HPV Testing Outperforms Pap Test for Detecting Precancerous Lesions in Large Trial

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NEW YORK (GenomeWeb) – Cervical cancer screening using human papillomavirus (HPV) testing leads to significantly fewer high-grade cervical pathologies four years later than standard liquid-based cytology (LBC) screening, according to a randomized trial of approximately 19,000 Canadian women.

Described today in *The Journal of the American Medical Association*, 48-month follow-up results from the Human Papillomavirus For Cervical Cancer screening trial, called HPV FOCAL, also showed that HPV testing detected precancerous lesions earlier and more accurately than LBC, also known as the Pap test.

Specifically, the incidence of cervical intraepithelial neoplasia of grade 3 or higher (CIN3+) four years after initial screening was 2.3 per 1,000 women among those randomized to receive HPV testing, while it was 5.5 per 1,000 women among those tested by LCB.

HPV infection causes nearly all cases of cervical cancer, which is the fourth most common cause of cancer in women globally, with 527,600 cases and 265,700 deaths reported in 2012. These numbers have since been declining due to screening programs and vaccinations. But although cervical cancer rates in the US declined by half between 1975 and 2014 due primarily to widespread Pap screening, the American Cancer Society anticipates 13,240 new cases of cervical cancer and 4,170 deaths in the US this year.

HPV FOCAL began about a decade ago and involves 224 collaborating clinicians in British Columbia. Participants were women ages 25 to 65, with a mean age of 45 years old. In the trial, researchers affiliated with the University of British Columbia, the British Columbia Centre for Disease Control, and six other labs and research centers sought to establish the efficacy of HPV testing as a standalone screening test with cytology triage of HPV positive women, as well as to determine the appropriate screening interval for women who test negative for HPV and the overall cost-effectiveness of HPV testing as a primary screening test.

The trial has already yielded eight publications, including a study evaluating the effect of screening methods on CIN grade 2 or higher and an evaluations of women's interest in self-

collection of specimens.

In the latest *JAMA* study, the authors wrote that overall, "primary HPV testing detected significantly more CIN3+ and CIN2+ cases in the first round and significantly reduced CIN3+ and CIN2+ rates 48 months later," as well as "confirmed that women who were HPV negative at baseline have lower rates of CIN2+ at 48 months than cytology-negative women at baseline."

An accompanying editorial by Stewart Massad, a professor of obstetrics and gynecology at the Washington University School of Medicine in St Louis, noted that the study completed recruitment in 2012, but that HPV vaccination was introduced in 2006 and has subsequently reduced the prevalence of HPV 16 and HPV 18, the most carcinogenic HPV types, as well as the prevalence of cervical precancers.

"This reduction is becoming more apparent as women who were adolescents at vaccination and at the time the study was launched are now aging into screening cohorts. Lower prevalence of cervical precancer has changed the accuracy of screening tests in ways that are only now being appreciated but that will further favor adoption of primary HPV screening by lowering its false-positive rate," according to the editorial.

Furthermore, the Qiagen Digene Hybrid Capture 2 High-Risk HPV DNA test (HC2) test that was used in the trial incorporates all carcinogenic HPV types in a single, pooled, positive or negative result, another potential limitation, according to the editorial, since detailed genotyping might allow for "nuanced risk stratification," including immediate referral to colposcopy for women who screen positive for HPV 16 or HPV 18.

Molecular tests for HPV that have been cleared by the US Food and Drug Administration include the HC2 and Roche Cobas tests, as well as assays from Gen-Probe and Hologic. The BD Onclarity HPV assay from Becton Dickinson, which detects 14 high-risk genotypes, was cleared earlier this year. All five available tests are cleared for use in co-testing scenarios, but only the Roche assay is also cleared for use as a standalone screening test.

The HPV FOCAL study data will likely now add to the body of evidence being considered by organizations that develop cancer screening guidelines, which are currently "wrestling with whether to recommend replacing co-testing with primary HPV testing as the optimal screening strategy," the editorial noted.

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