	53.10
T338I	13.10
G542X	5.63
2183AA->G	3.75
N1303K	2.50
3849+10kbC->T	1.88
Altro*	8.75
UN	**11.30**
Totale	100.00

≈2100 MUTAZIONI

CFTR variants in Chinese population

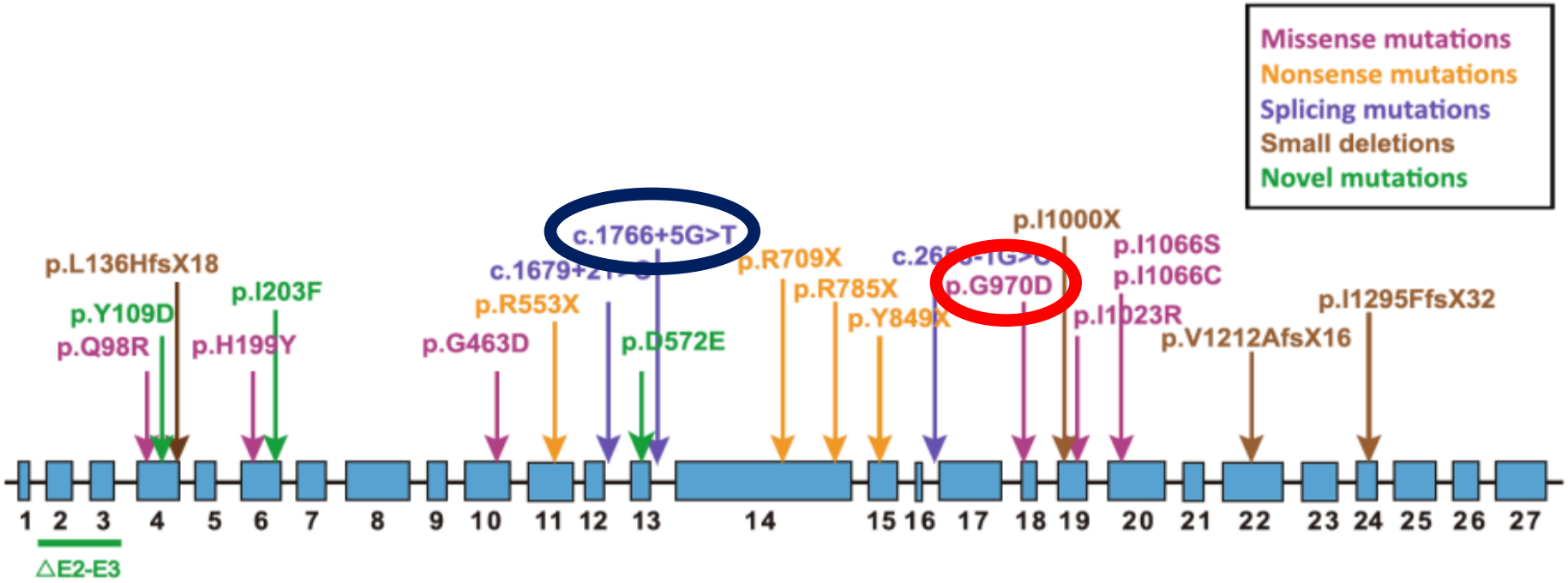


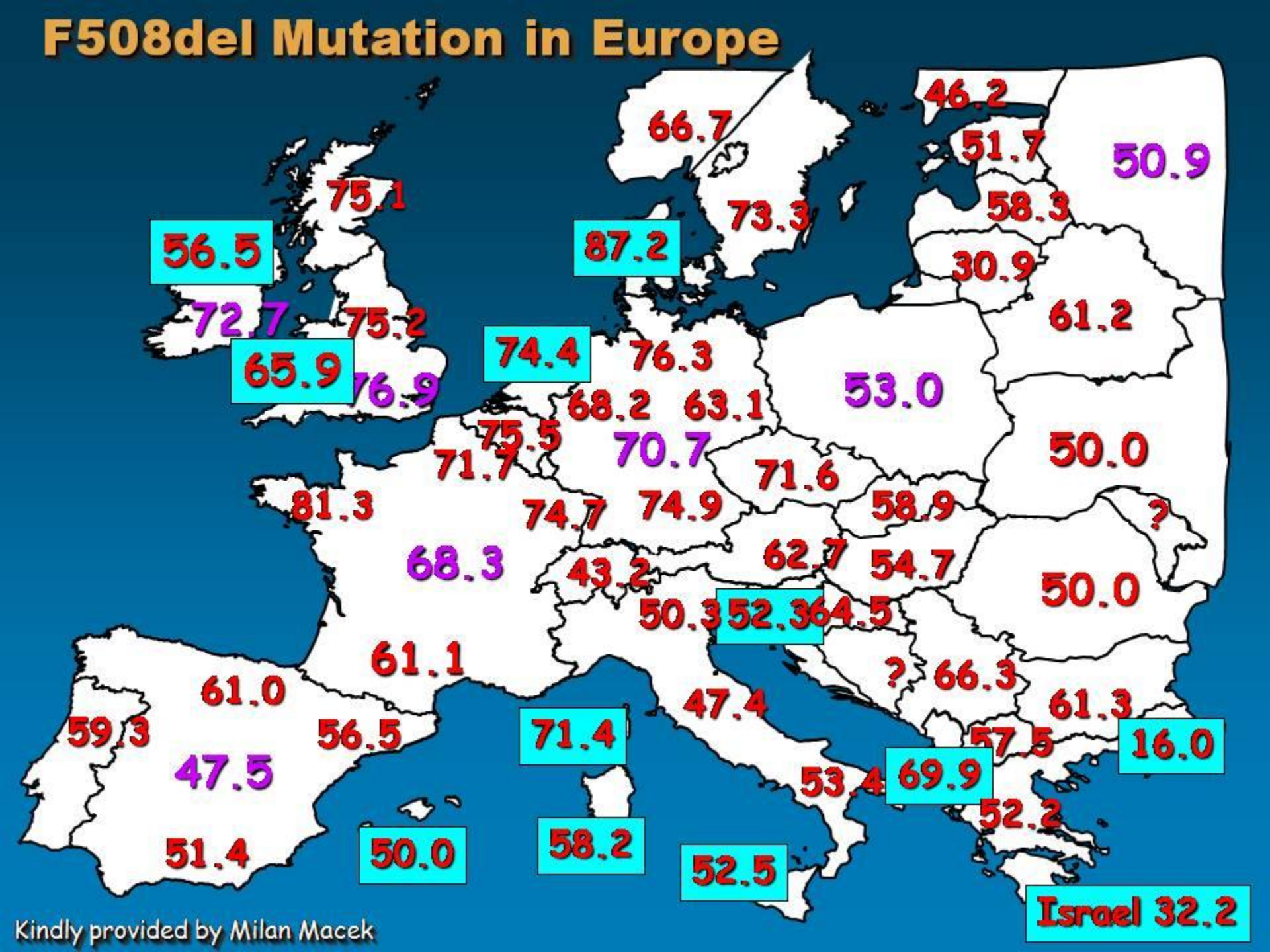
Fig. 1 *CFTR* mutations detected in this CF cohort. Different mutation types are shown in the colors indicated in the upper panel; the gross deletion of exons 2–3 is indicated with a green solid line in the lower panel. The novel mutations identified in the current study are highlighted in green

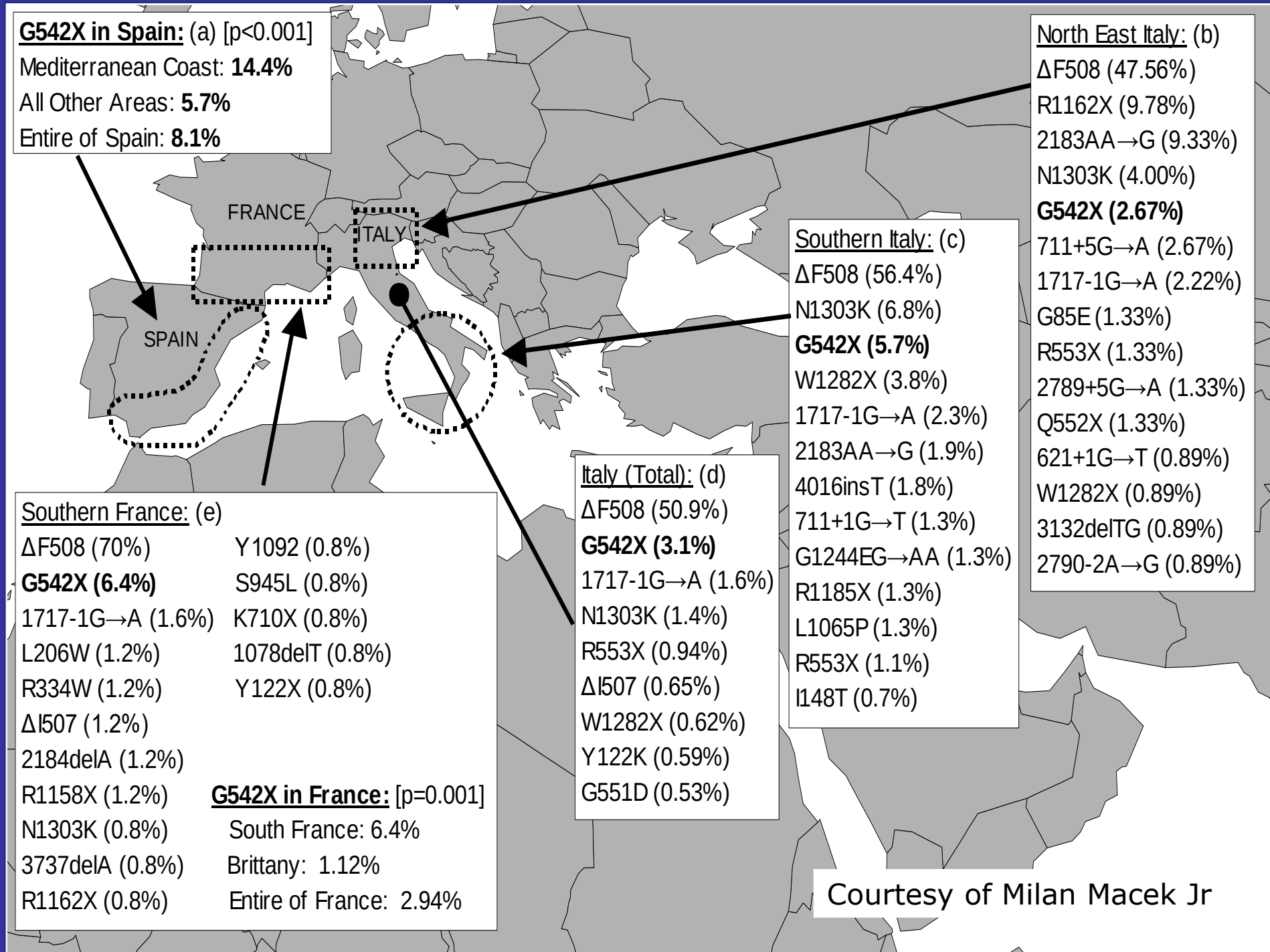
p.Phe508del assente o rara

p.Gly970Asp mutazione più frequente in China (assente in CFTR2)

c.1766+5G>T non identificata nella popolazione Caucasica (presente in CFTR2 come CF-causing)

F508del Mutation in Europe




G542X in Spain: (a) [p<0.001]
Mediterranean Coast: **14.4%**
All Other Areas: **5.7%**
Entire of Spain: **8.1%**
FRANCE
ITALY
SPAIN
North East Italy: (b)
ΔF508 (47.56%)
R1162X (9.78%)
2183AA→G (9.33%)
N1303K (4.00%)
G542X (2.67%)
711+5G→A (2.67%)
1717-1G→A (2.22%)
G85E (1.33%)
R553X (1.33%)
2789+5G→A (1.33%)
Q552X (1.33%)
621+1G→T (0.89%)
W1282X (0.89%)
3132delTG (0.89%)
2790-2A→G (0.89%)
Southern Italy: (c)
ΔF508 (56.4%)
N1303K (6.8%)
G542X (5.7%)
W1282X (3.8%)
1717-1G→A (2.3%)
2183AA→G (1.9%)
4016insT (1.8%)
711+1G→T (1.3%)
G1244EG→AA (1.3%)
R1185X (1.3%)
L1065P (1.3%)
R553X (1.1%)
I148T (0.7%)
Italy (Total): (d)
ΔF508 (50.9%)
G542X (3.1%)
1717-1G→A (1.6%)
N1303K (1.4%)
R553X (0.94%)
ΔI507 (0.65%)
W1282X (0.62%)
Y122K (0.59%)
G551D (0.53%)
Southern France: (e)
ΔF508 (70%)
G542X (6.4%)
1717-1G→A (1.6%)
L206W (1.2%)
R334W (1.2%)
ΔI507 (1.2%)
2184delA (1.2%)
R1158X (1.2%)
N1303K (0.8%)
3737delA (0.8%)
R1162X (0.8%)
Y1092 (0.8%)
S945L (0.8%)
K710X (0.8%)
1078delT (0.8%)
Y122X (0.8%)
G542X in France: [p=0.001]
South France: 6.4%
Brittany: 1.12%
Entire of France: 2.94%
Courtesy of Milan Macek Jr

Cystic Fibrosis Mutation Database

F508del occurs in 70% of CF chromosomes worldwide

CFMDB Statistics

There are currently **2124** mutations listed in this CFTR mutation database.

Statistics by mutation type:

Mutation Type	Count	Frequency %
Missense	816	38.42
Frameshift	343	16.15
Splicing	231	10.88
Nonsense	178	8.38
In frame in/del	43	2.02
Large in/del	59	2.78
Promoter	17	0.80
Sequence variation	269	12.66
Unknown	168	7.91

In collaboration with:

CFTR2 Clinical and Functional Translation of CFTR

CFTR2 was last updated on April 7, 2023

CYSTIC FIBROSIS FOUNDATION ADDING TOMORROWS

JOHNS HOPKINS MEDICINE

sequenom Laboratories

Welcome to the CFTR2 website

Our Purpose:

CFTR2 is a website that provides information for patients, researchers, and the general public about specific variants in what is commonly referred to as the cystic fibrosis (CF) gene.

For each variant or variant combination included in the database, the website will provide information about:

1. Whether the variant or variant combination is CF-causing, and

2. Information about sweat chloride, lung function, pancreatic status, and Pseudomonas infection rate in patients in the CFTR2 database with this variant or variant combination.

Information on the CFTR2 website is being updated as further analysis is completed. The most up-to-date clinical information and results of functional testing are available on individual variant pages. For a complete list of CFTR2 variants and their characterizations, please visit CFTR2 Variant List History.

What this site is intended to do:

- This website provides information for members of the general public, including cystic fibrosis patients and their family members, about what is currently known about specific genetic variants related to cystic fibrosis.
- Patients and their family members are encouraged to visit the section, "For patients and family members" first.
- This website also provides more in-depth research-related information for health care professionals and researchers.

What this site is NOT intended to do:

This website is not intended to help diagnose anyone with CF.

- The information about groups of patients contained on this website should not be used to predict the clinical course of individual patients.
- This website is not intended to provide medical advice to individual patients.
- This website is not intended to provide information about pancreatitis, diabetes mellitus, or other diseases associated with CF.

For more information about CF, click here.

Note: If you have questions about any of the information contained in this website, please consult your doctor.

In collaboration with:

CFTR2 Clinical and Functional Translation of CFTR

CFTR2 was last updated on April 7, 2023

CYSTIC FIBROSIS FOUNDATION ADDING TOMORROWS

JOHNS HOPKINS MEDICINE

seq

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Informa analysis and res variant charact

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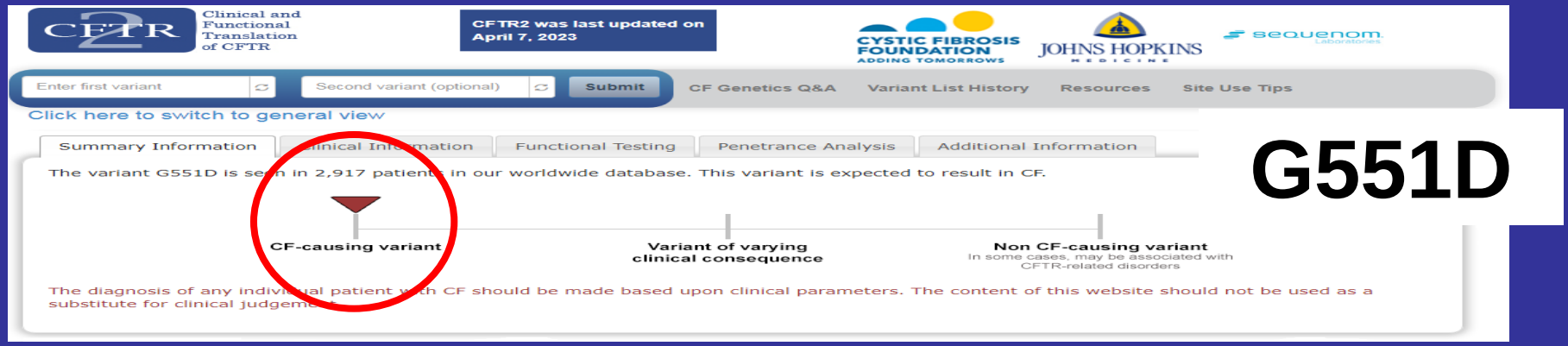
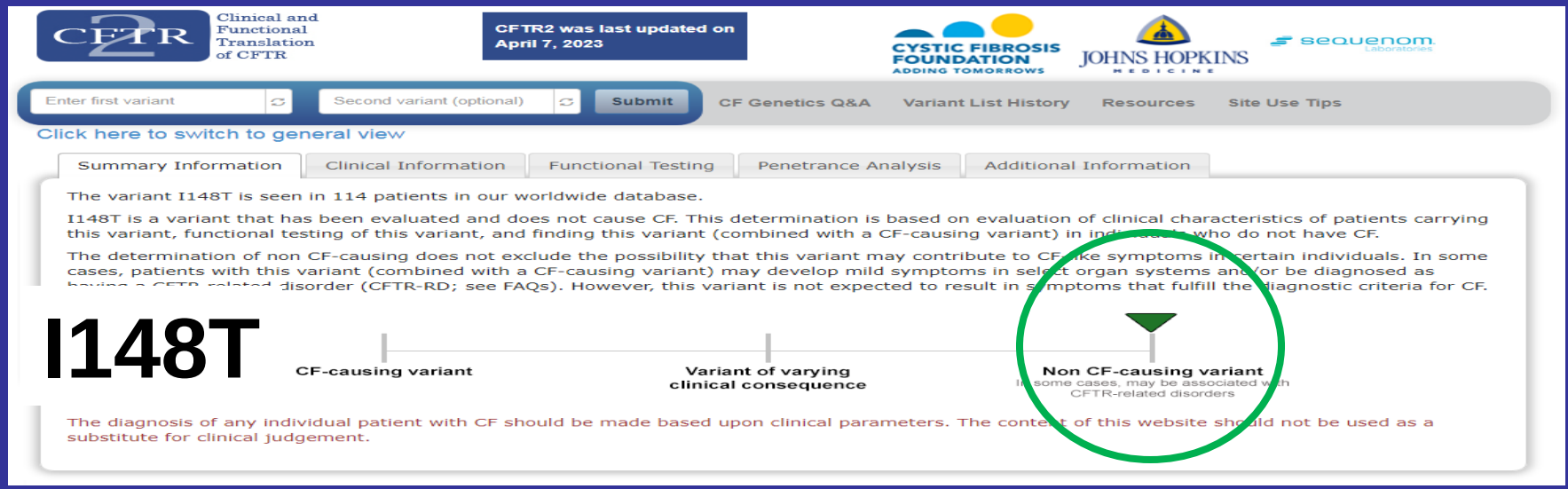
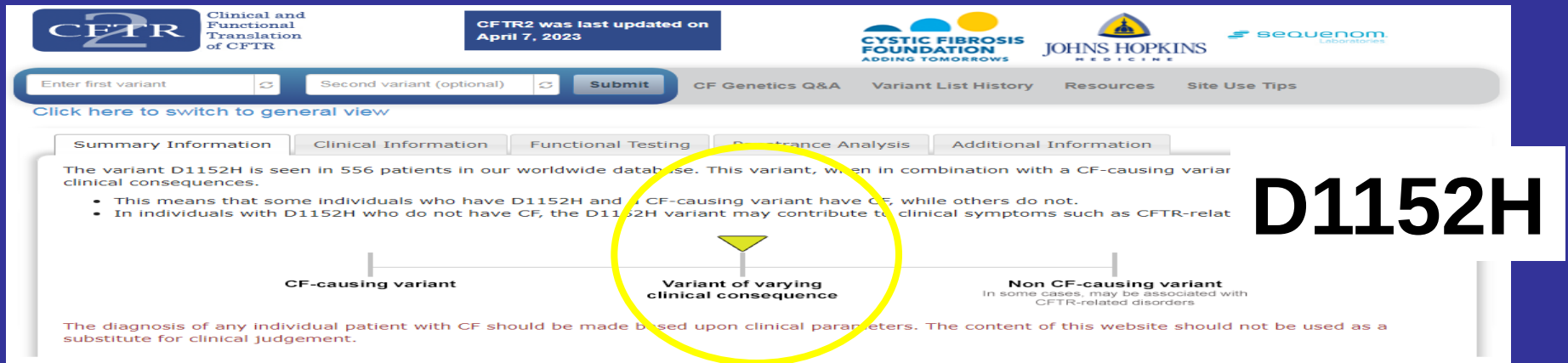
Mutation analysis is not the answer to every diagnostic dilemma:its limitations and role must be understood by the **clinician**,who **has to interpret and use it in the context of the clinical setting**



G551D



I148T

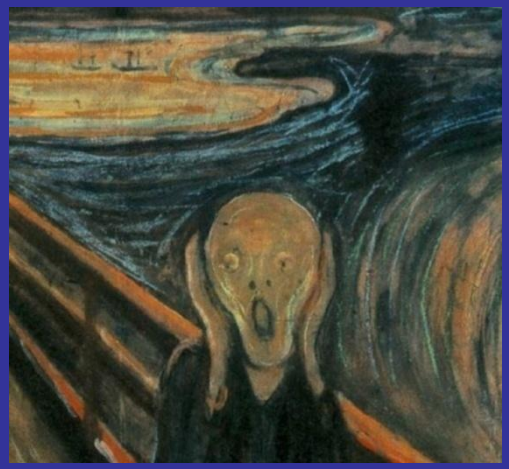


D1152H

http://www.genet.sickkids.on.ca/cftr/Home.html

↓

2124 variazioni di sequenza



CF-causing: 1245 (58%)
Variants of varying clinical consequence (*VCC*): 83 (3.9%)
Non CF-causing: 42 (1.9%)

The list of mutations that is acceptable as diagnostic evidence will need to be expanded.

The Clinical and Functional TRanslation of CFTR (CFTR2) Project

Raccoglie dati da registri di Europa e Nord-America

www.cftr2.org

Predicting a spectrum of disease is difficult

Table 4 Classification of *CFTR* mutations with regard to their potential for causing disease

Mutation group	*Examples*
CF-causing	F508del Mainly nonsense, frameshift, splicing (invariant dinucleotide): G542X, R553X, W1282X, 2183AA>G, 3659delC, 1717-1G>A, 3120+1G>A Missense that severely affects CFTR synthesis or function: G551D, N1303K, R347P 2789+5G>A, 3849+10kbC>T, 3272-26A>G, L206W[a], D1152H[a], (TG)13(T)5[a]
CFTR-related disorders associated	L206W[a], D1152H[a], (TG)13(T)5[a] [R117H;(T)7], (TG)12(T)5, L997F, V562I, [R668C;G576A;D443Y], [R74W;D1270N] (TG)11(T)5[b], S1235R[b]
No clinical consequences	875+40A>G, M470V (1540A>G), I506V (1648A>G), F508C (1655T>G), 1716G>A, 2694T>G, 4002A>G, 2752-15G>C (TG)11(T)5[b], S1235R[b]
Unproven or uncertain clinical relevance	Mainly missense mutations G622D, R170H, V938G, I125T Putative splice mutations: 406-6T>C, 2752-26A>G, 3601-17T>C

Only a fraction of mutations and patients have been characterized in detail and, with the exception of frequent mutations, only small numbers of patients have been available for the study of most mutations. Data shown here have to be interpreted with caution.

[a]Mutations that are associated with a wide phenotypic spectrum and which may belong either to group A or to group B.

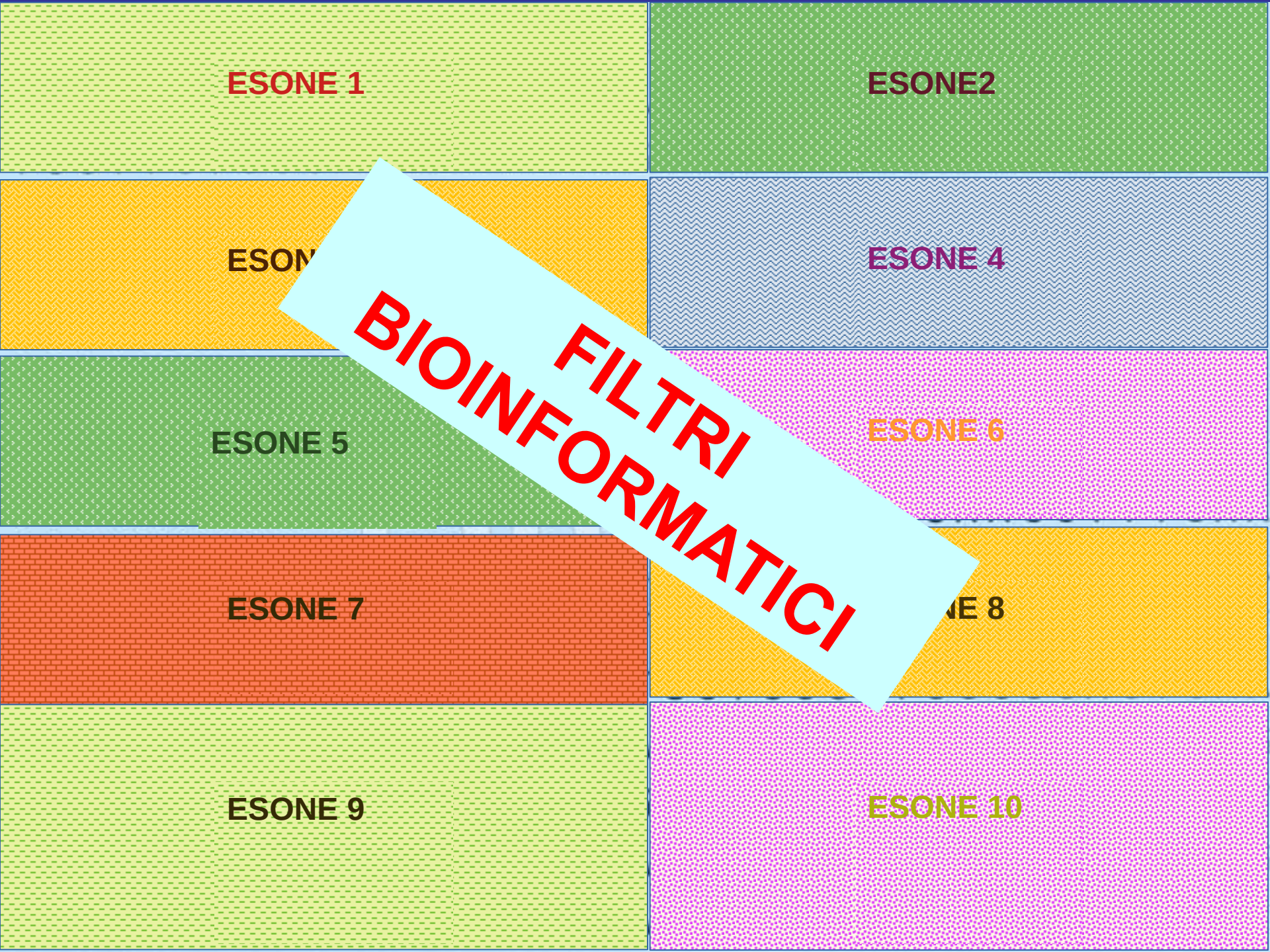
[b]Mutations that may belong either to group B or to group C.

IL TEST GENETICO

ELENCO DELLE MUTAZIONI RICERCATE:

1002-1110_1113delTAAG, 1078delT, 1119delA, 1138insG, 1154insTC, 1161delC, 1213delT, 1248+1G>A, 1249-1G>A, 124del23bp, 1259insA, 1288insTA, 1341+1G>A, 1343delG, 1429del7, 1461ins4, 1471delA, 1497delGG, 1504delG, 1525-1G>A, 1525-2A>G, 1548delG, 1609delCA, 1677delTA, 1716+1G>A, 1716+18672bpA>G, 1717-1G>A, 1717-8G>A, 175insT, 1782delA, 1802delC, 1811+1634A>G, 1811+1643G>T, 1811+1G>A, 1811+1G>C, 1812-1G>A, 1824delA, 182delT, 1833delT, 1845delAG/1846delGA, 185+1G>T, 1874insT, 1898+1G>A, 1898+1G>C, 1898+1G>T, 1898+3A>G, 1898+5G>T, 1924del7, 1949del84, 2055del9>A, 2075delA, 2105-2117del13insAGAAA, 2118del4, 2143delT, 2183AA>G, 2184delA, 2184insA, 2185insC, 2307insA, 2347delG, 2372del8, 2556insAT, 2585delT, 2594delGT, 2622+1G>A, 2711delT, 2721del11, 2732insA, 2789+5G>A, 2790-1G>C, 2869insG, 2896insAG, 2909delT, 2942insT, 2957delT, 296+1G>A, 296+1G>T, 296+2T>C, 296+3insT, 297-1G>A, 2991del32, 3007delG, 3028delA, 306delTAGA, 306insA, 3120+1G>A, 3120G>A, 3121-1G>A, 3121-2A>G, 3132delTG, 3143del9, 3171delC, 3171insC, 3199del6, 3271delGG, 3272-26A>G, 3349insT, 3500-2A>G, 3600+2insT, 3600+5G>A, 3600G>A, 365-366insT, 3659delC, 3667ins4, 3737delA, 3791delC, 3821delT, 3849+10kbC>T, 3849+40A>G, 3849+4A>G, 3849+5G>A, 3849G>A, 3850-1G>A, 3850-3T>G, 3876delA, 3878delG, 3905insT, 3941delTT, 4005+1G>A, 4005+2T>C, 4010del4, 4015delA, 4016insT, 4022insT, 4040delA, 405+3G>A, 405+3A>C, 406-1G>A, 406-2A>G, 4158delCTAAGCC, 4209TGTT>AA, 4218insT, 4259del5, 4279insA, 4326delTC, 4374-1G>A, 4374+1G>T, 4382delA, 4478insGA, 442delA, 444delA, 457TAT>G, 541delC, 574delA, 602del14, 621+1G>T, 663delT, 675del4, 711+1G>T, 711+3A>G, 711+5G>A, 712-1G>T, 849delG, 852del22, 935delA, 977insA, 991del5, A1006E, A455E, A46D, A559T, A561E, A613T, C276X, C524X, CFTRdele1, CFTRdele14b-17b, CFTRdele17a-18, CFTRdele2, CFTRdele2,3, CFTRdele22,23, CFTRdele22-24, D110E, D110H, D1152H, D1270N, D513G, D614G, D979V, E1104X, E1371X, E1473X, E193K, E193X, E474K, E504X, E56K, E585X, E60K, E60X, E822X, E831X, E92K, E92X, F1074L, F191V, F311L, F508del, G1061R, G1069R, G1244E, G1249R, G126D, G1349D, G178R, G194R, G27R, G27X, G330X, G542X, G550X, G551D, G551S, G628R, G673X G85E, G91R, G970D, G970R, H1054D, H1375P, H139R, H199R, H199Y, H609R, I1027T, I1234V, I1269N, I1366N, I336K, I502T, I507del, I601F, K598X, K710X, L102R, L1065P, L1077P, L1254X, L1324P, L1335P, L138ins, L15P, L165S, L206W, L227R, L346P, L453S, L467P, L558S, L571S, L732X, L88X, L927P, M1101K, M1101R, M1V, N1303K, P205S, P574H, P5L, P67L, P99L, Q1042X, Q1291R, Q1313X, Q1330X, Q1382X, Q1411X, Q1412X, Q1476X, Q220X, Q2X, Q30X, Q353X, Q359K/T360K, Q39X, Q414X, Q493X, Q525X, Q552X, Q685X, Q715X, Q720X, Q890X, Q98R, Q98X, R1066C, R1066H, R1070Q, R1070W, R1102X, R1158X, R1162X, R117C, R117H, R117L, R117P, R1283M, R334L, R334W, R347H, R347P, R352Q, R352W, R553X, R560K, R560S, R560T, R709X, R74W, R75X, R764X, R785X, R792X, R851X, S1118F, S1159F, S1159P, S1196X, S1251N, S1255P, S1255X, S13F, S1455X, S341P, S466X, S489X, S492F, S4X, S549N, S549R, S912X, S945L, T1036N, T338I, V1240G, V232D, V456A, V520F, W1089X, W1098C, W1098R, W1098X, W1145X, W1204X, W1282X, W19X, W216X, W401X, W496X, W57G, W57X, W846X, W882X, Y1032C, Y1092X, Y122X, Y161D, Y275X, Y563D, Y563N, Y569D, Y849X, Y913X

365 MUTAZIONI


ESONE 1
ESONE2
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NE 8
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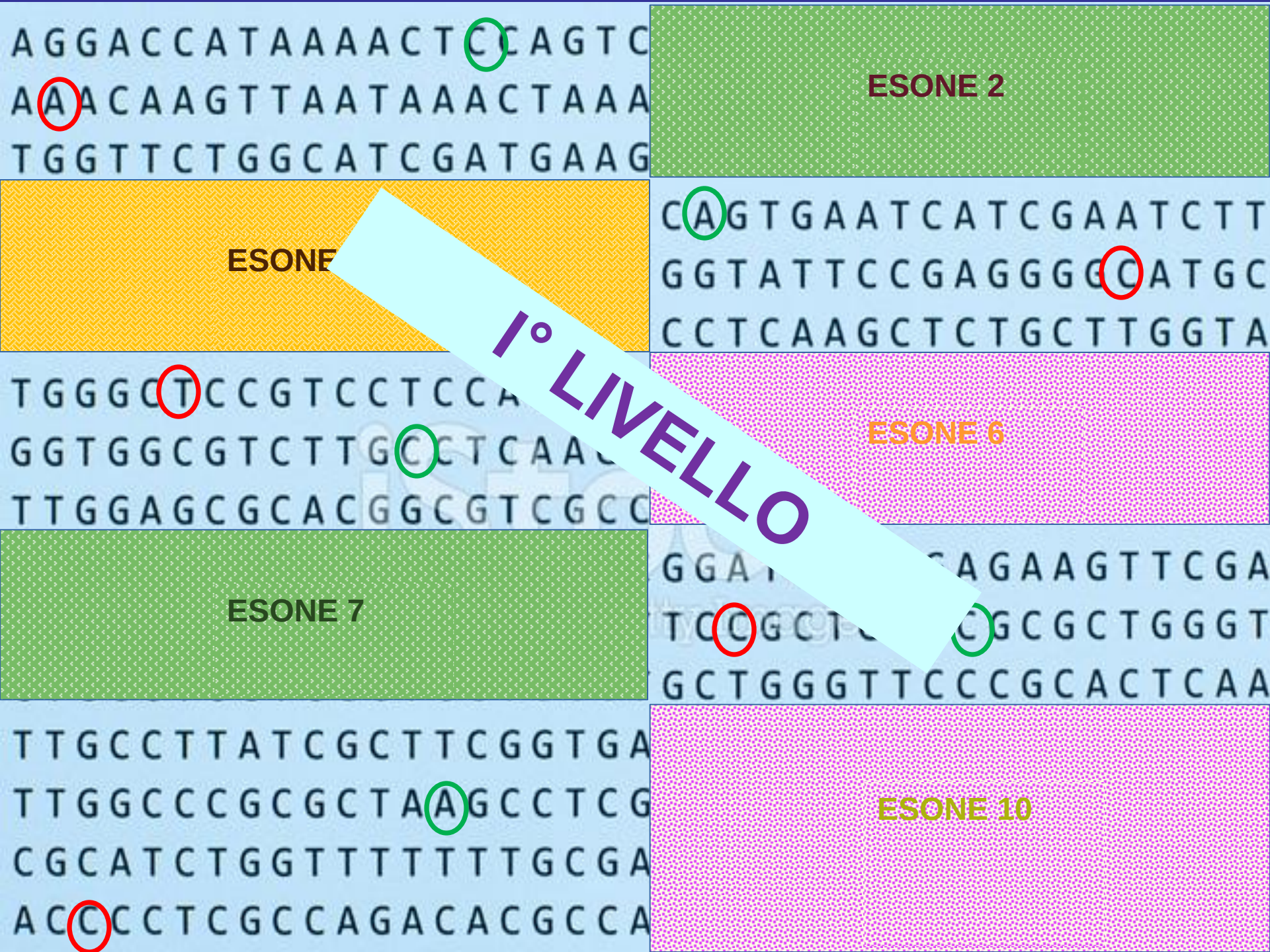
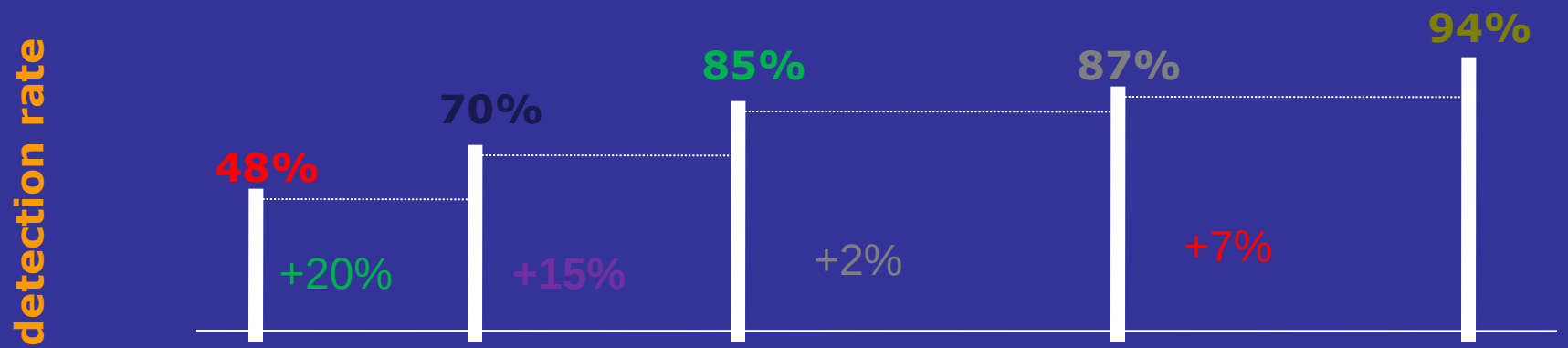
FILTRI
BIOINFORMATICI


ESONE 2
ESONE
I° LIVELLO
ESONE 6
ESONE 7
ESONE 10


II° LIVELLO



F508del

R1162X
2183AA>G
N1303K

+3 M

F508del
G551D
G542X
DI507
R553X
N1303K
W1282X
1717-1G>A
V520F
R560T
S549R
3849+10kbC>T
R1162X
3659delC
3905insT
G85E
621+1G>T
R117H
711+1G>T
1078delT
R347P
R347H
R334W
A455E
1898+1G>A
2183AA>G
2789+5G>A
3876delA

+25 M

F508del G551D
G542X DI507
R553X N1303K
W1282X 1717-1G>A
CFTRdel2.3(21Kb)
3199del6 3272-26A>G
S1251N 3120+1G>A
Q552X 394delTT
2184delA 711+5GA
R560T, 3849+10KbC>T
R1162X 3659delC
3905insT G85E
621+1G>T
711+1G>T
R347P R334W
A455E 1898+1G>A
2183AA>G 2789+5G>A
2143delT 1259insA
4016insT 4382delA
852del22Bp D579G
G1244E G1349D
I502T L1065P
R11 T338I
D1152H
8+3A>G R1070Q
R1066H 621+3A>G
E217G R334Q
R347H R347P

+26 M

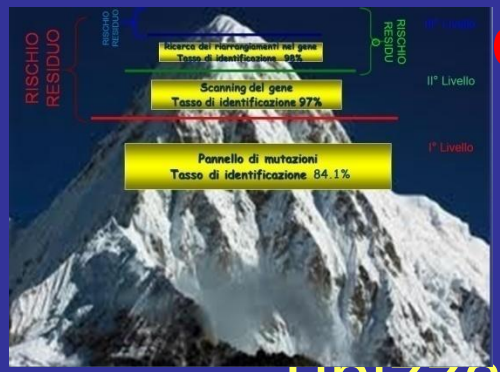
>2000 M

all exons scanning

VENETO

Mutazione	%
DF508	44.84
R1162X	9.00
2183AA->G	7.96
1717-1G->A	3.83
N1303K	3.54
711+5G->A	2.65
2789+5G->A	2.51
G542X	2.36
R553X	1.77
G85E	1.62
Q552X	1.47
DI507	1.18
3132delTG	0.59
3849+10kbC->T	0.44
621+1G->T	0.44
Altro*	2.36
UN	**13.40**
Totale	100.00

INDICAZIONI AL TEST



e dello stato di portatore nei familiari — I° livello / Mirata

molecolare nei partner dei portatori sani/affetti — I° livello / II° livello

Consanguineità — I° livello

Tipizzazione molecolare in pazienti affetti — II° livello

Diagnosi prenatale in coppie a rischio — Mirata

Coppie in gravidanza con quadri ecografici di anse intestinali iperecogene — I° livello / II° livello

Screening neonatale — I° livello

Tipizzazione genetica in pazienti con quadri clinici CF-Like — II° livello

Analisi molecolare in pazienti che accedono alla fecondazione medicalmente assistita

I° livello / II° livello

Test genetici

I test genetici

⇓ *generano*

Dati genetici

Dati genetici → peculiarita'

Sono diversi dagli altri dati "sensibili"

- caratterizzano l'identità biologica non solo del singolo ma anche della famiglia
- sono "immodificabili"
- possono spostare il rapporto temporale tra identificazione di mutazione e insorgenza di malattia
- possono permettere di predire il "rischio futuro" di malattia

FONDAZIONE IRCCS CA' GRANDA
OSPEDALE MAGGIORE POLICLINICO

Laboratorio di Genetica Medica
Settore di Genetica Molecolare
via Commenda 12, 20122 - Milano
tel: 02 55032432-2433

INDAGINI MOLECOLARI PER LA FIBROSI CISTICA

Milano, **16/02/2012**

Data prelievo **09/02/2012**

Nome paziente:

Cod. FC95/12

D.nascita **Sesso**

Reparto/Centro:

Motivo della richiesta: *Accertamenti pre-fecondazione assistita*

Materiale pervenuto: Sangue intero **Materiale utilizzato:** DNA estratto da leucociti del sangue periferico

Risultati **Presenza in eterozigosi della mutazione : c.3909C>G, p.Asn1303Lys (N1303K in eterozigosi)**

Interpretazione Il soggetto in esame è risultato portatore di una mutazione che causa Fibrosi Cistica ed è pertanto da considerarsi eterozigote per fibrosi cistica.
E' opportuno estendere l'indagine molecolare per la fibrosi cistica al partner ed ai familiari.

Si consiglia consulenza genetica

Il Biologo

Il responsabile del Laboratorio di Genetica Molecolare

Mutazioni studiate [delta]F508,G551D,G542X,[delta]I507,R553X,N1303K,W1282X,1717-1G->A,CFTRdel2.3(21Kb), 3199del6,3272-26A>G,S1251N,Q552X,R560T,3905insT,3120+1G>A,711+1G->T, 1898+1G->A,394delTT,2184delA,711+5GA,3849+10kbC->T,R1162X,3659delC,G85E, 621+1G->T,R117H,1078delT,R347P,R334W,A455E,2183AA->G,2789+5G->A,2143delT, E60X,1259insA,4016insT,4382delA,852del22Bp,D579G,G1244E,G1349D,I502T,L1065P, R1158X,T338I,S549R(A>C),991del5,D1152H,1898+3A->G,R1070Q,R1066H,621+3A->G, E217G,R334Q,R347H,L1077P,1677delTA,1706del17, E585X, R1066C, S912X.
Screening delezioni es.1, es.2 (ins.182bp), es.2, es.2-3, es. 14b-17b, es. 22-23, es. 22-24, es. 17a-18 (3120+1Kb del. 8.6Kb).
Le mutazioni ricercate coprono circa l'85% dei difetti che causano Fibrosi Cistica (frequenze analizzate su 1200 alleli CF - dati casistica interna).

Polimorfismi osservati

Con tecnica di sequenziamento sono stati inoltre indagati per la presenza di mutazioni i seguenti esoni del gene CFTR:

Metodiche utilizzate 13 CFTR19, CFTR17+TN Update,CFTR Italian Regional; CFTR Deletions +6 (reverse dot blot)

Riferimento numerazione sequenza NM_000492.3. Nomenclatura secondo HGVS V 2.0 (in parentesi nomenclatura tradizionale: Cystic Fibrosis Mutation Database: www.genet.sickkids.on.ca)

Il laboratorio di Genetica Molecolare partecipa ai controllio di qualità Europeo organizzato dal Cystic Fibrosis European Network.

Legge 196/03 sulla privacy

Laboratorio certificato UNI EN ISO 9001-2008

Componenti essenziali dei test genetici

Consulenza pre-test

*raccolta dati-albero
*informazione
*consenso

→ **ANALISI DI LABORATORIO** →

Consulenza post-test

*interpretazione risultati
*azioni conseguenti

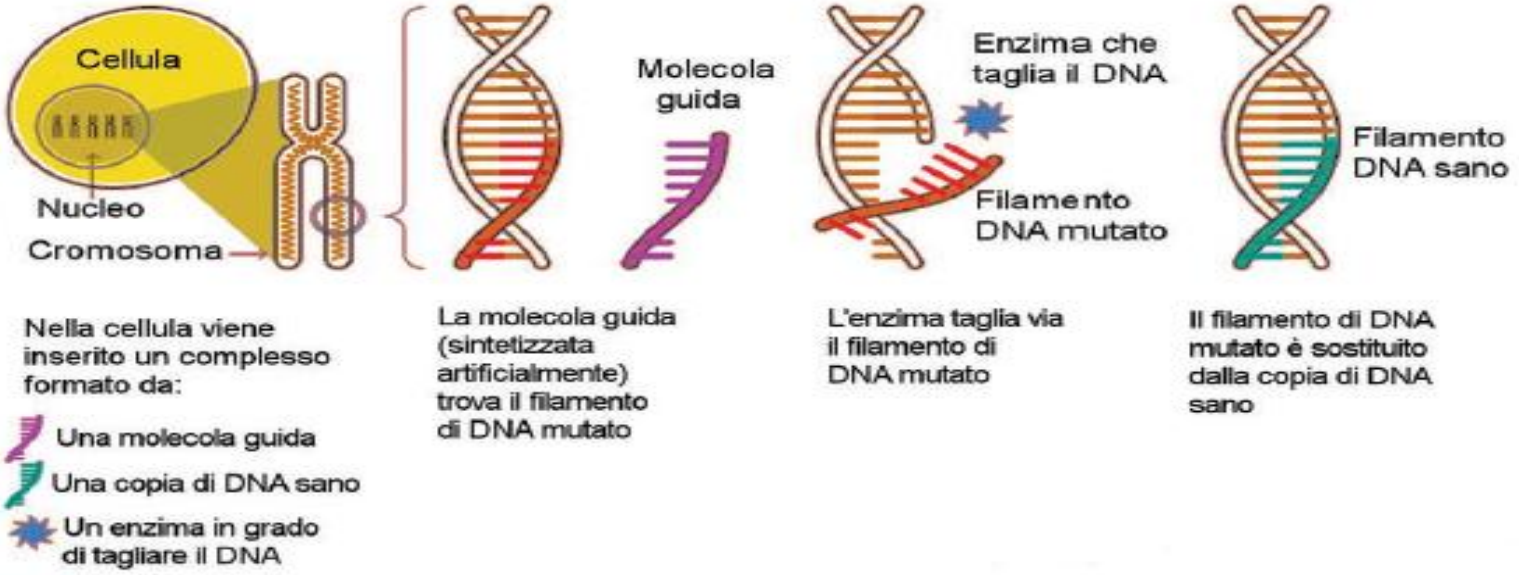
La consulenza genetica e il consenso informato costituiscono parte integrante dell'esecuzione dei test genetici pre e post-natali.

Terapia della FC

- Fisioterapia respiratoria quotidiana (rimozione secreti bronchiali e sostegno alla ventilazione)
- Terapia mucolitica ed antibiotica per liberare dal muco e combattere le infezioni (*Pseudomonas Aeruginosa*)
- Terapia nutrizionale ad elevato apporto calorico
- Assunzione enzimi pancreatici ad ogni pasto
- Terapia delle complicanze tardive della malattia (diabete, epatopatie, sterilità, calcolosi biliare)
- Trapianto polmonare (FC allo stadio terminale)

DNA EDITING

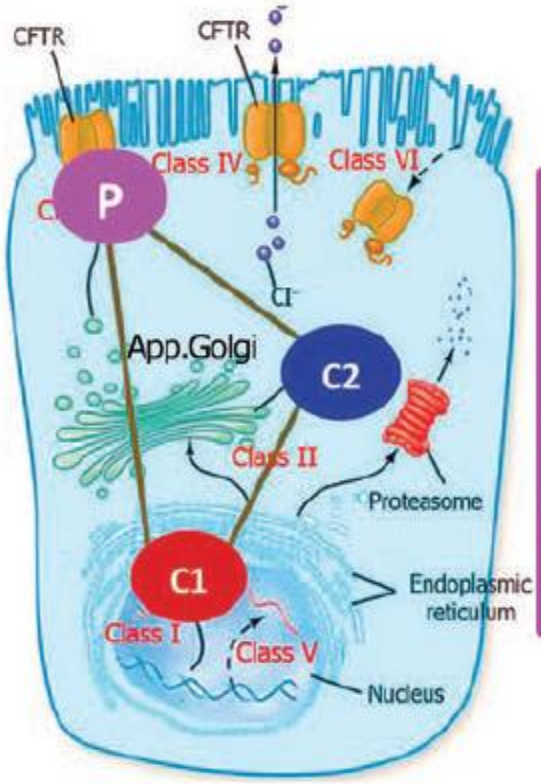
COME CRISPR/Cas9 RISCRIVE IL DNA



- Farmaco terapia del gene *(Protein-repair Therapy)*

Studio di molecole in grado di stimolare la sintesi, maturazione o la funzione della CFTR mutata
Alcune sostanze sono attualmente allo studio.

MODULATORI - *Tipologia*



Potenziatori

	fase
• Kalydeco (in commercio)	
• GLPG1837	(2)
• ABBV/GLPG2451	(1)
• ABBV/GLPG3067	(1)
• QBW-251	(2)
• CTP-656	(2)
• FDL-176	(1)
• PTI-808	(1)

Correttori C1

	fase
• Lumacaftor+Kalydeco -Orkambi (in commercio)	
• Tezacaftor+Kalideko -Symdeko (in commercio USA)	
• ABBV/GLPG2222	(2)
• ABBV/GLPG2851	(2)
• FDL-169	(1/2)
• PTI-801	(1/2)
• FFC/ARN23765	pred.

Correttori C2

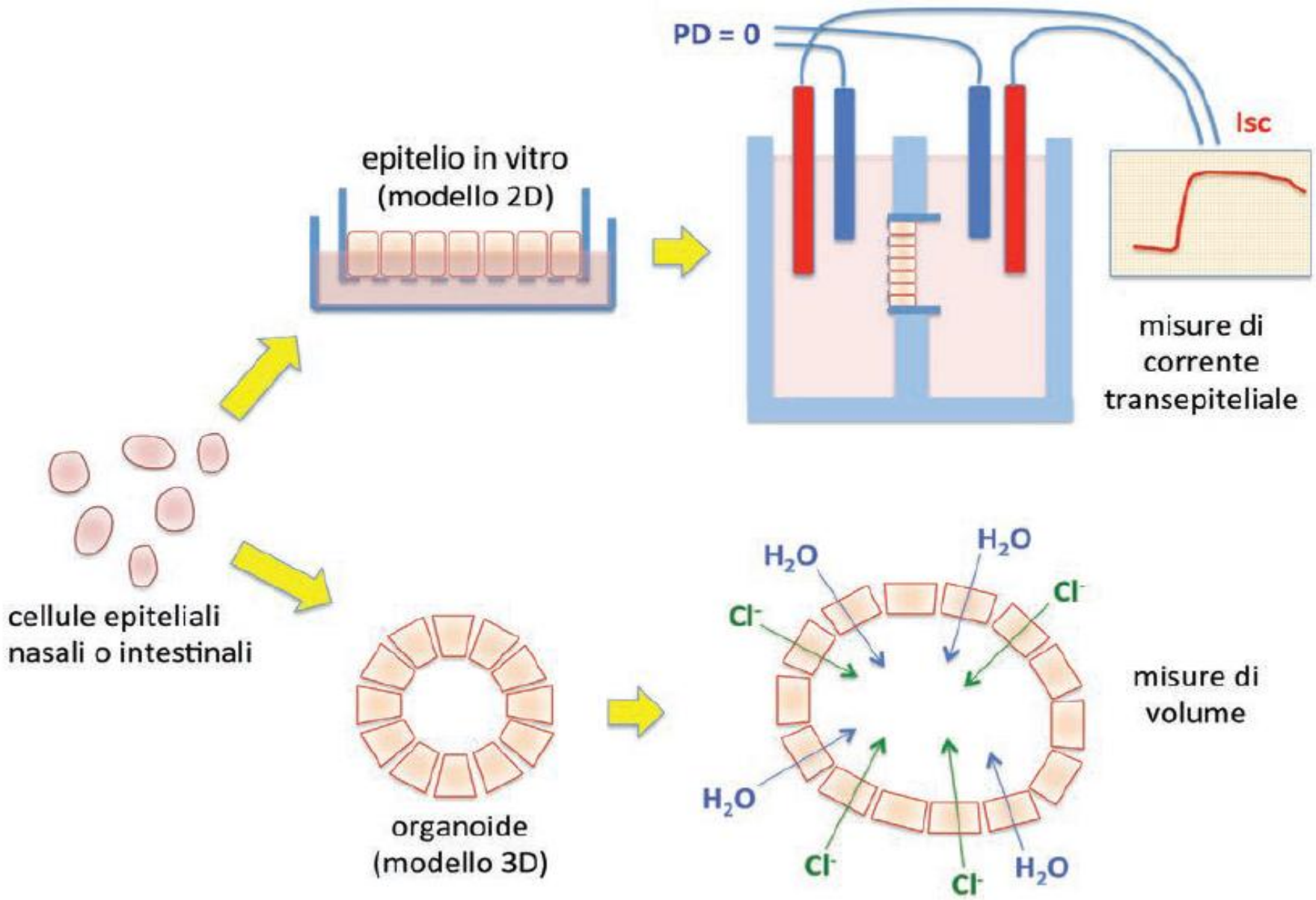
	fase
• VX-152	(2/3)
• VX-440	(2)
• VX-659	(2/3)
• VX-445	(1/2)
• ABBV/GLPG2737	(1)
• ABBV/GLPG3221	(1)
• FD2052160	pred.

Amplificatori: PTI-428 (fase 1)

Modulatori della proteina CFTR mutata per F508del e altre mutazioni.

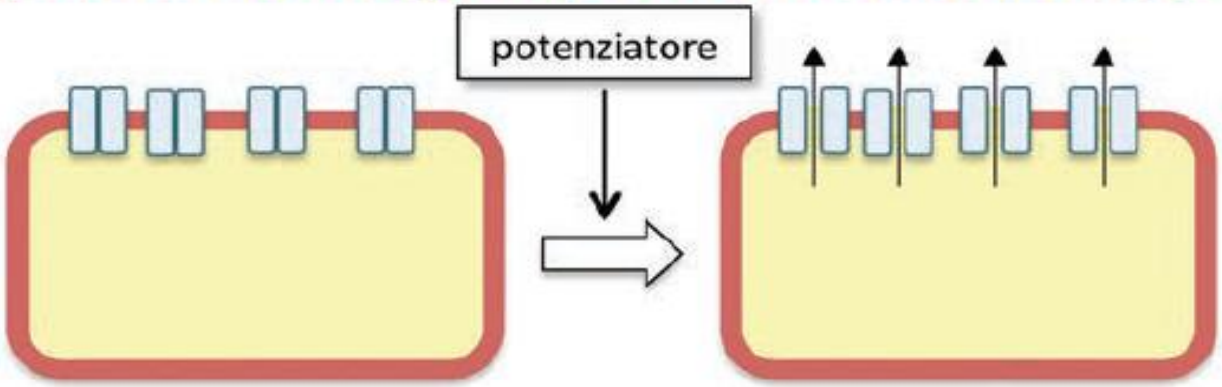
*I modulatori di CFTR mutata sono distinti in **Potenziatori (P)**, che intervengono su CFTR quando è sulla membrana della cellula, per potenziare la sua funzione di canale per il cloro, e in **Correttori (C1 e C2)** che intervengono nella maturazione di CFTR e nel suo percorso verso la membrana cellulare. Si ritiene che il meccanismo d'azione dei **Correttori C1 (Correttori di prima generazione)** sia rivolto direttamente a CFTR nelle prime fasi di maturazione fuori dal nucleo; quello dei **Correttori C2 (Correttori di seconda generazione)** sia rivolto alle proteine contenute nel citoplasma della cellula, che indirizzano CFTR sulla membrana o l'avviano alla degradazione. Una nuova categoria di modulatori, chiamati **Amplificatori** è in grado di aumentare la produzione della proteina CFTR, indipendentemente dal tipo di mutazione, e incrementa quindi l'azione di Potenziatori e Correttori.*

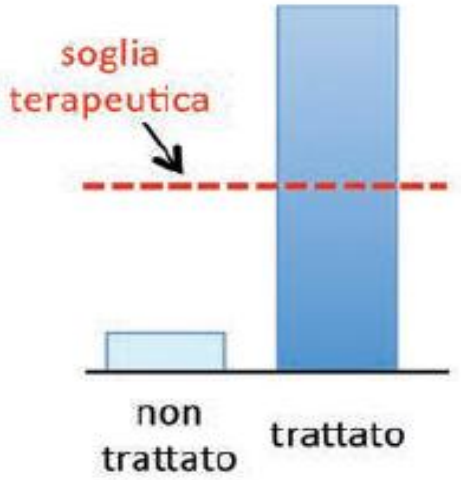
MODULATORI – "*In Vitro*"



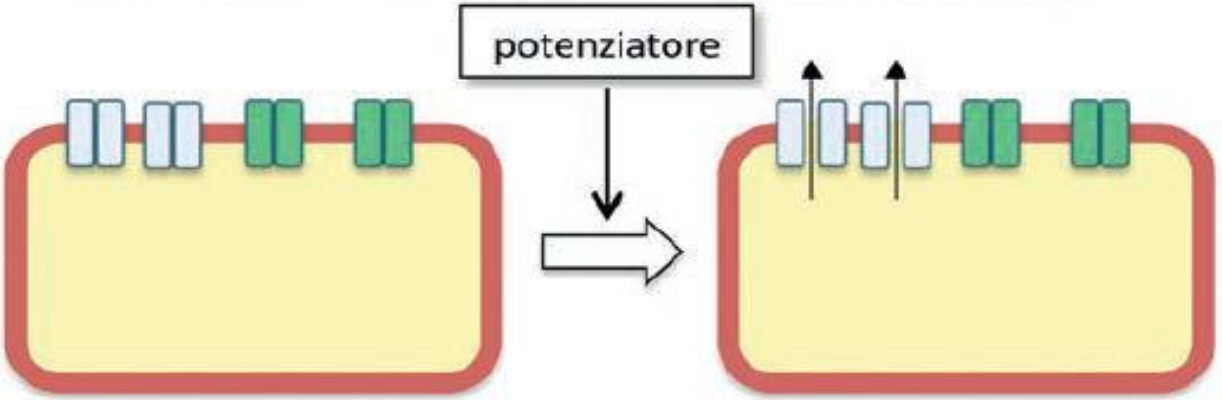
MODULATORI - *Effetti*

paziente omozigote per mutazione di classe 3

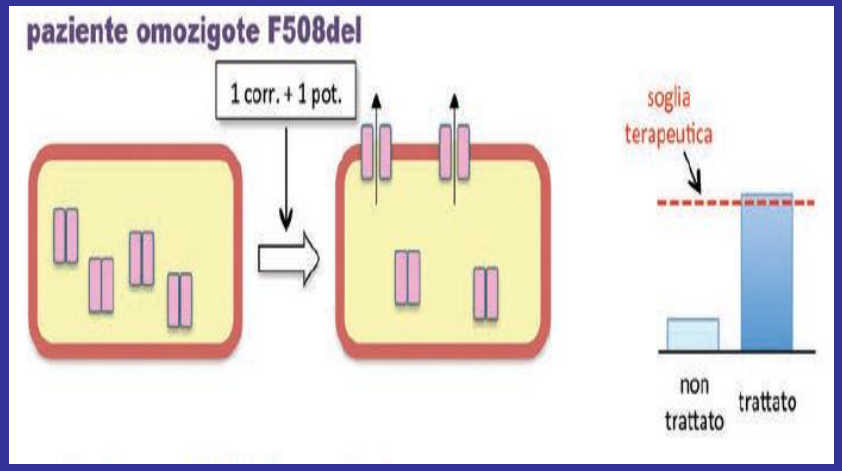


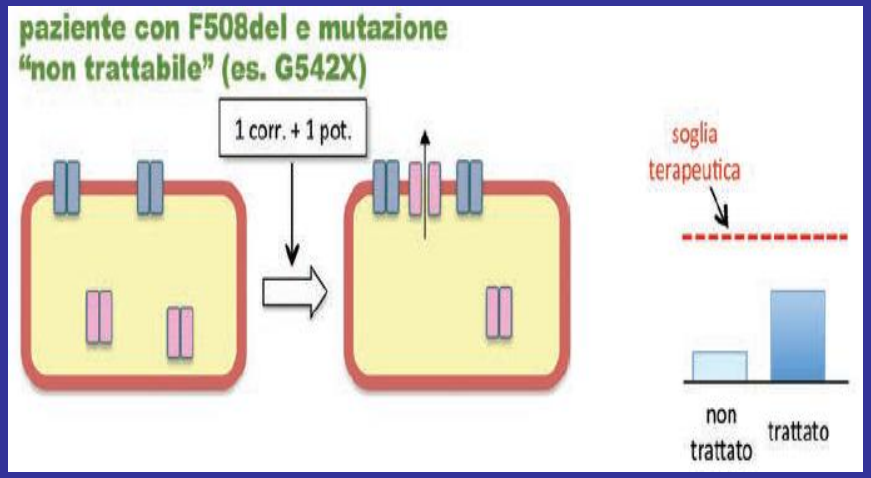


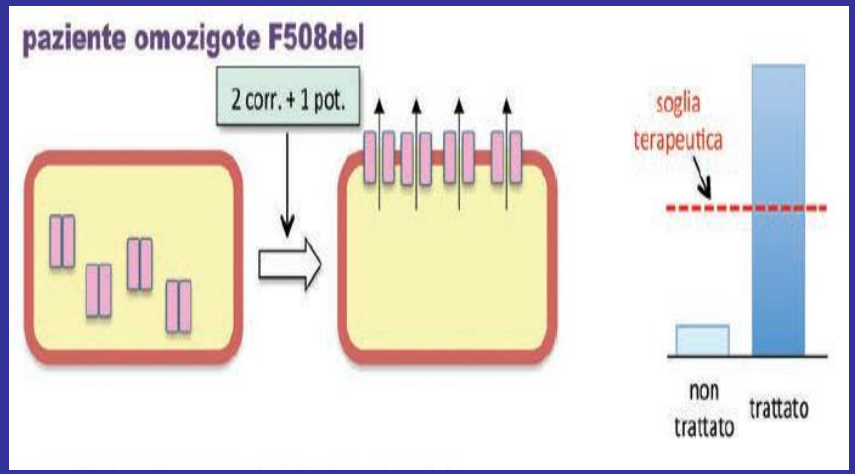
paziente con mutazione di classe 3 e mutazione "non trattabile" (es. G542X)

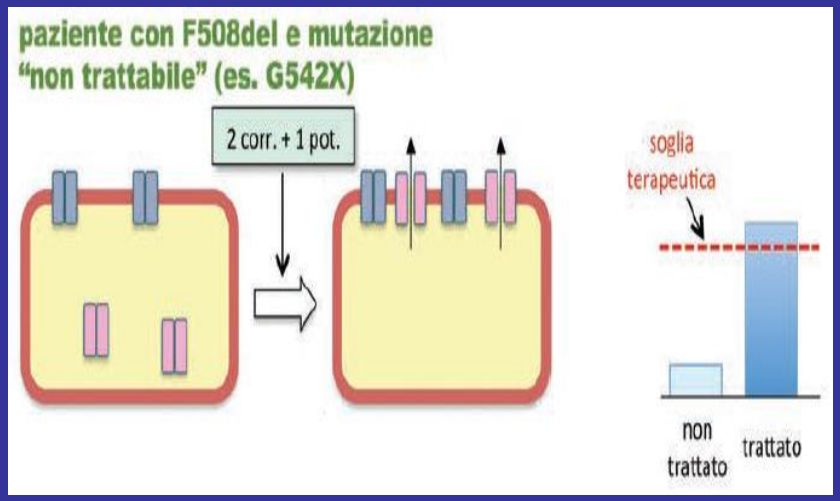


MODULATORI - *Combinazioni*

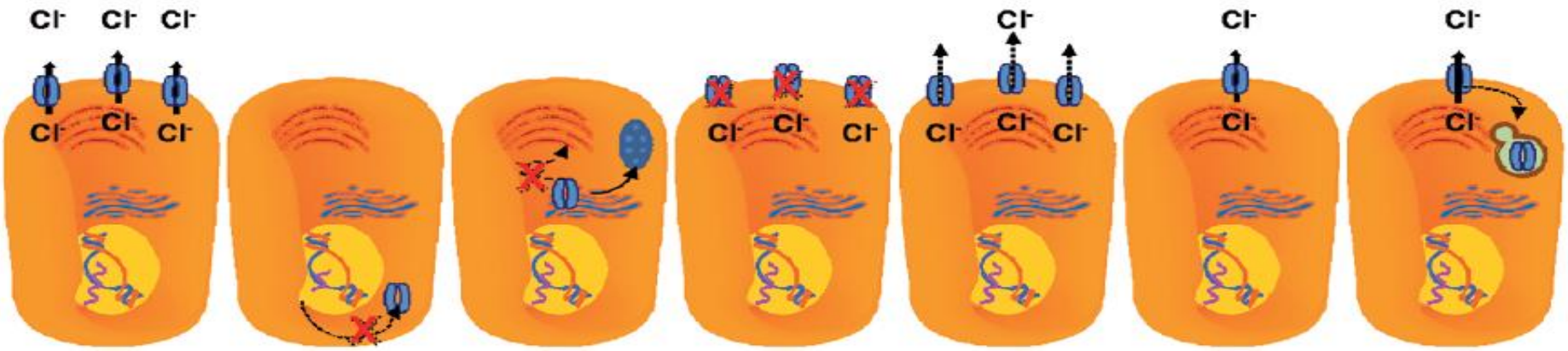








MODULATORI - *Riassunto*



CFTR	Classe I	Classe II	Classe III	Classe IV	Classe V	Classe VI
Tipo di difetto	Mancanza di sintesi	Difetto di ripiegamento	Mancanza di funzione	Ridotta funzione	Ridotta sintesi	Ridotta stabilità
Esempi di mutazioni	G542X R553X W1282X	G85E F508del N1303K	V520F S549R G551D	R117H R334W S1235R	A455E 2657+5G>A	Q1412X
Farmaci disponibili		Orkambi® Symdeko®	Kalydeco®	Kalydeco®		
Molecole in sviluppo	VX-659 MRT5005	VX-659 VX-445 FDL-169 GLPG2222 PTI-428 QR-010 PTI428 PTI801 MRT5005	VX-561 FDL-176 PTI808 MRT5005	VX-659 VX-445 QBW251 MRT5005	QBW251 MRT5005	MRT5005

BIBLIOGRAFIA

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Journal of Cystic Fibrosis 7 (2008) 179–196

Journal of Cystic Fibrosis
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Consensus on the use and interpretation of cystic fibrosis mutation analysis in clinical practice

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Journal of Cystic Fibrosis xx (2010) xxx–xxx

Journal of Cystic Fibrosis
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Review

Benchmarks for Cystic Fibrosis carrier screening: A European consensus document

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Guidelines for Diagnosis of Cystic Fibrosis in Newborns through Older Adults: Cystic Fibrosis Foundation Consensus Report

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(J Pediatr 2008;153:S4-S14)

European Journal of Human Genetics (2008), 1–15
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ARTICLE

Best practice guidelines for molecular genetic diagnosis of cystic fibrosis and CFTR-related disorders – updated European recommendations

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