VETERANS HEALTH ADMINISTRATION
OFFICE OF PATIENT CARE SERVICES
TECHNOLOGY ASSESSMENT PROGRAM

Brief Overview:

Bladder Cancer Surveillance

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TECHNOLOGY ASSESSMENT PROGRAM

An Effective Resource for Evidence-based Managers

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A SUMMARY FOR HTA REPORTS
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This summary form is intended as an aid for those who want to record the extent to which a HTA report meets the 17 questions presented in the checklist. It is NOT intended as a scorecard to rate the standard of HTA reports – reports may be valid and useful without meeting all of the criteria that have been listed.

BRIEF OVERVIEW
Bladder Cancer Surveillance
(NOVEMBER 2007)

Item	Yes	Partly	No
Preliminary			
1. Appropriate contact details for further information?	√		
2. Authors identified?	√		
3. Statement regarding conflict of interest?			√
4. Statement on whether report externally reviewed?	√		
5. Short summary in non-technical language?	√		
Why?			
6. Reference to the question that is addressed and context of the assessment?	√		
7. Scope of the assessment specified?	√		
8. Description of the health technology?		√	
How?			
9. Details on sources of information?	√		
10. Information on selection of material for assessment?	√		
11. Information on basis for interpretation of selected data?	√		
What?			
12. Results of assessment clearly presented?	√		
13. Interpretation of the assessment results included?	√		
What Then?			
14. Findings of the assessment discussed?	√		
15. Medico-legal implications considered?		√	
16. Conclusions from assessment clearly stated?	√		
17. Suggestions for further actions?	√		

Brief Overview:

Bladder Cancer Surveillance

ABBREVIATIONS IN THIS REPORT

ABC	advanced bladder cancer
ACR	American College of Radiology
BC	bladder cancer
BCG	bacillus Calmette-Guérin
BTA	bladder tumor antigen
AHRQ	Agency for Healthcare Research and Quality
CI	95% confidence interval
CIS	carcinoma in situ
EAU	European Association of Urology
EORTC	European Organization for Research and Treatment of Cancer
ESMO	European Society for Medical Oncology
FISH	fluorescence in situ hybridization
FU	follow up
LR	likelihood ratio
MMC	mitomycin C
NMIBC	non-muscle invasive bladder cancer
NMP	nuclear matrix protein
MSAC	Medical Services Advisory Committee (Australia)
OR	odds ratio
RBC	red blood cell
RR	relative risk
SD	standard deviation
TCC	transitional cell carcinoma
TUR	transurethral resection
QoL	quality of life
UC	urothelial cancer
USPSTF	US Preventive Services Task Force

Brief Overview:

Bladder Cancer Surveillance

INTRODUCTION

"A transitional cell epithelium lines the urinary tract from the renal pelvis to the ureter, urinary bladder, and the proximal two-thirds of the urethra. Carcinomas may occur at any point, but generally 90% develop in the bladder, 8% in the renal pelvis, and 2% in the ureter or urethra…In the United States, 90 to 95% of bladder tumors diagnosed are transitional cell tumors…

"Cigarette smoking is believed to contribute to up to 50% of the diagnosed urothelial cancers in men. The risk of developing a urothelial cancer is increased two- to fourfold relative to nonsmoking males and may persist for 10 years or longer after smoking is stopped…

"Once diagnosed, these tumors exhibit the tendency to recur over time and in new locations in the urothelial tract. As long as urothelium is present, continuous monitoring of the urothelial tract is required." Scher (2001).

"Bladder cancer is the second most common genitourinary malignancy in the United States, with an estimated 6,420 new cases in 2006 and a prevalence of roughly 500,000 cases. The preponderance of cases (65-80%) is non-muscle invasive (stage Ta/T1/Tis) at presentation, and the natural history of these cases is unique in its propensity for local recurrence over the course of a patient's life. Following transurethral resection (TUR), anywhere from 50 to 90% of NMIBCs will eventually recur…

"Given the large number of cases of non-muscle invasive disease, the potential economic consequences of standard practice, where patients are typically assigned to a lifetime of surveillance, are significant. In fact, bladder cancer has the distinction of being the most expensive tumor type per patient, due in large part to the high costs of lifelong surveillance, monitoring, and repeated treatments. An illuminating economic analysis estimated the annual direct costs of bladder cancer in the US alone at roughly $4 billion, with the cost per patient with bladder cancer from diagnosis to death estimated to be $96,000-$187,000. Clearly, innovations in bladder cancer management may have a substantial economic impact.

"The economic impact of further integration of biomarkers in the clinical practice of bladder cancer care may be manifest in a number of ways. At one extreme, established components of the current standard of care (e.g., cytology) may be completely replaced by a novel marker. Alternatively, validation of the performance of a given novel marker of panel of markers may facilitate the development of risk-adjusted management protocols that alter the frequency of regular cystoscopic examinations. Given the sheer numbers of patients undergoing "standard" bladder cancer surveillance, even slight modifications of these standards of care could have major impact. The potential quality of life "costs" of bladder cancer care, including regular invasive cystoscopic examinations, are also non-trivial from the patients' perspective." Nielson (2006).

"Over 50,000 cases of transitional cell carcinoma of the urinary bladder are diagnosed each year in the United States, leading to nearly 10,000 deaths. The median age at diagnosis is approximately 65 years with 70% to 80% if tumors confined to lamina propria, i.e., superficial tumors (stage Ta or T1). Carcinoma in situ (CIS) represents another form of superficial tumor characterized by diffuse malignant cells confined to the epithelium." Huncharek (2004).

"At present, cystoscopy and histology are still considered the gold standard methods for the detection of primary or recurrent urethral cancer (UC) of the bladder. Patients with bladder tumuor undergo 3-6 months of cystoscopy and cytology follow-up. Despite technical improvements, cystoscopy is an invasive method causing the patient some discomfort. Furthermore, flat tumours or carcinoma in situ *may be difficult to detect."* Mian (2005).

"…Once a pathologist confirms muscle-invasive tumor growth, lymphadenectomy and cystectomy or radiotherapy is recommended. In any case, a close follow-up of the patients is required as UCC is considered to be a pan urothelial disease and also due to possible monoclonal spread of urothelial cancer

cells. The probability of recurrence ad progression in superficial bladder cancer a 5 years ranges from 31 to 78% and from less than 1 to 45%, depending on grade and stage, respectively." Arentsen (2007).

Based on a review of the literature, the most important prognostic factors for recurrence are prior recurrence rate, number of tumors, and tumor size; whereas for progression, the most important prognostic factors are the T category, grade, and presence of CIS. Treatment with intravesical bacillus Calmette-Guerin reduces both the risk of recurrence and the risk of progression, and is the treatment of choice in high-risk papillary tumors and in patients with CIS...

"However, a limitation of nearly all these prognostic factor studies is that they date from the pre-BCG maintenance era, when most patients did not receive an immediate postoperative instillation of chemotherapy, and high-risk patients did not have a second-look TUR. Thus, current rates of recurrence and progression may be lower than those previously reported in the literature. Likewise, it is not clear if the prognostic importance of factors identified in previous studies would remain the same if patients are treated according to current recommendations: the use of an immediate instillation, and a second look TUR and maintenance BCG in high risk patients.

"Nevertheless, it is time to stop classifying all patients under the same heading, superficial, in order to properly convey the very different risk of progression to muscle invasive disease that is present in those patients. Nieder and Soloway (2006) propose a new nomenclature based on the pathological diagnosis and risk of progression:

- *"Papilloma, papillary urothelial neoplasms of low malignant potential (PUNLMP)*
- *"Ta, low grade*
- *"Ta, high grade*
- *"T1, high grade*
- *"CIS"*

Sylvester (2006).

"The diagnosis of both primary and recurrent bladder tumors currently relies upon both urine cytology and cystoscopy. Neither of these diagnostic tools is completely accurate. Prognostication of bladder cancer is largely based on pathologic tumor grade and stage. Over the past two decades, there is accumulating evidence that like many other cancers, bladder cancer, too, has a distinct molecular signature that separates it from other cancers and from normal bladder tissue. Bladder tumors of different grades and stages even possess unique, and specific genotypic and phenotypic characteristics. Although recognition of several of these markers is possible by analyzing tumor tissue, urine, and serum samples, few if any of these "molecular markers" for bladder cancer are widely used in clinical practice. These markers include some that can be applied during the diagnostic work-up of symptoms (e.g. hematuria), those under surveillance for recurrence of superficial disease and forecasting long-term prognosis, or response to chemotherapy.

"Cystoscopy, which is used in most studies of diagnostic markers as the reference standard, is itself not always accurate, with a sensitivity as low as 73% and specificity of 37%. The low effectiveness and invasive nature of conventional methods in the diagnosis of bladder cancer have prompted the search for newer and better ways to diagnose the disease…

"Although there are several candidate markers for assessing prognosis or response to chemotherapy, studies of large patient populations are lacking. Further studies involving larger numbers of patients are required to determine their accuracy and widespread applicability in guiding treatment of bladder cancer." Konety (2006).

"Urinary cytology is used routinely for the diagnosis and management of patients with urothelial carcinoma and its precursors. The diagnostic yield of urinary cytology in daily practice depends on the grade of the primary lesion and the type of specimen examined. Although diagnostic accuracy is very high for high-grade carcinoma and carcinoma in situ, cells of low-grade urothelial neoplasms often lack recognizable features, resulting in a low detection rate. The frequently encountered diagnosis of nonconclusive atypia is another important problem in urinary cytology because it leaves patients and physicians in uncertainty and may result in unnecessary procedures. In addition, there is a disturbingly high rate of false-positive results in cytologic samples of patients receiving intravesical therapy with cytotoxic agents or bacille Calmette-Guérin." Glatz (2006).

"Histopathologic grade and tumor stage remain the standards for predicting patient prognosis. Invasive TCC clearly has a poor prognosis highly associated with regional and distant metastases. In general,

invasive TCC are high-grade, poorly differentiated neoplasms. It has been shown, however, that histopathologically similar low-grade and noninvasive tumors with divergent karyotypes have different tumor behavior. Therefore, one cannot rely on histologic grade alone for prognostic purposes." Wolman (2007).

"The current reference standard for UC surveillance is cystoscopic examination with urine cytologic examination every 3 months during the first two years with decreasing frequency thereafter. Limitations of the present surveillance algorithm include the need for frequent invasive evaluation of the bladder mucosa by cystoscopy, the relatively low sensitivity of urine cytology of around 34%, and the frequent occurrence of cytologically equivocal ("atypical") results. This has led to the development of many adjunctive assays for the detection of UC recurrence, the goal of which is to identify patients for whom increased intensity of cystoscopy is a necessity while allowing safe extension of surveillance intervals for patients at minimal risk of recurrence. These adjunctive assays are urine-based immunoassays such as BTA Stat (Polymedco, Cortlandt Manor, NY) and NMP2 (Matritech, Newton MA), or cell-based assays such as ImmunoCyt (DiagnoCure, Quebec, Canada) and UroVysion (Abbott/Vysis, Downers Grove, IL)." Yoder (2007).

"Using the UroVysion test, it is possible to predict behavior of urothelial cancer with a significant impact on the follow-up of patients. The intermediate-risk group of urothelial cancer can be eliminated in the routine workup by classifying these patients according to their chromosomal pattern and defining those patients who can follow the low-risk scheme and those who must be monitored according to guidelines for high-risk superficial lesions." Pycha (2004).

"In comparison to the UroVysion test, cystoscopies are invasive procedures and are associated with known adverse effects. These include bladder rupture, stramnguria, bleeding and urinary tract infections, although it would appear that the incidence of these complications following cystoscopy is rare, and although minor complications are more common, they usually resolve within 48 hours and are likely to be of minimal clinical significance." MSAC (2005).

"The most common noninvasive method for monitoring bladder cancer is the detection of exfoliated tumor cells by urinary cytology. Cytology has high sensitivity for detecting high grade tumors but poor sensitivity for detecting low grade tumors, which are the most common type of bladder cancer. However, the limitations of cytology, especially for detecting recurrent low grade tumors, and the invasiveness of cystoscopy have increased interest in tests using urinary diagnostic markers." Messing (2005).

"…The "take home message" of this discussion is that for any novel biomarker to satisfy the requirements for clinical utility, it will require rigorous evaluation in well-designed prospective multicenter trials including heterogeneous groups of both bladder cancer cases and individuals without bladder cancer with potentially confounding conditions common to urological practice….." Sylvester (2006).

"There has been minimal progress in reducing the mortality from BC in more than 25 years. Despite some benefits for systemic chemotherapy, long-term survival for patients with metastatic disease only approaches 15%. Effective treatment starts with a proper diagnosis and appropriate categorization of disease potential. High grade BC can be a lethal disease, and labeling those cases as having "superficial" BC may not be in the best interest." Sylvester (2006).

BACKGROUND

VHA's Office of Patient Care Services (OPCS) asked the Technology Assessment Program (TAP) for a review of the literature on fluorescence in situ hybridization (FISH)/UroVysion ™ (Vysis, Inc.; Downers Grove IL) as a monitoring test for recurrent bladder cancer. The specific questions to be addressed are:

1. What are the indications/applications for UroVysion?
2. What is the quality of evidence for each indication?
3. What is the evidence for advantages of FISH versus alternative tests for recurrent bladder cancer?

METHODS

Systematic reviews

Cook (1997) and Mulrow (1997) define systematic reviews: *"Systematic reviews are scientific investigations in themselves, with pre-planned methods and an assembly of original studies as their "subjects". They synthesize the results of multiple primary investigations by using strategies that limit bias and random error…"*

The same authors further specify characteristics of systematic reviews and contrast them with traditional narrative reviews: the latter synthesize articles without reporting methods of selection or quality assessment criteria and thus do not qualify as reproducible science.

Systematic reviews:

- Ask a focused clinical question;
- Conduct a comprehensive search for relevant studies using an explicit search strategy;
- Uniformly apply criteria for inclusion and exclusion of studies;
- Rigorously and critically appraise included studies;
- Provide detailed analyses of the strengths and limitations of included studies.

Systematic reviews can be quantitative (i.e., meta-analytic, applying statistical methods to summarize study results) or qualitative; in either case the inferences or conclusions of the review must follow logically from the evidence presented. The rigor of this approach is illustrated by the place of systematic reviews in evidence grading schemes (Cook 1995; Guyatt 1995), where they receive the highest level designation.

Analytic framework: systematic reviews

In the broad context outlined by the review questions, TAP first identified available systematic reviews and technology assessments. Such reviews provide a rigorous and immediately accessible overview of the state of knowledge and research progress toward definitive answers to questions of effectiveness, adverse effects, and cost effectiveness for healthcare interventions. They synthesize otherwise unmanageable amounts of primary research literature, and thus provide an invaluable resource for rapidly responding to policy makers' information needs in broadly defined areas such as the evidence supporting various approaches to bladder cancer surveillance.

TAP also includes clinical guidelines, technology assessments, economic analyses, or decision analyses in which efficacy estimates or recommendations clearly were based on systematic reviews.

TAP excludes primary research unless studies meeting inclusion criteria for systematic reviews, were published subsequent to searches conducted for reviews, and would change the review's conclusions. Systematic reviews of risk factors for bladder cancer were also excluded as outside the scope of this overview. TAP does not abstract narrative reviews or consensus statements in detail (Table 2) although Table 1 indicates availability.

Analytic framework: diagnostic tests

Diagnostic testing has been the subject of much methodological discussion, summarized by Muir Gray (1997) and Sackett (1991). Briefly, evaluation of a diagnostic technology entails five levels (Banta and Luce, 1993):

1. *"Technical evaluation: the technical output gives accurate information concerning the structure of the body part imaged.*

2. *Diagnostic accuracy: this output concerns information that potentially improves the clinician's ability to diagnose disease and assess the patient's prognosis.*
3. *Diagnostic impact: the information can alter plans for additional diagnostic tests.*
4. *Therapeutic impact: the information can lead to changes in therapeutic plans for patients.*
5. *Health impact: the end result may be improved patient outcome."*

Search strategy/selection criteria

TAP searched Medline, the databases of the International Network of Agencies for Health Technology Assessment (INAHTA; www.inahta.org), and the Cochrane Library using the terms bladder cancer, monitoring, surveillance, or screening and publication types (review, meta-analysis) to identify systematic reviews and assessments published in English and which synthesize research in adult human subjects for the years 2001 to 2007. TAP updated all searches on October 18, 2007.

One author (KF) selected citations for full-text retrieval, reviewed all articles, abstracted information, and prepared this report.

RESULTS

TAP immediately identified one recent, comprehensive, and directly relevant technology assessment report (MSAC, 2005; Table 1), which serves as the starting point for this review and whose analytic framework (systematic reviews and stages of diagnostic test evaluation) TAP continues.

MSAC searches closed in March 2005 and the report provides extensive background on bladder cancer staging/grading, so TAP restricts attention to literature published after that date and does not duplicate background information.

Table 1 provides an overview of English-language reviews and guidelines, and Table 2 (Appendix) details their recommendations and findings.

Table 1. Categories and content of English-language reviews from TAP searches [but not cited by MSAC (2005)]

Study type	Citation	Content/Interventions
Surveillance of bladder cancer patients for disease recurrence		
Systematic reviews	MSAC (2005)	UroVysion FISH assay
	Malats(2005)	P53 as a prognostic marker for bladder cancer, recurrrence, progression, mortality
	Segal (2005)	Guideline: follow-up imaging (X-ray, ultrasound, CT) of bladder cancer
Narrative review/consensus statement	Lokeshwar (2005)	Bladder tumor markers: two articles from one consensus panel
	Habuchi (2005)	
	Black (2006)	Molecular markers for monitoring superficial urothelial cancer
	Arentsen (2007)	FISH
	Palou (2006)	Patient risk profiles
	Liou (2006)	Biomarkers for diagnosis and surveillance
	Schultz (2006)	Surviving for diagnosis and recurrence prognosis
	ESMO(2005)	Minimum recommendations for diagnosis, treatment and FU of invasive bladder cancer
Other components of bladder cancer management		
Quasi systematic review	Dalbagni (2007)	Management of superficial bladder cancer
Narrative review	Stein (2007)	Orthotopic urinary diversion in women with bladder cancer
Systematic reviews	ABC Meta-Analysis Collaboration (2006)	Adjuvant chemotherapy for invasive bladder cancer: two publications of the same review
	ABC Meta-Analysis Collaboration (2005)	
	Fahmy (2006)	Delay in surgical treatment of bladder cancer and survival
	Han (2006)	Intravesical BCG
	Lotan (2006)	Screening for bladder cancer using urine markers in a high risk population
	Rodgers (2006)	Diagnostic tests for hematuria
	Ruggeri (2006)	Adjuvant chemotherapy in muscle invasive bladder cancer
	Tinazzi (2006)	Reactive arthritis following BCG for bladder cancer
	Bennett (2005)	Hyperbaric oxygenation for tumor sensitization to radiotherapy
	Porter (2005)	Health-related QoL after radical cystectomy and urinary diversion
	Takkouche (2005)	Hair dyes and relative risk of cancer
	Advanced Bladder Cancer Overview Collaboration (2004)	Neoadjuvant chemotherapy for invasive bladder cancer
	Huncharek (2004)	Intravesical chemotherapy Vs BCG immunotherapy
	Huncharek (2003)	
	Huncharek (2001)	
	Sylvester (2004)	Single immediate postoperative instillation of chemotherapy
	USPSTF (2004)	Guideline: screening for bladder cancer in adults
	Shelley (2003)	Intravesical BCG versus MMC in superficial bladder cancer
	Panmar (2003)	Neoadjuvant chemotherapy for invasive bladder cancer
	Nabi (2003)	Urinary diversion/bladder reconstruction
Narrative review	Kurth (2007)	Prognostic factors (clinical, biologic) in NMIBC
	Stein (2007)	Orthotopic urinary diversion in women with bladder cancer
	Nieder (2005)	Management of stage T1 bladder tumors
	Carmack (2006)	Diagnosis and staging

SUMMARY AND DISCUSSION

To revisit the assessment questions:

1. What are the indications/applications for UroVysion? An FDA letter approving marketing of UroVysion (June 24, 2005) states approved indications:

> *"The UroVysion Bladder Cancer Kit (UroVysion Kit) is designed to detect aneuploidy for chromosomes 3, 7, 17, and loss of the 9p21 locus via fluorescence* in situ *hybridization (FISH) in urine specimens from persons with hematuria suspected of having bladder cancer. Results from the UroVysion Kit are intended for use, in conjunction with and not in lieu of current standard diagnostic procedures, as an aid for initial diagnosis of bladder cancer in patients with hematuria and subsequent monitoring for tumor recurrence in patients previously diagnosed with bladder cancer."*

2. What is the quality of evidence for each indication? Both indications cited by the FDA are supported by diagnostic accuracy studies as noted in MSAC (2005) and van Rhijn (2005), both in Table 2, with cytology as the reference standard.

3. What is the evidence for advantages of FISH versus alternative tests for recurrent bladder cancer? No evidence beyond diagnostic accuracy studies supports replacing cytology-based surveillance protocols with urine marker tests. A prediction model based on clinical variables is available (Sylvester, 2006; Table 2) but provides only ranges of probabilities for any individual patient and would still require individualized decision making.

CONCLUSIONS

TAP's overview of the post-2005 literature indicates both substantial recent publication activity and the lack of studies at the higher levels of diagnostic test evaluation necessary to change the conclusions of the MSAC (2005) review of UroVysion FISH. Additional diagnostic accuracy studies with imperfect cytology as the gold standard and narrative reviews contribute little to the body of knowledge.

The single post-MSAC comprehensive systematic review (van Rhijn, 2005; Table 2) further confirms that studies to that date were limited to the diagnostic accuracy level and do not support replacing cystoscopy- or cytology-based surveillance by urine markers. The single relevant trial of surveillance protocols (Denzinger, 2007) tested 5-amino-levulinic acid-induced fluorescence diagnosis against white light cystoscopy and found a statistical advantage to fluorescent diagnosis at 8 years. Yoder (2007) also report that 27% of patients without immediate cystoscopic evidence of recurrence will have positive FISH; 63% of "anticipatory positives" developed recurrent cancer during 29-month follow up, the majority of which were low-grade.

More recent primary research also fails to provide fully definitive answers. A direct comparison of UroVysion to cytology and quantitative cytology (Moonen, 2007) concludes that UroVysion provides no improvement over current cytology-based surveillance protocols. Another primary research report (Gudjonnson, 2007; available to TAP only in abstract form also confirms MSAC's conclusion (Table 2, Appendix) that UroVysion's low sensitivity limits clinical usefulness. With TAP's caveat regarding their relatively small (175 FU visits) diagnostic accuracy study and with insufficient detail in the abstract to judge study quality, Gudjonsson (2007) conclude:

> *"...the UroVysion urinary test has too low sensitivity to be considered as an alternative to cystoscopy in surveillance of patients with superficial bladder cancer. UroVysion is*

> *however valuable for detecting CIS in the bladder. Its use should be considered in patients with a history of high grade urothelial cancer, patients with equivocal cystoscopic findings and patients with inconclusive or atypical urine cytology."*

Finally, bladder cancer is a cigarette-associated disease for which many aspects of optimal management, including surveillance for recurrence with newer biomarkers, have yet to be fully defined, as does optimal allocation of societal resources to prevention versus treatment.

The optimal cut point for a FISH positive diagnosis remains to be determined, the test is not in a position to replace cytology, and no trial directly comparing FISH to other tests and reporting health outcomes in patients under surveillance for recurrent bladder non-muscle invasive cancer (stratified by grade and stage under a standardized nomenclature) has been reported or is in progress, from 2005 to 2007, nor has an economic evaluation based on the results of such a trial.

Three 2006 narrative summaries (Liou; Black; Nielsen) of biomarkers for detection and surveillance of urothelial cancer warrant repetition in 2007:

> *"The ideal urinary bladder tumor test is still unavailable, but the eventual "gold standard"' will consist of multiplex assays that analyze nucleic acids and proteins for detection. In addition, these tests would also reveal to the clinician both prognostic information and therapeutic targets for personalized medical treatment."* (Liou, 2006).

> *None of these markers has proved sensitive and specific enough to replace cystoscopy. Others, such as nuclear matrix protein 22 (NMP22) and UroVysion, appear to have some utility when used to complement or replace cytology. The other applications* (replacement or reduction in number of cystoscopies, predicting recurrence or progression, substitution or concurrent use with cytology, predicting or monitoring response to treatment) *have not been adequately studied for any given marker. While multiple molecular markers exist for bladder cancer, their full clinical utility will not be realized until more multicenter trials are conducted to verify their efficacy and safety in the monitoring of patients with superficial bladder cancer."* Black (2006).

> *"This assay (UroVysion FISH) received FDA approval in January 2005. Different studies have selected a threshold of either >10 or >20% aneuploid cells as the cutoff for a positive test. The lower threshold results in increased sensitivity for low-grade lesions and though such gains often come at the cost of slower specificity, at least one study utilizing the > 10% threshold did not find substantial sacrifices in terms of specificity. In ay event, standardization of the criterion for a positive test represents one outstanding issue that must be resolved for translation of this strategy to broader clinical application."* Nielsen (2006).

IMPLICATIONS FOR RESEARCH

As noted above, the optimal surveillance protocol for superficial bladder cancer patients has yet to be defined, as does a universally accepted nomenclature for grade and stage of tumor.

Large high quality trials directly comparing competing surveillance protocols for useful periods of follow up and reporting health and economic outcomes are needed.

APPENDIX

Table 2. Abstracted details of English-language systematic reviews and technology assessments: bladder cancer surveillance

Citation	Study type/details	Main recommendations/results
Assessment updated by TAP		
MSAC (2005)	Systematic review: What is the value of the UroVysion FISH assay in conjunction with cystoscopy versus cystoscopy alone to diagnose TCC in patients who have previously been diagnosed with TCC of the bladder who would undergo cystoscopy under local anesthetic? • Databases plus hand searching; • Systematic reviews and controlled trials of safety, effectiveness, or cost-effectiveness of UroVysion FISH assay; • 1966-March 2005; • Strategy: in the absence of controlled trials comparing health outcomes resulting from the use of UroVysion FISH assay with comparator tests, the effectiveness of the UroVysion FISH assay was inferred by evidence of the relative diagnostic accuracy of UroVysion FISH assay compared to cystoscopy; and its use to change clinical management. • Purpose of the assessment: to consider Urovysion use only in patients being monitored for bladder cancer recurrence and as a supplement to cystoscopy.	7 publications met criteria: **Safety:** • No included studies reported complications from the UroVysion test, cystoscopy, or any of the comparators; • Universal blood and body fluid precautions should be followed to ensure safety of staff involved in collection, transport, and analysis of urine samples. **Effectiveness:** 7 diagnostic accuracy studies • Quality of studies was fair, one high quality, one low quality, sample sizes from 19 to 451 (median, 86; total, 1072): patients with history of bladder cancer patients being investigated without history; patients without suspicion of bladder cancer; • Monitoring for recurrence: 558 patients (19-176; median, 51). **2x2 tables of results in patients being monitored:** • Could be constructed from 4 included studies, but single pooled estimate of test accuracy could not be obtained due to variation among studies (differences in types of patients, reference standards, and quality of studies); • Sensitivity ranged from 48-86%; Specificity from 34.3-100%. **Potential impact of UroVysion on clinical practice:** • Positive LRs: 1.3-21.1; • Negative LRs: 0.2-0.5; • Applying LRs to pretest probabilities of recurrence (based on risk and length of follow up): for most patients, the use of UroVysion did 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 been followed for at least one year. Current practice is to give these patients cystoscopy under LA and a large proportion undergo a second cystoscopy under GA due to high rates of recurrence; • Using Uroysion to determine type of anesthetic for cystoscopy means that only a small number will unnecessarily receive general anesthesia, while the majority will have only one cystoscopy; • In patients with a low risk of recurrence who are early in their FU, 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 at later stages in FU; • The problem of false negatives is not of clinical significance if UroVysion is used only in conjunction with cystoscopy. **Cost-effectiveness:** • Economic model comparing a clinical pathway where patients undergo cystoscopy under LA followed by cystoscopy under GA if first cystoscopy is positive to pathway where patients initially have UroVysion, then cystoscopy with LA or GA determined by Urovysion: at 3 months and at 5 years, costs with UroVysion exceeded the current practice pathway;

Citation	Study type/details	Main recommendations/results
		• At 5 years, cost of following UroVysion pathway was $7852 vs $5959 for current practice; • UroVysion pathway increased costs for patients until the first recurrence by $1876 Vs. current practice. **Conclusions:** *"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."* **Recommendations:** *"MSAC recommends that on the strength of evidence pertaining to UroVysion fluorescence in situ hybridization (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"*
Systematic reviews published after MSAC (2005): surveillance for bladder cancer		
Sylvester (2006)	Combined analysis of recurrence and progression among patients enrolled in EORTC trials: 7 trials	Individual patient (Stage TaT1 bladder cancer) multivariate analyses: • 2596 patients (median age 65, 80%) male after excluding ineligibles; stage TaT1 bladder cancer with or without CIS; • Median FU, 3.9 yrs, maximum, 14.8; • 47.8% had at least one recurrence at median of 2.7 yrs; • Variables of prognostic importance in univariate analyses: prior treatment, prior recurrence and rate, number of tumors, T category, grade, presence of CIS; • Multivariate model score for each patient: 0 (best prognosis) to 17 (worst); • Article provides tables of probabilities of recurrence with CI at one and five years. **Conclusions:** *"With these probabilities, the urologist can discuss the different options with the patient to provide the most appropriate treatment and frequency of follow up."*
Van Rhijn (2005)	Systematic review: urine markers for bladder cancer surveillance: • A marker was included if at least 2 studies from different authors/institutions were available; • Included: BTAstat; BTAtrak; NMP22; FDP; ImmunoCyt; Cytotometry; Quanticyt, Hb-dipstick; LewisX; FISH; Telomerase;Microsatellite; CYFRA21-1; cytokeratin20; BTA; NMP22; TBS, cytology;	• BTAstat, NMP22, Immunocyt, and cytology were evaluated in more than 750 patients, Telomerase, Cytokeratin20, and Hb-dipstick in less than 250; • Highest median sensitivities were reported for CRFA21-1 (85%), Cytokeratin20 (85%) and Microsatellite analysis (82%)' highest specificities for Cytology (94%), BTA (92%), and Microsatellite analysis (89%); • In comparison with recent reviews, media sensitivity was ≥5% lower for the surveillance group while specificity remained fairly constant between different patient groups; **Conclusions:** *"In our view, Microsatellite analysis, ImmunoCyt, NMP22, CFRA21-1, LewisX and FISH are the most promising markers for surveillance at this time. Nevertheless, clinical evidence is insufficient to warrant the substitution of the cystoscopic follow-up schemer by any of the currently available urine marker tests. Future studies may test some of the most sensitive and specific assays to reduce the cystoscopy frequency. However, our results show that initiators of these studies should anticipate a lower sensitivity than reported in the current literature."*

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TECHNOLOGY ASSESSMENT PROGRAM

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To enhance the health of veterans and the nation by providing and fostering technology assessment for evidence-based health care

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Integrity and pride in the work that we do

Quality products that are clinically valid and methodologically transparent

Objectivity in evaluating and presenting research evidence

Commitment to continuous quality improvement and to the guiding principles of evidence based practices

Flexibility in responding to changes in VA and the larger healthcare environment

Innovation in designing products and their dissemination to best meet VA's needs

Accessibility of products and services