Cervical screening by HPV testing: clinical results and HPV test selection criteria

Chris JLM.Meijer Dept of Pathology
Vrije Universiteit Medical Center
Amsterdam
The Netherlands
cjlm.meijer@vumc.nl
Cervical cancer worldwide

- **Worldwide:**
  - New cervical cancer cases 530,000/year
  - 3rd cancer in women
  - 275,000 women/year are dying of cervical cancer
  - 80% of cases in low resource countries: Africa, Mid- and south America and Eastern Europe

- **Incidence:** ASR/100,000  
  - Netherlands: 6.9  
  - South Korea incidence: 9.5

- **Mortality:** ASR/100,000  
  - Netherlands: 1.6  
  - South Korea incidence: 2.6

*Globocan IARC-WHO 2012*
Current cervical screening tool in many countries: Pap test (cytology)
Problems in cervical screening by cytology

- Low sensitivity: many false pos. and false neg smears
- Frequent repeat testing necessary
- Subjective; moderate reproducibility
- Require good training of technicians and strong QC
- Not all women are reached for cervical screening
hrHPV is the causative agent of cervical cancer

• Can HPV testing improve cervical screening?
Role of HPV in cervical carcinogenesis

1. Persistent infection with hrHPV necessary for cervical carcinogenesis
2. No HPV, no cancer
3. 14 hrHPV types responsible for >99% of all CxCa: HPV 16 and 18 cause ~70% of all CxCa
HPV testing in cervical screening

- HPV vs cytology
- Clinical validation of an HPV test
- Triage of HPV pos women
- HPV genotyping
HPV testing vs cytology

HPV testing is more sensitive for CIN2+ detection than cytology; more objective

HPV provides better protection against CIN3 and cancer than cytology after a screen negative test

For screening purposes HPV testing is as good as HPV & cytology (Combo)

The HPV test is a more sensitive screening tool than the Pap test

HPV testing detects more CIN2+ than the Pap test

---

<table>
<thead>
<tr>
<th>Study</th>
<th>CIN2+</th>
<th>DRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Developing countries</td>
<td>Pap test</td>
<td></td>
</tr>
<tr>
<td>Sankaranarayan, 2005 (IN)</td>
<td></td>
<td>0.88 (0.76,1.03)</td>
</tr>
<tr>
<td>Industrialised countries, CP</td>
<td>HPV test</td>
<td></td>
</tr>
<tr>
<td>Ronco, 2006* (IT)</td>
<td></td>
<td>1.43 (1.00,2.04)</td>
</tr>
<tr>
<td>Mayrand, 2007 (CA)</td>
<td></td>
<td>1.69 (0.83,3.45)</td>
</tr>
<tr>
<td>Naucler, 2007 (SE)</td>
<td></td>
<td>1.42 (1.06,1.91)</td>
</tr>
<tr>
<td>Ronco, 2008* (IT)</td>
<td></td>
<td>1.92 (1.28,2.87)</td>
</tr>
<tr>
<td>Leinonen, 2009* (FL)</td>
<td></td>
<td>1.37 (0.98,1.90)</td>
</tr>
<tr>
<td>Rijaart, 2012 (NL)</td>
<td></td>
<td>1.26 (1.04,1.52)</td>
</tr>
<tr>
<td>Subtotal (I²=0.0%,p=0.572)</td>
<td></td>
<td>1.39 (1.23,1.57)</td>
</tr>
<tr>
<td>Industrialised countries, LBC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kitchener, 2009 (UK)</td>
<td></td>
<td>1.06 (0.87,1.28)</td>
</tr>
<tr>
<td>Overall (I²=71.8%,p=0.001)</td>
<td></td>
<td>1.27 (1.06,1.52)</td>
</tr>
</tbody>
</table>

* restricted to women older than 35 years

---

Arbyn et al., Vaccine 2012
Performance HPV & Pap (combo) vs HPV test alone

Sole HPV testing is as nearly as sensitive as HPV&Pap:
For screening use sole HPV testing

Arbyn et al., Vaccine 2012
Meta-analysis of outcome of RCT: relative Detection rate of CIN3+ or CxCa in second round in women who were HPV neg or cytology neg at enrolment

<table>
<thead>
<tr>
<th>Study</th>
<th>DRR (95% CI)</th>
<th></th>
<th>Study</th>
<th>DRR (95% CI)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Naucler, 2007</td>
<td>0.53 (0.29, 0.98)</td>
<td></td>
<td>Naucler, 2007</td>
<td>0.14 (0.01, 2.77)</td>
<td></td>
</tr>
<tr>
<td>Kitchener, 2009</td>
<td>0.52 (0.28, 0.97)</td>
<td></td>
<td>Ronco, 2010†</td>
<td>0.05 (0.00, 0.92)</td>
<td></td>
</tr>
<tr>
<td>Ronco, 2010*</td>
<td>0.34 (0.15, 0.75)</td>
<td></td>
<td>Rijkeart, 2012</td>
<td>0.17 (0.04, 0.74)</td>
<td></td>
</tr>
<tr>
<td>Rijkeart, 2012</td>
<td>0.39 (0.27, 0.56)</td>
<td></td>
<td>Overall (I²=0.0%, p=0.681)</td>
<td>0.43 (0.33, 0.56)</td>
<td></td>
</tr>
<tr>
<td>Overall (I²=0.0%, p=0.785)</td>
<td>0.13 (0.04, 0.44)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* restricted to women of 35 years or older.
† continuity correction (+.5 in each cell because of zero cancer cases among HPV-negative women).

50% less CIN3+ and nearly no cancer in second round in HPV screen neg women compared to cytology screen negative women at enrolment

➢ HPV protects better against CIN3+ and Cancer than cytology
Cumulative detection of invasive carcinoma
Pooled data from POBASCAM, NTCC, Artistic and Swedescreeen (>160,000 women)

Figure 2: Cumulative detection of invasive cervical carcinoma
*Observations are censored 2.5 years after CIN2 or CIN3 detection, if any.

Ronco et al., Lancet 2013

A negative HPV test provides better protection against cancer than cytology
Take home messages

- Women who were at enrolment HPV screen neg, have in the second round 50% less CIN3+ and nearly no cancer compared to women who were cytology screen negative at enrolment.

- HPV testing provides better protection against CIN3+ and CxCa than cytology.
HPV testing in cervical screening

• HPV vs cytology

• Clinical validation of HPV tests

• Triage of HPV pos women

• HPV genotyping
Use of HPV DNA tests

- Epidemiological studies:
  - assessing burden of HPV infections
  - Prevalence of HPV in CIN lesions and cervical cancer

- Vaccine monitoring:
  - determining protection against HPV infections

- Screening/ diagnosis/ post-treatment monitoring for CIN 2+:
  hrHPV testing should be considered for the detection of CIN2/3 or cancer, not simply viral infections
  - Cervical screening
  - Triage women with AS-CUS
  - test of cure (Monitoring women for post-treatment CIN2+)
HPV testing in cervical screening

For screening purposes it is imperative to detect transforming HPV infections associated with (pre)cancer i.e. CIN2, CIN3, CxCa and ignore the other types of HPV infections (i.e. transient HPV infections)

Otherwise too many women without lesions enter into diagnostic evaluation. Increase COSTS!

- Clinical validation of HPV tests obligatory!
- International guidelines have been formulated
HPV tests vary in their property to detect the various types of HPV infections

Important distinctions:

• Analytical sensitivity and specificity
  ➢ Detect all hrHPV infections: both transient (irrelevant) and transforming infections

• Clinical sensitivity and specificity
  ➢ Detect mainly HPV infections associated with CIN2+/3+ (clinically relevant hrHPV infections):
Example: Case-control study: women with CIN3 vs women with normal cytology (≥30 years) and no CIN2+ in next 2 years

- In women with normal cytology false positivity rate of clinically non-validated test was significantly higher than that of a clinically validated test; true positive CIN3+ rate is similar

- Result: Unnecessary F-up, expensive, harmful, and overtreatment of women

Hesselink et al., 2008
Viral load analysis in concordant vs discordant SPF10/GP5+/6+-PCR samples

- Samples negative by GP5+/6+-PCR but positive with SPF10 had significantly lower viral loads. Low viral loads point to clinically irrelevant (transient) infections.
Clinical validation of other HPV assays

• In order to become validated for use in cervical screening candidate HPV assays should prove:
  – their value in large prospective screening studies
  or
  – non-inferiority to validated reference assays (HC2 or GP5+/6+-PCR) in cross-sectional clinical equivalence studies

• Consensus guidelines for test requirements have been developed by an international consortium

(Meijer et al. : Int J Cancer, 2009)
Candidate test should:

- **Have a clinical sensitivity** for CIN2+ not less than 90% of that of HC2 (women ≥ 30 years of screening population)
  - to be tested on at least 60 samples of women with CIN2+

- **Have a clinical specificity** for CIN2+ not less than 98% of that of HC2 (women ≥ 30 years of screening population)
  - to be tested on at least 800 samples of women without CIN2+

- Display intra-laboratory **reproducibility** and inter-laboratory agreement with a lower confidence bound ≥87%
  - to be tested on at least 500 samples of which 1/3 is positive with validated test

Clinically validated HPV assays for cervical screening

<table>
<thead>
<tr>
<th>Available HPV detection assays</th>
</tr>
</thead>
<tbody>
<tr>
<td>Many (&gt;40)</td>
</tr>
<tr>
<td>- Hybrid Capture 2</td>
</tr>
<tr>
<td>- Diassay (GP5+/6+-PCR)</td>
</tr>
<tr>
<td>- COBAS4800</td>
</tr>
<tr>
<td>- APTIMA</td>
</tr>
<tr>
<td>- HPV RealTime</td>
</tr>
<tr>
<td>- SPF10</td>
</tr>
<tr>
<td>- Amplicor</td>
</tr>
<tr>
<td>- Cervista</td>
</tr>
<tr>
<td>- PapilloCheck</td>
</tr>
<tr>
<td>- PGMY</td>
</tr>
<tr>
<td>- … (and so on)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HPV tests validated for cervical screening (cervical scrapings)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Hybrid Capture 2*</td>
</tr>
<tr>
<td>- Diassay (GP5+/6+-PCR)*</td>
</tr>
<tr>
<td>- COBAS4800**</td>
</tr>
<tr>
<td>- HPV RealTime**</td>
</tr>
<tr>
<td>- PapilloCheck**</td>
</tr>
<tr>
<td>- APTIMA**#</td>
</tr>
<tr>
<td>- HPV-Risk assay**</td>
</tr>
<tr>
<td>- AnyplexII HPV28: Clinical validation in preparation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HPV tests validated for cervical vaginal lavages (Delphi-screener)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Diassay (GP5+/6+-PCR)</td>
</tr>
<tr>
<td>- HPV-Risk assay</td>
</tr>
</tbody>
</table>

*Based on longitudinal studies
**Based on equivalence analysis according to guidelines
# Provided that data of long term NPV of mRNA testing become available
International guidelines for clinical validation of HPV tests have been adopted in countries where primary screening is already present or will be implemented:

The Netherlands, Australia, UK, Denmark, 5 regions of Italy.

www.gr.nl
www.msac.gov.au
HPV testing in cervical screening

- HPV vs cytology
- Clinical validation of HPV tests
- HPV genotyping
- Triage of HPV pos women
Why HPV genotyping?

- Different HPV-DNA genotype prevalences suggest different risks for CIN 3 and CxCa

- Q: Useful for management?
HPV types in cervical cancer worldwide: HPV 16 and HPV 18 most prevalent

HPV 16 and 18 have a preferential risk for hgCIN and CxCa

<table>
<thead>
<tr>
<th>HPV types</th>
<th>Squamous Cell Carcinoma</th>
<th>Adeno-carcinoma</th>
<th>CIN2/3 HSIL</th>
<th>CIN 1 LSIL normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>16/18</td>
<td>~70%</td>
<td>~91%</td>
<td>~53%</td>
<td>~25%</td>
</tr>
<tr>
<td>31/45</td>
<td>~6%</td>
<td>~4%</td>
<td>~7%</td>
<td>~11%</td>
</tr>
<tr>
<td><strong>Total</strong> (16/18/31/45)</td>
<td>~76%</td>
<td>~95%</td>
<td>~60%</td>
<td>~36%</td>
</tr>
</tbody>
</table>

Different prevalence of HPV types in normal smears, LSIL, HSIL and squamous and adenocarcinomas indicates different risks,

HPV genotypes in different cervical lesions

- Differences in prevalence of HPV types among lesion severity indicate a different risk for CIN3+ by different HPV types

Franceschi et al. JNCI 2005
Meta-analyses of type-specific HPV DNA prevalence in invasive cervical cancer and women with normal cytology

<table>
<thead>
<tr>
<th>HPV Type</th>
<th>Invasive cervical cancer</th>
<th>Normal cytology</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N tested</td>
<td>% pos</td>
</tr>
<tr>
<td>HPV16</td>
<td>14595</td>
<td>54.4</td>
</tr>
<tr>
<td>HPV18</td>
<td>14387</td>
<td>15.9</td>
</tr>
<tr>
<td>HPV33</td>
<td>13827</td>
<td>4.3</td>
</tr>
<tr>
<td>HPV45</td>
<td>9843</td>
<td>3.7</td>
</tr>
<tr>
<td>HPV31</td>
<td>11960</td>
<td>3.5</td>
</tr>
<tr>
<td>HPV58</td>
<td>10157</td>
<td>3.3</td>
</tr>
<tr>
<td>HPV52</td>
<td>9509</td>
<td>2.5</td>
</tr>
<tr>
<td>HPV35</td>
<td>9507</td>
<td>1.7</td>
</tr>
<tr>
<td>HPV59</td>
<td>6972</td>
<td>1.0</td>
</tr>
<tr>
<td>HPV51</td>
<td>7339</td>
<td>0.7</td>
</tr>
<tr>
<td>HPV56</td>
<td>7427</td>
<td>0.7</td>
</tr>
<tr>
<td>HPV39</td>
<td>7078</td>
<td>0.6</td>
</tr>
<tr>
<td>HPV68</td>
<td>6723</td>
<td>0.5</td>
</tr>
<tr>
<td>HPV73</td>
<td>5837</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Schiffman et al. Infectious agents and cancer 2009

No consequences for management because differences in CIN3+ risk are too small for different management algorithms.

Strong Preferential Increase

Small Preferential Increase

No Preferential Increase
HPV genotyping in cervical screening

- HPV genotyping should only be done in women who are hrHPV pos. with a clinically validated hrHPV test.

Alternative

- HPV genotyping should be done in women by a primary clinically validated HPV test which detect at the same time individual hrHPV genotypes

This algorithm is necessary because otherwise over-referral of many women with irrelevant (transient) HPV infections
Most clinically validated HPV tests have an HPV-DNA genotyping possibility for HPV 16, 18 and/or HPV 45.

**Signal amplification**

HC2 in combination with a separate HPV 16/18/45 Test

**Real time multiplex HPV-PCR**

*DNA based*
- Cobas 4800®, Roche: target L1, HPV 16/18 included
- HPV Risk test® Self-screen: target E6/7, HPV 16/18 included
- PapilloCheck® Bio-Greiner: Target E1, detects 14 hrHPV types
- Real time high risk HPV® Abbott: target L1, HPV 16/18 included

*RNA based*
- Aptima® Hologic: Target E6/7, HPV 16/18/45 testing possible
HPV detection and genotyping

AnyplexII HPV28 (seegene ®): Quantitative Real time PCR: Detects in one simple reaction step all 19 hrHPV types and 8 lrHPV types (multiplex PCR)

Key features

• Provide quantitative information: +++(>105 copies/rxn) or ++(102~105 copies/rxn) or +( <102 copies/rxn). High viral loads associated with (pre)cancer
• Only 2 tubes for 28 HPVs: 19 high-risk and 9 low-risk HPVs
• Compatible automated DNA extraction and PCR set-up instruments: Nimbus IVD and STARlet IVD (Hamilton)
• Compatible Real-time PCR instrument: CFX-96 (Bio-Rad)
• Provide whole process control for each reaction: human b-globin

Clinical validation in progress
HPV genotypes

Prevalence of HPV 16/18 increases preferentially in HPV infections without morphological changes (NILM) via CIN2/CIN3 to Cancer.

Risk for developing a persistent HPV infection is highest for HPV 16 and 18.

Risk for CIN3 after a persistent HPV infection is highest for HPV 16, followed by HPV 18.

Risk for development of CxCa is very high for HPV 16/18.

➢ These data argue for more intense clinical management for HPV 16/18 types.

Prevalence of all non-HPV 16/18 genotypes do not or slightly increase from HPV-NILM via CIN2/3, and stay the same in CxCa.

Risk for CxCa of non-HPV 16/18 HPV genotype is much lower than for HPV 16/18 and remains for all non-HPV16/18 types in the same low range.

➢ The data argue for similar clinical management of women with non-HPV 16/18 genotypes and for less intense management than for women with HPV 16/18 infections.
Use of HPV-DNA genotyping tests

- **Epidemiological studies:**
  - assessing burden of HPV-DNA genotype infections
  - Prevalence of HPV-DNA genotypes in CIN lesions and CxCancer

- **Vaccine monitoring:**
  - reveals protection or failure against vaccine type HPV infections

- **Cervical screening/ diagnosis/ post-treatment CIN2+ monitoring** *(only in combination with or incorporated in a clinically validated HPV test)*
  - Cervical screening, mainly HPV 16/18 and perhaps 45
  - test of cure (Monitoring women for post-treatment CIN2+)
    - differentiate between persistent and incident infections
    - HPV 16 pos. women have an increased risk for
HPV testing in cervical screening

• HPV vs cytology

• Clinical validation of HPV tests

• HPV genotyping

• Triage of HPV pos women
HPV testing recognizes viral infection, but we need to detect disease.

Detection women at RISK

HPV test detects both transient and clinical relevant infections

We are only interested in HPV infections associated with disease: high grade lesions and cancer.
HPV testing recognizes viral infection, but we need to detect disease: triage testing necessary

**HPV Testing (risk population)**

Women

HPV DNA test

HPV + Women

**Detection women at RISK**

Population at risk CxCa

**TRIAGE (disease)**

Detection of women with disease in need of Referral

Population with disease

- hrHPV infection
- Normal
- 20% precursor lesions
- High grade lesions 1-3% cancer
- Clinically relevant HPV infections
- Carcinoma
- Low grade lesions
- 80% No lesions
- 2-3 years
- 10-12 years
Evaluation of triage tests in longitudinal studies (VUSA-Screen and POBASCA)

- Cytology
- HPV 16/18 genotyping
- Combinations of these tests

➢ Aim to increase specificity without losing sensitivity

Rijkaart et al Int.J Cancer 2011; Dijkstra et al CEBP 2013
Evaluation of triage strategies of HPV positive women: considerations 1

- Strategies should have a high NPV for CIN3+ of ≥98%

- If the 3 year CIN3+ risk is:
  - >10%: immediate referral for colposcopy
  - 3-10%: short-term follow-up testing after 6-12 months
  - ≤2%: referral to next screening round (3 or 5 years)

Castle et al 2008; Dutch screening council 2010; Rijkaart et al Int J Cancer 2011
Dijkstra et al CEPB 2013
At maximum one follow-up test: loss to follow-up in each follow-up step (20-40%)

Colposcopy rates as low as possible -> low costs and less overtreatment:
  PPV for CIN3+ should be $\geq 20\%$: acceptable colposcopy referral rate

Easy to implement: negative test as final screen

Castle et al 2008; Dutch screening council 2010
Rijkaart et al; Int J Cancer 2011; Dijkstra et al 2013
# Triage strategies for hrHPV positive women

(4.2% of screening population, 30-60 yrs)

<table>
<thead>
<tr>
<th>Baseline triage test</th>
<th>Follow-up test 6 months</th>
<th>Follow-up test 12 months</th>
<th>NPV %</th>
<th>PPV %</th>
<th>Repeat tests %</th>
<th>Colpo rate %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytology</td>
<td>-</td>
<td>-</td>
<td>94.3</td>
<td>39.7</td>
<td>-</td>
<td>30.5</td>
</tr>
<tr>
<td>Cytology</td>
<td>-</td>
<td>-</td>
<td>95.1</td>
<td>42.2</td>
<td>-</td>
<td>21.6</td>
</tr>
<tr>
<td>Cytology / HPV16,18</td>
<td>-</td>
<td>-</td>
<td>98.8</td>
<td>28.5</td>
<td>-</td>
<td>54.5</td>
</tr>
<tr>
<td>Cytology / HPV16,18</td>
<td>-</td>
<td>-</td>
<td>97.1</td>
<td>26.0</td>
<td>-</td>
<td>43.4</td>
</tr>
</tbody>
</table>

- NPV of ≥ 98% for CIN3+: adequate for use in cervical screening

*Rijkaart et al 2011, Dijkstra et al 2014*
# Triage strategies for hrHPV positive women

(4.2% of screening population, 30-60 yrs)

<table>
<thead>
<tr>
<th>Baseline triage test</th>
<th>Follow-up test 6 months</th>
<th>Follow-up test 12 months</th>
<th>NPV %</th>
<th>PPV %</th>
<th>Repeat tests %</th>
<th>Colpo rate %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytology</td>
<td>-</td>
<td>-</td>
<td>94.3</td>
<td>39.7</td>
<td></td>
<td>30.5</td>
</tr>
<tr>
<td>Cytology</td>
<td>-</td>
<td>-</td>
<td>95.1</td>
<td>42.2</td>
<td></td>
<td>21.6</td>
</tr>
<tr>
<td>Cytology / HPV16,18</td>
<td>-</td>
<td>98.8</td>
<td>28.5</td>
<td></td>
<td></td>
<td>54.5</td>
</tr>
<tr>
<td>Cytology / HPV16,18</td>
<td>-</td>
<td>97.1</td>
<td>26.0</td>
<td></td>
<td></td>
<td>43.4</td>
</tr>
<tr>
<td>Cytology</td>
<td>Cytology</td>
<td>98.5</td>
<td>34.0</td>
<td>69.5</td>
<td>44.8</td>
<td></td>
</tr>
<tr>
<td>Cytology</td>
<td>Cytology</td>
<td>99.3</td>
<td>37.5</td>
<td>78.4</td>
<td>33.4</td>
<td></td>
</tr>
<tr>
<td>Cytology / HPV16,18</td>
<td>Cytology</td>
<td>99.6</td>
<td>25.6</td>
<td>45.5</td>
<td>62.1</td>
<td></td>
</tr>
<tr>
<td>Cytology / HPV16,18</td>
<td>Cytology</td>
<td>99.7</td>
<td>25.6</td>
<td>56.6</td>
<td>49.9</td>
<td></td>
</tr>
</tbody>
</table>

- Triage with cytology and HPV16/18 genotyping at borderline risk of ~ 2% risk
  - Trade-off in colpo referral rate
Presently two triage strategies have been adopted, because they are easy to implement and fulfill CIN3+ risk requirements

A) Baseline cytology and cytology in follow-up (6 or 12 months)
B) Baseline cytology & HPV16/18 genotyping and cytology in follow-up (6 or 12 months)

Take home message

- The exact algorithm to be used for triage depends on the quality of cytology and the minimum positive predictive value for CIN3+ referral acceptable by local health decision makers (resources available)
Primary HPV Screening will be implemented in

**The Netherlands**: Jan 2016
Women 30-60 years, 30,35,40, 50,60y. Triage with cytology at baseline and 6 months.
If HPV screen pos and triage test neg at 40,50, or 60y: repeat testing after 5 years

**Australia**: advice medical services advisory committee 4/04/2014:
Start primary HPV screening
Women: 25-69 years, 5 years interval, Triage by cytology and HPV 16/18 genotyping at baseline and cytology at 12 month

**Italy**: 5 regions start HPV screening in 2015
women 25-65 y, 5 years interval, Triage by cytology and HPV 16/18 genotyping
Nordic countries are considering or doing implementation pilot studies

[www.gr.nl](http://www.gr.nl); [www.msac.gov.au](http://www.msac.gov.au)
Indications for HPV genotyping

• Full HPV genotyping necessary for
  – evaluation of vaccine efficacy: to determine (cross) protection or vaccine failure
  – epidemiological studies
  – detection/exclusion new incident CIN2+ in women treated for high grade CIN
  – detection of persistent infection of a specific HPV genotype when hrHPV is present

• Partial HPV genotyping (HPV16, HPV 18/(45) is usefull for
  – management of HPV 16/18 pos women: highest risk for CIN3+
  – monitoring women treated for high grade CIN: HPV 16 pos women have a higher risk for recurrent CIN

➢ In clinical practice HPV testing should only be done following or integrated in a clinically validated HPV test
Acknowledgments

VU University Medical Center (VUmc)

Department of Pathology
- P. Snijders
- D. Heideman
- F. van Kemenade
- L. Rozendaal
- M. Gök
- B. Hesselink
- R. Steenbergen
- S. Wilting
- V. Verhoef
- M. Uijterwaal
- M. Dijkstra

Department of clinical epidemiology and biostatistics
- N. Fransen
- M. Verkuyten
- D. Boon
- M. Letting
- F. Topal
- D. Buma
- M. Bogaarts
- R. van Andel
- R. Pol
- M. Doeleman

Gynaecologic Oncology
- G. Kenter

EEC consortia
- PreHDICT
- CoHeaHr
- Mass-care

Dutch Cancer foundation
ZON-MW
Thank You