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

Expansion of a National Newborn Bloodspot Screening Program with Fourteen Conditions

Preparations in the Netherlands

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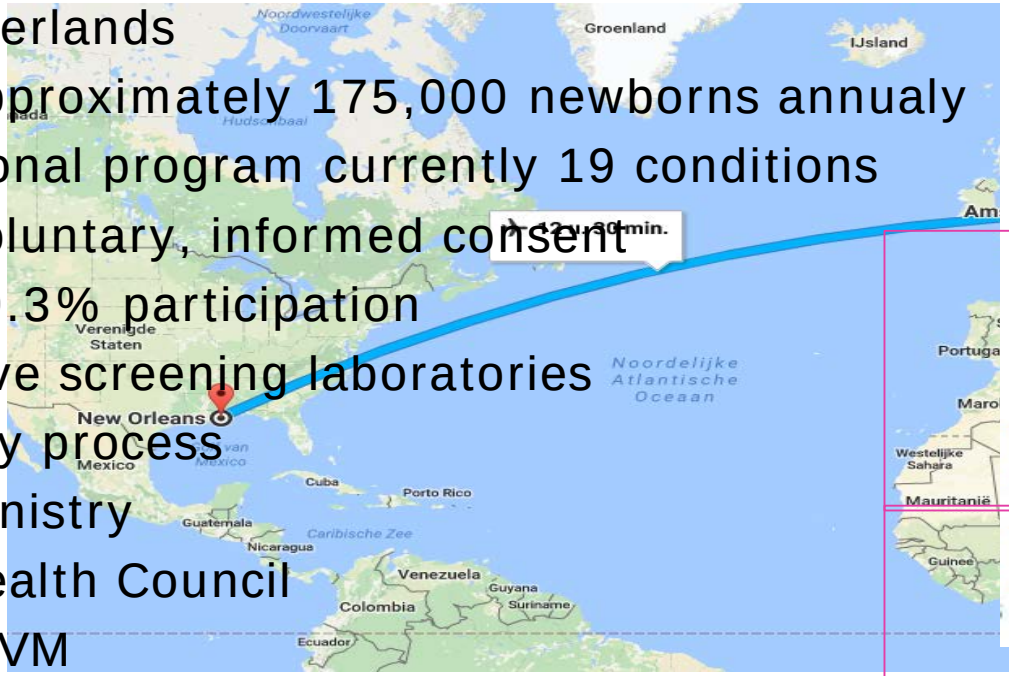
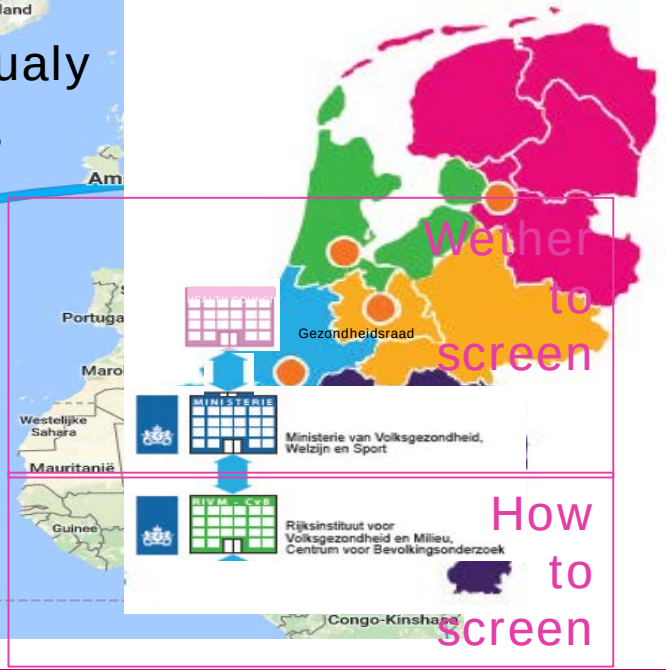
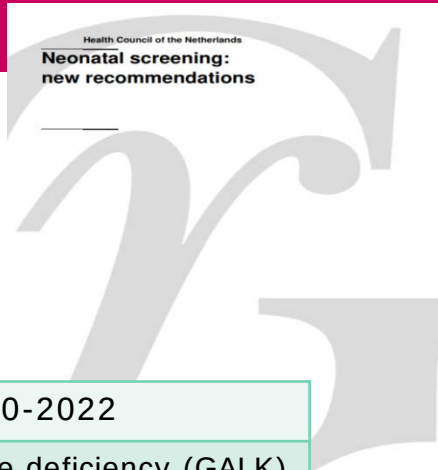
Program and process in the Netherlands

- Netherlands
  - Approximately 175,000 newborns annualy
- National program currently 19 conditions
  - Voluntary, informed consent
  - 99.3% participation
  - Five screening laboratories
- Policy process
  - Ministry
  - Health Council
  - RIVM







Policy advice & decision on expansion

- Expansion with 14 conditions in three phases
  - Health Council of NL advisory report (2015)
  - Primary program, Ministry decided on phased time frame

Phase I – 2017	Phase II – 2019	Phase III – 2020-2022
• *Alfa-thalassemia (HbH-disease)* • *Beta thalassemia major (TM)* • Organic cation transporter 2 (OCTN 2)	• Methylmalonic acidemia (MA) • Propionic acidemia (PA) • Carnitine-acylcarnitine translocase deficiency (CACT) • Carnitine palmitoyltransferase deficiency type 1 (CPT1) • Carnitine palmitoyltransferase deficiency type 2 (CPT2) • Methyl-acetoacetyl-CoA thiolase deficiency; ketothiolase deficiency (BKT)	• Galactokinase deficiency (GALK) • Guanidinoacetate methyltransferase deficiency (GAMT) • Mucopolysaccharidosis type 1 (MPS I) • Severe combined immune deficiency (SCID) • X-linked adrenoleukodystrophy (X-ALD)

Available in English from
https://www.gezondheidsraad.nl/sites/default/files/201508e_neonatalscreeningnewrecommendations.pdf

Implementation

- Feasibility study[1]
  - Primary process
  - Organization and responsibility
  - Quality assurance
  - Communication and education
  - Information tools
  - Monitoring and evaluation
- Additional details required
  - Stakeholder involvement through experts groups

1. Available in Dutch from: http://www.rivm.nl/Documenten_en_publicaties/Wetenschappelijk/Rapporten/2017/Juli/Uitvoeringstoets_uitbreiding_neonatale_hielprikscreening

Principles for screening

- **Whether** to screen: framework screening criteria
  - Wilson & Jungner principles
- **How** to screen: Checklist based on international examples:[2,3]
  - Australia; Canada; Denmark; UK; USA
- Additional details required
  - Test method
  - Disease variants and Dutch prevalence
  - Treatment consensus

Category 1: conditions that qualify for inclusion
- Neonatal screening prevents significant, irreversible damage and/or yields substantial health gains for the child
- A test of proven quality is available

Category 2A: conditions that require further study
- Neonatal screening prevents significant, irreversible damage and/or yields substantial health gains for the child
- A test of proven quality is not (yet) available

Category 2B: conditions that may be considered for inclusion after weighing the advantages and disadvantages, including cost-effectiveness
- Neonatal screening yields health gains
- A test of proven quality is available

Category 3: conditions that do not qualify for inclusion
- Neonatal screening yields no health gains
- There may be other advantages for quality of life, such as shortening the diagnostic process (without prevention or limitation of damage to health).

2. Jansen, M. E., Metternick-Jones, S. C., & Lister, K. J. (2017). International differences in the evaluation of conditions for newborn bloodspot screening: a review of scientific literature and policy documents. *EJHG* 25(1), 10-16.
3. English translation of checklist available via marleen.jansen@rivm.nl

Stakeholder involvement

- Eight multidisciplinary expert groups for eleven conditions
  - Background document
    - Scientific publications
    - Grey literature, international examples
  - Agenda meeting
    - Test, disease variants, treatment consensus
  - Outcome
    - Advice on current status and types of further research needed
  - Member check through summary of the minutes, advice, checklist
  - Evaluation of process

CACT; CPT1; CPT2 | GALK | GAMT | BKT | MMA; PA | MPS I | OCTN 2 | X-ALD

Advice for conditions and further research

- Retrospective studies: Dutch prevalence, cut-offs
- Post analytical tool with CLIR database: potentially applicable to multiple conditions

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GAMT

- Prevalence
  - Unknown in Netherlands, estimated at 1:250.000
- Test method
  - Off-label MS/MS
  - In-house
  - LC MS/MS
- Logistics
  - In-house: central lab or all labs
  - Analysis within 24 hours
- Advice
  - → Retrospective studies: Dutch prevalence, cut-offs
  - → Prospective pilot study

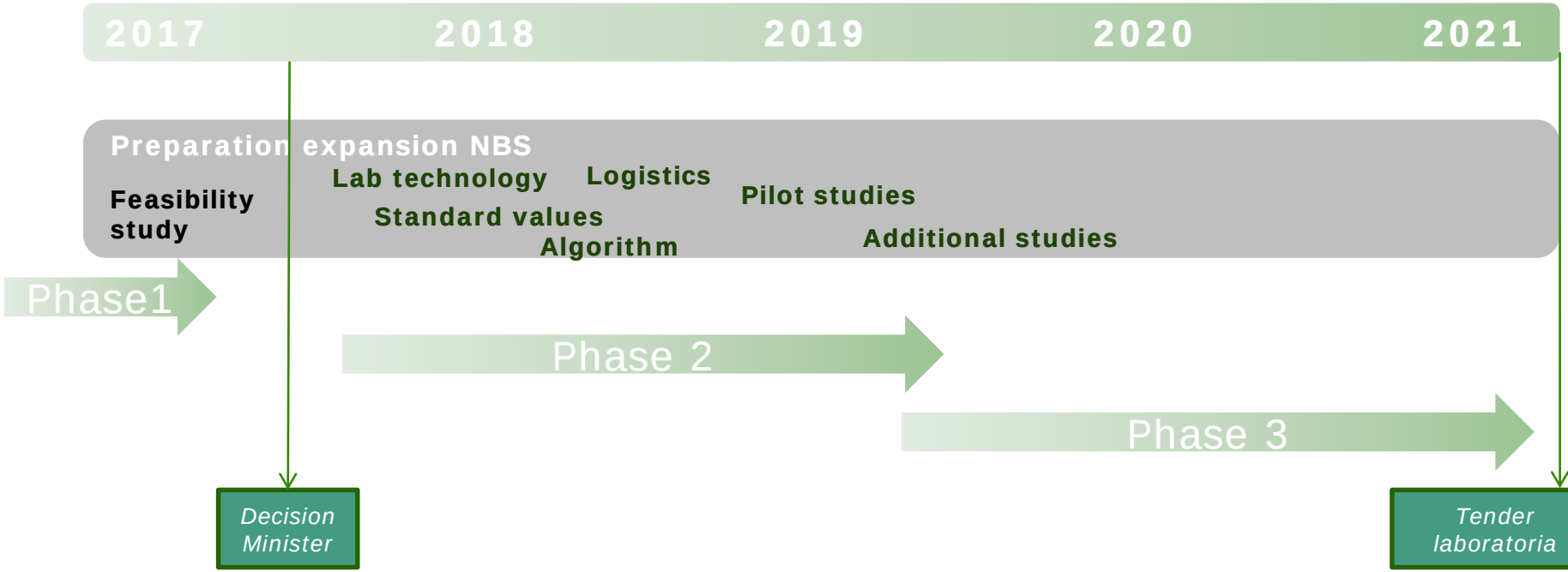
OCTN-2

- Prevalence
  - Unknown in Netherlands, estimated 1:20.000 – 1:200.000
- Disease variants
  - Broad spectrum: life threatening to apparent healthy
  - Genotype-phenotype relation unclear
  - Asymptomatic mothers
- Test method
  - Available MS/MS: C0 carnitine
- Logistics
  - Assess time point for reliable heel prick
- Advice

  → Retrospective studies: Dutch prevalence, cut-offs

  → Prospective pilot study

Estimated time frame



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- Experts participated groups

Extra slide – Topics on checklist

A. Test parameters
   I. Which analytes or parameters are tested, and about what disorders does the test provide information? If a test involves multiple steps, answer for each tier.
   II. If screening will inevitably identify carriers, it must be clear (i) how to deal with this information, and (ii) the consequences of this must be weighed

B. Analytical and clinical validity of the screening test
   I. A simple, rapid, specific, precise, accurate and safe test must be available, which can be performed on dried blood spots.
   II. The distribution of the biomarker in the target population must be known
   III. The test is acceptable for the target population.

C. Follow-up in the case of positive test result
   I. There must be an agreed policy for a positive screening result
   II. The benefit for individuals must outweigh the drawbacks (caused by the test)
   III. There must be an agreed policy for secondary findings and variants, discovered in the screening
   IV. The follow-up costs of the screening programme in the case of secondary findings/variants are reasonable in relation to costs on healthcare in general (value for money)

Extra slide – Participants in expert groups

- Pediatrician
- Clinical geneticist
- Clinical biochemist
- NBS Advisory committee member
- Medical ethicist
- Laboratory expert
- Scientific consultant
- Policy expert
- Evaluation consultant
- Patient advocate
- Program coordination