European Reference Network
for rare or low prevalence complex diseases

Network Neuromuscular Diseases (ERN EURO-NMD)

Newborn Screening in Neuromuscular Diseases

Satellite Scientific Symposium organized by ERN EURO-NMD
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NBS for Cystic Fibrosis: The German landscape

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Funded by the European Union

Cystic fibrosis

- Rare inborn genetic disease (1:3500)
- Autosomal recessive: *CFTR*-variants (> 2000 known, F508del 80%)
- Multiorgan involvement (main focus: Lung, Pancreas)

- Symptomatic treatment
- Causal treatment based on genetic background (*CFTR*-modulators)

- Number of pwCF in Germany: 4000 (2000) -> 7600 (2023); adults 36%->61%[1]
- Median age of survival (DE 2019-2023: 66,8 years)[1]

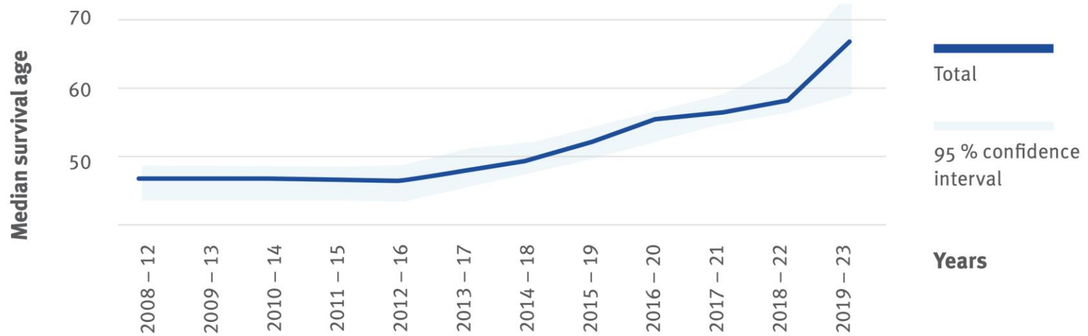
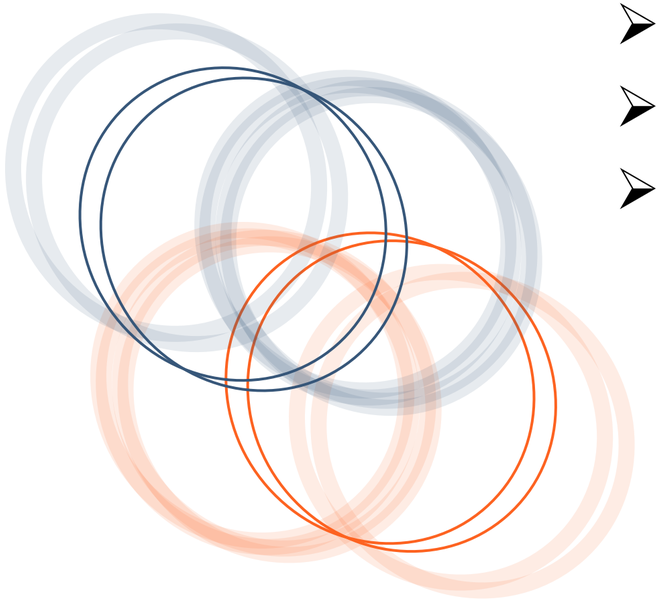


Figure 40: Median predicted survival age in the years 2012 – 2023

1. https://www.muko.info/englisch-version/registry

Newborn Screening in Germany

- 1969: PKU
- 1970s: Galaktosemia, Primary Hypothyrodism
- 2000s: Metabolic disorders (11), Adrenogentital Syndrom
- **2016: Cystic fibrosis**
- 2019: Severe combined immunodeficiency
- 2021: SMA, Sickle cell disease



➢ 19 target diseases in total

➢ 1:1300 newborns suffer from one of the target diseases

➢ More than 14000 diagnosis

Spiekerkötter, Krude. Dtsch Arztebl Int 2022; 119: 306–16
DOI: 10.3238/arztebl.m2022.0075

NBS for CF in Europe

- Started in 1970 in NZ -> National programs in Europe: 1997 Austria, 2002 France

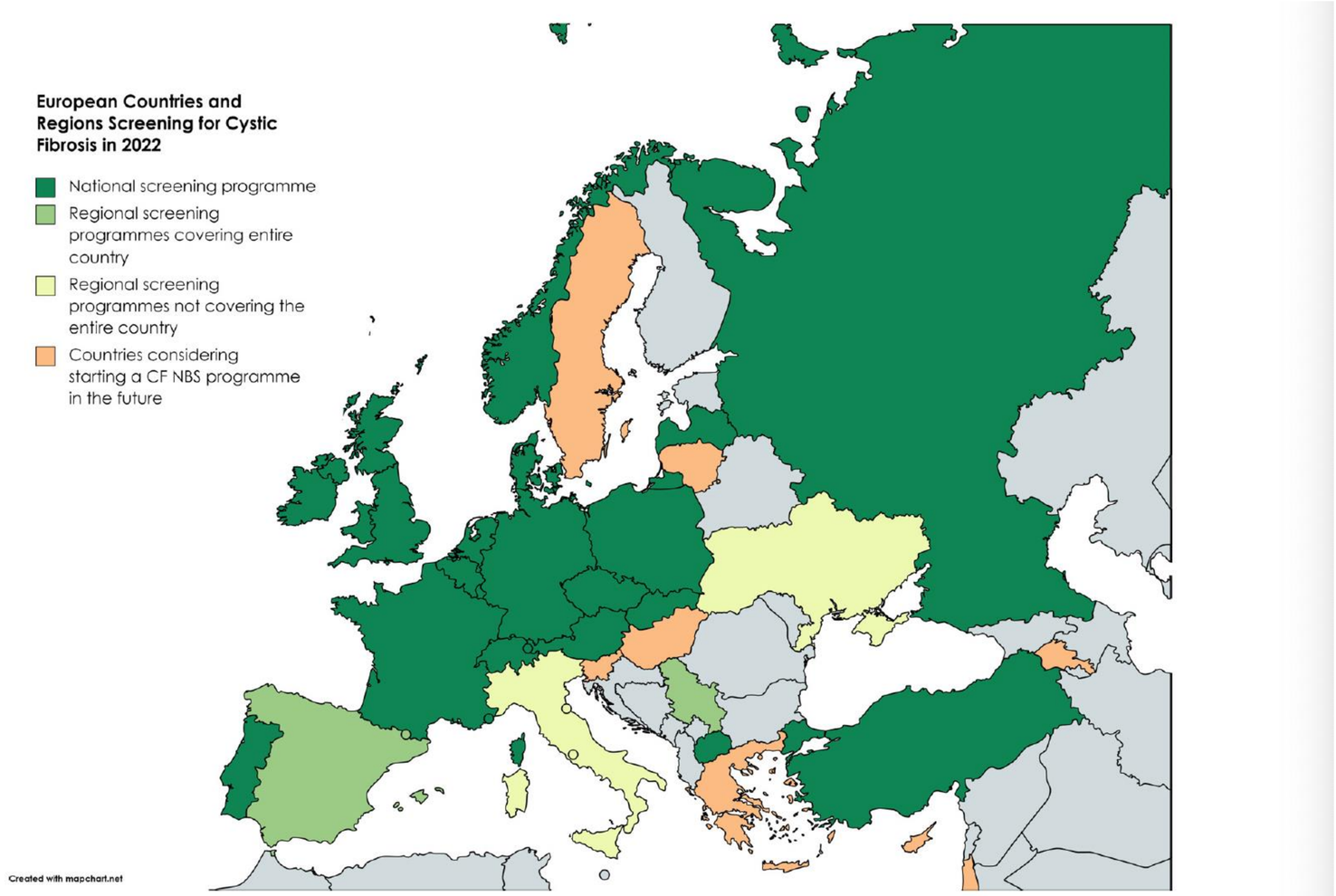


Fig. 1. The status of NBS for CF in Europe 2022.
National programmes are coloured dark green and regional programmes, light green. Countries considering or planning NBS for CF are coloured light orange and those with no plans, light grey.

Munck et al, JCF 2023:484

NBS for Cystic Fibrosis

- IRT = Immunoreactive trypsinogen
- Pancreatitis associated protein
- Genetic component: DNA, panel or extended gene analysis

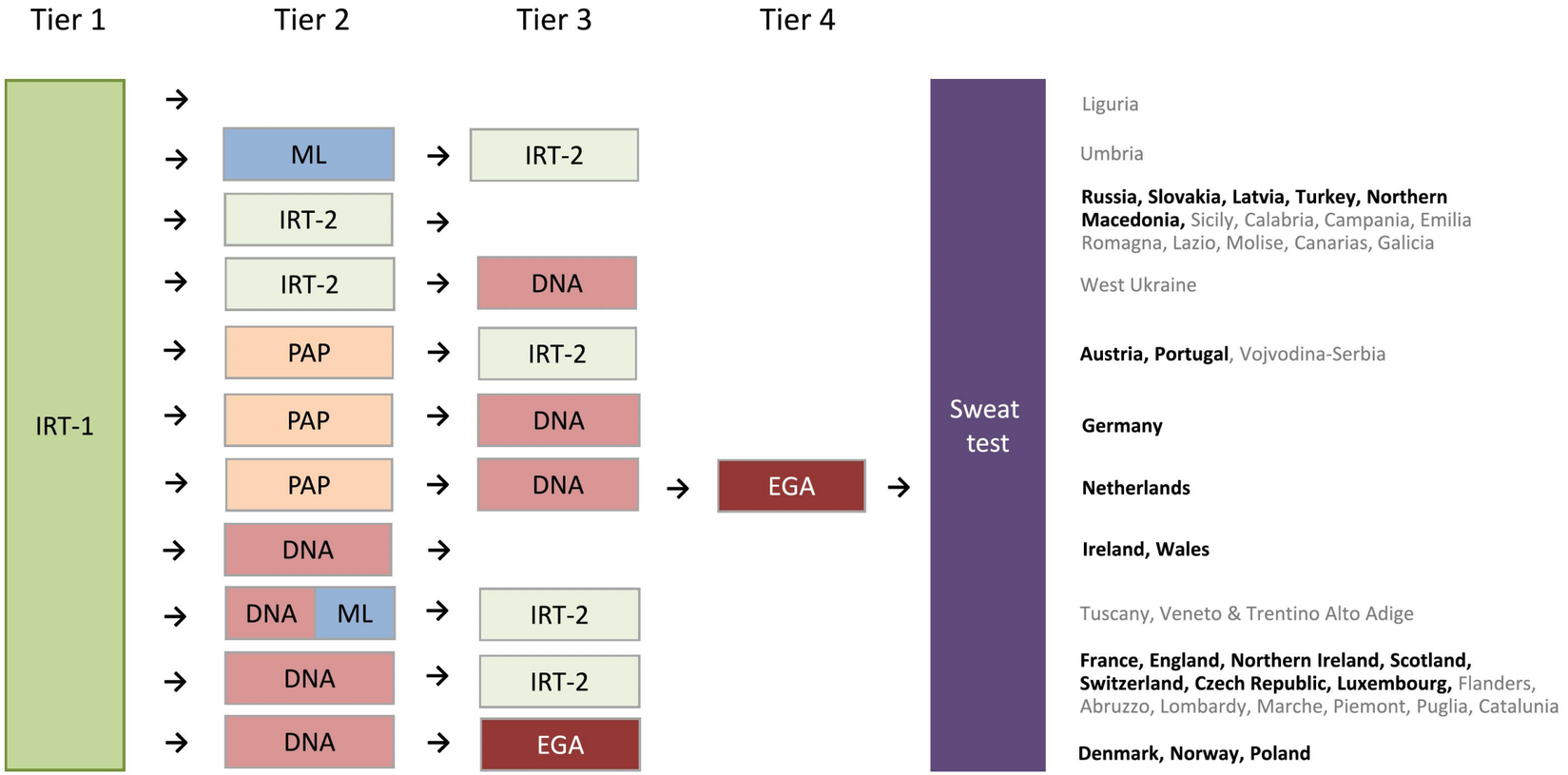
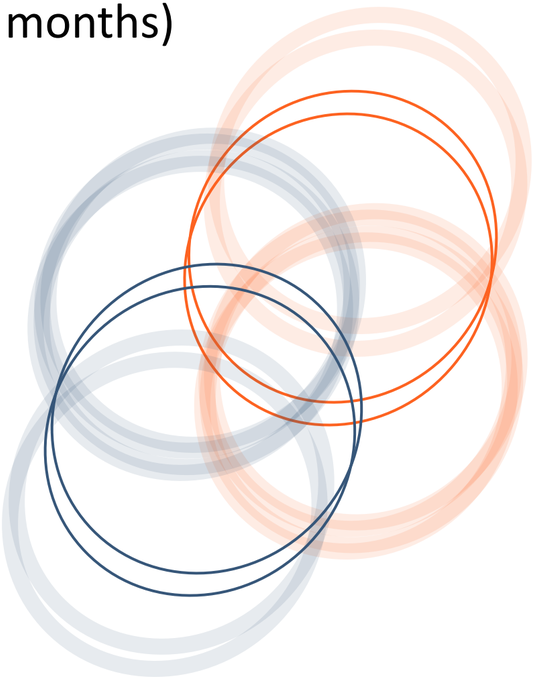


Fig. 2. Algorithm used for CF-NBS in 2019.
National programmes are written in black font and regional programmes in grey font.

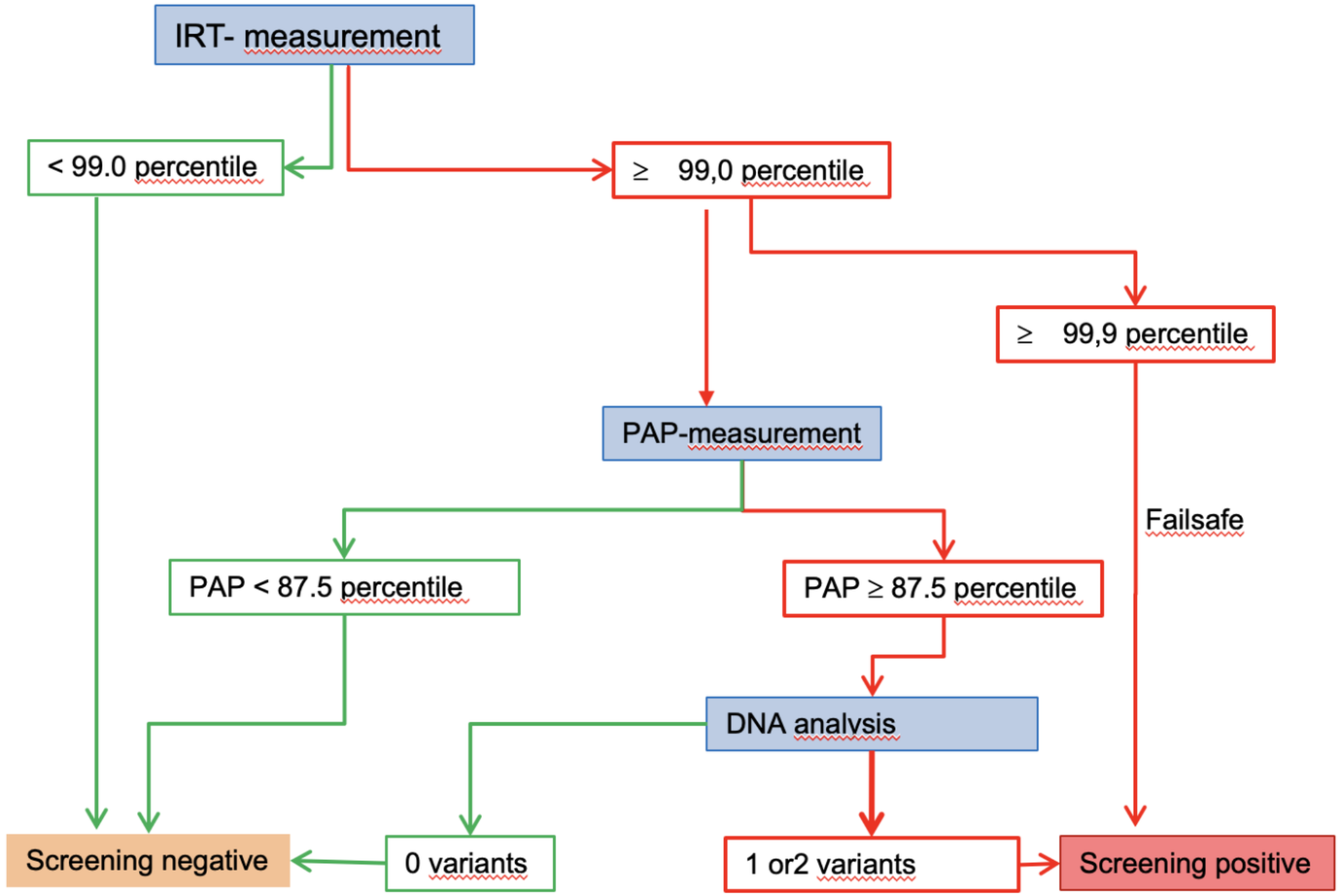
Munck et al, JCF 2023:484

NBS for Cystic Fibrosis in Germany

- Regional programs started in 1990s:
  - Saxony (since 1996; IRT-DNA (3 DNA variants)
  - Baden-Württemberg (since 2008; IRT-PAP-DNA (4 DNA variants)
  - Mecklenburg-Western Pomerania (since 2012; IRT-DNA)
- National program started 01.09.2016 (The Federal Joint Committee (Gba))
  - Benefit of NBS for CF ? > !
    - Age at diagnosis (2016: median 0,5 years, only 50% diagnosed in the first 12 months)
  - Screening-Algorithm ?
    - Balance between sensitivity and specifity!
    - Genetic component:
      - DNA panel: 31 most common CFTR-variants among German pwCF (German CF registry)
      - Avoiding/minimize carrier screening or « hide » carrier status!
      - Informed consent by doctors only, not by midwifes!



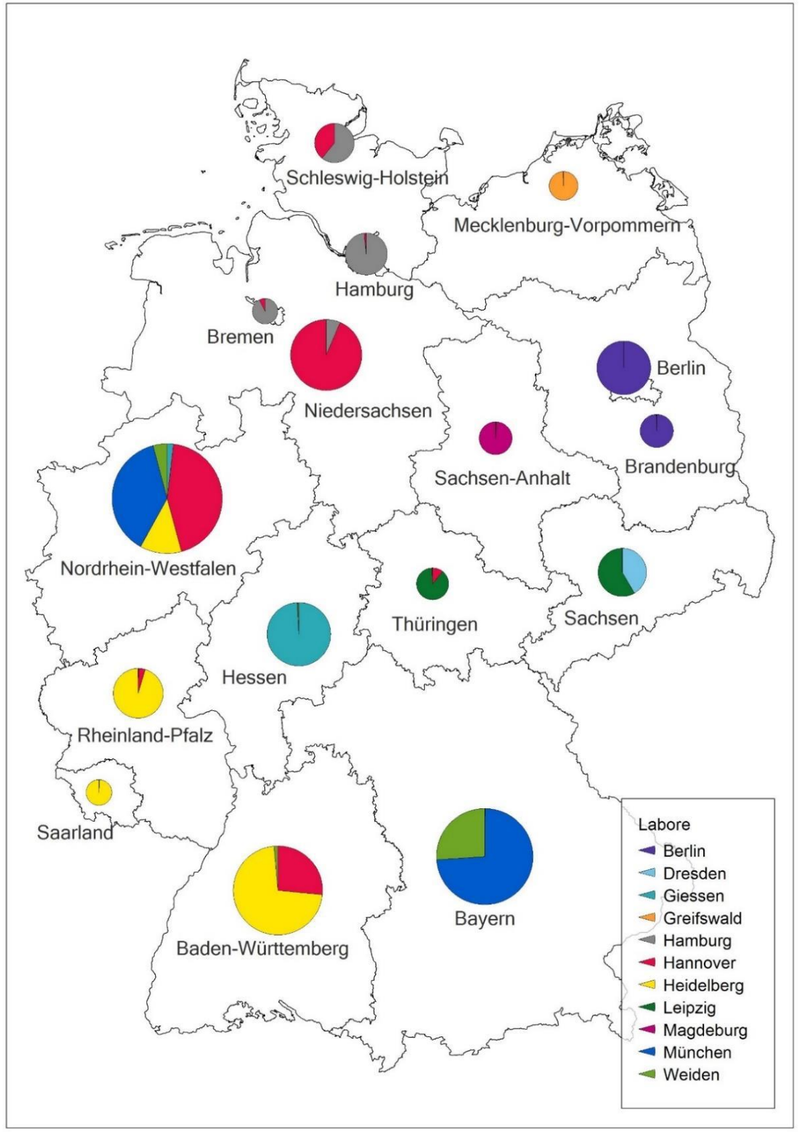
NBS for Cystic Fibrosis in Germany
Screening algorithm: IRT – PAP - DNA



DNA panel of 31 most common CFTR-variants among German pwCF (German CF registry)

Courtesy Brockow, DGNS

NBS for Cystic Fibrosis in Germany
Structure: 16 federal states - 11 screening labs



National Screening Report Germany 2021, https://www.screening-dgns.de

NBS for Cystic Fibrosis in Germany
Evaluation

National Screening Report*

German Society of Newborn Screening

DGNS

Since 2004

Quality report yearly

+ **Screening procedure**

- Limited feedback on diagnosis
  esp. late diagnosis

German CF Registry#

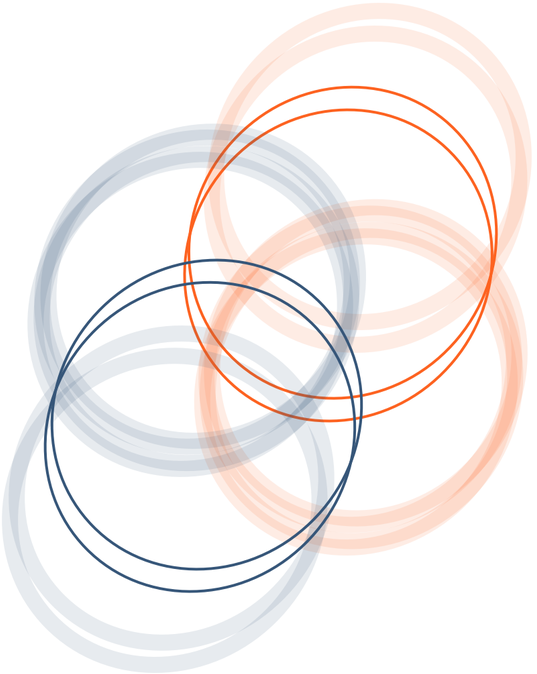
Mukoviszidose eV

DMR

Since 1995

Annual Report

+ Confirmed diagnosis
  incl. late diagnosis



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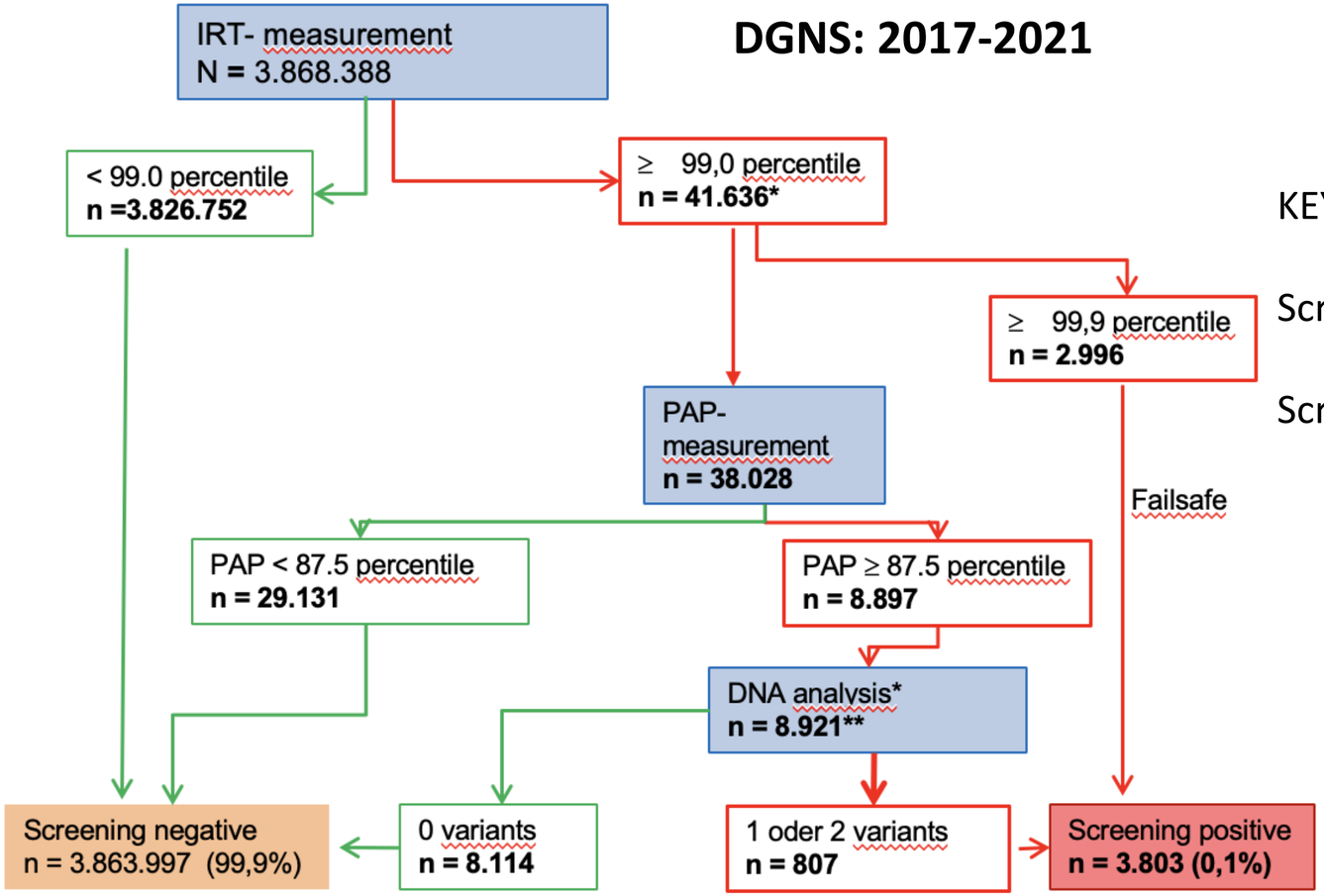
NBS for Cystic Fibrosis in Germany
Screening algorithm: IRT – PAP - DNA



KEYPOINTS

Screened for CF: 99% (additional IC!)

Screening positive: 0,1%

but 79% only by **failsafe net**

only 21% bei IRT-PAP-DNA

* DNA in case of abnormal PAP x IRT
DNA panel of 31 most common CFTR-variants among German pwCF (German CF registry)

German Society of Newborn Screening (DGNS) 2017-2021
Courtesy Brockow, DGNS

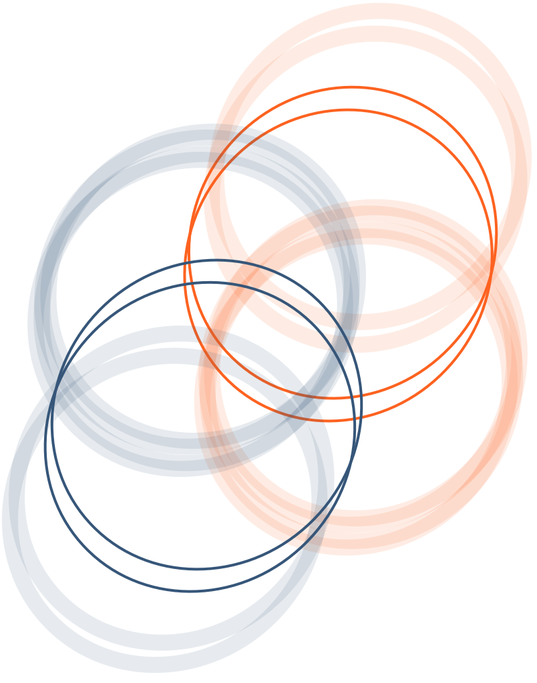
NBS for Cystic Fibrosis in Germany
« Screening positive" to confirmation

2016-2024
Screening lab inform maternity clinic
Maternity clinic inform parents
Parents contact sweat test lab (not obligatory: CF center)
Sweat test lab inform screening lab (not obligatory!)
-> No unified tracking system ! Quality control only !

Regional tracking systems
In Bavaria, Berlin, Hessen

REEVALUATION IN 2024:

2025-
Screening lab inform parents
Parents/screening lab contact CF center (oligatory)
CF center inform screening lab (obligatiory!)
Unified tracking system !



NBS for Cystic Fibrosis in Germany
Evaluation

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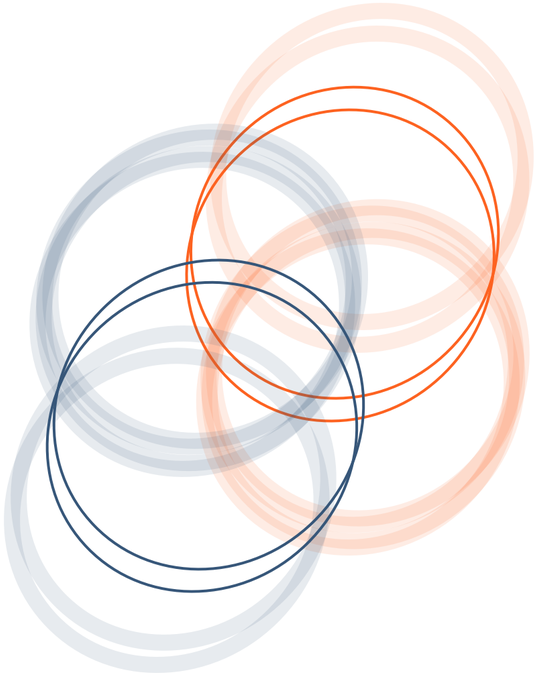


NBS for Cystic Fibrosis in Germany
Outcome

	DGNS 2017-2021	DMR2017-2021
CF	563	879
CFSPID	32	31
CF/CFSPID ?	172	
CF und CFSPID	767	910
Ratio CF:CFSPID	17,6:1	28,4:1

Reason for discrepancies:

DGNS: Lost to follow rate , incomplete information's on genetic

DMR: Born in Germany ?

Naehrlich, Bundesgesundheitsbl 2023
https://doi.org/10.1007/s00103-023-03778-1

Only in 1 out of 5 screening positive newborns CF is confirmed

3.919.150

NBS for Cystic Fibrosis in Germany
Outcome

Newborns with CF	2017-2021	Incidence (CF+CFSPID):
767 (DGNS)	3.919.150 life births	1:5246
910 (DMR)		1:4307

Age at diagnosis (2023): Median 0,1 years

False-negative screening results:

DGNS: 37 out of 767= **4,8%**

18x normal IRT (9x meconiumileus (MI); 15x normal PAP (4x MI), 4x no CFTR-Variant from screening panel

DMR: 49 von 910= **5,4%**

8x meconiumileus, 4x no CFTR-Variant from screening panel

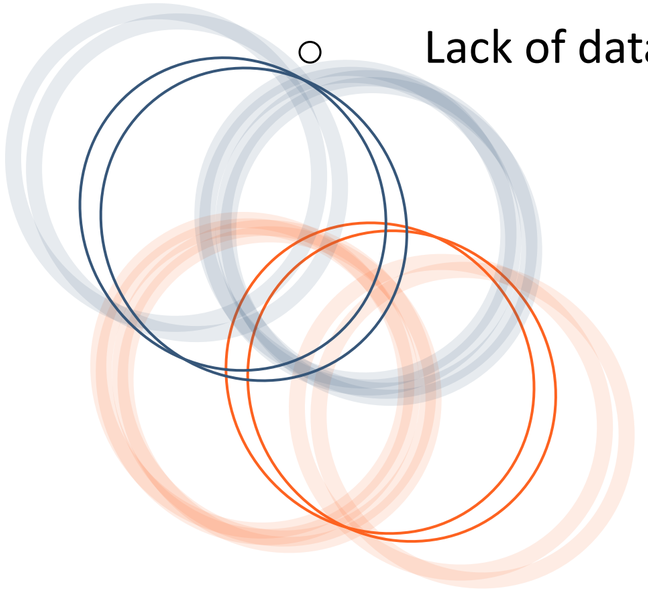
Naehrlich, Bundesgesundheitsbl 2023
https://doi.org/10.1007/s00103-023-03778-1

NBS for Cystic Fibrosis in Germany
Conclusion

Newborns screening for CF has led to earlier diagnosis in Germany

Lessons to be learned :

- Barrier of the additional Informed Consent for NBS for CF leads to 1% newborns not screened for CF!
- “Right not to know” (carrier status) leads to a low PPV of only 20%!
- ✓ Lack of tracking system leads to incomplete outcome analysis!
- Lack of data mapping between DGNS and DMR limit the long-term evaluation/epidemiologic knowledge.



- ❖ Data protection limit optimization
- ❖ Ethical concerns regarding (genetic) discrimination led to more uncertainty