Clinical Validation of the Cervista HPV HR Test According to the International Guidelines for Human Papillomavirus Test Requirements for Cervical Cancer Screening

Aniek Boers, a Rong Wang, a Lorian Slagter-Menkema, b Bettien M. van Hemel, b Hilde Ghyssaert, c Ate G. J. van der Zee, a G. Bea A. Wisman, a Ed Schuuring b

Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands; Department of Pathology and Medical Biology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands; Department of Pathology, AZ St. Jan Brugge-Oostende, Bruges, Belgium

This study demonstrates that both the clinical sensitivity and specificity of the Cervista HPV HR test for high-risk human papillomavirus (HPV) detection are not inferior to those of the Hybrid Capture 2 (HC2) test. The intra- and interlaboratory reproducibilities of Cervista were 92.0% (kappa, 0.83) and 90.4% (kappa, 0.80), respectively. The Cervista HPV HR test fulfills all the international HPV test requirements for cervical primary screening purposes.

It is well established that cervical cancer is caused by a persistent infection of cervical epithelial cells by any of the ~14 genotypes of high-risk human papillomavirus (hrHPV). This knowledge prompted the development of in vitro diagnostic tests for hrHPV testing in clinical specimens. Generally, these tests have a high sensitivity and high negative predictive value, making them potentially valuable tools for primary screening strategies. Systematic reviews have shown that primary screening using hrHPV testing has a higher sensitivity than that of cytology for detecting atypical cells of undetermined significance (ASCUS) and 31 samples with normal cytology (negative for intraepithelial neoplasia grade 2 or higher (CIN2+) were included in the validation process in strict accordance with that recommended by Meijer et al. (4).

The clinical performance of the Cervista HPV HR test was assessed relative to that of the HC2 test using data from the SHENCCAST II study, a large cohort of screening participants originally screened by cotesting using ThinPrep cytology and hrHPV testing, applying both the Cervista HPV HR and HC2 HPV tests, all performed on the same sample. A detailed description of the SHENCCAST II study, a multisite, population-based, and cross-sectional study conducted in Guangdong Province in China, which enrolled approximately 10,000 women, 25 to 59 years old, was reported previously (10). To calculate the relative clinical specificity and sensitivity, 7,218 samples without CIN 2+ lesions and 109 samples with CIN2+ lesions, respectively, were used for a noninferiority analysis of the Cervista assay versus the HC2 assay. The overall clinical specificities of the HC2 and the Cervista assays in 7,218 women aged ≥30 years without CIN2+ (controls) were similar, at 89% (95% confidence interval [CI], 88.0 to 89.5) and 91% (95% CI, 90.5 to 91.8), respectively (Table 1). To calculate the relative sensitivity on a representative population-based screening cohort, 78 randomly selected samples with abnormal cytology (≥atypical cells of undetermined significance [ASCUS]) and 31 samples with normal cytology (negative for in-
traepithelial lesion or malignancy [NILM]), all with histologically proven CIN2+ lesions (45 with CIN2, 61 with CIN3, and 3 with carcinoma), were selected (cases) from the SHENCCAST II data set. The overall clinical sensitivities of the HC2 and Cervista assays for detecting CIN2+ in women age ≥30 years were 94% (95% CI, 87.2 to 97.4) and 89% (95% CI, 81.6 to 94.2), respectively (Table 1). The noninferiority of the relative sensitivity and specificity of the Cervista HPV HR test versus the HC2 test was confirmed, as the null hypothesis of inferiority was rejected (t = 17.73, P < 0.0001 for specificity; t = 1.76 and P = 0.043 for sensitivity). Therefore, the Cervista HPV HR test met the criterion of noninferiority set forth by the international guidelines, i.e., it had a clinical sensitivity not less than 90% of the sensitivity of the HC2 test and a clinical specificity not less than 98% of the specificity of the HC2 test for detecting CIN2+ in women age ≥30 years.

The intra- and interlaboratory reproducibilities of the Cervista assay were evaluated on 510 cervical scraping samples selected from women age 30 to 60 years participating in the routine national population-based cervical screening program in the Netherlands. A detailed description of the sample selection and analysis of the intra- and interlaboratory reproducibilities is reported elsewhere (13). These samples comprised 186 HC2-positive and 324 HC2-negative randomly selected scrapings (36% hrHPV positivity), according to the international guidelines for HPV DNA testing. To determine the intralaboratory reproducibility, all 510 samples were tested twice (University Medical Center Groningen [UMCG] test 1 and UMCG test 2) with the Cervista assay, according to the manufacturer’s product insert (7), at a 1- to 3-week interval by the same experienced technician on the same Cervista system at the Department of Pathology of the University Medical Center Groningen (UMCG). The agreement between the two test results was 92.0% (lower bound of 95% CI, 89.7%; kappa, 0.83; P < 0.001) (Table 2). For the interlaboratory agreement, an aliquot (2 mL of PreservCyt) of the same samples was sent to an independent reference laboratory in Bruges (Department of Pathology, AZ St. Jan Brugge-Oostende, Bruges, Belgium), which routinely uses the Cervista assay. All samples were randomly renumbered and provided to the reference laboratory without any cytology or hrHPV test results. The agreement between the two laboratories was 90.4% (lower bound of the 95% CI, 88.4%; kappa, 0.80; P < 0.001) (Table 2). Thus, the intra- and interlaboratory agreements of the Cervista assay met the requirement of having a lower bound of the 95% CI of >87% and a kappa value of >0.5.

The present study validates the Cervista HPV HR test for use in primary screening for the detection of CIN2+ lesions in women age ≥30 years, in accordance with the international guidelines for HPV DNA testing in primary screening, and it includes a determination of: (i) the noninferiority of the Cervista test to the reference HC2 HPV test and (ii) the intra- and interlaboratory reproducibilities of the Cervista assay. The Cervista test met the criteria for noninferiority to the HC2 test (noninferiority test) set forth in the international guidelines (4). Thus, the Cervista HPV HR test fulfills all the requirements of the international guidelines and can be considered formally validated for the use of primary cervical cancer screening in women of age ≥30 years. Recently, we found that the specificity of the Cervista HPV HR test could be even further improved when the standard second cutoff (default setting of the manufacturer) was adapted (13).

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REFERENCES


