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NMP22 BladderChek™ point-of-care diagnostic test for bladder cancer.

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PRIORITISING SUMMARY

REGISTER ID: **000150**

NAME OF TECHNOLOGY: **NMP22 BLADDERCHEK™**

PURPOSE AND TARGET GROUP: **POINT-OF-CARE DIAGNOSTIC TEST FOR BLADDER 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
- ☒ No

ARTG number

- ☐ Not applicable

INTERNATIONAL UTILISATION:

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

IMPACT SUMMARY:

Matritech Inc. has developed the point-of-care diagnostic test, NMP22 BladderChek™ Test for the detection of bladder cancer. The test was approved in the United States in July 2002, and is not yet available in Australia.

BACKGROUND

The majority of cancers of the bladder start in the layer of cells which form the lining (urothelium) of the bladder. These are termed transitional cell or urothelial cell cancers (CancerBACUP 2005). The most common clinical presentation is blood in the urine or haematuria. Usually this is painless and the blood may be visible to the naked eye or microscopic. The diagnosis of bladder cancer may be delayed due to intermittent bleeding or may be attributed to other causes such as urinary tract infection or the presence of anticoagulant medications (Cancer News 2005).

Patients with suspected bladder cancer initially undergo voided urine cytology. A Pap smear is prepared from transitional cells which have sloughed off the urinary tract into the urine. This technique requires intact cells for examination (Grossman et al 2005). If urinary cytology is positive, then transitional cell cancer of the urothelium is almost certainly present. However, cytologic examinations may be negative in up to half of all patients with bladder cancer;

therefore, a negative study does not rule out bladder cancer. Voided urine cytology is frequently used as an adjunct to the gold standard cystoscopy with biopsy (Grossman et al 2005).

The NMP22 BladderChek™ test is a point-of-care immunochromatographic assay that detects elevated amounts of nuclear matrix protein NMP22, a proteomic marker for cancer. Measuring levels of NMP22 for the detection of bladder cancer has been established in different patient groups, including those with confirmed bladder cancer, patients post-transurethral resection of bladder and in conjunction with standard urine cytology and cystoscopy (Carpinito et al,1996, Soloway et al, 1996, Sawczuk et al, 2000 and Shariat et al, 2004).

The BladderChek™ is the only point-of-care test approved in the United States (Matritech 2005). The Matritech NMP22 BladderChek™ test is indicated for professional and prescription home use as an aid in monitoring bladder cancer patients, in conjunction with standard diagnostic procedures (United States Food and Drug Administration 2005).

CLINICAL NEED AND BURDEN OF DISEASE

Bladder cancer occurs most commonly in people between 50 and 70 years of age. It is twice as common in men as in women (CancerBACUP 2005). The incidence of bladder cancer is higher in people exposed to carcinogens in their occupation or environment and significantly higher in smokers.

In 2001 there were 2,954 new cases of bladder cancer in the Australian population, representing a crude rate of 15.2 per 100, 000. There was a higher incidence in males (24 per 100, 000) compared to females (7 per 100, 000), (AIHW 2005a).

In the year 2002-03 there were 15,672 hospitalisations for principal diagnosis C67 malignant neoplasm of bladder (AIHW 2005b).

DIFFUSION

The NMP22 BladderChek™ is not currently available in Australia. In the United States, the cost of using the test is almost half the cost of standard voided urine cytology tests. Given that this test is for point-of-care testing, it is likely that general practitioners and clinicians in hospital settings would incorporate its use in conjunction with cystoscopy. However, at this point it is unclear whether this has occurred in the United States. If further studies find that the NMP22BladderChek™ is better at detecting cancers than those missed by voided cytology (standard urine test) and cystoscopy (reference standard for detection), the test would receive a rapid uptake.

COMPARATORS

A combination of methods is used for the diagnosis of bladder cancer. The gold standard test is cystoscopy and biopsy. This procedure, performed under local anaesthetic, involves inserting a small, flexible, fibre-optic telescope (cystoscope) into the urethra to view the whole lining of the bladder and urethra. If abnormal tissue is observed, a general anaesthetic is administered and biopsies of the abnormal cells from the inside of the bladder, or the lining of the bladder are taken for pathologic examination (CancerBACUP 2005).

An intravenous urogram or pyelogram are further diagnostic tools employed in evaluating the urinary tract. This involves the injection of radioactive dye into a vein that can be viewed on an x-ray screen for any abnormalities in the kidneys, bladder and the rest of the urinary system.

Other non-invasive urine tests that measure NMP22 levels are not approved for point-of-care use and require laboratory analysis (Grossman et al 2005).

EFFECTIVENESS AND SAFETY ISSUES

A multi-site study examined the NMP22 BladderChek™ was tested in (level II diagnostic evidence) 1331 patients at elevated risk for bladder cancer (Grossman et al 2005). The performance of the NMP22 test was compared with voided urine cytology as an aid to detecting bladder cancer. Cystoscopy with biopsy was used as the reference standard. One of the sites included 26 patients with cancers other than bladder cancer. All patients with risk factors or symptoms of bladder cancer underwent testing with both the BladderChek™ and standard urine cytology before undergoing cystoscopy. All physicians and technicians were blinded to the BladderChek™, standard urine cytology and cystoscopy results.

Cystoscopy detected 79/1331 (6%) patients with bladder cancer, 685/1331 (51%) had 1 or more benign urological conditions and 567/1331 (43%) had no cystoscopic evidence of urinary tract disease. Of the 79 patients with cancer, 72 cancers were surgically removed and 7 (labelled TX) were not excised. The BladderChek™ test was positive (sensitive) in 44 (56%) of the 79 patients with cancer (95% CI [44%-67%]), whereas cytology identified 12/76 patients (16%), (95% [7% - 24%]).

Of the cancers with pathological staging data, 62 were superficial and 10 were muscle invasive. Pathological determination of grade was available for 70 of the 72 removed tumours. Of these, 27 were classified low grade, 18 were moderate and 25 were high grade. A total of 27 cancers were muscle invasive and/or high grade. Table 1 below provides the results of the sensitivity of BladderChek™ and voided cytology by stage and grade of cancer.

Of 79 confirmed malignancies, 10 were muscle invasive. The BladderChek™ identified four of these malignancies missed during cystoscopy. Initial cystoscopy detected 6 (60%) of these whereas the NMP22 test identified 9 (90%) with elevated levels of the protein marker. Voided cytology was positive in only 2 (22%) of the 9 patients with muscle-invasive disease for whom test results were available. The BladderChek™ was also positive for a patient diagnosed with carcinoma in situ after and an initial negative cystoscopic report.

This study reports that the BladderChek™ was more accurate in detecting both aggressive malignancies (high grade) when compared to urine cytology (74% vs 39%) and medium or low grade malignancies (47% vs 5%).

Table 1. Sensitivity of BladderChek™ Assay and Voided Cytology by Stage and Grade of Cancer

	BladderChek™		Voided Cytology	
	No. with Positive Test Result/Total No. with bladder cancer	Sensitivity % (95% CI)	No. with Positive Test Result/Total No. with bladder cancer	Sensitivity % (95% CI)
Stage				
Ta	14/30	46.7 (28.3- 65.7)	2/28	7.1 (1.0-23.5)
Tis	4/5	80.0 (28.4-99.5)	3/5	60.0 (14.7-94.7)
T1 #	13/27	48.2 (28.7-68.1)	5/27	18.5 (6.3-38.1)
T2, T2a	6/6	100 (54.1-100)	2/6	33.3 (4.3-77.7)
T3a, T3b*	3/4	75.0 (19.4-99.4)	0/3	0 (0-70.8)
TX**	4/7	57.1 (18.4-90.01)	0/7	0 (0-41.0)
Noninvasive: Ta-T1	31/62	50.0 (37.0-63.0)	10/60	16.7 (8.3-28.5)
Muscle Invasive: T2 –T3	9/10	90.0 (55.5-99.8)	2/9	22.2 (2.8-60.0)
Grade				
Well differentiated	13/27	48.2 (28.7-68.1)	0/25	0 (0-13.7)
Moderately differentiated	9/18	50.0 (26.0-74.0)	3/18	16.7 (3.6-41.4)
Poorly differentiated	18/25	72.0 (50.6-87.9)	9/24	37.5 (18.8-59.4)
GX	4/9	44.4 (13.7-78.8)	0/9	0 (0-33.6)

Ta, Tis, T1 were classified superficial, *T2 –T3 were classified aggressive, **TX – 7 tumours seen on cystoscopy but not excised

COST IMPACT

The current MBS fees for item numbers 36836 (cystoscopy with biopsy) and 73045 (urine cytology are $195.05 and $48.95 respectively (Medicare Benefits Schedule 2005). There were 1349 cystoscopy procedures performed between July 2003 and June 2004 and a total Medicare contribution of $160,777 (Health Insurance Commisssion 2005).

The average cost of voided cytology in the United States is approximately $US 56 compared to a cost of $US 24 for the BladderChek™ test (Grossman 2005).

ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

No issues were identified/raised in the sources examined.

OTHER ISSUES

It would be useful to assess the impact of using the NMP22 BladderChek™ test on survival of patients with bladder cancer. There is no study to date that assesses the ability of the test to detect cancers at an early stage or earlier than the standard diagnostic procedures.

CONCLUSION:

There has only been one study published on the effectiveness of the NMP22 BladderChek™ at the time of writing this summary, however the results were encouraging. BladderChek™ appears to have an increased sensitivity compared to cytology for the detection of bladder cancer. In addition, given it is a point-of-care service, the uptake of this diagnostic test in the Australian health care sector may be rapid.

HEALTH PACT ACTION:

Therefore it is recommended that this technology be monitored in 6 months time.

LIST OF STUDIES INCLUDED

Total number of studies
Level II diagnostic evidence 1

SOURCES OF FURTHER INFORMATION:

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Su, C. K., Yang, C. R. et al (2003). 'NMP22 in transitional cell carcinoma of the urinary bladder', *J Chin Med Assoc*, 66 (5), 294-298.

United States Food and Drug Administration (2005). *K021231. 510 (k) Summary* [Internet] Available from: http://www.fda.gov/cdrh/pdf2/k021231.pdf [Accessed 6th April, 2005].

SEARCH CRITERIA TO BE USED:

Bladder Neoplasms/ urine
Carcinoma, Transitional Cell/ urine
Neoplasm Recurrence, Local/ diagnosis/ urine
Nuclear Proteins/ urine

Tumor Markers, Biological/ urine