Neonatale screening op CF
6 februari 2009
Utrecht

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Definition US Commission on Chronic Illness 1951:

The presumptive identification of unrecognized disease or defect by the application of tests, examinations or other procedures which can be applied rapidly. Screening tests sort out apparently well persons who probably have a disease from those who probably do not. A screening test is not intended to be diagnostic. Persons with positive or suspicious findings must be referred to their physicians for diagnosis and necessary treatment.
Neonatal screening (heelprick)
<table>
<thead>
<tr>
<th>Hospital Name and ward</th>
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<tbody>
<tr>
<td>USE BLOCK LETTERS OR HOSPITAL ID LABEL</td>
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<tr>
<td>UR/Comments</td>
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<table>
<thead>
<tr>
<th>Doctor's name and initials</th>
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<table>
<thead>
<tr>
<th>Infant's full name</th>
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<tr>
<th>Twin</th>
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<th>Date of birth / / time</th>
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<th>Date of sample / / time</th>
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<table>
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<tr>
<th>Gestation: weeks</th>
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<tr>
<th>Current weight: g</th>
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<table>
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<th>Breast Feed</th>
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<th>□ Formula Type</th>
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<th>□ TPN</th>
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<th>□ Male</th>
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<table>
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<th>□ Female</th>
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<table>
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<tr>
<th>Relevant Family History</th>
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<th>Collectors Name</th>
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SOAK BLOOD FROM THE OTHER SIDE
PKU phenylketonuria

Autosomal recessive

Without treatment severe mental retardation

Treatment: diet with limitation of phenylalanine intake

1:18.000 newborns = 11 per year in NL

(Verkerk 1995)

Carrier frequency 1 in 67

Starting 1974 in NL
Preconceptional screening
Screening: phases of life

Preconceptional

Antenatal: during pregnancy

Neonatal: heelprick

Later in life (mammography, cholesterol)
Screening:

- Presymptomatic
  (no symptoms or complaints yet)
- Offer of health care
- Systematic offer
  (all newborns or all women aged 50-75)
- Sometimes voluntary, seldom “mandatory”
- Often low risk population; similar to self tests
Screening: goal

• **Prevention and treatment**
  • Early detection; treatment before symptoms occur
  • Early detection of risk; preventive interventions to reduce risk

• **Reproductive choices**, such as
  • Don’t get pregnant (again)
  • Prenatal diagnosis and selective abortion
  • Artificial insemination donor sperm
  • Preimplantation genetic diagnosis
Screening: goal neonatal screening

• Prevention and treatment
  • Early detection; treatment before symptoms occur
  • Early detection of risk; preventive interventions to reduce risk
Genomics

This knowledge will dramatically accelerate the development of new strategies for the diagnosis, prevention and treatment of disease, not just for single-gene disorders but for the host of more common complex diseases, e.g., diabetes, heart disease, schizophrenia, and cancer.
Neonatal screening NL 2006-2007

2006

- PKU
- Congenital hypothyroidism
- Adrenogenital syndrome

- Medication or diet to avoid
- Mental retardation or sudden death

- Biotinidase deficiency
- Cystische fibrosis (conditional; pilot 2008)
- Galactosemia
- Glutaric aciduria type I
- HMG-CoA-lyase deficiency
- Holocarboxylase synthase deficiency
- Homocystinuria
- Isovaleric acidemia
- Long-chain hydroxyacyl CoA dehydrogenase deficiency
- Maple syrup urine disease
- MCAD deficiency
- 3-methylcrotonyl-CoA carboxylase deficiency
- Sickle cell disease
- Tyrosinemia type I
- Very-long-chain acylCoA dehydrogenase deficiency
Neonatale screening NL

- Gezondheidsraad 2005
- Aangeboden aan staatssecretaris op 22 augustus 2005
- “Bij baby’s zijn met één hielprik veel meer behandelbare ziektes op te sporen”
- Voor CF eerst een betere opsporingsmethode ontwikkelen

www.gr.nl
Neonatal screening NL: the committee

- Dr GCML Page-Christiaens, Chairman
  gynaecologist, University Medical Centre, Utrecht
- Prof. MF Niermeijer, Vice-Chairman
  Professor of Clinical Genetics, University Medical Centre, Nijmegen
- Prof. MC Cornel
  Professor of Community Genetics, VU University Medical Centre, Amsterdam
- Prof. JJC Dute
  Professor of Health Law; Erasmus Medical Centre, Rotterdam
- Dr AH van Genip
  clinical chemist, University of Maastricht
- RM den Hartog-van Ter Tholen, adviser
  Ministry of Health, Welfare and Sport
- Prof. HSA Heymans
  Professor of Paediatrics; Academic Medical Centre, Amsterdam
- Dr JG Loeber
  biochemist; National Institute of Public Health and the Environment (RIVM), Bilthoven
- Dr GPA Smit
  paediatrician, Groningen University Hospital (AZG)
- Dr MF Verweij
  ethicist, Utrecht University

- Dr PA Bolluis, Secretary
  The Health Council, The Hague

Secretarial support: CJM Vianello-Roodbol
Layout: J van Kan
• Considerable, irreparable damage can be prevented (category 1)
  – Add 14 diseases (biotinidase deficiency, galactosemia, glutaric aciduria type I, HMG-CoA lyase deficiency, holocarboxylase synthase deficiency, homocystinuria, isovaleric acidemia, longchain hydroxyacyl-CoA dehydrogenase deficiency, maple syrup urine disease, MCAD deficiency, 3-methylcrotonyl-CoA carboxylase deficiency, sickle cell disease, tyrosinemia type I and very-long-chain acyl-CoA dehydrogenase deficiency).

• Less substantial or insufficient evidence of prevention of damage to health (category 2)
  – Consider adding cystic fibrosis if better test becomes available (improve specificity)

• No prevention of damage to health (category 3)
Why more diseases?

- More treatment available
  - Early detection: less health damage
- More tests available
  - MS/MS

• Should any disease for which treatment becomes available be screened for?
Screening criteria

• When to screen?
  – A variety of sets of criteria derived from W&J

• Important public health problem (prevalence & severity)
• Is treatment available? Does early treatment help?
• Course of disease known; frequency known
• Good test (high sensitivity; high specificity, high positive predictive value)
• Uniform treatment protocol; knowing whom to treat
• Etc
Balancing pros and cons

1. Treatment available? Effective? Available for all and for ever? Affordable?

2. Good test available?
   - False positives
   - Specificity (1-FP)
   - False negatives
   - Sensitivity (1-FN)
   - Positive predictive value

3. Unintended side effects
   - Mild phenotypes
   - Carriers identified

<table>
<thead>
<tr>
<th>Disease</th>
<th>Present</th>
<th>Absent</th>
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<tr>
<td>Test Result ↓</td>
<td></td>
<td></td>
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<tr>
<td>Positive</td>
<td>A</td>
<td>B</td>
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<tr>
<td>Negative</td>
<td>C</td>
<td>D</td>
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Balancing pros and cons

Good test available?

- False positives: many children referred to hospital; parents are worried; breastfeeding stopped (galactosemia); long time before result is certain (hypothyroidism).

- False negatives: pediatricians don’t consider the diagnosis any more, if it’s in the heelprick. Delay of diagnosis may occur in cases missed.

- Specificity and sensitivity should be (close to) 100%.
Balancing pros and cons

**Unintended side effects**

**Mild phenotypes:** when looking for serious cases of CF, also mild cases are identified, who might not have had symptoms for many years. Advantage to avoid long diagnostic quest? Disadvantage to worry from birth onwards?

**Carriers identified:** should parents be informed because the information is relevant to them?
- Recurrence risk for carrier couples
- Many carriers as compared to cases
Neonatale screening CF, GR 2005

- Behandelbare aandoening
- Of vroege diagnostiek tot een betere uitkomst leidt, is onderwerp van discussie -> grensgeval, categorie II
- Sensitiviteit geen 100% (m.n. Turkse en Marokkaanse mutaties niet allemaal bekend, dus niet allemaal in panel)
- Specificiteit geen 100% dus veel fout positieven (600 pasgeborenen zonder CF doorverwezen voor zweettest, 1200 tweede IRT test)