Newborn Screening for Cystic Fibrosis in Switzerland
- Evaluation after two years

R. Fingerhut, T. Torresani, S. Gallati, M.H. Schoeni, C. Kuehni,
C. Ruegg, M. Baumgartner, J. Barben
and the Swiss CF Screening Group
Final approval of CF-Screening

Retrospective analysis …
J Barben et al.
JCF 11 (2012) 332-6

Pilot study

NBS for CF in Switzerland - Consequences after Analysis of 4 Months Pilot Study
T Torresani et al.
JCF (2013) in press

Application to the health ministry

APHL 2013 – Atlanta
Legal Regulations

NBS = Genetic Screening
informed consent necessary
IRT/DNA protocol approved
CF-screening result pos./neg.
Cut-off definitions


from: Lehmann „Handbuch der Medizinischen Informatik“
Percentiles

95.0
99.0
99.2
99.5
99.9

CF pos. (n=27)
Equivocal CF (n=3)
CF pos. with meconium ileus and normal IRT
<table>
<thead>
<tr>
<th>Analyte</th>
<th>Intra-Assay CV</th>
<th>Inter-Assay CV</th>
<th>mean recovery [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRT</td>
<td>3.5 (at 31.6 ng/mL; n=12)</td>
<td>6.1 (at 31.6 ng/mL; n=30)</td>
<td>97.8</td>
</tr>
<tr>
<td></td>
<td>5.0 (at 67.6 ng/mL; n=12)</td>
<td>5.8 (at 67.6 ng/mL; n=30)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.7 (at 100.0 ng/mL; n=12)</td>
<td>5.7 (at 100.0 ng/mL; n=30)</td>
<td></td>
</tr>
</tbody>
</table>
IRT measurement on the 4th day of life (NBS card - term) or 15th day of life (2nd NBS card - preterm)

- ≥ 99.2nd percentile (≥ 50ng/ml)
- <99.2nd percentile (<50ng/ml)

- Screening for 7 CFTR mutations
- No CFTR mutation
- 1 or 2 CFTR mutations
- 2nd NBS card 2nd IRT measurement

- No further tests
- IRT from 1st test ≥ 60 ng/ml

- ≥ 99.2nd percentile (≥ 50ng/ml)
- <99.2nd percentile (<50ng/ml)

- Referral to CF centre
- Sweat test
- Additional diagnostic tests: DNA analysis, pancreas elastase, etc.

Diagnosis

Children with meconium ileus

F508del 3905insT G542X R553X W1282X 1717-1G>A N1303K
**Procedure in CF centre since 2012**

**Sweat test**
*Measurement of chloride and conductivity*

- **Cl ≥ 60 mmol/L**
  - Conductivity ≥ 80 mmol/L
  - DNA analysis
    - 32 CFTR mutations
    - (informed consent !)
    - 2 mutations
    - 1 mutation
  - total DNA analysis
  - CF diagnosis
  - Follow up and further investigations

- **Cl 30-59 mmol/L**
  - Conductivity 50-79 mmol/L
  - DNA analysis
    - 32 CFTR mutations
    - (informed consent !)
    - 1 mutation
    - 2 mutations
  - total DNA analysis
  - Equivocal CF or CF

- **Chloride < 30 mmol/L**
  - Conductivity < 50 mmol/L
  - Information about possible carrier status or atypical CF
    - Information sheet for parents
    - Information to GP about elevated IRT and normal sweat test
  - DNA analysis
    - 32 CFTR mutations
    - (informed consent !)
    - total DNA analysis if needed
  - CF, equivocal CF, CF carrier or healthy

- **Sweat test not possible**
  - DNA analysis
    - 32 CFTR mutations
    - (informed consent !)
  - CF, equivocal CF, CF carrier or healthy

**Feedback to the NGS laboratory – fill in assessment sheet for data base**
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition of success</th>
<th>Evaluation after two years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis of children with CF (compared to earlier years with clinical diagnosis)</td>
<td>≥15 per year</td>
<td>56 CF + 9 equivocal CF</td>
</tr>
<tr>
<td>Care of children with CF in a CF centre</td>
<td>&gt;90%</td>
<td>100 % (56/56)</td>
</tr>
<tr>
<td>Deniers of Guthrie test</td>
<td>Not elevated to earlier years (&lt;10 per year)</td>
<td>2011: 5 / 2012: 6</td>
</tr>
<tr>
<td>Recall rate (Percentage of children who required further investigations)</td>
<td>assumed &lt; 1%</td>
<td>0.58 % (168+805)/167’819</td>
</tr>
<tr>
<td>Positive predictive value (PPV)</td>
<td>&gt; 20%</td>
<td>29.2 % (49/186)</td>
</tr>
<tr>
<td>False negatives (without MI)</td>
<td>&lt;5% of all CF diagnosis</td>
<td>3.7 % (2/56)</td>
</tr>
<tr>
<td>Time to genetic diagnosis</td>
<td>Before NBS: 198 days (13-1033) Aim: &lt; 60 days</td>
<td>41 days (12-160)</td>
</tr>
<tr>
<td>Satisfaction of parents with a CF child</td>
<td>&gt;80% are satisfied</td>
<td>2011: 100% (18/18), 2012: 96%</td>
</tr>
<tr>
<td>Satisfaction of parents with positive screening but without CF diagnosis</td>
<td>&gt;70% are satisfied</td>
<td>2011: 86% (25/29), 2012: 86%</td>
</tr>
</tbody>
</table>
### Results after 2 years

#### Time from birth to CF diagnosis

<table>
<thead>
<tr>
<th>Parameter (days)</th>
<th>Mean</th>
<th>Median</th>
<th>Interquartile range</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth – genetic diagnosis</td>
<td>48.1</td>
<td>41</td>
<td>28-56</td>
<td>12-160</td>
</tr>
<tr>
<td>Birth – heel prick test</td>
<td>5.9</td>
<td>5</td>
<td>5-6</td>
<td>4-47</td>
</tr>
<tr>
<td>Heel prick test – notification of CF centre</td>
<td>13.2</td>
<td>10</td>
<td>8-15</td>
<td>1-115</td>
</tr>
<tr>
<td>Notification of CF centre – phone call to parents</td>
<td>7.2</td>
<td>5</td>
<td>3-9</td>
<td>0-44</td>
</tr>
<tr>
<td>Phone call to parents – visit in CF centre</td>
<td>1.9</td>
<td>1</td>
<td>1-2</td>
<td>0-10</td>
</tr>
<tr>
<td>Birth – visit in CF centre</td>
<td>31.8</td>
<td>25</td>
<td>20-32.5</td>
<td>4-314</td>
</tr>
<tr>
<td>Visit in CF centre – genetic diagnosis</td>
<td>19.8</td>
<td>16</td>
<td>8-26</td>
<td>1-80</td>
</tr>
<tr>
<td>Duration of genetic analysis</td>
<td>13.6</td>
<td>11.5</td>
<td>5-19</td>
<td>1-42</td>
</tr>
</tbody>
</table>
## Results after two years

### Children with meconium ileus

#### 2011

- **8 children with MI**
  - 1 without CF
  - 7 with CF

<table>
<thead>
<tr>
<th>No.</th>
<th>IRT</th>
<th>Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>77.7</td>
<td>F508del / 1717-1G&gt;A</td>
</tr>
<tr>
<td>2</td>
<td>119.5</td>
<td>F508del / F508del</td>
</tr>
<tr>
<td>3</td>
<td>89.9</td>
<td>F508del / F508del</td>
</tr>
<tr>
<td>4</td>
<td>102.3</td>
<td>F508del / F508del</td>
</tr>
<tr>
<td>5</td>
<td>54.4</td>
<td>F508del / F508del</td>
</tr>
<tr>
<td>6</td>
<td>88</td>
<td>F508del / F508del</td>
</tr>
<tr>
<td>7</td>
<td>39.5</td>
<td>F508del / F508del</td>
</tr>
</tbody>
</table>

#### 2012

- **7 children with MI**
  - 3 without CF
  - 4 with CF

<table>
<thead>
<tr>
<th>No.</th>
<th>IRT</th>
<th>Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>71.7</td>
<td>F508del / F508del</td>
</tr>
<tr>
<td>2</td>
<td>117.9</td>
<td>F508del / N1303K</td>
</tr>
<tr>
<td>3</td>
<td>50.5</td>
<td>W1282 / R347H</td>
</tr>
<tr>
<td>4</td>
<td>29.5</td>
<td>F508del/TG11_T5</td>
</tr>
</tbody>
</table>
### Newborn screening

**Situation in Switzerland 1965 - 2012**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Tested babies</th>
<th>Cases</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenylketonuria (+ Hyperphenylalaninemia)</td>
<td>3’705’005</td>
<td>465</td>
<td>1 : 7’968</td>
</tr>
<tr>
<td>Galaktosemia</td>
<td>3’536’372</td>
<td>87</td>
<td>1 : 40’648</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>2‘851’700</td>
<td>783</td>
<td>1 : 3’642</td>
</tr>
<tr>
<td>Biotinidase-Deficiency</td>
<td>2’116’336</td>
<td>37</td>
<td>1 : 57’198 (1 : 42’327)</td>
</tr>
<tr>
<td>Congenital adrenal hyperplesia</td>
<td>1‘692’673</td>
<td>179</td>
<td>1 : 9’456</td>
</tr>
<tr>
<td>MCAD Deficiency</td>
<td>634’760</td>
<td>58</td>
<td>1 : 10’944</td>
</tr>
<tr>
<td>Cystic Fibrosis</td>
<td>167’819</td>
<td>65</td>
<td>1:2’581</td>
</tr>
</tbody>
</table>
Screening for 7 CFTR mutations

IRT measurement on the 4th day of life (NBS card - term) or 15th day of life (2nd NBS card - preterm)

- ≥ 99.2nd percentile (≥ 50ng/ml)
- <99.2nd percentile (<50ng/ml)

No further tests

- No CFTR mutation
- IRT from 1st test ≥ 60 ng/ml

2nd NBS card 2nd IRT measurement

- ≥ 99.2nd percentile (≥ 50ng/ml)
- <99.2nd percentile (<50ng/ml)

No further tests

Blood taken for Further IRT measurement in screening lab

- Referral to CF centre
- Sweat test
  - normal
  - positive, borderline, unclear
  - Additional diagnostic tests: DNA analysis, pancreas elastase, etc.

Referral to CF centre

IRT from 1st test ≥ 50ng/ml

333 / year

81 / year
CF-Screening in Switzerland

Thanks to the Swiss CF Screening-Group

J. Barben  P. Eng  C. Kühni  N. Regamey  J. Spalinger
T. Torresani  S. Gallati  A. Möller  I. Rochat  R. Spinias
C. Barrazzone  G. Hafen  A. Mornand  B. Schiller  D. Trachsel
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