#### HPV DNA Testing & Cervical Cancer Screening

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Castle et al., AJOG, 2007

# **Optimal Cytology Screening Intervals**

Women ages 21-29

#### Screen with cytology alone every 3 years.

- Annual screening results in slightly greater cancer risk reduction (lifetime risk 3 per 1000 women) but twice the number of colposcopies compared to screening every 3 years
- No significant difference in cancer reduction between a 2- and 3-year screening interval (lifetime risk 4-6 vs 5-8 per 1000 women) with a 40% increase in number of colposcopies

#### Rationale/Evidence

Lifetime risk (%) of cervical cancer



#### Rationale/Evidence



# Screening Strategies for Women 30 Years & Older: Cotesting

Women ages 30-65

#### Recommendations

- Women ages 30-65 years<sup>\*</sup> should be screened with cytology alone every 3 years. (strong recommendation)
- For women 30-65 years of age with 2 or more consecutive negative cytology results, there is insufficient evidence to support a longer screening interval (i.e. >3 years).
- For women 30-65 years,<sup>\*</sup> there is sufficient evidence to recommend against annual screening. (strong recommendation)

\* For women who are DES exposed, immunocompromised, HIV positive or women who have not been previously screened or who have not been screened per the recommendations above, a different screening interval and/or a different screening strategy (besides cytology only) may be warranted.

## Cancer Antecedents: 136 Women Cotested 6 to 42 Months Prior to Diagnosis

| Cotest Result | Squamous | Nonsquamous | Total Number of Women |
|---------------|----------|-------------|-----------------------|
| Cotest +      | 50       | 46 (72%)    | 96 (71%)              |
| Pap + HPV-    | 9        | 2 (3%)      | 11                    |
| Pap- HPV+     | 14       | 28 (44%)    | 42                    |
| Pap+ HPV+     | 27       | 16 (25%)    | 43                    |
| Cotest -      | 22       | 18 (28%)    | 40 (29%)              |
| Total         | 72       | 64          | 136                   |

Pap neg HPV pos is by far the most important screening diagnosis prior to nonsquamous cancers

Dinkelspiel et al, WAGO Abstract, 2011

#### Why cotesting at 5 year intervals?

CIN3+ Risk Following a Negative Test



Dillner et al., BMJ, 2008

#### Why cotesting at 5 year intervals?

| Source     | Method    | Colpos | Cancers | Deaths |
|------------|-----------|--------|---------|--------|
| Oregon EPC | Q3 Cytol  | 758    | 8.50    | 1.55   |
|            | Q5 Cotest | 626    | 7.07    | 1.29   |
| Mayrand    | Q3 Cytol  | 416    | 8.97    | 1.65   |
|            | Q5 Cotest | 348    | 7.39    | 1.35   |

#### Per thousand, over a lifetime of screening, age 21+

Kulasingam et al: Decision Analysis for the USPSTF

#### Optimal Cytology Screening Intervals Women ages 30-65

Cotesting every 5 years has lower cancer risk and less colposcopies than cytology alone every 3 years:

✓ 3 years after a negative Pap (2003-2005) the risk of invasive cancer in KPNC is .018% (.008 - .041)

✓ 5 years after a negative cotest the risk of cancer is 0.016% (.003-.072)

#### Rationale

Women screening cytology - / HPV + should not go to immediate colposcopy

#### Immediate colposcopy could double the numbers of colposcopy currently done

- Cytology -/ HPV + 3.7%
- Cytology LSIL + 3.8%

Katki et. al. Lancet Oncol 2011

- Risk of CIN 3+ in women with Cytology-/HPV + within 12 months
  - Range 0.8% to 4.1%
  - Below clinical threshold for colposcopy

Kahn JNCI 2005, Wright Am J Clin Pathol 2011

#### Rationale

Cytology negative / HPV positive

HPV 16: Risk of CIN 3+ reaches threshold for colposcopy comparable to ASCCP Guidelines

#### Wright 2011 (ATHENA Study)

- 11.7% CIN 3+
  - Colposcopy within 12 wks
  - HPV 16/18 positive 9.8%
- Kahn JNCI 2005
  - 10% CIN 3+ by 12 months f/u
    - HPV 18 + 12% CIN3+ by 39 months f/u
- Kjaer JNCI 2010 (Age 20-29)
  - 10% CIN 3+ by 4 yrs f/u

#### **Proposed Testing Algorithm**



Cumulative incidence of Cancer by enrollment HPV test and Pap smear



# Screening Following Vaccination

- Currently cervical cancer prevention now includes HPV vaccination.
- Vaccination is likely to dramatically impact the functional characteristics of our current screening strategies.
- Although it is recognized that vaccine coverage in the US remains below target, it remains essential to identify parameters that will need to be met in order to change screening strategies safely.

#### Recommendation

Recommend that there be no change in population based screening practices based on HPV vaccination status

The committee recommends against changing age of screening or interval for the individual woman who has received HPV vaccinations.

## Vaccine efficacy of the bivalent vaccine for CIN3+ in the total vaccinated cohort\*

(irrespective of HPV DNA in lesion)

Vaccine efficacy: 95 – 100%

In HPV-naïve women

Women with <5-6 lifetime sex partners

Women who get all 3 vaccines on schedule

|            | Efficacy             |
|------------|----------------------|
| 15 – 17 yr | 65.5% (42.5 - 80)    |
| 18 – 20 yr | 49.5% (13.9 - 71.2)  |
| 21 – 25 yr | 19.5% (-22.7 - 47.4) |

TVC – received at least 1 dose and were included regardless of DNA or serostatus

Lehtinen M et al, Lancet Oncology 2011

# Estimated HPV Vaccine Coverage, Females 13-17 years

National Immunization Survey-Teen, 2007-2010



CDC. MMWR 2009,2010,2011

Percent

# Predicted reduction in CIN3 among 20- to 29-year-olds after onset of HPV vaccination based on US data



Based on model of Chesson et al (Vaccine 2011) and includes indirect effects (herd immunity). The model assumed 95% efficacy against HPV 16/18, with no cross-protection. HPV 16/18 were assumed to account for 58.6% of CIN3.

WG5: Looking to the FUTURE

# What are the strengths and weaknesses in the studies regarding individual issues?

- Strong evidence that HPV vaccination reduces rates of CIN 3+
- There are no observational or randomized clinical trials in HPV-vaccinated women looking at screening intervals or age of screening initiation.
- Populations in the vaccine studies were closely observed with intensive cytology screening starting at ages 15 or 16 years of age;
- Vaccine trial data based on ITT (TVC) analysis show that reduction in CIN 3+ is far less than those observed in the PP analyses and that abnormalities from all HPV types continue.

Vaccine study data show that vaccinated after infection gives less protection

### **Exiting Women from Screening**

Women Over 65 Recommendation

Women over 65 years of age with evidence of adequate negative prior screening and no history of CIN2+ within the last 20 years should not be screened for cervical cancer with any modality. Once screening is discontinued it should not resume for any reason, even if a woman reports having a new sexual partner.

#### **Exiting Women from Screening**

Women Over 65 Recommendation

- ✓ In well-screened women >65, CIN2+ prevalence is low and cancer is rare
- ✓ Potential for harms outweigh small potential benefit
- ✓ Most new HPV infections in women >65 should clear spontaneously

### **Exiting Women from Screening**

Women who have undergone hysterectomy recommendation

- Women at any age following a hysterectomy with removal of the cervix who have no history of CIN2+ should not be screened for vaginal cancer using any modality.
- Once screening is discontinued it should not resume for any reason, including if a woman reports having a new sexual partner.

#### **Risk Following Incident or Prevalent HPV Infection**



Months since enrollment or since 2nd visit after enrollment HPV-/Pap-

Katki et al, Lancet Oncology 2011

#### Rationale

- Another cohort study in Sweden found increased cervical cancer risk after CIN3 treatment with greater risk for women aged 50 years and older<sup>1</sup>
- Risk of recurrent CIN 2+ and CIN 3+
  - 3.5% and 0.4% respectively in women who had negative cytology screening at 6, 12 and 24 mos;
  - 2.4% and 0.4% in women who were negative for cytological and HPV cotesting at 24 mos

*Strander B, et al Eur J Cancer. 2007;43:1849-185 Kocken M, et al. Lancet Oncol. 2011 May;12(5):441-50.* 

#### Rationale

- Among 5,862 women who had hysterectomy for benign disease only 79 had abnl post surgery vagina cytology (1.1%).
  - Mean time from hysterectomy to abnormal Pap was 19 years.
  - The positive predictive value for detection of vaginal cancer was 0 (95% Cl = 0 to 33%).<sup>1</sup>
- A cross-sectional study of 5,330 vaginal Paps in women after hysterectomy found 1 dysplasia and no cancers.<sup>2</sup>

Pearce KF, et al . NEJM 1996; **335**: 1559–1562. Fox J, et al. Am J Obstet Gynecol 1999; **180**: 1104–1109.

### **Comparison of Guidelines**

|                                    | ACS-ASCCP-ASCP 2012  | USPSTF 2012   |
|------------------------------------|--|---|
| Age to start                       | Age 21   | Age 21  |
| Women ages<br>21-29                | Cytology every 3 years (liquid or<br>conventional) Recommend AGAINST annual<br>Pap   | Cytology every 3 years (liquid or conventional)   |
| Women ages<br>30-65                | Cotesting every 5 years (preferred)<br>or<br>Every 3 years with Pap alone (acceptable)<br>Recommend AGAINST more frequent<br>screening | Cotesting every 5 years<br>or<br>Every 3 years with Pap alone   |
| Women ages<br>>65                  | Discontinue after age 65 if 3 negative Pap<br>tests or 2 negative HPV tests in last 10 years<br>with most recent test in last 5 years  | Discontinue after age 65 if adequate prior<br>screening (3 negative Pap tests or 2 negative HPV<br>tests in last 10 years with most recent test in last<br>5 years) |
| Post-<br>Hysterectomy              | Discontinue if for benign reason   | Discontinue if for benign reason  |
| Screening after<br>HPV vaccination | Same as for unvaccinated   | Same as for unvaccinated  |