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Comparative performance of human papillomavirus messenger RNA versus DNA screening tests at baseline and 48 months in the HPV FOCAL trial

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ABSTRACT

Background: HPV FOCAL is a randomized trial comparing high-risk HPV [Hybrid Capture 2 (HC2)] vs. liquid-based cytology (LBC) for primary cervical screening.
Objective: The present study objective was to compare Aptima HPV (AHPV) and HC2 assay performance at the intervention arm baseline and 48 mo. screens in relation to the rates of cervical intraepithelial neoplasia (CIN) grade 2 or worse (CIN2+).
Study design: Women enrolled after December 2010 (n = 3475) were screened at baseline with both AHPV and HC2 (AHPV was blinded). Women with CIN2+ exited the trial; HC2 negative (−) women and those HC2 positive (+) with < CIN2 returned for 48 mo. screening with AHPV, HC2, and LBC.
Results: At baseline, 7.2% were AHPV + vs. 8.4% for HC2 (p = 0.06). Round 1 AHPV CIN2+ sensitivity (relative to HC2) was 96.0% (95%CI: 86.5–99.0; p = 0.15) and 100% (95%CI: 82.4–100) for CIN3+. AHPV and HC2 specificities (< CIN2) were 94.1% vs. 93.0% respectively (p = 0.05). At 48 mo., 4.8% and 5.2% were AHPV + and HC2+ respectively (p = 0.41), and both tests had the same CIN2+ and CIN3+ sensitivities (87.5% and 85.0% respectively). AHPV specificity (95.8%) was higher, but not significantly, than HC2 (95.3%; p = 0.38). Of 3226 baseline AHPV− women, 12/2,858 (0.4%) had CIN2+ vs. 13/2821 (0.5%) for the 3184 baseline HC2− women.
Conclusions: There was no significant difference in CIN2+ detection for AHPV vs. HC2 at baseline or at 48 mo. Baseline AHPV− and HC2− women had similar CIN2+ rates at 48 mo., demonstrating the safety of a four year screening interval for AHPV− women.

1. Background and objectives

Screening programsare beginning to replace Pap cytology with high-risk (hr) HPV for primary cervical cancer screening [1–3]. Multiple randomized trials utilizing the Hybrid Capture 2 High-Risk HPV DNA Test (HC2) [4–7], GP5/GP6 PCR-based hrHPV assays [8] and the cobas 4800 HPV test [9] have demonstrated earlier detection of high-grade cervical lesions (cervical intraepithelial neoplasia [CIN] grade 2 or worse [CIN2+]) compared to cytology, which reflects the safety of extending the re-screening interval following negative primary hrHPV DNA screening. HPV FOr CerviCAL Cancer Screening (HPV FOCAL; ISRCTN79347302) [4,7] is a randomized controlled trial designed to

Abbreviations: hr, high-risk; HPV, human papillomavirus; DNA, deoxyribonucleic acid; HC2, hybrid capture 2 HPV DNA test; CIN, cervical intraepithelial neoplasia; AHPV, Aptima HPV assay; CI, confidence interval; mRNA, messenger ribonucleic acid; LBC, liquid-based cytology; ASCUS, atypical squamous cells, undetermined significance; NILM, negative for intraepithelial lesions and malignancy; AHPV-G, Aptima HPV 16 18/45 Genotype assay; RLU, relative light units; BC, British Columbia; LSIL, low-grade squamous intraepithelial lesion; ASCH, atypical squamous cells, cannot rule out high-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; UNSAT, smear unsatisfactory

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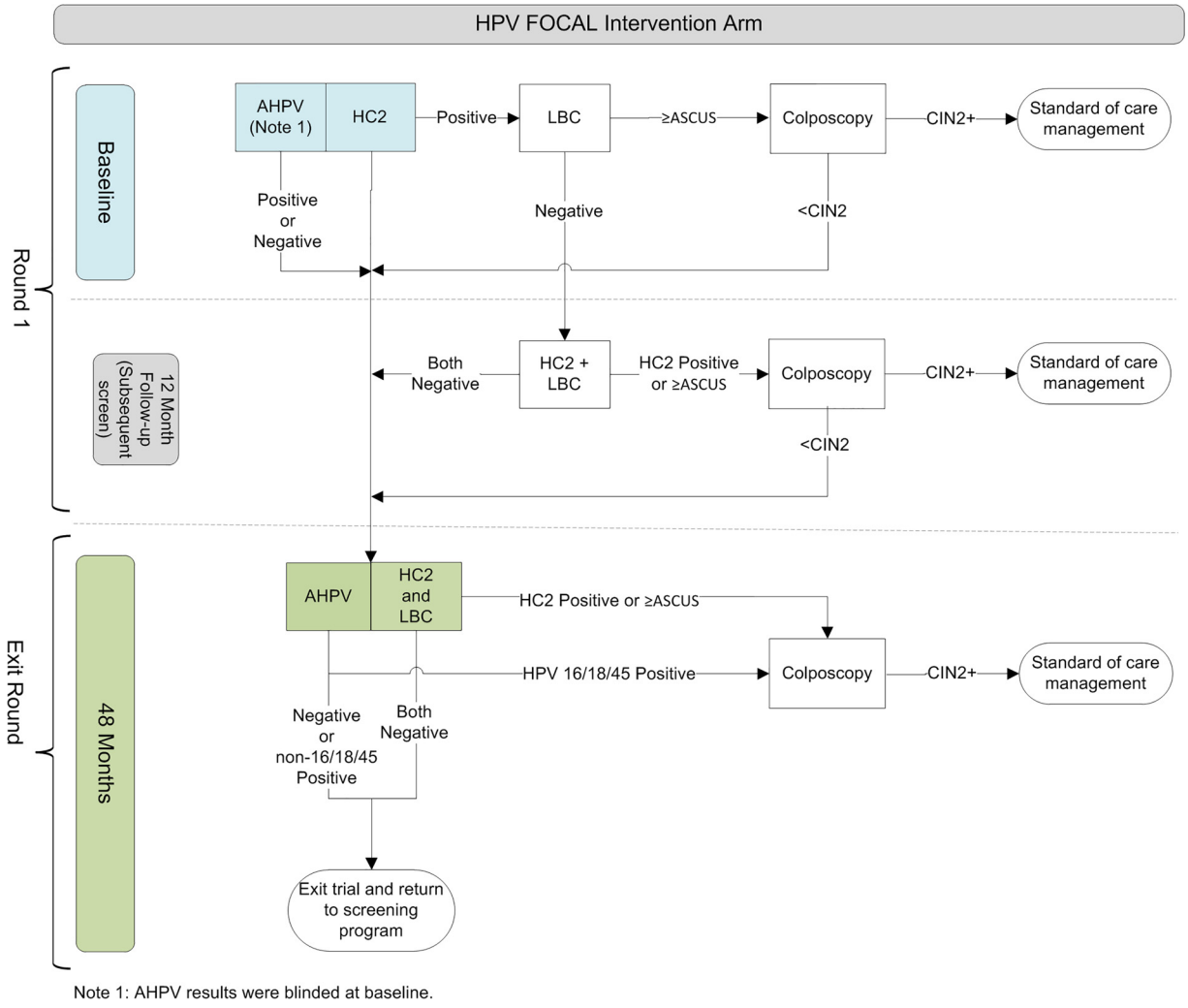

Fig. 1. HPV FOCAL Aptima Adjunct Study Design.
Abbreviations: AHPV: Aptima HPV assay; HC2: hybrid capture 2 HPV test; LBC: liquid-based cytology; ASCUS: atypical squamous cells, undetermined significance; CIN: cervical intraepithelial neoplasia.

establish the efficacy of HC2 screening together with liquid-based cytology (LBC) triage of HC2 positives (HC2+) (intervention arm) compared to LBC together with HC2 triage of atypical squamous cells of undetermined significance (ASCUS) (control arm) in women aged 25–65. Criteria have been developed [10] to assess the cross-sectional screening equivalence of DNA-based hrHPV assays by comparing their performance to either HC2 or GP5/GP6-based assays. The Aptima HPV Assay (AHPV) detects E6/E7 messenger RNA (mRNA) of 14 high-risk (hr) HPV types (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68), whereas HC2 detects DNA of the same HPV types, except HPV 66. Equivalent performance of AHPV and HC2 has been demonstrated in cross-sectional screening settings [11–13], but there is limited long-term follow-up data following a negative AHPV screen. In the CLEAR study, Reid et al. [14] showed equivalent performance of AHPV and HC2 at baseline in a colposcopy referral population, where follow-up of baseline AHPV and HC2 negative women for three years showed a CIN2+ risk of 0.3% for both tests. While AHPV screening fulfills the established Meijer criteria [15], because AHPV utilizes a mRNA target, concerns remain about the safety of a long re-screening interval following a negative baseline AHPV screen [16].

We previously reported that AHPV and HC2 had equivalent CIN2+ detection at round 1 of the HPV FOCAL Trial [11]. In this study, we report comparative AHPV and HC2 results for women at the FOCAL baseline and 48 mo. screens.

2. Study design

2.1. Study population

The HPV FOCAL trial subset reported here consists of women randomized to the intervention arm after December 2010 who were screened by both AHPV and HC2 (n = 3476) (Fig. 1). Round 1 includes the baseline and 12 mo. subsequent screens. At baseline, women HC2 positive (HC2+) and LBC ≥ ASCUS were referred immediately to colposcopy. Those HC2+ and LBC negative for intraepithelial lesions and malignancy (NILM) (LBC−) were re-screened by HC2 and LBC 12 mo. later, and those persistently HC2+ and/or LBC ≥ ASCUS were referred to colposcopy. At colposcopy, visible lesions were biopsied or endocervical curettage was performed for those with no visible lesions. Women diagnosed with CIN2+ at round 1 were offered standard of care treatment and exited the trial; those with < CIN2 were invited to return to trial follow-up and exited the trial at 48 mo. Baseline HC2 negative (HC2−) women, together with those baseline HC2+ and HC2−/LBC− at 12 mo., who returned to trial follow-up, also exited the trial at 48 mo. At the 48 mo. screen, women were co-tested with AHPV, HC2and LBC. Women with a positive 48 mo. screen, i.e., HC2+, LBC ≥ ASCUS or AHPV+ for HPV 16/18/45, were referred to colposcopy.