Evaluation of the Clinical Performance of the cobas 4800 HPV Test in Patients Referred for Colposcopy

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The clinical performance of the cobas human papillomavirus (HPV) test for detection of high-grade disease in a colposcopy-referred population was compared with that of Hybrid Capture 2 (HC2). The overall agreement between the tests was 92.3%. Clinical sensitivity and specificity for detection of cervical intraepithelial neoplasia grade 2 or greater (CIN2+) were 90.0% and 55.5% for cobas and 90.5% and 50.2% for HC2, respectively. In conclusion, both tests showed comparable performance for detection of CIN2+.

Testing for human papillomavirus (HPV) is now an important tool in managing women with cervical precancer. Many tests have been developed to detect HPV. Hybrid Capture 2 (HC2) was the first clinically validated HPV DNA detection assay. More recently, new tests, such as the cobas 4800 HPV test, have become available. The aim of this study was to evaluate the performance of the cobas compared to that of HC2 in a population of women with abnormal cervical cytology who were referred for colposcopy.

Women who attended colposcopy clinics at the National Maternity Hospital and the Coombe Women’s and Infants University Hospital, Dublin, Ireland, receiving colposcopy exams on the basis of abnormal cytology, were included in this study after giving consent. A cervical smear was taken at their first visit for HPV testing. HPV DNA testing was performed using HC2 (Qiagen) for the detection of 13 oncogenic HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) using the standard relative light unit (RLU) cutoff of 1.0 and the cobas (Roche Diagnostics), which detects HPV16 and HPV18 and 12 pooled high-risk (HR) HPV genotypes (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68). HPV genotyping was performed on a subset of discordant patient samples (those for whom adequate material remained; n = 23/43) using the linear array (LA) HPV genotyping test (Roche Diagnostics) for detection of 37 HPV genotypes (6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 45, 51, 52, 53, 54, 55, 56, 58, 59, 61, 62, 64, 66, 67, 68, 69, 70, 71, 72, 73 [MM9], 81, 82 [MM4], 83 [MM7], 84 [MM8], IS39, and CP6108). Agreement between the cobas and HC2 tests was calculated using Cohen’s kappa coefficient and clinical performance assessed by calculating the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and relative 95% confidence intervals (CI) for detecting cervical intraepithelial neoplasia grade 2 (CIN2+) and CIN3. Results were obtained from 558 women with a median age of 32 years (interquartile range of 28 to 39). The study population was composed of 465 women referred for colposcopy with minor cytological abnormalities, low-grade squamous intraepithelial lesions (LSIL), or atypical squamous cells of undetermined significance (ASCUS) and 96 women referred with high-grade squamous intraepithelial lesions (HSIL). The overall prevalence of HPV detected by the cobas was 62.7% (95% CI of 60.8% to 64.7%), compared to 65.8% (95% CI of 63.9% to 67.6%) for HC2. Agreement between the two tests was high at 92.3%, producing a kappa value of 0.832 (95% CI of 0.784 to 0.881). In 43 cases, the results did not match between the cobas and HC2 tests. LA was employed in all samples with adequate material remaining (n = 23). In total, 17/23 cases were HC2 positive and cobas HPV negative. Of these, 70.6% (12/17) were subsequently confirmed by LA as being positive for low-risk HPV types only, most notably...
Within the study population, there were 67 women who appeared normal by colposcopy examination and therefore had no biopsy specimen taken. A histological diagnosis was available for the remaining 474 patients presenting with abnormal cytology (ASCUS-HSIL). Biopsy confirmed CIN1, CIN2, and CIN3 were identified in 30.8% (146/474), 23.6% (112/474), and 20.8% (99/474), respectively. In 24.7% (117/474) of the cases, no CIN was detected on biopsy. The sensitivity and specificity of the cobas test for detection of CIN2+ were 90.0% (95% CI of 88.8 to 91.3) and 55.5% (95% CI of 52.5 to 58.5), respectively (Table 1). Results compare well with those of HC2, which demonstrated sensitivity of 90.5% (95% CI of 89.4 to 91.7) and specificity of 50.2% (95% CI of 47.2 to 53.2). There was no significant difference in PPV, 61% (95% CI of 59.3 to 64.5) and 59.3% (95% CI of 56.7 to 62.0), or NPV, 87.4% (95% CI of 85.8 to 89.1) and 86.8% (95% CI of 85.0 to 88.7), for the cobas and HC2 tests, respectively. When the disease endpoint was confined to the detection of CIN3, the NPV was markedly increased to 100% and 98.7% for the cobas and HC2 tests, respectively (Table 1). However, due to the lower prevalence of CIN3 lesions in the study population, the PPV of both tests was reduced to 30%.

The clinical performance of the cobas test for detection of CIN2+ in the 465 women presenting with LSIL and ASCUS was evaluated in those with confirmed histological diagnoses, resulting in 404 cases available for analysis. The sensitivity, specificity, PPV, and NPV for detection of CIN2+ in LSIL and ASCUS are reported (4, 5). A study by Stoler et al. on 1,578 women reported a higher specificity of 70.5% (95% CI of 68.1 to 72.7) and lower PPV of 14.0% (95% CI of 12.8 to 15.3) for detection of CIN2+ (4) than the current study. This may be, in part, due to the higher prevalence of high-grade disease in our ASCUS population than in the study by Stoler et al. (26.0% compared to 5.1%) (4). This can be attributed to a number of factors, most notably the different management strategies of ASCUS in different settings. In Ireland, ASCUS detected through organized, population-based screening is managed by repeat cytology. In comparison, in the United States, women with initial ASCUS are triaged by HPV detection (6). It is important to note that this study population represents a population of women receiving colposcopy exams on the basis of repeat minor cytological abnormalities and not a population undergoing primary screening. Therefore, it should be acknowledged that the population is enriched for cervical disease, which can produce a higher PPV than would be seen in a screening population.

In summary, the cobas test demonstrated a high level of agreement with HC2 for detection of HPV and comparable clinical performance. The strengths of this study are that enrollment was systematic through the Irish national screening program, Cervi
calCheck. Women were managed under a standard protocol outlined by CervicalCheck guidelines. These attributes allowed the test performance to be evaluated in a routine population-based setting. In addition, the clinical performance of the cobas was assessed in LSIL, which has not been previously reported. The weakness of the study is that test performance of the HPV tests is not evaluated in a primary screening setting. However, given the high prevalence of minor cytological abnormalities in Ireland, which account for over 13% of cervical smears (7), this study has particular relevance in an Irish setting.

The management of women at colposcopy is changing with the recognition that many low-grade lesions will regress spontaneously in addition to the known side effects and morbidities associated with excisional treatment. Tests that can further stratify women and identify those that do not need treatment will be useful in terms of returning women to routine screening, reducing long-term surveillance at colposcopy.

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We thank the colposcopy clinic staff at the National Maternity Hospital Dublin and the Coombe Women and Infants University Hospital, Dublin, for facilitating the study, as well as the women who took part.

Cara Martin and John O’Leary have had a cobas 4800 system placed with ASCUS in this study is equivalent to what is previously reported (4, 5). A study by Stoler et al. on 1,578 women reported a higher specificity of 70.5% (95% CI of 68.1 to 72.7) and lower PPV of 14.0% (95% CI of 12.8 to 15.3) for detection of CIN2+ (4) than the current study. This may be, in part, due to the higher prevalence of high-grade disease in our ASCUS population than in the study by Stoler et al. (26.0% compared to 5.1%) (4). This can be attributed to a number of factors, most notably the different management strategies of ASCUS in different settings. In Ireland, ASCUS detected through organized, population-based screening is managed by repeat cytology. In comparison, in the United States, women with initial ASCUS are triaged by HPV detection (6). It is important to note that this study population represents a population of women receiving colposcopy exams on the basis of repeat minor cytological abnormalities and not a population undergoing primary screening. Therefore, it should be acknowledged that the population is enriched for cervical disease, which can produce a higher PPV than would be seen in a screening population.

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Cara Martin and John O’Leary have had a cobas 4800 system placed
into their laboratory by Roche Diagnostics. All HPV testing kits and associated reagents for both the cobas 4800 HPV test and HC2 were purchased for this study. Roche Diagnostics and Qiagen are commercial partners in CERVIVA.

REFERENCES


