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Evaluation of oncogenic human papillomavirus RNA and DNA tests with liquid-based cytology in primary cervical cancer screening: the FASE study

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As human papillomavirus (HPV) testing becomes increasingly integrated into cervical disease management strategies, it is necessary for the clinical community to consider optimal HPV tests. The test used for the majority of the influential randomised controlled trials and – more locally – the UK National Cervical Screening Programme (UKNCSP) Sentinel Site project was the Hybrid Capture 2 (HC2) test. The HC2 is a well-established, clinically validated test that detects 13 high-risk HPV types in aggregate at the DNA level. The significant amount of existing clinical data associated with HC2 has ensured its current ‘gold-standard’ status against which the performance of other emerging HPV tests is assessed.

However, it is also well established that the sensitivity of HPV DNA testing exceeds its specificity (particularly in young women) due to the high prevalence of asymptomatic infection. Consequently, ways to enhance specificity have been context-driven (such as limiting testing to women aged >30 years) and test-driven. An alternative to DNA testing is

detection of E6/E7 transcripts apropos the evidence that deregulated expression of E6/E7 is necessary for initiation and maintenance of malignancy. There are two commercially available HPV tests that target E6/E7 mRNA, namely the PreTect HPV-Proofer™ (Norchip, Klokkestua, Norway) and the APTIMA™ HPV Assay (AHPV; GenProbe Inc., San Diego, CA, USA) with a respective target range of 5 and 14 high-risk HPV types. The similarity of the AHPV type range to HC2 (all 13 types plus one) make it a closer match for performance comparisons of the RNA versus DNA vein.

In the French APTIMA HPV Screening Evaluation study, Monsonogo *et al.* were the first to assess the clinical performance of the AHPV test, compared with HC2 (and cytology) in a population-based screening setting. A total of 4428 women were included in the analysis (with approximately 25% aged >30 years and the remainder aged up to 65 years). One-hundred and one cases of high-grade disease (CIN2+) were detected, although it was interesting that women aged under and over 30 years had similar histological results. Overall positivity of the HC2 and AHPV was 15.7% and 10.3% AHPV, respectively. When the full population was considered, AHPV was slightly less sensitive than HC2 for the detection of CIN2+ (92% vs 96.7% for 74 cases) whereas equivalent sensitivity of the tests (both >95%) was reached for the 27 cases of CIN3+. Specificity of the AHPV was higher than the HC2 (91.8 vs 86.4% for CIN2+) with the largest improvement in specificity observed in the under-30s. Both HPV tests were (perhaps unsurprisingly) more sensitive than liquid-based

cytology (LBC); however, specificity of the AHPV and LBC was equivalent.

These data are interesting and support other data (derived from different populations) in that E6/E7 mRNA tests appear to show a moderately higher specificity for cervical disease, without a significant compromise in sensitivity, particularly at the CIN3 level. Although increased specificity is welcomed, there is still room for improvement; in addition, the HC2 was considered positive at a cut-off of 1 (as per the manufacturer's instructions). An additional analysis where the cut-off for HC2 was raised to 2 (suggested by some to be a more clinically relevant threshold) would have been of interest. It should also be noted that although this is the first (relatively large) study to look at the performance of AHPV in a primary screening context, women were recruited as part of an opportunistic programme. The performance of cytology in itself and relative to both of the HPV tests may differ if executed via a call-recall nationalised programme. Consequently, the last sentence of the abstract “AHPV ... may be considered as an option for routine cervical cancer screening for women >20 years of age” may be slightly lofty at this stage.

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