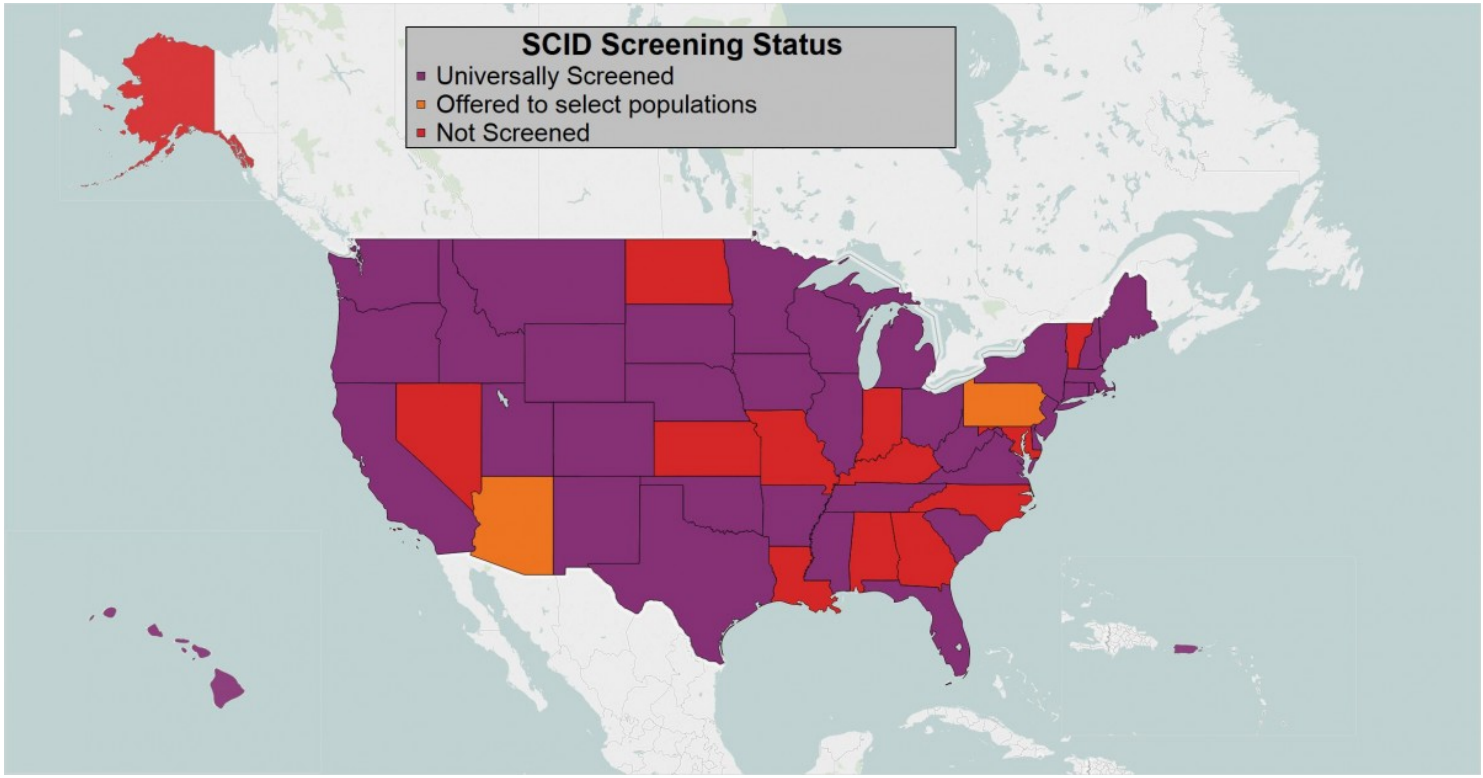
National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

Integration of SCID Screening into the Dutch Newborn Screening Program

Benefits and shortcomings of the available screening assays

SCID screening in USA

- About half of the states screens half of the newborns…

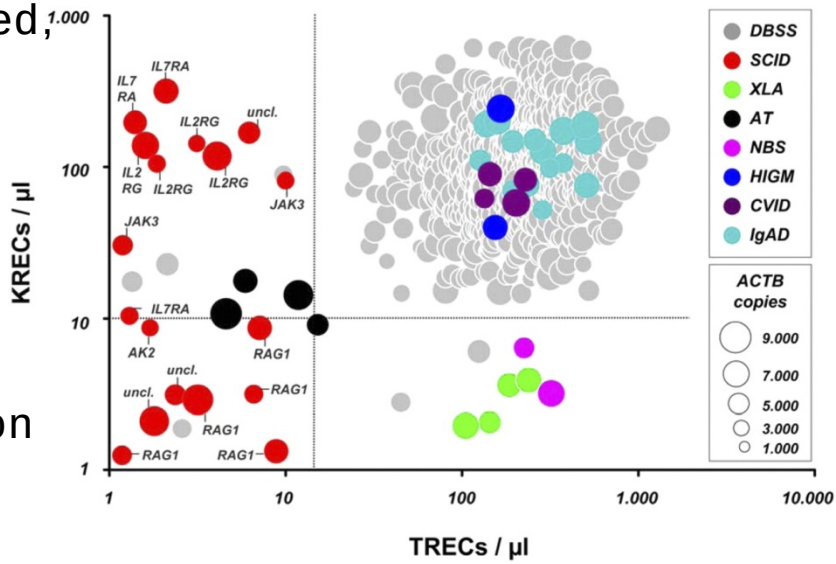


https://www.newsteps.org

Meanwhile,
on the continent..

Pilot SCID screening in Sweden

- Retrospective study with 2560 freshly collected, anonymized heelprick cards and 18 cards of SCID patients (and other (B-cell-related-) immunodeficiencies)
- Combined TREC*/KREC** - in house PCR
- National Board of Health and Welfare works on criteria for the evaluation of NBS diseases.

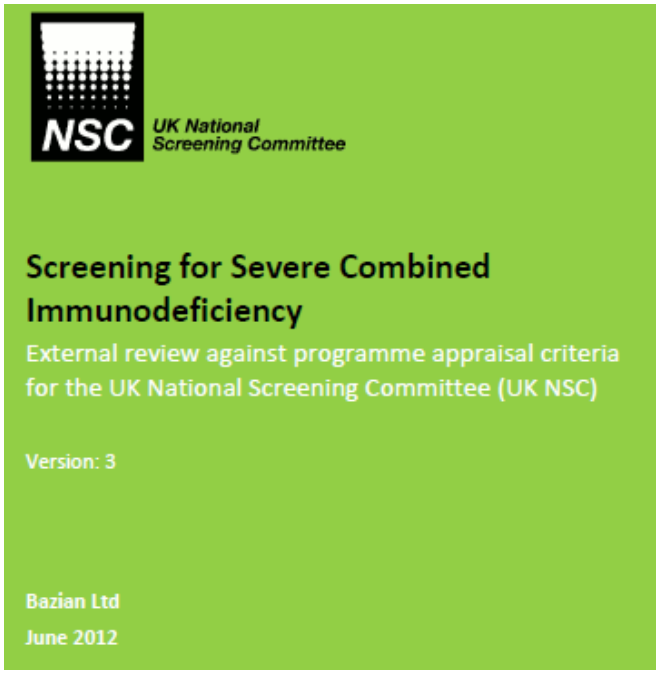


Borte et al., Blood 2012, 119(11)

* T-cell receptor excision circles

**kappa-deleting recombination excision circles

Pilot SCID screening in UK



Recommendation

Newborn screening for SCID is **not** recommended

insufficient information on:

- the epidemiology of the condition in the UK
- the performance of the test
- the management and outcomes of babies who are detected by screening but do not have SCID
- the clinical and cost effectiveness of screening compared to current practice

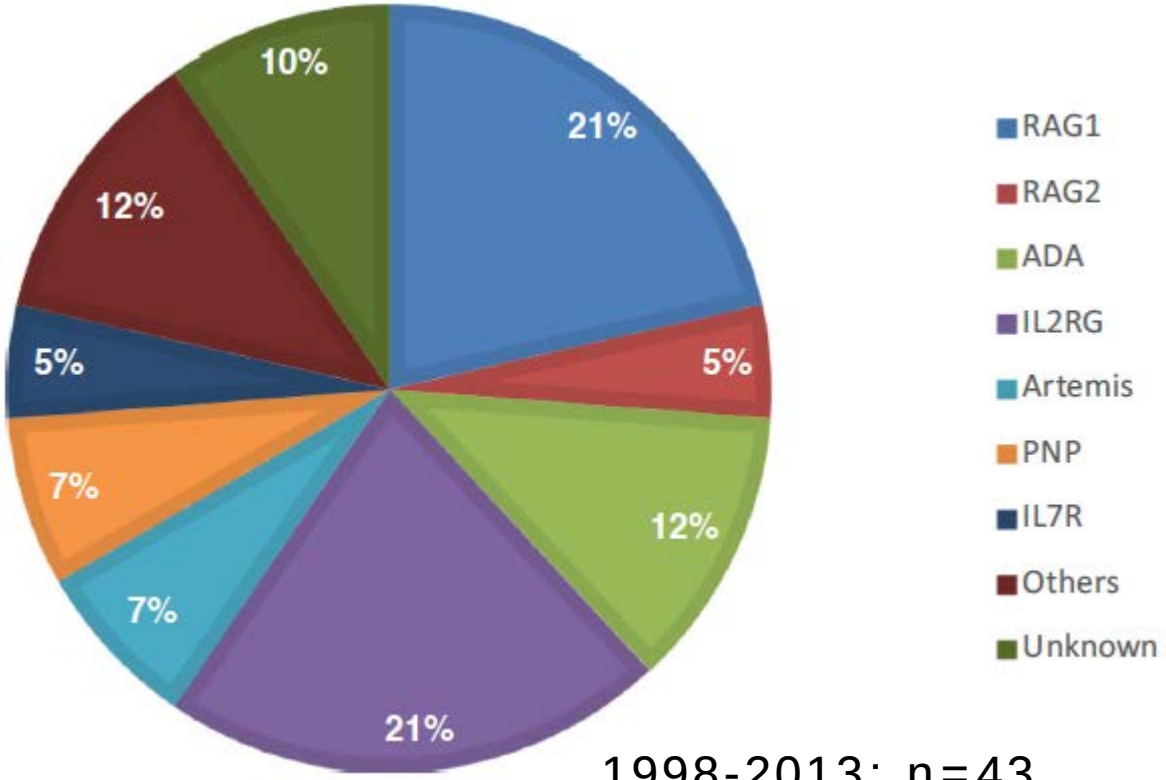
Adams et al., J Clin Immunol (2014), 34, 323-330

Dutch Health council on SCID screening

Neonatal Screening. New recommendations.
Dutch Health Council,
The Hague, Netherlands.
April 8, 2015

- Serious health problem
- Acceptable treatment (gene therapy or haematopoetic stem cell therapy)
- Suitable test (TREC, or TREC/KREC)
- Note-unintended findings (e.g. DiGeorge, Down syndrome, others)
- Note-cost-effectiveness study is needed

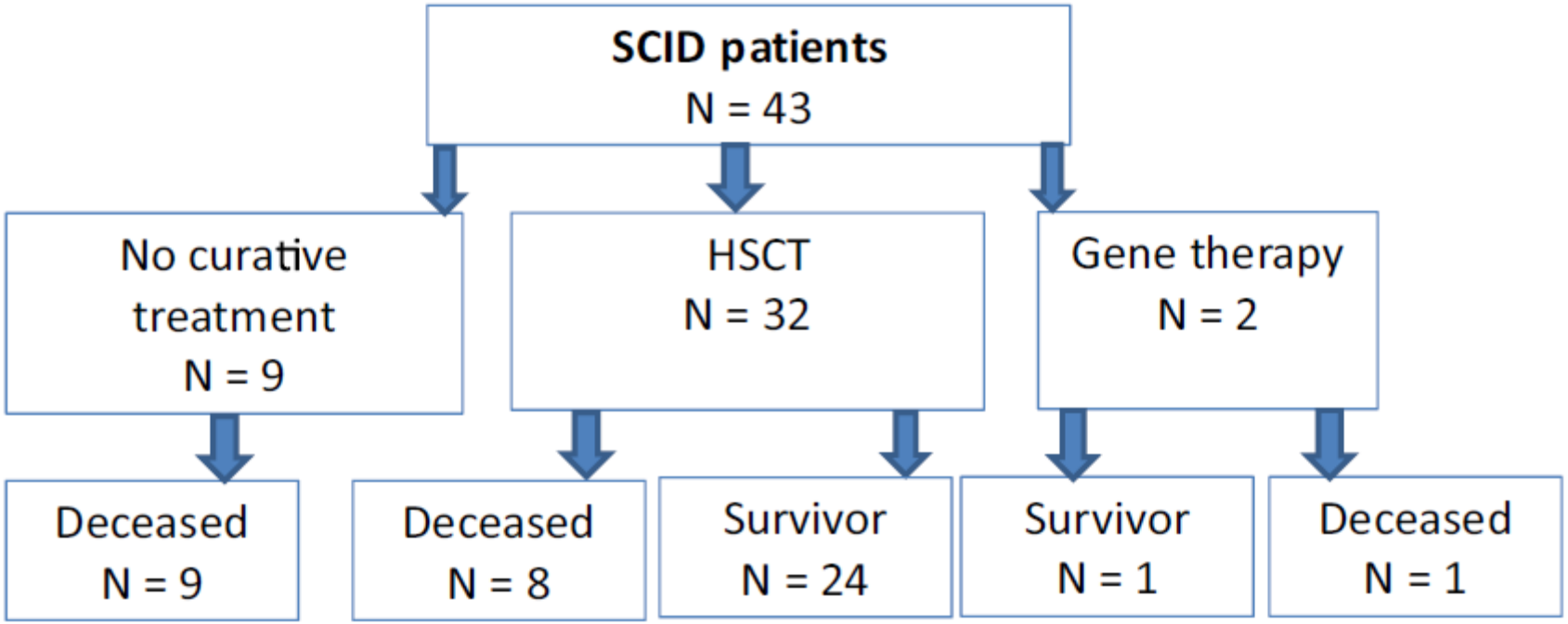
Distribution of SCID patients based on genetic diagnosis



1998-2013; n=43

Pagter et al., Eur J Pediatrics 2015

Fate of Dutch SCID patients



Pagter et al., Eur J Pediatrics 2015

Aims of Dutch retrospective SCID study

- To get first experience with DNA-analysis in the screening laboratory with two (commercially available) TREC (/KREC) assays
- To evaluate common SCID screening algorithms
- To get an idea of TREC in samples of premature births
- To align screening, diagnostic and treatment expertise
- To supply data for an extended prospective pilot screening with an analysis of costs

Samples

- Anonymized fresh heel prick cards (n=1295) from the Dutch Newborn Screening

- Filter paper cards with peripheral blood of 22 patients with a clinical, genetically confirmed, SCID diagnosis, (affected genes: ADA n=2, RAG1 n=6, RAG2 n=2, IL2Rg n=4, JAK3 n=2, XLF n=2, Artemis n=2, CD3E n=2) and of 27 patients with a primary immunodeficiency (PID), potentially SCID

- Reference samples of the Newborn Screening Translational Research Initiative (CDC, Atlanta, Georgia)

Methods

SCREEN-ID kit (TRM Leipzig*)

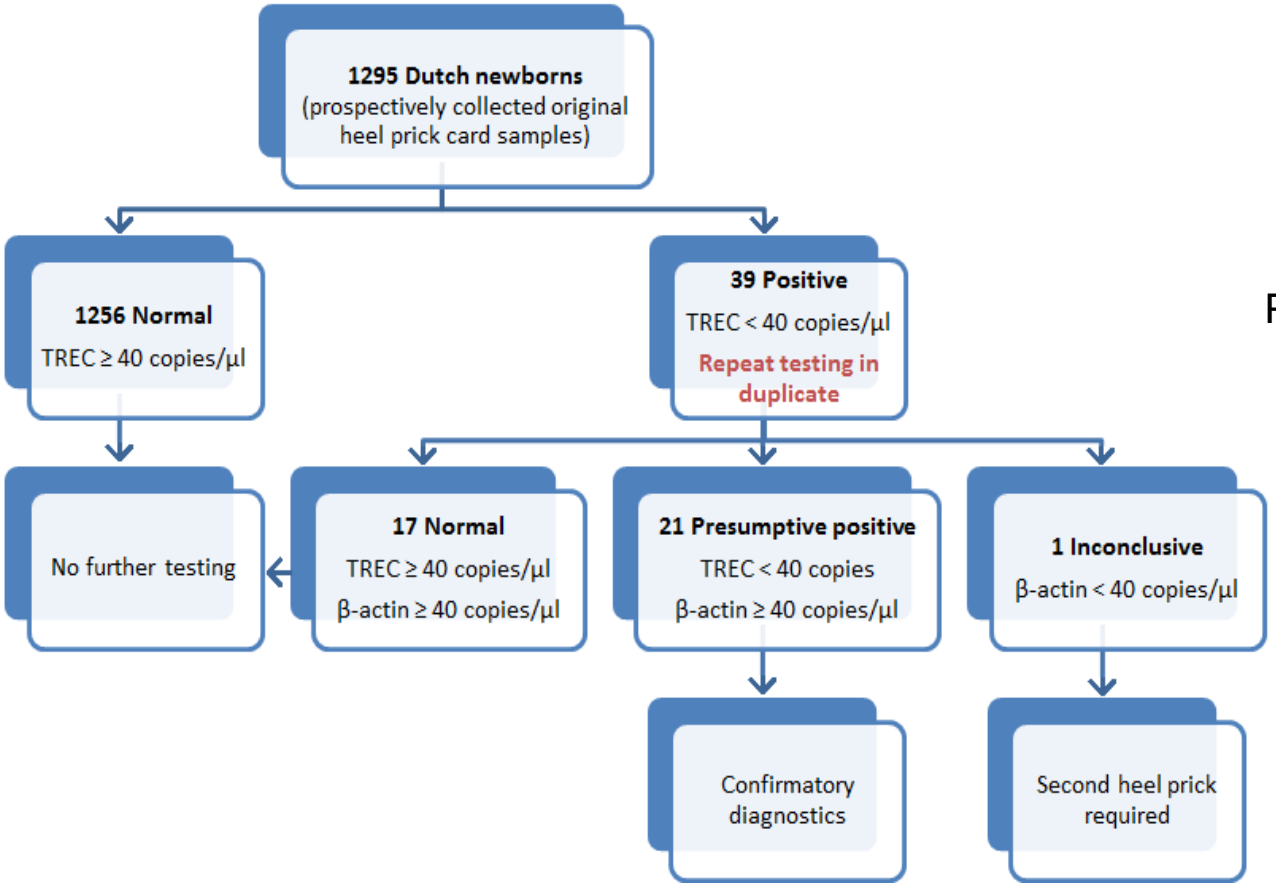
- Quantitative analysis of TREC, KREC and β-actin
- Real-time multiplex PCR

EnLite Neonatal TREC kit (PerkinElmer)

- Semi-quantitative analysis of TREC and β-actin
- End-point PCR

*Currently:
Mabtech Diagnostics, Nacka Strand, Sweden

Screening scheme



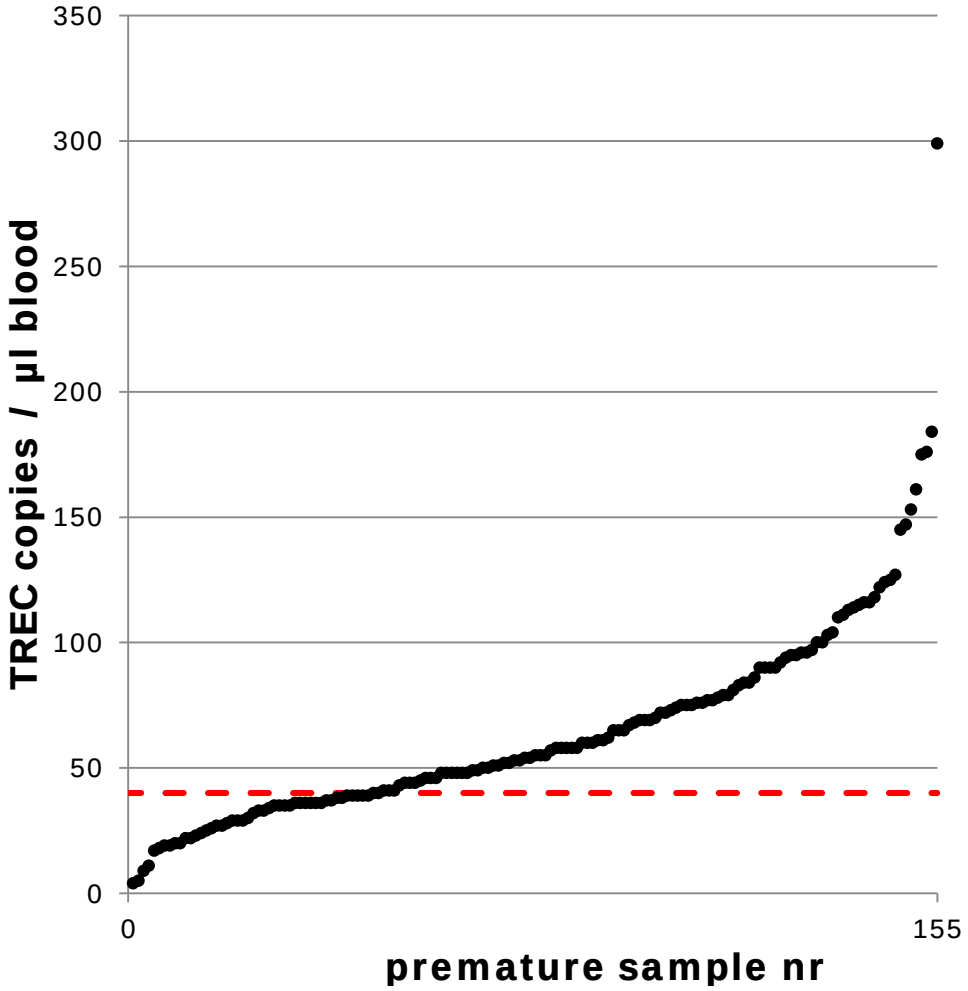
Re-test: 1.62%

Second sample: about 0.1%)

Results EnLite assay – samples of premature births

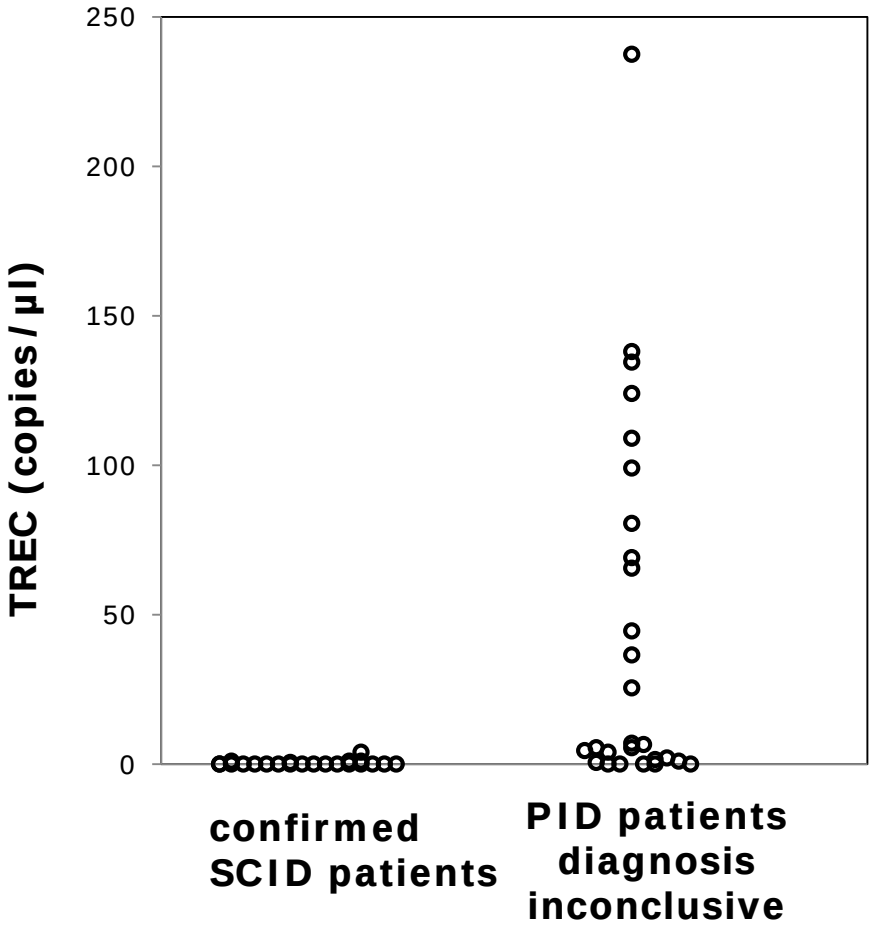
155 NBS cards of premature births (birth weight below ≤2500 g and GA ≤ 36.0 weeks)

- Average TREC-values; 65 copies/µl (median: 55)
- Re-test rate = 29%

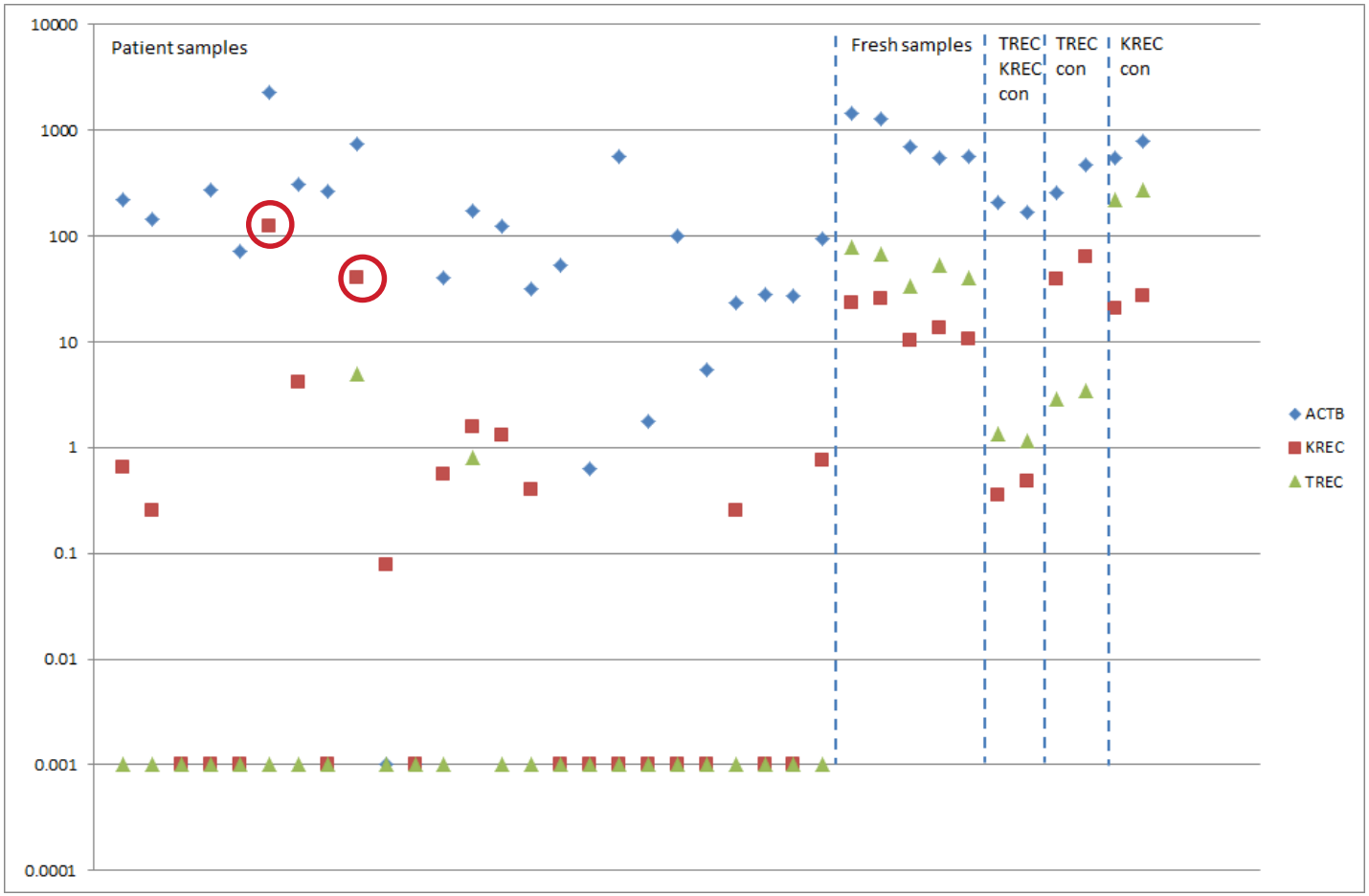


Results PE EnLite assay –SCID patients

- 22 confirmed SCID-patiënts (average TREC values: 0.47 copies/µl blood)
- 17 of 27 SCID-inconclusive diagnosis < cut off value of 40 copies/µl blood)



Results SCREEN-ID assay (KREC/TREC-assay)



What did we learn?

- Both assays work fine in the hands of experienced and well-trained technicians
- A basically equipped PCR laboratory is sufficient
- High throughput KREC analysis seems not feasible at this time (no commercial supply)
- Screening protocol with cut off of 40 TREC copies/µl blood (re-test rate 1.62 %) may be adapted, with adapted policy for premature newborns
- This became a joint project of screening laboratory and clinical immunological specialists with focus on diagnosis and treatment

What next?

"To supply data for an extended prospective pilot screening with a cost-analysis"

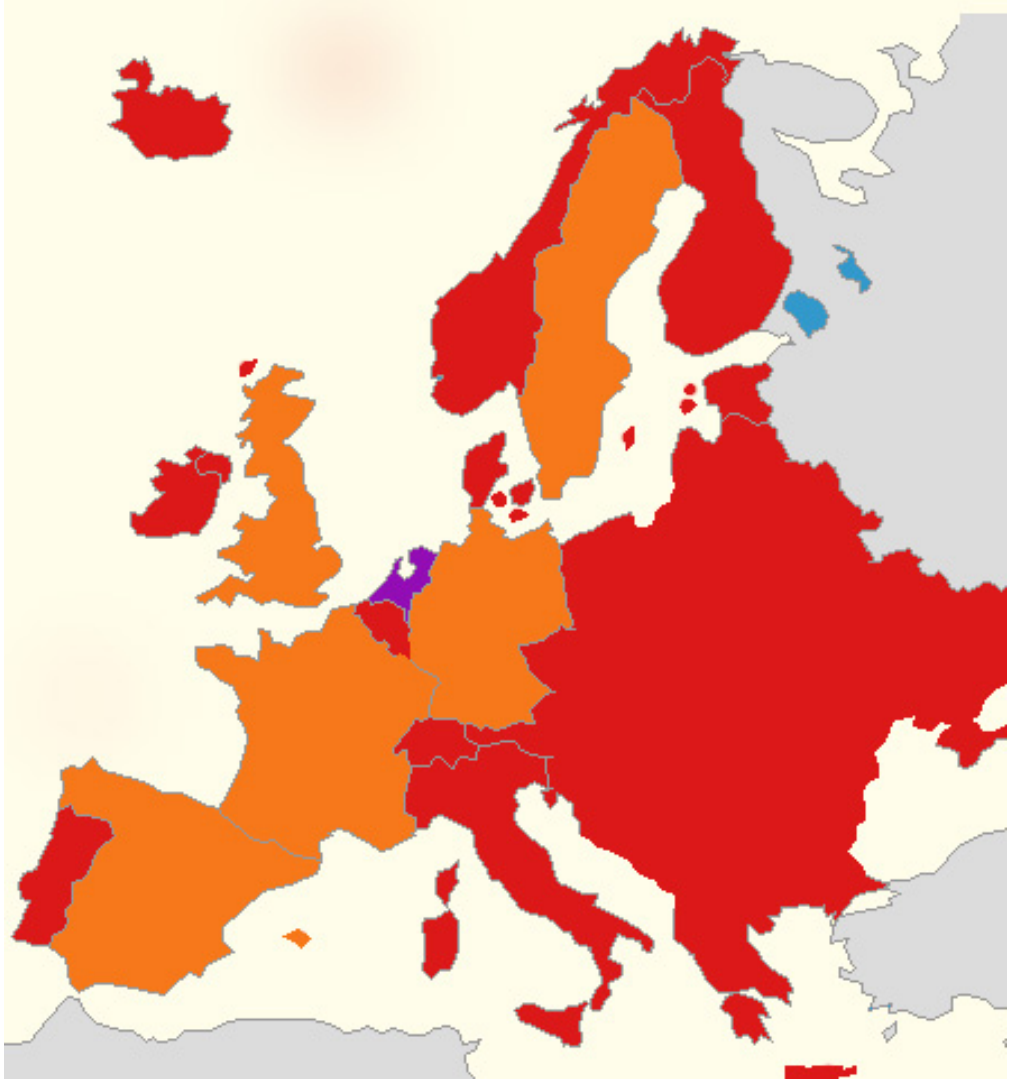
Prospective pilot screening in three laboratories (about 30.000 samples) to test

- ICT logistics
- High throughput prospective approach
- Referral of positive results (including into clinical diagnostic routine)
- Definition of applicable cut off values (also for samples of premature newborns)
- 330.000 euro
- TREC assay

Lennart Hammerstrøm (email 27.02.2016)

- Pilot program for both TREC and KREC (first in the world) in Stockholm
- 70.000 children screened
- Three severe PID children identified.
- First one, a SCID, successfully transplanted
- Request made for starting nationwide screening as of late this year.

Next (2018?) on the continent…



Next (2018?) on the continent…

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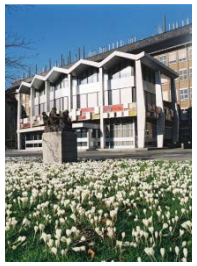

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Maartje Blom

Maartje Blom (RIVM/LUMC)

We recommend IJNS for your next publication…

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http://www.mdpi.com/journal/neonatalscreening