PAP + HPV CO-TESTING INCREASES CERVICAL CANCER DETECTION

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Clinical Background

Pap + HPV co-testing has been shown to be a useful and successful approach to reduce the incidence of cervical intraepithelial neoplasia grade 3 and cancer (CIN3+) and has thus been integrated into the 2012 screening guidelines for cervical cancer. As a quick reminder of traditional cervical screening guidelines, cervical cancer screening is not recommended for women under the age of 21 and Pap testing alone is recommended for women between the ages of 21 to 29, at three-year intervals. As a result of the high rate of transient HPV infection in this population, the 2012 guideline recommends that HPV testing not be used to screen this population, except as a reflex testing for atypical squamous cells of undetermined significance (ASCUS) Pap tests. In women between the ages of 30 and 65 years, Pap testing alone, at three-year intervals, is an acceptable option while Pap + HPV co-testing at five-year intervals is the preferred mode of screening.

In 2014, the United States Food and Drug Administration (FDA) approved the first assay to be used as a first-line primary cervical cancer screening to detect high risk HPV in women 25 years of age or older. Approval was based on results from the Addressing THE Need for Advanced HPV Diagnosis (ATHENA) observational clinical trial, which assessed HPV-alone screening in 42,209 women. In 2015, the largest retrospective analysis of cervical cancer screening was published, and is referred to as The Quest Study. The study correlated cervical pathology with Quest's antecedent screening results in more than a quarter of a million women. Findings demonstrated that screening with Pap + HPV co-testing detected CIN3 and, more importantly, invasive cervical cancer more reliably than HPV-alone screening. The authors suggested that abandoning co-testing in favor of HPV-alone screening would result in the failure to diagnose 2,400 women with cervical cancer (out of approximately 12,400 women diagnosed with cervical cancer each year). The study emphasized that Pap + HPV co-testing was the most sensitive method currently available for detecting cervical cancer and its precursors.

A Real-World Look at Cervical Cancer Screening

Researchers at Quest Diagnostics and the University of Pittsburgh Medical Center conducted a retrospective, cross-sectional analysis comparing three screening approaches for cervical cancer: Pap-alone, HPV-alone, and Pap + HPV co-testing. The researchers assessed cervical biopsy results from 256,648 women aged 30-65, who had co-testing performed within 1 year prior to cervical biopsy. The HPV assessment was conducted using the Digene Hybrid Capture 2 HPV DNA-based test (HC2) (Qiagen). The HC2 and other HPV DNA-based tests have shown comparability in several different studies. In the study, the investigators analyzed the respective contributions of Pap-alone, HPV-alone, and Pap + HPV co-testing screening to CIN3 and invasive cervical cancer.

Of the 526 women with confirmed cervical cancer, 18.6% tested negative for HPV during the prior year; 12.2% had a negative Pap test result; and 5.5% had a negative Pap + HPV co-test result (Figure 1). Of 526 Pap samples, 12 were unevaluable. These findings suggest that up to 19% of women with cancer may be falsely reassured by a negative HPV-alone screening result. In addition, screening with Pap + HPV co-testing identified 70% of cancers missed by HPV-alone screening. These results were even more pronounced in the 169 women in the study with cervical adenocarcinoma, a carcinoma that is often difficult to detect with screening: 26.6% tested negative with HPV; 20.7% had a normal Pap, and 8.3% tested negative with the Pap + HPV co-test.

The investigators also analyzed the ability of these three screening approaches to detect CIN3+. In this analysis, a positive Pap + HPV co-test result was found to
detect 98.8% of CIN3+ cases, compared with 94% for HPV-alone screening, and 91.3% for Pap-alone screening. The authors suggest that although HPV-alone testing is more sensitive than Pap-alone testing in the detection of CIN in general, some high-grade lesions and especially cervical cancers have lower HPV viral loads than more differentiated, lower-grade lesions. In some patients, this lower viral load may be below the detection threshold of HPV DNA-based tests. Similarly, older women and women with adenocarcinoma also have lower HPV viral loads. This may explain why Pap testing and co-testing detected more cases of invasive cancer than HPV-alone testing and why co-testing detected more cases of CIN3+ than HPV-alone testing. A possible limitation of the study is that it only included women who had both co-testing and biopsy results in the Quest system. However, the combination of the large number of women represented in the study, as well as the large number of cancers detected, point to the robust nature of the data.

Conclusions
The findings from the study are compelling because of the large, real-world population that emphasizes the unique relevance of the Quest Study to clinical practice. In clinical practice, the most important aspects of cervical cancer screening are the detection of high-grade lesions (and especially invasive cervical cancer) and the reassurance provided by a negative test. Although early detection and the ability to extend the screening interval following a negative screening test are important benefits of HPV-alone testing, they are secondary to the detection of high-grade lesions and invasive cervical cancer. By this measure, the combination of Pap + HPV co-testing provides the greatest reassurance following a negative test, and the greatest sensitivity in detecting high-grade cervical lesions (CIN3+ and cervical cancer). As women and their providers reluctantly begin to adjust to the lengthening of screening guideline intervals, the Quest Study reinforces the greater reassurance provided by Pap + HPV co-testing.12

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References
**THE QUEST STUDY:**

**Screening with HPV alone misses more cervical cancer.**

There is serious debate about how best to screen for cervical cancer today. Now, the largest retrospective study ever affirms that women’s lives are at risk if HPV alone screening is used.

| 1 in 5 Women with cervical cancer missed by screening with HPV alone. |

| 18.6% cancers missed by HPV alone. |

| 12.2% cancers missed by Pap alone. |

| 5.5% cancers missed by Pap+HPV. |

**WHY PAP+HPV IS PREFERRED:**

- **70%** Pap-HPV Together™ (co-testing) identified 70% of cancers missed by screening with HPV alone.

**ABOUT STUDY:**

- **>8.6 MILLION WOMEN** ages 30-65 received Pap+HPV screening.

- **256,648 WOMEN** then received cervical cancer biopsy based on screening results.

- **526 WOMEN** of that group were found to have biopsy-confirmed cervical cancer.

- **65X MORE CANCER CASES** than the clinical trial which led to FDA-approval of HPV alone screening.

**SCREENING METHODS BY AGE:**

- **PAP ALONE:**
  - **AGE**: 21-29

- **PAP+HPV:**
  - **AGE**: 30-65

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“...HPV-only testing would tragically miss many cervical cancers...”

- Dr. Marshall Austin

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* A positive HPV screening result may lead to further evaluation with cytology and/or colposcopy.

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