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Australia and New Zealand Horizon Scanning Network
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AN INITIATIVE OF THE NATIONAL, STATE AND TERRITORY GOVERNMENTS OF AUSTRALIA AND THE GOVERNMENT OF NEW ZEALAND

Horizon Scanning Technology Prioritising Summary

GeneSearch™ Breast Lymph Node (BLN) Assay for women undergoing sentinel lymph node biopsy for breast cancer

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PRIORITISING SUMMARY

REGISTER ID: **000295**

NAME OF TECHNOLOGY: **GENESEARCH™ BREAST LYMPH NODE (BLN) ASSAY**

PURPOSE AND TARGET GROUP: **WOMEN UNDERGOING SENTINEL LYMPH NODE BIOPSY FOR BREAST CANCER**

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
United States of America	✓		
Belgium		✓	
United Kingdom	✓		
France	✓		

IMPACT SUMMARY:

Veridex, LLC provides Genesearch BLN (Breast Lymph Node) with the aim of detecting the spread of breast cancer to lymph nodes within the breast and arm. In combination with permanent section Haematoxylin and Eosin (H&E) staining analysis of the lymph node, the data obtained from the GeneSearch™ BLN Assay can assist in staging of the patient. (FDA 2006) The technology would only be available through tertiary hospitals due to the requirement for a molecular biology diagnostic laboratory. The assay is for patients undergoing sentinel lymph node biopsy during breast cancer surgery. Currently, this technology is not in use in Australia.

BACKGROUND

Sentinel lymph node biopsy (SNB) for breast cancer is an emerging diagnostic technique that is undergoing clinical trials in Australia (e.g. SNAC trial). SNB is based on the idea that cancer spread occurs in a non-random fashion and is hence more likely to spread first to the lymph nodes to which the tumour drains (Giuliano et al 1994). The testing of "sentinel" lymph nodes is an indicator of how far the cancer has spread within the patient. If the sentinel nodes are found to be cancer positive the patient may undergo axillary clearance (AC). AC is the removal of all of the lymph nodes from the armpit, and is associated with significant morbidity such as wound infection; numbness of the arm, shoulder, armpit and chest; seroma; lymphoedema; and shoulder stiffness (Schijven et al 2003). If the sentinel nodes are negative for cancer the patient is prevented from undergoing potentially more damaging AC. Recently, the SNAC trial reported a positive outcome of SNB versus AC (Wetzig 2005). In Australia, 74% of breast cancer patients present with T1 stage (<20 mm) or ductal carcinoma *in situ* and the majority of these patients have metastasis negative lymph nodes (Malycha 2003). SNB is of most benefit to patients with negative nodes as they are prevented from undergoing AC.

The GeneSearch™ BLN Assay is *dependent* on the adoption of SNB in preference to immediate AC, as the assay is designed to be used intra-operatively to screen sentinel lymph nodes for clinically relevant (>0.2mm) breast cancer metastases. Specifically, the GeneSearch™ BLN Assay aims to improve the accuracy of metastasis detection during intra-operative sentinel lymph node biopsy. The GeneSearch™ BLN Assay consists of 2 parts; a RNA purification kit and a real time reverse-transcription polymerase chain reaction (RT-PCR) kit. The real time RT-PCR assay qualitatively detects the expression of two genes, Mammaglobin (MG) and Cytokeratin 19 (CK19). Mammaglobin and Cytokeratin are markers specific for breast cancer cells and are not expressed at high levels in normal lymph node tissue (Bernstein et al 2005; Schoenfeld et al 1997; Zehentner & Carter 2004). The assay involves the sectioning of the lymph node with alternative sections homogenised, the RNA extracted and real time RT-PCR performed on this RNA. If external RT-PCR controls are valid then the samples are compared against pre-determined thresholds for each gene and internal RT-PCR controls. The samples are then designated positive, negative or invalid, depending which markers are above or below these thresholds (Veridex 2006). The real time RT-PCR is performed on a Cepheid Smart Cycler® Diagnostic System. The alternate, spare lymph node sections can be embedded and used for post-operative permanent H&E staining to verify and supplement the information provided by the GeneSearch™ BLN Assay.

CLINICAL NEED AND BURDEN OF DISEASE

In Australia, the number of females diagnosed with breast cancer was estimated to be 13,261 in 2006 and is predicted to rise to 14,800 in 2011. The age-standardised

incidence of breast cancer in females was 117 per 100,000 in 2002, 80% above the 1983 level. In 2004 the age-standardised rate of death from breast cancer was 23.4 per 100,000 females, decreasing from 31.0 deaths per 100,000 in 1990. There were 2,641 female deaths due to breast cancer in 2004, with an average of 601 additional cases per year from 2000–2004 in which breast cancer was an associated cause but not the underlying cause of death (AIHW & NBCC 2006).

In 2003-04 there were 23,598 hospital separations where the primary cause of hospitalisation was breast cancer and on average each separation was 3.9 days (AIHW & NBCC 2006).

The GeneSearch™ BLN Assay is not applicable to all patients undergoing breast cancer surgery. Only the population undergoing SNB are candidates for testing with GeneSearch™ BLN Assay. The initial findings of the SNAC trial indicate that only 46% of women initially included into the trial passed the exclusion criteria, (54% were excluded due to tumour size greater then 3 cm or axillary involvement), and were hence suitable for SNB (Gill 2004).

DIFFUSION

The Veridex GeneSearch™ BLN Assay has pre-market approval in the USA and is CE marked as an *in vitro* diagnostic device in Europe (Veridex, Personal communication). The GeneSearch™ BLN Assay is used routinely at the site of the European clinical trial, Jules Bordet Institute, Brussels, Belgium (Veridex, Personal communication). It has not yet been marketed as an *in vitro* diagnostic device in the USA, Canada, Japan or Australia. The product has been in clinical trials as an investigational use only (IUO) device in the United States.

COMPARATORS

Following AC, histological analysis, using H&E staining, is conducted post-operatively on formalin-fixed and paraffin-embedded slices of sentinel nodes. This is the gold standard with regard to diagnosis of breast cancer metastasis (MSAC 2005). Intra-operative comparators include gross inspection of the target lymph node by the surgeon, or either frozen section or imprint cytology of the sentinel lymph nodes. Frozen section or imprint cytology require the availability of a pathologist to assess the test samples. The GeneSearch™ BLN Assay is aimed to replace intra-operative tests for breast cancer metastasis in sentinel lymph nodes (Table 1).

Table 1 GeneSearch™ BLN Assay compared to Intra-operative histology

	GeneSearch™ BLN Assay	Histology based tests (Frozen section (FS), imprint cytology (IC))
Advantages	Objective	Can determine metastasis size directly (FS only)
	Samples more of lymph node (less sampling error)	Can determine location of tumour within lymph node (FS only)
	Only requires verification of results by Pathologist	Can distinguish true from iatrogenic positives (FS only)
	Standardised Test	Slightly shorter to perform (10 - 40 minutes)
	Lower operator to operator variability	Greater Specificity (97.8 % vs. 94.3 %) (FS only)
	Greater sensitivity (95.6 % vs. 85.6 %)	
Disadvantages	Tissue used in assay cannot be subsequently used for histology	Subjective
	Less information for patient staging (no metastasis size measurements or location of tumour)	Requires more time from an expert Pathologist
	Take slightly longer to perform (35-50 minutes)	Higher operator to operator variability
		Not standardised, each lab has own methods
		Samples less of lymph node (greater sampling error)

Adapted from Cserni et al 2003

EFFECTIVENESS AND SAFETY ISSUES

There are no known contraindications for the GeneSearch™ BLN Assay. The GeneSearch™ BLN Assay is an *in vitro* test and therefore can have no direct negative impact on the patient. Histological information about the lymph node is completely destroyed during its processing within the assay. Due to the destruction of useful information the FDA has stated, in its pre-market approval, that the test may only be conducted as a *complementary* test to the post-operative gold standard, H&E staining of permanent lymph node sections (FDA 2006). H&E staining and the GeneSearch™ BLN Assay result in qualitatively different information and conflicts may arise between these two testing methods. The PPV of the GeneSearch™ BLN Assay was calculated to be 86% compared to H&E staining (FDA 2006). Although this would imply that 14% of patients testing positive with the GeneSearch™ BLN Assay would later test negative with H&E staining, evidence was presented at the FDA pre-market approval meeting indicating that the majority of these "false positives" are in fact true positives and that H&E staining itself misses some positives due to its limited sampling of the lymph node (FDA 2006).

Staging of the breast cancer patient within their disease course, which is critical for post-surgical treatment, is currently based on histological data obtained during SNB or AC. The information from the GeneSearch™ BLN Assay is qualitatively different to that obtained from the current histological methods e.g. the size of metastasis and its location with in the lymph node. Hence, some controversy exists about how best to stage patients solely tested with the GeneSearch™ BLN Assay (FDA 2006). Due to

this problem the FDA ruled that the GeneSearch™ BLN Assay must be conducted alongside post-operative H&E staining.

The GeneSearch™ BLN Assay is only useful when a SNB is a surgical option for a patient, as a patient undergoing AC can be staged using the established H&E staining post-operatively. In Australia, as reported by the RACS SNAC trial, half of the patients presenting were ineligible for SNB as they either had large (> 3 cm) or multicentric tumours, and therefore had AC immediately (Wetzig et al 2005). The GeneSearch™ BLN Assay is not applicable in the diagnosis of these patients as they are not candidates for SNB. No long-term morbidity/mortality data exist for patients undergoing SNB, and therefore, by extension, for patients being tested with the GeneSearch™ BLN Assay.

In the clinical trial conducted by Veridex, which was submitted to the FDA, the sensitivity of the GeneSearch™ BLN Assay was reported to be 87.6 % (95% CI [80.4, 92.9]) and the specificity was 94.2 % (95% CI [90.9 to 96.6]) (FDA 2006) (level III-2 diagnostic evidence).

COST IMPACT

A capital investment of $US 40000 is required for establishment of the GeneSearch™ BLN Assay at a particular site. The kit would cost $US 2250 for 30 tests (Veridex, personal communication). Each patient requires one test per lymph node and two controls (positive and negative). The test itself would cost about $US 300 per patient, assuming two lymph node tests and two controls are performed per patient, i.e. four tests per patient (Veridex, personal communication).

Through the reduced burden on pathologists and an increased sensitivity, and therefore reduction in second surgery costs, the GeneSearch™ BLN Assay is predicted to be more cost effective than current comparators (Veridex, personal communication), although this is not supported by evidence at this early stage in the product's development.

ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

A false positive test result from the GeneSearch™ BLN Assay could lead to the patient receiving AC rather than SNB alone. AC has been associated with significant morbidity versus SNB.

A false negative test result from the GeneSearch™ BLN Assay means that an existing metastasis/metastases were not detected and the incorrect surgical procedures and/or post-surgical treatment may be administered to the patient e.g. failure to perform AC. Although the patient may be monitored over the course of their disease course, and thus the false negative result may be later amended to the correctly positive result,

there is a significant risk, potentially fatal, to the patient receiving a false negative result.

OTHER ISSUES

All research on the GeneSearch™ BLN Assay was conducted by the Veridex or affiliates. The FDA gave pre-market approval for the GeneSearch™ BLN Assay with several conditions.

CONCLUSION:

As recently reported in the initial findings of the RACS SNAC trial (Wetzig 2005), SNB alone reduced the hospital stay to 1.8 days from 2.8 days for SNB plus AC. The Genesearch test is designed to increase the sensitivity of intra-operative diagnosis of the spread of metastatic breast cancer cells to sentinel lymph nodes of patients undergoing lumpectomy. Hence it may play a role in the uptake/improvement of SNB and therefore indirectly facilitate a reduction in breast cancer patient morbidity.

If the GeneSearch™ BLN Assay is to play a role in reducing the mortality of breast cancer patients it will be through more accurate diagnosis of breast cancer metastasis during SNB. As yet there is no data to indicate whether SNB itself lowers the mortality rate among breast cancer patients. Hence, it is unclear whether the GeneSearch™ BLN Assay would have any indirect effect on breast cancer mortality until further investigation into SNB concludes.

Based on the limited evidence available it is probable that the GeneSearch™ BLN Assay will diffuse into the Australian Health Care system. MSAC has recommended interim funding for SNB and, as the GeneSearch™ BLN Assay is complementary to SNB, it would be prudent to await further evidence and the full report of the RACS SNAC trial before further assessment is undertaken on the GeneSearch™ BLN Assay.

HEALTHPACT ACTION:

The GeneSearch™ assay may have benefits in terms of a standardised approach to the determination of nodal status. However, the widespread usefulness of this assay may depend on whether or not the assay, or the genes that are targeted in the assay, are patented. HealthPACT have therefore recommended that this technology be monitored in 12 months time.

SOURCES OF FURTHER INFORMATION:

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Zehentner, B. K. & Carter, D. (2004). 'Mammaglobin: a candidate diagnostic marker for breast cancer', *Clin Biochem*, 37 (4), 249-257.

LIST OF STUDIES INCLUDED

Total number of studies	
Level III-2 Diagnostic evidence	1

SEARCH CRITERIA TO BE USED:

Breast Neoplasms/*pathology/surgery
Lymphatic Metastasis
*Sentinel Lymph Node Biopsy
Axilla
Lymph Node Excision/*adverse effects
Sensitivity and Specificity
Tumor Markers, Biological