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A highly efficient assay for detection of high-risk human papillomavirus E7 proteins in cervical samples as a method of triage to colposcopy

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Background:

Cervical cancer is the fourth most common cancer in women worldwide. Human papillomavirus (HPV) is detected in 99.7% of cervical cancer cases. Nucleic acid-based cervical cancer screening methods frequently pick up HPV infections without underlying disease, thereby leading to low test specificity. Hence, implementation of a triage method to colposcopy for HPV-positive women in the screening

algorithm is necessary. Different triage methods such as cytology, methylation patterns of host and viral DNA, and p16/Ki67 overexpression are under investigation.

Overexpression of HPV oncoproteins E6 and E7 during disease progression leads to loss of cell cycle control and neoplastic transformation. Therefore, these proteins are potential biomarkers for detection of persistent HPV infection. Here we describe the performance of a novel assay for detection of high-risk (hr) HPV E7 proteins. The assay was developed, validated, and clinically evaluated during the EU-PIPAVIR project.

Material/methods:

An hrHPV E7 sandwich Enzyme Linked Immunosorbent Assay (ELISA) – recomWell HPV 16/18/45 - was developed for detection of hrHPV types 16, 18, and 45. Suitable for measurement of E7 protein are liquid-based cytological samples in PreserveCyte.

Cervical samples were obtained from 2424 women aged 30-60 who participated in different sub-studies of the PIPAVIR project. Exclusion criteria were history of cervical intraepithelial neoplasia (CIN) (treated or not), and pregnancy. Samples were characterized by cytology and HPV-genotyping; E7 measurements were performed with recomWell HPV 16/18/45. Women positive for cytology [atypical squamous cells of undetermined significance or worse] or hrHPV DNA were referred to colposcopy followed by biopsy, when needed, and/or endocervical curettage. Data were recorded using a web-based data capturing system.

Results:

Sensitivity (CIN2+/CIN3+/CxCa: 36.1/58.3/85.7%), specificity (>98%), positive predictive value (PPV) (CIN2+/CIN3+/CxCa: 59.5/56.8/16.2%) and negative predictive value (NPV) (>97.5%) were calculated across all studies with 1572 clinical samples.

1473 samples were analyzed for validity of E7-based triage for HPV16/18 positive women. 282 women were positive for hrHPV DNA testing and further subjected to colposcopy. For the detection of CIN2+ for HPV16/18 positive women without further triage, sensitivity and PPV were 100.0% and 11.11%, respectively. No triage of HPV16/18 positive women required 9 colposcopies to diagnose one case of CIN2+. The sensitivity of recomWell HPV16/18/45 was 100.0% (meaning that no CIN2+ case was missed) and PPV was 19.75%. The recomWell HPV16/18/45 identified all 16 CIN2+ cases, requiring 43.75% less colposcopies than no triage of HPV16/18 positive women.

Conclusions:

Detection of hrHPV E7 by ELISA is a feasible method for diagnosing HPV-induced, high-grade cervical dysplasia. Our results support the detection of HPV E7 oncoprotein as a method of triage to colposcopy for HPV16/18 positive women (instead of no triage) in the framework of a screening program based on primary HPV screening with HPV 16/18 genotyping.