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.

* T-cell receptor excision circles
**kappa-deleting recombination excision circles

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

- 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

1295 Dutch newborns
(prospectively collected original heel prick card samples)

1256 Normal
TREC ≥ 40 copies/μl
No further testing

39 Positive
TREC < 40 copies/μl
Repeat testing in duplicate

17 Normal
TREC ≥ 40 copies/μl
β-actin ≥ 40 copies/μl

21 Presumptive positive
TREC < 40 copies/μl
β-actin ≥ 40 copies/μl
Confirmatory diagnostics

1 Inconclusive
β-actin < 40 copies/μl
Second heel prick required

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 \( \leq 2500 \) g and GA \( \leq 36.0 \) weeks)

- Average TREC-values; 65 copies/\( \mu l \) (median: 55)
- Re-test rate = 29%
Results PE EnLite assay – SCID patients

- 22 confirmed SCID-patients (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...
Acknowledgements

**Erasmus University Medical Centre Rotterdam**
Mirjam van der Burg
Ingrid Pico-Knijnenburg

**Leiden University Medical Centre (LUMC)**
Robbert Bredius

**Academic Medical Centre Amsterdam**
Anita Boelen
Marja van Veen-Sijne

**Nat. Inst. Public Health and the Environment (RIVM)**
Maartje Blom

Maartje Blom (RIVM/LUMC)
We recommend IJNS for your next publication...

International Journal of Neonatal Screening

(ISSN 2409-515X)

The official journal of the International Society for Neonatal Screening (ISNS)

Editor-in-Chief

Dr. Ralph Fingerhut
Swiss Newborn Screening Laboratory, Zurich, Switzerland
ralph.fingerhut@kispi.uzh.ch

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