Cytopathology in focus: Review of FDA-approved molecular testing platforms for HPV

Recommended Reading

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January 2020—The Food and Drug Administration approved in 2001 the first testing modality for the detection of HPV in gynecological cytological specimens. To date, there are now five FDA-approved testing modalities, and molecular testing for high-risk HPV has become commonplace. Numerous studies have shown that high-risk HPV testing is more sensitive in detecting high-grade squamous intraepithelial lesion/cervical intraepithelial neoplasia grade two and above (HSIL/CIN2+) than cytology alone, but that cytology is more specific.

A fundamental understanding of each testing platform's methodology is required in order to properly interpret results and to recognize the limitations of each platform. Salazar, et al., in a recent article review the five FDA-approved molecular testing platforms for high-risk HPV and provide a reference table that highlights the key characteristics of each platform (**Table 1**) (Salazar KL, et al. A review of the FDA-approved molecular testing platforms for human papillomavirus. *J Am Soc Cytopathol.* 2019;8[5]:284–292). The article describes the methodology and limitations of each testing platform and the approved specimen types. The different platforms are then compared with a focus on inter-platform concordance.

The authors write that "HPV tests are more automated and reproducible than cytology, but are by no means perfect," adding that none of the platforms will identify every HSIL/CIN2+ or cancer. "This fact must be kept in mind," they say, "when correlating the results of HPV testing with cytology or biopsy findings."

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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 cotesting	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)

Table 1. Comparison of the 5 FDA-approved testing platforms (Abbreviations: N/A, not applicable; PCR, polymerase chain reaction. Reprinted from *Journal of the American Society of Cytopathology*, vol 8, Katrina L. Salazar, Daniel J. Duhon, Randall Olsen, Michael Thrall. A review of the FDA-approved molecular testing platforms for human papillomavirus, page 286, Copyright (2019), with permission from Elsevier.)