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Horizon Scanning Technology Prioritising Summary

BladderChek: diagnostic test for bladder cancer

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UPDATE PRIORITISING SUMMARY

REGISTER ID: **000150**

NAME OF TECHNOLOGY: **NMP22 BLADDERCHEK™**

PURPOSE AND TARGET GROUP: **DIAGNOSTIC TEST FOR BLADDER 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:

Matritech Inc. has developed the point-of-care diagnostic test, NMP22 BladderChek™ 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 (American Society of Clinical Oncology 2005). The most common clinical presentation is blood in the urine (haematuria). Haematuria is usually 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 (American Society of Clinical Oncology 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 (high positive predictive value). 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 (low negative predictive value). Voided urine cytology is frequently used as an adjunct to the gold standard test of 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 (American Society of Clinical Oncology 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 a principal diagnosis (C67) of 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 is has occurred in the United States. If further studies found that the NMP22BladderChek™ was 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. Voided cytology is the first diagnostic test used in assessing patients for bladder cancer before proceeding to further, invasive tests. 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 (American Society of Clinical Oncology 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).

APRIL 2005 - EFFECTIVENESS AND SAFETY ISSUES

A multi-site study (level II diagnostic evidence) examined NMP22 BladderChek™ testing of 1,331 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 79/1,331 (6%) patients with bladder cancer, 685/1,331 (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% CI 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 provides the results of the sensitivity of BladderChek™ and voided cytology by stage and grade of cancer.

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

Of 79 confirmed malignancies, 10 were muscle invasive. The BladderChek™ identified four of the malignancies missed during cystoscopy. Initial cystoscopy detected 6 (60%) of these malignancies 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 an initial negative cystoscopic report.

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

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.

APRIL 2005 - RECOMMENDATION:

There has been only one study published on the effectiveness of the NMP22 BladderChek™ at the time of writing this summary. However, given it is a point-of-care service the uptake may be rapid. It is therefore recommended that the following be conducted:

☐	Horizon Scanning Report	☐	Full Health Technology Assessment
☒	Monitor	☐	Archive

APRIL 2005 - SOURCES OF FURTHER INFORMATION:

AIHW (2005a) *Interactive Cancer Data.* [Internet] Available from: http://www.aihw.gov.au/cognos/cgi-bin/ppdscgi.exe?DC=Q&E=/Cancer/canceragerates v7 [Accessed April 06, 2005]
AIHW (2005b) *Interactive national hospital morbidity data.* [Internet] Available from: http://www.aihw.gov.au/cognos/cgi-in/ppdscgi.exe?DC=Q&E=/AHS/principaldiagnosis0203 [Accessed April 06, 2005]
American Society of Clinical Oncology (2005) *People Living With Cancer - Cancer Page – Bladder Cancer - Risk Factors and Prevention*: [Internet] Available from: http://www.plwc.org/plwc/MainConstructor/1,1744,_04-0018-00_12-001042-00_17-001029-00_21-008,00.asp [Accessed April 20, 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

HEALTH PACT DECISION:

- ☐ Horizon Scanning Report
- ☐ Full Health Technology Assessment
- ☐ Monitor
- ☐ Archive
- ☐ Refer

PRIORITY RATING

- ☐ **High**
- ☐ **Medium**
- ☐ **Low**

MAY 2006 - COMPARATORS

Published literature indicates that fluorescence in situ hybridization (FISH) is emerging as a valid test for bladder cancer surveillance (Jones 2006). A critical review of Medline literature (Jones 2006) indicated that FISH was superior in performance when compared to cytology, and was able to detect cancer before lesions were evident using cystoscopy. Notably the greatest advantage of FISH was the ability to detect high grade urothelial cancer and in particular, carcinoma in situ (Jones 2006).

Svatek et al (2006) investigated the possibility of urinary soluble Fas (sFas) as an effective and independent predictor of bladder cancer recurrence and invasiveness in patients who had a past history of non-muscle invasive bladder transitional cell carcinoma (TCC). This study showed that sFas outperformed NMP22 in the surveillance of patients with a past history of non-muscle invasive bladder TCC (Svatek et al 2006).

MAY 2006 UPDATE - SAFETY EFFECTIVENESS AND ISSUES

The gold standard for diagnosing bladder cancer is cystoscopy and biopsy.

Since the initial Prioritising Summary three studies investigating the effectiveness of the NMP22 assay compared to cytologic analysis and cystoscopy have been published. Moonen et al (2005) (level III-1 diagnostic evidence) described a study in which 106 patients provided a voided urinary specimen prior to cystoscopy or bladder tumour resection. The total sample included 28 patients presenting with haematuria, 57 patients in follow-up for superficial bladder cancer and 21 patients who provided a specimen prior to bladder tumour resection. Assessment of NMP22 assay results was performed without knowledge of cytology results.

For patients with haematuria, the sensitivity of both the NMP22 assay and cytology were 100 per cent when compared to cystoscopy, and the specificity was 92 and 100 per cent, respectively. In the superficial bladder cancer group of patients, the sensitivity and specificity of the NMP22 assay was 57 and 90 per cent respectively, compared to 43 and 93 per cent respectively for cytology. The positive predictive value (PPV) and negative predictive value (NPV) for the NMP22 assay were 41 and 95 per cent, respectively. The PPV and NPV were similar for cytology, at 43 and 93 per cent, respectively (Moonen et al 2005).

In addition, there was improvement in the sensitivity of the NMP22 assay as the stage of the tumour progressed. The NMP22 assay was more sensitive than cytology; 40% vs. 33% for stage Ta tumours, 83% vs. 67% for stage T1 and 100% vs. 86% for stages T2-T4 . Similarly, the sensitivity of the NMP22 assay also increased as the grade of the tumour increased, however the sensitivity of cytology assay was greater at a lower grade of tumour. For grade 1 tumours the sensitivity of the NMP22 assay and cytology were 29 per cent and 43 per cent respectively, 89 per cent and 56 per cent respectively for grade 2 tumours and both 62 per cent for grade 3 tumours.

A prospective study (level III-1 diagnostic evidence) was conducted whereby 131 patients with a previous history of superficial bladder cancer, on follow-up, were enrolled (Kumar et al 2006). A voided urine specimen was collected prior to cystoscopy and used to perform cytological analysis and the NMP22 assay. Findings from biopsies taken during cystoscopy were treated as a gold standard. All observers interpreting the test results were blinded to the results of the other tests.

Of the 131 patients in the study, 46 patients tested positive for recurrence by biopsy. Of these 46 patients, 39 were positive for the NMP22 assay and 19 were positive for cytology. The sensitivity and specificity of the NMP22 assay was 85 and 78 per cent, respectively (PPV = 67%, NPV = 90%). In comparison, the sensitivity and specificity of cytology was 41 and 96 per cent, respectively (PPV = 86%, NPV = 75%). The sensitivity of the NMP22 assay was greater than that of cytology particularly for low T stage malignancies as demonstrated in Table 1. The table also demonstrates that the sensitivity of the NMP22 assay was significantly greater than that of cytology in detecting lower grade tumours.

When the results of both the NMP22 assay and cytology were combined, 42 of the 46 tumours detected by cystoscopy were identified, which gave an overall sensitivity of 91 per cent (Kumar et al 2006).

Table 1 Sensitivity according to T stage and grade of tumour

N=46	NMP22 Test (%)	Urine cytology (%)	P-value
Stage			
Ta (n=21)	76.2 (16/21)	14.3 (3/21)	0.0002
T1 (n=17)	88.2 (15/17)	47 (8/17)	0.003
T2 or higher	100 (8/8)	100 (8/8)	
Grade			
G1 (n=11)	81.8 (9/11)	18.8 (2/11)	0.009
G2 (n=22)	81 (18/22)	27.2 (6/22)	0.0009
G3 (N=13)	92.3 (12/13)	84.6 (11/13)	0.54

A cross-sectional study investigated the use of NMP22 BladderChek in improving the detection of bladder cancer (Grossman et al 2006) (level II diagnostic evidence). Consecutive patients were recruited (n=668) across 23 clinical sites. Each patient submitted a voided urine sample before undergoing cystoscopy. The urine sample was sent for routine cytologic examination as well as being analysed for NMP22 protein by clinic staff. Physicians who performed the cystoscopies were blinded to the NMP22 results and staff that performed the NMP22 assays were blinded to cystoscopy results. Patients were classified as positive for bladder cancer if one or more tumours were observed during cystoscopy and, if removed, were considered malignant upon pathological examination.

Initially, cystoscopy detected 94/103 (91%) cancers, the remaining 9 were detected upon repeat evaluation as a result of continued suspicion or close follow-up. The NMP22 assay detected 43/94 (45.7%) tumours initially detected and 8/9 (89%) malignancies detected upon repeated evaluation (49.5%). Cytological results were available for 98/103 malignant samples detected and 552/565 samples without cancer. Of the malignant samples, cytology found 12/98 (12.2%) with cancerous or dysplastic cells. Combining the NMP22 test with cystoscopy improved the overall sensitivity to from 91 to 99 per cent, a difference that was statistically significantly ($p = 0.005$). In comparison, the combination of cytology with cystoscopy increased the overall sensitivity to 94 per cent, a difference that was not statistically significant ($p = 0.06$). The positive predictive value of the NMP22 assay and cytology were very similar at 42 and 41 per cent, respectively.

Similarly, the specificities of cytology and the NMP22 assay were compared. Cytology proved to be significantly more specific than NMP22 assay at 97 and 87 per cent, respectively ($p<0.001$). The NPV for the NMP22 assay was 91 per cent and 86 per cent for cytologic analysis (Grossman et al 2006).

MAY 2006 - RECOMMENDATION:

Voided cytology is often utilised as the first step in the diagnosis of bladder cancer, before invasive procedures such as cystoscopy and biopsy. The NMP22 assay had similar overall sensitivity and specificity values as cytology, however the sensitivity of the NMP22 assay was superior in patients with low grade and low stage tumours. NMP22 *combined* with cytology gave *increased* sensitivity and specificity. Studies reported conflicting positive predictive values for NMP22 (41-67%), which may result in a high number of patients undergoing an unnecessary invasive procedure. However, all studies reported good negative predictive values (90-93%) indicating that a high proportion of individuals testing negative do not have bladder cancer. The NMP22 assay is easy to use, non-invasive and provides a rapid result for the clinician. New non-invasive techniques (FISH and sFas) should also be investigated. Based on the good quality evidence it is therefore recommended that the following be conducted:

☒	Horizon Scanning Report	☐	Full Health Technology Assessment
☐	Monitor	☐	Archive

MAY 2006 - SOURCES OF FURTHER INFORMATION:

Grossman, H. B., Soloway, M. et al. (2006). 'Surveillance for recurrent bladder cancer using a point-of-care proteomic assay.' *Journal of the American Medical Association,* 295(3), 299-305.

Jones, J. S. (2006). 'DNA-based molecular cytology for bladder cancer surveillance.' *Urology,* 67(3 Suppl 1), 35-45; discussion 45-7.

Kumar, A., Kumar, R. et al. (2006). 'Comparison of NMP22 BladderChek Test and Urine Cytology for the Detection of Recurrent Bladder Cancer.' *Japanese Journal of Clinical Oncology,* 36(3), 172-5.

Moonen, P. M., Kiemeney, L. A. et al. (2005). 'Urinary NMP22 BladderChek test in the diagnosis of superficial bladder cancer.' *European Urology,* 48(6), 951-6; discussion 956.

Svatek, R. S., Herman, M. P. et al. (2006). 'Soluble Fas-A promising novel urinary marker for the detection of recurrent superficial bladder cancer.' *Cancer,* 106(8), 1701-7.

LIST OF STUDIES INCLUDED

Total number of studies	
Level II diagnostic evidence	1
Level III-1 diagnostic evidence	2

HEALTH PACT DECISION:

☐	Horizon Scanning Report	☐	Full Health Technology Assessment
☒	Monitor	☐	Archive
☐	Refer		

PRIORITY RATING

☐	**High**	☐	**Medium**	☐	**Low**

AUGUST 2007 – UPDATE

AUGUST 2007 – COMPARATORS

Comparators to BladderChek™ include a variety of other tests, both commercial and self-developed, these include: gene specific tests, in-house developed NMP-22 (the marker detected by the BladderChek™ kit) ELISAs, and tests for telomerase markers amongst others.

A combined assay for the tumour markers CYFRA21-1, telomerase and vascular endothelial growth factor (VEGF), showed a very high level of sensitivity compared to cytology, 94 vs 38 per cent in 100 patients who were known to be cancer positive. The patients were diagnosed with bladder transitional cell carcinoma, which was either superficial or invasive. In the testing of 50 patients who were bladder cancer negative but haematuria positive (a common cause of false positives), the specificity of the assays were reported to be 78, 84 88 and 92 per cent for CYFRA21-1, telomerase, VEGF, and cytology, respectively (Bian & Xu 2007).

In a study dividing patients into four groups - primary cancer, histologically confirmed cancer recurrence, post-operative cancer patients who were non-recurrent for six months; and healthy controls, it was found that NMP-22 was an effective marker for bladder cancer diagnosis. The sensitivity was reported to be 52 per cent and the specificity was 95 per cent. Further progression of the disease was linked to higher sensitivity of the NMP-22 assay (Darenkov et al 2006).

Several commercial kits are now available on the market to detect bladder cancer. A review of these kits compared to cytology, the current standard for bladder cancer diagnosis, reported that only UroVysion™ had a satisfactory sensitivity and specificity (80% and 94% respectively). The kits assessed in this review were ImmunoCyt / uCyt+, BTA TRAK, BTA stat, NMP22, NMP22 BladderChek, and UroVysion assays for bladder cancer (Feil & Stenzl 2006).

A PCR based assay testing the promoter hypermethylation of several markers was described by Hoque et al. This assay showed a sensitivity of 82 per cent (95% CI [75, 87]) and a specificity of 96 per cent (95% CI [90, 99]) for bladder cancer detection in 175 bladder cancer patients and 94 healthy subjects (Hoque et al 2006) (level III-3 diagnostic evidence).

A study assessing the diagnostic ability of a RT-PCR assay for the urinary survivin gene in 24 bladder cancer confirmed cases, 50 cases with bladder cancer history, 55 cases with haematuria, and 68 healthy subjects reported an overall sensitivity of 79 per cent and a specificity of 93 per cent. Within each group the sensitivity and specificity did not vary significantly from the overall figure, indicating the test was accurate in all the groups studied.(Kenney et al 2007).

The NMP-22 assay (in house developed) was reported to be superior to both cytology and urinary bladder cancer II (UBC II) assays for detecting the post-operative early recurrence of bladder cancer (Kibar et al 2006). This study included 60 patients with transitional cell carcinoma of the bladder and 30 subjects with unrelated urological diseases. Ten days after the primary cancer was operated upon urine samples were tested by UBC II, NMP-22 and cytology. Versus three month post operative cytoscopy, the NMP-22 assay had the highest sensitivity for early recurrence of cancer 52%, whereas UBC II and cytology sensitivities were reported at 19% and 14% respectively.

A study comparing a multiprobe FISH (fluorescence in situ hybridization) assay with standard urinary cytology for detection of superficial urothelial carcinoma of the bladder found that FISH had a much higher sensitivity (70.3% versus 35.1% for urinary cytology) and a statistically equivalent specificity (94.7% versus 100% for urinary cytology). This study involved 74 patients with superficial urothelial carcinoma, 19 patients with muscle-invasive tumours, and 19 healthy subjects (Marin-Aguilera et al 2007).

The investigation of 113 patients with haematuria for diagnosing bladder cancer reported that BladderChek™ had a sensitivity of 86% and specificity of 98% compared to 57% sensitivity and 97% specificity for urine cytology. This high specificity is a reflection of the exclusion from the study of patients with conditions known to reduce the specificity of the BladderChek™ assay, that is patients with stones, urethral catheters or urinary tract infections (Oehr & Schroeder 2006).

Table 1 presents a summary of sensitivity and specificity ranges of a variety of tests, designed to detect bladder cancer, as presented in a 2006 review. BladderChek™ was not assessed in this review but the marker that BladderChek™ is based on (NMP22) was reviewed.

Table 1 Sensitivity and specificity of urine based bladder markers

Bladder cancer marker	Mean sensitivity (range)	Mean specificity (range)
Cytology	48.00% (28%–76.47%)	95.72% (81%–100%)
NMP22	67.49% (31%–91.7%)	74.38% (5.1%–94.3%)
BTA stat	68.71% (52.8%–89%)	73.67% (54%–93%)
BTA TRAK	61.96% (17%–77.5%)	73.59% (50.5%–95%)
Telomerase	72.4% (46%–92%)	87.15% (69%–99%)
Hyaluronic acid and hyaluronidase	94% (91%–100%)	80.93% (70%–88.8%)
Flow cytometry and Quanticyt™ assay	58.08% (45%–72%)	80.62% (70.6%–93%)
Fluorescence in situ hybridization	77% (73%–81%)	98% (96%–100%)
ImmunoCyt™	58.2% (38.5%–86.1%)	78.77% (73%–83.9%)
Cytokeratin 20	82.83% (71%–94.4%)	73.37% (36%–96.7%)
Cytokeratins 8 and 18 (UBC)	60.7% (48.7%–70%)	83.82% (72%–95%)
Lewis X antibody	87.1% (79.8%–94.4%)	61.65% (36.9%–86.4%)
Hemoglobin dipstick	71.2% (47%–92.6%)	67.27% (51%–84%)
CYFRA 21-1	74.15% (69%–79.3%)	91.3% (88.6%–94%)
Survivin	64%	93%

Adapted from (Konety 2006), a review of 111 studies

AUGUST 2007 - EFFECTIVENESS AND SAFETY ISSUES

Five additional studies were identified examining effectiveness and safety of the BladderChek™ assay. Three of these studies examined use of the assay for diagnosis while the remaining two assessed its value in providing prognostic information.

Kitsukawa compared the BladderChek™ assay to NMP-22 ELISA and urinary cytology and found the BladderChek™ assay was the most sensitive yet the *least* specific of these tests. In 40 patients with confirmed bladder cancer, the sensitivities were 62.5, 55 and 27.5 per cent for BladderChek™, NMP-22 ELISA, and urine cytology, respectively. In 40 subjects *negative* for bladder cancer, the specificities were reported as 87.5, 90 and 100 per cent for BladderChek™, NMP-22 ELISA, and urine cytology, respectively (Kitsukawa et al 2006) (level III-2 diagnostic evidence). In the second diagnostic study involving 51 patients (43 cases with bladder cancer, and 8 cases with upper urothelial cancer) BladderChek™ showed the highest level of sensitivity, mainly due to its much higher sensitivity for lower grade cancers, compared to NMP-22 ELISA and urinary cytology.

The three assays performed similarly for high grade tumours (68.4%, 68.4% and 63.2% sensitivity for BladderChek™, NMP-22 and urine cytology respectively). However, sensitivity differed significantly when testing patients with *low grade* tumours (58.3%, 33.3% and 8.3% respectively). BladderChek™ assay gave false positive results if more than 10^5 erythrocytes and 10^3 white blood cells were present per microlitre of urine (Yokoyama et al 2004) (level III-3 diagnostic evidence).

In a diagnostic study involving 43 patients, BladderChek™ was assessed alongside standard urinary cytology against cytoscopy. It was found that the BladderChek™ assay had a greater sensitivity but a lower specificity compared to urinary cytology, 63.6% vs. 36.3% respectively for sensitivity and 62.5% vs. 100% respectively for specificity. All the samples positive by urine cytology were also detected as positive by the BladderChek™ assay. The higher false positive rate for the BladderChek™ assay was attributed to the presence of haematuria, pyuria, or cytolysis or normal urotherium (Minagawa et al 2006) (level IV diagnostic evidence).

A study, involving 2,871 patients, investigating the variability of the NMP-22 assay in the prognostic assessment of patients for either disease progression or recurrence reported there was no satisfactory cut-off level for an indicative level of NMP-22 that would distinguish between these conditions. The manufacturer's cut-off level gave a sensitivity of 57 per cent and a specificity of 81 per cent. Overall the test was more sensitive for latter stage disease vs early stage disease. It was concluded that there was no definitive cut off using this assay but rather a continuum with significant institutional variation (Shariat et al 2006) (level III-3 prognostic evidence). A second prognostic study which involved monitoring for superficial bladder cell carcinoma in patients after cancer treatment, reported that BladderChek™ had a low sensitivity compared to cystoscopy (28% vs. 100%).The specificity of BladderChek™ was better than cytoscopy at 94 vs. 87 per cent. The authors recommended against using the BladderChek™ assay for follow up of patients with superficial bladder cell carcinoma. In this study BladderChek™ displayed similar sensitivity and specificity to the NMP-22 and cytology assays (Aguilera Tubet et al 2005) (level IV prognostic evidence).

AUGUST 2007 - OTHER ISSUES

In the previous update (May 2006) a study by Grossman was assessed (Grossman et al 2006). Subsequently, criticism of the design and conclusions of this study was reported (Wilson 2006; Eggener & Herr 2006). These critiques focussed on the uneven application of the reference standard, the positive conclusion despite the moderate sensitivity reported, the lesser specificity versus cytology, and the fact that the poor sensitivity of cytology in the Grossman study, versus the sensitivity reported in the literature, may give a favourable bias to the NMP-22 assay.

There are many markers for diagnosis of bladder cancer, either currently being assessed and/or available commercially, which may be of equivalent or better at bladder cancer diagnosis than the BladderChek™ assay (Konety 2006).

AUGUST 2007 – SUMMARY OF FINDINGS

The BladderChek™ assay offers rapid point of care diagnosis of patients being assessed for bladder cancer; giving a moderately sensitive result. It lacks in specificity when compared to the standard, non-invasive test urinary cytology. To overcome the lack of specificity the clinician must exclude several other possible causes of symptoms otherwise BladderChek™ will have a high false positive rate. The fact that other tests and examinations must be concluded before BladderChek™ is accurate undermines its utility as a point of care test.

AUGUST 2007 HEALTHPACT ACTION:

Other tests have better sensitivity and specificity and are available commercially, and many more markers are currently being assessed for future clinical use. Therefore as point-of-care tests for bladder cancer are rapidly evolving and show much promise HealthPACT have recommended that this technology be monitored for more information in 24-months time.

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NUMBER OF STUDIES INCLUDED

Total number of studies	
level III-2 diagnostic evidence	1
level III-3 diagnostic evidence	1
level III-3 prognostic evidence	1
level IV diagnostic evidence	2