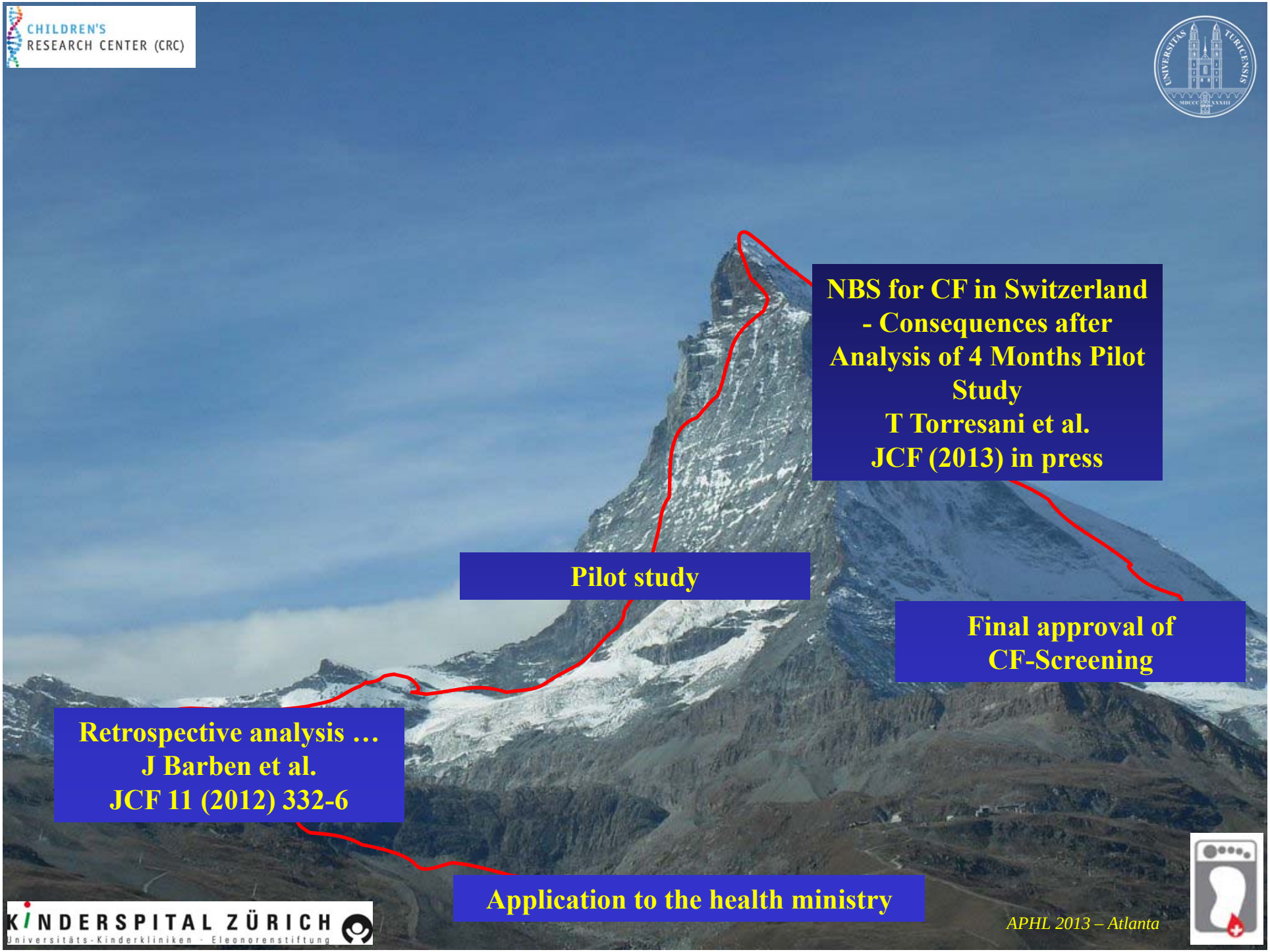
Newborn Screening for Cystic Fibrosis in Switzerland - Evaluation after two years

R. Fingerhut, T. Torresani, S. Gallati, M.H. Schoeni, C. Kuehni, C. Rueeg, M. Baumgartner, J. Barben and the Swiss CF Screening Group


CHILDREN'S
RESEARCH CENTER (CRC)
NBS for CF in Switzerland
- Consequences after
Analysis of 4 Months Pilot
Study
T Torresani et al.
JCF (2013) in press
Pilot study
Final approval of
CF-Screening
Retrospective analysis …
J Barben et al.
JCF 11 (2012) 332-6
Application to the health ministry
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Legal Regulations

NBS = Genetic Screening

informed consent necessary

IRT/DNA protocol approved

CF-screening result pos./neg.

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Cut-off definitions

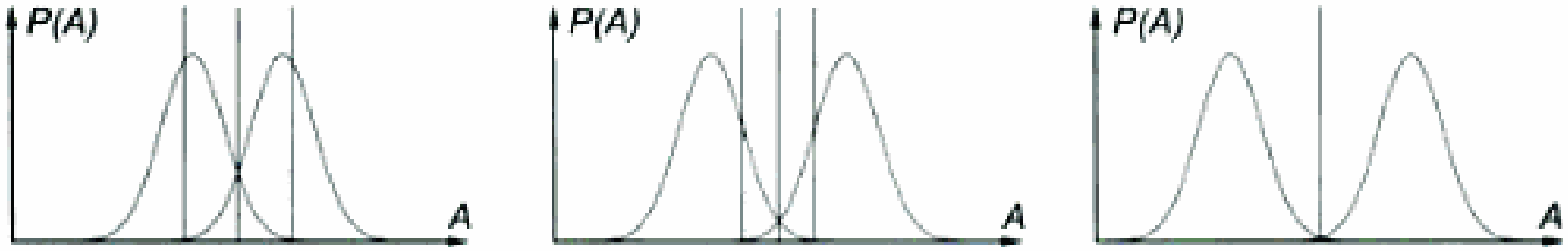
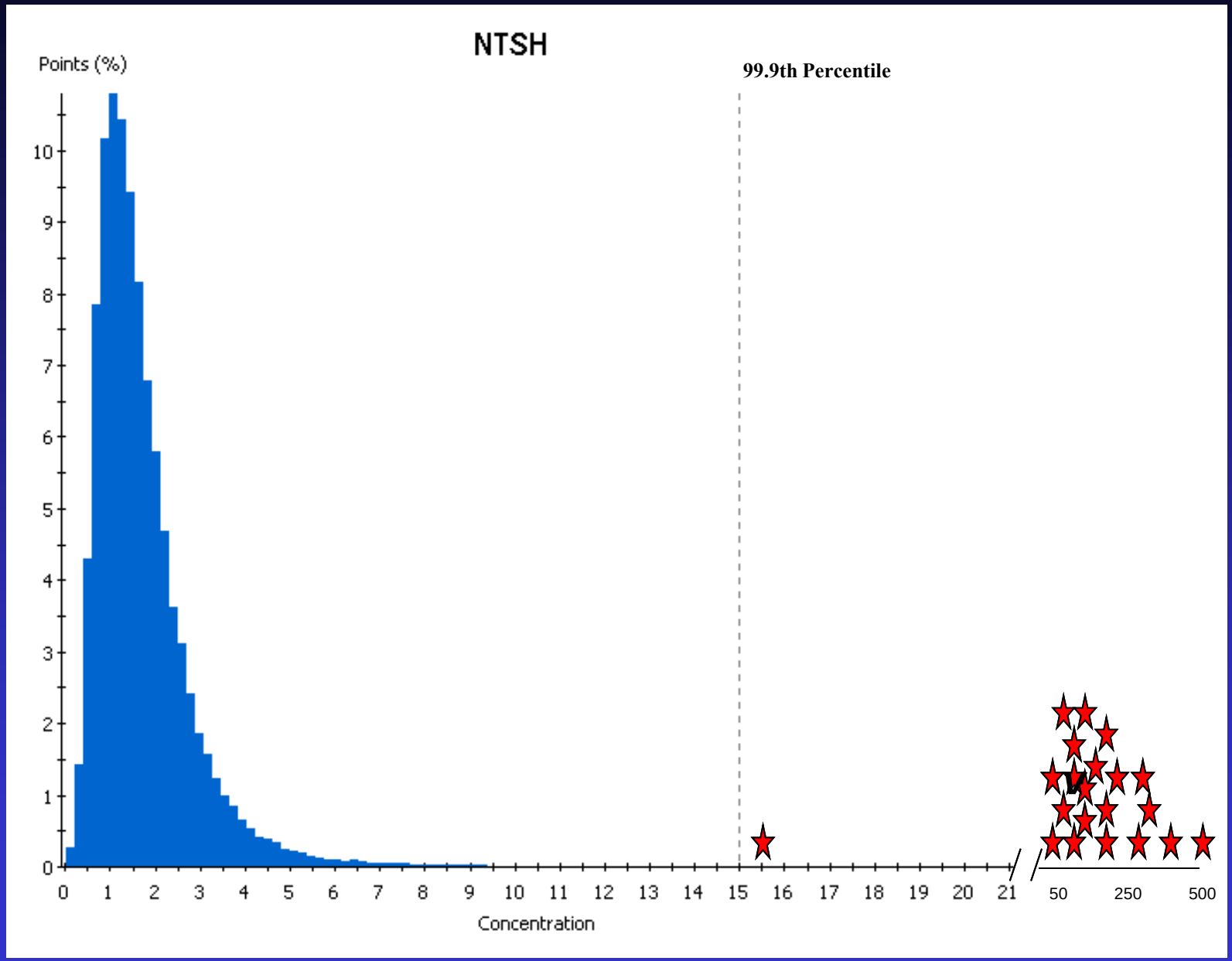
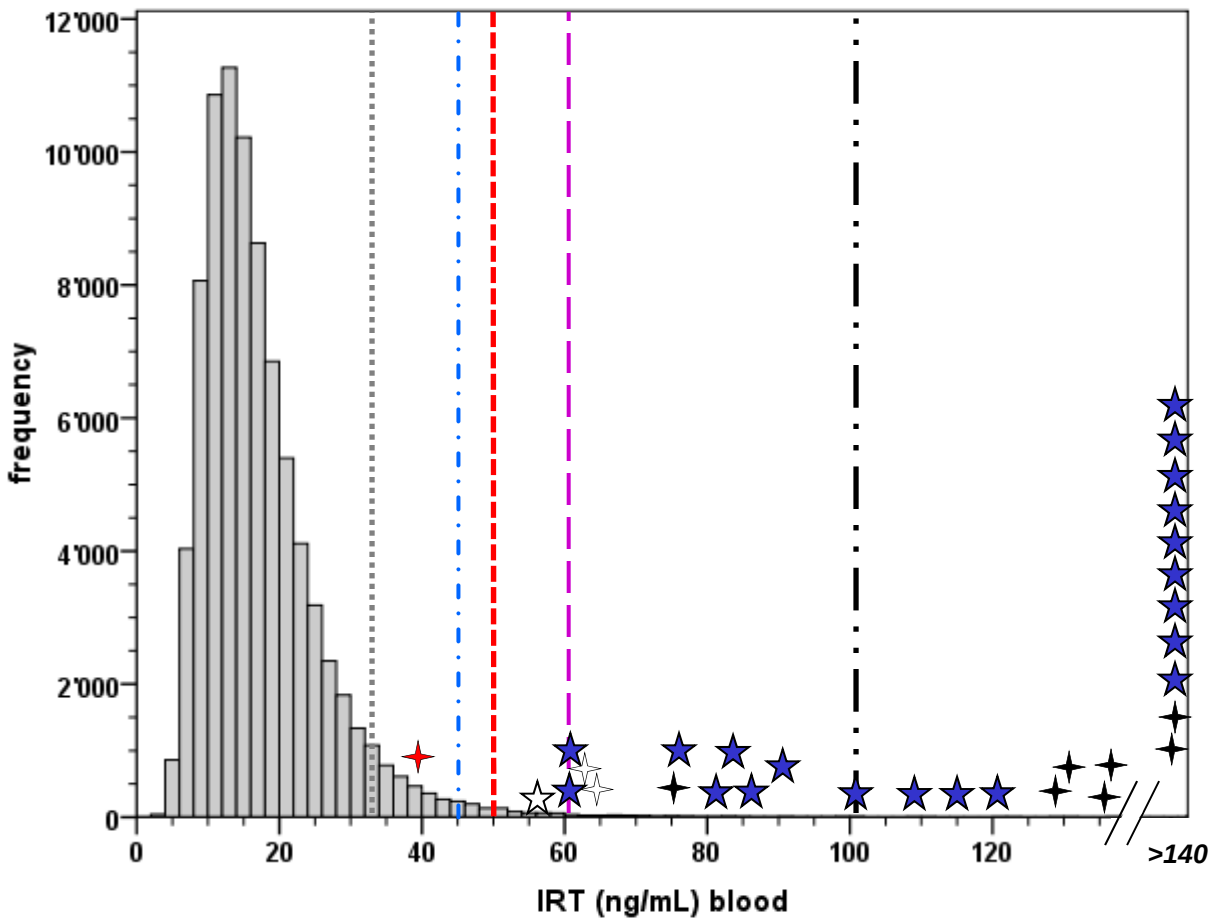


Abb. 12.1: Normalverteilte Ausprägungen des Merkmals *A*. Die vertikalen Linien markieren mögliche Schwellenwerte als Entscheidungskriterium.

from: Lehmann „Handbuch der Medizinischen Informatik“


NTSH
Points (%)
99.9th Percentile
0
1
2
3
4
5
6
7
8
9
10
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21
50
250
500
Concentration



Percentiles

95.0

99.0

99.2

99.5

99.9

- CF pos. (n=27)
- Equivocal CF (n=3)
- CF pos. with meconium ileus and normal IRT

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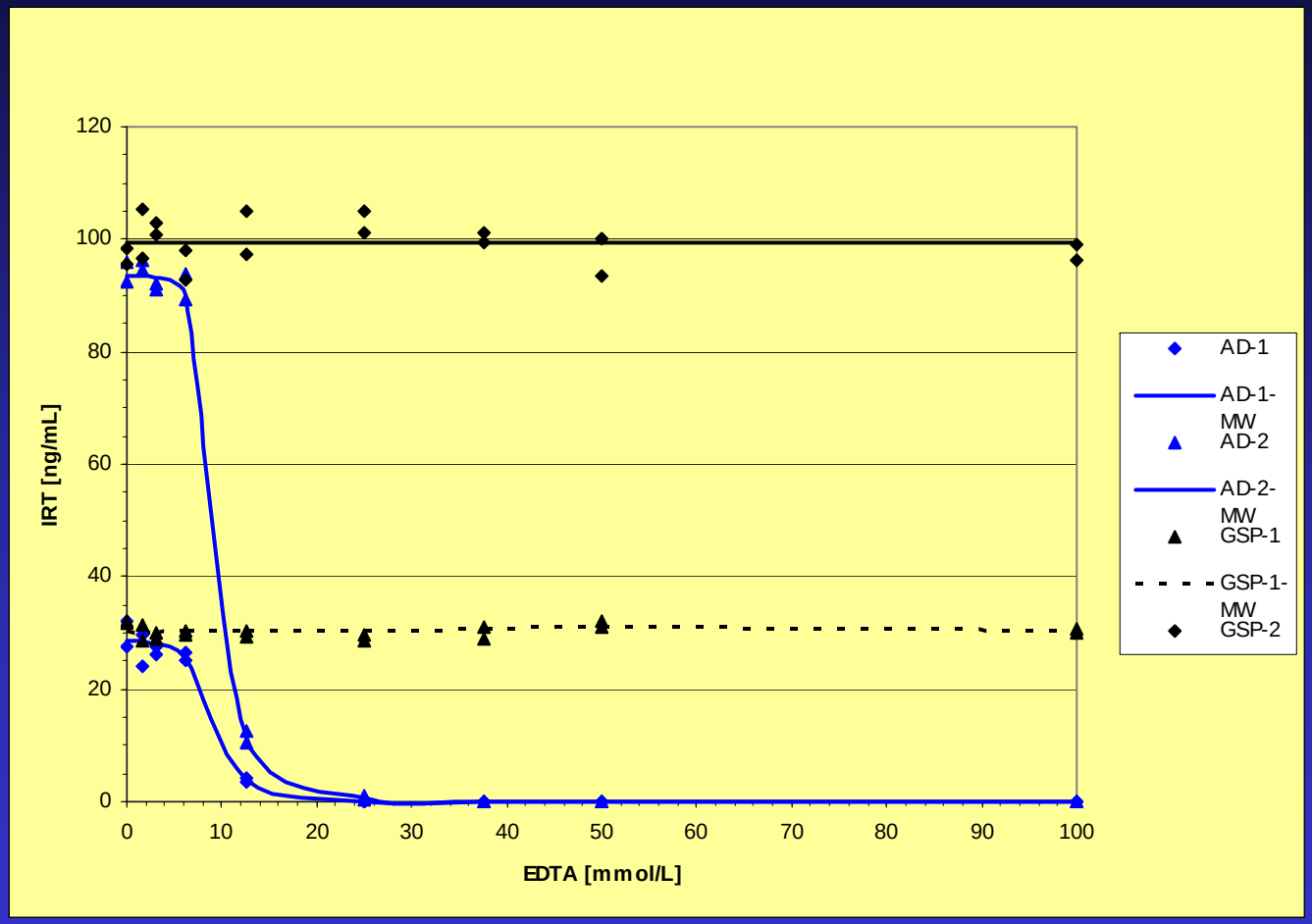
IRT-Determination with the GSP™



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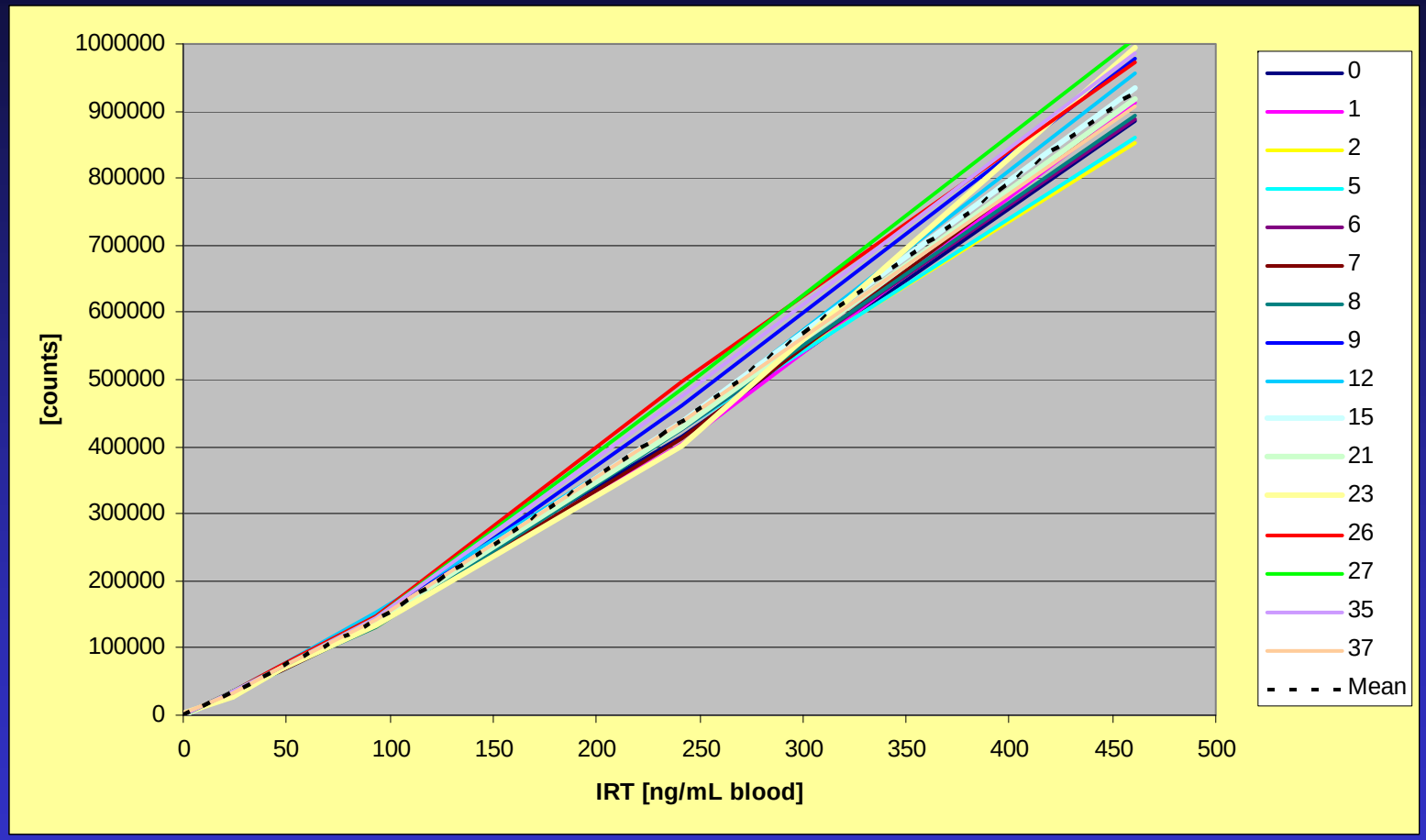
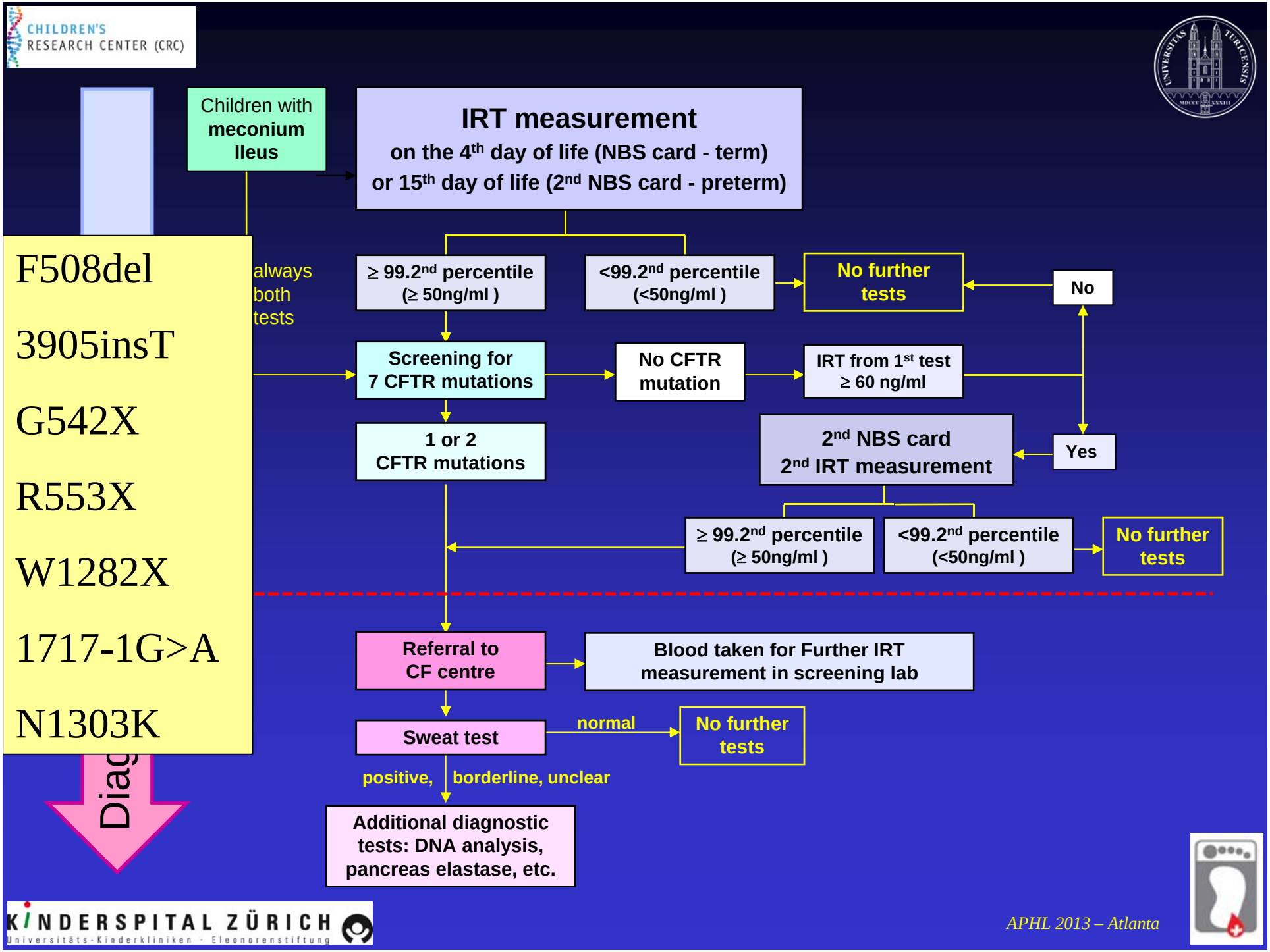

1000000
900000
800000
700000
600000
500000
400000
300000
200000
100000
0
[counts]
0
50
100
150
200
250
300
350
400
450
500
IRT [ng/mL blood]
0
1
2
5
6
7
8
9
12
15
21
23
26
27
35
37
Mean

Analyte	Intra-Assay CV	Inter-Assay CV	mean recovery [%]
IRT	3.5 (at 31.6 ng/mL; n=12) 5.0 (at 67.6 ng/mL; n=12) 2.7 (at 100.0 ng/mL; n=12)	6.1 (at 31.6 ng/mL; n=30) 5.8 (at 67.6 ng/mL; n=30) 5.7 (at 100.0 ng/mL; n=30)	97.8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Children with meconium Ileus
IRT measurement
on the 4th day of life (NBS card - term)
or 15th day of life (2nd NBS card - preterm)
F508del
3905insT
G542X
R553X
W1282X
1717-1G>A
N1303K
always both tests
≥ 99.2nd percentile (≥ 50ng/ml)
<99.2nd percentile (<50ng/ml)
No further tests
No
Screening for 7 CFTR mutations
No CFTR mutation
IRT from 1st test ≥ 60 ng/ml
1 or 2 CFTR mutations
2nd NBS card
2nd IRT measurement
Yes
≥ 99.2nd percentile (≥ 50ng/ml)
<99.2nd percentile (<50ng/ml)
No further tests
Referral to CF centre
Blood taken for Further IRT measurement in screening lab
Sweat test
normal
No further tests
positive, borderline, unclear
Additional diagnostic tests: DNA analysis, pancreas elastase, etc.
Diag
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Procedure in CF centre since 2012

Sweat test
Measurement of chloride and conductivity

Cl ≥ 60 mmol/L Conductivity ≥ 80 mmol/L	Cl 30-59 mmol/L Conductivity 50-79 mmol/L	Chloride < 30 mmol/L Conductivity < 50 mmol/L	Sweat test not possible
DNA analysis 32 CFTR mutations ***(informed consent !)***	DNA analysis 32 CFTR mutations ***(informed consent !)***	Information about possible carrier status or atypical CF • ***Information sheet for parents*** • ***Information to GP about elevated IRT and normal sweat test***	DNA analysis 32 CFTR mutations, total DNA analysis if needed ***(informed consent !)***
2 mutations → CF diagnosis	2 mutations → Equivocal CF or CF		CF, equivocal CF, CF carrier or healthy
1 mutation → total DNA analysis	1 mutation → total DNA analysis		
total DNA analysis: 2 mut. → CF diagnosis	total DNA analysis: 2 mut. → Equivocal CF or CF		
total DNA analysis: 1 mutation → Follow up and further investigations	total DNA analysis: 1 mutation → Follow up and further investigations		

Feedback to the NGS laboratory – fill in assessment sheet for data base

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Summary of the pilot study

Parameter	Definition of success	Evalution after two years
Diagnosis of children with CF (compared to earlier years with clinical diagnosis)	**≥15 per year**	**56 CF + 9 equivocal CF**
Care of children with CF in a CF centre	**>90%**	**100 %** (56/56)
Deniers of Guthrie test	**Not elevated to earlier years (<10 per year)**	**2011: 5 / 2012: 6**
Recall rate (Percentage of children who required further investigations)	**assumed < 1%**	**0.58 %** ((168+805)/167'819)
Positive predictive value (PPV)	**> 20%**	**29.2 %** (49/186)
False negatives (without MI)	**<5% of all CF diagnosis**	**3.7 %** (2/56)
Time to genetic diagnosis	**Before NBS: 198 days** (13-1033) **Aim: < 60 days**	**41 days** (12-160)
Satisfaction of parents with a CF child	**>80% are satisfied**	**2011: 100%** (18/18), **2012: 96%**
Satisfaction of parents with positive screening but without CF diagnosis	**>70% are satisfied**	**2011: 86%** (25/29), **2012: 86%**

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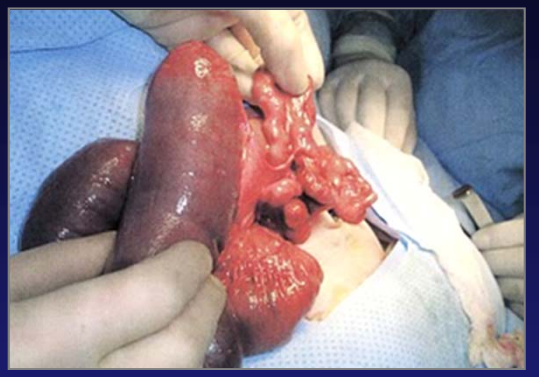
Results after 2 years

Time from birth to CF diagnosis

Parameter (days)	Mean	Median	Interquartile range	Range
Birth – genetic diagnosis	48.1	41	28-56	12-160
Birth – heel prick test	5.9	5	5-6	4-47
Heel prick test – notification of CF centre	13.2	10	8-15	1-115
Notification of CF centre – phone call to parents	7.2	5	3-9	0-44
Phone call to parents – visit in CF centre	1.9	1	1-2	0-10
Birth – visit in CF centre	31.8	25	20-32.5	4-314
Visit in CF centre – genetic diagnosis	19.8	16	8-26	1-80
Duration of genetic analysis	13.6	11.5	5-19	1-42

Results after two years

Children with meconium ileus



2011

8 children with MI

- 1 without CF
- 7 with CF

No.	IRT	Mutation
1	77.7	F508del / 1717-1G>A
2	119.5	F508del / F508del
3	89.9	F508del / F508del
4	102.3	F508del / F508del
5	54.4	F508del / F508del
6	88	F508del / F508del
7	39.5	F508del / F508del

2012

7 children with MI

- 3 without CF
- 4 with CF

No.	IRT	Mutation
1	71.7	F508del / F508del
2	117.9	F508del / N1303K
3	50.5	W1282 / R347H
4	29.5	F508del/TG11_T5

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Newborn screening

Situation in Switzerland 1965 - 2012

Disease	Tested babies	Cases	Frequency
Phenylketonuria (+ Hyperphenylalaninemia)	**3'705'005**	**465**	**1 : 7'968**
Galaktosemia	**3'536'372**	**87**	**1 : 40'648**
Hypothyroidism	**2'851'700**	**783**	**1 : 3'642**
Biotinidase-Deficiency	**2'116'336**	**37** **(+ 13 mild forms)**	**1 : 57'198** **(1 : 42'327)**
Congenital adrenal hyperplesia	**1'692'673**	**179**	**1: 9'456**
MCAD Deficiency	**634'760**	**58**	**1 : 10'944**
Cystic Fibrosis	**167'819**	**65**	**1:2'581**

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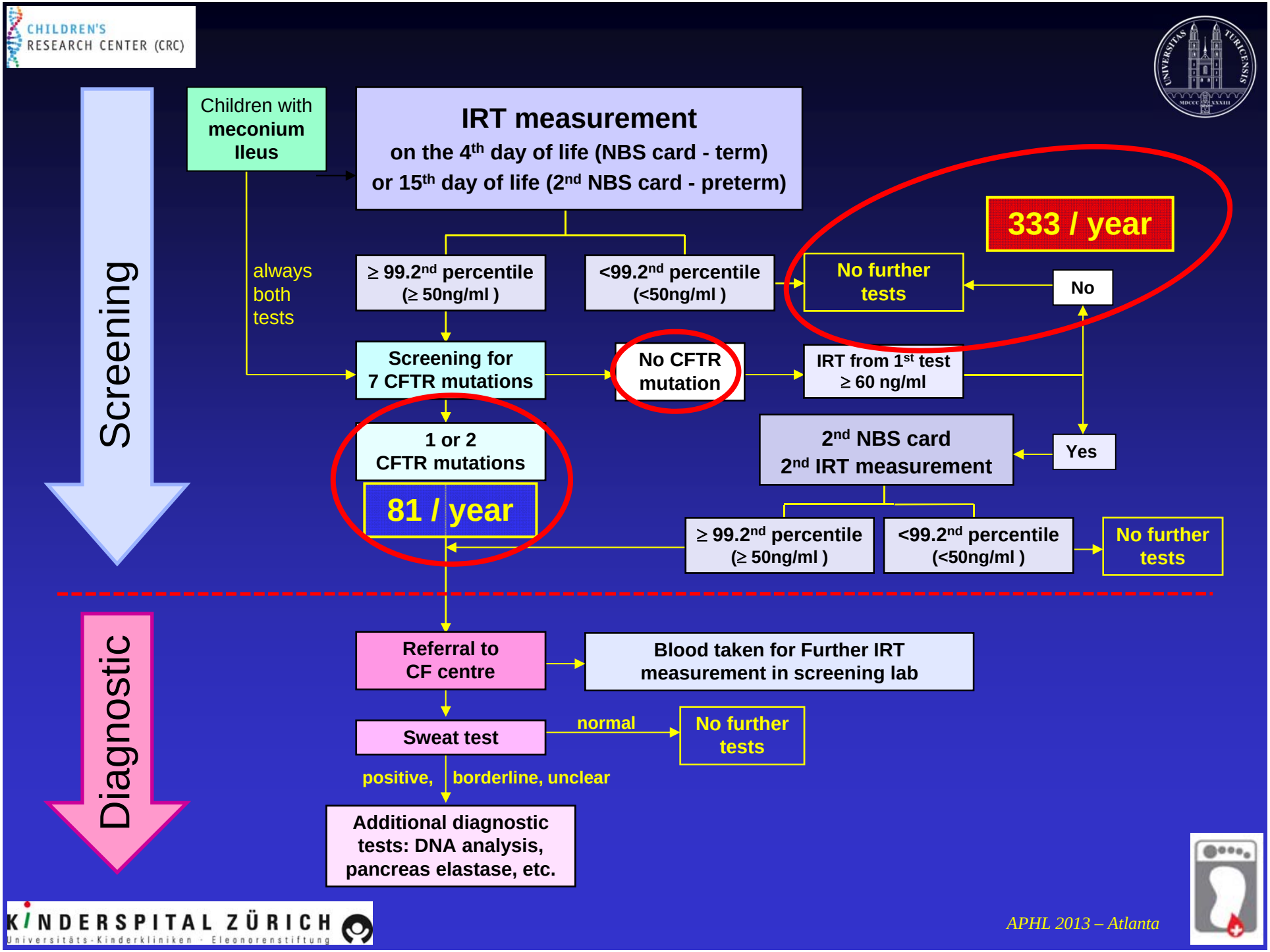
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<99.2nd percentile (<50ng/ml)
No further tests
333 / year
No
Screening for 7 CFTR mutations
No CFTR mutation
IRT from 1st test ≥ 60 ng/ml
1 or 2 CFTR mutations
81 / year
2nd NBS card
2nd IRT measurement
Yes
≥ 99.2nd percentile (≥ 50ng/ml)
<99.2nd percentile (<50ng/ml)
No further tests
Diagnostic
Referral to CF centre
Blood taken for Further IRT measurement in screening lab
Sweat test
normal
No further tests
positive, borderline, unclear
Additional diagnostic tests: DNA analysis, pancreas elastase, etc.
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CF-Screening in Switzerland

Thanks to the Swiss CF Screening-Group

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M. Baumgartner	*J. Hammer*	*D. Müller*	*M.H. Schöni*	*M. Zanolari*
C. Casaulta				

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Thanks to the Colleagues from the Screening-Lab:

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