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ORIGINAL ARTICLE

An automated quantitative DNA image cytometry system detects abnormal cells in cervical cytology with high sensitivity

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Objective: To evaluate the performance of an automated DNA-image-cytometry system as a tool to detect cervical carcinoma.

Methods: Of 384 liquid-based cervical cytology samples with available biopsy follow-up were analyzed by both the Imager System and a high-risk HPV test (Cobas).

Results: The sensitivity and specificity of Imager System for detecting biopsy proven high-grade squamous intraepithelial lesion (HSIL, cervical intraepithelial neoplasia [CIN]2-3) and carcinoma were 89.58% and 56.25%, respectively, compared to 97.22% and 23.33% of HPV test but additional HPV 16/18 genotyping increased the specificity to 69.58%. The sensitivity and specificity of the Imager System for predicting HSIL+ (CIN2-3+) lesions among atypical squamous cells of undetermined significance samples were 80.00% and 70.53%, respectively, compared to 100% and 11.58% of HPV test whilst the HPV 16/18 genotyping increased the specificity to 77.89%. Among atypical squamous cells-cannot exclude HSIL, the sensitivity and specificity of Imager System for predicting HSIL+ (CIN2-3+) lesions upon follow up were 82.86% and 33.33%%, respectively, compared to 97.14% and 4.76% of HPV test and the HPV 16/18 genotyping increased the specificity to 19.05%. Among low-grade squamous intraepithelial lesion cases, the sensitivity and specificity of the Imager System for predicting HSIL+ (CIN2-3+) lesions were 66.67% and 35.71%%, respectively, compared to 66.67% and 29.76% of HPV test while HPV 16/18 genotyping increased the specificity to 79.76%. The overall results of imager and high-risk HPV test agreed in 69.43% (268) of all samples.

Conclusions: The automated imager system and HPV 16/18 genotyping can enhance the specificity of detecting HSIL+ (CIN2-3+) lesions.

KEYWORDS
automated DNA-image-cytometry, cervical cancer, DNA ploidy, HPV DNA test, screening

1 | INTRODUCTION

The Papanicolaou (Pap) test has contributed tremendously to the prevention of cervical cancer since its invention. Countries with a well-organised cervical screening programme have demonstrated reduction in incidence and mortality rates of cervical cancer.[1-4] Despite its proven success, Pap test exhibits several limitations.[5] The sensitivity of Pap test for detecting cervical cancer and precursors varies among laboratories, although the specificity is generally high.[6] The invention of LBC has overcome some of the limitations of conventional smear by reducing unsatisfactory and suboptimal smears.[7] However, there still exist cervical cancer cases found in women who

previously received *proper* screening.[8] Moreover, despite international standardisation in diagnostic criteria, subjective assessment of cellular morphological features and associated interobserver variability still exists.[9] Molecular tests such as high-risk (HR)-HPV DNA/RNA detection and immunocytochemical markers have been emerging as replacement or adjunct tests in primary screening, *co-testing* with cytology in women older than 30 years, reflex triage test for borderline cervical cytology including atypical squamous cells of undetermined significance (ASC-US)[10] and low-grade squamous intraepithelial lesion (LSIL), the latter in postmenopausal women.[11-14]

Computer assisted analysis represents another direction to enhance the accuracy and to reduce the labour involved in Pap smear evaluation.[15,16] Currently, ThinPrep Imaging System (Hologic Inc, Marlborough, MA, USA) and the FocalPoint Slide Profiler (Becton, Dickinson and Company, Franklin Lakes, NJ, USA) have successfully been adopted to facilitate the cytology slide evaluation process.[17-19] The former incorporates the use of DNA sensitive dye while the latter adopts algorithms to assess cell changes. Both involve the use of computerised devices to detect higher risk fields of view (FOV; ThinPrep) or cases (FocalPoint) but the final interpretation and diagnosis still depends on human (cytotechnologists and pathologists).

Completely automated reporting of cervical cytology continues to be developed. Structural and numerical chromosomes instability, largely caused by the HPV oncoproteins E6 and E7, is an early and important hallmark of cervical cancer development.[20,21] DNA ploidy evaluation by flow cytometry[22-24] and DNA image cytometry has been explored as a screening test for cervical cancer.[25,26] MotiSavant (Motic, Xiamen, China), one of the more commonly used automatic imaging system,[27] is composed of a scanning microscope, a camera and two software: MotiCytometer1.1 for image acquisition and MotiClassify for scoring the images of nuclei.[28] Neoplastic changes were judged based on three criteria: number of aneuploid cell, number of proliferating cells, and presence or absence of aneuploidy peak in the histogram (when the number of cells is plotted against DNA content) and scatter diagram (when nuclear area is plotted against DNA index; Figure 1).[29]

Relatively few studies have addressed the differences between the performances of DNA cytometry and HPV tests. Here, we compared the performances of MotiSavant DNA cytometry and Cobas HPV test which has been approved by US Food and Drug Administration for cervical cancer screening.

2 | MATERIALS AND METHODS

2.1 | Clinical samples

Four hundred and forty-one ThinPrep cervical cytology residues of various diagnostic categories were retrieved from the archives of the University of Hong Kong Cervical Cytology laboratory. Negative for intraepithelial (NIL) samples were confirmed by at least two consecutive follow up negative Pap smears. All cases except NIL or HPV negative ASC-US had biopsy data. The cases were reported between 2004 and 2013 and the residues were stored in an air-conditioned storage room at approximately 22°C. The diagnoses of most of these cases were made with the assistance of a ThinPrep Imaging System. The mean age of the patients was 39.8 year (range: 18-86 year). All the ASC-US cases have been evaluated with Cobas HPV test (Roche Molecular Diagnostic, Pleasanton, CA, USA) for triage management according to the guidelines set by Hong Kong College of Obstetricians and Gynaecologists. Women with ASC-US tested positive for HR-HPV were referred for colposcopy whereas HR-HPV negative patients were monitored with repeated cytology at 12-month intervals. Among the 139 ASC-US, 94 were HR-HPV positive. More HR-HPV positive ASC-US cases have been recruited for study to increase the number of cases with biopsy follow up data. The most serious biopsy finding during the follow-up period was identified. The use of archived cytology specimens for research purpose was approved by the institutional review board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (HKU/HA HKW IRB UW 12-397).

2.2 | HPV test

The HR-HPV status of the samples was evaluated using Cobas HPV test following the manufacturer's instruction. Cobas HPV test can identify HPV 16 and 18 in addition to 12 other HR-HPV genotypes.

2.3 | Preparation of Feulgen stained smears for review by Imager system

Feulgen stain was used for quantitative image analysis of DNA content in cells as previously described.[30] Cells in 6 mL ThinPrep® cytology residues were collected by centrifugation and resuspended in distilled water. Two drops of the diluted sample were mixed with 100 μL GluCute Cell Adheren. Two drops of the cell-GluCute mixture were dropped onto a slide, and fixed in Bohm-Sprenger fixative. The slides were then rinsed, and then acidolysed by 5N hydrochloric acid before stained in filtrated Feulgen DNA staining reagent.

2.4 | Scanning and analysis of DNA image

Samples slides were scanned by a MotiSavant (Motic Inc., Xiamen, China). Each screening was completed when the number of screened cell has reached 8000 or the entire pre-set area has been screened. MotiClassify was used for classifying each scanned nuclear image. Screened images of the nuclei of each sample were displayed in descending order according to their DNA index (Figure 1B,D,F,H). Overlapping nuclei misidentified as single nuclei by the software was unflagged for analysis manually.

2.5 | Interpretation of image data

Three criteria were used by MotiClassify to evaluate the degree of abnormality of a sample: DNA index, proliferation activity and presence of aneuploid peak. For each criterion, an integer score of 2, 3 or 4 was given (except aneuploid peak, which was only scored as 2 or 4; Table 1). Ultimately, the integrated DNA-cytometry result of a

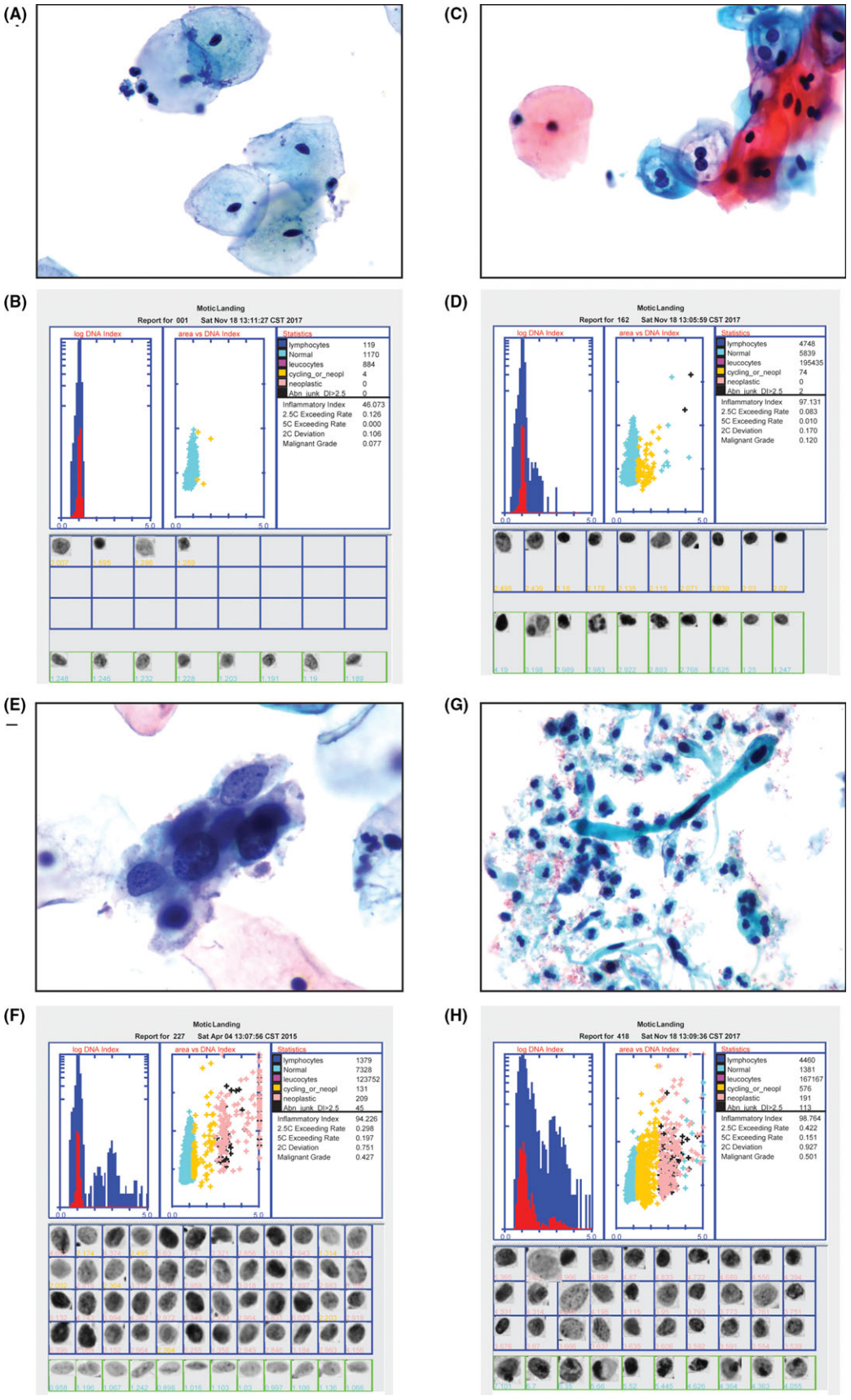

FIGURE 1 DNA image analysis of cervical smear by the Imager system. Photomicrographs showing the cytological features of (A) negative, (C) low-grade squamous intraepithelial lesion, (E) high-grade squamous intraepithelial lesion and (G) squamous cell carcinoma and corresponding DNA imager layout of cases with scores of (B) 2 (Case 1), (D) 3 (Case 162), (F) 4 (Case 227) and (H) 4 (Case 418), respectively

TABLE 1 Scoring criteria

1. No. of cells with DI ≥ 2.5	
0	2
1-2	3
3 or above	4
2. % of proliferating cell	
<5%	2
≥5% or <10%	3
≥10%	4
3. Aneuploid peak	
Absent	2
Present	4

sample was equal to the highest of the individual scores. Integrated results of 2, 3 and 4 were interpreted as *Normal*, *Suspicious* and *Abnormal*, respectively. For the purpose of this study, a more stringent approach was adopted. *Normal* and *Suspicious* was regarded as test negative, whereas *Abnormal* was regarded as test positive.

2.6 | Satisfactory criteria for analysis

All samples with *Suspicious* or *Abnormal* DNA-cytometry result were included in analysis regardless of the number of cell counted on their slides. Samples with *Normal* result but fewer than 1000 counted cells were excluded from study.

2.7 | Statistical analysis

The performance of the Imager system as cervical cancer detection tool was evaluated by calculating the sensitivity and specificity of the test to detect any cytology sample with HSIL or worse (HSIL+, cervical intraepithelial neoplasia [CIN] 2-3+) biopsy results. The performance in ASC-US triage was evaluated by calculating the sensitivity and specificity of the test to identify samples with HSIL+ (CIN 2-3+) detected in follow-up biopsy. The difference between proportions of Imager or HPV test positive in each diagnostic category was tested with *Z*-test. The differences between the sensitivities or specificities of the two tests under various settings were investigated by McNemar's test. The concordance between HR-HPV test and Imager test was evaluated by calculating the Cohan's κ.

3 | RESULTS

3.1 | Imager test was less sensitive but more specific than pooled HPV test in identifying high-grade lesions

Out of the 441 LBC samples processed, 384 (87.07%) were satisfactorily evaluated by both the imager and Cobas test, including 21 NIL, 87 LSIL, 58 HSIL, and 26 squamous cell carcinoma (SCC), 105 ASC-US, 31 atypical glandular cells (AGC) and 56 atypical squamous cells-cannot exclude HSIL (ASC-H; Table 2). Cases with unsatisfactory imager analysis or invalid HPV test were excluded.

None of the NIL (0/21, 0%) and a relatively low percentage of ASC-US (36/105, 34.29%) were Imager test positive (Table 2). In contrast, HR-HPV could be found in 23.81% of NIL and 89.52% of ASC-US samples (Table 2). The proportion of Imager positive cases was significantly lower than the proportion of HR-HPV positive cases in NIL, ASC-US, AGC, and ASC-H samples (Table 2), suggesting that most discrepancies between Imager test and HPV test occurred in <LSIL cases. Overall, the two tests agreed in 268 (69.43%) of the samples and the Cohen's κ was 0.284 (95% confidence interval [CI]: 0.197-0.370).

Biopsy data confirmed the diagnosis of LSIL (CIN1; n = 202), HSIL (CIN2-3; n = 105), and carcinoma (n = 39). The carcinoma group includes 34 squamous cell carcinomas, four adenocarcinomas and one adenosquamous carcinoma. Biopsy examination of two patients with AGC revealed underlying endometrial adenocarcinoma and ovarian adenocarcinoma. These two cases were excluded from the evaluation of the sensitivity and specificity of the Imager and HPV tests but were included for concordance test.

The sensitivity and specificity of Imager test for identifying biopsy confirmed HSIL (CIN2-3) and carcinoma (SCC/adenocarcinoma/adenosquamous carcinoma) were 89.58% (95% CI: 83.40%-94.05%) and 56.25% (95% CI: 49.72%-62.62%) respectively (Table 3). Cobas HR-HPV test showed higher sensitivity than Imager (97.22% vs 89.58%, $P = .0055$) but Imager test has significantly higher specificity (56.25% vs 23.33%, $P < .0001$; Table 3). Detection of HPV18 alone achieved the highest specificity of 89.92% while detection of HPV 16 and detection of HPV 16 or 18 also improved the specificity of HPV tests to 75.21% and 69.58%, respectively.

3.2 | Imager was less sensitive than HPV test in triage of ASC-US or low-grade lesions

To evaluate Imager as a triage tool for equivocal cytology findings, we first examined whether HR-HPV and Imager test positive result could identify patients with ASC-US who subsequently had biopsy confirmed HSIL+ (CIN2-3 or carcinoma) during follow up. In this series, more HPV positive ASC-US cases were included to increase the number of cases with colposcopy biopsy follow up. The number of HPV positive and HPV negative ASC-US with satisfactory imager analysis and follow up data was 94 and 11 respectively in this series. As shown in Table 4, Cobas HPV test was able to highlight all HSIL+ (CIN 2-3+) cases (sensitivity = 100.00% [95% CI: 69.15%-100.00%]), but with low specificity (11.58% [95% CI: 5.92%-19.77%]). On the other hand, Imager test was less sensitive (80.00% [95% CI: 44.39%-97.48%]) but more specific (70.53% [95% CI: 60.29%-79.44%]; Table 4). Such improvement in specificity can also be achieved by detection of HPV 16 alone (83.16%), HPV 18 alone (93.68%) and HPV 16 or 18 (77.89%) but not by detection of Non16/18 HR-HPV (33.68%).

The performance of the two tests for triage of AGC (Table 5), ASC-H and LSIL (data not shown) displayed similar patterns. Imager

TABLE 2 Number of Imager test and high-risk (HR)-HPV positive cases in each category of diagnosis among LBC samples

Diagnosis	Number of sample	Number of satisfactory imager evaluated cases	Number of Imager positive[a] sample (% satisfactory imager evaluated cases)	Number of HR-HPV positive sample (% satisfactory imager evaluated cases)	*P*-value*
NIL	23	21	0 (0.00)	5 (23.81)	.0173
ASC-US	139	105	36 (34.29)	94 (89.52)	.0000
AGC	36	31	20 (64.52)	28 (90.32)	.0151
ASC-H	61	56	43 (76.79)	54 (96.43)	.0023
LSIL	91	87	56 (64.37)	61 (70.11)	.4179
HSIL	60	58	55 (94.83)	56 (96.55)	.6455
SCC	31	26	24 (92.31)	26 (100.00)	.1499
Total	441	384	234 (60.94)	324 (84.38)	.0000

[a]The highest of the individual scores among the three criteria was taken as the integrated DNA-cytometry result of a sample. Integrated results of 2, 3 and 4 were interpreted as *Normal*, *Suspicious* and *Abnormal*, respectively. In this study, only *Abnormal* was regarded as test positive whereas *Normal* and *Suspicious* were regarded as test negative.

*Z-test, proportion Imager positive vs proportion HR-HPV positive.

NIL, negative for intraepithelial; ASC-US, atypical squamous cells of undetermined significance; AGC, atypical glandular cells; ASC-H, atypical squamous cells-cannot exclude HSIL; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; SCC, squamous cell carcinoma

TABLE 3 Sensitivity and specificity of Imager test and HPV tests in detection of high-grade squamous intraepithelial lesion+ (cervical intraepithelial neoplasia 2-3+) lesions in a screening cohort

Test	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)
Cytology[a]	56.94% (48.44%-65.16%)	99.17% (97.02%-99.90%)	97.62% (91.66%-99.71%)	79.33% (74.31%-83.77%)
Imager	89.58% (83.40%-94.05%)	56.25% (49.72%-62.62%)	55.13% (48.51%-61.61%)	90.00% (84.04%-94.29%)
HR-HPV	97.22% (93.04%-99.24%)	23.33% (18.13%-29.20%)	43.21% (37.75%-48.80%)	93.33% (83.80%-98.15%)
HPV16	78.32% (70.66%-84.77%)	75.21% (69.22%-80.56%)	65.50% (57.86%-72.59%)	85.24% (79.71%-89.74%)
HPV18	16.91% (11.03%-24.29%)	89.92% (85.37%-93.43%)	48.94% (34.08%-36.94%)	65.44% (60.01%-70.59%)
HPV16 or HPV18	80.56% (73.14%-86.67%)	69.58% (63.34%-75.34%)	61.38% (54.03%-68.35%)	85.64% (79.92%-90.24%)
Non16/18 HR-HPV	88.81% (82.47%-93.47%)	37.24% (31.09%-43.70%)	45.85% (39.87%-51.91%)	84.76% (76.44%-91.03%)

[a]Most of these cases were diagnosed with the assistance of ThinPrep Imaging System.

PPV, positive predictive value; NPV, negative predictive value; HR, high risk

test demonstrated lower sensitivity but higher specificity than pooled HR-HPV test. Detection of HPV 16, HPV18 and HPV 16 or 18 improve the specificity.

3.3 | Interpersonnel variability

To access whether the interpretation of Motisavant findings needs professional training background, 32 of the slides were given to a non-cytotechnologist for operation through the scanning and MotiClassify result interpretation process. The absolute agreement between the results by cytotechnologist and non-cytotechnologist was 75%, and the Cohen's κ was 0.559 (95% CI: 0.340-0.778).

4 | DISCUSSION

The history of DNA image cytometry can be traced back to 1960s when Sandritter et al reported that measuring the DNA content of cells cytophotometrically could distinguish tumour and normal cells. In such measurements, an atypical DNA distribution pattern (DNA stem line) lying between diploid and tetraploid or octoploid values are indicative of abnormal cells.[31] The technique was later shown to be applicable to cells in effusions, proposing DNA image detected aneuploidy as a very sensitive and specific marker of neoplastic cells.[32,33] Since the procedure is quick, it has even been suggested for intraoperative evaluation of tumours.[34] Another advantage of DNA cytometry is its relative adaptability of automation and that quantitation of DNA content could be done at remote centres, enabling virtual cytology.[26,35]

Detecting cervical cancer cells using DNA image cytometry was adopted about a decade ago.[27,36,37] Sun et al[37] reported the sensitivity and specificity of imager for detecting HSIL+ (CIN2-3+) to be 82% and 71%, respectively, compared to 52% and 92%, respectively, for conventional cytology, while Zhang et al[38] stated their sensitivity and specificity to be 70.0% and 77.1%, respectively. Another study evaluating a similar DNA image cytometry system CytoSavant reported high specificity (96.9 $\pm$ 0.6%) but moderate sensitivity (54.4 $\pm$ 7%).[36] In this study, we evaluated the performance of MotiSavant, an automatic DNA cytometry system[28] in detecting cervical cancer and precursor cells in comparison to HPV test.

TABLE 4 Sensitivity and specificity of Imager test and HPV tests in detection of high-grade squamous intraepithelial lesion+ (cervical intraepithelial neoplasia 2-3+) lesions in triage of atypical squamous cells of undetermined significance

Test	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)
Imager	80.00% (44.39%-97.48%)	70.53% (60.29%-79.44%)	22.22% (10.12%-39.15%)	97.10% (89.92%-99.65%)
HR-HPV	100.00% (69.15%-100.00%)	11.58% (5.92%-19.77%)	10.64% (5.22%-18.70%)	100.00% (71.51%-100.00%)
HPV16	30.00% (6.67%-65.25%)	83.16% (74.10%-90.06%)	15.79% (3.38%-39.58%)	91.86% (83.95%-96.66%)
HPV18	0.00% (0.00%-30.85%)	93.68% (86.76%-97.65%)	0.00% (0.00%-45.93%)	89.90% (82.21%-95.05%)
HPV16 or HPV18	30.00% (6.67%-65.25%)	77.89% (68.22%-85.77%)	12.50% (2.66%-32.36%)	91.36% (83.00%-96.45%)
Non16/18 HR-HPV	70.00% (34.75%-93.33%)	33.68% (24.31%-44.11%)	10.00% (4.11%-19.52%)	91.43% (76.94%-98.20%)

PPV, positive predictive value; NPV, negative predictive value; HR, high risk

TABLE 5 Sensitivity and specificity of Imager test and HPV tests in detection of high-grade squamous intraepithelial lesion+ (cervical intraepithelial neoplasia 2-3+) lesions in triage of atypical glandular cells

Test	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)
Imager	92.86% (66.13%-99.82%)	58.82% (32.92%-81.56%)	65.00% (40.78%-84.61%)	90.91% (58.72%-99.77%)
HR-HPV	100.00% (76.84%-100.00%)	17.65% (3.80%-43.43%)	50.00% (30.65%-69.35%)	100.00% (29.24%-100.00%)
HPV16	69.23% (38.57%-90.91%)	47.06% (22.98%-72.19%)	50.00% (26.02%-73.98%)	66.67% (34.89%-90.08%)
HPV18	41.67% (15.17%-72.33%)	76.47% (50.10%-93.19%)	55.56% (21.20%-86.30%)	65.00% (40.78%-84.61%)
HPV16 or HPV18	78.57% (49.20%-95.34%)	35.29% (14.21%-61.67%)	50.00% (28.22%-71.78%)	66.67% (29.93%-92.51%)
Non16/18 HR-HPV	92.86% (66.13%-99.82%)	35.29% (14.21%-61.67%)	54.17% (32.82%-74.45%)	85.71% (42.13%-99.64%)

PPV, positive predictive value; NPV, negative predictive value; HR, high risk

The samples used in this study were LBC residues of archived cases. Our laboratory started to use ThinPrep Imaging system (Hologic) for cervical cancer cell detection more than a decade ago. Indeed, about three-quarters of the cases successfully evaluated by MotiSavant in this study were reported under assistance of the ThinPrep Imaging System (297/384, 77.34%). Using this system, the cells stained by DNA quantity-sensitive dyes are checked. In every smear, 22 FOV considered most worrying by the system are identified and their *x-y* axes recorded. These 22 FOV are then recalled using the Review Scope and evaluated by cyto-technicians. If no abnormal cells are found in these 22 FOV, the smear can be reported as negative after the quality control procedures have been followed. Otherwise, the whole smear will need to be manually checked for abnormal cells. Since this DNA quantity sensitive dye produces staining colour similar to that of usual Pap stain, the smears can be manually evaluated irrespective of whether the ThinPrep Imaging System has been used. As most of the cytology diagnoses were made with the assistance of the ThinPrep imaging system, our comparison between the automatic MotiSavant DNA Imager test and *cytology* (Table 3) might provide a rough comparison between the two systems. We found that the MotiSavant DNA imager was more sensitive (89.58% vs 56.94%) but cytology with help of ThinPrep imaging system achieved nearly 100% specificity for screening HSIL+ (CIN2-3+; Table 3). This high specificity of ThinPrep imager assisted screening agrees with that previously reported.[39] Similarly, another computer-assisted screening system BD FocalPoint, which ranks slides based on the probability of abnormality using algorithms to assess cell changes and laboratory customised stain, could also identify HSIL+ (CIN2-3+) with nearly 100% specificity.[40] Hence, it seems the human interpretation element adds specificity to the identification of cervical cancer and precursor cells at the expense of manpower limitation.

The performance of a similar semi-automated DNA image analysis system CytoSavant has previously been compared with Hybrid Capture II (HC2) HPV test in a study carried out in North America.[41] CytoSavant showed comparable specificity and negative predictive value (NPV) to HC2, but lower sensitivity and positive predictive value (PPV).[41] In this study, MotiSavant also demonstrated lower sensitivity but higher specificity than HR-HPV pooled test when applied to samples from an Asian screening population.[7] In addition, sensitivity/specificity as well as PPV and NPV of HPV 16 and 18 genotyping was also evaluated and compared using Cobas HPV test (Tables 3 and 4). Our findings show that HPV 16/18 genotyping as well as the MotiSavant Imager test could enhance the specificity in identifying cases with subsequent biopsy proven HSIL+ lesions.

Overall, the two tests agreed in 70% of the samples but the concordance increased to 94% among cases of HSIL and SCC. Most of the discrepancies were found in NIL, ASC-US, AGC, ASC-H and LSIL. The discrepancies in negative or borderline samples can be explained by the high sensitivity of HPV test in identifying a risk factor and not established lesions.

The LBC samples employed in this study were reported between 2004 and 2013 and the residues were stored in an air-conditioned storage room at approximately 22°C. Several studies dedicated to investigating the impact of long-term room temperature storage on molecular tests of LBC sample have demonstrated that such samples are generally stable for long period. For example, using samples stored in PreservCyt solution at room temperature for Aptima HPV

RNA to triage women with LSIL achieved good sensitivity and specificity.[42] Parallel comparison of LBC samples stored at –80°C and room temperature detected no difference in DNA quality, cytomorphology, and immunoreactivity during at least 1 year of storage.[43] Our previous studies on HPV DNA tests also showed the satisfactory quality of these archived samples for such evaluation.[11,44]

In this study we evaluated the performances of MotiSavant DNA imager and Cobas HPV test in cervical cancer screening by performing both tests on the same set of non-random samples selected to encompass various biopsy proven diagnostic categories. We found that the performance of the automated MotiSavant DNA imager was comparable with the ThinPrep Imaging System or Cobas HR-HPV test, the current commonly used cervical cancer screening tools (Table 3). The HR-HPV test combined with 16/18 genotyping seems to excel in achieving high sensitivity and specificity. Indeed, HR-HPV test is advocated to be the tool for primary screening as co-testing to be combined with cytology. However, one also needs to bear in mind the existence of HPV negative cervical carcinoma as highlighted by some studies.[45] Moreover, while cervical cytology is not targeted towards detection of carcinoma other than that from cervix, it provides a valuable opportunity of incidental detection of carcinoma from endometrium, ovaries or even extra-uterine location as found in our previous study on AGC.[46] Automated DNA imager or morphological evaluation of cytology smears with or without computer assisted examination may exhibit advantages from this angle. An automated imager such as MotiSavant, however, carries the additional benefit that well trained and adequately staffed professional cytotechnologists and pathologists are not required. As illustrated by a small-scale comparison on 32 cases in our study, good concordance in scoring MotiSavant imager by non-cytotechnologists and cytotechnologists was demonstrated. Large scale study in this aspect is necessary before conclusion can be drawn.

Whether and how the automated MotiSavant DNA imager, conventional or LBC with or without computer-assisted screening and HR-HPV test should be adopted in cervical cancer screening depends on various factors that may vary in different populations. Such factors may include the coverage of HPV vaccine, relative costs of these devices and availability of screening infrastructure. Cost-effective analysis should be conducted in populations of different culture and resources before a decision is made.

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AUTHORS' CONTRIBUTION

Conceptualisation: O.W., O.T., A.C.; formal analysis: O.W.; investigation: M.H., O.T., A.N., E.T., J.C.; writing – original draft preparation: O.W.; writing – review and editing: O.W., P.I., A.C.; supervision: A.C.

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