Supplementary material

Modelling of NIPT

Figure 3 presents an overview of the current screening strategy in Belgium. In Figure 4, the current first trimester biochemistry screening and second trimester screening is replaced by NIPT at week 12.

In the next part of this supplementary file, we present and explain the three models in detail (current screening, NIPT 2\textsuperscript{nd} line and NIPT 1\textsuperscript{st} line) with inclusion of the number of pregnant women and T21 pregnancies at different moments in the model.
Figure 3 – Current screening strategy

- Participation in T21 testing?
  - Y: Immediate inv. test?
    - Y: NT >3.5mm?
      - Y: screening >1:300?
        - N: invasive testing?
          - Y: pr.rel. misc. hosp. leak.
            - N: invasive testing?
              - Y: result inv. testing
                - +: pregnancy term.?
                  - Y: spontaneous miscarriage?
                    - N: Births
                - -: Spontaneous miscarriage?
                  - +: invasive testing?
                    - N: Births
                  - Y: terminations
              - N: Spontaneous miscarriage?
                - +: invasive testing?
                  - N: Births
                - -: terminations
          - N: Spontaneous miscarriage?
            - +: invasive testing?
              - N: Births
            - -: terminations
    - N: Immediate inv. test?
      - Y: NT >3.5mm?
        - Y: screening >1:300?
          - N: invasive testing?
            - Y: pr.rel. misc. hosp. leak.
              - N: invasive testing?
                - Y: result inv. testing
                  - +: pregnancy term.?
                    - Y: spontaneous miscarriage?
                      - N: Births
                  - -: Spontaneous miscarriage?
                    - +: invasive testing?
                      - N: Births
                    - -: terminations
                - -: Spontaneous miscarriage?
                  - +: invasive testing?
                    - N: Births
                  - -: terminations
          - N: Spontaneous miscarriage?
            - +: invasive testing?
              - N: Births
            - -: terminations
      - N: Spontaneous miscarriage?
        - +: invasive testing?
          - N: Births
        - -: terminations

Hosp.leak.: hospitalization for leakage; inv.: invasive; pr.rel.misc.: procedure-related miscarriage; term.: termination.
Hosp.leak.: hospitalization for leakage; inv.: invasive; pr.rel.misc.: procedure-related miscarriage; rep.: repeat; term.: termination.
Supplementary material

In this part of the supplementary file we transparently present the three screening models: current screening, NIPT 2nd line, and NIPT 1st line. The figures of the models are copies from the original excel file, including exact numbers. These numbers represent (singleton) pregnancies and the number of T21 foetuses is added between brackets. All transitions are mentioned on the figures and explained with a short reference to the full text of the report. Small differences in numbers (maximum 1 unit) might be possible due to the presentation of rounded numbers. In the original calculations, full details with non-rounded numbers were taken into account.

Current screening:

Part 1:

- 1 : 131567 pregnant women at week 10 including 350 T21 foetuses (part 2.1.3.4 and Table 9).
- 2 : Exclusion of 1.8% twin pregnancies (part 2.1.3.3 and Table 9). 129199 singleton pregnancies and 2368 twin pregnancies.
- 3 : Impact of miscarriage between week 10 and 40 (part 2.1.3.4 and Table 9). 2368 x (1-0.05) = 2250, 8 x (1-0.36) = 5.
- 4a → 4e : Impact of miscarriage between week 10 and 15 (part 2.1.3.4 and Table 9).
- 5a, 5b, 5c : 1st and 2nd trimester screenings (part 2.1.6.1 and Table 12): number of tests, cost per activity, and % of screening uptake. E.g. 5a) 26 056/129 199 = 20.17%.
- 6a, 6b, 6c : For simplicity, numbers are recalculated to week 14 and we assume that further steps are taken at week 14 (although in reality this might be between week 11 and 20). This has no meaningful impact on results since afterwards spontaneous pregnancy termination is modelled in one step between week 14 and 40.
- 6d : The remaining pregnant women that did not participate in screening (124 608 – 21 560 – 51 583 – 25 130 = 26 335).
- 7a, 7b : Total number of singleton pregnant women (not) participating in screening. Number of T21 fetusses (292 in total) is mentioned between brackets.
- 8a, 8b : 398 pregnant women with an ultrasound detected NT>3.5mm are referred directly for invasive testing. They are divided proportionally among the screening (n=314) and no-screening (n=84) participants (see 2.1.6.3). It was assumed that women opting for an invasive test based on NT had an increased prevalence of a T21 pregnancy of 1:10.
Part 2:

- 9a, 9b: Exclusion of the high-risk pregnancies (NT>3.5mm): 26 335 – 84 = 26 251; 98 273 – 314 = 97 959.
- 10, 10: Results of the current screening. E.g. True negatives: (97 959 – 199) x specificity of 95.0343% = 92 906; True positives: 199 x sensitivity of 72.5352% = 144 (part 2.1.6.1).
- 11, 11: After a positive screening test result, we assume 87.5% of women choose to have an invasive diagnostic test (part 2.1.6.3). Thus (4855+144) x 87.5% = 4374.
- 12: In Belgium, there was a total of 7586 of invasive tests (part 2.1.6.3). This leaves us with 3212 (7586 – 4374) invasive tests. We already identified 398 (314+84) pregnant women with an ultrasound detected NT>3.5mm. We assume another 1000 invasive tests for T21 detection are performed in pregnant women (often at low risk) who wish to have more certainty than can be provided with the current screening, and/or are referred based on age over 35 (despite existing guidelines). The remaining 1814 invasive tests are performed for non-T21 indications, including structural anomalies detected with ultrasound not related to T21 detection. The 1000 and 84 invasive tests are specifically for T21 and were not counted before and represent another 0.87% of the pregnant population. This slightly increase the overall uptake (of any type of) testing for Down from 78.87 to 79.74%.
- 13, 13: After CVS or amniocentesis, an incremental procedure related foetal loss of on average 1% was assumed in our model (e.g. 4374 x 1% = 44). We also included a 1% risk of hospitalization for one week for leakage. The costs for such a stay in an acute hospital in Belgium are €3515 (part 2.1.6.3).
- 14: One of the outcomes in our model is the number of procedure related miscarriages and the number of such miscarriages related to T21 detection. The latter excludes the miscarriages related to the 1814 invasive tests performed for non-T21 indications.
- 15: In the ‘no screening uptake’ group, there are 23 437 singleton pregnant women (26 251 – 1000 – 1814 = 23 437).

Part 3:

- 16, 16: In our model we assume the invasive diagnostic test is 100% sensitive and 100% specific (part 2.1.6.3). E.g. (4374 – 126) – (44 – 1.3) = 4205 and 126 – 1.3 = 125.
- 17, 17: T21 pregnancy termination was induced in 95.45% (part 2.1.6.4). E.g. 125 x 95.5% = 119
- 18 → 18: Spontaneous miscarriage is taken into account (part 2.1.6.5, 2.1.3.4 and Table 9). E.g. 18a) (125 – 119) x 0.25 = 1.4; 4205 x 0.0144 + 1.4 = 62; 18c) 48 x 0.25 = 12; (23 437 – 48) x 0.0144 + 12 = 350.
The total number of singleton births at week 40 with the number of Down births between brackets. E.g. 19a) \((4205 + 125) - (119 + 62) = 4149\); \(125 - (119 + 1.4) = 4.3\); 19c) \(23437 - 350 = 23087\); \(48 - 12 = 35.7\).
Part 1 (current screening)

1. Women who are 10 weeks pregnant (singletons)
   - High-risk total: 20,17%
   - Total: 25,651
   - Cost: €80,42
   - Week 10 twin pregnancies: 2,368

2. Women who are 11 weeks pregnant (singletons)
   - High-risk total: 20,17%
   - Total: 25,651
   - Cost: €80,42
   - Week 11 twin pregnancies: 2,368

3. Women who are 12 weeks pregnant (singletons)
   - High-risk total: 20,17%
   - Total: 25,651
   - Cost: €80,42
   - Week 12 twin pregnancies: 2,368

4. Women who are 13 weeks pregnant (singletons)
   - High-risk total: 20,17%
   - Total: 25,651
   - Cost: €80,42
   - Week 13 twin pregnancies: 2,368

5. Women who are 14 weeks pregnant (singletons)
   - High-risk total: 20,17%
   - Total: 25,651
   - Cost: €80,42
   - Week 14 twin pregnancies: 2,368

6. Women who are 15 weeks pregnant (singletons)
   - High-risk total: 20,17%
   - Total: 25,651
   - Cost: €80,42
   - Week 15 twin pregnancies: 2,368

7. Week 40 N° of twin births: 2,250
NIPT 2nd line:

Part 1:
- \(\square \rightarrow \square\): See current screening

Part 2:
- All blue hexagons: See current screening
- \(\square\): NIPT is offered to 4999 (4855+144) women at increased risk after current screening (part 2.1.4.2). We assume the first NIPT is repeated in 4% of cases. We assume the second NIPT test is performed about one week later and therefore also take into account the number of miscarriage during 1 week (4999 x 4% x (1 – (0.015 – 0.01)) = 199). Each NIPT test costs €460 (part 2.1.6.2).
- \(\square, \square, \square\): We assume that after repeat testing there is no result in 2% of cases: 11b) 4999 x 2% = 100; 144 x 2% = 3. For the remaining 98% the results of NIPT screening are calculated: E.g. True negatives: (4855 x specificity of 99.84%) x (98%) = 4750; True positives: (144 x sensitivity of 99.30%) x (98%) = 140 (part 2.1.6.2).
- \(\square, \square\): After a positive NIPT screening test result or no NIPT result (but previously a positive test result after current screening), we assume 87.5% of women chooses to have an invasive diagnostic test (part 2.1.6.3). Thus (100 + 140 + 8) x 87.5% = 217.
- \(\square\): Same reasoning as for \(\square\) (1% hospitalizations for leakage and 1% procedure related miscarriages) but with other underlying numbers as mentioned on the figure.

Part 3:
- All blue hexagons: See current screening
- \(\square \rightarrow \square\): Same reasoning as for \(\square \rightarrow \square\) but with other underlying numbers as mentioned on the figure.
NIPT 1st line:

Part 1:
- All blue hexagons: See current screening
  - : The current first and second trimester screening is replaced by NIPT and we assume the NIPT is performed at week 12 (part 2.1.4.3). Taking into account the number of spontaneous miscarriages, recalculating 98,273 singleton pregnant women from week 14 to 12 results in 99,281 pregnant women. Furthermore, we assume that the 1000 women who are directly referred to invasive testing based on age (despite existing guidelines) or the wish to have more certainty than can be provided with the current testing, will now opt to have a NIPT test. Recalculating from week 14 to 12, this results in 1010 extra NIPT tests.
  - : One week later, 3991 repeat tests are performed (98,774 + 1005) x 4% = 3991.

Part 2:
- All blue hexagons: See current screening.
  - : see in part 1.
  - : The 314 pregnant women with an ultrasound detected NT>3.5mm continue to be referred directly for invasive testing (part 2.1.4.3). The 1000 extra NIPT tests are taken into account, thus 98 273 – 314 + 1000 = 98 959.
  - : We assume that after repeat testing there is no result in 2% of cases: 10b) 98 959 x 2% = 1979; 201 x 2% = 4. For the remaining 98% the results of NIPT screening are calculated: E.g. True negatives: ((98 959 – 201) x specificity of 99.84%) x (98%) = 96 628; True positives: (201 x sensitivity of 99.30%) x (98%) = 196 (part 2.1.6.2).
  - : In case no NIPT result is obtained after a repeat NIPT the current screening strategy is applied (part 2.1.4.3).
  - : Results of the current screening. E.g. True negatives: (1979 – 4) x specificity of 95.0343% = 1877; True positives: 4 x sensitivity of 72.5352% = 2.9 (part 2.1.6.1).
  - : After a positive NIPT screening test result or a positive current screening test result (after a NIPT no result), we assume 87.5% of women chooses to have an invasive diagnostic test (part 2.1.6.3). Thus (196 + 155 + 2.9 + 98) x 87.5% = 395.
  - : The number of invasive tests in the ‘no screening uptake’ arm is 2212 instead of 3212 (excluding those 1000 pregnant women: see point 5).
  - : Same reasoning as for but with other underlying numbers as mentioned on the figure.

Part 3:
- All blue hexagons: See current screening.
- \[16 \rightarrow 19\]: Same reasoning as for \[16 \rightarrow 19\] but with other underlying numbers as mentioned on the figure.
Part 1 (NIPT 1st line)

- **1st NIPT**
  - **1** women who are 10 weeks pregnant (singletons)
    - 131567 (350)
  - **2** women who are 10 weeks pregnant (singletons)
    - 129199 (342)
  - **3** women who are 11 weeks pregnant (singletons)
    - 127191 (327)
  - **4a** women who are 12 weeks pregnant (singletons)
    - 125886 (313)
  - **4b** women who are 13 weeks pregnant (singletons)
    - 125244 (300)
  - **4c** women who are 14 weeks pregnant (singletons)
    - 124608 (292)
  - **4d** women who are 15 weeks pregnant (singletons)
    - 123979 (284)
  - **4e** women who are 15 weeks pregnant (singletons)
    - 123979 (284)

- **Repeat NIPT**
  - **5a** extra women who are 10 weeks pregnant
    - 1010 (5)
    - 99281 (342)
  - **5b** extra women who are 12 weeks pregnant
    - 1005 (5)
    - 98774 (342)
  - **5c** extra women who are 11 weeks pregnant
    - 1000 (5)
    - 98273 (342)

- **No screening uptake**
  - high-risk: 84 (8)
  - total: 26335 (62)

- **Screening uptake**
  - high-risk: 314 (31)
  - total: 98273 (230)

- **Week 10 twin pregnancies**
  - total: 2368 (8)

- **Week 15 twin pregnancies**
  - total: 2284 (7)

- **Week 40 No. of twin births**
  - total: 2250 (5)
Supplementary material

Scenario analyses
Several scenario analyses are modelled:

- In Belgium, the overall uptake (of any type of) testing for Down is currently about 80%. If NIPT would be offered in first line, there is a possibility that the screening uptake of primary NIPT will be higher than for the current screening. A large survey in the UK suggests an uptake of primary NIPT of 88.2% (972/1103; 95%CI 86.1–90%), including respondents who would currently decline T21 screening. A scenario with 90% NIPT uptake in first line is presented without changing any other input variable (see Table 4).

- In the reference case, the price of NIPT is set at €460. If NIPT would be used in 1st line, the eligible population would be much larger and scale effects could result in lower prices. Also evolution in technology will help. A threshold analysis is performed, changing the price of NIPT to keep the short-term costs per case of T21 detected at the same level as in the current screening scenario. This price was about €150. Results with this lower price are presented in Figure 2 and Table 4.

- In the reference case, a cut-off risk of 1:300 for T21 is used. Based on Belgian context-specific data, this results in a referral of about 5% of all pregnant women for definitive prenatal diagnosis using an invasive test, while the sensitivity is 72.5% (AML data). Lowering of the threshold is considered in the NIPT triage scenario. The cut-off risk with specificity closest to 95% (1:300), 90% (1:600), 85% (1:1100), 80% (1:1700) and 75% (1:2400) were selected plus the lowest reported cut-off risk of 1:3000 which has a specificity of 71%. Sensitivity and specificity are modelled with beta distributions reflecting the parameters from the AML data (see Table 5). Results are presented in Table 6.

- In Belgium, based on expert opinion, the sensitivity of the current screening could be improved by increasing the quality of the current screening, especially the quality of the nuchal translucency measure. An absolute increase of 5% in the current screening sensitivity was applied to model this, i.e. being 77.5% instead of 72.5%, without changing specificity. These results are also presented in Table 6.
### Table 4 – Changing the uptake and price of NIPT

<table>
<thead>
<tr>
<th>Test strategy Uptake</th>
<th>NIPT 1&lt;sup&gt;st&lt;/sup&gt; line 80%</th>
<th>NIPT 1&lt;sup&gt;st&lt;/sup&gt; line 90%</th>
<th>NIPT 1&lt;sup&gt;st&lt;/sup&gt; line 80%</th>
<th>NIPT 1&lt;sup&gt;st&lt;/sup&gt; line 90%</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIPT price</td>
<td>€460</td>
<td>€460</td>
<td>€150</td>
<td>€150</td>
</tr>
<tr>
<td>Uptake 80%</td>
<td>122,560</td>
<td>122,542</td>
<td>122,560</td>
<td>122,542</td>
</tr>
<tr>
<td>Uptake 90%</td>
<td>90%</td>
<td>45%</td>
<td>63%</td>
<td>45%</td>
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<tr>
<td>N° of births</td>
<td>122,560</td>
<td>122,542</td>
<td>122,560</td>
<td>122,542</td>
</tr>
<tr>
<td>N° of Down born</td>
<td>63</td>
<td>45</td>
<td>63</td>
<td>45</td>
</tr>
<tr>
<td>N° of Down born (false neg. screening)</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
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<tr>
<td>N° of T21 detected</td>
<td>215</td>
<td>240</td>
<td>215</td>
<td>240</td>
</tr>
<tr>
<td>N° of proc.rel. miscarriages</td>
<td>26</td>
<td>27</td>
<td>26</td>
<td>27</td>
</tr>
<tr>
<td>N° of T21 proc.rel. misc.</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
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</tbody>
</table>

### (Down) births, diagnosis and miscarriages

<table>
<thead>
<tr>
<th></th>
<th>1st &amp; 2nd trim. screening cost</th>
<th>NIPT cost</th>
<th>Cost invasive tests</th>
<th>Cost hosp.leakage &amp; pregn.term.</th>
<th>Total cost (Short term)</th>
<th>Short term cost/T21 detected</th>
<th>Extra cost per extra T21 detected§</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>€89,123</td>
<td>€47,969,932</td>
<td>€2,435,450</td>
<td>€279,539</td>
<td>€50,774,045</td>
<td>€236,436</td>
<td>€839,936</td>
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<td>€100,718</td>
<td>€54,191,054</td>
<td>€2,486,456</td>
<td>€303,308</td>
<td>€57,081,536</td>
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<td>€89,123</td>
<td>€15,642,369</td>
<td>€2,435,450</td>
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<td>€18,446,482</td>
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<td>€100,718</td>
<td>€17,670,996</td>
<td>€2,486,456</td>
<td>€303,308</td>
<td>€20,561,478</td>
<td>€85,769</td>
<td>€106,160</td>
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</tbody>
</table>

**Proc.rel. misc.:** procedure-related miscarriage; § The extra cost per extra case of T21 diagnosed was compared with NIPT 2<sup>nd</sup> line (i.e. the previous best alternative) but with a price of €460 for NIPT (we assume such a lower price would in first instance only be probable with high volumes of NIPT such as in 1<sup>st</sup> line).
<table>
<thead>
<tr>
<th>Cut-off risk</th>
<th>Sensitivity</th>
<th>Uncertainty</th>
<th>Specificity</th>
<th>Uncertainty</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:300</td>
<td>72.54%</td>
<td>Beta(103;39)</td>
<td>95.03%</td>
<td>Beta(117 144; 6121)</td>
</tr>
<tr>
<td>1:600</td>
<td>80.99%</td>
<td>Beta(115;27)</td>
<td>90.88%</td>
<td>Beta(112 018; 11 247)</td>
</tr>
<tr>
<td>1:1100</td>
<td>84.51%</td>
<td>Beta(120;22)</td>
<td>85.41%</td>
<td>Beta(105 283; 17 982)</td>
</tr>
<tr>
<td>1:1700</td>
<td>87.32%</td>
<td>Beta(124;18)</td>
<td>80.17%</td>
<td>Beta(98 817; 24 448)</td>
</tr>
<tr>
<td>1:2400</td>
<td>87.32%</td>
<td>Beta(124;18)</td>
<td>75.18%</td>
<td>Beta(92 675; 30 590)</td>
</tr>
<tr>
<td>1:3000</td>
<td>88.73%</td>
<td>Beta(126;16)</td>
<td>71.46%</td>
<td>Beta(88 087; 35 178)</td>
</tr>
</tbody>
</table>

*Source: AML data*
Table 6 – Varying the sensitivity of the current screening approach or risk cut-off if NIPT is used in 2nd line

<table>
<thead>
<tr>
<th>Test strategy</th>
<th>Current screening</th>
<th>NIPT 2nd line + 77.5% sensitivity*</th>
<th>NIPT 2nd line (1/300)</th>
<th>NIPT 2nd line (1/600)</th>
<th>NIPT 2nd line (1/1100)</th>
<th>NIPT 2nd line (1/1700)</th>
<th>NIPT 2nd line (1/2400)</th>
<th>NIPT 2nd line (1/3000)</th>
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</thead>
<tbody>
<tr>
<td><strong>(Down) births, diagnosis and miscarriages</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N° of births</td>
<td>122,543</td>
<td>122,546</td>
<td>122,554</td>
<td>122,529</td>
<td>122,509</td>
<td>122,490</td>
<td>122,476</td>
<td>122,463</td>
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<tr>
<td>N° of Down born</td>
<td>96</td>
<td>90</td>
<td>97</td>
<td>86</td>
<td>82</td>
<td>78</td>
<td>78</td>
<td>77</td>
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<tr>
<td>N° of Down born (false neg. screening)</td>
<td>41</td>
<td>34</td>
<td>42</td>
<td>29</td>
<td>24</td>
<td>20</td>
<td>20</td>
<td>18</td>
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<tr>
<td>N° of T21 detected</td>
<td>170</td>
<td>178</td>
<td>169</td>
<td>184</td>
<td>190</td>
<td>194</td>
<td>194</td>
<td>197</td>
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<tr>
<td>N° of proc.rel. miscarriages</td>
<td>76</td>
<td>34</td>
<td>34</td>
<td>35</td>
<td>36</td>
<td>37</td>
<td>38</td>
<td>39</td>
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<tr>
<td>N° of T21 proc.rel. misc.</td>
<td>58</td>
<td>16</td>
<td>16</td>
<td>17</td>
<td>18</td>
<td>19</td>
<td>20</td>
<td>21</td>
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<tr>
<td><strong>Costs for testing during pregnancy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>NIPT cost</td>
<td>€0</td>
<td>€2,395,686</td>
<td>€2,390,929</td>
<td>€4,343,507</td>
<td>€6,901,721</td>
<td>€9,357,267</td>
<td>€11,687,078</td>
<td>€13,428,890</td>
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<tr>
<td>Cost hosp.leakage &amp; pregn.term.</td>
<td>€415,728</td>
<td>€276,151</td>
<td>€268,375</td>
<td>€284,228</td>
<td>€293,214</td>
<td>€301,016</td>
<td>€304,292</td>
<td>€308,923</td>
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<tr>
<td>Total cost (Short term)</td>
<td>€14,754,829</td>
<td>€13,135,542</td>
<td>€13,114,935</td>
<td>€15,168,714</td>
<td>€17,835,800</td>
<td>€20,394,149</td>
<td>€22,813,130</td>
<td>€24,626,040</td>
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<tr>
<td>Short term cost/T21 detected</td>
<td>€86,944</td>
<td>€74,063</td>
<td>€77,696</td>
<td>€82,746</td>
<td>€94,188</td>
<td>€105,016</td>
<td>€117,474</td>
<td>€125,249</td>
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<tr>
<td>Extra cost per extra T21 detected§</td>
<td>/</td>
<td>/</td>
<td>/§§</td>
<td>€142,110</td>
<td>€442,346</td>
<td>€531,269</td>
<td>/§§§</td>
<td>€1,750,512</td>
</tr>
</tbody>
</table>

Proc.rel. misc.: procedure-related miscarriage; * In this scenario, we assume NIPT is used in 2nd line after current screening (1/300) but with an improved sensitivity of 77.5% instead of 72.5%. § This is calculated in a deterministic way since the simulations fall into different quadrants making the average of all simulations unreliable. §§ This is the initial comparator, thus no extra cost per extra T21 detected is calculated. §§§ Due to the same sensitivity and a lower specificity in comparison with the previous situation (based on the data of AML), this scenario is an example of extended dominance.