UroVysion fluorescence in situ hybridisation (FISH) assay

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Assessment report

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The Medical Services Advisory Committee (MSAC) is an independent committee which has been established to provide advice to the Minister for Health and Ageing on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost-effectiveness. This advice will help to inform government decisions about which medical services should attract funding under Medicare.

The MSAC recommendations do not necessarily reflect the views of all individuals who participated in the MSAC evaluation.

This report was prepared by the Medical Services Advisory Committee with the assistance of Ms Alisa Higgins, Mr Simon Eckermann and Dr Sarah Lord from the NHMRC Clinical Trials Centre. This report was edited by Matthew Stevens, ScienceScape Editing, Sydney. The report was endorsed by the Minister for Health and Ageing on 28 March 2006.

Publication approval number: 3836

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The procedure

Fluorescence *in situ* hybridisation (FISH) is a technique which detects chromosomal and genetic aberrations at the cellular level by using fluorescent-labelled nucleic acid probes. In bladder cancer, numerous chromosomal abnormalities have been identified which are associated with both the development and progression of the disease. The UroVysion FISH assay consists of a four-colour, four-probe mixture of DNA probe sequences homologous to specific regions on chromosomes 3, 7, 9 and 17. The assay is designed to detect aneuploidy of chromosomes 3, 7 and 17, and the loss of the 9p21 locus on chromosome 9. This set of probes was selected for testing on the basis of reports in the scientific literature that associated these changes in DNA (chromosome copy number changes or deletion of the locus) with bladder cancer (Vysis 2005). The Vysis UroVysion probe mixture contains chromosome enumeration probe (CEP) 3 SpectrumRed, CEP 7 SpectrumGreen and CEP 17 SpectrumAqua, which hybridise to the centromere regions of chromosomes 3, 7 and 17 respectively, and locus-specific identifier (LSI) 9p21 SpectrumGold, which hybridises to the *p16* gene at 9p21.

The process of performing FISH using the UroVysion assay first involves fixing cells from urine samples on microscope slides. The DNA is denatured to its single-stranded form and allowed to hybridise with the UroVysion DNA probes. Following hybridisation, unbound probe is removed by a series of washes, and the nuclei are counterstained with DAPI (4,6-diamidino-2-phenylindole), a DNA-specific stain that fluoresces blue (Vysis 2005). Specific hybridisation of the UroVysion probes is viewed through a fluorescence microscope equipped with appropriate excitation and emission filter sets allowing visualisation of the red, green, aqua, and gold fluorescent signals. The probes specific for chromosomes 3, 7, and 17 and the 9p21 region are counted by microscopic examination of the nuclei, which are easily distinguished by the DAPI staining. Interpretation of results involves recording the DNA probe profile (the number of probe signals of each colour) to determine whether there is aneusomy of chromosomes 3, 7 or 17, or deletion of the 9p21 locus.

Medical Services Advisory Committee—role and approach

The Medical Services Advisory Committee (MSAC) was established by the Australian Government to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Minister for Health and Ageing on the evidence relating to the safety, effectiveness and cost-effectiveness of new and existing medical technologies and procedures, and under what circumstances public funding should be supported.

A rigorous assessment of evidence is thus the basis of decision-making when funding is sought under Medicare. A team from the National Health and Medical Research Council's Clinical Trials Centre was engaged to conduct a systematic review of literature on the UroVysion FISH assay for the detection of bladder cancer recurrence. An advisory panel with expertise in this area then evaluated the evidence and provided advice to MSAC.

MSAC's assessment of the UroVysion FISH assay for detecting recurrent bladder cancer

The evaluators worked with members of the advisory panel to develop specific questions on the use of the UroVysion FISH assay for detecting recurrence of transitional cell carcinoma (TCC) of the bladder. The question addressed in this review is:

- What is the value of the UroVysion FISH Assay in conjunction with cystoscopy versus cystoscopy alone to diagnose recurrence of TCC in patients who have previously been diagnosed with TCC of the bladder who would undergo cystoscopy under local anaesthetic?

A comprehensive search strategy was developed to identify systematic reviews and controlled trials of the safety, effectiveness or cost-effectiveness of the UroVysion FISH assay. In addition to electronic database searches, reference lists of identified publications were hand-searched, and publications were provided by the company submitting the application. Seven publications met criteria for inclusion in the report.

Clinical need

Bladder cancer is one of the most common cancers in Western society. In Australia in 2001, bladder cancer was the fifth most common cancer among men and the eight most common cancer overall (AIHW 2004b). It was associated with 3.1% of all cancer deaths among men, and 2.5% of cancer deaths overall (AIHW 2004b). The incidence of bladder cancer has steadily increased between 1991 and 2001 at an average rate of 0.1% per annum for males and 0.7% per annum for females (AIHW 2004b). Furthermore, in Australia in 2002–03, there were 15 672 hospital separations (both public and private) for malignant neoplasm of the bladder (ICD-10-AM principal diagnosis code C67), which corresponds to 4.01 separations per 10 000 population (AIHW 2004a). These separations included 47 248 patient days, with an average length of stay for each separation of 3.02 days (AIHW 2004a).

Recurrence of bladder cancer is common: 60% to 80% of patients with papillary tumours experience recurrence after initial destruction of the papillary lesions (Newling *et al.* 1995). Tumours are most likely to recur in the first year after transurethral resection (Debruyne & Witjes 1999), and patients are closely monitored for recurrence after their initial presentation and treatment. In patients who initially present with superficial tumours, the majority of recurrent tumours are also superficial, but about 15% of patients will develop tumour progression with bladder muscle invasion (Van Erps & Denis 1999).

Safety

None of the seven studies included in this review reported complications from the UroVysion test, cystoscopy or any of the comparators. As the UroVysion FISH Assay is a non-invasive test performed on voided urine, there are minimal or no risks to the safety of the patient providing the urine sample. As urine is a body fluid, universal blood and body fluid precautions should be followed to ensure the safety of staff involved in the collection, transport and analysis of the urine samples.

In comparison to the UroVysion test, cystoscopies are invasive procedures and are associated with known adverse effects. These include bladder rupture, stranguria, bleeding and urinary tract infections, although it would appear that the incidence of serious complications following cystoscopy is rare, and although minor complications are more common, they usually resolve spontaneously within 48 hours and are likely to be of minimal clinical significance.

Effectiveness

Seven diagnostic accuracy studies were identified for inclusion in the review. In general, the quality of the studies was fair, with one study of high quality and one study of low quality. The studies include a total of 1072 patients, with sample sizes ranging from 19 to 451, and a median of 86. These sample sizes include patients with a history of bladder cancer, patients being investigated for bladder cancer who have no history of bladder cancer, and healthy controls or patients without suspected bladder cancer. Considering only those patients being monitored for bladder cancer recurrence, there were a total of 558 patients, with sample sizes ranging from 19 to 176, and a median of 51.

Four of the included studies provided sufficient data for the reconstruction of two-by-two tables of results in patients being monitored for recurrence. The other three studies presented only values of sensitivity or specificity. Owing to statistically significant heterogeneity in the estimates of UroVysion accuracy across studies, a single pooled estimate of test accuracy could not be obtained. The sensitivity of the UroVysion test ranged from 48% to 86%, and the specificity ranged from 34.3% to 100%. Differences in the types of patients included in the trials, the reference standard used and the quality of the trials is likely to have contributed to the variation between studies.

The potential impact of the UroVysion test on clinical practice was determined from the results of the studies, which were used to gain estimates of the likelihood ratios (LRs) of the UroVysion test. The positive LRs ranged from 1.3 to 21.1, and the negative LRs ranged from 0.2 to 0.5. Applying these LRs to various pretest probabilities of recurrence (based on risk of recurrence and period of follow-up) revealed that for most patients, the use of the UroVysion test does not greatly increase the probability of detecting recurrence. Clinical impact is likely to be greatest in patients with a high risk of recurrence who have undergone at least one year of follow-up. In these patients, current practice is to give patients a cystoscopy under local anaesthetic (LA), and a large proportion undergo a second cystoscopy under general anaesthetic (GA) (owing to high rates of recurrence). Using the result of the UroVysion test to determine the type of anaesthetic for cystoscopy means that only a small number of patients will unnecessarily undergo cystoscopy under GA (owing to a false positive UroVysion test), while the majority of patients will have to undergo only one cystoscopy (compared with current practice). The post-test probabilities show that in patients with a low risk of recurrence who are early in their follow-up, the chance of missing a recurrence following a negative UroVysion test is small, but the probability of missing a recurrence increases in patients with higher risks or in patients at later stages in their follow-up. This problem of false negatives is not of clinical significance if the UroVysion test is only to be used in conjunction with cystoscopy, as the recurrence will be detected by cystoscopy.

Cost-effectiveness

The reviewers developed an economic model comparing a clinical pathway where patients undergo cystoscopy under LA followed by a cystoscopy under GA if they have a positive result to a pathway where patients initially undergo the UroVysion test, the result of which informs whether a patient undergoes cystoscopy under LA or GA. The model showed that at both the 3-month follow-up and at 5 years (cumulative costs over a 5-year follow-up period), the costs of following the UroVysion clinical pathway exceeded the costs of following the current-practice clinical pathway. At 5 years, the cost of following the UroVysion pathway was $7835, compared to $5959 for following current practice. Therefore, the UroVysion clinical pathway increased the expected cost for patients until first recurrence by $1876 over current practice.

As the cost analysis is conditional on the rate of recurrence, the costs of procedures, the sensitivity and specificity of the UroVysion test, and the specificity of LA cystoscopy, one-way sensitivity analysis and a best-case scenario were used to allow for the uncertainty of the parameters used in the model. In general, under any plausible variation of evidence of accuracy, costs or rates of recurrence, the use of the UroVysion test remained more costly than current practice given the expected diagnostic pathways. As diagnostic pathways with and without the UroVysion test are expected to have equivalent clinical outcomes, the UroVysion clinical pathway was dominated by (more expensive while having equivalent effects relative to) current practice.

Recommendation

MSAC recommended that on the strength of evidence pertaining to UroVysion fluorescence in situ hybridisation (FISH) assay public funding should not be supported for this procedure.

The clinical usefulness of the test is limited by the sensitivity and expense of the test and the cost effectiveness was not demonstrated.

- The Minister for Health and Ageing accepted/rejected this recommendation on 28 March 2006. -

Introduction

The Medical Services Advisory Committee (MSAC) has reviewed the use of the UroVysion fluorescence *in situ* hybridisation (FISH) assay, which is a diagnostic test for the detection of bladder cancer recurrence. MSAC evaluates new and existing diagnostic technologies and procedures for which funding is sought under the Medicare Benefits Schedule (MBS) in terms of their safety, accuracy, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. MSAC takes an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

MSAC's terms of reference and membership are outlined in Appendix A. MSAC is a multidisciplinary expert body, comprising members drawn from such disciplines as diagnostic imaging, pathology, surgery, internal medicine and general practice, clinical epidemiology, health economics, consumer health and health administration.

This report summarises the assessment of current evidence for the UroVysion FISH assay for detection of bladder cancer recurrence.

Background

The UroVysion fluorescence *in situ* hybridisation assay

The Vysis® UroVysion™ FISH assay is a non-invasive diagnostic test used in conjunction with cystoscopy for monitoring for tumour recurrence in patients previously diagnosed with transitional cell carcinoma (TCC) of the bladder (urothelial carcinoma). It is a multitarget, multicolour FISH probe set that is designed to detect aneuploidy of chromosomes 3, 7 and 17, and loss of the 9p21 locus in voided urine. The UroVysion FISH assay is a complex pathology test that will need to be done in selected accredited laboratories by a pathologist.

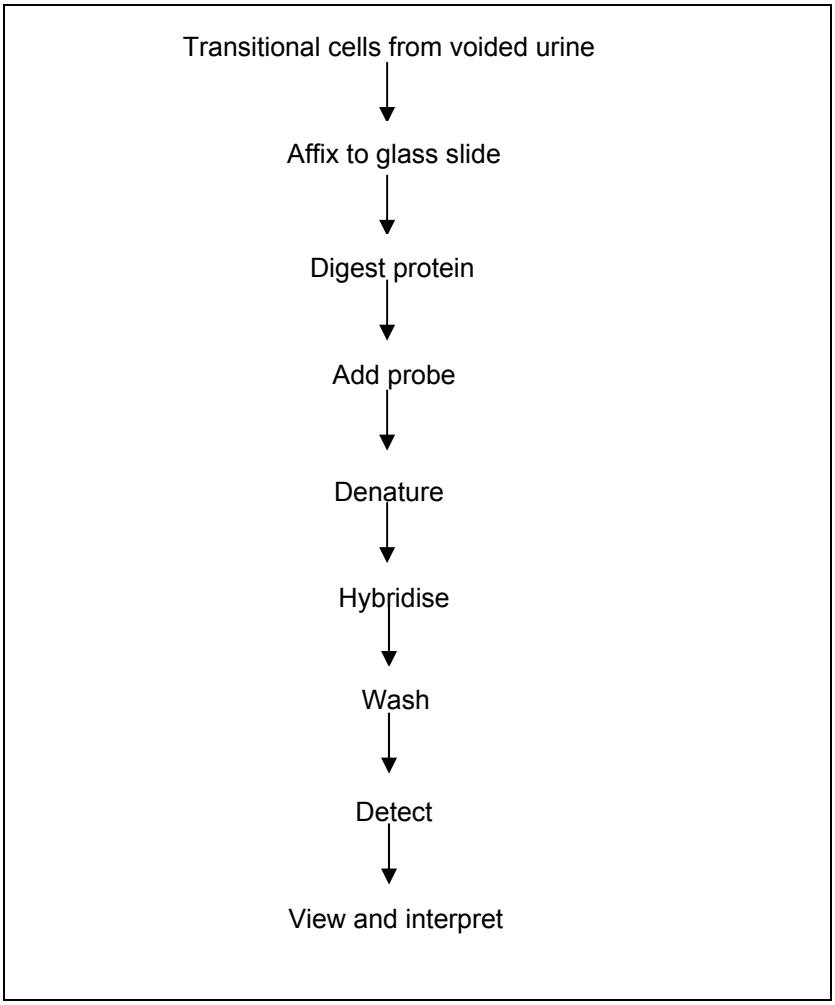
Fluorescence *in situ* hybridisation

FISH is a technique which detects chromosomal and genetic aberrations at a cellular level by using fluorescent-labelled nucleic acid probes. Hybridisation refers to the formation of base pairs between nucleic acids, and *in situ* refers to the fact that the hybridisation occurs 'in place', that is, in the nuclei of the bladder cells, which are affixed to a glass slide.

DNA is a molecule with a unique double helical structure. The two strands of DNA have a backbone of sugars and phosphates, with a nitrogen-containing base attached to each sugar. These two strands are complementary to each other, with the base sequence on one strand determining the base sequence on the other strand. DNA is organised into chromosomes within the nuclei of all cells. DNA may be denatured (separated) into two single strands by conditions that disrupt the stabilising hydrogen bonds between bases. This process of separating the DNA into two separate strands may be reversed, and complementary strands reform when the denaturant (such as heat) is removed. When complementary strands from two different sources are mixed, some of the reformed structures will be composed of a strand from each source. These molecules are termed hybrids. In a hybridisation assay, the two sources are the sample (eg, DNA strands in transitional cells from voided urine) and the probe (eg, UroVysion probes). The probe is a known fragment of nucleic acid (labelled to enable detection) which has a complementary sequence to the target DNA. After hybridisation, the mixture is washed to remove unbound probe from the slide so that the remaining probe can be detected. In FISH, fluorescent groups are chemically linked to probes, enabling the probes to be visualised under a microscope after hybridisation has occurred.

The general steps of *in situ* hybridisation are outlined in Figure 1.

Figure 1 Generalised steps of *in situ* hybridisation (adapted from Kenny-Moynihan & Unger 2003)



The UroVysion FISH assay

Cancer usually arises as a result of acquired genetic changes (Bradley *et al.* 1995). In bladder cancer, numerous chromosomal abnormalities have been identified which are associated with both the development and progression of the disease. The UroVysion FISH assay consists of a four-colour, four-probe mixture of DNA probe sequences homologous to specific regions on chromosomes 3, 7, 9 and 17, which are commonly altered in bladder cancer. The assay is designed to detect aneuploidy of chromosomes 3, 7 and 17, and the loss of the 9p21 locus. This set of probes was selected for testing on the basis of reports in the scientific literature that associated these changes in DNA (chromosome copy number changes or deletion of the locus) with bladder cancer (Vysis 2005). The Vysis UroVysion probe mixture contains chromosome enumeration probe (CEP) 3 SpectrumRed, CEP 7 SpectrumGreen and CEP 17 SpectrumAqua, which hybridise to the centromere regions of chromosomes 3, 7 and 17 respectively, and locus-specific identifier (LSI) 9p21 SpectrumGold, which hybridises to the *p16* gene at 9p21. These probes are premixed and predenatured in hybridisation buffer. Unlabelled blocking DNA is included with the probes to suppress sequences contained within target loci that are common to other chromosomes.

The process of performing FISH using the UroVysion assay first involves fixing cells from urine samples on microscope slides. The DNA is denatured to its single-stranded form and allowed to hybridise with the UroVysion DNA probes. Following hybridisation, unbound probe is removed by a series of washes, and the nuclei are counterstained with DAPI (4,6-diamidino-2-phenylindole), a DNA-specific stain that fluoresces blue (Vysis 2005). Specific hybridisation of the UroVysion probes is viewed through a fluorescence microscope equipped with appropriate excitation and emission filter sets allowing visualisation of the red, green, aqua, and gold fluorescent signals. The probes specific for chromosomes 3, 7 and 17 and the 9p21 region are counted by microscopic examination of the nucleus, which is easily distinguished by the DAPI staining.

Interpretation of results involves scanning a specimen slide for cells that have abnormal-appearing nuclei (such as a large or irregular shape), since these are likely to have experienced some sort of cancer-associated genetic change (Vysis 2005). The DNA probe profile (the number of probe signals of each colour) is then recorded to determine whether there is aneusomy of chromosomes 3, 7 or 17, or deletion of the 9p21 locus. If no nuclei appear abnormal, the probe signal pattern of the remaining cells is reviewed to identify cancer-associated changes in the absence of changes in cell morphology.

The definition of a positive UroVysion FISH assay differs among studies evaluating the role of UroVysion, and there are no universally accepted criteria for defining positivity (Placer *et al.* 2002). The most common definition of a positive test result is ≥5 cells with a gain of two or more chromosomes, or ≥50% of nuclei with 9p21 loss. Most definitions require a minimum of 50 cells to be examined, and many require 100.

Intended purpose

The UroVysion FISH assay is intended for use in patients who have been previously diagnosed with TCC of the bladder who are being monitored for recurrence. While it may be used for diagnosing bladder cancer in patients who have not previously had such a diagnosis, the purpose of this report is to consider its use only in patients being monitored for recurrence.

The UroVysion FISH assay is intended to be used in conjunction with cystoscopy to monitor for bladder cancer recurrence. While the UroVysion kit may also be considered as a replacement test for cystoscopy, the purpose of this report is to consider its use as a supplement to cystoscopy. The role of the UroVysion FISH assay is outlined in the clinical flow chart in Appendix F.

Clinical need / burden of disease

Definition and classification

Bladder cancer is a disease in which the cells lining the urinary bladder lose the ability to regulate their growth and start dividing uncontrollably. This abnormal growth results in a mass of cells that form a tumour. The types of bladder cancer include TCC, adenocarcinoma, squamous carcinoma, sarcoma, lymphoma, small cell anaplastic carcinoma, pheochromocytoma and choriocarcinoma (AJCC 2002). Of these, TCC of the bladder is the most common type of bladder cancer and accounts for more than 90% of bladder cancers (NCCN & ACS 2003).

TCC, also known as urothelial carcinoma, arises from the urothelial cells that line the bladder, ureters, renal pelvis and proximal urethra, although it is far more common in the bladder than in other parts of the urinary tract (Newling *et al.* 1995). There are two main types of TCC of the bladder—papillary carcinoma and carcinoma *in situ* (also termed flat carcinoma). Papillary tumours have a low potential for invasion, and while they often recur, they tend to remain non-invasive (Newling *et al.* 1995). Carcinoma *in situ* refers to flat lesions of the urothelium with enough cellular anaplasia to be recognised as at least a grade 2 tumour (refer to Table 3 for a description of grades). In contrast to papillary tumours, at least half of carcinoma *in situ* tumours progress to invasive disease (Newling *et al.* 1995).

TCCs of the bladder are staged using the American Joint Commission for Cancer Tumour-Node-Metastasis (TNM) classification. The definitions of T, N and M are outlined in Table 1. The pathological classification is designated pTNM and is based on subsequent evidence from surgery and from the pathological specimens obtained after cystectomy (Newling *et al.* 1995).

Table 1 AJCC tumour-node-metastasis classification for bladder cancer (AJCC 2002)

Primary tumour (T)		Regional lymph nodes (N)		Distant metastasis (M)	
TX	Primary tumour cannot be assessed	NX	Regional lymph nodes cannot be assessed	MX	Distant metastasis cannot be assessed
T0	No evidence of primary tumour	N0	No regional lymph node metastasis	M0	No distant metastasis
Ta	Non-invasive papillary carcinoma	N1	Metastasis in a single lymph node, 2 cm or less in greatest dimension	M1	Distant metastasis
Tis	Carcinoma *in situ*: 'flat tumour'	N2	Metastasis in a single lymph node, more than 2 cm but not more than 5 cm in greatest dimension; or multiple lymph nodes, none more than 5 cm in greatest dimension		
T1	Tumour invades subepithelial connective tissue	N3	Metastasis in a lymph node, more than 5 cm in greatest dimension		
T2	Tumour invades muscle				
pT2a	Tumour invades superficial muscle				
pT2b	Tumour invades deep muscle				
T3	Tumour invades perivesical tissue				
pT3a	As for T3 – microscopically				
pT3b	As for T3 – macroscopically				
T4	Tumour invades any of the following – prostate, uterus, vagina, pelvic wall, abdominal wall				
T4a	Tumour invades prostate, uterus, vagina				
T4b	Tumour invades pelvic or abdominal wall				

The TNM classification is used to determine the stage of the disease, from stage 0 to stage IV. Table 2 outlines the different groupings for each stage. Stages 0 and 1 are referred to as superficial disease, as the tumour is confined to the mucosa or submucosa. Seventy to eighty per cent of patients with TCC of the bladder have superficial tumours at initial presentation (Van Erps & Denis 1999).

Table 2 AJCC stage groupings for bladder cancer (AJCC 2002)

Stage	Primary tumour classification	Regional lymph nodes classification	Distant metastasis classification
Stage 0a	Ta	N0	M0
Stage 0is	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2a	N0	M0
	T2b	N0	M0
Stage III	T3a	N0	M0
	T3b	N0	M0
	T4a	N0	M0
Stage IV	T4b	N0	M0
	Any T	N1	M0
	Any T	N2	M0
	Any T	N3	M0
	Any T	Any N	M1

The histologic grade of a tumour is a qualitative assessment of the differentiation of the tumour expressed as the extent to which a tumour resembles normal tissue at that site (AJCC 2002). The histologic grades of bladder cancer are shown in Table 3.

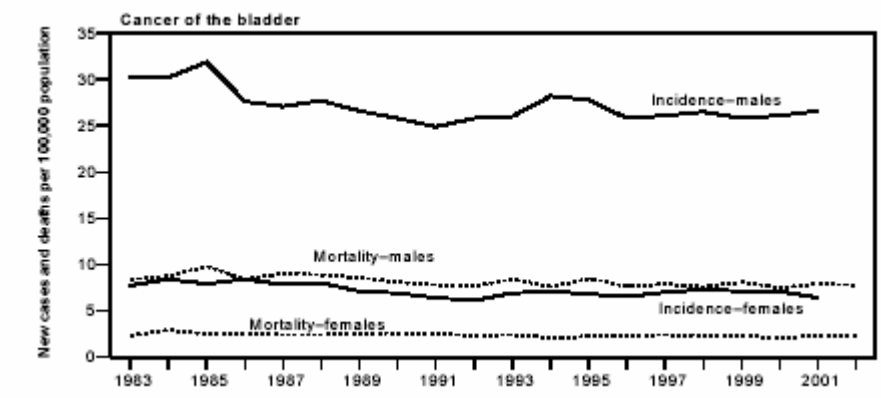
Table 3 AJCC histologic grades for bladder cancer (AJCC 2002)

Grade	Definition
GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3–4	Poorly differentiated or undifferentiated

Incidence and prevalence

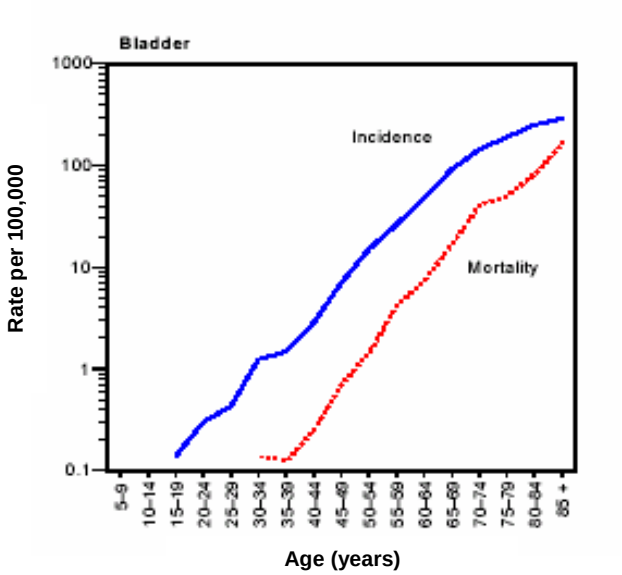
Bladder cancer is one of the most common cancers in Western society. In Australia in 2001, bladder cancer was the fifth most common cancer among men and the eight most common cancer overall (AIHW 2004b). It was associated with 3.1% of all cancer deaths among men, and 2.5% of cancer deaths overall (AIHW 2004b). The incidence of bladder cancer has steadily increased between 1991 and 2001, at an average rate of 0.1% per annum for males and 0.7% per annum for females (AIHW 2004b). During the same period, mortality decreased for both males and females—by 0.2% and 0.5% per annum respectively (AIHW 2004b). The changes in bladder cancer incidence and mortality from 1983 to 2002 are shown in Figure 2.

Figure 2 Trends in age-standardised incidence and mortality rates for bladder cancer, Australia, 1983–2002 (AIHW 2004b)



Bladder cancer occurs most commonly in males, with 2258 new cases of bladder cancer in males in Australia in 2001 compared to only 696 new cases in women (AIHW 2004b). The age-standardised rate for males (26.6 per 100 000 population) is four-times that for females (6.4 per 100 000 population) (AIHW 2004b). The incidence of bladder cancer and mortality are also known to increase with age (Figure 3). Known predisposing factors include smoking, exposure to chemicals, and schistosomiasis. In Australia, 43% of bladder cancer in males and 36% of bladder cancer in females are attributed to smoking (AIHW 2004b).

Figure 3 Age-specific bladder cancer incidence and mortality rates for Australian males (AIHW 2004b)



Recurrence of bladder cancer is common: 60% to 80% of patients with papillary tumours experience recurrence after initial destruction of the papillary lesions (Newling *et al.* 1995). Tumours are most likely to recur in the first year after transurethral resection (TUR) (Debruyne & Witjes 1999), and patients are closely monitored for recurrence after their initial presentation and treatment. Recurrences may be regrowths after incomplete resection, a result of implantation of tumour cells during resection, or new occurrences (Debruyne & Witjes 1999). The factors known to be associated with the risk of recurrence are the number of tumours present at diagnosis, the recurrence rate in the previous period, the tumour size (larger tumours being associated with greater risk), and the anaplasia grade of the tumour (Oosterlinck *et al.* 2001).

In patients who initially presented with superficial tumours, most recurrent tumours are also superficial, but about 15% of patients will develop tumour progression with bladder muscle invasion (Van Erps & Denis 1999). Once the tumour has invaded the detrusor muscle, the prognosis is poor, with a high risk for the development of metastases. In patients with superficial tumours at initial presentation, the risk of progression to invasive disease is highest in patients with T1G3 tumours, at up to 50% (Oosterlinck *et al.* 2001). The risk of progression is also high for patients with Tis tumours or patients with multifocal tumours (Oosterlinck *et al.* 2001).

Health service usage

In Australia in 2002–03, there were 15 672 hospital separations (both public and private) for malignant neoplasm of bladder (ICD-10-AM principal diagnosis code C67), which corresponds to 4.01 separations per 10 000 population (AIHW 2004a). These separations included 47 248 patient days, with an average length of stay for each separation of 3.02 days (AIHW 2004a).

The number of cystoscopies, the principal diagnostic and therapeutic tool used in bladder cancer, performed in Australian hospitals from 2000 to 2003 is shown in Table 4 and Figure 4. These data include cystoscopies in which no biopsy or therapeutic procedure was performed and cystoscopies in which a biopsy or therapeutic procedure such as

resection or destruction of the lesion was performed. Table 4 and Figure 4 also show the number of cystectomies that were performed in Australian hospitals from 2000 to 2003. The total number of procedures performed, particularly cystoscopies, has increased steadily from 2000 to 2003.

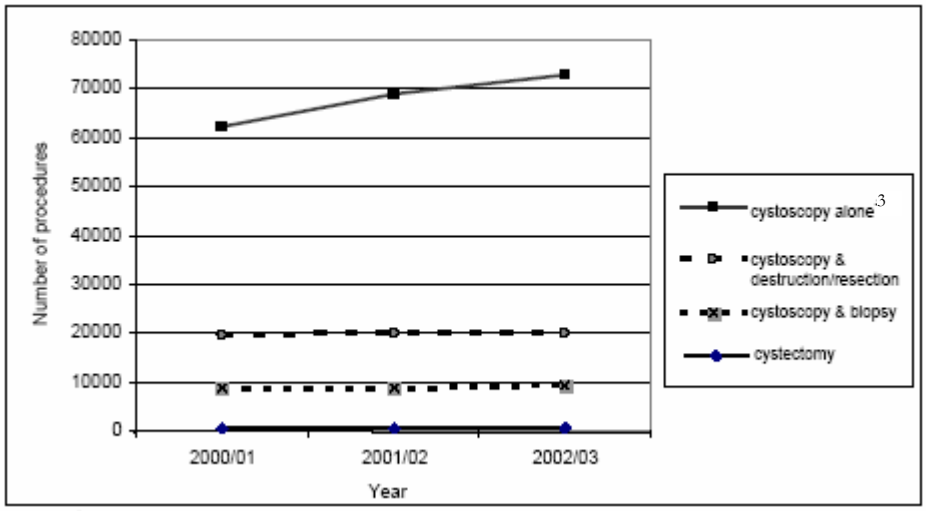
Table 4 Number of bladder procedures performed in Australian hospitals 2000–2003[1]

ICD-10-AM – MBS extended code(s)	Procedure description	Number of procedures performed		
		2000–2001	2001–2002	2002–2003
36812[2]	Examination procedures on bladder —cystoscopy	62 257	68 921	72 925
36840	Endoscopic laser destruction or resection of single bladder tumour	13 446	13 784	13 904
36485	Endoscopic destruction or resection of single bladder tumour >2 cm in diameter or multiple bladder tumours	6 167	6221	6 272
36836	Biopsy of bladder – endoscopic biopsy of bladder	8 683	8 832	9 691
	Cystectomy			
37000	– Laparoscopic partial excision of bladder or partial excision of bladder	239	264	238
37014	– Total excision of bladder	516	517	494

[1] Source: AIHW 2004c

[2] The number of cystoscopies performed includes those performed on patients without a history of bladder cancer, so the number performed on patients undergoing surveillance for bladder cancer will be a proportion of this number.

Figure 4 Australian hospital procedures 2000–2003[1,2]



[1] Source: AIHW 2004c

[2] The ICD-10-AM codes 1095, 1096 and 1099 have been aggregated to create an overall number of procedures (cystoscopies) performed with destruction or resection of a bladder tumour(s).

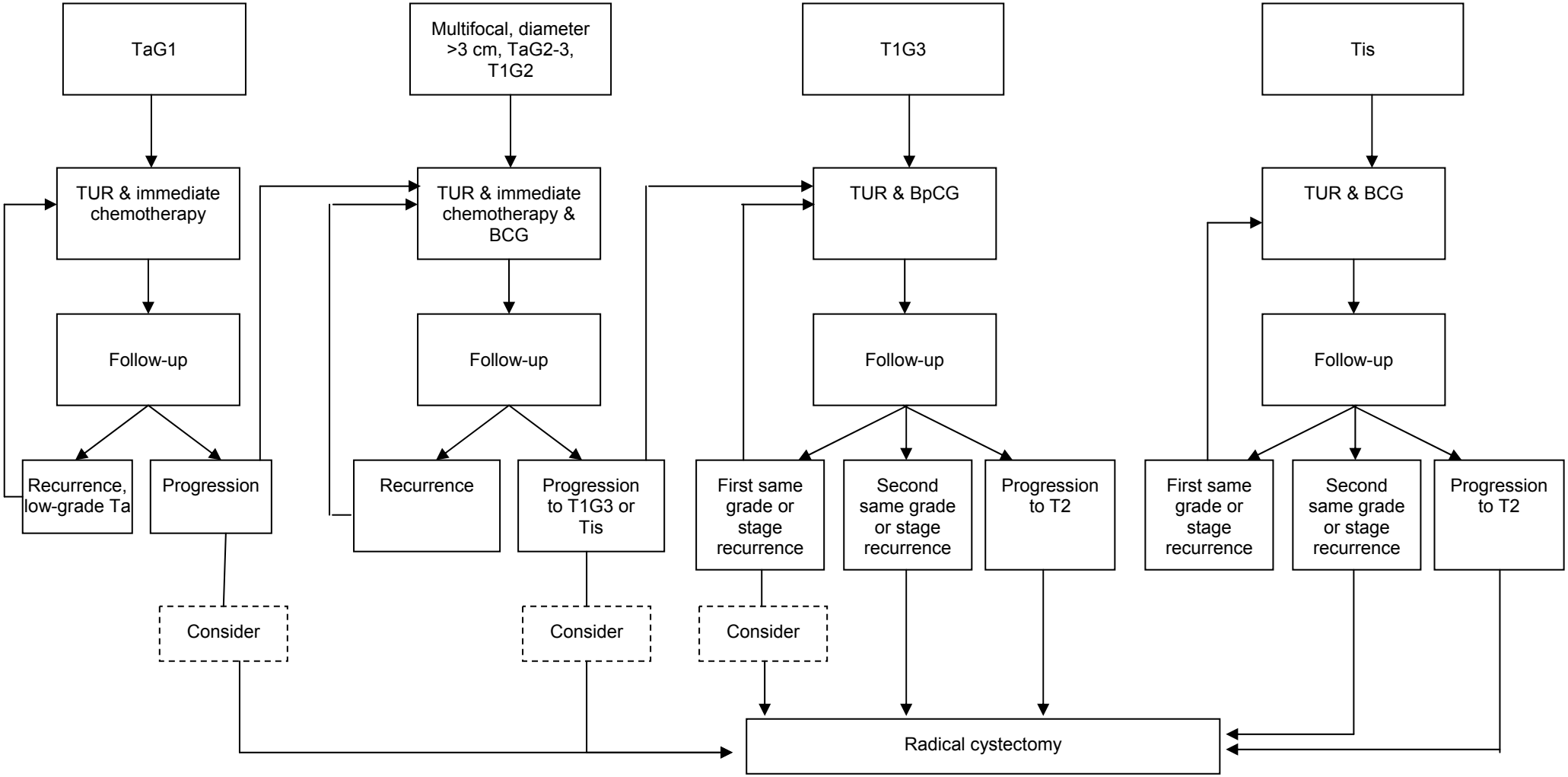
[3] The number of cystoscopies performed includes those performed on patients without a history of bladder cancer, so the number performed on patients undergoing surveillance for bladder cancer will be a proportion of this number.

Current treatment

The techniques used for treating TCC of the bladder depend on the stage of the disease. The main treatments are TUR, cystectomy, intravesical Bacillus Calmette-Guérin (BCG), chemotherapy (intravesical and systemic) and radiation therapy. The role of each of these treatments is outlined in the following paragraphs, and a clinical flow chart outlining the role of each treatment for stages Ta, T1 and Tis of the disease is shown in Figure 5. For stage T2 and above, patients would usually be treated with a cystectomy (refer to cystectomy section, page 12) and thus would not be at risk of local recurrence.

The effectiveness of each of the treatments is based primarily on three evidence-based publications—two by the UK's National Institute for Clinical Excellence (NICE 2002a, b), which provide guidance for improving outcomes in urological cancers based on research evidence that addresses clinical effectiveness and service, and the European Association of Urology's guidelines on bladder cancer (Oosterlinck *et al.* 2001).

Figure 5 Treatment flow chart for transitional cell carcinoma in stages Ta, T1 and Tis (adapted from Soloway *et al.* 2002)



Transurethral resection

TUR involves destruction of the bladder tumour using a resectoscope (a thin lighted tube inserted into the bladder via the urethra). Alternatively, the bladder tumour may be destroyed using laser energy. The procedure may be performed under regional or general anaesthesia and is commonly performed as a day procedure. TUR is used as the primary form of therapy for patients with superficial bladder cancer. As the majority of patients with superficial bladder cancer will develop recurrences, adjuvant therapy such as intravesical immunotherapy or intravesical chemotherapy may be used.

Partial or radical cystectomy

A radical cystectomy is standard treatment for patients with muscle-invasive tumours, although some invasive tumours may be treated with a partial cystectomy and bladder preservation. A radical cystectomy involves surgical removal of the bladder as well as the tissue and some of the organs surrounding the bladder (the prostate and the seminal vesicles in males, and the uterus, ovaries, fallopian tubes and part of the vagina in females), while a partial cystectomy involves removal of part of the bladder.

Intravesical immunotherapy

Intravesical immunotherapy involves the instillation of a treatment directly into the bladder, and uses the body's immune system to fight the cancer. The aim of intravesical therapy is to prevent or delay tumour recurrence or progression or to treat tumours than cannot be fully resected.

Bacillus Calmette-Guérin (BCG)

BCG is a bacterium that is used as a form of intravesical immunotherapy in treating bladder cancer. The body's immune system responds to the BCG, and immune cells are attracted to the bladder and activated to fight cancer cells. The optimal dosage of intravesical BCG following TUR is yet to be established. Current practice involves weekly instillations of BCG for six weeks to provoke an immunological response.

A meta-analysis of 24 randomised clinical trials conducted by the European Organisation for Research and Treatment of Cancer (Sylvester *et al.* 2002) found that intravesical BCG significantly reduces the risk of progression after TUR in patients with superficial bladder cancer who receive maintenance treatment (OR 0.73, $P = 0.001$).

The side-effects of BCG are primarily local irritation of the bladder, but systemic effects such as flu-like symptoms, sepsis, prostatitis and hepatitis can occur (Oosterlinck *et al.* 2001). The use of BCG is contraindicated when open wounds in the bladder or urethra are present, such as immediately after TUR.

Intravesical chemotherapy

Epirubicin and mitomycin C are the most commonly used intravesical chemotherapeutic agents. Epirubicin is an anthracycline which inhibits DNA synthesis. Mitomycin-C is an alkylating agent that binds to DNA, resulting in synthesis inhibition and strand breakage.

It has low absorption and, as a result, minimal systemic side-effects. The chemotherapeutic agents are dissolved in physiological solution or water and are kept in the bladder for 1 to 2 hours (Oosterlinck *et al.* 2001). A single instillation of epirubicin or mitomycin C within 6 hours of TUR reduces the disease recurrence rate by about 50% (Oosterlinck *et al.* 2001). In patients at a high risk of recurrence (for example, recurrent multiple Ta-T1, G1-G2 tumours), a further 4- to 8-week course of intravesical chemotherapy may be indicated (Oosterlinck *et al.* 2001). The benefit from maintenance intravesical chemotherapy remains unclear (Oosterlinck *et al.* 2001).

The potential side-effects of intravesical chemotherapy relate to systemic absorption and local effects. Chemical cystitis and allergic skin reactions in the genital area have been reported (Oosterlinck *et al.* 2001).

Radiotherapy

Radical radiotherapy is used as a treatment for patients with invasive bladder cancer who are not fit for surgery or who wish to avoid cystectomy (NICE 2002a). There is currently no evidence that radical radiotherapy leads to long-term survival in patients with invasive bladder cancer (NICE 2002a). In addition, there is no clear evidence as to whether radiotherapy is more or less effective than surgery for preventing disease progression and death when both are options (NICE 2002a).

Existing procedures

The existing procedures used to diagnose bladder cancer recurrence include cystoscopy, cytology and tumour marker tests.

Cystoscopy

Cystoscopy involves the insertion of a cystoscope into the urinary tract via the urethra to see the bladder. It may be performed under general or local anaesthetic (GA or LA). It is the current standard of care for monitoring patients for bladder cancer recurrence. It enables characteristic information about a tumour, such as multifocality, appearance and size to be determined, and enables specimens for pathological diagnosis to be obtained. The sensitivity of cystoscopy is limited to tumours that can be seen, but as the true incidence of unseen bladder cancer cannot be determined, the sensitivity of cystoscopy cannot be quantified.

When cystoscopies are performed under GA, a TUR may be performed if a tumour is found. In Australia, most cystoscopies performed for monitoring of bladder cancer recurrence are performed under LA (Advisory Panel, February 2005). Those performed under GA are performed in patients considered at high risk for recurrence, such as patients undergoing their first surveillance cystoscopy (at 3 months) after a Grade 3 tumour, a carcinoma *in situ*, multiple tumours or intravesical therapy.

Cystoscopy can be considered an invasive and expensive procedure. The potential complications associated with cystoscopy include bladder perforation, urinary tract infection, and urethral inflammation, although the risk of these complications is very small.

Cytology

Cytology is a diagnostic tool which can be used in addition to cystoscopy to detect bladder cancer recurrence. It involves microscopic examination of bladder cells obtained from a urine specimen or a bladder washing. Cell features suggestive of malignancy are most often associated with the nucleus and include hyperchromasia or hypochromasia, irregular nuclear membranes, and increased nuclear to cytoplasmic ratio (Van Erps & Denis 1999).

Urinary cytology does not enable the location of the malignancy in the urinary tract to be determined. The accuracy of urinary cytology is affected by the grade of the tumour, with a much greater accuracy for high-grade tumours. The reported sensitivity of urinary cytology varies between 20% and 40% in the most common low-grade lesions, irrespective of the manner of collection of the sample (Burchardt *et al.* 2000). The low sensitivity of urinary cytology is due to the normal cytological appearance of well-differentiated tumours, and the fact that well-differentiated tumours are more cohesive and less commonly shed into the urine (Stein & Skinner 1999). Urinary cytology results may also be altered by factors such as the presence of a urinary tract infection, an indwelling catheter or the use of intravesical therapies. This can result in false-positive results in up to 12% of patients (Burchardt *et al.* 2000). In a meta-analysis of 26 trials evaluating urinary cytology for detecting primary bladder cancer, the sensitivity of cytology across all tumour grades was found to be 55% (95% CI 48%–62%) and the specificity was 94% (95% CI 90%–96%) (Glas *et al.* 2003). The specificity of cytology was found to be significantly higher than the specificity of BTA Stat and NMP22 (see next section) (Glas *et al.* 2003). Despite the high specificity of urinary cytology, its low sensitivity and low overall accuracy enable urinary cytology to be used only as an adjunct to other diagnostic procedures such as cystoscopy. Cytology is used infrequently and isn't a major part of the current clinical pathway or the average clinical pathway.

As cytology is a non-invasive procedure, it is usually not associated with any complications or adverse effects.

Tumour markers

Tumour marker studies use chemical or immunologic tests to detect specific substances released into the urine by malignant cells. Over the past few decades, numerous markers of bladder cancer have been reported, including the BTA Stat and BTA TRAK tests, NMP22, the FDP test, ImmunoCyt and telomerase. For tumour markers to be of value, the test should be non-invasive, rapid, easy to obtain, use and interpret, and most importantly, accurate, with high sensitivity and specificity (Burchardt *et al.* 2000).

NMP22

The nuclear matrix is a three-dimensional web of RNA and proteins that provide the structural foundation for the nucleus of a cell. It participates in DNA replication, transcription, RNA processing and gene expression. Several nuclear matrix proteins (NMPs) are organ specific and have been found to be cancer-specific. Of these, NMP22 is a potential urothelial-specific cancer marker. The NMP22 test is an enzyme immunoassay that detects NMP22, which is shed from the cell nucleus into urine during apoptosis (Burchardt *et al.* 2000). The concentration of NMP22 in voided urine is

significantly higher in patients with TCC than in those without the disease (Burchardt *et al.* 2000).

The reported sensitivity of the NMP22 test varies between 68% and 100%, with reported specificity ranging from 61% to 96% (Burchardt *et al.* 2000). The reported values depend on the concentration of NMP22 used to determine the presence of disease (that is, the cut-off value for a positive test), and on the patient group tested. High false-positive rates have been reported for urolithiasis, benign prostatic hyperplasia and other benign urological diseases (Burchardt *et al.* 2000).

BTA Stat and BTA TRAK tests

The BTA (bladder tumour antigen) assay was originally a latex agglutination assay that detected basement membrane antigen in voided urine, but as conditions such as cystitis cause cellular destruction resulting in the release of basement membrane, its specificity was found to be diminished (Gaston & Pruthi 2004). The newer BTA Stat and BTA TRAK tests detect complement factor H-related protein, which is believed to be specific to bladder cancer. BTA Stat is a qualitative point-of-care test, and BTA TRAK is a quantitative test. BTA Stat and BTA TRAK can both give false positives in the presence of urinary tract inflammation, recent genitourinary tumours or bladder stones (Dey 2004).

In a systematic review of tumour markers for primary bladder cancer, including eight studies evaluating BTA Stat and five evaluating BTA TRAK, the sensitivity of BTA Stat was found to be 70% (95% CI 66%–74%) and its specificity 75% (95% CI 64%–84%), and those for BTA TRAK were 66% (95% CI 62%–71%) and 65% (95% CI 45%–81%) respectively (Glas *et al.* 2003).

FDP test

The FDP test involves determining the concentration of fibrin or fibrinogen degradation products (FDP) in voided urine, which are associated with the presence of bladder cancer. The test consists of a lateral-flow immunoassay device that uses monoclonal antibodies to qualitatively detect FDP (Burchardt *et al.* 2000). It is a rapid, point-of-care dipstick assay. A systematic review conducted by Glas *et al.* (2003) included two studies evaluating FDP. In those two studies, the sensitivity of the FDP test ranged from 78% to 91% and the specificity, reported in only one study, was 76% (Glas *et al.* 2003)

ImmunoCyt

The ImmunoCyt test is a combination of cytology with an immunofluorescence assay. It detects cellular markers specific for bladder cancer by using three fluorescent monoclonal antibodies (Dey 2004). In a systematic review evaluating commonly available bladder tumour markers, Lotan and Roehrborn (2003) identified one study evaluating the ImmunoCyt test. This study showed a sensitivity of 86% and a specificity of 79%.

Telomerase

Telomeres are the nucleotide sequences of eukaryotic chromosomes that occur on the ends of chromosomes and that remain uncopied after each cycle of DNA replication (Dey 2004). Telomerase is a ribonucleoprotein polymerase that helps maintain the length of telomeres. Telomerase is not usually present in adult somatic tissue, but is present in many types of cancer (Dey 2004). Measurement of telomerase in exfoliated cells in voided

urine can be used as a marker for bladder cancer. False positive results may occur in cases of chronic or severe inflammation (Dey 2004).

In the systematic review by Glas *et al.* (2003), ten studies evaluating telomerase were included. Meta-analysis of the results of these trials found a sensitivity of 75% (95% CI 71%–79%) and a specificity of 86% (95% CI 71%–94%).

Reference standard

A reference standard for the detection of bladder cancer would necessitate removal of the bladder to enable a detailed pathological and histological examination of all of the tissue. As this is not appropriate, the reference standard used for the detection of TCC of the bladder is not perfect. The standard used is cystoscopy, usually with histopathology from a bladder biopsy or resection. Occasionally, direct visualisation without resection (where the tumour is destroyed by laser treatment or diathermy) is considered positive for bladder cancer where the cystoscopy result was unequivocal. Patients are defined as negative for bladder cancer in the case of a negative cystoscopy or a positive or suspicious cystoscopy with negative histopathology (where sufficient histopathological tissue was available). Cystoscopy may result in misclassification of patients owing to false negatives (that is, a negative cystoscopy resulting in a patient being classified as not having the disease when the disease is in fact present). On the other hand, false positives are unlikely to occur, as while a cystoscopy may give a false positive, histological confirmation is required for a patient to be classified as disease positive for the reference standard (unless the cystoscopy was unequivocal and the tumour was destroyed by laser treatment or ablation).

Comparators

The comparator for the UroVysion FISH assay in conjunction with cystoscopy is cystoscopy alone. This is outlined in the clinical flow chart in Appendix F, which shows that in current practice, patients with a history of TCC of the bladder undergo regular follow-up to monitor for recurrence. This follow-up consists of regular cystoscopies, usually under LA, to allow visualisation of any recurrent tumours. Those patients who are found to have a recurrence then undergo a cystoscopy under GA to allow for treatment such as a TUR to occur. The proposed diagnostic pathway which includes the UroVysion FISH assay is the UroVysion test, followed by cystoscopy with LA in patients with a negative UroVysion result, or cystoscopy under GA in patients with a positive UroVysion result.

Given the above pathways, the comparator is cystoscopy under LA. Cystoscopy under GA is not considered a comparator as, in clinical practice, there is a subset of patients (considered high-risk, such as those undergoing their first surveillance cystoscopy after a Grade 3 tumour) who would always undergo cystoscopy under GA (Advisory Panel, February 2005), regardless of the result of the UroVysion test. UroVysion is not intended to alter practice in this subgroup of patients.

Cytology has not been chosen as a comparator, as expert opinion holds that this procedure is infrequently used to monitor for bladder cancer recurrence in Australian practice (Advisory Panel, February 2005).

Marketing status of the technology

Diagnostic devices which (i) are used *in vitro*, (ii) do not contain any components of human origin, (iii) will not be supplied in Australia as a home-use test, and (iv) will not be supplied as a pharmaceutical benefit are exempt from inclusion on the Australian Register of Therapeutic Goods. As the UroVysion FISH assay meets these criteria, it is exempt from inclusion in the Register. Exempt goods are still required to comply with labelling requirements, relevant standards and the advertising provisions of the *Therapeutics Goods Act (1989)*.

The Therapeutic Goods Administration is currently developing a new legislative framework under which *in vitro* diagnostic devices will be regulated.

Current reimbursement arrangement

There is currently no item on the MBS for the UroVysion FISH assay. The currently funded techniques for monitoring of bladder cancer recurrence are cystoscopy (item number 36812, or item numbers 36836, 36840 and 39845 with biopsy or resection) and cytology (item number 73045). Table 5 shows the MBS fee associated with each of these procedures.

Table 5 Bladder cancer recurrence diagnostic procedures—Medicare Benefits Schedule services rendered 2000–2004[1]

Item number	Item description	Fee
36812	Cystoscopy with urethroscopy with or without urethral dilatation	$141.40
36836	Cystoscopy, with biopsy of bladder	$195.05
36840	Cystoscopy, with resection, diathermy or visual laser destruction of bladder tumour or other lesion of the bladder, not being a service to which item 36845 applies	$274.25
36845	Cystoscopy, with diathermy, resection or visual laser destruction of multiple tumours in more than 2 quadrants of the bladder or solitary tumour greater than 2 cm in diameter	$586.65
73045	Cytology (including serial examinations) for malignancy, if performed on (a) specimens resulting from washings or brushings from sites not specified in item 73043; or (b) a single specimen of sputum or urine; or (c) 1 or more specimens of other body fluids.	$48.95

[1] Source: HIC 2005

Approach to assessment

Research questions

The evaluation team worked with members of the advisory panel to develop specific questions addressing the use of the UroVysion FISH assay for detecting recurrence of TCC of the bladder. These questions were formulated *a priori* from information on current practice (ie, use of diagnostic tests for bladder cancer recurrence in Australia), the disease area and the purpose of the therapy. A flow chart (Appendix F), depicting the clinical pathways for monitoring recurrence of TCC of the bladder, was developed in conjunction with the advisory panel. This flow chart was used to define the role of the UroVysion FISH assay in detecting recurrence of TCC of the bladder.

A review question was developed and is covered in this report:

- What is the value of the UroVysion FISH Assay in conjunction with cystoscopy versus cystoscopy alone to diagnose recurrence of TCC in patients who have previously been diagnosed with TCC of the bladder who would undergo cystoscopy under local anaesthetic?

Assessment strategy

In the absence of controlled trials comparing health outcomes resulting from the use of the UroVysion FISH assay with comparator tests, the effectiveness of the UroVysion FISH assay was inferred by evidence of:

a. the relative diagnostic accuracy of the UroVysion FISH assay compared to cystoscopy

b. the use of the UroVysion FISH assay to change clinical management decisions.

This strategy is justified by the evidence of the effectiveness of treatment for TCC of the bladder.

Review of literature

MSAC's recommendations are based primarily on the findings of a systematic literature review conducted by the National Health and Medical Research Council's (NHMRC) Clinical Trials Centre. The medical literature was searched to identify relevant studies and reviews for the period between 1966 and March 2005. Searches were conducted via the electronic databases listed in Table 6.

Table 6 Electronic databases searched

Database	Period covered
Medline	1966 – March 2005
EMBASE	1980 – March 2005
Premedline	As at 2 March 2005
Current Contents	2 March 2005 (previous 6 months)
The Cochrane Library	Issue 1, 2005

Search strategy

The search strategy was developed using the key elements of the clinical question. The search strategies shown in Tables 7 to 9 were used to identify papers in the various databases outlined in Table 6.

Table 7 Medline and The Cochrane Library search strategy

Number	Search Strategy
1	exp In Situ Hybridization, Fluorescence/
2	exp Nucleic Acid Hybridization/
3	limit 2 to yr = 1977 – 1992
4	exp Microscopy, Fluorescence/
5	limit 4 to yr = 1977 – 1992
6	(FISH adj5 assay).mp.
7	urovysion.mp.
8	(fluorescence adj5 hybrid$).mp
9	1 or 3 or 5 or 6 or 7 or 8
10	exp Carcinoma, Transitional Cell/
11	exp Bladder Neoplasms/
12	exp Neoplasm Recurrence, Local/
13	(bladder adj3 (cancer or neoplasm$)).mp.
14	(transitional adj3 cell adj3 (carcinoma or cancer$)).mp.
15	(urothelial adj3 (carcinoma or cancer$)).mp.
16	or/10–15
17	9 and 16

Table 8 EMBASE search strategy

Number	Search History
1	exp Fluorescence in Situ Hybridization/
2	(FISH adj5 assay).mp.
3	urovysion.mp.
4	(fluorescence adj5 hybrid$).mp.
5	or/1–4
6	exp Transitional Cell Carcinoma/
7	exp Bladder Tumor/
8	exp Bladder Carcinoma/
9	exp Tumor Recurrence/

10	exp Recurrent Cancer/
11	(bladder adj3 (cancer or neoplasm$)).mp.
12	(transitional adj3 cell adj3 (carcinoma or cancer$)).mp.
13	(urothelial adj3 (carcinoma or cancer$)).mp.
14	or/6–13
15	5 and 14

Table 9 Premedline and Current Contents search strategy

Number	Search History
1	urovysion.mp.
2	(FISH adj assay).mp.
3	(fluorescence adj5 hybrid$).mp.
4	or/1–3
5	(bladder adj3 (cancer or neoplasm$)).mp.
6	(transitional adj3 cell adj3 (carcinoma or cancer$)).mp.
7	(urothelial adj3 (carcinoma or cancer$)).mp.
8	or/5–7
9	4 and 8

Reference lists of publications were also searched for additional relevant citations that may have been inadvertently missed in searches of major databases. In addition, the company submitting the application provided publications which were reviewed to determine whether any of the provided publications met criteria for inclusion in the review and had been inadvertently missed in searches of major databases.

In addition to the databases listed in Table 6, the websites of international health technology assessment agencies listed in Table 10 were also searched.

Table 10 Electronic databases and heath technology assessment websites searched in this review.

Organisation	Database or website
NHS Centre for reviews and Dissemination databases	
Economic evaluation database (EED)	www.york.ac.uk/inst/crd/
Database of abstracts of reviews of effectiveness (DARE)	
Heath Technology Assessment (HTA)	
Health Technology Assessment International (HTAi)	www.htai.org
International Network of Agencies for Health Technology Assessment (INAHTA)	www.inahta.org
British Columbia Office of Health Technology Assessment (Canada)	www.chspr.ubc.ca
Swedish Council on Technology Assessment in Healthcare (Sweden)	www.sbu.se
Oregon Health Resources Commission (US)	www.ohppr.state.or.us/index.html
Minnesota Department of Health (US)	www.health.state.mn.us/htac/index.htm
Canadian Coordinating Office for Health Technology Assessment (Canada)	www.ccohta.ca
Alberta Heritage Foundation for Medical Research (Canada)	www.ahfmr.ca
Veteran's Affairs Research and Development Technology Assessment Program (US)	www.va.gov/resdev
National Library of Medicine Health Service / Technology Assessment text (US)	www.ncbi.nlm.nih.gov
Office of Health Technology Assessment Archive (US)	www.wws.princeton.edu/~ota
Institute for Clinical Evaluative Science (Canada)	www.ices.on.ca
DIMDI – German Institute for Medical Documentation and Information	www.dimdi.de
National Information Centre of Health Services Research and Health Care Technology (US)	www.nlm.nih.gov/nichsr
Finnish Office for Health Technology Assessment (FinOHTA) (Finland)	www.stakes.fi/finohta/linkit/
Institute Medical Technology Assessment (Netherlands)	www.bmg.eur.nl/imta/
Agence nationale d'accreditation et d'évaluation en santé (France)	www.anaes.fr
Agence d'évaluation des technologies et des modes d'intervention en santé (AETMIS)	www.aetmis.gouv.qc.ca/en/index.php
Health Technology Board for Scotland	www.htbs.co.uk
National Coordinating Centre for HTA (NCCHTA)	www.hta.nhsweb.nhs.uk
Centre for Health Program Evaluation	chpe.buseco.monash.edu.au

Search results

Existing reviews

The searches of the health technology assessment agency databases and websites (Table 10) did not identify any systematic reviews or health technology assessments meeting criteria for inclusion in this review.

Published literature

The search strategy retrieved a total of 501 non-duplicate citations. The numbers of non-duplicate citations retrieved from each database are presented in Table 11.

Table 11 Number of non-duplicate citations retrieved from each database

	Medline	Pre-Medline	Current Contents	EMBASE	Cochrane Library	Total
Number of citations	407	14	11	69	0	501

Eligibility criteria for studies

The 501 non-duplicate citations were evaluated independently by two reviewers to determine whether they met the exclusion criteria outlined in Table 12. Discrepancies in the results of this screening process were resolved by discussion.

Table 12 Study exclusion criteria

1. Not an appropriate clinical study

Reports excluded were those describing animal, laboratory or scientific studies, technical reports or case reports. Non-systematic narrative reviews, letters and conference abstracts were also excluded in this category.

Case series where the use or reporting of the reference standard is based on the UroVysion result (positive/negative) were excluded.

Case-control studies where patients were selected for inclusion in the study on the basis of their known disease status were excluded.

Retrospective case referent studies (reporting on subjects all known to have the condition of interest) were excluded.

2. Wrong patient group

Studies were to include patients being monitored for bladder cancer recurrence. Studies with <10 patients being monitored for recurrence were excluded.

3. Wrong diagnostic test

Studies were to perform the UroVysion FISH assay.

4. Wrong reference standard or comparator

Studies were to use cystoscopy with biopsy or resection as the reference standard. Studies performing laser treatment or diathermy for unequivocal positive cystoscopy findings without biopsy were also included.

Studies were to use cystoscopy as a comparator.

5. Wrong outcomes

Studies had to report on at least one of the following:

- diagnostic accuracy with sufficient data to calculate sensitivity and/or specificity
- impact on clinical management
- patient outcomes (morbidity, mortality, adverse events)

Studies in which the results for patients being monitored for recurrence could not be identified separately from patients being investigated for possible bladder cancer (who have no history of bladder cancer) were excluded.

6. Not in English

Owing to time constraints, only studies published in English were eligible for inclusion.

On the basis of these criteria, 494 citations were excluded from the review. The reasons for exclusion are listed in Table 13.

Table 13 Reasons for exclusion

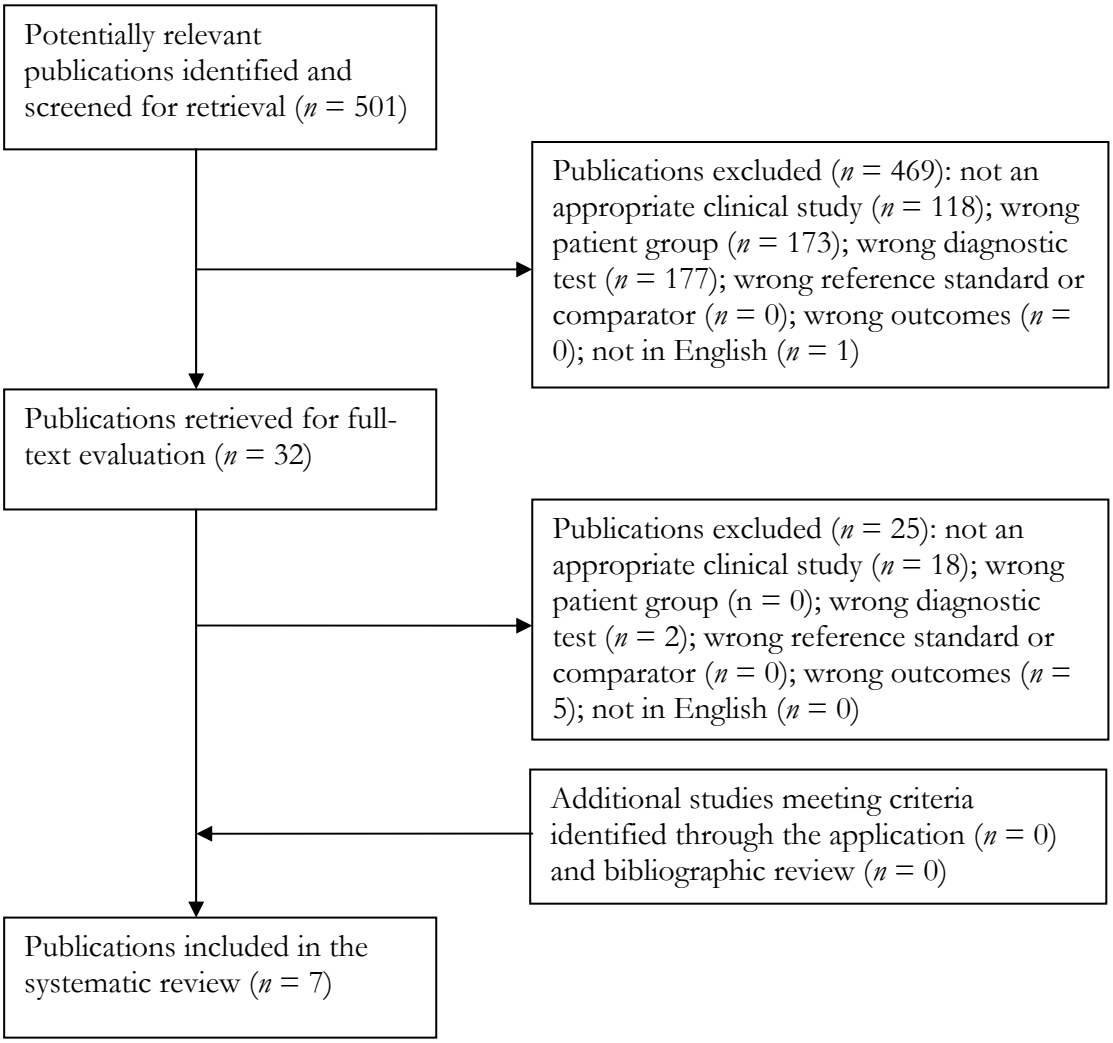
Reason for exclusion	Number	%[a]
1. Not an appropriate clinical study	136	27.14%
2. Wrong patient group	173	34.53%
3. Wrong diagnostic test	179	35.73%
4. Wrong reference standard or comparator	0	0%
5. Wrong outcomes	5	1.00%
6. Not in English	1	0.20%
Total	494	98.60%

[1] Percentage of frequency is calculated as a percentage of the total 501 citations identified.

Of those publications excluded for not being an appropriate clinical study, two were case referent studies and two were case-control studies, where patients were selected for inclusion in the study on the basis of their known disease status. All of the five publications excluded for having the wrong outcomes included both patients with a history of bladder cancer being monitored for recurrence and patients without a history of bladder cancer being investigated for possible malignancy. In these publications, the results for only those patients being monitored for recurrence were not available separately. A complete list of studies which were retrieved in full text and subsequently excluded is given in Appendix E.

The QUOROM flow chart (Figure 6) summarises the results of the literature search and the application of the study exclusion criteria.

Figure 6 QUOROM flow chart summarising the results of the literature search and the application of entry criteria



The 7 publications meeting criteria for inclusion in the review are studies of diagnostic test accuracy. No studies of change in clinical management or patient outcomes were identified.

Study appraisal

Assessment of eligible studies

The evidence presented in the selected studies was assessed and classified using the NHMRC (1999) Dimensions of Evidence and the MSAC (2005) Diagnostic Test Guidelines. These dimensions (Table 14) consider important aspects of the evidence supporting a particular diagnostic test and include three main domains: strength of the evidence, size of the effect and relevance of the evidence. The first domain is derived directly from the literature identified for a particular diagnostic test. The last two require expert clinical input as part of their determination.

Table 14 Dimensions of Evidence (adapted from NHMRC 1999 and MSAC 2005)

Type of evidence	Definition
Strength of the evidence	
Appropriate comparison	Did the study evaluate a direct comparison of the index test strategy with the comparator test strategy?
Applicable population	Did the study evaluate the index test in a population that is representative of the subject characteristics (age and sex) and clinical setting (disease prevalence, disease severity, referral filter and sequence of tests) for the clinical indication of interest?
Study quality	The methods used by investigators to minimise bias within the study design—refer to Quality Appraisal section, next.
Size of effect	The distance of the study estimate from the 'null' value and the inclusion of only clinically important effects in the confidence interval.
Relevance of evidence	The usefulness of the evidence in clinical practice, particularly the appropriateness of the outcome measures used.

The strength of evidence for studies of diagnostic accuracy is defined as follows:

High: studies which have an appropriate comparison, applicable population and high quality.
Fair: studies which have either an appropriate comparison or applicable population and fair or high quality.
Low: studies which have neither an appropriate comparison nor applicable population, or have poor quality.

Where available, the design of studies evaluating the effectiveness of a test and any subsequent intervention on patient outcomes was also ranked using the NHMRC levels of evidence (NHMRC 1999) (Table 15)

Table 15 Designations of levels of evidence (Modified from NHMRC 1999)

Level of evidence	Study design
I	Evidence obtained from a systematic review of all relevant randomised controlled trials
II	Evidence obtained from at least one properly-designed randomised controlled trial
III-1	Evidence obtained from well-designed pseudorandomised controlled trials (alternate allocation or some other method)
III-2	Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a control group
III-3	Evidence obtained from comparative studies with historical control, two or more single-arm studies, or interrupted time series without a parallel control group
IV	Evidence obtained from case series, either post-test or pre-test/post-test

Quality appraisal

The quality of a study refers to the extent to which it is has been designed and conducted to reduce bias in the estimation of the outcome. The potential sources of bias vary according to whether the study is designed to measure the impact of the test on health outcomes (where the ideal is a randomised trial of alternative tests) or to estimate the diagnostic accuracy of the test (for which the ideal is cross-sectional analytic studies of consecutive patients all followed up with a valid reference standard).

A structured appraisal to assess the quality of all included studies was performed. As no studies of effectiveness were identified, the criteria used to appraise the quality of effectiveness studies have not been presented. Checklists used to assess the quality of diagnostic test accuracy have not yet been validated (Jaeschke *et al.* 1994, Bossuyt *et al.* 2003, Whiting *et al.* 2004). The quality of studies of diagnostic test accuracy for this review will be assessed using a modified version of the QUADAS tool (see Table 16). The QUADAS tool has recently been developed by experts in the field after consideration of the growing body of evidence relating to sources of bias and variation relevant to studies of diagnostic test accuracy (Whiting *et al.* 2004).

Table 16 Quality assessment of studies of diagnostic test accuracy—the QUADAS tool (Whiting *et al.* 2003)

Item		Yes	No	Unclear
1.	Was the spectrum of patients representative of the patients who will receive the test in practice?	( )	( )	( )
2.	Were selection criteria clearly described?	( )	( )	( )
3.	Is the reference standard likely to correctly classify the target condition?	( )	( )	( )
4.	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	( )	( )	( )
5.	Did the whole sample or a random selection of the sample receive verification using a reference standard of diagnosis?	( )	( )	( )
6.	Did patients receive the same reference standard regardless of the index test result?	( )	( )	( )
7.	Was the reference standard independent of the index test (ie, the index test did not form part of the reference standard)?	( )	( )	( )
8.	Was the execution of the index test described in sufficient detail to permit replication of the test?	( )	( )	( )
9.	Was the execution of the reference standard described in sufficient detail to permit its replication?	( )	( )	( )
10.	Were the index test results interpreted without knowledge of the results of the reference standard?	( )	( )	( )
11.	Were the reference standard results interpreted without knowledge of the results of the index test?	( )	( )	( )
12.	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	( )	( )	( )
13.	Were uninterpretable or intermediate test results reported?	( )	( )	( )
14.	Were withdrawals from the study explained?	( )	( )	( )

Of the 14 criteria listed in the QUADAS tool, item 7 was not considered relevant to this review, as the reference standard is always independent of the index test, and as such, item 7 was not included in the quality assessment of included studies. The four criteria which are considered essential components in this review for a classification of a high-quality study of diagnostic test accuracy are described below. These four criteria are the selection and application of the reference standard, methods and criteria used for the selection of the study population, the execution and interpretation of the index test and presentation of results.

Selection and application of the reference standard

When an imperfect reference standard is used, the sensitivity and specificity of the test are distorted. The direction of the resulting bias depends upon whether the new test and the imperfect reference standard have a tendency to misclassify the same patients. When

there is no such tendency, the sensitivity and specificity of the new test will be underestimated when evaluated against the imperfect reference standard. When the new test and the standard tend to misclassify the same patients (that is, the classification errors between the two tests are highly correlated), the sensitivity and specificity of the new test will be overestimated (Valenstein 1990). When different reference standards are used, 'differential verification bias' may occur. This refers to bias due to the different performance of these different tests. 'Partial verification bias' refers to the use of the reference standard according to the result of the index test (positive or negative).

In studies of the diagnostic accuracy, the performance of the UroVysion FISH assay would ideally be compared to a perfect reference standard, but a perfect reference standard does not exist for the diagnosis of bladder cancer. The reference standard which is used is cystoscopy, with biopsy or resection to confirm the findings of a positive cystoscopy (and to allow histopathology to be performed). This, however, is an imperfect reference standard, as it is possible for cystoscopy findings to be negative in a patient who has bladder cancer. In this review, a study that includes cystoscopy with biopsy or resection as confirmation for positive cystoscopies were graded as high quality. The selection and application of the reference standard is addressed by questions 3, 5 and 6 within the QUADAS tool. Answering yes to each of these questions is considered essential to minimise bias and classify a study as high quality. Studies in which the reference standard was considered inappropriate (answering no to question 3) were classified as low quality.

Methods and criteria used for the selection of the study population

The evaluation of the test in a selected, non-consecutive sample introduces the potential for bias (for example, if the test is used only in those with more severe disease) and compromises the applicability of the results to clinical practice. There is empirical evidence that this problem is greater when data are assessed retrospectively (Lijmer *et al.* 1999). Studies that select a prospective sample of patients on the basis of the same eligibility criteria for testing that will be used in practice were graded as high quality. Studies that enrolled patients retrospectively were graded as fair quality owing to the potential for bias using this method. The selection of the study population is addressed by questions 1 and 2 in the QUADAS tool.

Execution and interpretation of the index test

The accuracy of a test varies according to the additional information available to those interpreting the test (Whiting *et al.* 2004). This is referred to as review bias. In this review, studies that report that the UroVysion FISH assay and the reference standard were interpreted independently (blind to the results of the other test) were graded as high quality. This is addressed by questions 10 and 11 in the QUADAS tool. In addition, an appropriate description of the methods used in performing the UroVysion FISH assay, including the definition of a positive result, was required in order to define a study as high quality. This is addressed by question 8 in the QUADAS tool.

Presentation of results

Studies that do not report on the proportion of eligible patients who were excluded from the analysis (for example, owing to test failure) limit the interpretation of the study findings in clinical practice. To be defined as high quality, studies must have reported any uninterpretable test results, which is addressed by question 13 in the QUADAS tool. In

addition, it was considered essential that studies present all data so that 2×2 tables can be reconstructed for calculations of sensitivity, specificity and LRs. Where 2×2 tables are unable to be reconstructed from available data in the publication, studies could not be classified as high quality.

Data analysis

The characteristics of the study population, type of diagnostic test, reference standard, comparator, study quality and relevant endpoints were extracted for each trial. Where appropriate, the results of eligible studies were statistically synthesised, and pooled results are presented.

Data extraction

Data were extracted using a standardised instrument designed for this review. Data were extracted independently by two reviewers, and any discrepancies were resolved by discussion or a third reviewer if required. The data extraction tables are provided in Appendixes C and D. Where the publications presented percentages only, raw numbers have been determined on the basis of the percentages and the number of patients on which each test was performed. Where raw numbers only are available, percentages have been calculated from the number of patients known to have had the test performed. Where possible, 2×2 tables (Figure 7) to determine data accuracy were reconstructed from data available.

Measurement of test accuracy

The accuracy of a test is determined by its ability to identify the target condition compared to a reference standard test that is used as a proxy for true disease status. Subjects who test positive by the reference standard are classified as having the disease, and those who test negative are classified as disease free.

Results of the test of interest (index test) and reference standard for a group of tested subjects can be summarised in a 2×2 table, as shown in Figure 7.

Figure 7 Two-by-two table displaying the data used to determine test accuracy

		Reference standard: disease +	Reference standard: disease –
Index test	+	true positive (TP)	false positive (FP)
	–	false negative (FN)	true negative (TN)
		TP + FN	TN + FP

Total number of subjects tested = TP + TN + FP + FN
Number of subjects with disease = TP + FN
Number of subjects without disease = TN + FP

As shown, subjects who test positive for the disease of interest by both the index test and the reference standard are recorded as true positives (TP). Subjects without the target condition who test negative by both tests are recorded as true negatives (TN). When there is discordance between the results of the index test and reference standard, the index test result is recorded as a false positive (FP) if it detects the target condition and

the reference standard does not. A false negative (FN) is recorded if the reference standard detects the target condition and the index test does not.

The primary measures of test accuracy used in this review are the sensitivity and specificity of the test and the positive and negative LRs.

Sensitivity and specificity

The sensitivity of a test is the probability of a positive test in subjects with the disease of interest. The specificity of a test is the probability of a negative result in subjects without the disease. The sensitivity and specificity of a test are always considered together and vary according to the threshold used to define a positive test. Sensitivity and specificity vary according to the spectrum of disease (for example, variation in disease severity) in the patient group tested.

Calculation:
Sensitivity = TP / (TP + FN)
Specificity = TN / (TN + FP)

If the sensitivity of a test is sufficiently high, a negative result rules out the disorder. Therefore, high sensitivity is particularly important if the penalty for missing disease is high. If the specificity of a test is sufficiently high, a positive result rules in the disorder. Therefore, high specificity is particularly important if a false positive result can harm the patient.

Positive and negative likelihood ratios

The likelihood ratio of a test is the probability of the test result in patients with the disease compared to those without the disease. This ratio combines the sensitivity and specificity of the test into a single measure that can be used to assist clinical decision-making.

Calculation:
Positive likelihood ratio (LR+) = sensitivity / (1 – specificity)
Negative likelihood ratio (LR–) = (1 – sensitivity) / specificity

In general, positive LRs > 10 and negative LRs < 0.1 can provide convincing diagnostic evidence. Positive LRs > 5 and negative LRs < 0.2 can provide strong diagnostic evidence. An LR of 1 indicates that the test does not provide any useful diagnostic information.

The advantage of using LRs are that they can be used to calculate the post-test probability of disease while adapting for varying prior probabilities drawn from different clinical presentations by using Bayes's theorem, as shown next.

Bayes's theorem

Post-test odds of disease = likelihood ratio × pretest odds of disease,
where odds of disease = probability of disease / (1 – probability of disease).

Where possible, 2×2 tables were reconstructed from the data reported in the included studies to calculate the point estimates for each of these measures and their 95% confidence intervals (95% CI).

Assessment of heterogeneity

The true positive rate (sensitivity) and false positive rate (1 – specificity) from studies assessing the same target condition were plotted in receiver operating characteristic (ROC) space for the assessment of non-random variation in the study results (study heterogeneity), for the presence of a threshold effect for a positive test, and to fit a summary ROC curve to provide a summary of test accuracy and compare tests. The Meta-Disc program was used in the assessment of heterogeneity (Zamora *et al.* 2004). Study heterogeneity was assessed statistically using the LR test.

Conduct of meta-analysis

Pooled estimates of the sensitivity, specificity and positive and negative LRs of the test were calculated if no variation due to a threshold effect or other sources was detected. Studies were excluded from this analysis when the absolute numbers of true positive, true negative, false positive and false negative results for the test could not be extracted from the published paper.

A random effects model (DerSimonian Laird method) was used for this analysis to incorporate variation among studies (Zamora *et al.* 2004). Where appropriate, a chi-squared test was used to compare the pooled sensitivity and specificity between the UroVysion FISH assay and comparator tests, and $P < 0.05$ was considered statistically significant.

Expert advice

An advisory panel with expertise in urology, oncology and pathology was established to evaluate the evidence and provide advice to MSAC from a clinical perspective. In selecting members for advisory panels, MSAC's practice is to approach the appropriate medical colleges, specialist societies and associations and consumer bodies for nominees. Membership of the advisory panel is provided in Appendix B.

Results of assessment

Seven publications were identified as meeting the criteria for inclusion in this review. All were studies of the diagnostic accuracy of the UroVysion FISH assay.

Study descriptions

Seven publications representing seven diagnostic accuracy studies survived the exclusion criteria outlined in Table 12. The details of the study population, tests performed, study inclusion/exclusion criteria and endpoints for each of these studies are presented in Appendix C. The results of the included studies are presented in Appendix D. Table 17 presents the main characteristics of each of the included studies. All studies performed the UroVysion FISH assay in patients being monitored for bladder cancer recurrence. Four types of comparators were studied: cystoscopy, cytology, uCyt+ and the BTA Stat test. The studies included a total of 1072 patients, with sample sizes ranging from 19 to 451, and a median sample size of 86. The samples included patients with a history of bladder cancer, patients being investigated for bladder cancer who had no history of bladder cancer, and healthy controls or patients without suspected bladder cancer. Considering only those patients being monitored for bladder cancer recurrence, there were a total of 558 patients, with the sample sizes in each study ranging from 19 to 176, and a median sample size of 51.

Halling *et al.* (2000) studied 308 patients, including 150 with a history of TCC of the bladder, 115 with a history of bladder cancer being evaluated for a variety of genitourinary signs and symptoms, and 43 healthy controls. The UroVysion test, cystoscopy and cytology were performed in all patients, and 121 patients had biopsies or surgical resections. The voided urine samples used for the FISH analysis were collected immediately before cystoscopy, and cytology results were obtained from specimens obtained no more than 2 weeks before the date of biopsy or resection. Results were presented for all 265 patients being investigated for bladder cancer (whether new or recurrent). Separate results for patients undergoing surveillance for recurrence are limited to specificity alone.

Kipp *et al.* (2005) studied 37 patients receiving intravesical therapy for superficial bladder cancer. Urine specimens for the UroVysion test were collected just before the first intravesical therapy in 31 patients and just before or within 2 months following the last intravesical therapy in all patients. For the purpose of this review, only follow-up UroVysion test results have been used. It appears that the UroVysion test and cystoscopy were performed in all patients, although it is not stated that cystoscopy was performed in all patients. In addition, cytology was performed in a subset of patients, but the UroVysion test and cytology were not directly compared, as there was not enough sample to perform both tests in most patients. Patient clinical follow-up ranged from 6 to 29 months, with a median of 16 months.

Placer *et al.* (2002) studied 86 consecutive patients, 31 of whom were undergoing bladder cancer follow-up, 35 of whom had no history of malignancy, and 10 of whom had prostatism with no history or clinical evidence of TCC of the bladder who acted as controls. The UroVysion test and cystoscopy with biopsy or resection were performed in all patients, although the UroVysion test was unable to be assessed in six patients because of insufficient hybridisation or insufficient cells. Urinary cytology was performed in 83

patients. Results were presented for the 76 patients being investigated for bladder cancer (whether new or recurrent). Separate results for patients undergoing surveillance for recurrence are limited to sensitivity and specificity alone; 2×2 tables could not be reconstructed owing to inconsistencies in the reported data.

Pycha *et al.* (2004) studied 51 consecutive patients under follow-up after complete TUR of intermediate-risk urothelial carcinoma which had occurred at least 6 months previously (with a mean follow-up period of 14.2 months). Two of the 51 patients were not evaluated because of intense granulocytosis and insufficient urothelial cells. The remaining 49 patients were all tested by liquid-based cytology, uCyt+, the UroVysion test and cystoscopy (with resection or biopsy if the cystoscopy was positive). The uCyt+ test is also known as ImmunoCyt, and is a combination of cytology with an immunofluorescence assay, as described in the Background section of this assessment. In this study, patients were classified as having recurrent bladder cancer if there was a histological confirmation of recurrence (from a biopsy or resection during cystoscopy). The timing of the cystoscopies relative to the UroVysion test is not known.

Sarosdy *et al.* (2002) conducted a multicentre prospective study of 451 patients, of whom 176 had a history of TCC of the bladder in the past 9 months, and the remaining 275 were healthy volunteers or patients with benign genitourinary disease, non-bladder genitourinary cancer or genitourinary trauma who acted as controls. The UroVysion test in the 275 controls was a separate study (reported in the same publication). All 176 patients with a history of TCC had the UroVysion test, the BTA Stat test, cytology and cystoscopy (with biopsy, resection or ablation when positive). Among the 176 patients, there were 309 visits, with 251 of these visits being classified as assessable. Only one visit per patient was included in the data analysis, being the earliest visit at which recurrence was recorded in patients with recurrence, and the latest trial visit for patients without recurrence.

Skacel *et al.* (2003) performed a retrospective study on 120 urine samples from patients with atypical, suspicious and negative cytology for whom concurrent and follow-up bladder biopsy data were available. The primary purpose of the study was to analyse the efficacy of the UroVysion test for resolving equivocal results of urinary cytology. Ninety-four of the patients had a previous diagnosis of biopsy-proven TCC of the bladder, while 26 had no history of bladder cancer and were being investigated for haematuria or unexplained urgency. Archived urine samples were used, 47 being collected via a voided urine specimen and 73 via instrumented urine specimens. All included specimens had an accompanying bladder biopsy within 7 days after cytology examination. Before the UroVysion test was performed, the specimens were re-reviewed to confirm the original cytological diagnosis. Results were presented for all 120 patients (whether with a history of bladder cancer or not). Separate results for the 94 patients with a previous diagnosis of TCC are limited to sensitivity alone.

Varella-Garcia *et al.* (2004) conducted a prospective study in 19 patients being monitored for recurrence of bladder cancer. All patients underwent the UroVysion test, cytology and cystoscopy, and patients who had tumours identified on cystoscopy received biopsy or surgery.

Table 17 Descriptive characteristics of included studies

Author & year	Strength of evidence[1]	*N*	Study population	Index test	Comparators	Reference standard
Halling *et al.* (2000)	Fair	308 (150 patients undergoing follow-up; 115 patients under investigation for haematuria or other genitourinary signs or symptoms; 43 healthy controls)	All patients (excluding controls for whom characteristics are not reported): 200 male, 65 female; mean age 69.7 years, median 71 years (range 36–94)	UroVysion FISH assay (positive = ≥5 cells with polysomy)	Cytology	Cystoscopy with biopsy (unclear when biopsy performed) with clinical follow-up
Kipp *et al.* (2005)	Low	37 (all patients receiving intravesical therapy for superficial bladder cancer)	Follow-up patients: 36 male, 1 female Mean age 72.2 years, median 75.3 (range 50.2–86.4) Initial tumour stage: Ta 17 patients, T1 5 patients, Tis 15 patients	UroVysion FISH assay (positive = ≥5 cells with polysomy, ≥10 cells with trisomy or >20% cells with 9p21 homozygous deletion)	Not identified	Cystoscopy/biopsy or cytology; Tumour recurrence scored as positive for positive biopsy, positive cystoscopy or positive cytology
Placer *et al.* (2002)	Fair	86 (34 patients undergoing follow-up; 42 patients under investigation for symptoms suggestive of bladder cancer, 10 controls)	All patients: 76 male, 10 female; mean age 70 years (range 28–90)	UroVysion FISH assay (positive = ≥5 cells with polysomy or >50% cells with loss of both 9p21 signals)	Cytology	Cystoscopy with biopsy or resection for positive cystoscopies
Pycha *et al.* (2004)	Fair	51 (all patients under follow-up following TUR)	Follow-up patients: Mean age 72.2 years (range 52–93) Initial tumour stage or grade: pTaG1 16 patients, pTaG2 30 patients, pT1G2 5 patients (2 patients not assessed)	UroVysion FISH assay (positive = ≥5 cells with polysomy)	Liquid-based cytology and uCyt+	Cystoscopy with biopsy or resection for suspicious cystoscopies
Sarosdy *et al.* (2002)	Fair	451 (176 patients undergoing follow-up; 275 controls)	Follow-up patients: 132 male, 44 female; mean age 71 years (range 36–98) Initial tumour stage: Ta 67%, T1 11%, ≥T2 2%, Tis 16%, unknown 3% Initial tumour grade: G1 40%, G2 32%, G3 26%, unknown 2%	UroVysion FISH assay (positive result reported as being performed according to the manufacturer's specifications)	Cytology and BTA Stat	Cystoscopy with biopsy or where a lesion was fulgurated or ablated on cystoscopy. A case was considered positive only if the cystoscopy was unequivocal
Skacel *et al.* (2003)	Fair	120 (94 patients undergoing follow-up; 26 patients under investigation for haematuria or unexplained urgency)	All patients: sex and age not reported	UroVysion FISH assay (positive = ≥5 cells with gain of 2 or more of chromosomes 3, 7 or 17, or ≥12 cells with 9p21 deletion or ≥10% of cells with isolated trisomy of 1 of chromosomes 3, 7 or 17)	Liquid-based cytology	Cystoscopy with biopsy and a minimum of 12 months' post-biopsy follow-up
Varella-Garcia *et al.* (2004)	High	19 (all undergoing follow-up)	Follow-up patients: 16 male, 3 female Mean age 68 years (range 58–80)	UroVysion FISH assay (positive = >16% cells with polysomy or >48% cells with 9p21 homozygous loss among at least 50 scored nuclei)	Cytology	Cystoscopy with biopsy or resection for positive cystoscopies

[1] The components of strength of the evidence are outlined in Table 14. High is defined as studies which have an appropriate comparison, applicable population and high quality. Fair is defined as studies which have either an appropriate comparison or applicable population and fair or high quality. Low is defined as studies which have neither an appropriate comparison or applicable population or low quality.

Table 17 shows that there was a predominance of males in the included studies; the average age of patients ranged from 68 to 72.2 years, with a median average age of 70.5 years; and, where reported, Ta was the most common initial tumour stage. The UroVysion FISH assay was performed for all patients in all studies, but the definition of a positive UroVysion test differed between studies. Most studies required at least 5 cells with polysomy. As outlined in the Background section of this report, there are no universally accepted criteria for defining positivity (Placer *et al.* 2002). The difference in criteria between studies may mean that sensitivity and specificity estimates are not directly comparable between studies.

The reference standard used also differed among the seven studies. As discussed in the Background section, there is an imperfect reference standard for the detection of bladder cancer recurrence – cystoscopy with histopathology from a bladder biopsy or resection in patients with positive or suspicious cystoscopies, unless the positive cystoscopy result was unequivocal and the lesion was destroyed (for example, by laser treatment or diathermy), in which case the patient is considered positive for bladder cancer. The reference standard was considered appropriate in six of the seven studies, of which most classed a patient as positive for bladder cancer (recurrence) only if the patient had a positive or suspicious cystoscopy with positive histology. In the study by Kipp *et al.* (2005), a patient was classified as positive if there was a positive biopsy, positive cystoscopy or positive cytology. This is considered an inappropriate reference standard, as both a positive cystoscopy alone (that is, without positive histology) and positive cytology are known to have false positive rates (and, thus, this reference standard will overestimate the number of patients with bladder cancer).

Study appraisal

Quality assessment

Study quality was assessed using the QUADAS tool as outlined in Table 16, with question 7 removed as it was not considered relevant (refer to the Approach to Assessment section of this report for more detailed information). Table 18 presents summary results of the quality of the seven studies included in this review.

Table 18 Quality assessment of included studies

QUADAS tool question	Author & year						
	Halling *et al.* (2000)	Kipp *et al.* (2005)	Placer *et al.* (2002)	Pycha *et al.* (2004)	Sarosdy *et al.* (2002)	Skacel *et al.* (2003)	Varella-Garcia *et al.* (2004)
1. Was the spectrum of patients representative of the patients who will receive the test in practice?	Y	Y	Y	Y	Y	U	Y
2. Were selection criteria clearly described?	N	N	N	Y	Y	Y	N
3. Is the reference standard likely to correctly classify the target condition?	Y	N	Y	Y	Y	Y	Y
4. Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	Y	N	U	U	Y	Y	Y
5. Did the whole sample or a random selection of the sample receive verification using a reference standard of diagnosis?	U	U	Y	Y	Y	Y	Y
6. Did patients receive the same reference standard regardless of the index test result?	Y	U	Y	U	Y	Y	Y
8. Was the execution of the index test described in sufficient detail to permit replication of the test?	Y	Y	Y	Y	U	Y	Y
9. Was the execution of the reference standard described in sufficient detail to permit its replication?	N	N	N	N	N	N	N
10. Were the index test results interpreted without knowledge of the results of the reference standard?	Y	Y	Y	U	Y	Y	Y
11. Were the reference standard results interpreted without knowledge of the results of the index test?	Y	U	U	U	Y	Y	Y
12. Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	N	N	U	U	U	U	U
13. Were uninterpretable or intermediate test results reported?	Y	N/A	Y	Y	N	N/A	N/A
14. Were withdrawals from the study explained?	N/A	N/A	N/A	Y	Y	N/A	N/A

Y = yes; N = no; U = unclear; N/A = not applicable

Table 18 shows that, in general, the included studies did not perform well when assessed using the QUADAS tool (with question 7 excluded), with no study receiving yes answers to all questions, and many studies being classified as unclear on dot points owing to a lack of reporting.

The four criteria which were considered essential components in this review for a classification of a high-quality study of diagnostic test accuracy were the selection and application of the reference standard, methods and criteria used for the selection of the study population, the execution and interpretation of the index test, and presentation of results. The selection of the reference standard was appropriate in all studies except for Kipp *et al.* (2005), for reasons discussed previously. In addition, the application of the reference standard was unclear in two studies (Placer *et al.* 2002, Pycha *et al.* 2004), with the timing of the cystoscopy relative to the UroVysion test being unclear. If the reference standard and index test (that is, cystoscopy and the UroVysion test) are not performed at similar time periods (or, more accurately, the urine specimen is not obtained at a similar time to the cystoscopy), then the patient's disease status may change between the two tests.

The methods and criteria used for the selection of the study population were defined and appropriate in fewer than half of the included trials. Four of the included studies did not report the inclusion/exclusion criteria used to select patients (Halling *et al.* 2000, Placer *et al.* 2002, Varella-Garcia *et al.* 2004, Kipp *et al.* 2005), and a further study selected patients retrospectively (Skacel *et al.* 2003). Patients selected retrospectively may not be representative of the patient group of interest, owing to the opportunity for selectively including or excluding patients with certain characteristics or ranges of results (known as selection bias). In Skacel *et al.* (2003), the patients selected had archived urine samples and had bladder biopsies performed at the time of the original urine sample collection, as well as at least 12 months of bladder biopsy follow-up. These patients may not be representative of those in whom the UroVysion test will be used in clinical practice, as it is possible that patients who have had biopsies performed are more likely to have a recurrence.

The execution and interpretation of the index test was appropriate in all included studies, with the exception of Sarosdy *et al.* (2002) and Pycha *et al.* (2004). In Sarosdy *et al.* (2002), the UroVysion test was performed according to the instructions on the product labelling, but it is unclear what these instructions were, or what the criteria used to define a positive test were. In Pycha *et al.* (2004), it is unclear whether the results of the reference standard (that is, the cystoscopy with or without biopsy or resection) were available to those interpreting the UroVysion test. If those interpreting the UroVysion test were not blinded to the results of the reference standard, review bias may occur, in that the interpretation of the UroVysion test may have been influenced by knowledge of the reference standard. All other included studies reported that those interpreting the UroVysion test were not aware of the results of the reference standard.

The presentation of results was considered an essential component in defining the quality of a study. All studies other than Sarosdy *et al.* (2002) reported on uninterpretable test results or test failure. In all of the studies except Halling *et al.* (2000), 2×2 tables were able to be reconstructed, although in two of these studies (Placer *et al.* 2002, Skacel *et al.* 2003), 2×2 tables could only be reconstructed for all patients, and separate tables for patients being monitored for recurrence could not be constructed. Furthermore, in two studies (Placer *et al.* 2002, Sarosdy *et al.* 2002), data in the 2×2 tables (with subsequent

calculations) disagreed with values presented in the text. In this situation, data from the tables were used in this assessment.

On the basis of the criteria considered essential components for high-quality studies, only one of the included studies was classified as high quality (Varella-Garcia *et al.* 2004), one was classified as low quality (Kipp *et al.* 2005), and the remaining five studies were classified as fair quality (for further detail, refer to Appendix C).

Generalisability of results

In drawing conclusions from this review, it is essential to consider the population of patients to whom the results apply. The spectrum of patients in each of the included studies differs, and factors such as tumour grade, tumour stage and tumour number are known to influence the accuracy of the UroVysion test. In clinical practice, the results of this review should be applied only to patients who are similar to those in the included studies.

In evaluating the included studies and drawing conclusions from their results, it is also important to consider the applicability of the results to clinical practice in Australia. None of the seven included trials were conducted in Australia, and practice in other countries (including UroVysion technique, pathology practice, cystoscopy practice) may differ. Furthermore, only one of the included studies described the cystoscopy technique used (Varella-Garcia *et al.* 2004 reported that flexible cystoscopy was performed in the outpatient clinic), and no study reported whether the cystoscopy was performed under general or local anaesthetic. Therefore, the results must be interpreted with caution, particularly as the rate of false negatives may differ with different cystoscopy techniques.

Is it safe?

None of the seven studies included in this review reported complications from the UroVysion test, cystoscopy or any of the comparators. As the UroVysion FISH Assay is a non-invasive test performed on voided urine, there are minimal or no risks to the safety of the patient providing the urine sample. As urine is a body fluid, universal blood and body fluid precautions should be followed to ensure the safety of staff involved in the collection, transport and analysis of the urine sample.

In comparison to the UroVysion test, cystoscopies are invasive procedures and are associated with known adverse effects. These include minor complications such as bleeding, urinary frequency, stranguria and urinary tract infections. Serious adverse events such as bladder rupture are rare, although there are minimal data on the incidence rates, as most reports of serious adverse effects are case reports.

Burke *et al.* (2002) investigated the morbidity after flexible cystoscopy in 420 patients. They found that flexible cystoscopy is well tolerated, although gross haematuria, urinary frequency and dysuria are common. Fifty per cent of patients reported dysuria, with then pain resolving in less than 24 hours in more than half of the patients and in less than 48 hours in more than 85% of the patients. Thirty-seven per cent of patients reported urinary frequency, most of less than 48 hours. Nineteen per cent of patients reported gross haematuria, with the haematuria resolving in less than 48 hours in more than 80% of these patients. In addition, 2.7% of patients developed urinary tract infections.

Vriesema *et al.* (2000) conducted a study investigating patient opinion of urinary tests versus cystoscopy in patients undergoing follow-up for superficial bladder cancer. They found that subjective morbidity due to cystoscopy was low, with stranguria the most frequently noted side-effect. They found that stranguria always occurred in 27% of patients, and regularly occurred in 19%, but it usually resolved spontaneously within 2 days. On the basis of the above studies, it would appear that the incidence of serious complications following cystoscopy is rare, and the minor complications that occur are likely to resolve spontaneously within 48 hours and therefore are of minimal clinical significance.

The adverse effects which may occur as a result of the use of the UroVysion test in clinical practice relate to false positives resulting in patients undergoing a cystoscopy under GA (when the patient would otherwise have undergone a cystoscopy under LA). Denholm *et al.* (1990) reported on morbidity following cystoscopy in 100 patients undergoing LA flexible cystoscopy and 100 patients undergoing GA rigid cystoscopy. They found that the incidence of postoperative symptoms was 33% following flexible cystoscopy and 76% following rigid cystoscopy, and patients undergoing surveillance cystoscopy had lower morbidity in both groups. No major postoperative complications were reported, only minor complications such as dysuria, frequency and haematuria. The difference between the GAL and LA complications should be interpreted with caution, as the study was non-randomised and the indications for cystoscopy differed between the groups: more patients in the LA group underwent surveillance cystoscopy, whereas more patients in the GA group were underwent cystoscopy for investigation of genitourinary symptoms. No additional data were identified specifically quantifying the risk of LA versus GA in patients undergoing a urological procedure. The risks of a GA compared to LA, however, are minor, and unlikely to be of clinical importance in patients undergoing cystoscopy.

Is it effective?

All seven studies provided information about the performance of the UroVysion test in patients being monitored for bladder cancer. Four provided sufficient information to enable 2×2 tables to be reconstructed (Sarosdy *et al.* 2002, Pycha *et al.* 2004, Kipp *et al.* 2005, Varella-Garcia *et al.* 2004. The ROC plane showing the characteristics of these four studies is shown in Figure 8, and the sensitivity and specificity of the UroVysion test from each of the seven studies are shown in Table 19.

Table 19 Summary of sensitivity and specificity estimates for patients being monitored for bladder cancer recurrence

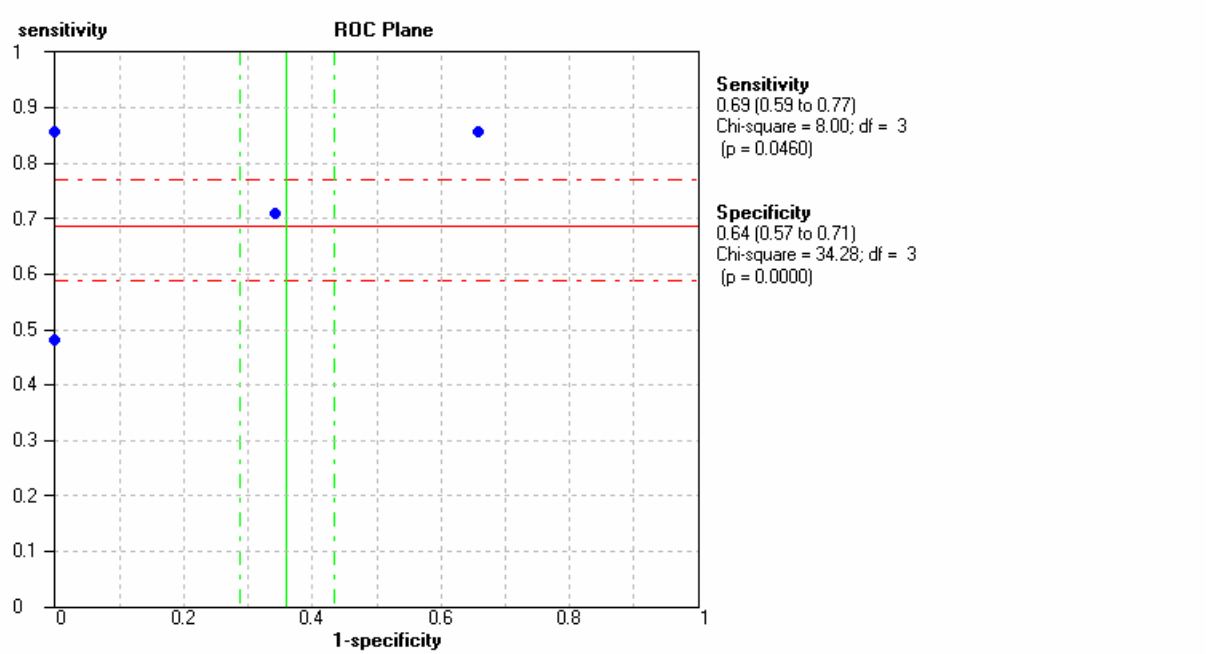
Study	*n*[1]	Sensitivity (95% CI)	Specificity (95%CI)
Halling *et al.* (2000)	150	–	76.1% (CI unknown)
Kipp *et al.* (2005)	37	48.0% (27.8%–68.7%)	100% (73.5%–100%)
Placer *et al.* (2002)	31	70.6% (CI unknown)	79.2% (CI unknown)
Pycha *et al.* (2004)	49	85.7% (57.2%–98.2%)	34.3% (19.1%–52.2%)
Sarosdy *et al.* (2002)	176	71.0% (58.1%–81.8%)	65.8% (56.3%–74.4%)
Skacel *et al.* (2003)	94	86% (CI unknown)	–
Varella-Garcia *et al.* (2005)	19	85.7% (42.1%–99.6%)	100% (73.5%–100%)

[1] *n*: Number of patients being monitored for bladder cancer recurrence for which results are available.

Table 19 shows that there is large variation in both the sensitivities and specificities reported in the included studies. Given the variability in the reported values of sensitivity and specificity, it is not appropriate to pool the estimates to obtain one overall estimate. The sensitivity ranged from 48.0% in the trial by Kipp *et al.* (2005) to 86% in the trials by Skacel *et al.* (2003) (test for heterogeneity: $\chi^2 = 8.00$, $P = 0.046$). The specificity ranged from 34.3% in the trial by Pycha *et al.* (2004) to 100% in the trials by Kipp *et al.* (2005) and Varella-Garcia *et al.* (2005) (test for heterogeneity: $\chi^2 = 34.28$, $P < 0.001$).

The ROC plane shown in Figure 8 explores whether a diagnostic test threshold explains some of the variability among trial results. The diagnostic test threshold refers to the variation that may occur among results of different studies owing to either implicit or explicit use of different thresholds to define a positive result (Irwig *et al.* 1995). Where a diagnostic test threshold effect exists, a curvilinear pattern in seen among the points on the ROC plane. As a curvilinear pattern is not obvious among the points in the ROC plane (Figure 8), a threshold effect does not explain the variability in the four studies. Thus, an ROC curve has not been fitted to the data. Differences in the types of patients included in the trials, the reference standard used and the quality of the trials are likely to contribute to some of the heterogeneity among results.

Figure 8 ROC plane



The poor-quality trial by Kipp *et al.* (2005) found a low sensitivity (48.0%) relative to the other included studies. This may be due to the reference standard that was used in the trial, where a patient was defined as having a recurrence if they had a positive biopsy, positive cystoscopy or positive cytology. Given the known poor accuracy of cytology, patients may have been classed as having a recurrence due to positive cytology when there was no recurrence present. This misclassification would result in a lower reported sensitivity of the UroVysion test. Furthermore, the trial by Kipp *et al.* (2005) included only patients who were receiving intravesical therapy, and thus this different patient group may explain the low sensitivity found relative to the results of the other included studies. A low specificity (34.3%) was found in the trial by Pycha *et al.* (2004). This trial is of similar quality to most of the included trials (fair quality), and the patient group is not dissimilar

to those in most included studies. Hence, the low specificity in the trial by Pycha *et al.* (2004) does not appear to be explained by either the trial quality or the type of included patients.

Further variation among the results in Table 19 may be explained by differences in the number and type of patients enrolled in the trial and the prevalence of recurrence. The stage and grade of the initial tumour in patients being monitored for recurrence is known to affect the sensitivity and specificity of the UroVysion test, but as only three studies (Sarosdy *et al.* 2002, Pycha *et al.* 2004, Kipp *et al.* 2005) provided information about the initial tumour grade or stage, it is difficult to examine whether difference between studies account for differences in results. Only one of the included studies presented results (in patients being monitored for bladder cancer recurrence) of the UroVysion test by the stage or grade of recurrence (Sarosdy *et al.* 2002). The results table in Appendix D shows that in the trial by Sarosdy *et al.* (2002), the sensitivity of the UroVysion test improves with either higher grades or higher stages. The results are shown in Table 20.

Table 20 Sensitivity of the UroVysion test by stage and grade (Sarosdy *et al.* 2002)

Stage	Sensitivity (*n*)
TaG12	62% (16/26)
TaG3	83% (5/6)
T1G2	100%(2/2)
T1G3	75% (3/4)
T2	100% (3/3)
Tis	100% (7/7)
Grade	**Sensitivity (*n*)**
1	55% (12/22)
2	78% (7/9)
3	94% (17/18)

The above results suggest that if a higher proportion of patients in a study have a higher stage or higher grade tumour, the sensitivity of the UroVysion test would be expected to be higher. An additional three of the included studies (Halling *et al.* 2000, Placer *et al.* 2002, Skacel *et al.* 2003) presented the sensitivity of the UroVysion test by stage or grade of the recurrent tumour, but these results were available only in all patients, and were not available only in patients with a history of bladder cancer (that is, the patient group which is the focus of this review). These three studies all showed an improvement in sensitivity, with an increase in stage or grade.

Clinical interpretation

In current clinical practice in Australia, patients with a history of TCC of the bladder undergo regular follow-up to monitor for recurrence. This follow-up consists of regular cystoscopies, usually under LA, to allow visualisation of any recurrent tumours. Those patients who are found to have a recurrence then undergo a cystoscopy under GA to allow for treatment such as a TUR.

The results of the UroVysion test may be used in clinical practice to inform whether a patient undergoes a cystoscopy under LA or GA. A further role of the UroVysion test

could involve using the results to delay cystoscopy (for example, until the next scheduled cystoscopy in routine follow-up, thereby reducing the number of cystoscopies performed). The clinical impact of the UroVysion tests in these situations can be considered by using the estimates of the accuracy of the UroVysion test from the included studies to patients classified according to their risk of recurrence. This is done using estimates of the LRs of the test.

Table 21 shows the positive and negative LRs for the four studies for which 2×2 tables could be reconstructed. A positive LR refers to how much more frequent a positive UroVysion result is among those with a recurrence than in those without a recurrence. Conversely, a negative LR refers to how much more frequent a negative UroVysion result is among those without a recurrence than in those with a recurrence.

Table 21 Positive and negative likelihood ratios

Study	Positive LR (95% CI)	Negative LR (95%CI)
Kipp *et al.* (2005)	12.5 (0.8–195.0)	0.5 (0.4–0.8)
Pycha *et al.* (2004)	1.3 (0.9–1.8)	0.4 (0.1–1.6)
Sarosdy *et al.* (2002)	2.1 (1.5–2.8)	0.4 (0.3–0.7)
Varella-Garcia *et al.* (2005)	21.1 (1.4–326.6)	0.2 (0.05–0.8)

Statistical testing revealed significant heterogeneity among the positive LRs from the four studies ($\chi^2 = 14.01$, $P = 0.003$). The heterogeneity among the negative LRs was not significant ($\chi^2 = 2.49$, $P = 0.48$), but the test may be underpowered to detect differences between studies.

In general, positive LRs >10 and negative LRs <0.1 can provide convincing diagnostic evidence. In Table 21, the studies by Kipp *et al.* (2005) and Varella-Garcia *et al.* (2005) provide strong evidence for the use of the UroVysion test to diagnose recurrence, but the trials by Pycha *et al.* (2004) and Sarosdy *et al.* (2002) do not show a use for the UroVysion test (as a positive test is only slightly more likely in a patient with recurrence and, thus, the test does not provide additional clinical information which may change patient management). Thus, the evidence for the use of the UroVysion test in the diagnosis of recurrence is inconsistent. The negative LR from the Varella-Garcia *et al.* (2005) trial shows that the UroVysion test may be of use in excluding recurrence, but the negative LRs of 0.4 or 0.5 from each of the other three trials do not provide sufficient evidence to rule out recurrence, so a cystoscopy would still be performed in clinical practice.

Using Bayes's theorem as outlined on page 29, the post-test probability of a patient having recurrence (or of missing a recurrence) can be determined using different pretest probabilities of recurrence and the LRs. Given the variation in LRs within the included studies, the post-test probabilities have been calculated for each of the reported LRs to determine the potential impact on clinical decision-making for a range of possible LRs. The pretest probabilities are based on known recurrence rates from a cohort study of 1529 patients with primary superficial bladder cancer followed for a period of 5 years (Millan-Rodriguez *et al.* 2000). In the study, recurrence rates at various time points are presented, both overall and for individual risk groups. The study shows that for all risk groups (low, intermediate and high), the risk of recurrence increases with time (for example, a low-risk patient at 3 months has a probability of recurrence of 2%, increasing to 15% at 1 year and 45% at 5 years). The study also shows that the probability of

recurrence varies between risk groups (for example, at the 3-month follow-up, a low-risk patient has a 2% probability of recurrence, an intermediate-risk patient has a 4% probability, and a high-risk patient has a 9.4% probability). The post-test probabilities are shown in Table 22.

Table 22 Post-test probability of recurrence given various pretest probabilities and likelihood ratios

Pretest probability of having recurrence[1]	Positive LR	Post-test probability of detecting recurrence	Negative LR	Post-test probability of missing recurrence
2% (probability of recurrence in low-risk patient at 3 months)	1.3	2.58%	0.2	0.41%
	2.1	4.11%	0.4	0.81%
	12.5	20.33%	0.5	1.01%
	21.1	30.10%		
4% (probability of recurrence in intermediate-risk patient at 3 months)	1.3	5.14%	0.2	0.83%
	2.1	8.05%	0.4	1.64%
	12.5	34.25%	0.5	2.04%
	21.1	46.78%		
9.4% (probability of recurrence in high-risk patient at 3 months)	1.3	11.88%	0.2	2.03%
	2.1	17.89%	0.4	3.98%
	12.5	56.46%	0.5	4.93%
	21.1	68.64%		
15% (probability of recurrence in low-risk patient at 1 year)	1.3	18.66%	0.2	3.41%
	2.1	27.04%	0.4	6.59%
	12.5	68.81%	0.5	8.11%
	21.1	78.83%		
26% (probability of recurrence in intermediate-risk patient at 1 year)	1.3	31.35%	0.2	6.57%
	2.1	42.46%	0.4	12.32%
	12.5	81.45%	0.5	14.94%
	21.1	88.11%		
39% (probability of recurrence in high-risk patient at 1 year)	1.3	45.39%	0.2	11.34%
	2.1	57.31%	0.4	20.37%
	12.5	88.89%	0.5	24.22%
	21.1	93.10%		
45% (probability of recurrence in low-risk patient at 5 years)	1.3	51.54%	0.2	14.06%
	2.1	63.21%	0.4	24.66%
	12.5	91.09%	0.5	29.03%
	21.1	94.52%		
53% (probability of recurrence in intermediate-risk patient at 5 years)	1.3	59.45%	0.2	18.40%
	2.1	70.31%	0.4	31.09%
	12.5	93.38%	0.5	36.05%
	21.1	95.97%		
61% (probability of recurrence in high-risk patient at 5 years)	1.3	67.03%	0.2	23.83%
	2.1	76.66%	0.4	38.49%
	12.5	95.13%	0.5	43.88%
	21.1	97.06%		

[1]The probabilities are taken from a cohort study of 1529 patients by Millan-Rodriguez *et al.* (2000), where risk groups are defined as follows:
Low risk: Grade 1 stage Ta; Grade 1 stage T1 with single tumour
Intermediate risk: Grade 1 stage T1 with multiple tumours; Grade 2 stage Ta; Grade 2 stage T1 with single tumour
High risk: Grade 2 stage T1 with multiple tumours; Grade 3 stage Ta; Grade 3 stage T1; CIS

Table 22 shows that among patients at low risk of recurrence, a positive UroVysion test increases the probability of a recurrence, but this increase is only small—for example, the probability of a low-risk patient having a recurrence at their 3-month follow-up increases from 2% to a maximum of 30.10% in the best-case scenario of a positive LR of 21.1. Thus, if the UroVysion test were used in this population to determine whether a patient undergoes a cystoscopy under GA, 69.90% of patients would undergo a GA unnecessarily. The clinical value of the UroVysion test is improved when patients have a higher risk of recurrence. For example, in patients with a high-risk of recurrence at their 1-year follow-up, the probability of recurrence increases from 39% to 93.10% in the best-case scenario (that is, a positive LR of 21.1). In this situation, only 6.90% of patients would undergo a GA unnecessarily, while most patients would correctly undergo only one cystoscopy instead of two. This scenario assumes a positive LR of 21.1. In reality, the true LR is unknown and is likely to be lower than 21.1. In this situation, the benefit of a positive UroVysion test is less clear.

Table 22 also shows the probability of missing a recurrence. In the situation where the UroVysion test is always used in conjunction with cystoscopy, this is not of major concern, as the tumour would be detected by cystoscopy. However, if the UroVysion test were to be used to delay performing a cystoscopy, this is of much greater clinical importance. In patients with very-low risks of recurrence (for example, low-risk patients at their three-month follow-up), the probability of missing a recurrence is very small. However, in patients with an intermediate or high probability of recurrence, a significant proportion of recurrent tumours may be missed if a negative UroVysion test results in a delayed cystoscopy. For example, in high-risk patients at the 1-year follow-up, up to 24.2% of recurrent tumours will be missed by the UroVysion test. Under the best-case scenario of a negative LR of 0.2, more than 11% of recurrent tumours will still be missed.

The clinical value of the UroVysion test in informing the choice of whether follow-up cystoscopy is performed under LA or GA is considered in the economic analysis (next main section).

Other information

Four of the included studies report on patients with positive UroVysion tests and negative cystoscopies that were subsequently followed up over time. In the study by Sarosdy *et al.* (2002), 36 patients with positive UroVysion results had negative cystoscopies. Continued longitudinal follow-up showed that 15 (41.1%) of these 36 patients had visually evident tumours on subsequent cystoscopy confirmed by biopsy, with a time to tumour diagnosis of between 3 and 16 months. Halling *et al.* (2000) reported on 11 patients with positive UroVysion tests but negative biopsies who had a follow-up biopsy (follow-up time ranging from 3 to 12 months); seven (64%) had a positive biopsy. Skacel *et al.* (2003) reported on nine patients with a positive UroVysion test with concurrent negative biopsies. Eight (89%) had biopsy-proven TCC within 12 months of the date when the sample for the UroVysion test was obtained. Placer *et al.* (2002) reported on five patients with positive UroVysion tests and negative cystoscopy. After 1 year of follow-up, a recurrence was detected in one (20%) of the five patients.

It is possible that the cases reported above represent patients with tumours at the time of the UroVysion test (where the lesions are missed by urologists performing the cystoscopies or malignant cells are shed before the tumour is visible grossly), or that the positive UroVysion test was indicating premalignant changes in cells. In the study by

Sarosdy *et al.* (2002), among patients with negative cystoscopies there was a significant difference in the time to recurrence between those with positive UroVysion tests and those with negative UroVysion tests ($P = 0.003$). In the absence of a positive cystoscopy, treatment of a tumour is unlikely to occur (for example, in the absence of a visually evident tumour, a resection cannot be performed).

Test failures

Four of the included studies report UroVysion test failures, but the remaining three studies do not report any. Halling *et al.* (2000) reported that among 75 patients with biopsy-proven urothelial carcinoma, there were inadequate cells for FISH in two cases (2.7%). These 75 patients included both patients who were being monitored for recurrence and patients without a history of urothelial carcinoma being investigated for possible carcinoma. Among the 47 cases with a history of urothelial carcinoma that had a negative biopsy, FISH results were available in 46. The reason why a FISH result was not available in one patient is not reported. Placer *et al.* (2002) report that among 86 patients, it was impossible to count assessable FISH signals in six cases (6.9%) because of insufficient hybridisation or insufficient cells. As with Halling *et al.* (2000), these patients included both patients who were being monitored for recurrence and patients without a history of urothelial carcinoma being investigated for possible carcinoma, as well as ten control patients. Pycha *et al.* (2004) reported that 2 of 51 patients could not be evaluated owing to intense granulocytosis and insufficient urothelial cells. Sarosdy *et al.* (2002) reported on 251 assessable office visits by 176 patients. Among these, 234 provided evaluable FISH results, and of these, one visit per patient was included. The reasons why 17 of the visits did not provide evaluable FISH results are not presented.

As some of the studies reporting test failures do not report failures specifically in patients being monitored for recurrence, it is not possible to estimate the proportion of UroVysion tests performed which are likely to be failures in the patient group of interest. Assuming that the failure rate is similar in both those being monitored for recurrence and those without a history of bladder cancer being investigated for signs and symptoms of possible cancer, it appears that there will be test failures in only a small percentage of patients.

What are the economic considerations?

Economic evaluation compares the expected cost and effects of alternative diagnostic strategies in a defined treatment population.

When considering the cost-effectiveness of diagnostic procedures, the following questions should be asked:

1. How accurate is the test?
2. How does using the test change practice or treatment paths of patients?
3. What are the cost and effect implications of changes in practice and treatment paths?

With respect to the first question, previous analysis in this report has assessed the evidence of the accuracy of the UroVysion test in diagnosing recurrence of bladder cancer.

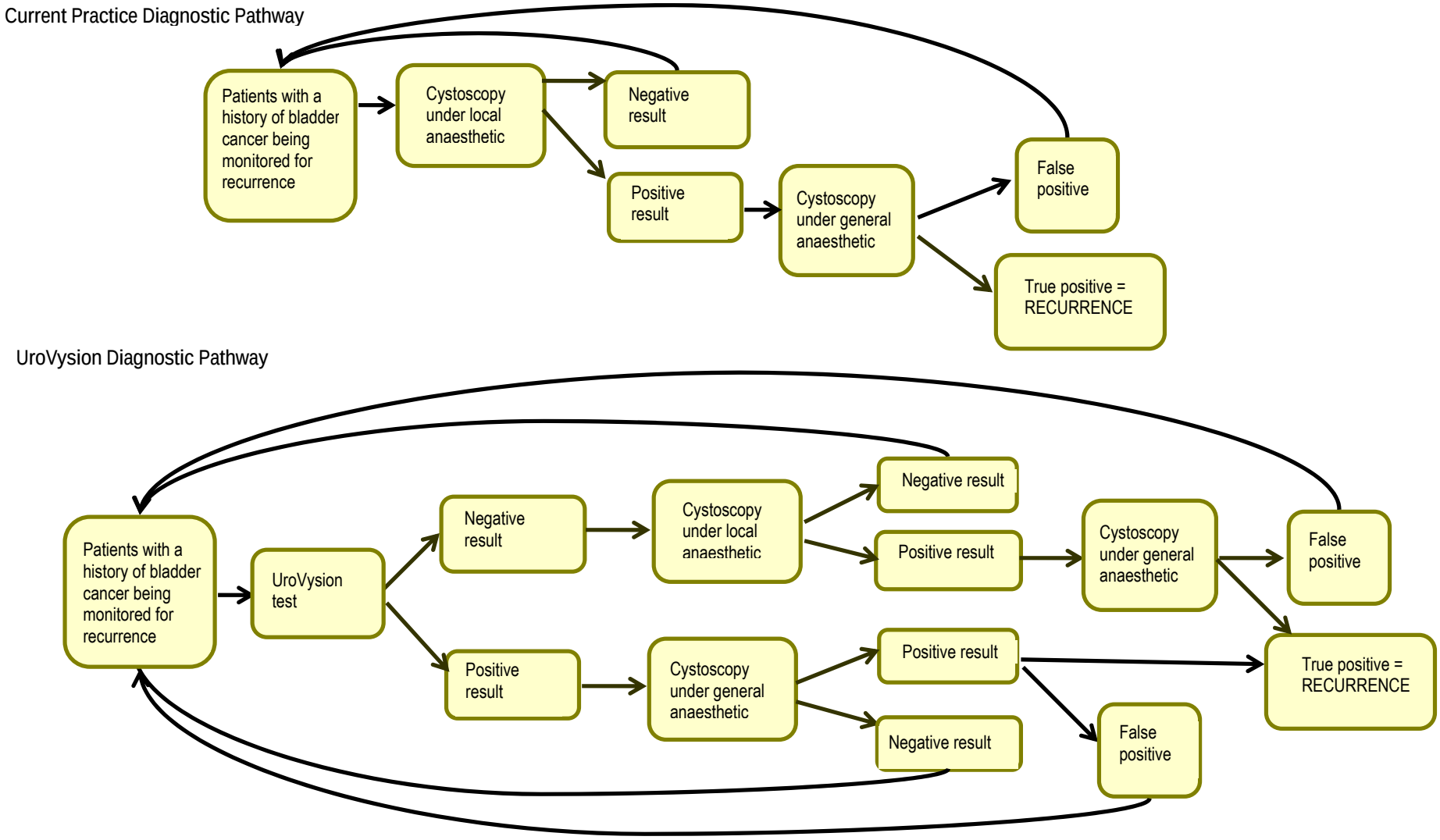
With respect to the second question, diagnostic pathways for use of the UroVysion FISH assay relative to those of current practice have been identified on the basis of the expert opinion of the advisory panel. In current practice, patients with a history of TCC of the bladder undergo regular follow-up to monitor for recurrence. This follow-up consists of regular cystoscopies, usually under LA, to allow visualisation of any recurrent tumours. Those patients who are found to have a recurrence then undergo a cystoscopy under GA to allow for treatment such as a TUR to occur. The proposed diagnostic pathway which includes the UroVysion FISH assay has been identified as the UroVysion test, followed by cystoscopy with LA in patients with a negative UroVysion result, and cystoscopy under GA in patients with a positive UroVysion result. These pathways are shown in Figure 9.

With respect to the third question, the expected incremental cost of using the UroVysion FISH assay clinical pathway relative to the current practice diagnostic pathway has been modelled in patients with a history of TCC of the bladder undergoing regular surveillance for recurrence. Based on expert opinion, this surveillance occurs at 3, 6, 12, 18 and 24 months and then yearly until recurrence or completion of the model at 5 years (Advisory Panel, February 2005). The model is based on the diagnostic pathways outlined (see Figure 9), evidence of the accuracy of the test, the probability of recurrence over time, and the costs associated with treatment.

Existing literature

None of the seven publications assessed in this review presented information regarding the economic impact of the UroVysion test. A further literature search was conducted to determine whether any economic evaluations of the UroVysion test exist. This literature search involved adding the search term (cost$ or econ$).mp to the literature searches outlined in Tables 7 to 9, as well as searching the electronic databases and heath technology assessment websites outlined in Table 10. No economic evaluations of the UroVysion FISH assay were identified by the literature search.

Figure 9 Diagnostic pathways – current clinical practice, and proposed use of the UroVysion test



Approach of the modelled economic evaluation

The economic evaluation is designed to estimate the costs of the alternative clinical pathways for the monitoring of bladder cancer recurrence as outlined in Figure 9. In the model, only the costs of the cystoscopy procedures and the UroVysion test are considered. The alternative diagnostic pathways modelled have no expected difference in the rates of patients with recurrence treated by resection at any stage. This suggests that there are no expected differences in health outcomes in treating the recurrence of bladder cancer across these diagnosis strategies. The disutility (adverse effects) of undergoing two cystoscopy procedures (which applies to patients who have a positive result at the initial cystoscopy under LA and then require a second cystoscopy under GA to allow for biopsy and treatment) and the disutility of a GA compared to an LA have not been considered in the model. It is the expert opinion of the advisory panel that any such disutility is minimal and not of clinical significance. Therefore, there is no expected difference in effect in the alternative diagnostic pathways considered. As differences in costs but no differences in effects are expected in comparing the modelled diagnostic alternatives, the economic evaluation conducted is a cost-minimisation analysis.

The diagnostic accuracy of the UroVysion test will affect which patients undergo cystoscopy under GA and which under LA. A high sensitivity will ensure a high rate of true positive classifications and a low number of false negative classifications (ie, patients with a recurrence who are incorrectly classified as not having a recurrence), thus reducing the number of patients undergoing two cystoscopies. A high specificity will ensure a low number of false positive classifications (ie, patients without recurrence who are classified as positive by the UroVysion test and therefore classified incorrectly as having a recurrence), ensuring that only a small number of patients without recurrence undergo a cystoscopy under GA. Current evidence suggests the UroVysion test has average sensitivity of 68.5% and average specificity of 64.2%. These estimates were obtained using the results of the four studies which provided sufficient information to enable 2×2 tables to be reconstructed. The sensitivity and specificity results for the studies were pooled, and each study was weighted according to its sample size (Figure 8).

The model considers the costs incurred over 5 years where patients undergo cystoscopy at 3, 6, 12, 18 and 24 months, followed by yearly cystoscopies until recurrence or 5 years. This follow-up regimen is based on current practice and the expert opinion of the advisory panel. The model shown in Figure 10 allows estimation of the costs and effects of the initial monitoring of patients at 3 months. The cumulative expected cost of monitoring patients until their first recurrence (which does not differ in diagnostic strategies compared) when monitored at 3, 6, 12, 18, 24, 36, 48 and 60 months must also be considered. This is best undertaken with a Markov model, where recurrence is an absorbing state and the transition probability of recurrence differs at each stage (stage 1 = 3 months, 2 = 6 months, 3 = 12 months, 4 = 18 months, 5 = 24 months, 6 = 36 months, 7 = 48 months, 8 = 60 months), given evidence of the cumulative probability of recurrence. A Markov model of expected costs until first recurrence or monitoring until 60 months is shown in Figure 11. All patients begin (at stage 0) in a state of no recurrence, then in stage 1 follow (by diagnostic arm) a diagnostic path conditional on their transition into recurrence. Patients recurring are absorbed while those not recurring enter the next period of monitoring as no recurrence (stage 2), and so on. Costs are accumulated over stages until 60 months (end of stage 8), when the model finishes.

Figure 10 Diagnostic pathways for UroVysion FISH assay relative to current practice at 3 months

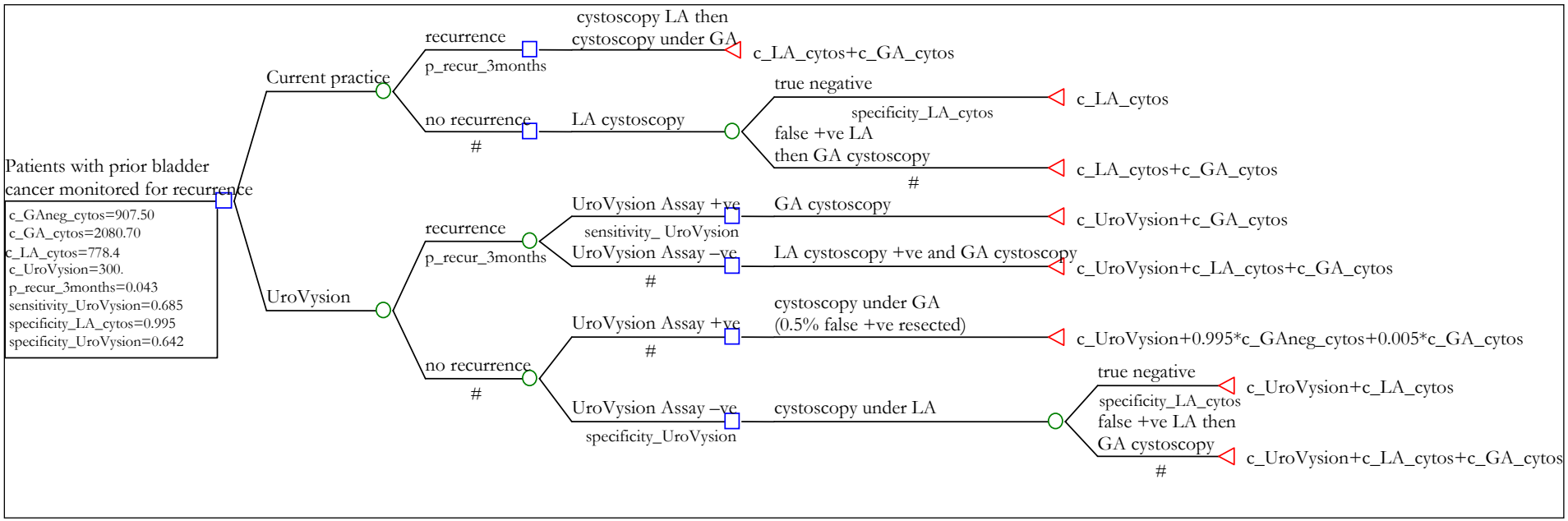
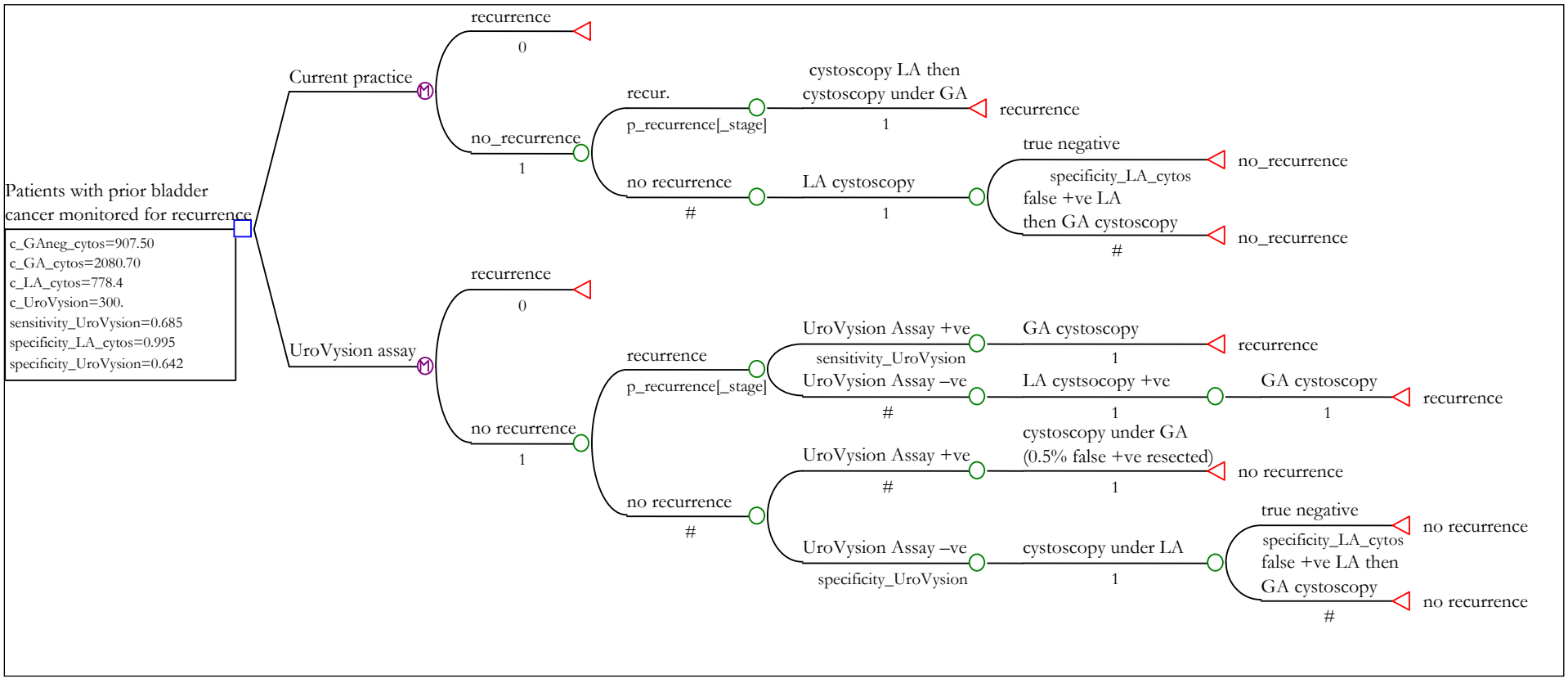


Figure 11 Diagnostic pathways for UroVysion FISH assay relative to current practice at 5 years



Main assumptions

The assumptions and sources of data for event probabilities are outlined in Table 23, and the costs of procedures used in the model are summarised in Table 25.

Each of these components of the model is discussed in the following sections.

Table 23 Assumptions used in the economic model

Assumption	Value	Source
Proportion of patients with recurrence following initial diagnosis and treatment of TCC of the bladder:		
3 months	4.3%	Millan-Rodriguez *et al.* (2000); refer to text of this present report for explanation of how values were derived from the article
6 months	13.2%	
12 months	24.2%	
18 months	31.2%	
24 months	35.6%	
3 years	41.2%	
4 years	46.8%	
5 years	51.4%	
Proportion of patients with false positive cystoscopy results	6%	Estimate from included studies in this review (refer to text)
Proportion of patients with recurrence which is detected by the UroVysion test (sensitivity)	68.5%	Estimate from included studies in this review (refer to text)
Proportion of patients without recurrence correctly classified as negative by the UroVysion test (specificity)	64.2%	Estimate from included studies in this review (refer to text)
Proportion of patients with recurrence who undergo MBS procedure 36840	10%	Advisory Panel estimate
Proportion of patients with recurrence who undergo MBS procedure 36845	90%	Advisory Panel estimate
Proportion of patients undergoing MBS procedure 36840 who have laser treatment or diathermy and therefore do not have pathology	100%	Advisory Panel estimate
Proportion of patients undergoing MBS procedure 36845 who have an overnight stay	100%	Advisory Panel estimate
Length of procedure (minutes):		
MBS Item No. 36812	12 minutes	Advisory Panel estimate
MBS Item No. 36840	19 minutes	
MBS Item No. 36845	32 minutes	
Proportion of patients over 70 years of age	50%	Median average age of patients in studies included in this review = 70.5 years

Probability of events

Expected costs for each diagnostic strategy depend on the expected recurrence rates at 3, 6, 12, 18, 24, 36, 48 and 60 months. Evidence of these recurrence rates is reported in Table 23. These recurrence rates over time are taken from the large cohort study by Millan-Rodriguez *et al.* (2000), in which 1529 patients with primary superficial bladder cancer were followed over 5 years. In the study, recurrence rates at various time points

are presented, both overall and for individual risk groups. The risk groups were classified as follows:

Low risk:
- Grade 1 stage Ta
- Grade 1 stage T1, single tumour

Intermediate risk:
- Grade 1 stage T1, multiple tumours
- Grade 2 stage Ta
- Grade 2 stage T1, single tumour

High risk:
- Grade 2 stage T1, multiple tumours
- Grade 3 stage Ta
- Grade 3 stage T1
- Carcinoma *in situ*

The recurrence rates at various time points used in the economic analysis assume that 40% of the patients are low risk, 40% are intermediate risk and 20% are high risk. These proportions are based on the distribution of patients in the included studies, where known. Table 24 reports the transition probability given the probability of recurrence.

Table 24 Transition probabilities for stages of the Markov model given cumulative rate of patients with recurrence

	Recurrence rate	Transition probability[1]
3 months	4.3%	0.043
6 months	13.2%	0.092998955
12 months	24.2%	0.126728111
18 months	31.2%	0.092348285
24 months	35.6%	0.063953488
36 months	41.2%	0.086956522
48 months	46.8%	0.095238095
60 months	51.4%	0.086466165

[1]Transition probability at time t = ((recurrence rate(t) – recurrence rate(t – 1)) / (1 – recur rate(t – 1))

Sensitivity and specificity of cystoscopy under local anaesthetic in current practice

The sensitivity of cystoscopy under LA in detecting recurrent tumours is assumed to be 100%. Three of the included studies allowed calculation of the rate of cystoscopies with resection under GA where pathology was negative for cancer (Placer *et al.* 2002, Sarosdy *et al.* 2002, Varella-Garcia *et al.* 2004). These studies suggest that the false positive rate for cystoscopy is 6%. Under the assumption that all positive LA cystoscopy leads to cystoscopy under GA, this evidence can be used as indirect evidence to determine the specificity of cystoscopy, conditional on the rate of recurrence. The average recurrence rate per period across the monitoring regimen at 3, 6, 12, 18, 24, 36, 48 and 60 months in Table 24 is approximately 8%. If 6% of all resected tumours are negative, this would imply that approximately 0.5% (6% of 8.5%) of the 92% of patients without recurrence undergo a cystoscopy with resection or ablation. This suggests that 0.5% of patients do not have recurrence but are referred for a cystoscopy under GA (with resection or diathermy) after a positive LA cystoscopy. It therefore follows that the specificity of cystoscopy in detecting recurrence is 0.915/0.92 = 99.5%.

The probability of a positive UroVysion test in patients with recurrence (that is, the sensitivity of the UroVysion test) is estimated as 68.5% from the average across patients from studies included in this review (see Table 19). The probability of a negative UroVysion test in patients without a recurrence (that is, the specificity of the UroVysion test) is estimated as 64.2% from evidence for patients in studies included in this review (see Table 19). One-way sensitivity analyses and best and worst case scenarios have been used to allow for variation in these rates.

Surgical procedures

Two MBS item numbers refer to the treatment of recurrent superficial tumours (36840 and 36845). As item number 36840 may be performed in the absence of bladder cancer, the number of items claimed does not allow an accurate representation of the proportions. Therefore, an assumption about the proportion of patients with recurrence undergoing each procedure is required. It is the expert opinion of the advisory panel that 90% of patients with recurrence will undergo item 36845, and the remaining 10% will undergo item 36840.

The length of each of the cystoscopy procedures is required to enable the anaesthetic costs for each procedure to be calculated. As data regarding the length of the procedures were not available, the expert opinion of the advisory panel was used. In addition to procedure length, the proportion of patients aged over 70 years is required, as there is an additional anaesthetic fee charged when patients are aged over 70. As the median average age of patients in studies included in this review is 70.5 years, it is assumed that half of the patients undergoing the procedure are over 70. Further assumptions relating to the procedures have been outlined in Table 23.

Resource use and costs

All health utilisation and cost data were derived from Australian sources. The costs of the cystoscopy procedure, anaesthetic and pathology are based on MBS schedule fees, while the theatre and accommodation costs for each procedure are based on median revenue costs for two Australian private hospitals. Further details about the calculation of theatre and accommodation costs are shown in Appendix G. The costs of the UroVysion test are based on information provided by the applicant. A detailed costing based on the Pathology Services Table Committee's costing template was not available.

Table 25 Costs used in the economic model

Procedure	Cost ($AU)	Source
Cystoscopy under local anaesthetic:		
Cystoscopy with urethroscopy with or without urethral dilatation	$141.40	MBS Item No. 36812
Theatre cost	$285.00	Refer to Appendix G
Accommodation cost (day only)	$342.00	Refer to Appendix G
Cystoscopy with resection or diathermy under general anaesthetic:		
Cystoscopy:		
1. Cystoscopy, with resection, diathermy or visual laser destruction of bladder tumour or other lesion of the bladder, not being a service to which item 36845 applies	$274.25	MBS Item No. 36840
2. Cystoscopy, with diathermy, resection or visual laser destruction of multiple tumours in more than 2 quadrants of the bladder or solitary tumour greater than 2 cm in diameter	$586.65	MBS Item No. 36845

Procedure	Cost ($AU)	Source
Anaesthetic fee:		
1. MBS Item No. 36840		
a. Examination of a patient in preparation for administration of an anaesthetic relating to a clinically relevant service	$36.40	MBS Item No. 17603
b. Initiation and management of anaesthesia for transurethral procedures (including urethrocystoscopy) (4 basic units)	$67.40	MBS Item No. 20910
c. Anaesthesia (16–20 minutes)	$33.70	MBS Item No. 23021
d. Anaesthesia where the patient is less than 12 months of age or 70 years or greater (1 basic unit)	$16.85	MBS Item No. 25015
2. MBS Item No. 36845		
a. Examination of a patient in preparation for administration of an anaesthetic relating to a clinically relevant service	$36.40	MBS Item No. 17603
b. Initiation and management of anaesthesia for TUR of bladder tumour(s) (5 basic units)	$84.25	MBS Item No. 20912
c. Anaesthesia (31–35 minutes)	$50.55	MBS Item No. 23031
d. Anaesthesia where the patient is less than 12 months of age or 70 years or greater (1 basic units)	$16.85	MBS Item No. 25015
Pathology – Examination of complexity level 5 biopsy material with 1 or more tissue blocks, including specimen dissection, all tissue processing, staining, light microscopy and professional opinion or opinions – 1 or more separately identified specimens	$190.75	MBS Item No. 72830
Theatre cost		
1. MBS Item No. 36840	$496.00	Refer to Appendix G
2. MBS Item No. 36845	$605.00	Refer to Appendix G
Accommodation cost:		
1. MBS Item No. 36840 (day only)	$361.00	Refer to Appendix G
2. MBS Item No. 36845 (overnight)	$608.00	Refer to Appendix G
Cystoscopy (negative) under general anaesthetic:		
Cystoscopy with urethroscopy with or without urethral dilatation	$141.40	MBS Item No. 36812
Anaesthetic fee:		
a. Examination of a patient in preparation for administration of an anaesthetic relating to a clinically relevant service	$36.40	MBS Item No. 17603
b. Initiation and management of anaesthesia for transurethral procedures (including urethrocystoscopy) (4 basic units)	$67.40	MBS Item No. 20910
c. Anaesthesia (15 minutes or less)	$16.85	MBS Item No.23010
d. Anaesthesia where the patient is less than 12 months of age or 70 years or greater (1 basic unit)	$16.85	MBS Item No. 25015
Theatre cost	$285.00	Refer to Appendix G
Accommodation cost (day only)	$352.00	Refer to Appendix G
UroVysion FISH assay:		
UroVysion kit	$150.00	Applicant
Laboratory fees	$150.00	Applicant

Using the probabilities outlined in Table 24, and the costs of procedure components outlined in Table 25, the total for each procedure can be calculated. These total costs are shown in Table 26.

Table 26 Summary of total costs for procedures

Procedure	Total cost ($AU)
UroVysion test	$300
Cystoscopy under local anaesthetic	$778.40
Cystoscopy with resection or diathermy under general anaesthetic	$2080.70
Cystoscopy (negative) under general anaesthetic	$907.50

Model results

If we populate the decision model with data from Tables 24 and 26, Figure 12 shows the expected costs of the diagnostic pathway for UroVysion relative to the current practice diagnostic pathway after the first monitoring at 3 months. Figure 13 shows the expected costs for the diagnostic pathways in patients until recurrence up to 5 years.

Figure 12 shows that the use of the UroVysion test (following the diagnostic pathway previously outlined) would have a higher cost than current practice by an average of $320 ($1197 vs $877) per patient in the first cycle (that is, at the initial 3-month follow-up). This incremental cost can be attributed to:

1. the cost of the UroVysion FISH assay ($300) plus ...
2. the additional costs of general versus local anaesthetics in patients in whom the UroVysion test is positive but subsequent cystoscopy under GA is negative (this amount is $31, determined from the following calculation: ((1 – true recurrence rate) × ((1 – specificity UroVysion) – (1 – specificity LA cystoscopy))) × ($907.50 – $778.4) = 0.957 × (0.358 – 0.005) × $129.10 = $43), less ...
3. the reduction of costs from avoiding a cystoscopy with LA in patients who test positive by the UroVysion test and go directly to a cystoscopy under GA in which a recurrence is confirmed (this amount is $23, determined from the following calculation: true recurrence rate × sensitivity × cost LA cystoscopy = 0.043 × 0.685 × $778.4 = $23).

Therefore, the additional cost of the UroVysion test is not offset by the reduction in the number of patients who undergo two cystoscopies.

Figure 12 Expected cost of diagnostic pathways for UroVysion FISH assay relative to current practice at 3 months

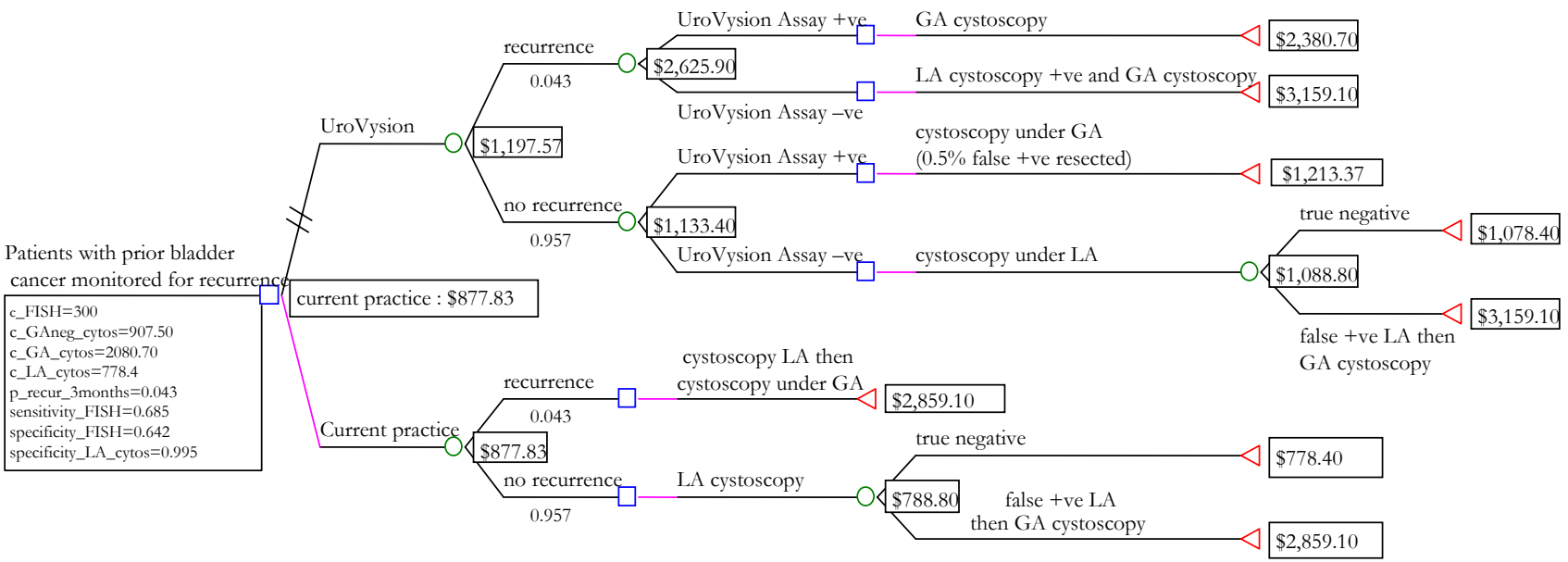


Figure 13 Expected cost of diagnostic pathways for UroVysion FISH assay relative to current practice at 5 years

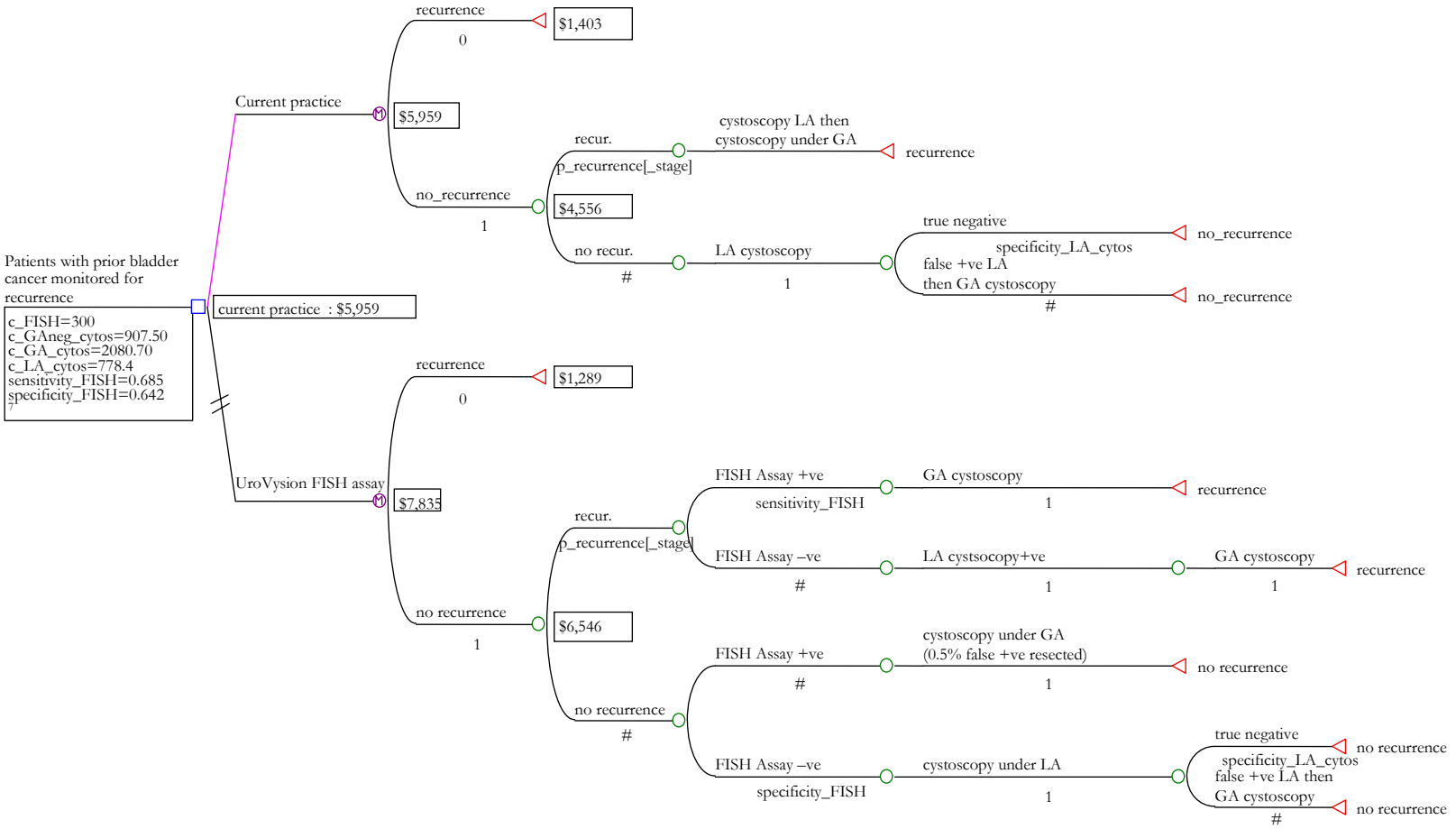


Figure 13 shows that over 5 years, the total cost of following the UroVysion pathway is $7835, compared to $5959 for following current practice. Therefore, the UroVysion clinical pathway increases the expected cost for patients until first recurrence by $1876 over current practice in monitoring cycles at 3, 6, 12, 18, 24, 36, 48 and 60 months.

Sensitivity analysis

The cost analysis is conditional on the rate of recurrence, the costs of procedures, the sensitivity and specificity of the UroVysion test, and the specificity of LA cystoscopy. One-way sensitivity analysis and a best case scenario have been used to allow for the uncertainty of these parameters in the model. The parameters tested in the sensitivity analyses and the best case scenario and the values used are shown in Table 27.

Without a detailed costing, the true cost of performing the UroVysion test in Australia is uncertain. Changes in the costs of the test have been considered in the sensitivity analyses, however, based on the retail price of the test in the United States, it is possible that the upper limit of $400 may be a conservative estimate.

The best-case scenario occurs when all patients have high risk and the sensitivity of the UroVysion test is high. Thus, for the best case scenario, the probability of recurrence was changed to the probability of recurrence in high-risk patients. As the sensitivity of the UroVysion test differs according to the stage or grade of a tumour (see Table 20), the sensitivity estimate used with the high-risk recurrence rate should be appropriate for the high risk group. In the best case scenario, a sensitivity of 94% is used. This is the sensitivity for Grade 3 tumours from the study by Sarosdy *et al.* (2002), which is the only included study which provided information on the sensitivity of the UroVysion test in different tumour grades in patients being monitored for recurrence.

Table 27 Inputs varied in the economic model sensitivity analysis

Assumption	Values used in sensitivity analysis	Source	Justification
Total cost of UroVysion	$200–$400	Assumption	50% increase or decrease in cost
Proportion of patients with recurrence who undergo MBS procedure 36845	50%–90%	Assumption	
Proportion of patients with recurrence following initial diagnosis and treatment of TCC of the bladder: 3 months 6 months 12 months 18 months 24 months 3 years 4 years 5 years	9.4% 24% 39% 44% 50% 56% 58% 61%	Millan-Rodriguez *et al.* (2000)	Assumes all patients are high risk
Proportion of patients with recurrence which is detected by the UroVysion test (sensitivity)	48%–86%	Kipp *et al.* (2005); Skacel *et al*. (2003)	Minimum and maximum sensitivity reported in studies included in this review
Proportion of patients without recurrence correctly classified as negative by the UroVysion test (specificity)	34.3%–100%	Pycha *et al.* (2004); Kipp *et al.* (2005)	Minimum and maximum specificity reported in studies included in this review

The results of the sensitivity analysis are shown in Table 28.

Table 28 One-way sensitivity analyses results for the incremental cost of the UroVysion diagnostic pathway vs current practice

Variable (lower bound–upper bound)	Incremental cost of the UroVysion test @ lower bound (total UroVysion cost – total current practice cost)	Incremental cost of the UroVysion test @ higher bound (total UroVysion cost – total current practice cost)
Cost of the UroVysion test ($200–$400)	$1249 ($7208–$5959)	$2502 ($8461–$5959)
Cost of GA cystoscopy ($1724 with 50% 36845, $2081 with 90% 36845)	$1876 ($7649–$5773)	$1876 ($7835–$5959)
Sensitivity of the UroVysion test (48%–86%)	$1954 ($7913–$5959)	$1809 ($7768–$5959)
Specificity of the UroVysion test (35%–100%)	$2091 ($8050–$5959)	$1618 ($7577–$5959)

Table 28 shows that for a range of sensitivities, a range of specificities, a range of costs of cystoscopy with resection or diathermy under GA, and a range of UroVysion costs, the total cost of following the UroVysion clinical pathway is always higher than the total cost of following current practice. A best case scenario, where the UroVysion test is used only in higher-risk patients (Stages 2 and 3, where risk of bladder recurrence is 9.4% at 3 months and 61.5% at 5 years) and is assumed to have a sensitivity of 94%, was also modelled. The expected cost of the UroVysion diagnostic pathway in this model was $1355 higher than for the current practice clinical pathway ($6839 vs $5484). In this best

case scenario, if the cost of the UroVysion FISH assay were $200 rather than $300, then this incremental cost falls to $822 ($6307 vs $5485).

In general, the above results show that under any plausible variation of evidence of accuracy, costs or rates of recurrence, the use of the UroVysion test remains more costly than current practice given the expected diagnostic pathways. As diagnostic pathways with and without the UroVysion test are expected to have equivalent clinical outcomes, the UroVysion clinical pathway is dominated by (more expensive while having equivalent effects relative to) current practice.

Conclusions

The specific question addressed in this review was:

- What is the value of the UroVysion FISH assay in conjunction with cystoscopy versus cystoscopy alone to diagnose recurrence of TCC in patients who have previously been diagnosed with TCC of the bladder who would undergo cystoscopy under local anaesthetic?

Safety

None of the seven studies included in this review reported complications from the UroVysion test, cystoscopy or any of the comparators. As the UroVysion FISH assay is a non-invasive test performed on voided urine, there are minimal or no risks to the safety of the patient providing the urine sample. As urine is a body fluid, universal blood and body fluid precautions should be followed to ensure the safety of staff involved in the collection, transport and analysis of the urine sample.

In comparison to the UroVysion test, cystoscopies are invasive procedures and are associated with known adverse effects. These include bladder rupture, stranguria, bleeding and urinary tract infections, although it would appear that the incidence of serious complications following cystoscopy is rare, and while minor complications are more common, they usually resolve spontaneously within 48 hours and are likely to be of minimal clinical significance.

Effectiveness

Conclusions pertaining to the effectiveness of the UroVysion test are based on seven cross-sectional studies of diagnostic accuracy which met criteria for inclusion in this review. These studies included a total of 558 patients with a history of bladder cancer being monitored for recurrence, and had sample sizes ranging from 19 to 176. Most studies were of fair quality, one of high quality and one of low quality. Four of the studies provided sufficient data for the reconstruction of 2×2 tables of results of patients being monitored for recurrence, while the remaining three studies presented only values of sensitivity or specificity for this patient group. Owing to statistically significant heterogeneity in the estimates of UroVysion accuracy across studies, a single pooled estimate of test accuracy could not be obtained. The sensitivity of the UroVysion test ranged from 48% to 86%, and the specificity ranged from 34.3% to 100%. Differences in the types of patients included in the trials, the reference standard used and the quality of the trials are likely to have contributed to the variations between studies.

The potential impact of the UroVysion test on clinical practice was determined by using the results of the studies to gain estimates of the LRs of the UroVysion test. The positive LRs ranged from 1.3 to 21.1, and the negative LRs ranged from 0.2 to 0.5. Applying these LRs to various pretest probabilities of recurrence (based on risk of recurrence and period of follow-up) revealed that for most patients, the use of the UroVysion test does not greatly increase the probability of detecting recurrence. Clinical impact is likely to be greatest in patients with a high risk of recurrence who have undergone at least 1 year of

follow-up. In these patients, using the UroVysion test to inform the choice of anaesthetic for cystoscopy means that only a small number of patients will unnecessarily undergo cystoscopy under GA, and most patients with have to undergo only one cystoscopy, rather than two. The post-test probabilities show that in patients with a low risk of recurrence who are early in their follow-up, the chance of missing a recurrence following a negative UroVysion test is small, but the probability of missing a recurrence increases in patients with higher risks or in patients at later stages in their follow-up. This problem of false negatives is not of clinical significance if the UroVysion test is to be used only in conjunction with cystoscopy, as the recurrence will be detected by cystoscopy.

Cost-effectiveness

Conclusions pertaining to the cost-effectiveness of the UroVysion test are based on an economic model comparing a clinical pathway where patients undergo cystoscopy under local anaesthetic followed by a cystoscopy under general anaesthetic for those who have a positive cystoscopy to a pathway where patients initially undergo the UroVysion test, the result of which informs whether a patient undergoes cystoscopy under local or general anaesthetic. The model showed that at both the 3-month follow-up and 5 years (cumulative costs over a 5-year follow-up period), the costs of following the UroVysion clinical pathway exceeded the costs of following the current practice clinical pathway. At five years, the cost of following the UroVysion pathway was $7835, compared to $5959 for following current practice. Therefore, the UroVysion clinical pathway increased the expected cost for patients until first recurrence by $1876 over current practice.

As the cost analysis is conditional on the rate of recurrence, the costs of procedures, the sensitivity and specificity of the UroVysion test, and the specificity of LA cystoscopy, one-way sensitivity analysis and a best case scenario were used to allow for the uncertainty of the parameters used in the model. In general, under any plausible variation of evidence of accuracy, costs or rates of recurrence, the use of the UroVysion test remained more costly than current practice given the expected diagnostic pathways. As diagnostic pathways with and without the UroVysion test are expected to have equivalent clinical outcomes, the UroVysion clinical pathway was dominated by (more expensive while having equivalent effects relative to) current practice.

Recommendation

MSAC recommended that on the strength of evidence pertaining to UroVysion fluorescence in situ hybridisation (FISH) assay public funding should not be supported for this procedure.

The clinical usefulness of the test is limited by the sensitivity and expense of the test and the cost effectiveness was not demonstrated.

- The Minister for Health and Ageing accepted/rejected this recommendation on 28 March 2006. -

Appendix A MSAC terms of reference and membership

The MSAC's terms of reference are to:

- advise the Minister for Health and Ageing on the strength of evidence pertaining to new and emerging medical technologies and procedures in relation to their safety, effectiveness and cost-effectiveness and under what circumstances public funding should be supported;
- advise the Minister for Health and Ageing on which new medical technologies and procedures should be funded on an interim basis to allow data to be assembled to determine their safety, effectiveness and cost-effectiveness;
- advise the Minister for Health and Ageing on references related either to new and/or existing medical technologies and procedures; and
- undertake health technology assessment work referred by the Australian Health Ministers' Advisory Council (AHMAC) and report its findings to AHMAC.

The membership of the MSAC comprises a mix of clinical expertise covering pathology, nuclear medicine, surgery, specialist medicine and general practice, plus clinical epidemiology and clinical trials, health economics, consumers, and health administration and planning:

Member	**Expertise or Affiliation**
Dr Stephen Blamey (Chair)	general surgery
Associate Professor John Atherton	cardiology
Professor Syd Bell	pathology
Dr Michael Cleary	emergency medicine
Dr Paul Craft	clinical epidemiology and oncology
Dr Kwun Fong	thoracic medicine
Dr Debra Graves	medical administrator
Dr David Gillespie	gastroenterology
Professor Jane Hall	health economics
Professor John Horvath	Chief Medical Officer, Department of Health and Ageing
Dr Terri Jackson	health economics
Professor Brendon Kearney	health administration and planning
Associate Professor Frederick Khafagi	nuclear medicine
Associate Professor Donald Perry-Keene	endocrinology
Dr Ray Kirk	health research
Dr Ewa Piejko	general practice

Ms Sheila Rimmer	consumer health issues
Ms Samantha Robertson	Acting Assistant Secretary Department of Health and Ageing
Professor Ken Thomson	radiology
Dr Douglas Travis	urology
Dr Mary Turner	Australian Health Ministers' Advisory Council Representative
Dr David Wood	orthopaedics

Appendix B Advisory Panel

Advisory Panel for MSAC Application 1084— UroVysion fluorescence *in situ* hybridisation

Dr Douglas Travis (Chair) MBBS FRACS Head of Urology Western Health	MSAC member
Associate Professor Lynda Campbell MBBS FRCPA FHGSA Director, Victorian Cancer Cytogenetics Service St. Vincent's Hospital, Melbourne	nominated by the Royal College of Pathologists of Australasia
Dr Paul Craft MPH FRACP Director, Medical Oncology Unit Canberra Hospital	MSAC member
Mr Craig Ellis BA BSW (Hons) Cert Adv Eng Cert EFM Consumer Representative, The Consumer's Health Forum of Australia Inc.	nominated by the Consumer's Health forum of Australia
Dr Shane La Bianca MBBS, FRACS Head of Urology Fremantle Hospital & Director, Urology West SJOG Healthcare Murdoch	nominated by the Urological Society of Australasia

Evaluators

Ms Alisa Higgins BPhysio(Hons) MPH Project Officer	NHMRC Clinical Trials Centre
Dr Sarah Lord MBBS MSc(Epi) Epidemiologist	NHMRC Clinical Trials Centre
Mr Simon Eckermann BEc(Hons) BMSC Grad Dip HEc Health Economist	NHMRC Clinical Trials Centre

Department of Health and Ageing

Ms Alex Lloyd MSAC Project Manager	Health Technology Section

Appendix C Studies included in the review and their characteristics

The references included in the report are listed below. Details of the characteristics of each of these studies are presented in Table 29.

Halling KC, King W, Sokolova IA, Meyer RG, Burkhardt HM, Halling AC, *et al.*, 2000, A comparison of cytology and fluorescence *in situ* hybridization for the detection of urothelial carcinoma, *Journal of Urology*, 164(5), 1768–1775.

Kipp BR, Karnes RJ, Brankley SM, Harwood AR, Pankratz VS, Sebo TJ, *et al.*, 2005, Monitoring intravesical therapy for superficial bladder cancer using fluorescence *in situ* hybridization, *Journal of Urology*, 173, 401–404.

Placer J, Espinet B, Salido M, Sole F, Gelabert-Mas A, 2002, Clinical utility of a multiprobe FISH assay in voided urine specimens for the detection of bladder cancer and its recurrences, compared with urinary cytology, *European Urology*, 42(6), 547–552.

Pycha A, Lodde M, Comploj E, Negri G, Egarter-Vigl E, Vittadello F, *et al.*, 2004, Intermediate-risk urothelial carcinoma: an unresolved problem? *Urology*, 63(3), 472–475.

Sarosdy MF, Schellhammer P, Bokinsky G, Kahn P, Chao R, Yore L, *et al.*, 2002, Clinical evaluation of a multi-target fluorescent *in situ* hybridization assay for detection of bladder cancer, *Journal of Urology*, 168(5), 1950–1954.

Skacel M, Fahmy M, Brainard JA, Pettay JD, Biscotti CV, Liou LS, *et al.*, 2003, Multitarget fluorescence *in situ* hybridization assay detects transitional cell carcinoma in the majority of patients with bladder cancer and atypical or negative urine cytology, *Journal of Urology*, 169(6), 2101–2105.

Varella-Garcia M, Akduman B, Sunpaweravong P, Di Maria MV, Crawford ED, 2004, The UroVysion fluorescence *in situ* hybridization assay is an effective tool for monitoring recurrence of bladder cancer, *Urologic Oncology*, 22(1), 16–19.

Table 29 Characteristics of studies included in the review

Studies of diagnostic accuracy							
Author & Year	**Strength of evidence[1]**	**Setting**	***N***	**Index test, comparator and reference standard**	**Study population**	**Endpoints[2]**	**Study quality**
Halling *et al.* (2000)	Fair	Setting and dates of enrolment not reported	265 patients: 150 patients undergoing follow-up for previous bladder cancer 115 patients under investigation for haematuria or other genitourinary signs and symptoms An additional 43 healthy donors were recruited as controls	**Index test:** UroVysion FISH assay (voided urine); positive result defined as ≥5 cells with polysomy **Comparator(s):** Cytology **Reference standard:** Cystoscopy with biopsy (unclear when biopsy performed) with clinical follow-up	**All patients** (excluding controls for whom characteristics are not reported)**:** **Sex:** 200 male, 65 female **Age:** mean 69.7 years, median 71 years (range 36–94) **Inclusion/exclusion criteria:** not reported	Specificity	**Fair quality:** **Patient selection or spectrum:** • Appropriate **Reference standard:** • Appropriate reference standard • Unclear which patients had biopsies performed **Test and its interpretation:** • FISH appropriately described • Results interpreted without knowledge of alternative test results **Exclusions or missing data:** • Reasons for exclusions reported • Unable to replicate 2×2 table owing to missing data

[1] The components of strength of the evidence are outlined in Table 14. High is defined as studies which have an appropriate comparison, applicable population and high quality. Fair is defined as studies which have either an appropriate comparison or applicable population and fair or high quality. Low is defined as studies which have neither an appropriate comparison nor applicable population or are low quality.

[2] Only the endpoints where results are available separately for patients being monitored for recurrence have been reported.

Table 29 continued Characteristics of studies included in the review

Studies of diagnostic accuracy							
Author & Year	**Strength of evidence[1]**	**Setting**	***N***	**Index test, comparator and reference standard**	**Study population**	**Endpoints[2]**	**Study quality**
Kipp *et al.* (2005)	Low	Mayo Clinic, USA March 2001 – August 2002	37 patients	**Index test:** UroVysion FISH assay; positive result defined as ≥5 cells with polysomy, ≥10 cells with trisomy or >20% of cells with 9p21 homozygous deletion **Comparator(s):** not identified **Reference standard:** Cystoscopy, biopsy or cytology; Tumour recurrence scored as positive for positive biopsy, positive cystoscopy or positive cytology	**All patients** **Sex:** 36 male, 1 female **Age:** mean 72.2 years, median 75.3 years (range 50.2–86.4) **Initial tumour stage:** Ta 17 patients T1 5 patients Tis 15 patients **Inclusion criteria:** • Patients receiving intravesical therapy for superficial bladder cancer	Accuracy Sensitivity Specificity Positive predictive value Negative predictive value Time to recurrence Onset of muscle invasive disease	**Low quality:** **Patient selection or spectrum:** • Appropriate **Reference standard:** • Inappropriate reference standard as tumour recurrence scored as positive for positive biopsy, positive cystoscopy or positive cytology **Test and its interpretation:** • FISH appropriately described • Results of FISH interpreted without knowledge of reference standard results; unclear whether results of reference standard interpreted without knowledge of FISH results **Exclusions or missing data:** • No uninterpretable or intermediate test results • Able to replicate 2×2 table for post-therapy results

[1] The components of strength of the evidence are outlined in Table 14. High is defined as studies which have an appropriate comparison, applicable population and high quality. Fair is defined as studies which have either an appropriate comparison or applicable population and fair or high quality. Low is defined as studies which have neither an appropriate comparison nor applicable population or are low quality.

[2] Only the endpoints where results are available separately for patients being monitored for recurrence have been reported.

Table 29 continued Characteristics of studies included in the review

Studies of diagnostic accuracy							
Author & Year	**Strength of evidence[1]**	**Setting**	***N***	**Index test, comparator and reference standard**	**Study population**	**Endpoints[2]**	**Study quality**
Placer *et al.* (2002)	Fair	Spain, single centre Dates of enrolment not reported	86 patients in total: 34 patients undergoing follow-up for previous bladder cancer 42 patients with no known history of bladder cancer but clinical features suggestive of malignancy 10 controls with prostatism with no known history or clinical evidence of bladder cancer	**Index test:** UroVysion FISH assay (voided urine); positive result defined as ≥5 cells with polysomy or presence of >50% of cells with a loss of both 9p21 signals **Comparator(s):** Cytology **Reference standard:** Cystoscopy with biopsy or tumour resection for positive cystoscopies	**All patients** **Sex:** 76 male, 10 female **Age:** mean 70 years (range 28–90) **Inclusion/exclusion criteria:** not reported	Sensitivity Specificity	**Fair quality:** **Patient selection or spectrum:** • Appropriate—prospective, consecutive enrolment **Reference standard:** • Appropriate reference standard • All patients received reference standard **Test and its interpretation:** • FISH appropriately described • Unclear whether results interpreted without knowledge of alternative test results **Exclusions or missing data:** • Reasons for exclusions reported

[1] The components of strength of the evidence are outlined in Table 14. High is defined as studies which have an appropriate comparison, applicable population and high quality. Fair is defined as studies which have either an appropriate comparison or applicable population and fair or high quality. Low is defined as studies which have neither an appropriate comparison nor applicable population or are low quality.

[2] Only the endpoints where results are available separately for patients being monitored for recurrence have been reported.

Table 29 continued Characteristics of studies included in the review

Studies of diagnostic accuracy							
Author & Year	**Strength of evidence[1]**	**Setting**	***N***	**Index test, comparator and reference standard**	**Study population**	**Endpoints[2]**	**Study quality**
Pycha *et al.* (2004)	Fair	Setting and dates of enrolment not reported	51 patients, of whom 2 were not evaluated owing to intense granulocyt-osis and insufficient urothelial cells	**Index test:** UroVysion FISH assay (voided urine); positive result defined as ≥5 cells with polysomy **Comparator(s):** Liquid-based cytology and uCyt+ **Reference standard:** Cystoscopy with biopsy or tumour resection for suspicious cystoscopies	**All patients** **Sex:** not reported **Age:** mean 72.2 years (range 52–93) **Initial tumour stage or grade:** pTaG1 multifocal 16 (31.4%) pTaG2 30 (58.8%) pT1G2 5 (9.8%) Not assessed at FISH 2 (3.9%) **Inclusion criteria:** • Patients under follow-up after complete TUR of intermediate-risk urothelial carcinoma at least 6 months previously	Accuracy Sensitivity Specificity Positive predictive value Negative predictive value	**Fair quality:** **Patient selection or spectrum:** • Appropriate—prospective, consecutive enrolment **Reference standard:** • Appropriate reference standard • All patients received reference standard **Test and its interpretation:** • FISH appropriately described • Unclear whether results interpreted without knowledge of alternative test results **Exclusion or missing data:** • Reasons for exclusions reported

[1] The components of strength of the evidence are outlined in Table 14. High is defined as studies which have an appropriate comparison, applicable population and high quality. Fair is defined as studies which have either an appropriate comparison or applicable population and fair or high quality. Low is defined as studies which have neither an appropriate comparison nor applicable population or are low quality.

[2] Only the endpoints where results are available separately for patients being monitored for recurrence have been reported.

Table 29 continued Characteristics of studies included in the review

Studies of diagnostic accuracy							
Author & Year	**Strength of evidence[1]**	**Setting**	***N***	**Index test, comparator and reference standard**	**Study population**	**Endpoints[2]**	**Study quality**
Sarosdy *et al.* (2002)	Fair	Locations not reported, 21 centres Accrual completed 2000	176 patients with a history of TCC of the bladder in the previous 9 months 275 healthy volunteers and patients with benign genitourinary disease, non-bladder genitor-urinary cancer and genitourinary trauma were recruited as controls	**Index test:** UroVysion FISH assay (voided urine); positive result reported as being performed according to manufacturer specifications **Comparator(s):** Cytology and BTA Stat test **Reference standard:** Cytoscopy with biopsy or where a lesion was fulgurated or ablated on cystoscopy, a case was considered positive only if the cystoscopy was unequivocal	**<u>All patients</u> (**excluding controls)**:** **Sex:** 132 male, 44 female **Age:** mean 71 years (range 36–98) **Initial tumour stage:** Ta 67% T1 11% ≥T2 2% Tis 16% Unknown 3% **Initial tumour grade:** G1 40% G2 32% G3 26% Unknown 2% **Inclusion criteria:** • Patients with a history of TCC of the bladder within the past 9 months • Written consent obtained	Accuracy Sensitivity Specificity Positive predictive value Negative predictive value	**Fair quality:** **Patient selection or spectrum:** • Appropriate—prospective enrolment **Reference standard:** • Appropriate reference standard • All patients received reference standard **Test and its interpretation:** • FISH described only as being performed according to the instructions on product labelling—unclear of what definition of positive used • Results interpreted without knowledge of alternative test results **Exclusions or missing data:** • Reasons for exclusions reported • Able to replicate 2×2 table

[1] The components of strength of the evidence are outlined in Table 14. High is defined as studies which have an appropriate comparison, applicable population and high quality. Fair is defined as studies which have either an appropriate comparison or applicable population and fair or high quality. Low is defined as studies which have neither an appropriate comparison nor applicable population or are low quality.

[2] Only the endpoints where results are available separately for patients being monitored for recurrence have been reported.

Studies of diagnostic accuracy							
Author & Year	**Strength of evidence[1]**	**Setting**	***N***	**Index test, comparator and reference standard**	**Study population**	**Endpoints[2]**	**Study quality**
Skacel *et al.* (2003)	Fair	USA, single-centre 1996–2001	120 patients in total: 94 patients under surveillance for bladder cancer recurrence 26 patients with no history of bladder cancer with haematuria or unexplained urgency	**Index test:** UroVysion FISH assay (voided urine *n* = 47, instrumented urine *n* = 73); positive result defined as ≥5 cells with gain of 2 or more of chromosomes 3, 7 or 17, or ≥12 cells with 9p21 deletion or ≥10% of cells with isolated trisomy of 1 of chromosomes 3, 7 or 17 **Comparator(s)** Liquid-based cytology **Reference standard:** Cystoscopy with biopsy and a minimum of 12 months' biopsy follow-up	**All patients** **Sex:** not reported **Age:** not reported **Inclusion criteria:** • Patients who had archived urine specimens who had concurrent bladder biopsy and at least 12 months' bladder biopsy follow-up	Sensitivity	**Fair quality:** **Patient selection or spectrum:** • Inappropriate—retrospective **Reference standard:** • Appropriate reference standard • All patients received reference standard **Test and its interpretation:** • FISH appropriately described • Results interpreted without knowledge of alternative test results **Exclusions or missing data:** • No uninterpretable or intermediate test results • Able to replicate 2×2 table for post-therapy results

Table 29 continued Characteristics of studies included in the review

[1] The components of strength of the evidence are outlined in Table 14. High is defined as studies which have an appropriate comparison, applicable population and high quality. Fair is defined as studies which have either an appropriate comparison or applicable population and fair or high quality. Low is defined as studies which have neither an appropriate comparison nor applicable population or are low quality.

[2] Only the endpoints where results are available separately for patients being monitored for recurrence have been reported.

Table 29 continued Characteristics of studies included in the review

Studies of diagnostic accuracy							
Author & Year	**Strength of evidence[1]**	**Setting**	***N***	**Index test, comparator and reference standard**	**Study population**	**Endpoints[2]**	**Study quality**
Varella-Garcia *et al.* (2004)	High	Location, number of centres not reported Feb 2001 – June 2001	19 patients	**Index test:** UroVysion FISH assay (voided urine); positive result defined as >16% cells with polysomy or >48% of cells with 9p21 homozygous loss among at least 50 nuclei scored **Comparator(s):** Cytology **Reference standard:** Cystoscopy with biopsy or tumour resection for positive cystoscopies	**Sex:** 16 men, 3 women **Age:** mean 68 years (range 58–80) **Inclusion criteria:** • Patients with a history of bladder cancer being monitored for recurrence • Informed consent obtained	Accuracy Sensitivity Specificity Positive predictive value Negative predictive value	**High quality:** **Patient selection or spectrum:** • Appropriate—prospective enrolment **Reference standard:** • Appropriate reference standard • All patients received reference standard **Test and its interpretation:** • FISH appropriately described • Results interpreted without knowledge of alternative test results **Exclusions or missing data:** • No uninterpretable or intermediate test results • Able to replicate 2×2 table for post-therapy results

[1] The components of strength of the evidence are outlined in Table 14. High is defined as studies which have an appropriate comparison, applicable population and high quality. Fair is defined as studies which have either an appropriate comparison or applicable population and fair or high quality. Low is defined as studies which have neither an appropriate comparison nor applicable population or are low quality.

[2] Only the endpoints where results are available separately for patients being monitored for recurrence have been reported.

Appendix D Results of studies included in the review

Details of the results of the studies included in this review are presented in Table 30.

Table 30 Results of studies included in the review

Results of studies of diagnostic accuracy						
Author & Year	**N[1]**	**Index test, comparator and reference standard**	**Prevalence**	**UroVysion outcomes**	**Comparator outcomes**	**Other**
Halling *et al.* (2000)	265 patients: 150 undergoing follow-up 115 patients under investigation 43 controls	**Index test:** UroVysion FISH assay (voided urine); positive result defined as ≥5 cells with polysomy **Comparator(s):** Cytology **Reference standard:** Cytoscopy with biopsy (unclear when biopsy performed) with clinical follow-up	**In patients with history of bladder cancer:** 45.3% (39/86) **In all patients** (excluding controls): 28.3% (75/265)	**Patients with history of bladder cancer:** **Specificity:** 76.1% (35/46) **In all patients:** **Sensitivity:** 80.8% (59/73) *By stage:* pTa: 64.9% (24/37) pT1–T4: 94.7% (18/19) pTis: 100% (17/17) *By grade:* G1: 36.4% (4/11) G2:76.0% (19/25) G3: 97.3% (36/37) **Specificity** (calculated for patients without a history of bladder cancer and negative cystoscopy)**:** 96.2% (75/78)	**Patients with history of bladder cancer:** **Specificity:** 85.0% (34/40) **In all patients:** **Sensitivity:** 58.0% (40/69) *By stage:* pTa: 47.2% (17/36) pT1–T4: 60.0% (9/15) pTis: 77.8% (14/18) *By grade:* G1: 27.3% (3/11) G2: 54.2% (13/24) G3: 70.6% (24/34) **Specificity** (calculated for patients without a history of bladder cancer and negative cystoscopy)**:** 98.0% (48/49)	Among the 75 patients with biopsy-proven urothelial carcinoma, FISH and cytology were performed on 73 and 69 patients respectively. There were inadequate cells for FISH in 2 cases. Cytology was not performed, because a diagnosis of invasive urothelial carcinoma had already been established in 4 patients and for unknown reasons in 2 patients. The sensitivity of FISH was significantly better than cytology for pTis (P = 0.046), pT1–T4 (P = 0.025), grade 3 (P = 0.003) and all tumours (P = 0.001) **Among the patients with a history of urothelial carcinoma:** Of the 11 patients with a positive FISH or negative cystoscopy, 7 had a follow-up biopsy (follow-up time 3–12 months) that revealed cancer (1pTis, 3 pTa, 3 pT3). Tumour progression had occurred for 4 of the 7 patients. **Specificity among controls:** UroVysion: 100%

[1] For further details refer to Table 29

Table 30 continued Results of studies included in the review

Results of studies of diagnostic accuracy						
Author & Year	**N[1]**	**Index test, comparator and reference standard**	**Prevalence**	**UroVysion outcomes**	**Comparator outcomes**	**Other**
Kipp *et al.* (2005)	37 patients	**Index test:** UroVysion FISH assay; positive result defined as ≥5 cells with polysomy, ≥10 cells with trisomy or >20% of cells with 9p21 homozygous deletion **Comparator(s):** not identified **Reference standard:** Cystoscopy, biopsy or cytology; tumour recurrence scored as positive for positive biopsy, positive cystoscopy or positive cytology	67.6%	**Accuracy:** 64.9% (24/37) **Sensitivity:** 48.0% (12/25) **Specificity:** 100% (12/12) **TP:** 100% (12/12) **FP:** 0% (0/12) **TN:** 48.0% (12/25) **FN:** 52.0% (13/25)	N/A	**Time to recurrence:** Patients with a positive UroVysion result after intravesical therapy were 4.6 × (HR 95% CI 1.9–11.1, *P* < 0.001) more likely to have a recurrence on follow-up than those with a negative UroVysion result **Time to muscle invasive tumour:** Patients with a positive UroVysion result after intravesical therapy were 9.4 × (HR 95% CI 1.9–45.3, *P* = 0.001) more likely to have a muscle invasive tumour on follow-up than those with a negative UroVysion result
Pycha *et al.* (2004)	51 patients, of which 2 were not evaluated owing to intense granulocytoses and insufficient urothelial cells	**Index test:** UroVysion FISH assay (voided urine); positive result defined as ≥5 cells with polysomy **Comparator(s):** Liquid-based cytology and uCyt+ **Reference standard:** Cystoscopy with biopsy or tumour resection for suspicious cystoscopies	28.6% (14/49)	**Accuracy:** 49.0% (24/49) **Sensitivity:** 85.7% (12/14) **Specificity:** 34.3% (12/35) **TP:** 34.3% (12/35) **FP:** 65.7% (23/35) **TN:** 85.7% (12/14) **FN:** 14.3% (2/14)	N/A	Liquid-based cytology and uCyt+ reported as being conducted in the methods, but no results presented

[1] For further details refer to Table 29

TP = true positive; TN = true negative; FP = false positive; FN = false negative

Table 30 continued Results of studies included in the review

Results of studies of diagnostic accuracy						
Author & Year	**N[1]**	**Index test, comparator and reference standard**	**Prevalence**	**UroVysion outcomes**	**Comparator outcomes**	**Other**
Placer *et al.* (2002)	86 patients: 34 undergoing follow-up 42 patients under investigation 10 controls	**Index test:** UroVysion FISH assay (voided urine); positive result defined as ≥5 cells with polysomy or presence of >50% of cells with a loss of both 9p21 signals **Comparator(s):** Cytology **Reference standard:** Cystoscopy with biopsy or tumour resection for positive cystoscopies	**In patients with history of bladder cancer:** 54.8% (17/31) **In all patients** (excluding controls): 52.8% (47/89)	**Patients with history of bladder cancer:** **Sensitivity:** 70.6% (12/17) **Specificity[2]:** 79.2% **In all patients:** **Accuracy:** 82.5% (66/80) **Sensitivity:** 80.4% (37/46) *By stage:* pTa: 64.0% (16/25) pT1: 100% (12/12) pT2–T4: 100% (9/9) *By grade:* G1: 53.3% (8/15) G2: 83.3% (10/12) G3: 100% (19/19) **Specificity:** 85.3% (29/34) **TP:** 88.1% (37/42) **FP:** 11.9% (5/42) **TN:** 76.3% (29/38) **FN:** 23.7% (9/38)	**Patients with history of bladder cancer:** **Sensitivity:** 47.1% (8/17) **Specificity[2]:** 87.5% **In all patients:** **Accuracy:** 73.5% (61/83) **Sensitivity:** 63.8% (30/47) *By stage:* pTa: 42.3% (11/26) pT1: 91.7% (11/12) pT2–T4: 88.9% (8/9) *By grade:* G1: 25.0% (4/16) G2: 66.7% (8/12) G3: 94.7% (18/19) **Specificity:** 86.1% (31/36) **TP:** 85.7% (30/35) **FP:** 14.3% (5/35) **TN[3]:** 64.6% (31/48) **FN[3]:** 33.4% (17/48)	In 6 cases (6.9%), it was not possible to count assessable signals in the UroVysion test owing to insufficient hybridisation or inadequate cells Cytology performed in 83 (96.5%) cases There was a significant difference ($P < 0.05$) in the sensitivity of UroVysion and cytology **Specificity among controls:** UroVysion: 100% Cytology: 90.9%

[1] For further details refer to Table 29
[2] 2×2 tables unable to be reconstructed from data given owing to discrepancies
[3] Values from reconstructed 2×2 table; value disagrees with text negative predictive value of 62.2%

Table 30 continued Results of studies included in the review

Results of studies of diagnostic accuracy							
Author & Year	**N[1]**	**Index test, comparator and reference standard**	**Prevalence**	**UroVysion outcomes**	**Comparator outcomes**		**Other**
Sarosdy *et al.* (2002)	176 patients undergoing follow-up 275 controls	**Index test:** UroVysion FISH assay (voided urine); positive result reported as being performed according to manufacturer's specifications **Comparator(s):** Cytology and BTA Stat test **Reference standard:** Cystoscopy with biopsy or where a lesion was fulgurated or ablated on cystoscopy. A case was considered positive only if the cystoscopy was unequivocal	35.2% (62/176)	**Accuracy:** 67.6% (119/176) **Sensitivity:**71.0% (44/62) *By stage[2]:* TaG12: 62% (16/26) TaG3: 83% (5/6) T1G2: 100% (2/2) T1G3: 75% (3/4) T2: 100% (3/3) Tis: 100% (7/7) *By grade[3]:* G1: 55% (12/22) G2: 78% (7/9) G3: 94% (17/18) **Specificity:** 65.8% (75/114) **TP:** 53.0% (44/83) **FP:** 47.0% (39/83) **TN:** 80.6% (75/93) **FN:** 19.4% (18/93) **In BCG treated patients[4]:** **Accuracy:** 75.0% (60/80) **Sensitivity:** 84.6% (22/26) **Specificity:** 70.4% (38/54) **TP:** 57.9% (22/38) **FP:** 42.1% (16/38) **TN:** 90.5% (38/42) **FN:** 9.5% (4/42)	**Cytology[5]:** **Sensitivity:** 26% *By stage[2]:* TaG12: 23% (6/26) TaG3: 33% (2/6) T1G2: 100% (2/2) T1G3: 50% (2/4) T2: 33% (1/3) Tis: 33% (2/6) *By grade[3]:* G1: 18% (4/22) G2: 44% (4/9) G3: 41% (7/17) ***In BCG treated patients[4]:*** **Accuracy:** 71.3% (57/80) **Sensitivity:** 34.6% (9/26) **Specificity:** 88.9% (48/54) **TP:** 60.0% (9/15) **FP:** 40.0% (6/15) **TN:** 73.8% (48/65) **FN:** 26.2% (17/65)	**BTA Stat:** **Sensitivity:** 50.0% (31/62) *By stage[2]:* TaG12: 38% (10/26) TaG3: 100% (6/6) T1G2: 100% (2/2) T1G3: 75% (3/4) T2: 67% (2/3) Tis: 43% (3/7) *By grade[3]:* G1: 27% (6/22) G2: 78% (7/9) G3: 72% (13/18) ***In BCG treated patients[4]:*** **Accuracy:** 59.3% (48/81) **Sensitivity:** 69.2% (18/26) **Specificity:** 54.5% (30/55) **TP:** 41.9% (18/43) **FP:** 58.1% (25/43) **TN:** 78.9% (30/38) **FN:** 21.1% (8/38)	**Time to recurrence:** Time to recurrence was significantly less in patients with positive FISH or negative cystoscopy than in those with negative FISH or negative cystoscopy (P = 0.014); 36 of the patients with a positive FISH or negative cystoscopy were followed up for 3–16 months and 15 (41.1%) were found to have a biopsy-confirmed tumour; 68 of the patients with a negative FISH or negative cystoscopy were followed up for 3–19 months and 13 (19.1%) were found to have a biopsy-confirmed tumour **Specificity among controls:** 94.5% (260/275) ranging from 66.7% in non-genitourinary cancer to 100% in healthy volunteers

[1] For further details refer to Table 29. [2] Stage not assigned in 3 cases. [3] Grade not assigned in 2 cases

[4] Values calculated from numerators of data in Table 3 in reference; data in table and text disagree, and data in reconstructed 2×2 tables do not agree with denominators in table

[5] Cytology results inconclusive in 1 case

Table 30 continued Results of studies included in the review

Results of studies of diagnostic accuracy						
Author & Year	**N[1]**	**Index test, comparator and reference standard**	**Prevalence**	**UroVysion outcomes**	**Comparator outcomes**	**Other**
Skacel *et al.* (2003)	120 patients : 94 undergoing follow-up 26 patients under investigation	**Index test:** UroVysion FISH assay (voided urine *n* = 47, instrumented urine *n* = 73); positive result defined as ≥5 cells with gain of 2 or more of chromosomes 3, 7, 17, as ≥12 cells with 9p21 deletion or ≥10% of cells with isolated trisomy of 1 of chromosomes 3, 7 or 17 **Comparator(s):** Liquid-based cytology **Reference standard:** Cystoscopy with biopsy and a minimum of 12 months' biopsy follow-up	**In patients with history of bladder cancer:** Unknown **In all patients:** 52.8% (82/120) when not considering 12 month follow-up after negative biopsy 75% (90/120) when considering negative disease state to be negative biopsy and negative follow-up at 12 months	**Patients with history of bladder cancer:** **Sensitivity:** 86% **In all patients:** **Accuracy:** 82.5% (99/120) **Sensitivity:** 85.4% (70/82) *By stage:* pTa: 82.8% (53/64) pT1: 83.3% (5/6) pT2: 100% (6/6) pT4: 100% (3/3) pTis: 100% (3/3) *By grade:* G1: 82.6% (19/23) G2: 80.0% (28/35) G3: 95.8% (23/24) **Specificity:** 76.3% (29/38) **TP:** 88.6% (70/79) **FP:** 11.4% (9/79) **TN:** 70.7% (29/41) **FN:** 29.3% (12/41) Among patients with negative biopsy and negative 12 month follow-up, **Specificity[2]:** 96.6% (28/29)	**Patients with history of bladder cancer:** No results available **In all patients:** **Sensitivity[3]:** 75.6% (62/82)	Among 9 patients with positive FISH or negative concurrent biopsy, 8 (89%) developed biopsy-proven TCC within 3–12 months (mean 5.5)

[1] For further details refer to Table 29

[2] Table and text disagree; results from table presented

[3] Suspicious cytology results classed as positive for the purpose of sensitivity calculations

Table 30 continued Results of studies included in the review

Results of studies of diagnostic accuracy						
Author & Year	**N[1]**	**Index test, comparator and reference standard**	**Prevalence**	**UroVysion outcomes**	**Comparator outcomes**	**Other**
Varella-Garcia *et al.* (2005)	19 patients	**Index test:** UroVysion FISH assay (voided urine); positive result defined as >16% cells with polysomy or >48% of cells with 9p21 homozygous loss among at least 50 nuclei scored **Comparator(s):** Cytology **Reference standard:** Cytoscopy with biopsy or tumour resection for positive cystoscopies	36.8% (7/19)	**Accuracy:** 94.7% (18/19) **Sensitivity:** 85.7% (6/7) **Specificity:** 100% (12/12) **TP:** 100% (6/6) **FP:** 0% (0/6) **TN:** 92.3% (12/13) **FN:** 7.7% (1/13)	**Accuracy:** 78.9% (15/19) **Sensitivity:** 42.9% (3/7) **Specificity:** 100% (12/12) **TP:** 100% (3/3) **FP:** 0% (0/3) **TN:** 75.0% (12/16) **FN:** 25.0% (4/16)	

[1] For further details refer to Table 29

Appendix E Excluded studies

The following is a list of publications which were retrieved in full text for possible inclusion in the review and found to meet one of the exclusion criteria outlined in Table 12.

Amiel GE, Shu T, Lerner SP, 2004, Alternatives for cytology in the management of non-muscle invasive bladder cancer, *Current Treatment Options in Oncology*, 5, 377-389.

Bubendorf L, Grilli B, 2004, UroVysion multiprobe FISH in urinary cytology, *Methods in Molecular Medicine*, 97, 117–131.

Bubendorf L, Grilli B, Sauter G, Mihatsch MJ, Gasser TC, Dalquen P, 2001, Multiprobe FISH for enhanced detection of bladder cancer in voided urine specimens and bladder washings, *American Journal of Clinical Pathology*, 116(1), 79–86.

Dahmoush L, Cohen MB, 2004, FISHing and beyond in urinary cytology, *Diagnostic Cytopathology*, 31(4), 201.

Dalquen P, Kleiber B, Grilli B, Herzog M, Bubendorf L, Oberholzer M, 2002, DNA image cytometry and fluorescence *in situ* hybridization for noninvasive detection of urothelial tumors in voided urine, *Cancer*, 96(6), 374–379.

Eissa S, Kassim S, El Ahmady O, 2003, Detection of bladder tumours: role of cytology, morphology-based assays, biochemical and molecular markers, *Current Opinions in Obstetrics and Gynecology*, 15(5), 395–403.

Friedrich MG, Toma MI, Hellstern A, Pantel K, Weisenberger DJ, Noldus J, *et al.*, 2003, Comparison of multitarget fluorescence *in situ* hybridization in urine with other noninvasive tests for detecting bladder cancer, *BJU International*, 92(9), 911–914.

Grossman HB, 1998, New methods for detection of bladder cancer, *Seminars in Urologic Oncology*, 16(1), 17-22.

Halling KC, 2003, Vysis UroVysion for the detection of urothelial carcinoma, *Expert Review of Molecular Diagnostics*, 3(4), 507–519.

Halling KC, King W, Sokolova IA, Karnes RJ, Meyer RG, Powell EL, *et al.*, 2002, A comparison of BTA Stat, hemoglobin dipstick, telomerase and Vysis UroVysion assays for the detection of urothelial carcinoma in urine, *Journal of Urology*, 167(5), 2001–2006.

Jichlinski P, 2003, New diagnostic strategies in the detection and staging of bladder cancer, *Current Opinions in Urology*, 13(5), 351–355.

Konety BR, Williams RD, 2004, Superficial transitional (Ta/T1/CIS) cell carcinoma of the bladder, *BJU International*, 94(1),18-21.

Kruger S, Mess F, Bohle A, Feller AC, 2003, Numerical aberrations of chromosome 17 and the 9p21 locus are independent predictors of tumor recurrence in non-invasive transitional cell carcinoma of the urinary bladder, *International Journal of Oncology*, 23(1), 41–48.

Kurth KH, 1997, Diagnosis and treatment of superficial transitional cell carcinoma of the bladder: facts and perspectives, *European Urology*, 31(Suppl 1), 10–19.

Lane T, Oliver T, 2002, A study comparing various non-invasive methods of detecting bladder cancer in urine, *BJU International*, 90(4),477.

Little B, 2003, Non-invasive methods of bladder cancer detection, *International Urology & Nephrology*, 35(3), 331-43.

Lubbe L, Nowack R, May M, Ullmann K, Gunia S, Kaufmann O, *et al.*, FISH—a new noninvasive method for the diagnosis of urinary bladder carcinomas, *Clinical Laboratory*, 50(7–8), 395–402.

Meloni AM, Peier AM, Haddad FS, Powell IJ, Block AW, Huben RP, *et al.*, 1993, A new approach in the diagnosis and follow-up of bladder cancer. FISH analysis of urine, bladder washings, and tumors, *Cancer Genetics and Cytogenetics*, 71(2), 105–118.

Mian C, Lodde M, Comploj E, Negri G, Egarter-Vigl E, Lusuardi L, *et al.*, 2003, Liquid-based cytology as a tool for the performance of uCyt+ and UroVysion multicolour-FISH in the detection of urothelial carcinoma, *Cytopathology*, 14(6), 338–342.

Parry WL, Hemstreet GP III, 1988, Cancer detection by quantitative fluorescence image analysis, *Journal of Urology*, 139(2), 270–274.

Quek ML, Sanderson K, Daneshmand S, Stein JP, 2004, New molecular markers for bladder cancer detection, *Current Opinions in Urology*, 14, 259–264.

Sandberg AA, Berger CS, 1994, Review of chromosome studies in urological tumors. II. Cytogenetics and molecular genetics of bladder cancer, *Journal of Urology*, 151(3), 545–560.

Skacel M, Liou LS, Pettay JD, Tubbs RR, 2002, Interphase fluorescence *in-situ* hybridization in the diagnosis of bladder cancer, *Frontiers in Bioscience*, 7, e27–e32.

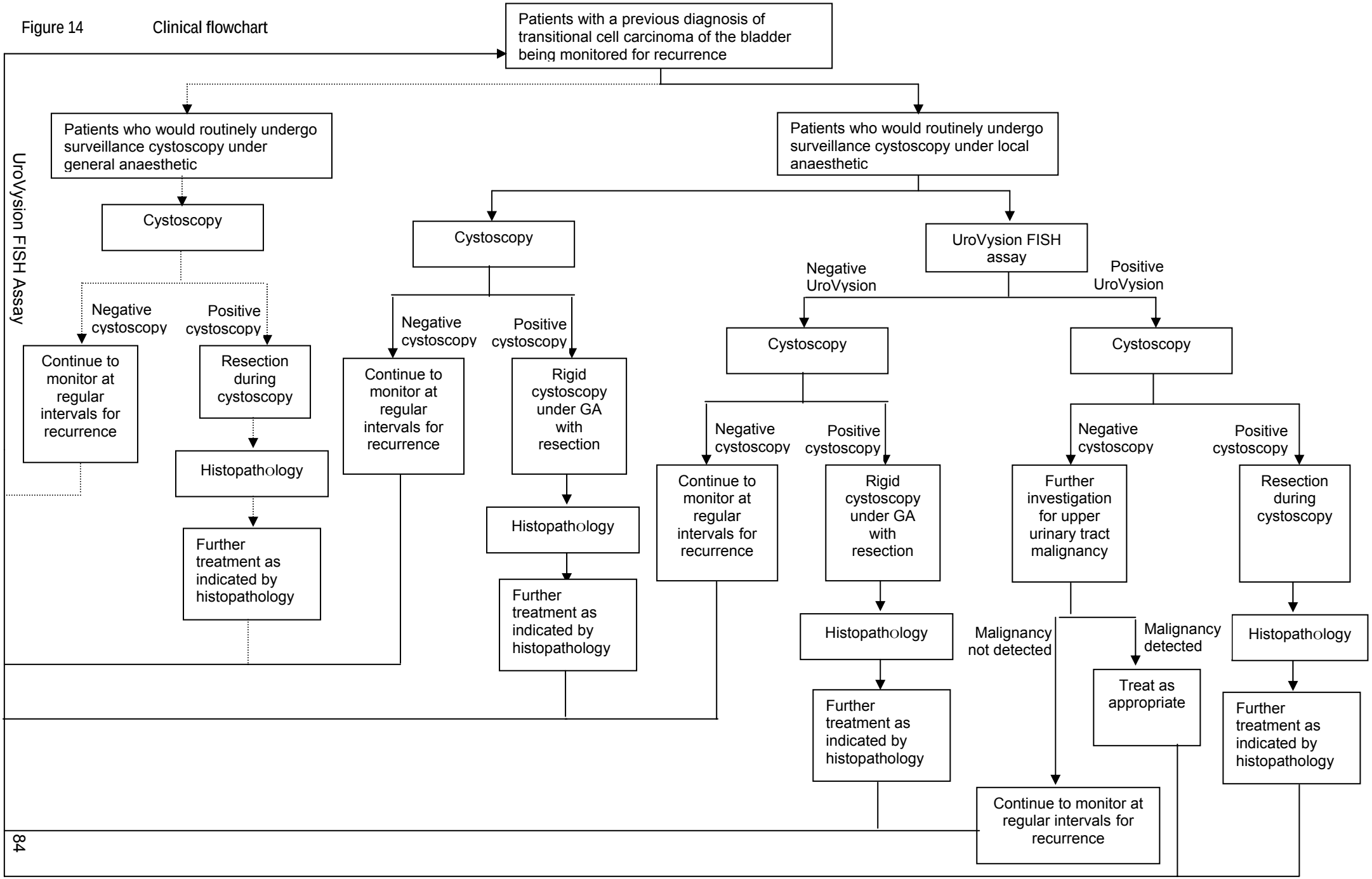
Sokolova IA, Halling KC, Jenkins RB, Burkhardt HM, Meyer RG, Seelig SA, *et al.*, 2000, The development of a multitarget, multicolor fluorescence *in situ* hybridization assay for the detection of urothelial carcinoma in urine, *Journal of Molecular Diagnostics*, 2(3), 116–123.

Veeramachaneni R, Nordberg ML, Shi R, Herrera GA, Turbat-Herrera EA, 2003, Evaluation of fluorescence *in situ* hybridization as an ancillary tool to urine cytology in diagnosing urothelial carcinoma, *Diagnostic Cytopathology*, 28(6), 301–307.

Appendix F Clinical flow chart

The following flow chart outlines the role of the UroVysion FISH assay in the diagnosis and treatment pathway for patient with a history of bladder cancer being monitored for recurrence.

Figure 14 Clinical flowchart



Appendix G Economic evaluation—additional costing information

Table 31 shows the sources and costings that were used to determine theatre and accommodation costs for each of the three cystoscopy procedures included in the economic analysis (MBS item numbers 36812, 36840 and 36845).

Table 31 Theatre and accommodation costs for cystoscopy procedures

Health fund	Procedure								
	MBS Item No. 36812			*MBS Item No. 36840*			*MBS Item No. 36845*		
	Theatre cost	Accommodation cost (day only)	Total	Theatre cost	Accommodation cost (day only)	Total	Theatre cost	Accommodation cost (overnight)	Total
Alliance[1]	$299	$342	$641	$531	$342	$873	$643	$530	$1173
Medibank Private[2,3]	–	–	$634	–	–	$826	–	–	$1336
HCF[1,3]	–	–	$634	–	–	$885	$610	$572	$1182
Westfund[1]	$308	$339	$647	$535	$339	$874	$600	$558	$1158
ACA[4]	$285	$397	$682	$479	$397	$876	$583	$645	$1228
Australian Unity[4]	$285	$397	$682	$479	$397	$876	$583	$644	$1227

[1] Estimate obtained from Nepean Private Hospital, NSW, April 2005. [2] Mean of estimates obtained from Nepean Private Hospital and Sydney Adventist Hospital, NSW, April 2005
[3] Medibank Private & HCF provide combined costs only for theatre and accommodation. [4] Estimate obtained from Sydney Adventist Hospital, NSW, April 2005

The median theatre cost and the median accommodation cost for each procedure were used in the base case analysis of the economic evaluation. Where total costs only were available (Medibank Private and HCF), estimates were made of theatre and accommodation costs based on the proportion of total cost made up by theatre costs in health funds for which separate theatre and accommodation costs were available. These median costs are shown in Table 32.

Table 32 Median theatre and accommodation costs for cystoscopy procedures

MBS Item No.	Median theatre cost ($AU)	Median accommodation cost ($AU)
36812	$285	$352
36840	$496	$361
36845	$605	$608

Abbreviations

ABS	Australian Bureau of Statistics
ACS	American Cancer Society
AIHW	Australian Institute of Health and Welfare
AJCC	American Joint Committee on Cancer
BCG	Bacillus Calmette-Guérin
BTA	bladder tumour antigen
CDHA	Commonwealth Department of Health and Ageing
CEP	chromosome enumeration probe
CI	confidence interval
DAPI	4,6-diamidino-2-phenylindole
DHA	Department of Health and Ageing
DNA	deoxyribonucleic acid
EMBASE	medical database at http://www.embase.com/
FDA	United States of America Food and Drug Administration
FDP	fibrin or fibrinogen degradation product
FISH	fluorescence *in situ* hybridisation
FN	false negative
FP	false positive
GA	general anaesthetic
HTA	heath technology assessment
ICD-10-AM	International Statistical Classification of Diseases and Related Health Problems, 10th revision, Australian Modification
LA	local anaesthetic
LR	likelihood ratio
LSI	locus-specific identifier
MBS	Medical Benefits Schedule

MSAC	Medical Services Advisory Committee
N or *n*	number of patients
NCCN	National Comprehensive Cancer Network
NHMRC	National Health and Medical Research Council
NICE	National Institute for Clinical Excellence (UK)
NMP	nuclear matrix protein
NS	not significant
OR	odds ratio
QUADAS	quality assessment of diagnostic accuracy studies
QUOROM	quality of reporting of meta-analyses
RACGP	Royal Australian College of General Practitioners
RNA	ribonucleic acid
ROC	receiver operating characteristic
TCC	transitional cell carcinoma
TN	true negative
TNM	tumour-node-metastasis
TP	true positive
TUR	trans-urethral resection

Glossary

Anaplasia	A loss of differentiation of cells; a characteristic of tumour tissue
Aneuploidy	An abnormal number of copies of a chromosome (that is, more than or less than two)
Aneusomy	See aneuploidy
Centromere	The constricted portion of a chromosome where the paired chromosome strands are joined
Chromosome	A structure in the nucleus containing DNA which transmits genetic information and is associated with RNA; in man, the normal number of chromosomes present in somatic cells is 46
Cystectomy	Removal or resection of the bladder
Cystoscopy	Direct visual examination of the bladder and urinary tract with a cystoscope (a long thin lighted tube which is inserted through the urethra)
Cytology	The study of cells—their origin, structure, function and pathology
Denature	Destruction of the usual nature of a substance—in relation to DNA, it is unravelling of the two strands of DNA using, for example, heat, a change in pH or other physical or chemical means
Deoxyribonucleic acid (DNA)	A nucleic acid that carries the genetic information in the cell and is capable of self-replication and synthesis of RNA. DNA consists of two long chains of nucleotides twisted into a double helix and joined by hydrogen bonds between the complementary nitrogen bases
Haematuria	Blood in the urine
Homologous	In relation to chromosomes, homologous refers to pair of chromosomes containing the same gene sequences
Homozygous	Possessing a pair of identical alleles at a given locus (that is, a given position on a chromosome)
Hybridisation	A process in which complementary strands of DNA from different sources are mixed, and some of the reformed structures will consist of one strand from each source
In situ	In the natural place (that is, occurring in the urinary cells)

Intravesical	Within the bladder
Locus	The position of a gene on a chromosome
Morphology	The form or structure of an organism, organ or part
Negative likelihood ratio	The probability of a negative test result in patients with the disease compared to those without the disease
Polysomy	An excess of a particular chromosome (that is, having more than 2 copies of a chromosome in a cell)
Positive likelihood ratio	The probability of a positive test result in patients with the disease compared to those without the disease
Sensitivity	The probability that a person having the disease is correctly identified by a clinical test
Specificity	The probability that a person without the disease is correctly identified by a clinical test
Stranguria	Slow and painful discharge of urine, due to spasm of the urethra and bladder
Transitional cell carcinoma (TCC)	A malignant neoplasm derived from transitional epithelium and occurring primarily in the urinary bladder, ureters or renal pelves
Transurethral resection (TUR)	Removal of a tumour in a procedure conducted through the urethra
Trisomy	Having an extra chromosome of one type in a cell (that is, having three copies of a chromosome)
Urothelial carcinoma	See transitional cell carcinoma

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