

## Human Papillomavirus DNA versus Papanicolaou Screening Tests for Cervical Cancer NEJM, 2007; 357: 1579-1588

### Background

- Cervical cancer is the second most common cancer in women worldwide, despite the fact that screening with cervical cytologic testing (the Papanicolaou test) has been available for over 50 years
- Testing cervical specimens for DNA of high-risk types of HPV has entered clinical practice, but this practice is used mainly to triage for colposcopy those women with Pap smears labeled as ASCUS
- Nonrandomized studies indicate that HPV testing is more sensitive than Pap testing for identifying cervical cancer and its precursors, however there have been no published, randomized, controlled trials comparing HPV testing to Pap testing

### Hypothesis

The authors hypothesize that HPV testing as a stand-alone screening test is more sensitive than Pap testing and therefore is better able to identify cervical cancers and their high-grade precursors.

### Study Design

Study Type: blinded and randomized controlled trial

Setting: 30 clinics in Montreal and St. John's, Canada

Inclusion Criteria: women, ages 30 to 69 years and willingness to sign written informed consent

Exclusion Criteria: hx of cervical lesion, women without a cervix, hx of cervical cancer, women that are pregnant, hx of pap smear within the last year or women that are unable to provide consent

Randomization: Assignment of the tests was done at the coordination center by computer-assisted block randomization stratified according to clinic, with randomly variable block sizes.

Patient characteristics: Randomization produced similar groups. The participants in the Montreal group were slightly younger and less likely to be married than those in the St. John's group. At least 95% of the participants had previously had a Pap smear.

#### Outcomes:

- In this study, a result of ASCUS or AGC, or worse was considered positive in the pap test.
- The hybrid capture 2 test was used for HPV testing. Specimens were considered positive if the ratio of relative light units (RLUs) of the specimen to the mean RLU of positive control triplicates was at least 1 (equivalent to 1 pg of HPV DNA per milliliter).
- High grade (grade 2 or higher) cervical intraepithelial neoplasia is the accepted end point for cervical screening.
- This study differentiated between liberal and conservative definitions. The conservative definition is considered the gold standard because diagnoses are confirmed by the LEEP procedure.

### Results

	CIN2+	CIN-			CIN2+	CIN-	
HPV+	40	515	PPV 7	Pap+	24	242	PPV 8.5
HPV-	1	809	NPV 100	Pap-	17	1082	NPV 99.8
	Sens 97.4	Spec 94.3			Sens 56.4	Spec 97.3	

\*Patient numbers are taken from those who completed verification of disease status

\*Calculations (sensitivity, specificity, PPV, NPV) are estimates corrected for verification bias from combined study groups

### Comments

- HPV testing has a higher sensitivity which may make it a better screening test.
  - o More likely that a patient with cervical cancer will be +, however more false +'s.
  - o More referrals for colposcopy = more expensive
  - o But can this lead to prolonged screening intervals
- Screening must continue even though HPV vaccines are now available
- These data may underestimate the sensitivity of a Pap smear in the U.S. (liquid based cytologic testing).
- Screening algorithms do not decrease sensitivity compared to Pap smear alone, but decrease colposcopy referrals
- Cotesting does not improve sensitivity compared to HPV alone, is not cost effective, and leads to increased colposcopy referrals.

