Cervical Cancer Screening via HPV testing and/or Cytology

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I declare I have no conflict of Interest
Every Year, 530,000 new cases of cervical cancer

Estimated Cervical Cancer Incidence Worldwide in 2008
275,000 Deaths from Cervical Cancer
WHO Recommendation

Screen:
- Breast cancer
- Cervical cancer
- Colo-rectal cancer

Nationwide

Develop your own national strategy
WHO Recommendations for Cervical Screening

- Not necessary under 25 yrs of age
- Not necessary after 65 yrs of age
- Never screen annually

<table>
<thead>
<tr>
<th>Target age group:</th>
<th>Screen Interval:</th>
<th>Screening Test:</th>
</tr>
</thead>
<tbody>
<tr>
<td>33-64</td>
<td>Once in a lifetime</td>
<td>Cytology</td>
</tr>
<tr>
<td>30-59</td>
<td>10 years</td>
<td>HPV-DNA Test</td>
</tr>
<tr>
<td>35-49</td>
<td>7 years</td>
<td>VIA/VILI</td>
</tr>
<tr>
<td>30-49</td>
<td>5 years</td>
<td>Parallel and sequential</td>
</tr>
<tr>
<td>30-39</td>
<td></td>
<td></td>
</tr>
<tr>
<td>35-39</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cervical Cancer: Last century

1900- Orphans leaving disease (killing one of every 5 women with child).
First Epidemiological Studies:
Nuns never get cervical cancer
Second wife of a man gets the disease whose first wife was also died because of cervical cancer

1940- Introduction of cytology (G. Papanikolaou)
1960 - Screening programs
1990- HPV and today
Cervical Cancer: Last century

Cytology based screening programs have reduced more than 75% of incidence and mortality from cervical cancer in the last 50 years.

Especially in developed countries.

England- 1971-1995
Cancer Screening

European Union

Breast

- Belgium
- Cyprus
- Estonia
- Finland
- France
- Germany
- Hungary
- Luxembourg
- Netherlands
- Spain
- Sweden
- UK

12 Countries

Cervical

- Finland
- Sweden
- Denmark
- Netherlands
- UK
- Hungary
- Slovenia
- Germany

8 Countries

Colorectal

- UK
- France
- Italy
- Finland

0 Countries

has started
Cytology Based Screening

• It is a very difficult and complex service to provide.

• Even if the main barriers for cytological screening were overcome relatively low sensitivity of pap-test remains a big problem.

• Cervical cancer still occurs even in women who are living in developed countries and being routinely screened.
Problems in Cytology Based Screening

- A single pap-test has a very low sensitivity for CIN2+ lesions
- Pap-test has a high false negative rate
- Reproducibility of pap-test is low
- Pap-test is less effective in detecting adenocarcinoma of cervix
Problems in Cytology Based Screening

• A single pap-test has a very low sensitivity for CIN2+ lesions

  • The sensitivity of a single pap-test is 50-60%
    
  
  • It has to be repeated frequently
  
  • If the interval is increased to 3 years without 3 consecutive negative results cervical cancer risk increases 3 times.

    Kitchener HC, Castle PE, Cox JT. Chapter 7: Achievements and limitations of cervical cytology screening. Vaccine 2006;24:S63-70
Problems in Cytology Based Screening

• Pap-test has a high false negative rate

Screening history of 2275 cervical cancer cases:

<table>
<thead>
<tr>
<th>Screen History (%)</th>
<th>Italian Data\textsubscript{1}</th>
<th>Kaiser Data\textsubscript{2}</th>
<th>Sweden Data\textsubscript{3}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not screened</td>
<td>62%</td>
<td>56%</td>
<td>64%</td>
</tr>
<tr>
<td>Normal Cytology</td>
<td>14%</td>
<td>32%</td>
<td>24%</td>
</tr>
<tr>
<td>Abnormal cytology &amp; Inadequate follow-up</td>
<td>24%</td>
<td>13%</td>
<td>7%</td>
</tr>
<tr>
<td></td>
<td>n=262</td>
<td>n=833</td>
<td>n=1180</td>
</tr>
</tbody>
</table>

1 Amadori A, et al. Int J Gyn Can 1998, 8; 251-256
3 Andrae B, et al. JNCI 2008, 100; 622-629
Problems in Cytology Based Screening

- Reproducibility of pap-test is low
  - Inter-observer and inter-laboratory variability is high
  - This variability lessens its clinical confidence
  - Variability increases with the difference in training
  - It is important especially if screening is newly began

Problems in Cytology Based Screening

• Reproducibility of pap-test is low

<table>
<thead>
<tr>
<th>Proportion (%)</th>
<th>Lab A</th>
<th>Lab B</th>
<th>Lab C</th>
<th>Lab D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>96,2</td>
<td>94,6</td>
<td>91,8</td>
<td>90,1</td>
</tr>
<tr>
<td>Abnormal</td>
<td>3,8</td>
<td>5,2</td>
<td>8,1</td>
<td>9,9</td>
</tr>
<tr>
<td>ASC-US/LSIL</td>
<td>2,1</td>
<td>1,1</td>
<td>1,2</td>
<td>2,3</td>
</tr>
<tr>
<td>CIN2+ Sensitivity of cytology</td>
<td>42,0</td>
<td>51,0</td>
<td>60,5</td>
<td>73,0</td>
</tr>
</tbody>
</table>

Wright TC et al. Insights from ATHENA. 2013
Problems in Cytology Based Screening

• Pap-test is less effective in detecting adenocarcinoma of cervix

  • Cervical adenocarcinoma incidence is increasing despite the cytology based screening
    
    Ault KA et al. 2011 Int J Can. 128, 1344-1353

  • AIS is increasing especially <40 yrs.
    

  • 85-90% of adenocarcinomas are related to HPV16/18, since 70% of SCC are related to them.

Problems in Cytology Based Screening

- Pap-test is less effective in detecting adenocarcinoma of cervix

<table>
<thead>
<tr>
<th>Hystology (n)</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cytology</td>
</tr>
<tr>
<td>CIN3 (254)</td>
<td>52%</td>
</tr>
<tr>
<td>AIS (16)</td>
<td>63%*</td>
</tr>
<tr>
<td>Adenoca ve Adenosq ca (1)</td>
<td>100%</td>
</tr>
<tr>
<td>SCC (3)</td>
<td>100%</td>
</tr>
</tbody>
</table>

*25% difference

Are there any other more efficient methods for cervical screening?

- HPV test can detect 25-50% of cases missed with a single pap-test
Cervical Cancer Pathogenesis and Preventive Models

A

<table>
<thead>
<tr>
<th>Normal</th>
<th>HPV Infection</th>
<th>Precancer</th>
<th>Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clearance</td>
<td>Progression</td>
<td>Regression</td>
<td>Invasion</td>
</tr>
</tbody>
</table>

B

Population prevalence (not to scale)

Age

Pap-based screening
Co-testing
Vaccination and HPV screening
Screen and treat

Symbols:
A: C: H:
Clinical Use of HPV Tests

- Triage of women with cytological abnormality
  - HPV is more accurate than repeat cytology
- Follow-up after treatment of CIN lesions
  - HPV testing picks up more quickly, with higher sensitivity and not lower sensitivity
- Primary screening for cervical cancer and pre-cancerous lesions

HPV Test

- HPV is the causative agent for 100% of cervical cancer.
  Munoz N. Int J Cancer 2004 Aug 20;111(2)278-85

- HPV tests have begun to be used clinically

- First metaanalyses have shown high sensitivity of HPV tests

- Randomised controlled trials have been conducted for primary screening

- First round results

- Primary screening in Europe and the World

- Second round results
Metaanalyses have shown the high sensitivity of HPV tests.

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytology</td>
<td>53%</td>
<td>97%</td>
</tr>
<tr>
<td>HPV test</td>
<td>96%</td>
<td>92%</td>
</tr>
</tbody>
</table>

Mayrand MH et al. Int J Cancer 2006 119;615-623
First Round Results for Primary HPV Screen

Joint European Cohort

Cumulative incidence of CIN3+ (per 10,000)

- Cytology-
- HPV-
- Cytology-/HPV-

Time since initial testing (months)

Dillner, J. et al. BMJ 2008;337:a1754
Other Results from the Indian Study

- 4 arm randomised controlled trial:
- N=131.476

- One single HPV test significantly reduces mortality
- HPV- cases has 4 fold lower risk for cancer
- HPV is the most objective and reproducible test

Sankaranarayanan R et al. 2009. NEJM 360;14
Problems in HPV Screening

• Too much HPV positive cases without cytoabnormality
  ▫ Overdiagnosis of regressive lesions
    • It has to be done age appropriate
    • Second Round Data
      • POBASCAM, Swedescreeen, ARTISTIC,NTCC
      • Reflex Cytology / HPV Genotyping / Moleculer Testings

• HPV Alone or in combination with Pap
• HPV tests are more costly
  ▫ It increases screen interval
• Communication Problems
Problems in HPV Screening

- It has to be done age appropriate

Sensitivity increases especially in women older than 35 years of age

Cuzick J et al. 2006 Int J Cancer
Problems in HPV Screening

- Too much HPV positive cases without cytoabnormality
  - Overdiagnosis of regressive lesions
    - It has to be done age appropriate
  - Second Round Data
    - POBASCAM, Swedescreen, ARTISTIC, NTCC
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- HPV Alone or in combination with Pap
- HPV tests are more costly
  - It increases screen interval
- Communication Problems
4 over 8 randomised controlled trials have announced 2nd round results: longitudinal outcomes.

HPV – cases has a significantly lower risk for CIN3+ and cervical cancer compared to cytology – ones.

4 over 8 randomised controlled trials have announced 2nd round results: longitudinal outcomes

HPV vs. Pap

- **Second round screening lesser CIN3+**
- **First and second round total detection rates is higher for CIN3+**
  - Earlier detection of preinvasive lesions
- **Second round screening higher CIN2+**
  - Loss of specificity can be compensated with
    - Reflex cytology or
      - Low Risk
      - Moderate Risk (6% CIN3+ over 5 years)
      - High Risk (17% CIN3+ over 5 years)
    - HPV Genotyping
      - HPV 16/18 and others
    - Molecular Tests (p16Ki67)
      - Strict regulations are needed

Rijkaart DC/ Int J Cancer (2012)
Katki HA, Lancet Oncology 2011
RCT 94.370 Women HPV or Cytology

<table>
<thead>
<tr>
<th>Screening</th>
<th>HPV Screening</th>
<th>Pap Screening</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CIN2</td>
<td>CIN3/AIS</td>
</tr>
<tr>
<td>Round one</td>
<td>108</td>
<td>98</td>
</tr>
<tr>
<td>Round two</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Total Over</td>
<td>116</td>
<td>106</td>
</tr>
</tbody>
</table>

Ronco et al, Lancet Oncol, 2010
Second Round Screening Higher CIN2+

HPV vs. Pap

- Second round screening lesser CIN3+
- First and second round total detection rates is higher for CIN3+
  - Earlier detection of preinvasive lesions
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      - HPV 16/18 and others
    - Molecular Tests (p16Ki67)
      - Strict regulations are needed

Rijkaart DC/ Int J Cancer (2012)
Katki HA, Lancet Oncology 2011
Management Options Based on risk of CIN2+
Reflex Cyto and HPV Genotyping
Compensation

<table>
<thead>
<tr>
<th></th>
<th>Risk for CIN2+</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV Neg, Pap Neg</td>
<td>0.1%</td>
<td>Rescreen 5 years</td>
</tr>
<tr>
<td>Neg Pap</td>
<td>1%</td>
<td>Rescreen 3 years</td>
</tr>
<tr>
<td>ASC-US or HPV +, Pap -, 16/18 -</td>
<td>5%</td>
<td>12 mths Follow Up</td>
</tr>
<tr>
<td>ASC-US and HPV + or LSIL or HPV 16/18 +, Pap -</td>
<td>10%</td>
<td>Colpo+ 12 mths Follow Up After Colpo</td>
</tr>
<tr>
<td>ASC-H or AGC</td>
<td>50%</td>
<td>Colpo + 6 Mths Follow Up After Colpo</td>
</tr>
<tr>
<td>H-SIL</td>
<td>80%</td>
<td>LEEP</td>
</tr>
</tbody>
</table>
Combined or HPV only?  
Relative Cross Sectional Accuracy with 2. Round Trials  
Primary Only HPV Screening is Sufficient

Table 3. Relative accuracy of virological versus cytological screening or of combined screening versus testing with one test in order to find underlying CIN2 or CIN3 or worse.

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Outcome</th>
<th>Relative sensitivity (95% CI)</th>
<th>Range</th>
<th>Relative specificity (95% CI)</th>
<th>Range</th>
<th>Nb of studies†</th>
</tr>
</thead>
<tbody>
<tr>
<td>HC2 / cyto (ASC-US+)</td>
<td>CIN2+</td>
<td>1.23 (1.15-1.31)</td>
<td>0.91-2.93</td>
<td>0.97 (0.96-0.98)</td>
<td>0.86-1.10</td>
<td>28/25†</td>
</tr>
<tr>
<td>HC2 / cyto (ASC-US+)**</td>
<td></td>
<td>1.37 (1.22-1.54)</td>
<td>1.06-2.25</td>
<td>0.97 (0.96-0.98)</td>
<td>0.93-1.00</td>
<td>12/10†</td>
</tr>
<tr>
<td>HC2 / cyto (LSIL+)</td>
<td></td>
<td>1.40 (1.27-1.54)</td>
<td>1.09-2.37</td>
<td>0.92 (0.90-0.94)</td>
<td>0.67-1.03</td>
<td>20/19†</td>
</tr>
<tr>
<td>HC2 / cyto (ASC-US/LSIL+)</td>
<td></td>
<td>1.27 (1.18-1.36)</td>
<td>0.91-2.93</td>
<td>0.96 (0.94-0.97)</td>
<td>0.67-1.10</td>
<td>33/30†</td>
</tr>
<tr>
<td>HC2 / cyto (ASC-US+)</td>
<td>CIN3+</td>
<td>1.27 (1.12-1.44)</td>
<td>0.97-2.63</td>
<td>0.97 (0.96-0.99)</td>
<td>0.88-1.10</td>
<td>20/18†</td>
</tr>
<tr>
<td>HC2 / cyto (ASC-US+)**</td>
<td></td>
<td>1.43 (1.15-1.77)</td>
<td>1.01-2.12</td>
<td>0.97 (0.96-0.98)</td>
<td>0.93-1.00</td>
<td>8/6†</td>
</tr>
<tr>
<td>HC2 / cyto (LSIL+)</td>
<td></td>
<td>1.36 (1.21-1.53)</td>
<td>0.97-2.32</td>
<td>0.93 (0.91-0.96)</td>
<td>0.84-1.03</td>
<td>13/12†</td>
</tr>
<tr>
<td>Cyto (ASC+) &amp; HC2 / Cyto (ASC-US+)</td>
<td>CIN2+</td>
<td>1.42 (1.36-1.48)</td>
<td>1.06-2.30</td>
<td>0.94 (0.93-0.94)</td>
<td>0.89-0.96</td>
<td>13</td>
</tr>
<tr>
<td>Cyto (ASC+) &amp; HC2 / Cyto (ASC-US+)</td>
<td>CIN3+</td>
<td>1.33 (1.29-1.37)</td>
<td>1.02-2.18</td>
<td>0.92 (0.90-0.92)</td>
<td>0.85-0.96</td>
<td>10/9</td>
</tr>
<tr>
<td>Cyto (ASC-US+) &amp; HC2 / HC2</td>
<td>CIN2+</td>
<td>1.05 (1.04-1.07)</td>
<td>1.00-1.19</td>
<td>0.95 (0.94-0.96)</td>
<td>0.81-0.99</td>
<td>10</td>
</tr>
<tr>
<td>Cyto (ASC-US+) &amp; HC2 / HC2</td>
<td>CIN3+</td>
<td>1.02 (1.01-1.03)</td>
<td>1.04-1.04</td>
<td>0.93 (0.92-0.95)</td>
<td>0.81-0.99</td>
<td>6</td>
</tr>
<tr>
<td>GP5+/6+ / cyto (ASC-US+)</td>
<td>CIN2+</td>
<td>1.33 (1.13-1.25)</td>
<td>0.75-1.50</td>
<td>0.94 (0.85-0.93)</td>
<td>0.89-0.99</td>
<td>3/2</td>
</tr>
<tr>
<td>Cobas-4800 / cyto (ASC-US+)</td>
<td>CIN2+</td>
<td>1.77 (1.55-1.89)</td>
<td>-</td>
<td>0.97 (0.97-0.97)</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Other L1-based PCR / cyto (ASC-US+)</td>
<td>CIN2+</td>
<td>1.04 (0.87-1.25)</td>
<td>0.75-1.50</td>
<td>0.97 (0.92-1.02)</td>
<td>0.86-1.08</td>
<td>7</td>
</tr>
<tr>
<td>E6/E7 based PCR / cyto (ASC-US+)</td>
<td>CIN2+</td>
<td>1.63 (1.27-2.09)</td>
<td>-</td>
<td>0.90 (0.88-0.92)</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>APTIMA / cyto (ASC-US+)</td>
<td>CIN2+</td>
<td>1.35 (1.20-1.55)</td>
<td>1.33-1.50</td>
<td>0.98 (0.94-1.02)</td>
<td>0.96-1.00</td>
<td>2</td>
</tr>
<tr>
<td>HPV Pretec Procter</td>
<td>CIN2+</td>
<td>1.22 (0.79-1.87)</td>
<td>-</td>
<td>1.00 (0.97-0.92)</td>
<td>-</td>
<td>1</td>
</tr>
</tbody>
</table>

† When 2 values are given for number of studies: 1st value = number of studies where relative sensitivity was assessable and the 2nd = number of studies where the specificity could be assessed. † The meta-analysis of relative sensitivity includes RCTs with a control arm where only cytology was used, the meta-analysis of relative specificity does not include these RCTs. **Restricted to studies conducted in N-America or Europe after exclusion of Kitchener, 2009. † Exclusion of Sankaranarayanan, 2005.
HPV Only vs. HPV+ Cytology

Figure 6. Relative sensitivity of HPV testing only vs combined testing (HPV+cytology).
Cost Effectiveness

- It increases screen interval

NPV of the test is very high. Intervals can be lengthened to 5 years with enough confidence

Dillner, J. et al. BMJ 2008;337:a1754
A recent Dutch Microsimulation Analysis

Conclusion

We carried out an extensive simulation study, using a Dutch model, to investigate under which realistic European conditions HPV testing is to be preferred to cytology screening as a primary test for the detection of cervical cancer. Primary HPV screening was preferred in most of the scenarios considered. Primary cytology screening was only preferred in scenarios with low costs of cytology and in scenarios with high prevalence of HPV in combination with high costs of HPV testing. Therefore most European countries should seriously consider switching from primary cytology to HPV screening. Such screening must, however, only be implemented in situations where screening is already well controlled.

de Kok I MCM, et al. BMJ 2012;344
Communication Problems

- Individual with risk, not presence of disease
- The only risk is gynecologists for overtreatment
- They are the luckiest since they will only be followed, not treated
Additional Benefits of HPV Screening

Additional Benefits of HPV Screening

- It is more easy to make genotyping if the woman is primarily screened with HPV test.
- 71% of SCCs and 90% of AIS are because of HPV16/18

![Graph showing HPV genotypes and their associated cancer cases.](image)

**Figure 2** - Percentages and numbers of cervical cancer cases attributed to the most frequent HPV genotypes in all world regions combined (women 15 years of age and older).

*Munoz N. Int J Cancer 2004 Aug 20;111(2)278-85*
Additional Benefits of HPV Screening

- It is objective and requires less complex quality assurance system than cytology
- It can be automated and centralised
- HC2 results have been consistent in all over the world
- Longer screen intervals
  - Increase adherence for treatment
- Self HPV Testings
  - Women can collect samples themselves reducing the number of visits
- HPV Vaccination
- Future of screening policies
  - Vaccination
  - 3 or less screening per life
  - Eradication of cervical cancer
Current Status For HPV Tests in Primary Screening

In Europe
- The trend is towards HPV testing instead of pap
  - Triage with pap
- Completed trials
- Most countries are piloting
- Adopted in national screening (Netherlands, Italy)

Cuzick, J. Clinical workshop IPV 2012, Puerto Rico

In the USA
- 2012 ACS/ASCCP and 2013 ACOG guidelines for cervical screening have recommended co-testing as preferred strategy
  - Triage with HPV16/18 or 12 mths followup for HPV+/Cyto- cases

Turkish Cervical Cancer Screening

ASR: 4/100,000
Ann case: 1500
Ann mort: 750

It is in force since 1992
Target: 30-65 yrs women
Interval: 5 yrs

Had been done by cytology
Coverage rate: 15%
Public awareness is low

Target Pop: 15,000,000
Family Phy.s involved

HPV Screening
Genotyping for every 13 High risk types
Reflex cytology and genotyping for + ones
Local production
THANK YOU
Figure 8. Five-year cumulative incidence of CIN3+ among women attending cervical cancer screening who are at baseline cyto-negative (a), cyto-positive/hrHPV-negative (b), cyto-negative/hrHPV-positive (c) and cyto-positive/hrHPV-positive (d). Pooled from 6 European cohorts. * The Portland study reported cumulative incidences over 4 years (Sherman et al., JNCI, 2003).
Table 4. Relative accuracy of other HPV tests compared to the Hybrid Capture-2 Assay (at RLU≥1) to find underlying CIN2 or CIN3 or worse in primary screening.

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Outcome</th>
<th>Relative sensitivity (95% CI)</th>
<th>Range</th>
<th>Relative specificity (95% CI)</th>
<th>Range</th>
<th>Nb. of studies [Reference]</th>
</tr>
</thead>
<tbody>
<tr>
<td>GP5/6+ / HC2</td>
<td>CIN2+</td>
<td>1.00 (0.96-1.04)</td>
<td>0.98-1.00</td>
<td>0.99 (0.91-1.07)</td>
<td>0.95-1.1</td>
<td>2 [4,51]</td>
</tr>
<tr>
<td>careHPV (at RLU≥0.5) / HC2</td>
<td></td>
<td>0.93 (0.85-1.01)</td>
<td>-</td>
<td>0.98 (0.96-1.01)</td>
<td>-</td>
<td>1 [52]</td>
</tr>
<tr>
<td>Cobas-4800 / HC2</td>
<td></td>
<td>0.98 (0.88-1.10)</td>
<td>-</td>
<td>1.00 (0.98-1.03)</td>
<td>-</td>
<td>1 [24]</td>
</tr>
<tr>
<td>Abbott RT PCR / HC2</td>
<td></td>
<td>1.00 (0.96-1.04)</td>
<td>0.99-1.03</td>
<td>1.01 (0.99-1.03)</td>
<td>1.00-1.02</td>
<td>1 [26,27]</td>
</tr>
<tr>
<td>Papillochk / HC2</td>
<td></td>
<td>0.98 (0.96-1.01)</td>
<td>-</td>
<td>0.99 (0.98-1.00)</td>
<td>-</td>
<td>1 [25]</td>
</tr>
<tr>
<td>APTIMA / HC2</td>
<td></td>
<td>1.02 (0.86-1.20)</td>
<td>0.95-1.12</td>
<td>1.07 (1.05-1.08)</td>
<td>1.06-1.08</td>
<td>2 [49,53]</td>
</tr>
<tr>
<td>careHPV (at RLU≥0.5) / HC2</td>
<td>CIN3+</td>
<td>0.91 (0.76-1.09)</td>
<td>-</td>
<td>0.98 (0.96-1.01)</td>
<td>-</td>
<td>1 [52]</td>
</tr>
<tr>
<td>Cervista / HC2</td>
<td></td>
<td>0.97 (0.93-1.02)</td>
<td>-</td>
<td>1.03 (1.02-1.04)</td>
<td>-</td>
<td>1 [54]</td>
</tr>
<tr>
<td>Abbott RT PCR / HC2</td>
<td></td>
<td>1.00 0†</td>
<td>-</td>
<td>1.02 (1.00-1.03)</td>
<td>-</td>
<td>1 [26]</td>
</tr>
<tr>
<td>MALDITOF / HC2</td>
<td></td>
<td>0.96 (0.92-1.01)</td>
<td>-</td>
<td>1.02 (1.01-1.03)</td>
<td>-</td>
<td>1 [54,55]</td>
</tr>
<tr>
<td>APTIMA / HC2</td>
<td></td>
<td>1.02 (0.93-1.11)</td>
<td>1.00-1.07</td>
<td>1.07 (1.05-1.08)</td>
<td>1.06-1.08</td>
<td>2 [49,53]</td>
</tr>
</tbody>
</table>

† 95% CI not computable since Abbott RT PCR and HC2 both showed 100% sensitivity for CIN3+. 