Screening for Cystic Fibrosis

Guillaume Thouvenin
CF center
Hôpital Armand Trousseau - Paris
International Meeting on Pulmonary Rare Diseases 2019

SORBONNE UNIVERSITÉ
CRÉATEURS DE FUTURS DEPUIS 1257

Hôpitaux Universitaires Est Parisien
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VAINCRE LA MUCOVISCIDOSE

Conflict of interest

- **No direct conflict of interest related to the subject**

Screening for cystic fibrosis (CF)

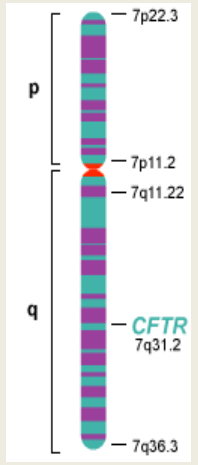
- Historical model of neonatal blood spot screening for pulmonary rare diseases
- Prooved efficacy of the model
- implemented in several countries all over the world
- Source of inspiration for others pulmonary rare diseases

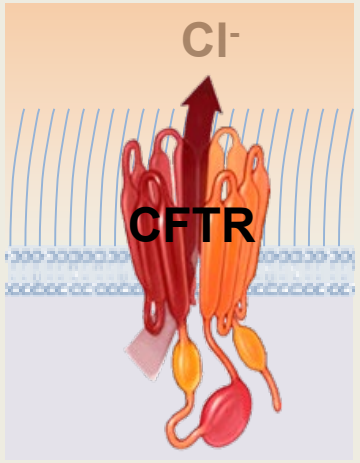
Screening for CF

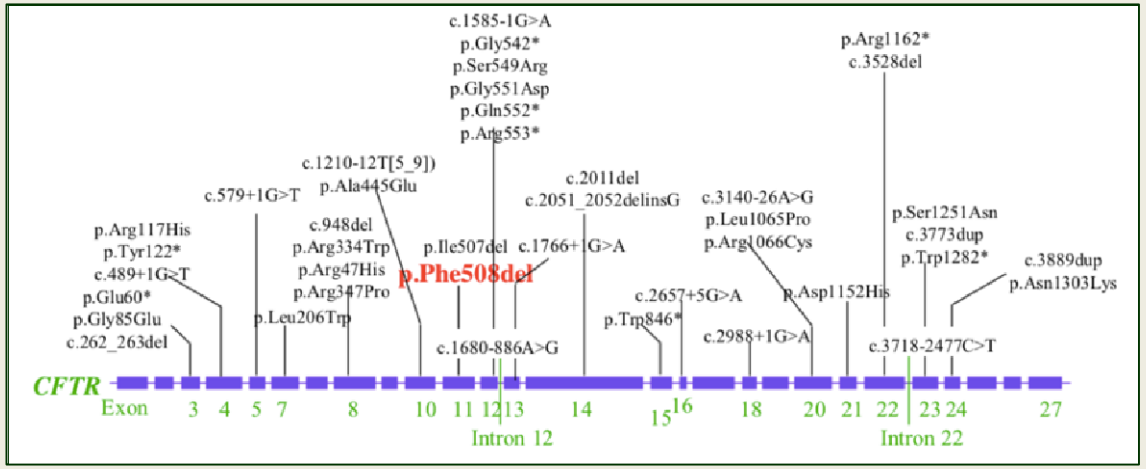
- CF screening algorithm
- Limits of the screening for CF
- Impact of the screening for CF patients
- Relevant for other rare pulmonary diseases ?

Cystic Fibrosis

- Cystic fibrosis in 1936
- CF as a genetic disease in 1946
- Sweat chloride test in 1948
- In the late 1970s, elevations in pancreatic immunoreactive trypsinogen (IRT)
- DNA mutation in chromosome 7 in 1989 (*CFTR* gene)



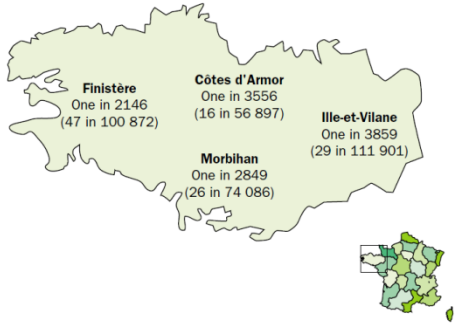




Crossley Lancet 1979
E. Girodon, Hôpital Cochin, Paris

Screening for CF in France

- 10 years experience of a exhaustive CF neonatal screening program in Brittany (1989-1998)
- 343 756 children
- 118 CF children
  - 112 positive neonatal screening tests (5 with negative sweat test)
- Incidence on prenatal diagnosis:
  - 39 / 134 couples with an affected child
- National CF neonatal screening program in 2002
  - Reduction in the age of diagnosis
  - Increase of life expectancy
  - Increase of quality of life
  - Reduce in morbidity in the early year of life (hospitalisations, nutritional and biochemical deficit)



Incidence of cystic fibrosis in Brittany, France, during 1989–98

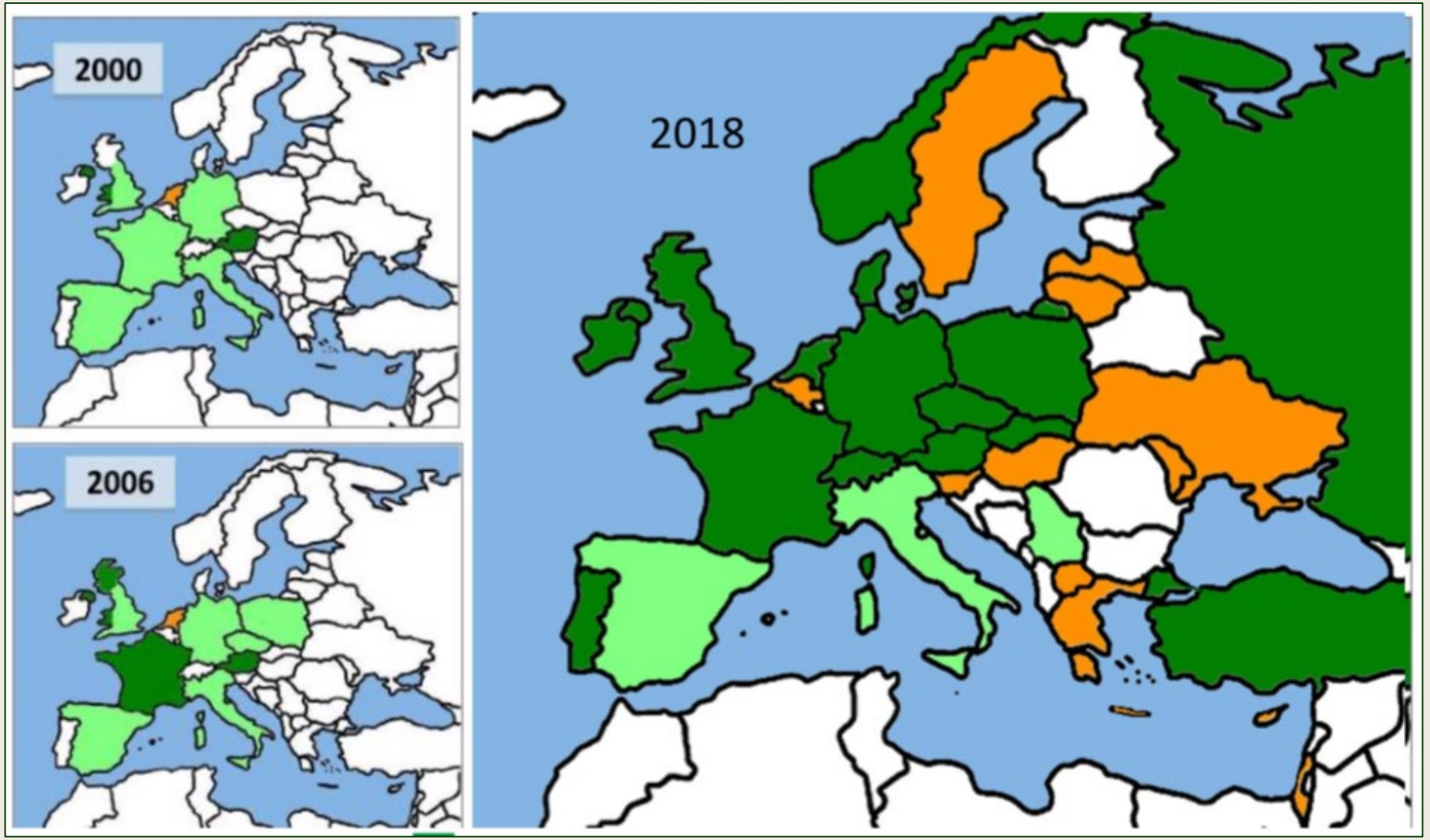
Genotype	Number of cases (n=117)	Mean (SD) immunoreactive trypsin concentration (µg/L)	Mean (SD) sweat chloride concentration (mEq/L)
ΔF508/ΔF508	62 (53·0%)	1513·1 (587·2)	100·6 (23·3)
ΔF508/other severe	28 (23·9%)	1347·1 (585·8)	97·3 (22·9)
ΔF508/other mild	13 (11·1%)	1261·8 (611·7)	66·9 (41·9)
Other severe/other severe	6 (5·2%)	1686·7 (607·6)	112·7 (26·7)
Other severe or mild/other mild	8 (6·8%)	1095·3 (500·1)	71·4 (28·8)

A CFTR mutation is "severe" when associated with pancreatic insufficiency. A "severe" genotype is the result of homozygosity for one severe mutation or compound heterozygosity for two severe mutations; a "mild" genotype results from the combination of two mild mutations or one mild and one severe mutation.

Table 2: **Immunoreactive trypsin and sweat chloride concentrations according to genotype**

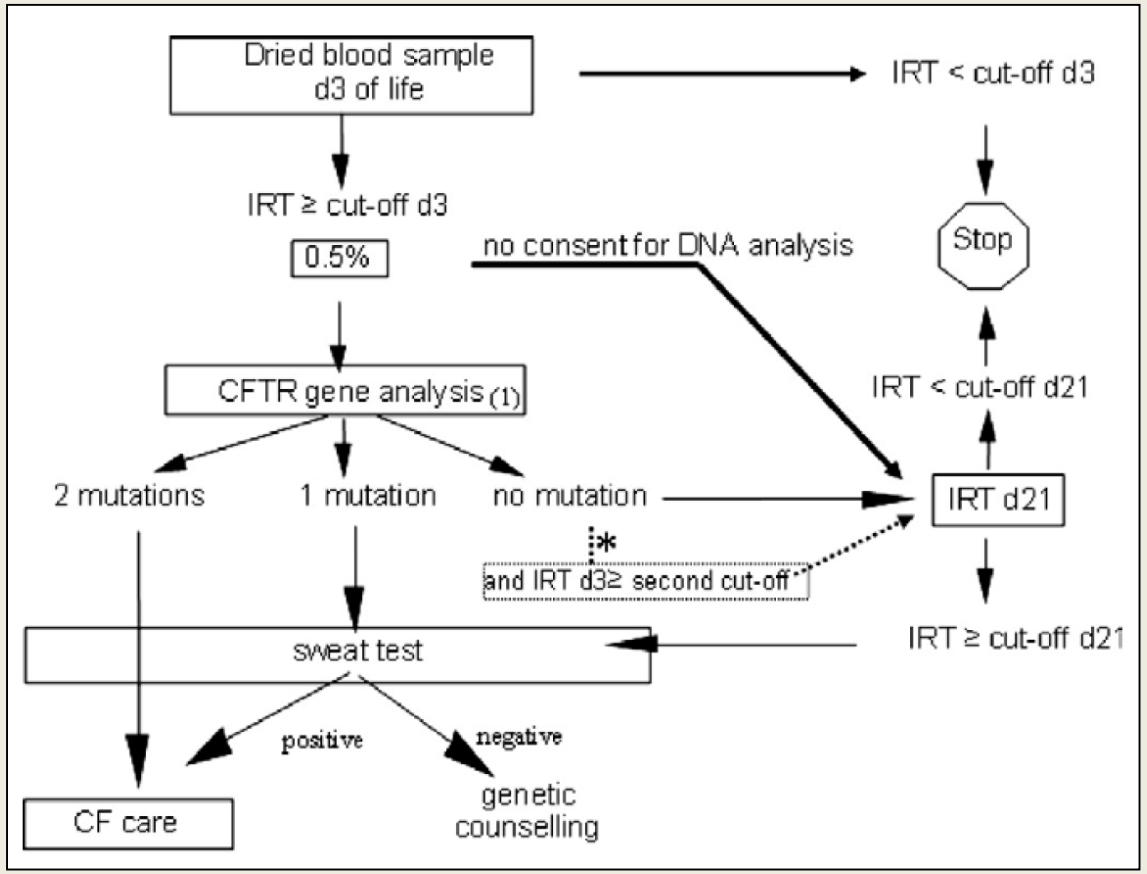
Chatfield, ADC 1991 *Wilken, Lancet 1995*
Farrell, NEJM 1997 *Scotet, Lancet 2000*

Expansion of national neonatal screening program for CF in Europe



Barben, JCF 2017

French screening algorithm for CF



- Spot blood test at day 3 (Guthrie)
- Informed consent form signed

- If positive CF screening test:
  - Parents phoned by nearest CF center team
  - Diagnosis process (sweat test)

- Central monitoring process:
  - Collecting data from screening laboratory centers
  - Collecting data from CF centers

  - Linked to French CF registry
  - Optimizing screening strategy

Munck, JPEDS 2008
Munck, J Med Screen 2017

ECFS best practice guidelines

Study period	2002–2014	2002–2004	2005–2014
Pending infant status			
N (% of referrals to a CF centre)	39 (0.5)	0	39 (0.75)
Positive predictive value (95% CI)	0.26 [0.25; 0.27]	0.16[0.15; 0.18]	0.31[0.30; 0.32]
Incidence [95% CI][a]	1/4913 [1/5135; 1/4709]	1/4374 [1/4824;1/4001]	1/5061 [1/5321;1/4825]
Number of newborn screened up to 2013	9,233,593	1,928,969	7,304,624
Diagnosis confirmed, N	1883	441	1442
(CF or CFSPID)	(1621 or 262)	(379 or 62)	(1242 or 200)
False negative w/o MI, PND, N	108	25	83
(*CF or CFSPID*)	(86 or 22)	(19 or 6)	(67 or 16)
Sensitivity overall (95% CI)	0.946	0.946	0.946
	[0.936; 0.956]	[0.926; 0.967]	(0.934; 0.957)

Table 3. Age and symptoms at initial visit to a CF centre of infants diagnosed with CF and identified CFSPID[a] (period 2002–2014, number of newborn screened: 10,046,581).

	CF	CFSPID	p-value
Number of cases with age reported, (%)	1378[b]/1474[c] (93.5)	245[b]/280[c] (87.5)	<0.001[f]
Age at initial visit, d[a]	35 [28; 45]	46 [35; 60]	<0.0001[e]
Seen at ⩽ 35 days, N (%)	735/1378[b] (53.3)	63/245[b] (25.7)	<0.0001[f]
Seen at ⩽ 56 days, N (%)	1211/1378[b] (87.9)	172/245[b] (70.2)	<0.0001[f]
Symptoms at initial visit, N (%)	1106/1765[d] (62.6)	25/280[d] (8.9)	<0.0001[f]

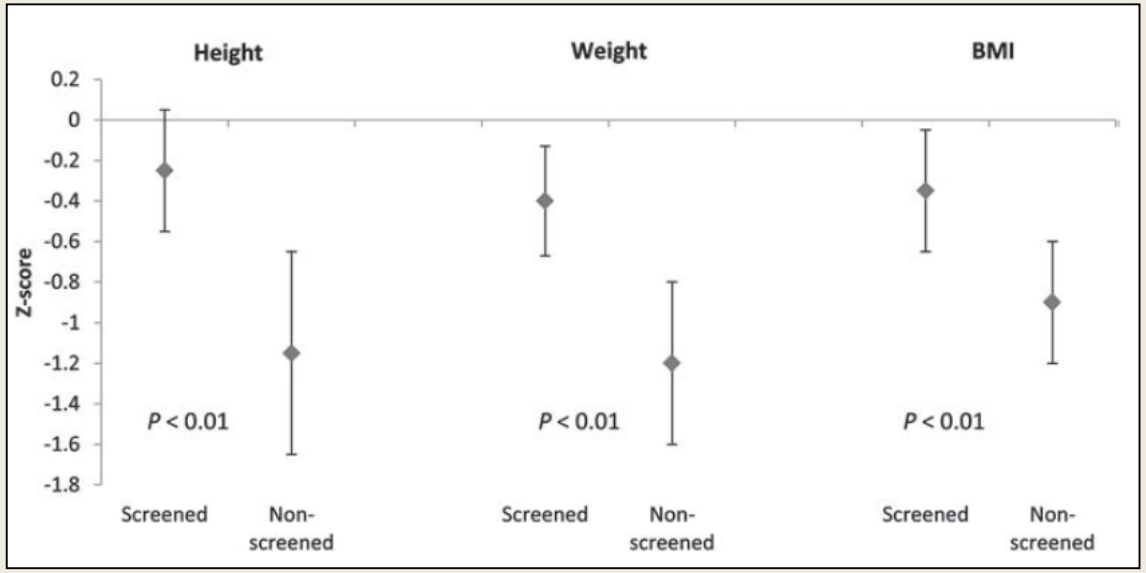
Castellani, JCF 2018 *Munck, J Med Screen 2017*

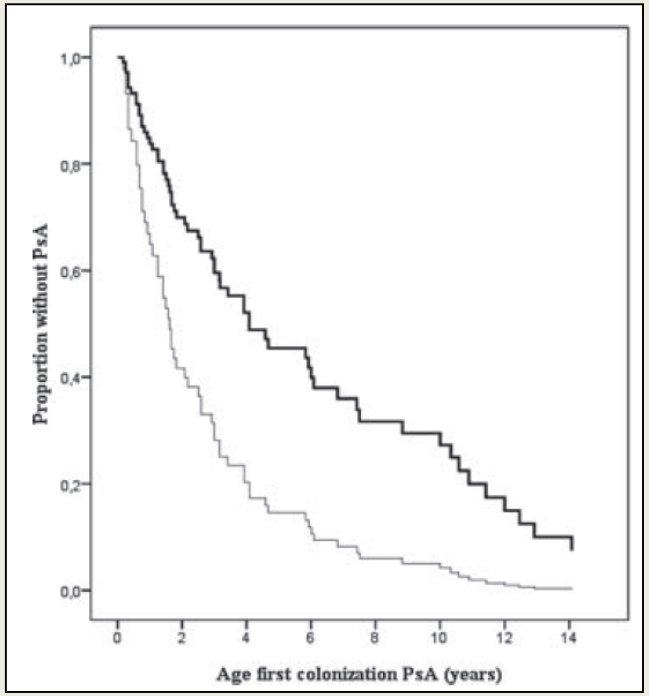
Limits

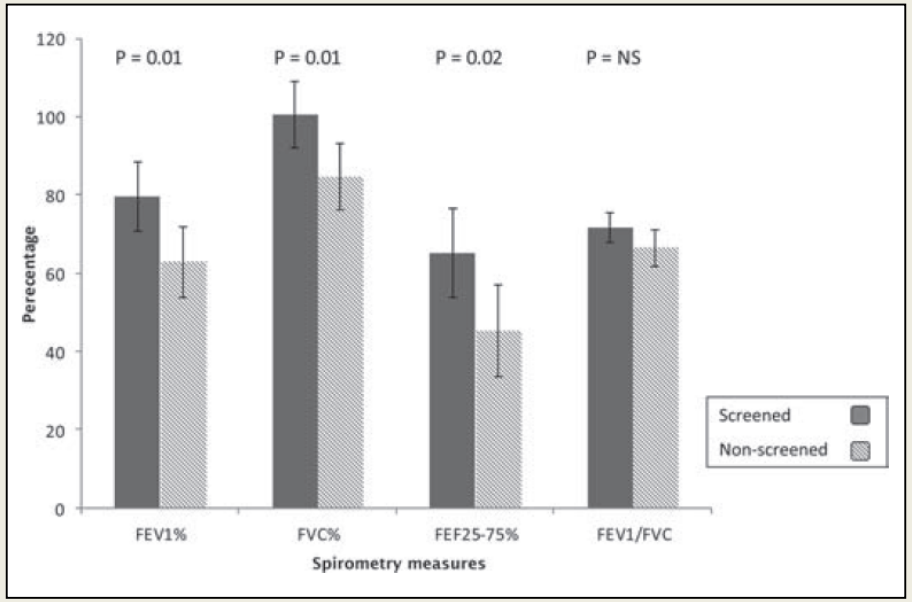
- **False positive test results**
- **Ethical problems of**
  - **CF carriers mutations without symptoms**
  - **Only detection of frequent mutations (ethnic minorities)**
- **Inconclusive diagnosis (CFSPID) : NBS screening positive**
  - **With negative sweat chloride test**
  - **Mutations without clear phenotypic characterisation**

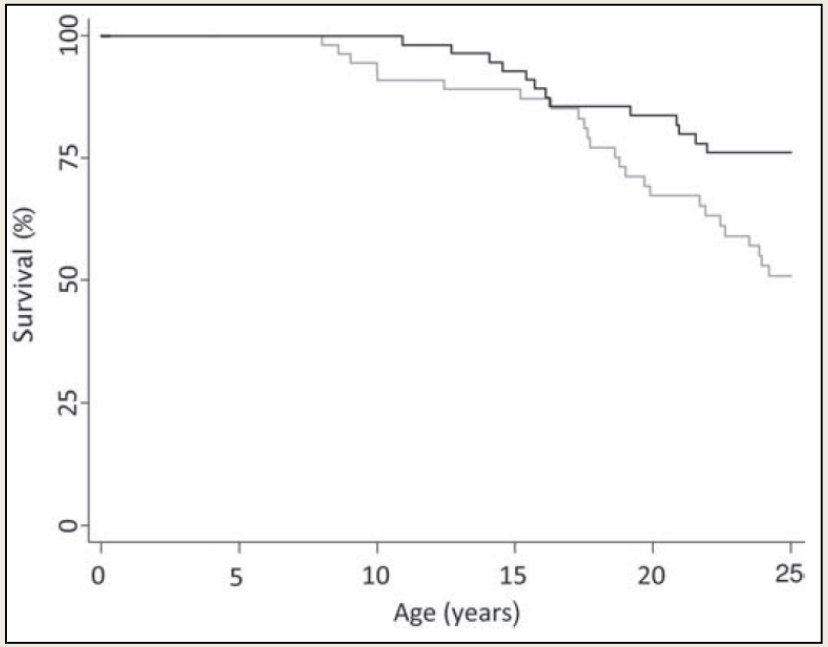
Cavanagh, J Gen Couns 2010
Sermet 2017
Sarles JCF 2014
Castellani, Lancet 2017

- New South Wales cohort (1981)
- Retrospective observational study
- 3 yrs before / after NBS
- 2 step IRT protocol
- Follow up from birth to 25 yrs old
- Age at diagnosis: 1.6 months vs 7,1 months









Dijk, Arch Dis Child 2011

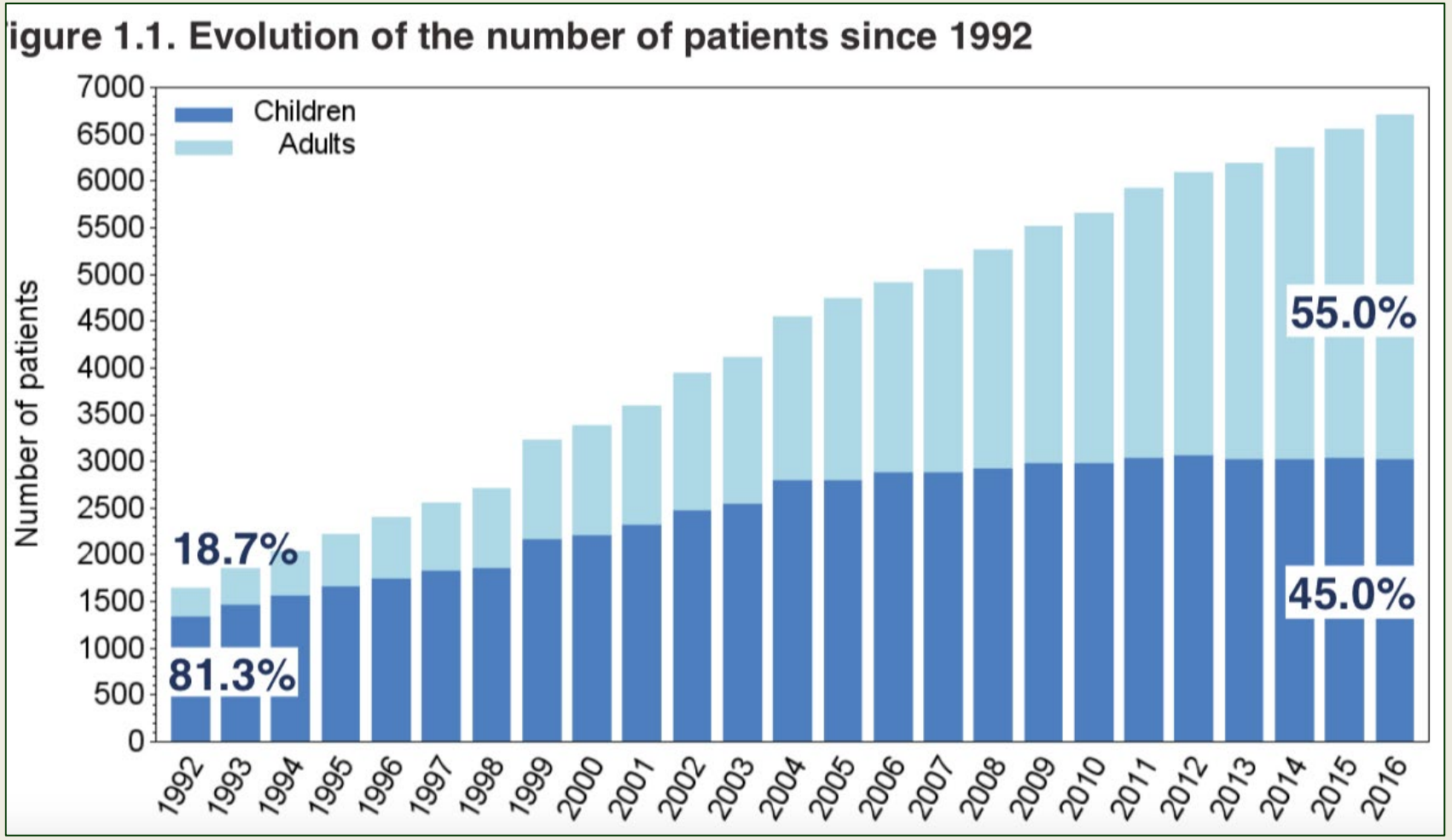
Impact for CF patients

- 12 studies comparing before / after neonatal screening for CF
- Survival improvement
- Respiratory improvement
  - Reduced airway inflammation
  - Improved lung structure
  - Improved lung function
  - Delayed chronic airway infection
  - Lower incidence of Pseudomonas airway colonization
- Nutritional improvement (in early life +++)
- Reducing hospitalizations
- Quality of life improved

VanDevanter, JCF 2016

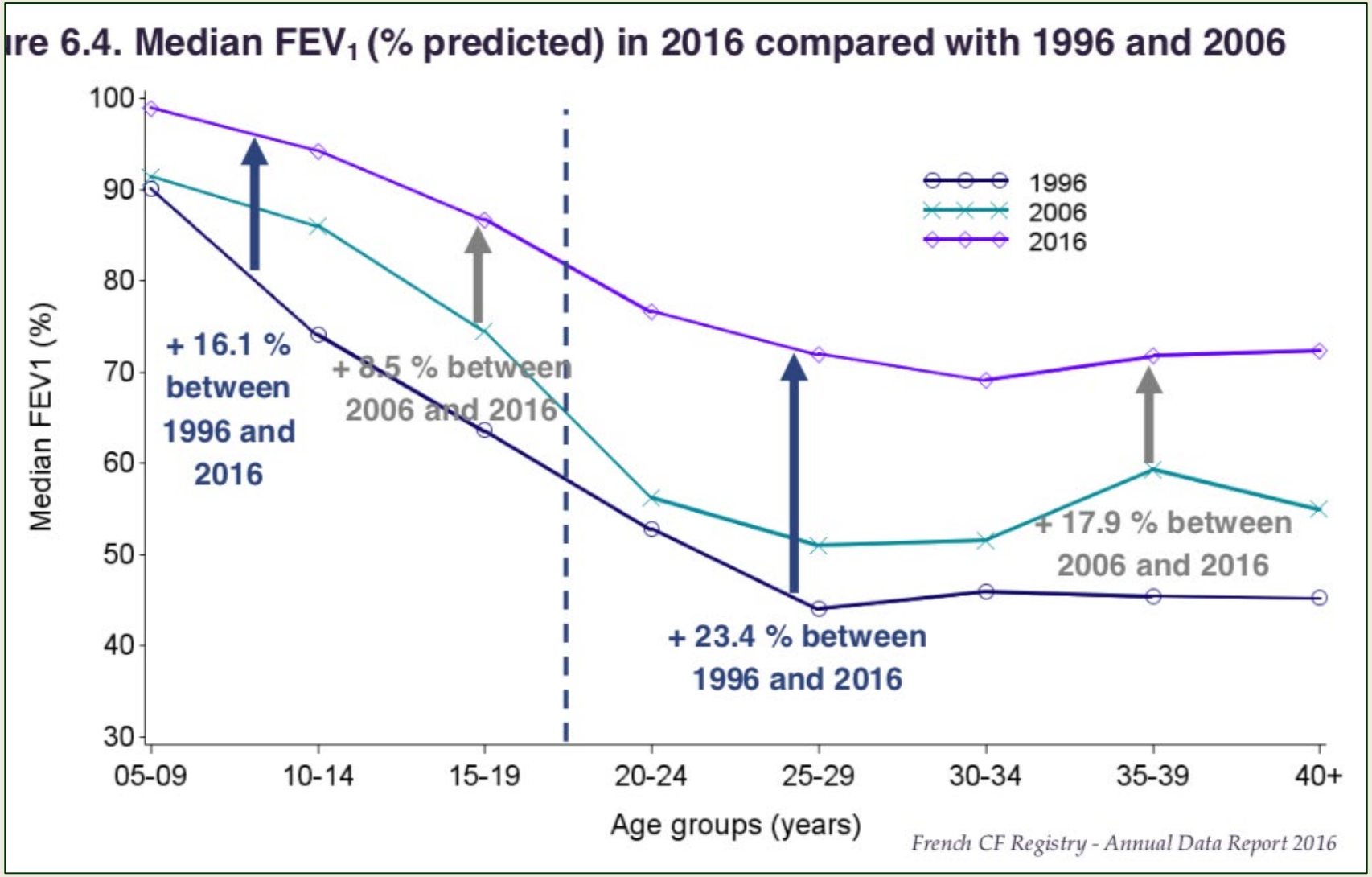
Bihouee 2014
Ramsey, AJRCCM 2014
Leung, JAMA 2017
Coffey, JPEDS 2017
Zhang, Pediatrics 2017
Tridello, EJR 2018

Demographic data

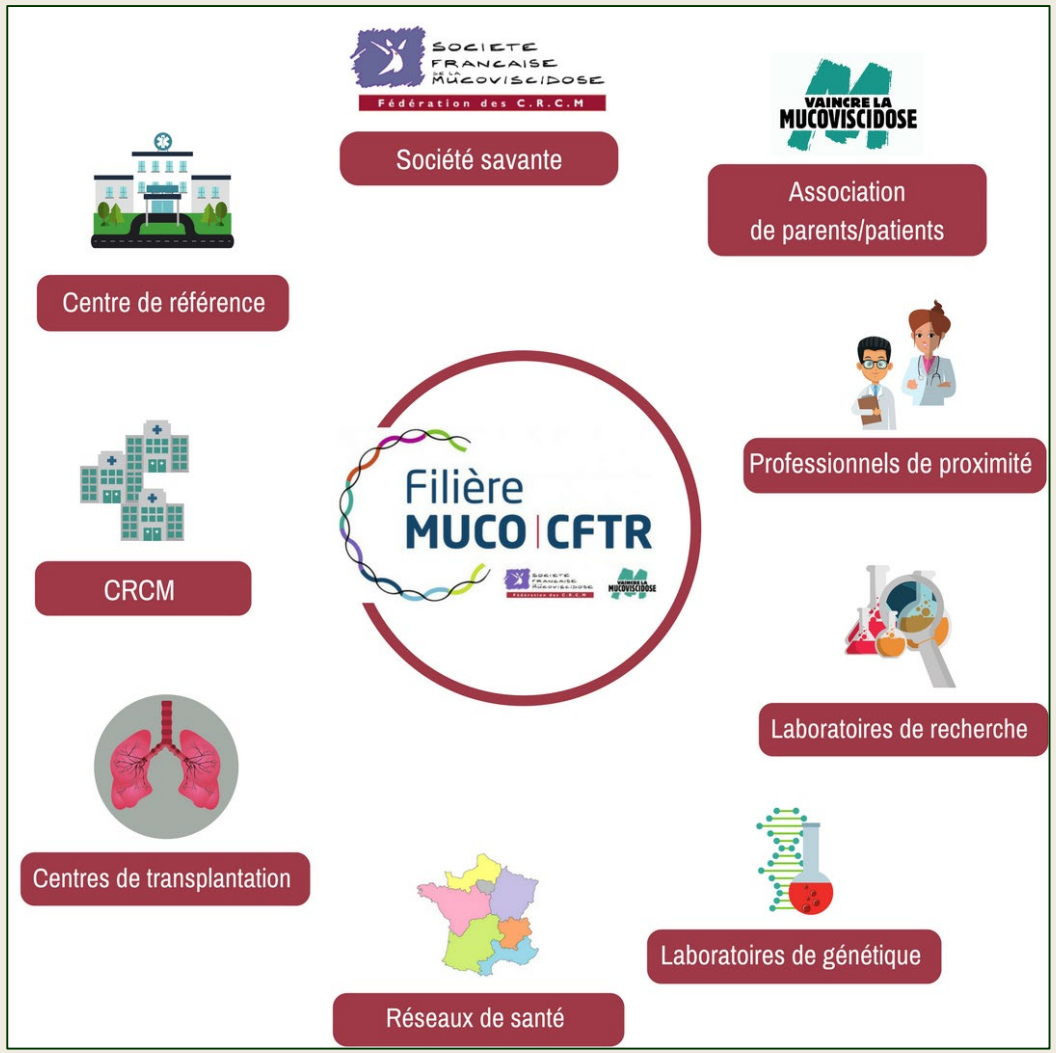


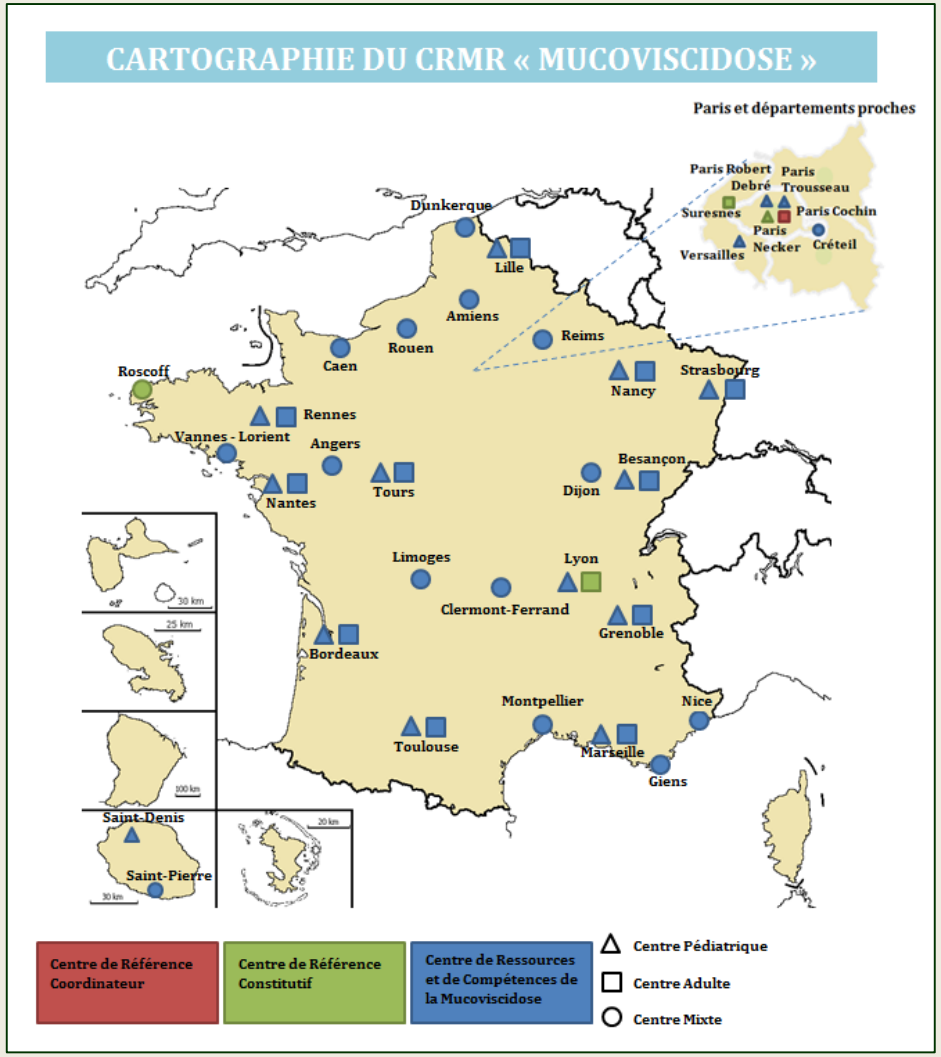
French CF registry data

Lung function tests



French CF network





National Network

- **Proactive multidisplinary approach**
- **Guidelines for diagnosis and management**
  - **National French guidelines 2017**
  - **Lahiri Pediatrics 2016**
  - **Farrell JPEDS 2017**
  - **NICE 2016 (Villanueva)**
- **Research project :**
  - **110 research teams in France**
  - **Exhaustive national registry**
    - ***Corvol et al., Nature Com 2015***
    - ***Munck et al., J Pediatr Gastroenterol Nutr 2018***
- **Patients education programs (Gethem®)**

Scully, Ann neurol 2015
https://muco-cftr.fr/

WHO screening criteria

Box 2. **Synthesis of emerging screening criteria proposed over the past 40 years**

- The screening programme should respond to a recognized need.
- The objectives of screening should be defined at the outset.
- There should be a defined target population.
- There should be scientific evidence of screening programme effectiveness.
- The programme should integrate education, testing, clinical services and programme management.
- There should be quality assurance, with mechanisms to minimize potential risks of screening.
- The programme should ensure informed choice, confidentiality and respect for autonomy.
- The programme should promote equity and access to screening for the entire target population.
- Programme evaluation should be planned from the outset.
- The overall benefits of screening should outweigh the harm.

Wilson and Jungner

Ask yourself the good questions

- **Does the disease fit the screening criteria ?**
  - **Severe disease ?**
  - **Impact of early diagnosis ?**
  - **Incidence of the disease (prenatal diagnosis) ?**
- **Does a reliable screening or diagnostic test exist ?**
  - **Is it easy to do ? (painless, available)**
- **Does a good medical support organisation exist ?**
  - **Or do you have to create it ?**
  - **Or an effective therapy (CFTR modulator therapies ?)**
- **Is it a cost-effectiveness strategy ?**

Van den Akker-van Marle, Pediatrics 2005
Sims, Lancet 2007

Thank you for your attention

Service de pneumologie
Hôpital Trousseau
Annick Clement
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Nadia Nathan
Aline Tamalet
Guillaume Aubertin
Jessica Taytard
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Corinne Troadec

CRCM Hôpital Trousseau
Virginie Travers
Melisa Zemouri
Cécile Combes
Alexia Challan-Belval
Sandrine Yadan
Béatrice Dubern
Patrick Tounian

Nicole Beydon

Equipe "Mucoviscidose : Physiopathologie & Phénogénomique"
Harriet Corvol
Loic Guillot
Olivier Tabary
Philippe Le Rouzic
Michel Chignard
Viviane Balloy
Julie Mesinele
Tobias Foussignière

UF de génétique moléculaire
Hopital Trousseau
Serge Amselem
Estelle Escudier
Marie Legendre
Gregory Jouvion

RespiFil - RespiRare
Céline Lustremant
Delphine Habouria
Barbara Girerd
Laura Downham
Flore Mathurin

French CF network

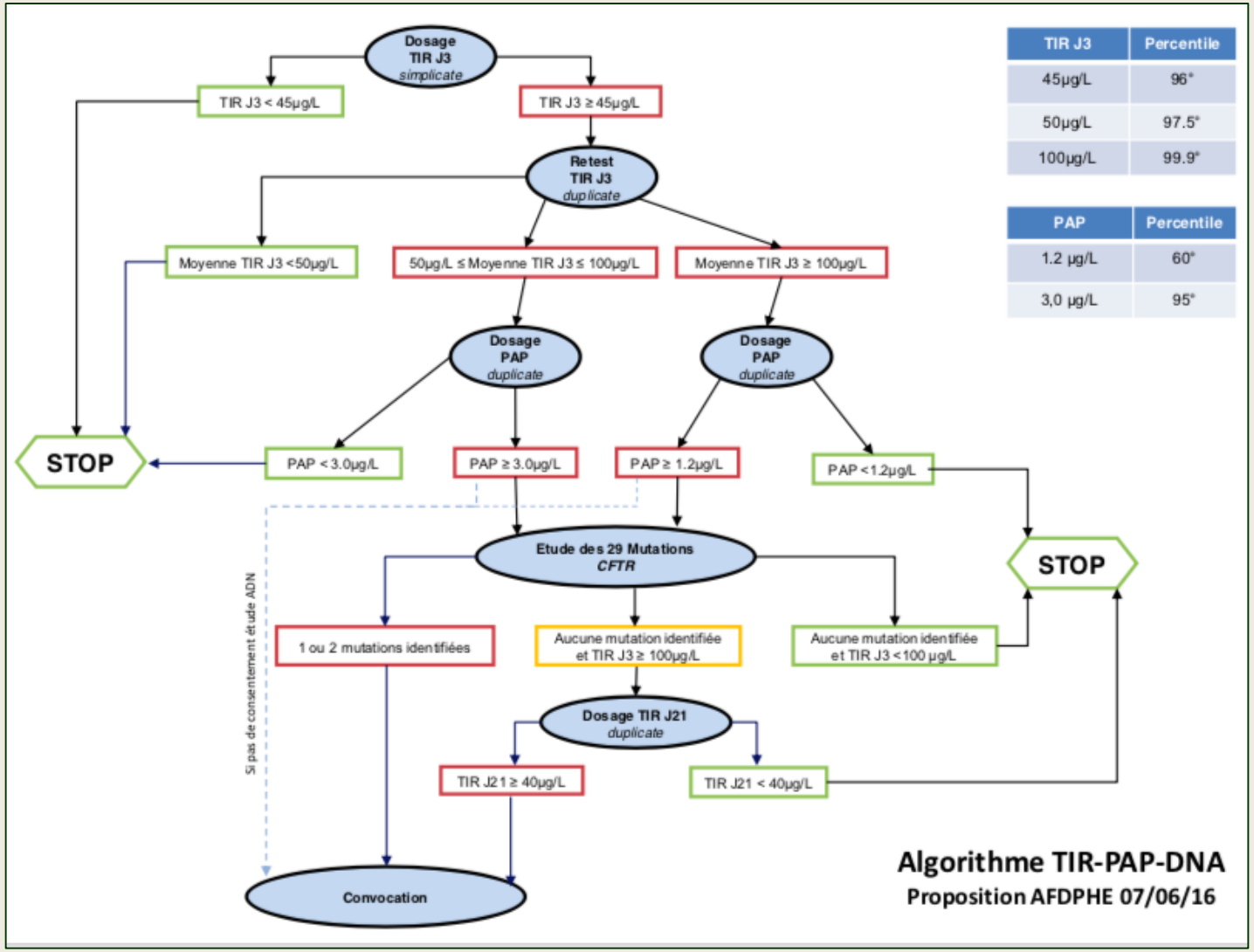
- Patients association in 1965
- Systematic neonatal screening in 2002
- CF network in 2002
- French CF society in 2004
- Filière muco CFTR in 2014 (PNMR2)

Conclusion

- **Screening for CF : a valid public health strategy**
  - **Severe and common disease**
  - **National CF network**
    - **Diagnosis**
    - **Monitoring and treatments**
  - **Registry and research**

Plan

- CF screening algorithm
- Impact of the screening for CF patients:
  - Benefits of early medical care
  - Research
- Limits of the screening for CF
  - Impact of the screening for non CF patients
  - Cost questions … ?
- Transposition for other rare pulmonary diseases ?
  - Network organization, registry
  - Disease severity
  - Homogenic model



TIR J3	Percentile
45µg/L	96°
50µg/L	97.5°
100µg/L	99.9°

PAP	Percentile
1.2 µg/L	60°
3,0 µg/L	95°

TIR-PAP/TIR-*CFTR* mutations

Avantages

- Porteurs sains non repérés
- Moins de CFSPID
- Un peu moins cher (TS)
- Plus éthique (minorités)

Inconvénients

- VPP basse
- Pas d'anticipation de qui a/n'a pas de mucoviscidose quand le TS échoue
- Pas de détection d'HZ pour les couples

- **Réception du courrier de l'ARDPHE/CRDN** (que je me suis envoyé)
  Vérification du dossier médical de l'enfant (CHU). Vivant et en bonne santé ?

- **Mini-staff : choix d'une date « Mucoviscidologue » (3) / Puer (3) - dispo 1/2j. Plan B proche prévu, si indisponibilité des parents**
- **Appel des parents, le matin vers 8h, le jour de convocation.**
  - Appel en N° masqué sur les numéros laissés sur le carton de DNN
  - Répétitiondesappelssiéchec;recherched'unelignefixe(Internet/MT);siéchec message laissé (« contrôle biologique »); si échec appel de N° non masqué; si échec envoie du MT au domicile.
  - Fiched'appelrenseignée.Echangeprogressif:contrôlebiologique/DNN/Muco nom du médecin / durée 2h / lieu de rencontre/numéro de tel.
  - Présencedes2parentsdemandée.

- **Réception des parents au CRCM.**
  - Entretien synthétique sur le motif d'appel (Pédiatre) et déroulement du test (PDE)
  - Démarragedutestdelasueur(1ou2)–1hautotal.Stim5mn+Reccueil30mn
  - Accompagnementpendanttouteladuréedutest;examenclinique;arbre généalogique; éventualités évoquées. Soit environ 3h.
  - Annonce du diagnostic. Propositions de dates à environ j3/j8. vs Cs génétique

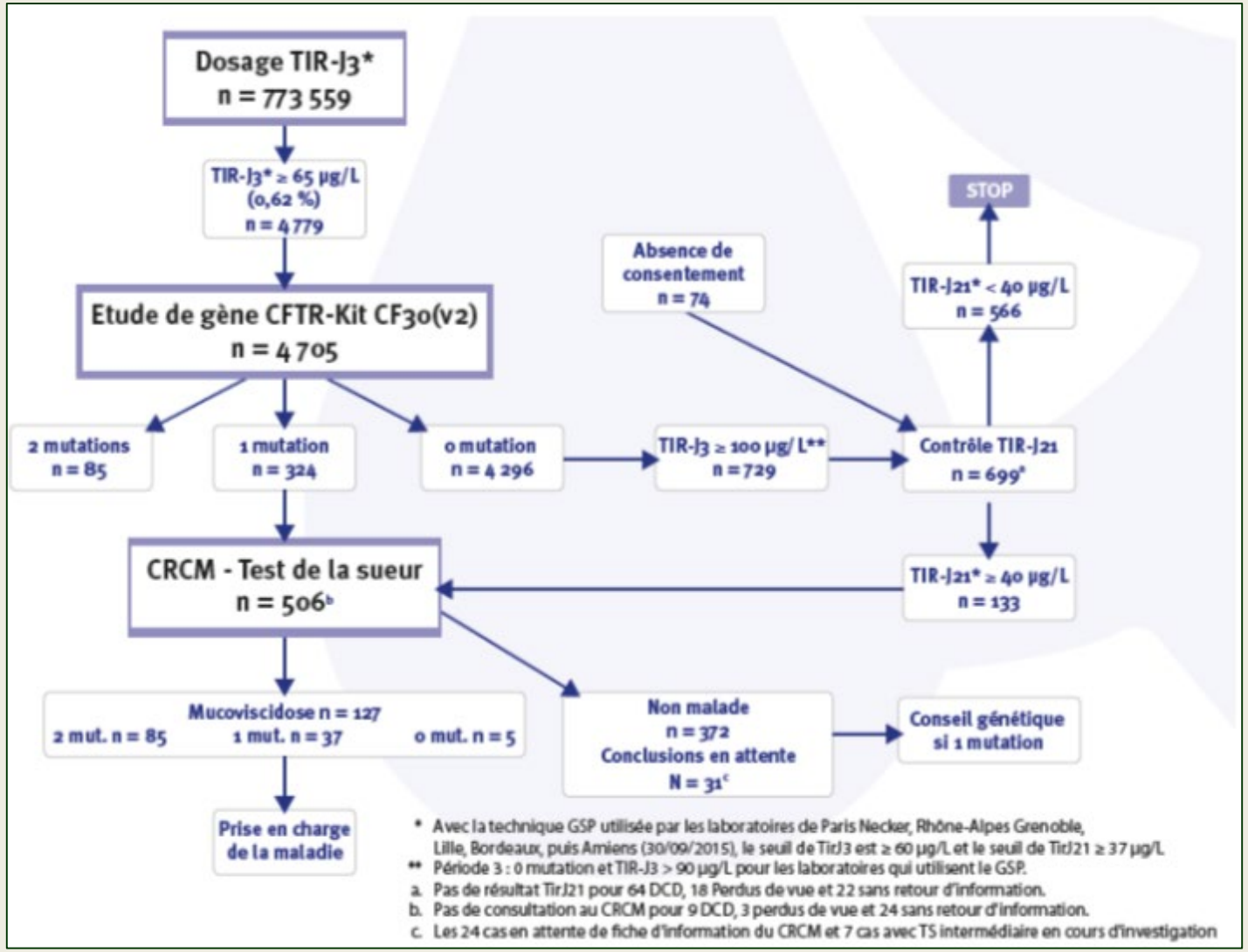
- **I. Premier contact:**
  - S'identifier clairement, décliner sa fonction, son lieu d'exercice,
  - s'assurer de l'identité de la personne qui répond au téléphone,
  - s'enquérir de la disponibilité du parent et de sa capacité à écouter.

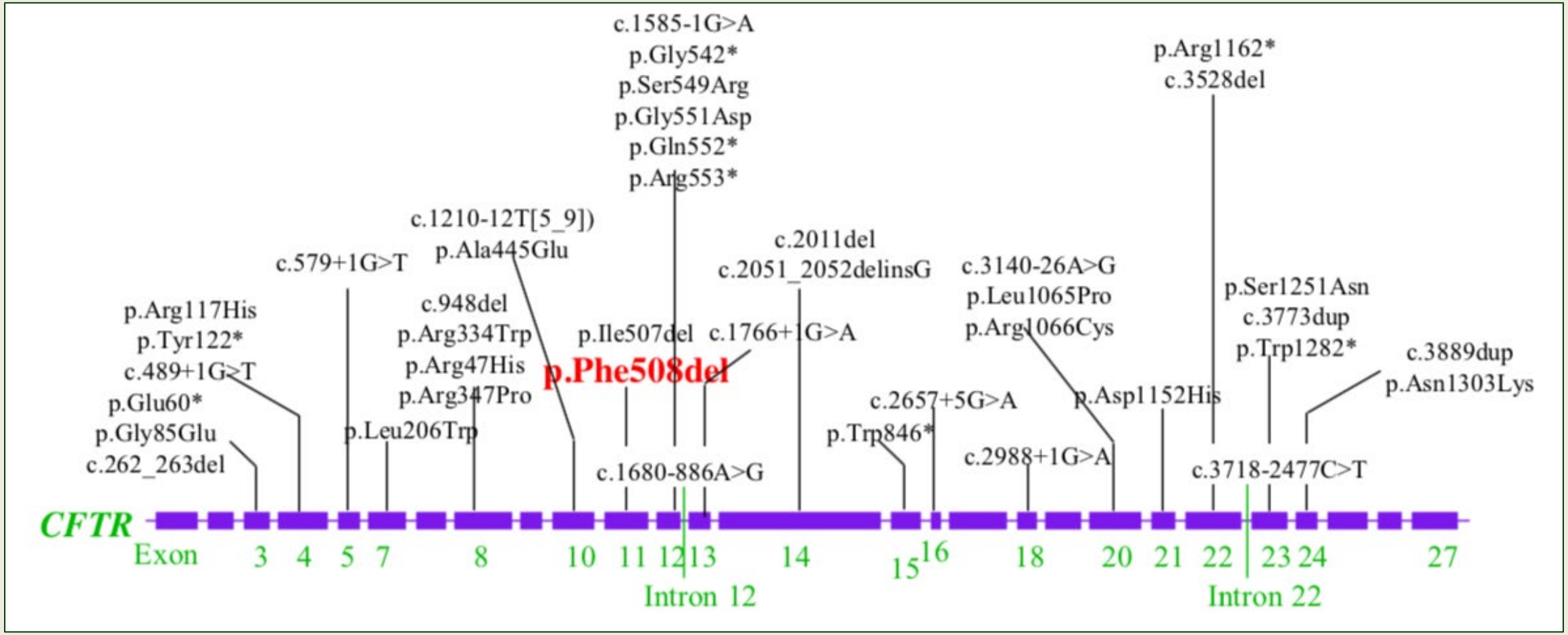
- **II. Annonce du résultat du Guthrie -> réalisation d'un test supplémentaire (sans pour autant cibler la mucoviscidose)**
  - Donner des informations claires, compréhensives et précises (poids des mots),
  - Répondre avec sincérité et loyauté.

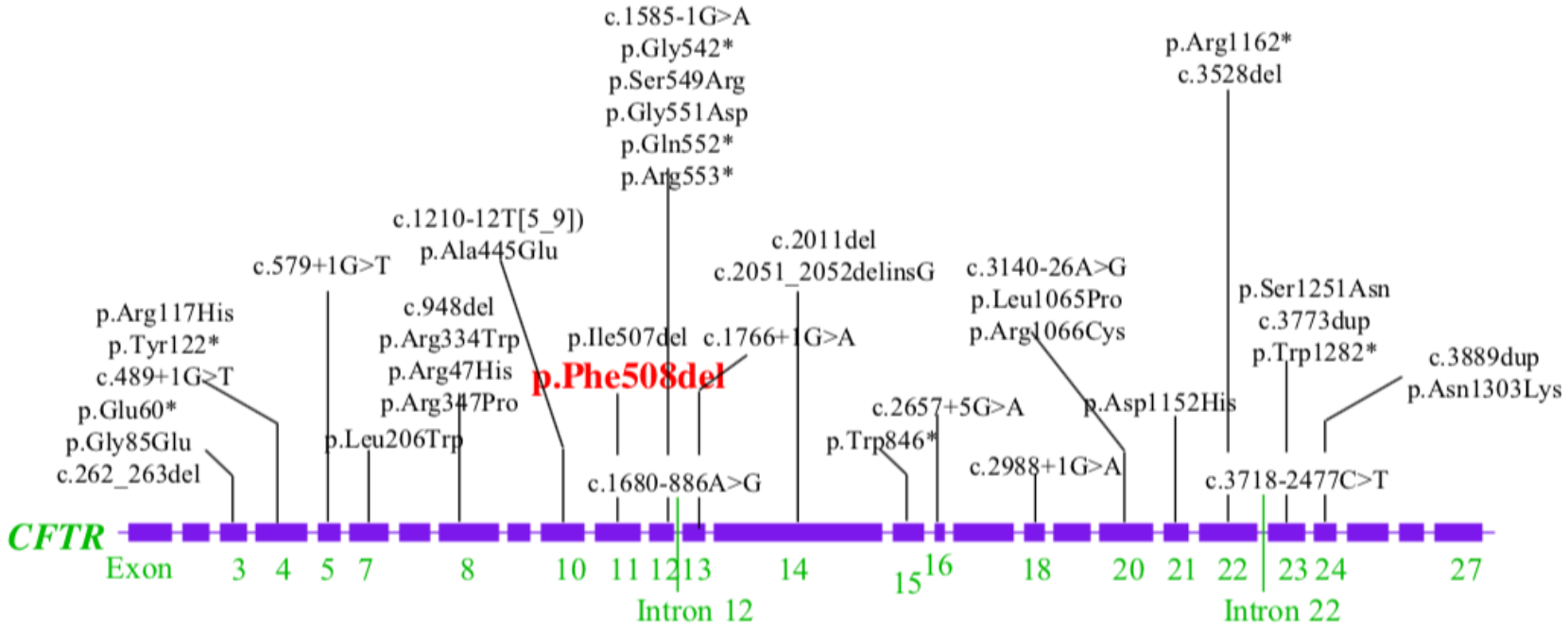
- **III. Informations sur le déroulement pratique du test -> 24 heures après**
  - Préciser le lieu du test, l'itinéraire jusqu'à l'HCE...
  - Stipuler par qui ils vont être accueillis, le caractère indolore du test, à quelle moment sera restitué le résultat, ce qu'ils doivent emmener (couches, lait...).
  - Donner un numéro de téléphone en cas de difficultés

- **IV Validation de la présence des deux parents**

2016


Dosage TIR-J3*
n = 773 559
TIR-J3* ≥ 65 µg/L
(0,62 %)
n = 4 779
Etude de gène CFTR-Kit CF30(v2)
n = 4 705
2 mutations
n = 85
1 mutation
n = 324
0 mutation
n = 4 296
Absence de
consentement
n = 74
TIR-J3 ≥ 100 µg/ L**
n = 729
Contrôle TIR-J21
n = 699a
STOP
TIR-J21* < 40 µg/L
n = 566
TIR-J21* ≥ 40 µg/L
n = 133
CRCM - Test de la sueur
n = 506b
Mucoviscidose n = 127
2 mut. n = 85
1 mut. n = 37
0 mut. n = 5
Non malade
n = 372
Conclusions en attente
N = 31c
Conseil génétique
si 1 mutation
Prise en charge
de la maladie
* Avec la technique GSP utilisée par les laboratoires de Paris Necker, Rhône-Alpes Grenoble, Lille, Bordeaux, puis Amiens (30/09/2015), le seuil de TirJ3 est ≥ 60 µg/L et le seuil de TirJ21 ≥ 37 µg/L
** Période 3 : 0 mutation et TIR-J3 > 90 µg/L pour les laboratoires qui utilisent le GSP.
a. Pas de résultat TirJ21 pour 64 DCD, 18 Perdus de vue et 22 sans retour d'information.
b. Pas de consultation au CRCM pour 9 DCD, 3 perdus de vue et 24 sans retour d'information.
c. Les 24 cas en attente de fiche d'information du CRCM et 7 cas avec TS intermédiaire en cours d'investigation


c.1585-1G>A
p.Gly542*
p.Ser549Arg
p.Gly551Asp
p.Gln552*
p.Arg553*
p.Arg1162*
c.3528del
c.1210-12T[5_9])
p.Ala445Glu
c.579+1G>T
c.2011del
c.2051_2052delinsG
c.3140-26A>G
p.Leu1065Pro
p.Arg1066Cys
p.Ser1251Asn
c.3773dup
p.Trp1282*
p.Arg117His
p.Tyr122*
c.489+1G>T
p.Glu60*
p.Gly85Glu
c.262_263del
c.948del
p.Arg334Trp
p.Arg47His
p.Arg347Pro
p.Ile507del
p.Phe508del
c.1766+1G>A
c.3889dup
p.Asn1303Lys
c.2657+5G>A
p.Trp846*
p.Asp1152His
p.Leu206Trp
c.2988+1G>A
c.1680-886A>G
c.3718-2477C>T
CFTR
Exon 3 4 5 7 8 10 11 12 13 14 15 16 18 20 21 22 23 24 27
Intron 12
Intron 22



- > **2000** variations de séquence (http://www.genet.sickkids.on.ca/cftr/)
- **Tous types** de variants ; variants ponctuels ++ dont faux-sens : 50%
- 50 délétions / duplications de grande taille
- Distribution et fréquence variables selon les origines géographiques / ethniques
- **Impacts variés** sur l'expression du gène et/ou de la protéine CFTR