Newborn Screening for Galactosaemia

some countries do, others do not

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Galactosemias Network (GalNet)
(www.galactosemianetwork.org)

Galactosemia Network (GalNet)

Annual members meeting

Athens, Sep 3, 2018

- NBS: some countries have NBS galactosemia, others do not. Agreed on a review NBS for galactosemia lead by Matthias Gautschi

⇨ **«brainstorming»**

⇨ **How is it done in YOUR country?**

NBS = Newborn screening

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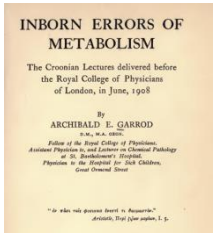
Phenylketonuria (PKU): the «IEM Prototype»

Archibald E. Garrod

~1908

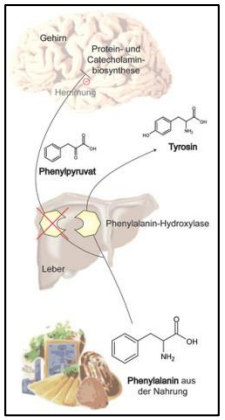
Chemical Individuality



I. Asbjörn Fölling

1934

PKU

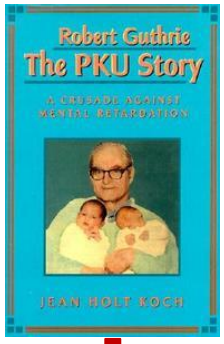


Horst Bickel

1953

diet

Robert Guthrie



~1962

NBS

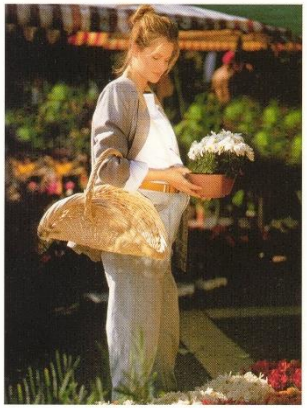
NBS = Newborn screening

Enthusiasm at 1st PKU diagnosis by NBS in Switzerland

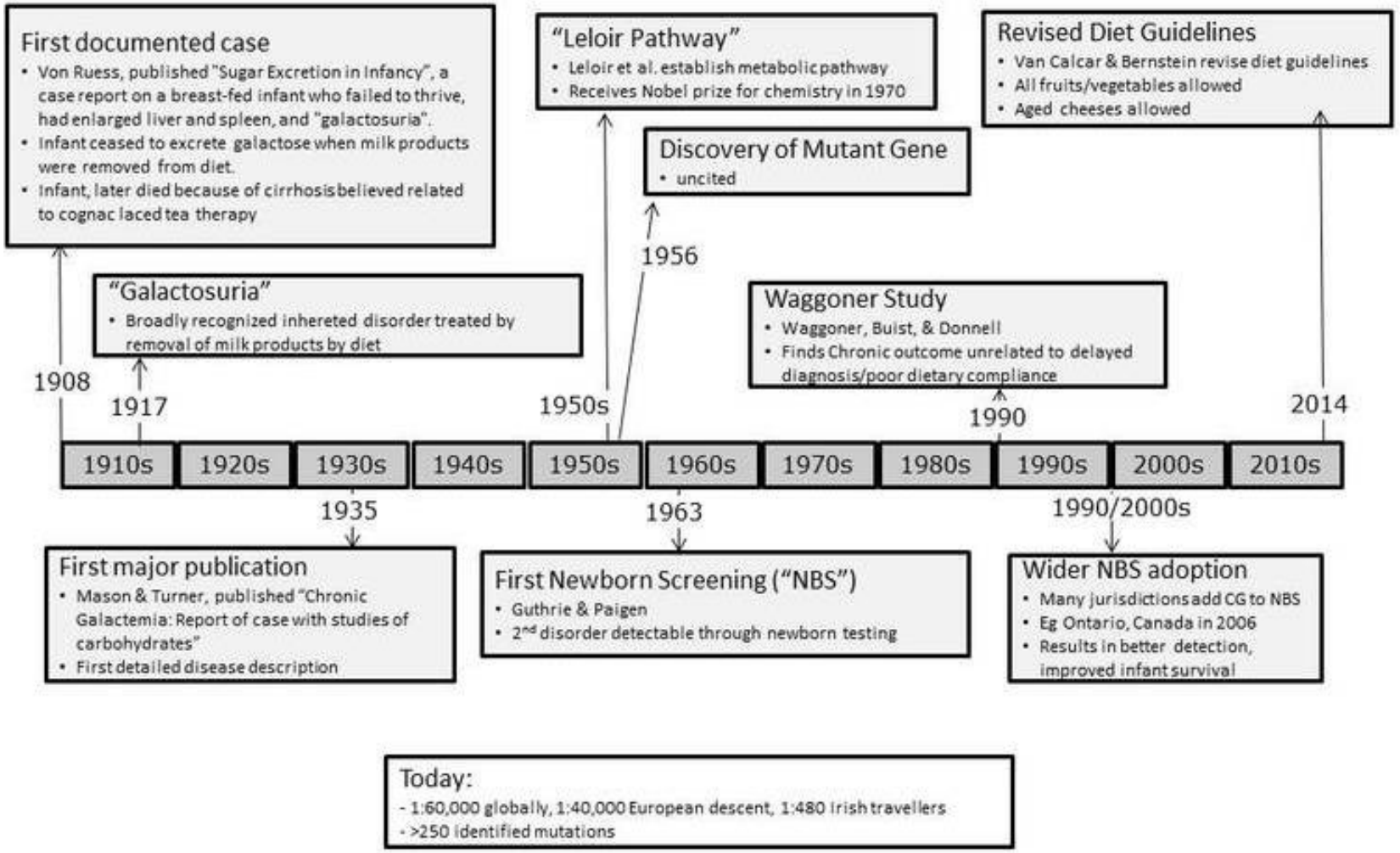
Start in 1965

- without Therapy
- Severe PM retardation
- Epilepsy
- Eczema
- Mouse smell

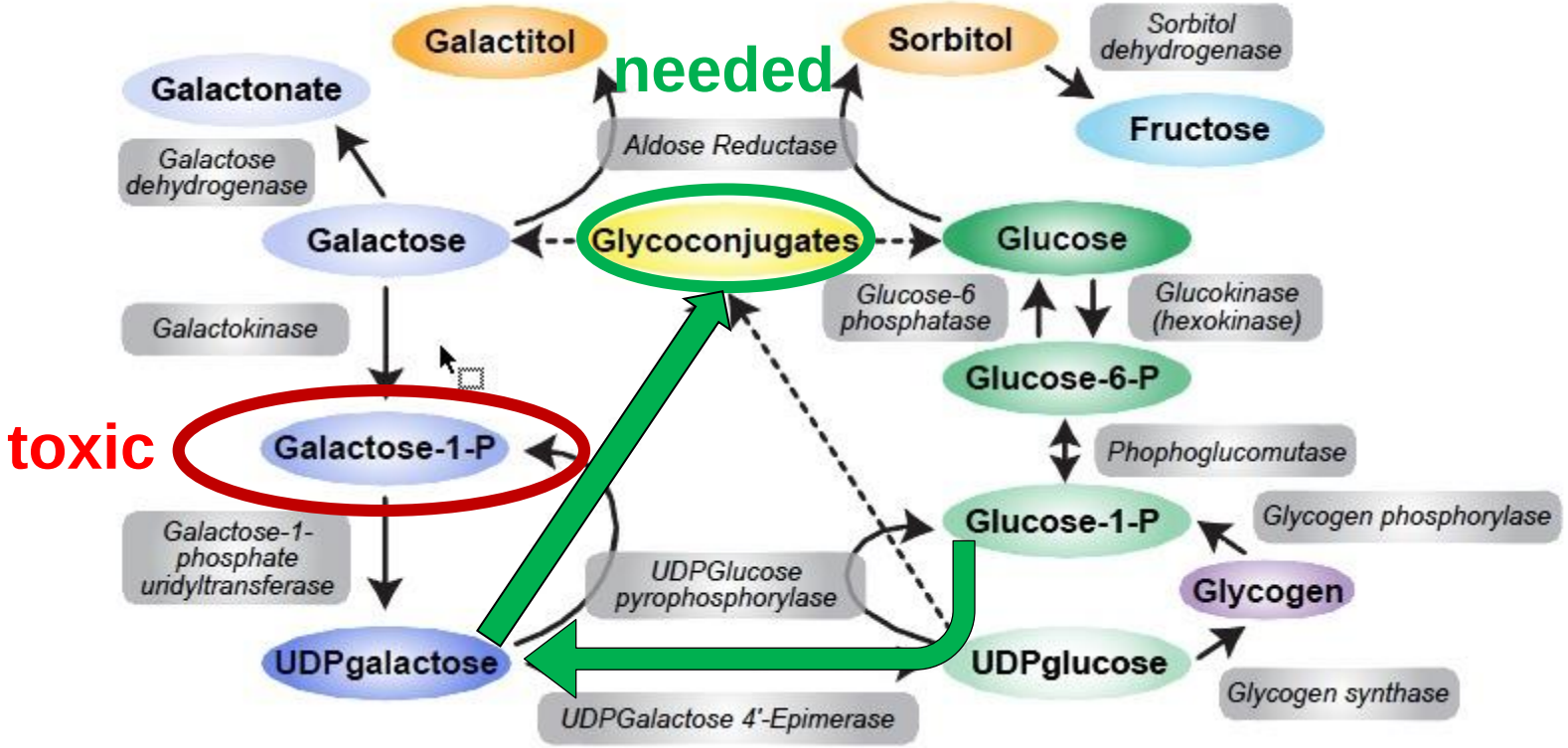
- with Therapy
- NORMAL
- … but do not forget
- Maternal PKU!



History of Galactosemia



Hypothesis of «salvage pathway»
= Rationale for «total exclusion diet» (R. Gitzelmann)



Start of NBS in many countries
Objective: «2nd PKU»

Cartoon from Berry GT, *GeneRev*, last update 2017

Outcome of GALT-deficiency: disappointing…

Holton (2001):

"It is now generally accepted that, even with early diagnosis and good dietary treatment, neuropsychological development is ignificantly impaired."

Gitzelmann (2000):

- multicenter, long-term studies only retrospective
- no prospective study
- negative selection of patients

"They [the studies] have spread unfounded pessimism among physicians and dieticians who must overcome it for the benefit of their patients."

Long-term outcome with=without NBS!?

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US & EU Recommendations for NBS programmes

Table 2. Core panel of inherited metabolic disorders recommended by ACMG to be included in the uniform NBS program.

Condition	Incidence[a]	NACB recommendations[b] (i)	(ii)	(iii)	EUNENBS recommendation	Methodology used for NBS[c]
GALT	1:45 000	ND	ND	ND	Group 1B	Fluorescence

ND = not discussed

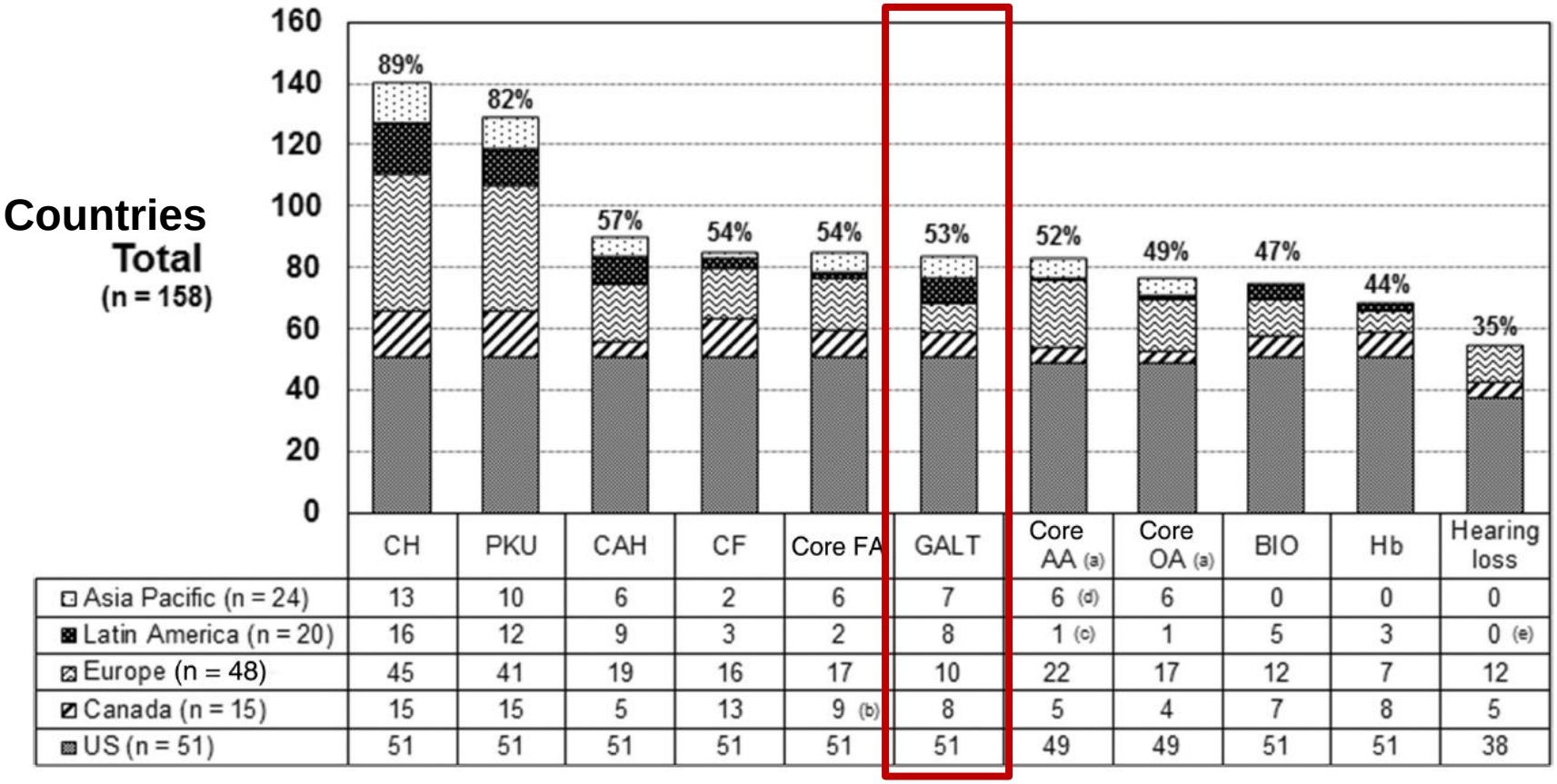
Group 1B = high prevalence and feasible screening test
«they consider that the health gain for … GALT is proven.»

Objective: *Harmonization* of NBS programmes

But: Galactosemia is *outside the box*

Martinez-Morillo E et al, 2016

NBS programmes in the World and in Europe



Countries Total (n = 158)	CH	PKU	CAH	CF	Core FA	GALT	Core AA (a)	Core OA (a)	BIO	Hb	Hearing loss
Asia Pacific (n = 24)	13	10	6	2	6	7	6 (d)	6	0	0	0
Latin America (n = 20)	16	12	9	3	2	8	1 (c)	1	5	3	0 (e)
Europe (n = 48)	45	41	19	16	17	10	22	17	12	7	12
Canada (n = 15)	15	15	5	13	9 (b)	8	5	4	7	8	5
US (n = 51)	51	51	51	51	51	51	49	49	51	51	38

In Europe (10/40): Austria, Belgium (part), Germany, Greece, Hungary, Ireland, Italy (part?), Netherlands, Spain (part?), Sweden, Switzerland

Martinez-Morillo E et al, 2016; Loeber JG et al, 2012

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GALT NBS in Switzerland

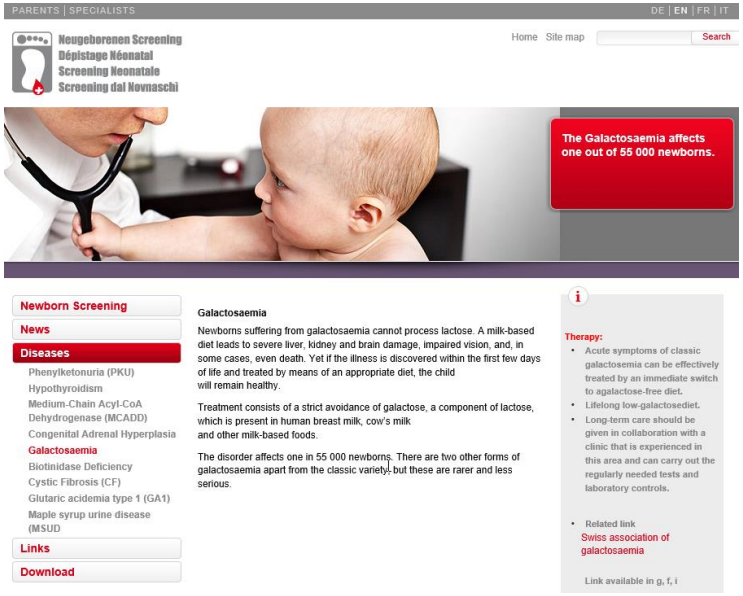
~90‘000 newborns/year

start in 1966 for Galactosemia

Screening on 4th day (72-95h)

Classical Galactosemia: 1/54‘000
mild Galactosemia: 1/5‘300
=> C:V = 1:10

Gal-Epimerase deficiency 1/160‘000
Gal-Kinase deficiency 1/1‘500‘000



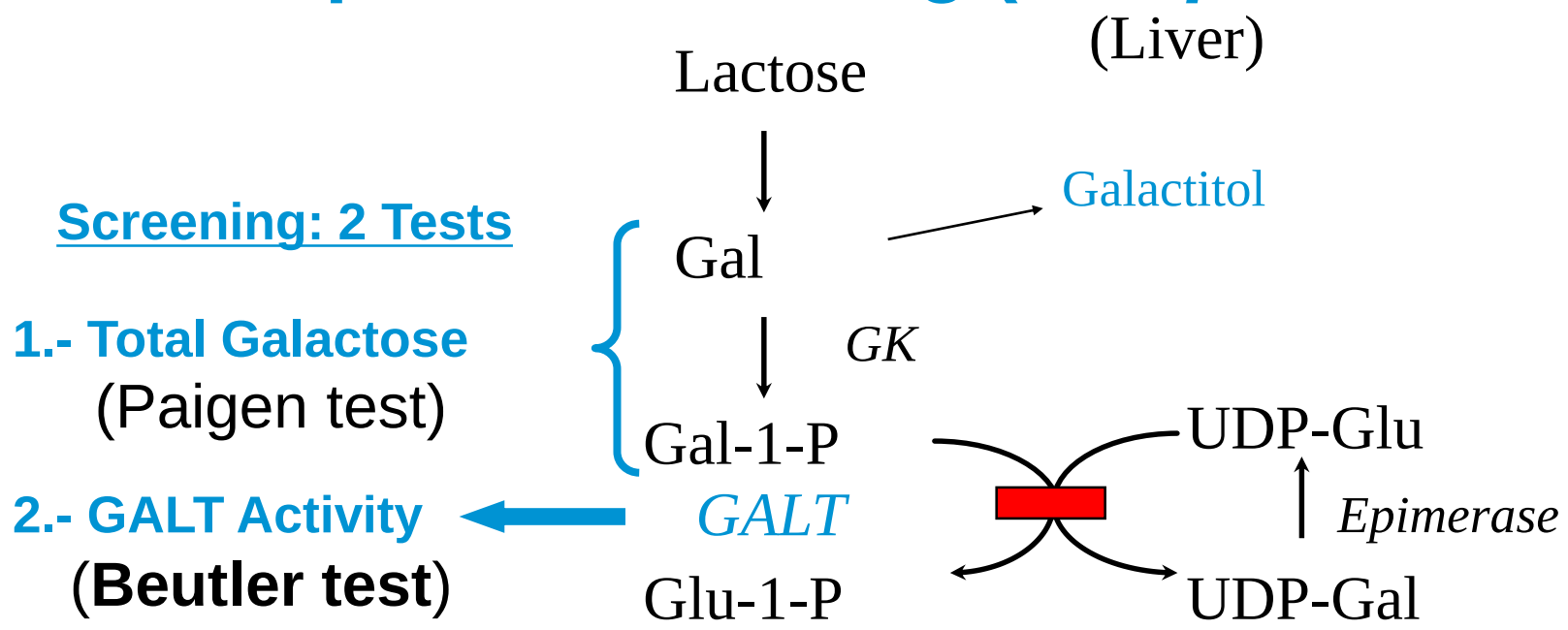
In contrast, e.g. France & UK have opted against NBS

See survey in England (1988-90)
Schottland until 2002 & Poland until 1978/1994
(stopped: too many ***false positives***)

Rely on ***awareness***! => ***no*** false positives!

What is the best approach?

Principle of Screening (*Lab procedure*)



Screening: 2 Tests

1.- Total Galactose
(Paigen test)

2.- GALT Activity
(**Beutler test**)

Galactose-1-P + UDP-glucose $\xrightarrow{GALT}$ Glucose-1-P + UDP-galactose

Glucose-1-P $\xrightarrow{PGM}$ Glucose-6-P

Glucose-6-P + $NADP^+$ $\xrightarrow{G6P\text{-}DH}$ Gluconate-6-P + $NADPH^+$

Cut-offs:
tot Gal: ≤ 800 µmol/L?
GALT activity: >30%?

Instructions for the Screening (*Sampling*)

When*	Birth weight >2000 g	72 – 96 hours
	Birth weight < 2000 g	1. Test: 72 – 96 hours 2. Test: end of 2nd week or at the end of hospitalization
	Newborn with transfusion or blood exchange	1. Test: pre-transfusion 2. Test: 3-5 days after transfusion birth w. < 2000 g end of 2nd week
What	Capillary puncture	Never use EDTA-blood!!!!
How	1 drop / circle Correct and complete patient data	Dry for 2-3 hours (do not expose to sunlight or heat) and send 2 times a day in a plastic envelope

*Take blood 1-2 hours after a lactose-containing meal

Protocol for pathological screening result

Total Gal ↑↑ GALT null	Classical Galactosemia	Clinitest, ASAT, ALAT, Bili, Amino acids P/U Gal/Gal-1P in RBC Enz. GALT typisation	Stop breastfeeding Lactose free, low-galactose nutrition
Total Gal ↑ GALT ↓	Double Heterozygosity (1 classical + 1 mild mutation)	Clinitest, ASAT, ALAT, Bili, Amino acids P/U Gal/Gal-1P in RBC Enz. GALT-Typisation	Continue breastfeeding, sometimes reduced
Total Gal ↑ GALT normal	Porto-cava Shunt Gal-Kinase Gal-Epimerase Contamination	Clinitest, ASAT, ALAT, Bili, Amino acids P/U Gal/Gal-1P in RBC Enzymatic assay	Continue breastfeeding (stop only if Kinase Def.)
Total Gal norm GALT ↓	Heat inactivation Sunlight / Radiator Heterozygote G6PD / PGM def	Repeat the Guthrie test Enzymatic assay	Continue breastfeeding Specific action

Germany: Recall rate and confirmed cases

3.1.4 *Galaktosämie*

Labor	Erstscreening gesamt	Erstscreening ≥36h	Recall ≥36h	Recall-rate(%)*	bestätigte Fälle[a]
1	60681	59374	25	0,04	1
3	16464	16437	0		0
5	61072	59885	19	0,03	1
6	13500	13095	3		0
7	54925	53283	16	0,03	1
8	182945	179378	40	0,02	2
9	137382	134165	13	0,01	3
10	37650	36832	6	0,02	2
11	17864	17308	3		0
12	92664	90575	31	0,03	1
13	66282	64753	5	0,01	2
14	32797	31925	7	0,02	1
15	9647	9347	1		0
Gesamt	**783873**	**766157**	**169**	**0,02**	**14**

* Recallraten werden nur für eine Recallrate ≥ 0,01% und n > 5 angegeben.

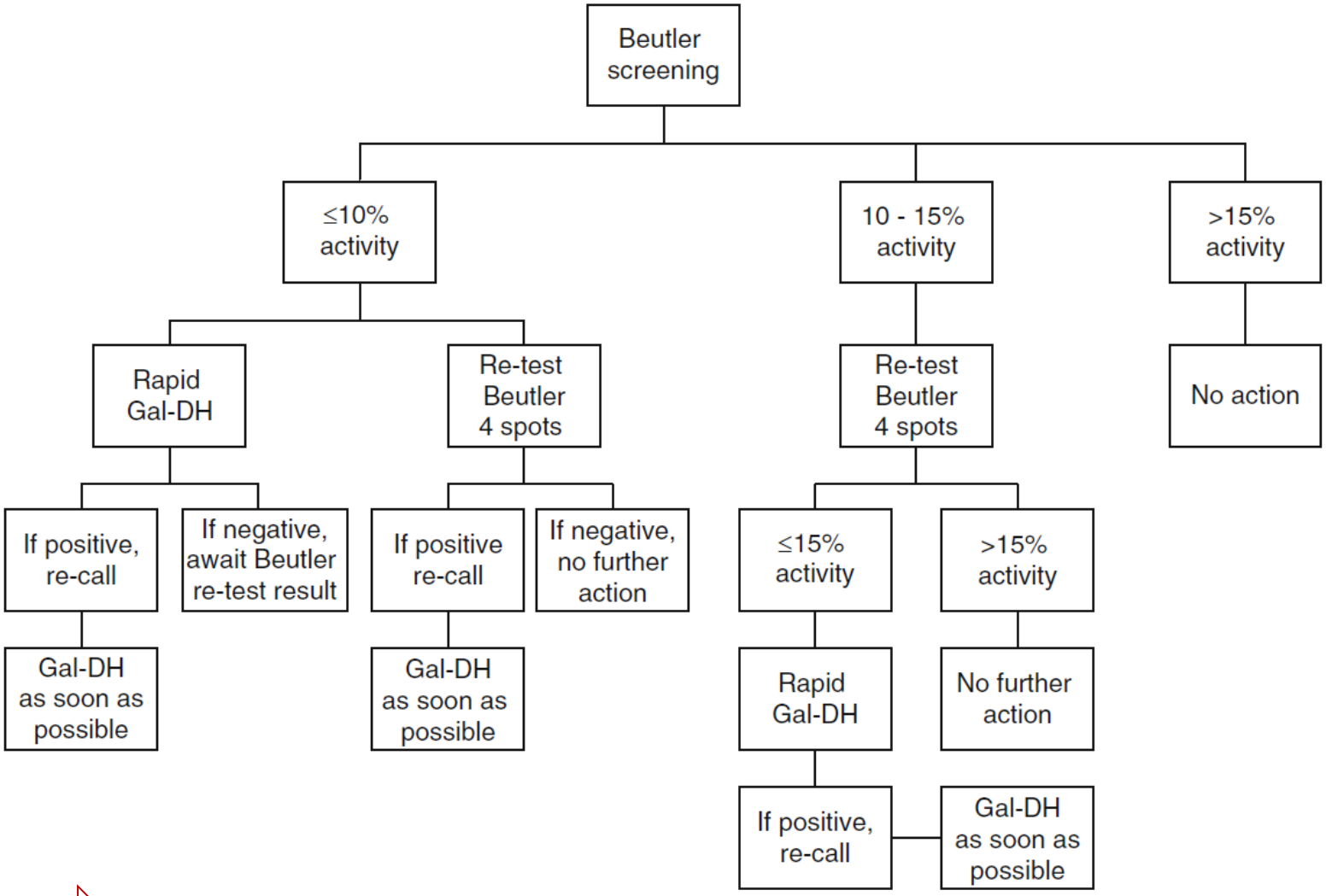
[a] nur klassische Galaktosämie

Germany: Diversity of cut-offs within one country

7.4 Galaktosämie

Labor	Parameter	Normbereich	Methode
1	GALT Galaktose	>3,5 U/g Hb <20 mg/dl	Fluorometrie quantitativ BIORAD Quantase
3	GALT Galaktose	>2,3 U/g Hb <15 mg/dl	Fluorometrie (PE)
5	GALT Galaktose	3,5 U/g Hb 15 mg/dl	Colorimetrie quantitativ BIORAD Quantase
6	GALT	>3,5 U/g Hb	Fluorometrie (PE)
7	GALT	3,5 U/g Hb	Fluorometrie quantitativ
8	GALT Galaktose	>20% Tagesmittel <30 mg/dl	Fluorometrie quantitativ Colorimetrie quantitativ
9	GALT Galaktose	>5,3 U/g Hb <20 mg/dl	Fluorometrie (PE) BIORAD Quantase
10	GALT Galaktose	>3,5 U/gHb 1111 µmol/l	Fluorometrie (PE) BIORAD Quantase
11	GALT	3,5 U/g Hb	Fluorometrie (PE)
12/13	GALT Galaktose	>20% < 15 mg/dl	Colorimtrie non Kit / Fluoro. quant.(non-kit)
14/15	GALT Galaktose	<2,3 U/g Hb <15 mg/dl	Fluorometrie quantitativ BIORAD Quantase

Sweden: a successful model



Objective: *Optimization* of sequence / cut-offs

Ohlsson A et al, 2011

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Wilson–Jungner Criteria, 1968 => Gal

Principles of Practice of screening for Disease (Public Health Paper Nr 34, WHO Geneva)

1. Condition is an important health problem **yes**
2. Natural history of the disease well understood **yes/no**
3. Detectable at early stage (presymptomatic) **yes?**
4. Benefit of pre-symptomatic treatment **no?**
5. Suitable screening test **yes, but false positives**
6. Reliable confirmatory test **yes**
7. Sufficient medical expertise (screening) **yes**
8. Sufficient medical expertise (clinical workload) **yes, but**
9. Physical and psychosocial risks less than benefits **yes**
10. Costs balanced against benefits **yes?**

one test - one disease - one therapy

Courtesy Dr. Jean-Marc Nuoffer

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Conclusions: requirements for a good NBS => Gal?

- **Specific** – few false positives => how many? How to improve?
- **Sensitive** – few false negatives => really none or any???
- **Predictive** – diagnosed newborns will have the disease
- **Acceptable** – low risk of procedure

Consider: (what do we know about that?)

- Avoid/minimise any harm => IEM reference centers, GL…
- Privacy / autonomy aspects
- Ethical, legal, societal aspects
- Consequences of genetic condition for the whole family

- reduce diagnostic delay, improve access to therapy & research

≤ 14d!? **= incentive for NBS**

Conclusions

- «Already the great variability of approaches to NBS for Galactosemia, including set-up, cut-offs etc. clearly shows the ***remaining uncertainties*** and the ***lack of evidence***.»

- Can we improve? And how?

Jumbo-Lucioni PP et al, 2012; Varela-Lema L et al, 2016

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THANK YOU FOR YOUR ATTENTION

6. Open **Discussion: What is YOUR point of view?**