[redacted] CERVICAL SCREENING
TEST KIT

HEALTH TECHNOLOGY ASSESSMENT SECTION
MEDICAL DEVELOPMENT DIVISION
MINISTRY OF HEALTH MALAYSIA
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DISCLAIMER

Technology review is a brief report, prepared on an urgent basis, which draws on restricted reviews from analysis of pertinent literature, on expert opinion and / or regulatory status where appropriate. It has been subjected to an external review process. While effort has been made to do so, this document may not fully reflect all scientific research available. Additionally, other relevant scientific findings may have been reported since completion of this review.

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DISCLOSURE

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EXECUTIVE SUMMARY

Introduction

Cancer of the cervix is the third most common cancer among women and fifth most common cancer in the entire general population in Malaysia. There are a total of 847 cases diagnosed in 2007 registered at National Cancer Registry. Cervical cancer incidence rate increased with age after 30 years old and has its peaks at ages 65 – 69 years.

In Malaysia, the cervical cancer screening programme was established in 1969 to ensure early detection of cervical cancer among the target group of women aged 20 – 65 years. In 1995, the Ministry of Health launched the “Healthy Life Style Campaign against Cancer”, an open invitation to women aged 20 – 65 years to have Papanicolaou (Pap) smear taken every three years for free. However, only 47.3% of Malaysian women have been screened via Pap smears.

Currently, the cervical cancer screening in Malaysia uses the conventional Pap smears. However, there is a new technology named [redacted] Cervical Screening Test Kit.

[redacted] Cervical Screening Test Kit.is used for the detection elevated levels of E6 oncoprotein expressed by human papillomavirus (HPV) types 16 and 18. The manufacturer claims that it can demonstrate outstanding clinical performance with high specificity and high positive predictive value. Thus it can be used to triage patients with high-risk HPV and other abnormal screening results to avoid unnecessary treatment procedures.

This test is used to analyze cells extracted from cervical cytology swab specimens. It is based on the capture and detection of HPV E6 oncoproteins using high-affinity monoclonal antibodies (mAb) in a lateral-flow assay format. This technology relies on the capillary migration of the analyte through a nitrocellulose membrane, where specific capture antibodies are immobilized. The analyte is detected by an alkaline phosphatase (AP) conjugated mAb. The mAb-AP-analyte complex on the test is visualized by the addition of an enzyme substrate, producing a coloured line. A positive result is a visible test line.

The [redacted] Cervical Screening Test Kit is claimed to have high specificity, high positive predictive value, and stable at room temperature and does not require any complex equipment which allows cervical cancer detection to be carried at point-of-care. However, it is not known whether the claim is supported

by scientific evidence. Thus, this technology review was conducted following a request from Senior Principal Assistant Director, Disease Control Division.

Objective/aim

The objective of this technology review is to assess the safety, efficacy/effectiveness and cost-effectiveness of [redacted] Cervical Screening Test Kit at point-of-care.

Results and conclusions

There was limited good level of evidence retrieved on the efficacy/effectiveness of [redacted] Cervical Screening Test Kit. However, there was no retrievable evidence on safety and cost-effectiveness of this test. The test is certified with CE-IVD and the market price for this test is MYR 126 per kit for private sector.

Based on the above review, the evidence seems to indicate potential benefit of [redacted] Cervical Screening Test Kit in detecting HPV 16 and 18 in CIN2+, CIN3+ and cervical cancer. It may be feasible to be used as point-of-care. However, other factors such as cost of equipments and consumables also training need to be considered.

Methods

Literature was searched through electronic databases which included MEDLINE(R), Cochrane Database of Systematic Reviews, Health Technology Assessment, Embase, NHS Economic Evaluation Database, Database of Abstracts of Review of Effects, PubMed, other websites; INAHTA, U.S. FDA, NIHR Centre for Reviews and Dissemination – CRD Database, EuroScan International Network, Australia and New Zealand Horizon Scanning Network, Health Policy Advisory Committee on Technology (HealthPACT) and general databases such as Google Scholar.

The search was limited to human study. The last searched was conducted on 27 June 2014.

A critical appraisal of all relevant literature was performed using Critical Appraisal Skills Programme (CASP) checklists and the evidence graded according to the NHS Centre for Reviews and Dissemination (CRD) University of York, Report Number 4 (2nd Edition) for diagnostic accuracy studies.

[redacted] **CERVICAL SCREENING TEST KIT**

1. INTRODUCTION

Cancer of the cervix is the third most common cancer among women and fifth most common cancer in the entire general population in Malaysia. There are a total of 847 cases diagnosed in 2007 registered at National Cancer Registry. Cervical cancer incidence rate increased with age after 30 years old and has its peaks at ages 65 – 69 years. [1]

Cancer can grow on the cervix and it can take 10 to 15 years (or more) for abnormal cells to turn into cancer. Cervical cancer is often asymptomatic in its early stages. Physical symptoms of cervical cancer may include abnormal vaginal bleeding, vaginal discomfort, malodorous discharge and dysuria. The most common finding in patients with cervical cancer is an abnormal Papanicolaou (Pap) test result. Thus, cervical cancer screening programme is crucial in detecting pre-cancerous lesion to allow early treatment.

Almost all cervical cancer caused by HPV infection. Studies have shown that HPV infection responsible for more than 90% of the cases of invasive cervical cancer worldwide, and it is related to 80% of pre-cancerous changes in the cervix.

According to the International Agency for Research on Cancer, the specialised cancer agency of the World Health Organization, cervical cancer is the fourth most common cancer affecting women worldwide with 528 000 new cases every year, after breast, colorectal and lung cancers. It is also the fourth most common cause of cancer death as 266 000 deaths in 2012 among women worldwide.[2]

Cervical cancer can be prevented by identifying pre-cancerous lesions early using Pap smear screening test and treating these lesions before they progress to cancer. A cervical screening test is a method of detecting abnormal cells in the cervix. The screening is not a test for cancer but it is a test to check the health of the cells of the cervix.

Based on guidelines from the American Cancer Society, the American Society for Colposcopy and Cervical Pathology, the American Society for Clinical Pathology, the US Preventive Services Task Force and the

American College of Obstetricians and Gynaecologists, current screening recommendations are as follows. [3]

i. < 21 years: No screening recommended
ii. 21 – 29 years: Cytology (Pap smear) alone every three years
iii. 30 – 65 years: HPV and cytology contesting every five years (preferred) or cytology alone every three years (acceptable)
iv. > 65 years: No screening recommended if adequate prior screening has been negative and high risk is not present

In Malaysia, the cervical cancer screening programme was established in 1969 to ensure early detection of cervical cancer among the target group of women aged 20 – 65 years.[4] In 1995, the Ministry of Health launched the "Healthy Life Style Campaign against Cancer", an open invitation to women aged 20 – 65 years to have Pap smear taken every three years for free.[5] However, only 47.3% of Malaysian women have been screened via Pap smears.[5]

Currently, the cervical cancer screening in Malaysia uses the conventional Pap smears. However, there is a new technology named [redacted] Cervical Screening Test Kit.

[redacted] Cervical Screening Test Kit is used for the detection of elevated levels of E6 oncoprotein expressed by human papillomavirus (HPV) types 16 and 18.[6] The manufacturer claims that it can demonstrate outstanding clinical performance with high specificity and high positive predictive value. Thus it can be used to triage patients with high risk HPV and other abnormal screening results to avoid unnecessary treatment procedures.[7]

E6 oncoprotein is necessary for oncogenic transformation of HPV-infected cervical epithelial cells. Detection of elevated levels of E6 oncoprotein in cells from cervical swab specimens indicates an existing precancerous or cancerous lesion, or elevated risk of pre-cancer or cancer.[8]

This test is used to analyze cells extracted from cervical cytology swab specimens. It is based on the capture and detection of HPV E6 oncoproteins using high-affinity monoclonal antibodies (mAb) in a lateral-flow assay format. This technology relies on the capillary migration of the analyte through a nitrocellulose membrane, where specific capture

antibodies are immobilized. The analyte is detected by an alkaline phosphatase (AP) conjugated mAb. The mAb-AP-analyte complex on the test is visualized by the addition of an enzyme substrate, producing a coloured line. A positive result is a visible test line.[8]

The [redacted] Cervical Screening Test Kit is claimed to have high specificity, high positive predictive value, and stable at room temperature and does not require any complex equipment which allows cervical cancer detection to be carried at point-of-care. However, it is not known whether the claim is supported by scientific evidence. Thus, this technology review was conducted following a request from Senior Principal Assistant Director, Disease Control Division

2. OBJECTIVE/AIM

The objective of this technology review is to assess the safety, efficacy/effectiveness and cost-effectiveness of [redacted] Cervical Screening Test Kit at point-of-care.

3. TECHNICAL FEATURES

3.1 INDICATION

The [redacted] Cervical Screening Test Kit, [redacted] is a qualitative test that detects elevated levels of E6 oncoprotein expressed by HPV types 16 and 18. The test is indicated as an aid to further assess the likelihood that malignancy is present when used in conjunction with independent clinical evaluations. The test is not intended as a screening or stand-alone diagnostic assay.

3.2 MECHANISM OF ACTION

The [redacted] Cervical Screening Test Kit analyses cell lysates generated from cervical cytology swab specimens. The lysate is incubated with mAbs to oncoprotein E6 of HPV subtypes 16 and 18 (E6 16/18) conjugated with AP. A nitrocellulose test strip with capture mAb to E6 16/18 striped at two locations on the strip is placed into the specimen lysate mix containing the AP mAbs to E6 16 and 18. The cell lysate/mAb mix migrates up the test strip by a capillary action forming a complex with the capture mAb if the E6 oncoprotein 16 or 18 are present in the mix. If

one or both oncoproteins are present a purple line is visible at the specific location for HPV subtypes 16 or 18 on the strip.

Following the wash and development steps, E6 oncoprotein appears as a purple test line if present in the specimen. The result is positive if a purple test line can be visualized or negative if no test line is present.

In detail, the test results are read and interpreted as follows:

	
If the control line is only visible, the test is negative.	If the control line and the 18 line are visible, the test is positive E6 18.

	• No control line • Control or test lines appear as broken, do not cover full width of strip • There is overall strong dark purple background • There are background streaks or dots obscuring the lines
If the control line and the 16 line are visible, the test is positive E6 16.	Any criteria from the above are invalid result.

The test is stable at room temperature and requires no complex equipment.

3.3 [redacted] CERVICAL SCREENING TEST KIT PRODUCTS

The [redacted] Cervical Screening Test Kit products are as follows:

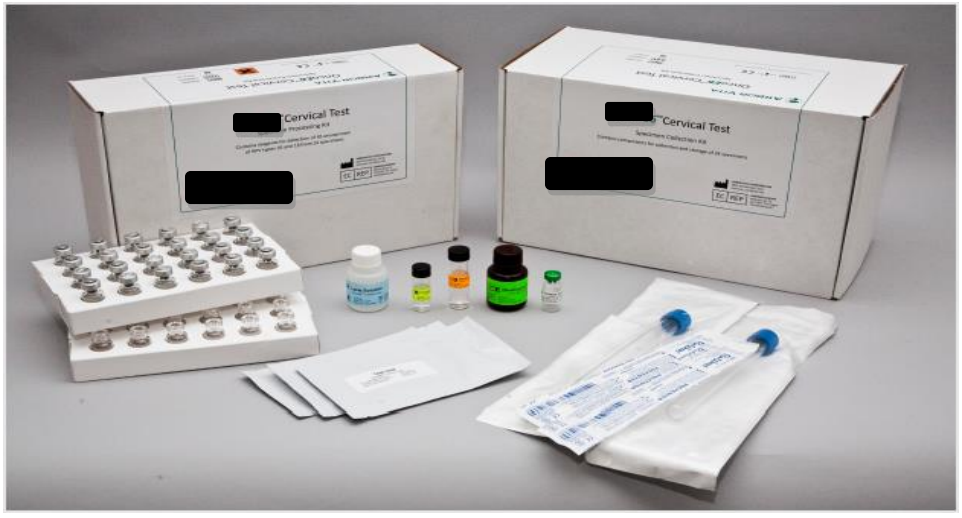
a. [redacted] Cervical Test Specimens Collection Kit (Refer Picture 1)

This specimen collection kit contains material for collection and storage of 24 specimens (which are 24 swabs for specimen collection – sterile polyester tipped and 24 tubes for specimen storage).

b. [redacted] Cervical Test Specimen Processing Kit (Refer Picture 1)

This specimen processing kit contains material and reagents for 24 tests which are

- 1 bottle for Lysis Solution A
- 1 vial of Conditioning Solution B
- 24 vials of Detector Reagent C
- 1 vial of Wash Solution D
- 1 bottle of Developing Solution E
- 1 vial of Positive Control
- 24 tubes for Lysis
- 24 vials for Wash
- 24 tubes for Development
- 8 test units – 3 test strips each

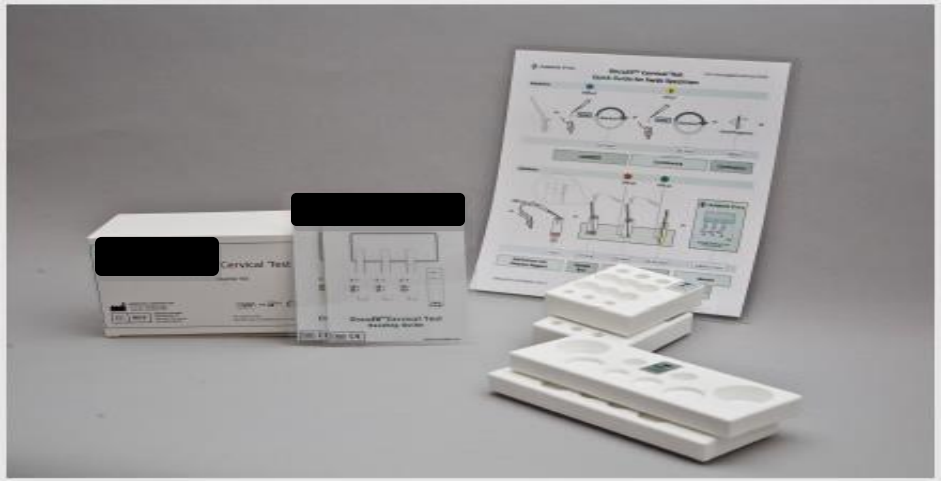


Picture 1: The [redacted] Cervical Test Specimens Collection and Processing Kit

Other the [redacted] Cervical Screening Test Kit products are as follows:

a. [redacted] Cervical Screening Starter Kit (Refer Picture 2)

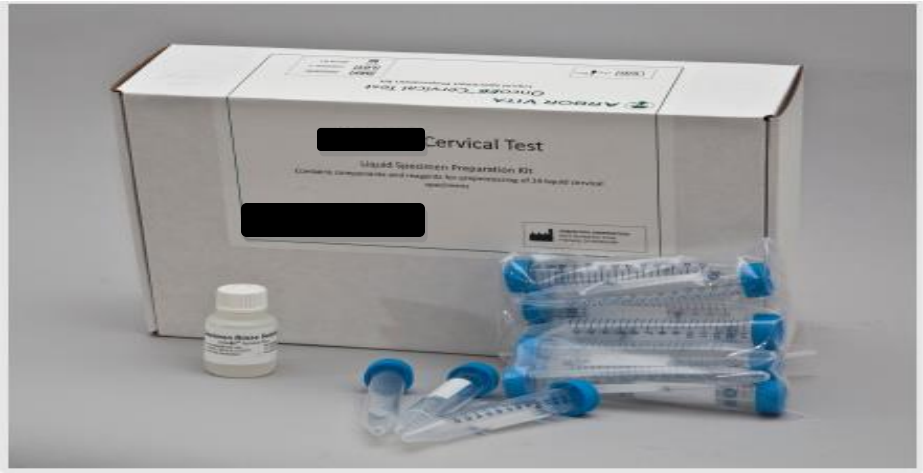
This kit provides the essential accessories to make the work flow of [redacted] Cervical Screening Test Kit smooth. It contains solution stand, test platforms, reading guides and quick guide.



Picture 2: The [redacted] Cervical Screening Starter Kit

b. [redacted] Cervical Screening Liquid Specimen Preparation Kit (Refer Picture 3)

This kit enables liquid cytology specimen to be used with [redacted] Cervical Screening Test Kit.



Picture 3: The [redacted] Cervical Screening Liquid Specimen Preparation Kit

In addition, other equipments (Refer Picture 4) are required for the [redacted] Cervical Screening Test Kit but not supplied are as follows:

- Microcentrifuge (1.5 to 2ml tubes, > 10 000xg)
- Micropipettes (calibrated)
- Tube rotator (8RPM)
- Timer
- Thermometer (calibrated)

Picture 4: Other equipments required for the [redacted] Cervical Screening Test Kit

4. METHODS

4.1. Searching

These scientific databases were searched such as:

- MEDLINE(R) In-process and other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to present
- Embase 1996 to 2014 Week 21
- EBM Reviews – Database of Abstracts of Review of Effects – 2nd Quarter 2014
- EBM Reviews – Cochrane Database of Systematic Reviews – 2005 to April 2014
- EBM Reviews – Health Technology Assessment – 2nd Quarter 2014

- EBM Reviews – NHS Economic Evaluation Database – 2nd Quarter 2014

Other databases or websites as below were also searched

- PubMed
- U.S. FDA
- NIHR Centre for Reviews and Dissemination – CRD Database
- INAHTA website
- EuroScan International Network
- Australia and New Zealand Horizon Scanning Network
- Health Policy Advisory Committee on Technology (HealthPACT)

Google was used to search for additional web-based materials and information. The search was limited to human study only. The last search was conducted on 27 June 2014. Appendix 1 showed the detailed search strategies.

4.2. Selection

Two reviewers screened the titles and abstracts against the inclusion and exclusion criteria and then evaluated the selected full-text articles for final article selection.

The inclusion and exclusion criteria were:

Inclusion criteria

Population	Women Cervical cancer Cervical cancer screening programme
Interventions	[redacted] Cervical Screening Test Kit
Comparators	Pap smear [redacted] Human papillomavirus E6, E7 mRNA
Outcomes	• Safety (CE mark) • Efficacy/effectiveness (Short term – detection of pre-cancerous and cancer state of cervical cancer, diagnostic accuracy of the OncoE6™ Cervical Test • Cost-effectiveness
Setting	Point-of-care

Study design	Systematic Review, Health Technology Assessment, Randomised Controlled Trial, Diagnostic StudyCohort Study, Cross Sectional Study, Case Series, Case Report, Pre and post Intervention Study, Economic Evaluation
Type of publication	English full text articles, human studies

Exclusion criteria

Study design	Animal study, Laboratory study, Narrative review
Language	Non English full text article

Relevant articles were critically appraised using Critical Appraisal Skills Programme (CASP) and the evidence graded according to the NHS Centre for Reviews and Dissemination (CRD) University of York, Report Number 4 (2nd Edition) for diagnostic accuracy studies (Appendix 2).

Data were extracted and summarized in the evidence table as in Appendix 3.

5. RESULTS AND DISCUSSION

There were two published literatures on [redacted] Cervical Screening Test Kit included in this technology review.

5.1. SAFETY

There was no retrievable evidence of safety for [redacted] Cervical Screening Test Kit.

The [redacted] Cervical Screening Test Kit is certified with CE-IVD (In Vitro Diagnostic).

5.2. EEFICACY/ EFFECTIVENESS

There were two published literature on [redacted] Cervical Screening Test Kit retrieved from the available scientific database.

Schweizer J et al. conducted a study by using the [redacted] Cervical Screening Test Kit on various sources of cervical swab specimens. There

were 160 cervical swab specimens collected from three different groups. The first group of specimens consisted of 16 specimens with negative histology from Planned Parenthood, California. The second group consisted of 55 specimens (one specimen from women with cervical intraepithelial neoplasia (CIN) grade one [CIN1], 14 specimens from women with CIN three [CIN3], 29 specimens from women with CIN3 or cervical cancer [CIN3+] and 11 specimens from women with cervical cancer) from a clinical trial being conducted in India, which were acquired via Bio-Imagene, California. The third group consisted of 89 specimens (eight specimens with negative histology, 28 specimens from women with CIN1, 43 specimens from women with CIN3, and ten specimens from women with cervical cancer). All specimens were run for HPV oncoprotein testing (HPV 16/18/45) based on the instruction of use of [redacted] Cervical Screening Test Kit. In addition, all specimens were also tested for another 37 HPV genotypes. However, those specimens were not tested and compared to the reference standard test and also not blinded. As a result, 51 out of 75 (68%, with 95% confidence interval [CI] 56% to 78%) HPV 16/18/45 DNA-positive specimens from women with a CIN3+ diagnosis tested positive for HPV 16/18/45 E6 oncoprotein. None of the 16 HPV 16/18/45 DNA-positive cervical specimens from women with a negative histology or CIN1 diagnosis tested positive for HPV 16/18/45 E6 oncoprotein. Fourty-five out of specimens (88%) from 51 tested positive for HPV 16/18/45 E6 oncoprotein were positive for the same HPV genotype (40 HPV 16 and five HPV 18). Two of the 37 specimens (5.4%) from women with a negative or CIN1 diagnosis showed a weak positive test line for HPV 16 E6 oncoprotein and negative for HPV DNA. None of the 32 specimens from women with a CIN3+ diagnosis tested positive for HPV 16 E6 oncoprotein. The test was only run for HPV 16/18/45 E6 oncoprotein and the sensitivity of [redacted] Cervical Screening Test Kit was not available. The author concluded that E6 detection from cervical swab specimens was both feasible and potentially more specific for CIN3+ than HPV DNA detection for the same HPV genotypes. [8, level 3]

Another study was conducted by Fang-Hui Z et al. in rural China. About 11,350 eligible women were identified in the three counties, but only 7 543 were recruited into the study based on five eligible criteria. Women were excluded if they were not married and reported never had sexual intercourse. Two vaginal specimens were used from those eligible women, which were clinician-collected and self-collected specimens. All specimens were run for four types of tests, which were E6 oncoprotein by using

[redacted] Cervical Screening Test Kit, HPV DNA test by using *care*HPV and HC2 and visual inspection acetic acid (VIA). In addition, women who tested positive and 10% from negative result for any tests either by clinician-collected or self-collected specimens were referred to colposcopy. The reference standard test used was colposcopy and biopsy. However, all patients were not blinded during the test. In addition, all positive results were further undergoing for colposcopy and biopsy but only 10% of negative results to be referred for colposcopy and biopsy. As a result, out of 7 543 women who were recruited into the study, about 7 539 were eligible and had valid [redacted] Cervical Screening Test Kit results. A total of 2 290 (30.4%) women tested positive by at least one of the screening test and were referred for colposcopy; 118 (5.2% of 2 290) did not undergo colposcopy and/or had biopsies. About 5 249 (69.9%) tested negative by all tests. A random sample of 9.2% (485 women) was referred to colposcopy and all complied, of whom 22 had visible lesions that were biopsied but not CIN2+. The percentage of specimen tested positive was 1.8% for HPV E6, 14.4% and 14.5% for clinician- and self-collected specimens tested by *care*HPV, 14.5% and 17.9% for clinician- and self-collected specimens tested by HC2 and 7.3% for VIA. Furthermore, the percentage of E6 positive specimen increased steadily with increasing severity of diagnosis: 0.8% for negative histology, 8.5% for CIN1, 17.8% for CIN grade two [CIN2], 48.8% for CIN3 and 84.6% for cervical cancer. The [redacted] Cervical Screening Test Kit was 42.4% sensitive for CIN2+ and 53.5% sensitive for CIN3+. The [redacted] Cervical Screening Test Kit was very specific, at 99% for CIN2+ and CIN3+, resulting the positive predictive value (PPV) for CIN2+ (46.9%) and for CIN3+ (40.8%) compared with high-risk HPV (HR-HPV) DNA detection methods (i.e., 10 – 13% PPV for CIN2+ and 7 – 9% for CIN3+). Clinician-collected specimens tested for HR-HPV DNA by HC2 and *care*HPV were the most sensitive for CIN2+ (95.8% for both) and CIN3+ (97.0% for both). The sensitivity for CIN2+ and CIN3+ was higher with the clinician-collected specimens than with self-collected specimens for HC2 (95.8% versus 91.7% for CIN2+, p=0.2 and 97.0% versus 90.9% for CIN3+, p=0.06). In addition, the sensitivity for CIN2+ and CIN3+ was higher with the clinician-collected specimens than with self-collected specimens also for *care*HPV (95.8% versus 82.6% for CIN2+, p<0.0001 and 97.0% versus 83.8% for CIN3+, p=0.0001). The HR-HPV DNA testing was the least specific for CIN2+ and CIN3+, with the specificities in the mid- 80% range. In comparison [redacted] Cervical Screening Test Kit to VIA, VIA was equally sensitive for CIN2+ and CIN3+ (p=0.5 for CIN2 and

p=0.8 for CIN3+) but much less specific for CIN2+ and CIN3+ (p<0.0001) and the PPV for CIN2+ and CIN3+ were comparable with HR-DNA detection in this study. The result of [redacted] Cervical Screening Test indicated that the test had high specificity but the sensitivity was low. Furthermore, there was no detail result of [redacted] Cervical Screening Test pertaining to the colposcopy. The author concluded that HPV E6 oncoprotein detection by [redacted] Cervical Screening Test was very specific for the presence of cervical pre-cancer and cancer, especially CIN3+ caused by the targeted HPV genotypes and as a result, had a remarkable PPV in a screening population. In addition, the HR-HPV DNA testing of the clinician-collected specimen by both HC2 and *care*HPV was very sensitive for CIN2+ and CIN3+ but not specific due to the high prevalence of HPV infection at all ages. The sensitivity for CIN2+ and CIN3+ of HR-HPV DNA testing of self-collected specimens was very good but less sensitive than using clinician-collected specimens. [9, level 2]

5.3 COST/COST-EFFECTIVENESS

There was no retrievable evidence of cost/cost-effectiveness for [redacted] Cervical Screening Test Kit.

The cost for this test is MYR 126 per kit for private sector.

5.4 LIMITATIONS

This review has few limitations. The selection of studies was made by two reviewers. Although there was no restriction in language during the search but only English full text articles were included in this report.

6. CONCLUSION

There was limited good level of evidence retrieved on the efficacy/effectiveness of [redacted] Cervical Screening Test Kit. However, there was no retrievable evidence on safety and cost-effectiveness of this test. The test is certified with CE-IVD and the market price for this test is MYR 126 per kit for private sector.

Based on the above review, the evidence seems to indicate potential benefit of [redacted] Cervical Screening Test Kit in detecting HPV 16 and 18 in CIN2+, CIN3+ and cervical cancer. It may be feasible to be used at

point-of-care. However, other factors such as cost of equipments and consumables also training need to be considered.

7. REFERENCES (Modified Vancouver)

1. National Cancer Registry Report. Malaysia Cancer Statistics – Data and Figure. 2007. Non-Communicable Disease Section, Disease Control Division, Ministry of Health.

2. World Health Organization. International Agency for Research on Cancer. Press Release (N^0 223): Latest World Cancer Statistics, Global Cancer Burden Rises to 14.1 million New Cases in 2012, Marked Increase in breast cancers must be addressed. Dated 12 December 2013. Available from: http://www.iarc.fr/en/media-centre/pr/2013/pdfs/pr223_E.pdf. Accessed on 19/05/2014.

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5. Othman N H, Rebolj M. Challenges to Cervical Cancer Screening in a Developing Country: The Case of Malaysia. Asian Pacific Journal of Cancer Prevention. 2009; 10: 747 – 752.

6. [redacted] Cervical Test: Instruction for Use. Available from: http://www.[redacted]%20Cervical%20Test_IFU.pdf. Accessed on 19/05/2014

7. [redacted] Cervical Test: Available from: http://www.[redacted]-cervical-test.html. Accessed on 19/05/2014

8. Schweizer J, Lu PS, Mahoney CW et al. Feasibility Study of a Human Papillomavirus E6 Oncoprotein Test for Diagnosis of Cervical Precancer and Cancer. J. Clin. Microbol. 2010; 48(12):4646-4648.

9. Fang-Hui Z, Jeronimo J, You-Lin Q et al. An Evaluation of Novel Lower –Cost Molecular Screening Tests for Human Papilomavirus in Rural China. Cancer Prev. Res. 2013; 6(9): 938 – 948.

8. APPENDIX

8.1. Appendix 1

LITERATURE SEARCH STRATEGY

Ovid MEDLINE® In-process & other Non-Indexed citations and OvidMEDLINE® 1948 to present

1. General women.tw.
2. Uterine Cervical Neoplasms/
3. (cervical cancer* adj1 uterine).tw.
4. cancer* uterine cervical.tw.
5. (cancer adj4 cervix).tw.
6. (cervical neoplasm* adj1 uterine).tw.
7. (cervi* adj1 (neoplasm* or cancer*)).tw.
8. neoplasm* uterine cervical.tw.
9. 2 or 3 or 4 or 5 or 6 or 7 or 8
10. Uterine Cervical Dysplasia/
11. (uterine cervical adj1 dysplasia).tw.
12. cervical dysplasia uterine.tw.
13. (cervix adj1 dysplasia).tw.
14. 10 or 11 or 12 or 13
15. Cervical Intraepithelial Neoplasia/
16. (intraepithelial neoplas* adj 1 cervical).tw.
17. (cervical intraepithelial adj1 neoplas*).tw.
18. 15 or 16 or 17
19. Cervical screening programme.tw.
20. Cervical cancer screening programme.tw.
21. 1 or 9 or 14 or 18 or 19 or 20
22. [redacted].tw.
23. Human papillomavirus E6 oncoprotein/
24. Human papillomavirus E6 oncoprotein*.tw.
25. (E6 adj1 (protein or oncoprotein)).tw.
26. 23 or 24 or 25
27. Oncoprotein/
28. Oncogene protein.tw.
29. 27 or 28
30. 22 or 26 or 29
31. 21 and 30

OTHER DATABASES

EBM Reviews – Database of Abstracts of Review of Effects	Same MeSH, keywords, limits used as per MEDLINE search
EBM Reviews – Cochrane Database of Systematic Reviews	
EBM Reviews – Health Technology Assessment	
EBM Reviews – NHS Economic Evaluation Database	
INAHTA	[redacted] Cervical Screening Test Kit
U.S. FDA	
NIHR Centre for Reviews and Dissemination – CRD Database	
EuroScan International Network	
Australia and New Zealand Horizon Scanning Network	
Health Policy Advisory Committee on Technology (HealthPACT)	
Google Scholar	

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((((((((((((((((((((((((((((((General women) OR uterine cervical neoplasms[MeSH Terms]) OR Cervical neoplasm*, uterine[Title/Abstract]) OR Neoplasm*, uterine cervical[Title/Abstract]) OR Uterine Cervical Neoplasm* [Title/Abstract]) OR Neoplasm*, cervical[Title/Abstract]) OR Cervical neoplasm*[Title/Abstract]) OR Neoplasm*, cervix[Title/Abstract]) OR Cervix neoplasm*[Title/Abstract]) OR Cancer of the Uterine Cervix[Title/Abstract]) OR Cancer of the Cervix[Title/Abstract]) OR Cervical Cancer[Title/Abstract]) OR Uterine cervical cancer* [Title/Abstract]) OR Cancer*, uterine cervical[Title/Abstract]) OR Cervical cancer*, uterine[Title/Abstract]) OR Cancer of Cervix[Title/Abstract]) OR Cervix Cancer[Title/Abstract]) OR Cancer*, cervix[Title/Abstract]) OR Uterine Cervical Dysplasia[MeSH Terms]) OR Cervical Dysplasia, Uterine[Title/Abstract]) OR Dysplasia, Uterine Cervical[Title/Abstract]) OR Cervix Dysplasia[Title/Abstract]) OR Dysplasia, Cervix[Title/Abstract]) OR Cervical Intraepithelial Neoplasia[MeSH Terms]) OR Intraepithelial Neoplasia, Cervical[Title/Abstract]) OR Neoplasia, Cervical Intraepithelial[Title/Abstract]) OR Cervical Intraepithelial Neoplasm*[Title/Abstract]) OR Intraepithelial Neoplasm*, Cervical[Title/Abstract]) OR Neoplasm*, Cervical Intraepithelial[Title/Abstract]) OR Cervical screening programme) OR Cervical cancer screening programme)) AND (((((([redacted]) OR E6 protein, Human papillomavirus type 18[MeSH Terms]) OR E6 *protein, HPV-18[Title/Abstract]) OR v-protein E6, human papilloma virus type 18[Title/Abstract]) OR oncogene protein E6, human papilloma virus type 18[Title/Abstract])) OR human papillomavirus e6 oncoprotein[Title/Abstract])

8.2. Appendix 2

HIERARCHY OF EVIDENCE FOR TEST ACCURACY STUDIES

Level	Description	
1.	A blind comparison with reference standard among an appropriate sample of consecutive patients	
2.	Any one of the following	Narrow population spectrum
3.	Any two of the following	Differential use of reference standard
4.	Any three or more of the following	Reference standard not blind Case control study
5.	Expert opinion with no explicit critical appraisal, based on physiology, bench research or first principles.	

SOURCE: NHS Centre for Reviews and Dissemination (CRD) University of York, Report Number 4 (2nd Edition)

8.3. Appendix 3

Evidence Table : Efficacy
Question : Is [redacted] Cervical Screening Test safe, effective/efficacious and cost-effectiveness compare to Pap smear test or HPV [redacted] E6, E7 mRNA for cervical cancer screening?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
1. Schweizer J, Lu PS, Mahoney CW et al. Feasibility Study of a Human Papillomavirus E6 Oncoprotein Test for Diagnosis of Cervical Precancer and Cancer. J. Clin. Microbol. 2010; 48(12):4646-4648.	Diagnostic study A set of cervical swab specimens were collected using a Dacron swab and stored without buffer or specimen transport medium at less than -60C. The specimen set (160 specimens) was assembled as a convenience sample from three sources. The [redacted] Cervical Test is based on detection of HPV-E6 oncoprotein in cervical swabs sample. It detects E6 oncoprotein of HPV type 16, type 18, and/or type 45 on three distinct test lines. The Dacron swab collection tip is placed in 0.933 ml of extraction buffer for 30 min. Then, 87µL or proprietary buffer was added and the mixture was incubated with mixing for another 30 min.	4	160 specimens from three different groups of people First group – 16 specimens (negative histology). Second group – 55 specimens (1 specimen from a woman with CIN1, 14 specimens from women with CIN3, 29 specimens from women with CIN3 or cervical cancer (CIN3+), 29 specimens from women with cervical cancer)	Human papillomavirus type 16, 18, and/or 45 E6 oncoproteins test	Another 37 HPV genotypes test	Not mention	➢ 51 of 75 (68%; 95% CI, 56 to 78%) of HPV16/18/45 DNA-positive specimens from women with a CIN3+ diagnosis tested positive for HPV16/18/45 E6 oncoprotein. ➢ None of the 16 (95% CI of 0 to 37%) HPV16/18/45 DNA-positive cervical specimens from women with a negative or CIN1 diagnosis tested positive for HPV16/18/45 E6 oncoprotein. ➢ 45 of 51 (88%) of the E6 and DNA positive tests were positive for the same HPV genotype (40 HPV 16 and 5 HPV 18). ➢ 2 of 37 specimens (5.4%) form women with a negative or CIN1 diagnosis showed a weak positive test line for HPV16 E6 oncoprotein and negative for HPV DNA. ➢ None of the 32 specimens from women with a CIN3+ diagnosis tested positive for HPV 16 E6 oncoprotein.	

Evidence Table : Efficacy
Question : Is [redacted] Cervical Screening Test safe, effective/efficacious and cost-effectiveness compare to Pap smear test or HPV [redacted] E6, E7 mRNA for cervical cancer screening?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
Continued 1. Schweizer J, Lu PS, Mahoney CW et al. Feasibility Study of a Human Papillomavirus E6 Oncoprotein Test for Diagnosis of Cervical Precancer and Cancer. J. Clin. Microbol. 2010; 48(12):4646-4648.	The extracted, lysed specimen was clarified by centrifugation in a microcentrifuge at 13 000 X g for 10 min. An aliquot of the specimen of the specimen lysate (0.12ml) was combined with a detector monoclonal antibody (mAb) cocktail consisting two anti-E6 mAb. Then, the above step is placed into the vial containing alkaline phosphatase. After development and removal of the lateral-flow strip for the alkaline phosphatasae substrate vial, test outcome was obtained via visual inspection.	4	Third group – 89 specimens (8 specimens with negative histology, 28 specimens from women with CIN1, 43 specimens from women with CIN3, 10 specimens form women with cervical cancers) • Total negative histology specimens – 16 • Total CIN1 specimens – 29 • Total CIN3 specimens – 57 • Total CIN3 or CIN3+ specimens – 29 • Total cervical cancer specimens – 21				The author concluded that E6 detection from cervical swab specimens is both feasible and potentially more specific for CIN3+ than HPV DNA detection for the same HPV genotypes.	

Evidence Table : Efficacy
Question : Is [redacted] Cervical Screening Test safe, effective/efficacious and cost-effectiveness compare to Pap smear test or HPV [redacted] E6, E7 mRNA for cervical cancer screening?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
2. Fang-Hui Z, Jeronimo J, You-Lin Q et al. An Evaluation of Novel Lower – Cost Molecular Screening Tests for Human Papilomavirus in Rural China. Cancer Prev. Res. 2013; 6(9): 938 – 948.	Diagnostic study Recruitment took place from October 2010 through June 2011. There were five eligible criteria for the recruitment of patient. Women were excluded if they were not married and reported never having had sexual intercourse. First, participants were given instruction s on how to self-collect a vaginal specimen conducted in private room. Then, women underwent a routine pelvic exam by female clinicians, which two specimens were collected for OncoE6 test and HR-HPV DNA test. Women who tested positive and 10% from negative result for any tests either by clinician-collected or self-collected specimens were referred to colposcopy.	4	Women ages 25 to 65 years. 11 350 eligible women were identified in the three counties and only 7 543 recruited into the study. Two vaginal specimens used are clinician-collected and self-collected specimens.	E6 oncoprotein	HPV DNA test (*care*HPV, HC2) VIA (visual inspection acetic acid)	Not mention	➢ Out of 7 543 recruited into the study, about 7 539 were age eligible and had valid OncoE6 cervical test results. ➢ A total of 2 290 (30.4%) women tested positive by at least one of the screening test and were referred to colposcopy. ➢ 5 249 (69.6%) tested negative by all tests and random sample of 9.2% (485 women) were referred to colposcopy. ➢ The percent test positive was 1.8% for HPV E6, 14.4% and 14.5% for clinician- and self-collected specimens tested by *care*HPV, 14.5% and 17.9% for clinician- and self-collected specimens tested by HC2 and 7.3% for VIA. ➢ The percent E6 positive increased steadily with increasing severity of diagnosis: 0.8% for negative histology, 8.5% for CIN1, 17.8% for CIN2, 48.8% for CIN3 and 84.6% for cervical cancer.	

Evidence Table : **Efficacy**
Question : **Is [redacted] Cervical Screening Test safe, effective/efficacious and cost-effectiveness compare to Pap smear test or HPV [redacted] E6, E7 mRNA for cervical cancer screening?**

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
Continued 2. Fang-Hui Z, Jeronimo J, You-Lin Q et al. An Evaluation of Novel Lower – Cost Molecular Screening Tests for Human Papilomavirus in Rural China. Cancer Prev. Res. 2013; 6(9): 938 – 948.							➢ The [redacted] E6 oncoprotein was 42.4% sensitive for CIN2+ and 53.5% sensitive for CIN3+. ➢ The [redacted] E6 oncoprotein was very specific , at 99% for CIN2+ and CIN3+, resulting a very high positive predictive value (PPV) for CIN2+ (46.9%) and for CIN3+ (40.8%) compared with HR-HPV DNA detection methods. ➢ Clinician-collected specimens tested for HR-HPV DNA by HC2 and *care*HPV were the most sensitive for CIN2+ (95.8% for both) and CIN3+ (97.0% for both). ➢ The sensitivity for CIN2+ and CIN3+ was more with the clinician-collected specimens than with self-collected specimens for HC2 (95.8% versus 91.7% for CIN2+, p=0.2 and 97.0% versus 90.9% for CIN3+, p=0.06). ➢ In addition, the sensitivity for CIN2+ and CIN3+ was more with the clinician-collected specimens than with self-collected specimens also for *care*HPV (95.8% versus 82.6% for CIN2+, p<0.0001 and 97.0% versus 83.8% for CIN3+, p=0.0001).	

Evidence Table : **Efficacy**
Question : **Is [redacted] Cervical Screening Test safe, effective/efficacious and cost-effectiveness compare to Pap smear test or HPV [redacted] E6, E7 mRNA for cervical cancer screening?**

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
Continued 2. Fang-Hui Z, Jeronimo J, You-Lin Q et al. An Evaluation of Novel Lower – Cost Molecular Screening Tests for Human Papilomavirus in Rural China. Cancer Prev. Res. 2013; 6(9): 938 – 948.							➢ The HR-HPV DNA testing was the least specific for CIN2+ and CIN3+, with the specificities in the mid- 80% range. ➢ In comparison [redacted] E6 oncoprotein to VIA, VIA was equally sensitive for CIN2+ andCIN3+ (p=0.5 for CIN2 and p=0.8 for CIN3+) but much less specific for CIN2+ and CIN3+ (p<0.0001) and its PPV for CIN2+ and CIN3+ were comparable with HR-DNA detection in this study. ➢ The author summarized that HPV E6 oncoprotein detection by [redacted] E6 oncoprotein was very specific for the presence of cervical pre-cancer and cancer, especially CIN3+ caused by the targeted HPV genotypes and as a result, had a remarkable PPV in a screening population. ➢ In addition, the HR-HPV DNA testing of the clinician-collected specimen by both HC2 and *care*HPV was very sensitive for CIN2+ and CIN3+ but not specific due to the high prevalence of HPV infection at all ages.	

Evidence Table : **Efficacy**
Question : **Is [redacted] Cervical Screening Test safe, effective/efficacious and cost-effectiveness compare to Pap smear test or HPV [redacted] E6, E7 mRNA for cervical cancer screening?**

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
Continued 2. Fang-Hui Z, Jeronimo J, You-Lin Q et al. An Evaluation of Novel Lower – Cost Molecular Screening Tests for Human Papilomavirus in Rural China. Cancer Prev. Res. 2013; 6(9): 938 – 948.							➢ The sensitivity for CIN2+ and CIN3+ of HR-HPV DNA testing of self-collected specimens was very good but less than using clinician-collected specimens.	