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Horizon Scanning Technology Prioritising Summary

TamPap home based self sampling for HPV

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PRIORITISING SUMMARY

REGISTER ID: **000326**

NAME OF TECHNOLOGY: **TAM PAP**

PURPOSE AND TARGET GROUP: **HOME-BASED SELF-SAMPLING FOR HUMAN PAPILLOMA VIRUS (HPV) TESTING**

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
Australia		✓	

IMPACT SUMMARY

Tam Pap Pty Ltd provides Tam Pap with the aim of providing the means for home sampling for the purpose of the detection of human papilloma virus (HPV). The technology is available through General Practitioners and online for women wanting to self-sample for the purpose of finding out their HPV status. It is proposed that the HPV status of a woman may be predictive of her risk status regarding cervical cancer. This prioritising summary investigates the evidence for self sampling and the relationship between HPV status and cervical cancer.

BACKGROUND

The Tam Pap test is aimed at women not participating, for various reasons such as fear, embarrassment, cultural beliefs, or inconvenience etc, in the national organised cervical cancer screening program. It is proposed that the women may take a vaginal

sample using a tampon in their own home and send this sample to a pathology testing laboratory using the directions provided by the Tam Pap kit. The pathology laboratory would test the sample for HPV and the results would then be forwarded to the client's nominated general practitioner. The kits are distributed via pharmacies and are also available for purchase through a website.

CLINICAL NEED AND BURDEN OF DISEASE

Cervical cancer is the 18th ranked cause of cancer related mortality in women, causing 238 deaths in Australia in 2003. The cervical cancer death rate increases with geographical remoteness from major cities and affects indigenous Australians at nearly three times the incidence rate compared to the incidence for the remainder of the population.

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. From 1991 to 2000 there was a 33 per cent reduction in cervical cancer incidence and 36 per cent reduction in associated mortality (Canfell et al 2006). In 2001 there were 735 new cases of cervical cancer, compared to 1,078 new cases in 1990 before the start of the National Cervical Cancer Screening Program. There has been a decline in the age-standardised death rate from 64 per 100,000 women in 1983 to 2.2 per 100,000 women in 2003.

Human Papilloma Virus (HPV) is associated with up to 99.7 per cent of cervical cancers (Walboomers et al 1999). HPV is the most common sexually transmitted disease and is estimated to infect 50 per cent of sexually active women in their lifetime (Koutsky et al 1988). HPV is classified into types, not all of which are associated with cervical cancer. Only the oncogenic types are thought to play a role in cancer. Even infection with one of the predominant oncogenic HPV types may not result in cancer. Persistence of the HPV infection is another major factor in the causation of cervical cancer (Nobbenhuis et al 1999), with persistent infection with an oncogenic type of HPV providing the highest cancer risk.

Although the National Cervical Cancer Screening Program appears to have had an impact on the incidence and mortality associated with cervical cancer, a large proportion of Australian women do not participate in the program. There is, thus, a need to screen the proportion of women who fall outside the current screening program.

DIFFUSION

Tam Pap Pty Ltd has recently launched the Tam Pap kit, but the TGA has limited marketing of the kit to health practitioners and pharmacists. The kit is ordered through a website (http://tampappayments.com/order.php) or by telephone.

COMPARATORS

While the Papinicolou (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). Reasons for not participating in the screening program are many and include cultural objections, discomfort, inconvenience, embarrassment etc. To overcome these problems self-collection of samples by women for Pap smear or HPV testing have been investigated in several settings around the world (Szarewski et al 2007; Petignat et al 2007; Stenvall et al 2007).

Another method of home sampling that has been trialled is cervicovaginal lavage. A study comparing a home sample obtained by cervicovaginal lavage to clinician-performed cervicovaginal lavage and Pap smear found that neither lavage method was useful for cytology. In contrast, in women with high grade cervical intraepithelial neoplasia the test outcome for high risk HPV had a high level of concordance between the patient sampled lavage (81% HPV positive) and the clinician sampled Pap smear (91% HPV positive) and lavage (91% HPV positive). The authors concluded that the home sampling technique was useful for reaching women not participating in organised Pap Test programs, but that the home sampling method did not fully match the standards of an organised program (Nobbenhuis et al 2002).

EFFECTIVENESS AND SAFETY ISSUES

As no information was found regarding the specific safety or effectiveness of the Tam Pap product, this summary will review the evidence for general self sampling and HPV testing for the purpose of cervical cancer screening.

HPV Testing

Nucleic acid based tests for HPV are beginning to be used in diagnostic laboratories around the world as an adjunct to conventional Pap testing for screening, the secondary triage of patients with abnormal Pap tests, and the follow-up of patients after cancer treatment (Franco 2003). A systematic review of HPV testing within the current screening program concluded that there was sufficient evidence for advocating HPV testing in certain situations, such as management of women with borderline or mildly dyskaryotic smears, especially in women over 30 years of age. The women over 30 years who test positive to high-risk HPV should be immediately referred for colposcopy, and women aged under 30 who test negative can be less intensively

monitored. The review also found that although HPV testing using a nucleic acid based test had a higher sensitivity than cytology, it also lacked specificity compared to cytology. The false positive rate was higher in younger women, where it was also noted that the specificity of cytology is also lacking (Cuzick et al 2000) (level III-3 screening evidence)[1].

A study involving 4,075 women (mean age 25) compared a polymerase chain reaction (PCR) based HPV test, and a liquid-based RNA-DNA hybridisation capture with signal amplification HPV assay (signal amplification) to conventional Pap cytology. The results showed that, regarding women who were CIN 3[2] or higher, the sensitivity of Pap cytology was lower (61.3%, 95% CI [48.5, 70.9]) compared to HPV PCR (88.2%, 95% CI [78.9%-93.8%]) and HPV signal amplification (90.8%, 95% CI [83.1%-95.8%]). The test specificity was 82.4% (95% CI [81.8-83.1]) for Pap cytology, 78.8% (95% CI [77.9-79.7]) for PCR, and 72.6% (95% CI [69.4-75.0]) for signal amplification. Several testing strategies were investigated and it was found that referring all women with atypical cells of undetermined significance (ASCUS) or greater (as determined by Pap cytology) for colposcopy had a sensitivity of 61.3 per cent compared to 60.3 percent if the ASCUS or greater subjects were screened by signal amplification and only those testing positive were referred for colposcopy. The latter strategy was significantly more specific (88.9%), compared to the first strategy (82.4%). The authors concluded that HPV testing, due to its high sensitivity, may have a role in testing patients who are not likely to be available for further testing, in for example national organised screening programs (Kulasingam et al 2002) (level III-3 screening evidence).

A review of 13 studies comparing the use of HPV testing against Pap cytology for screening of asymptomatic women concluded that on average HPV testing is 27 per cent more sensitive and Pap cytology is eight per cent more specific. A combination of both HPV testing and Pap cytology yielded high negative predictive values, which may allow the interval between screening visits to be extended. No outcomes, based on mortality or cancer incidence, were reported (Franco 2003) (level III-3 screening evidence).

A Canadian randomised controlled trial is currently underway, having fulfilled recruiting requirements in 2005. This study has 10,171 women enrolled and will compare HPV testing to Pap cytology as a primary screening tool in women aged over 30 years. The interim results showed 2.8 per cent of subjects had an abnormal Pap test, 6.1 per cent had a positive HPV result and 1.1 per cent had both (Mayrand et al 2006) (level II screening evidence).

[1] Although these reviews were conducted systematically, the papers reviewed are of poor quality. The reviews were therefore given the same level of evidence as the studies reviewed.
[2] Cervical Intraepithelial Neoplasia (CIN) grade 3 encompasses severe dysplasia and carcinoma *in situ* in which dysplastic cells extend into the upper third and potentially the full thickness of the epithelium.

Self sampling

Self sampling is being investigated as a means to increase the number of women reached by organised cervical cancer screening programs.

A study involving 103 women referred for colposcopy, therefore a high HPV prevalence group, were sampled by a clinician and also self-sampled in a clinic and then self-sampled at home over the next three weeks. The sampling protocol used 2 dacron swabs and a tampon per sampling time point. The tampon sampling time was progressively increased over the three weeks, from 10 seconds in the clinic to overnight in the last sampling. For women found to have cervical intraepithelial neoplasia (CIN) by biopsy, both tampons and swab sampling were found to be equally effective at detecting high-risk HPV. For women with normal biopsy histology the 1hr, 4hr and overnight tampons were as effective as the concurrent swabs at detecting high-risk HPV (Harper et al 2002) (level III-3 intervention evidence).

A study of 920 women presenting for a routine Pap test utilised an additional sampling method consisting of self sampling using a cotton swab, followed by a Pap test performed by a clinician and a cotton swab sample collected by a clinician. The self sampling was conducted in the clinic but was not supervised nor directed; rather the women were only given written instructions as would be in the case with a home sampling kit. The women with abnormal Pap cytology, positive HPV tests, unsatisfactory smears, and a random five per cent of negative HPV tested women were examined by colposcopy. The colposcopy results were used as the standard against which the other tests were measured. The test sensitivity for high grade disease (CIN 2+) was 81 (95% CI [60-92]), 100 (95% CI [85-100]), and, 81 (95% CI [60-92]) per cent for the self sampled HPV test, the clinician sampled HPV test, and the Pap cytology test, respectively. For combined high and low grade disease the test sensitivity was 77 (95% CI [65-86]), 80 (95% CI [68-88]) and 48 (95% CI [36-61]) per cent for the self sampled HPV test, the clinician sampled HPV test, and the Pap cytology test, respectively. For combined high and low grade disease the test specificity was 85 (95% CI [82-87]), 87 (95% CI [85-89]) and 97 (95% CI [96-98]) per cent for the self sampled HPV test, the clinician sampled HPV test, and the Pap cytology test, respectively. The authors conclude that self sampling is a viable alternative for women not participating in organised cervical cancer screening (Szarewski et al 2007) (level III-2 screening evidence).

A systematic review and meta-analysis of self sampling for HPV testing reviewed 18 studies involving a total of 5,441 participants. Self sampling methods used in the studies included Dacron or cotton vaginal swabs, tampons, cytobrush or cervicovaginal lavage. HPV detection methods were nucleic acid based and were either second-generation hybrid capture 2 (HC-2) assays, or PCR assays. The review found self- or clinician- sampling did not affect the detection of HPV significantly. For all the studies analysed the combined mean detection rates for self- and clinician-sampling methods were 27.4 per cent (95% CI [26.2-28.6]) and 28 per cent (95% CI

[26.8,29.1]), respectively. The two largest studies in the review showed very close agreement between detection rates for either sampling method. Using combined self- and clinician- sampling, over either sampling method, individually added 6.4 per cent to the detection rate over self-sampling and 5.8 per cent over clinician-sampling. For high-risk HPV the results were similar with an approximate 6 per cent gain by combining the results from self- and clinician- samples over either sampling method individually. Although the assessment methods were not standardised, the six studies that queried the acceptability of self- versus clinician- sampling found that the vast majority of women preferred self-sampling. The authors, due to the variations in the outcomes of the individual studies, were not able to recommend a particular sampling method, with regard to either the type of sampling method or who performed the sampling. The individual studies also did not give long term outcomes such as rates of severe disease/death due to cervical cancer but rather just focussed on the narrower goal of determining the better method of sampling for the detection of HPV (Petignat et al 2007) (level III-3 screening evidence)[3].

In summary, most of the studies identified agree that self sampling is a viable alternative to clinician sampling, and that the diagnostic outcomes of self obtained samples are very close to those obtained by clinicians. Swabs or tampons seem to yield the best results, but other modalities are also viable. The majority of appropriate studies agree that HPV testing is a useful tool and should play some role in cervical cancer screening. The exact role of HPV testing, as yet, cannot be definitively determined as long term disease-based outcomes and cost effectiveness data are lacking. Most published information agrees that HPV testing is best suited to a role in conjunction with some form of cytology such as the Pap test.

COST IMPACT

The TamPap home testing kit costs AUD$49.95 and is purchased by the patient.

A United States study that modelled the cost of a variety of HPV and Pap cytology testing strategies found that the maximal saving of lives occurred using both HPV testing and Pap cytology at 2 years intervals until death (up to 100 years). This outcome had an incremental cost of $US 76,183 per Quality adjusted life year (QALY). This scenario resulted in 225 cases of cervical cancer and 51 deaths versus the no-screening scenario where 3,382 cases occurred and 1,822 deaths. The scenario that most closely mimics the Australian national program, in this case Pap testing every 2 years until 65, had 796 cases and 352 deaths at a cost of $US 34,529 per QALY. The HPV screening was equally cost effective as Pap cytology at any designated age of screening cessation and all screening intervals (Mandelblatt et al 2002).

[3] Although this review was conducted systematically, the studies reviewed are of poor quality. The review was therefore given the same level of evidence as the studies reviewed.

ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

It is currently uncertain how the results of the Tam Pap test will be conveyed to the patient and within what framework the results will be interpreted, given that the test is aimed at women who find the current system of screening unacceptable. 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. Given the highly emotive nature of the issue of sexual activity in young people, there exists the possibility that a home sampled test for a STD could be used coercively to investigate sexual activity of unwilling subjects. The psychological stress associated with potential false positive results and subsequent unnecessary invasive medical investigations is an issue that needs consideration.

OTHER ISSUES

Pap testing within the National Cervical Cancer Screening Program is a very successful Australian public health program. The Tam Pap test enters into this arena and its role is uncertain. If this test reaches women who are not currently participating in the organised national screening program, it may play a positive role in bringing some form of screening to the unscreened. If Tam Pap causes confusion or uncertainty towards the established national screening program, or results in a reduction in the current Screening Program participation rate, then it could damage the success of the current program. Currently, no literature was found to support the exclusive use of HPV testing as a screening tool, except in the case where it may reach women currently not participating in organised Pap cytology based screening. The vast majority of studies involving both HPV testing and Pap cytology, recommended the combination of both tests as an improvement to the current Pap cytology alone system. Viable combinations were either, concurrent testing with both methods, or using HPV testing to triage certain patients with certain Pap cytology outcomes. Younger and especially older women who test negative with a HPV test are most probably reflecting their true HPV status, due to the high sensitivity of HPV testing. The interpretation of the tests of younger women who test positive is more problematic, with many of these women likely to spontaneously clear the virus. Also a proportion of these “HPV positive” women are falsely positive and will be subject to unnecessary stress and/or invasive examinations such as colposcopy or biopsy causing potential risk to the women and adding a cost burden to the health care system. Older women testing positive are more likely to be truly HPV positive and are at the most risk of developing or having cervical cancer.

SUMMARY OF FINDINGS

HPV testing as the basis for screening for cervical cancer is highly sensitive, yet lacks specificity. It shows better performance when used as a screening test in women over 30 or 35 years of age. In younger women test results are more difficult to interpret,

with most HPV infections clearing spontaneously and posing no threat for the development of cervical cancer. The lack of specificity and uncertainty of the meaning of results for younger women make exclusive HPV testing only useful for those who are not going to be tested any other way. Specifically, there was little information and no studies identified for the Tam Pap kit. It is therefore recommended to monitor this controversial new technology.

HEALTHPACT ACTION:

HealthPACT agreed that over-the-counter HPV testing is unlikely to affect conventional Pap smear testing for cervical cancer and have therefore recommended that further assessment of this technology is no longer warranted.

NUMBER OF STUDIES INCLUDED

Total number of studies	
Level II screening evidence	1
Level III-2 screening evidence	1
Level III-3 screening evidence	2

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SOURCES OF FURTHER INFORMATION

No other sources were identified.

SEARCH CRITERIA TO BE USED:

Female
Humans
Mass Screening
Uterine Cervical Neoplasms/ diagnosis/ epidemiology
Papillomavirus Infections/ diagnosis
Tumor Virus Infections/ diagnosis
Uterine Cervical Dysplasia/ diagnosis/pathology/ virology
Uterine Cervical Neoplasms/ diagnosis/pathology/ virology
Vaginal Smears
DNA, Viral/isolation & purification
Polymerase Chain Reaction
Sexually Transmitted Diseases
Nucleic Acid Amplification Techniques
Nucleic Acid Hybridization