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Horizon Scanning Technology Prioritising Summary

Cervista™ HPV 16/18 for the identification of strains of the human papillomavirus associated with cervical cancer

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PRIORITISING SUMMARY

REGISTER ID: **000427**

NAME OF TECHNOLOGY: **CERVISTA™ HPV 16/18**

PURPOSE AND TARGET GROUP: **FOR THE IDENTIFICATION OF STRAINS OF THE HUMAN PAPILLOMAVIRUS (HPV) ASSOCIATED WITH CERVICAL CANCER**

STAGE OF DEVELOPMENT (IN AUSTRALIA):

☒	Yet to emerge	☐	Established
☐	Experimental	☐	Established *but* changed indication or modification of technique
☐	Investigational	☐	Should be taken out of use
☐	Nearly established		

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

☐	Yes	ARTG number
☐	No	
☒	Not applicable	

INTERNATIONAL UTILISATION:

COUNTRY	LEVEL OF USE		
	Trials Underway or Completed	Limited Use	Widely Diffused
United States	✓		

IMPACT SUMMARY:

Hologic™ (Massachusetts, USA) provides the Cervista™ HPV 16/18 with the aim of identifying two of the viral strains of human papillomavirus (HPV) that are associated with high-grade cervical cancer. The technology would be made available through general practitioners for women aged 30 years or more or for women who returned an ambiguous Pap smear. The Cervista™ HPV 16/18 was approved by the United States Food and Drug Administration in March 2009 but does not require Australian TGA approval.

BACKGROUND

Cervical cancer may arise from the squamous cells that cover the outer surface of the cervix (squamous cell carcinoma) or from the glandular cells in the cervical canal (adenocarcinoma). The majority of cervical cancers are squamous cell carcinoma (>60%), and approximately 20 per cent are adenocarcinomas (AIHW 2009).

Abnormal changes in the squamous cells or growth in the layers of the cervix are referred to as cervical intra-epithelial neoplasia, or CIN. Low-grade changes are referred to as CIN1, high-grade as CIN2 and CIN3 represents severe changes and is equivalent to in situ carcinoma (National Screening Unit 2008).

There is a significant body of evidence that infection with a high-risk type of human papillomavirus (HPV) is necessary, but not sufficient, for development of cancer of the cervix, with over 99.7% of cervical cancers testing positive for HPV DNA (Walboomers et al 1999). Although almost all cases of cervical cancer are associated with a HPV infection, cervical cancer remains a rare outcome of infection with HPV. Low-grade cervical abnormalities may occur after an acute infection with HPV, however the majority of these will regress without any treatment. High-grade abnormalities may occur after persistent HPV infection (AIHW 2009). HPVs are small double-stranded DNA viruses and there are currently more than a 100 known genotypes of HPV. Of these, approximately 40 are capable of infecting the anogenital area and are sexually transmitted. Cervical cancer is causally related to infection with at least 14 oncogenic or high-risk genotypes of HPV, with the majority of cancers associated with infection with HPV genotypes 16, 18, 39, 45 and 73. Approximately 70 per cent of all cervical cancers are associated with HPV types 16 and 18 (AIHW 2009). HPV18 is the most prevalent and HP16 the second most prevalent genotype identified in adenocarcinomas, which are more frequently missed by cytology screening than squamous cell carcinoma (Meijer et al 2006).

A number of tests already exist for the testing of high-risk HPV genotypes including the Digene Hybrid Capture-II, a DNA hybridisation test. The Capture-II can identify the 13 high-risk (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68) and five low-risk (6, 11, 42, 43, 44) genotypes of HPV. The Hybrid Capture-II was assessed by the Medical Services Advisory Committee in 2002 for women with cytological prediction of low-grade abnormality and again in 2003 for use as a cervical screening tool[1]. The 2002 MSAC report found that HPV testing was more sensitive but less specific than cytology, however the evidence could not support the use, or the public funding, of the Hybrid Capture-II test for triaging of women with ambiguous cervical screening results. The 2003 MSAC assessment also found there to be insufficient evidence to support public funding of the Hybrid Capture-II test either as a stand-alone screening test or combined with screening by cytology (Pap or liquid-based smear). Hologic Inc also produces the Cervista™ HPV HR test which screens for 14 high-risk genotypes (the same as the Capture-II with the addition of genotype 66). In August 2009, the MSAC found that although HPV triage for Pap smear(using the Hybrid Capture-II for 13 high-risk genotypes), compared with repeat recall cytology at one year, was safe and effective, it was not cost effective in the Australian setting at the current price of

[1] Completed MSAC references

HPV testing. The MSAC did not support public funding for HPV triage testing in cervical cancer.

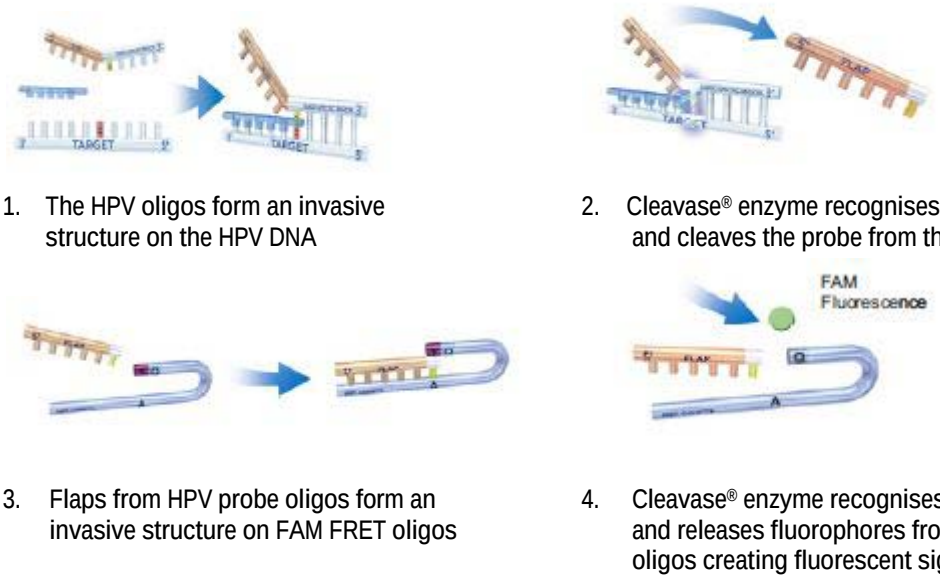
These "pooled" tests are *qualitative*, not quantitative, and only identify whether a women is positive for one or more of the high-risk genotypes but do not identify which specific genotype. It has been suggested that as women positive for HPV 16 and 18 are at a greater risk of developing high-grade (CIN3+) cervical cancer, a triage test should be developed which only identifies women positive for HPV16 and 18 (Meijer et al 2006).

The new Hologic Cervista HPV 16/18 is a *qualitative* assay which identifies the presence of DNA sequences to the two specific high-risk genotypes HPV16 and18. It is recommended for use in women aged 30 years or older, or those with questionable cytological results, to gain a better understanding of their risk for cervical cancer. Thus, an ambiguous Pap smear (or an ASC-US[2] smear), which identifies abnormal cells by microscopic examination of cervical cell samples, could be followed by the Cervista™ HPV 16/18, informing the clinician about the presence of high-risk types of HPV and a woman's risk of developing cervical cancer. Although the Cervista™ assay is designed to *only* use the same cervical sample obtained by the ThinPrep® Pap Test and *not* a conventional Pap smear (FDA 2009), residual cells from a conventional Pap smear (approximately 80% of the smear sample) may be placed in a ThinPrep® collection vial and used for HPV testing (personal communication Hologic Australia). In 2002, the MSAC considered the ThinPrep® Pap Test, however public funding was not supported for this technique. Australian women may be offered a ThinPrep® Pap Test if a previous Pap smear was unsatisfactory due to the presence of inflammatory cells or blood, or if the women has a history of unsatisfactory Pap smears.

The Cervista assay uses a signal amplification method for detection of specific HPV16/18 nucleic acid sequences. The primary reaction occurs on the targeted DNA sequence and a secondary reaction produces a fluorescent signal. In the primary reaction, two types of sequence specific oligonucleotides (oligos) (i.e. a probe oligo and an "Invader" oligo) bind to the DNA target sequence. When these oligos overlap by at least one base pair on the target sequence, an invasive structure forms that acts as a substrate for the Cleavase® enzyme, which cleaves the flap of the probe at the position of the overlap (Figure 1). The cleaved flaps bind to a universal hairpin FRET oligo. Cleavase® recognises this structure and cleaves the FRET oligos, producing a fluorescent signal indicating the presence of a HPV genotype. An internal control is also provided in the kit. A positive result is represented by a FAM fluorescent signal that lies above an empirically derived cut-off value. For each reaction, a negative

[2] ASC-US smear result = atypical cells of undetermined significance

result is represented by a FAM fluorescent signal that lies below the same empirically derived cut-off value (FDA 2009).



1. The HPV oligos form an invasive structure on the HPV DNA
2. Cleavase® enzyme recognises the structure and cleaves the probe from the oligo
3. Flaps from HPV probe oligos form an invasive structure on FAM FRET oligos
4. Cleavase® enzyme recognises structure and releases fluorophores from FRET oligos creating fluorescent signal.

Figure 1 A graphic illustration of the principles of the Cervista HPV 16/18 test (Day et al 2009)

OTHER ISSUES

On October 1st 2009, New Zealand released new guidelines for cervical screening, including the recommendation of HPV testing in three clinical situations:

- ASC-US/LSIL triage of women over 30 years. If the HPV test is negative then the woman will have a follow-up smear in one year. If the HPV test is positive, then the woman will be referred for a colposcopy;
- Post treatment of CIN2/3; or
- Management of discordant results (National Screening Unit 2009).

Eight New Zealand pathology laboratories are contracted to provide cytological services for the programme and some of these laboratories will provide HPV testing. Several commercially available HPV tests will be used by these laboratories, rather than a single defined product, and these include Hologic's Cervista™ HPV HR, Roche's Amplicor HPV, Abbott's RealTi*me* High Risk (HR) HPV and the Diagene Capture-II (personal communication NZ National Cervical Screening Programme). All of these assays are qualitative and test for the 13 or 14 high-risk genotypes. HPV testing is not recommended for women under the age of 30 years as HPV infection is common in this age group and is usually self resolving. It is hoped that HPV testing will determine more accurately those women who require further assessment. A negative test indicates that a woman is unlikely to develop cancer in the next few years, however a positive HPV test does not indicate that a woman has cancer (National Screening Unit 2009).

The HPV vaccine has also been introduced in New Zealand and is included on the National Immunisation Schedule at no cost for girls aged 12 years (National Screening Unit 2009).

Recently in Australia, the National Cervical Screening Program has been affected by two major changes in policy and management In 2006, the NHMRC guidelines (NHMRC 2005) were introduced into clinical practice. The guidelines recognised that changes in cervical cells are a result of an infective rather than a neoplastic process. The Guidelines recommend less intervention for women with low-grade squamous intraepithelial lesions, giving HPV infection an opportunity to resolve without treatment. In addition, in 2007, a vaccine against HPV types 16, 18, 6, and 11 was introduced under the National Immunisation Program. The vaccine is expected to lower cervical cancer incidence and mortality rates, however due to the slow progression of cervical cancer the effect of vaccine administration may not be evident for some time (AIHW 2009).

CLINICAL NEED AND BURDEN OF DISEASE

In 1991 Australia introduced the National Cervical Cancer Screening Program. This program aims to screen all sexually active women in the age group 18-69 yrs, testing is recommended every 2 years. This program has lead to a significant reduction in the incidence of cervical cancer and associated mortality. Cervical cancer is now the 13th most common cancer affecting Australian women, with an age-standardised (world) incidence of 5.9 new cases per 100,000 women in 2005. Cervical cancer is the 19th most common cause of cancer mortality, with an age-standardised (world) mortality of 1.5 deaths per 100,000 women in 2006. This compares favourably with 2002 worldwide figures of an age-standardised (world) incidence of cervical cancer of 16.2 new cases per 100,000 women, and an age-standardised (world) mortality rate from cervical cancer of 9.0 deaths per 100,000 women (AIHW 2009).

The number of colposcopies performed in Australia in the 12-month period from January 2008 to December 2008 was 8,831 (MBS item numbers 35644, 35645, 35646, 35647), with the majority (7,512) performed using the MBS item number 35647 (Fee: $188.15).[3]

A similar trend has been observed in New Zealand after the introduction of a National Cervical Screening Program in 1991. The age-standardised incidence of cervical cancer in 1991 was 12 per 100,000 and in 2002 this rate had decreased to 7 per 100,000. The incidence rate is much higher in Māori women compared to the general population, and was estimated to be 12.4 per 100,000 in 2002. Mortality rates have also decreased with the introduction of a national screening program. Between 1990 and 2001, mortality fell from 5 per 100,000 to 2 per 100,000, a decline of 60 per cent.

[3] http://www9.health.gov.au/mbs/search.cfm

Mortality in Māori women was also higher than in the general population but has decreased from 11 per 100,000 in 1996 to 6 per 100,000 in 2001 (MoH 2005).

DIFFUSION

The Cervista™ HPV 16/18 is not currently in use in Australia or New Zealand.

COMPARATORS

Cervical cancer affects the cells of the cervix and unlike many cancers these cells may show precancerous changes or abnormalities, which may be detected before progression to cancer occurs with screening with the Papanicolaou (Pap) test (AIHW 2009). While the Papanicolaou (Pap) test is problematic and unreliable in many respects it has been the backbone of the most successful cancer reduction program in the Australian health system. The main failing of the Pap test is its sensitivity which has been estimated to be as low as 30 per cent (30-87%), while the specificity – more important for a screening test - is much higher, falling in the range of 86-100 per cent (Nanda et al 2000). Although the success of the Australian Cervical Cancer Screening program is undoubted, reaching 73 per cent of eligible women in each three year period, many women do not participate in the screening for a variety of reasons and the impact of this is evident in the fact that 50 per cent of invasive cervical cancers occur in women not adequately screened (Sasieni et al 1996; van der Graaf et al 1988).

SAFETY AND EFFECTIVENESS ISSUES

To date, the only published information in respect to the use of the Cervista HPV 16/18 assay is the safety and effectiveness data provided to the FDA in support of Hologic's application for FDA approval. A great deal of data has been published since the 2002 and 2003 MSAC applications on the use of assays which are used to detect either the 13 or 14 high-risk HPV genotypes. The most recent of these studies compared the use of the Cervista HPV HR test to PCR[4] with bidirectional DNA sequencing of 189 cervical smear samples. Indeterminate Cervista results were obtained in 2/189 (1.1%) samples. Accuracy of the Cervista assay compared to PCR was 91.4 per cent, 95% CI [86.5, 95.0]. The assay was performed in several pathology centres over different time periods. The inter-run reproducibility agreement (between days and within site) was 98.8 per cent and the inter-site reproducibility agreement (between sites) was 98.7 per cent. In addition, there was no cross-reactivity with DNA obtained from non-oncogenic HPV genotypes or from other infectious agents (Day et al 2009) (level III-2 diagnostic evidence).

Preliminary laboratory-based studies of the Cervista HPV 16/18 demonstrated good precision between operators (94-100%), depending on the DNA copy number or number of HPV positive cells/ml, when the same sample was assayed twice daily and

[4] PCR = polymerase chain reaction

in duplicate over a 21-day period. Reproducibility of the Cervista was assessed at three sites using HPV16, HPV18 and HPV negative DNA extracted and sequenced from cervical samples. Each sample was tested at all three sites on five, non-consecutive days and reproducibility was 100 per cent. Inconclusive results were obtained when samples were contaminated with contraceptive jelly and anti-fungal creams but not with blood, mucous or the PreservCyt® solution. There was no cross-reactivity with DNA obtained from non-oncogenic HPV genotypes or from other infectious agents including Herpes simplex and *Chlamydia trachomatis* (FDA 2009).

The initial clinical study enrolled 1,514 women, over 18 years (mean age 33.7 ± 11.76 years), with an ASC-US result. All women underwent testing colposcopic examination and testing with the two Cervista assays HPV16/18 and HPV HR using the original ThinPrep® smear sample (level III-1 diagnostic evidence). Cervista HPV 16/18 results were obtained from 1,398 and colposcopy was completed on 1,476 women, however only 1,312 women with a known disease status were available for analysis. The outcomes for these women are summarised in Table 1.

Table 1 Cervista HPV HR and HPV 16/18 results compared to colposcopy

Cervista HPV HR	Cervista HPV 16/18	Disease (central histology)					Total
		-ve colposcopy, no biopsy	No CIN	CIN 1	CIN 2	CIN 3	
Positive	HPV16 +ve	39	83	40	25	14	201
	HPV18 +ve	11	22	9	0	1	43
	HPV16 + 18 +ve	1	3	5	2	2	13
	HPV16 + 18 -ve	109	273	98	15	5	500
Negative	HPV16 and/or 18 +ve	3	3	1	0	0	7
	HPV16 + 18 -ve	210	304	29	5	0	548
Total		373	688	182	47	22	1312

Three possible outcomes could result from the study: women could be HPV HR positive and HPV 16/18 positive, HPV HR positive and HPV 16/18 negative[5] or HPV HR negative. For women who were CIN 2 by colposcopy/ histology the likelihood ratio of women having the disease and being positive for HPV HR and HPV 16/18 was 3.72. The likelihood ratio of having the disease and being HPV HR positive and HPV 16/18 negative was 0.75 (less likely to have disease) and was 0.16 when HPV HR negative. For women who were CIN 3 by colposcopy/ histology the likelihood ratio of women having the disease and being positive for HPV HR and HPV 16/18

[5] As the HPV HR tests for 14 genotypes including HPV 16 and 18 it is possible for this test to be positive whilst the HPV 16/18 is negative

was 4.15. The likelihood ratio of having the disease and being HPV HR positive and HPV 16/18 negative was 0.59 (less likely to have disease) and was 0.0 when HPV HR negative. These results demonstrate that women positive for HPV 16/18 and not just the 14 high-risk genotypes are more likely to have cervical cancer. The sensitivity and specificity of the Cervista HPV 16/18 test in women who were CIN 2 or CIN 3 *and* had a positive HPV HR result are summarised in Table 2. PCR sequencing was the conducted on the samples that were HPV HR positive. The level of agreement for samples positive for PCR and HPV 16/18 was 94.1 per cent (95% CI [89.8, 96.7]) and for those negative for PCR and negative for HPV 16/18 was 85.7 per cent (95% CI [82.4, 88.4]).

Table 2 Performance of Cervista HPV 16/18 in women who are HPV HR positive

CIN 2		
Sensitivity	68.8% (44/64)	95% CI [56.6, 78.8]
Specificity	69.3% (480/693)	95% CI [65.7, 72.6]
CIN 3		
Sensitivity	77.3% (17/22)	95% CI [56.6, 89.9]
Specificity	67.3% (495/735)	95% CI [63.9, 70.6]

Preliminary PCR sequencing data was also presented in the FDA submission of an ongoing study recruiting 2,026 women ≥ 30 years with a normal Pap smear result (no intraepithelial lesion or malignancy). ThinPrep® smear samples were then tested with Cervista HPV HR and HPV 16/18. It is hoped that at least 1,000 of these women will be followed-up for three years. The level of agreement for samples positive for PCR and HPV 16/18 was 94.4 per cent (95% CI [74.2, 99.0]) and for those negative for PCR and negative for HPV 16/18 was 82.1 per cent (95% CI [77.6, 85.9]).

COST IMPACT

The Cervista HPV 16/18 or HPV HR costs approximately $20-25 per test. A ThinPrep® smear test costs approximately $12, however the cost of supplying the ThinPrep® collection vial is only about $2 of this cost (personal communication Hologic Australia).

Although the 2002 MSAC systematic review on the use of HPV testing for women with an ambiguous smear test initially concluded that additional testing was not cost-effective, the cost analysis was found to be sensitive to the prevalence of high grade lesions in women. It was noted that further cost-effectiveness research was required. It would be of interest to source the cost-effectiveness data used to produce the 2009 New Zealand cervical screening guidelines.

ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

It is currently uncertain how the results of the HPV testing will be conveyed to the patient and within what framework the results will be interpreted. Counselling issues and the stigma of being diagnosed with a sexually transmitted disease, without the counselling support of a trained practitioner, are concepts that have been highlighted as reasons against patient access to medical technology outside of established systems.

SUMMARY OF FINDINGS

Women presenting with an ambiguous smear test result may benefit from triaging with an additional test for HPV status. Testing for the 13 or 14 HPV genotypes considered to confer high-risk for the development of cervical cancer would appear to be of some benefit, however further stratification of testing just for the high-risk HPV16 and HPV18 genotypes may reduce the number of women referred on for invasive colposcopy. In preliminary studies, the Cervista HPV 16/18 appears to have good agreement with the gold standard of PCR bidirectional sequencing and has reasonable sensitivity and specificity for women diagnosed with CIN 2 and CIN 3 abnormalities.

HEALTHPACT ACTION:

Although New Zealand have recently adopted HPV testing in conjunction with conventional Pap smears, the cervical cancer screening programme in Australia is not ready to screen women for HPV. Therefore HealthPACT has recommended that further assessment of this technology is no longer warranted.

NUMBER OF INCLUDED STUDIES

Total number of studies	
Level III-1 diagnostic evidence	1

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SEARCH CRITERIA TO BE USED:

Cervical Intraepithelial Neoplasia/*diagnosis

Cervix Uteri/*virology

Female

Mass Screening/*methods

Papillomavirus Infections/*virology

Sensitivity and Specificity