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Agreement between careHPV and Hybrid capture 2 (HC2) in detecting high-risk HPV in women in Tanzania

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Conflicts of Interest

None

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ABSTRACT

Introduction: visual inspection of the cervix with acetic acid is used to control the burden of cervical cancer in low and middle-income countries. This method has some limitations and HPV
DNA testing may be an alternative, but it is expensive and requires a laboratory setup. A cheaper and faster HPV tests have been developed. This study describe the agreement between a fast HPV test (careHPV) and hybrid capture 2 (HC2) in detection of high-risk HPV among Tanzanian women.

**Material and methods:** study involving women attending routine cervical cancer screening at Ocean Road Cancer Institute and Kilimanjaro Christian Medical Centre in Tanzania. They were offered HIV testing. Two cervical samples were subsequently obtained, the 1st sample was processed at the clinics by using careHPV and the 2nd sample was transported to Denmark and Germany for cytology and hc2 analysis, respectively. Kappa statistic was calculated to assess the agreement between careHPV and HC2. The sensitivity, specificity and predictive values of careHPV was calculated using HC2 as reference. The analyses were done for the overall study population and stratified by testing site and HIV status.

**Results:** A total of 4080 women were enrolled with 437 being excluded due to invalid information, lack of careHPV or hc2 results. Overall agreement between the tests was substantial with a kappa value of 0.69 (95% CI: 0.66-0.72), sensitivity and specificity of careHPV was 90.7% (95% CI: 89.6 – 91.8) and 84.2% (95% CI: 81.2 – 86.8) respectively. the agreement was similar in the stratified analyses where the kappa values were 0.75 (95% CI:0.70-0.79) in women aged 25-34, 0.66 (95% CI:0.62-0.70) in women aged 35-60, 0.73 (95% CI: 0.70-0.77) at Ocean Road Cancer Institute, 0.64 (95% CI: 0.60-0.69) at Kilimanjaro Christian Medical Centre, 0.73 (95% CI: 0.68-0.79) in HIV positive and 0.66 (95% CI: 0.63-0.70) in HIV negative women. The kappa value of 0.64 (95% CI: 0.39 – 0.88) for cervical high-grade lesions indicates a substantial agreement between careHPV and HC2 in detecting HPV among women with cervical high-grade lesions.

**Conclusions:** a substantial agreement was found between careHPV and HC2 in detecting HPV overall as well as detecting HPV among women with cervical high-grade lesions. However, given the limited resources available in low and middle-income countries, the HPV testing assay should be weighed against the cost effectiveness of the test.

**Keywords:**
careHPV, Hybrid capture 2, HPV, Tanzania, women, agreement,
INTRODUCTION

Despite being preventable, cervical cancer ranks as the fourth most common cancer globally [1]. A disproportional high percentage (86%) of cervical cancer cases and deaths occur in low and middle-income countries (LMICs) and it is evident that the disease mainly affects women who lack access to cervical cancer screening and treatment [2]. Practically, all cervical
cancer cases are caused by persistent infection with high-risk human papillomavirus (HPV) types. Among HIV infected women, the risk of cervical cancer is increased since impaired immune status is associated with an increased risk of HPV persistence and progression of pre-cancerous lesions into cancerous lesion [3].

Although cervical cancer is a lethal disease, it can be prevented if appropriate measures are taken in time. For example, in some LMICs, lifetime risk of getting cervical cancer was reduced by more than thirty per cent in women screened once or twice by visual inspection with acetic acid (VIA) or HPV DNA testing [4]. Other strategies have also been employed to prevent the disease, like HPV vaccination to girls and boys, where more than 80 countries globally have implemented HPV vaccination programs [5,6]. However, in LMICs where the burden of cervical cancer is highest and where the need for vaccination is most pronounced, significant financial barriers hamper the introduction of HPV vaccination [7].

HPV DNA testing is currently used as a primary cervical cancer screening method in a number of high-income countries [8,9]. Hybrid Capture 2 (HC2; Qiagen, Inc., Valencia, CA, USA) was the first high-risk HPV test approved by U.S. Food and Drug Administration [10] and has extensively been used worldwide [11]. HC2 detects at least 13 high-risk HPV types (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68) [12]. However, HC2 HPV testing requires a sophisticated environment with highly qualified personnel, which cannot be afforded by most LMICs. On this ground, careHPV (Qiagen), a rapid and less expensive derivative of HC2, has been developed. It has been documented that the careHPV test performs well in clinical trials conducted by well-trained lab personnel [12-15]. However, the performance of the test in resource constrained settings has not been thoroughly documented. Further, in the evaluation of screening programmes relying on careHPV testing, it should be acknowledged that the various high-risk HPV genotypes included in the test have different carcinogenic potentials. If marginally carcinogenic HPV types are included in rapid HPV tests it may add an increased number of women being screened false positive. This can lead to misuse of constraint financial resources, which may be a problem in LMICs. Additionally, it may lead to overtreatment and increased morbidity associated with the treatment [16]. This study aims to evaluate the test agreement between careHPV and HC2 in detecting high-risk HPV in a low resource setting and to assess the agreement stratified by age, testing site, HIV status, and cytology result.

MATERIAL AND METHODS

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Enrolment and data collection

The present study is a sub-study of a larger research study, Comprehensive Cervical Cancer Prevention in Tanzania (CONCEPT), which aims to improve prevention of cervical cancer in Tanzania. The CONCEPT study is linked to the existing national cervical cancer screening programmes in Dar es Salaam and Kilimanjaro Regions.

Data were collected among women attending cervical cancer screening at Ocean Road Cancer Institute (ORCI) in Dar es Salaam, and Kilimanjaro Christian Medical Centre (KCMC) and Mawenzi Regional Hospital in Kilimanjaro Region. Women aged 25-60 were eligible for the study. Exclusion criteria included having menstruation, being pregnant or having a history of hysterectomy or precancerous lesion.

All women underwent gynaecological examination performed by qualified health care providers. Firstly, cervical specimens were obtained for careHPV analysis, liquid based cytology and HC2 DNA analyses in the mentioned order. Thereafter VIA was performed according to the National standard guideline for cervical cancer screening [17]. Details of enrollment procedure are described elsewhere [18].

HIV analysis

HIV testing was offered to all women with unknown HIV status as part of routine cervical cancer screening. The testing was performed according to the Tanzanian HIV/AIDS guideline [19]. Venous blood was obtained and tested by use of a rapid immunoassay test (SD bio-line HIV 1/2 3.0 rapid test; Standard Diagnostics, South Korea). The positive results were confirmed by a supplementary quick HIV-1/2 test (HIV-1/2 Determine; Abbott Laboratories). Discordant results were further confirmed using Uni-gold (Recombigen® HIV-1/2; Trinity Biotech, USA). All HIV positive women were connected to HIV care and treatment clinics at the respective sites.

HPV DNA detection

careHPV testing
Laboratory staffs (two from ORCI and two from KCMC) attended a two days training course led by a lab technician from the manufacturing company (Qiagen Inc.). An introduction to the principles behind careHPV testing was provided the first day together with a demonstration of the careHPV test kit and the careHPV machine. The second day was allocated to practical training where the trainees got hands on experience on how to perform the careHPV analyses. Laboratory staff from ORCI and KCMC used laboratory facility at ORCI to run test samples, each did the test on separate occasion independent of the other and got similar results. All samples from Mawenzi hospital were taken to KCMC for analysis.

Specimens for careHPV testing were obtained among all participating women using the careBrush as recommended by the manufacturer. The obtained specimens were stored in careHPV collection medium (Qiagen) and kept at room temperature (max 25 °C) in the laboratories at ORCI and KCMC. They were kept for maximum 14 days and analysed by the careHPV test using a careHPV machine when we reached a number of 90 samples. The machine can 14 high-risk HPV types (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68). The careHPV test targets HPV DNA from lysed cells which is denatured and hybridized by complementary RNA, then captured by antibodies coated on the magnetic beads. The captured hybrids are detected by alkaline phosphatase conjugate, which reacts with an added chemiluminescent substrate to produce light which is proportional to the number of bound alkaline phosphatase molecules per target [12].

The HC2 assay detects a pool of 13 high-risk HPV types (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68). The careHPV assay is broadly based on the HC2 assay and targets 14 high-risk HPV types. Both HC2 and careHPV positivity were calculated at 1.0 RLU/CO (approximately equal to 1.0 pg DNA per mL) according to the manufacturer’s recommendation [12]. In one of our recent papers we showed that among all women, careHPV had a sensitivity of 88.9% (95% CI: 82.4–93.9) and a specificity of 78.9% (95% CI: 77.5–80.3) while the HC2 test had a slightly higher sensitivity of 91.1% (95% CI: 85.0–95.3) and a slightly higher specificity of 83.7% (95% CI: 82.4–84.9) [18].

**HC2 testing**

A second cervical sample was obtained for HC2 testing and liquid-based cytology using ThinPrep® Pap Test Plastic Spatula (Innogenetics, Gent, Belgium). The samples were kept in PreServCyt solution (Hologic, Inc., Marlborough, USA) and firstly shipped to Denmark for analysis.
cytological assessment and thereafter to Germany (Section for Experimental Virology, Tubingen University) for HPV DNA testing and genotyping.

HPV DNA testing was done using the HC2 DNA test (www.qiagen.com) with a high-risk cocktail probe. A threshold of 1.0 pg HPV DNA/ml, which corresponds to 1.0 relative light unit coefficient, was used, as recommended by United States Food and Drug Authority.

HC2 HPV positive samples were further analyzed to determine the HPV genotype using the LiPA Extra test (FujiRebio Gent, Belgium). DNA was isolated with the help of the Qiasymphony device (Qiagen) from 200 μl of the remaining denatured cervical samples. The LiPA Extra test is a lineblot assay based on the principle of reverse hybridization. It covers 18 putative high-risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 26, 53, 66, 73, and 82), 7 LR HPV types (6, 11, 40, 43, 44, 54, and 70), and three additional types (69, 71, and 74) [20]. Subsequently, 5 μl of DNA solution was used for the LiPA Extra SPF-PCR assay. Polymerase chain reaction products were then denatured, and a 10 μl aliquot was hybridized to an HPV genotype detection strip. The resulting strip reading was performed using a scanner and the LiRAS prototype software (Innogenetics Inc.)

Liquid based cytology

All samples underwent cytological assessment at the Department of Pathology at Lillebaelt Hospital, Vejle, Denmark. They were processed at the ThinPrep5000 Autoloader Instrument, Hologic® according to manufactures instruction and stained with ThinPrep Stain®. The slides were scanned by the Thin Prep Imaging System® with selection of 22 fields of view which was reviewed by cytotechnologist in review scopes. The specimens were evaluated for adequacy and for abnormal cells. If abnormal cells were detected, the slides were consulted with a gynae-pathologist who made the final diagnosis. The specimens were diagnosed according to the Bethesda Nomenclature for System for Cervical Cytology 2014 [21]: negative for intraepithelial lesion or malignancy (NILM), atypical squamous cell of undetermined significance (ASCUS), atypical squamous cell in which high grade squamous intraepithelial lesion cannot be excluded (ASC-H), low grade squamous intraepithelial lesion (LSIL), high grade squamous intraepithelial lesion (HSIL), atypical glandular cell (AGC), adenocarcinoma in situ (AIS), and adenocarcinoma. No abnormal cells were detected in the inadequate samples and for the purpose of this study they were included in the NILM group. Women with HSIL or worse were referred for colposcopy and biopsy according to the national guidelines.

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Statistical analyses

The kappa statistic was calculated to analyze the agreement of the careHPV assay against HC2 in the detection of HPV genotypes. Kappa values were interpreted as poor/slight agreement (0.00 - 0.20), fair agreement (0.21 - 0.40), moderate agreement (0.41 - 0.60), substantial agreement (0.61 - 0.80), or almost perfect agreement (0.81 - 1.00) [22]. The analytical sensitivity, specificity, positive and negative predictive value (PPV/NPV) of careHPV was calculated with 95% CI using HC2 as reference. The analyses were done for the overall study population and stratified by age, testing site and HIV status. Agreement between the careHPV test result and genotypes identified by LiPaExtra was determined by percentage overall agreement and percentage agreement for the individual HPV genotypes. Also kappa statistic was calculated to analyze agreement of careHPV against HC2 in detection of precancerous lesion. All analyses were performed using the Stata version 15 (Stata Corp., College Station, TX, USA).

Ethical approval

The ethical approval for this study, obtained from National institute for medical research for medical research in Tanzania with reference number NIMR/HQ/R.8a/Vol. IX/1955 dated 11/05/2015.

RESULTS

A total of 4080 women were enrolled into the CONCEPT study. After inclusion, 37 study participants were excluded (6 women with invalid ID number, 14 women with no questionnaire and 17 women who lacked vaginal samples). An additional 4 women were excluded due to lack of careHPV results and 396 women were excluded due to insufficient material for cytological assessment and HC2 HPV analysis. The 3643 women who were included in the analysis did not differ significantly in terms of age, marital situation and parity from the 396 women who were excluded from the analysis.

The majority of the women were aged 35 – 54 years (67.6%) and married (70.8%). Most of the participants (64.8%) had primary education, and 55% reported that they had three or more children whilst a small proportion reported never to have given birth (6.5%). Most participants (82.2%) were HIV-negative.
The high-risk HPV prevalence was 23.6% (858/3643) by careHPV and 19.1% (695/3643) by HC2. The overall agreement between tests was 89.5% (3260/3643) with a kappa value of 0.69. Among women aged 25 – 34 the prevalence of high-risk HPV was 26.6% by careHPV and 24.5% by HC2. The corresponding figures for women aged 35 – 60 were 22.4% and 17.1%. The agreement in women aged 25 – 34 was 90.3 (88.3 – 92.1) with a Kappa value of 0.75. The corresponding figures in women aged 35-60 was 89.2 (88.0 – 90.4) and 0.66. At ORCI, the prevalence of high-risk HPV was 23.8% as detected by careHPV and 21.1% by HC2. At KCMC, the corresponding figures were 23.3% and 17.3%, respectively. At ORCI, the agreement was 90.8% (1533/1689) with a kappa value of 0.73. The corresponding figures at KCMC were 88.4% (1727/1954) and 0.64.

Among 652 HIV positive women, 242 (37.1%) were found to have HPV infection when tested with careHPV whereas 220 (33.7%) were HPV positive when tested with HC2. In the 2991 HIV negative women, 616 (20.6%) tested HPV positive with careHPV and 475 (15.9%) with HC2. In HIV positive women, the agreement between the two tests was 87.7% (572/652) with a kappa value of 0.73. In HIV negative women the agreement was 89.9% (2688/2991) with a kappa value of 0.66.

The sensitivity and specificity with which the careHPV test detected HPV infection in comparison with HC2 was 90.7% and 84.2%, respectively. When looking at age, the careHPV test had slightly higher sensitivity (92.2% vs 90.3%) and specificity (84.5% vs 84.0%) in women aged 25 – 34 years in comparison with women aged 35-60 years. In the stratified analyses based on health facility, the careHPV test performed slightly better at ORCI than at KCMC with a sensitivity of 92.4% vs 89.3% and a specificity of 84.6% vs 83.8%. When focusing on HIV status, the careHPV test had a slightly poorer sensitivity and a higher specificity in HIV positive women than in HIV negative women (table 2).

The agreement between careHPV and HC2 according to genotypes is summarized in Table 3. For Alpha 9 species, which include HPV types 16, 31, 33, 35, 52, 58, the agreement ranged from 88.5% to 94.6%, being highest for HPV 16 and lowest for HPV 52. For Alpha 7 species, which include HPV types 18, 39, 45, 59 and 68, the agreement ranged from 84.4% to 93.9%, with a relatively lower agreement for HPV 18 (86.5%) and HPV 39 (84.4%).

The agreement of the tests in relation to cytology, where the population was restricted to those with cytology results (n=3620), showed an overall prevalence of HSIL of 3.7% (133/3620). As shown in Table 4, the prevalence of high-risk HPV detected by careHPV or HC2 increased with severity of the lesion. The agreement between careHPV and HC2 according to...
lesion grade was 94.0% for HSIL+, 90.1% for LSIL, 89.3% for ASCUS and 89.3% for women with normal cytology. The kappa test values of 0.64 for both HSIL+ and LSIL indicate a substantial agreement between careHPV and HC2 in detecting HPV among women with HSIL+ and LSIL.

**DISCUSSION**

We found a substantial agreement in HPV detection between careHPV and HC2, although careHPV detected more high-risk HPV types than HC2 (24% vs. 19%) and proved to have a lower specificity. Compared with HC2, no cases of HSIL+ were overlooked by careHPV testing.

A main strength of the study is that it relies on two clinically validated PCR-based HPV DNA test assays on paired samples. Furthermore, the analyses of the careHPV samples were performed in local laboratories at KCMC and ORCI, which is the most relevant setting for testing careHPV before it is scaled up in routine screening settings. Also the study had a fairly large sample size that allowed us to evaluate the test performance according to the women’s age, the testing site, and HIV status. Further, the samples were obtained by the same staff using the same technique, this ensured that the samples were comparable.

One potential limitation is the time span between the analyses of the careHPV and HC2 samples, hence the HC2 samples were kept in PreServCyt solution for 9-12 months before being shipped to Germany. This may have affected the amount of HPV DNA in the HC2 samples, however, HPV DNA is generally considered to be stable for more than 2.5 years when stored in PreServCyt solution [23]. Thus, we assume that the difference in time span has not significantly affected our results and conclusion.

Finally, histological results should have been available for all women, however, in a setting with high prevalence rates of HIV positive women, we found it unethical to obtain biopsies on all women. Instead we relied on cytological assessment to document whether careHPV testing had overlooked any potential high grade cervical lesions.

The overall agreement between the two tests was substantial. The findings are similar to studies done in various settings [24,25,26]. This can be explained by the test design; CareHPV is a derivative of HC2 so most of the relevant components are similar and thus the two tests.
provide almost identical results [12]. However, the careHPV test was slightly more likely to test HPV positive than the HC2 test.

The careHPV test performed equally well among HIV positive and HIV negative women. Other studies have likewise reported an excellent agreement between careHPV and HC2 among HIV positive women as well as HIV negative women [25,27]. Our results together with findings from other studies indicate the careHPV test has potential for scaling up HPV testing in both HIV positive and HIV negative women. However, although the careHPV sampling and testing is cheaper than HC2 testing, it may still be rather costly in a low-income setting like Tanzania. To address this problem alternative solutions, like e.g. using simple cotton swab smeared on a glass slide followed by low-cost PCR-based techniques to detect HR HPV infections, have been examined with promising results (28).

Another important finding of our study is that there was no difference in the performance of careHPV test between ORCI, the national cancer institute and KCMC, a zonal referral hospital. This finding also has implications for the future scale up of cervical cancer screening in Tanzania, where screening is challenged by a low coverage due to limited availability of screening facilities resulting in long travel distances for the women. In future, by coupling careHPV testing with HPV self-collection, the screening service could be brought even closer to women, especially to older women living in remote areas. Such an approach is supported by the findings from a qualitative study conducted in Tanzania where the majority of the women preferred self-sampling over provider-based sampling [29].

When considering implementing HPV-testing to identify women at highest risk of HSIL+, it is of great importance that the screening is coupled with systematic treatment. This can be implemented by a see-and-treat approach where HPV positive women undergo colposcopy, digital cervicography or VIA - and if positive - subsequent treatment. However, such an approach requires good organisational compliance of the target population as well as well-trained health staff who are skilled in performing colposcopy or VIA. If these obstacles are overcome, a see-and-treat approach may help reduce false positive cases which will minimize ‘over treatment’ and further help reduce unnecessary referrals.

The analytical performance of the careHPV test for the detection of HC2 positive women showed that careHPV was slightly less sensitive and less specific in detecting high-risk HPV DNA. However, various studies, including our own research, have documented that the clinical performance of the two tests are comparable [1830 ,31]. Thus, it may be reasoned that the
observed differences in analytical sensitivity of careHPV may not affect its usefulness as a screening test. Though, given the relative low specificity of careHPV that poses a risk of false positive testing, large multi-country studies should be considered with the aim of acquiring a reliable cut off point. Such information will help balance the best possible testing cut off while having in mind the cost effectiveness of the screening [32].

Compared to results related to HC2 positive samples, careHPV captured 94% of HPV 16 and 87% of HPV 18. This is comparable to detection rates reported by Yu Q et al [33]. HPV 16 and 18 are jointly responsible for 70% of cervical cancers [34], thus careHPV has the potential to detect most of the expected cases of cervical cancer when compared to HC2. Also it captured other less carcinogenic types like HPV 39, 59, 68, 51 and 56 as in the study performed by Secondy et al [35]. The higher HPV positivity rate found by careHPV could be due to the test’s ability to identify these less carcinogenic HPV types. This may be associated with a waste of resources, which may be a problem especially in LMICs where economic means are constrained [16]. While having this in mind, it may be considered limiting the range of HPV types in the care HPV test to the most carcinogenic ones to improve the cost effectiveness of the testing.

The ability of careHPV to detect most of HSIL+ is important and in agreement with research done in various countries [36]. This increases the confidence in ability of the careHPV test to detect pre-cancerous lesion and makes it a trustworthy supplement to VIA or cytology in cervical cancer screening programs in LMICs. Further, in resource-limited countries like Tanzania with few pathologists and well-equipped laboratory facilities, the introduction of careHPV testing might help minimize referrals to tertiary hospitals for specialized care.

Although we found a substantial agreement in HPV detection between careHPV and HC2, it may be argued that the careHPV assay is still inferior to the HC2 assay and needs some improvement for better implementation. Further, the careHPV test has been launched as a low cost HPV test, however, in resource-limited settings, the price may still be considered rather costly for national scale up.

CONCLUSION

The careHPV test has a substantial agreement with HC2 in detecting HPV overall as well as detecting HPV among women with cervical high-grade lesions and should thus be considered integrated in routine cervical cancer screening programs in LMICs. However, given the limited
resources available in LMICs, the cut off level as well as the HPV types to be included in the HPV testing assay should be weighed against the cost effectiveness of the test.

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Legends

Table 1. Agreement of paired careHPV and HC2 testing for detection of HPV among 3643 women. Overall and stratified for testing site and HIV status.

Table 2. Analytical performance of careHPV for detection of HC2 positive women. Overall and stratified for testing site and HIV status.

Table 3: HPV genotypes and agreement of CareHPV and HC2 by HPV genotype.

Table 4: Agreement of CareHPV and HC2 by cytology.
Table 1. Agreement of paired careHPV and HC2 testing for detection of HPV among 3643 women. Overall and stratified for testing site

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ORCI Ocean Road Cancer Institute; KCMC Kilimanjaro Christian Medical Centre.

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<table>
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<th>Age (years)</th>
<th>Sensitivity %</th>
<th>Specificity %</th>
<th>PPV %</th>
<th>NPV %</th>
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<td>90.7 (89.6 – 91.8)</td>
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<td>96.1 (95.3 – 96.7)</td>
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<td>83.8 (79.4 – 87.5)</td>
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<td>64.0 (60.0 – 67.8)</td>
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</table>

ORCI Ocean Road Cancer Institute; KCMC Kilimanjaro Christian Medical Centre.
Table 3: HPV genotypes and agreement of CareHPV and HC2 by HPV genotype

<table>
<thead>
<tr>
<th>HPV Type</th>
<th>Positive N</th>
<th>Negative N</th>
<th>% agreement</th>
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<tr>
<td>HC2 positive</td>
<td>695</td>
<td>585</td>
<td>110</td>
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<td>α 9 variant</td>
<td>129</td>
<td>70</td>
<td>37</td>
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<tr>
<td>α 7 variant</td>
<td>89</td>
<td>77</td>
<td>12</td>
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<td>α 5-6 variant</td>
<td>72</td>
<td>65</td>
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Table 4: Agreement of CareHPV and HC2 by cytology

<table>
<thead>
<tr>
<th>Cytology</th>
<th>N=3620</th>
<th>CareHPV</th>
<th>HC2</th>
<th>% agreement (95% CI)</th>
<th>Kappa (95% CI)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Pos (%)</td>
<td>Neg (%)</td>
<td>Pos (%)</td>
<td>Neg (%)</td>
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<tr>
<td>Normal</td>
<td>3190</td>
<td>560 (17.6)</td>
<td>2630 (82.4)</td>
<td>387 (12.1)</td>
<td>2803 (87.9)</td>
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<td>98 (50.0)</td>
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<td>101 (51.5)</td>
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<td>LSIL</td>
<td>101</td>
<td>80 (79.2)</td>
<td>21 (20.8)</td>
<td>90 (89.1)</td>
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<td>HSIL+</td>
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ASCUS, atypical squamous cell of undetermined significance; LSIL, low grade squamous intraepithelial lesion; HSIL, high grade squamous intraepithelial lesion.