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Technology matters: The clinical utility of HPV mRNA testing compared to DNA testing

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The importance of HPV testing for cervical cancer screening

Cervical cancer, historically the most common gynecologic cancer and a leading cause of cancer death among women in the United States, has decreased dramatically in incidence and mortality over the past few decades, in large part due to developments in screening. While Papanicolaou (Pap) smear testing was once the only method of cervical cancer screening, advances in technologies using human papillomavirus (HPV) detection have led to additional options.[1] To reflect the new capabilities of HPV testing, screening guidelines were updated by the American Cancer Society, the American Society for Colposcopy and Cervical Pathology, and the American Society for Clinical Pathology in 2011. Then in 2014, an HPV DNA test for primary screening was approved by the US Food and Drug Administration for women over 25 years of age.[1] Currently, the American College of Obstetricians and Gynecologists advises that women between the ages of 30 and 65 should be screened by Pap smear every 3 years or Pap and HPV testing every 5 years.[1]

If HPV screening alone is used, however, it should not be performed in women under the age of 25, and if negative, should be repeated no sooner than every 3 years.[1]

Along with these updated guidelines, the methods by which HPV is detected continue to evolve. HPV DNA tests, developed first, detect any HPV present in the cell whether the virus is active or latent.[2-4] Newer modalities that detect HPV mRNA, rather than DNA, detect only active infections. Once the HPV virus integrates into the host genome, becoming an active infection, the host cell produces HPV mRNA and HPV proteins.[2-4] Therefore, HPV mRNA testing methods are most likely to lead to identification of clinically-relevant disease.

However, as screening methods continue to advance, confusion has arisen surrounding the roles of these various methods and applications in clinical practice. In particular, clinicians have many questions regarding the HPV virus, its role in cervical cancer, and the clinical utility of HPV mRNA testing compared to traditional DNA testing.

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How does HPV lead to the development of cervical cancer?

HPV is the most common sexually transmitted disease, infecting over 80 percent of sexually-active women at least once in their lifetime.[5] High-risk HPV (hrHPV) genotypes, which are the focus of this article, have a prevalence of 20.4 percent in women aged 18 to 59 and are responsible for the majority of cervical cancers.[6,7] In fact, two hrHPV genotypes in particular, HPV16 and HPV18, are collectively responsible for over 70 percent of cervical cancers worldwide.[1,8,9]

To cause neoplastic cervical disease, HPV, a double-stranded DNA virus, first enters cervical epithelial cells. Upon entering, the virus can either stay in its free episomal form or linearize and integrate into the DNA of the host cell.[10,11] Following integration, HPV causes the malignant transformation of cervical cells via expression of two oncogenic proteins: E6 and E7.[9] E6 regulates degradation of tumor suppressor protein p53, which under normal conditions regulates cell growth and enables DNA repair enzymes to mend chromosomal damage.[11-13] E7 inhibits the retinoblastoma (Rb) protein, another important regulator of the cell cycle.[11,13] When p53 and Rb are inactivated, chromosomal mutations and uncontrolled growth occur.[11-13]

E6 and E7 not only cause damage individually, but they also have a synergistic effect that transforms the HPV-infected cell into a precancerous cell.[13] This process is typically slow, with progression of a high-grade lesion to cervical cancer taking approximately 10 years.[8]

How do HPV assays correlate with the life cycle of HPV infection?

The detection of HPV DNA signifies the presence of the virus but not necessarily a clinically-relevant infection that will progress to cervical cancer. A positive HPV DNA assay indicates that the virus is present in the cell but does not distinguish between active disease versus a latent infection or a recent infection that is likely to be cleared by the immune system.[2-4]

Even if HPV infects the cervical epithelial cells, the infection often resolves spontaneously. Up to 70 percent of HPV infections regress on their own.[14-16] Regression is more likely with lower grade lesions and those that do not integrate into the host genome.[15,16] In cases where cervical dysplasia progresses, however, spontaneous resolution is less likely. Among cervical intraepithelial neoplasia (CIN)2 lesions, 40 percent regress within 2 years, and regression becomes even less likely for CIN3.[17,18] Once the HPV DNA integrates into the genome, the host cell begins to produce HPV mRNA and HPV proteins.[2-4] Typically, the more severe the lesion, the higher number of E6 and E7 mRNA copies are present.[2,3,4,17] The FDA-approved Aptima HPV assay detects the presence of E6 and E7 mRNA, indicating an active and therefore potentially oncogenic infection.[2-4]

How does performance compare for HPV DNA and mRNA tests?

Six HPV tests are currently approved for cervical cancer screening by the FDA.[18,19] Five of those detect HPV DNA: the Hybrid Capture 2 High-Risk DNA test (Qiagen), Cervista HPV High-Risk DNA test (Hologic), Cobas 4500 PCR test (Roche), Digene HC2 HPV DNA test (Qiagen), and Onclarity HPV Assay (Becton Dickinson). Aptima, Hybrid Capture 2, Cervista, and Cobas each detect 14 hrHPV types, while Digene detects 13 hrHPV types.[18] Onclarity (Becton Dickinson), which was recently approved by the FDA in February 2018, detects 14 types of hrHPV.[19] The Aptima HPV assay is the only FDA-approved test that detects HPV mRNA, and detects 14 hrHPV types.[18]

Numerous clinical trials have demonstrated similar sensitivity among the various HPV detection assays.[1,20] In most studies, sensitivity is well over 90 percent, reaching 99 percent in some trials, indicating that false negatives are rare.[21-42]

While all of the FDA-approved tests are highly sensitive for detecting CIN2+, mRNA testing is the most specific for detecting biopsy-confirmed CIN3+. A positive result from a test with high specificity confers an improved level of confidence in detecting meaningful cervical lesions while minimizing false positives. As such, the high specificity of the Aptima assay confers the lowest rate of false-positive results compared to other commercially-available, FDA-approved assays.[43-45]

The largest trial performed on the Aptima HPV mRNA test to date is the CLEAR trial, consisting of over 11,000 women.[21] The CLEAR study consisted of two arms: women with atypical squamous cells of undetermined significance (ASCUS; referral population) and women negative for intraepithelial malignancy (NILM; screening population) on routine cytology screening.[21] All women in the ASCUS arm were referred for colposcopy—regardless of HPV status—while in the NILM arm, only women with a positive Aptima HPV result were referred. The study revealed that Aptima had similar sensitivity and superior specificity when compared to FDA-approved DNA testing mechanisms for the detection of CIN2 and CIN3.[21]

These findings have been confirmed in numerous additional trials. As shown in the following graphs, Aptima HPV mRNA testing has consistently shown equal sensitivity and superior specificity when compared to HPV DNA testing assays.[21-42] Table 1 shows a summary of individual head-to-head studies assessing sensitivity for biopsy-confirmed CIN3+, while Table 2 shows the comparative specificity for biopsy-confirmed CIN2+ for HPV DNA and mRNA assays.

Table 1: High-Risk HPV Tests and Clinical Sensitivity for CIN3+

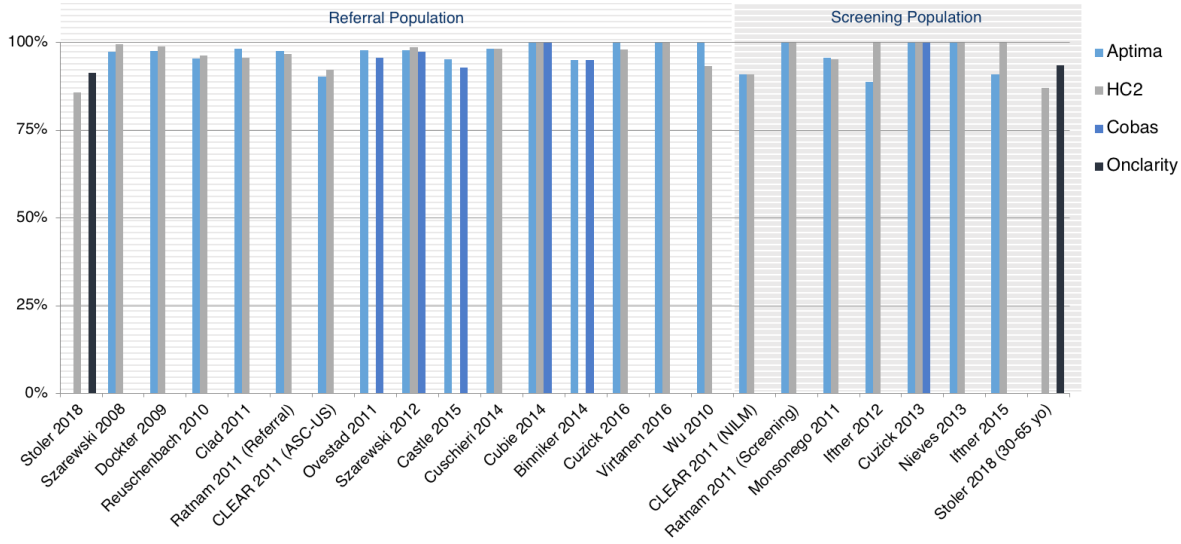
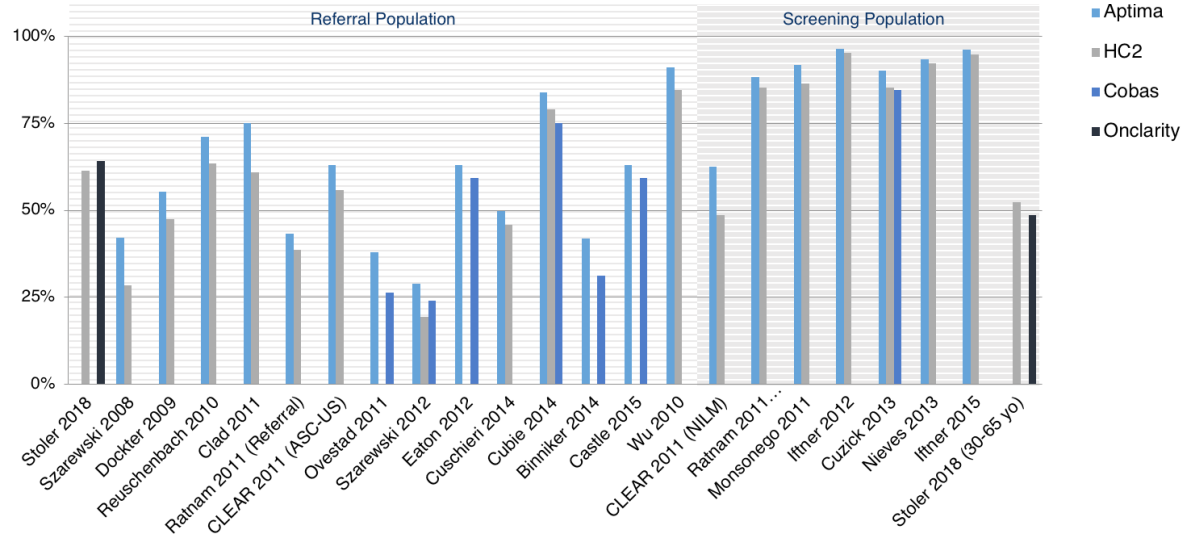


Table 2: High-Risk HPV Tests and Clinical Specificity for CIN2+



What is the clinical significance of detecting only active infections?

To illustrate the benefits of HPV mRNA testing, consider the cases of Lin and Corrine.

Case #1: Lin undergoes HPV DNA testing

Lin presents as a new patient for an annual well-woman examination. She is 30 years old with regular menses and has no complaints or concerns. She uses oral contraceptives for birth control and is in a long-term monogamous relationship.

At her examination, she has a Pap test with concurrent HPV testing performed; the laboratory uses DNA testing for HPV. The Pap is normal, but the DNA test is positive for HPV, and genotyping reveals that she is positive for HPV16. Per current guidelines, her OB/GYN schedules her for a colposcopy.

Lin experiences a lot of anxiety regarding the procedure. She also accuses her fiancé of infidelity since she has a positive HPV test, and she knows that HPV is sexually transmitted.

After the procedure, she has an abnormal amount of bleeding and requires extensive application of Monsel's solution and pressure. She experiences a distressing amount of foul-smelling, coffee ground discharge for a week and is placed on pelvic rest until the lesion heals. Lin reports feeling "dirty" and "infected," and she continues to experience distress while awaiting her diagnosis, which affects her sleep and her relationship. Ultimately her biopsy comes back as CIN1, and Lin does not require additional treatment. Her positive HPV test is thus considered "false positive" since it does not correlate with clinically-relevant disease.

Case #2: Corrine undergoes HPV mRNA testing

Now, consider the case of Corrine, also visiting her OB/GYN for cervical cancer screening. In this case, the doctor sends Corrine's Pap sample to a laboratory that performs an HPV mRNA test on the residual sample. Her HPV mRNA assay, which detects E6 and E7 mRNA present in active infections, comes back negative, providing reassurance that Corrine is unlikely to harbor serious cervical disease (CIN2+). Corrine continues her daily life activities and does not undergo additional invasive testing; she returns to her OB/GYN 5 years later for routine co-testing.

Significance of false-positive cervical cancer screening

Although colposcopy is thought to be a safe and relatively harmless procedure, it can lead to complications. Minor adverse events including pain, bleeding, or discharge occur in up to 82 percent of women.[46] Although uncommon, excessive bleeding or infection can occur, and other rare complications such as acetic acid burns to the vagina or cervix have also been reported in literature.[47]

Just as important, abnormal screening tests and colposcopies can lead to patient anxiety and reduced quality of life.[46,48] Many women report experiencing sadness, intrusive thoughts, and high levels of anger after an abnormal cervical screening test.[48] In fact, up to 90 percent of women report fear and worry, 67 percent report depression, 44 percent report poor concentration, and 29 percent report sleep disturbances once they are diagnosed with a cervical abnormality.[49] The anxiety is related not only to the procedure itself, but the implications of that procedure.[49] After colposcopy, 40 percent of patients report worries about having cancer, while 24 percent worry about fertility and 60 percent worry about their general health.[50]

Negative body image and sexual function are also consequences of colposcopy. A randomized controlled trial revealed that patients undergoing colposcopy had decreased sexual interest, decreased frequency of intercourse, and decreased arousal compared to controls.[49] Nineteen percent of women stated that their sex lives were adversely affected by the procedure, and up to 14 percent of women reported negative impacts to their sex lives for up to 9 months afterwards.[51]

Will precancerous lesions be missed with HPV mRNA testing?

Data from numerous clinical trials have demonstrated that the Aptima HPV mRNA assay has equal sensitivity to the DNA-based assays for detecting moderate to severe cervical dysplasia, but with the added benefit of increased specificity.[21-41] Additionally, the risk of CIN3+ developing over 5 years after an initial baseline negative HPV mRNA test remains low.[25,41,52,53]

A large study of 342 women with ASCUS and LSIL showed that screening with the Aptima HPV mRNA assay achieved high long-term sensitivity in predicting future cervical dysplasia.[52] In this trial, no mRNA HPV-negative women developed CIN3 over 4.5 years.[52] Cubie et al followed patients for 1 year and found that the Aptima HPV mRNA assay detected all cases of CIN3, while achieving sensitivity similar to DNA assays for CIN 2+.[25]

Waldstrom et al also demonstrated sustained sensitivity for mRNA HPV testing, reporting a sensitivity above 95 percent over 3 years.[41] Most recently, the FOCAL trial demonstrated that over a 4-year period, Aptima HPV testing had an equal sensitivity and superior sensitivity when compared to Hybrid Capture DNA testing.[53]

Overall, these studies show that Aptima yields reassuring results as a cervical cancer screening test over the long term.

Conclusion

Based on multiple clinical trials, HPV mRNA testing predicts the development of moderate to severe cervical dysplasia with similar sensitivity and improved specificity compared to HPV DNA testing methods. By utilizing mRNA testing, care paradigms can shift more selectively toward patients with active, oncogenic infections, and false-positive testing and unnecessary procedures can be avoided. This, in turn, can improve quality of life and treatment planning for these patients.

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