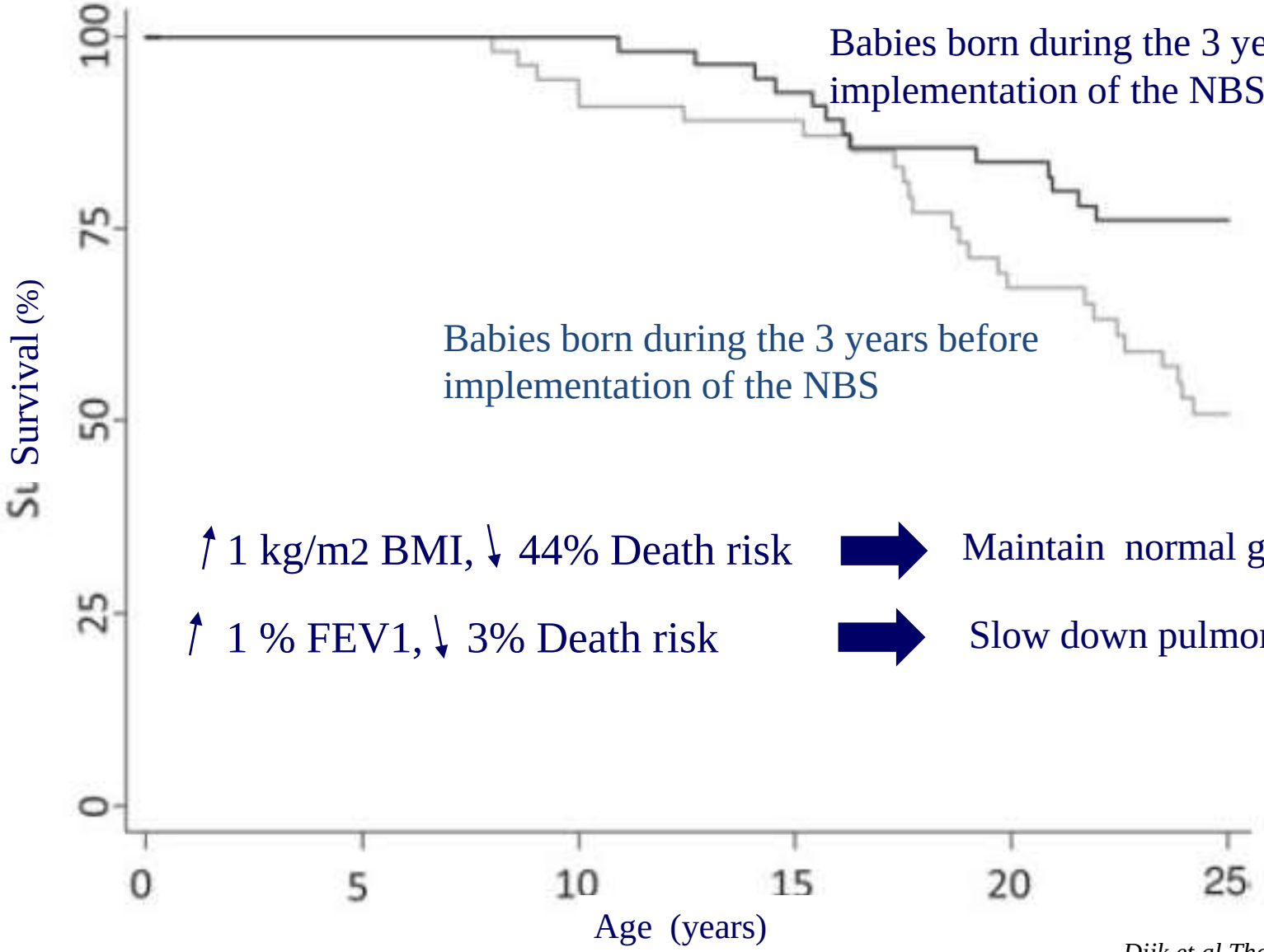
Neonatal screening in France
Main results and ethical challenges

I Sermet-Gaudelus, E Girodon, and
French working group for CF diagnosis

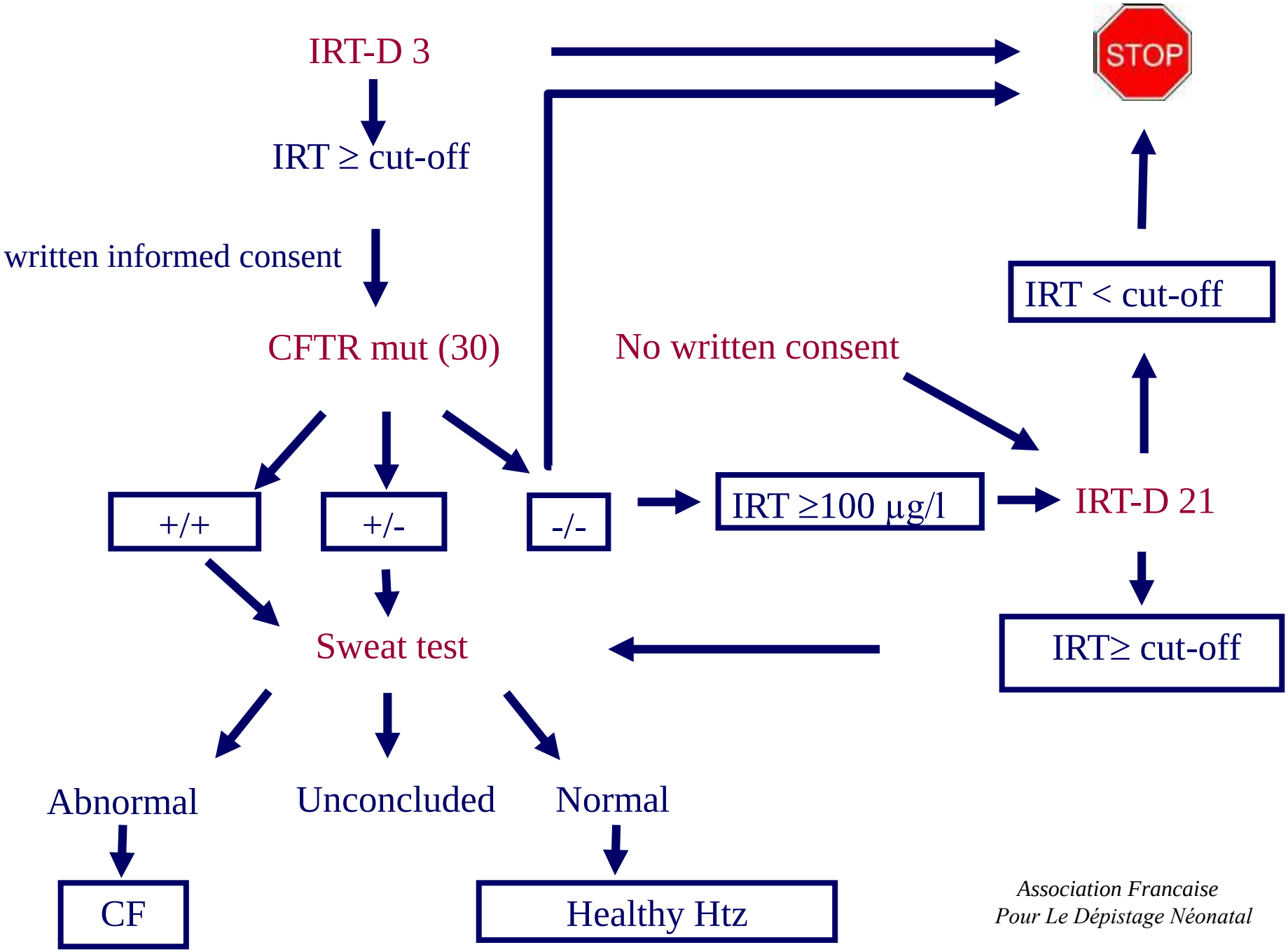
NBS improves survival
25 yrs follow-up of the Australian cohort



↑ 1 kg/m2 BMI, ↓ 44% Death risk → Maintain normal growth

↑ 1 % FEV1, ↓ 3% Death risk → Slow down pulmonary disease

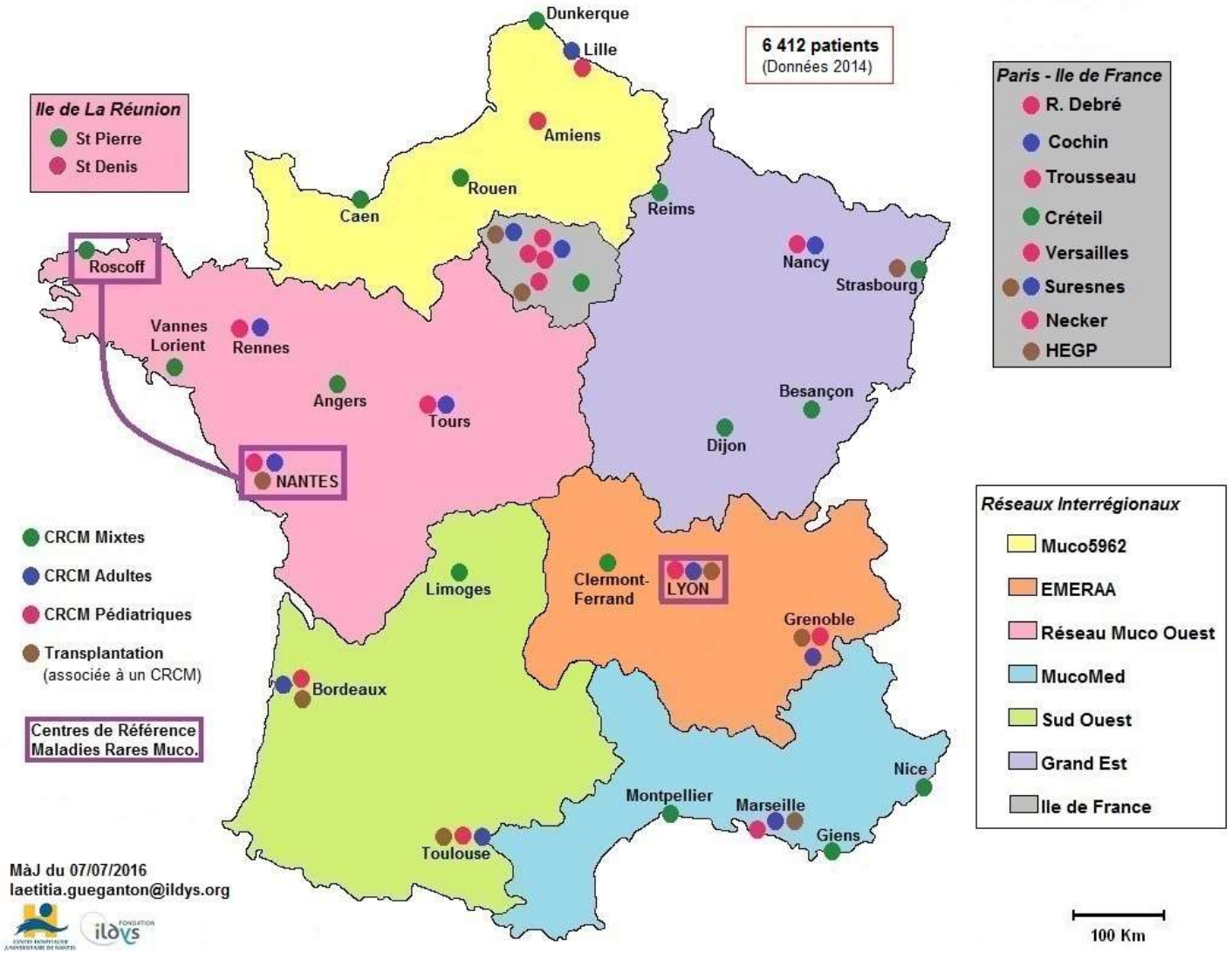
Dijk et al Thorax 2012


IRT-D 3
STOP
IRT ≥ cut-off
written informed consent
IRT < cut-off
CFTR mut (30)
No written consent
+/+
+/-
-/-
IRT ≥100 µg/l
IRT-D 21
IRT≥ cut-off
Sweat test
Abnormal
Unconcluded
Normal
CF
Healthy Htz
Association Francaise
Pour Le Dépistage Néonatal

	2002-2016	2003- 2004	2005-2016	p
NB screened	10,046,581	1,928,969	9,921,525	
+ IRT d3 (%NBS)	0.54	0.72	0.49	<0.0001
+ IRT d21 (%NBS)	0.019	0.063	0.009	<0.001
Infants referred at a CFC (% of positive IRT)	14.6	19.3	12.9	<0.0001
Diagnosis confirmed	2157	379	1686	NS
Incidence[95%CI]	1/4913 [1/5135;1/4709]	1/4374 [1/4824;1/4001]	1/5061 [1/5321;1/4825]	NS
PPV [95%CI]*	0.26 [0.25;0.27]	0.16 [0.15;0.18]	0.31 [0.30;0.32]	<0.0001
Sensitivity [95%CI]**	0.950 [0.939;0.960]	0.952 [0.931;0.973]	0.949 [0.937;0.961]	NS

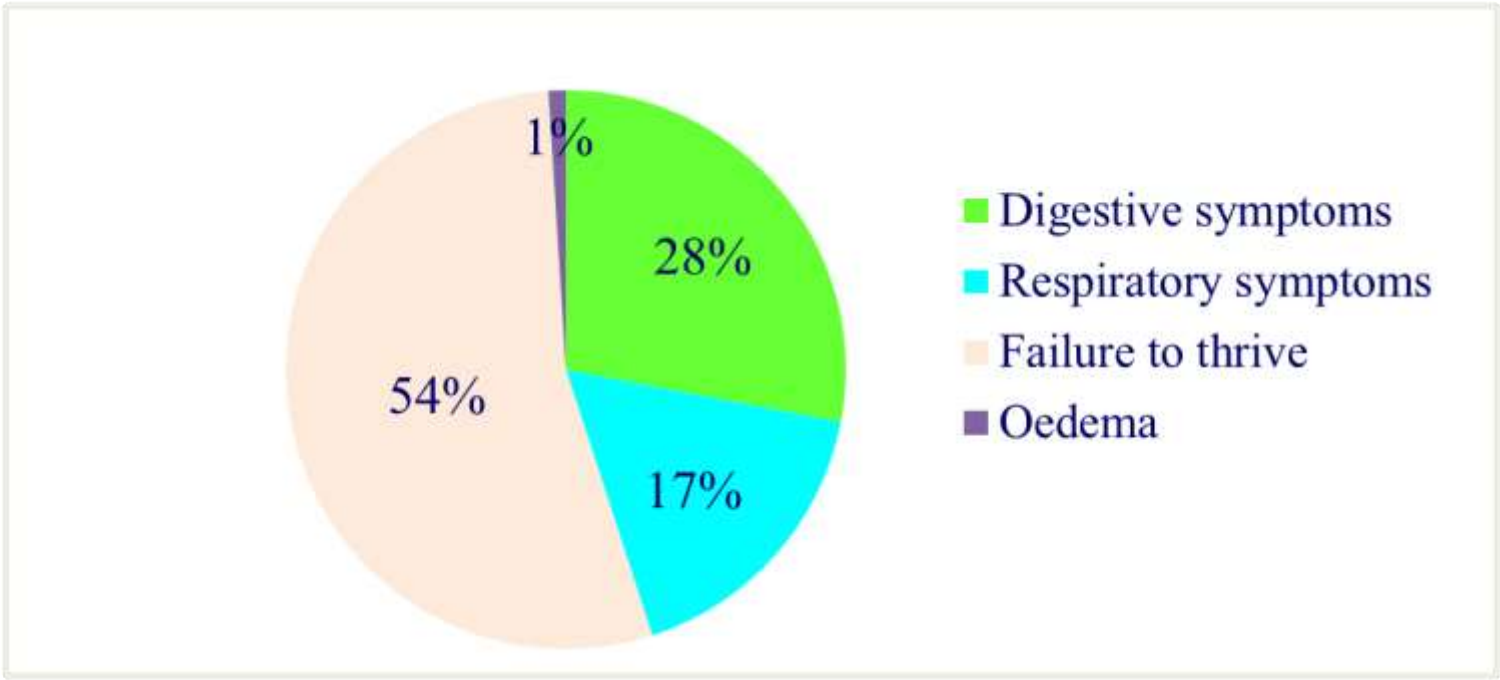
*True diagnosis from the number of positive tests
**Positive tests/ nbre of CF patients

Equity in access to care



First visit and initial follow up

Age at initial visit, d	35[28;45]
-seen ≤35 days, %	53
-seen ≤56 days, %	88
Symptoms at initial visit,%	63



Société Francaise de Mucoviscidose

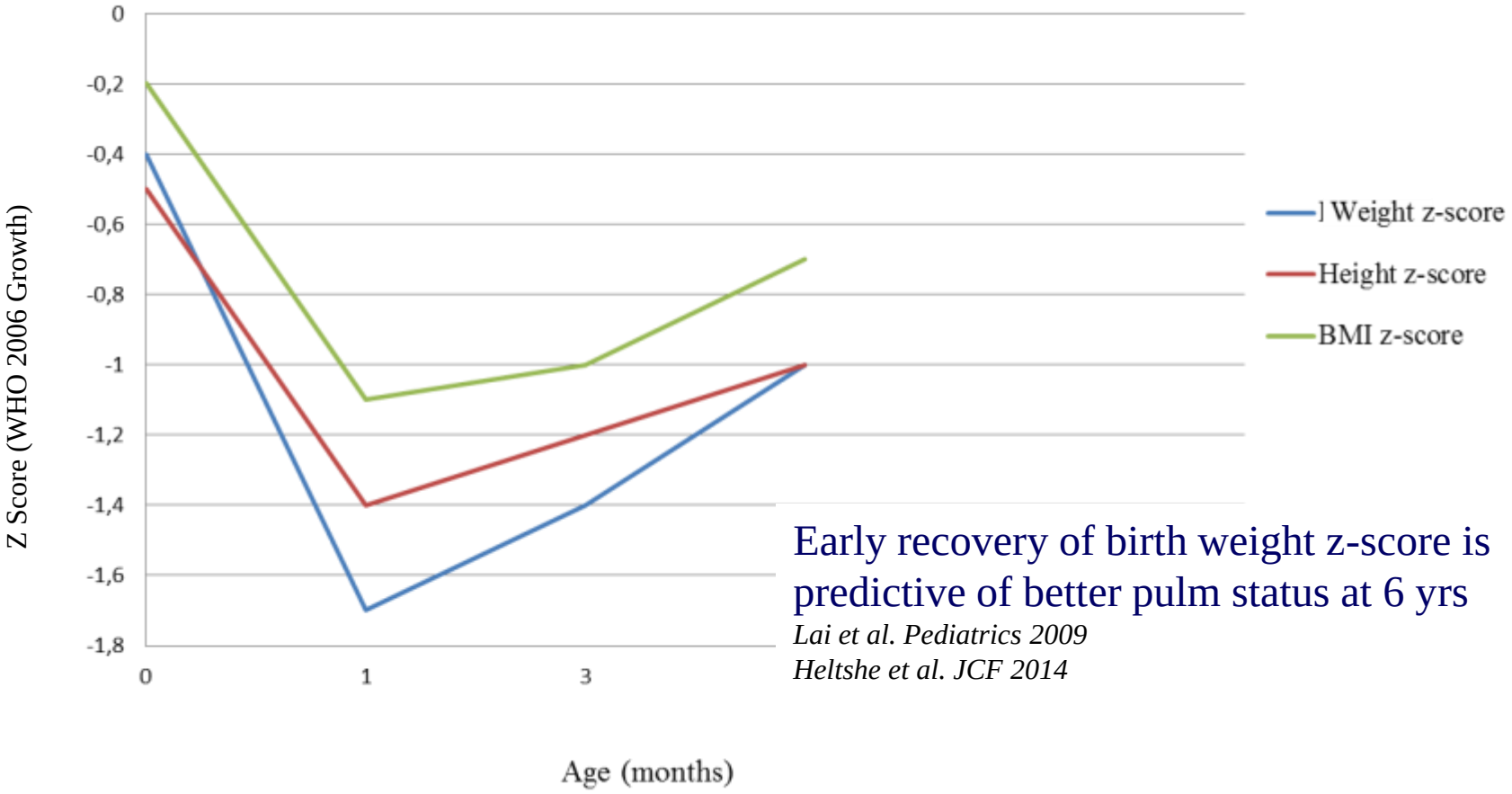
Digestive evaluation

	Initial 1.2 [1-1.05]	M3 3.1[2.8-3.3]	M6 6 [5.7-6.5]
Stools Liquid/Normal (%)	68/27	51/45	39/52
Median number/day	5 [3-6]	3[2-4]	2[2-3]
Elastase < 200µg/g (%)	79		81
Hb < 12 g/dl (%)	23		0
Albuminémie < 30 g/l (%)	9		0
Vitamine A < local threshold (%)	40		19
Vitamine E <local thershold (%)	30		4
Vitamine D < 30 ng/ml (%)	63		43

Feeding

	Initial	M3	M6
Breast Feeding (%)	43	28	21
Excl/non excl (%)	66/34	54/46	48/52
Enriched calories (%)	0	7	29
Enriched NaCl (%)	0	71	90
Bottle (%)	57	73	80
Enriched calories (%)	0	38	47
Enriched NaCl (%)	0	88	93

Initial growth
No catch up at 6 months (ongoing study)



Early recovery of birth weight z-score is predictive of better pulm status at 6 yrs

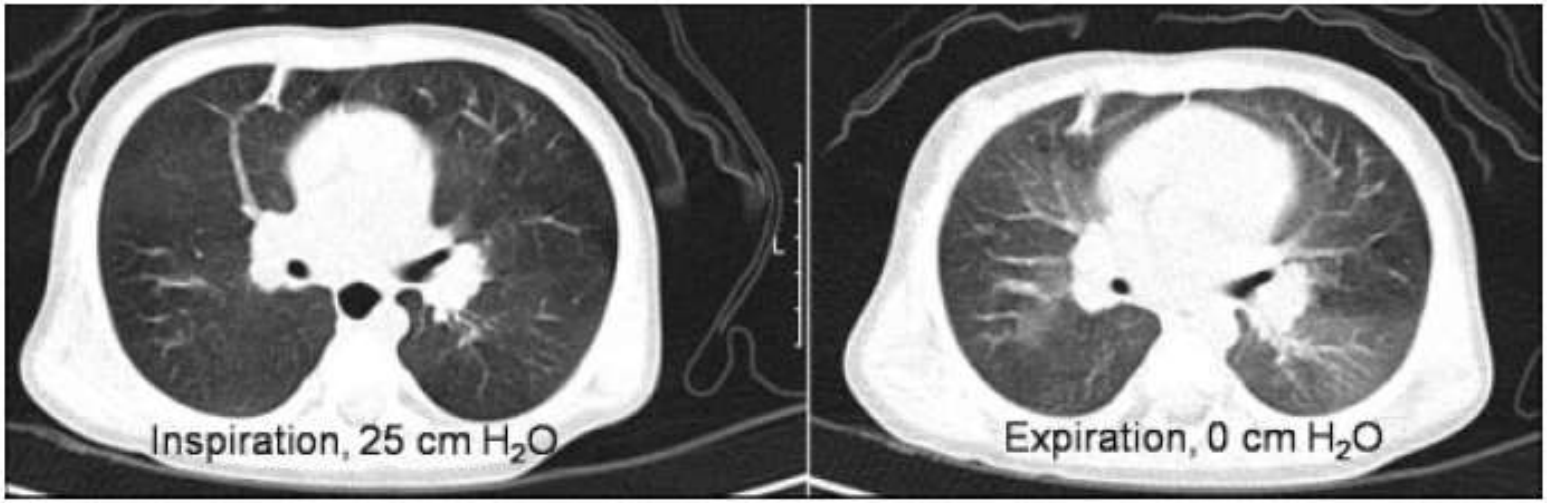
Lai et al. Pediatrics 2009

Heltshe et al. JCF 2014

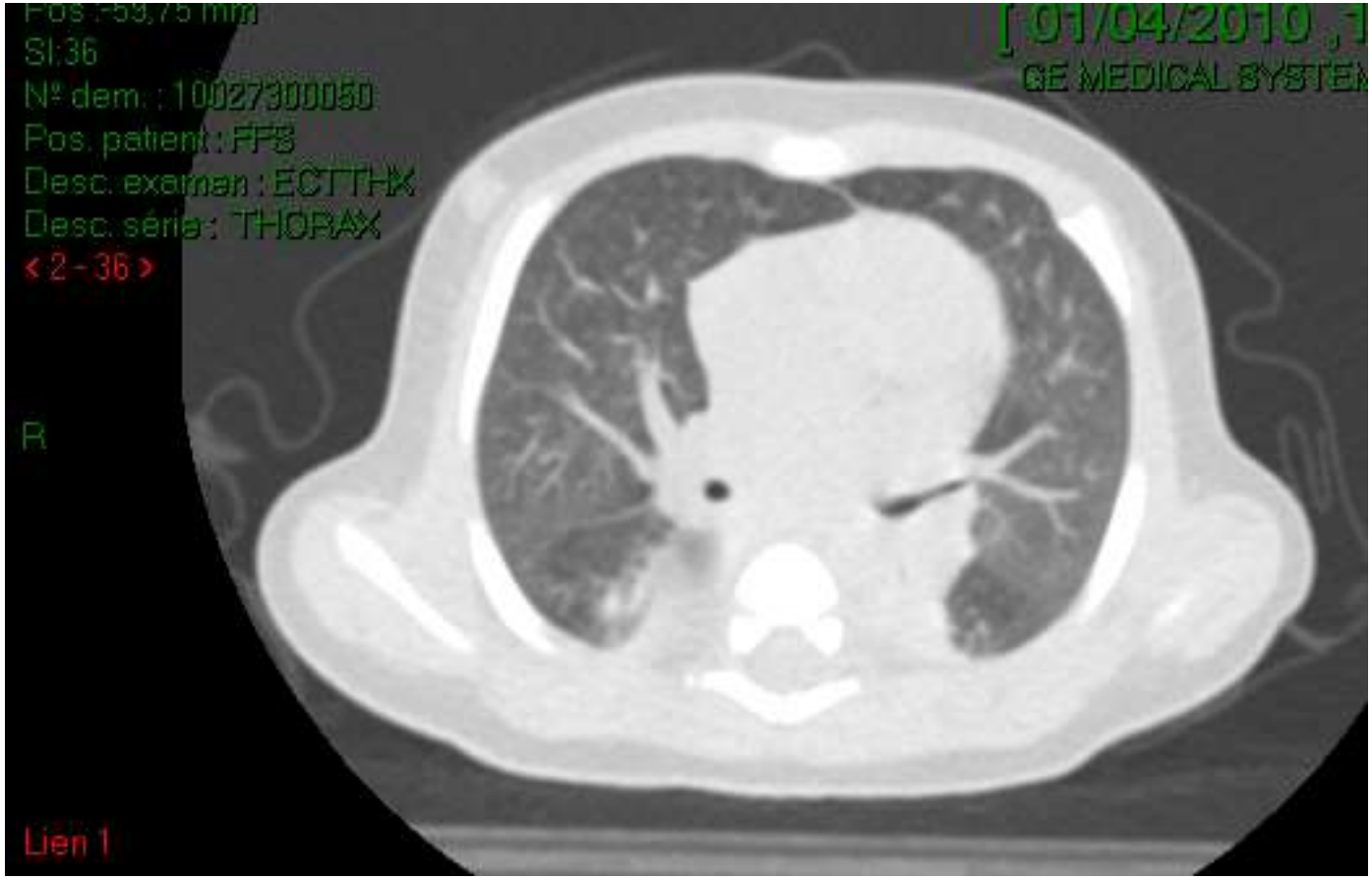
Pathogens in Sputum

	M3	M6
Sampled/Abnormal(%)	90/49	95/58
- *Haemophilus influenzae* (%)	17	32
- *SASM/SARM* (%)	85/0	72/2
-*Pneumococcus* (%)	6	5
-*Pseudomonas aeruginosa* (%)	11	9
-*X Maltophilia/A Xylosoxidans* (%)	4/0	7/2

Early lung damage



Trapped air on expiratory scans

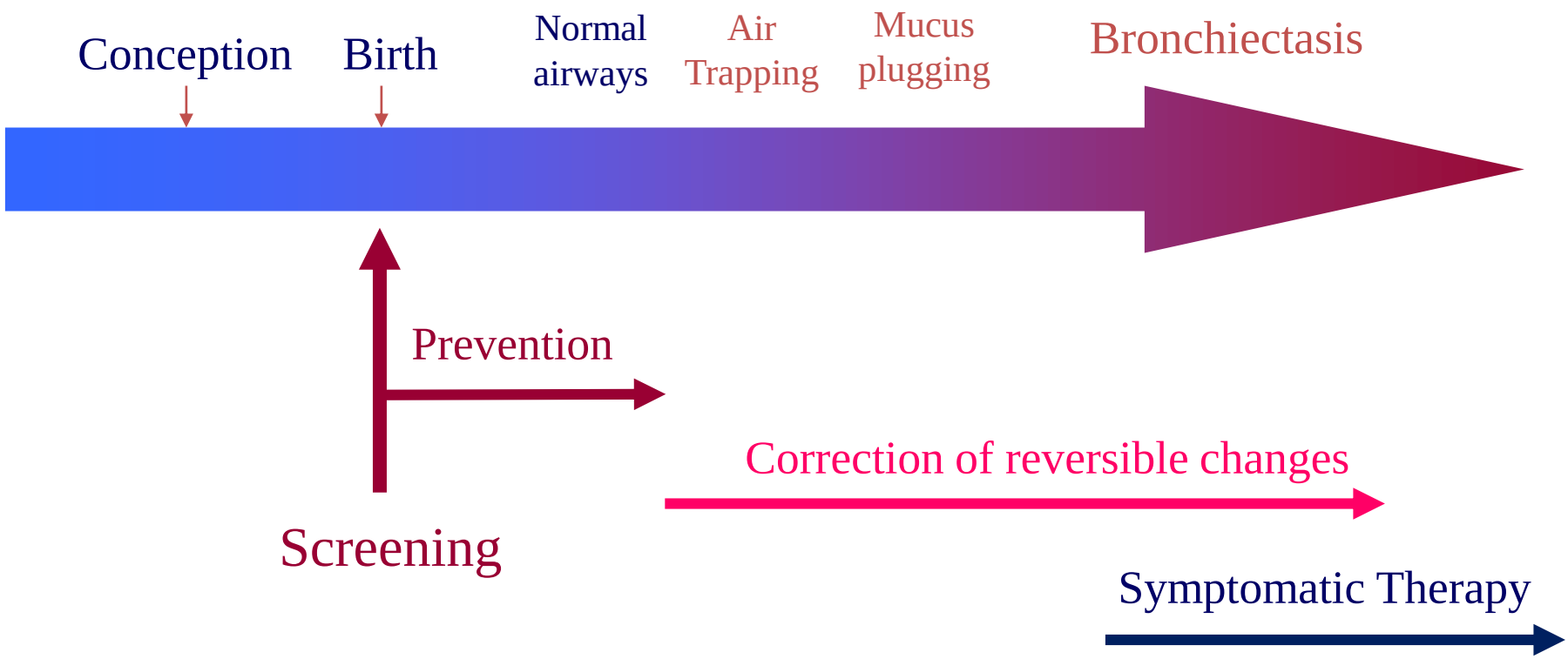


CD, 3 months, asymptomatic, TS 36 et 42 mmol/l, F508del/3849 + 10kb C > T

Distension, bronchial wall thickening, condensation

Guidelines for standardized follow-up

Initiate therapy early may prevent or correct reversible changes

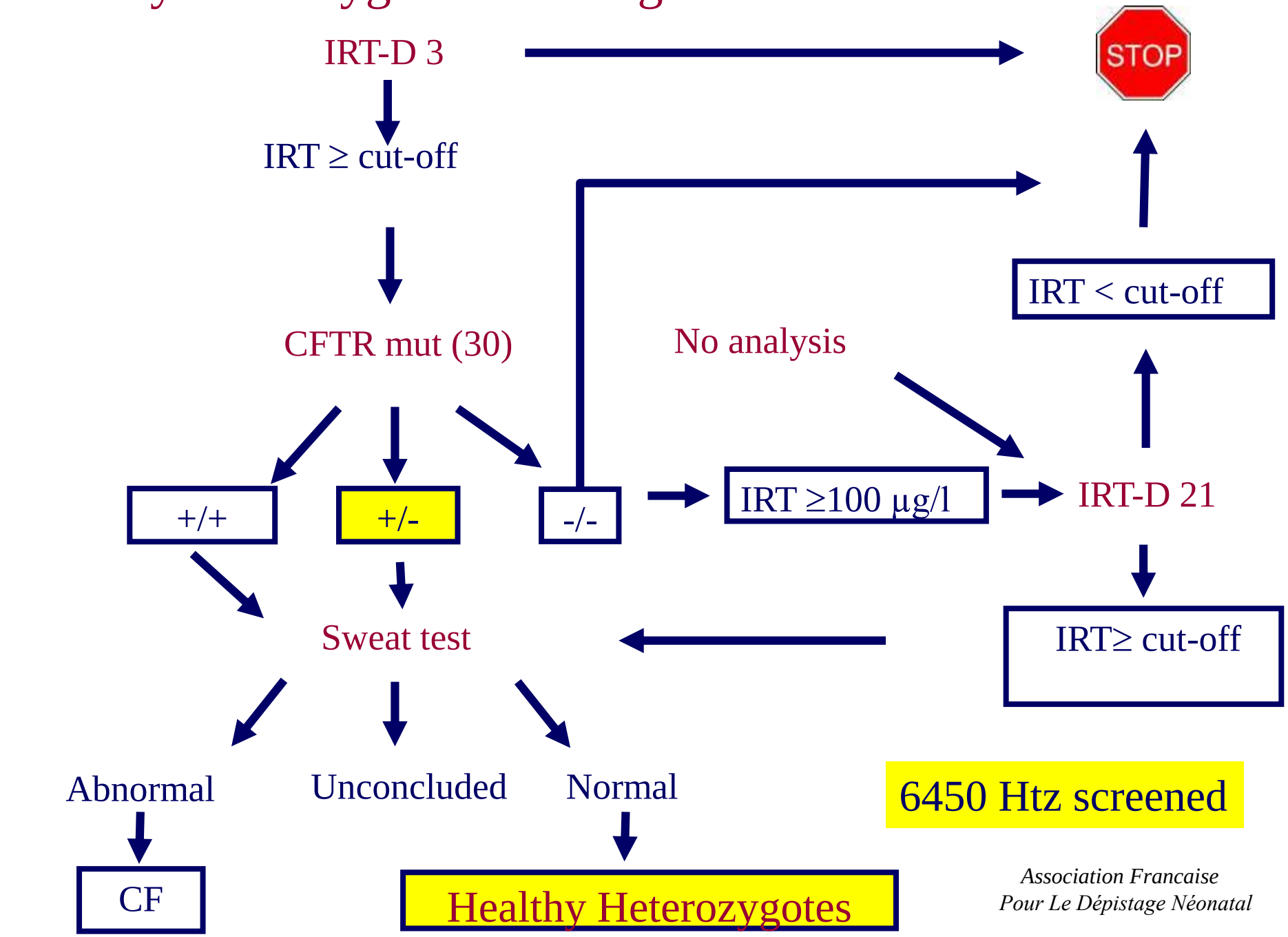


« Prise en charge du Nourrisson dépisté atteint de forme typique de mucoviscidose ».

Sputum induction, defined nutritional targets, lung imaging

Sermet-Gaudelus et al. Arch Fr Ped 2012

Healthy heterozygote screening



Association Francaise
Pour Le Dépistage Néonatal

« Positive » impact of heterozygote screening
Domino effect

The knowledge of their heterozygosity by the previously screened, now adults, modifies their behavior.

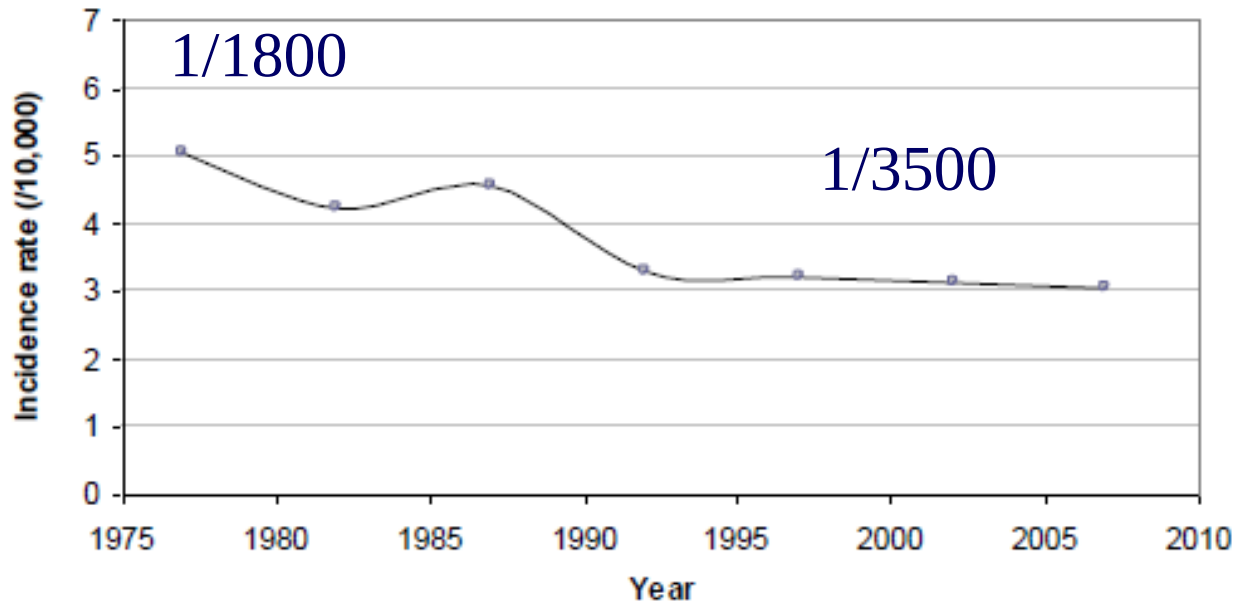


Figure 2 Evolution of the birth incidence rate of cystic fibrosis in Brittany by 5-year period, over the period 1975-2009.

Scotet et al. Orphanet Journal of Rare Diseases 2012

Heterozygote screening is unethical

Comité national d' Ethique (N°5701/**2007)**

- « It is unethical to screen healthy controls ONLY in the families with hypertrypsinemic neonate » (1/2000 versus 1/30)
- « Loss of chance for ethnic minorities »
- « It is unethical not to be able to provide a comprehensive information » (genetic counseling)

- No information to the parents about their Htz status
- Results are stored in a biobank and can be communicated after clear demand (written consent)

Heterozygote screening is unethical

Heterozygosity is not a disease

- Genetic screening is prohibited in a subject < 18 yrs if no direct benefit nor any disease (R.1131-5 issu du décret du 23 juin 2000)
- Information is not asked by the parents
- Information given when adult, if asked

Avoid « instrumentalisation » of heterozygote status

- Minimal risk for a CF baby
- Incomplete reverse cascade screening creates inequity : only some family members will be positively screened

Alternative strategy to avoid Htz screening
Pancreatic Activation Protein (PAP)

Screening protocol	IRT/DNA	IRT/PAP
IRT positive	2441	8487
Screening test positive, recalled for ST	313	951
Classical CF	68	69
Classical CF with MI	5	8
Atypical CF	12	5
False positives (negative ST)	228	869
HZ	165	
Negative ST after failsafe procedure	63	
Test negative	552,602	551,964
Classical CF	6	5
Classical CF with MI	4	1
Atypical CF	0	7
Detection rate (%)	91.9	93.2
PPV (%)	27.1	8.6

Sarles et al. J Cyst Fibr 2014

TIR-PAP/TIR-*CFTR* mutations

Performances	Sensitivity	PPV	Carrier
IRT/PAP	medium	very low	good
IRT/PAP/DNA	→	↗	↘

Advantages

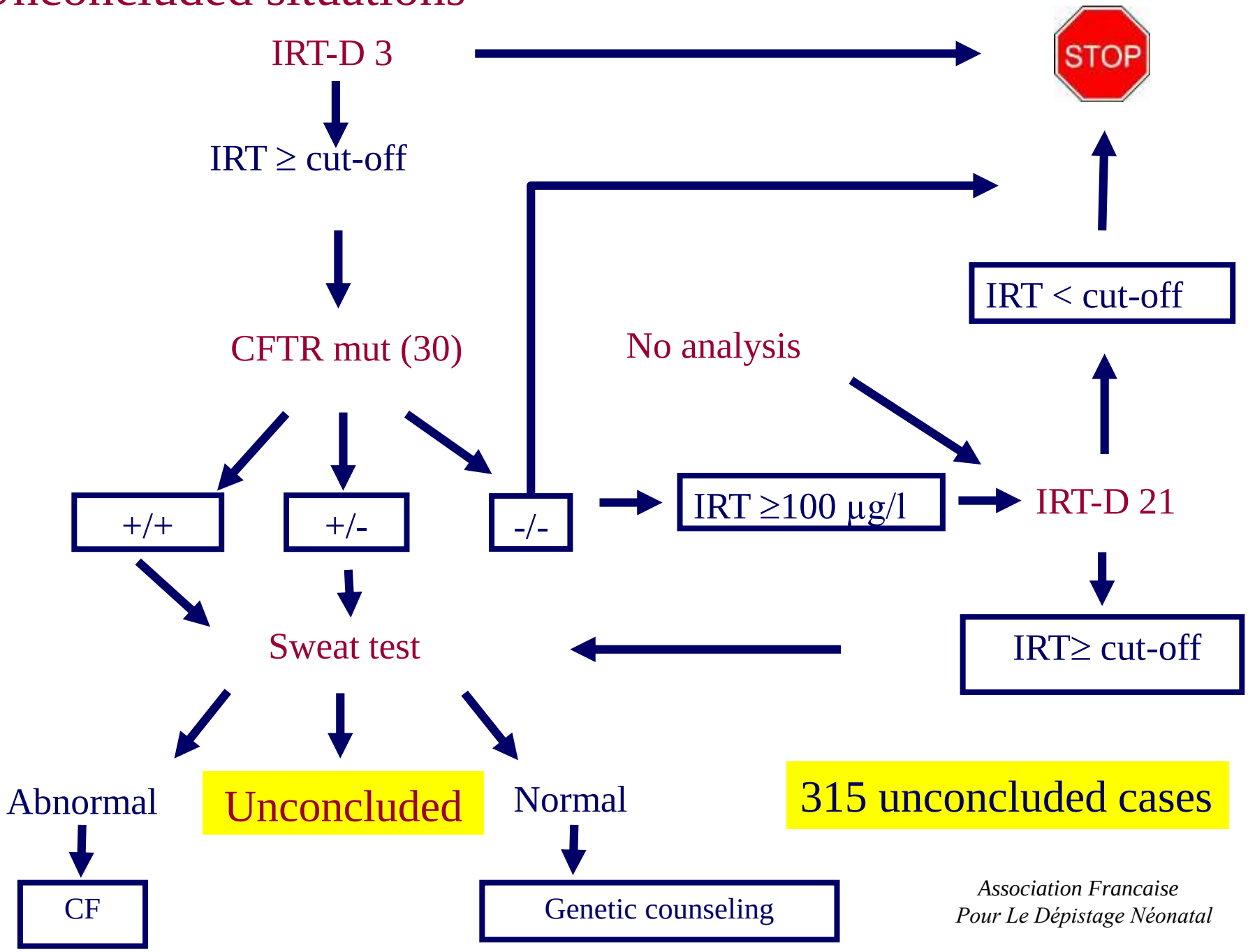
- Less Htz screening
- Also for ethnical minorities
- Less costful

Drawbacks

- Lower pos predict value
- PAP cut offs may change % IRT, age
- Possibly more sweat test

Haute Autorité de Santé 2014

Unconcluded situations

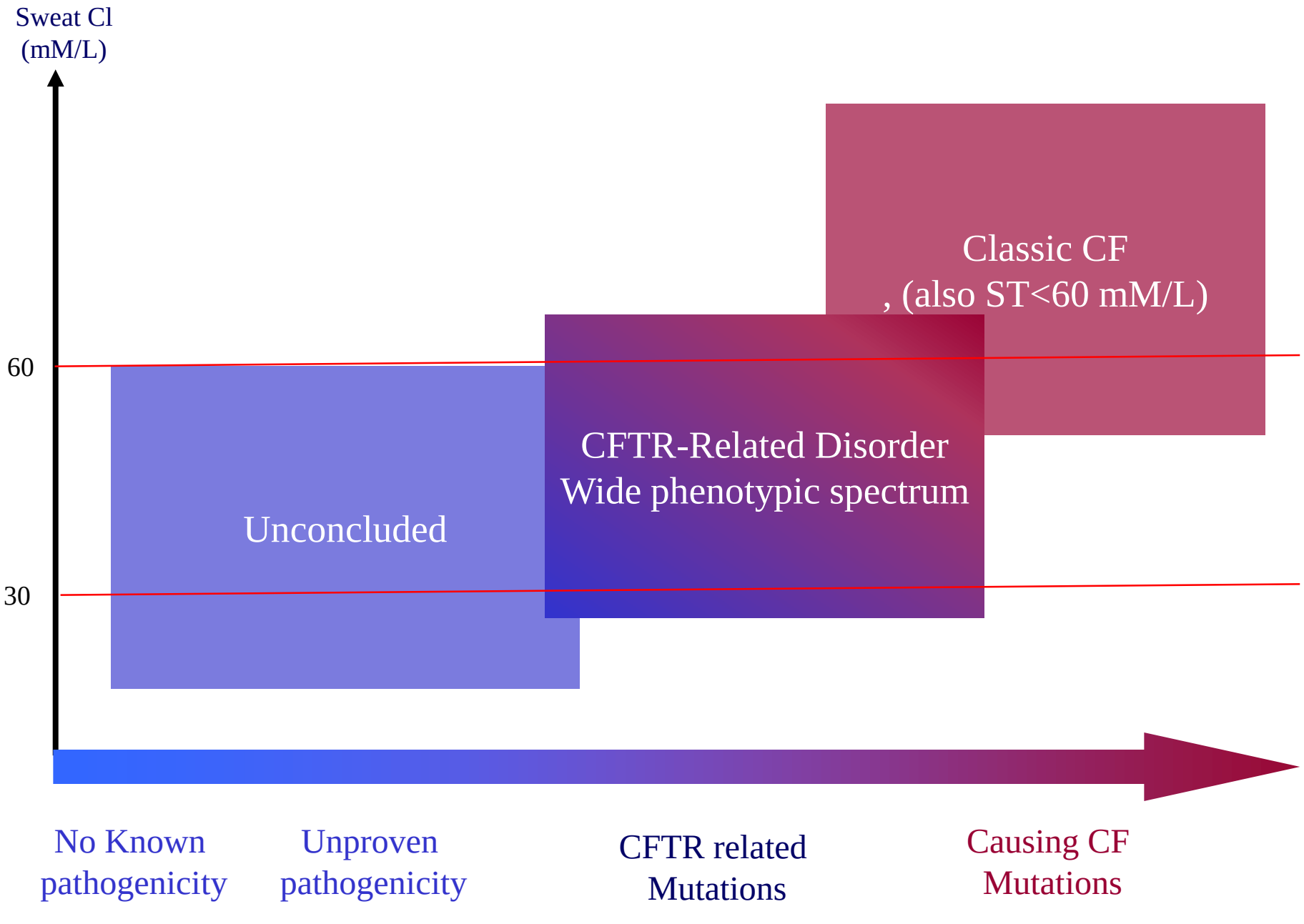


Association Francaise
Pour Le Dépistage Néonatal

2 Situations

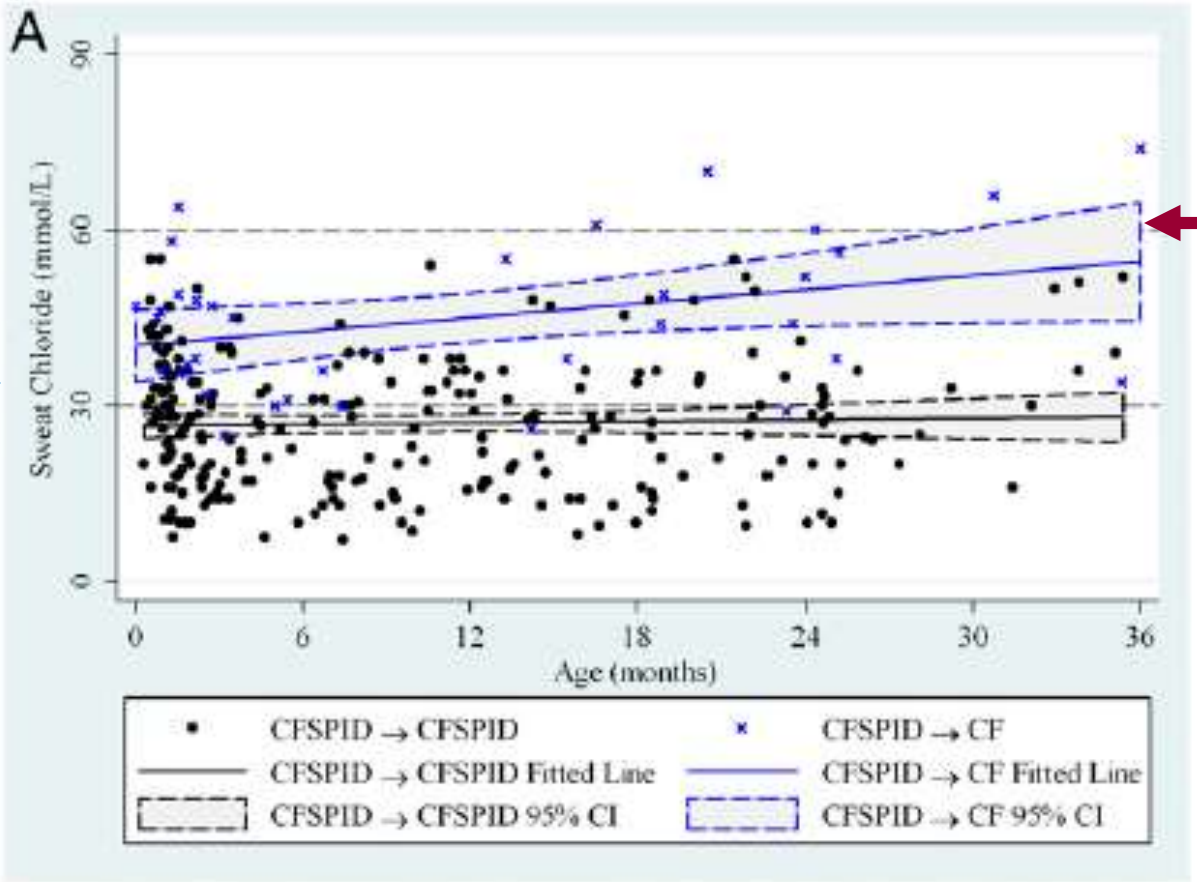
Sweat test	Mutations
30 to 59 mMoL/L	At most 1 CF causing
< 60 mMol/L	2 *CFTR* mutations with at least 1 of unknown pathogenic potential

Sermet-Gaudelus et al. Arch Fr Ped 2017
Farrell et al. J Pediatrics 2017



Groupe de travail de la SFM, Dépistage et formes difficiles

Only a very low proportion will develop CF or CFTR-RD



Ren et al. Pediatrics 2011

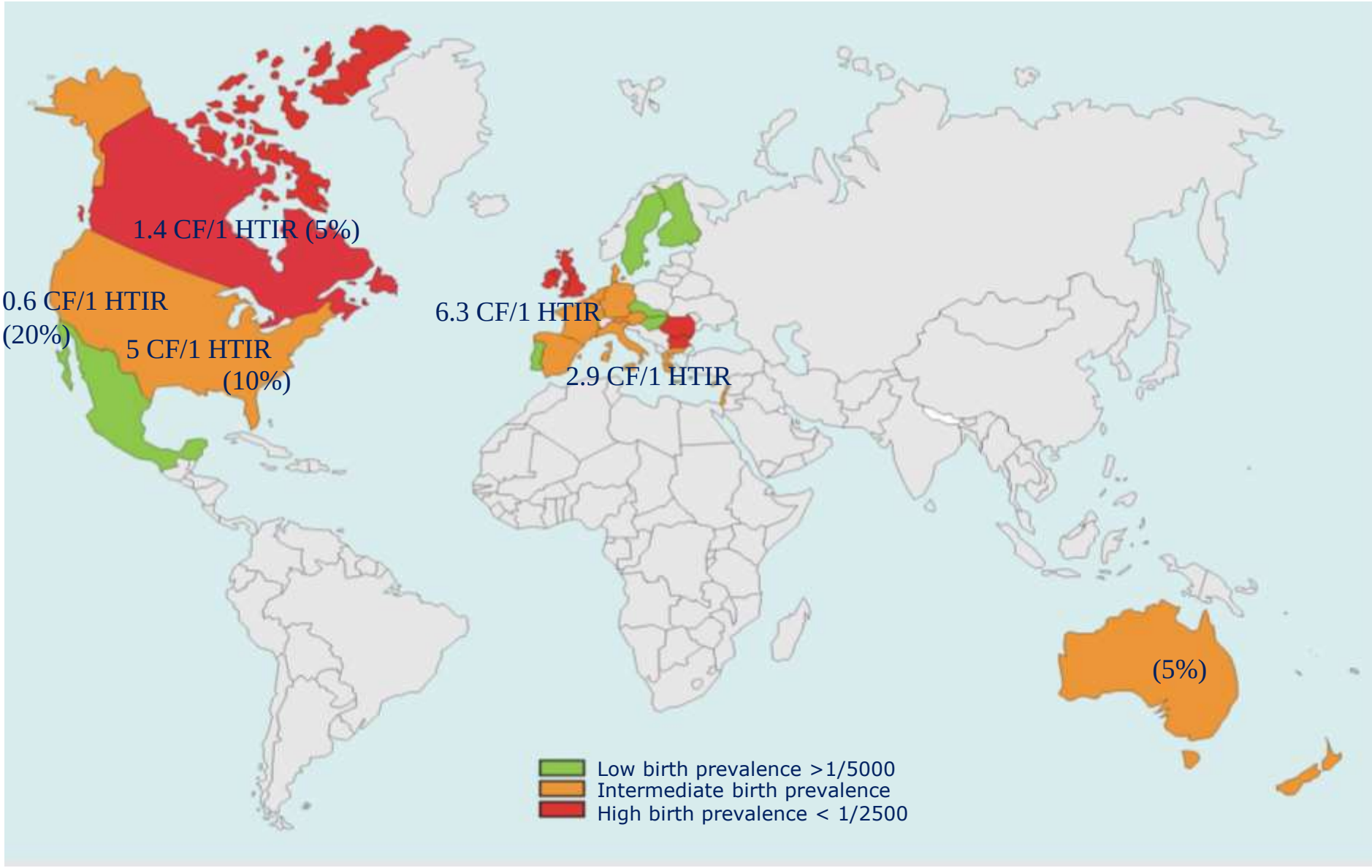
No Known pathogenicity

Unproven pathogenicity

CFTR related Mutations

Causing CF Mutations

Frequency according to screening algorithm



p.Arg117His

- 7.2% of HIRT newborns
- 6/1000 CF babies
- 53% of the nonconcluded cases
- Population study: F508del/R117H-7T: 97% asymptomatic; 1/3650 expected with classic CF

Thauvin Robinet. J Med Genet 2009

Considering this very low penetrance (0.03%) R117H was excluded from the newborn screening test panel on January 1st, 2015

2015: CF/unconcluded ratio 9/1 (versus 6.3/1)

These challenging unconcluded situations raise a dilemma for our medical practice

Beneficence (e.g., doing good)

- Babies who turn out to have clinical CF will benefit from treatments to delay the onset of complications

Non Maleficence» (e.g., not doing harm)

- Risk : identify at risk a child who will never develop the disease
  - Parent-child relationship
  - Antenatal diagnosis
  - Nocious effect of overmedicalisation
  - Adult : job, insurance, life partner

Unconcluded situations
Not a disease, nor a syndrom, nor even a clinical entity !
Reflects genetic diversity

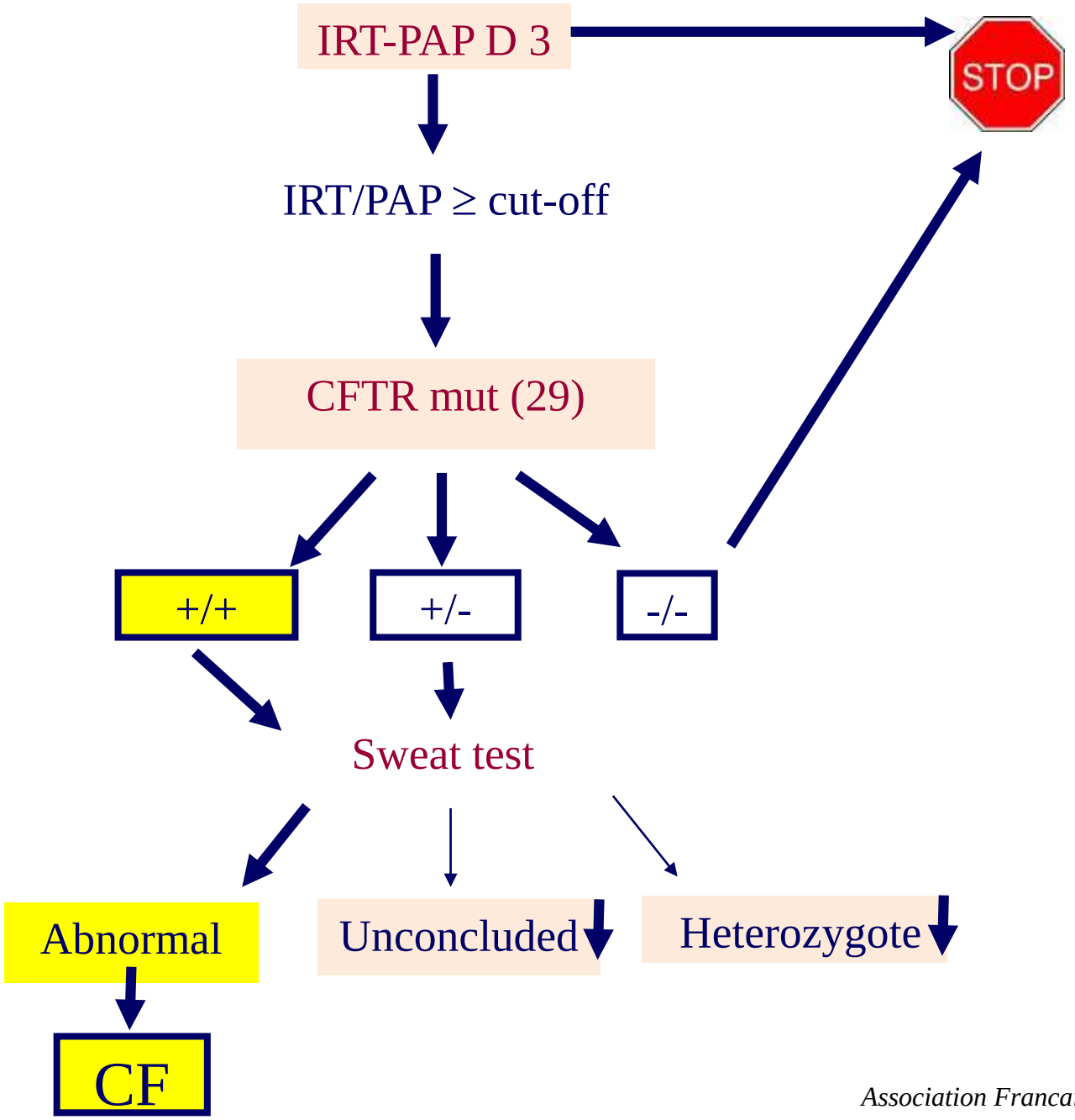
"labeling those children might be highly detrimental. Associating them to a defined clinical entity carries a potential for stigmatization whereas most of them will never develop the disease »

No label, No name

Sermet-Gaudelus et al.Arch Fr Ped 2017

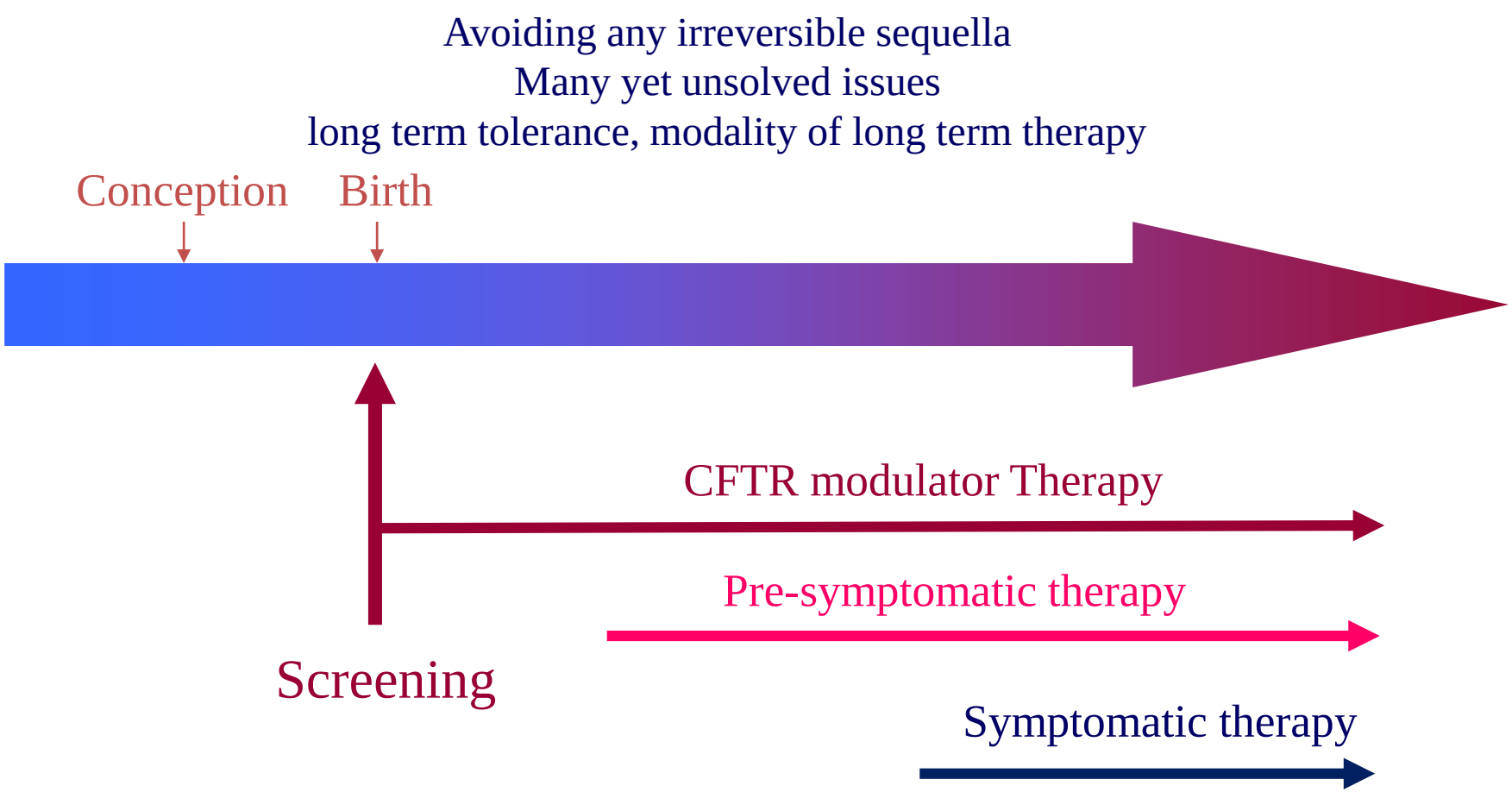
Explain uncertainty

- Clear and fair explanation to the parents, no categorization (preferred option of « watchful waiting », autonomy,)
- Follow-up with the primary care physician, informed of the uncertain diagnosis, the specificities of the clinical management and the need to promptly refer the patient if symptoms suggestive of CF
- This recommendation contrasts with the management advocated by the American/European guidelines which suggests active surveillance, and classification (metaboli syndrom, CFSPID)



Association Francaise
Pour Le Dépistage Néonatal

Shift the paradigm of pre-symptomatic therapy to neonatal implementation of mutation targeted therapy



Pediatric CF Center
Necker Enfants Malades
Sociéte francaise de Mucoviscidose
Groupe de travail: diagnostic et formes difficiles