DGNS Jahrestagung 2015, Burg Nürnberg

Die Cut-Off-Frage im Screening auf Congenitale Hypothyreose

…sollte nicht alles klar sein nach mehr als 30 Jahren…?

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CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN

Berliner Centrum für seltene Erkrankungen

The initial aim: to prevent the burden of severe CH

(…a fairly old story…)

Treatment with

thyroid extract

NEONATAL

SCREENING
To avoid mental retardation

1977

W. Osler **1897**
Trans Congress of American Physicians and Surgeons, 4,169-206

Clinical features (if any) of severe CH

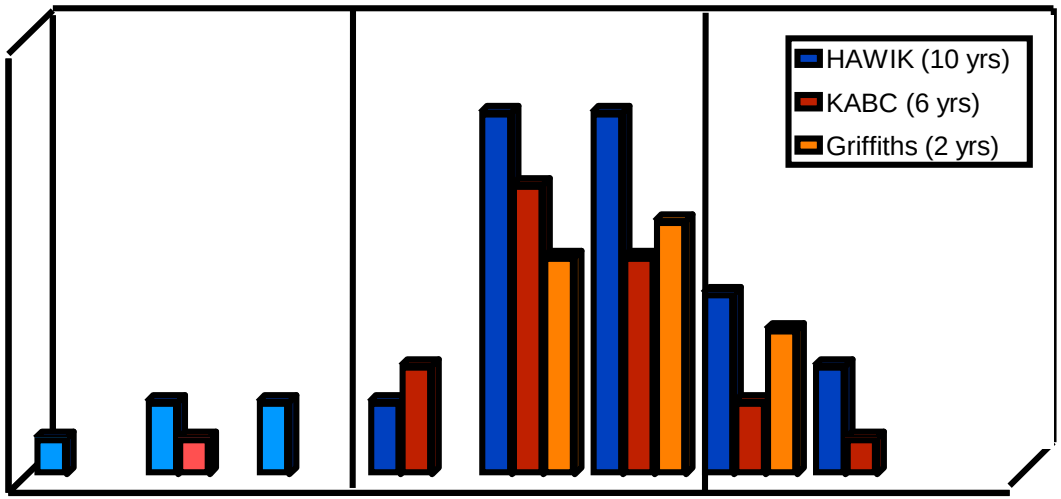
- Brittle Hair
  low hairline
- Coarse facial features
- Prolonged jaundice
- Umbilical hernia
- Dry skin
- Reduced motoric activity
- Sleepiness, poor feeding

L-T4-Treatment

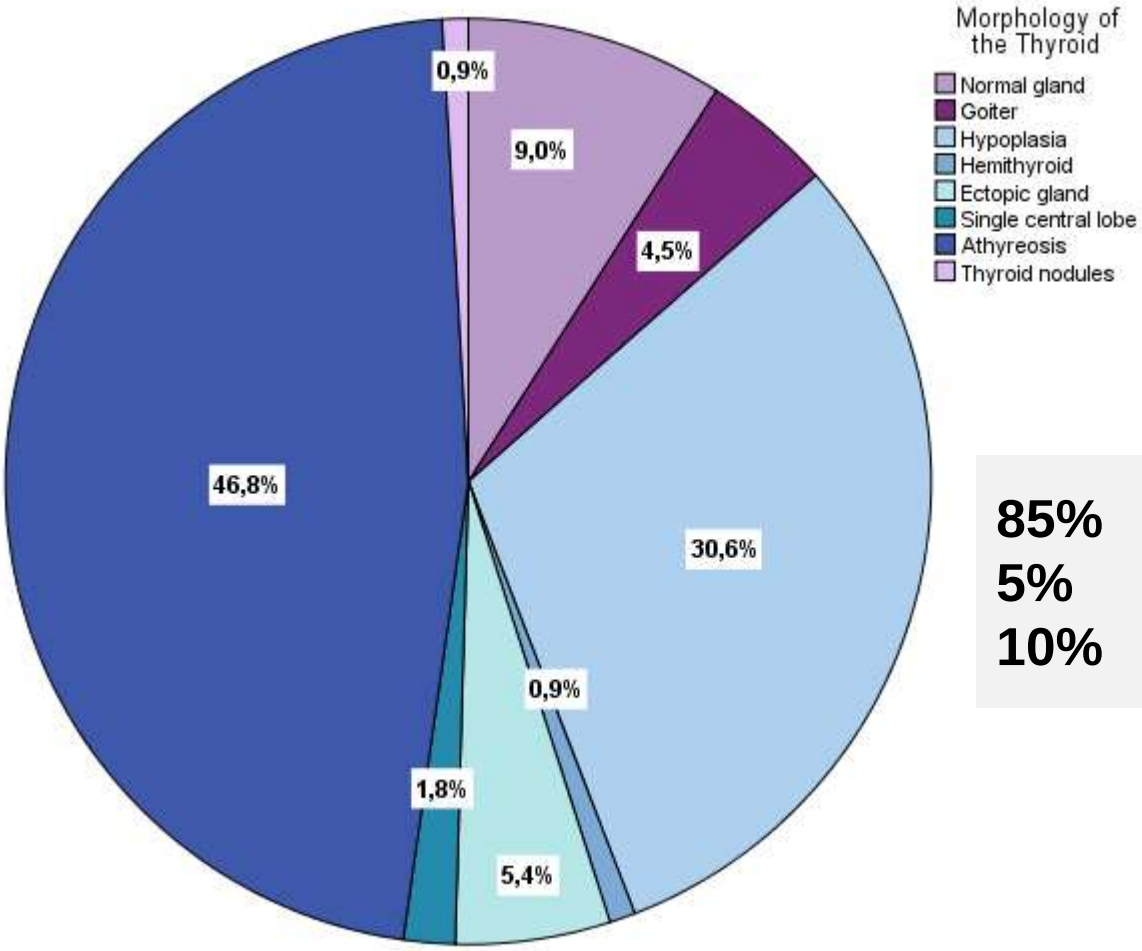
Outcome in congenital hypothyroidism: today

(15µg/KG body weight, TSH normal after 2 weeks Tx)

IQ/EQ values of the first 103 children diagnosed in the Berlin TSH Screening program



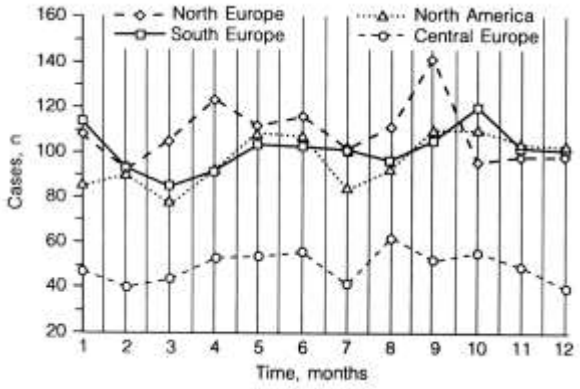
CH morphology (Berlin data): 85% thyroid dysgenesis



85%	**Dysgenesis**
5%	**Goiter**
10%	**normal thyroid**

Epidemiology of Congenital Hypothyroidism:

no seasonal influence



incidence

Europe	1 : 3.500
USA	1 : 3.800
Canada	1 : 3.290
Japan	1 : 3.850
New Zealand	1 : 3.980
Australia	1 : 3.415
Wales	1 : 1.748 ?
Italy	1 : 1.783 ?

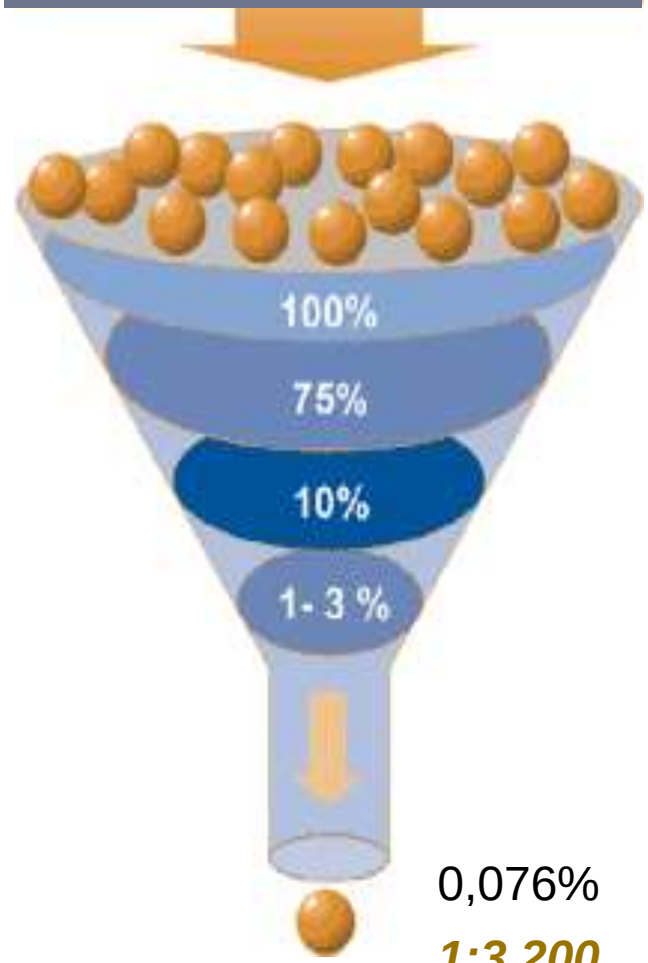
What's going on there…?

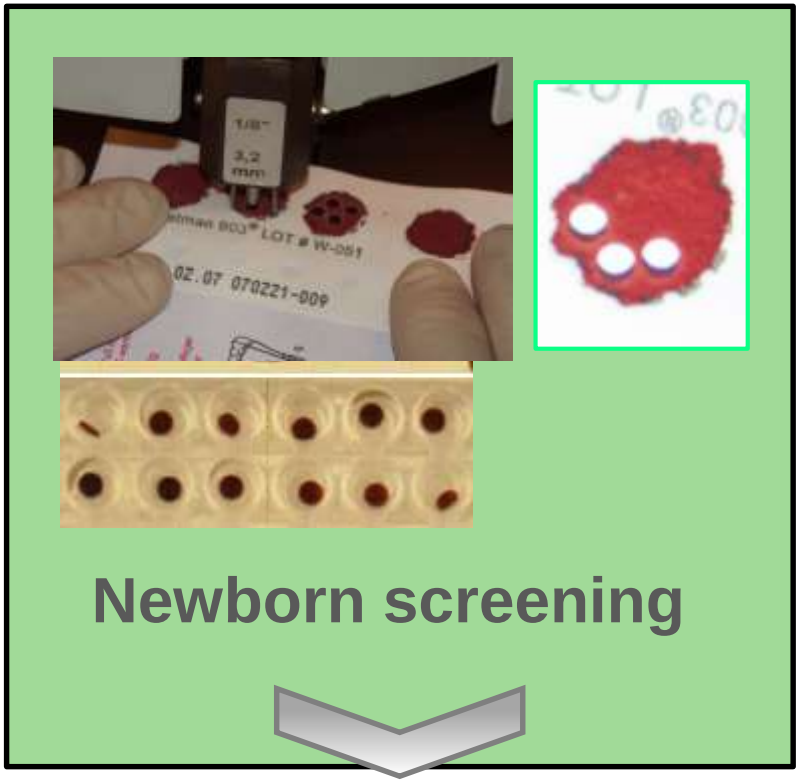
African American Population	1 : 11 000 – 1 : 32 000

Newborn screening – basic principle

All Newborns

680.000 births in Germany

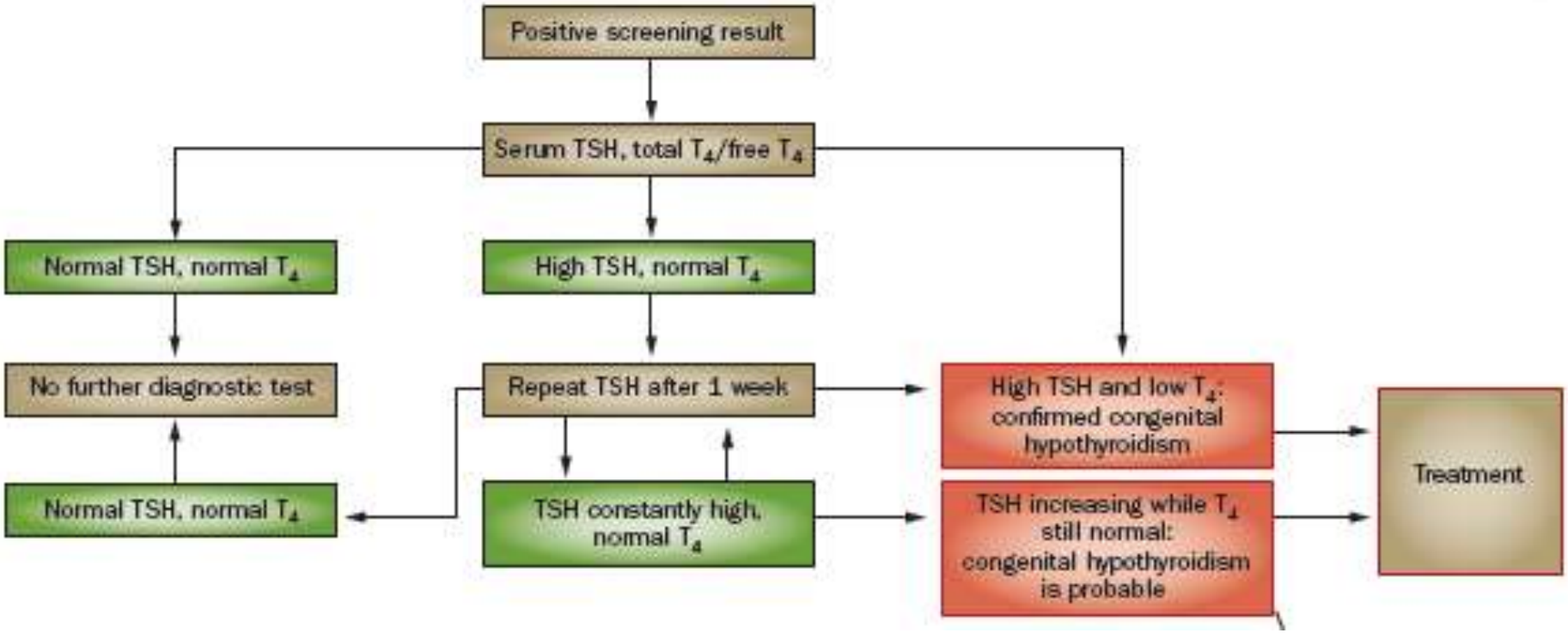




0,076% — **518** — **Confirmed affected**

1:3.200 — *195* — *Cong. Hypothyroidism*

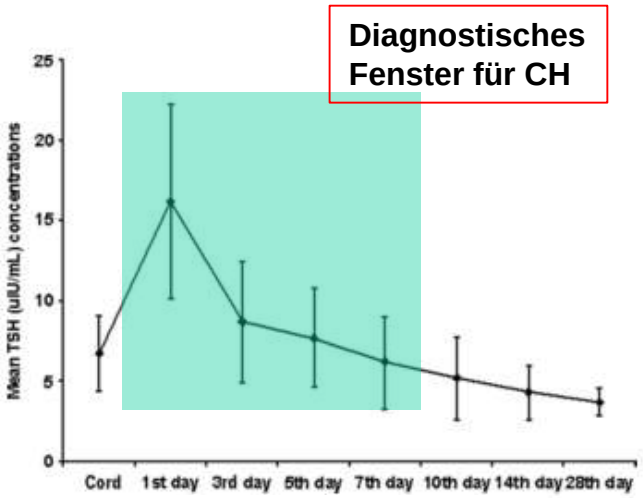
The critical decision: Confirmation diagostic – who to treat?

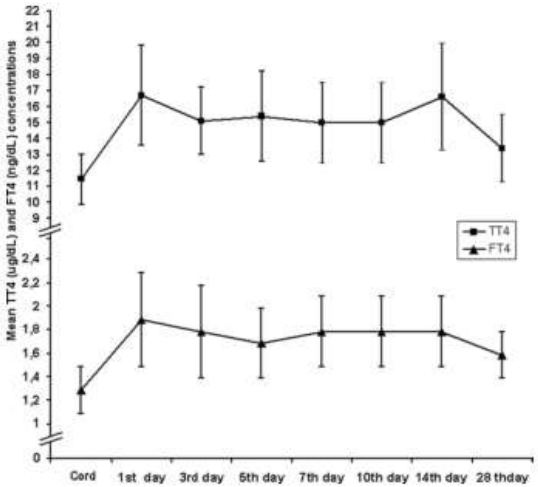


Hypothyroidism a deficiency of thyroid hormone (T3/T4)

- **Low peripheral thyroid hormone (T4/fT4) is required for confirmation**
- **No diagnosis based on elevated TSH alone (!)**
- **IF TSH > 40 mU/l → low T4 is likely but has to be checked**
- fT3 is un-reliable in newborns

Perinatale SD-Funktion
Referenzbereiche sind essentiell !!





		TSH (ml/Ul)		TT4 (μg/dl)		FT4 (ng/dl)	
Age	*n*	2.5th	97.5th	2.5th	97.5th	2.5th	97.5th
Cord	47	2.22	10.66	7.79	13.14	1.07	2.02
1st day	29	2.69	26.50	10.07	20.89	1.20	2.61
3rd day	39	2.83	18.58	9.93	17.64	1.20	3.30
5th day	28	2.12	13.08	9.28	19.51	1.06	2.30
7th day	30	1.34	12.08	8.05	20.15	1.13	2.69
10th day	82	1.19	10.72	9.21	19.26	1.18	2.49
14th day	22	1.72	7.87	9.71	21.81	1.13	2.23
28th day	19	2.02	4.79	8.03	16.82	1.23	1.94
Adult	50	1.07	3.77	7.88	13.80	0.91	1.42

		TT3 (ng/ml)		FT3 (pg/ml)	
Age	*n*	2.5th	97.5th	2.5th	97.5th
Cord	47	0.50	1.24	1.15	2.81
1st day	29	1.04	3.38	2.25	7.47
3rd day	39	1.01	2.99	2.19	5.22
5th day	28	1.08	2.56	2.16	5.88
7th day	30	1.16	3.37	2.06	5.64
10th day	82	1.43	3.26	3.10	5.65
14th day	22	1.05	3.87	2.34	6.20
28th day	19	1.36	2.67	3.10	4.94
Adult	50	0.94	1.94	1.60	4.23

The Journal of Maternal-Fetal and Neonatal Medicine, 2012; 25(2): 120–124

The “bitter” reality among paediatric endocrinologists

Treatment

Newborns with s-TSH higher than 20 mU/L and normal or low FT4 were considered to have congenital hypothyroidism and promptly started on L-T4 treatment. Infants with repeatedly increased s-TSH levels between 10 and 19.9 mU/L after the first month of birth also received substitution therapy with L-T4. Replacement therapy with L-T4

Screening for congenital hypothyroidism: Definition of the disease:

The pre-screening view:

Incidence of congenital hypothyroidism: retrospective study of neonatal laboratory screening versus clinical symptoms as indicators leading to diagnosis

J ALM, L HAGENFELDT, A LARSSON, K LUNDBERG

Same cohort investigated „clinically“ without screening and 5 year later blood spot of PKU screening reinvestigated for TSH, cutoff 40mU/L

before screening: 1:6500, age of diagnosis: 5 months, IQ 45-116

after screening: 7 clinically not diagnosed cases, IQ 84-120

BRITISH MEDICAL JOURNAL VOLUME 289 3 NOVEMBER 1984

TABLE II—*Development and serum hormone concentrations at 5 years of age in 31 children with raised thyrotrophin concentrations in the neonatal period (filter paper blood sample)*

Case No	Sex	Neonatal plasma thyrotrophin (mU/l)	Age at start of treatment (months)	Follow up at 5 years: Griffiths developmental quotient	Neurological development: gross motor/fine and visual motor	Serum thyrotrophin (mU/l)	Serum thyroxine (nmol/l)	Serum triiodothyronine (nmol/l)
Patients with diagnosed congenital hypothyroidism (n = 15)								
1	M	>100	<1	80	—	—	—	
2	F	>100	<1	106	N/N	—	—	
3	F	>100	<1	107	N/N	—	—	
4	F	>100	<1	116	N/N	—	—	—
5	F	>100	2	58	R/R	—	—	—
6	F	>100	3	87	R/R	—	—	—
7	F	>100	5	—	—	—	—	—
8	F	>100	5	98	N/N	—	—	—
9	M	>100	7	90	N/N	—	—	—
10	M	>100	14	76	N/N	—	—	—
11	F	>100	14	82	R/R	—	—	—
12	M	>100	16	45	R/R	—	—	—
13	F	>100	33	85	N/N	—	—	—
14	F	>100	37	79	R/R	—	—	—
15	F	>100	41	111	N/N	—	—	—
Mean (SD)				87 (20)				
Patients with undiagnosed congenital hypothyroidism (n = 7)								
16	F	>100		94	N/N	40	69	1·5
17	F	>100		97	N/N	30	88	2·3
18	F	>100		105	N/N	16	95	2·0
19	F	96		—	—	19	84	2·7
20	M	84		84	N/N	83	103	2·4
21	M	66		120	N/N	20	117	2·4
22	M	45		101	N/R	6	86	2·2
Mean (SD)				100 (12)		31 (25)	92 (15)	2·2 (0·4)
Euthyroid children (n = 9)								
23	F	>100		112	N/N	5		
24	M	>100		103	N/N	3		
25	F	70		—	N/N	2		
26	F	62		109	N/R	2		
27	F	61		—	—	3		
28	F	56		106	N/N	<1		
29	M	46		114	N/N	4	107	1·8
30	M	42		98	N/N	3	93	2·6
31	F	42		—	—	2	113	—
Mean (SD)				107 (6)		2·9 (1·2)	103 (13)	2·6 (0·4)
Controls (mean (SD))				103 (11)		3·1 (1·6)	103 (16)	2·2 (0·4)

N = Normal (neurological development scores within ±1 year for chronological age).
R = Retarded (neurological development scores >1 year below chronological age).
Conversion: SI to traditional units—Thyroxine: 1 nmol/l ≈ 0·08 µg/100 ml. Triiodothyronine: 1 nm

Clinically diagnosed

Clinically not diagnosed

Clinically not diagnosed and transiently elevated TSH

CH neonatal screening: the success and the burden.....

THE PSYCHOSOCIAL BURDEN OF A FALSE POSITIVE RESULT.....

J Inherit Metab Dis (2006) 29:677–682
DOI 10.1007/s10545-006-0381-1

ORIGINAL ARTICLE

A review of the psychosocial effects of false-positive results on parents and current communication practices in newborn screening

J. Hewlett · S. E. Waisbren

In families with false-positive recalls:

- **50% reported persistent anxiety**
- **148% enhanced depression levels in situation**
- **18% persistent anxiety**

The challenge:

- Detecting and treating Congenital Hypothyreoidism

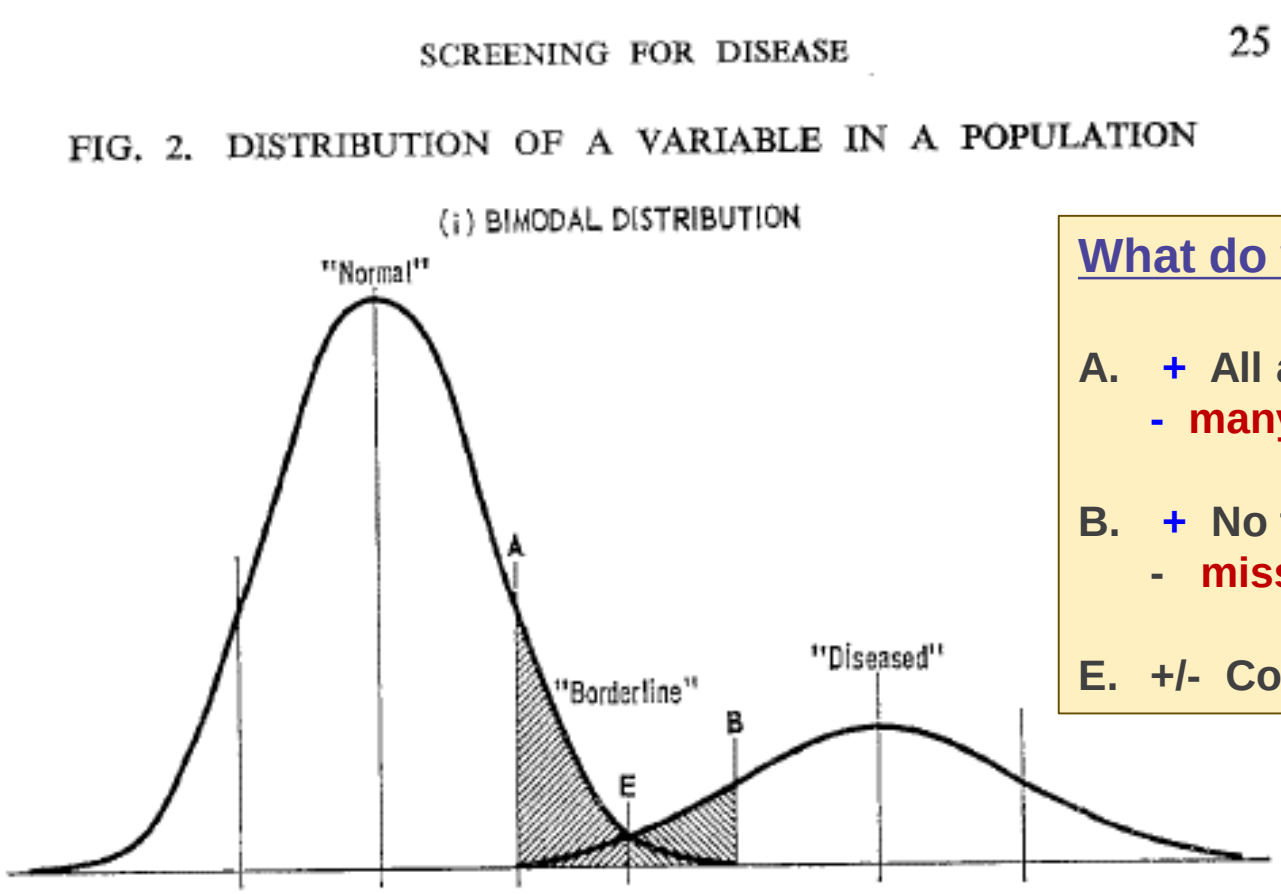
To diagnose the treatable diasease

and at the same time

To avoid the detection of variants that need NOT to be treated

>>>>Need: A precise definition of the disease!

The „Cut-off“ as important tool what to detect..?



What do we want to find?

A. + All affected (even mild)
- many false-positives

B. + No false positive
- missed some affected

E. +/- Compromise(s)

The recent TSH cut-off data:

TSH screening cutoff mU/L

Arch Dis Child. 2010 Mar;95(3):169-73. Epub 2009 Aug 12.

Difficulties in selecting an appropriate neonatal thyroid stimulating hormone (TSH) screening threshold.

> 6

Korada SM, Pearce M, Ward Platt MP, Avis E, Turner S, Wastell H, Cheetham T.

Institute of Health and Society, Newcastle University, Sir James Spence Institute, Royal Victoria Infi rmary, Newcastle upon Tyne, UK.

J Clin Endocrinol Metab. 2010 Sep;95(9):4283-90. Epub 2010 Jun 30.

Screening for congenital hypothyroidism: the significance of threshold limit in false-negative results.

10/20

Mengreli C, Kanaka-Gantenbein C, Girginoudis P, Magiakou MA, Christakopoulou I, Giannoulia-Karantana A, Chrousos GP, Dacou-Voutetakis C.

Department of Biochemical Laboratories, Institute of Child Health, Aghia Sophia Children's Hospital, 11527-Goudi, Athens, Greece. chmengreli@ich.gr

Clin Endocrinol (Oxf). 2009 Nov;71(5):739-45. Epub 2009 Mar 28.

A 7-year experience with low blood TSH cutoff levels for neonatal screening reveals an unsuspected frequency of congenital hypothyroidism (CH).

20>12>10

Corbetta C, Weber G, Cortinovis F, Calebiro D, Passoni A, Vigone MC, Beck-Peccoz P, Chiumello G, Persani L.

Laboratory for Neonatal Screening, Buzzi Children Hospital, Milan, Italy.

The UK-approach: Lowering the TSH cutoff to 6 mU/L

Arch Dis Child. 2010 Mar;95(3):169-73. Epub 2009 Aug 12.

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Institute of Health and Society, Newcastle University, Sir James Spence Institute, Royal Victoria Infi rmary, Newcastle upon Tyne, UK.

Table 1 TSH on initial testing on all infants screened from April 2005 to March 2007 (term and preterm infants)

TSH	First sample	First TSH (%)
<1.0	48012	73.37
1.1–2.0	13584	20.76
2.1–3.0	2757	4.21
3.1–4.0	660	1.01
4.1–5.0	198	0.30
5.1–6.0	79	0.12
6.1–7.0	38	0.06
7.1–8.0	29	0.04
8.1–9.0	13	0.02
9.1–10.0	7	0.01
10.1–20	37	0.05
>20	24	0.04
Total	65438	

TSH, thyroid stimulating hormone.

Recall:

Serum TSH >5 = treated

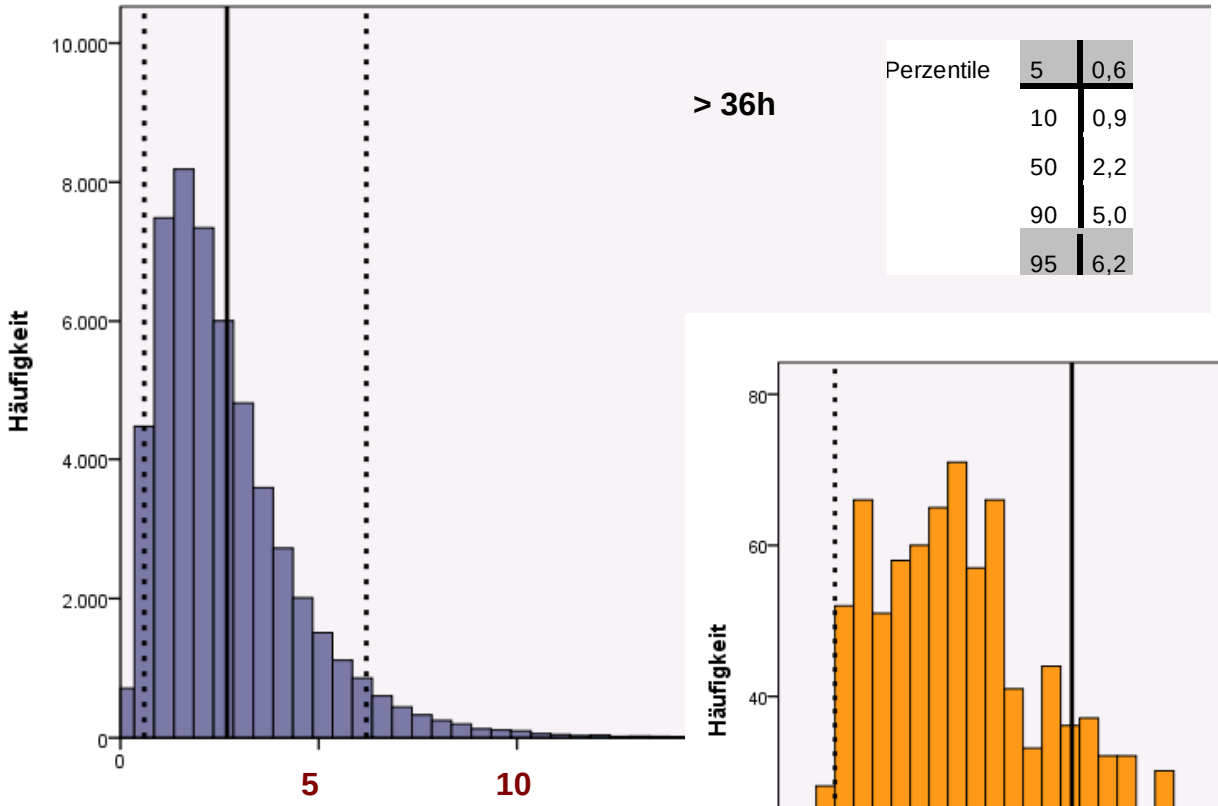
all fT4s → normal

No imaging mentioned

Infant	First TSH (mU/l)	Second TSH (mU/l)	Serum TSH (mU/l)	FT4 (pmol/l)	Days old (serum)
1	6.3	6.1	8.7	18.0	17
2	6.1	6.4	21.4	18.4	16
3	8.2	9.4	24.3	17.2	35
4	6.7	20.8	44.7	18.0 ??	29

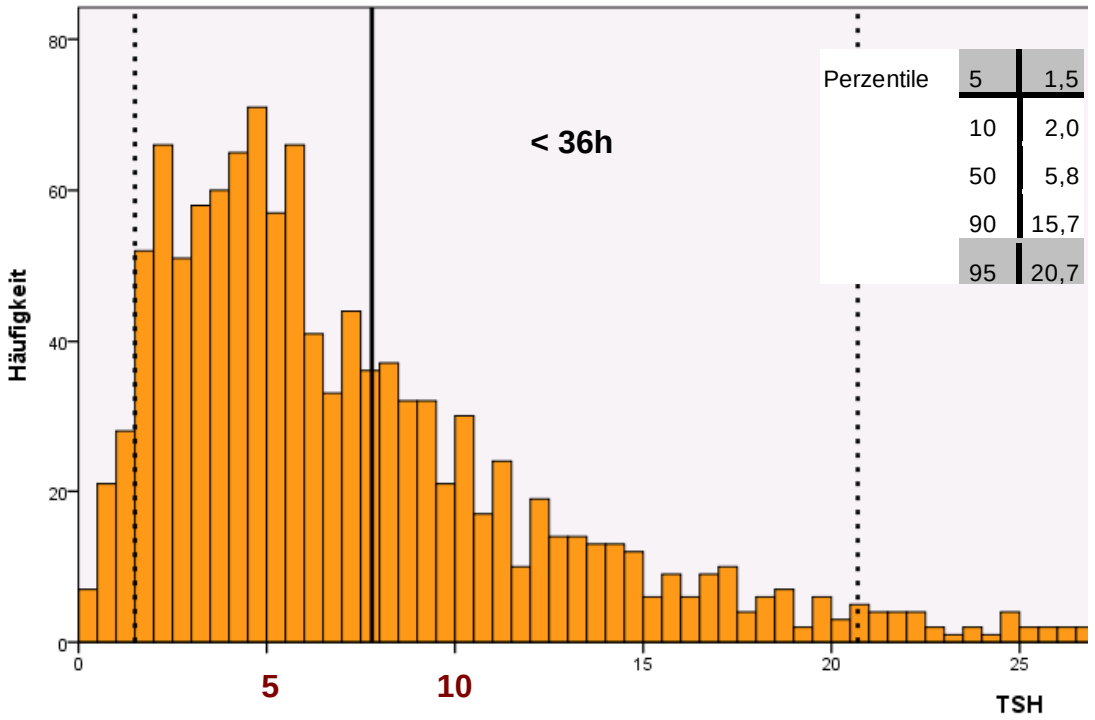
CH definition = „finally treated“ !

NEED TO BE CONSIDERED:
Screening TSH value as a function of age of testing



> 36h

Perzentile	5	0,6
	10	0,9
	50	2,2
	90	5,0
	95	6,2



< 36h

Perzentile	5	1,5
	10	2,0
	50	5,8
	90	15,7
	95	20,7

Data from Berlin screening program, 2012

NEED TO BE CONSIDERED:
Screening TSH value as a function of age of testing

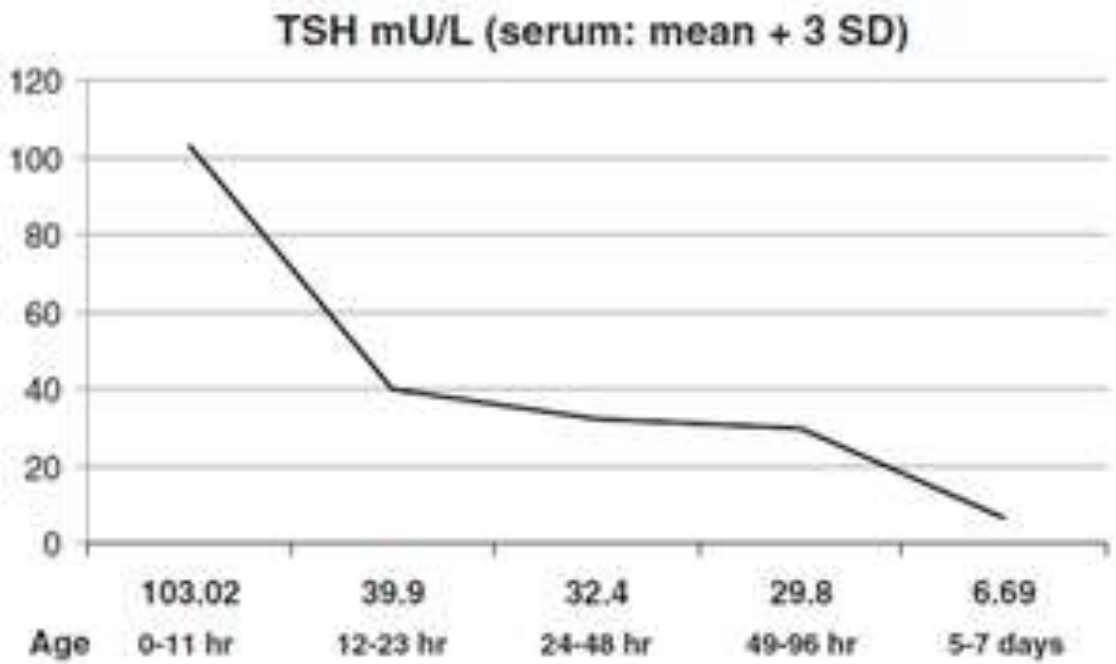
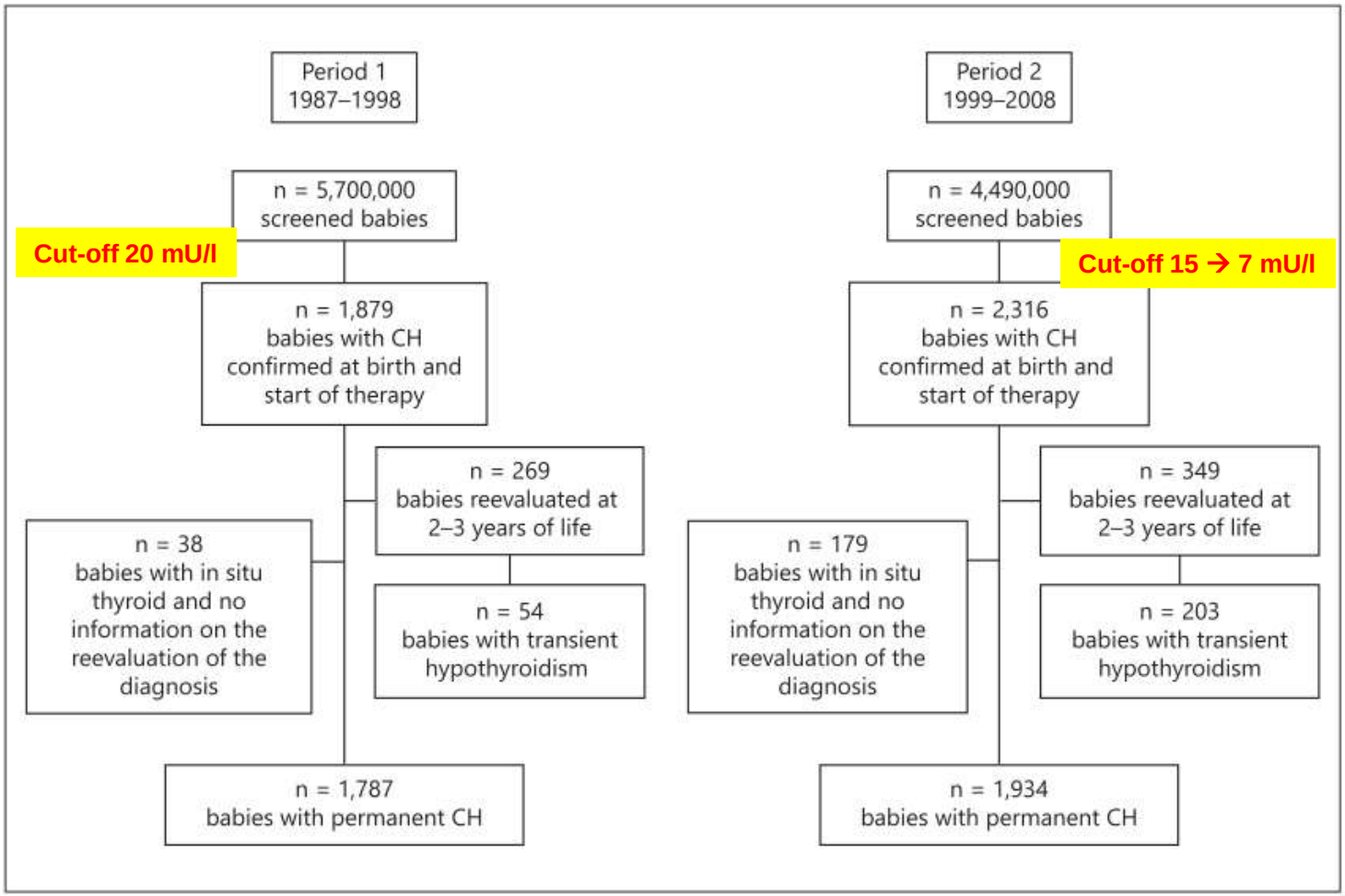


Fig. 2 Age-related thyroid stimulating hormone (TSH) cutoff; linear plot = mean+3 standard deviations (SD) (Oregon Newborn Screening Program, 2009; unpublished data)

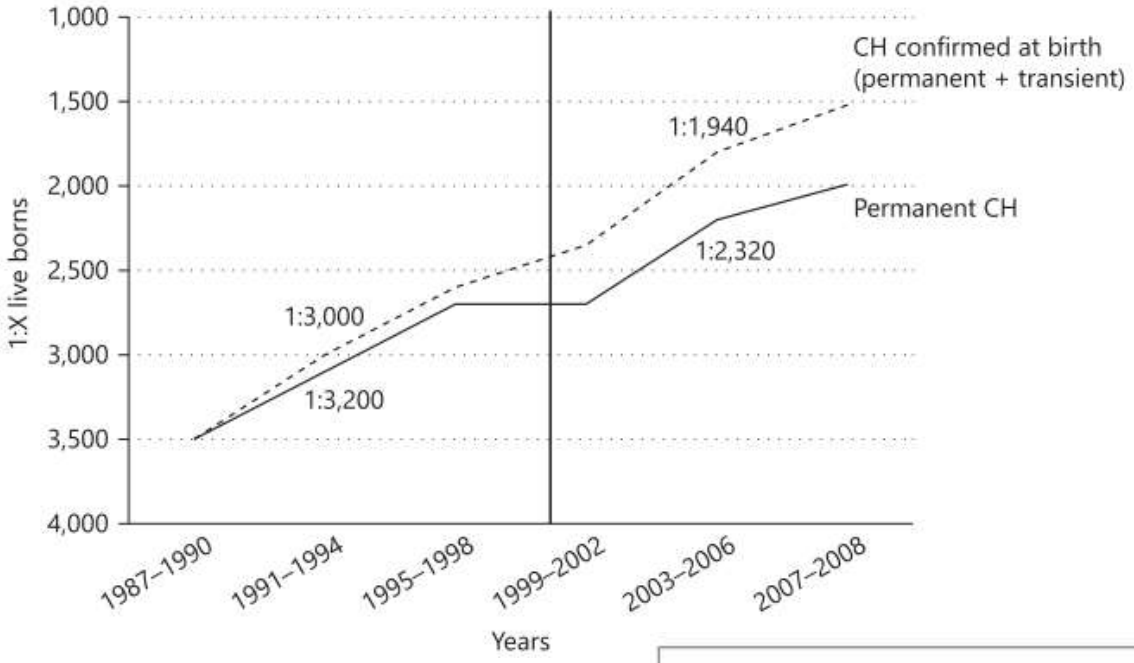
From: S. H. LaFranchi J Inherit Metab Dis (2010)

…might explain part of the controversy…

Italy: Lowering the TSH cut-off: Outcome…



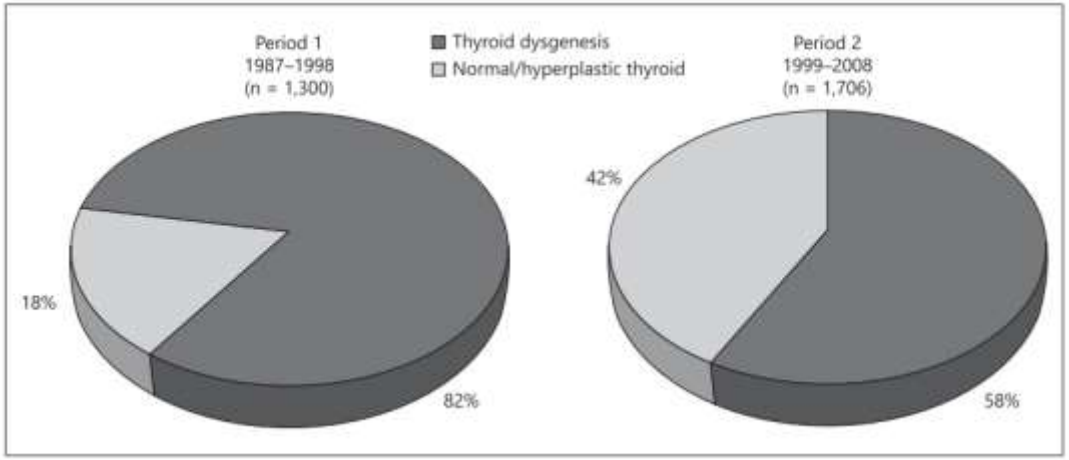
Etiology of CH in Italy: Effect of lower TSH cut-off



Multiple Factors Influencing the Incidence of Congenital Hypothyroidism Detected by Neonatal Screening

Antonella Olivieri[a] Cristina Fazzini[a] Emanuela Medda[b] The Italian Study Group for Congenital Hypothyroidism

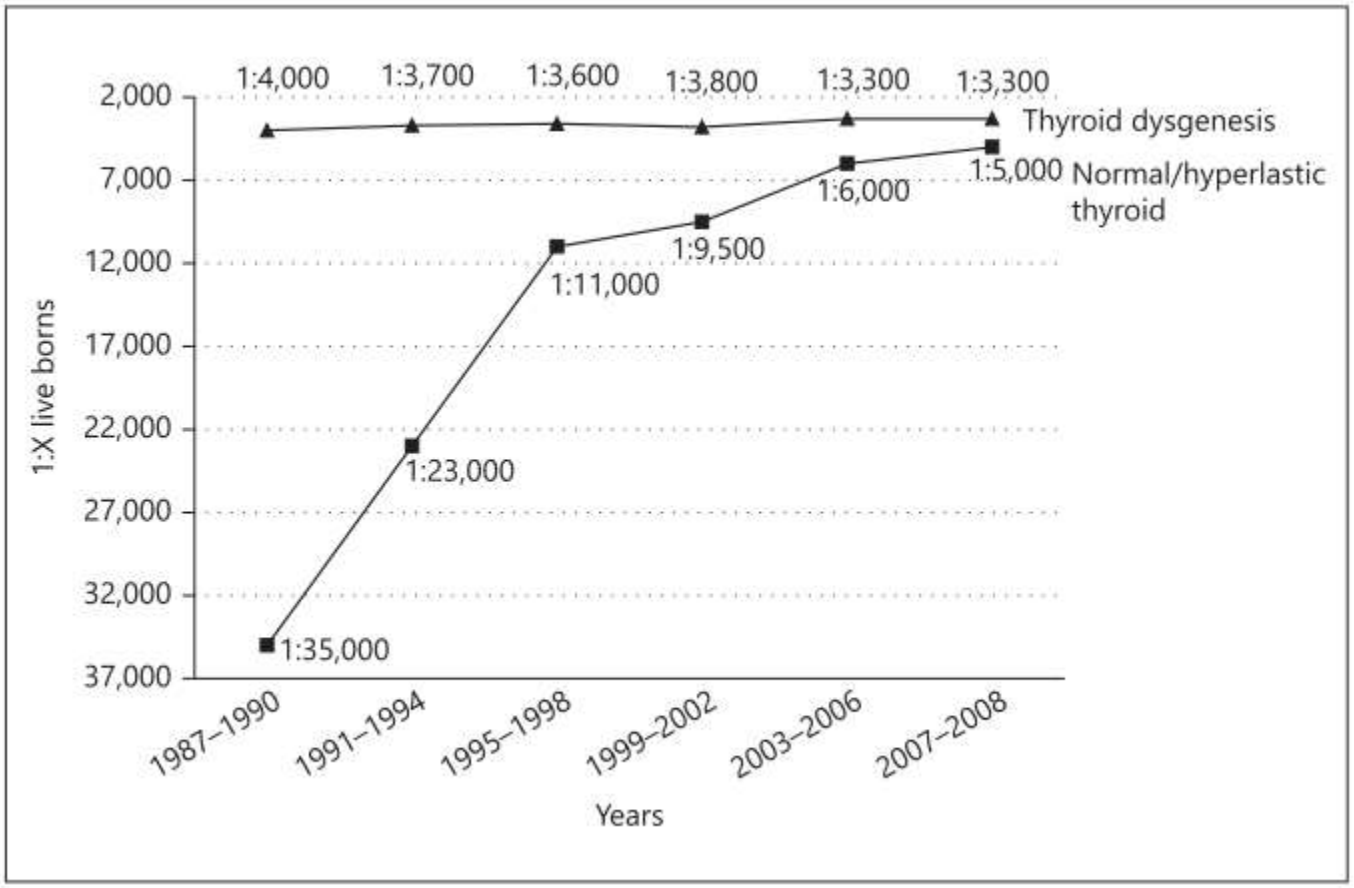
Horm Res Paediatr 2015;83:86–93



Bei Re-Evaluation:

- **14% persistierende SD-Störung**
- **86% normale fT4-Spiegel**

Italy: One or two diseases…?



Impact of lower TSH cut-offs

Programms which lowered the TSH cut-off (worldwide):

Impact of lowering TSH cutoff on incidence of congenital hypothyroidism.

Program	Initial year (s)	Initial TSH cutoff (mU/L)	Later year(s)	Later TSH cutoff (mU/L)	Initial incidence	Later incidence
Western Australia[53]	1981–1987	>25	1988–1998	>15	1:5747	1:2825
Lombardy Italy[5]	1999–2002	>20	2003–2005	>12/→>10	1:2654	1:1154
North England[54]	1994	>20	2003	>10→>6	1:2702	1:1078
Greece[55]	1979–2000	>20	2000–2002	>10	1:3384	1:1749
Quebec[56]	1990–2000	>15[a]	2001–2009	>5[a]	1:2898	1:2450
Brazil[57]	2005	>20	2007	>10	1:3616	1:1030

[a] TSH cutoff in 1st NBS specimen >30 mU/L; change shown is for the TSH cutoff on 2nd NBS test.

Screening for congenital hypothyroidism:
A worldwide view of strategies

George Ford, MD, Fellow, Pediatric Endocrinology,
Stephen H. LaFranchi, MD, Professor of Pediatrics,
Endocrinology *

Best Practice & Research Clinical Endocrinology & Metabolism 28 (2014) 175–187

The recent TSH cut-off data:

Arch Dis Child. 2010 Mar;95(3):169-73. Epub 2009 Aug 12.

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Korada SM, Pearce M, Ward Platt MP, Avis E, Turner S, Wastell H, Cheetham T.

Institute of Health and Society, Newcastle University, Sir James Spence Institute, Royal Victoria Infirmary, Newcastle upon Tyne, UK.

- **Increasing the incidence to 1:1.500 (double)**
- **mainly cases with normal gland**
- **Much higher recall-rate (up to 1.2%)**
- **most cases with normal fT4/T4**
- **no data availbale about untreated outcome!!**

J Clin Endocrinol Metab. 2010 Sep;95(9):4283-90. Epub 2010 Jun 30.

Screening for congenital hypothyroidism: the significance of threshold limit in false-negative results.

Mengreli C, Kanaka-Gantenbein C, Pirpilidis P, Matsinos YG, Christakopoulou I, Giannoulia-Karantana A, Chrousos GP, Dacou-Voutetakis C.

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Laboratory for Neonatal Screening, Buzzi Children Hospital, Milan, Italy.

Potential neurodevelopmental damage is the „killing argument“ in debates around CH…

The relation between serum and filter paper TSH level in neonates with congenital hypothyroidism

Ali Hassan Ayyad, Mahin Hashemipour[1], Silva Hovsepian[2], Ali Mehrabi Kooshki[3], Mahmoud Afshari[4]

Advanced Biomedical Research | 2014

In sum, it seems that considering the findings of this study the cutoff point for recall should be changed to 7.5 for appropriate screening outcome, but on the other hand considering the low cost of filter paper and importance of missing any case of CH, changing of cutoff point is not considered necessary. However,

…there is a price to pay… →

TSH cutoff (mU/liter whole blood)	Newborns recalled, n	Recall rate (%)	Infants with CH, n
30	173	0.05	114
20	376	0.12	144
10	3784	1.20	200

3408 recalls for 56 cases

The main question: Mental development (!)

- Severe primary CH → mental developmental delay
  - This is challenged by data from non-screened population studies
  - Mental disability in severe (clinical diagnosed) CH → 30%
- Over-estimation of mental disability?
  - Is there a developmental risk for milder forms of CH?
    - *__no__* data available ☹
  - Is newborn screening of milder forms justified…?
    - Junger criteria: …"*the natural course of the disease must be known and understood*…"
- **Is there an over-treatment problem in CH…?**

Intellectual outcome of clinical diagnosed CH

Table 1 Prevalence of congenital hypothyroidism among unscreened populations using active case finding

Reference	Country	Birth years	Age at evaluation (years)	Birth cohort (N)	No with clinically detected congenital hypothyroidism	Prevalence
Jacobsen *et al*[31]	Denmark	1970–1975	3–8	436 959	72	1:6100
Alm *et al*[32]	Sweden	1969–1975	2	767 698	112	1:6900
Alm *et al*[27]	Sweden	1977–1978	5	100 239	15	1:6700
de Jonge *et al*[33]	The Netherlands	1972–1974	1–4	594 951	94	1:6300
Birrell *et al*[28]	UK: Northern England	1963–1975	5–15	480 000	72	1:6700
Hulse *et al*[30]	UK: Kent and East Sussex	1965–1978	3–8	433 900	65	1:6700
	Pooled			2 813 747	430	1:6500

Table 2 Indicators of intellectual disability associated with congenital hypothyroidism among unscreened populations

						Indicator of intellectual disability			
Reference	Country	No tested	Birth years	Age at testing (years)	Measure	Mean IQ	Percentage with low IQ	IQ range	Percentage in special schools
Alm *et al*[26]	Sweden	39	1969–1971	7–9	Wechsler Intelligence Scale for Children	88	8% <70 16% <75	50–113	8
Alm *et al*[27]	Sweden	14	1977–1978	5	Griffith's Developmental quotient	87	14% <70 28% <80	45–116	Not reported
Frost *et al*[29]	England	45	1965–1975	7–15	Wechsler Intelligence Scale for Children—revised	82	NR	40–112	13
Hulse *et al*[30]	England	94	1957–1975	7 or older	Wechsler Intelligence Scale for Children—revised	82	27% <70	NR	29

IQ, intelligence quotient; NR, not reported.

Prevention of intellectual disability through screening for congenital hypothyroidism: how much and at what level?

Scott D Grosse[1] Guy Van Vliet[2,3]

Arch Dis Child 2011;**96**:374–379.

- **In vorhandenen Daten max. 30% mit IQ < 75**
- **Ausgangs Inzidenz ca 50% der Screening-Inzidenz**
- **“Neues” Bild dermentale Folgen von CH…?**
- **gesundheitsökonomische Betrachtung (teurer aber nicht besser)…?**

Treating patients not numbers: the benefit and burden of lowering TSH newborn screening cut-offs

Heiko Krude,[1] Oliver Blankenstein[2]

(1) What is the definition – either clinical or laboratory – of the new, mild disease?
(2) What are the appropriate age related fT4/T4 levels in the newborn period to discriminate between mild hypothyreosis and normal children?
(3) What is the cognitive outcome of untreated children with a newborn TSH of 5–10 mU/l?

Arch Dis Child February 2011 Vol 96 No 2

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- The assumption that 40% or more of people with clinically-diagnosed CHT in high-income countries developed intellectual disability in the absence of screening is an overestimate, and the true percentage is probably about 25%.
- No evidence is available that children with mild or subclinical CHT who have moderately elevated TSH levels developed overt disability, and it is invalid to extrapolate from outcomes among persons with severe CHT to

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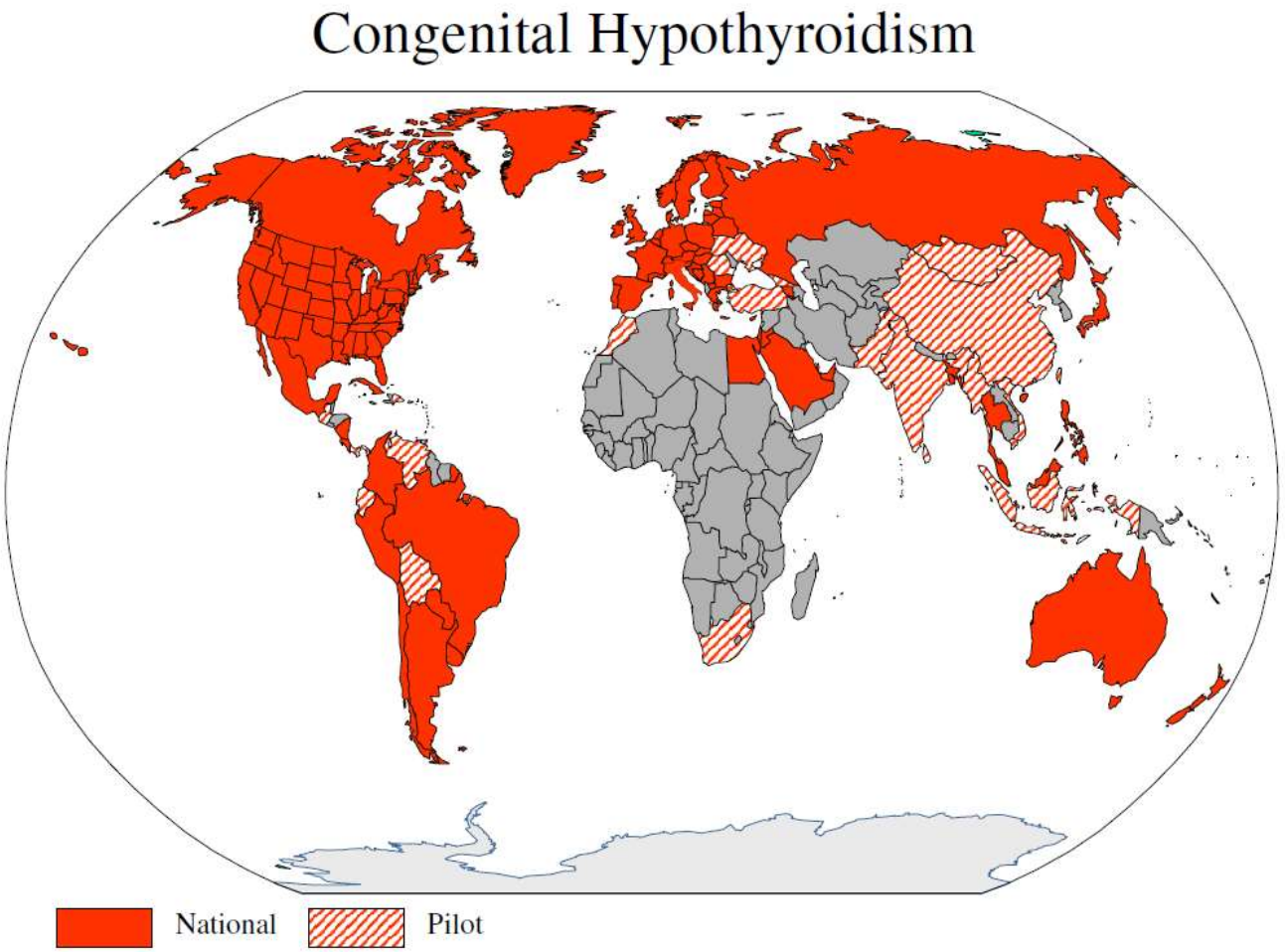
Broader view on CH-screening: world perspective



➔ **Ca. 30.000 (true) affected babies without newborn screening**

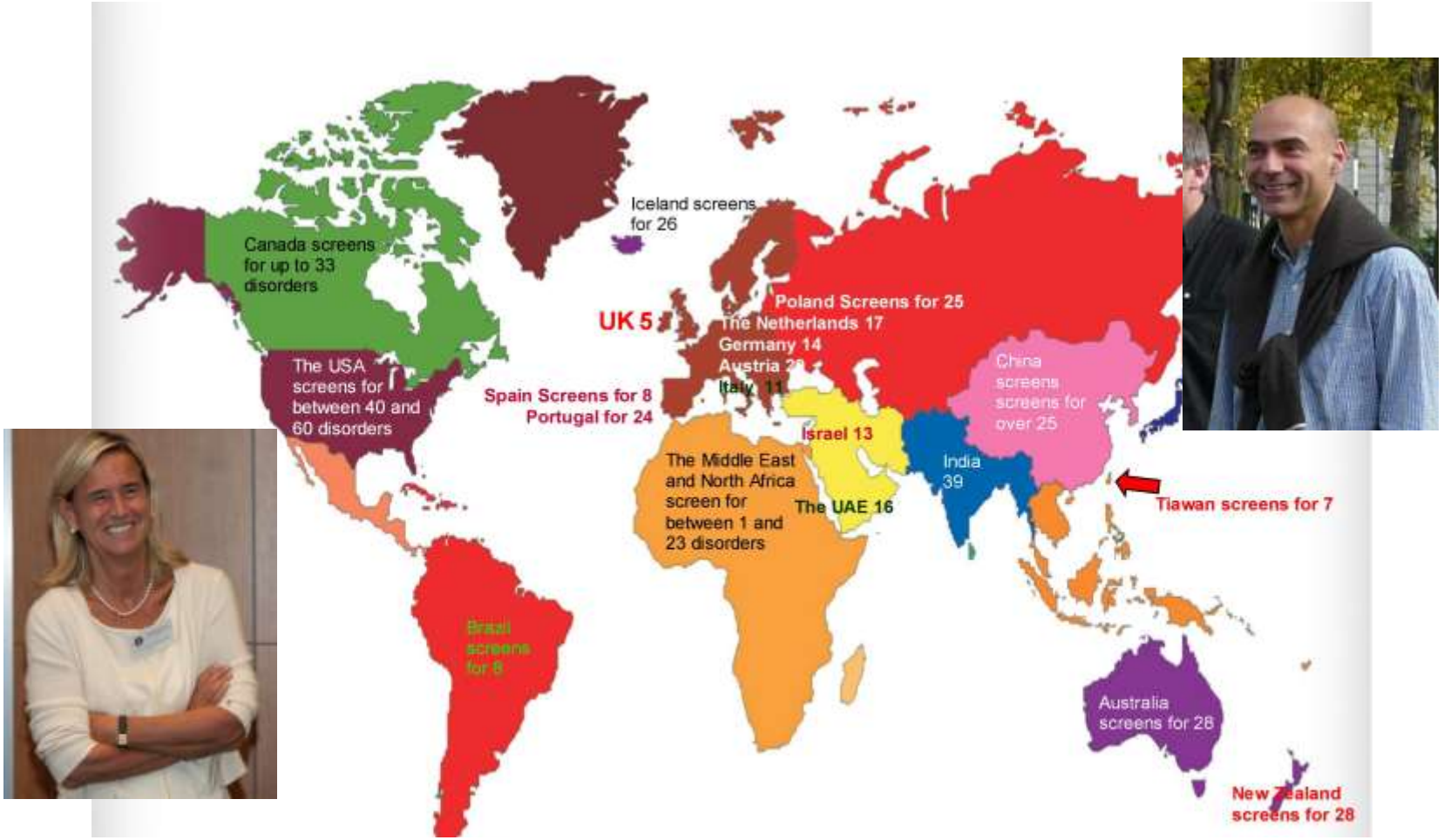
Conclusions & points to discuss

- **Newborn screening for CH is one of the most successful programs in medicine ever ☺**
- **Age-dependent TSH cut-offs would make sense…**
- **Paediatric endorcinologists and the screening programs have to *consent* in whom they want to find (and treat)**
  - **Lowering TSH cutoff < 15 will increase recall- and false-positive-rates**
- **Ages appropriated reference range for TSH and (f)T4 are critical for making correct diagnoses.**
  - **If you don‘t know and T4 is in the normal rage: → wait and re-check! (there‘s no danger in waiting)**
- **CAVE: *Dilution* of true severe disease with „near-normal variants”**

Open problems in screening for CH → still a lot to do…!

- **80% of births worldwide without CH screening**
  - **No chance for early treatment in 30.000 affected babies/year**
- **Develop screening for Central CH**
  - **Dutch approach (incidence 1:15.000)**
  - **fT4-Screening (Japan)..?**
- **Screening is only (the first) part of the process**
  - **…outcome is dependent from all parts**
  - **Changing cut-offs will significantly increase total costs (even when the method is already there)**
- **“Mild CH” is a new screening disease**
  - **Evaluation according Wilson & Jungner criteria**
  - **Is there mental disability in the natural course..?**

Thank you for your attention !



appr. 35 Mio Children screened each year worldwide

80.000 or 480.000 recalls per year…??