Scientific Publications of PapilloCheck®
Abstracts of Selected Publications

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Comparison of the PapilloCheck® DNA micro-array Human Papillomavirus detection assay with Hybrid Capture II and PCR-enzyme immunoassay using the GP5/6+ primer set.

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BACKGROUND: Cervical screening detects precancerous cells and routine screening could be improved by testing for Human Papillomavirus (HPV), the virus that causes cervical cancer. HPV infection is common and the benefit of HPV testing would be identification of women who are HPV negative and at low risk of developing cancer.

STUDY DESIGN: The aim of this study was to evaluate the Greiner Bio-One PapilloCheck® micro-array assay (PapilloCheck®) for detection of HPV in comparison with Hybrid Capture II (hc2) and PCR-enzyme immunoassay (PCR-EIA) using the GP5/6+ primers.

RESULTS: Samples from a cytologically defined population (n=878) were analysed and 187 samples also had histology information. Overall, 674 out of 878 samples gave a consistent result (76.8%; 95% CI 73.83-79.52%) on all three platforms. The genotype results obtained by PapilloCheck® and PCR-EIA were compared and 94% were consistent (95% CI 92.1-96.4%). The main difference was the poor Kappa agreement for detection of high risk (HR) type 35 (Kappa=0.190) with all inconsistent results being HR positive by PCR-EIA assay but negative on the PapilloCheck® platform. There was no statistically significant difference between the performance of each assay when HR HPV positive samples were linked with clinical result (cytology and histology grade).

CONCLUSIONS: Overall, PapilloCheck® proved to be a sensitive, reproducible, robust molecular assay for HPV genotyping with the potential for high throughput of specimens in a clinical setting.

Comparison of the clinical performance of PapilloCheck® human papillomavirus detection with that of the GP5+/6+-PCR-enzyme immunoassay in population-based cervical screening.

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We compared the clinical performance of the PapilloCheck® assay with the high-risk HPV GP5+/6+-PCR method, followed by enzyme immunoassay readout (GP5+/6+-PCR-EIA) on cervical samples originating from women of a population-based cervical screening cohort tested by combined cytology and GP5+/6+-PCR-EIA (POBASCAM trial). A random sample of 1,437 controls (defined as women with normal cytology (age 40-60 years) without evidence of ≥CIN2 within up to 8 years), and 192 cases (women aged 30-60 years with ≥CIN3 detected within up to 3 years of follow-up) were subjected to PapilloCheck® analysis. When all 17 (probably) hrHPV types were taken into account PapilloCheck® had a clinical sensitivity for ≥CIN3 of 96.4% (95%CI 93.7-99.7) and a clinical specificity for ≥CIN2 of 96.3% (95%CI 95.3-97.3). After restricting PapilloCheck® analysis to the 14 hrHPV types targeted by GP5+/6+-PCR-EIA the clinical sensitivity and specificity figures were 96.8% (95%CI 95.2-98.3) and 96.6% (95%CI 95.7-97.7), respectively. By comparison, these figures were 96.4% (95%CI 93.9-98.9) and 97.7% (95%CI 96.9-98.5), respectively, for GP5+/6+-PCR-EIA. When including all 17 (probably) hrHPV types non-inferiority score testing revealed that the clinical sensitivity for ≥CIN3 of PapilloCheck® was non-inferior (P<0.0001), but the specificity for ≥CIN2 inferior to that of GP5+/6+-PCR-EIA (P=0.08), using lower bounds of 90% and 98%, respectively. When restricting the analysis to the 14 hrHPV types targeted by GP5+/6+-PCR-EIA both clinical sensitivity and specificity of PapilloCheck® were non-inferior to that of GP5+/6+-PCR-EIA (non-inferiority score test; P=0.0001 and P=0.007, respectively). Thus, when considering the 14 hrHPV types detectable with hrHPV GP5+/6+-PCR-EIA the PapilloCheck® assay is clinically compatible to the GP5+/6+-PCR-EIA assay.
Which high-risk HPV assays fulfil criteria for use in primary cervical cancer screening?

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Several countries are in the process of switching to high-risk human papillomavirus (hrHPV) testing for cervical cancer screening. Given the multitude of available tests, validated assays which assure high-quality screening need to be identified. A systematic review was conducted to answer the question which hrHPV tests fulfil the criteria defined by an international expert team in 2009, based on reproducibility and relative sensitivity and specificity compared to Hybrid Capture-2 or GP5+/6+ PCR–enzyme immunoassay. These latter two hrHPV DNA assays were validated in large randomized trials and cohorts with a follow-up duration of 8 years or more. Eligible studies citing the 2009 guideline were retrieved from Scopus (http://www.scopus.com) and from a meta-analysis assessing the relative accuracy of new hrHPV assays versus the standard comparator tests to detect high-grade cervical intraepithelial neoplasia or cancer in primary screening. The cobas 4800 HPV test and Abbott RealTime High Risk HPV test were consistently validated in two and three studies, respectively, whereas the PapillioCheck® HPV-screening test, BD Onclarity HPV assay and the HPV-Risk assay were validated each in one study. Other tests which partially fulfil the 2009 guidelines are the following: Cervista HPV HR Test, GP5+/6+ PCR–LMNX, an in-house E6/E7 RT quantitative PCR and MALDI-TOF (matrix-assisted laser desorption ionization time-of-flight). The APTIMA HPV assay targeting E6/E7 mRNA of hrHPV was also fully validated. However, the cross-sectional equivalency criteria of the 2009 guidelines were set up for HPV DNA assays. Demonstration of a low risk of CIN3+ after a negative APTIMA test over a longer period is awaited to inform us about its utility in cervical cancer screening at 5-year or longer intervals.

Clinical and analytical performance of the PapillioCheck® HPV-Screening assay using the VALGENT framework

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Background: The benefit of HPV testing for cervical cancer screening and disease management has been shown in many recent studies and is part of several new evidence-based guidelines. Assessment of emerging HPV tests in this context is essential, using well-annotated samples, such as those generated via the Validation of Genotyping Tests-HPV (VALGENT) framework.

Objective: Our aim was to assess the PapillioCheck® HPV assay in terms of absolute and relative accuracy for primary cervical cancer screening, using a standard comparator test (GP5+/6 + EIA) already validated in randomised trials.

Study design: Type-specific HPV prevalence was stratified by age and cytology grade and compared with the luminex typing assay incorporating a GP5+6+ PCR (GP5+/6+ LMNX Assay). Clinical outcomes were compared with GP5+/6 + EIA.

Results: Prevalence of hrHPV types (high-risk HPV) increased with severity of cytology. The concordance between PapillioCheck® and the GP5+/6+ LMNX Assay was excellent when assessed at the qualitative hrHPV presence/absence level also at the type-specific level in the whole population and in women over 30 years of age. Absolute clinical sensitivity and specificity of the PapillioCheck® was high and ranged between 95.5% and 98.2% for sensitivity and between 82.7% and 91.6% for specificity, depending on the outcome and population.

Conclusion: The sensitivity and specificity of this assay for the outcomes of CIN2+ were similar to those of the standard comparator assay, GP5+/6+ EIA.
The PapilloCheck® Assay for Detection of High-Grade Cervical Intraepithelial Neoplasia

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Human papillomavirus (HPV) testing is used in primary cervical screening, as an adjunct to cervical cytology for the management of low grade abnormal cytology, and in a test of cure. PapilloCheck® (Greiner Bio-One) is a PCR-based DNA microarray system that can individually identify 24 HPV types, including the 13 high-risk (HR) types identified by Hybrid Capture 2 (HC2).
Here, we compare PapilloCheck® with HC2 for the detection of high-grade cervical intraepithelial neoplasia (CIN2+) in a total of 8,610 cervical cytology samples from the ARTISTIC population-based cervical screening study. We performed a retrospective analysis of 3,518 cytology samples from round 1 ARTISTIC enriched for underlying CIN2+ (n=723) and a prospective analysis of 5,092 samples from round 3 ARTISTIC. Discrepant results were tested using the Roche reverse line blot (RLB) or Linear Array (LA) assay. The relative sensitivity and specificity of HR PapilloCheck® compared with that of HC2 for the detection of CIN2+ in women aged over 30 years were 0.94 (95% confidence interval [CI], 0.91, 0.97) and 1.05 (95% CI, 1.04, 1.05), respectively. HC2 missed 44 (7%) CIN2+ lesions, while HR PapilloCheck® missed 74 (11%) CIN2+ lesions. Thirty-six percent of HC2-positive normal cytology samples were HR HPV negative by both PapilloCheck® and RLB/LA, indicating that the use of HR PapilloCheck® rather than HC2 in population-based primary screening would reduce the number of additional tests required (e.g., reflex cytology) in women where underlying CIN2+ is extremely unlikely. HR PapilloCheck® could be a suitable HPV detection assay for use in the cervical screening setting.

A Head-to-Head Analytical Comparison of Cobas 4800 HPV, PapilloCheck® HPV Screening, and LMNX Genotyping Kit HPV GP for Detection of Human Papillomavirus DNA in Cervical and Cervicovaginal Swabs

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High-risk human papillomavirus (hrHPV) infection is a cause of cervical cancer development. The addition of hrHPV testing to cervical cancer screening and monitoring of cervical intraepithelial neoplasia treatment improves the efficacy of screening and treatment, respectively. Self-sampling for hrHPV testing seems a promising tool for increasing patient participation in cervical cancer screening. In this project, 1,198 cervical swabs obtained by physicians and 176 cervicovaginal swabs obtained by self-sampling (not collected in parallel) were analyzed for the presence of 14 hrHPV genotypes using three commercially available assays in comparison. HPV DNA was detected in 21.2% of all samples (21% of cervical swabs and 22.7% of cervicovaginal swabs). The cobas 4800 HPV Test was the most sensitive (0.983) and specific (0.992) for hrHPV detection overall. The PapilloCheck® HPV Screening and LMNX Genotyping Kit HPV GP had comparable specificity with that of the cobas (0.989 and 0.955, respectively), but lesser sensitivity (0.997 and 0.909, respectively). In physician-obtained cervical swabs, the cobas showed the highest sensitivity and specificity (0.980 and 0.934, respectively) for hrHPV detection, whereas in cervicovaginal swabs, the cobas had the highest sensitivity (1.00), but the PapilloCheck® had the highest specificity (0.993). In conclusion, all of the detection methods evaluated were highly sensitive and specific for hrHPV detection from both clinician-collected cervical swabs and self-sampled cervicovaginal swabs.
Effectiveness of Human Papillomavirus Vaccination on Prevalence of Vaccine Genotypes in Young Sexually Active Women in France.

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BACKGROUND: Effectiveness of human papillomavirus (HPV) vaccines in the context of both guidelines, which recommend vaccination at 14 years and modest vaccine coverage, is poorly documented. METHODS: Residual specimens from females aged <25 years undergoing chlamydia testing were collected, together with demographic, sexual behaviour, and vaccine status data. Human papillomavirus genotypes were determined using the PapilloCheck® test system. We compared vaccine type (VT; types 6, 11, 16, 18) prevalence according to vaccination status and identified factors associated with VT prevalence. RESULTS: Of 3736 eligible samples, 822 were from vaccinated women according to immunization record, 1021 from women self-reporting vaccination, and 1893 from unvaccinated women. Adjusted vaccine effectiveness for confirmed vaccinated compared with unvaccinated women was 95.93% (95% confidence interval [CI] = 90.22-98.32) against VT HPV and 38.37% (95% CI = 12.68-56.51) against cross-reactive genotypes (HPV 31, 33, 45), respectively. Vaccine type HPV prevalence was significantly lower (0.61%) among confirmed-vaccinated women than among those who self-reported vaccination or unvaccinated women (1.76% and 15.0%, respectively). Factors associated with prevalent VT in multivariable analysis were vaccine status, positive Chlamydia trachomatis and ≥4 partners in the preceding year. CONCLUSION: Our study demonstrates evidence of high effectiveness of HPV prophylactic vaccines at an individual level, supporting that wider implementation will help to reduce cervical cancer and precursors incidence.

Papillomavirus genotyping on formaldehyde fixed paraffin-embedded tissues in vulvar-intraepithelial neoplasia.

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PURPOSE: Few studies have described the epidemiology of human papillomavirus (HPV) in vulvar intraepithelial neoplasia (VIN). The aim of this study was to genotype HPV on formalin fixed paraffin-embedded tissues in VIN lesions. METHODS: A 5-year retrospective study was conducted by including all patients attending the teaching hospital of Nice with a diagnosis of VIN between 1st January 2010 and 31st December 2014. For all patients, HPV genotyping was performed with the PapilloCheck® microarray kit, routinely used on cervical cytology samples, and optimized for formaldehyde fixed paraffin-embedded tissues in VIN. RESULTS: Forty patients were included in the study: 39 patients had usual VIN and one presented with differentiated VIN. Among the 39 patients with usual VIN, the prevalence of HPV was 90% (35/39). Thirty-two patients had high grade VIN (82%) and seven low grade VIN (18%). In high grade VIN, the most represented HPV types were: HPV 16 (21/32 66%), HPV 56 (3/32 9%) and HPV 33 (2/32 6%). In low grade VIN, the most represented HPV types were: HPV 16 (4/7 57%) and HPV 6 (3/7 43%). Interestingly, 5/39 (13%) of patients diagnosed with usual VIN also had co-existing lichen sclerosus. CONCLUSIONS: We have optimized a HPV genotyping technique, routinely used on cervical cytology samples, and on paraffin fixed embedded tissue showing VIN. Moreover, we have identified five patients with lichen sclerosus co-existing with usual VIN. This association has rarely been reported and proves that these two entities can coexist.
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