HPV Testing
For Cervical Cancer Screening

Robert Schlaberg, MD, MPH
Objectives

• Understand the role of HR-HPV in cervical cancer development
• Know the use of HR-HPV testing in current cervical cancer screening guidelines
• Be able to compare testing principles used in current FDA-cleared HR-HPV assays
Cervical Cancer

• Most frequent --> #14 (cancer death in women)
  – 12,000 cases, 4,200 deaths, (50% unscreened)
  – Goal: detection of preinvasive disease
  – Early detection: 5-year survival rate >90%

• Persistent HR HPV infection
  – Almost 100% of cervical cancers HR HPV+
  – HPV16 (55-60%), HPV18 (10-15%)

• Cause all common/most rare histologic types
  – Squamous cell carcinoma (80-90%)

Am J Clin Pathol 2012;137:516-542
Cervical Carcinogenesis

- Sexual/genital skin-to-skin contact
- Peak: few years after median sexual debut
- 90% clearance within 1-2 years
- 1 & 2-year persistence strongly predicts CIN3+
- Progression
- Invasion
Squamous Cervical Precursor Lesions

- **LSIL**: Low-grade squamous intraepithelial lesion  
  ~ koilocytic atypia (HPV) and/ or CIN1
- **HSIL**: High-grade squamous intraepithelial lesion  
  ~ CIN2/3

*J Clin Invest* 2006;116:1167-1173
# Natural History of Cervical Precancer

<table>
<thead>
<tr>
<th>Degree of Dysplasia</th>
<th>Regression (%)</th>
<th>Persistence (%)</th>
<th>Progression to CIN3 (%)</th>
<th>Progression to Invasive Cancer (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIN I</td>
<td>60</td>
<td>30</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>CIN II</td>
<td>40</td>
<td>40</td>
<td>15</td>
<td>5</td>
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<tr>
<td>CIN III</td>
<td>33</td>
<td>55</td>
<td>N/A</td>
<td>&gt;12*</td>
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</tbody>
</table>

* untreated: 30% over 30-year period  
  treated: 1% over 30-year period  

*Am J Clin Pathol* 2012;137:516-542  
HPV - Biology

- Double-stranded, circular DNA, ~8kb
- Oncogenes (E6, E7)
- >100 types (~40 infect genital tract)
  - **Low risk** (condyloma acuminata): 6, 11, 42, 43, 44, 54, 61, 70, 72, and 81
  - **High risk** (cervical dysplasia/cancer): 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, (73, 82)
  - **Indeterminate risk**
- Squamous epithelium
  - Skin, cervix, larynx, oropharynx, anus, esophagus, conjunctiva
HPV Replication

J Clin Invest 2006;116:1167-1173
HPV Infection

- Most common viral STI
- Incidence ~ 6 million/y; prevalence ~20 million
- Lifetime risk ~ 50-75%
- Clearance 70% at 1 yr, 90% at 2 yrs

CDC: Sexually Transmitted Disease Surveillance, 2009

Lancet 2007; 370: 890–907
HPV – Pathogenic Spectrum

• **HR HPV** - Squamous cell carcinoma
  – Uterine cervix, vulva, vagina, anus, penis
  – Oropharynx (tonsil, base of tongue), esophagus

• **LR HPV**
  – Genital warts
  – Recurrent respiratory papillomatosis
  – Low-grade cervical abnormalities

~70%: HPV16 and 18
Cervical Cancer Screening

• Pap test
  – Identifies dysplasia / pre-cancer / cancer
  – Higher specificity/lower sensitivity

• HPV test
  – Identifies women at risk
  – High negative predictive value (CIN, cancer)
  – Higher reproducibility

• Combined approach
  – Co-testing with cytology (≥30y)
  – ASCUS-triage: follow-up interval (≥21y)
Clinical Specimens (HC II)

- **Digene Cervical Sampler** (Qiagen)
  - Media optimized for HC2 assay
  - FDA-approved
  - 2 wks (2-30°C), 3 wks (4°C), 3 mo (-20°C)

- **ThinPrep** (PreservCyt, 20ml)
  - 3 weeks from collection (cytology)
  - FDA-approved
  - HCII, Invader, cobas, APTIMA

- **SurePath** (TriPath, 10ml)
  - 4 weeks from collection (cytology)
  - Not FDA-approved
  - Full validation required
The Analytical Sensitivity of HC2 is 5,000 copies of HPV DNA

The Analytical Sensitivity of PCR methods can be <10 copies of HPV DNA

Adapted from J Pathol 2003; 201:1-6
Viral Load (RLU) & Histology

1: $0 < \text{RLU/CO values} \leq 1$
2: $1 < \text{RLU/CO values} \leq 10$
3: $10 < \text{RLU/CO values} \leq 100$
4: $100 < \text{RLU/CO values} \leq 1,000$
5: $\text{RLU/CO values} > 1,000$

Eur J Clin Microbiol Infect Dis. 2012 Mar 1
2012 Cervical Screening Guidelines

- American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology
  *Am J Clin Pathol* 2012;137:516-542

- Not applicable for
  - Women with h/o cervical cancer
  - Women with exposure to diethylstilbestrol (DES)
  - Immunocompromised women (e.g. HIV+)

- U.S. Preventive Services Task Force
  *Ann Intern Med* 2012 Mar 14
<table>
<thead>
<tr>
<th>Population</th>
<th>Page Numbers</th>
<th>Recommended Screening Method*</th>
<th>Management of Screen Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aged &lt;21 y</td>
<td></td>
<td>No screening</td>
<td></td>
<td>HPV testing should not be used for screening or management of ASC-US in this age group</td>
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<tr>
<td>Aged 21-29 y</td>
<td></td>
<td>Cytology alone every 3 y</td>
<td>HPV-positive ASC-US(^\d) or cytology of LSIL or more severe: Refer to ASCCP guidelines(^\d)</td>
<td>HPV testing should not be used for screening in this age group</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Cytology negative or HPV-negative ASC-US(^\d): Rescreen with cytology in 3 y</td>
<td></td>
</tr>
<tr>
<td>Aged 30-65 y</td>
<td></td>
<td>HPV and cytology “cotesting” every 5 y (preferred)</td>
<td>HPV-positive ASC-US(^\d) or cytology of LSIL or more severe: Refer to ASCCP guidelines(^\d)</td>
<td>Screening by HPV testing alone is not recommended for most clinical settings</td>
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<td>HPV positive, cytology negative:</td>
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<td>Option 1: 12-mo follow-up with cotesting</td>
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<td>Option 2: Test for HPV or HPV16/18 genotypes</td>
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<td></td>
<td>• If HPV16 or HPV16/18 positive: refer to colposcopy</td>
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<td></td>
<td>• If HPV16 or HPV16/18 negative: 12-mo follow-up with cotesting</td>
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<td>Aged &gt;65 y</td>
<td></td>
<td>No screening following adequate negative prior screening</td>
<td>Women with a history of CIN2 or a more severe diagnosis should continue routine screening for at least 20 y</td>
<td></td>
</tr>
<tr>
<td>After hysterectomy</td>
<td></td>
<td>No screening</td>
<td>Applies to women without a cervix and without a history of CIN2 or a more severe diagnosis in the past 20 y or cervical cancer ever</td>
<td></td>
</tr>
<tr>
<td>HPV vaccinated</td>
<td></td>
<td>Follow age-specific recommendations (same as unvaccinated women)</td>
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</tbody>
</table>

ASCCP, American Society for Colposcopy and Cervical Pathology; ASC-US, atypical squamous cells of undetermined significance; CIN2, cervical intraepithelial neoplasia grade 2; HPV, human papillomavirus; LSIL, low-grade squamous intraepithelial lesion.

\(^\d\) Women should not be screened annually at any age by any method.

\(^\d\) ASC-US cytology with secondary HPV testing for management decisions.
Rationale For Screening Interval

- Cytology
- HPV
- Cytology-/HPV-
Main Points

• No annual screening at any age

• Age <21: no screening
  – No reduction over past 4 decades
  – Prevention through vaccination

• Age 21-29: cytology q3 yrs, no cotesting
  – q1 year: 2x colposcopies, slight cancer reduction

• Age 30-65: cotesting q5 yrs or cytology q3 yrs
  – Incident cancer equal/lower with cotesting
  – Cotesting: better detection of adenocarcinoma

Am J Clin Pathol 2012;137:516
Main Points, Cont.

• **Age >65 and no history of CIN2+ in last 20 yrs**
  – STOP

• **Age >65 with history of CIN2+ in last 20 yrs**
  – Continue **routine screening** for at least 20 yrs

• **Hysterectomy, no history of CIN2+**
  – STOP

• **Vaccinated women**
  – Same

Am J Clin Pathol 2012;137:516
Cytology-neg & HPV-pos

• No direct referral to colposcopy
• **Option 1**: repeat cotesting after 12 months
  – Either test positive (LSIL+) -> colposcopy
  – Both negative -> return to normal screening
• **Option 2**: immediate HPV16 ± HPV18
  – HPV16 and/or HPV18-positive -> colposcopy
  – HPV16 and 18 negative -> cotest after 12 months
  – Follow-up see option 1
ASC-US & HPV-\textit{neg}

- Continue with \textit{routine} screening

ASC-US & HPV-\textit{pos}

- Direct referral to \textit{colposcopy}

LSIL+ & Irrespective of HPV

- Direct referral to \textit{colposcopy}
FDA-Cleared HPV Tests

- **Hybrid Capture 2 High-Risk HPV DNA Test** *(Qiagen)*
  - Probe hybridization (whole genome); HR, (LR)
- **Cervista HPV HR** *(Hologic)*
  - Invader; HR, IC; HPV16, HPV18
- **cobas HPV Test** *(Roche)*
  - Real-time PCR; HR, IC; HPV16, HPV18
- **APTIMA HPV Assay** *(Gen-Probe)*
  - TMA; HR, IC
Hybrid Capture

• RNA probes targeting most of genome, hybrid
• Capture Ab, AP-conjugated mAb
• **Signal** amplification
• 13 HR types targeted
  – Cross-hybridization: HR: 66; LR: 8, 9, 43, 45, 47
• No extraction
• No target amplification
• No internal control
Invader

- DNA extraction
- Probes for 14 HR HPV types
  - Probe and Invader oligonucleotides anneal
  - Cleavase: overlapping probes
  - Release of 5' flap
  - Flap + FRET probe -> signal
- **Signal** amplification
- No target amplification
- Internal control (histone 2)
Real-Time PCR

- DNA extraction
- Primers/probes for 14 HR types
- Multiple primer/probe sets
- **Target** amplification
- Internal control (β-globin)
- Optional/simultaneous: HPV16/18 typing
TMA

- E6/E7 mRNA
- 14 HR types
  - Target capture, amplification (TMA), detection (hybridization protection assay)
- Target amplification
- Internal control
- Separate RUO assay: HPV16 vs. 18/45
Performance and Workflow

• Sample volume requirements
• Prequot vs. postquot samples
• Sample preservative
• Screening vs. triage
• Clinical sensitivity and specificity
• Throughput
• Automation vs. manual steps
• Cross-contamination risk
One Test Comparison Study

- Referral population, $n=1099$
- CIN2+ $n=359$ (33%), CIN3+ $n=224$ (20%)
- ThinPrep samples

Table 2: HPV positivity and type-specific results of different tests

<table>
<thead>
<tr>
<th>Test:</th>
<th>Number tested (Number with single mild or less smear)</th>
<th>positive (%)</th>
<th>HPV 16 positive (%)</th>
<th>HPV 18 positive (%)</th>
<th>Other HPV positive (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qiagen: Hybrid Capture 2</td>
<td>1067 (649)</td>
<td>85.8</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Roche: Cobas</td>
<td>1095 (670)</td>
<td>82.3</td>
<td>31.9</td>
<td>10</td>
<td>71.1</td>
</tr>
<tr>
<td>Abbott: Real-time PCR</td>
<td>1095 (670)</td>
<td>79.4</td>
<td>30.5</td>
<td>8.5</td>
<td>67.6</td>
</tr>
<tr>
<td>BD HPV</td>
<td>1097 (670)</td>
<td>82.0</td>
<td>30.5</td>
<td>9.4</td>
<td>71.4</td>
</tr>
<tr>
<td>Gen-probe: APTIMA</td>
<td>1097 (670)</td>
<td>79.0</td>
<td>30.0</td>
<td>11.8**</td>
<td>-</td>
</tr>
<tr>
<td>Norchip: PreTect HPV-Proofer</td>
<td>1057 (641)</td>
<td>43.9</td>
<td>26.2</td>
<td>7.8</td>
<td>42.8</td>
</tr>
<tr>
<td>mtm laboratories: p16$^{INK4a}$</td>
<td>974 (591)</td>
<td>58.9</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

* Other HPV only for those negative for HPV 16 and HPV 18
** tested HPV 18/45 combined
<table>
<thead>
<tr>
<th>Test (no. assessed)</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>PPV (95% CI)</th>
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<td><strong>Qiagen: Hybrid Capture 2</strong></td>
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<tr>
<td>CIN3+</td>
<td>98.7 (96.1-99.7)</td>
<td>-</td>
<td>24.0 (21.3-26.9)</td>
</tr>
<tr>
<td>CIN2+</td>
<td>96.3 (93.8-98.0)</td>
<td>19.5 (16.7-22.6)</td>
<td>37.4 (34.2-40.6)</td>
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<tr>
<td>CIN2</td>
<td>92.4 (86.5-96.3)</td>
<td>-</td>
<td>-</td>
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<tr>
<td><strong>Roche: Cobas</strong></td>
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<td>CIN3+</td>
<td>97.3 (94.2-99.0)</td>
<td>-</td>
<td>23.9 (21.1-26.8)</td>
</tr>
<tr>
<td>CIN2+</td>
<td>95.2 (92.5-97.2)</td>
<td>24.0 (20.9-27.2)</td>
<td>37.6 (34.5-40.9)</td>
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<td>-</td>
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<tr>
<td>CIN2+</td>
<td>93.3 (90.1-95.6)</td>
<td>27.3 (24.1-30.7)</td>
<td>38.2 (35.0-41.5)</td>
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<tr>
<td>CIN2</td>
<td>86.7 (79.7-91.9)</td>
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<tr>
<td><strong>BD HPV</strong></td>
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<td>CIN3+</td>
<td>97.8 (94.8-99.3)</td>
<td>-</td>
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</tr>
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<td>95.0 (92.2-97.0)</td>
<td>24.2 (21.2-27.5)</td>
<td>37.8 (34.6-41.0)</td>
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<td>CIN2</td>
<td>90.4 (84.1-94.8)</td>
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<tr>
<td><strong>Gen-Probe: APTIMA</strong></td>
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<tr>
<td>CIN3+</td>
<td>97.8 (94.8-99.3)</td>
<td>-</td>
<td>25.1 (22.3-28.2)</td>
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<td>CIN2+</td>
<td>95.3 (92.5-97.2)</td>
<td>28.8 (25.6-32.2)</td>
<td>39.3 (36.1-42.7)</td>
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<td>CIN2</td>
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<td><strong>mtm laboratories: p16INK4a</strong></td>
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<tr>
<td>CIN3+</td>
<td>90.2 (85.3-93.9)</td>
<td>-</td>
<td>32.2 (28.4-36.2)</td>
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<tr>
<td>CIN2+</td>
<td>85.7 (81.5-89.3)</td>
<td>54.7 (50.8-58.6)</td>
<td>49.1 (45.0-53.3)</td>
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<td>CIN2</td>
<td>78.2 (69.9-85.1)</td>
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<td><strong>Norchip: PreTect HPV-Proofer</strong></td>
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<tr>
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<td>80.3 (74.4-85.3)</td>
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<td>37.7 (33.3-42.3)</td>
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<td>CIN2+</td>
<td>74.1 (69.1-78.6)</td>
<td>70.8 (67.3-74.2)</td>
<td>55.4 (50.7-60.0)</td>
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<tr>
<td>CIN2</td>
<td>63.6 (54.6-71.9)</td>
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<tr>
<td><strong>Cytology (mild or worse)</strong></td>
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<tr>
<td>CIN3+</td>
<td>92.9 (88.7-95.9)</td>
<td>-</td>
<td>33.1 (29.4-36.9)</td>
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<tr>
<td>CIN2+</td>
<td>88.9 (85.1-91.9)</td>
<td>58.1 (54.5-61.7)</td>
<td>50.7 (46.7-54.7)</td>
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<td>CIN2</td>
<td>82.2 (74.7-88.3)</td>
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<tr>
<td>Test (no. assessed)</td>
<td>Women with referral less or equal to single mildly dyskaryosis</td>
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<td>---------------------------------------------------------------</td>
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<td>CIN3+</td>
<td>100.0 (92.7-100.0)</td>
<td>-</td>
<td>9.2 (6.9-11.9)</td>
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<td>19.9 (16.5-23.5)</td>
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<td>87.9 (77.9-94.6)</td>
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<tr>
<td>mtm laboratories: p16INK4a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CIN3+</td>
<td>83.7 (69.3-93.2)</td>
<td>-</td>
<td>12.5 (8.9-16.9)</td>
</tr>
<tr>
<td>CIN2+</td>
<td>76.2 (66.9-84.0)</td>
<td>57.2 (52.7-61.6)</td>
<td>27.8 (22.7-33.3)</td>
</tr>
<tr>
<td>CIN2</td>
<td>71.0 (58.1-81.8)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Norchip: PreTect HPV-Proofer</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>CIN3+</td>
<td>80.9 (66.7-90.9)</td>
<td>-</td>
<td>16.6 (12.0-22.1)</td>
</tr>
<tr>
<td>CIN2+</td>
<td>73.6 (64.4-81.6)</td>
<td>72.1 (68.1-75.9)</td>
<td>35.4 (29.2-41.9)</td>
</tr>
<tr>
<td>CIN2</td>
<td>68.3 (55.3-79.4)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cytology (mild or worse)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CIN3+</td>
<td></td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>CIN2+</td>
<td></td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>CIN2</td>
<td></td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>
Future Issues

• Vaginal self sampling (screening uptake)
  – *J Natl Cancer Inst* 2012;104:178–188

• Primary screening
  – *J Natl Cancer Inst* 2012;104:178–188
  – *BJOG* 2012;119:650–652

• Screening and prognostic testing in other cancers
Self-Collected Vaginal Samples

Gynecol Oncol 105(2007):530
Oropharyngeal SCC & HPV Testing

- >36,000 cases/y
- >7,000 deaths/y
- RF: tobacco, alcohol <-> HPV
- HPV-associated
  - Increasing, mostly oropharyngeal
  - Younger, often without tobacco/alcohol
  - Better response to radiation, better survival
  - HPV 16 >> HPV 18
Increasing Incidence

Figure 2. Age-standardized incidence of tonsillar and base of tongue cancers, Stockholm, Sweden, 1970–2006.

Figure 3. Estimated age-standardized incidence of human papillomavirus (HPV)—positive and HPV-negative tonsillar cancer squamous cell carcinoma cases per 100,000 person-years, Stockholm, Sweden, 1970–2006. Error bars indicate 95% confidence intervals. Data from Násman et al. (18), with permission of John Wiley and Sons (www.interscience.wiley.com).

Ramqvist et al., EID 2010,16,11,
HPV In Oropharyngeal Cancers

A. Overall Survival According to Tumor HPV Status

- HPV-positive
- HPV-negative

No. at Risk
HPV-positive: 206, 193, 179, 165, 151, 73
HPV-negative: 117, 89, 76, 65, 51, 22

Hazard ratio for death, 0.38 (0.26–0.55); P<0.001

Years since Randomization

B. Progression-free Survival According to Tumor HPV Status

- HPV-positive
- HPV-negative

No. at Risk
HPV-positive: 206, 168, 155, 148, 136, 65
HPV-negative: 117, 73, 59, 49, 37, 15

Hazard ratio for relapse or death, 0.40 (0.29–0.57); P<0.001

Years since Randomization

C. Overall Survival According to p16 Expression

- p16-positive
- p16-negative

No. at Risk
p16-positive: 215, 203, 190, 176, 162, 77
p16-negative: 101, 73, 60, 49, 34, 15

Hazard ratio for death, 0.29 (0.20–0.43); P<0.001

Years since Randomization

D. Progression-free Survival According to p16 Expression

- p16-positive
- p16-negative

No. at Risk
p16-positive: 215, 177, 164, 156, 143, 66
p16-negative: 101, 59, 46, 37, 25, 11

Hazard ratio for relapse or death, 0.33 (0.24–0.46); P<0.001

Years since Randomization

Open Questions

• Specimen
  – Cytology specimens (FNA, brush)
  – Surgical specimens

• Modality
  – In-situ hybridization for HPV
  – Molecular testing for HPV (E6 mRNA)
  – Immunohistochemistry for p16
Questions?