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REVIEW ARTICLE

A review of the FDA-approved molecular testing platforms for *human papillomavirus*

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Review

Abstract The advent of US Food and Drug Administration (FDA)-approved molecular testing for *human papillomavirus* (HPV) has resulted in a dramatic shift from cytological testing alone to a combination of cytology and molecular testing for primary HPV screening. HPV testing has quickly become an essential component of daily practice in most laboratories and clinical practices. Although the principle of HPV testing is now familiar, it is important to understand the mechanisms behind these platforms in order to properly interpret the results and understand the limits of each method. HPV tests are more automated and reproducible than cytology, but are by no means perfect. None of these platforms will identify every HSIL/CIN2+ or cancer. This fact must be kept in mind when correlating the results of HPV testing with cytology or biopsy findings. The goal of this paper is to review the FDA- approved molecular testing platforms for HPV, including methodology, limitations, and specifications. The concordance between the platforms will also be discussed. Package inserts of the 5 FDA- approved molecular testing platforms for HPV, as well as a literature review of the platforms, were reviewed and assimilated into the article. Due to the multiple modalities available for detection of hrHPV, the concordance between these assays becomes important. Prior publications have compared HC2, Cervista, cobas, and Aptima, with most studies comparing to HC2 because it is considered the reference standard. With the newly approved BD platform, concordance studies were reviewed as well.

Contents

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Introduction

In the past 2 decades, the field of medicine has experienced a dramatic shift with the utilization of molecular testing platforms, ranging from the rapid identification of infectious organisms to specific gene targeting mutations in malignancies. The practice of genomic medicine has entrenched itself into everyday practice; nevertheless, the understanding of the available testing modalities is not widespread throughout the medical community.

One of the most well-known and widespread applications of such testing is for the detection of the *human papillomavirus* (HPV) in gynecological cytology specimens. With the American Cancer Society incorporating HPV testing into their cervical cancer screening guidelines, the need for molecular testing modalities to be available to all clinicians and patient populations became essential.

Since 2001, the US Food and Drug Administration (FDA) has approved 5 testing modalities for the detection of HPV in cytological specimens: Hybrid Capture 2 HPV DNA test by Qiagen (Hilden, Germany, 2001), Cervista HPV HR test by Hologic (Marlborough, Massachusetts, 2009), cobas 4800 HPV test by Roche (Basel, Switzerland, 2011), the Aptima HPV assay by Gen Probe (San Diego, California, 2011, purchased by Hologic in 2012), and BD Onclarity HPV assay by Becton Dickinson (Franklin Lakes, New Jersey, 2018).

Multiple studies have researched the sensitivity and specificity of HPV testing compared with HPV cytology and have found that HPV testing is more sensitive in detecting high-grade squamous intraepithelial lesion/cervical intraepithelial neoplasia grade 2 and above (HSIL/CIN2+) in all ages, but cytology has a higher specificity.[1] The studies were conducted in both Europe and North America and support the use of HPV testing as a primary screening tool. In women younger than 30 years, screening with HPV testing results in large numbers of positive results and increases the need for additional testing.[2] Cytology, along with the supplement of molecular testing, can improve both sensitivity and specificity and decrease false negative reporting.

This review aims to give an overview of the 5 FDA approved tests and discuss limitations of the current testing platforms.

Human papillomavirus

HPV is the most common sexually transmitted infection in the United States and has malignant transformation potential, especially in the cervix, anogenital region, and head and neck sites.

HPV is a non-enveloped, double-stranded DNA virus with over 200 known genotypes. The 14 most clinically relevant high-risk types include (in order of worldwide frequency): 16, 18, 58, 33, 45, 31, 52, 35, 59, 39, 51, 56, 66, and 68. The key genes involved in the pathogenesis of the virus include *L1* (viral capsid), *E6*, and *E7*. The *E6* and *E7* genes work by inhibiting apoptosis and enhancing viral propagation by inhibiting Rb, p53, and p21, causing an accumulation of p16 in infected cells. Expression of viral *E6* and *E7* oncogene mRNA is highly associated with squamous intraepithelial lesion (SIL) development[3,4] and is necessary and sufficient for cell immortalization, neoplastic transformation, and development of invasive cancer.[3-7] It should also be noted that the presence of hrHPV genomic DNA in the female genital tract is common and can be transient in nature[8,9]; most cervical HPV infections resolve without developing carcinoma.[10,11]

HPV molecular testing platforms

The 5 testing platforms will now be described. Table 1 compiles the information in tabular form.

Hybrid Capture 2 HPV DNA test by Qiagen

The Hybrid Capture 2 (HC2) HPV DNA test by Qiagen was first approved in 2001 by the FDA for use with ThinPrep specimens. This nucleic acid hybridization assay uses signal amplification for the qualitative detection of 13 hrHPV DNA strains in cervical specimens.

The cervical specimen types that are approved for use with the HC2 system include DNAPap Cervical Sampler, HC Cervical Sampler, broom-type collection devices placed in Cytyc PreservCyt Solution, TriPath Imaging SurePath Preservative fluid, or Specimen Transport Medium. The use of SurePath medium has been reported to interfere with DNA-

Table 1 Comparison of the 5 FDA-approved testing platforms.

Test	Hybrid Capture II	Cervista	cobas	Aptima	BD Onclarity
Manufacturer	Qiagen	Hologic	Roche	Gen Probe (Hologic)	Becton Dickinson
Year FDA approved for reflex HPV testing and HPV/Papanicolaou co-testing	2001	2009	2011	2011	2018
Year approved for primary screening	N/A	N/A	2014 (ThinPrep only)	N/A	2018 (SurePath only)
Method	DNA (non-PCR based) Signal amplification: full genome probe	DNA (non-PCR based) Signal amplification: L1, E6, and E7 genes	DNA (PCR based); Target amplification: L1 gene target	mRNA (PCR based); Target amplification: *E6/E7* gene target	DNA (PCR based); Target amplification: *E6/E7* gene target
Genotypes detected	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68 with genotyping of 16 and 18	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68; genotyping as separate test (16, 18/45)	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68; simultaneous, discrete identification of 16, 18, and 45
Clinical trial	ASC-US/LSIL Triage Study (ALTS), 2006 CAP	Cervista HPV HR	ATHENA[12]	CLEAR trial	Onclarity trial (baseline phase)[13]
Clinical validation	Extensive	Limited	Limited	Limited	Limited
Sensitivity for CIN2/3	63.6%-100%[2,14-24]	92.8%-100%[25]	71.1%-99%[2,15-21,26]	55.3%-100%[2,14,17-20,22-24,26-30]	85.7%-100%[18,31-33]
Specificity for CIN2/3	6.2%-98.4%[2,14-24]	–	24%-86.2%[2,15-21,26]	28.8%-99.2%[2,14,17-20,22-24,26-30]	17%-98.8%[18,31-34]
Built-in internal control	No	Yes (HIST2H2BE)	Yes (ß-globin)	Yes, an internal control transcript (HPV16 E6/7 transcript) is added to each reaction at the target capture step	Yes (ß-globin)

Abbreviations: N/A, not applicable; PCR, polymerase chain reaction.

based HPV tests including HC2[35]; however, other studies have shown HC2 positive rates and CIN2+ detection rates were comparable for ThinPrep and SurePath collection systems[36] and the use of HC2 with SurePath is a clinically valid method.[37] It should be noted that SurePath specimens require sample conversion prior to testing with this assay.

Multiple studies have reported cross-reactivity with these HPV types: 6, 11, 26, 34, 40, 42, 53, 54, 55, 61, 66, 67, 70, 71, 72, 73, 81, 82, and 84.[38-45] Some of these, such as type 66, have significant carcinogenic potential, but many do not. In a large primary screening cohort of 2859 Danish women ranging in age from 30 to 65 years, the proportion of positive test results in women with biopsy follow-up that showed less than CIN2+ that was attributable to cross-reactivity was 25% for HC2.[44] The consequence of this cross-reactivity will depend on the region's relative prevalence of each HPV type.

The effects of blood, douching liquid, anti-fungal cream, and contraceptive jelly were tested in all specimen types with positive and negative controls. No false positives were observed in Specimen Transport Medium specimens; however, false-negative results occurred in the presence of high levels of anti-fungal cream or contraceptive jelly. No false-positive or false-negative results were observed with any of the 4 agents using the PreservCyt solution. The lack of an internal control in the HC2 test means that false-negative results due to these factors are reported as negative rather than as test failures.

Limitations include:

- Cross-reactivity with many low-risk HPV types
- Low levels of HPV infection can result in false-negative results
- DNAPap/HC Cervical sampler should not be used for pregnant women[31]
- High concentrations of anti-fungal cream, contraceptive jelly, or douche may cause false-negative results if DNA levels are near the assay cutoff[31]
- Cross-reactivity with the bacterial plasmid pBR322 may give false positive results[31]
- If no pellet is observed after centrifugation, the amount of cellular material may not be sufficient, possibly resulting in a false-negative result[31]
- PreservCyt Solution specimens containing less than 4 mL after the ThinPrep slides are prepared are considered inadequate[31]

Cervista HPV HR test by Hologic

The Cervista HPV HR test by Hologic was first approved in 2009 by the FDA for use with ThinPrep specimens. This assay uses signal amplification for detection of specific nucleic acid sequences targeting the *L1*, *E6*, and *E7* genes. The test targets 14 hrHPV types. The test cannot determine the specific HPV type present and cannot evaluate for the persistence of any specific type. However, a separate test is available to identify types 16 and 18. Glacial acetic acid treatment has a deleterious effect on Cervista performance.[46] The approved cervical specimens, preservation system collection media, and collection devices that may be tested with the Cervista HPV HR test include ThinPrep Pap Test PreservCyt Solution and Rovers Cervex Brush, Wallach Papette, or endocervical brush/spatula.[47]

Limitations include:

- Test exhibits cross-reactivity to 2 HPV types of unknown risk (HPV types 67 and 70)[47]
- Performance has not been adequately established for HPV-vaccinated individuals[47]
- Interference was observed in cervical specimens contaminated with high levels (2%) of contraceptive jelly and/or anti-fungal creams; false-negative results may be obtained under these circumstances[47]
- PreservCyt Solution specimens containing volumes less than 2 mL after the ThinPrep Pap test slides are prepared are considered inadequate[47]
- High levels of human DNA may create non-specific signal resulting in false-positive results[48]

Cobas 4800 HPV test by Roche

The cobas HPV Test is a qualitative test that amplifies target L1 DNA by PCR and nucleic acid hybridization for the detection of 14 hrHPV types. The test specifically identifies HPV 16 and 18 without the need for a separate test.

Roche cobas was originally approved in 2011 for use on ThinPrep specimens. In 2016, the FDA approved this assay for SurePath specimens as well. This test has been approved for primary screening in women aged 25 years and older, but only for ThinPrep. Acceptable specimens for testing in conjunction with cytology include ThinPrep PreservCyt vials with collection by an endocervical brush/spatula or a cervical broom specimen placed in SurePath Preservative Fluid.[49]

Unlike HC2, which has been in clinical use for many years and has therefore had many of its limitations exposed, the cobas test has only been on the market a relatively short time. Already, however, there are indications that the test may have previously unsuspected limitations. A recent large retrospective study performed by Zhou et al. of 253 cases with follow-up confirmation of CIN2+ following cytology and cobas testing showed that 8.7% of the CIN2+ lesions were preceded by negative HPV results.[50] Because the test is being used for primary screening, false-negative results are of paramount importance. The study from Denmark mentioned in the HC2 section also analyzed cross-reactivity in the cobas test. The authors found cross-reactivity to types 61 and 70, accounting for 26% of the cases that did not show CIN2+ in follow-up, comparable to the percentage for HC2.[44]

Limitations include:

- Performance of the test has not been adequately established in HPV-vaccinated women[49]

- Effects of other potential variables including vaginal discharge, use of tampons, or douching have not been evaluated[49]
- Has not been validated for specimens that have been previously treated with glacial acetic acid[49]
- Concentrations of whole blood in the vial exceeding 1.5% in ThinPrep PreservCyt or 2% in SurePath Preservative fluid (dark red or brown in color) may cause a false-negative result[49]
- Cross-contamination can cause false-positive results; the cross-contamination rate in a non-clinical study was 0.71% for the cobas 4800 system[49]
- The β-globin internal control is not epithelial-cell specific, meaning that there can be a positive control due to inflammatory cells despite low numbers of epithelial cells

Aptima HPV assay by Gen Probe/Hologic

The Aptima HPV Assay, approved by the FDA in 2011 for use with ThinPrep specimens, is a nucleic acid amplification test for the qualitative detection of E6/E7 viral messenger RNA (mRNA) from 14 hrHPV types. This test does not include genotyping. However, a separate test can be performed to identify types 16 and 18/45.

Approved collection devices and solutions include ThinPrep Pap Test vials containing PreservCyt Solution or the Aptima Cervical Specimen Collection and Transport Kit.[32] The Aptima test is designed to be less sensitive than the Roche cobas test, but more specific for HSIL/CIN2+. By targeting messenger RNA rather than DNA, the test aims to identify only transcriptionally active virus. This means that positive results are more likely to reflect the presence of squamous intraepithelial lesions because inactive viral DNA incorporated into cells but not driving viral replication will not be detected.

Like the Roche cobas test, Aptima has been fairly recently introduced. This means that it has undergone much less evaluation in clinical practice than HC2. Therefore, it is likely that there are test limitations that are still unknown or poorly understood. The Danish study by Preisler et al. examined Aptima in addition to HC2 and Roche cobas. For Aptima, cross-reactivity was seen to types 26, 61, 62, 67, 70, 82, and 83. Twenty-one percent of the cases that did not show CIN2+ on follow-up were attributed to this cross-reactivity.[44] Cross-reactivity to types 26, 67, 70, and 82 was also seen in testing of the assay performed during development.[32]

Limitations include:

- Non-cervical specimen types have not been evaluated[32]
- Performance has not been evaluated for HPV-vaccinated individuals[32]
- Personal lubricants that contain polyquaternium 15 may interfere with the performance of the assay when present at concentrations greater than 0.025% (v/v or w/v) of a test sample[32]
- Anti-fungal medications that contain tioconazole may interfere with the performance of the assay when present at concentrations greater than 0.075% (w/v) of a test sample[32]
- The effects of other potential variables such as vaginal discharge, use of tampons, douching, and so on, and specimen collection variables have not been evaluated[32]
- Cross-contamination of samples can cause false-positive results; the carry-over rate of the Aptima HPV Assay on the Tigris DTS System and the Panther System was 0.7% and 0.4% respectively, as determined in non-clinical studies[32]

BD Onclarity HPV assay by Becton Dickinson

The BD Onclarity HPV Assay was most recently FDA approved in early 2018. The fully automated assay utilizes target amplification of DNA by real-time PCR and nucleic acid hybridization for detection of 14 hrHPV types with extended genotyping for individual detection of types 16, 18, 31, 45, 51, and 52.

Approved collection devices and solutions include cervical specimens collected using either an endocervical broom or a brush/spatula combination with the BD SurePath Preservation Fluid Collection Vial.[32] Of note, 1 study compared the performance of this assay with samples collected in PreservCyt versus those collected in SurePath. Each woman in this study had 2 samples taken at the same time—one for PreservCyt and one for SurePath. Overall there was an agreement of 97.1% between the 2 transport media.[51] Genotyping on formalin-fixed, paraffin-embedded tissue has also been researched with one study looking at samples with both exfoliative cytology and tissue with a histologic diagnosis of CIN2+. In this study, genotyping for the exfoliated cells was performed by Linear Array (LA; Roche Molecular Systems, Pleasanton, California), and the overall agreement of HPV status between exfoliated cells and formalin-fixed, paraffin-embedded specimens was 90% for Onclarity.[52]

Unlike most of the other FDA-approved assays, this test has been evaluated for HPV-vaccinated individuals. The sensitivity is lower (80%) and the specificity is higher (52.1%) in vaccinated women compared with unvaccinated women (100% and 46%, respectively).[32]

Limitations include:

- Non-cervical specimen types have not been evaluated[32]
- Performance has not been evaluated in women with prior ablative or excisional therapy or who are pregnant[32]
- False negative results may occur for specimens containing >8% (v/v) mucin, > 7% (w/v) acyclovir cream, or >8% (w/v) clindamycin vaginal cream[32]
- Effects of other variables such as vaginal discharge, tampon use, douching, and so forth, and specimen collection variables have not been evaluated[32]

Discussion

Because of the multiple modalities available for detection of hrHPV, the concordance between these assays becomes important. Prior publications have compared HC2, Cervista, cobas, Aptima, and BD Onclarity with most studies comparing to HC2 since it is considered the reference standard.[53]

HC2 versus Aptima

Large randomized trials and reviews have shown accuracy of both the HC2 assay and the Aptima assay in triaging women with atypical squamous cells of undetermined significance (ASC-US) cytology to detect underlying high-grade neoplasia compared with repeat cytology.[54-58] In a meta-analysis of multiple studies comparing HC2 and Aptima, the sensitivity was similar but the specificity of Aptima for CIN2+ was significantly higher in the setting of ASC-US cytology.[58] By targeting messenger RNA the Aptima test appears to be able to successfully reduce the number of positive results that do not correspond to a CIN2+ lesion, relative to the less specific HC2 test.

HC2 versus Cobas

In the ATHENA study, cervical samples from 1578 women with ASC-US cytology and follow-up biopsies were analyzed on HC2 and cobas. The sensitivity and negative predictive value for HC2 were 87.2% and 99.1%, respectively, and they were 90% and 99.2%, respectively, for cobas.[15] Gate et al. compared HPV testing results of over 1800 samples from US women 30 years or older who had cotesting performed at Kaiser Permanente Northern California. In their study, HC2 and cobas had an 85.9% agreement. When there were discordant results, cobas tended to call more results HPV positive. These discordant samples were then tested on LA, an HPV genotyping assay that is commonly used in research, and found that the cobas-positive/HC2-negative samples were more likely to be called positive for HPV 16 or another carcinogenic HPV genotype detected by LA. Those that were cobas-negative/HC2-positive were more likely to be positive by LA for one or more low-risk HPV genotypes phylogenetically related to high-risk genotypes.[59]

A study by Levi et al. compared HC2 to cobas in cytology specimens collected in ThinPrep media and SurePath media. With 1122 SurePath and 249 ThinPrep specimens processed within a week of collection, there was no statistically significant difference in the positive hrHPV result percentages between the 2 liquid-based preparations with either assay ($P = 0.17$) and the two assays had a concordance rate of 94% and a kappa coefficient of 0.72. The sensitivities of HC2 and cobas for ThinPrep samples were not significantly different (93.1% and 93.5%, respectively); nevertheless, the sensitivities for SurePath showed a larger difference between HC2 and cobas (86.7% and 93.3%, respectively). There was no significant difference between the specificities of the 2 assays between the 2 liquid-based preparations. LA was used in the discordant cases and found the cobas had a lower cross-reactivity to low-risk HPV genotypes compared with HC2.[60]

HC2 versus BD Onclarity

In a 2014 study by Wright et al., the performance of BD Onclarity was compared with that of HC2. The cervical samples were collected at the same time—1 in BD SurePath medium for Onclarity and 1 in Specimen Transport Medium for HC2. The cohort of 541 women from multiple US centers was composed of predominantly younger women (median age 28 years) or women at high risk for cervical disease. The positivity rates of both assays were comparable across all categories.[31] Similar results were found in a study that validated the Onclarity assay using the international guidelines for HPV test requirements in women 30 years and older for cervical cancer screening.[61] Bottari et al. found an overall agreement between Onclarity and HC2 of 94.6% based on 567 samples in PreservCyt from women in a referral population.[62] The kappa coefficient between Onclarity and HC2 in a study of 276 Danish women referred for colposcopy was 92% for samples collected in SurePath media.[33]

Cobas versus Aptima

In a study by Castle et al., almost 1000 samples were tested in a blinded fashion comparing cobas to Aptima HPV assay as well as Aptima's separate genotyping assay for HPV 16, 18, or 45. These samples came from women who were referred for colposcopy due to an ASC-US Papanicolaou cytology result. They found that the Aptima HPV assay was more specific than cobas, but equally sensitive for CIN2+ diagnoses and had a kappa value of 0.815. The women in this study were part of a multicenter U.S. clinical study for women 30 years and older with normal Papanicolaou cytology and women 21 years and older with ASC-US Papanicolaou cytology (clinical evaluation of Aptima mRNA [CLEAR] study).[26]

A study by Ge et al. compared 1866 Papanicolaou tests with cobas HPV testing and biopsy follow-up with 175 Papanicolaou tests with Aptima HPV testing and biopsy follow-up. Both tests were 97% sensitive for CIN2+. However, Aptima had a higher positive predictive value for CIN2+, 25% versus 16% for cobas, because a lower percentage of Aptima positive cases had follow-up biopsies that were negative or low-grade.[63]

Aptima versus Cervista

Nolte et al. compared Aptima and Cervista in 208 specimens and found only 88% agreement between the results.[48]

A much larger study by Munson et al. assessed 4056 cytology specimens from women who were at least 20 years old and found an 88.7% concordance between Aptima and Cervista.[64] Both studies found that most of the discordant results were due to higher Cervista positivity rates, with similar rates of detection of CIN2+, indicating that Aptima offers better specificity without loss of sensitivity.

Multiple comparisons

A systematic review by de Thurah et al. summarized the work of 16 studies that compared the different HPV testing assays; these studies had samples from a variety of countries around the world. Overall, de Thurah et al. concluded that various HPV assays (HC2, Abbott RealTIme, Amplicor, Aptima, BD Onclarity, Cervista, CLART, cobas, GP5+/6+, and LA) have similar overall clinical accuracy in detecting CIN2+, but are frequently discordant when compared with one another.[65]

Mesher et al. compared various assays including HC2, cobas, and Aptima for triage of women with low-grade cytological abnormalities. Their cohort consisted of 1228 English women ranging in age from 18 to 67 years with Papanicolaou tests interpreted as borderline or mildly dyskarytotic. In this setting, the sensitivities for HC2, cobas, and Aptima were 96%, 94.9%, and 94.1%, respectively, and the specificities were 23.3%, 25%, and 34.7%, respectively. The concordance kappa coefficients were as follows: HC2/cobas 0.63; HC2/Aptima 0.69; and cobas/Aptima 0.72. They concluded that in women with low-grade cytology, triaging with these HPV testing assays can reduce the number of unnecessary referrals without loss of sensitivity.[19] In another referral population from England, 1099 cervical samples were analyzed on HC2, cobas, and Aptima with the following results: sensitivities were 96.3%, 95.2%, and 95.3% and specificities were 19.5%, 24%, and 28.8%, respectively. Szarewski et al. concluded that these HPV assays offer high sensitivities for high-grade disease, although these findings may not necessarily be extrapolated to a screening population and further research is required.[17]

Few studies have focused on a screening population when comparing the different HPV testing assays; most are referral population studies. Cuzick et al compared 6 HPV assays (HC2, cobas, Abbott RealTime, BD Onclarity, Aptima, and NorChip) in a screening population of 6000 women. Residual ThinPrep samples available at a hospital in England were assayed using each test and all but the NorChip assay had high sensitivity (94.7% to 100%) for high-grade lesions that were positive by cytology. The specificity of these high sensitivity tests ranged from 84.3% to 90.2% with Aptima having the highest specificity.[18] In a separate study of a screening population of 2881 Danish women ranging in age from 30 to 65 years, the positive agreement between multiple assays were as follows: HC2/cobas 52.2%, HC2/Aptima 57.5%, and cobas/Aptima 44.9% with kappa coefficients of 0.64, 0.70, and 0.57, respectively.[66] They found that agreement between assays was lower among women 30 years old or more, in primary screening samples, and in women with concurrent normal cytology. They concluded that design differences among the available platforms result in high levels of disagreement, an issue that becomes more pronounced and problematic in the settings of primary screening and HPV-positive/cytology-negative results.

Conclusions

The advent of FDA-approved molecular tests for HPV has resulted in a dramatic shift from cytological testing alone to a combination of cytology and molecular testing for primary HPV screening. HPV testing has quickly become an essential component of daily practice in most laboratories and clinical practices. Although the principle of HPV testing is now familiar, it is important to understand the mechanisms behind these platforms in order to properly interpret the results and understand the limits of each method. HPV tests are more automated and reproducible than cytology, but are by no means perfect. None of these platforms will identify every HSIL/CIN2+ or cancer. This fact must be kept in mind when correlating the results of HPV testing with cytology or biopsy findings.

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