SIFC
SOCIETÀ ITALIANA
PER LO STUDIO DELLA FIBROSI CISTICA

Gruppo di Lavoro Screeening Neonatale

Indicatori di attività nei programmi regionali di screening neonatale per fibrosi cistica

Carlo Castellani
CFC GE

POTENZIALE CONFLITTO D'INTERESSI DA DICHIARARE

Nessun conflitto d'interessi in relazione all'attività del Gruppo

Partecipanti

Carlo Castellani, Genova	coordinatore
Carla Carducci, Roma	
Laura Claut, Milano	
Carlo Corbetta, Milano	
Vito Terlizzi, Firenze	
Antonella Tosco, Napoli	

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Short Communication

Defining key outcomes to evaluate performance of newborn screening programmes for cystic fibrosis

Anne Munck[a], Kevin W Southern[b], Carlo Castellani[c], Karin M de Winter-de Groot[d], Silvia Gartner[e], Nataliya Kashirskaya[f], Barry Linnane[g], Sarah J Mayell[h], Marijke Proesmans[i], Dorota Sands[j], Olaf Sommerburg[k], Jürg Barben[l,*], For the European CF Society Neonatal Screening Working Group (ECFS NSWG)

Newborn Screening Parameters (P) to be collected by each country (or region)

1. Number of live births per year
2. Number of infants screened per year
3. Number of infants with an inadequate dried blood sample per year
4. Number of infants with positive tier 1 test (IRT or IRT/PAP) per year
5. Number of infants with a positive NBS result (NBS+) with 2 *CFTR* variant or 1 *CFTR* variant referred for diagnostic assessment (including sweat testing)
6. Number of infants NBS+ with 0 *CFTR* variant and a positive IRT safety net (if applicable) referred for diagnostic assessment (including sweat testing)
7. Number of infants NBS+ with a confirmed CF diagnosis per year
8. *Number of infants NBS+ with a confirmed CF diagnosis and 2 CFTR variants identified from the NBS protocol* [1]
9. *Number of infants NBS+ with a confirmed CF diagnosis and 1 CFTR variant identified from the NBS protocol* [1]
10. *Number of infants NBS+ with a confirmed CF diagnosis and 0 CFTR variants identified from the NBS protocol* [1]
11. Number of infants NBS+ with a CRMS/CFSPID designation per year
12. Number of infants NBS+ with a pending conclusion per year [2]
13. Number of infants who did not complete the NBS algorithm per year
14. Number of infants NBS+ with one *CFTR* variant [3] and sweat chloride <30mmol/L if required by the protocol (reported as a carrier)
15. Number of false negatives without MI: cases clinically diagnosed with CF based on symptoms, family history and without MI, born in the previous year (affected but not detected by NBS)
16. Number of false negatives including MI: cases clinically diagnosed with CF based on symptoms, family history and including MI, born in the previous year (affected but not detected by NBS) [4]
17. Total number of infants diagnosed with CF during this year (True+ and False-) [4]
18. Number of infants with a true negative NBS result
19. Number of infants NBS+ result but not diagnosed as CF or CRMS/CFSPID
20. Mean age (median, min and max) in days, where date of birth is day 0 and when the newborn is first assessed by a CF specialist team

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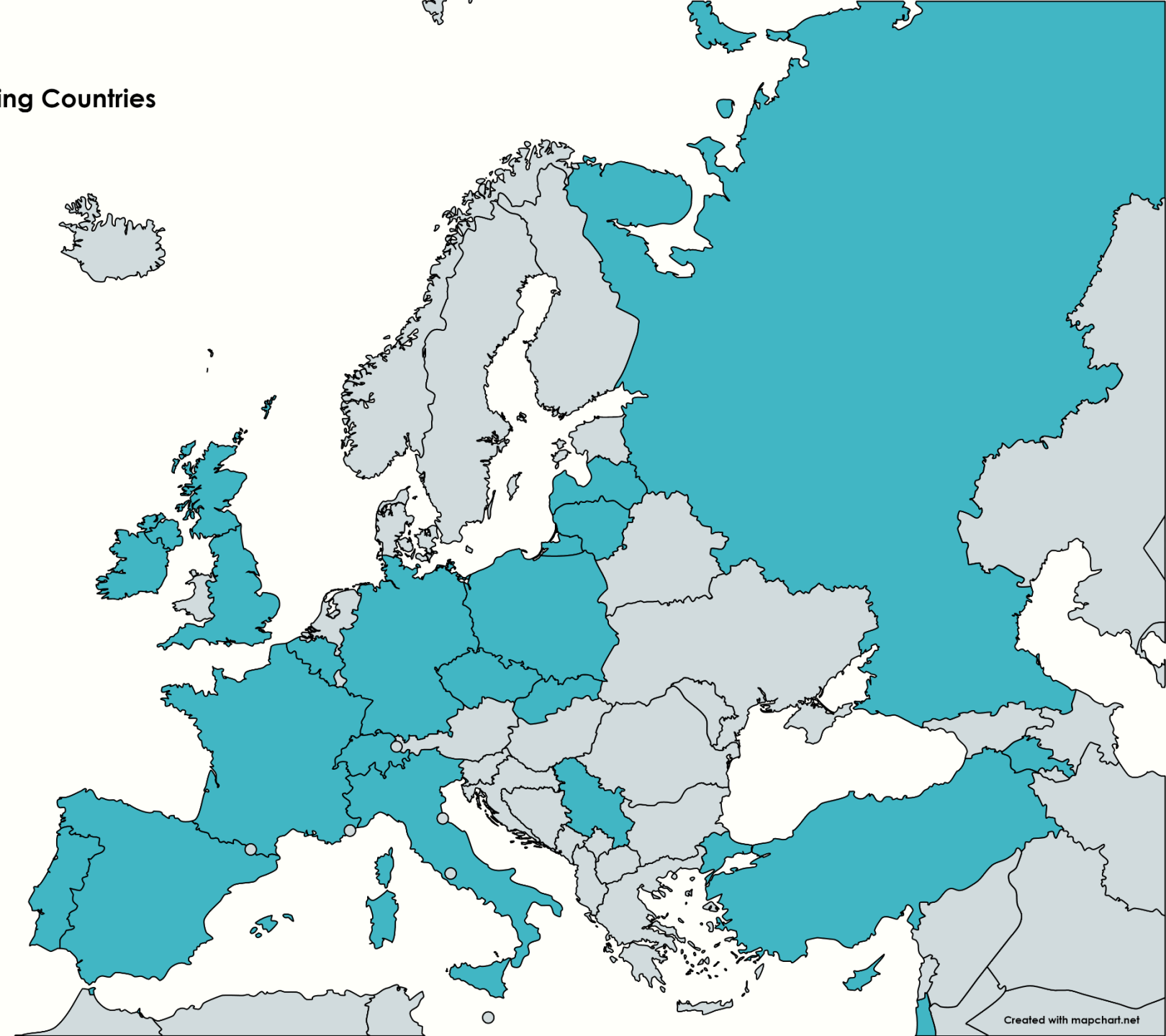
Key outcome	Definition	Parameters
1. Coverage of the NBS programme	Proportion of infants screened for CF per year	P2/P1
2. First-tier or IRT/PAP (if applicable) a) Proportion of first-tier IRT or IRT/PAP b) Proportion of repeat tests required for inadequate dried blood sample (%)	 a) Proportion of infants with a first-tier IRT or IRT/PAP ≥ cut-off per year b) Proportion of infants with an inadequate first dried blood sample per year	P4/P2 P3/P2
3. NBS outcome (diagnosis or designation)		
a) CF (number (%)) if applicable	*a) CF: Sweat chloride concentration (SCC) ≥60mmol/L and/or 2 CF-causing mutations (CFTR2 database)* Number of infants with a CF diagnosis per year	**P7**
	Proportion of infants carrying 2 CFTR variants within the programme protocol [1]	P8/P7
	Proportion of infants carrying 1 CFTR variant within the programme protocol [1]	P9/P7
	Proportion of infants carrying 0 CFTR variant within the programme protocol [1]	P10/P7
b) CRMS/CFSPID (number (%))	*b) CRMS/CFSPID: An infant with a positive NBS result and* *1) SCC <30mmol/L and 2 CFTR variants (mutations), at least one of unclear phenotypic consequences OR* *2) Intermediate SCC (30-59mmol/l) and 1 or 0 CF-causing variants (mutation)* [2,3] Proportion of infants with a CFSPID diagnosis per year	**P11**/P5+P6
c) Pending conclusion, infants screened positive for whom the CF physician needs additional information to conclude CF, no CF, CRMS/CFSPID (number (%) (i.e. waiting for ST or genetic result)	*c) Not yet with a conclusion* Proportion of infants with a pending conclusion per year	**P12**/P5+P6
d) Lost to follow-up (number (%))	*d) Cases screened positive on IRT that could not follow the algorithm (including deaths)* Proportion of infants who did not complete the NBS algorithm	**P13/P4**
4. Carriers (if applicable), number (%))	*Infants carrying one CFTR variant with a SCC <30mmol/L if required by the protocol* Proportion of infants with one CFTR variant and SCC <30mmol/L/year if required by the protocol	**P14**/P5
5. CF cases missed by NBS without MI (number, (%)) **CF cases missed by NBS including MI** (number, (%)) (Please record babies born in the index year and then diagnosed within two years. For example, for the 2019 data collection include diagnoses subsequently made in 2020). Please outline on the first page how you have collected these data	*Cases diagnosed CF based on symptoms or family history who were screened negative* Proportion of CF cases clinically diagnosed on symptoms or family history born during the intended analysis	**P15/P7** and **P16/P7**
6. Performances for CF a) Sensitivity, **%** b) Specificity, % c) Positive predictive value, %	a) Proportion of cases with CF diagnosis after positive NBS out of all CF cases including clinically diagnosed CF (to calculate the sensitivity you need the number for this year which makes a follow-up of at least 1-2 years necessary until children are clinically diagnosed) b) Proportion of cases with negative NBS not CF affected out of all CF not affected c) Proportion of cases with CF diagnosis after positive NBS out of all NBS positive cases	**P7/P17** P18/P19 **P7**/P5+P6
7. Performances for CRMS/CFSPID Ratio CF:CRMS/CFSPID	Ratio of CF to CRMS/CFSPID	**P7:P11**
8.Timeliness at initial visit at a CF centre a) CF b) CRMS/CFSPID	*Mean age (median, min and max) in days, where date of birth is day 0 and when newborn is first assessed by a CF specialist team* (may be before age at sweat test)	P20

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All established programmes

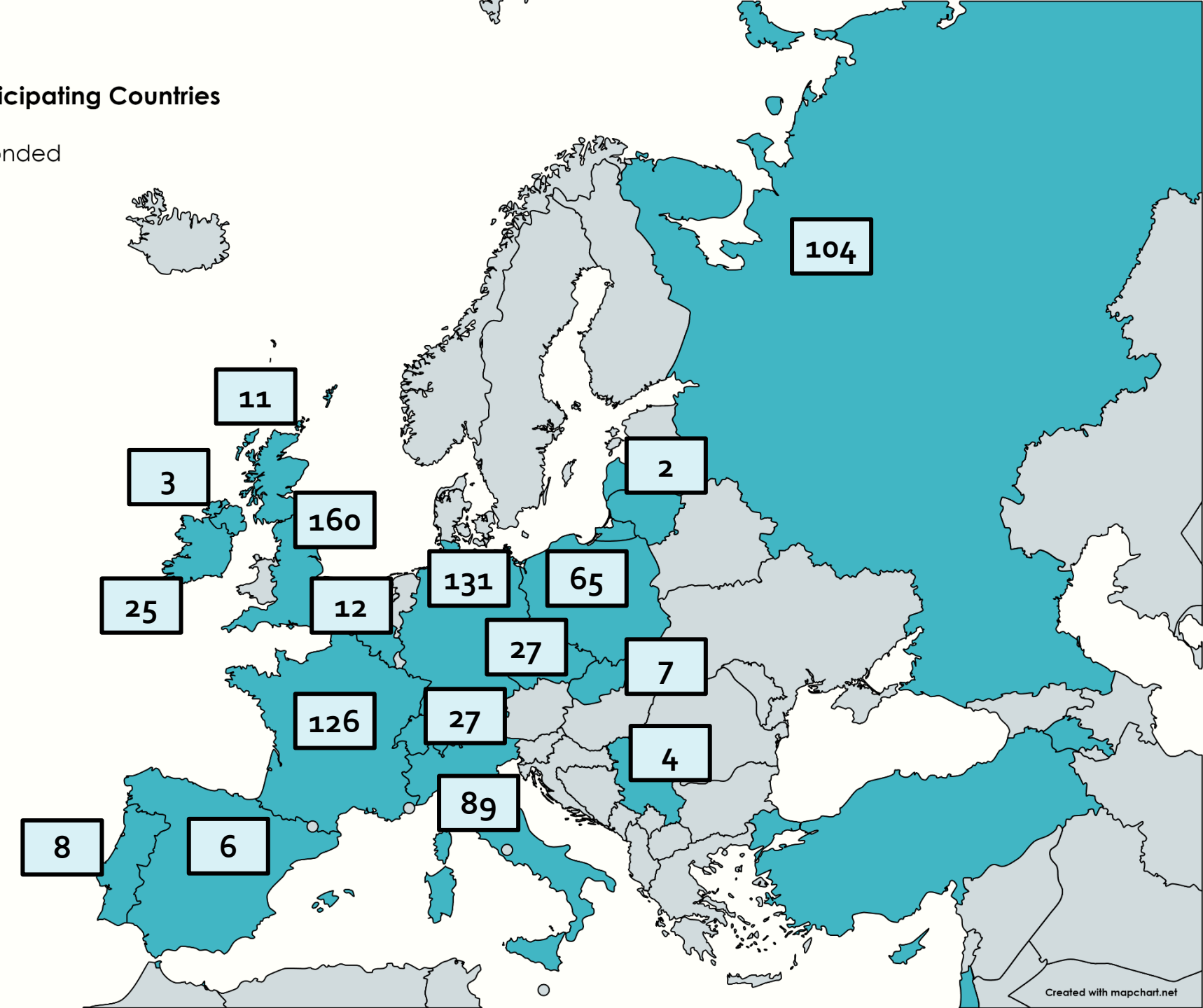
Regional programmes: Belgium, Italy, Serbia and Spain



https://mapchart.net/europe.html

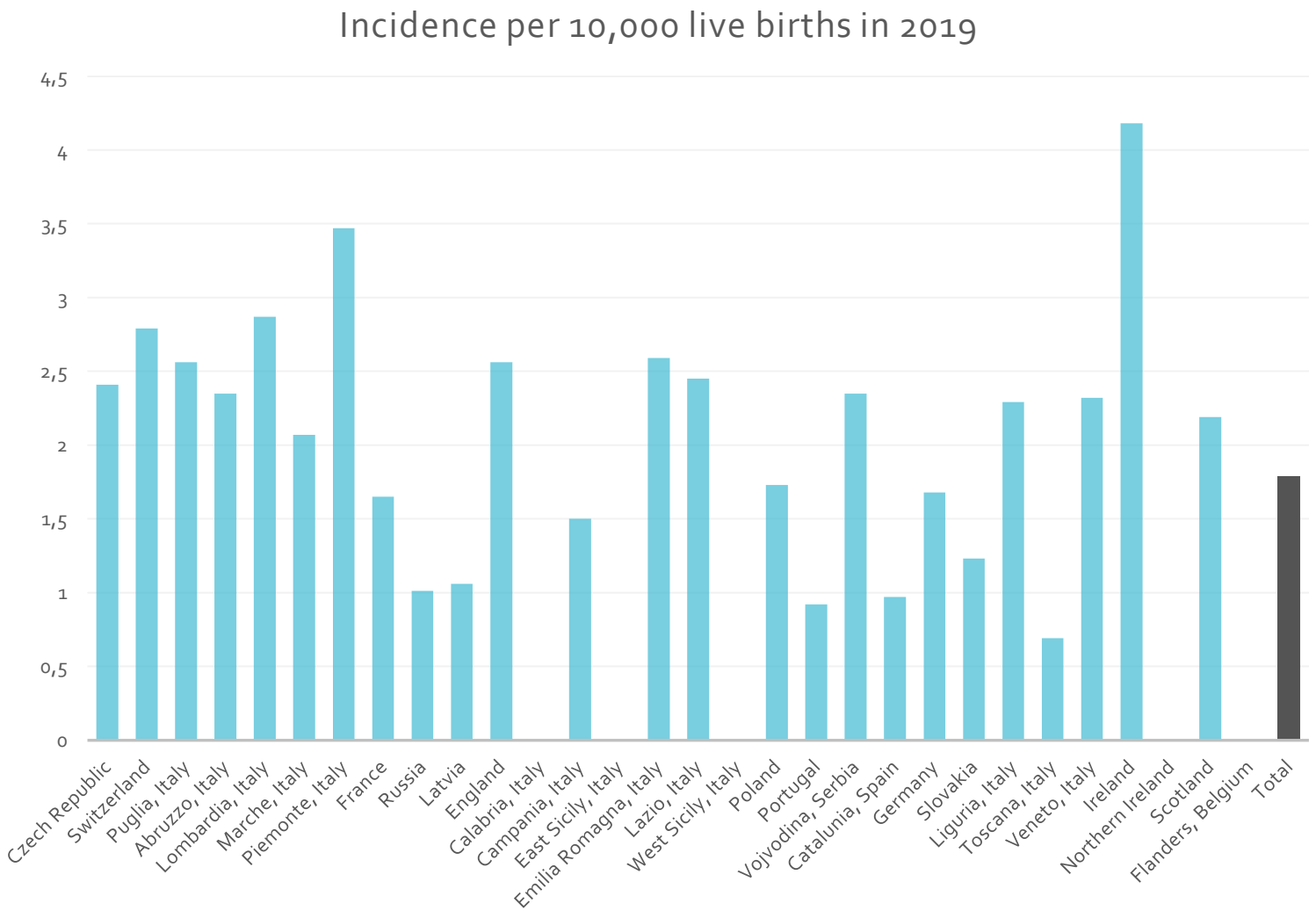
4,443,036 screened

To diagnose 804 children



https://mapchart.net/europe.html

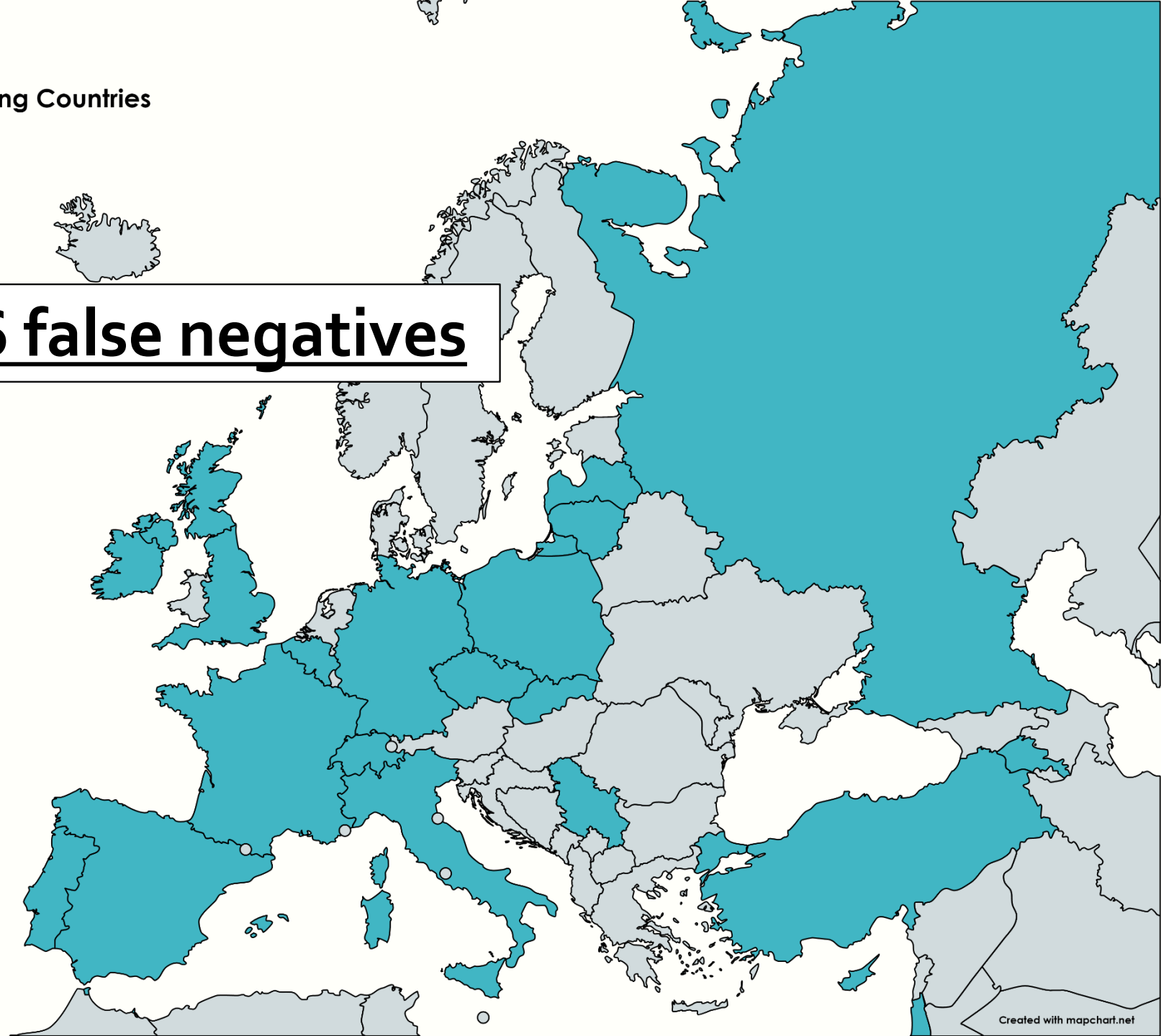
Incidence of CF per 10,000 live births



4,443,036 screened

26 false negatives

4,326,588 true negatives = 97.4% of all children screened



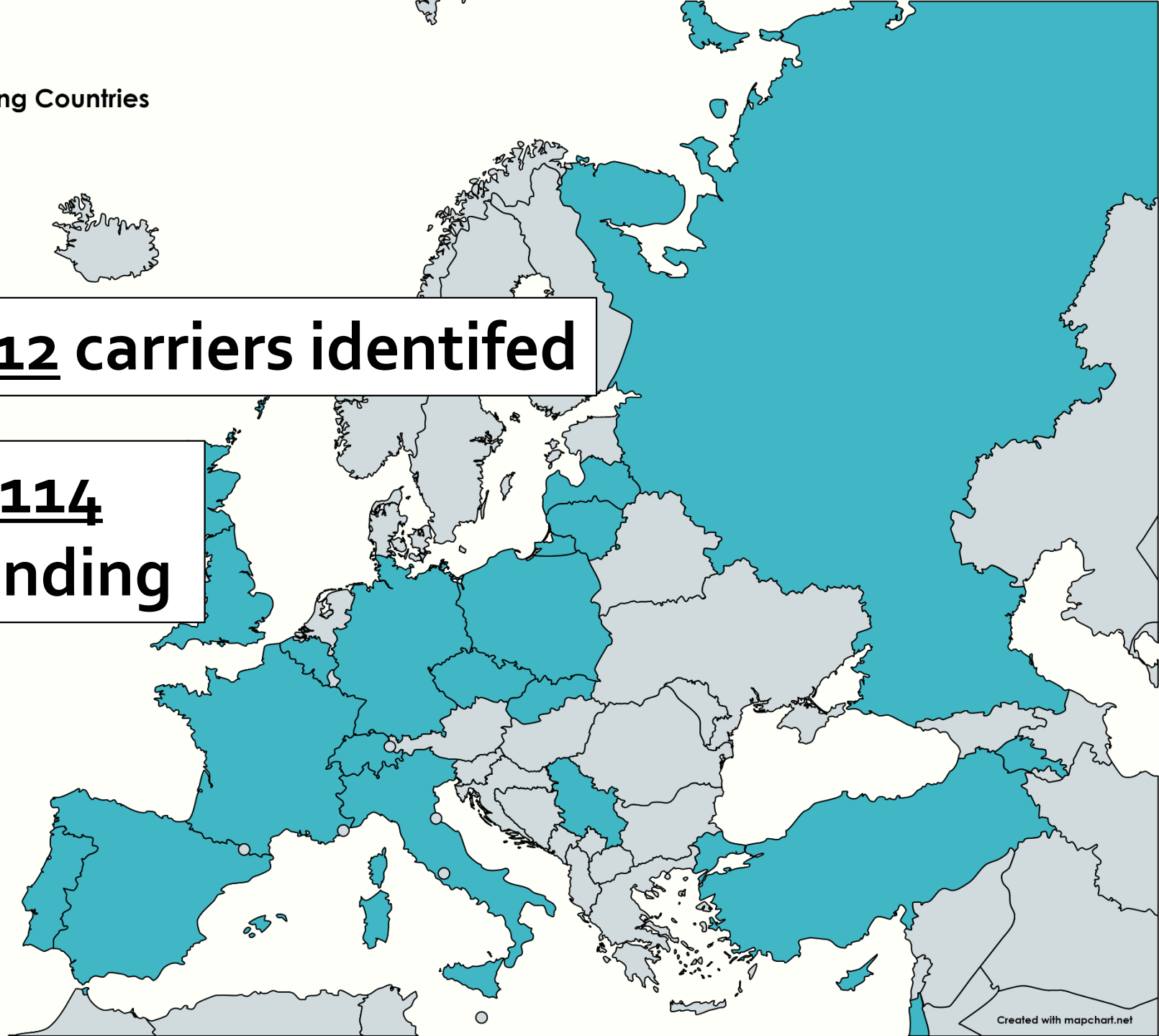
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4,443,036 screened

1112 carriers identifed

114 pending

981 lost to follow up

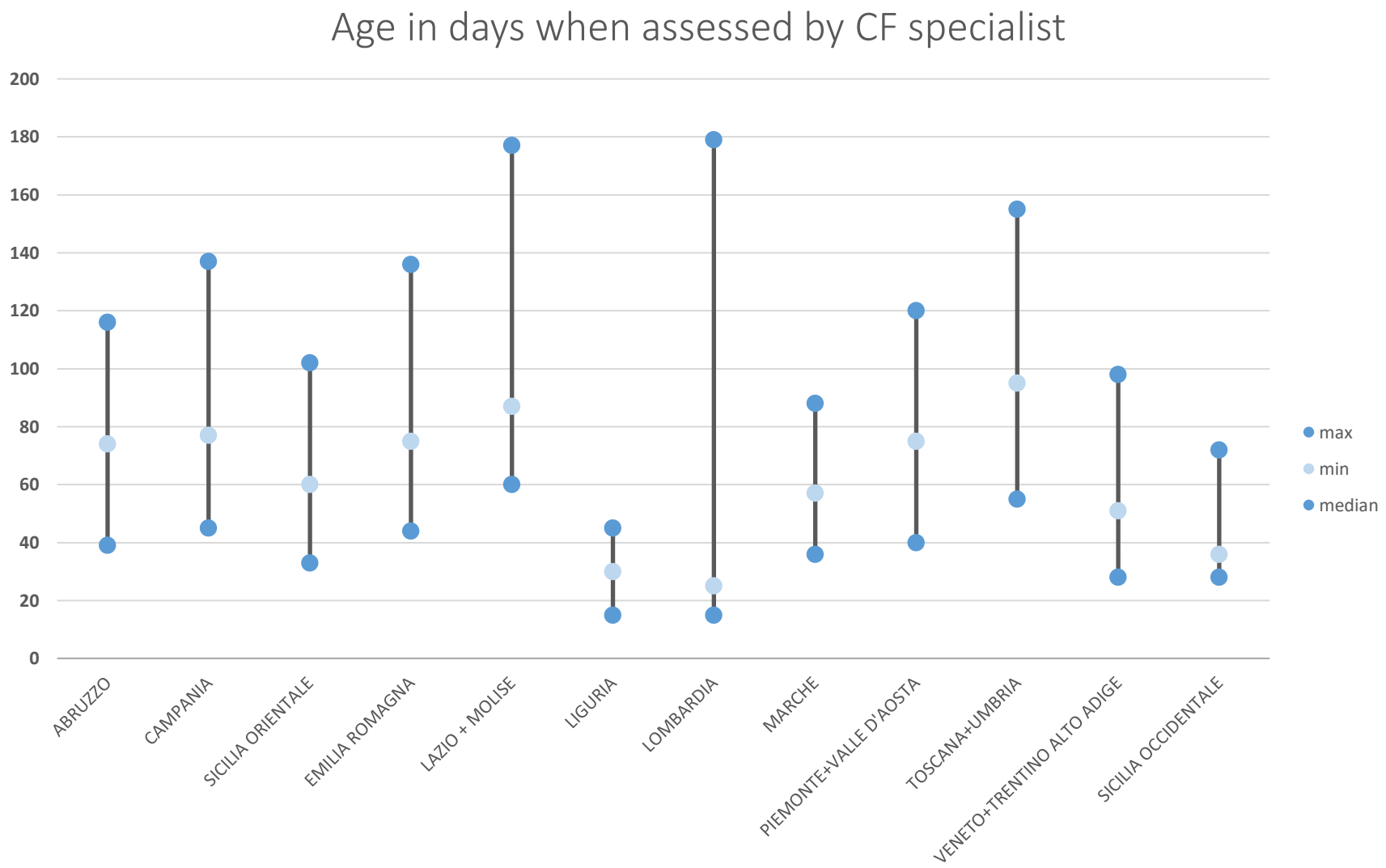


https://mapchart.net/europe.html

Screening algorithms

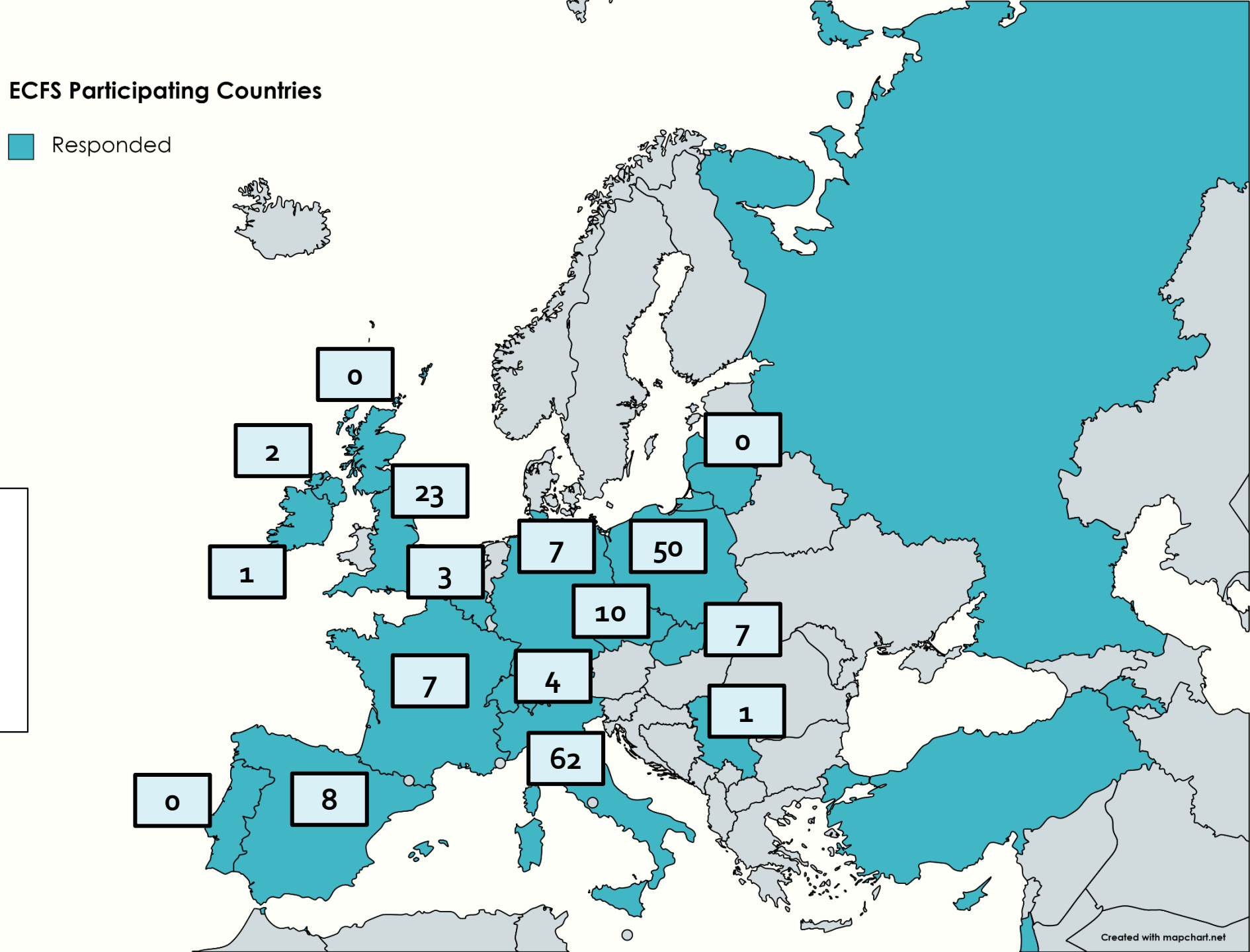
Region	Sensitivity without MI
Puglia, Italy	90%
Abruzzo, Italy	75%
Lombardia, Italy	88,9%
Marche, Italy	100%
Piemonte, Italy	10%
Calabria, Italy	No FC
Campania, Italy	88,9%
East Sicily, Italy	100%
Emilia Romagna, Italy	100%
Lazio, Italy	100%
West Sicily, Italy	100%
Liguria, Italy	100%
Toscana, Italy	100%
Veneto, Italy	92,3%

Median age at time of review

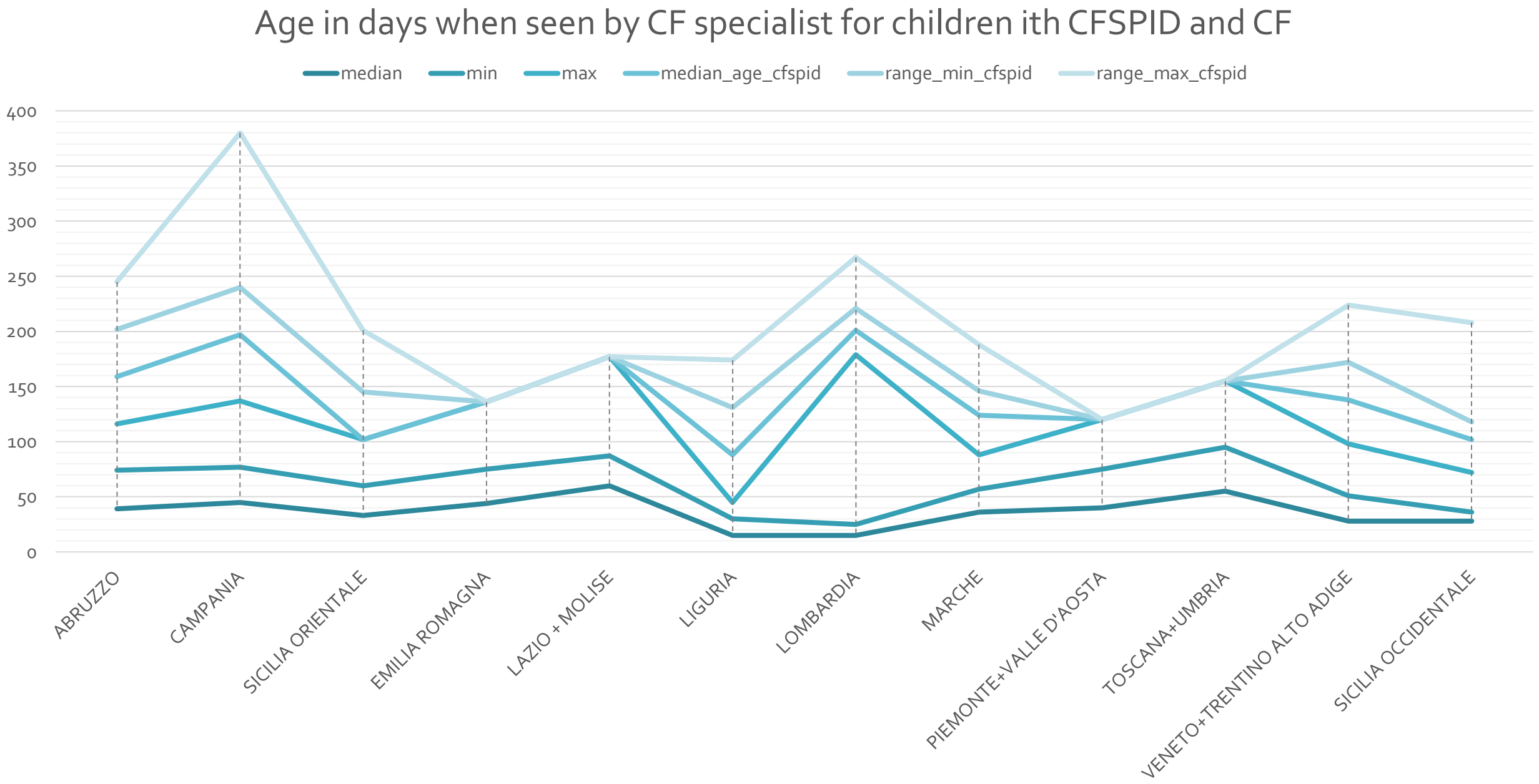


4,443,036 screened

To diagnose CFSPID in 178 children



https://mapchart.net/europe.html


Age in days when seen by CF specialist for children ith CFSPID and CF
median
min
max
median_age_cfspid
range_min_cfspid
range_max_cfspid
400
350
300
250
200
150
100
50
0
ABRUZZO
CAMPANIA
SICILIA ORIENTALE
EMILIA ROMAGNA
LAZIO + MOLISE
LIGURIA
LOMBARDIA
MARCHE
PIEMONTE+VALLE D'AOSTA
TOSCANA+UMBRIA
VENETO+TRENTINO ALTO ADIGE
SICILIA OCCIDENTALE

Considerazioni

I dati sono da verificare con un terzo round di consultazioni

Incongruenze Centri / Laboratori

Un anno fornisce un quadro parziale

Progettualità

Collaborazione con SIMMESN a lungo termine

Collaborazione con RIFC

Confronto pannelli mutazionali

Ringraziamo

Presidente e Direttivo SIMMESN

Direttori Centri Fibrosi Cistica

Laboratori Regionali Screening Neonatale