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Horizon Scanning Technology Prioritising Summary

Diagnostic tests for ovarian cancer

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PRIORITISING SUMMARY

REGISTER ID: **000431**

NAME OF TECHNOLOGY: **DIAGNOSTIC TESTS FOR THE DETECTION OF OVARIAN CANCER**

PURPOSE AND TARGET GROUP: **FOR THE EARLY DETECTION OF OVARIAN CANCER IN SYMPTOMATIC WOMEN**

STAGE OF DEVELOPMENT (IN AUSTRALIA):

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

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:

HealthLinx Ltd, Australia produces the OvPlex™ diagnostic test with the aim of providing early detection of ovarian cancer. The technology is available on a direct-to-consumer basis through ARL Pathology in Melbourne, Australia, for women with symptoms suggestive of ovarian cancer[1]. In September 2009 the FDA approved the OVA-1 test (Vermillion Inc, USA) OVA1 is a biomarker assay which aims to identify women who will benefit from referral to a gynaecological oncologist for surgery, despite negative results from other clinical and radiographic tests for ovarian cancer. Ovasure, another biomarker assay marketed by LabCorp was recently withdrawn from the United States market after criticism by the FDA (see links) (Greene et al 2008).

[1] Although HealthLinx Ltd have stated in communications with the evaluators that the OvPlex test is designed for women with symptoms of ovarian cancer, this is not explicitly stated on their web site.

BACKGROUND

Ovarian cancer can either originate in the ovary (primary ovarian cancer) or result from metastases from another site, such as the breast or colon. Benign or malignant ovarian cancer can develop from three cell types: epithelial, germ cells (cells that form the egg) or the stromal cells which produce ovarian hormones. Approximately 60 per cent of *all* ovarian cancers and 90 per cent of primary ovarian cancer are of the epithelial type. Stromal and germ cell tumours account for approximately 10-15 and 25 per cent of ovarian cancers, however these types may be more common in younger, premenopausal women. Ovarian cancer spreads primarily through the peritoneal cavity and common sites of metastasis are the small and large bowel, the omentum, the liver, the diaphragm and spread to retroperitoneal lymph nodes is common (AHRQ 2006).

There is currently no effective method of screening for ovarian cancer. As ovarian cancer presents with few, if any specific symptoms, the first presentation of many women occurs at an advanced stage of the disease: stage III, where the cancer has spread beyond the pelvis to organs of the upper abdominal cavity, or stage IV, where the cancer has spread outside of the peritoneal cavity. Cancers detected at these stages have a high case-fatality rate. Stage I ovarian cancer, which is limited to the ovaries, has a survival rate of over 90 percent. Therefore a test able to detect early signs of ovarian cancer may reduce morbidity and mortality (AHRQ 2006).

Ovarian cancer diagnostic tests currently offered in Australia (OvPlex™) and in the United States (OVA-1 and previously OvaSure) are biomarker assays which test for the presence of various biomarkers in the blood that are associated with ovarian cancer. The OvPlex™ diagnostic test, is based on the presence of five biomarkers: CA-125, C-reactive protein (CRP), serum amyloid A (SAA), interleukin 6 (IL-6) and interleukin 8 (IL-8) (Edgell et al 2010). An algorithm is used to analyse the plasma concentrations of the five biomarkers and the results are expressed as the "OvPlex™ Index", or the probability that the woman has ovarian cancer. To obtain a test, women are advised to order the OvPlex™ kit from ARL Pathology and take the kit, including the enclosed request form to their doctor. Results will then be forwarded to the doctor within 10-20 working days (ARL Pathology 2009). The OvaSure test was developed based on the paper by Visintin et al and used the following biomarkers: leptin, prolactin, osteopontin, insulin-growth factor II and macrophage inhibitory factor. The OVA-1 test is a qualitative serum test that combines the results of five immunoassays into a single numerical score. This test uses five biomarkers: transthyretin, apolipoprotein A-1, beta2-microglobulin, transferrin and CA-125 (Medical News Today 2009).

CLINICAL NEED AND BURDEN OF DISEASE

In 2005, ovarian cancer was the ninth most common cancer in Australian women with 1,205 new cases diagnosed and an age standardised incident rate of 2.7 per 100,000 women. The risk of developing ovarian cancer is 1:120 to age 75 years and 1:77 to age 85 years. The incidence of ovarian cancer is expected to rise gradually each year, with an estimated annual change in incidence of 27 cases per year. In 2005, ovarian cancer was ranked sixth in terms of the number of cancer deaths in women with 888 women dying, representing 5.2 per cent of all cancer deaths in females. The age standardised mortality rate was 7.6 per 100,000 women and the total person-years of life lost due to death before age 75 years or 85 years was 6,713 and 12,938, respectively. Interestingly, the age standardised mortality rate from ovarian cancer is not expected to change. The estimated proportion of women with ovarian cancer, based on 1998-2004 data, surviving at one-year was 66 per cent, 40 per cent at 5-years and approximately 26 per cent at 10-years (AIHW and AACR 2008).

In New Zealand in 2005, ovarian cancer was the seventh most common cancer diagnosed with 301 new registrations, accounting for 3.4 per cent of all new cancer registrations. Ovarian cancer was ranked the fourth most common cause of cancer mortality with 190 women dying, representing five per cent of all cancer deaths in females. The age-standardised death rate was 6.1 deaths per 100,000 females. Rates of new cases of ovarian cancer and death from ovarian cancer were much higher in women of Pacific Islander origin compared to Māori and non-Māori and non-Pacific women (Ministry of Health 2009).

DIFFUSION

Only the OvPlex™ diagnostic test is currently offered on a direct-to-consumer basis in Australia.

COMPARATORS

Currently, there is no high-quality, standard screening technique for the routine early detection of ovarian cancer. Current methods in use in Australia include bimanual pelvic examination, transvaginal ultrasound, and serum cancer antigen 125 (CA-125) levels. CA-125 levels have been found to be higher in some cancer patients, in particular ovarian cancer, however this test is not accurate enough to be used as a population screening tool (Anderiesz & Quinn 2003). The development of a symptom index has also been suggested as a useful tool for the monitoring of women's health, in particular symptoms such as increased abdominal size, persistent bloating, pelvic pain and urinary urgency may be an indication of the early stages of ovarian cancer (Goff et al 2004).

SAFETY AND EFFECTIVENESS ISSUES

The gold standard for diagnosis of ovarian cancer is histology.

Only one peer-reviewed paper, published February 2010, was identified that discussed the OVA-1 test, however the evaluators were unable to access this paper. From its title it would appear to discuss the process of the development of a biomarker assay and achieving FDA approval (Fung 2010).

As background to diagnostic testing for ovarian cancer, a recent systematic review reported on the use of CA 125 levels as a biomarker. Seventeen primary studies were included in the review, comparing CA 125 levels to histological analysis. All of the included studies were of low quality due to the lack of blinding. A total of 2,374 symptomatic women were analysed with study population sizes ranging from 53 to 290 women. Normal or benign lesions were reported in 1,695 (71.3%), a borderline diagnosis in 73 (3.07%) and ovarian cancer in 606 (25.5%) of patients. There was a moderate agreement of 77 per cent (kappa = 0.51) between CA 125 levels and histology. CA 125 had a pooled sensitivity of 80 per cent, 95% CI [76, 82], and a pooled specificity of 75 per cent, 95% CI [73, 77] for the detection of borderline or malignant ovarian tumours. The diagnostic odds ratio, or the odds of a positive test result in participants *with* the ovarian cancer compared to the odds of a positive test result in those *without* ovarian cancer, was 21.2 (95%CI [12, 37]). The I^2 statistic reported for sensitivity and specificity (89% and 96%) indicates that there was a high degree of heterogeneity between studies. Based on the high diagnostics odds ratio, the authors felt that the use of CA 125 levels was a useful preoperative test for predicting benign or malignant disease and this may be important when making decisions such as when to conduct laparoscopy or laparotomy. However it should be noted that CA 125 levels may be elevated in other gynaecological diseases and only 50 per cent of patients with stage 1 ovarian cancer will have an elevated CA 125 level (Medeiros et al 2009).

The 2004 paper by Zhang et al (2004) analysed a series of serum samples from patients with epithelial ovarian cancer (n=57, stage I/II invasive cancer n=42, stage IIIA invasive cancer n=2, stage I/II borderline tumour n=13) and healthy women (n=79). Proteomic profiles were compared between the healthy controls and those with cancer. Protein peaks of interest were purified and identified. Three potential biomarkers were identified. Two peaks were down-regulated in the cancer group and identified as apolipoprotein A1 and transthyretin (pre-albumin). The remaining peak was up-regulated in the cancer group and was identified as an amino acid fragment of human inter-α tyrpsin inhibitor. Levels of these biomarkers were then analysed in an independent validation set of serum samples: healthy controls (n=63), epithelial cancer (n=138), recurrent ovarian cancer (n=15) and a benign pelvic mass (n=166) (level III-3 diagnostic evidence). Apolipoprotein A1 and transthyretin were both able

to discriminate between healthy controls and cases of epithelial cancer, recurrent cancer and benign pelvic masses. Levels of the amino acid fragment were only significantly different in patients with recurrent cancer. Of interest was the fact that CA 125 levels were able to discriminate between controls and epithelial ovarian cancer and pelvic masses but not recurrent cancer. Combining these biomarkers with the detection of CA 125 levels increased sensitivity for the detection of ovarian cancer (74%, 95% CI [52, 90]) , however it should be remembered that sensitivity will be increased when the population is enriched for a particular condition and when the prevalence in a given tested population is high (Zhang et al 2004).

A similar study was conducted in 2008 by Vistintin et al, after an earlier study had already characterised four potential biomarkers for ovarian cancer: leptin, prolactin, osteopontin and macrophage inhibitory factor. Insulin-growth factor II and CA 125 were included as additional biomarkers. During phase one, the characterisation or training phase of the study, 181 samples from healthy controls and 113 samples from newly diagnosed women with ovarian cancer were analysed. During phase two, or the testing phase of the study, 181 samples from healthy controls and 43 samples from newly diagnosed women with ovarian cancer were analysed (level III-3 diagnostic evidence). The authors reported sensitivity, specificity, positive predictive (PPV) and negative predictive (NPV) values of 95.3, 99.4, 99.3 and 99.2 per cent (Visintin et al 2008). However, these estimates were derived by using the combined data from the training and validation phases. The training sample set should only be used to select the classifier and then the test set of samples should be used to evaluate the selected classifier. Using this principle, a lower sensitivity (84%) and specificity (95%) would result (McIntosh et al 2008). In addition, the PPV value is dependent on the prevalence of disease. In an enriched population such as that described by Visintin et al, the prevalence of ovarian cancer was high (156 cancer patients and 362 healthy controls). The prevalence of ovarian cancer in a general, asymptomatic screening population is low and has been estimated to be 1:2500 (0.04%). This would reduce the PPV to 6.5 per cent instead of the reported 99.3 per cent. As the PPV represents the proportion of women that test positive for ovarian cancer who actually have ovarian cancer, a PPV of 6.5 per cent means that of 15 women testing positive, only one will actually have ovarian cancer. The remaining 14 false positive women may undergo further diagnostic procedures that may be harmful to their mental and physical health (Greene et al 2008). In a symptomatic population, suspected of cervical cancer, the prevalence of disease would likely fall between the extremes of a non-symptomatic and a cancer-prevalent population. The study by Vistintin et al was used as a basis for the ovarian cancer diagnostic test, Ovasure, which, as previously mentioned in the Impact Summary, has been withdrawn from the market after concerns expressed by the FDA.

In November 2009, the OvPlex™ web site described a Phase II biomarker trial which has since been published by Edgell et al (2010). This study evaluated a panel of biomarkers (see Background) in healthy controls (n=212, mean age 47 ± 0.8years) and women with ovarian cancer (n=150, mean age 59 ± 1.0 years): stage I (n=28), stage II (n=63), stage III (n=46), stage IV (n=7) and undiagnosed (n=6). Plasma concentrations of the individual biomarkers for all patients are summarised in Table 1. Two-sample comparisons of plasma concentrations of cases versus controls were significantly different ($p<0.01$) for all biomarkers.

Table 1 Biomarker plasma concentrations

Mean ± SE	Controls (n=212)	All stages ovarian cancer (n=150)	Early stage cancer(I/II)* (n=91)
CA-125 (U/ml)	19 ± 1	1,419 ± 258	1,008 ± 180
CRP (μg/ml)	11 ± 1	88 ± 9	97 ± 14
SAA (ng/ml)	5 ± 1	113 ± 14	118 ± 18
IL-6 (pg/ml)	31 ± 9	62 ± 11	77 ± 17
IL-8 (pg/ml)	42 ± 19	138 ± 42	197 ± 69

SE = standard error, CRP = C-reactive protein, SAA = serum amyloid A, IL-6 = interleukin 6, IL-8 = interleukin 8
* Early stage cancer patients are a subset of the 150 patients with all stages of ovarian cancer

A model was constructed using 82 cancer patients and 97 healthy controls (unmatched for age and menopausal status). This model was then validated using this panel of biomarkers, compared to CA-125 alone, for patients with *all stages* of cancer, using samples from 68 cancer patients and 115 controls. For only *early stage (I/II) cancer*, 39 patients were evaluated with the biomarker panel and compared to CA-125 (level III-3 diagnostic evidence). With the inclusion of CA-125 in the OvPlex™ biomarker panel, incorporation bias has been introduced[2] into the analysis of diagnostic accuracy. The result is to make the test appear more powerful in differentiating a positive case from a negative case than it really is.

Samples were analysed for expressed biomarker levels and an algorithm was constructed, which reported a predicted posterior probability value (ρP) or the likelihood that a sample came from a women with ovarian cancer. These ρP values were used to generate receiver operator characteristic curves (ROC) for the biomarker panel. Two cut-off values for ρP were reported: 0.3 and 0.5 and the cut-off value for CA-125 was ≥35 U/ml[3]. Data from the validation study are summarised in Table 2. In this test population, with a high prevalence of ovarian cancer, the OvPlex™ assay had

[2] Incorporation bias = occurs when the diagnostic test under consideration is used to determine the reference standard, or the reference standard is used to determine the results of the diagnostic test (Worster & Carpenter 2008).
[3] The reference range for CA-125 is 0-35 U/ml. Values within this range are considered normal (Crawford & Peace 2005)

a sensitivity and specificity slightly higher or equivalent, depending on the cut-off value used, than those obtained with CA-125. The sensitivity for both the OvPlex™ and CA-125 assays decreased as the number of cancer patients (or prevalence) in the sample population decreased from 37 to 25 per cent, and would be expected to fall even further if a true population prevalence of ovarian cancer (0.04%) was approached. The number of false positives reported when using the CA 125 and the OvPlex™ assays were 12 and 10 ($\rho P \geq 0.3$), respectively, and seven ($\rho P \geq 0.5$) for the validation population. With regard to the number of false negatives, for the CA-125 assay alone there were five (7.4%) and four (10.3%) false negatives for all and early ovarian cancer patients, respectively. This compared favourably to the OvPlex™ assay, depending on the ρP cut-off value used, with a $\rho P \geq 0.3$ reporting four (5.9%) and three (7.7%) false negatives for all and early ovarian cancers, respectively. Using a $\rho P \geq 0.5$ cut-off, there were five (7.4%) and four (10.3%) false negatives using the the OvPlex™ assay for all and early ovarian cancers, respectively (Edgell et al 2010).

Table 2 Performance of OvPlex™ vs CA 125

	All stages ovarian cancer (n=68) Controls (n=115)			Early stage ovarian cancer (n=39) * Controls (n=115)		
	CA 125 ≥ 35 U/ml	OvPlex™ ρP ≥ 0.3	OvPlex™ ρP ≥ 0.5	CA 125 ≥ 35 U/ml	OvPlex™ ρP ≥ 0.3	OvPlex™ ρP ≥ 0.5
Sensitivity (%)	92.6	94.1	92.6	89.7	92.3	89.7
Specificity (%)	89.6	91.3	93.9	89.6	91.3	93.9
False +ve (%)	10.4	8.7	6.1	10.4	8.7	6.1
False –ve (%)	7.4	5.9	7.4	10.3	7.7	10.3

* Early stage cancer patients are a subset of the 150 patients with all stages of ovarian cancer

Table 3 Comparison of the AUC of the ROC curves for CA-125 and OvPlex™

	All stages ovarian cancer (n=68)	Early stage ovarian cancer (n=39)
CA-125	0.960	0.937
OvPlex™	0.988	0.985
Difference	2.8%	4.8%
Mann–Whitney test p (two-tailed)	$p < 0.01$	$p < 0.01$

ROC curves were generated and the area under the curve was used as a measure of diagnostic efficiency (Table 3). The area under the curve was reported to be significantly ($p<0.01$) greater for the OvPlex™ assay than for CA-125 alone for the all stages and early ovarian cancer cohorts.

It should be noted that this study presents preliminary estimates of the likely diagnostic accuracy of the test compared to CA-125 testing. However, the OvPlex™

biomarker panel also includes the CA-125 biomarker, which means that incorporation bias is introduced with the comparison of the biomarker panel with the individual biomarker. Therefore there has been considerable statistical adjustment in the study to cope with the non-independence of the results. Further, the results are currently too preliminary to be able to assess the diagnostic accuracy of OvPlex™ with any degree of certainty. This study by Edgell et al (2010) is a retrospective case-control study, and thus compares women with a known disease status, ovarian cancer, with healthy controls. As such, this type of study is considered open to several types of bias including spectrum bias[4] and selection bias[5] and thus the results are potentially not applicable to the women who are currently directly accessing the test.

The ideal study design, according to the NHMRC levels of evidence (Merlin et al 2009), to assess the diagnostic accuracy of a test, is one where there is a blinded comparison of the results of consecutive persons with a defined clinical presentation (in this case those women suspected of having ovarian cancer on the basis of symptoms) who receive both the new test and a valid reference standard (in this case histology).

COST IMPACT

ARL Pathology provides the OvPlex™ test for $200. A Medicare rebate or private health insurance rebate is not currently available for this test. If another pathology provider is used, a collection fee of $30 applies. Testing will not proceed until full payment is received (ARL Pathology 2009).

In Australia during 2000-01, total expenditure on ovarian cancer was $25 million. Of this, $19 million was spent on patients admitted to hospital, $1 million on out-of-hospital costs and $2 million on prescription pharmaceuticals. In 2000-01, ovarian cancer has an estimated lifetime treatment cost per case of $19,677 (AIHW 2006).

CA-125 levels may be determined using the MBS item number 66650 (fee $24.50).

ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

Technologies that are available on a direct-to-market basis do not require regulatory control by the TGA and can therefore be offered to women of all ages and health status. Direct marketing to consumers may have social consequences, such as increasing the burden on the health care system to cope with false positive or false negative test results. Women should discuss the need to undergo a test such as the

[4] Spectrum bias refers to the evaluation of a diagnostic test in a biased group of patients which leads to an overestimation of the sensitivity and specificity of the test. This is due to the diagnostic test being compared in a *healthy* population versus a population with *advanced disease.*

[5] Selection bias refers to the manner in which cases or controls were selected to take part in a study. Are the characteristics of patient samples analysed in the study the same as those in the target population that would receive the test?

OvPlex™ with their doctor and need to fully understand the implications of test results.

OTHER ISSUES

The lead author and three of the co-authors of the Edgell paper (2010) are employees of HealthLinx Ltd.

The Victorian Government announced In November 2009 an investment of $750,000 towards a biomarker trial for OvPlex™, the world's first commercially available early stage ovarian cancer diagnostic. The Victorian Government funding will go towards the biomarker trial being conducted in Victoria, with samples from the collaborators clinics in Queensland, Singapore and the UK. HealthLinx is working in conjunction with Victorian-based HealthScope, Mercy Hospital for Women, Victorian Bio Bank, Brisbane-based Mater Hospital and the UK-based University of Liverpool and South Essex Cancer Network. The biomarker trial will screen blood samples using the original five biomarker panel as well as two new novel biomarkers, HTX005 and HTX010.

SUMMARY OF FINDINGS

There is a clear need to establish a diagnostic test for ovarian cancer which is able to distinguish women with early stage, asymptomatic cancer from healthy women. The tests included in this assessment are aimed at women who have symptoms suggestive of ovarian cancer. The available studies are at the 'proof of concept stage' in that sensitivity and specificity estimates have been calculated on the basis of populations with a high prevalence of disease. To determine the diagnostic accuracy of the OvPlex™ test a large, symptomatic population would need to be tested that is likely to contain women with and without disease. These initial studies should provide a basis for further research. The need and consequences of testing should be discussed between the consumer and a health professional.

HEALTHPACT ASSESSMENT:

Based on the poor quality of evidence of studies conducted in inappropriate populations, and in light of ethical concerns and the potential to do harm associated with this direct-to-consumer test, it is recommended that this summary be disseminated to CTEPC, consumer health groups, the College of General Practitioners and the National Breast and Ovarian Cancer Centre. As the technology currently available in Australia is offered on a direct-to-consumer basis and does not impact directly on the health system. HealthPACT does not intend to further review this technology at this time.

NUMBER OF INCLUDED STUDIES

Total number of studies	
Level III-3 evidence	3

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SEARCH CRITERIA TO BE USED:

Amino Acid Sequence
Apolipoprotein A-I/blood
CA-125 Antigen/blood
Immunoassay
Ovarian Neoplasms/*blood/diagnosis/pathology
Tumor Markers, Biological/*blood