Improvement of the validity of the Dutch combined IRT/PAP/InnoLipa/EGA newborn screening program for CF by re-evaluating mutation classification and optimizing cut-off values.
Program until June 30 2016

● National program started May 1 2011
● Four step screening strategy
● After screening → referral for a sweat test at a designated CF center
● Aim: To identify patients with (classical) Cystic Fibrosis
● Standard of care: Sensitivity ≥ 95%*

* JCF 2014:13, S23
Screening strategy until June 30 2016
Performance of the strategy

● Between May 1 2011 and June 30 2014
  – 556.978 children screened
  – 86 CF patients referred
  – 9 CF patients missed
  – Sensitivity: 91% (CI 83-95%)

● Sensitivity below standard of care!

See poster Jeannette Dankert-Roelse
Evaluation of the screening protocol

● Re-evaluation InnoLiPA panel

● Evaluation screening strategy based on screening results between May 1 2011 and June 30 2014 and data from CHOPIN study* from 2008

* Thorax 2012; 67, 289-95
Re-evaluation InnoLiPa panel

- 35 mutations:
  - Classified as disease-causing CF mutations (A)
  - R117H-7T/9T mutations: Unknown (O) → no clinical relevance (N)

- Effect:
  - No EGA after one R117H-7T/9T in InnoLiPa
  - A/N genotype still referred for sweat test!

- Re-assigned InnoLiPA panel used for evaluation
Evaluation of the screening strategy

- 11 scenarios were compared with the existing strategy by
  - Sensitivity
  - Specificity
  - Positive Predictive Value
  - Negative Predictive Value
  - Cost
  - Carriers referred

- 7 scenarios with sensitivity ≥95%
  - IRT*PAP too drastic
<table>
<thead>
<tr>
<th>Strategy</th>
<th>Current</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PAP if IRT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥60</td>
<td>≥60</td>
<td>≥40</td>
<td>≥40</td>
<td>≥40</td>
<td>≥40</td>
<td>≥40</td>
<td>≥40</td>
</tr>
<tr>
<td><strong>InnoLiPa if</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IRT≥60 PAP≥3.0 or IRT≥100 PAP≥1.6</td>
<td>IRT≥60 PAP≥3.0 or IRT≥100 PAP≥1.2 or IRT≥124 PAP N/A</td>
<td>IRT≥40 PAP≥3.0 or IRT≥100 PAP≥1.2 or IRT≥300 PAP N/A</td>
<td>IRT≥40 PAP≥3.0 or IRT≥100 PAP≥1.2 or IRT≥124 PAP N/A</td>
<td>IRT≥40 PAP≥4.0 or IRT≥60 PAP≥3.0 or IRT≥100 PAP≥1.2 or IRT≥124 PAP N/A</td>
<td>IRT≥40 PAP≥4.0 or IRT≥60 PAP≥3.0 or IRT≥100 PAP N/A</td>
<td>IRT≥40 PAP≥4.0 or IRT≥60 PAP≥3.0 or IRT≥100 PAP N/A</td>
<td></td>
</tr>
<tr>
<td><strong>Safety net</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IRT≥100</td>
<td>IRT≥100</td>
<td>IRT≥100</td>
<td>IRT≥80</td>
<td>IRT≥80</td>
<td>IRT≥100</td>
<td>IRT≥100</td>
<td></td>
</tr>
<tr>
<td><strong>Sensitivity (CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>91% (83-95%)</td>
<td>95% (88-98%)</td>
<td>96% (89-99%)</td>
<td>98% (92-100%)</td>
<td>98% (92-100%)</td>
<td>96% (89-99%)</td>
<td>97% (89-99%)</td>
<td></td>
</tr>
<tr>
<td><strong>PPV</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>65%</td>
<td>60%</td>
<td>57%</td>
<td>58%</td>
<td>58%</td>
<td>60%</td>
<td>55%</td>
<td></td>
</tr>
<tr>
<td><strong>Cost per screened newborn</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>€3.25</td>
<td>€3.42</td>
<td>€4.08</td>
<td>€4.15</td>
<td>€4.37</td>
<td>€3.92</td>
<td>€4.41</td>
<td></td>
</tr>
</tbody>
</table>
Changes starting July 1 2016

● Classification R117H-7T/9T mutations from “unknown” to “no clinical relevance”

● New strategy, chosen based on
  - Sensitivity
  - number of referred carriers
  - cost per year of life saved
Screening strategy starting July 2016

CF scheme The Netherlands starting 1-7-2016

Step 1
IRT

Step 2
PAP

Step 3
Lineblot

Step 4
EGA

code mutations: A = clinically relevant; N = clinically not relevant; O = clinical relevance inconclusive
Expected performance after improvement

<table>
<thead>
<tr>
<th></th>
<th>Expected after July 1 2016</th>
<th>Between May 1 2011 and June 30 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>95% (CI 0.88-0.98%)</td>
<td>91% (CI 0.83-0.95%)</td>
</tr>
<tr>
<td>Specificity</td>
<td>99.99%</td>
<td>99.99%</td>
</tr>
<tr>
<td>PPV</td>
<td>60%</td>
<td>65%</td>
</tr>
<tr>
<td>NPV</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>CFSPID/year</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Carriers/year</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>Costs per test</td>
<td>€3.42</td>
<td>€3.25</td>
</tr>
</tbody>
</table>
Acknowledgments

● Optimalisation workgroup
  – Jeannette Dankert-Roelse
  – Paul Verkerk
  – Yvonne Schönbeck
  – Rendelien Verschoof-Puite
  – Vincent Gulmans
  – Philis Lakeman
  – Karin de Winter-de Groot
  – Hans Gille
  – Bernadette Jakobs
  – Annemarie van der Stee
  – Peter Schielen

● Laboratories
  – Anita Boelen
  – Marja van Veen
  – Guido Diependaal
  – Evelien Kemper
  – Carolien van Rijswijk
  – Johan Timmers
  – Henk Engel
  – Gerda Beltman

marelle.bouva@rivm.nl