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Abstract

Systematic review of the clinical effectiveness and cost-effectiveness of photodynamic diagnosis and urine biomarkers (FISH, ImmunoCyt, NMP22) and cytology for the detection and follow-up of bladder cancer

G Mowatt,[1]* S Zhu,[1] M Kilonzo,[2] C Boachie,[1] C Fraser,[1] TRL Griffiths,[3] J N'Dow,[4] G Nabi,[4] J Cook[1] and L Vale[1,2]

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Objective: To assess the clinical effectiveness and cost-effectiveness of photodynamic diagnosis (PDD) compared with white light cystoscopy (WLC), and urine biomarkers [fluorescence in situ hybridisation (FISH), ImmunoCyt, NMP22] and cytology for the detection and follow-up of bladder cancer.

Data sources: Major electronic databases including MEDLINE, MEDLINE In-Process, EMBASE, BIOSIS, Science Citation Index, Health Management Information Consortium and the Cochrane Controlled Trials Register were searched until April 2008.

Review methods: A systematic review of the literature was carried out according to standard methods. An economic model was constructed to assess the cost-effectiveness of alternative diagnostic and follow-up strategies for the diagnosis and management of patients with bladder cancer.

Results: In total, 27 studies reported PDD test performance. In pooled estimates [95% confidence interval (CI)] for patient-level analysis, PDD had higher sensitivity than WLC [92% (80% to 100%) versus 71% (49% to 93%)] but lower specificity [57% (36% to 79%) versus 72% (47% to 96%)]. Similar results were found for biopsy-level analysis. The median sensitivities (range) of PDD and WLC for detecting lower risk, less aggressive tumours were similar for patient-level detection [92% (20% to 95%) versus 95% (8% to 100%)], but sensitivity was higher for PDD than for WLC for biopsy-level detection [96% (88% to 100%) versus 88% (74% to 100%)]. For more aggressive, higher-risk tumours the median sensitivity of PDD for both patient-level [89% (6% to 100%)] and biopsy-level [99% (54% to 100%)] detection was higher than those of WLC [56% (0% to 100%) and 67% (0% to 100%) respectively]. Four RCTs comparing PDD with WLC reported effectiveness outcomes. PDD use at transurethral resection of bladder tumour resulted in fewer residual tumours at check cystoscopy [relative risk, RR, 0.37 (95% CI 0.20 to 0.69)] and longer recurrence-free survival [RR 1.37 (95% CI 1.18 to 1.59)] compared with WLC. In 71 studies reporting the performance of biomarkers and cytology in detecting bladder cancer, sensitivity (95% CI) was highest for ImmunoCyt [84% (77% to 91%)] and lowest for cytology [44% (38% to 51%)], whereas specificity was highest for cytology [96% (94% to 98%)] and lowest for ImmunoCyt [75% (68% to 83%)]. In the cost-effectiveness analysis the most effective strategy in terms of true positive cases (44) and life-years (11.66) [flexible cystoscopy (CSC) and ImmunoCyt followed by PDD in initial diagnosis and CSC followed by WLC in follow-up] had an incremental cost per life-year of over £270,000. The least effective strategy [cytology followed by WLC in initial diagnosis (average cost over 20 years £1403, average life expectancy 11.59)] was most likely to be considered cost-effective when society's willingness to pay was less than £20,000 per life-year. No strategy was cost-effective more than 50% of the time, but four of the eight strategies in the probabilistic sensitivity analysis (three involving a biomarker or PDD) were each associated with a 20% chance of being considered cost-effective. In sensitivity analyses the results were most sensitive to the pretest probability of disease (5% in the base case).

Conclusions: The advantages of PDD's higher sensitivity in detecting bladder cancer have to be weighed against the disadvantages of a higher false-positive rate. Taking into account the assumptions made in the model, strategies involving biomarkers and/or PDD provide additional benefits at a cost that society might be willing to pay. Strategies replacing WLC with PDD provide more life-years but it is unclear whether they are worth the extra cost.

Contents

List of abbreviations

5-ALA	5-aminolaevulinic acid
AUA	American Urological Association
BAUS	British Association of Urological Surgeons
BCG	bacillus Calmette–Guerin
BM	biomarker
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CIS	carcinoma in situ
CSC	flexible cystoscopy
CT	computerised tomography
CTL	cytology
DOR	diagnostic odds ratio
EAU	European Association of Urology
EORTC	European Organisation for Research and Treatment of Cancer
FDA	Food and Drug Administration
FISH	fluorescence in situ hybridisation
GC	gemcitabine, cisplatin
GST	glutathione S-transferase
HAL	hexaminolaevulinate
HRG	Healthcare Resource Group
HSROC	hierarchical summary receiver operating characteristic
ICER	incremental cost-effectiveness ratio
IVP	intravenous pyelography
MDT	multidisciplinary team
MRI	magnetic resonance imaging
MVAC	methotrexate, vinblastine, adriamycin, cisplatin
NAT	*N*-acetyltransferase
NCRI	National Cancer Research Institute
NICE	National Institute for Health and Clinical Excellence
NMP22	nuclear matrix protein
NPV	negative predictive value
PDD	photodynamic diagnosis
PPIX	protoporphyrin IX
PPV	positive predictive value
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trial
ReBIP	Review Body for Interventional Procedures
RR	relative risk
SIGN	Scottish Intercollegiate Guidelines Network
SROC	summary receiver operating characteristic
TCC	transitional cell carcinoma
TUR	transurethral resection
TURBT	transurethral resection of bladder tumour
WHO	World Health Organization
WLC	white light cystoscopy
WMD	weighted mean difference

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

Executive summary

Background

Bladder cancer is the sixth most common cancer in the UK, affecting more than 10,000 people each year. Around 75–85% of patients are diagnosed as having non-muscle-invasive disease, which, despite treatment, has a probability of recurrence at 5 years of 31% (95% CI 24% to 37%) to 78% (95% CI 73% to 84%). Inspection of the bladder [flexible cystoscopy using white light (CSC)] facilitated with local anaesthesia and voided urine cytology (involving the examination of cells in voided urine to detect the presence of cancerous cells) are currently the routine initial investigations of the bladder in patients with haematuria or other symptoms suggestive of bladder cancer. If CSC or urine cytology are suspicious, a rigid white light cystoscopy (WLC) under general or regional anaesthesia is performed with transurethral resection of bladder tumour (TURBT) where applicable. However, WLC may fail to detect some tumours. Photodynamic diagnosis (PDD) is a technique that could potentially be used to enhance tumour detection. Also, since the mid-1990s many urine biomarker tests for detecting bladder cancer have been developed, including fluorescence in situ hybridisation (FISH), ImmunoCyt and nuclear matrix protein (NMP22).

Objectives

This review aims to assess the clinical and cost-effectiveness of PDD compared with WLC, and urine biomarkers (FISH, ImmunoCyt, NMP22) and cytology for the detection and follow-up of bladder cancer.

Methods

Electronic searches were undertaken to identify published and unpublished reports. The databases searched included MEDLINE, MEDLINE In-Process, EMBASE, BIOSIS, Science Citation Index, Health Management Information Consortium (HMIC) and the Cochrane Controlled Trials Register as well as current research registers. The date of the last searches was April 2008. The types of studies considered for test performance were randomised controlled trials (RCTs), non-randomised comparative studies and diagnostic cross-sectional studies that reported the absolute numbers of true and false positives and negatives. Only RCTs were considered for studies reporting effectiveness. Participants had symptoms suspicious for bladder cancer or were previously diagnosed with non-muscle-invasive disease. The tests considered were (1) PDD compared with WLC or (2) FISH, ImmunoCyt, NMP22 or cytology, with a reference standard of histopathological examination of biopsied tissue.

One reviewer screened the titles and abstracts of all reports identified by the search strategy and data extracted included full-text studies, with checking by a second reviewer. Two reviewers independently assessed the quality of the diagnostic studies using a modified version of the QUADAS instrument and the quality of the effectiveness studies using a checklist adapted from Verhagen and colleagues.

The results of the individual studies were tabulated and sensitivity, specificity, positive and negative likelihood ratios, and diagnostic odds ratios (DORs) calculated. Separate summary receiver operating characteristic (SROC) curves were derived for different levels of analysis. Meta-analysis models were fitted using hierarchical summary receiver operating characteristic (HSROC) curves. Summary sensitivity, specificity, positive and negative likelihood ratios and DORs for each model were reported as median and 95% confidence interval (CI). For studies reporting effectiveness outcomes meta-analysis was employed to estimate a summary measure of effect, with dichotomous outcome data combined using relative risk (RR). Results were reported using a fixed-effect model in the absence of statistical heterogeneity.

An economic model was constructed to assess the cost-effectiveness of alternative diagnostic and follow-up strategies for the diagnosis and management of patients suspected of having bladder cancer. The model described care pathways from initial presentation, through diagnosis and treatment over a 20-year time horizon. A total of 26 different strategies were considered in the

economic model, which represented plausible ways in which the tests might be used for the diagnosis and follow-up of patients with bladder cancer. Of these 26, eight strategies that appeared to perform best in the deterministic analysis were further considered in a probabilistic analysis. The clinical effectiveness data from the systematic review (summarised below) were incorporated into the model. In the base-case analysis it was assumed that the underlying risk of disease within the target population was 5%. Costs for treatments and interventions with strategies were derived from the literature review in the UK setting, in particular NHS resources. The mean cost per test for PDD was £1371, WLC £937, CSC £441, cytology £92, NMP22 £39, ImmunoCyt £54 and FISH £55. TURBT cost from £2002 to £2436 depending upon whether it was assisted by WLC or PDD respectively. Additional subsequent treatments were also included, which were based upon those typically adopted within the UK NHS. A cost–utility analysis was not possible as part of the base-case analysis because of a lack of relevant utility data. Hence, cost-effectiveness (life-years, cases of true positives) and cost–consequence analyses were conducted. Sensitivity analyses were conducted to assess the uncertainties in estimates and assumptions.

Results

A total of 27 studies enrolling 2949 participants reported PDD test performance. In the pooled estimates for patient-level analysis, based on direct evidence, PDD had higher sensitivity than WLC (92%, 95% CI 80% to 100% versus 71%, 95% CI 49% to 93%) but lower specificity (57%, 95% CI 36% to 79% versus 72%, 95% CI 47% to 96%). In the pooled estimates for biopsy-level analysis, based on direct evidence, PDD also had higher sensitivity than WLC (93%, 95% CI 90% to 96% versus 65%, 95% CI 55% to 74%) but lower specificity (60%, 95% CI 49% to 71% versus 81%, 95% CI 73% to 90%).

Across studies, the median sensitivities (range) of PDD and WLC for detecting lower risk, less aggressive tumours were broadly similar for patient-level detection [92% (20% to 95%) versus 95% (8% to 100%)], but sensitivity was higher for PDD than for WLC for biopsy-level detection [96% (88% to 100%) versus 88% (74% to 100%)]. However, for the detection of more aggressive, higher risk tumours the median sensitivity of PDD for both patient-level [89% (6% to 100%)] and biopsy-level [99% (54% to 100%)] detection was higher than those of WLC [56% (0% to 100%) and 67% (0% to 100%) respectively]. The superior sensitivity of PDD was also reflected in the detection of carcinoma in situ (CIS) alone, both for patient-level [83% (41% to 100%) versus 32% (0% to 83%)] and biopsy-level [86% (54% to 100%) versus 50% (0% to 68%)] detection.

Four RCTs enrolling 709 participants comparing PDD with WLC reported effectiveness outcomes. The use of PDD at TURBT resulted in fewer residual tumours at check cystoscopy (pooled estimate RR 0.37, 95% CI 0.20 to 0.69) and longer recurrence-free survival (pooled estimate RR 1.37, 95% CI 1.18 to 1.59) compared with WLC. The advantages of PDD at TURBT in reducing tumour recurrence (pooled estimate RR 0.64, 95% CI 0.39 to 1.06) and progression (pooled estimate RR 0.57, 95% CI 0.22 to 1.46) in the longer term were less clear.

A total of 71 studies reported the performance of biomarkers (FISH, ImmunoCyt, NMP22) and cytology in detecting bladder cancer. In total, 14 studies enrolling 3321 participants reported on FISH, 10 studies enrolling 4199 participants reported on ImmunoCyt, 41 studies enrolling 13,885 participants reported on NMP22 and 56 studies enrolling 22,260 participants reported on cytology. In the pooled estimates, based on indirect evidence, sensitivity was highest for ImmunoCyt and lowest for cytology. FISH (76%, 95% CI 65% to 84%), ImmunoCyt (84%, 95% CI 77% to 91%) and NMP22 (68%, 95% CI 62% to 74%) all had higher sensitivity than cytology (44%, 95% CI 38% to 51%). However, cytology had higher specificity (96%, 95% CI 94% to 98%) than FISH (85%, 95% CI 78% to 92%), ImmunoCyt (75%, 95% CI 68% to 83%) or NMP22 (79%, 95% CI 74% to 84%).

Cost-effectiveness

Although the differences in outcomes and costs between these strategies appear to be small, the decision about which strategy to adopt depends upon society's willingness to pay for additional gain. The most effective strategy in terms of true positive cases (44) and life-years (11.66) was a strategy of CSC and ImmunoCyt followed by PDD in initial diagnosis and CSC followed by WLC in follow-up. This strategy had, however, an incremental cost per life-year of over £270,000. The least effective strategy was cytology followed by WLC in initial diagnosis and follow-up (total average cost over 20 years = £1403 and average

life expectancy = 11.59). This strategy was most likely to be considered cost-effective when society's willingness to pay was less than £20,000 per life-year. Over most of the ranges of willingness to pay values there appeared to be no strategy that would have a likelihood of being cost-effective more than 50% of the time, but four of the eight strategies included in the probabilistic sensitivity analysis were each associated with an approximately 20% chance of being considered cost-effective. Three of these four strategies involved the use of a biomarker or PDD.

Sensitivity analyses

The sensitivity analyses indicated that the order of the least to the most costly strategies remained the same when discount rates, RR rates and performance of CSC were changed. The results were most sensitive to the pretest probability of disease (5% in the base case). At a 1% probability it is most likely that the least costly (and least effective) strategy of cytology followed by WLC for both diagnosis and follow-up would be cost-effective. At a 20% prevalence the more effective strategies (in terms of diagnostic performance) are more likely to be worth their increased cost.

Discussion

PDD has higher sensitivity (fewer false negatives) than WLC and so will detect cases of bladder cancer missed by WLC, but its lower specificity will result in more false positives. The advantages of PDD's higher sensitivity in detecting bladder cancer overall, and also more aggressive, higher risk tumours, have to be weighed against the disadvantages of a higher false-positive rate, which leads to additional, unnecessary biopsies of normal tissue being taken and potentially additional unnecessary investigations being carried out and the resulting anxiety caused to patients and their families.

In the four studies reporting effectiveness outcomes, such as tumour recurrence, the administration of single-dose adjuvant chemotherapy following TURBT, which can reduce recurrence rates by up to 50% in the first 2 years, varied, making it difficult to assess what the true added value of PDD might be in reducing recurrence rates in routine practice.

Based on indirect comparisons, all three biomarkers had higher sensitivity, but lower specificity, than cytology in detecting bladder cancer. A urine biomarker test such as ImmunoCyt could potentially replace some cytology tests if higher sensitivity (fewer false negatives) is considered more important than higher specificity (fewer false positives). However, if higher specificity is considered more important then cytology would remain the test of choice.

Linking diagnostic performance to long-term outcomes required a number of assumptions to be made about the structure of the economic model and its parameters. Some assumptions were based on non-UK study data; it is unclear whether such data are applicable to the UK setting. One assumption concerned starting age and the length of time over which the benefits from a diagnostic strategy may accrue. In the base-case analysis a time period of 20 years and starting age of 67 years were used, although the impact of shorter time horizons and older starting age were explored in the sensitivity analyses. When either the time horizon was reduced or the starting age was increased, the incremental cost per life-year increased as the costs of initial diagnosis and treatments were not offset by survival and life-year gains.

Conclusions

Implications for service provision

PDD has higher sensitivity than WLC in detecting bladder cancer and is better at detecting more aggressive, higher risk tumours, including CIS, but has lower specificity. Based on limited evidence, the use of PDD at TURBT compared with WLC results in fewer residual tumours at check cystoscopy and longer recurrence-free survival, whereas the advantages of PDD at TURBT in reducing tumour recurrence and progression in the longer term are less clear. In the pooled estimates ImmunoCyt had the highest sensitivity and cytology had the highest specificity, with all three biomarkers having higher sensitivity, but lower specificity, than cytology.

Taking into account the assumptions made in the model, the strategy of CSC and ImmunoCyt followed by PDD in initial diagnosis and CSC followed by WLC in follow-up is likely to be the most costly and the most effective (£2370 per patient and 11.66 life-years). There appeared to be no strategy that would have a likelihood of being cost-effective more than 50% of the time over most of the ranges of willingness to pay values. Nevertheless, strategies involving biomarkers and/

or PDD provide additional benefits at a cost that society might be willing to pay. Strategies involving cytology are unlikely to be considered worthwhile. Strategies that replaced WLC with PDD provided more life-years but it is less clear whether they would be worth the extra cost.

Recommendations for research

Further research is required in the following areas:

- RCTs including economic evaluations comparing PDD with rigid WLC at TURBT plus adjuvant immediate single-dose intravesical chemotherapy in patients diagnosed with bladder tumours at CSC.
- Diagnostic cross-sectional studies comparing FISH with ImmunoCyt, NMP22 BladderChek point of care test and voided urine cytology within the setting of the British Association of Urological Surgeons and the Renal Association diagnostic algorithm for the diagnosis of patients with haematuria. Data produced should be incorporated into an economic evaluation.
- Studies to collect health state utilities are needed. These may come from further prospective studies or as part of future RCTs.
- The trade-off between process of care and short-term (diagnostic outcomes) and longer-term outcomes needs to be explored using recognised preference elicitation methodology in a way that can be incorporated into future economic evaluations.
- The impact that an incorrect diagnosis (false-negative result) has on patients either at diagnosis or at follow-up in terms of future survival, quality of life and costs.

Chapter 1
Background

Description of health problem

Introduction

Bladder cancer, or more precisely malignant neoplasm of the bladder,[1] is a disease in which the cells lining the urinary bladder lose the ability to regulate their growth and start dividing uncontrollably.[2] This abnormal growth results in a mass of cells that form a tumour. People with a suspicion of bladder cancer mainly present with urinary symptoms including gross haematuria, microscopic haematuria and urinary tract symptoms. Bladder cancers can be broadly categorised into two main groups depending upon their extent of penetration into the bladder wall: non-muscle invasive and muscle invasive. The majority of diagnosed patients (75–85%) present with non-muscle-invasive disease, which as described in the next subsection is characterised by a probability of recurrence at 5 years from 31% (95% CI 24% to 37%) to 78% (95% CI 73% to 84%) despite treatment.[3] The remaining cancers are muscle invasive and/or metastatic.

Aetiology, pathology and prognosis

Aetiology

The aetiology of bladder cancer appears to be multifactorial, with environmental and genetic factors as well as endogenous molecular factors having potential roles. The risk of developing bladder cancer before the age of 75 years is 2–4% for men and 0.5–1% for women.[4] Cigarette smoking and specific occupational exposures are the main known risk factors for bladder cancer.[5] In Europe it is estimated that up to half of bladder cancer cases in men and one-third of cases in women are caused by cigarette smoking.[6,7]

Occupational exposure to chemicals in Europe accounts for up to 10% of male bladder cancers. Most carcinogens have a latent period of 15–20 years between exposure and the development of tumours. The proportion may be higher in countries with less well-regulated industrial processes. Bladder cancer has an important place in the history of occupational disease. In 1895, Rehn reported cases of bladder cancer in a German aniline dye factory. It was then recognised that aromatic amines and polycyclic aromatic hydrocarbons, by-products of the catabolic process, were the key aetiological factors. Aromatic amines were widely used in the manufacture of dyes and pigments for textiles, paints, plastics, paper and hair dyes, and in drugs and pesticides and in the rubber industry. In 1953, bladder cancer became a prescribed industrial disease in the UK.[8] Occupational studies of hairdressers have produced conflicting results. Within the EU, the Scientific Committee on Cosmetic Products and Non-Food Products aims to set up a 'high-risk' permanent and semi-permanent register of hair dye formulations.

Several dietary factors have been related to bladder cancer, but the results of different studies have been controversial. A meta-analysis[9] of 38 articles supported the hypothesis that vegetable and fruit intake reduced the risk of bladder cancer. Phenacetin, chlornaphazine and cyclophosphamide also increase the risk of bladder cancer.[10] In comparison to other carcinogenic agents, the latency period is relatively short. Acrolein, a metabolite of cyclophosphamide, is responsible for the ninefold increased risk of bladder cancer associated with cyclophosphamide. In addition, chronic infection by *Schistosoma haematobium* is a cause of squamous cell carcinoma of the bladder. Patients treated with pelvic radiotherapy for cervical and prostate cancers also have an increased risk of developing bladder cancer.[11,12]

Drug- and carcinogen-metabolising enzymes are important in the processing of lipophilic chemicals to products that are more water-soluble and can be excreted. These enzyme systems are partly controlled by genetic polymorphism. In the liver, chemicals are oxidised by the cytochrome P450 superfamily and detoxified by N-acetylation, predominantly by *N*-acetyltransferases (NAT). Aromatic amines are usually detoxified by NAT2. NAT2 slow acetylator genotypes are at increased risk of bladder cancer [relative risk (RR) 1.4], and this may be especially true in smokers.[13] Approximately 50% of Caucasians and 25% of Asians are slow acetylators. Glutathione S-transferase (GST) is the product of the *GSTM1*

gene and is involved in the detoxification of polyaromatic hydrocarbons. Approximately 50% of Caucasians and Asians have a homozygous deletion of the *GSTM1* gene, which is associated with a RR of 1.4.[14] There is no clear evidence that the underlying pathogenesis of bladder cancer differs by gender.[10]

Pathology

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 most common type of bladder cancer is transitional cell carcinoma (TCC), which accounts for more than 90% of bladder cancers in the UK; other forms of bladder cancer include squamous carcinoma, adenocarcinoma (urachal and non-urachal), small cell carcinoma, sarcoma and lymphoma. TCC, also known as urothelial carcinoma, arises from changes in the urothelial cells that line the bladder, ureters, renal pelvis and proximal urethra, although TCC is approximately 50 times more common in the bladder than in other parts of the urinary tract.[15] The 2002 TNM staging system of the International Union against Cancer (UICC) 2002 is the most recent pathological staging system (*Table 1*).[16] About 25% of newly diagnosed TCCs of the bladder are muscle invasive (T2–T4); the remainder are non-muscle invasive, either papillary (70%) or a flat lesion of the urothelium termed carcinoma in situ (CIS) (5%).

For more than three decades, the preferred grading system in the UK for bladder TCC has been the World Health Organization (WHO) 1973 classification,[17] which has been repeatedly validated

TABLE 1 *International Union against Cancer (UICC) 2002 TNM staging system*

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				

and shown to be of clinical relevance for treatment and prognosis. WHO 1973 divides TCC into three grades on the basis of cytological and architectural disorder, grade 1 being well differentiated, grade 2 moderately differentiated and grade 3 poorly differentiated. WHO 2004 is the latest version of the bladder TCC classification. Current reporting guidelines recommend providing the urologist with both classifications. The main differences are two grades of carcinoma (high grade and low grade) and the introduction of the term papillary urothelial neoplasm of low malignant potential (PUNLMP) to replace the best differentiated grade 1 tumours, avoiding the term carcinoma. However, there has been considerable resistance in the UK to adopting the WHO 2004 classification, which was not prospectively validated before its introduction and which has subsequently not demonstrated either improved reproducibility or clinical relevance over WHO 1973.[18] In this report we will therefore only quote the WHO 1973 classification.

Prognosis

The natural history of treated non-muscle-invasive bladder cancer (Ta/T1/CIS), a group of heterogeneous cancers, can be summarised as any of the following:

- no further recurrence
- local recurrence, which can occur on a single occasion or on multiple occasions; it can involve single or multiple tumour recurrences, but recurrent tumours are usually of the same stage and grade as the primary tumour
- local progression – an increase in local stage over time to muscle invasion or the appearance of distant metastases and subsequent death.

On average, non-muscle-invasive bladder cancer has a probability of recurrence at 5 years from 31% (95% CI 24% to 37%) to 78% (95% CI 73% to 84%) and of progression of between 0.8% (95% CI 0% to 1.7%) and 45% (95% CI 35% to 55%) after initial treatment.[3] The rates of recurrence and progression vary depending upon the stage, grade and number of tumours at the time of first presentation. Of the newly diagnosed non-muscle-invasive bladder tumours, approximately 30% are multifocal at presentation. There is little information on the predictive role of environmental and genetic risk factors on tumour recurrence, progression and mortality. Tumours are most likely to recur within 5 years after transurethral resection of bladder tumour (TURBT),[19] and therefore patients are closely monitored for recurrence following their initial presentation and treatment. According to the European Organisation for Research and Treatment of Cancer (EORTC), the risk factors relating to recurrence and progression include the number of tumours present at diagnosis, the recurrence rate in the previous period, the tumour size (larger tumours being associated with greater risk), stage, grade and the presence of concomitant CIS.[20] The poor prognosis of T1G3 TCC is well described; 50% progression rate if associated with concomitant CIS.[21] If primary CIS is diffuse, 50% of these patients die of metastatic TCC within a year or two if maintenance intravesical immunotherapy with bacillus Calmette–Guerin (BCG) is not instituted. Once the tumour has invaded the detrusor muscle, 50% of patients have occult metastatic disease at presentation.

Epidemiology

Bladder cancer is the sixth most common cancer in the UK.[22] Bladder cancer is the most frequently occurring tumour of the urinary system and accounts for 1 in every 28 new cases of cancer diagnosed each year in the UK. During the last three decades there has been a gradual decrease in the incidence of bladder cancer (*Figure 1*).[22] However, changing trends in the incidence of bladder cancer over time are difficult to interpret because of different and changing classifications and coding practices of the condition.[5]

Incidence and prevalence

Bladder cancer is the fourth most common cancer in men and the tenth most common in women in the UK.[22] In 2005, the estimated male and female crude incidence rates of bladder cancer were 24.6 and 9.3 per 100,000 population with 6091 and 2403 new cases, respectively, in England, and 43.0 and 17.2 per 100,000 population with 619 and 260 new cases, respectively, in Wales (*Table 2*).[22]

Although the overall incidence of bladder cancer in the UK has remained much higher in men than in women in the last five decades, it has shown a slow decrease between 1993 and 2005 (*Figure 1*) following a rapid rise between 1971 and 1993.[22,23] In addition, in England and Wales, the prevalence of bladder cancer increased by 57% between 1971 and 1998, particularly in women.[23]

Variation in incidence by age

The mean age at which bladder cancer is diagnosed in the UK is 71.3 years. The incidence and mortality rate of bladder cancer rapidly increase with increasing age (*Figures 2* and *3*).

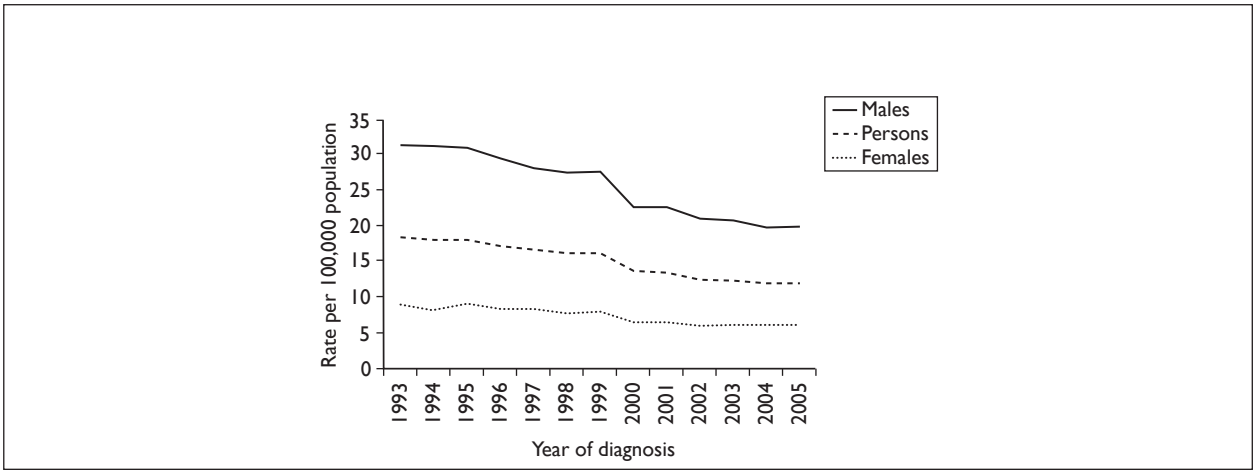


FIGURE 1 *Age-standardised (European) incidence rates of bladder cancer by sex, UK, 1993–2004.*

TABLE 2 *Number of new cases and rates of bladder cancer in the UK, 2005*

	England	Wales	Scotland	N. Ireland	UK
Cases					
Male	6091	619	468	132	7310
Female	2403	260	247	58	2968
Total	8494	879	715	190	10,278
Crude rate per 100,000 population					
Male	24.6	43.0	19.1	15.6	24.8
Female	9.3	17.2	9.4	6.6	9.7
Total	16.8	29.8	14.0	11.0	17.1
Age-standardised rate (European) per 100,000 population					
Male	19.6	31.6	15.5	15.0	19.8
Female	5.7	10.1	5.6	4.4	5.9
Total	11.7	19.6	9.8	9.1	11.9

Source: Cancer Research UK.[22]

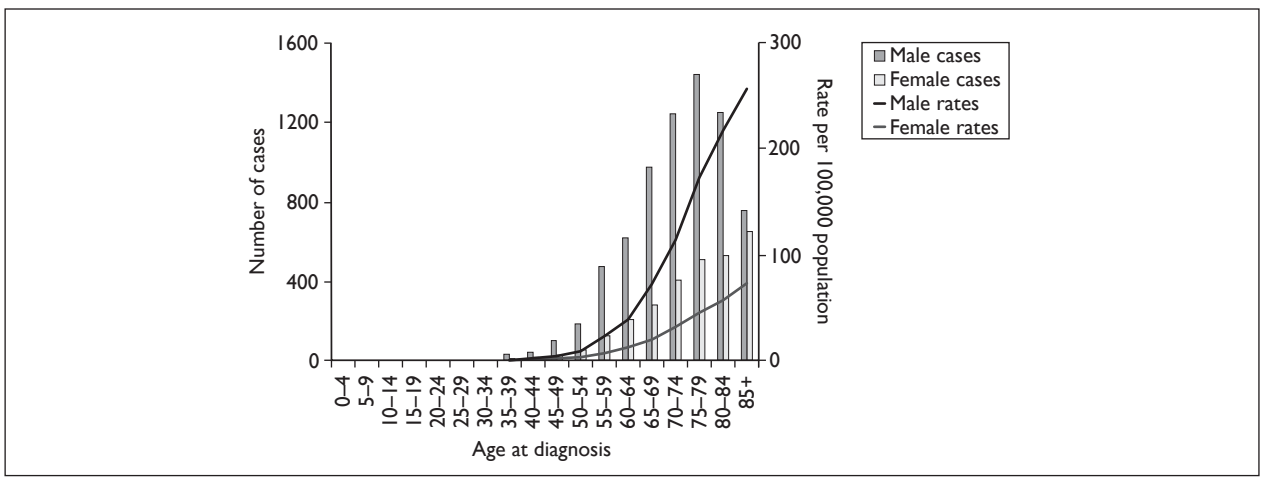


FIGURE 2 *Numbers of new cases and age-specific incidence rates of bladder cancer by sex, England and Wales, 2005.*

Bladder cancer commonly occurs in older people and is rare in people under 50 years of age.

Variation in incidence by deprivation and geography

In the UK the incidence of bladder cancer also varies according to socioeconomic status and geographical area. Data from Cancer Research UK[22] show that the incidence is likely to be slightly increased in areas of deprivation, with the lowest incidence found in the most affluent groups.

Geographical patterns of bladder cancer incidence are difficult to interpret because of differences in the way in which bladder tumours are classified between cancer registries, for example differences between UK and Northern Ireland. Such differences also hinder reliable international comparisons.

Impact of the health problem

Significance for patients in terms of ill-health

Although most non-muscle-invasive bladder cancers are unlikely to be life-threatening they are associated with high recurrence and variable progression rates, which result in an impaired quality of life. Untreated bladder cancer is associated with significant morbidity, such as haematuria, dysuria, irritative urinary symptoms, urinary retention, incontinence, ureteral obstruction and pelvic pain. In addition to the physical damage caused, bladder cancer also has a severe effect on work status, sexual life and mental health. A consequence of our population living longer will be an increased incidence of bladder cancer with resulting increased morbidity and mortality. At the same time, less smokers in the population may slow the rate of increase.

In the UK and also in other countries, unlike other common cancers, men with bladder cancer have consistently higher survival rates than women and this also extends to stage-specific survival. Although men seem to be diagnosed at a slightly earlier stage than women, the reasons for this male survival advantage remain unclear.

Patients with non-muscle-invasive tumours have 5-year survival rates of between 80% and 90%.[5] However, patients with muscle-invasive bladder cancer have 5-year survival rates of less than 50%, because, although radical treatment deals effectively with locally invasive disease, many patients die from metastatic disease, which may have been micrometastatic at presentation.[24] Early detection while the tumour is still at a non-muscle-invasive stage is therefore very important.

Patients with early bladder cancer may fall into one of three different groups: (1) those with low-risk disease in whom the main risk is recurrent low-risk disease with a small chance of ever dying of bladder cancer; (2) those with high-risk superficial disease in whom there is a high chance of disease progression and subsequent death from bladder cancer; and (3) those with muscle-invasive disease in whom there is imminent risk of death from bladder cancer. In groups 2 and 3, inaccurate diagnosis/follow-up may have life-threatening consequences, whereas in group 1 the main impact of follow-up is to prevent morbidity rather than mortality. Therefore the clinical needs

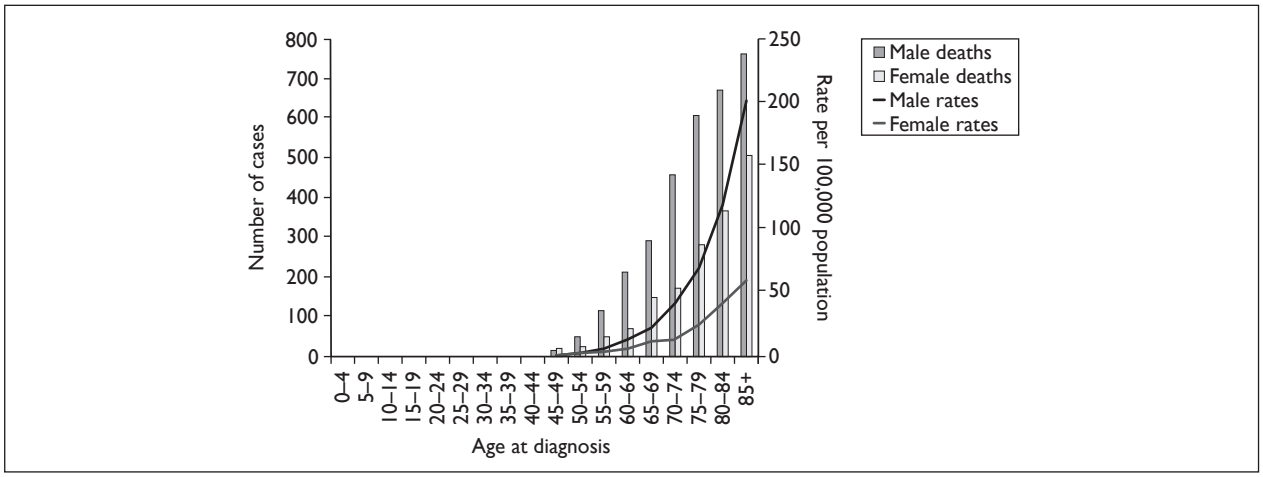


FIGURE 3 *Numbers of deaths from and age-specific mortality rates of bladder cancer by sex, UK, 2006.*

of these groups differ with respect to diagnostic performance.

Significance for the NHS

Bladder cancer is considered to be the most expensive cancer in terms of lifetime and treatment costs because of the high recurrence rates. A higher incidence of non-muscle-invasive disease, longer survival requiring lifelong surveillance and treatment of recurrences are some of the reasons for the higher cost of non-muscle-invasive disease compared with muscle-invasive bladder cancers. However, annual research fund allocation for bladder cancer from the National Cancer Research Institute (NCRI) UK is less than those for other cancers.

Current service provision

Diagnosis

Haematuria is presence of blood in the urine and is the most common symptom of bladder cancer. Bladder cancer is detected in approximately 10% of patients with gross haematuria and 3–5% of those with microscopic haematuria aged over 40 years.[25,26] Less commonly, individuals may note disturbance in their urinary habits including complaints of dysuria (painful urination), increased frequency, urgency of urination, failed attempts to urinate and urinary tract infection. These symptoms can raise suspicion of diffuse CIS. Other symptoms that may be attributed to a mass in the bladder or ureteral obstruction are likely to indicate that bladder cancer may be muscle-invasive disease.[5,24,27]

History, physical examination and radiology

The clinical workup for potential bladder cancer should start with a history and a complete physical examination with careful attention to potential risk factors, such as the patient's smoking history and occupation. Clinicians must look for cancer in all areas of the urinary tract. Most haematuria clinics in the UK perform an ultrasound of the upper tracts and kidney, ureter and bladder radiography. In some centres, intravenous pyelography (IVP) is also performed routinely; in others, computerised tomography (CT) urography has replaced ultrasound and IVP in this setting.

Cystoscopy and pathology

In many centres, voided urine for cytological analysis is usually collected before flexible cystoscopy. Flexible cystoscopy is an invasive procedure in which an endoscope is passed within the urethra, prelubricated with local anaesthetic gel. Its purpose is to evaluate the urethra and to look for tumours and irregularities in the bladder such as red patches (which may prove to be CIS on biopsy), diverticula and trabeculations. A urine culture should be performed if dipstick analysis suggests a urinary tract infection.

Transurethral resection and/or biopsy

If a bladder tumour is identified on flexible cystoscopy, arrangements are made for the patient to return as an inpatient for TURBT and/or biopsy under general anaesthesia. Depending on the location of the tumour, resection may be aided on occasion by muscle paralysis to avoid complications arising from an obturator nerve jerk. The exophytic tumour is first resected and then a separate deep resection is obtained. Both specimens are sent separately for histological assessment. Biopsies of any red areas may also be taken and submitted for analysis. Haemostasis is then achieved by using a rollerball electrode followed by insertion of an irrigating catheter. As part of clinical staging, a bimanual examination is performed to identify if there is a residual mass at the end of the procedure. If a mass is detected, it is noted whether it is mobile (clinical T3) or fixed (clinical T4).

Imaging techniques

If bladder cancer is detected, accurate disease staging and grading are critical. There is much debate over the role of imaging techniques, such as magnetic resonance imaging (MRI) and CT, in the staging of bladder cancer.[27] A staging CT scan of chest, abdomen and pelvis and/or MRI of pelvis are therefore not usually performed in patients with papillary non-muscle-invasive TCC. The role of CT in patients with muscle-invasive disease is primarily to provide extra information on local staging, lymph node status and visceral metastases. The primary role of MRI in patients with muscle-invasive TCC is to provide further information on local stage.

Management of disease

The management of non-muscle-invasive bladder cancer is based on: (1) the pathological findings of the biopsy specimen, with attention to histological type, grade and depth of invasion; (2) the presence of associated CIS; (3) the number of tumours; (4) previous recurrence rate if applicable; and (5) size of tumour. Depending on these findings, treatment options include cystoscopic follow-up only (either flexible or rigid cystoscopy under general

anaesthesia), cystoscopic follow-up and intravesical chemotherapy and immunotherapy courses or radical cystectomy.

The goals of current treatment for patients with non-muscle-invasive bladder cancer are to prevent disease recurrence or progression to muscle-invasive disease to avoid loss of the bladder and, ultimately, to enhance survival. The current treatment strategies for patients with bladder cancer depend on three main types of bladder cancer, non-muscle-invasive disease, muscle-invasive disease and metastases, as recommended in the multidisciplinary team (MDT) guideline.[28]

Non-muscle-invasive disease

Initial treatment

- TURBT of all malignant tissue is the recommended primary treatment for non-muscle-invasive disease and should be followed as soon as possible (ideally within 6 hours, otherwise within 24 hours) by a single instillation of intravesical chemotherapy.
- Tumours should then be assessed depending on stage, grade, size, multiplicity and the presence of recurrence at cystoscopy after 3 months:
  - low risk – patients at low risk of recurrence and progression have TaG1 TCC or solitary T1G1 TCC
  - intermediate risk – those at intermediate risk have TaG2 TCC or multifocal T1G1 TCC
  - high risk – broadly speaking, patients with Ta/T1G3 TCC, CIS or multifocal T1G2 TCC are classified as being at high risk of not only recurrence but also progression.

Follow-up of low- and intermediate-risk non-muscle-invasive bladder cancer

Follow-up of non-muscle-invasive disease is by cystoscopy, the frequency and duration of follow-up depending on the risk at presentation and the presence of recurrences. Multiplicity at presentation and a tumour recurrence at 3 months have consistently been shown to be key practical predictors of future recurrence, and so many urologists in the UK tailor their cystoscopic follow-up of low- and intermediate-risk patients based on these two factors:

(a) If patients have a solitary tumour at diagnosis and no tumour recurrence at 3 months they are then followed up at 9 months and then annually for 4 further years. If at the end of this 5-year follow-up period they have remained tumour free they are discharged. During the follow-up visits patients undergo flexible cystoscopy and in some centres cytology and/or biomarker tests. Not all patients with a tumour recurrence will receive TURBT; some may have a cystodiathermy and biopsy.

(b) Patients with multiple tumours at presentation and no recurrence at 3 months or a solitary tumour at presentation with recurrence at 3 months need more intense follow-up and are followed up every 3 months for the first year and annually if they remain tumour free until 10 years and are then discharged. During the follow-up visits patients undergo cystoscopy and in some centres cytology and/or biomarker tests. Those who present with a tumour at the follow-up visit undergo either TURBT or cystodiathermy and biopsy. These patients may be considered for a course of six intravesical instillations of mitomycin C or epirubicin.

(c) Patients with multiple tumours at presentation and recurrence at 3 months have the highest risk of recurrence and are followed up every 3 months for the first 2 years and then annually thereafter. They are usually offered a course of six intravesical instillations of mitomycin C or epirubicin. Those who present with a tumour at follow-up visits undergo either TURBT or cystodiathermy and biopsy. During the follow-up visits patients undergo cystoscopy and in some centres cytology and/or biomarker tests. Cystoscopies in the first 2 years are usually under general anaesthesia using a rigid cystoscope.[29]

Follow-up of high-risk non-muscle-invasive bladder cancer

If diagnosed with T1G3 TCC, patients are offered an early re-resection to ensure that the tumour is not muscle invasive. All patients in this group are usually offered an induction course of six intravesical BCG instillations followed by a maintenance regimen of a further 21 instillations over a 3-year period. Some may opt for primary radical cystectomy. Patients who opt for bladder sparing undergo their first bladder check at 3 months. If they remain tumour free they are followed up every 3 months for the first 2 years and then every 6 months thereafter. During the follow-up visits patients undergo cystoscopy and in some centres cytology and/or biomarker tests. Patients found to have a non-muscle-invasive recurrence at 3 months have four options: they can undergo cystectomy, have a second induction course of BCG

and then reassess, have three further instillations of BCG and then reassess, or have endoscopic control.

Muscle-invasive disease

Initial treatment

Once again, initial treatment comprises TURBT. If muscle invasion is confirmed on histological analysis, patients undergo CT of the chest, abdomen and pelvis and in some centres MRI scanning of the pelvis. In the absence of metastatic disease and other significant comorbidity, treatment options for patients with muscle-invasive disease include radical cystectomy with ileal conduit formation, radical cystectomy with formation of a neobladder, or radical radiotherapy. Neoadjuvant systemic chemotherapy is usually recommended before radical cystectomy or radiotherapy.

Follow-up

- Follow-up after radiotherapy is by regular (usually 6-monthly) cystoscopy. The first check cystoscopy is usually performed at about 4 months post completion of radiotherapy.
- Follow-up after cystectomy is by clinical assessment and CT scanning.
- A CT scan should be performed (at around 6 months following surgery for most patients) to assess for lymph or local recurrence. Subsequent CT scanning may be required in some cases but need not be carried out routinely.
- Non-muscle-invasive recurrences are dealt with endoscopically. Intravesical chemotherapy or BCG should be considered if recurrences are multiple or frequent.
- Non-muscle-invasive recurrences after radiotherapy are dealt with endoscopically. Intravesical chemotherapy, or in advanced cases salvage cystectomy, should be considered.
- Muscle-invasive recurrences after radiotherapy are best dealt with by salvage cystectomy if the patient's condition allows (in other cases chemotherapy may be appropriate).
- Recurrence after cystectomy may be treated with radiotherapy or chemotherapy.

Metastatic disease

Radiotherapy can provide effective palliation for symptoms of locally advanced disease such as haematuria. Chemotherapy may be appropriate in cases of metastatic disease in which the patient has a good performance status and renal function. Treatment is purely palliative and should be selected according to the patient's needs but may include systemic chemotherapy with GC (gemcitabine and cisplatin) or MVAC (methotrexate, vinblastine, adriamycin, cisplatin). Combinations with cisplatin are more effective than those without.[30,31] Gemcitabine plus cisplatin has equivalent survival to MVAC but is much less toxic.

Non-transitional cell carcinoma bladder cancer

Careful case-by-case management of non-TCC bladder cancer patients is required including discussion by the specialist MDT. Specialist histopathological review may be required, with consideration to the fact that the primary tumour may not be arising from the bladder.

Current service cost

It is difficult to estimate the current bladder cancer service cost in the UK because of the variation in practice in the diagnosis and follow-up of patients based on their risk categorisation. It is anticipated that the costs of the higher risk patients will be greater than those of the low-risk patients because of more follow-up interventions. The total cost of treatment and 5-year follow-up of patients with bladder cancer diagnosed during 2001–2 was £55.39 million; the total cost of superficial disease was £35.25 million and that of invasive disease was £20.2 million. The total cost for patients undergoing radical radiotherapy was over twice that for those undergoing cystectomy (£8.1 versus £3.6 million)[32] In the USA it is estimated that $1.7 billion is spent on bladder cancer.[33]

An estimate of the current cost to the UK NHS can be generated by using the total cost of each strategy (see *Tables 39* and *42*) and combining it with the values in *Table 2*. If it assumed that the current practice for diagnosis in the UK is flexible cystoscopy and cytology for initial diagnosis followed by white light rigid cystoscopy [CSC_CTL_WLC (CSC_WLC)] the cost per low-risk patient will be £6302.25. Therefore the total annual cost to the NHS will be £64,765,481. There is also evidence that costs are likely to increase with improved survival because patients need several courses of treatment.

Variation in services and/or uncertainty about best practice

All urology departments offer haematuria clinics and subsequent TURBT if appropriate either in the same hospital or in a hub hospital. Radiotherapy and systemic chemotherapy are available in cancer centres. Radical surgery for

prostate and bladder cancer should be provided by teams carrying out a cumulative total of at least 50 such operations per annum. These procedures should be performed by surgeons performing at least five of either radical cystectomy or prostatectomy each year.[34]

Relevant national guidelines, including National Service Frameworks

The relevant national guidelines are:

- National Institute for Clinical Excellence (2002). *Improving outcomes in urological cancers*. NHS guidance on cancer services[34]
- National Institute for Clinical Excellence (2003). *Laparoscopic cystectomy of the urinary bladder*. IPG026[35]
- Scottish Intercollegiate Guidelines Network (SIGN) (2005). *Management of transitional cell carcinoma of the bladder*[36]
- National Institute for Health and Clinical Excellence (2007). *Intravesical microwave hyperthermia with intravesical chemotherapy for superficial bladder cancer*. IPG235[37]
- NHS Pan-Birmingham Cancer Network (2006/2007). *Guidelines for the management of bladder cancer*[38]
- UK National Screening Committee (NSC) (2002). *Evaluation of urinary tract malignancy (bladder cancer) screening against NSC criteria*[39]
- British Association of Urological Surgeons (BAUS) Section of Oncology and Uro-oncology Group (2007). *MDT (multi-disciplinary team) guidance for managing bladder cancer*[28]
- European Association of Urology (EAU) (2009). *Guidelines on TaT1 (non-muscle-invasive) bladder cancer*[3]
- European Association of Urology (EAU) (2009). *Guidelines on bladder cancer: muscle invasive and metastatic*[40]
- American National Comprehensive Cancer Network (NCCN) (2009). *NCCN clinical practice guidelines in oncology. Bladder cancer including upper tract tumours and urothelial carcinoma of the prostate*[24]
- American Urological Association (AUA) (2007). *Guideline for the management of nonmuscle invasive bladder cancer (stages Ta,T1 and Tis)*.[5]

Only two of the above guidelines specifically mention photodynamic diagnosis (PDD):

> The evidence suggests potential benefits from photodynamic techniques for patients with superficial bladder cancer undergoing initial resection of their tumour. Its role in patients developing recurrence during followup is less clear.
>
> SIGN (2005)[36]

> The benefit of fluorescence-guided TURBT for recurrence-free survival was shown in several small randomised clinical trials, but its value remains to be proven in improving the outcome of patients for progression rates or survival. The additional costs of the equipment should be considered.
>
> EAU (2009)[3]

Various guidelines, including those of the EAU and AUA, recommend the use of voided urinary cytology, both in the diagnosis and surveillance of non-muscle-invasive bladder carcinoma. However, there are no equivalent recommendations for the use of biomarkers. Although the international consensus panel on the use of biomarkers in bladder cancer realised the importance of non-invasive diagnosis and surveillance of non-muscle-invasive disease, it concluded that, although none of the non-invasive tests could replace cystoscopy, many markers together with cystoscopy could improve the current practice of managing patients with bladder cancer.[41]

Description of the technologies under assessment

Summary of interventions

Photodynamic diagnosis

Principles

Fluorescence

Fluorescence occurs when a molecule absorbs one colour of light and emits another colour. Essentially, photons of light are absorbed by tissue and excite electrons in the tissue. The electron then returns to its resting state and the photon is emitted with less energy, i.e. longer wavelength, resulting in a different colour emission. Fluorescence cystoscopy is based on the principle that specific fluorochromes have increased affinity for neoplastic tissue compared with normal urothelium. When light of an appropriate wavelength is used to look at the surface of bladder to which the fluorochrome has been applied, different signal intensities are given off by neoplastic and non-neoplastic tissue. To minimise autofluorescence from cellular components such as collagen, a longpass eye filter is needed. A

filter allowing only wavelengths > 600 nm would be ideal, but this would result in the image being very dark. A compromise is therefore to use a 450-nm yellow filter and therefore accept some autofluorescence. This does not affect colour reproduction in the white light mode.

Over the last 40 years, several agents have been evaluated for their ability to improve visualisation of urothelial cancer. These include tetracyclines, fluorescein, methylene blue and synthetic porphyrin compounds. However, these have been abandoned because of several side effects, including cutaneous toxicity lasting several weeks with synthetic porphyrins.

Photosensitisers

5-Aminolaevulinic acid-mediated fluorescence cystoscopy A major breakthrough was the discovery that 5-aminolaevulinic acid (5-ALA), in a suitable dose, could be safely applied to the bladder surface and permit detection of tumours by fluorescence without serious adverse effects. 5-ALA is an initial substrate of heme biosynthesis. Exogenous application of 5-ALA induces an accumulation of fluorescent porphyrins, predominantly protoporphyrin IX (PPIX), in epithelial tissue. Using a blue–violet light with a wavelength of 450 nm, PPIX appears as fluorescent red whereas normal urothelium appears blue. This is because PPIX accumulates up to 10 times more in neoplastic cells than in normal tissue. The mechanism of accumulation of fluorescent PPIX in urothelial cancer is unclear. Several theories, including a difference in the metabolic rate of neoplastic tissue, hyperproliferation and inflammation-induced increased permeability to ALA, have been proposed. These are supported by the observations that increased PPIX can be detected in urothelial hyperplasia, inflammation and granulation tissue. 5-ALA is usually administered intravesically 2–3 hours before cystoscopy at a dose of 1.5 g. The procedure requires special endoscopes and a specific light source (D-light™, Karl Storz).

Hexaminolaevulinate-mediated fluorescence cystoscopy 5-ALA absorption is limited because of its positive electric charge. The esterification of 5-ALA as hexylester aminolaevulinate makes ALA more lipophilic, which enables it to cross the cell membrane more easily. A consequence of this is more rapid cellular uptake and higher fluorescence than with ALA.[42] Hexaminolaevulinate (HAL) needs therefore only be administered 1 hour before cystoscopy and the dose is typically a 85-mg solution of HAL hydrochloride in 50 ml of phosphate buffered saline (Hexvix®).

Hypericin-mediated fluorescence cystoscopy Recently, hypericin has been proposed as an additional photosensitiser. Hypericin consists of a hydroxylated phenanthroperylenequinone that is extracted from the *Hypericum perforatum* plant, which is present in St John's wort. Within an organic solution, hypericin produces an intense, prolonged, red fluorescence signal. This is because its pigment produces single oxygen species upon exposure to light of an appropriate wavelength. Most studies have used hypericin at a concentration of 8 µmol/l and instilled it 1–2 hours before cystoscopy.

Procedure

Before TURBT, a 12F LoFric or two-way urethral catheter is inserted by a nurse on the ward and intravesical photosensitiser instilled. The catheter is removed immediately. In theatre, under general or spinal anesthesia, the bladder is first inspected using white light rigid cystoscopy. The bladder is then reinspected using blue–violet light. Normal-appearing bladder should appear blue. Normal-appearing bladder neck and/or prostate appear red because of tangential views that cause them to be artefactually red. This, however, acts as a useful positive control. Within the bladder, any red areas are considered to be suspicious and require biopsy.

The bladder tumour is then resected in white light. A further inspection of the bladder with blue–violet light will then identify any residual tumour that may have been missed on WLC.

Equipment

- Photosensitiser, e.g. 5-ALA, HAL, hypericin.
- Rigid cystoscope with longpass yellow filter for wavelengths > 450 nm.
- Fluid light cable – this blocks residual infrared light and lowers intrinsic autofluorescence; however, a disadvantage is that it cannot be autoclaved.
- Switchable bandpass filter – this enables the surgeon to interchange between white light and blue–violet light without changing cystoscopes.
- Xenon lamp – powerful, especially in the blue light spectra.
- Camera controller.
- Video monitor.
- Colour charge-coupled device (CCD) camera (on chip integration) – this is suitable for working in low light conditions. The

fluorescent image is 10 times less intense than white light; allows increased red light intensity.
- Beam splitter cube.

Extra personnel involved
Unlike white light cystoscopy, PDD requires the instillation of a photosensitiser via a urethral catheter before TURBT. This is usually performed by a nurse on the ward.

Procedure time compared with conventional cystoscopy
On the ward, catheterisation and instillation of the photosensitiser and then removal of the catheter takes about 15 minutes. In theatre, fluorescence-guided TURBT takes an extra 10 minutes compared with conventional white light TURBT alone.

Urinary biomarkers
Urinary biomarkers are molecular substances that can be objectively measured in urine and evaluated as indicators of physiological or disease processes in the urinary tract or in various systems of the body. In principle, this could act as a source of vital information for diagnosis, prognosis and predicting response to therapies. The explosion of interest in urinary biomarker research, in particular related to bladder cancer, is driven by the fact that there is a lack of non-invasive methods of diagnosis and disease surveillance. The current standard of care – endoscopic inspection of the inside of the urinary bladder – is not only invasive but can also miss up to 10% of bladder tumours.[43] The urinary measurement of biomarkers could provide a diagnostic means that could either complement cystoscopy to enhance its performance or replace it as a mode of diagnosis and surveillance.

From a methodological perspective, urinary markers fall into a few broad groups, in particular soluble urinary proteins, cell-based biomarkers and nucleic acid biomarkers. As a complete review of each specific biomarker is beyond the scope of this chapter, the present study focused on four urinary biomarkers approved by the US Food and Drug Administration (FDA) for clinical use in urological practice. These are urinary cytology, nuclear matrix protein (NMP22), fluorescence in situ hybridisation (FISH) and ImmunoCyt.

Place of biomarkers in the treatment pathway
There are several potential strategies worth considering aimed at making use of urinary biomarkers in the care pathways of bladder cancer. They could be used:

- Alone or as an adjunct to urinary cytology to improve the detection rate of cancer in high-risk populations.
- To provide a less expensive and more objective alternative to the urinary cytology test.
- To replace or supplement direct cystoscopic surveillance of non-muscle-invasive bladder cancer. They may also serve to decrease the number of invasive procedures, provided that adequate cancer control is maintained on follow-up, and thereby reduce the health-care cost and improve the comfort of patients.

The critical issue remains the operating characteristics of these markers compared with cystoscopy, the current standard of care. False-positive results are likely to generate further unnecessary investigations in addition to fear and anxiety in patients' minds; alternatively, false-negative results may prove to be detrimental, such as progression to muscle invasion.

Setting
Urinary cytology
Urinary cytology involves examination of cells from the urinary tract under microscopy. A urinary sample is transported to the laboratory and cells are retrieved by a conventional cytospin method. Cells are examined under a microscope by a cytopathologist for the presence or absence of malignant changes using the standard Papanicolaou method. The test is laboratory based and results are observer dependent with the potential for inter- and intraobservational variation.

Nuclear matrix protein
NMP22 is a patented proteomic technology that has been commercialised by Matritech. Two products are marketed for the diagnosis of bladder cancer, the NMP22® Test Kit and the NMP22® BladderChek® Test. The NMP22 BladderChek Test is the only in-office test approved by the FDA for the diagnosis of bladder cancer. It is a non-invasive test performed on a single urine sample. Bladder cancer cells release NMP22 protein into urine, which is detected by putting 4–5 drops of urine on a prepared card. A change in colour is considered as a 'positive test' result. The levels of NMP22 in urine from healthy individuals are very small but can be significantly elevated in patients with urothelial cancers. The test has also been approved

by the FDA for point of care use in the diagnosis of bladder cancer.

Fluorescence in situ hybridisation
The basis of this test is the detection of abnormal DNA sequences on chromosomes 3, 7, 17, and the loss of the 9p21 locus in cancer cells shed into the urine of patients with bladder cancer. The retrieved cells from voided urine specimens are fixed on microscopy slides and visualised using a four-colour, four-probe mixture of DNA probe sequences homologous to specific regions on the aforementioned chromosomes. This is a laboratory test and has been commercialised by Abbott under the market name of UroVysion™ Bladder Cancer Kit (UroVysion Kit).

ImmunoCyt
The ImmunoCyt test uses a cocktail of three monoclonal antibodies labelled with fluorescent dyes that bind to two antigens, a mucin glycoprotein (green) and a carcinoembryonic antigen (red), expressed by bladder tumour cells in urine specimens. A voided urine specimen is transported to the laboratory and cells retrieved from it are fixed to a microscope slide. The antibodies are added to the slide and the stained slide examined under fluorescent microscopy by a cytopathologist.

Equipment required and personnel involved
Urine cytology requires the support of skilled laboratory cytotechnicians and cytopathologists within pathology laboratories. This means that results take longer to obtain and are not available on the same day. In addition to these requirements, the FISH and ImmunoCyt tests require specific kits and specialised fluorescence microscopes for visualisation of labelled cancer cells. Also, the FISH technique requires a special filter for cell retrieval. The only biomarker test approved for point of care diagnosis of bladder cancer is NMP22 detection using the commercially available NMP22 Test Kit. The test provides instantaneous results and can be performed by medical personnel with minimal training.

Identification of important subgroups

Photodynamic diagnosis

- It is important to distinguish the role of fluorescence-guided TURBT for primary tumours from its role in bladder tumour recurrence. Its role in patients developing recurrence during follow-up is less clear.
- It is important to realise that the use of different photosensitisers may lead to different results in terms of sensitivity and specificity.

Biomarkers/cytology
The diagnostic performance of urinary biomarkers can be scrutinised in the background of two clinical settings: the ability to accurately diagnose bladder cancer in high-risk populations and their potential to accurately predict recurrences in patients known to have non-muscle-invasive disease. Urinary biomarkers can either complement or replace current invasive tests such as cystoscopy. The second clinical scenario in which the diagnostic utility of urinary biomarkers comes under sharp focus is their ability to perform across all grades and stages of non-invasive bladder cancer disease. For example, urinary cytology performs well (high sensitivity) in high-grade disease, whereas its performance decreases (low sensitivity) in low-grade disease – this is why it is not a plausible replacement for cystoscopy, both at the point of diagnosis and at follow-up in the care pathways of non-muscle-invasive bladder cancer disease.

Current usage in the NHS

Photodynamic diagnosis
In most UK centres PDD is not available. Moreover, in centres in which the service is available, it is used to a varying extent. In a few centres (less than five) it is used routinely for all first-time TURBTs. In others it may be used only during follow-up when CIS is suspected, such as a normal-appearing bladder on WLC but positive urine cytology.

Two further factors are likely to influence the uptake of PDD within the wider NHS:

- Fluorescence cystoscopy has been identified as a new technology that has been signalled by the NCRI to the National Horizon Scanning Centre for early review.
- In 2008 the NHS Technology Adoption Centre took forward a PDD implementation project involving three NHS trusts. The experience gained from the project will support the wider NHS in overseeing issues associated with the adoption of new technologies.

Biomarkers/cytology
Although urinary cytology is the most common urinary biomarker used for the diagnosis and follow-up of non-muscle-invasive bladder cancer in the NHS, the practice varies across the UK.[44] There are few reports of NMP22 being used as a diagnostic biomarker in patients with haematuria

from UK centres.[45] The clinical use of FISH and ImmunoCyt as urinary markers in patients with bladder cancer has not been reported in the UK.

Anticipated costs associated with the technologies

The anticipated costs associated with the technologies will depend on the strategies used in the diagnosis and follow-up of patients. The average unit cost of diagnosing bladder cancer using PDD is £1371, rigid white light cystoscopy £937, flexible cystoscopy £441, cytology £92.37, NMP22 £39.3, FISH £54.8 and ImmunoCyt £54.8; and the cost of treatment using PDD-assisted TURBT is £2436, WLC-assisted TURBT £2002, mitomycin £73, BCG £89, cystectomy £6856, chemotherapy £50.22, radical radiotherapy £1050 and palliative treatment £12,825 (see Chapter 6 for details). The modelling results indicate that using the most effective strategy (the one with the highest number of true positives and the lowest number of false negatives), which includes either of the two biomarkers FISH or ImmunoCyt and PDD as the initial strategy and either FISH or ImmunoCyt with WLC as the follow-up strategy, will cost £5919.28 per low-risk patient per year.

Chapter 2
Definition of the decision problem

Decision problem

Accurate diagnosis of bladder cancer is crucial for people who may potentially have the disease to allow for early detection and to reduce the risk of tumour recurrence and progression. The ideal test for diagnosis and follow-up of bladder cancer would be non-invasive, highly sensitive and specific, inexpensive and easy to perform and would provide reproducible results. Many of the tests meet some, but not all, of these criteria. Currently, a common diagnostic scenario in the UK is that people suspected of having bladder cancer are first examined with flexible cystoscopy and voided urine cytology, followed by white light rigid cystoscopy-assisted TURBT or biopsies for those considered positive or suspicious for the disease. However, insufficient sensitivity or specificity of the three tests can result in the incomplete detection or overtreatment of primary and recurrent disease.

As patients are living longer and recurrence of disease is becoming a major issue there is a need to identify the most appropriate methods for diagnosing patients with bladder cancer and subsequently following them up. A variety of tests have been developed that have been used as alternatives to, or alongside, existing investigations. As described in Chapter 1, urinary biomarkers for bladder cancer are non-invasive assay tests that can detect protein, genetic or chromosomal aberrations, even at early stages of disease. Some are point of care tests whereas others require laboratory analysis. These tests are considered to be attractive and potentially cost-effective as they may offer the potential to avoid unnecessary cystoscopies and labour-intensive cytology. Biomarkers have the potential to play a role in the initial diagnosis of patients either in addition to or as a replacement for urine cytology, and in monitoring during follow-up.

PDD has been used alongside rigid cystoscopy with the aim of improving detection of CIS and papillary tumours during TURBT, thereby potentially reducing the residual tumour rate at the 6-week check following TURBT and consequently also reducing recurrence and progression of disease. PDD has also been described as a safe and straightforward technique to learn.

The following sections provide a description of the care pathways that show the plausible strategies for the primary diagnosis and follow-up of people with bladder cancer.

Inclusion criteria (see Chapter 3)

Key issues

The key issues to be addressed are:

- Can PDD improve detection of bladder cancer (1) at the time of TURBT for newly diagnosed disease and (2) during follow-up of patients with non-muscle-invasive disease?
- Can PDD reduce recurrence and/or progression of non-muscle-invasive bladder cancer compared with WLC?
- Can urine biomarkers (FISH, ImmunoCyt, NMP22) improve detection of bladder cancer during (1) initial diagnosis of patients suspected of having bladder cancer and (2) follow-up of patients diagnosed with non-muscle-invasive disease?
- What is the incremental cost-effectiveness of PDD during TURBT for newly diagnosed non-muscle-invasive bladder cancer and during follow-up?
- What is the incremental cost-effectiveness of biomarkers during the initial diagnosis of patients suspected of having bladder cancer and during follow-up of those diagnosed with non-muscle-invasive disease?

Care pathways

Care pathways describing plausible strategies for the initial diagnosis and follow-up of people with bladder cancer were developed. The basic care pathway was based on discussions with the clinical experts involved in this study and a brief description of this is provided within Chapter 1.

***Initial diagnosis and treatment (*Figure 4)**

The pathway begins with an initial presentation of symptoms or asymptomatic microscopic haematuria and varies in terms of where and when

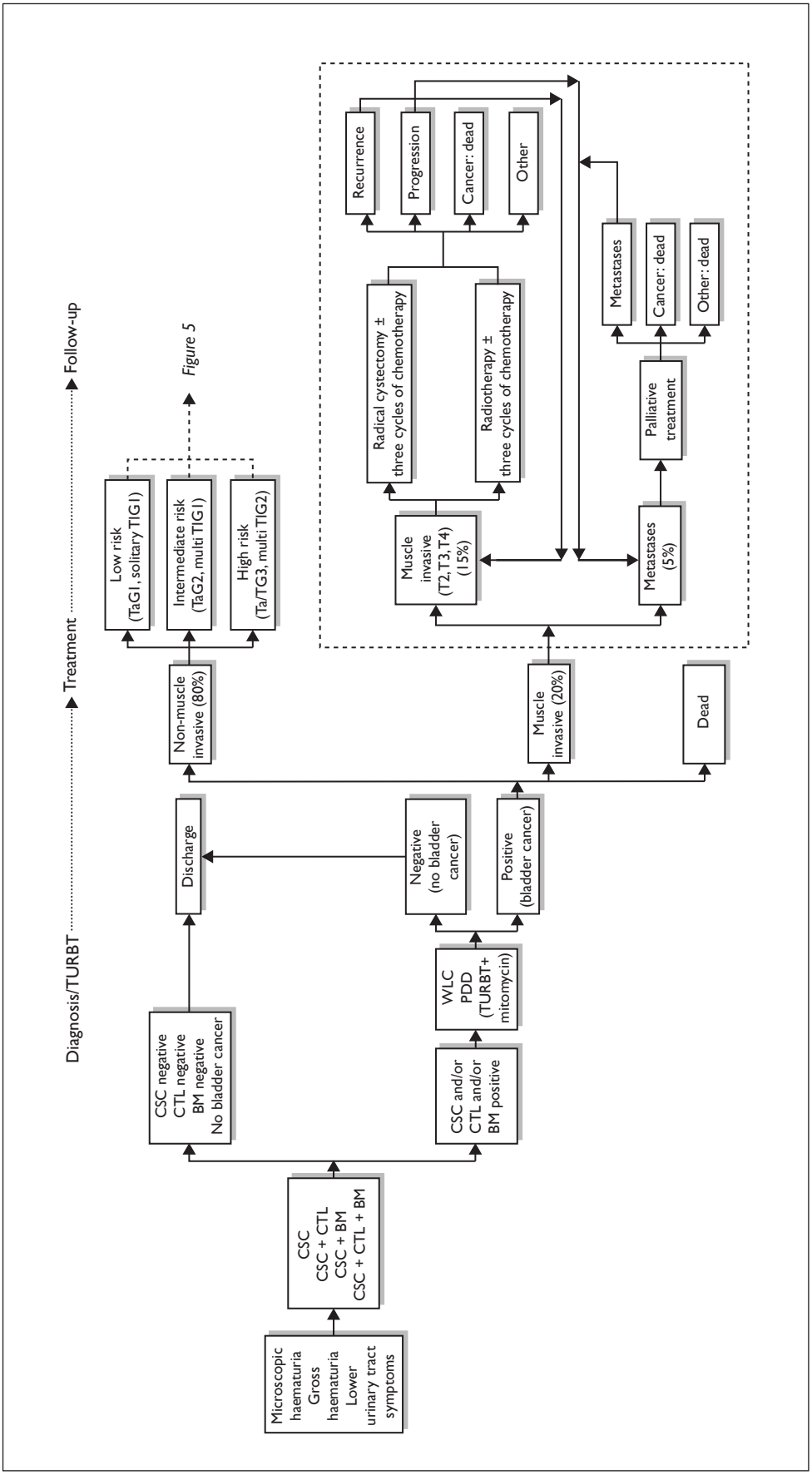


FIGURE 4 *Developed care pathway – initial diagnosis/treatment. BM, biomarkers; CSC, flexible cystoscopy; CTL, cytology.*

biomarkers and PDD might be used. Patients who present with either microscopic or gross haematuria or lower urinary tract symptoms are tested using flexible cystoscopy and cytology. Biomarkers could be used at this point either in addition to these two tests or instead of cytology. The results of these tests can be either negative or positive. Patients who have two/three negative results are discharged. Discharged patients who later re-present with similar symptoms go back to the beginning of the care pathway. Patients with one or more positive results for these tests as outlined in *Table 3* undergo TURBT during which PDD may be used with the aim of improving the detection of tumours, thereby potentially reducing the rate of residual tumours and increasing the detection of CIS and small papillary tumours.

After TURBT is performed for newly diagnosed bladder cancer, the standard UK management is that the patient also receives a single instillation of adjuvant intravesical mitomycin C, ideally within 6 hours of resection but not later than 24 hours if possible. Biopsies are taken and the results of the histological analysis may be either negative or positive for bladder cancer. Those who have a negative histology result are then discharged. Discharged patients whose symptoms are not resolved may subsequently re-present at the beginning of the care pathway. For the purposes of this review, although patients who have a negative bladder cancer test result are considered as discharged, it is noted that some who initially had a positive result may be at risk of upper tract urothelial cancer or renal cancer and consequently will require further tests, and, if positive, treatment.

Those patients whose histological results confirm the presence of bladder cancer are classified into muscle-invasive or non-muscle-invasive disease. For those with muscle-invasive disease, treatment options are outlined in *Figure 4*. Essentially, those amenable to potential cure are offered either radical cystectomy with bilateral pelvic lymphadenectomy or radiotherapy. Treatment with surgery or radiotherapy is usually preceded by three cycles of systemic neoadjuvant cisplatin-based chemotherapy. The rationale for chemotherapy is that over 50% of patients with muscle-invasive disease have occult metastatic disease at presentation. It is noted that practice at individual centres may vary. The decision for cystectomy or radiotherapy is primarily based on patient choice and medical fitness. The presence of concomitant CIS and upper tract dilatation are also factors that favour cystectomy. For patients with more advanced metastatic disease, the treatment is palliative.

TABLE 3 *Different test results*

Cystoscopy	Cytology	Biomarkers
–	–	–
–	–	+
–	+	–
+	–	–
–	+	+
+	–	+
+	+	–
+	+	+

–, negative; +, positive.

Follow-up of patients with non-muscle-invasive bladder cancer (Figure 5)

The key factors increasing the risk of recurrence and progression in patients with non-muscle-invasive bladder cancer are: (1) tumour multiplicity, (2) greater tumour diameter, (3) previous recurrence rate, (4) higher T-stage, (5) concomitant CIS and (6) higher histological grade. A brief summary is provided in the following sections and a further short review on the management of bladder cancer, required for the description of the model structure, is provided in Chapter 6 (see Model structure, Markov model).

High risk

Broadly speaking, patients with Ta/T1G3 TCC, CIS or multifocal T1G2 TCC are classified as being at high risk of not only recurrence but also progression. If diagnosed with T1G3 TCC they are offered an early re-resection to ensure that they are not muscle invasive. All patients in this group are usually offered an induction course of six intravesical BCG instillations followed by a maintenance regimen of a further 21 instillations over a 3-year period. Some may opt for primary radical cystectomy. Patients who opt for bladder sparing undergo their first bladder check at 3 months. If they remain tumour free they are followed up every 3 months for the first 2 years and then every 6 months thereafter. During the follow-up visits, patients undergo cystoscopy and in some centres cytology and/or a biomarker test. Patients found to have a non-muscle-invasive recurrence have four options: they can undergo cystectomy, have a second induction course of BCG and then reassess, have three further instillations of BCG and then reassess, or receive endoscopic control.

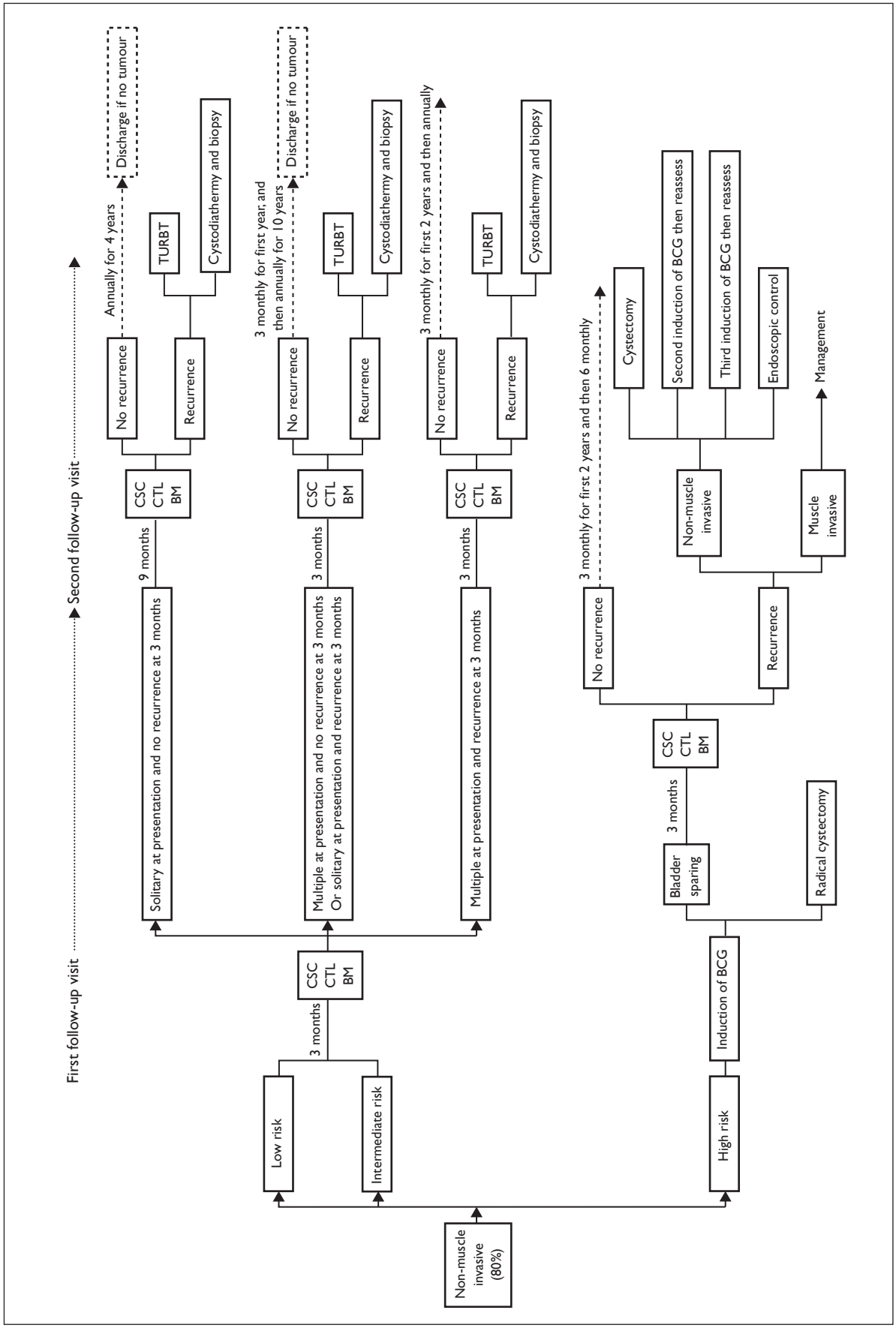


FIGURE 5 *Developed care pathway – follow-up. BM, biomarkers; CSC, flexible cystoscopy; CTL, cytology.*

Low and intermediate risk

Patients at low risk of recurrence and progression have TaG1 TCC or solitary T1G1 TCC. Those at intermediate risk have TaG2 TCC or multifocal T1G1 TCC. Multiplicity at presentation and a tumour recurrence at 3 months have consistently been shown to be key practical predictors of future recurrence, and many urologists in the UK tailor their cystoscopic follow-up of low- and intermediate-risk patients based on these two factors for these reasons:

(a) Patients who have a solitary tumour at diagnosis and no tumour recurrence at 3 months are followed up at 9 months and then annually for 4 further years. If at the end of this 5-year follow-up period they have remained tumour free they are discharged. During the follow-up visits these patients undergo flexible cystoscopy and in some centres cytology and/or biomarker tests. Although most patients with a tumour recurrence will receive TURBT, some may have a cystodiathermy and biopsy.
(b) Patients with multiple tumours at presentation and no recurrence at 3 months or a solitary tumour at presentation with recurrence at 3 months need more intense follow-up and are followed up every 3 months for the first year and annually if they remain tumour free until 10 years and are then discharged. During the follow-up visits patients undergo cystoscopy and in some centres cytology and/or biomarker tests. Those who present with a tumour at the follow-up visit undergo either TURBT or cystodiathermy and biopsy. These patients may be considered for a course of six intravesical instillations of mitomycin C or epirubicin.
(c) Patients with multiple tumours at presentation and recurrence at 3 months have the highest risk of recurrence and are followed up every 3 months for the first 2 years and then annually thereafter. They are usually offered a course of six intravesical instillations of mitomycin C or epirubicin. Those who present with a tumour at the follow-up visit undergo either TURBT or cystodiathermy and biopsy. During the follow-up visits patients undergo cystoscopy and in some centres cytology and/or biomarker tests. Cystoscopies in the first 2 years are usually under general anaesthesia using a rigid cystoscope.

During the follow-up period the status of patients may change and they may develop muscle-invasive tumours. It is also possible that patients may die at any time during follow-up from causes related to bladder cancer or from unrelated causes. The outlined care pathways in *Figures 4* and *5* identify the areas in which PDD and biomarkers could be used in conjunction with the standard tests to diagnose patients with suspected bladder cancer and to follow up those who have been diagnosed with non-muscle-invasive disease. These patient care pathways will be used to inform the economic model and to establish whether the use of PDD and urine biomarkers reduces recurrence or decreases progression at follow-up as a consequence of altered treatment.

Aim of the review

The aim of this review is to assess the clinical and cost-effectiveness of PDD and urine biomarker tests in the detection and follow-up of non-muscle-invasive bladder cancer.

This aim is addressed through:

- a systematic review of PDD, and urine biomarker tests (FISH, ImmunoCyt and NMP22) and cytology alone or in combination, in the diagnosis and follow-up of bladder cancer
- a structured review of the management of patients diagnosed with bladder cancer with associated costs and outcomes
- economic modelling of the cost-effectiveness and cost–utility of alternative approaches in the diagnosis and follow-up of patients with non-muscle-invasive bladder cancer.

The specific objectives of the review are to:

- estimate the incremental cost-effectiveness of PDD compared with white light rigid cystoscopy, and biomarkers and urine cytology, in initial diagnosis and follow-up
- assess the performance of PDD (1) at the time of TURBT for newly diagnosed bladder cancer and (2) during follow-up of patients with non-muscle-invasive disease
- assess the performance of urine biomarkers and cytology in (1) initial diagnosis of bladder cancer and (2) during follow-up of patients with non-muscle-invasive disease
- assess whether PDD reduces recurrence and/or progression of non-muscle-invasive disease compared with WLC.

Structure of the remainder of the report

The remainder of the report is structured as follows. Chapter 3 describes the methods for reviewing test performance and effectiveness, Chapter 4 assesses the diagnostic accuracy, and clinical effectiveness in terms of recurrence/progression rates, of PDD compared with WLC and Chapter 5 assesses the test performance of urine biomarkers (FISH, ImmunoCyt, NMP22) and cytology. Chapter 6 assesses the cost-effectiveness of the tests, Chapter 7 discusses factors relevant to the NHS and other parties, Chapter 8 is a discussion of the findings and Chapter 9 presents the review's conclusions, including implications for the NHS and for research.

Chapter 3

Methods for reviewing test performance and effectiveness

Identification of studies

Studies were identified by searching electronic databases and relevant websites, contact with experts in the field and the scrutiny of bibliographies of retrieved papers. Highly sensitive electronic searches were conducted to identify reports of published and ongoing studies on the diagnostic performance of the tests of interest, as well as the effectiveness of PDD-assisted TURBT. The databases searched were MEDLINE (1966 to March Week 3 2008), MEDLINE In-Process (1 April 2008), EMBASE (1980 to Week 13 2008), BIOSIS (1985 to 27 March 2008), Science Citation Index (1970 to 1 April 2008), Health Management Information Consortium (HMIC) (March 2008) and the Cochrane Controlled Trials Register (Cochrane Library, Issue 1 2008) as well as current research registers [National Research Register (NRR) Archive (September 2007), Current Controlled Trials (CCT) (March 2008), ClinicalTrials.gov (March 2008) and WHO International Clinical Trials Registry (March 2008)]. Additional databases searched

TABLE 4 *Search results*

Database	Number retrieved
Primary reports	
MEDLINE (1966 to March Week 3 2008)/EMBASE (1980 to Week 13 2008)/MEDLINE In-Process (1 April 2008) multifile search (after deduplication in Ovid)	5373
Science Citation Index (1970 to 1 April 2008)	206[a]
BIOSIS (1985 to 27 March 2008)	60[a]
CENTRAL (Cochrane Library, Issue 1 2008)	2[a]
HMIC (March 2008)	2[a]
Total	5643
Background	
CDSR (Cochrane Library, Issue 1 2008)	1
DARE (March 2008)	21
HTA database (March 2008)	15
Medion (March 2008)	0
Total	37
Total assessed for review	5680
Ongoing studies	
NRR	33
CCT	7
ClinicalTrial.gov	1
WHO International Clinical Trials Registry	0
Total	41

a The numbers retrieved from the searches in Science Citation Index, BIOSIS, HMIC and CENTRAL refer to the additional reports found after excluding those identified from the MEDLINE/EMBASE multifile search.

for systematic reviews and other background information included the Cochrane Database of Systematic Reviews (CDSR) (Cochrane Library, Issue 1 2008), Database of Abstracts of Reviews of Effectiveness (DARE) (March 2008), Health Technology Assessment (HTA) database (March 2008) and Medion (March 2008). A total of 5680 reports were identified (*Table 4*). In addition, the details of 41 potentially relevant ongoing studies were noted. Reference lists of all included studies were scanned to identify additional potentially relevant studies. Full details of the search strategies used and websites consulted are documented in Appendix 1.

Inclusion and exclusion criteria

Types of studies

The types of studies considered for reporting test performance were:

- direct (head-to-head) studies in which the index test and reference standard test were performed independently in the same group of people
- randomised controlled trials (RCTs) in which people were randomised to the index and comparator test(s) and all received the reference standard test.

In the event that there was insufficient evidence from direct and randomised studies we considered undertaking indirect (between-study) comparisons by meta-analysing studies that compared each single test or combination of tests with the reference standard test, and making comparisons between meta-analyses of the different tests. However, this type of study design is less reliable than direct studies as differences in diagnostic accuracy are susceptible to confounding factors between studies. The following types of studies were considered:

- Observational studies, including case series, in which the sample is created by identifying all people presenting at the point of testing (without any reference to the test results).
- Case–control studies in which two groups are created, one known to have the target disease and one known not to have the target disease, when it is reasonable for all included to go through the tests. We excluded case–control studies when the control group consisted of completely healthy volunteers, or when the control group consisted of completely healthy volunteers and people with benign urinary conditions and it was not possible to calculate results for the control group minus the healthy volunteers, such that the spectrum of disease and non-disease was unlike that to be encountered in a diagnostic situation.

Studies reporting test performance had to report the absolute numbers of true positives, false positives, false negatives and true negatives, or provide information allowing their calculation. Studies reporting patient- and/or biopsy-level analysis (for PDD) and patient- or specimen-level analysis (for biomarkers/cytology) were considered.

For assessment of the effectiveness of PDD-assisted TURBT compared with WLC-assisted TURBT in terms of outcomes such as recurrence or progression we focused on RCTs.

Types of participants

The participants considered were people (1) suspected of having bladder cancer or (2) previously diagnosed with non-muscle-invasive bladder cancer and having follow-up cystoscopic examination.

Index and comparator tests

The following tests and comparators were considered:

- PDD (using the photosensitising agents 5-ALA, HAL or hypericin) compared with WLC
- urine biomarkers (FISH, ImmunoCyt, NMP22) or cytology either alone or compared with each other.

Studies reporting the test performance of combinations of the above tests were also considered.

If the evidence allowed, the following subgroup analyses were planned:

- number of tumours on first cystoscopic examination
- type (e.g. CIS) and grade of tumour (WHO 1973 or 2004 classification)
- tumour recurrence at the first 3-month cystoscopic examination following TURBT
- diagnostic performance of the different PDD photosensitising agents

- diagnostic performance of the different categories of urine biomarkers
- for urine biomarkers, whether the urine sample was voided or obtained by bladder wash.

Numerous biomarkers exist that potentially could have been included in the review but to make the task manageable within the given time frame the review's steering committee agreed that the review should focus only on those biomarkers regarded as being most clinically relevant. These were seen as being either those approved by the US FDA or the three generally regarded as most useful – FISH, ImmunoCyt and NMP22 – with cytology also included. It was agreed that the Chairman of the BAUS Section of Oncology should be contacted to canvass the views of the Section's Executive Committee on the most relevant biomarkers to consider. Following this, the Chairman on behalf of the Section suggested that the review should assess ImmunoCyt, NMP22, FISH and cytology, and consequently these were the tests that were included in the review.

Reference standard

The reference standard considered both for studies reporting PDD and for studies reporting biomarkers was histopathological examination of biopsied tissue.

Types of outcomes

The following outcomes were considered:

- for PDD:
  - test performance in detecting non-muscle-invasive bladder cancer
  - recurrence rate of bladder tumour over time following initial resection
  - progression to muscle-invasive disease
- for urine biomarkers/cytology:
  - test performance in detecting non-muscle-invasive bladder cancer.

In any studies reporting the above outcomes, the following outcomes were also considered if reported:

- altered treatment as a result of the tests
- acceptability of the tests
- interpretability of the tests
- quality of life (disease-specific and generic instruments)
- adverse effects.

Exclusion criteria

The following types of report were excluded:

- animal models
- preclinical and biological studies
- reviews, editorials and opinions
- case reports
- abstracts, as usually insufficient methodological details are reported to allow critical appraisal of study quality
- reports investigating technical aspects of a test
- non-English language studies.

In addition, studies reporting biomarkers or cytology in which the number of participants in the analysis was less than 100 were excluded. Studies reporting cytology that predated the publication year of the earliest of the included biomarker studies were also excluded.

Data extraction strategy

One reviewer screened the titles (and abstracts if available) of all reports identified by the search strategy. Full-text copies of all studies deemed to be potentially relevant were obtained and two reviewers independently assessed them for inclusion. Any disagreements were resolved by consensus or arbitration by a third party.

Data extraction forms for studies reporting PDD and studies reporting biomarkers/cytology were developed and piloted. One reviewer extracted details of study design, participants, index, comparator and reference standard tests and outcome data, and a second reviewer checked the data extraction. Any disagreements were resolved by consensus or arbitration by a third party.

Quality assessment strategy

Two reviewers independently assessed the quality of the included diagnostic studies using QUADAS, a quality assessment tool developed for use in systematic reviews of diagnostic studies.[46] QUADAS was developed through a formal consensus method and was based on empirical evidence. The original QUADAS checklist contained 14 questions. The QUADAS tool was adapted to make it more applicable to assessing the quality of studies of tests for detecting bladder cancer (see Appendix 2 for an example of the modified checklist for PDD).

Questions 1, 3–7 and 10–14 of the original QUADAS tool were retained (questions 1–11 in the modified version). Three questions in the original QUADAS tool that related to the quality of reporting rather than methodological quality were omitted from the modified version (questions 2, 8 and 9). These questions related to the description of: (a) the selection criteria, (b) the execution of the index test and (c) the execution of the reference standard test. Two questions were added to the modified checklist on: (a) whether the study provided a clear definition of what was considered to be a 'positive' result and (b) whether data on observer variation were reported and within an acceptable range. In addition, a third question was added that related only to studies reporting biomarkers and/or cytology, on whether a prespecified cut-off value was used.

Two reviewers (from GM, CB or CR) independently assessed the quality of all included diagnostic studies using the modified version of QUADAS. Each question was checked as 'yes', 'no' or 'unclear'. Each item was worded so that a rating of 'yes' was always optimal in terms of methodological quality. Any disagreements were resolved by consensus or arbitration by a third party.

Two reviewers (from GM, CB or CR) independently assessed the quality of RCTs comparing WLC-assisted TURBT with PDD-assisted TURBT using a checklist adapted from Verhagen and colleagues[47] and developed through the Review Body for Interventional Procedures (ReBIP). ReBIP is a joint venture between the Medical Care Research Unit at Sheffield University and the Health Services Research Unit at the University of Aberdeen and works under the auspices of the National Institute for Health and Clinical Excellence's (NICE) Interventional Procedures Programme (IPP). The checklist for RCTs contained 14 questions (see Appendix 3). Any disagreements were resolved by consensus or arbitration by a third party.

Data analysis

Diagnostic accuracy of PDD/ urine biomarker tests

The results of the individual studies were tabulated and sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratios and diagnostic odds ratios (DORs) calculated. If reported in a given study, a separate 2×2 table was derived for patient-level and biopsy-level analyses.

Sensitivity describes the proportion of those with disease who have positive test results, whereas specificity is the proportion of those without disease who have negative test results. A positive likelihood ratio describes how many times more likely it is that a person with disease will receive a positive test result than a person without disease whereas a negative likelihood ratio describes how many times more likely it is that a person with disease will receive a negative test result than a person without disease. A positive predictive value (PPV) describes the proportion of those with positive test results who have the disease, whereas a negative predictive value (NPV) is the proportion of those with negative test results who do not have the disease. A DOR is a single indicator of test performance and is the ratio of the odds of testing positive in those with the disease relative to the odds of testing positive in those without the disease. It can be calculated from the sensitivity and specificity values. The DOR summarises the results into a single indicator of test performance; however, information contained in sensitivity and specificity is lost and in particular a DOR cannot distinguish between tests with high sensitivity and low specificity and vice versa.

Hierarchical summary receiver operating characteristic (HSROC) curves were produced for each test when three or more studies reported sufficient data. A separate HSROC curve was derived for patient-level analysis and biopsy-level analysis when possible. Meta-analysis models were fitted using the HSROC model[48] in SAS 9.1 using the NLMIXED function (SAS Institute). This HSROC model takes account of the diseased and non-diseased sample sizes in each study and allows estimation of random effects for the threshold and accuracy effects.[48,49] HSROC models for PDD and WLC were fitted individually based upon the data for the individual alone, which allowed for an asymmetric summary receiver operating characteristic (SROC) curve. Additionally, two models that fitted the data simultaneously were also run, to formally assess the evidence for a difference in diagnostic accuracy between the tests. A fuller model was run that allowed for a difference between the tests in all three constituent diagnostic accuracy parameters (threshold, accuracy and shape of SROC curve) and also a simpler nested model was run that did not allow for a difference in

diagnostic accuracy in any of the three parameters. The SROC curves from the HSROC models were produced and are shown on the corresponding SROC plots along with the individual study estimates. Summary sensitivity, specificity, positive and negative likelihood ratios and DORs for each model were reported as point estimate and 95% confidence interval (CI).

The presentation of test performance in terms of the detection of stage and grade of non-muscle-invasive bladder cancer was considered in the two broad categories of: (1) less aggressive, lower risk tumours (pTa, G1, G2) and (2) more aggressive, higher risk tumours (pT1, G3, CIS). The median (range) sensitivity of PDD and WLC across studies, for both patient- and biopsy-based detection of tumours, was reported for each category and also separately for CIS.

WLC-assisted TURBT compared with PDD-assisted TURBT

For relevant outcomes (e.g. recurrence rate after WLC-assisted TURBT compared with PDD-assisted TURBT), when appropriate, meta-analysis was employed to estimate a summary measure of effect. The dichotomous outcome data were combined using the Mantel–Haenszel (RR) method. For the estimates of RR, 95% CIs and p-values were calculated. The results were reported using a fixed-effect model in the absence of statistical heterogeneity. Chi-squared tests and I^2 statistics were used to explore statistical heterogeneity across studies. Possible reasons for heterogeneity were explored using sensitivity analysis. When there was no obvious reason for heterogeneity, the results were reported using random-effects methods. In the event that a quantitative synthesis was considered to be inappropriate or not feasible, we provided a narrative synthesis of results.

Chapter 4

Results – photodynamic diagnosis

Number of studies identified

From the electronic searches for primary reports, 113 records were selected as being possibly relevant to the review of PDD. In total, 33 of these were non-English language papers and were not considered further. The full-text reports of the remaining 80 were obtained and assessed: 44 met the inclusion criteria for this review; 25 were excluded; and 11 were retained for background information. *Figure 6* shows a flow diagram outlining the screening process, with reasons for exclusion of full-text papers.

Number and type of studies included

Appendix 4 lists the 31 studies, published in 44 reports, that were included in the review of test performance and effectiveness. In total, 27 studies, published in 36 reports,[50–85] met the inclusion criteria for studies reporting the diagnostic accuracy of PDD. Four RCTs, published in eight reports,[86–93] met the inclusion criteria for studies comparing the effectiveness of PDD-assisted TURBT with the effectiveness of WLC-assisted TURBT in terms of outcomes such as recurrence or progression.

Number and type of studies excluded

A list of the 25 potentially relevant studies identified by the search strategy for which full-text papers were obtained but which subsequently failed to meet the inclusion criteria is given in Appendix 5. These studies were excluded because they failed to meet one or more of the inclusion criteria in terms of the type of study, participants, test, reference standard or outcomes reported.

Characteristics of the included studies

Appendix 6 shows the characteristics of the included studies. *Table 5* shows summary information for the PDD studies reporting diagnostic accuracy and *Table 6* shows summary information for the RCTs comparing PDD with WLC and reporting recurrence and/or progression.

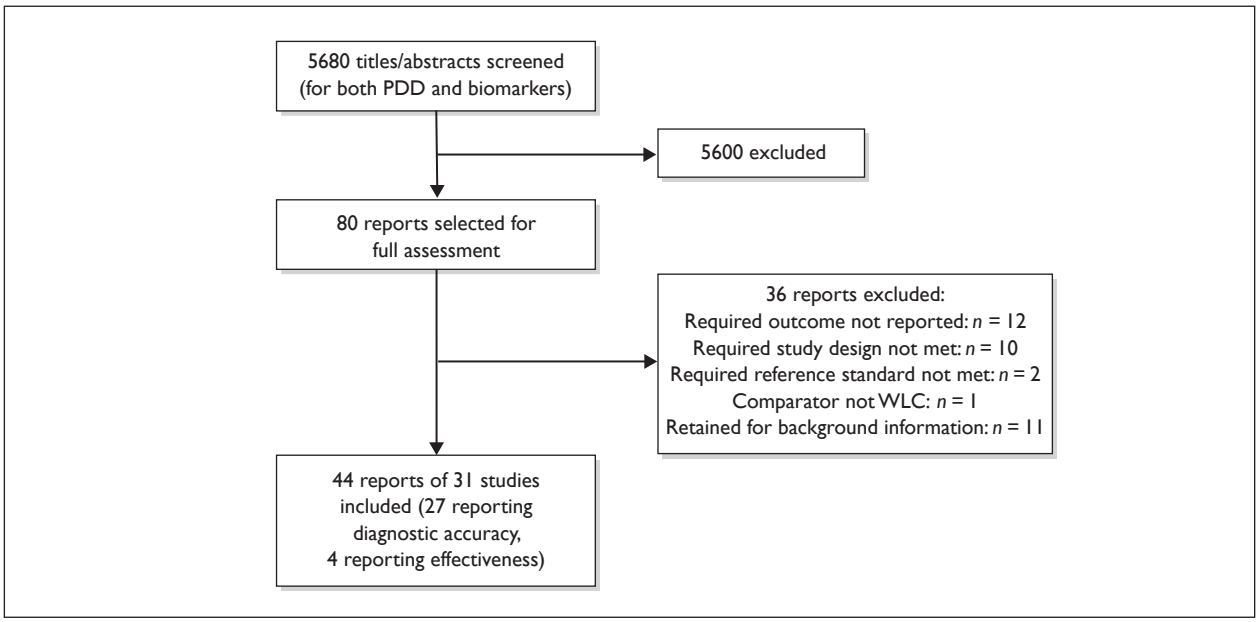


FIGURE 6 *Flow diagram outlining the screening process for the photodynamic diagnosis part of the review.*

TABLE 5 *Summary of the characteristics of the PDD diagnostic accuracy studies*

Characteristic	Number	Number of studies
Patients		
Enrolled	2949	27
Analysed	2807	
Suspicion of or previously diagnosed BC[a]		
Suspicion of BC	946 (41%)	19 (70%)
Previously diagnosed BC	1381 (59%)	
Not reported	481	8 (30%)
Age		
Median (range) of means (years)	67 (52–72)	20 (74%)
Not reported	–	7 (26%)
Sex[b]		
Men	1647 (76%)	18 (67%)
Women	510 (24%)	
Not reported	656	9 (33%)
Agent used		
5-ALA	2113 (75%)	18 (67%)
HAL	464 (17%)	5 (19%)
Hypericin	81 (3%)	2 (7%)
5-ALA or HAL	149 (5%)	2 (7%)

BC, bladder cancer.

a Suspicion of or previously diagnosed BC. The totals for this section sum to 2808 rather than 2807 because (1) in the study by Fradet and colleagues,[57] of 196 patients included in the analysis, 62 presented with a suspicion of BC, 133 had previously diagnosed disease (total of 195) and information was missing for one patient, and (2) in the study by Kriegmair and colleagues,[70] 29 patients were reported to have presented with suspicion of BC and 77 with previously diagnosed BC (total of 106), but only 104 patients were included in the analysis.

b Sex. This section sums to 2813 rather than 2807 because the study by Koenig and colleagues[67] reported gender information for those enrolled ($n = 55$) rather than those analysed ($n = 49$).

The 27 diagnostic studies enrolled 2949 participants, with 2807 included in the analysis. In 19 studies[51,53,57–63,65,66,70–72,77,78,80,81,84] involving 2327 participants, 946 (41%) presented with a suspicion of bladder cancer and 1381 (59%) had previously diagnosed bladder cancer. In two[72,78] of these studies the whole patient population ($n = 102$) had a suspicion of bladder cancer and in three[51,58,84] the whole population had previously diagnosed bladder cancer ($n = 117$). The remaining eight studies[50,52,54,56,67,73,76,85] did not report this information. In total, 18[50,53,54,56,58,59,61–63,67,70–73,77,78,84,85] (67%) of 27 studies used 5-ALA as the photosensitising agent, five[57,60,65,66,81] (19%) used HAL, two[52,76] (7%) used hypericin and two[51,80] used either 5-ALA or HAL but did report the number of patients receiving each agent.

Across 20 studies[50,51,53,56,57,59–63,65–67,70,71,76,77,80,81,84] providing information on patient age, the median (range) of means was 67 years (52–72 years). In total, 18 studies[50,53,54,57,60–63,65–67,70,71,76,77,80,81,84] provided information on the gender of 2157 participants, of whom 1647 (76%) were men and 510 (24%) were women.

Sixteen studies[50,51,53,56,59–63,65,71,76,77,80,81,85] gave details of when they took place, with an earliest start date of February 1994[63] and latest end date of March 2006.[51] Nine studies took place in Germany,[54,56,58,61,70,71,80,84,85] three in the Netherlands,[59,60,81] two each in Italy[51,53] and Singapore[50,76] and one each in Belgium,[52] Switzerland,[63] France,[72] Austria,[73] Poland,[78] South Korea[62] and China,[77] and four had multinational

TABLE 6 *Summary of the characteristics of the RCTs reporting recurrence/progression*

Characteristic	Number	Number of studies
Patients		
Enrolled	709	4
Analysed	544	
Suspicion of or previously diagnosed BC		
Suspicion of BC	48	1
Previously diagnosed BC	74	
Not reported	422	3
Age[a]		
PDD groups (years)	68 (68–69)	3
WLC groups (years)	70 (all three studies)	
Whole study population (years)	67	1
Sex		
Men	396 (73%)	4
Women	148 (27%)	
Agent used		
5-ALA	544	4
Outcomes reported		
Recurrence-free survival	–	2
Residual tumour at first cystoscopy	–	4
Recurrence of tumour	–	2
Progression to muscle-invasive disease	–	2
Length of follow-up		
8 years		1
5 years		1
2 years		1
10–14 days		1

BC, bladder cancer.

a Age. Babjuk and colleagues,[86] Denzinger and colleagues[89] and Kriegmair and colleagues[92] provided information on patient age separately for the PDD and WLC groups – the information in the table is the median (range) of means across the three studies. Daniltchenko and colleagues[88] reported the mean age for the study population overall.

settings, taking place in the USA/Canada,[57] Germany/the Netherlands,[66] Germany/USA[67] and Switzerland/Norway/Sweden/Germany.[65]

The four RCTs reporting recurrence/progression enrolled 709 participants, of whom 544 were included in the analysis. In the study by Babjuk and colleagues,[86] of 128 patients enrolled, six were excluded because of no histological evidence of bladder cancer ($n = 2$), muscle-invasive bladder cancer ($n = 3$) and multiple T1G3 tumour with concomitant CIS treated with immediate cystectomy ($n = 1$). In the study by Daniltchenko and colleagues,[88] 115 patients were randomised, with 13 patients subsequently excluded because of muscle-invasive bladder cancer. In the study by Denzinger and colleagues,[89] 301 patients were randomised to the PDD ($n = 151$) and WLC ($n = 150$) arms. A total of 63 patients were subsequently excluded from the PDD arm because of no positive tumour confirmation ($n = 38$), invasive tumour or indication for cystectomy

($n = 23$), or no follow-up examinations ($n = 2$), and 47 patients were excluded from the WLC arm because no tumour could be found ($n = 22$), muscle-invasive urothelial carcinoma was diagnosed or cystectomy was indicated ($n = 23$) or follow-up was refused after the first resection ($n = 2$, one with pTaG1 and one with pT1G2). In the study by Kriegmair and colleagues,[92] of 165 patients randomised, 129 patients had histological proof of TCC and were considered evaluable.

The outcomes reported for the studies included recurrence-free survival,[86,89] residual tumour rate at first cystoscopy following TURBT,[86,88,89,92] recurrence during follow-up[88,89] and progression to muscle-invasive disease.[88,89]

Although the selection criteria for all four studies allowed the inclusion of patients with either a suspicion of or previously diagnosed bladder cancer, only the study by Babjuk and colleagues[86] provided details of these groups. Babjuk and colleagues reported that 20/60 (33%) of the PDD group and 28/62 (45%) of the WLC group presented with a suspicion of bladder cancer whereas 40/60 (67%) of the PDD group and 34/62 (55%) of the WLC group had previously diagnosed bladder cancer. The remaining studies by Daniltchenko and colleagues,[88] Denzinger and colleagues[89] and Kriegmair and colleagues[92] involving 422 patients did not provide separate details of those with a suspicion of bladder cancer and those with previously diagnosed disease. All four studies used 5-ALA as the photosensitising agent.

Three studies[86,89,92] provided information on patient age separately for the PDD and WLC groups, with the median (range) of means 68 years (68–69 years) for the PDD groups and 70 years (all three studies) for the WLC groups. The study by Daniltchenko and colleagues[88] reported the mean age for the whole patient population as 67 years. All four studies provided information on the gender of the 544 patients analysed, of whom 396 (73%) were men and 148 (27%) were women. There were 197 men in the PDD groups and 199 in the WLC groups, and there were 67 women in the PDD groups and 81 in the WLC groups. All four studies gave details of when they took place, with an earliest start date of 1997[89] and latest end date of December 2003.[86] One (single centre) study took place in Germany,[89] one in the Czech Republic,[86] and the remaining two were multicentre, with both taking place in Germany/Austria.[88,92] The follow-up periods for the studies were 8 years for Denzinger and colleagues,[89] 5 years for Daniltchenko and colleagues,[88] 2 years for Babjuk and colleagues[86] and 10–14 days for Kriegmair and colleagues,[92] although Kriegmair and colleagues compared PDD and WLC with the aim of evaluating residual tumour following TURBT, hence the short follow-up period.

Quality of the included studies

Figure 7 summarises the quality assessment for the PDD diagnostic studies, and *Figure 8* summarises the quality assessment for the four RCTs that compared PDD with WLC and reported recurrence/progression of disease. The results of the quality assessment of the individual studies are shown in Appendix 7.

The diagnostic studies were assessed using a modified version of the QUADAS tool containing 13 questions. In 96% (26/27) of studies the spectrum of patients who received the tests was considered to be representative of those who would receive the test in practice. For this question we considered patients to be representative if the patient population either had a suspicion or a history of bladder cancer or contained patients from both groups, or the majority or all of the patient population presented with either gross or microhaematuria or contained a mixture of patients with either indication. In all studies the reference standard (histological assessment of biopsied tissue) was considered likely to correctly classify bladder cancer, and the time period between PDD and the reference standard was considered to be short enough to be reasonably sure that the patient's condition had not changed between the tests.

In all studies partial verification bias was avoided in that all patients who underwent PDD also received a reference standard test. However, in only 55% (15/27) of studies[50–54,57–60,63,65,67,70,72,84] were patients considered to have received the same reference standard regardless of the PDD test result. This question was checked 'yes' if random biopsies were taken from normal-appearing areas (i.e. test negative) and 'no' if biopsies were taken only from suspicious looking areas (i.e. test positive). In effect the patients in those studies in which random biopsies of normal-appearing areas were taken received an enhanced reference standard. In all studies test review bias was avoided in that the PDD results were interpreted without knowledge

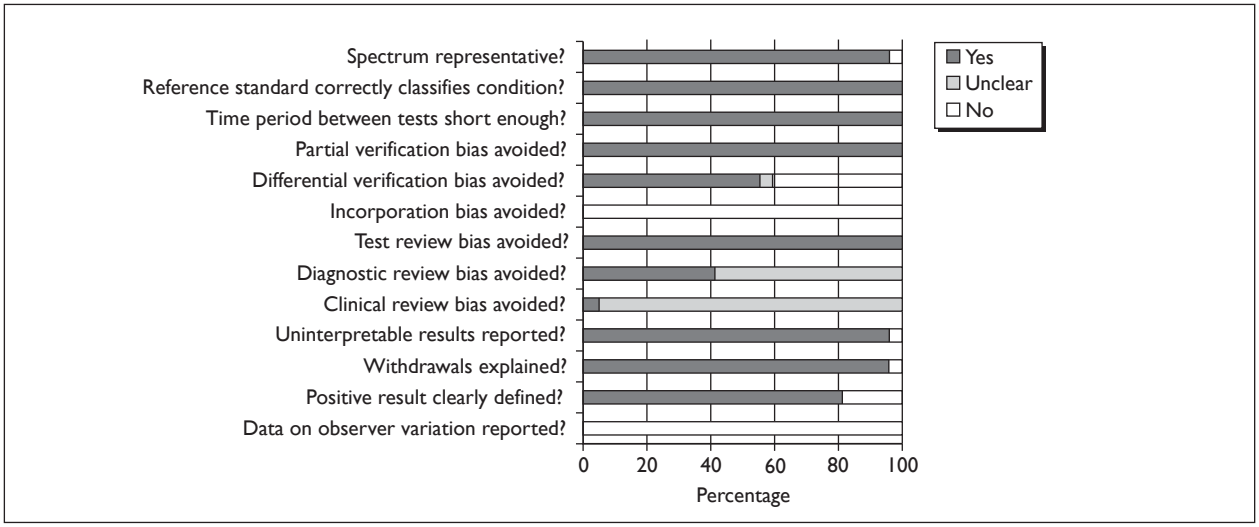


FIGURE 7 *Summary of quality assessment of PDD diagnostic studies (*n = *27).*

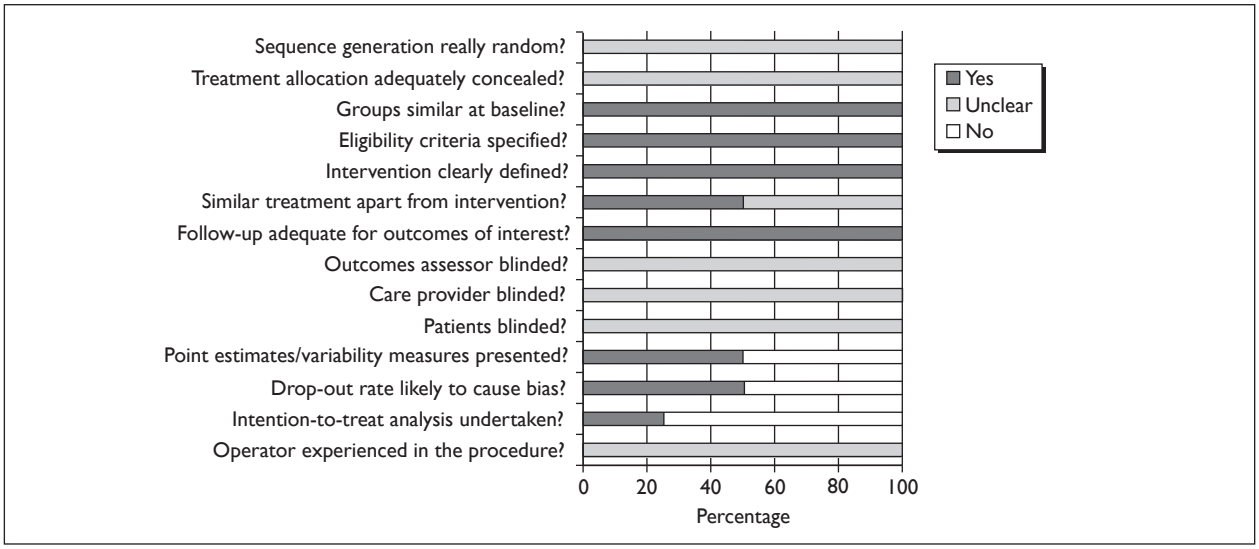


FIGURE 8 *Summary of quality assessment of RCTs reporting recurrence/progression (*n = *4).*

of the results of the reference standard test. We considered that this would always be the case, as lesions considered suspicious during PDD are biopsied during the procedure and it is only later that the reference standard results are known following histological assessment of the biopsied tissue.

In 96% (26/27) of studies, either uninterpretable or intermediate test results were reported or there were no uninterpretable or intermediate test results, and withdrawals from the study were explained or there were none. The exception to this was the study by Koenig and colleagues,[67] in which 55 patients were included but only 49 reported in the analysis. In 81% (22/27) of studies[50,52–54,56,58–63,65–67,70–73,76–78,84] a clear definition of what was considered to be a positive result was provided. In 96% (26/27) of studies it was unclear whether the same clinical data were available when the PDD test results were interpreted as would be available when the test was used in practice, the exception being the study by Ehsan and colleagues,[54] which stated that a detailed review of personal medical history was conducted for each patient before PDD. In this context clinical data were defined broadly to include any information relating to the patient

such as age, gender, presence and severity of symptoms, and other test results. In 59% (16/27) of studies[50,53,54,56,58,60,67,70–73,77,78,81,84,85] it was unclear whether the reference standard results were interpreted without knowledge of the results of the PDD test. All of the studies were judged to suffer from incorporation bias in that PDD was not considered to be independent of the reference standard test as the biopsies used for the reference standard were obtained via the PDD procedure. None of the studies provided information on observer variation in interpretation of test results.

The four RCTs,[86,88,89,92] comparing PDD with WLC, were assessed using the 14-question checklist adapted from Verhagen and colleagues.[47] In all four studies the groups were considered to be similar at baseline in terms of prognostic factors, eligibility criteria for the study were specified, and length of follow-up was considered adequate in relation to the outcomes of interest reported by the studies.

In all four studies it was unclear whether the sequence generation was really random, whether the treatment allocation was adequately concealed, whether the outcome assessors, care providers or patients were blinded to the PDD or WLC intervention, or whether the surgeon undertaking the operation was experienced in performing the procedure. In the studies by Denzinger and colleagues[89] and Kriegmair and colleagues[92] the withdrawal rate was considered likely to cause bias. In the studies by Babjuk and colleagues[86] and Denzinger and colleagues[89] the groups were considered to have been treated in the same way apart from the intervention received, whereas in the remaining two studies[88,92] this was unclear. In the studies by Daniltchenko and colleagues[88] and Denzinger and colleagues[89] point estimates and measures of variability were presented for the primary outcome measures. Only the study by Kriegmair and colleagues[92] included an intention to treat analysis.

Assessment of diagnostic accuracy

Overview

This section reports the diagnostic accuracy of PDD compared with WLC against a reference standard of histological assessment of biopsied tissue for the detection of non-muscle-invasive bladder cancer. The following levels of analysis are presented: patient, biopsy, stage/grade and photosensitising agent used. For patient and biopsy levels of analysis figures are included showing the sensitivity and specificity of the individual studies, SROC curves and pooled estimates with 95% CIs for sensitivity, specificity, positive and negative likelihood ratios and DORs for PDD and WLC. For the stage/grade level of analysis the median (range) sensitivity and specificity across studies are presented for PDD and WLC. Appendix 8 shows the studies that reported sufficient information (true and false positives and negatives for both PDD and WLC) to allow their inclusion in the pooled estimates for patient- and biopsy-level analysis, and also those studies comparing PDD with WLC that reported the sensitivity of the tests in detecting tumour stage/grade. Individual study results are given in Appendix 9. The results of studies reporting sensitivity and specificity for PDD but not WLC were examined to assess whether they differed from those of the comparative studies.

Patient-level analysis

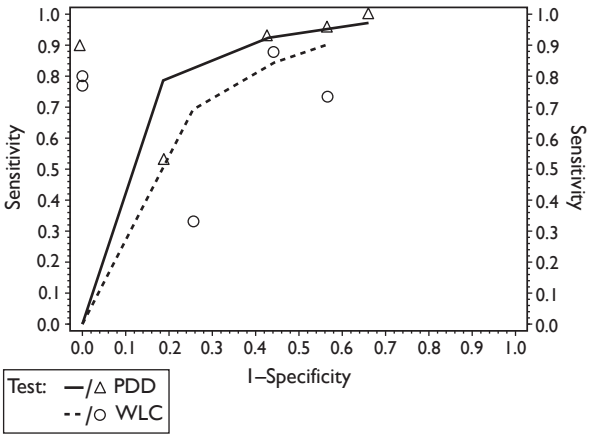
Although biopsy-level analysis is useful to validate the accuracy of the test, patient-level data are more useful in determining management. Five studies[65,66,73,80,81] comparing PDD with WLC and enrolling 386 people, with 370 included in the analysis, provided sufficient information to allow their inclusion in the pooled estimates for patient-level analysis. In four studies,[65,66,80,81] of 318 patients included in the analysis, 131 (41%) had symptoms suggestive of bladder cancer and 187 (59%) had a history of non-muscle-invasive bladder cancer. The study by Riedl and colleagues[73] did not report this information. Three of the studies[65,66,81] used HAL as the photosensitising agent and two[73,80] used 5-ALA. In two[65,73] of the studies random biopsies of normal-appearing areas were taken.

Figure 9 shows the sensitivity and specificity of the individual studies, SROC curves and pooled estimates for the sensitivity and specificity of PDD and WLC for patient-based detection of bladder cancer. The pooled sensitivity (95% CI) for PDD was 92% (80% to 100%) compared with 71% (49% to 93%) for WLC, whereas the pooled specificity (95% CI) for PDD was 57% (36% to 79%) compared with 72% (47% to 96%) for WLC. The pooled estimates show that PDD had higher sensitivity but lower specificity than WLC, with the CIs for the two techniques overlapping. None of the five studies comparing PDD with WLC reported test performance separately for the group of patients newly presenting with a suspicion of bladder cancer or for the group with a history of non-muscle-invasive disease. The DOR values (95% CI) were

Sensitivity and specificity: individual study results

	PDD			WLC		
Study ID	*n*	Sens	Spec	*n*	Sens	Spec
Jichlinski 2003[65]	52	96	43	52	73	43
Jocham 2005[66]	146	53	81	146	33	74
Riedl 1999[73]	52	100	33	52	76	100
Tritschler 2007[80]	100	93	57	100	88	55
Witjes 2005[81]	20	89	100	20	79	100

SROC plots for PDD and WLC: patient level



Pooled analysis of patient level PDD data

Number of studies	5
Sensitivity % (95% CI)	92 (80 to 100)
Specificity % (95% CI)	57 (36 to 79)
Positive likelihood ratio (95% CI)	2.17 (1.16 to 3.19)
Negative likelihood ratio (95% CI)	0.13 (0.01 to 0.32)
DOR (95% CI)	16.50 (1.00 to 42.23)

Pooled analysis of patient level WLC data

Number of studies	5
Sensitivity % (95% CI)	71 (49 to 93)
Specificity % (95% CI)	72 (47 to 96)
Positive likelihood ratio (95% CI)	2.57 (0.53 to 4.61)
Negative likelihood ratio (95% CI)	0.40 (0.12 to 0.67)
DOR (95% CI)	6.44 (1.00 to 14.24)

FIGURE 9 *Patient-level analysis: sensitivity, specificity, SROC curve and pooled estimates.*

16.50 (1.00 to 42.23) for PDD and 6.44 (1.00 to 14.24) for WLC, with higher DORs indicating a better ability of the test to differentiate between those with and those without bladder cancer. Across studies the median (range) PPVs were 91% (59% to 100%) for PDD and 89% (56% to 100%) for WLC, and NPVs were 60% (32% to 100%) for PDD and 23% (20% to 87%) for WLC. However, it should be noted that predictive values are affected by disease prevalence, which is rarely constant across studies, and therefore these data should be interpreted with caution.

Three studies[72,77,78] enrolling and analysing 153 patients reported patient-based detection for PDD only and were not included in the pooled estimates. All three studies used 5-ALA and, in one,[72] random biopsies of normal-appearing areas were taken. Across these three studies the median (range) sensitivity and specificity for PDD were 91% (64% to 100%) and 67% (36% to 67%) respectively. In two[72,78] of the studies the whole patient populations ($n = 102$) had a suspicion of bladder cancer with no previous history of the disease. Landry and colleagues[72] reported a sensitivity of 64% for PDD, compared with 91% reported by Szygula and colleagues,[78] whereas both studies reported a specificity of 67%.

Studies that reported patient-level analysis but only for CIS are considered in the section on stage/grade analysis.

Biopsy-level analysis

A total of 14 studies[50,53,54,56,59–63,65,70,76,81,85] comparing PDD with WLC and enrolling 1751 people, with 1746 included in the analysis, provided sufficient information to allow their inclusion in the pooled estimates for biopsy-level analysis (number of biopsies: 8574 for PDD analysis, 8473 for WLC analysis). In nine studies,[53,59–63,65,70,81] involving 1408 people, 560 (40%) had symptoms suggestive of bladder cancer and 848 (60%) had a history of non-muscle-invasive bladder cancer. The studies by Cheng and colleagues,[50] Ehsan and colleagues,[54] Filbeck and colleagues,[56] Sim and colleagues[76] and Zumbraegel and colleagues[85] did not report this information. Ten studies[50,53,54,56,59,61–63,70,85] used 5-ALA as the photosensitising agent and three[60,65,81] used HAL, while the study by Sim and colleagues[76] used hypericin. In eight studies[50,53,54,59,60,63,65,70]

random biopsies of normal-appearing areas were taken.

Figure 10 shows the sensitivity and specificity of the individual studies, SROC curves and pooled estimates for the sensitivity and specificity of PDD and WLC for biopsy-level detection of bladder cancer. In the pooled estimates, PDD had higher sensitivity (93%, 95% CI 90% to 96%) than WLC (65%, 95% CI 55% to 74%), whereas WLC had higher specificity (81%, 95% CI 73% to 90%) than PDD (60%, 95% CI 49% to 71%). The pair of CIs for both sensitivity and specificity did not overlap, providing evidence of a difference in diagnostic performance between the techniques. Across the 14 studies the sensitivity for PDD ranged from 76%[65] to 98%[54,62,70] compared with 17[53] to 88%[60] for WLC, and specificity ranged from 32%[85] to 100%[81] for PDD compared with 46[85] to 100%[81] for WLC. In the pooled analysis the DOR values (95% CI) were 20.29 (9.20 to 31.37) for PDD and 7.76 (3.39 to 11.93) for WLC. Across studies the median (range) PPVs were 61% (40% to 100%) for PDD and 70% (38% to 100%) for WLC, and the median (range) NPVs were 92% (20% to 99%) for PDD and 78% (13% to 91%) for WLC.

None of the 14 studies comparing PDD with WLC reported biopsy-level detection separately for the group of patients newly presenting with a suspicion of bladder cancer or for the group with a history of non-muscle-invasive disease.

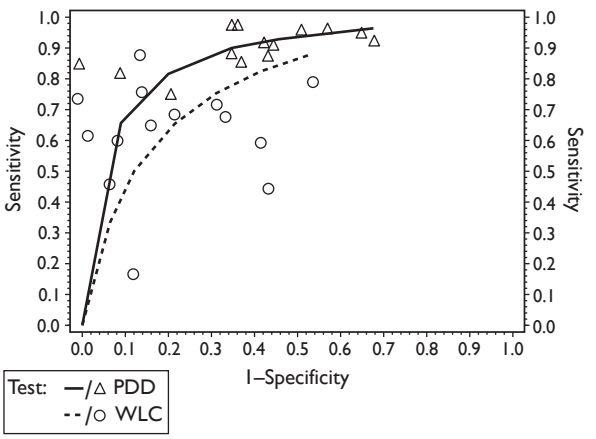
Six studies[58,67,71,73,77,84] involving 428 patients reported biopsy-level detection for PDD only and were not included in the pooled estimates. All six studies used 5-ALA and in four[58,67,73,84] random biopsies of normal-appearing areas were taken. Across the six studies the median (range) sensitivity and specificity for PDD were 95% (87% to 98%) and 51% (36% to 67%) respectively. In two[58,84] of these studies the whole patient population ($n = 68$) had a history of non-muscle-invasive bladder cancer. Frimberger and colleagues[58] and Zaak and colleagues[84] reported sensitivities of 95% and 90% and specificities of 67% and 61%, respectively, for PDD.

Studies that reported biopsy-level analysis but only for CIS are included in the section on stage/grade analysis.

Sensitivity and specificity: individual study results

	PDD			WLC		
Study ID	*n*	Sens	Spec	*n*	Sens	Spec
Cheng 2000[50]	175	89	65	175	66	84
De Dominicis 2001[53]	179	87	63	179	17	88
Ehsan 2001[54]	151	98	65	151	60	58
Filbeck 1999[56]	347	96	35	347	69	66
Grimbergen 2003[59]	917	97	49	917	69	78
Hendricksen 2006[60]	217	94	58	123	88	86
Hungerhuber 2007[61]	4630	92	56	4630	76	86
Jeon 2001[62]	274	98	43	274	59	91
Jichlinski 1997[63]	215	89	57	215	46	57
Jichlinski 2003[65]	421	76	79	414	46	93
Kriegmair 1996[70]	433	98	64	433	73	69
Sim 2005[76]	179	82	90	179	62	98
Witjes 2005[81]	28	85	100	28	74	100
Zumbraegel 2003[85]	408	94	32	408	80	46

SROC plots for PDD and WLC: patient level



Pooled analysis of biopsy level PDD data		Pooled analysis of biopsy level WLC data	
Number of studies	14	Number of studies	14
Sensitivity % (95% CI)	93 (90 to 96)	Sensitivity % (95% CI)	65 (55 to 74)
Specificity % (95% CI)	60 (49 to 71)	Specificity % (95% CI)	81 (73 to 90)
Positive likelihood ratio (95% CI)	2.33 (1.73 to 2.92)	Positive likelihood ratio (95% CI)	3.38 (2.01 to 4.75)
Negative likelihood ratio (95% CI)	0.12 (0.06 to 0.17)	Negative likelihood ratio (95% CI)	0.44 (0.33 to 0.54)
DOR (95% CI)	20.29 (9.20 to 31.37)	DOR (95% CI)	7.76 (3.39 to 11.93)

FIGURE 10 *Biopsy-level analysis: sensitivity, specificity, SROC curve and pooled estimates.*

Formal comparison of PDD and WLC in patient- and biopsy-based analysis

In addition to the two HSROC models of the diagnostic accuracy of PDD and WLC individually, two HSROC models were run that simultaneously modelled PDD and WLC diagnostic accuracy using all of the data from the 14 studies. There was strong evidence of a difference in diagnostic accuracy between the tests, with the model that allowed for a difference in diagnostic accuracy in the three constituent parameters (threshold, accuracy and shape of SROC curve) having a substantially better Bayesian information criterion than the simplified diagnostic accuracy model, for both patient- and biopsy-level analysis (difference of 1408.0 and 20.7 respectively). These results are supported by noting that the intervals for the summary sensitivity and specificity at biopsy level from the models in which the tests were modelled separately (*Figure 10*) did not overlap for either measure. PDD had a greater sensitivity than WLC but at the cost of a lower specificity. The point estimates of the patient-level analysis were similar to those from the biopsy-level analysis, although the intervals were substantially wider, as might be expected because of the smaller number of studies and observations available for this level of analysis.

Stage/grade analysis

Studies reporting the sensitivity of PDD compared with WLC in the detection of stage and grade of tumour categorised this information in different ways, including pTa, pTaG1, pTaG1–2, pTaG2, pTaG2–3, pTaG3, pTa-T1, G1–2, pT1, pT1G1, pT1G1–2, pT1G2, pT1G3, > pT1, CIS, G3, pT2G2, pT2G3, ≥ pT2, ≥ pT2G3 and pT4G3 (see Appendix 8). Some studies reported the detection of stage/grade at the patient level and others reported this information at biopsy level.

For the purposes of this review, the presentation of test performance in terms of the detection of stage and grade of non-muscle-invasive bladder cancer was considered in two broad categories:

1. less aggressive, lower risk tumours (pTa, G1, G2)
2. more aggressive, higher risk tumours (pT1, G3, CIS).

Table 7 shows the median (range) sensitivity of PDD and WLC across studies, for both patient- and biopsy-based detection of tumours, within the broad categories of less aggressive/lower risk and more aggressive/higher risk (including CIS), and also separately for CIS.

TABLE 7 *Sensitivity of PDD and WLC in detecting stage/grade of tumour*

	PDD sensitivity (%), median (range)	WLC sensitivity (%), median (range)	Number of patients (biopsies)[a]	Number of studies
Less aggressive/lower risk				
Patient-based detection	92 (20 to 95)	95 (8 to 100)	266	3
Biopsy-based detection	96 (88 to 100)	88 (74 to 100)	1206 (5777)	7
More aggressive/higher risk including CIS				
Patient-based detection	89 (6 to 100)	56 (0 to 100)	563	6
Biopsy-based detection	99 (54 to 100)	67 (0 to 100)	1756 (7506)	13
CIS				
Patient-based detection	83 (41 to 100)	32 (0 to 83)	563	6
Biopsy-based detection	86 (54 to 100)	50 (0 to 68)	1756 (7506)	13

a The number of biopsies is the overall total reported by the studies. In some studies more biopsies were taken for PDD than for WLC and in these cases the higher number used for PDD has been used in the table. In the less aggressive/lower risk category, Hendricksen and colleagues[60] reported 217 biopsies for PDD and 123 for WLC and Koenig and colleagues[67] reported 130 biopsies for PDD and 67 for WLC. Hendricksen and colleagues and Koenig and colleagues were also included in the more aggressive/higher risk category, as was Jichlinski and colleagues,[65] who reported 421 biopsies for PDD and 414 for WLC. The studies by Hendricksen and colleagues, Jichlinski and colleagues and Koenig and colleagues were also amongst those reporting detection of CIS.

Less aggressive, lower risk tumours (pTa, G1, G2)

Nine studies[54,56,60–62,66,67,80,81] involving 1452 patients reported the sensitivity of PDD compared with WLC for the detection of less aggressive, lower risk tumours. The stages/grades reported by these studies included pTa,[54,62,66,80] pTaG1,[60,61,67] pTaG1–2,[56] pTaG2[60,61,67,81] and G1–2.[80] Across three studies[66,80,81] involving 266 patients reporting patient-based tumour detection, the median (range) sensitivities of PDD at 92% (20% to 95%) and WLC at 95% (8% to 100%) were broadly similar. Across seven studies[54,56,60–62,67,81] involving 1206 patients reporting biopsy-based tumour detection ($n = 5777$ biopsies overall), the median (range) sensitivity of PDD at 96% (88% to 100%) was higher than that of WLC at 88% (74% to 100%) (*Table 7*).

None of the studies reported the specificity of PDD or WLC in detecting less aggressive, lower risk tumours.

More aggressive, higher risk tumours (pT1, G3, CIS)

Sixteen studies[50,51,53,54,56,57,60–62,65–67,70,80,81,85] involving 2155 patients reported the sensitivity of PDD compared with WLC for the detection of more aggressive, higher risk tumours. The stages/grades reported by these studies included pTaG2–3,[53] pTaG3,[60,61,67,81] pTa-T1,[50,70] pT1,[54,62,66,80] pT1G1,[61] pT1G1–2,[60,61,67] pT1G2[60,61,67] pT1G3,[56,60,61,67,81] > pT1,[56] G3[80] and CIS.[50,51,53,54,56,57,60–62,65–67,70,80,81,85]

Across six studies[51,57,65,66,80,81] involving 563 patients reporting patient-based tumour detection, the median (range) sensitivity of PDD at 89% (6% to 100%) was much higher than that of WLC at 56% (0% to 100%). Across 13 studies[50,53,54,56,57,60–62,65,67,70,81,85] involving 1756 patients reporting biopsy-based tumour detection ($n = 7506$ biopsies overall), the median (range) sensitivity of PDD at 99% (54% to 100%) was also much higher than that of WLC at 67% (0% to 100%) (*Table 7*).

None of the studies reported the specificity of PDD or WLC in detecting more aggressive, higher risk tumours, other than for CIS, discussed in the following section.

Carcinoma in situ

Although CIS is included in the more aggressive/higher risk category reported above, it may also be useful to consider separately the performance of PDD compared with WLC for the detection of CIS. The same 16 studies[50,51,53,54,56,57,60–62,65–67,70,80,81,85] reporting the sensitivity of PDD compared with WLC for the detection of more aggressive/higher risk tumours also provided this information specifically for CIS.

Across six studies[51,57,65,66,80,81] involving 563 patients reporting patient-based tumour detection, the median (range) sensitivity of PDD for detecting CIS was 83% (41% to 100%), much higher than the sensitivity of 32% (0% to 83%) for WLC. Across 13 studies[50,53,54,56,57,60–62,65,67,70,81,85] involving 1756 patients reporting biopsy-based tumour detection ($n = 7506$ biopsies overall), the median (range) sensitivity of PDD was 86% (54% to 100%), also much higher than that of WLC at 50% (0% to 68%) (*Table 7*).

Three studies[51,57,70] reported the specificity of PDD and WLC in detecting CIS and one study[52] reported this information only for PDD (*Table 8*). The specificity reported for PDD ranged from 61%[70] to 99%[52] whereas that for WLC ranged from 68%[70] to 97%.[51] Two[51,70] of the three studies comparing PDD with WLC reported higher specificity for WLC whereas the third study[57] reported similar specificities for both techniques. In the PDD studies HAL was associated with higher

TABLE 8 *Specificity of PDD and WLC in detecting carcinoma in situ*

Study	Unit of analysis	Number in study	Number without CIS	PDD agent	Specificity (%)	
					PDD	WLC
Colombo 2007[51]	Patient	49	31	5-ALA/HAL	71	97
Fradet 2007[57]	Patient	196	138	HAL	82	83
D'Hallewin 2000[52]	Biopsy	281	139	Hypericin	99	NR
Kriegmair 1996[70]	Biopsy	329	323	5-ALA	61	68

NR, not reported.

values than 5-ALA, with hypericin associated with the highest value. However, these results should be interpreted with caution as they are based on only a small number of studies.

Photosensitising agent used

Table 9 shows the median (range) sensitivity and specificity across studies for the different photosensitising agents used, for both patient- and biopsy-level detection of bladder cancer. Four studies using 5-ALA[72,73,77,78] and three using HAL[65,66,81] reported patient-level detection of bladder cancer. Across the studies using 5-ALA the median (range) sensitivity and specificity were 96% (64% to 100%) and 52% (33% to 67%), respectively, compared with 90% (53% to 96%) sensitivity and 81% (43% to 100%) specificity for HAL.

A total of 15 studies using 5-ALA,[50,53,54,56,58,59,61,63,67,70,71,73,77,84,85] three using HAL[60,65,81] and one using hypericin[76] reported biopsy-level detection of bladder cancer. Across the studies using 5-ALA the median (range) sensitivity and specificity were 95% (87% to 98%) and 57% (32% to 67%), respectively, compared with 85% (76% to 94%) sensitivity and 80% (58% to 100%) specificity for HAL. The study by Sim and colleagues[76] reported 82% sensitivity and 91% specificity for hypericin.

The results for both patient- and biopsy-based detection suggest that 5-ALA may have slightly higher sensitivity than HAL, whereas HAL may have higher specificity than 5-ALA, but this should be interpreted with caution as factors other than the photosensitising agent used may have contributed to the sensitivity and specificity values reported by the studies.

Four studies reported sensitivity and specificity at both patient and biopsy level, two using 5-ALA[73,77] and two using HAL.[65,81]

Side effects of photosensitising agents

5-Aminolaevulinic acid

A total of 18 studies used 5-ALA as the photosensitising agent. Seven studies[53,61,63,71–73,78] involving 1320 patients reported that no side effects were associated with the instillation of 5-ALA. Jeon and colleagues,[62] in a study involving 62 patients, reported that there were no systemic or serious local side effects following 5-ALA bladder instillation.

Cheng and colleagues,[50] in a study involving 41 patients, reported that besides two (5%) patients who complained of urgency and were unable to retain ALA for more than 2 hours, there were no clinically significant short-term side effects such as urinary tract infections and phototoxicity. At the 1-month follow-up no phototoxicity or other complications were reported.[50] Koenig and colleagues,[67] in a study involving 49 patients, reported that none showed signs of systemic side

TABLE 9 *Sensitivity and specificity according to photosensitising agent used*

Agent	Sensitivity (%), median (range)	Specificity (%), median (range)	Number of patients (biopsies)	Number of studies
Patient-based detection				
5-ALA	96 (64 to 100)	52 (33 to 67)	205	4
HAL	90 (53 to 96)	81 (43 to 100)	218	3
Hypericin	–	–	–	0
Biopsy-based detection				
5-ALA	95 (87 to 98)	57 (32 to 67)	1949 (8296)	15
HAL	85 (76 to 94)	80 (58 to 100)	122 (666)	3
Hypericin	82	91	41 (179)	1

Two studies included in the table reported only patient- and/or biopsy-based detection of CIS rather than non-muscle-invasive bladder cancer overall. D'Hallewin and colleagues[52] used hypericin and reported biopsy-based detection of CIS whereas Fradet and colleagues[57] used HAL and reported both patient- and biopsy-based detection of CIS.
Two studies used either 5-ALA or HAL but did not report the number of patients receiving each agent and are not included in the table.[51,80]

effects of PDD such as phototoxicity. One patient reported transient (< 24 hours) dysuria and one patient developed a urinary tract infection, which was treated with antibiotics.[67] Song and colleagues,[77] in a study involving 51 patients, reported that one cases of acute cystitis was accompanied by haemorrhagic lesion attributed to the instillation procedure (i.e. chemical cystitis).

Kriegmair and colleagues,[71] in a study involving 104 patients, reported that no serious side effects were observed during or after 5-ALA instillation. However, following instillation seven patients reported urgency. After the PDD procedure, more severe alginuresis symptoms and pollakiuria were detected in four patients. Significant gram-negative bacteriuria was detected in three patients but the symptoms improved rapidly with appropriate antibiotics and spasmolytic agents. Phototoxicity was not detected in any patient.[71]

Five studies[54,56,58,59,84] did not mention side effects.

Hexaminolaevulinate

Five studies used HAL as the photosensitising agent. In the studies by Jichlinski and colleagues[65] and Witjes and colleagues[81] adverse events were reported in 40 of 52 and 4 of 20 patients, respectively, although none was considered to be related to HAL instillation. Fradet and colleagues[57] and Jocham and colleagues[66] both reported that HAL was well tolerated. In the study by Fradet and colleagues,[57] 800 adverse events were reported by 240 of the 298 patients in the safety set, of which 19 (2.4%) were considered to be related to HAL instillation, none of which was serious. Twenty patients experienced a total of 23 serious adverse events, including one death due to an aortic aneurysm, which was unrelated to HAL instillation.[57] In the study by Jocham and colleagues[66] 75 adverse events were reported by 47 of 162 patients, of which two (2.7%) were considered treatment related, with both occurring in the same patient (urinary retention and micturition urgency).

The study by Hendricksen and colleagues[60] did not mention side effects.

5-Aminolaevulinic acid/ hexaminolaevulinate not reported separately

Two studies[51,80] involving 149 patients used 5-ALA or HAL but did not report the number of patients who received each agent. In the study by Colombo and colleagues,[51] no systemic side effects related to the PDD procedure were reported and any local side effects were referred to as negligible. Tritschler and colleagues[80] did not mention side effects.

Hypericin

Two studies used hypericin. D'Hallewin and colleagues,[52] in a study involving 40 patients, reported that there were no significant local or systemic side effects caused by the instillation of hypericin. In the study by Sim and colleagues,[76] involving 41 patients, there were no reports of urinary tract infections, contracted bladder, photosensitivity or allergies. One patient developed microscopic haematuria from cystitis, which resolved on conservative management.[76]

Recurrence/progression of disease

Overview

This section presents the results of the four RCTs[86,88,89,92] comparing PDD with WLC and reporting the effectiveness outcomes of recurrence-free survival, residual tumour rate at first cystoscopy following TURBT, recurrence rate during follow-up and tumour progression. Random-effects meta-analyses using RR as the effect measure are presented comparing PDD and WLC in terms of these outcomes.

The RCTs enrolled 709 participants, with 544 included in the analysis. In the study by Daniltchenko and colleagues[88] the groups were randomised to WLC or PDD, whereas in the studies by Babjuk and colleagues,[86] Denzinger and colleagues[89] and Kriegmair and colleagues[92] the groups were randomised to WLC or WLC and PDD. The follow-up periods varied from 10–14 days for the study by Kriegmair and colleagues,[92] which evaluated residual tumour following TURBT, to 2 years for the study by Babjuk and colleagues,[86] 5 years for the study by Daniltchenko and colleagues[88] and 8 years for the study by Denzinger and colleagues.[89] All four studies used 5-ALA as the photosensitising agent. Individual study results are given in Appendix 9.

In the study by Babjuk and colleagues[86] none of the randomised patients with grade 1 or grade 2 tumours received adjuvant intravesical therapy during the study. All patients with grade 3 tumours (six in the PDD group and seven in the WLC group) received intravesical BCG immunotherapy, based on a standard 6-week course followed by three, weekly instillations (3-

week course) at 3, 6 and 12 months.[86] In the study by Daniltchenko and colleagues[88] none of the randomised patients received adjuvant intravesical therapy throughout the study. In the study by Denzinger and colleagues[89] patients with a solitary primary tumour staged pTaG1–G2 did not receive recurrence prophylaxis. Patients with multifocal involvement of the bladder staged pTaG1–G2 or pT1G1–G2 underwent mitomycin therapy, and those with primary stage pT1G3, CIS or treatment failure with mitomycin received BCG therapy, with weekly instillations of 120 mg BCG given for 6 weeks.[89] The study by Kriegmair and colleagues[92] did not state whether adjuvant intravesical therapy was given, although the primary outcome of this study was to evaluate residual tumour 10–14 days following TURBT.

The four RCTs were reported in eight reports. The study for which Denzinger and colleagues[89] is considered the primary report was also reported by Filbeck and colleagues,[91] Burger and colleagues[87] and Denzinger and colleagues.[90] The primary report gave information on recurrence-free survival at 2, 4, 6 and 8 years and also tumour recurrence throughout this follow-up period, overall and for low-, intermediate- and high-risk groups, as well as reporting residual tumour rate at secondary transurethral resection (TUR). Filbeck and colleagues[91] reported residual tumour rate 6 weeks after initial resection and recurrence-free survival at 12 and 24 months. Burger and colleagues[87] reported recurrence-free survival, and tumour recurrence and progression at 7.1 years, and Denzinger and colleagues[90] reported recurrence-free survival and tumour recurrence and progression for a subgroup of patients who presented with initial T1 high-grade bladder cancer.

The study for which Daniltchenko and colleagues[88] is considered the primary report was also reported by Riedl and colleagues.[93] Daniltchenko and colleagues[88] reported tumour recurrence and progression during follow-up whereas Riedl and colleagues reported residual tumour rate at the control TUR.[93]

Recurrence-free survival

The studies by Babjuk and colleagues[86] and Denzinger and colleagues[89] involving a total of 313 patients reported recurrence-free survival at 12 and 24 months. In a random-effects meta-analysis comparing PDD and WLC in terms of recurrence-free survival, the direction of effect of the pooled estimate at both time points favoured PDD over WLC, although the difference was statistically significant only at 24 months (*Figure 11*). There was evidence of substantial statistical heterogeneity

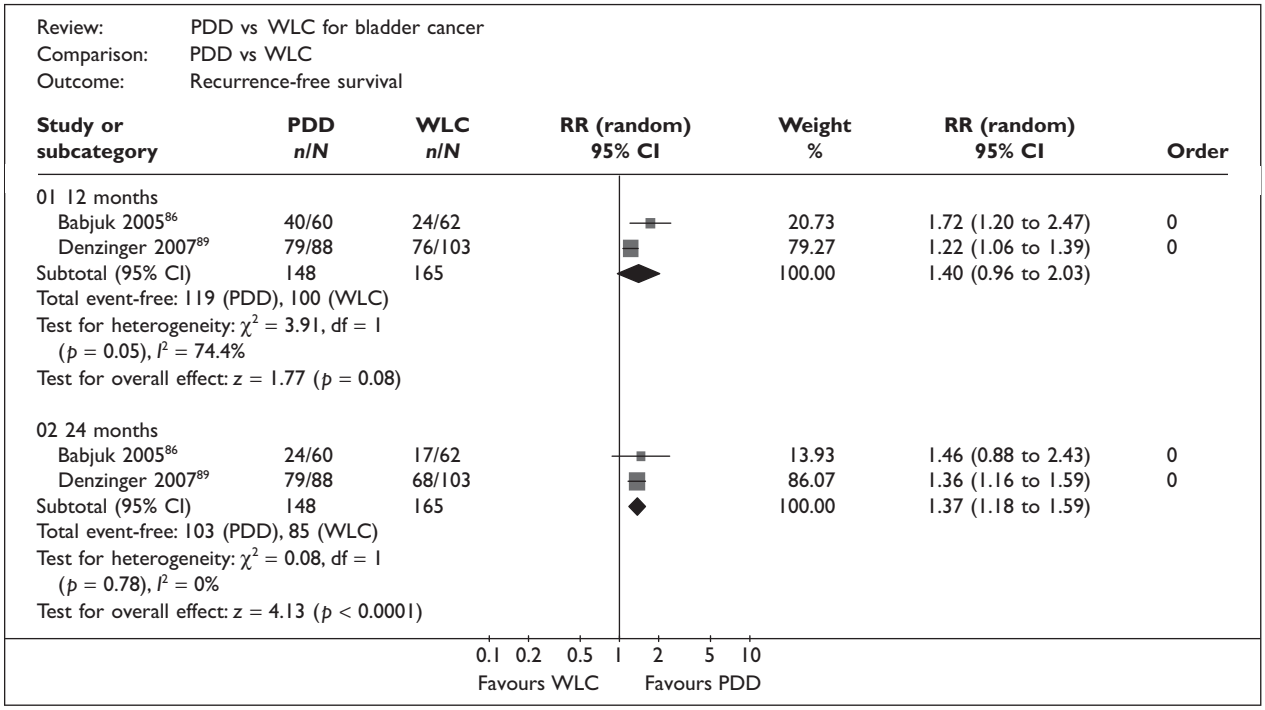


FIGURE 11 *Recurrence-free survival.*

between the studies at the 12-month time point ($I^2 = 74.4\%$).

Denzinger and colleagues[90] also reported on a subgroup of 46 patients who were diagnosed with T1 high-grade bladder cancer, with recurrence-free survival rates of 80% (17/21) in the PDD group compared with 52% (13/25) in the WLC group at the 8-year follow-up.

Residual tumour rate at first cystoscopy following transurethral resection

The studies by Babjuk and colleagues,[86] Daniltchenko and colleagues,[88] Denzinger and colleagues[89] and Kriegmair and colleagues[92] involving a total of 534 patients reported residual tumour rate at first cystoscopy following TUR. The timing of the cystoscopy varied between the studies, with Kriegmair and colleagues[92] reporting the residual tumour rate 10–14 days after the initial resection, Denzinger and colleagues[89] and Riedl and colleagues[93] reporting it 6 weeks after initial resection, and Babjuk and colleagues[86] assessing the residual tumour rate 10–15 weeks after TUR.

Figure 12 shows a random-effects meta-analysis comparing PDD with WLC in terms of residual tumour (pTa and pT1) detected at first cystoscopy following the initial TUR. The pooled estimates show that PDD resulted in both statistically

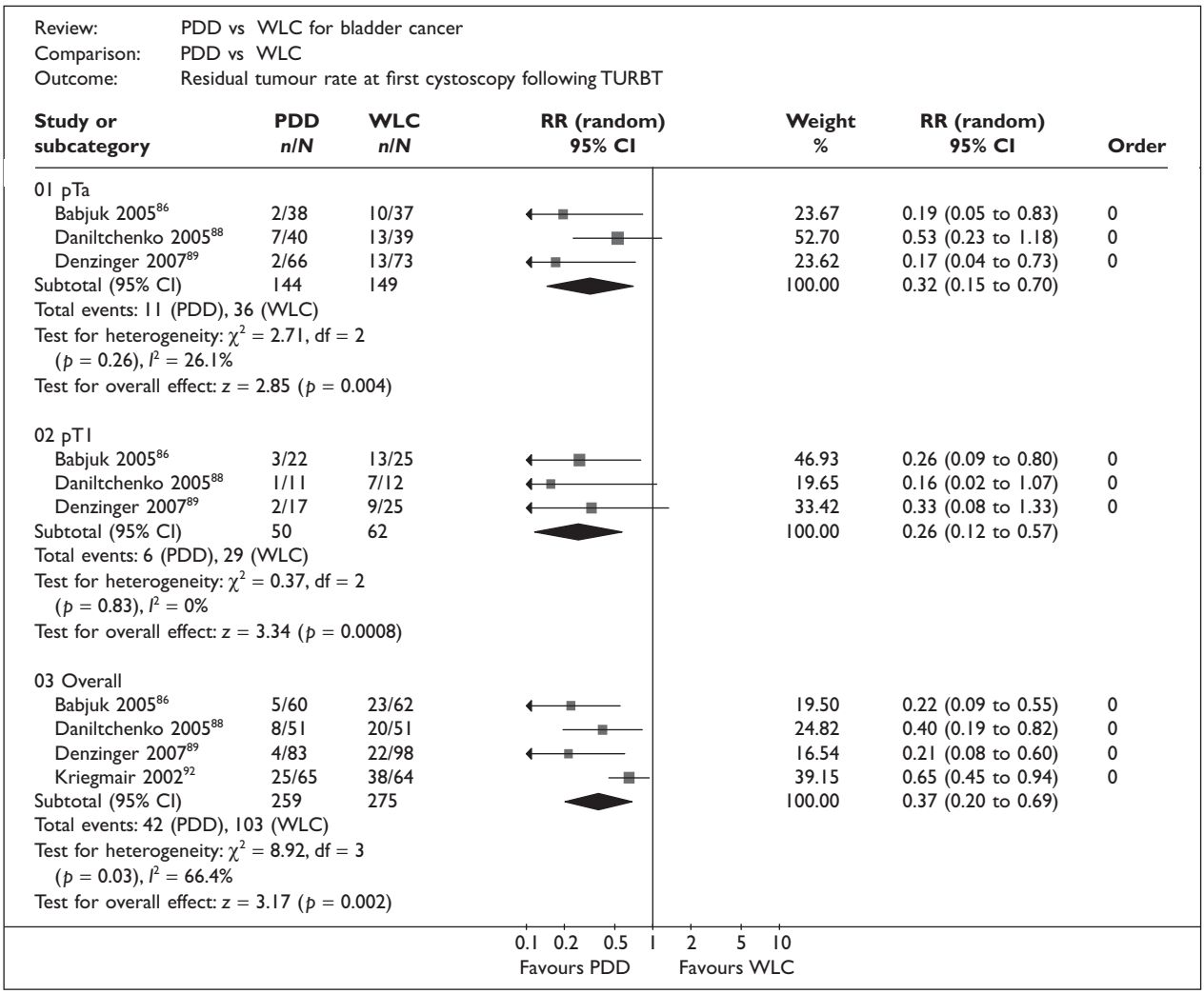


FIGURE 12 *Residual tumour (pTa and pT1) at first cystoscopy following TUR. Notes: 1. In the figure, the numbers of patients shown for the study by Denzinger and colleagues[89] do not include five each from the PDD and WLC groups who at initial resection had CIS. At 6 weeks after initial resection none of the five patients in the PDD group were found to have residual CIS but four of five (80%) in the WLC group were found to have residual CIS. 2. Kriegmair and colleagues[92] reported that in an intention to treat analysis 61.5% (40/65) of patients in the PDD group and 40.6% (26/64) of patients in the WLC group were tumour free. For the purposes of the meta-analysis this was interpreted as 25/64 patients in the PDD group and 38/64 patients in the WLC group having residual tumour.*

significantly fewer residual pTa tumours (RR 0.32, 95% CI 0.15 to 0.70) and fewer pT1 tumours (RR 0.26, 95% CI 0.12 to 0.57), with an overall RR of 0.37 (95% CI 0.20 to 0.69) in favour of PDD (Kriegmair and colleagues[92] reported overall rates only).

The studies by Babjuk and colleagues[86] and Daniltchenko and colleagues[88] also reported residual tumour according to grade, and *Figure 13* shows a fixed-effect meta-analysis comparing PDD with WLC in terms of the grade of residual tumour detected at first cystoscopy following the initial TUR. The pooled estimates for G3 were not statistically significant, whereas those for G1 (RR 0.13, 95% CI 0.03 to 0.71), G2 (RR 0.32, 95% CI 0.16 to 0.64) and overall (RR 0.31, 95% CI 0.18 to 0.53) showed a statistically significant difference in favour of PDD. In the study by Babjuk and colleagues[86] none of the patients with grade 1 or grade 2 tumours received adjuvant intravesical therapy whereas all those with grade 3 tumours received intravesical BCG immunotherapy. In the study by Daniltchenko and colleagues[88] none of the patients received adjuvant intravesical therapy.

Tumour recurrence rate during follow-up

The studies by Daniltchenko and colleagues[88] and Denzinger and colleagues[89] involving a total of 293 patients reported tumour recurrence rate during

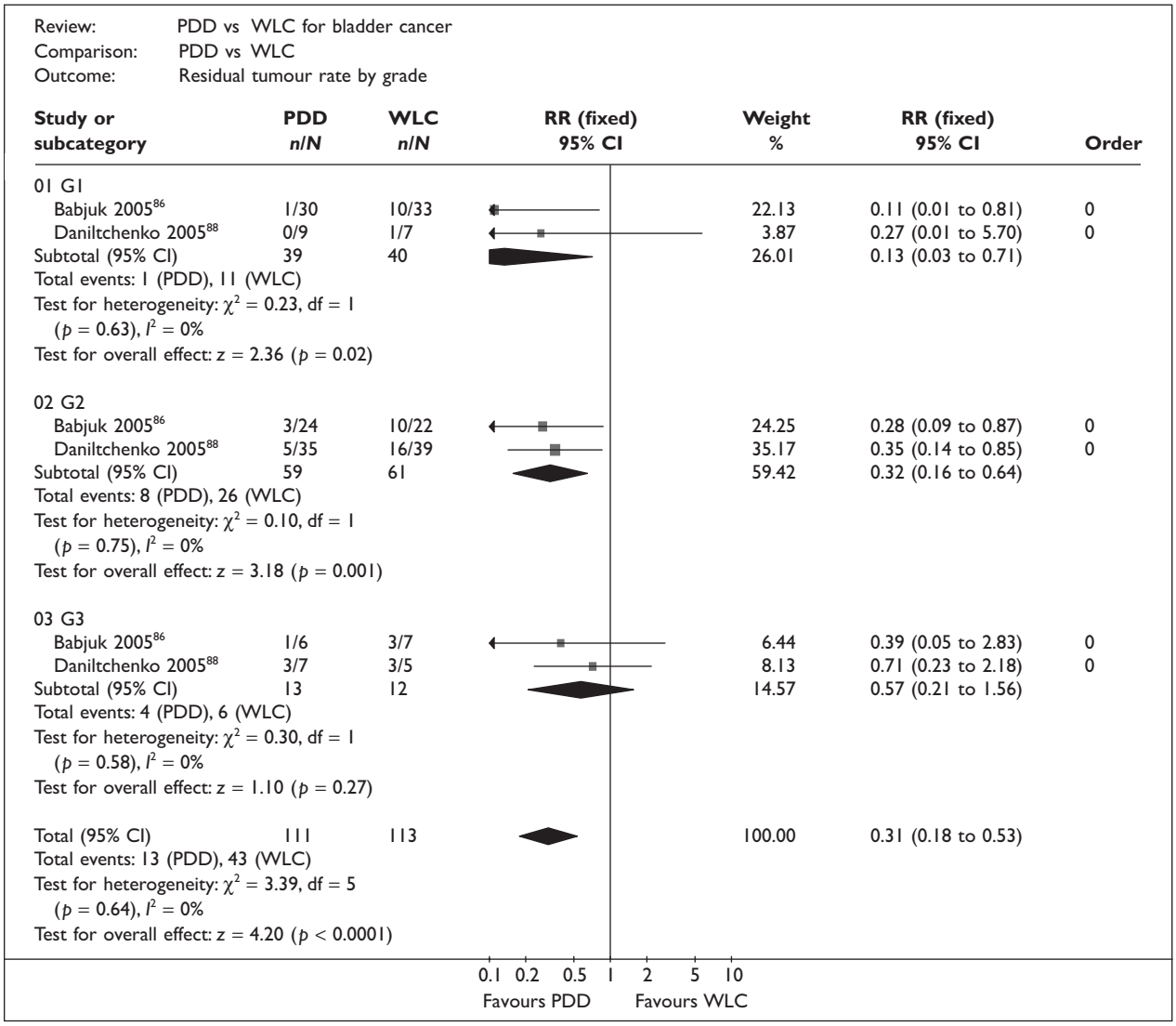


FIGURE 13 *Residual tumour (G1, G2 and G3) at first cystoscopy following transurethral resection.*

the follow-up period. The follow-up period for the study by Daniltchenko and colleagues was 5 years[88] whereas that for the study by Denzinger and colleagues was 8 years.[89]

Figure 14 shows a random-effects meta-analysis comparing PDD with WLC in terms of the number of patients who experienced tumour recurrence during the follow-up period. Although the direction of effect for both studies favoured PDD it was statistically significant only in the study by Denzinger and colleagues, and the pooled estimate did not show a statistically significant difference between PDD and WLC (RR 0.64, 95% CI 0.39 to 1.06).[89] There was evidence of substantial statistical heterogeneity between the studies ($I^2 = 71.1\%$).

In the study by Daniltchenko and colleagues[88] none of the randomised patients received adjuvant intravesical therapy. In the study by Denzinger and colleagues[89] patients with a solitary primary tumour staged pTaG1–G2 (low-risk group) did not receive adjuvant intravesical therapy. Patients with multifocal involvement of the bladder staged pTaG1–G2 or pT1G1–G2 (intermediate-risk group) underwent mitomycin therapy, and those with primary stage pT1G3, CIS or treatment failure with mitomycin (high-risk group) received BCG therapy, with weekly instillations of 120 mg BCG given for 6 weeks.[89] *Table 10* shows the recurrence rates for the low-, intermediate- and high-risk groups over the 8-year follow-up in the study by Denzinger and colleagues.[89] Although there were consistently fewer recurrences for PDD compared with WLC across all risk groups, the difference in recurrence rates between PDD and WLC was smaller in the intermediate- and high-risk groups, both of which received adjuvant intravesical therapy, albeit with wide CIs.

In the subgroup of 46 patients initially diagnosed with T1 high-grade bladder cancer, Denzinger and colleagues[89] reported recurrence rates of 14% (3/21) in the PDD group compared with 44% (11/25) in the WLC group during the follow-up period.

Time to recurrence

The studies by Babjuk and colleagues[86] and Daniltchenko and colleagues[88] reported time to recurrence of bladder tumours. In the study by Babjuk and colleagues[86] this was a median of 17.05 months for the PDD group and 8.05 months for the WLC group. Babjuk and colleagues[86] also reported a median time to recurrence in patients with multiple tumours of 13.54 months for the PDD group and 4.45 months for the WLC group. Daniltchenko and colleagues[88] reported a median (range) time to recurrence of 12 months (2 to 58) for the PDD group and 5 months (2 to 52) for the WLC group.

Tumour progression during follow-up

The studies by Daniltchenko and colleagues[88] and Denzinger and colleagues[89] also reported tumour progression during their follow-up periods of 5 years and 8 years respectively.

Figure 15 shows a fixed-effect meta-analysis comparing PDD with WLC in terms of the numbers of patients who experienced tumour progression

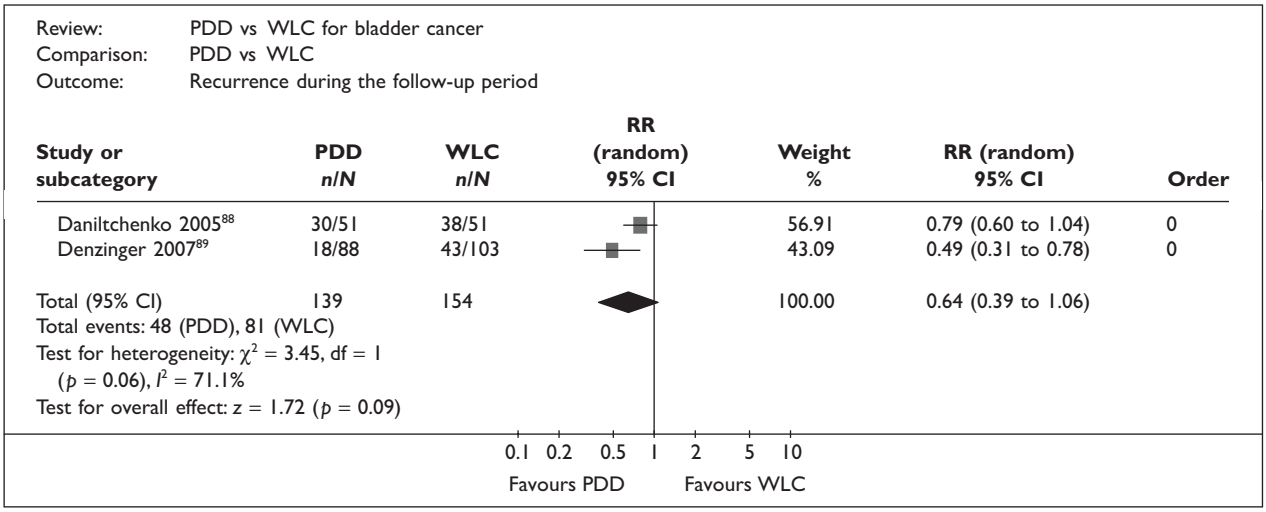


FIGURE 14 *Tumour recurrence rates during the follow-up period.*

TABLE 10 *Tumour recurrence by risk group in the Denzinger study*[89]

		Recurrence rate (*n*/*N*)	
Risk group	**Intravesical therapy?**	**PDD**	**WLC**
Low	No	7% (6/88)	19% (20/103)
Intermediate	Yes	7% (6/88)	13% (13/103)
High	Yes	7% (6/88)	10% (10/103)

during the follow-up period. The direction of effect of the study by Daniltchenko and colleagues[88] favoured PDD (four versus nine events) whereas in the study by Denzinger and colleagues[89] there were two cases in each group. The pooled estimate had wide CIs reflecting the small number of events (RR 0.57, 95% CI 0.22 to 1.46).

In the subgroup of patients diagnosed with T1 high-grade bladder cancer, Denzinger and colleagues[90] reported progression to muscle-invasive disease (≥ T2) of 19% (4/21) in the PDD group compared with 12% (3/25) in the WLC group during the follow-up period.

Summary – assessment of diagnostic accuracy and recurrence/progression of disease

Assessment of diagnostic accuracy

A total of 31 studies, published in 44 reports, met the inclusion criteria for the PDD part of the review. In total, 27 studies (36 reports) reported the diagnostic accuracy of PDD. As measured by the modified QUADAS checklist, in all studies partial verification bias was avoided (all patients received a reference standard test) and test review bias was avoided (PDD and WLC were interpreted without knowledge of the results of the reference standard test). In 96% (26/27) of studies uninterpretable or intermediate test results were reported or there were none, and withdrawals from the study were explained or there were none. However, all of the studies were judged to suffer from incorporation bias in that PDD was considered not to be independent of the reference standard test as biopsies used in the reference standard test were obtained via the PDD procedure.

In both patient- and biopsy-based detection of bladder cancer PDD had higher sensitivity but lower specificity than those of WLC. Five studies involving 370 patients reported patient-based detection. In the pooled estimates the sensitivity for PDD was 92% (95% CI 80% to 100%) compared with 71% (95% CI 49% to 93%) for WLC, whereas the specificity for PDD was 57% (95% CI 36% to 79%) compared with 72% (95% CI 47% to 96%) for WLC, with the CIs for the two techniques overlapping. A total of 14 studies involving 1746

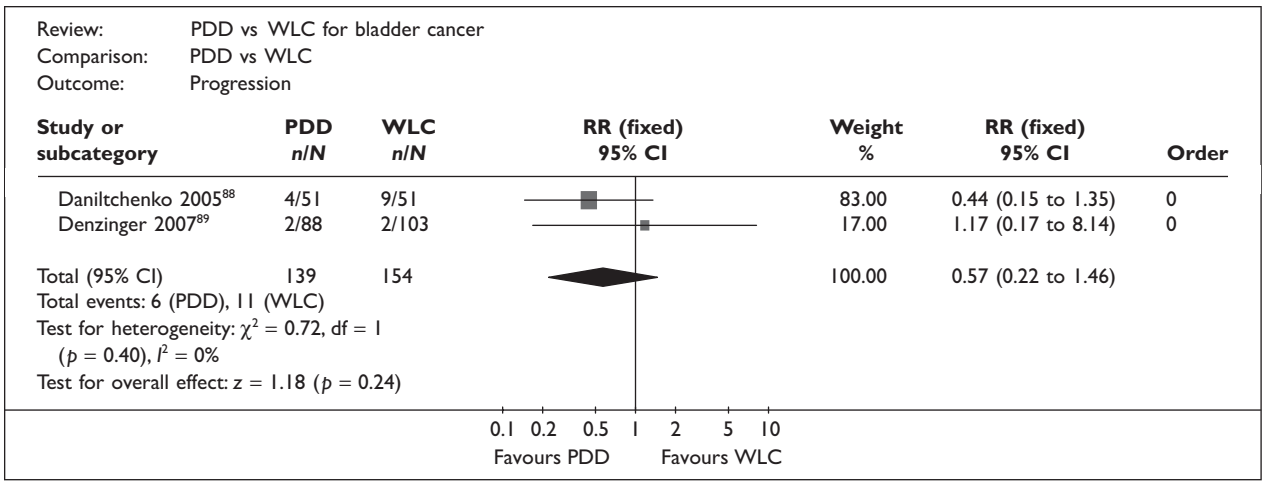


FIGURE 15 *Tumour progression rates during the follow-up period.*

patients reported biopsy-based detection (number of biopsies: 8574 for PDD analysis, 8473 for WLC analysis). In the pooled estimates the sensitivity for PDD was 93% (95% CI 90% to 96%) compared with 65% (95% CI 55% to 74%) for WLC, whereas the specificity for PDD was 60% (95% CI 49% to 71%) compared with 81% (95% CI 73% to 90%) for WLC. The pair of CIs for both sensitivity and specificity did not overlap, providing evidence of a difference in diagnostic performance between the techniques.

Studies reporting the sensitivity of PDD compared with WLC for detecting stage/grade of bladder cancer categorised this information in different ways. For the purposes of this review the detection of stage/grade was considered in two broad categories:

1. less aggressive, lower risk tumours (pTa, G1, G2)
2. more aggressive, higher risk tumours (pT1, G3, CIS).

Across three studies[66,80,81] involving 266 patients reporting patient-based detection of lower risk, less aggressive tumours, the median (range) sensitivity of PDD at 92% (20% to 95%) was broadly similar to that of WLC at 95% (8% to 100%). Across seven studies[54,56,60–62,67,81] involving 1206 patients reporting biopsy-based detection ($n = 5777$ biopsies overall), the median (range) sensitivity of PDD was slightly higher at 96% (88% to 100%) compared with 88% (74% to 100%) for WLC. Across six studies[51,57,65,66,80,81] involving 563 patients reporting patient-based detection of more aggressive, higher risk tumours, the median (range) sensitivity of PDD at 89% (6% to 100%) was higher than that of WLC at 56% (0% to 100%). Across 13 studies[50,53,54,56,57,60–62,65,67,70,81,85] involving 1756 patients reporting biopsy-based detection ($n = 7506$ biopsies overall), the median (range) sensitivity of PDD at 99% (54% to 100%) was again much higher than that of WLC at 67% (0% to 100%) (*Table 7*). These results suggest that PDD is much better than WLC in detecting more aggressive, higher risk tumours. However, the results for patient- and biopsy-based detection for less aggressive, lower risk tumours and patient-based detection for more aggressive, higher risk tumours should be interpreted with caution as they are based on only a small number of studies.

When CIS was considered separately, across six studies[51,57,65,66,80,81] involving 563 patients reporting patient-based detection, the median (range) sensitivity of PDD for detecting CIS at 83% (41% to 100%) was much higher than that of WLC at 32% (0% to 83%). Across 13 studies[50,53,54,56,57,60–62,65,67,70,81,85] involving 1756 patients reporting biopsy-based detection of CIS ($n = 7506$ biopsies overall), the median (range) sensitivity of PDD at 86% (54% to 100%) was also much higher than that of WLC at 50% (0% to 68%). The results for patient-based detection should be interpreted with caution as they are based on only a small number of studies. However, the median sensitivity across studies reported for patient-based detection of CIS (83%) was similar to that reported for biopsy-based detection of CIS (86%). Only three studies reported the specificity of PDD and WLC for detecting CIS. Two studies[51,70] reported higher specificity for WLC (97% versus 71% and 68% versus 61% respectively), whereas the third[57] reported similar specificity for both techniques (83% for WLC versus 82% for PDD).

Of the studies comparing PDD with WLC that were included in the pooled estimates in the present review, two[65,73] of five reporting patient-based analysis and eight[50,53,54,59,60,63,65,70] of 14 reporting biopsy-based analysis undertook random biopsies of normal-appearing areas. Ten[50,53,54,56,60–62,70,81,85] of these 14 studies also reported detection of CIS lesions. *Table 11* shows, for patient- and biopsy-level analysis and also for detection of CIS lesions, the sensitivity and specificity for PDD and WLC for those studies included in the pooled estimates that undertook random biopsies compared with those that did not. There did not appear to be any systematic pattern to the performance of the tests based on whether or not random biopsies were undertaken.

Most studies ($n = 18$) used 5-ALA as the photosensitising agent, with five using HAL, two hypericin and two either 5-ALA or HAL. In patient-based detection of bladder cancer, across four studies using 5-ALA[72,73,77,78] and three using HAL,[65,66,81] the median (range) sensitivity and specificity for 5-ALA were 96% (64% to 100%) and 52% (33% to 67%), respectively, compared with 90% (53% to 96%) sensitivity and 81% (43% to 100%) specificity for HAL. In biopsy-based detection of bladder cancer, across 15 studies[50,53,54,56,58,59,61,63,67,70,71,73,77,84,85] using 5-ALA, the median (range) sensitivity and specificity for 5-ALA were 95% (87% to 98%) and 57% (32% to 67%), respectively, compared with 85% (76% to 94%) and 80% (58% to 100%) for HAL. One study, by Sim and colleagues,[76] used hypericin, reporting 82% sensitivity and 91% specificity. The results for both patient- and biopsy-based detection suggest that

TABLE 11 *Test performance of studies undertaking/not undertaking random biopsies*

		PDD		WLC	
	Number of studies	**Median sensitivity (%) (range)**	**Median specificity (%) (range)**	**Median sensitivity (%) (range)**	**Median specificity (%) (range)**
Patient-level analysis					
Random biopsies	2	98 (96 to 100)	38 (33 to 43)	75 (73 to 76)	72 (43 to 100)
No random biopsies	3	89 (53 to 93)	81 (57 to 100)	79 (33 to 88)	74 (55 to 100)
Biopsy-level analysis					
Random biopsies	8	92 (76 to 98)	64 (49 to 79)	63 (17 to 88)	81 (57 to 93)
No random biopsies	6	93 (82 to 98)	50 (32 to 100)	72 (61 to 80)	89 (46 to 100)
Detection of CIS					
Random biopsies	5	77 (70 to 100)	–	23 (0 to 67)	–
No random biopsies	5	93 (63 to 100)	–	57 (5 to 64)	–

5-ALA may have slightly higher sensitivity than HAL, whereas HAL may have higher specificity than 5-ALA, but this should be interpreted with caution as factors other than the photosensitising agent used may have contributed to the sensitivity and specificity values reported by the studies.

In total, 20 studies reported side effects. Twelve studies[51–53,61–63,65,71–73,78,81] involving 1543 patients reported that there were no side effects or no serious side effects associated with the photosensitising agent used (5-ALA, eight studies; HAL, two studies; 5-ALA/HAL not reported separately, one study; hypericin, one study). In four studies[50,67,71,77] involving 245 patients and using 5-ALA, reported side effects associated with the agent included nine patients who complained of urgency,[50,70] four with alginuresis symptoms and pollakiuria,[70] three with significant gram-negative bacteriuria,[70] one with acute cystitis accompanied by haemorrhagic lesion,[77] one with transient dysuria[67] and one who developed a urinary tract infection.[67] Two studies[57,66] involving 460 patients and using HAL reported 21 non-serious side effects that were associated with the agent. One study[76] involving 41 patients and using hypericin reported that one patient developed microscopic haematuria from cystitis.

In summary, the evidence suggests that PDD has clinically important better sensitivity but lower specificity than WLC in the detection of bladder cancer and, in terms of stage/grade, has higher sensitivity than WLC in the detection of more aggressive, higher risk tumours (pT1, G3, CIS).

Assessment of recurrence/ progression of disease

Four RCTs (eight reports) reporting recurrence/ progression enrolled 709 participants, with 544 included in the analysis. The follow-up periods varied from 10–14 days for the study by Kriegmair and colleagues[92] (although the aim of this study was to evaluate residual tumour following TURBT) to 2 years for the study by Babjuk and colleagues,[86] 5 years for the study by Daniltchenko and colleagues[88] and 8 years for the study by Denzinger and colleagues.[89] All four studies used 5-ALA as the photosensitising agent.

The study by Daniltchenko and colleagues[88] reported that none of the patients received adjuvant intravesical therapy. In the study by Babjuk and colleagues[86] only patients with grade 3 tumours received intravesical therapy. In the study by Denzinger and colleagues[89] patients with a solitary primary tumour staged pTaG1–G2 did not receive intravesical therapy, whereas those with multifocal tumours staged pTaG1–G2 or pT1G1–G2 underwent mitomycin therapy and those with primary stage pT1G3, CIS or treatment failure with mitomycin received BCG therapy. The study by

Kriegmair and colleagues[92] did not state whether intravesical therapy was given.

In all four studies the PDD and WLC groups were similar at baseline in terms of prognostic factors, eligibility criteria for the studies were specified, and length of follow-up was considered adequate in relation to the outcomes of interest reported by the studies. However, in all four studies it was unclear whether the sequence generation was really random or whether the treatment allocation was adequately concealed.

The studies by Babjuk and colleagues[86] and Denzinger and colleagues[89] (involving a total of 313 patients) reported recurrence-free survival at 12 and 24 months. In a random-effects meta-analysis the direction of effect of the pooled estimate at both time points favoured PDD over WLC, although the difference was statistically significant only at 24 months (RR 1.37, 95% CI 1.18 to 1.59).

The studies by Babjuk and colleagues,[86] Daniltchenko and colleagues,[88] Denzinger and colleagues[89] and Kriegmair and colleagues[92] involving a total of 534 patients reported residual tumour rate at first cystoscopy following TURBT. In a random-effects meta-analysis PDD was associated with both statistically significantly fewer residual pTa tumours (RR 0.32, 95% CI 0.15 to 0.70) and pT1 tumours (RR 0.26, 95% CI 0.12 to 0.57), with an overall pooled estimate RR of 0.37 (95% CI 0.20 to 0.69) in favour of PDD. Babjuk and colleagues[86] and Daniltchenko and colleagues[88] also reported residual tumour according to grade (G1, G2 and G3). In a fixed-effect meta-analysis the pooled estimates for G1 (RR 0.13, 95% CI 0.03 to 0.71) and G2 (RR 0.32, 95% CI 0.16 to 0.64) were statistically significant in favour of PDD, as was the overall pooled estimate (RR 0.31, 95% CI 0.18 to 0.53).

Daniltchenko and colleagues[88] and Denzinger and colleagues,[89] in studies involving a total of 293 patients, reported tumour recurrence rate during the follow-up period (5 years and 8 years respectively). In a random-effects meta-analysis of the number of patients who experienced tumour recurrence, although the direction of effect for both studies favoured PDD it was statistically significant only in the study by Denzinger and colleagues,[89] and the direction of effect in the pooled estimate also favoured PDD but was not statistically significant (RR 0.64, 95% CI 0.39 to 1.06). In the study by Denzinger and colleagues[89] the recurrence rates were consistently lower for PDD than for WLC across all three risk groups. However, the difference in the recurrence rates between PDD and WLC was smaller in the intermediate-risk [PDD 7% (6/88), WLC 13% (13/103)] and high-risk [PDD 7% (6/88), WLC 10% (10/103)] groups that received adjuvant intravesical therapy than in the low-risk group that did not [PDD 7% (6/88), WLC 19% (20/103)].

Two studies[86,88] reported time to recurrence, both favouring PDD. Babjuk and colleagues[86] reported a median time to recurrence of 17.05 months for the PDD group and 8.05 months for the WLC group, whereas Daniltchenko and colleagues[88] reported a median (range) time to recurrence of 12 (2 to 58) months for the PDD group and 5 (2 to 52) months for the WLC group.

The studies by Daniltchenko and colleagues[88] and Denzinger and colleagues[89] also reported tumour progression during their respective 5- and 8-year follow-up periods. In a fixed-effect meta-analysis of the number of patients who experienced tumour progression, the direction of effect of the study by Daniltchenko and colleagues favoured PDD whereas that of the study by Denzinger and colleagues favoured WLC, although neither was statistically significant. The pooled estimate favoured PDD but again was not statistically significant (RR 0.57, 95% CI 0.22 to 1.46).[88,89]

In summary, the evidence suggests that, compared with WLC, the use of PDD at TURBT results in less residual tumour being found at the first cystoscopy following TURBT, longer recurrence-free survival of patients and a longer time to recurrence following TURBT, and may be associated with a lower rate of tumour recurrence over time. However, as these results are based on only a few studies they should be interpreted with caution. It should also be borne in mind that the administration of adjuvant intravesical therapy varied across the studies. Adjuvant intravesical therapy following TURBT is standard practice in the UK and much of Europe and can reduce recurrence by up to 50% in the first 2 years. The fact that in two studies[86,89] only some patients received intravesical therapy and in one[88] none did, while in the fourth study[92] this information was not reported, makes it difficult to assess what the true added value of PDD might be in reducing recurrence rates in routine practice.

Chapter 5

Results – biomarkers and cytology

Number of studies identified

From the electronic searches for primary reports, 501 records were selected as being possibly relevant to the review of biomarkers and cytology. In total, 133 of these were non-English language papers and were excluded from further assessment. The full-text reports of the remaining papers were obtained and assessed: 83 met the inclusion criteria for this review; 241 were excluded; and 44 were retained for background information. *Figure 16* shows a flow diagram outlining the screening process, with reasons for exclusion of full-text papers.

Number and type of studies included

Appendix 10 lists the 71 studies, published in 83 reports, that were included in the review of test performance.

Number and type of studies excluded

A list of the potentially relevant studies identified by the search strategy for which full-text papers were obtained but which subsequently failed to meet the inclusion criteria is given in Appendix 11. These studies were excluded because they failed to meet one or more of the inclusion criteria in terms of the type of study, participants, test(s), reference standard or outcomes reported.

Overview of the biomarkers/cytology chapter

This chapter contains a section on each of the individual tests followed by a section on studies that directly compared tests and concludes with a summary section. The section on each test contains information on the characteristics of the included

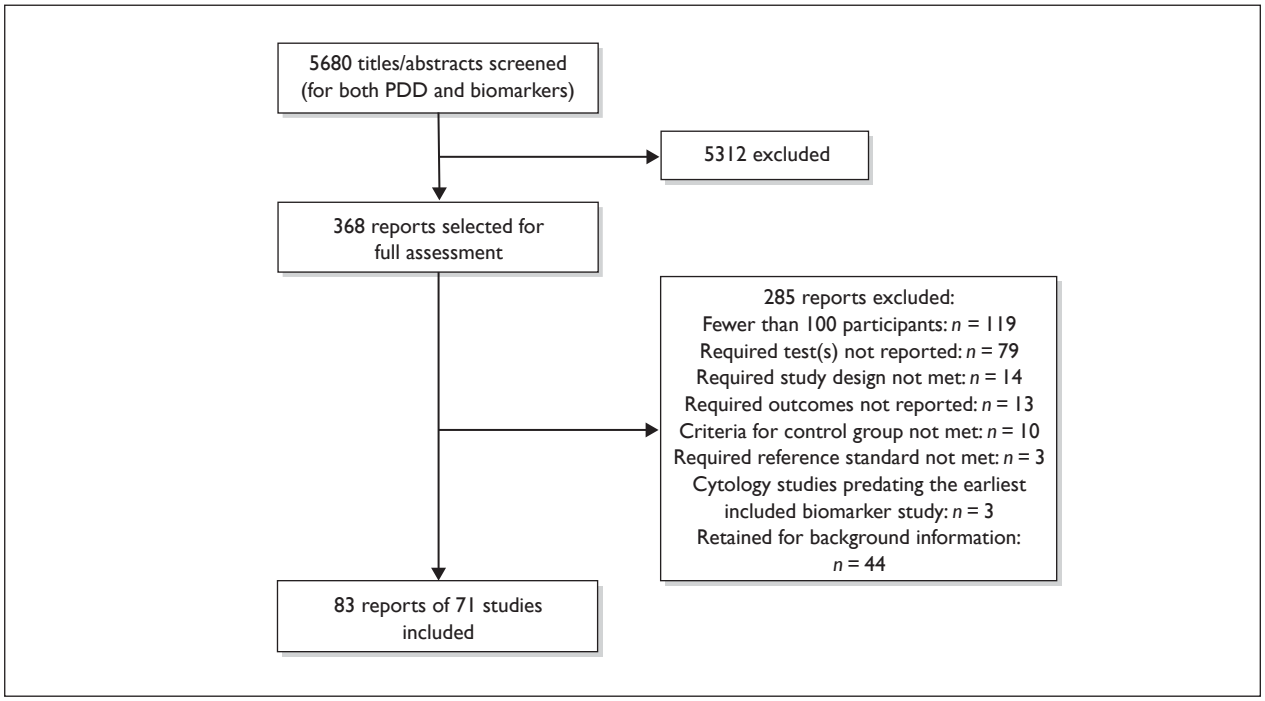


FIGURE 16 *Flow diagram outlining the screening process for the biomarkers part of the review.*

studies, methodological quality of the studies, results of the pooled estimates for patient-level analysis, and also information on specimen-level analysis, stage/grade analysis and unevaluable test results. The methodological quality of the biomarker and cytology studies was assessed using a modified version of the QUADAS tool containing 14 questions. For patient-level analysis, pooled estimates with 95% CIs for sensitivity, specificity, positive and negative likelihood ratios and DORs are presented. For specimen and stage/grade level of analysis the median (range) sensitivity and specificity across studies are presented. If the number of specimens reported by a study was one per patient included in the analysis then this was considered as a patient-level analysis. Studies reporting patient- and specimen-level analysis for CIS are included in the section on stage/grade analysis. As described in the previous chapter, for the purposes of this review, the presentation of test performance in terms of the detection of stage and grade of non-muscle-invasive bladder cancer was considered in two broad categories: (1) less aggressive, lower risk tumours (pTa, G1, G2) and (2) more aggressive, higher risk tumours (pT1, G3, CIS).

Appendix 12 shows the characteristics of the included biomarker/cytology studies, Appendix 13 shows the results of the quality assessment of the individual studies, Appendix 14 shows the studies that reported sufficient information (true and false positives and negatives) to allow their inclusion in the pooled estimates for each of the tests for patient-level analysis, and also those studies that reported specimen-level analysis and also the

TABLE 12 *Summary of the characteristics of the FISH studies*

Characteristic	Number	Number of studies
Study design[a]		
Cross-sectional diagnostic study	2704	12
Case–control	617	2
Patients		
Enrolled	3321	14
Analysed	2961	
Suspicion of or previously diagnosed BC[a,b]		
Suspicion of BC	1012 (45%)	12 (86%)
Previously diagnosed BC	1234 (55%)	
Not reported	765	2 (14%)
Age		
Median (range) of means/medians (years)	70 (63 to 72)	7 (50%)
Not reported	–	7 (50%)
Sex[c]		
Men	1073 (71%)	7 (50%)
Women	439 (29%)	
Not reported	1799	7 (50%)

BC, bladder cancer.

a In the study design and suspicion of or previously diagnosed BC rows the figures in the number column refer to numbers of patients.

b Suspicion of or previously diagnosed BC. The totals for this section sum to 3011 rather than 3321 because (1) in the study by Kipp and colleagues,[99] of 124 participants enrolled, 41 presented with a suspicion of BC, 81 had previously diagnosed disease (total of 122) and two had previous cancer of the upper urinary tract and did not fall into either category, and (2) two case–control studies[107,108] contained some participants with benign urological conditions who did not fall into either category.

c Sex. This section sums to 3311 rather than 3321 because the study by Moonen and colleagues[102] reported gender information for those analysed ($n = 95$) rather than those enrolled.

sensitivity of the tests in detecting tumour stage/grade, Appendix 15 shows the individual study results and Appendix 16 shows the cut-offs used by the studies reporting FISH that were included in the pooled estimates.

Fluorescence in situ hybridisation

Characteristics of the included studies

A description of each of the 14 included FISH studies is given in Appendix 12, which contains the characteristics of all of the included biomarker and cytology studies listed alphabetically by surname of first author. *Table 12* shows summary information for the 14 FISH studies.

Twelve studies, reported in 13 papers,[94–106] were diagnostic cross-sectional studies, of which two[101,104] reported consecutive recruitment, and the remaining two[107,108] were case–control studies. Two studies were multicentre (21 centres,[108] 23 centres[103]).

The 14 studies enrolled 3321 participants, with 2961 included in the analysis. In 12 studies[94,95,97,99,101–108] reporting this information, 1012 (45%) presented with a suspicion of bladder cancer and 1234 (55%) had previously diagnosed bladder cancer. In one[103] of these studies the whole study population ($n = 497$) had a suspicion of bladder cancer and in two[102,106] the whole study population had previously diagnosed bladder cancer ($n = 355$). Two studies[98,100] did not report this information.

Across seven studies[97,99,101–103,106,107] providing information on patient age for the whole study population, the median (range) of means/medians was 70 years (63 to 72 years) (Yoder and colleagues[106] reported median rather than mean age). Seven studies[94,97,99,102,103,106,107] provided information on the gender of 1512 participants, of whom 1073 (71%) were men and 439 (29%) were women.

Seven studies[94,99,102–104,106,108] gave details of when they took place, with an earliest start date of 1996[104] and latest end date of March 2007.[99] Seven studies took place in the USA,[97,99,103–106,108] three in Germany[95,98,107] and one each in the Netherlands[102] and Israel,[94] and two had multinational settings, taking place in Austria/Italy[101] and the USA/Belgium.[100]

Methodological quality of the included studies

Figure 17 summarises the quality assessment across the 14 FISH studies. The results for the quality assessment of the individual studies are shown in Appendix 13. In all studies the spectrum of patients who received the tests was considered to be representative of those who would receive the test in practice (Q1). For this question we considered patients to be representative if the patient population either had a suspicion or a history of bladder cancer or contained patients from both groups, or the majority or all of the patient population presented with either gross or microhaematuria or contained a mixture of patients with either indication. In all studies the reference standard (cystoscopy with histological assessment of biopsied tissue) was considered likely to correctly classify bladder cancer (Q2). In all studies partial verification bias was avoided in that all patients who underwent a FISH test also received a reference standard test (Q4), differential verification bias was avoided in that patients received the same reference standard regardless of the index test result (Q5) and incorporation bias was avoided in that the reference standard was independent of the index test (Q6). In all studies either uninterpretable or intermediate test results were reported or there were none (Q10), and withdrawals from the study were explained or there were none (Q11).

In 10 studies (71%) the time period between FISH and the reference standard was considered to be short enough (1 month or less) to be reasonably sure that the patient's condition had not changed in the intervening period (Q3). In nine studies (64%) test review bias was avoided in that the FISH results were interpreted without knowledge of the results of the reference standard test (Q7). However, in nine studies (64%) it was unclear whether the reference standard results were interpreted without knowledge of the results of the FISH test (diagnostic review bias, Q8) and in eight studies (57%) it was unclear whether the same clinical data were available when test results were interpreted as would be available when the test is used in practice (clinical review bias, Q9). In this context clinical data were defined broadly to include any information relating to the patient such as age, gender, presence and severity of symptoms, and other test results.

In 13 studies (93%) a prespecified cut-off value was used (Q12); in 10 studies (71%) a clear definition of what was considered to be a positive test result was

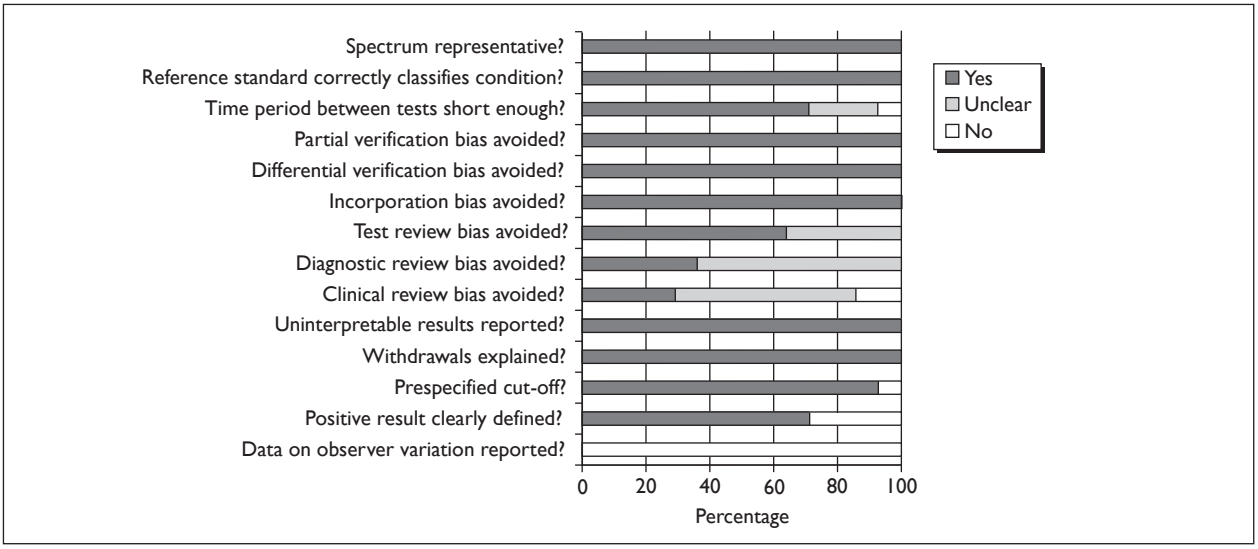


FIGURE 17 *Summary of quality assessment of FISH studies (n = 14).*

provided (Q13); and none of the studies provided information on observer variation in interpretation of test results (Q14).

Assessment of diagnostic accuracy

Patient-level analysis

A total of 12 studies[95,97–101,103–108] enrolling 3101 people, with 2535 included in the analysis, provided sufficient information to allow their inclusion in the pooled estimates for patient-level analysis. The cut-offs used by these studies to define a positive test result were considered sufficiently similar for all of them to be included in the pooled estimates (see Appendix 16 for a description of the cut-offs used by each of the FISH studies). *Figure 18* shows the sensitivity and specificity of the individual FISH studies, pooled estimates and SROC curve for patient-based detection of bladder cancer. The pooled sensitivity and specificity (95% CI) were 76% (65% to 84%) and 85% (78% to 92%), respectively, and the DOR (95% CI) value was 18 (3 to 32). Across the 12 studies the sensitivity for FISH ranged from 53%[107] to 96%,[101] and specificity ranged from 45%[101] to 97%.[104] The median (range) PPV across studies was 78% (27% to 99%) and the median (range) NPV was 88% (36% to 97%). However, as previously mentioned, predictive values are affected by disease prevalence, which is rarely constant across studies, and therefore these data should be interpreted with caution.

Most of the included studies in the pooled estimates contained a mixture of patients with a suspicion of bladder cancer and those with previously diagnosed bladder cancer, although two studies[98,100] did not report this information. In the study by Sarosdy and colleagues[103] all of the participants ($n = 497$) had a suspicion of bladder cancer (sensitivity 69%, specificity 78%) and in the study by Yoder and colleagues[106] all of the participants ($n = 250$) had previously diagnosed bladder cancer (sensitivity 64%, specificity 73%).

Specimen-level analysis

The study by Moonen and colleagues,[102] enrolling 105 participants, all of whom had been previously diagnosed with bladder cancer, reported specimen-level analysis ($n = 103$), with sensitivity and specificity of 39% and 90% respectively.

Stage/grade analysis

Studies reporting the sensitivity of FISH in the detection of stage and grade of tumour categorised this information in different ways, including pTa, pTaG1, pTaG1–2, pTaG2, pTaG3, G1, G2, pT1, pT1G2, pT1G3, pT1–4, CIS, G3, pT2, pT2–4, ≥ pT2 and pT4 (see Appendix 14). All of the studies apart from that by Moonen and colleagues[102] reported the detection of stage/grade at the patient level (if the number of specimens reported by a study was one per patient included in the analysis then this was considered as a patient-level analysis).

For the purposes of this review the presentation of test performance in terms of the detection of stage

Sensitivity and specificity: individual study results

Study ID	*n*	Sens %	Spec %
Friedrich 2003[95]	103	67	89
Halling 2000[97]	151	81	96
Junker2006[98]	121	60	83
Kipp 2008[99]	124	62	87
May 2007[107]	166	53	74
Meiers 2007[100]	624	93	90
Mian 2003[101]	57	96	45
Sarosdy 2002[108]	392	71	84
Sarosdy2006[103]	473	69	78
Skacel 2003[104]	111	85	97
Sokolova 2000[105]	179	85	92
Yoder 2007[106]	250	64	73

Pooled analysis of FISH at patient level	
Number of studies	12
Sensitivity % (95% CI)	76 (65 to 84)
Specificity % (95% CI)	85 (78 to 92)
Positive likelihood ratio	5.0 (2.5 to 7.6)
Negative likelihood ratio	0.28 (0.17 to 0.40)
DOR (95% CI)	17.7 (3.2 to 32.2)

SROC plot

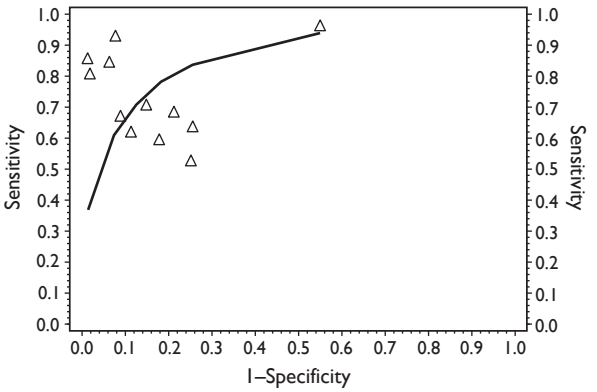


FIGURE 18 *FISH patient-level analysis: sensitivity, specificity, pooled estimates and SROC curve.*

and grade of non-muscle-invasive bladder cancer was considered in two broad categories:

1. less aggressive, lower risk tumours (pTa, G1, G2)
2. more aggressive, higher risk tumours (pT1, G3, CIS).

Table 13 shows the median (range) sensitivity of FISH, for both patient- and specimen-based detection of tumours, within the broad categories of less aggressive/lower risk and more aggressive/higher risk (including CIS), and also separately for CIS.

TABLE 13 *Sensitivity of FISH in detecting stage/grade of tumour*

	FISH sensitivity (%), median (range)	**Number of patients (specimens)[a]**	**Number of studies**
Less aggressive/lower risk			
Patient-based detection	65 (32 to 100)	2164	10
Specimen-based detection	27 (22 to 37)	95 (103)	1
More aggressive/higher risk including CIS			
Patient-based detection	95 (50 to 100)	2164	10
Specimen-based detection	60 (50 to 67)	95 (103)	1
CIS			
Patient-based detection	100 (50 to 100)	1067	8
Specimen-based detection	NR	NR	1

NR, not reported.
a The numbers of patients and specimens are the totals included in the overall analysis by the studies.

Less aggressive, lower risk tumours (pTa, G1, G2)

In total, 10 studies[95,97,99–101,103–105,107,108] involving 2164 patients reported the sensitivity of FISH for the patient-based detection of less aggressive, lower risk tumours. Across these studies the median (range) sensitivity of FISH was 65% (32% to 100%) (*Table 13*). The study by Moonen and colleagues[102] reported specimen-based detection (95 patients, 103 specimens), with a median (range) sensitivity of 27% (22% to 37%).

More aggressive, higher risk tumours (pT1, G3, CIS)

In total, 10 studies[95,97,99–101,103–105,107,108] involving 2164 patients reported the sensitivity of FISH for the patient-based detection of more aggressive, higher risk tumours. Across these studies the median (range) sensitivity of FISH was 95% (50% to 100%) (*Table 13*). The study by Moonen and colleagues[102] reported specimen-based detection (95 patients, 103 specimens), with a median (range) sensitivity of 60% (50% to 67%).

Carcinoma in situ

Although CIS is included in the more aggressive/higher risk category reported above, it may also be useful to consider separately the performance of biomarkers or cytology for the detection of CIS. Eight studies[95,97,99,101,104,105,107,108] involving 1067 patients reported the sensitivity of FISH for the patient-based detection of CIS. Across these studies the median (range) sensitivity of FISH was 100% (50% to 100%) (*Table 13*).

Number of tumours

None of the included studies reported the sensitivity of FISH in detecting varying numbers of tumours.

Size of tumours

None of the included studies reported the sensitivity of FISH in detecting varying sizes of tumour.

Unevaluable tests

Five studies[98,101–103,108] reported that 65 of 1059 tests (6.1%) could not be evaluated. The other studies did not specifically report this information.

ImmunoCyt

Characteristics of the included studies

A description of each of the 10 included ImmunoCyt studies is given in Appendix 12, which contains the characteristics of all of the included biomarker and cytology studies listed alphabetically by surname of first author. *Table 14* shows summary information for the 10 ImmunoCyt studies.

All 10 studies, reported in 12 papers,[101,109–119] were diagnostic cross-sectional studies. Six reported consecutive recruitment.[101,109,110,112,116,118] Two studies were multicentre (four centres,[111] 19 centres[116]).

The 10 studies enrolled 4199 participants, with at least 3091 included in the analysis (the study by Mian and colleagues[113] enrolled 942 participants but did not report the number included in the analysis). In nine studies[101,109–114,116,118] reporting this information, 890 participants (27%) presented with a suspicion of bladder cancer and 2405 (73%) had previously diagnosed bladder cancer. In one of these studies[118] the whole patient population ($n = 301$) had a suspicion of bladder cancer and in three[110,111,113] the whole population had previously diagnosed bladder cancer ($n = 1499$). One study[119] did not report this information.

Across six studies[101,109,112–114,116] providing information on patient age for the participant group as a whole, the median (range) of means was 68 years (66 to 73 years). Four studies[112,114,116,118] provided information on the gender of 1371 participants, of whom 1076 (78%) were men and 295 (22%) were women.

Six studies[111–114,118,119] gave details of when they took place, with an earliest start date of November 1997[112] and latest end date of July 2007.[118] The studies took place in Austria,[112] France,[116] Germany,[118] Italy,[113] Sweden,[114] Canada[119] and the USA,[111] with three having multinational settings, all taking place in Austria/Italy,[101,109,110] although they did not state that they were multicentre.

Methodological quality of the included studies

Figure 19 summarises the quality assessment for the 10 ImmunoCyt studies. The results for the quality assessment of the individual studies are shown in Appendix 13. In all studies the spectrum of patients who received the tests was considered to be representative of those who would receive the test in practice (Q1). In all studies the reference standard (cystoscopy with histological assessment of biopsied tissue) was considered likely to correctly classify bladder cancer (Q2). In all studies partial verification bias was avoided in that all patients who underwent an ImmunoCyt test also received a reference standard test (Q4), differential

TABLE 14 *Summary of the characteristics of the ImmunoCyt studies*

Characteristic	Number	Number of studies
Study design		
Cross-sectional diagnostic study	4199	10
Patients[a]		
Enrolled	4199	10
Analysed	3091+	
Suspicion of or previously diagnosed BC		
Suspicion of BC	890 (27%)	9 (90%)
Previously diagnosed BC	2405 (73%)	
Not reported	904	1 (10%)
Age		
Median (range) of means (years)	68 (66 to 73)	6 (60%)
Not reported	–	4 (40%)
Sex[b]		
Men	1076 (78%)	4 (40%)
Women	295 (22%)	6 (60%)
Not reported	2819	

BC, bladder cancer.
a Patients. The number for patients analysed is given as 3091+ because the study by Mian and colleagues[113] enrolled 942 participants and reported a specimen-based analysis but did not report the number of participants included in the analysis.
b Sex. This section sums to 4190 rather than 4199 because the study by Schmitz-Drager and colleagues[118] reported gender information for 292 of 301 participants enrolled.

verification bias was avoided in that patients received the same reference standard regardless of the index test result (Q5) and incorporation bias was avoided in that the reference standard was independent of the index test (Q6). In all studies either uninterpretable or intermediate test results were reported or there were none (Q10) and a prespecified cut-off value was used (Q12). In eight studies (80%) the time period between ImmunoCyt and the reference standard was considered to be short enough (1 month or less) to be reasonably sure that the patient's condition had not changed in the intervening period (Q3). In nine studies (90%) withdrawals from the study were explained or there were none (Q11) and a clear definition of what was considered to be a positive result was provided (Q13).

In all 10 studies (100%) it was unclear whether diagnostic review bias had been avoided (Q8), in nine studies (90%) it was unclear whether clinical review bias had been avoided (Q9) and in seven studies (70%) it was unclear whether test review bias had been avoided (Q7). One study (10%) provided information on observer variation in interpretation of test results (Q14).

Assessment of diagnostic accuracy

Patient-level analysis

Eight studies[101,109,111,112,114,116,118,119] enrolling 3041 participants, with 2896 included in the analysis, provided sufficient information to allow their inclusion in the pooled estimates for patient-level analysis. The 'common' cut-off used by all of these studies to define a positive test result was at least one green or one red fluorescent cell. *Figure 20* shows the sensitivity and specificity of the individual studies, pooled estimates and SROC curve for ImmunoCyt patient-based detection of bladder cancer. The pooled sensitivity and specificity (95% CI) were 84% (77% to 91%) and 75% (68% to 83%), respectively, and the DOR value

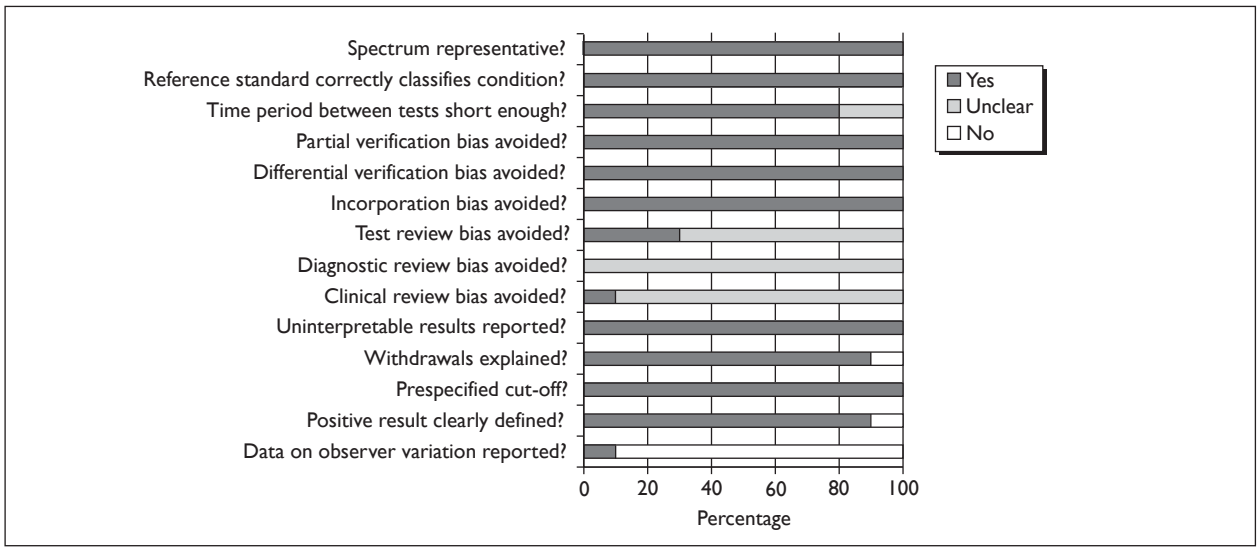


FIGURE 19 *Summary of quality assessment of ImmunoCyt studies (n = 10).*

(95% CI) was 16 (6 to 26). Across the studies the sensitivity for ImmunoCyt ranged from 73%[116] to 100%,[114] and specificity ranged from 62%[119] to 88%.[118] The median (range) PPV across studies was 54% (26% to 70%) and the median (range) NPV was 93% (86% to 100%).

Most of the included studies in the pooled estimates contained a mixture of patients with a suspicion of bladder cancer and those with previously diagnosed bladder cancer, although one study[119] did not report this information. In the study by Schmitz-Drager and colleagues[118] all of the participants ($n = 280$) had a suspicion of bladder cancer (sensitivity 85%, specificity 88%) and in the study by Messing and colleagues[111] all of the participants ($n = 326$) had previously diagnosed bladder cancer (sensitivity 81%, specificity 75%).

Specimen-level analysis

Two studies[110,113] enrolling 1158 participants, all of whom had been previously diagnosed with bladder cancer, reported specimen-level analysis ($n = 2220$ specimens). Across the two studies the median (range) sensitivity and specificity were 78% (71% to 85%) and 76% (73% to 78%) respectively.

Sensitivity and specificity: individual study results

Study ID	*n*	Sens %	Spec %
Lodde 2003[109]	225	87	67
Messing 2005[111]	326	81	75
Mian 1999[112]	249	86	79
Mian 2003[101]	181	86	71
Olsson 2001[114]	114	100	69
Piaton 2003[116]	651	73	82
Schmitz-Drager 2008[118]	280	85	88
Tetu 2005[119]	870	74	62

Pooled analysis of ImmunoCyt at patient level	
Number of studies	8
Sensitivity % (95% CI)	84 (77 to 91)
Specificity % (95% CI)	75 (68 to 83)
Positive likelihood ratio	3.4 (2.3 to 4.5)
Negative likelihood ratio	0.22 (0.12 to 0.31)
DOR (95% CI)	15.7 (5.5 to 25.9)

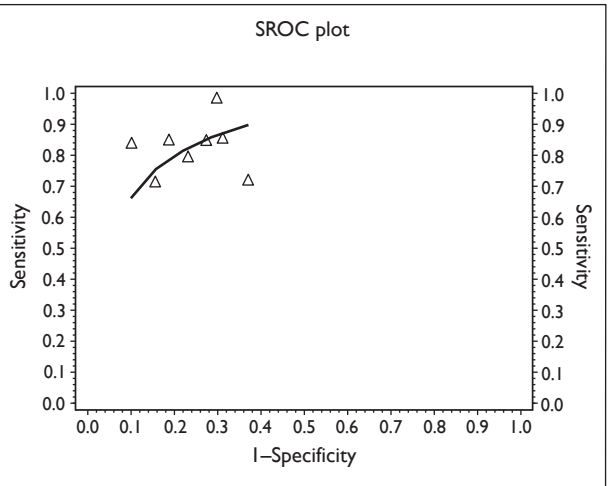


FIGURE 20 *ImmunoCyt patient-level analysis: sensitivity, specificity, pooled estimates and SROC curve.*

Stage/grade analysis

Studies reporting the sensitivity of ImmunoCyt in the detection of stage and grade of tumour categorised this information in different ways, including pTa, pTaG1–2, pTa pT1G3, pTa+CIS, G1, G2, pT1, pT1G1–2, CIS, G3, pT2 and ≥ pT2 (see Appendix 14). All of the studies providing this information, apart from that by Mian and colleagues,[113] reported the detection of stage/grade at the patient level (if the number of specimens reported by a study was one per patient included in the analysis then this was considered as a patient-based analysis).

Table 15 shows the median (range) sensitivity of ImmunoCyt, for both patient- and specimen-based detection of tumours, within the broad categories of less aggressive/lower risk and more aggressive/higher risk (including CIS), and also separately for CIS.

Less aggressive, lower risk tumours (pTa, G1, G2)

Six studies[101,109,111,112,116,119] involving 2502 patients reported the sensitivity of ImmunoCyt for the patient-based detection of less aggressive, lower risk tumours. Across these studies the median (range) sensitivity of ImmunoCyt was 81% (55% to 90%) (*Table 15*). The study by Mian and colleagues[113] reported specimen-based detection (942 participants enrolled, 1886 specimens), with a median (range) sensitivity of 82% (79 to 84%).

More aggressive, higher risk tumours (pT1, G3, CIS)

Six studies[101,109,111,112,116,119] involving 2502 patients reported the sensitivity of ImmunoCyt for the patient-based detection of more aggressive, higher risk tumours. Across these studies the median (range) sensitivity of ImmunoCyt was 90% (67% to 100%) (*Table 15*). The study by Mian and colleagues[113] reported specimen-based detection (942 participants enrolled, 1886 specimens), with a median (range) sensitivity of 91% (84% to 100%).

Carcinoma in situ

Six studies[101,109,111,112,116,119] involving 2502 patients reported the sensitivity of ImmunoCyt for the patient-based detection of CIS. Across these studies the median (range) sensitivity of ImmunoCyt was 100% (67% to 100%). The study by Mian and colleagues,[113] with specimen as the unit of analysis, reported 100% sensitivity for detecting CIS (*Table 15*).

Number of tumours

None of the included studies reported the sensitivity of ImmunoCyt in detecting varying numbers of tumours.

Size of tumours

Messing and colleagues,[111] in a study involving 326 patients, reported ImmunoCyt sensitivities of 71%, 84% and 60% in detecting tumours of < 1 cm, 1–3 cm and > 3 cm respectively.

TABLE 15 *Sensitivity of ImmunoCyt in detecting stage/grade of tumour*

	ImmunoCyt sensitivity (%), median (range)	Number of patients (specimens)[a]	Number of studies
Less aggressive/lower risk			
Patient-based detection	81 (55 to 90)	2502	6
Specimen-based detection[b]	82 (79 to 84)	942 (1886)	1
More aggressive/higher risk including CIS			
Patient-based detection	90 (67 to 100)	2502	6
Specimen-based detection[b]	91 (84 to 100)	942 (1886)	1
CIS			
Patient-based detection	100 (67 to 100)	2502	6
Specimen-based detection[b]	100	942 (1886)	1

a The numbers of patients and specimens are the totals included in the overall analysis by the studies.
b Specimen-based detection. In the study by Mian and colleagues[113] 942 participants were enrolled but it was unclear how many were included in the analysis.

Unevaluable tests

All 10 studies[101,109–114,116,118,119] provided information on unevaluable tests. Overall, 279 of 5292 tests (5%) could not be evaluated. Across studies, the median (range) percentage of tests that were unevaluable was 5% (1% to 10%).

Observer variation

Messing and colleagues[111] reported that after 1 day of training pathologists were able to pass an interobserver training test, achieving 100% concordance on five slides. At one participating laboratory 40% of cases were reviewed by two observers independently. There was 90% agreement between observers with the final diagnosis of disputed cases agreed on by the two pathologists who reviewed these cases together.[111]

NMP22

Characteristics of the included studies

A description of each of the 41 included NMP22 studies is given in Appendix 12, which contains the characteristics of all of the included biomarker and cytology studies listed alphabetically by surname of first author. *Table 16* shows summary information for the 41 NMP22 studies.

Thirty-one studies, reported in 37 papers,[45,80,95,120–153] were diagnostic cross-sectional studies. Three[45,126,127] reported consecutive recruitment. A total of 10 studies, reported in 11 papers,[154–164] were case–control studies. Four studies were multicentre (23 centres,[126] 23 centres,[127] 13 centres,[135] three centres[149]).

The 41 studies enrolled 13,885 participants, with 13,490 included in the analysis. Five studies[80,126,127,131,150] involving 2426 participants used the NMP22 BladderChek point of care test. In 33 studies[45,80,95,122,123,125–132,134–142,144,147–151,153,158,159,162,164] 4478 participants (41%) presented with a suspicion of bladder cancer and 6536 (59%) had previously diagnosed bladder cancer. In five[126,135,141,153,162] of these studies the whole patient population analysed ($n = 2202$) had a suspicion of bladder cancer and in 10[123,127,129–131,138,142,144,147,149] the whole population analysed had previously diagnosed bladder cancer ($n = 4799$). Eight studies[120,121,154–157,161,163] did not report this information.

Across 24 studies[80,123,125–129,131,134,136,138,140,141,144,147,149–151,153,154,156,158,159,162] providing information on patient age for the whole study population, the median (range) of means was 66 years (53 to 71 years). A total of 29 studies[80,121–123,125–127,129–131,135–142,144,147,149–151,153,156,158,159,162,163] provided information on the gender of 10,804 participants, of whom 7818 (72%) were men and 2986 (28%) were women.

In total, 16 studies[80,121,122,126,127,135,136,139,150,151,153,155,158,159,162,164] gave details of when they took place, with an earliest start date of August 1995[135] and latest end date of April 2006.[150] Nine studies took place in the USA,[126,127,129,139,148,149,153,158,159] four in Italy[122,123,144,154] and Spain,[128,142,161,162] three in Austria,[134,147,151] Germany[80,95,132] and Japan,[135,136,164] two in the UK,[45,141] Turkey[137,163] and India[131,150] and one in Greece,[125] Poland,[130] Switzerland,[121] Sweden,[155] the Netherlands,[138] South Korea[157] and China,[156] and two had multinational settings, taking place in Germany/USA[140] and Saudi Arabia/USA.[120]

Methodological quality of the included studies

Figure 21 summarises the quality assessment for the 41 NMP22 studies. The results for the quality assessment of the individual studies are shown in Appendix 13. In all studies the reference standard (cystoscopy with histological assessment of biopsied tissue) was considered likely to correctly classify bladder cancer (Q2) and withdrawals from the study were explained or there were none (Q11). In 40 studies (98%) the spectrum of patients who received the tests was considered to be representative of those who would receive the test in practice (Q1) and incorporation bias was avoided (Q6). In 39 studies (95%) partial verification bias was avoided (Q4), intermediate test results were reported or there were none (Q10) and a clear definition of what was considered to be a positive result was provided (Q13).

In 36 studies (88%) differential verification bias was avoided (Q5), in 32 studies (78%) the time period between NMP22 and the reference standard was considered to be short enough (1 month or less) to be reasonably sure that the patient's condition had not changed in the intervening period (Q3) and in 24 studies (58%) a prespecified cut-off value was used (Q12).

However, in 39 studies (95%) it was unclear whether clinical review bias had been avoided (Q9), in 29 studies (71%) it was unclear whether test review bias had been avoided (Q7) and in 27 studies (66%) it was unclear whether diagnostic review bias had been avoided (Q8). A total of 40 studies (98%) did

TABLE 16 *Summary of the characteristics of the NMP22 studies*

Characteristic	Number	Number of studies
Study design		
Cross-sectional diagnostic study	11,236	31
Case–control	2649	10
Patients		
Enrolled	13,885	41
Analysed	13,490	
Suspicion of or previously diagnosed BC[a]		
Suspicion of BC	4478 (41%)	33 (80%)
Previously diagnosed BC	6536 (59%)	
Not reported	1812	8 (20%)
Age		
Median (range) of means (years)	66 (53 to 71)	24 (59%)
Not reported	–	17 (41%)
Sex[b]		
Men	7818 (72%)	29 (71%)
Women	2986 (28%)	12 (29%)
Not reported	2858	

BC, bladder cancer.

a Suspicion of or previously diagnosed BC. This section sums to 12,826 rather than 13,885 because Giannopoulos and colleagues[125] reported this information for those analysed ($n = 213$) rather than those enrolled ($n = 234$), Lahme and colleagues[132] reported it for 84 of 169 participants enrolled, Oge and colleagues[137] reported it for those analysed ($n = 76$) rather than enrolled ($n = 114$), Ramakumar and colleagues[159] reported it for 57 of 196 participants enrolled, Sanchez-Carbayo and colleagues[162] reported it for 112 of 187 participants enrolled, Shariat and colleagues[147] reported it for those analysed ($n = 2871$) rather than those enrolled ($n = 2951$) and Takeuchi and colleagues[164] reported this information for 48 of 669 participants enrolled.

b Sex. This section sums to 13,662 rather than 13,885 because Chang and colleagues[156] reported this information for 331 of 399 participants enrolled, Sanchez-Carbayo and colleagues[162] reported it for 112 of 187 participants enrolled and Shariat and colleagues[147] reported it for those analysed ($n = 2871$) rather than those enrolled ($n = 2951$).

not report information on observer variation in interpretation of test results (Q14).

Assessment of diagnostic accuracy

Patient-level analysis

A total of 28 studies[45,80,95,121–123,126–128,130–132,134,137,139–142,144,147,148,150,151,153,159,160,162,163] enrolling 10,565 participants, with 10,119 included in the analysis, provided sufficient information to allow their inclusion in the pooled estimates for patient-level analysis, using a 'common' cut-off of 10 U/ml to define a positive test result. *Figure 22* shows the sensitivity and specificity of the individual studies, pooled estimates and SROC curve for NMP22 patient-based detection of bladder cancer. The pooled sensitivity and specificity (95% CI) were 68% (62% to 74%) and 79% (74% to 84%), respectively, and the DOR value (95% CI) was 8 (5 to 11). Across the 28 studies the sensitivity for NMP22 ranged from 33%[45] to 100%,[153] and specificity ranged from 40%[80] to 93%.[142] The median (range) PPV across studies was 52% (13% to 94%) and the median (range) NPV was 82% (44% to 100%).

Most of the included studies in the pooled estimates contained a mixture of patients with a suspicion of bladder cancer and those with previously diagnosed bladder cancer, although three studies[121,160,163] did not report this information. In four studies[126,141,153,162] all of the participants ($n = 1893$) had a suspicion of

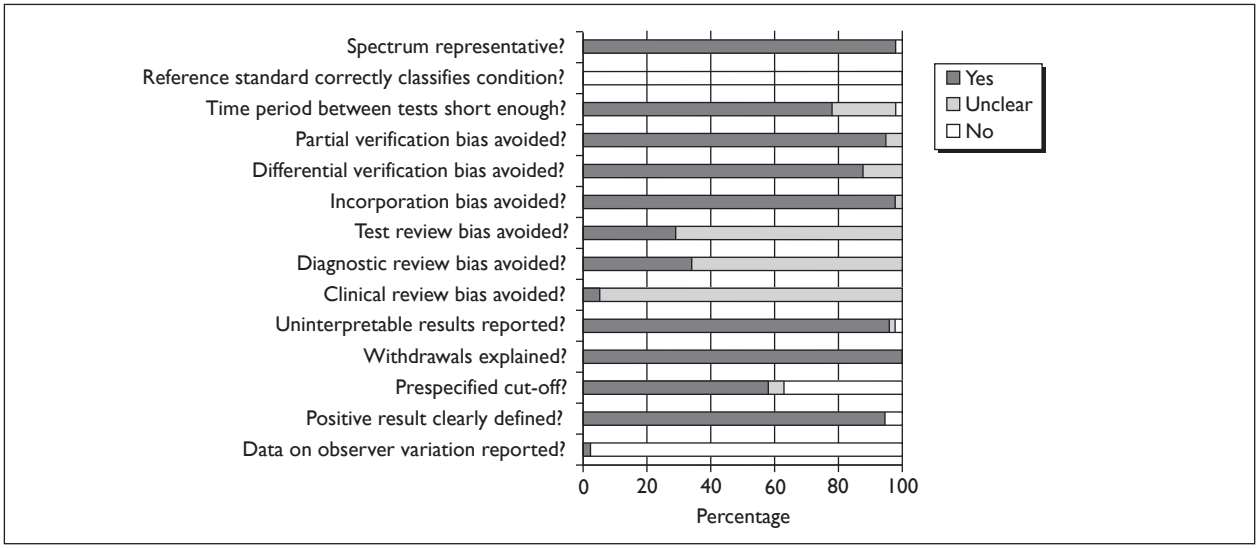


FIGURE 21 *Summary of quality assessment of NMP22 studies (n = 41).*

bladder cancer [median (range) sensitivity and specificity across studies 71% (56% to 100%) and 86% (80% to 87%) respectively]. In seven studies[123,127,130,131,142,144,147] all of the participants ($n = 4284$) had previously diagnosed bladder cancer [median (range) sensitivity and specificity across studies 69% (50% to 85%) and 81% (46% to 93%) respectively].

NMP22 BladderChek point of care test

Five studies[80,126,127,131,150] involving 2426 participants used the NMP22 BladderChek point of care test. Across these studies, using a cut-off of 10 U/ml for a positive test result, the median (range) sensitivity and specificity for patient-based detection of bladder cancer were 65% (50% to 85%) and 81% (40% to 87%), respectively, compared with 68% (95% CI 62% to 74%) sensitivity and 79% (95% CI 74% to 84%) specificity for the 28 studies included in the pooled estimates. (The five studies using the NMP22 BladderChek test were also included in the pooled estimates.) In the study by Grossman and colleagues[126] all of the participants ($n = 1331$) had a suspicion of bladder cancer (sensitivity 56%, specificity 86%). In the studies by Grossman and colleagues[127] and Kumar and colleagues[131] all of the participants ($n = 799$) had previously diagnosed bladder cancer [median (range) sensitivity and specificity across studies 68% (50% to 85%) and 83% (78% to 87%) respectively].

Specimen-level analysis

Three studies enrolling 655 participants reported specimen-level analysis ($n = 705$ specimens for Oosterhuis 2002[138] and Stampfer 1998;[149] Bhuiyan 2003[120] did not report numbers) using a cut-off of 10 U/ml for a positive test result. Across the three studies the median (range) sensitivity and specificity were 49% (25% to 50%) and 92% (68% to 94%) respectively.

Stage/grade analysis

Studies reporting the sensitivity of NMP22 in the detection of stage and grade of tumour categorised this information in different ways, including pTa, pTaG1, pTaG1–2, PTaG2, pTa pT1, pTa pT1 CIS, pTa+CIS, pTaG3–pT1, G1, G2, G1–2, G1 G3, pT1, pT1G2, CIS, G3, pT2, pT2 pT2a, pT2G2, pT2–3, pT2–4, ≥ pT2, pT3, pT3a 3b and pT4 (see Appendix 14). Almost all of the studies providing this information and using a cut-off of 10 U/ml for a positive test result reported the detection of stage/grade at the patient level (if the number of specimens reported by a study was one per patient included in the analysis then this was considered as a patient-based analysis); the exception was those studies by Oosterhuis and colleagues[138] and Stampfer and colleagues.[149]

Table 17 shows the median (range) sensitivity of ImmunoCyt, for both patient- and specimen-based detection of tumours, within the broad categories of less aggressive/lower risk and more aggressive/higher risk (including CIS), and also separately for CIS.

Less aggressive, lower risk tumours (pTa, G1, G2)

A total of 18 studies[45,95,121,123,126–128,131,132,134,137,141,142,144,150,151,159,162] involving 4685 patients reported

Sensitivity and specificity: individual study results

Study ID	*n*	Sens %	Spec %
Casella 2000[121]	235	52	84
Casetta 2000[122]	102	64	63
Chahal 2001b[45]	211	33	92
Del Nero 1999[123]	105	83	87
Friedrich 2003[95]	103	70	65
Grossman 2005[126]	1331	56	86
Grossman 2006[127]	668	50	87
Gutierrez Banos 2001[128]	150	76	91
Kowalska 2005[130]	98	53	46
Kumar 2006[131]	131	85	78
Lahme 2001[132]	109	63	61
Mian 2000[134]	240	56	79
Oge 2001[137]	76	74	69
Ponsky 2001[139]	608	88	84

Study ID	*n*	Sens %	Spec %
Poulakis 2001[140]	739	79	70
Ramakumar 1999[159]	196	53	60
Saad 2002[141]	120	81	87
Sanchez-Carbayo 1999[160]	187	81	91
Sanchez-Carbayo 2001a[142]	232	69	93
Sanchez-Carbayo 2001b[162]	112	61	80
Serretta 2000[144]	179	75	55
Shariat 2006[147]	2871	57	81
Sharma 1999[148]	199	67	86
Sozen 1999[163]	140	73	81
Talwar 2007[150]	196	67	81
Tritschler 2007[80]	100	65	40
Wiener 1998[151]	291	48	69
Zippe 1999[153]	330	100	86

Pooled analysis	
Number of studies	28
Sensitivity % (95% CI)	68 (62 to 74)
Specificity % (95% CI)	79 (74 to 84)
Positive likelihood ratio	3.2 (2.4 to 4.0)
Negative likelihood ratio	0.41 (0.33 to 0.49)
DOR (95% CI)	7.8 (4.5 to 11.1)

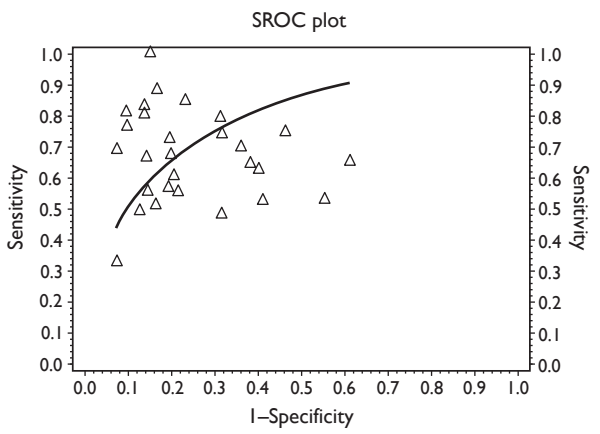


FIGURE 22 *NMP22 patient-level analysis: sensitivity, specificity, pooled estimates and SROC curve.*

TABLE 17 *Sensitivity of NMP22 in detecting stage/grade of tumour*

	NMP22 sensitivity (%), median (range)	Number of patients (specimens)[a]	Number of studies
Less aggressive/lower risk			
Patient-based detection	50 (0 to 86)	4685	18
Specimen-based detection	33	191 (431)	1
More aggressive/higher risk including CIS			
Patient-based detection	83 (0 to 100)	7556	19
Specimen-based detection	82 (25 to 100)	191 (431)	1
CIS			
Patient-based detection	83 (0 to 100)	3453	11
Specimen-based detection	25	191 (431)	1

a The numbers of patients and specimens are the totals included in the overall analysis by the studies.

the sensitivity of NMP22 for the patient-based detection of less aggressive, lower risk tumours. Across these studies the median (range) sensitivity of NMP22 was 50% (0% to 86%) (*Table 17*). The study by Oosterhuis and colleagues[138] reported a sensitivity of 33% for specimen-based detection (191 participants, 431 specimens).

More aggressive, higher risk tumours (pT1, G3, CIS)

A total of 19 studies[45,95,121,123,126–128,131,132,134,137,141,142,144,147,150,151,159,162] involving 7556 patients reported the sensitivity of NMP22 for patient-based detection of more aggressive, higher risk tumours. Across these studies the median (range) sensitivity of NMP22 was 83% (0% to 100%) (*Table 17*). In the study by Oosterhuis and colleagues[138] (191 participants, 431 specimens), the median (range) sensitivity for specimen-based detection was 82% (25% to 100%).

Carcinoma in situ

A total of 11 studies[95,126,127,134,137,141,142,144,150,159,162] involving 3453 patients reported the sensitivity of NMP22 for the patient-based detection of CIS. Across these studies the median (range) sensitivity of NMP22 was 83% (0% to 100%). Oosterhuis and colleagues[138] (191 participants, 431 specimens) reported a sensitivity of 25% for specimen-based detection of CIS.

Number of tumours

Three studies reported the sensitivity of NMP22 in detecting bladder cancer in patients with varying numbers of tumours, although none of the studies used a cut-off of 10 U/ml. Poulakis and colleagues[140] in a study involving 739 patients reported NMP22 (cut-off ≥ 8.25 U/ml) sensitivities of 79%, 90% and 97% in patients with one, two to three, and more than three tumours respectively. Takeuchi and colleagues[164] in a study involving 669 patients reported NMP22 (cut-off ≥ 12 U/ml) sensitivities of 44%, 60% and 91% in patients with one, two to four, and five or more tumours respectively. Sanchez-Carbayo and colleagues[161] in a study involving 187 patients reported NMP22 (cut-off ≥ 14.6 U/ml) sensitivities of 72% and 75% in patients with single and multiple tumours respectively.

Size of tumours

Three studies reported the sensitivity of NMP22 in detecting bladder cancer in patients with varying sizes of tumours, although again none of the studies used a cut-off of 10 U/ml. Boman and colleagues[155] in a study involving 250 patients reported NMP22 (cut-off ≥ 4 U/ml) sensitivities of 65%, 54%, 73% and 89% in detecting new tumours of ≤ 10 mm, 11–20 mm, 21–30 mm and > 30 mm, respectively, and 41%, 67% and 60% in detecting recurrent tumours of ≤ 10 mm, 11–20 mm and > 21 mm respectively. Takeuchi and colleagues[164] in a study involving 669 patients reported NMP22 (cut-off ≥ 12 U/ml) sensitivities of 32%, 65% and 92% in detecting tumours < 10 mm, 10–30 mm and > 30 mm respectively. Sanchez-Carbayo and colleagues[161] in a study involving 187 patients reported NMP22 (cut-off > 14.6 U/ml) sensitivities of 83%, 81% and 93% in detecting tumours < 5 mm, 5–30 mm and > 30 mm respectively.

Unevaluable tests

None of the NMP22 studies specifically reported this information.

Cytology

Characteristics of the included studies

A description of each of the 56 included cytology studies is given in Appendix 12, which contains the characteristics of all of the included biomarker and cytology studies listed alphabetically by surname of first author. *Table 18* shows summary information for the 56 cytology studies.

A total of 47 studies, reported in 56 papers, were diagnostic cross-sectional studies,[45,80,97,98,100–103,105,109–129,131–133,135,136,139–141,145,146,148–153,165–174] of which 11[45,101,109,110,112,116,118,126,127,165,174] reported consecutive recruitment. Nine studies[107,108,155,157–159,162–164] were case–control studies and 11 studies[103,108,111,116,126,127,135,149,165,170,174] were multicentre (*Table 19*).

The 56 studies enrolled 22,260 participants, with 19,219 included in the analysis. Eight studies[80,114,120,121,151,155,167,171] involving at least 872 patients reported bladder wash cytology. In 46 studies[45,80,97,101–103,105,107–114,116,118,122–124,126–129,131,132,135,136,139–141,148–151,153,158,159,162,164,165,168,170–172,174] 7888 participants (45%) presented with a suspicion of bladder cancer and 9487 (55%) had previously diagnosed bladder cancer. In 10[103,118,126,135,141,153,162,164,168,172] of these studies the whole patient population analysed ($n = 4290$) had a suspicion of bladder cancer and in 11[102,108,110,111,113,123,127,129,131,170,174] the whole population analysed had previously diagnosed bladder cancer ($n = 5710$). In total, 10 studies[98,100,119–121,155,157,163,166,167] did not report this information.

TABLE 18 *Summary of the characteristics of the cytology studies*

Characteristic	Number	Number of studies
Study design		
Cross-sectional diagnostic study	19,842	47
Case–control	2418	9
Patients		
Enrolled	22,260	56
Analysed	19,219	
Suspicion of or previously diagnosed BC		
Suspicion of BC	7888 (45%)	46 (82%)
Previously diagnosed BC	9487 (55%)	
Not reported	3057	10 (18%)
Age		
Median (range) of means (years)	67 (54 to 73)	33 (59%)
Not reported	–	23 (41%)
Sex		
Men	9702 (73%)	36 (64%)
Women	3639 (27%)	20 (36%)
Not reported	8578	

BC, bladder cancer.

TABLE 19 *Multicentre cytology studies*

Study	Number of centres
Bastacky 1999[165]	3
Grossman 2005[126]	23
Grossman 2006[127]	23
Karakiewicz 2006[170]	10
Messing 2005[111]	4
Miyanaga 1999[135]	13
Piaton 2003[116]	19
Raitanen 2002[174]	18
Sarosdy 2002[108]	21
Sarosdy 2006[103]	23
Stampfer 1998[149]	3

Across 33 studies[80,97,101–103,107,109,112–114,116,123,124,126–129,131,136,140,141,149–151,153,158,159,162,166,170–172,174] providing information on patient age for the whole study population, the median (range) of means was 67 years (54 to 73 years). A total of 36 studies provided information on the gender of 13,341 participants, of whom 9702 (73%) were men and 3639 (27%) were women.

In total, 30 studies[80,102,103,108,111–114,118,119,121,122,126,127,135,136,139,150,151,153,155,158,159,162,164–168,174] gave details of when they took place, with an earliest start date of 1990[165] and latest end date of July 2007.[118] Fifteen studies took place in the USA,[97,103,105,108,111,126,127,129,139,148,149,153,158,159,165] seven in Germany,[80,98,107,118,132,168,171] four in the UK,[45,141,166,172] three each in Italy[113,122,123] and Japan,[135,136,164] two each in Austria,[112,151] Spain,[128,161] Sweden[114,155] and India[131,150] and one each in Belgium,[167] Finland,[174] France,[116] Greece,[124] Switzerland,[121] the Netherlands,[102] Turkey,[163] Canada[119] and South Korea,[157] while seven had multinational settings, with three taking place in Austria/Italy[101,109,110] and the others taking place in Germany/USA,[140] USA/Belgium,[100] Saudi Arabia/USA[120] and Austria/Germany/Italy/Spain/Sweden/Switzerland/Egypt/Japan/Canada/USA.[170]

Methodological quality of the included studies

Figure 23 summarises the quality assessment for the 56 cytology studies. The results for the quality assessment of the individual studies are shown in Appendix 13. In all studies the reference standard

(cystoscopy with histological assessment of biopsied tissue) was considered likely to correctly classify bladder cancer (Q2). In 55 studies (98%) the spectrum of patients who received the tests was considered to be representative of those who would receive the test in practice (Q1), incorporation bias was avoided (Q6), uninterpretable test results were reported or there were none (Q10) and withdrawals from the study were explained or there were none (Q11). In 54 studies (96%) partial verification bias was avoided (Q4) and in 49 (88%) differential verification bias was avoided (Q5). In 41 studies (73%) the time period between cytology and the reference standard was considered to be short enough (1 month or less) to be reasonably sure that the patient's condition had not changed in the intervening period (Q3), in 40 studies (71%) a prespecified cut-off value for a positive test result was stated (Q12) and in 37 studies (66%) a clear definition of what was considered to be a positive result was provided (Q13).

However, in 48 studies (86%) it was unclear whether clinical review bias had been avoided (Q9), in 40 studies (71%) it was unclear whether diagnostic review bias had been avoided (Q8) and in 31 studies (55%) it was unclear whether test review bias had been avoided (Q7). A total of 53 studies (95%) did not report information on observer variation in interpretation of test results (Q14).

Assessment of diagnostic accuracy

Patient-level analysis

A total of 36 studies[45,80,97,100,101,107,109,111,112,116,118,119,122–124,126–128,131,132,135,136,139–141,148,150,151,153,157,159,164,166,170,172,174] reporting voided urine cytology, enrolling 15,161 participants with 14,260 included in the analysis, provided sufficient information to allow their inclusion in the pooled estimates for patient-level analysis. *Figure 24* shows the sensitivity and specificity of the individual studies, pooled estimates and SROC curve for cytology patient-based detection of bladder cancer. The pooled sensitivity and specificity (95% CI) were 44% (38% to 51%) and 96% (94% to 98%), respectively, and the DOR value (95% CI) was 19 (11 to 27). Across the 36 studies the sensitivity for cytology ranged from 7%[136] to 100%,[172] and specificity ranged from 78%[80] to 100%.[135] The median (range) PPV across studies was 80% (27% to 100%) and the median (range) NPV was also 80% (38% to 100%).

Most of the included studies in the pooled estimates contained a mixture of patients with a suspicion of bladder cancer and those with previously diagnosed bladder cancer. In seven studies[118,126,135,141,153,164,172] all of the participants ($n = 3331$) had a suspicion of bladder cancer [median (range) sensitivity and specificity across studies 44% (16% to 100%) and 99% (87% to 100%) respectively]. In six studies[111,123,127,131,170,174]

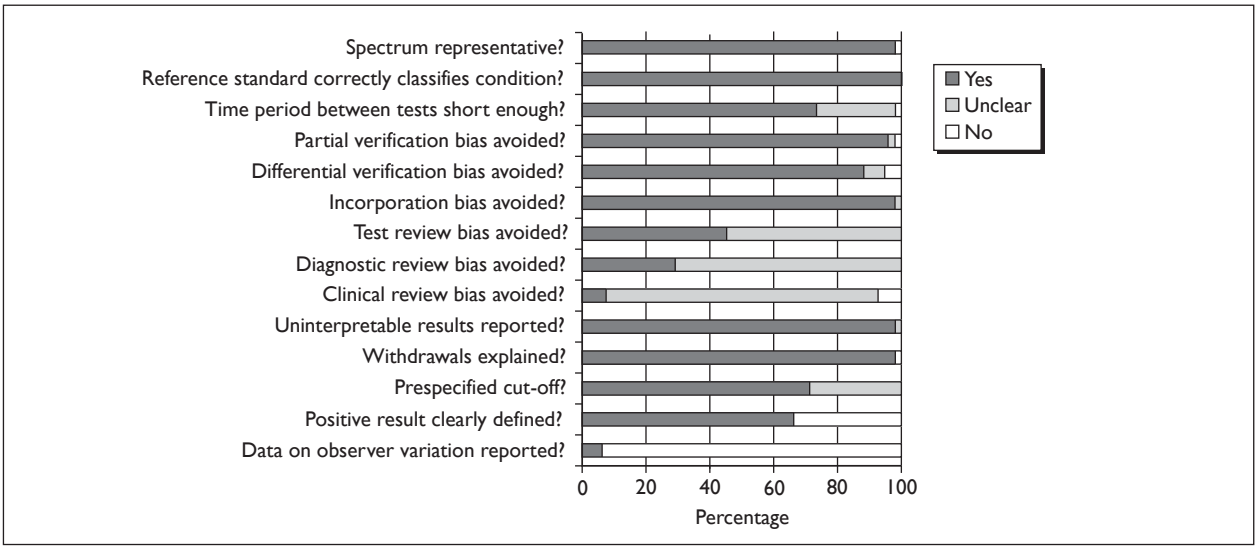


FIGURE 23 *Summary of quality assessment of cytology studies (n = 56).*

Sensitivity and specificity: individual study results

Study ID	*n*	Sens %	Spec %
Casetta 2000[122]	196	73	80
Chalhal 2001a[166]	285	49	94
Chahal 2001b[45]	211	24	97
Del Nero 1999[123]	105	47	83
Giannopoulos 2000[124]	147	38	92
Grossman 2005[126]	1287	16	99
Grossman 2006[127]	650	12	97
Gutierrez Banos 2001[128]	150	70	93
Halling 2000[97]	118	58	98
Karakiewicz 2006[170]	2542	45	95
Kumar 2006[131]	131	41	96
Lahme 2001[132]	109	45	93
Lee 2001[157]	106	56	89
Lodde 2003[109]	225	41	94
May 2007[107]	166	71	84
Meiers 2007[100]	624	73	87
Messing 2005[111]	326	23	93
Mian 1999[112]	249	47	98

Study ID	*n*	Sens %	Spec %
Mian 2003[101]	181	45	94
Miyanaga 1999[135]	309	55	100
Miyanaga 2003[136]	137	7	98
Piaton 2003[116]	651	62	85
Ponsky 2001[139]	608	62	85
Potter 1999[172]	336	100	99
Poulakis 2001[140]	739	62	96
Raitanen 2002[174]	441	35	90
Ramakumar 1999[159]	112	44	95
Sadd 2002[141]	120	48	87
Schmitz-Drager 2008[118]	280	44	96
Sharma 1999[148]	278	56	93
Takeuchi 2004[164]	669	44	100
Talwar 2007[150]	196	21	99
Tetu 2005[119]	870	29	98
Tritschler 2007[80]	85	44	78
Wiener 1998[151]	291	59	100
Zippe 1999[153]	330	33	100

Pooled analysis	
Number of studies	36
Sensitivity % (95% CI)	44 (38 to 51)
Specificity % (95% CI)	96 (94 to 98)
Positive likelihood ratio	10.8 (6.7 to 15.1)
Negative likelihood ratio	0.58 (0.51 to 0.64)
DOR (95% CI)	18.6 (11.0 to 26.6)

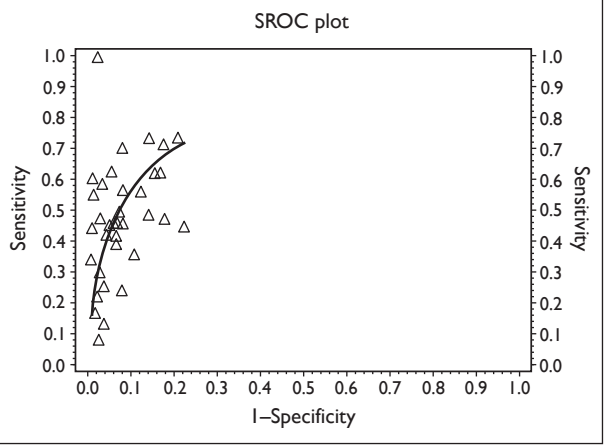


FIGURE 24 *Cytology patient-level analysis: sensitivity, specificity, pooled estimates and SROC curve.*

all of the participants ($n = 4195$) had previously diagnosed bladder cancer [median (range) sensitivity and specificity across studies 38% (12% to 47%) and 94% (83% to 97%) respectively]. Four studies[100,119,157,166] did not report this information.

Specimen-level analysis

Eight studies,[102,110,113,120,129,149,168,171] with at least 1143 patients included in the analysis, reported specimen-level analysis ($n = 3487$) of voided urine cytology. (The study by Mian and colleagues[113] enrolled 942 patients but did not report the number analysed, and in the study by Planz and colleagues[171] it was unclear how many patients underwent voided urine cytology and how many underwent bladder wash cytology.) Across these studies the median (range) sensitivity and specificity were 42% (38% to 76%) and 94% (58% to 99%) respectively.

Cytology using bladder wash

Eight studies[80,114,120,121,151,155,167,171] involving at least 872 patients reported bladder wash cytology. (It was unclear in the studies by Boman and colleagues[155] and Planz and colleagues[171] how many patients the specimen-based analysis related to.) Across four studies[80,114,121,151] reporting patient-based detection of bladder cancer ($n = 608$) the median (range) sensitivity and specificity were 58% (53% to 76%) and 90% (62% to 100%) respectively (Olsson and colleagues[114] did not report specificity). This compares with 44% (95% CI 38% to 51%)

sensitivity and 96% (95% CI 94% to 98%) specificity for the 36 voided urine cytology studies included in the pooled estimates.

Across four studies[120,155,167,171] reporting specimen-based detection of bladder cancer (n = at least 1076) the median (range) sensitivity and specificity were 50% (38% to 62%) and 94% (83% to 99%) respectively. (Bhuiyan and colleagues[120] reported sensitivity and specificity but not the number of specimens upon which this was based, and Olsson and colleagues[114] did not report specificity.) This compares with a median (range) sensitivity of 42% (38% to 76%) and specificity of 94% (58% to 99%) across the eight studies reporting specimen-based analysis for voided urine cytology.

All of the studies reporting bladder wash cytology contained a mixture of patients with a suspicion of bladder cancer or previously diagnosed bladder cancer, or did not report numbers for these groups of patients.

Stage/grade analysis

Studies reporting the sensitivity of cytology in the detection of stage and grade of tumour categorised this information in different ways, including pTa, pTaG1, pTaG1–2, PTaG2, pTaG3, pTa pT1, pTa pT1 CIS, pTa+CIS, ≥ pTa+CIS, pTa pT1G3, pTaG3–pT1, G1, G2, G1–2, pT1, pT1G1, pT1G2, pT1G1–2, pT1G3, pT1G3+CIS, pT1–T3b, pT1–4, CIS, CIS–pT1, G3, pT2, pT2 pT2a, pT2G2, pT2G3, pT2–3, pT2–4, ≥ pT2, pT3, pT3a 3b, pT3G3 and pT4 (see Appendix 14). If the number of specimens included in the analysis was one per patient then this was considered as a patient-based analysis.

Table 20 shows the median (range) sensitivity of voided urine cytology, for both patient- and specimen-based detection of tumours, within the broad categories of less aggressive/lower risk and more aggressive/higher risk (including CIS), and also separately for CIS.

Less aggressive, lower risk tumours (pTa, G1, G2)

A total of 29 studies[45,97,100,101,103,107–109,111,112,116,119,123,124,126–128,131,132,140,141,150,151,157,159,164,166,170,174] involving 12,566 patients reported the sensitivity of voided urine cytology for the patient-based detection of less aggressive, lower risk tumours. Across these studies the median (range) sensitivity of cytology was 27% (0% to 93%) (*Table 20*). Across three studies[102,113,168] reporting the sensitivity of voided urine cytology for specimen-based detection of less aggressive, lower risk tumours (469+ participants, 2411 specimens), the median (range) sensitivity was 27% (8% to 78%).

TABLE 20 *Sensitivity of voided urine cytology in detecting stage/grade of tumour*

	Cytology sensitivity (%), median (range)	Number of patients (specimens)[a]	Number of studies
Less aggressive/lower risk			
Patient-based detection	27 (0 to 93)	12,566	29
Specimen-based detection[b]	27 (8 to 78)	469+ (2411)	3
More aggressive/higher risk including CIS			
Patient-based detection	69 (0 to 100)	12,566	29
Specimen-based detection[b]	79 (68 to 93)	608+ (3003)	4
CIS			
Patient-based detection	78 (0 to 100)	6870	17
Specimen-based detection[b]	81 (76 to 93)	513+ (2895)	3

a The numbers of patients and specimens are the totals included in the overall analysis by the studies.
b Specimen-based detection: 469+, 608+, 513+. The '+' represents the study by Mian and colleagues,[113] in which 942 participants were enrolled but it was unclear how many were included in the analysis.

More aggressive, higher risk tumours (pT1, G3, CIS)

A total of 29 studies[45,97,100,101,103,107–109,111,112,116,119,123,124,126–128,131,132,140,141,150,151,157,159,164,166,170,174] involving 12,566 patients reported the sensitivity of voided urine cytology for the patient-based detection of more aggressive, higher risk tumours. Across these studies the median (range) sensitivity of cytology was 69% (0% to 100%) (*Table 20*). Across four studies[102,113,167,168] reporting the sensitivity of voided urine cytology for specimen-based detection of more aggressive, higher risk tumours (608+ participants, 3003 specimens), the median (range) sensitivity was 79% (68% to 93%).

Carcinoma in situ

A total of 17 studies[97,101,107–109,111,112,116,119,124,126,127,140,141,150,159,174] involving 6870 patients reported the sensitivity of voided urine cytology for patient-based detection of CIS. Across these studies the median (range) sensitivity of cytology was 78% (0% to 100%). Across three studies[113,167,168] reporting the sensitivity of voided urine cytology for specimen-based detection of CIS (513+ participants, 2895 specimens), the median (range) sensitivity was 81% (76% to 93%).

Number of tumours

Three studies reported the sensitivity of cytology in detecting bladder cancer in patients with varying numbers of tumours. Poulakis and colleagues[140] in a study involving 739 patients reported cytology sensitivities of 48%, 68% and 86% in patients with one, two to three, and more than three tumours respectively. Raitanen and colleagues[174] in a study involving 570 patients reported on a subgroup of 129 patients with no previous history of bladder cancer in which cytology sensitivities were 57%, 54% and 71% in patients with one, two and more than three tumours respectively. Takeuchi and colleagues[164] in a study involving 669 patients reported cytology sensitivities of 33%, 30% and 82% in patients with one, two to four, and five or more tumours respectively.

Size of tumours

Three studies reported the sensitivity of cytology in detecting bladder cancer in patients with varying sizes of tumours. Boman and colleagues[155] in a study involving 250 patients reported cytology sensitivities of 35%, 33%, 55% and 87% in detecting new tumours ≤ 10 mm, 11–20 mm, 21–30 mm and > 30 mm, respectively, and 30%, 91% and 100% in detecting recurrent tumours ≤ 10 mm, 11–20 mm and > 21 mm respectively. Messing and colleagues[111] in a study involving 326 patients reported cytology sensitivities of 18%, 26% and 20% in detecting tumours < 10 mm, 10–30 mm and > 30 mm respectively. Takeuchi and colleagues[164] in a study involving 669 patients reported cytology sensitivities of 21%, 47% and 75% in detecting tumours < 10 mm, 10–30 mm and > 30 mm respectively.

Unevaluable tests

Six studies[101,103,114,118,119,174] specifically reported unevaluable tests. Overall, 54 of 2566 tests (2%) could not be evaluated. Across studies, the median (range) percentage of tests that were unevaluable was 1% (0.6% to 4%).

Observer variation

Two studies reported observer variation. Hughes and colleagues[129] reported that all 128 specimens were independently reviewed by two cytopathologists, who were approximately 80% concordant in their interpretation of the cases. In the case of approximately 20% of specimens about which there was disagreement concerning the cytological diagnosis, the cytospin was reviewed by the two pathologists simultaneously and an agreement was reached.[129] Sarosdy and colleagues[108] reported that local site results were available in 43 cases and there was agreement with study central cytology in 36 (84%). Of the remaining seven cases, four were positive at the site and negative at the study testing laboratory, and three were negative at the investigation site and positive at the study testing laboratory.[108] Study site cytology was available in three cases of CIS and eight cases of G3 tumour, with 100% agreement between study site and central laboratory cytopathology interpretation in these 11 cases.[108]

Studies directly comparing tests

FISH versus cytology

Five[97,98,100,101,107] of the studies included in the pooled estimates for FISH and for cytology directly compared the two tests. The studies enrolled 1377 participants, with 1119 included in the analysis for FISH and 1198 for cytology. *Figure 25* shows the sensitivity and specificity of the individual studies, pooled estimates and SROC curves for these five studies. The pooled estimate (95% CI) for the sensitivity of FISH was 81% (66% to 97%) compared with 54% (39 to 80%) for cytology, whereas the pooled estimate (95% CI) for the specificity of FISH was 82% (68% to 97%) compared with 92% (84% to 99%) for cytology.

ImmunoCyt versus cytology

Six[101,109,111,112,116,118] of the studies included in the pooled estimates for ImmunoCyt and for cytology directly compared the two tests. The studies enrolled 2016 participants, with 1912 included in the analysis. *Figure 26* shows the sensitivity and specificity for the individual studies, pooled estimates and SROC curves for these six studies. The pooled estimate (95% CI) for the sensitivity of ImmunoCyt was 82% (76% to 89%) compared with 44% (35% to 54%) for cytology, whereas the pooled estimate (95% CI) for the specificity of ImmunoCyt was 85% (71% to 85%) compared with 94% (91% to 97%) for cytology.

NMP22 versus cytology

In total, 16[45,80,123,126–128,131,132,139–141,148,150,151,153,159] of the studies included in the pooled estimates for NMP22 and for cytology directly compared the two tests. The studies enrolled 5623 participants, with 5563 included in the analysis for NMP22 and 5402 for cytology. *Figure 27* shows the sensitivity and specificity for the individual studies, pooled estimates and SROC curves for these 16 studies. The pooled estimate (95% CI) for the sensitivity of NMP22 was 70% (59% to 80%) compared with 40% (31% to 49%) for cytology, whereas the pooled estimate (95% CI) for the specificity of NMP22 was 81% (74% to 88%) compared with 97% (95% to 99%) for cytology.

Studies reporting combinations of tests

In total, 16 studies reported the sensitivity and specificity of combinations of tests in detecting bladder cancer, including FISH and cytology,[94,102] FISH and cystoscopy,[99] ImmunoCyt and cytology,[101,109–113,116,119] ImmunoCyt and cystoscopy,[118] NMP22 and cytology,[131,164] NMP22 and cystoscopy[126,127] and cytology and cystoscopy.[118,127] Although not explicitly stated in the reports, the definition of a positive test result for the combined tests was a positive result on either of the tests included in the combination. The exception to this was the study by Daniely and colleagues,[94] which reported the test performance of FISH combined with cytology.

FISH and cytology

Two studies[94,102] reported the sensitivity and specificity of FISH and cytology used in combination. In a patient-level analysis ($n = 115$), Daniely and colleagues[94] reported sensitivity and specificity of 100% and 50%, respectively, for FISH and cytology used in combination (results were not presented separately for the individual tests). A test was reported as positive if at least one cell abnormality in both cytology and FISH was found. In the case of abnormal FISH and normal cytology, a minimum of four cells with a gain of two or more

Sensitivity and specificity of studies comparing FISH and cytology

	FISH			Cytology		
Study ID	*n*	Sens %	Spec %	*n*	Sens %	Spec %
Halling 2000[97]	151	81	96	118	58	98
Junker 2006[98]	121	60	81	109	24	91
May 2007[107]	166	53	74	166	71	84
Meiers 2007[100]	624	93	90	624	73	87
Mian 2003[101]	57	96	45	181	45	94

Pooled analysis of FISH and cytology

	FISH	Cytology
Number of studies	5	5
Sensitivity % (95% CI)	81 (66 to 97)	54 (39 to 80)
Specificity % (95% CI)	82 (68 to 97	92 (84 to 99)
Positive likelihood ratio	4.6 (0.9 to 8.3)	6.7 (0.3 to 13.1)
Negative likelihood ratio	0.23 (0.04 to 0.42)	0.50 (0.22 to 0.77)
DOR (95% CI)	20.1 (<0.1 to 46.0)	13.4 (<0.1 to 31.0)

BIC difference between this and simpler model: 166.3–163.9 = 2.4

SROC plot of FISH and cytology

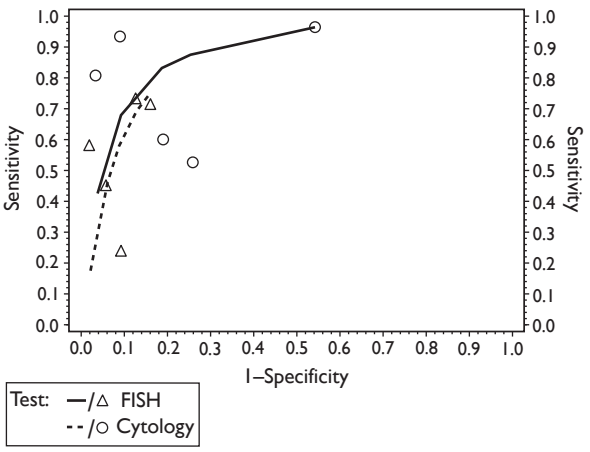


FIGURE 25 *FISH vs cytology – patient-level analysis: sensitivity, specificity, pooled estimates and SROC curve.*

Sensitivity and specificity of studies comparing ImmunoCyt and cytology

	ImmunoCyt			Cytology		
Study ID	*n*	Sens %	Spec %	*n*	Sens %	Spec %
Lodde 2003[109]	225	87	67	225	41	94
Messing 2005[111]	326	81	75	326	23	93
Mian 1999[112]	249	86	79	249	47	98
Mian 2003[101]	181	86	71	181	45	94
Piaton 2003[116]	651	73	82	651	62	85
Schmitz-Drager 2008[118]	280	85	88	280	44	96

Pooled analysis of ImmunoCyt and cytology

	ImmunoCyt	Cytology
Number of studies	6	6
Sensitivity % (95% CI)	82 (76 to 89)	44 (35 to 54)
Specificity % (95% CI)	85 (71 to 85)	94 (91 to 97)
Positive likelihood ratio	3.8 (2.7 to 4.9)	7.2 (4.0 to 10.5)
Negative likelihood ratio	0.22 (0.15 to 0.30)	0.59 (0.50 to 0.69)
DOR (95% CI)	17.0 (9.5 to 24.5)	12.2 (6.1 to 18.3)

BIC difference between this and simpler model: 183.2–197.2 = –14

SROC plot of ImmunoCyt and cytology

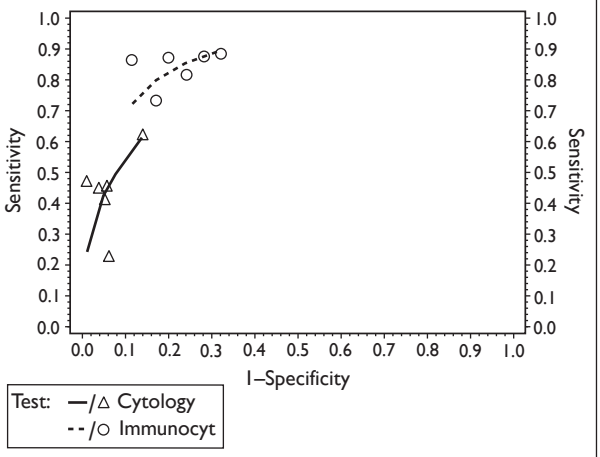


FIGURE 26 *ImmunoCyt vs cytology – patient-level analysis: sensitivity, specificity, pooled estimates and SROC curve.*

chromosomes or 12 or more cells with homozygous loss of the 9p21 locus was required for a positive diagnosis. The study by Moonen and colleagues[102] involving 105 patients reported a specimen-based analysis ($n = 103$), with sensitivity and specificity of 39% and 90%, respectively, for FISH, 41% and 90% for cytology and 53% and 79% for the tests used in combination.

FISH and cystoscopy

In a patient-based analysis, Kipp and colleagues[99] in a study involving 124 patients reported the sensitivity and specificity of FISH and cystoscopy (not stated whether flexible or rigid) used in combination. They reported sensitivity and specificity of 62% and 87%, respectively, for FISH, 67% and 85% for cystoscopy and 87% and 79% for the tests used in combination. A definition of what constituted a positive test result for the combined tests was not given.

ImmunoCyt and cytology

Eight studies reported sensitivity and specificity for the tests of ImmunoCyt and cytology used in combination. Six studies[101,109,111,112,116,119] involving 1997 patients reported patient-based detection and two studies[110,113] involving 1137 patients reported specimen-based detection (2220 specimens).

The median (range) sensitivities and specificities of ImmunoCyt, cytology, and ImmunoCyt and cytology across the studies reporting patient- and specimen-based detection are shown in *Table 21*. The sensitivity of the tests in combination for both patient- and specimen-based detection (87% and 88% respectively) was slightly higher than that of ImmunoCyt alone (84% and 78%), whereas the specificity (68% and 76%) was much lower than that of cytology alone (94% and 97%).

ImmunoCyt and cystoscopy

In a patient-based analysis ($n = 280$), Schmitz-Drager and colleagues[118] reported sensitivity and specificity of 85% and 88%, respectively, for ImmunoCyt, 84% and 98% for cystoscopy (not stated whether flexible or rigid) and 100% and 87% for the tests used in combination.

NMP22 and cytology

In a patient-based analysis, two studies[131,164] involving 800 patients reported the sensitivity and specificity of NMP22 and cytology used in combination. The study by Kumar and colleagues[131] involving 131 patients used the NMP22 BladderChek point of care test with a cut-off of 10 U/ml. They reported sensitivity and specificity of 85% and 78%, respectively, for NMP22, 41%

Sensitivity and specificity of studies comparing NMP22 and cytology

	NMP22			Cytology		
Study ID	*n*	Sens %	Spec %	*n*	Sens %	Spec %
Chahal 2001b[45]	211	33	92	211	24	97
Del Nero 1999[123]	105	83	87	105	47	83
Grossman 2005[126]	1331	56	86	1287	16	99
Grossman 2006[127]	668	50	87	650	12	97
Gutierrez Banos 2001[128]	150	76	91	150	70	93
Kumar 2006[131]	131	85	78	131	41	96
Lahme 2001[132]	109	63	61	109	45	93
Ponsky 2001[139]	608	88	84	608	62	85
Poulakis 2001[140]	739	79	70	739	62	96
Ramakumar 1999[159]	196	53	60	112	44	95
Saad 2002[141]	120	81	87	120	48	87
Sharma 1999[148]	278	56	93	278	29	100
Talwar 2007[150]	196	67	81	196	21	99
Tritschler 2007[80]	100	65	40	85	44	78
Wiener 1998[151]	291	48	69	291	59	100
Zippe 1999[153]	330	100	86	330	33	100

Pooled analysis of NMP22 and cytology

	NMP22	Cytology
Number of studies	18	18
Sensitivity % (95% CI)	70 (59 to 80)	40 (31 to 49)
Specificity % (95% CI)	81 (74 to 88)	97 (95 to 99)
Positive likelihood ratio	3.6 (2.3 to 5.0)	12.2 (4.3 to 20.2)
Negative likelihood ratio	0.38 (0.25 to 0.50)	0.62 (0.53 to 0.71)
DOR (95% CI)	9.6 (3.8 to 15.4)	19.8 (5.9 to 33.7)

BIC difference between this and simpler model: 511.5–526.7 = –15.2

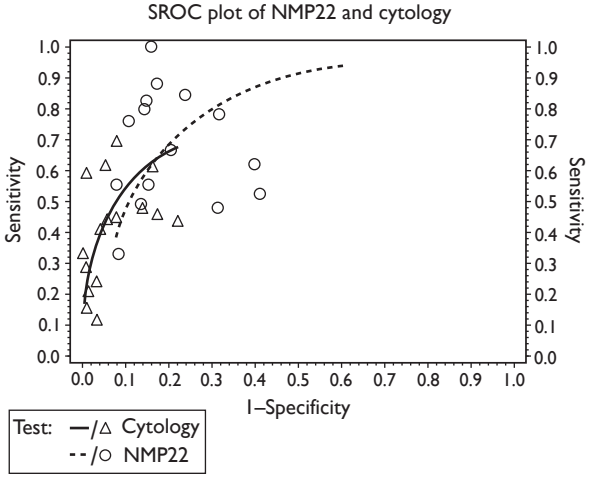


FIGURE 27 *NMP22 vs cytology – patient-level analysis: sensitivity, specificity, pooled estimates and SROC curve.*

TABLE 21 *Median (range) sensitivity and specificity across studies reporting ImmunoCyt plus cytology*

Test	Sensitivity (%), median (range)	Specificity (%), median (range)
Patient-based detection (n = 6 studies)		
ImmunoCyt	84 (73 to 87)	73 (62 to 82)
Cytology	43 (23 to 62)	94 (85 to 98)
ImmunoCyt + cytology	87 (81 to 90)	68 (61 to 79)[a]
Specimen-based detection (n = 2 studies)		
ImmunoCyt	78 (71 to 85)	76 (73 to 78)
Cytology	44 (39 to 49)	97 (95 to 99)
ImmunoCyt + cytology	88 (86 to 89)	76 (73 to 78)

a The median (range) specificity for ImmunoCyt + cytology is based on five studies as Piaton and colleagues[116] did not report specificity for the tests in combination.

and 96% for cytology and 91% sensitivity for the tests used in combination (specificity was not reported).[131] The study by Takeuchi and colleagues[164] involving 669 patients used a cut-off of 12 U/ml for NMP22. They reported sensitivity and specificity of 58% and 80%, respectively, for NMP22, 44% and 100% for cytology and 60% sensitivity for the tests used in combination (specificity was not reported). In both studies the sensitivity for the tests in combination was slightly higher than that for NMP22 alone, although there was a wide difference in the sensitivity values for NMP22 reported by the two studies.

NMP22 and cystoscopy

In a patient-based analysis ($n = 1999$), two studies by Grossman and colleagues[126,127] reported the sensitivity and specificity of the NMP22 BladderChek point of care test and cystoscopy (not stated whether flexible or rigid) used in combination. Both studies used a cut-off of 10 U/ml to define a positive NMP22 test result. In the first study[126] sensitivity was 56% and specificity 86% for NMP22 (1331 patients), whereas in 79 patients diagnosed with bladder cancer the sensitivity of cystoscopy and the tests used in combination was 89% and 94% respectively. In the second study[127] sensitivity was 50% and specificity 87% for NMP22 (668 patients), whereas in 103 patients diagnosed with bladder cancer the sensitivity of cystoscopy and the tests used in combination was 91% and 99% respectively.

Cytology and cystoscopy

In a patient-based analysis ($n = 280$), Schmitz-Drager and colleagues[118] reported sensitivity and specificity of 44% and 96%, respectively, for cytology, 84% and 98% for cystoscopy (not stated whether flexible or rigid) and 88% and 95% for the tests used in combination. In 103 patients diagnosed with bladder cancer Grossman and colleagues[127] reported sensitivity of 12% for cytology, 91% for cystoscopy and 94% for the tests used in combination.

Summary

A total of 71 studies, published in 83 reports, met the inclusion criteria for studies reporting the test performance of biomarkers (FISH, ImmunoCyt, NMP22) and cytology in detecting bladder cancer. In total, 14 studies enrolling 3321 participants reported on FISH, 10 studies enrolling 4199 participants reported on ImmunoCyt, 41 studies enrolling 13,885 participants reported on NMP22 and 56 studies enrolling 22,260 participants reported on cytology. The vast majority of the studies were diagnostic cross-sectional studies ($n = 59$, 83%), with the remainder being case–control studies ($n = 12$, 17%).

Pooled estimates with 95% CIs for sensitivity, specificity, positive and negative likelihood ratios and DORs for each of the tests were undertaken for patient-level analysis. *Table 22* shows the pooled estimates for sensitivity, specificity and DOR for each of the tests. Sensitivity was highest for ImmunoCyt at 84% (95% CI 77% to 91%) and lowest for cytology at 44% (95% CI 38% to 51%). ImmunoCyt (84%, 95% CI 77% to 91%) had higher sensitivity than NMP22 (68%, 95% CI 62% to 74%), with the lack of overlap of the CIs supporting evidence of a difference in sensitivity between the tests in favour of ImmunoCyt. FISH (76%, 95% CI 65% to 84%), ImmunoCyt (84%, 95% CI 77% to 91%) and NMP22 (68%, 95% CI 62% to 74%) all had higher sensitivity than cytology (44%, 95% CI 38% to 51%), and again the lack of overlap between the biomarker and cytology CIs supporting evidence of a difference in sensitivity in favour of the biomarkers over cytology.

Although sensitivity was highest for ImmunoCyt and lowest for cytology, this situation was reversed for specificity, which was highest for cytology at 96% (95% CI 94% to 98%) and lowest for ImmunoCyt at 75% (95% CI 68% to 83%). Cytology (96%, 95% CI 94% to 98%) had higher specificity than FISH (85%, 95% CI 78% to 92%), ImmunoCyt (75%, 95% CI 68% to 83%) or NMP22 (79%, 95% CI 74% to 84%), with the lack of overlap between the cytology and biomarker CIs supporting evidence of a difference in specificity in favour of cytology over the biomarkers.

DORs (95% CI) ranged from 8 (5 to 11) to 19 (6 to 26), with higher DORs indicating a better ability of the test to differentiate between those with bladder cancer and those without. Based on the DOR values, FISH and cytology performed similarly well [18 (3 to 32) and 19 (11 to 27) respectively], ImmunoCyt slightly less so [16 (6 to 26)] and NMP22 relatively poorly [8 (5 to 11)]. However, as the DOR CIs for each of the tests all overlapped these results should be interpreted with caution.

Across studies the median (range) PPV was highest for cytology at 80% (27% to 100%) and FISH at 78% (27% to 99%), followed by ImmunoCyt at

TABLE 22 *Summary of pooled estimate results for biomarkers and cytology for patient-based detection of bladder cancer*

Test	Number of studies	Number analysed	Common cut-off	Sensitivity (%) (95% CI)	Specificity (%) 95% CI)	DOR (95% CI)
FISH	12	2535	Gain of more than one or more than two chromosomes[a]	76 (65 to 84)	85 (78 to 92)	18 (3 to 32)
ImmunoCyt	8	2896	At least one green or one red fluorescent cell	84 (77 to 91)	75 (68 to 83)	16 (6 to 26)
NMP22	28	10,119	≥ 10 U/ml	68 (62 to 74)	79 (74 to 84)	8 (5 to 11)
Cytology	36	14,260	Cytologist subjective judgement	44 (38 to 51)	96 (94 to 98)	19 (11 to 27)

a FISH, common cut-off – see Appendix 16 for a detailed description of the cut-offs used by each of the FISH studies.

TABLE 23 *Summary of median (range) sensitivity of tests across studies for patient-level detection of stage/grade of bladder cancer*

Test	Number of studies (patients)[a]	Less aggressive/lower risk, median (range) sensitivity across studies	Number of studies (patients)[a]	More aggressive/higher risk including CIS, median (range) sensitivity across studies	Number of studies (patients)[a]	CIS, median (range) sensitivity across studies
FISH	10 (2164)	65 (32 to 100)	10 (2164)	95 (50 to 100)	8 (1067)	100 (50 to 100)
ImmunoCyt	6 (2502)	81 (55 to 90)	6 (2502)	90 (67 to 100)	6 (2502)	100 (67 to 100)
NMP22	18 (4685)	50 (0 to 86)	19 (7556)	83 (0 to 100)	11 (3453)	83 (0 to 100)
Cytology	29 (12,566)	27 (0 to 93)	29 (12,566)	69 (0 to 100)	17 (6870)	78 (0 to 100)

a The number of patients refers to the number included in the overall analysis by the studies.

TABLE 24 *Pooled estimates for sensitivity and specificity for tests being directly compared within studies*

Comparison	Number of studies (patients)[a]	Test	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	Test	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
FISH vs cytology	5 (1119; 1198)	FISH	81 (66 to 79)	82 (68 to 97)	Cytology	54 (39 to 80)	92 (84 to 99)
ImmunoCyt vs cytology	6 (1912; 1912)	ImmunoCyt	82 (76 to 89)	85 (71 to 85)	Cytology	44 (35 to 54)	94 (91 to 97)
NMP22 vs cytology	16 (5563; 5402)	NMP22	70 (59 to 80)	81 (74 to 88)	Cytology	40 (31 to 49)	97 (95 to 99)

a The numbers in parentheses separated by a semicolon represent the number of patients included in the analysis for each of the tests being compared, e.g. (1119; 1198), 1119 patients were included in the analysis for FISH, 1198 were included in the analysis for cytology.

54% (26% to 70%) and NMP22 at 52% (13% to 94%). The median (range) NPV was highest for ImmunoCyt at 93% (86% to 100%), followed by FISH at 88% (36% to 97%), NMP22 at 82% (44% to 100%) and cytology at 80% (38% to 100%).

Table 23 summarises the sensitivity of the tests in detecting stage/grade of tumour. ImmunoCyt had the highest median sensitivity across studies (81%) for detection of less aggressive/lower risk tumours whereas FISH had the highest median sensitivity across studies (95%) for detection of more aggressive/higher risk tumours. For detection of CIS the median sensitivity across studies for both FISH and ImmunoCyt was 100%. Cytology had the lowest sensitivity across studies for detecting less aggressive/lower risk tumours (27%), more aggressive/higher risk tumours (69%) and also CIS (78%). The median sensitivity across studies for each test was consistently higher for the detection of more aggressive/higher risk tumours than it was for the detection of less aggressive, lower risk tumours.

Some of the studies included in the pooled estimates for the individual tests also directly compared tests, e.g. FISH versus cytology. *Table 24* shows the pooled estimates for sensitivity and specificity for those tests being directly compared in studies and reporting a patient-level analysis. In each set of comparisons cytology had lower sensitivity but higher specificity than the biomarker with which it was being compared. ImmunoCyt had a statistically significant higher sensitivity (82%, 95% CI 76% to 89%) than that of cytology (44%, 95% CI 35% to 54%), whereas cytology had a statistically significant higher specificity (94%, 95% CI 91% to 97%) than that of ImmunoCyt (85%, 95% CI 71% to 85%). Similarly, NMP22 had a statistically significant higher sensitivity (70%, 95% CI 59% to 80%) than that of cytology (40%, 95% CI 31% to 49%), whereas cytology had a statistically significant higher specificity (97%, 95% CI 95% to 99%) than that of NMP22 (81%, 95% CI 74% to 88%).

In studies reporting the sensitivity and specificity of tests used in combination, sensitivity was generally higher but specificity lower for the combined tests compared with the higher value of the individual tests. Most combinations of tests were reported by only one or two studies, apart from the combination of ImmunoCyt and cytology, which was reported by eight studies.

In studies specifically reporting unevaluable tests, rates were 6.1% (65/1059, five studies) for FISH, 5% (279/5292, 10 studies) for ImmunoCyt and 2% (54/2566, six studies) for cytology. None of the NMP22 studies specifically reported unevaluable tests.

Chapter 6
Assessment of cost-effectiveness

Using the care pathways described in Chapter 2, an economic model was developed to estimate the cost-effectiveness of several management strategies for the initial diagnosis and follow-up of bladder cancer. This chapter describes how the data to estimate cost-effectiveness were derived and how these data were used in the economic model. The perspective adopted for the cost-effectiveness analysis was that of the NHS.

Economic model for initial diagnosis and follow-up of bladder cancer

Model structure

Based on the care pathway described in Chapter 2, the model structure was developed following consultation with clinicians and taking into consideration the approaches adopted by the existing economic evaluations[153,158,175–180] identified from the literature. The approach attempts to model patients passing through the whole sequence of care and determine the overall impact on costs and the clinical consequences. *Figure 28* shows a simplified model structure for the primary diagnosis and follow-up management of bladder cancer. Within this model people with suspected bladder cancer will receive tests and investigations to diagnose bladder cancer. Subsequent management will depend upon the findings of these tests and the nature of any bladder cancer detected. The absorbing state in the model is death from either bladder cancer or other causes.

The cost-effectiveness analysis was performed in two parts. The first part considered the diagnostic tests and consisted of a decision tree model element and the second part considered the follow-up of patients after diagnosis using a Markov model.

Decision tree model

The decision tree, constructed using TreeAge Software, displays the temporal and logical sequence of a clinical decision problem. Although this decision tree does not explicitly specify the time over which diagnosis takes as part of the model structure, going from initial presentation to final diagnosis may take weeks or even months.

As described in Chapters 1 and 2 there does not appear to be a single standard strategy in the UK. Flexible cystoscopy alone or combined with cytology followed by white light rigid cystoscopy are the main diagnostic tests performed. Cytology or biomarkers followed by WLC or PDD for the initial diagnosis of bladder cancer are less commonly used in the UK, but the use of cytology or biomarkers followed by WLC or PDD may be feasible. The aim of this model is to reflect the costs and consequences of these tests compared with one 'standard' strategy, 'flexible cystoscopy followed by WLC'.

Interventions of diagnosis and follow-up

The interventions included in the model were flexible cystoscopy, cytology, three types of biomarkers (NMP22, FISH, ImmunoCyt), WLC and PDD. Although flexible cystoscopy combined with cytology and a biomarker as the first suite of tests may be an option for the primary diagnosis of bladder cancer, there is little information about the results of these tests used in combination, as reported in Chapters 4 and 5. *Table 25* summarises the potential strategies that are considered in the model. These options were based on advice from clinical experts about strategies that are currently in use or those that can potentially be used.

Strategies 1–6 consider the use of a single test for initial diagnosis. These options might represent situations that clinical practice might move towards although they may not be currently used in practice. Strategies 7–16 represent alternative situations in which two or more tests are used in the initial phase of diagnosis. Across all strategies the choice of second level diagnostic test varies between WLC and PDD. The strategies also differ in terms of the tests used for follow-up surveillance. In our study we have assumed that a single test is used for initial surveillance with any positives confirmed by WLC.

It should be noted that none of our strategies explicitly considers the use of ultrasound. Ultrasound might be considered part of all of the

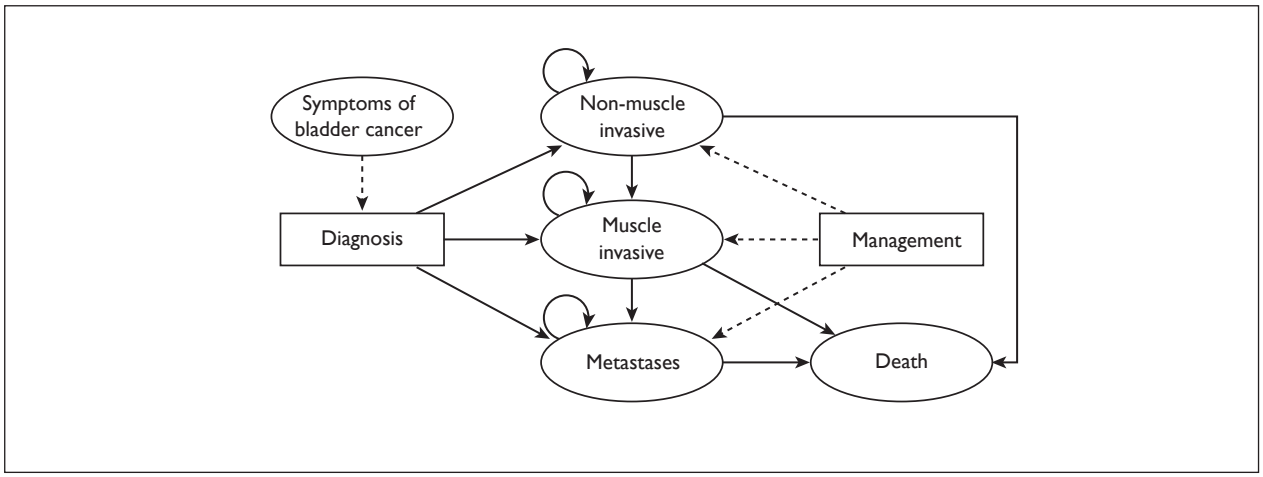


FIGURE 28 *Model structure.*

strategies when the patient population is restricted to haematuria. In such a situation this would have no impact on incremental costs (as all patients under all strategies incur the test) although it may alter the likelihood of subsequent testing.

Figure 29 illustrates a simplified model structure for the decision tree model for diagnosis of bladder cancer when a single test is used as part of the initial diagnosis (i.e. strategies 1–6). *Figure 30* illustrates the model structure for the situation in which two tests are used as part of the initial testing

TABLE 25 *Diagnostic strategies*

	Primary diagnosis					Follow-up surveillance				
	Initial test			Second test		Initial test			Second test	
Strategy	CSC	CTL	BM	WLC	PDD	CSC	CTL	BM	WLC	PDD
1	✓			✓		✓			✓	
2	✓				✓	✓			✓	
3		✓		✓			✓		✓	
4		✓			✓		✓		✓	
5			✓	✓				✓	✓	
6			✓		✓			✓	✓	
7	✓	✓		✓		✓			✓	
8	✓	✓			✓	✓			✓	
9	✓	✓		✓			✓		✓	
10	✓	✓			✓		✓		✓	
11	✓		✓	✓		✓			✓	
12	✓		✓		✓	✓			✓	
13	✓		✓	✓				✓	✓	
14	✓		✓		✓			✓	✓	
15	✓	✓	✓	✓		✓				
16	✓	✓	✓		✓	✓				

BM, biomarker; CSC, flexible cystoscopy; CTL, cytology.

(strategies 7–14). When three tests are used in combination (strategies 15 and 16) a similar model structure to that in *Figure 30* is developed (figure not shown).

In *Figure 29* a patient may, for example, arrive in a hospital with symptoms of haematuria. Taking the patient's history and symptoms into account, the physician may perform an invasive test (flexible cystoscopy) or a non-invasive test (e.g. cytology and biomarkers). The results of these tests could be either negative or positive. The negative test result could be either a false or a true negative. If the first single test in *Figure 29* is negative, it is assumed that there appears to be no evidence of bladder cancer and the patient is deemed not to have bladder cancer. If the result of the first test is positive (which might be either a true or a false positive) the patient will be further investigated using the second test, which will be either PDD or WLC. As with the first test there are four potential test results: true negative, false negative, true positive and false positive. As there is a risk of death associated with the use of general anaesthesia required for rigid cystoscopy, there is a chance that the patient may die whilst undergoing or as a result of undergoing the second test.

For the strategies in which two tests form part of the initial diagnosis (strategies 7–14) the first test that a patient receives will be flexible cystoscopy (*Figure 30*). If the result is negative (it might be either a true or a false negative) it is assumed that the patient will be further tested using cytology or a biomarker. If the result of cytology or a biomarker is negative the patient will be deemed not to have bladder cancer. If the result of the first test is positive (which might be either a true or a false positive) the patient will be further investigated using the second test, which will be either PDD or WLC. Patients who test positive with cytology or a biomarker will be handled in a similar manner. As with the first test there are four potential test results: true negative, false negative, true positive and false positive. As there is a risk of death associated with the use of general anaesthesia required for rigid cystoscopy, there is a chance that the patient may die whilst undergoing or as a result of undergoing the second test.

Strictly speaking, *Figure 30* describes the situation in which only those negative on flexible cystoscopy (CSC) receive either cytology (CTL) or a biomarker (BM) test. In practice, because of the way that services might be organised, the different tests may be performed during the same visit, i.e. those who are positive with flexible cystoscopy may also receive either cytology or a biomarker test. The implications of this are that, given the cost data available for this study, the average cost per patient in actual practice would be increased compared with the practice described in *Figure 29* (there will be no impact on effectiveness as all positives go through to the next level of testing). It should be noted that the practice of conducting additional tests at the same time as flexible cystoscopy is likely to be adopted because it is logistically easier to organise, i.e. the real opportunity costs of current practice are less than would be predicted from the unit costs available for this study. For this reason we have assumed that a more realistic estimate of costs will be provided by a model following the structure set out in *Figure 30* but we have provided an additional analysis to illustrate the effect on

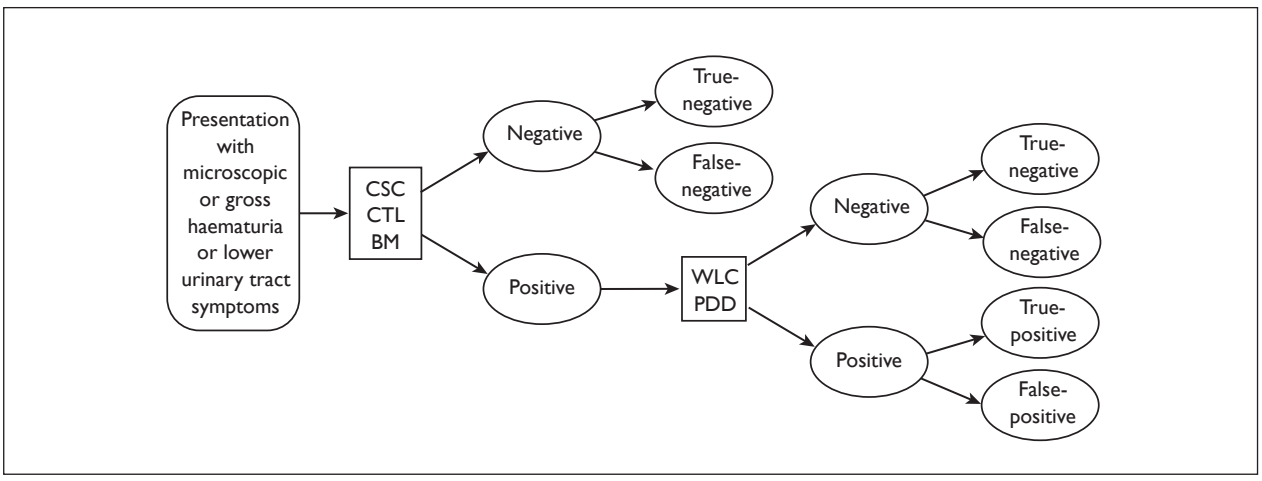


FIGURE 29 *Decision tree model structure for single diagnostic technology as the first test. BM, biomarker; CSC, flexible cystoscopy; CTL, cytology.*

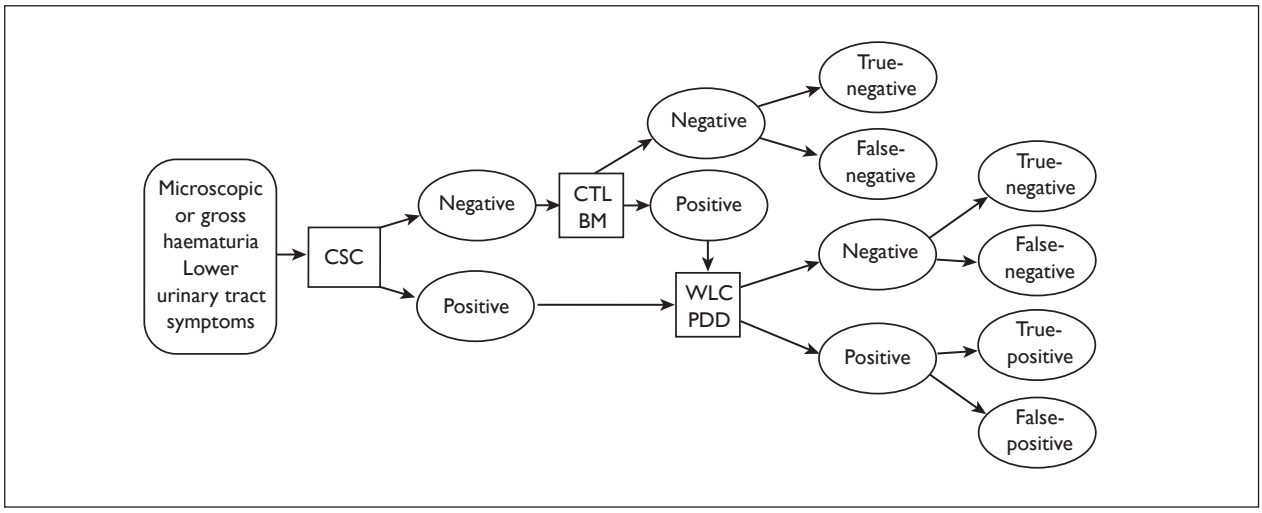


FIGURE 30 *Decision tree model structure for flexible cystoscopy combined with cytology or biomarker as the first test. BM, biomarker; CSC, flexible cystoscopy; CTL, cytology.*

costs when two or more tests are conducted on all patients presenting for initial diagnosis.

Estimation of probabilities required for the decision tree model

The probabilities used to populate the decision model were calculated according to the standard conventions of Bayes' theorem. The essence of the calculations is that, once the sensitivity and specificity of a test are known, along with the a priori probability of disease, the posterior probabilities of disease and absence of disease can be determined. Accordingly, if a patient has an abnormal test result, the probability of disease – the 'true positive rate', also referred to as the 'positive predictive value' (PPV) – is represented as p(BC+|T+), and if the patient has a normal test result, the probability of disease – the 'false-negative rate' – is similarly presented as p(BC+|T–). These are calculated as follows:

$$p(BC+|T+) = p(T+|BC+)\ p(BC+)/(p(T+|BC+)\ p(BC+) + p(T+|BC–)\ p(BC–))$$

$$p(BC+|T–) = p(T–|BC+)\ p(BC+)/(p(T–|BC+)\ p(BC+) + p(T–|BC–)p(BC–))$$

where BC = bladder cancer, T+ = test positive, T– = test negative, p(T+|BC+) = sensitivity, p(BC+) = prior probability of disease (prevalence or incidence), p(T+|BC–) = 1–specificity, p(BC–) = 1–prevalence (or incidence), p(T–|BC+) = 1–sensitivity and p(T–|BC–) = specificity.

When two tests are connected in series, the calculations are the same except that the prior probability of disease (prevalence or incidence) for the second test is the calculated 'true positive rate' of the first test.

To illustrate this in the construction and analysis of the bladder cancer primary diagnosis tree (Appendix 17, *Figure 37*), the strategy 'flexible cystoscopy (CSC) followed by WLC' is considered. The probability of a test positive result following flexible cystoscopy is:

$$pPos\_CSC = (Sens\_CSC*priori) + (1–Spec\_CSC)*(1–priori)$$

where Sens_CSC = sensitivity of flexible cystoscopy, Spec_CSC = specificity of flexible cystoscopy and priori is the prevalence or incidence rate for patients with suspected bladder cancer before the flexible cystoscopy test.

From this, the probability of a:

- negative result for flexible cystoscopy is 1–pPos_CSC
- false negative for flexible cystoscopy is pFN_CSC = (1–Sens_CSC)*priori/((1–Sens_CSC)*priori + Spec_CSC*(1–priori))
- true negative is 1–pFN_CSC
- positive result for WLC following a positive flexible cystoscopy result is pPos_CSC_WLC = (Sens_WLC*pPPV_CSC) + (1–Spec_WLC)*(1–pPPV_CSC), where Sens_WLC = sensitivity of WLC, Spec_WLC = specificity of WLC and pPPV_CSC = positive predictive value of flexible cystoscopy = (Sens_CSC*priori)/pPos_CSC

- true positive for WLC following a positive flexible cystoscopy result is pTP_CSC_WLC = (Sens_WLC*pPPV_CSC)/pPos_CSC_WLC
- false positive for WLC following flexible cystoscopy is 1 – pTP_CSC_WLC
- false negative for WLC following flexible cystoscopy is pFN_CSC_WLC = [Spec_WLC*(1 – pPPV_CSC)]/(1 – pPos_CSC_WLC)
- true negative is 1 – pFN_CSC_WLC
- the NPV after a negative result for CSC is pNPV_CSC = [Spec_CSC*(1 – priori)]/(1 – pPos_CSC).

The probabilities for the remaining strategies in the tree are calculated in a similar manner.

It is important to quantify the false-positive and false-negative values for each strategy, as these provide valuable information to the clinician in addition to the cost and number of true cases detected. The implications of false-positive results within the model are the cost of testing and treating patients and the associated morbidity and discomfort of further investigation and treatment. False-positive results may also induce adverse psychological responses in patients in terms of the needless distress that a positive result might cause and by leading to questioning of future results that are negative. In the case of false-negative results the patient may have a serious or life-threatening condition that is missed, resulting in a potentially poorer prognosis following late detection, such as CIS missed by WLC, as well as psychological distress from false reassurance. In the decision model patients with a false-negative evaluation following the first (flexible cystoscopy, cytology or biomarkers) or second (PDD/WLC) test may be subsequently correctly diagnosed as their continuing symptoms worsen. In the case of true negative results, it is assumed that the patients will not need further investigation.

Management of bladder cancer

Patients with true-positive results (confirmed bladder cancer) are classified into two types: non-muscle-invasive and muscle-invasive disease (*Figure 31*). Those with muscle-invasive tumours will not be discharged but are managed usually with either surgery (radical cystectomy) or radical radiotherapy with or without chemotherapy and routine checking thereafter and treatment. All patients with non-muscle-invasive tumours will undergo a follow-up test at 3 months after the primary diagnosis because of the high chance of recurrence and a chance of progression. For each risk group there are similar outcomes considered in initial diagnosis: true positive, false positive, true negative and false negative (Appendix 17, *Figure 37*).

It is assumed that the first test used in the follow-up of patients will be the same as the test used for primary diagnosis and the second test will be WLC. To illustrate the construction and analysis of each risk group, strategy 'flexible cystoscopy (CSC) followed by WLC in primary diagnosis and follow-up by CSC' is considered. In the case of each group, the probability of:

- true positive is pTP_Riskgroup = Sens_CSC* Recurrence rate of risk group at 3 months
- true negative is pTN_Riskgroup = Spec_CSC*(1 – Recurrence rate of risk group at 3 months)

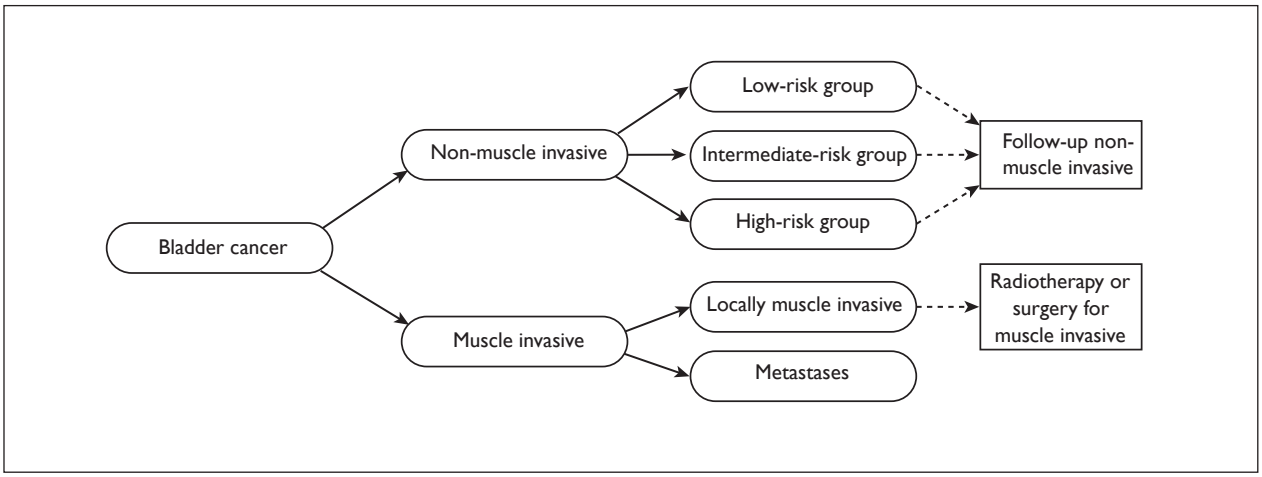


FIGURE 31 *Classification of bladder cancer.*

- false negative is pTP_Riskgroup = (1 – Sens_CSC)* Recurrence rate of risk group at 3 months
- false positive is pFN_Riskgroup = (1 – Spec_CSC)*(1 – Recurrence rate of risk group at 3 months).

As described in the care pathway reported in Chapter 2, bladder cancer treatment options will depend on classification of disease (*Table 26*).

To determine the efficiency of each strategy the terminal nodes (Appendix 17, *Figure 37*) of the tree were assigned a value of either '1' or '0'. This enabled the following solutions to be calculated: mean cost per case detected – achieved by assigning the value '0' to dead terminal node and the value '1' to the others.

Markov model

At the end of each branch of the decision tree the patients will enter one of the predefined states of the Markov model (Appendix 17, *Figures 36* and *38*). The health states within the Markov model are considered to reflect possible paths of recurrence and progression of bladder cancer based on information of the primary diagnosis and following the follow-up visit carried out 3 months after initial treatment of the bladder cancer.

As indicated in the care pathways described in Chapter 2, there are two elements in the Markov models: non-muscle invasive (TaT1) and muscle invasive (T2 or > T2). In the case of muscle-invasive disease, patients have a serious and life-threatening condition and high mortality and morbidity rates; they are thus not discharged from care but receive regular checks with CT or MRI and they receive either radiotherapy or chemotherapy treatment. Alternatively, the patient may receive palliative care after the initial major treatment if there is recurrence or progression of the tumour (*Table 26*).

Although a non-muscle-invasive tumour is not as likely to result in a serious life-threatening condition, it has high recurrence rates. As discussed in Chapter 1, the recurrence rate of non-muscle-invasive disease depends upon a number of prognostic risk factors: stage, grade, size of the tumour and number of previous recurrences. Prognostic risk factors are essential to predict future courses of the tumour in terms of recurrence and progression. Prognostic factors for recurrence and progression have been investigated by several clinical groups. The most frequent factor related to recurrence, in almost all series, has been multiplicity (Appendix 18, *Table 55*). Intravesical instillations have been defined as a protective factor. Kurth and colleagues[181] reported factors affecting recurrence and progression from the data of two trials involving 576 patients. The trials considered factors such as tumour size, grade, and recurrence rate per year and concluded that the most significant prognostic factors for recurrence were multiplicity, recurrence at 3 months, size of the tumour and site of involvement (Appendix 18, *Table 55*).[20,181–195] Parmar and colleagues[191] considered multiplicity and recurrence at 3 months as the main prognostic factors in recurrence. These two parameters provided the most predictive information related to recurrence, and they were independent of the stage (*Table 27*). However, the Medical Research Council classification in Parmar's study is only used to predict the risk of recurrence, not progression.[191]

Grade, associated CIS and stage are factors globally related to progression in the series that have investigated prognostic factors (Appendix

TABLE 26 *Management of bladder cancer*

Type of bladder cancer		Initial treatment
Non-muscle invasive	Low risk	TURBT and one dose of mitomycin
	Intermediate risk	TURBT and one dose of mitomycin
	High risk	TURBT, one dose of mitomycin and BCG induction
Muscle invasive		Three cycles of chemotherapy and cystectomy or three cycles of chemotherapy and radiotherapy or palliative treatment

18, *Table 56*).[20,181,183–185,187,192,196] Millán-Rodriguez and colleagues[187] developed three risk groups based on 1529 patients with primary non-muscle-invasive bladder cancer. The trial used recurrence prognostic factors such as multiplicity, tumour size and CIS and progression prognostic factors such as grade, CIS and multiplicity.

Although different studies have analysed the factors involved in recurrence and progression, there is no universally agreed prognostic risk group classification (*Table 27*). It is not possible to use the risk stratification illustrated in Kurth's study[181] in the model because of the complexity of data requirements for recurrence and progression. The risk groups and their proportions will be defined later in this chapter depending on the two studies that have the best data available for recurrence and progression.

Markov model structure for non-muscle-invasive disease

At the end of each risk group branch of non-muscle-invasive disease in the decision tree (Appendix 17, *Figure 36*) the patient will enter one of the following states of the Markov model shown in *Figure 32*: (1) no tumour recurrence; (2) recurrence; (3) progression to muscle-invasive disease; and (4) death. There are two diagnostic results of non-tumour recurrence, i.e. true negative and false negative, as well as true positive and false positive for tumour recurrence.

The patients with a false-negative result in the model will be followed using the follow-up strategy of non-tumour recurrence. The cycle length considered is 1 year, although the risk groups in the care pathway will be followed at different time periods: 12 months for low risk, 6 months for intermediate risk and 3 months for high risk. The absorbing state is 'death', which can be reached from any of the other states.

Markov model for local muscle-invasive disease

At the end of each risk group branch of local muscle-invasive disease in the decision tree (Appendix 17, *Figure 38*) the patient will enter

TABLE 27 *Studies of risk group classification*

Study		Risk factors	Proportion (%)
Millán-Rodriguez 2000[187]	Low risk	TaG1, single T1G1	11.5
	Intermediate risk	TaG2, multi T1G1	44.6
	High risk	Multi T1G2	43.9
		TaG3, T1G3	
		CIS	
Oosterlinck 2001[190]	Low risk	Single TaG1 and < 3 cm diameter	NA
	Intermediate risk	TaT1 excluding low and high risks	NA
	High risk	T1G3, CIS, multifocal or highly recurrent	NA
Parmar 1989[191]	Low risk	Single tumour and no recurrence at first follow-up	60
	Intermediate risk	Single tumour and no recurrence at first follow-up or multiple tumour no recurrence at first follow-up	30
	High risk	Multiple or highly recurrent	10
Kurth 1995[181]	Low risk	G1 and no recurrence in 2 years	52.5
		G1, size (< 1.5 cm) and recurrence (< 3 cm) in 2 years	
		G2, small size (< 1.5 cm) and no recurrence in 2 years	
	Intermediate risk	The others excluding low and high risks	40.7
	High risk	G1, great size (> 3 cm) and > 3 recurrences in 2 years	6.7
		G2, great size (> 3 cm) and recurrence in 2 years	
		G3	

NA, no details are available.

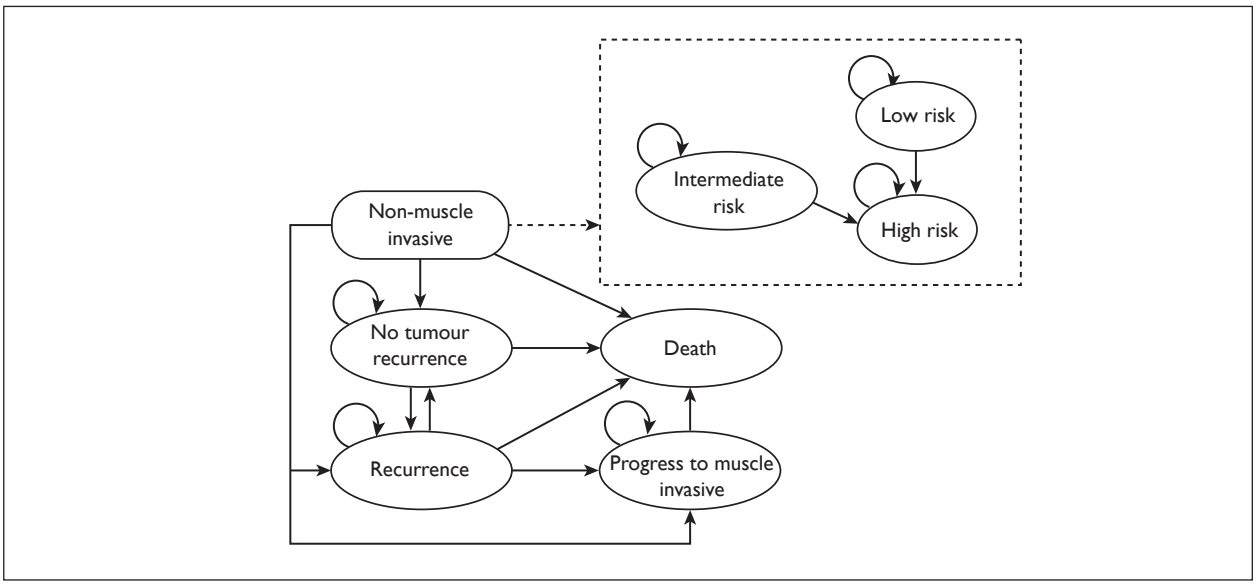


FIGURE 32 *Markov model structure for non-muscle-invasive tumour.*

one of the following states of the Markov model shown in *Figure 33*: (1) no tumour; (2) recurrence; (3) progression to metastases; and (4) death. Cycle length will be the same as that of non-muscle-invasive disease.

Estimation of parameters used in the model

Parameters used in the decision tree and Markov models were calculated within the model or estimated from the systematic reviews of diagnostic performance reported in Chapters 4 and 5 and the epidemiology of bladder cancer reported in Chapter 1, as well as other relevant cost-effectiveness data identified from the literature.

The details of the data for the probabilities, costs and utilities used in the models are described below.

Probabilities

Sensitivity and specificity of diagnostic test

The data on the sensitivity and specificity of each diagnostic test were taken from the systematic review and are summarised in *Table 28*. For flexible cystoscopy assessment there were no data available from the systematic review. It is therefore assumed that the accuracy of flexible cystoscopy used in the models is the same as that of white light rigid cystoscopy. This assumption is relaxed in the sensitivity analysis in which the performance of

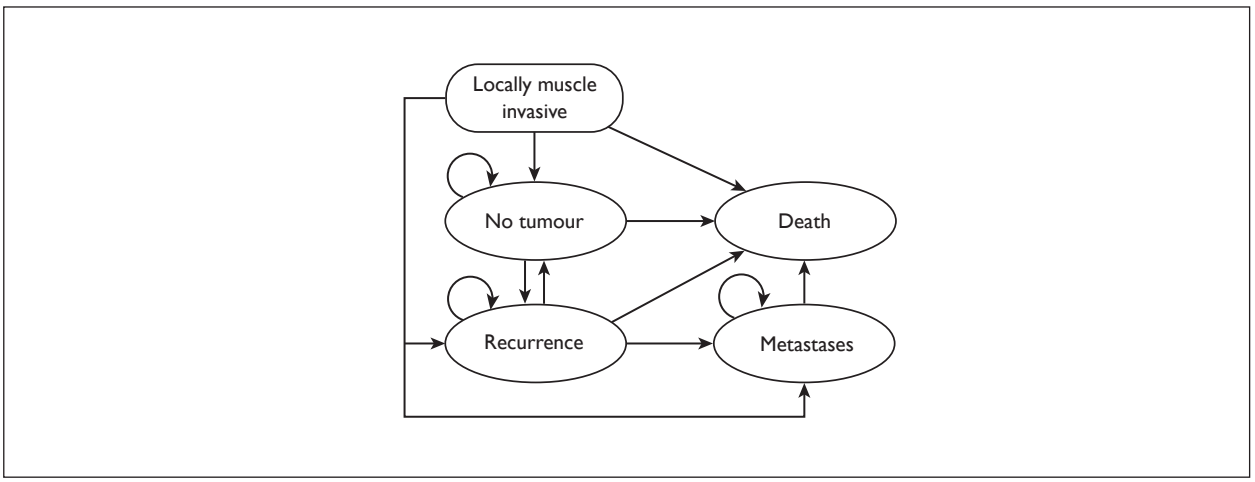


FIGURE 33 *Markov model for local muscle-invasive follow-up.*

TABLE 28 *Data on diagnostic performance*

Diagnosis	Sensitivity	95% CI	Specificity	95% CI	Source
CSC	0.71	0.49 to 0.93	0.72	0.47 to 0.96	Systematic review based on WLC
CTL	0.44	0.38 to 0.51	0.96	0.94 to 0.98	Systematic review
NMP22	0.68	0.62 to 0.74	0.79	0.74 to 0.84	Systematic review
ImmunoCyt	0.84	0.79 to 0.91	0.75	0.68 to 0.83	Systematic review
FISH	0.76	0.65 to 0.84	0.85	0.78 to 0.92	Systematic review
PDD	0.92	0.8 to 1.0	0.57	0.36 to 0.79	Systematic review
WLC	0.71	0.49 to 0.93	0.72	0.47 to 0.96	Systematic review

CSC, flexible cystoscopy; CTL, cytology.

flexible cystoscopy is increased by 5%, 10% and an extreme 20% compared with white light rigid cystoscopy.

Prevalence rate

The prevalence rate was not derived from existing data in the literature as the prevalence of bladder cancer varies considerably among subgroups with different symptoms, from 1% to 20% (for men over 50 years of age).[179] In the model base-case analysis it was assumed that the prevalence rate is 5% and in a sensitivity analysis a range of prevalence rates was considered to identify those prevalence rates for which different diagnostic strategies may be considered worthwhile. This approach of repeating the analysis for different prevalence rates was felt to be more informative than defining prevalence using a wide uniform (i.e. uninformative) distribution.

Proportions of types and their subgroups for bladder cancer

The proportions of the two main types of bladder cancer were assessed based on the literature and clinical opinions detailed in Chapter 1. With reference to the available information presented in the previous section and in *Table 27*, as well as discussions with the clinical members of the research team, prognostic risk groups in non-muscle-invasive disease within this model have been categorised by using a combination of Millán-Rodriguez and colleagues'[187] classification at initial diagnosis and Parmar and colleagues'[191] classifications at 3 months' follow-up, i.e. low risk, intermediate risk and high risk. These classifications are shown in *Table 29*, which also provides details on the proportions of patients in each risk group of non-muscle-invasive bladder cancer.

Table 30 summarises the values of these proportions used in the decision tree and Markov models.

Recurrence, progression and mortality of non-muscle-invasive disease

Table 31 shows the probabilities of recurrence, progression and mortality for the three risk groups of non-muscle-invasive disease used in the model for a 20-year time horizon. As referred to above, the first 5-year probabilities of recurrence, progression and mortality caused by cancer of the three risk groups used in the model were calculated from the study by Millán-Rodriguez and colleagues.[187] The following 15-year probabilities of recurrence, progression and mortality caused by cancer in these groups were estimated by using mean values of relevant data of the last 3 years in the 5-year data available in the study by Millán-Rodriguez and colleagues.[187] This was a retrospective cohort study of 1529 patients with primary non-muscle-invasive bladder cancer in Spain in the years 1968–96. Of the patients treated with TURBT and random biopsy, half were treated using additional BCG and one-third using additional intravesical instillation (mainly mitomycin C, thiotepa and doxorubicin). However, the characteristics of the patients, such as gender and mean age, were not reported, and the follow-up was less than 5 years.[187]

TABLE 29 *Risk group stratification*

Risk groups	Subgroups (cancer at diagnosis)	Factors defined in follow-up at 3 months	Proportion (%)
Low: TaG1, single T1G1	Group 1: single TaG1, single T1G1	No tumour recurrence	10
	Group 2a: single TaG1, single T1G1	Tumour recurrence[a]	
	Group 2b: multi TaG1	No tumour recurrence	
	Group 3: multi TaG1	Tumour recurrence[a]	
Intermediate: TaG2, multi T1G1, single T1G2	Group 1: single TaG2, single T1G2	No tumour recurrence	45
	Group 2a: single TaG2, single T1G2	Tumour recurrence[a]	
	Group 2b: multi TaG2, multi T1G1	No tumour recurrence	
	Group 3: multi TaG2, multi T1G1	Tumour recurrence[a]	
High: TaG3, T1G3, CIS, multi T1G2		Tumour recurrence or not	45

a If TaG3, T1G3, CIS, multi T1G2 recurrence, then joins high-risk treatment pathway.

TABLE 30 *Proportions of types and their subgroups for bladder cancer*

Type of bladder cancer	Proportion	Subgroups of bladder cancer considered	Proportion
Non-muscle invasive	75%	Low risk	10%
		Intermediate risk	45%
		High risk	45%
Muscle invasive	25%	Local muscle invasive	75%
		Metastases	25%

Recurrence, progression and mortality of muscle-invasive disease

When patients move into the Markov model for muscle-invasive disease, the model requires estimates of the annual rates of recurrence, progression and mortality caused by cancer. The probabilities of recurrence, progression and mortality of muscle-invasive disease and metastases used in the model for 20 years are presented in *Table 32*. The first 5-year probabilities of recurrence, progression and mortality caused by local muscle-invasive disease used in the model were obtained from a retrospective cohort study in Canada by Stein and colleagues[197] in which a cohort of 1054 patients with muscle-invasive bladder cancer were treated by radical cystectomy between 1971 and 1997. The mean age of the patients was 66 years, 80% of the patients were male[197] and data were available for 10 years of follow-up. The last 10-year probabilities used in the model are assumed to be the same as the data reported for between 5 and 10 years in the study by Stein and colleagues. The last column of *Table 32* presents the probabilities of mortality for metastases provided by von der Maase and colleagues[198] and there are data available for 5 years of follow-up. The last 5-year probabilities used in the model are assumed to be the same as rates reported for between 3 and 5 years in von der Maase and colleagues.[198] This RCT investigated the long-term survival of patients with metastatic bladder cancer treated with chemotherapy in Denmark. Of the 405 patients, 137 had locally advanced disease and 268 had metastatic disease. The median survival time was 8.3 months.

All-cause mwortality rates in the UK

As patients progress through the model over time, values of annual rates of age-specific general or all-cause mortality are required. These were taken from the published UK life tables for the years 2004–6.[199] As discussed in Chapter 1, Cancer

TABLE 31 *Probabilities of recurrence, progression and mortality in non-muscle-invasive bladder cancer*

Time (years)	Recurrence (%)			Progression (%)			Mortality caused by cancer (%)		
	Low	Intermediate	High	Low	Intermediate	High	Low	Intermediate	High
3 months	2	4	9.4	0	0.2	1.3	0	0	0
1	15	26	39	0	0.4	8	0	0.4	1
2	10	13	11	0	0.8	5	0	0	3
3	5	6	6	0	0.6	3	0	0.3	1
4	8	5	2	0	0.8	1	0	0.3	2
5	7	3	3	0	1	2	0	0	2
6	7	5	4	0	0.8	2	0	0.2	2
7	7	5	4	0	0.8	2	0	0.2	2
8	7	5	4	0	0.8	2	0	0.2	2
9	7	5	4	0	0.8	2	0	0.2	2
10	7	5	4	0	0.8	2	0	0.2	2
11	7	5	4	0	0.8	2	0	0.2	2
12	7	5	4	0	0.8	2	0	0.2	2
13	7	5	4	0	0.8	2	0	0.2	2
14	7	5	4	0	0.8	2	0	0.2	2
15	7	5	4	0	0.8	2	0	0.2	2
16	7	5	4	0	0.8	2	0	0.2	2
17	7	5	4	0	0.8	2	0	0.2	2
18	7	5	4	0	0.8	2	0	0.2	2
19	7	5	4	0	0.8	2	0	0.2	2
20	7	3	4	0	0.8	2	0	0.2	2

Research UK reported that 70% of all primary bladder cancer affects men and therefore the all-cause mortality for the model cohort was weighted to reflect this (*Figure 34*). Further data related to the rate of all-cause mortality are shown in *Table 57* in Appendix 18.

Other probabilities

Mortality rates of WLC/PDD and TURBT

White light rigid cystoscopy (WLC), PDD and TURBT are invasive procedures. As with all surgical procedures requiring general anaesthetic, death due to complications in the perioperative period is a potential risk. There are no available data on mortality rates associated with WLC or PDD. The probability of death during WLC and PDD in *Table 33* was therefore obtained from a study by Farrow and collegues,[200] which examined 108,878 anaesthetic cases in Cardiff between 1972 and 1977. The probability of death during TURBT in *Table 33* was obtained from Kondas and colleagues,[201] which evaluated 1250 TURBT cases in Cardiff during 18 years.

Relative risk for progression comparing no treatment (false negative) with treatment (true positive)

As some patients who have bladder cancer show negative results during the initial diagnosis or follow-up, it was believed that the risk of progression in the case of a false negative without relevant treatment was higher than that of a true positive with treatment. However, there are no data available in relation to false-negative diagnoses. Although there are some studies investigating disease-free survival or survival for different types of drug treatment as an adjunct to initial treatment (TURBT) for bladder cancer, there is no identified study that compares survival with and without TURBT. Using information from the Millán-Rodriguez and colleagues' study[187] it was assumed that the base-case RR for progression comparing no treatment (TURBT) with treatment (TURBT) was 2.56, that is the RR compared TURBT plus BCG with TURBT alone. The uncertainty around this value was tested as part of the sensitivity analysis.

TABLE 32 *Probabilities of recurrence, progression and mortality in muscle-invasive bladder cancer*

	Local muscle-invasive disease after cystectomy			Metastases
Time (years)	**Recurrence (%)**	**Progression (%)**	**Mortality (%)**	**Mortality (%)**
3 months	0	6.25	3	10.5
1	0	25	12	42
2	0	13	11	80
3	0	8	9	50
4	0	4	8	50
5	0	4	8	50
6	0	4	7	50
7	0	4	6	50
8	0	4	5	50
9	0	4	5	50
10	0	4	5	50
11	0	4	5	
12	0	4	5	
13	0	4	5	
14	0	4	5	
15	0	4	5	
16	0	4	5	
17	0	4	5	
18	0	4	5	
19	0	4	5	
20	0	4	5	

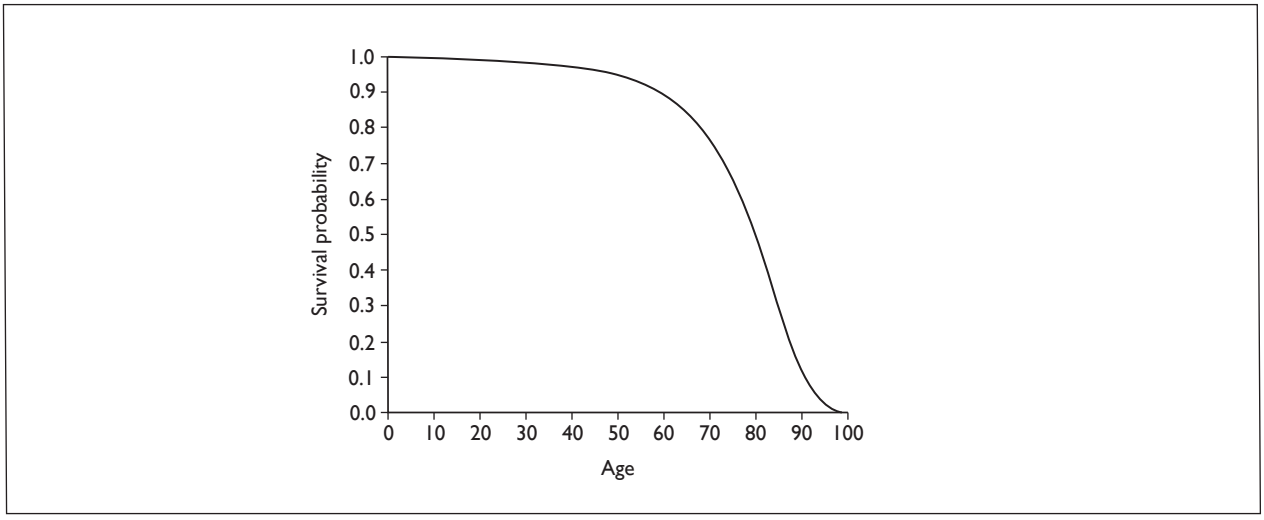


FIGURE 34 *Kaplan–Meier plot for sex- and age-adjusted survival (30% female, 70% male) in the UK.*

Relative risks for recurrence and progression comparing PDD with WLC treatment

One of the issues that could be considered in the model is whether the recurrence and progression rates of non-muscle-invasive disease differ based on the type of intervention used in the treatment (PDD or WLC). Although there is some evidence in Chapter 4 that PDD may reduce recurrence and progression for non-muscle-invasive disease compared with WLC, there are no reliable data related to recurrence and progression of non-muscle-invasive bladder cancer following PDD or WLC in primary diagnosis. It was therefore assumed that recurrence and progression rates are not different between PDD and WLC so that the base-case RR for recurrence and progression comparing PDD and WLC is 1. This assumption was tested as part of the sensitivity analysis.

Probability of detecting missed bladder cancer after false-negative results

There is no evidence to suggest when patients who have false-negative results should be detected. Therefore assumptions were made about when such patients were identified. The probabilities of detecting false-negative cases are described in *Table 33*.

Costs

Table 34 shows the cost estimates for the tests and investigations used within the model. The costs of flexible cystoscopy, WLC or WLC-assisted TURBT were identified from 2006 NHS reference costs.[202] The cost of flexible cystoscopy was based on the NHS reference cost with Healthcare Resource Group (HRG) (day case) code L21 'Bladder cancer endoscopic procedure without complications (cc)'. The cost of WLC was based on the NHS reference cost with HRG (elective inpatient) code LB15C 'Bladder minor procedure 19 years and over without cc'. The day unit cost of WLC-assisted TURBT was based on the NHS reference cost with HRG (elective inpatient) code L21 'Bladder intermediate endoscopic procedure without cc'. Based on the 2006 report by Karl Storz Endoscopy (UK), the cost of WLC-assisted TURBT is calculated by multiplying the cost per day by 2 days. [Karl Storz Endoscopy (UK), 2006, personal communication]. Also reported in *Table 34* are the costs of PDD. Compared with WLC, PDD incurs the following additional costs:

- extra equipment: photosensitiser (HAL, ALA), colour CCD camera (on chip integration), xenon lamp, fluid light cable
- extra personnel involved: unlike WLC, PDD requires the instillation of a photosensitiser via a urethral catheter prior to TURBT; this is usually performed by a nurse on the ward
- procedure time: on the ward, catheterisation and instillation of photosensitiser and then removal of catheter takes about 15 minutes; in theatres, fluorescence-guided TURBT takes an extra 10 minutes compared with conventional white light TURBT alone.

The additional cost of extra equipment, personnel and time of PDD were obtained from a business report prepared by Karl Storz (UK) [Karl Storz Endoscopy (UK), 2006, personal communication] (*Table 35*). It was assumed that the lifespan of PDD equipment is 5 years, a 3.5% discount rate is used in equivalent annual cost and the average number of PDD tests per year is 100.

The costs associated with the additional resources are shown in *Table 36* and these costs were added to the costs of WLC to obtain the costs of PDD and PDD-assisted TURBT.

TABLE 33 *Other probabilities*

Other probabilities	Value	Source
Mortality rate of WLC/PDD	0.5%	Farrow 1982[200]
Mortality rate of TURBT	0.8%	Kondas 1992[201]
False negatives: probability detected in first 3 months	50%	Assumption
Relative risk for progression (no treatment vs treatment)	2.56	Millán-Rodriguez 2000[187]
Relative risk for recurrence (PDD vs WLC)	1	Assumption
Relative risk for progression (PDD vs WLC)	1	Assumption
False negatives: probability detected in first year	50%	Assumption
False negatives: probability detected in second year	75%	Assumption
False negatives: probability detected after second year	100%	Assumption

TABLE 34 *Cost of diagnostic tests and initial treatments for bladder cancer*

Parameter	Base case (£)	Range	Unit	Source
PDD	1371	1136 to 1758	Procedure	Health Care Financial
WLC	937	702 to 1324	Procedure	NHS reference costs[202]
CSC	441	362 to 680	Session	NHS reference costs[202]
Cytology	92.37	Uniform distribution	Session	NHS reference costs[202]
NMP22	39.30	25 to 54.8	Test	MediChecks.com
ImmunoCyt	54.8	Uniform distribution	Session	NHS reference costs[202]
FISH	54.8	40 to 60	Test	NHS reference costs[202]
PDD-assisted TURBT	2436	2006 to 2994	Procedure	Health Care Financial
WLC-assisted TURBT	2002	1572 to 2560	Procedure	NHS reference costs[202]
CT scan	325	Uniform distribution	Procedure	Rodgers 2006[179]

CSC, flexible cystoscopy.

TABLE 35 *Estimated additional costs for extra capital resource of PDD*

Additional capital resource	Cost
Total cost of the extra equipment for PDD	£17,950
Lifespan of the equipment (years)	5
Average number of PDD tests per year	100
3.5% discount rate for 5 years	0.2215
Equivalent annual cost	£3976
Additional cost per test	£40
Cost of hexyl-5-aminolaevulinic acid per test	£286
Annual service and maintenance costs (after year 1)	£1795
Cost of service and maintenance per patient	£18
Total average cost per test	£344

TABLE 36 *Estimated additional costs for incorporating the PDD procedure*

Additional procedure	Additional cost
Extra nurse time for catheterising patients and instillation of 5-ALA	£40
Extra staffing cost (operation)	£35
Additional equipment of PDD	£344
Consumables (catheter, etc.)	£15
Total	£434

The states related to 'true negative' and 'false negative' only incur diagnostic costs. However, the states for 'true positive' and 'false positive' incur both diagnostic and relevant treatment costs. For example, for strategy CSC_WLC, the costs of 'true positive of low risk' and 'false positive of low risk' are equal to cost_CSC. The costs of 'true negative of low risk' and 'false negative of low risk' are equal to cost_CSC + cost_TURBT. For muscle-invasive disease relevant diagnostic and treatment costs were also considered.

The cost of NMP22 was based on the marketing price in the UK.[203] As the costs of ImmunoCyt and FISH are not available in the UK market, these costs were calculated from a systematic review conducted for NICE[179] as well as from 2005 NHS reference costs[202] with HRG code L13 'Minor pathology test'. The cost of cytology was estimated using HRG code L14 'Intermediate pathology test'[179] and the cost of a CT scan was estimated by using data from the same source.[179]

Table 37 reports the costs of treatments for bladder cancer. The cost of cystectomy was based on 2006 NHS reference costs with HRG code LB389B 'Cystectomy with urinary diversion and reconstruction without cc'. The unit day cost of palliative treatment was also obtained from NHS reference costs with HRG code SD01A 'Inpatient specialist palliative care 19 years and over'. Following consultation with clinical experts, an assumption was made that the palliative treatment requires a range of 3–6 months. The cost of palliative treatment was estimated by multiplying the unit cost per day by 135 days. This figure is uncertain as it would of course depend upon the type of care necessary. However, the proportion of patients likely to need this care is relatively small and the likely differences between strategies will also be small.

The unit cost of radical radiotherapy was obtained from Aberdeen Royal Infirmary (Dr Ghulam Nabi, University of Aberdeen, May 2008, personal communication). Radical radiotherapy requires from 30 to 40 sessions. The cost of radiotherapy was calculated by multiplying the unit cost by 35 sessions. The costs of the three drug treatments – mitomycin, BCG and cisplatin – were derived from the *British National Formulary (*http://bnf.org).

Discount rate

Discount rates used for costs and outcomes were those recommended in the recent NICE guideline[204] on the conduct of technology assessment reviews. Annual discount rates of 3.5% with a range from 0% to 6% were used in the model.

Estimation of total cost of strategies

The total cost for each strategy was determined using recursive costing in the decision tree and the Markov model. At the end point in the decision tree model this is achieved by setting the cost variable as 0 at the root node. As the tree expands from left to right, the 'cost' variable is modified by adding new cost variables to the variable 'cost'. In this way, the value of 'cost' at each terminal node is unique to the path from the root node to that terminal node. In the example strategy being used, flexible cystoscopy followed by WLC, the value of 'cost' at the 'true-positive' terminal node would be the costs of flexible cystoscopy and WLC and the additional treatment cost depending on the type of bladder cancer.

Discounted costs are considered in the Markov model to estimate the cost for each diagnostic strategy by using the following formulation:

$$\text{Cost}_{\text{strategy}} = \sum \text{cost}_{\text{cycle}} / (1 + \text{discount rate})^{\text{cycle}}$$

TABLE 37 *Cost of treatment and management of bladder cancer*

Parameter	Base case (£)	Range	Quantity	Unit	Source
Mitomycin	73.88	Uniform distribution	40 mg	Cycle	*British National Formulary*
BCG	89	Uniform distribution	12.5 mg	Cycle	*British National Formulary*
Cystectomy (w/o cc)	6856	3656 to 8437		Procedure	NHS reference costs[202]
Chemotherapy (cisplatin)	50.22	25.37 to 100		Cycle	*British National Formulary*
Radical radiotherapy	1050	900 to 1200	35 (30–40)	£30/day	Aberdeen Royal Infirmary
Palliative treatment (outpatient)	12,825	8550 to 17,100		£95/day	NHS reference costs[202]
Discount	3.5%	0% to 6%			NICE guideline[204]

w/o cc, without complications.

Distribution of parameters

For probabilities of recurrence, progression and mortality of bladder cancer and all-cause mortality rate, no distribution was assigned, as the number of observations or studies used to calculate the risk was very large. The estimates of sensitivity and specificity of the three biomarker tests and cytology were assigned normal distributions, which appear to fit the data that have small and symmetric ranges. The estimates for the performance of flexible cystoscopy, WLC and PDD were assigned beta distributions, which are more flexible to deal with data that have large and skewed ranges. Diagnoses and treatment costs were assigned log-normal distributions as this distribution appeared to best fit the data that have skewed or symmetric ranges.

Quality of life measures

To conduct a cost–utility analysis, quality of life (QoL) (utilities) data are required. The best estimates of QoL (utilities) data for a UK setting may be provided by using generic measures such as EQ-5D or SF-6D (which might be derived from responses to the SF-36 or SF-12). A structured literature search was conducted in EMBASE, MEDLINE and other relevant databases using the key words related to urological cancer, EQ-5D and SF-36 (Appendix 1). However, no QoL data were identified relating to bladder cancer. The only available QoL data were for other urological cancers. After discussions with clinical experts involved in this study it was decided not to use QoL estimates for other urological cancers as a proxy as these values were not considered to be generalisable to the population who have bladder cancer, although as reported later sensitivity analysis was conducted that explored the impact of using these data.

Data analysis

Cost-effectiveness analysis

The base-case analysis was based on the costs and outcomes for a hypothetical cohort of 1000 people with a mean age of 67 years reported in the systematic review in Chapter 4. The base-case model analysis was run for 5% prevalence rates and a 20-year time horizon. Two different measures of incremental cost-effectiveness have been considered as they provide slightly different information. These measures are the incremental cost per true positive case detected and incremental cost per life-year gained. The cases of true positives might be considered to be the key clinical outcome to reflect the diagnostic performance and life-years are a natural outcome to reflect survival.

The incremental cost-effectiveness is presented both with and without dominated and extendedly dominated options. For the estimation of incremental cost per life-year gained the results are presented as cost-effectiveness scatter plots and cost-effectiveness acceptability curves (CEACs). CEACs illustrate the likelihood that the strategy is cost-effective at various threshold values for society's willingness to pay for an additional life-year. Probabilistic sensitivity analysis was based mainly on the non-dominated strategies in the base-case model as changes in the estimates of parameters in these particular strategies are more likely to change the conclusions.

Cost–consequence analysis

The cost-effectiveness analysis results were presented as true positive cases detected and life-years. Further information can be obtained by considering the different outcome of diagnostic performance and longer-term effectiveness within the model for each strategy included in this study. The diagnostic performance of each strategy is reported in terms of false negative, false positive, true negative, correct diagnosis and incorrect diagnosis. Here, data along with information on life expectancy and cost can be presented in the form of a cost–consequence analysis. As such these data can be useful to aid in the interpretation of cost-effectiveness analyses and, had one been possible as part of the base-case analysis, a cost-utility analysis as they help to identify what factors might be drivers of the results.

Sensitivity analysis

Sensitivity analyses were carried out to explore uncertainties within the model. Sensitivity analyses concentrated on various assumptions made about estimates of main parameters used in the base-case model. As mentioned above the results of the sensitivity analyses focused on the non-dominated strategies in the base-case model. A cost–consequence analysis can be used to highlight the choices and trade-offs that can be made between outcomes.

Prevalence rates of patients who have symptoms of bladder cancer

Although considerable efforts were made to identify estimates for prevalence rates for patients who have symptoms of bladder cancer, no reliable data were available. In the base-case analysis a

prevalence rate of 5% was used. Existing data in the literature suggest that prevalence rates range from 1% to 20%. Sensitivity analysis was performed to explore the effects of a decrease to 1% and increases to 10% and 20%. The same distribution of parameters adopted in the base-case analysis was used.

Relative risk of progression comparing no treatment (false negative) and treatment (true positive)

As mentioned earlier there was little information available to investigate the risk of progression of no treatment for patients who have bladder cancer when they have negative results in the initial diagnosis. Bladder cancer missed in the initial diagnosis and at follow-up would not be treated and would subsequently have a higher risk of progression and mortality. The base-case analysis assumed that the RR of no treatment (TURBT) compared with treatment would be 2.56 based on the Millán-Rodriguez and colleagues' study.[187] A range of this RR was considered to investigate those values for which diagnostic strategies may be considered worthwhile. Based on available evidence on the RR for progression comparing TURBT with TURBT plus BCG or other drugs, a sensitivity analysis was performed with the assumption that the RR for progression comparing TURBT with no TURBT decreased to 1.

Relative risks of recurrence and progression comparing PDD with WLC

There are no reliable data on recurrence and progression when PDD is used for initial diagnosis and follow-up, although PDD is likely to reduce recurrence and progression compared with WLC as described in Chapter 4. It was assumed in the base-case model that the RRs of recurrence and progression comparing PDD with WLC would be 1, i.e. any gains from the use of PDD would flow from improvements in diagnostic performance as measured by sensitivity and specificity alone, as opposed to gains that might arise from a more complete removal of the cancer facilitated by the increased information provided by PDD. Results in Chapter 4 suggested that the RRs of recurrence and progression comparing PDD with WLC were 0.64 and 0.56 and these values were used in the sensitivity analysis.

Sensitivity and specificity of flexible cystoscopy

There were no data related to the sensitivity and specificity of flexible cystoscopy, although it is likely that the performance of flexible cystoscopy could be better than that of WLC. The assumption was made in the base-case analysis that the performance of flexible cystoscopy would be the same as that of WLC. Expert opinion (TR Leyston Griffiths, University of Leicester, July 2008, personal communication) suggested that the performance of flexible cystoscopy is better than that of WLC; sensitivity analysis was therefore performed assuming that both sensitivity and specificity of flexible cystoscopy are increased from 5% to 25% compared with WLC.

Proportion of risk groups for non-muscle-invasive bladder cancer

The risk groups used in the model were defined by combining two classifications based on the best available data. There were large differences in the proportions for risk groups in the two studies. The base case assumed that the proportion of risk would be the same as in the Millán-Rodriguez and colleagues' study,[187] in which the proportion of the high-risk group is much higher than that of the low-risk group. As mentioned in Chapter 1 it is likely that the proportion of the low-risk group in non-muscle-invasive disease is the same as that in the study by Parmar and colleagues.[191] Thus, it was assumed in the sensitivity analysis that the proportion of the high-risk group decreased from 30% in the base-case analysis to 10% and that the proportion of the low-risk group increased from 10% in the base-case analysis to 30%. The distributions of parameters were the same as those used in the base case.

Starting age and 10-year time horizon

As mentioned in Chapter 1 the incidence and mortality rate of bladder cancer are likely to increase as age increases. The base-case analysis was carried out on the assumption that the starting age of the cohort would be 67 years, based on the results from the systematic review, and considered a 20-year time horizon with constant mortality rates of bladder cancer except for the first 5 years. The sensitivity analysis used the reported mean age of bladder cancer patients in the UK of 71 years. The prevalence and mortality rate of bladder cancer associated with age may imply that the most cost-effective strategy in the base case may no longer be considered to be cost-effective.

Annual discount rate

As recommended in the NICE guidelines, an annual discount rate of 3.5% for cost and outcomes was used in the base-case model. A range from 0% to 6% for discount rate was considered in the sensitivity analysis.

Follow-up diagnostic strategies

White light rigid cystoscopy was considered as the second-line test in follow-up for each strategy in the base-case model as it is commonly used to follow bladder cancer in the UK if the result of the first test in follow-up is positive. Sensitivity analysis was performed to investigate whether alternative strategies associated with PDD in follow-up may be more cost-effective than those involving WLC, although PDD is more expensive than WLC.

Quality of life measures

As addressed in the previous section cost–utility analysis was not conducted in the base case. Sensitivity analysis was performed using the QoL data from other urological cancers to produce quality-adjusted life-years (QALYs). The utility values identified for urological cancers are included in *Table 38*. A prediagnosis utility value of 0.78 was identified and the rest of the values were based on a reduction in utility for undergoing the different tests and treatments.

Subgroup analysis

Depending on data availability it was intended that subgroup analysis would be performed on:

- type of tumour detected, e.g. CIS, low risk and high risk
- tumour recurrence at the first 3-month cystoscopic examination following TURBT
- diagnostic performance of the different PDD photosensitising agents.

Results

Deterministic and probabilistic results

The cost-effectiveness analysis aggregates the diagnostic performance and the time spent in the various health states of the model. As described previously cost–utility analysis was not performed because QoL data suitable for incorporation into the economic model were not available.

TABLE 38 *Utility values*

Utility and disutility	Assumption of reduction in utility	Value	Range	Source
Prediagnosis	NA[a]	0.78	0.52 to 1.0	UK EQ-5D
CSC	–0	0.78	0.518 to 1.0	Kulkarni 2007[205]
CTL	–0	0.78	0.52 to 1.0	Assumption
NMP22	–0	0.78	0.52 to 1.0	Assumption
ImmunoCyt	–0	0.78	0.52 to 1.0	Assumption
FISH	–0	0.78	0.52 to 1.0	Assumption
WLC	–0.05	0.73	0.66 to 0.73	Kulkarni 2007[205]
PDD	–0.05	0.73	0.66 to 0.73	Kulkarni 2007[205]
TURBT	–0.05	0.73	0.66 to 0.73	Kulkarni 2007[205]
BCG	–0.016	0.764	0.534 to 0.764	Kulkarni 2007[205]
Cystectomy (alone)	NA[b]	0.624	0.39 to 0.78	Kulkarni 2007[205]
Chemotherapy	–0.28	0.60	0.08 to 0.62	Kulkarni 2007[205]
Radiotherapy	–0.13	0.65	0.49 to 0.65	Pickard 2007[206]
Non-muscle-invasive	–0	0.78	0.24 to 0.73	Kulkarni 2007[205]
Muscle-invasive	–0	0.78	0.52 to 1.0	UK EQ-5D
Metastases with palliative treatment	–0.29	0.49	0.518 to 1.0	Kulkarni 2007[205]

CSC, flexible cystoscopy; NA, not applicable.
a Not applicable as this is the starting value from which reductions are made.
b Not applicable data based on that from Kulkarni and colleagues 2007.[205]

Deterministic results

The cost-effectiveness of the 26 strategies for initial diagnosis and follow-up were considered over a 20-year time horizon.

Base case: diagnostic performance and life-years and costs per patient

Table 39 shows the results for a hypothetical cohort of 1000 patients. The table reports performance of the strategies, from the least to the most costly. For each strategy the diagnostic performance of the strategy and the average cost and life expectancy over a 20-year time horizon are shown. It is important to remember when interpreting these data that in the base-case analysis the prevalence of disease is 5% (i.e. 50 people out of the 1000 in the cohort have bladder cancer).

Of the strategies shown, strategy 26, flexible cystoscopy and ImmunoCyt followed by PDD in initial diagnosis and flexible cystoscopy followed by WLC in follow-up [CSC_IMM_PDD (CSC_WLC)], has the best performance in terms of the highest number of true positives and lowest number of false negatives and the highest number of life-years but it also has the worst performance in terms of the highest number of false positives ($n = 188$), the lowest number of true negatives and the highest cost. Strategy 1, CTL_WLC (CTL_WLC), reports the lowest numbers of true positives and false positives and life-years saved and the highest values for true negatives and false negatives.

Cost–consequence analysis

The results presented in *Table 39* can be used to consider the trade-offs between the different treatment strategies and this can be further illustrated using the data presented in *Table 40*. *Table 40* reports the strategies that perform the best in terms of the different outcome measures considered. The results for all strategies are reported in Appendix 19 (*Tables 58* and *59*). For example, CSC_IMM_PDD (CSC_WLC) is the best-performing strategy in terms of having the lowest false-negative and the highest true-positive rates and longest survival. However, it is associated with the highest rates of false positives and the lowest rates of true negatives.

This table and *Table 39* illustrate the trade-offs that exists between those strategies that can correctly identify those without disease but will result in all of the harms from an incorrect diagnosis compared with those strategies that are better able to identify disease if it is present but also result in additional anxiety and cost for those incorrectly initially diagnosed as positive.

Cost-effectiveness analysis

Incremental cost per true positive case detected

The cost-effectiveness results for diagnostic performance are presented in *Table 41* using incremental cost per true positive detected. In terms of mean true positive cases and costs, most of the strategies associated with flexible cystoscopy or WLC in the initial diagnosis [except for CTL_WLC (CTL_WLC) and FISH_WLC (FISH_WLC)] are dominated by those that involve PDD or biomarkers and can be eliminated because they are less effective and more costly than the non-dominated strategies. The lower part of the table reports the incremental cost-effectiveness ratios (ICERs) when dominated and extendedly dominated strategies are omitted.

The results in *Table 41* show that strategy 26 (CSC_IMM_PDD) has the highest number of true positive cases detected ($n = 44$) and is the most costly strategy (£2370) per patient. Strategy 1 (CTL_WLC) has the lowest cost per patient (£1043) and produces the least number of true positives ($n = 16$). It is also highlighted in the table that total cost increases when moving from WLC to PDD and the number of cases detected also increases when PDD is used.

Incremental cost per life-year

The base-case analysis was also presented in terms of incremental cost per life-year (*Table 42*). The results presented for life-years are similar to those presented in *Table 41*. As can be seen from *Table 42* many strategies are dominated, that is they provide no more or even less benefits at the same or increased cost. Further strategies are extendedly dominated, that is providing a mix of a lower cost but less effective strategy and a higher cost but more effective strategy would be more efficient. The strategy of FISH_WLC (FISH_WLC) is extendedly dominated by the strategy of CTL_PDD (CTL_WLC) and it can be eliminated as its ICER is greater than that of FISH_PDD (FISH_WLC) as well as CSC_IMM_PDD. Furthermore, even for those strategies that are not dominated or extendedly dominated the incremental cost per life-year gained might be higher than society is willing to pay. Reference values for society's willingness to pay for a life-year are not available but given that people will be in less than full health it is likely that the incremental cost per QALY

TABLE 39 *Results of the deterministic model for the 20-year time horizon*

Strategy		Diagnostic performance						Average limitation outcome	
	First line tests (second line tests)	True positive	True negative	False positive	False negative	Correct diagnosis	Incorrect diagnosis	Life-years	Cost
1	CTL_WLC (CTL_WLC)	16	939	11	34	955	45	11.59	£1043
2	CTL_PDD (CTL_WLC)	20	934	16	30	954	46	11.6	£1094
3	FISH_WLC (FISH_WLC)	27	910	40	23	937	63	11.62	£1171
4	FISH_PDD (FISH_WLC)	35	889	61	15	924	76	11.64	£1235
5	NMP22_WLC (NMP22_WLC)	24	894	56	26	918	82	11.61	£1242
6	NMP22_PDD (NMP22_WLC)	31	864	86	19	895	105	11.62	£1321
7	IMM_WLC (IMM_WLC)	30	884	67	20	913	87	11.63	£1345
8	IMM_PDD (IMM_WLC)	39	848	102	11	887	113	11.65	£1458
9	CSC_CTL_WLC (CTL_WLC)	30	868	82	20	898	102	11.62	£1662
10	CSC_FISH_WLC (FISH_WLC)	33	847	103	17	880	120	11.63	£1807
11	CSC_NMP22_WLC (NMP22_WLC)	32	835	115	18	867	133	11.62	£1851
12	CSC_CTL_PDD (CTL_WLC)	39	824	126	11	863	137	11.65	£1859
13	CSC_WLC (CSC_WLC)	25	876	75	25	901	99	11.6	£1920
14	CSC_IMM_WLC (IMM_WLC)	34	828	122	16	862	138	11.63	£1941
15	CSC_CTL_WLC (CSC_WLC)	30	868	82	20	898	102	11.62	£1997
16	CSC_FISH_WLC (CSC_WLC)	33	847	103	17	880	120	11.66	£2005
17	CSC_FISH_PDD (FISH_WLC)	43	792	158	7	835	165	11.63	£2042
18	CSC_NMP22_WLC (CSC_WLC)	32	835	115	18	867	133	11.62	£2070
19	CSC_PDD (CSC_WLC)	33	836	114	17	869	131	11.63	£2082
20	CSC_NMP22_PDD (NMP22_WLC)	42	774	176	8	816	184	11.65	£2089

TABLE 39 *Results of the deterministic model for the 20-year time horizon (continued)*

Strategy		Diagnostic performance						Average limitation outcome	
	First line tests (second line tests)	True positive	True negative	False positive	False negative	Correct diagnosis	Incorrect diagnosis	Life-years	Cost
21	CSC_IMM_WLC (CSC_WLC)	34	828	122	16	862	138	11.63	£2105
22	CSC_CTL_PDD (CSC_WLC)	39	818	132	11	857	143	11.64	£2145
23	CSC_IMM_PDD (IMM_WLC)	44	762	188	6	806	194	11.66	£2195
24	CSC_FISH_PDD (CSC_WLC)	43	792	158	7	835	165	11.66	£2270
25	CSC_NMP22_ PDD (CSC_ WLC)	42	774	176	8	816	184	11.65	£2318
26	CSC_IMM_PDD (CSC_WLC)	44	762	188	6	806	194	11.66	£2370

would be greater than £20,000 for all strategies apart from 2, 3 and 4. The incremental cost per QALY for strategy 8 may be greater than £20,000 but less than £30,000 as long as the average annual QoL score is 0.65.

Probabilistic results

The cost-effectiveness point estimates do not provide any information on uncertainty surrounding the model parameters. The results of the probabilistic analysis revealed the level of uncertainty concerning results as illustrated in the CEACs in *Figure 35*.

As can be seen in *Figure 35* none of the eight strategies considered is likely to be cost-effective more than 50% of the time when society is willing to pay relatively little for an additional life-year except for strategy 1 [CTL_WLC (CTL-WLC)]. Nevertheless, there are four strategies that are each associated with an approximately 20% chance of being considered cost-effective over much of the range of willingness to pay values considered. It is notable that three of the four strategies involve the use of biomarkers for diagnosis and follow-up, while the fourth uses cytology.

As mentioned in the methods section of this chapter, the cost-effectiveness estimates for those strategies that involve more than one test as part of the initial diagnosis may be underestimated. Adding in these potential extra costs had virtually no effect on the point estimates of cost-effectiveness or on the likelihood that a particular strategy would be likely to be considered cost-effective.

Sensitivity analysis and subgroup analysis

Changing prevalence rates in patients who have symptoms of bladder cancer

As prevalence rates increase, people with suspected bladder cancer have more positive results and the costs and outcomes associated with diagnostic performance for each strategy are increased. However, the outcomes associated with long-term survival may be decreased, because fewer people within the cohort are disease free. *Table 43* describes the results of the sensitivity analysis for changes in the prevalence rate. The non-dominated or non-extendedly dominated strategies are the same as in the base-case analysis and are excluded from the table. At low probabilities of disease (i.e. 1%) it is likely that the least costly strategy, strategy 1 [CTL_WLC (CTL_WLC)], is likely to be cost-effective. The probability of IMM_PDD (IMM_WLC), FISH_PDD (FISH_WLC) and CSC_FISH_PDD (FISH_WLC) being also considered as cost-effective strategies at different thresholds of society's willingness to pay for an additional life-year in the base case did not vary

TABLE 40 *Ranking by diagnostic and life-year performance and cost*

Ranking	True negative	True positive	False positive	False negative	Correct diagnosis	Incorrect diagnosis	Life-years	Cost
1	CTL_WLC	CSC_IMM_PDD	CTL_WLC	CSC_IMM_PDD	CTL_WLC	CTL_WLC	CSC_IMM_PDD	CTL_WLC
	(CTL_WLC)	(CSC_WLC)	(CTL_WLC)	(CSC_WLC)	(CTL_WLC)	(CTL_WLC)	(CSC_WLC)	(CTL_WLC)
2	CTL_PDD	CSC_IMM_PDD	CTL_PDD	CSC_IMM_PDD	CTL_PDD	CTL_PDD	CSC_IMM_PDD	CTL_PDD
	(CTL_WLC)	(IMM_WLC)	(CTL_WLC)	(IMM_WLC)	(CTL_WLC)	(CTL_WLC)	(IMM_WLC)	(CTL_WLC)
3	FISH_WLC	CSC_FISH_PDD	FISH_WLC	CSC_FISH_PDD	FISH_WLC	FISH_WLC	CSC_FISH_PDD	FISH_WLC
	(FISH_WLC)	(FISH_WLC)	(FISH_WLC)	(FISH_WLC)	(FISH_WLC)	(FISH_WLC)	(CSC_WLC)	(FISH_WLC)
4	NMP22_WLC	CSC_FISH_PDD	NMP22_WLC	CSC_FISH_PDD	FISH_PDD	FISH_PDD	CSC_FISH_PDD	FISH_PDD
	(NMP22_WLC)	(CSC_WLC)	(NMP22_WLC)	(CSC_WLC)	(FISH_WLC)	(FISH_WLC)	(FISH_WLC)	(FISH_WLC)
5	FISH_PDD	CSC_NMP22_ PDD	FISH_PDD	CSC_NMP22_ PDD	NMP22_WLC	NMP22_WLC	CSC_NMP22_ PDD	NMP22_WLC
	(FISH_WLC)	(NMP22_WLC)	(FISH_WLC)	(NMP22_WLC)	(NMP22_WLC)	(NMP22_WLC)	(NMP22_WLC)	(NMP22_WLC)
6	IMM_WLC	CSC_NMP22_ PDD	IMM_WLC	CSC_NMP22_ PDD	IMM_WLC	IMM_WLC	CSC_NMP22_ PDD	NMP22_PDD
	(IMM_WLC)	(CSC_WLC)	(IMM_WLC)	(CSC_WLC)	(IMM_WLC)	(IMM_WLC)	(CSC_WLC)	(NMP22_WLC)
7	CSC_WLC	IMM_PDD	CSC_WLC	IMM_PDD	CSC_WLC	CSC_WLC	IMM_PDD	IMM_WLC
	(CSC_WLC)	(IMM_WLC)	(CSC_WLC)	(IMM_WLC)	(CSC_WLC)	(CSC_WLC)	(IMM_WLC)	(IMM_WLC)
8	CSC_CTL_WLC	CSC_CTL_PDD	CSC_CTL_WLC	CSC_CTL_PDD	CSC_CTL_WLC	CSC_CTL_WLC	CSC_CTL_PDD	IMM_PDD
	(CSC_WLC)	(CSC_WLC)	(CSC_WLC)	(CSC_WLC)	(CSC_WLC)	(CSC_WLC)	(CTL_WLC)	(IMM_WLC)
9	CSC_CTL_WLC	CSC_CTL_PDD	CSC_CTL_WLC	CSC_CTL_PDD	CSC_CTL_WLC	CSC_CTL_WLC	CSC_CTL_PDD	CSC_CTL_WLC
	(CTL_WLC)	(CTL_WLC)	(CTL_WLC)	(CTL_WLC)	(CTL_WLC)	(CTL_WLC)	(CSC_WLC)	(CTL_WLC)
10	NMP22_PDD	FISH_PDD	NMP22_PDD	FISH_PDD	NMP22_PDD	NMP22_PDD	FISH_PDD	CSC_FISH_WLC
	(NMP22_WLC)	(FISH_WLC)	(NMP22_WLC)	(FISH_WLC)	(NMP22_WLC)	(NMP22_WLC)	(FISH_WLC)	(FISH_WLC)

Note: For true test results correct diagnosis and higher life-year values are better and for false test results incorrect diagnosis and lower cost values are better.

TABLE 41 *Results of the deterministic model for the 20-year time horizon (per case)*

Strategy number	Strategy	Average cost	Incremental cost	True positive cases detected	Incremental number of cases detected	ICER
1	CTL_WLC (CTL_WLC)	£1043		16		
2	CTL_PDD (CTL_WLC)	£1094	£51	20	4	£13
3	FISH_WLC (FISH_WLC)	£1171	£77	27	7	£11
4	FISH_PDD (FISH_WLC)	£1235	£64	35	8	£8
5	NMP22_WLC (NMP22_WLC)	£1242	£6	24	–11	Dominated
6	IMM_WLC (IMM_WLC)	£1321	£86	30	–5	Dominated
7	NMP22_PDD (NMP22_WLC)	£1345	£109	32	–3	Dominated
8	IMM_PDD (IMM_WLC)	£1458	£223	39	4	£56
9	CSC_CTL_WLC (CTL_WLC)	£1662	£204	30	–9	Dominated
10	CSC_FISH_WLC (FISH_WLC)	£1807	£349	33	–5	Dominated
11	CSC_NMP22_WLC (NMP22_WLC)	£1851	£393	32	–7	Dominated
12	CSC_CTL_PDD (CTL_WLC)	£1859	£401	39	0	Dominated
13	CSC_WLC (CSC_WLC)	£1920	£462	25	–14	Dominated
14	CSC_IMM_WLC (IMM_WLC)	£1941	£483	34	–5	Dominated
15	CSC_CTL_WLC (CSC_WLC)	£1997	£539	30	–9	Dominated
16	CSC_FISH_PDD (FISH_WLC)	£2005	£547	43	4	£137
17	CSC_FISH_WLC (CSC_WLC)	£2042	£37	33	–10	Dominated
18	CSC_NMP22_WLC (CSC_WLC)	£2070	£65	32	–11	Dominated
19	CSC_PDD (NMP22_WLC)	£2082	£77	33	–10	Dominated
20	CSC_NMP22_PDD (NMP22_WLC)	£2089	£84	42	–1	Dominated
21	CSC_IMM_WLC (CSC_WLC)	£2105	£100	34	–9	Dominated
22	CSC_CTL_PDD (CSC_WLC)	£2145	£140	39	-4	Dominated
23	CSC_IMM_PDD (IMM_WLC)	£2195	£190	44	1	£190
24	CSC_FISH_PDD (CSC_WLC)	£2270	£75	43	–1	Dominated
25	CSC_NMP22_PDD (CSC_WLC)	£2318	£123	42	–2	Dominated
26	CSC_IMM_PDD (CSC_WLC)	£2370	£175	44	0	Dominated
Results without dominated and extendedly dominated options						
1	CTL_WLC (CTL_WLC)	£1043		16		
2	CTL_PDD (CTL_WLC)	£1094	£51	20	4	£13
3	FISH_WLC (FISH_WLC)	£1171	£77	27	7	£11
4	FISH_PDD (FISH_WLC)	£1235	£64	35	8	£8
8	IMM_PDD (IMM_WLC)	£1458	£223	39	4	£56
16	CSC_FISH_PDD (FISH_WLC)	£2005	£547	43	4	£137
23	CSC_IMM_PDD (IMM_WLC)	£2195	£190	44	1	£190

Note: In this table the ICER is the incremental cost per additional true positive case detected.

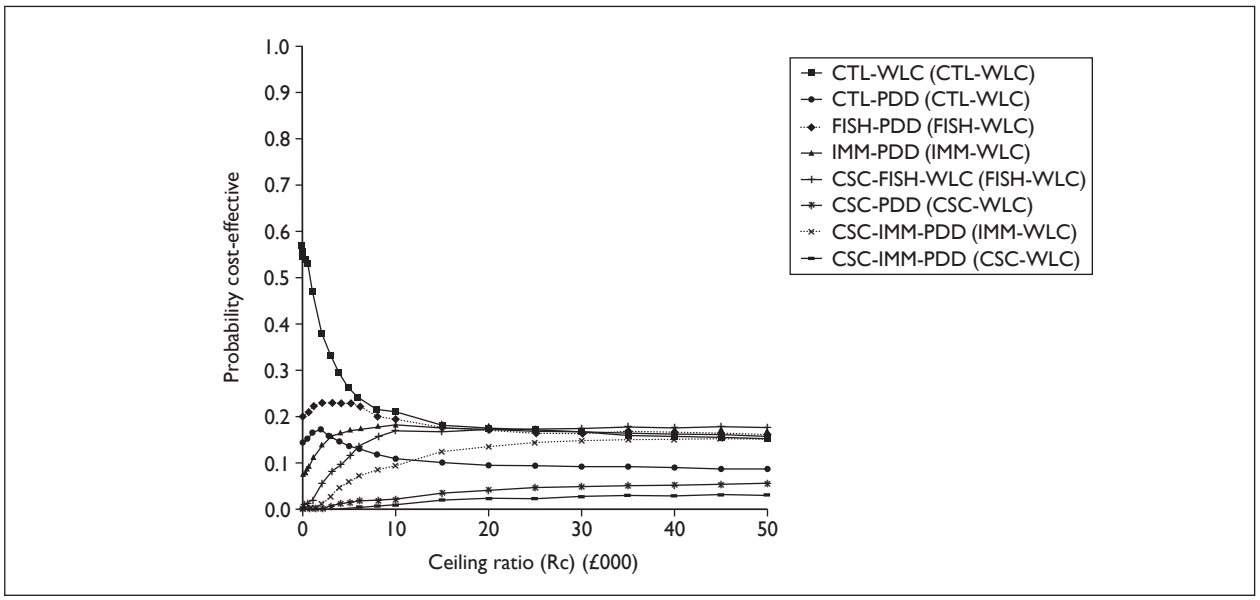


FIGURE 35 *Cost-effectiveness acceptability curves determined by society's willingness to pay for a life-year for the eight strategies.*

greatly when either lower or higher prevalence rates were used in the analysis. However, *Figure 35* shows that CSC_FISH_PDD (FISH_WLC) had an increased probability of being considered cost-effective when the prevalence rate increased to 20%. For example, the probability of CSC_FISH_PDD (FISH_WLC) being considered the most cost-effective strategy would be greater than 22% when society is willing to pay more than £20,000 per extra life-year. The CEACs for these sensitivity analyses are shown in Appendix 20.

Changes in the sensitivity and specificity of flexible cystoscopy

When the sensitivity and specificity of flexible cystoscopy were increased, life-years associated with 'flexible cystoscopy' strategies increased and relevant costs decreased. Results of the changes in the sensitivity and specificity of flexible cystoscopy are presented in *Table 44* and, as this table shows, the strategies involving flexible cystoscopy generally become more likely to be considered cost-effective as its diagnostic performance increases. Nonetheless, at perhaps the most plausible increase of 5% in sensitivity and specificity for flexible cystoscopy compared with those of WLC the probabilities that strategies involving flexible cystoscopy are cost-effective are not greatly changed. The CEACs for these sensitivity analyses are shown in Appendix 21.

Relative risk rate of progression of bladder cancer comparing no treatment with treatment

In the sensitivity analysis the speed of progression and rate of mortality for those falsely diagnosed as negative and hence not treated were altered. As might be expected, reducing these rates would decrease the cost-effectiveness of those strategies associated with fewer false negatives. Hence, the probability that CTL_WLC (CTL_WLC) would be considered cost-effective increased from 18% in the base-case analysis (RR 2.56) to 28% when the RR was 1 and society's willingness to pay for a life-year was £20,000 (*Table 45*). The CEACs for these sensitivity analyses are shown in Appendix 22.

Relative risk rate of recurrence and progression comparing PDD with WLC

As indicated in Chapter 4, PDD is more likely to reduce the recurrence and progression of bladder cancer, decreasing these rates, and would therefore increase the cost-effectiveness of strategies associated with it. FISH_PDD (FISH_WLC) had an increased probability of being considered cost-effective when the RRs of recurrence and progression were decreased to 0.64 and 0.56 respectively (*Tables 46* and *47* respectively). The CEACs for these sensitivity analyses are shown in Appendices 23 and 24 respectively.

TABLE 42 *Results of the deterministic model for the 20-year time horizon (per life-year)*

Strategy number	Strategy	Cost	Incremental cost	Life-years	Incremental years	ICER
1	CTL_WLC (CTL_WLC)	£1043		11.59		
2	CTL_PDD (CTL_WLC)	£1094	£51	11.60	0.01	£3423
3	FISH_WLC (FISH_WLC)	£1171	£77	11.62	0.01	£5575[a]
4	FISH_PDD (FISH_WLC)	£1235	£64	11.64	0.02	£2762
5	NMP22_WLC (NMP22_WLC)	£1242	£6	11.61	–0.03	Dominated
6	IMM_WLC (IMM_WLC)	£1321	£86	11.62	–0.02	Dominated
7	NMP22_PDD (NMP22_WLC)	£1345	£109	11.63	–0.01	Dominated
8	IMM_PDD (IMM_WLC)	£1458	£223	11.65	0.01	£28,864
9	CSC_CTL_WLC (CTL_WLC)	£1662	£204	11.62	–0.03	Dominated
10	CSC_FISH_WLC (FISH_WLC)	£1807	£349	11.63	–0.02	Dominated
11	CSC_NMP22_WLC (NMP22_WLC)	£1851	£393	11.62	–0.02	Dominated
12	CSC_CTL_PDD (CTL_WLC)	£1859	£401	11.65	0	Dominated
13	CSC_WLC (CSC_WLC)	£1920	£462	11.60	–0.04	Dominated
14	CSC_IMM_WLC (IMM_WLC)	£1941	£483	11.63	–0.02	Dominated
15	CSC_CTL_WLC (CSC_WLC)	£1997	£539	11.62	–0.03	Dominated
16	CSC_FISH_PDD (FISH_WLC)	£2005	£547	11.66	0.01	£60,284
17	CSC_FISH_WLC (CSC_WLC)	£2042	£37	11.63	–0.03	Dominated
18	CSC_NMP22_WLC (CSC_WLC)	£2070	£65	11.62	–0.03	Dominated
19	CSC_PDD (CSC_WLC)	£2082	£77	11.63	–0.03	Dominated
20	CSC_NMP22_PDD (NMP22_WLC)	£2089	£84	11.65	–0.01	Dominated
21	CSC_IMM_WLC (CSC_WLC)	£2105	£100	11.63	–0.03	Dominated
22	CSC_CTL_PDD (CSC_WLC)	£2145	£140	11.64	–0.01	Dominated
23	CSC_IMM_PDD (IMM_WLC)	£2195	£190	11.66	< 0.01	£309,256[a]
24	CSC_FISH_PDD (CSC_WLC)	£2270	£75	11.66	0	Dominated
25	CSC_NMP22_PDD (CSC_WLC)	£2318	£123	11.65	–0.01	Dominated
26	CSC_IMM_PDD (CSC_WLC)	£2370	£175	11.66	< 0.01	£237,863
Results without dominated and extendedly dominated options						
1	CTL_WLC (CTL_WLC)	£1043		11.59		
2	CTL_PDD (CTL_WLC)	£1094	£51	11.60	0.01	£3423
4	FISH_PDD (FISH_WLC)	£1235	£141	11.64	0.04	£3806
8	IMM_PDD (IMM_WLC)	£1458	£223	11.65	0.01	£28,864
16	CSC_FISH_PDD (FISH_WLC)	£2005	£547	11.66	0.01	£60,284
26	CSC_IMM_PDD (CSC_WLC)	£2370	£365	11.66	< 0.01	£270,375

a Extendedly dominated.

TABLE 43 *Sensitivity analysis associated with prevalence rate*

	Deterministic results					Probability of cost-effectiveness for different threshold values for society's willingness to pay for a life-year (%)				
Strategy	**Average cost**	**Incremental cost**	**Average life-years**	**Incremental life-years**	**Incremental cost/ life-year**	**£10,000**	**£20,000**	**£30,000**	**£40,000**	**£50,000**
Base case, prevalence = 5%										
CTL_WLC (CTL_WLC)	£1043		11.59			21	18	17	16	15
CTL_PDD (CTL_WLC)	£1094	£51	11.60	0.01	£3423	11	10	9	9	9
FISH_PDD (FISH_WLC)	£1235	£141	11.64	0.04	£3806	20	17	16	17	17
IMM_PDD (IMM_WLC)	£1458	£223	11.65	0.01	£28,864	18	18	17	17	17
CSC_FISH_PDD (FISH_WLC)	£2005	£547	11.66	0.01	£60,284	17	18	18	18	18
CSC_PDD (CSC_WLC)	£2082	£77	11.63	–0.03	Dominated	2	4	5	5	6
CSC_IMM_PDD (IMM_WLC)	£2195	£190	11.66	< 0.01	Extendedly dominated	9	14	15	15	16
CSC_IMM_PDD (CSC_WLC)	£2370	£365	11.66	< 0.01	£270,375	1	3	3	3	3
Prevalence = 1%										
CTL_WLC (CTL_WLC)	£319		11.79			35	30	29	28	27
CTL_PDD (CTL_WLC)	£349	£30	11.79	< 0.01	£12,120	5	4	4	4	4
FISH_PDD (FISH_WLC)	£499	£150	11.79	< 0.01	£51,884	18	15	14	14	13
IMM_PDD (IMM_WLC)	£680	£180	11.79	0	Dominated	13	13	13	13	12
CSC_PDD (CSC_WLC)	£1148	£648	11.78	–0.01	Dominated	16	19	19	21	21
CSC_FISH_PDD (FISH_WLC)	£1306	£806	11.79	–0.01	Dominated	3	4	5	6	6
CSC_IMM_PDD (IMM_WLC)	£1427	£928	11.78	–0.01	Dominated	10	14	15	16	16
CSC_IMM_PDD (CSC_WLC)	£1450	£951	11.78	–0.01	Dominated	0	0	0	0	0

Strategy	Deterministic results					Probability of cost-effectiveness for different threshold values for society's willingness to pay for a life-year (%)				
	Average cost	Incremental cost	Average life-years	Incremental life-years	Incremental cost/ life-year	£10,000	£20,000	£30,000	£40,000	£50,000
Prevalence = 10%										
CTL_WLC (CTL_WLC)	£1951		11.34			15	12	11	11	11
CTL_PDD (CTL_WLC)	£2033	£82	11.37	0.03	Extendedly dominated	11	10	10	9	9
FISH_PDD (FISH_WLC)	£2168	£217	11.45	0.11	£2018	19	16	16	15	15
IMM_PDD (IMM_WLC)	£2449	£281	11.47	0.02	£13,597	18	16	16	15	15
CSC_FISH_PDD (FISH_WLC)	£2899	£451	11.50	0.03	£17,555	22	23	22	22	22
CSC_IMM_PDD (IMM_WLC)	£3177	£278	11.50	0.01	£48,035	12	15	16	17	17
CSC_PDD (CSC_WLC)	£3271	£93	11.43	–0.08	Dominated	2	4	5	6	6
CSC_IMM_PDD (CSC_WLC)	£3545	£368	11.50	< 0.01	£235,672	2	4	5	5	5
Prevalence = 20%										
CTL_WLC (CTL_WLC)	£3765		10.85			7	5	4	4	4
CTL_PDD (CTL_WLC)	£3904	£139	10.90	0.06	Extendedly dominated	9	8	7	7	7
FISH_PDD (FISH_WLC)	£4019	£254	11.07	0.22	£1150	19	17	16	16	15
IMM_PDD (IMM_WLC)	£4411	£392	11.12	0.05	Extendedly dominated	19	19	18	18	18
CSC_FISH_PDD (FISH_WLC)	£4667	£648	11.17	0.11	£6148	26	25	24	23	22
CSC_IMM_PDD (IMM_WLC)	£5119	£452	11.19	0.02	£28,183	17	21	21	21	21
CSC_PDD (CSC_WLC)	£5628	£509	11.03	–0.16	Dominated	2	3	4	4	4
CSC_IMM_PDD (CSC_WLC)	£5871	£751	11.19	< 0.01	£233,858	1	4	6	8	9

TABLE 44 *Sensitivity analysis associated with changes to the sensitivity and specificity of flexible cystoscopy*

	Deterministic results					Probability of cost-effectiveness for different threshold values for society's willingness to pay for a life-year (%)				
Strategy	**Average cost**	**Incremental cost**	**Average life-years**	**Incremental life-years**	**Incremental cost/ life-year**	**£10,000**	**£20,000**	**£30,000**	**£40,000**	**£50,000**
Base case, CSC=WLC (sens=0.71, spec=0.72)										
CTL_WLC (CTL_WLC)	£1043		11.59			21	18	17	16	15
CTL_PDD (CTL_WLC)	£1094	£51	11.60	0.01	£3423	11	10	9	9	9
FISH_PDD (FISH_WLC)	£1235	£141	11.64	0.04	£3806	20	17	16	17	17
IMM_PDD (IMM_WLC)	£1458	£223	11.65	0.01	£28,864	18	18	17	17	17
CSC_FISH_PDD (FISH_WLC)	£2005	£547	11.66	0.01	£60,284	17	18	18	18	18
CSC_PDD (CSC_WLC)	£2082	£77	11.63	–0.03	Dominated	2	4	5	5	6
CSC_IMM_PDD (IMM_WLC)	£2195	£190	11.66	<0.01	Extendedly dominated	9	14	15	15	16
CSC_IMM_PDD (CSC_WLC)	£2370	£365	11.66	<0.01	£270,375	1	3	3	3	3
CSC=WLC+5.0% (sens=0.76, spec=0.77)										
CTL_WLC (CTL_WLC)	£1043		11.59			22	19	18	17	16
CTL_PDD (CTL_WLC)	£1094	£51	11.60	0.01	£3423	12	11	10	10	10
FISH_PDD (FISH_WLC)	£1235	£141	11.64	0.04	£3806	20	18	17	17	17
IMM_PDD (IMM_WLC)	£1458	£223	11.65	0.01	£28,864	16	16	15	15	15
CSC_FISH_PDD (FISH_WLC)	£1952	£494	11.66	0.01	£55,236	15	16	16	17	17
CSC_PDD (CSC_WLC)	£1986	£34	11.63	–0.02	Dominated	3	5	6	6	6
CSC_IMM_PDD (IMM_WLC)	£2149	£197	11.66	0	Dominated	12	15	16	17	17
CSC_IMM_PDD (CSC_WLC)	£2293	£341	11.66	0	Dominated	1	1	2	2	2

Strategy	Deterministic results					Probability of cost-effectiveness for different threshold values for society's willingness to pay for a life-year (%)				
	Average cost	Incremental cost	Average life-years	Incremental life-years	Incremental cost/ life-year	£10,000	£20,000	£30,000	£40,000	£50,000
CSC=WLC+10.0% (sens=0.81, spec=0.82)										
CTL_WLC (CTL_WLC)	£1043		11.59			21	18	16	15	15
CTL_PDD (CTL_WLC)	£1094	£51	11.60	0.01	£3423	9	7	8	7	7
FISH_PDD (FISH_WLC)	£1235	£141	11.64	0.04	£3806	20	18	17	17	16
IMM_PDD (IMM_WLC)	£1458	£223	11.65	0.01	£28,864	17	16	17	17	16
CSC_PDD (CSC_WLC)	£1881	£423	11.64	0	Dominated	3	5	6	7	7
CSC_FISH_PDD (FISH_WLC)	£1892	£434	11.66	0.01	£49,145	17	19	19	20	20
CSC_IMM_PDD (IMM_WLC)	£2096	£204	11.66	0	Dominated	12	15	16	16	17
CSC_IMM_PDD (CSC_WLC)	£2211	£319	11.65	0	Dominated	1	1	2	2	2
CSC=WLC+25.0% (sens=0.96, spec=0.97)										
CTL_WLC (CTL_WLC)	£1043		11.59			14	11	10	10	9
CTL_PDD (CTL_WLC)	£1094	£51	11.60	0.01	£3423	9	8	7	7	7
FISH_PDD (FISH_WLC)	£1235	£141	11.64	0.04	£3806	16	15	15	14	14
IMM_PDD (IMM_WLC)	£1458	£223	11.65	0.01	Extendedly dominated	17	17	18	18	18
CSC_PDD (CSC_WLC)	£1552	£317	11.67	0.03	£10,485	17	17	18	18	18
CSC_FISH_PDD (FISH_WLC)	£1706	£154	11.66	–0.01	Dominated	17	17	18	18	18
CSC_IMM_PDD (IMM_WLC)	£1931	£379	11.65	–0.02	Dominated	8	10	10	10	10
CSC_IMM_PDD (CSC_WLC)	£1964	£412	11.65	–0.02	Dominated	4	5	6	6	6

Sens, sensitivity; spec, specificity.

TABLE 45 *Sensitivity analysis associated with relative risk for progression comparing no treatment with treatment of bladder cancer*

	Deterministic result					Probability of cost-effectiveness for different threshold values for society's willingness to pay for a life-year (%)				
Strategy	**Average cost**	**Incremental cost**	**Average life-years**	**Incremental life-years**	**Incremental cost/life-year**	**£10,000**	**£20,000**	**£30,000**	**£40,000**	**£50,000**
Base case, RR = 2.56										
CTL_WLC (CTL_WLC)	£1043		11.59			21	18	17	16	15
CTL_PDD (CTL_WLC)	£1094	£51	11.60	0.01	£3423	11	10	9	9	9
FISH_PDD (FISH_WLC)	£1235	£141	11.64	0.04	£3806	20	17	16	17	17
IMM_PDD (IMM_WLC)	£1458	£223	11.65	0.01	£28,864	18	18	17	17	17
CSC_FISH_PDD (FISH_WLC)	£2005	£547	11.66	0.01	£60,284	17	18	18	18	18
CSC_PDD (CSC_WLC)	£2082	£77	11.63	–0.03	Dominated	2	4	5	5	6
CSC_IMM_PDD (IMM_WLC)	£2195	£190	11.66	< 0.01	Extendedly dominated	9	14	15	15	16
CSC_IMM_PDD (CSC_WLC)	£2370	£365	11.66	< 0.01	£270,375	1	3	3	3	3
RR = 2.0										
CTL_WLC (CTL_WLC)	£1040		11.63			24	22	21	20	19
CTL_PDD (CTL_WLC)	£1092	£52	11.64	0.01	£5707	11	9	9	9	8
FISH_PDD (FISH_WLC)	£1242	£150	11.66	0.02	£7115	20	18	17	17	17
IMM_PDD (IMM_WLC)	£1464	£222	11.66	0	£51,443	16	16	15	15	14
CSC_FISH_PDD (FISH_WLC)	£2008	£544	11.66	0	£127,281	16	18	18	19	19
CSC_PDD (CSC_WLC)	£2110	£102	11.64	–0.02	Dominated	3	4	5	6	6
CSC_IMM_PDD (IMM_WLC)	£2198	£190	11.66	0.00	Dominated	10	12	13	14	14
CSC_IMM_PDD (CSC_WLC)	£2378	£370	11.67	< 0.01	£897,929	1	2	2	3	3

Strategy	Deterministic result					Probability of cost-effectiveness for different threshold values for society's willingness to pay for a life-year (%)				
	Average cost	Incremental cost	Average life-years	Incremental life-years	Incremental cost/life-year	£10,000	£20,000	£30,000	£40,000	£50,000
RR = 1.5										
CTL_WLC (CTL_WLC)	£1026		11.66			30	26	24	23	23
CTL_PDD (CTL_WLC)	£1081	£55	11.66	0	£11,311	10	9	9	9	9
FISH_PDD (FISH_WLC)	£1243	£162	11.67	0.01	£24,861	19	18	16	16	16
IMM_PDD (IMM_WLC)	£1465	£223	11.67	< 0.01	£204,841	13	13	13	13	13
CSC_FISH_PDD (FISH_WLC)	£2008	£543	11.67	< 0.01	£2,836,313	15	16	17	17	18
CSC_PDD (CSC_WLC)	£2133	£124	11.66	–0.01	Dominated	3	5	6	6	6
CSC_IMM_PDD (IMM_WLC)	£2200	£191	11.67	0	Dominated	8	11	13	13	13
CSC_IMM_PDD (CSC_WLC)	£2384	£376	11.67	0	Dominated	2	2	2	3	3
RR = 1.0										
CTL_WLC (CTL_WLC)	£999		11.69			32	28	26	25	25
CTL_PDD (CTL_WLC)	£1066	£67	11.69	< 0.01	£123,479	11	10	10	10	10
FISH_PDD (FISH_WLC)	£1239	£173	11.68	–0.01	Dominated	17	15	14	14	14
IMM_PDD (IMM_WLC)	£1463	£398	11.68	–0.01	Dominated	14	12	13	13	12
CSC_FISH_PDD (FISH_WLC)	£2006	£940	11.68	–0.01	Dominated	14	17	17	17	17
CSC_PDD (CSC_WLC)	£2149	£1083	11.68	–0.02	Dominated	3	6	7	8	8
CSC_IMM_PDD (IMM_WLC)	£2200	£1134	11.68	–0.02	Dominated	8	11	12	12	12
CSC_IMM_PDD (CSC_WLC)	£2389	£1323	11.68	–0.02	Dominated	1	2	2	2	2

TABLE 46 *Sensitivity analysis associated with relative risk for recurrence comparing PDD with WLC*

	Deterministic result					Probability of cost-effectiveness for different threshold values for society's willingness to pay for a life-year (%)				
Strategy	**Average cost**	**Incremental cost**	**Average life-years**	**Incremental life-years**	**Incremental cost/life-year**	**£10,000**	**£20,000**	**£30,000**	**£40,000**	**£50,000**
Base case (RR_R = 1.0)										
CTL_WLC (CTL_WLC)	£1043		11.59			21	18	17	16	15
CTL_PDD (CTL_WLC)	£1094	£51	11.60	0.01	£3423	11	10	9	9	9
FISH_PDD (FISH_WLC)	£1235	£141	11.64	0.04	£3806	20	17	16	17	17
IMM_PDD (IMM_WLC)	£1458	£223	11.65	0.01	£28,864	18	18	17	17	17
CSC_FISH_PDD (FISH_WLC)	£2005	£547	11.66	0.01	£60,284	17	18	18	18	18
CSC_PDD (CSC_WLC)	£2082	£77	11.63	–0.03	Dominated	2	4	5	5	6
CSC_IMM_PDD (IMM_WLC)	£2195	£190	11.66	<0.01	Extendedly dominated	9	14	15	15	16
CSC_IMM_PDD (CSC_WLC)	£2370	£365	11.66	<0.01	£270,375	1	3	3	3	3
RR_R = 0.9										
CTL_WLC (CTL_WLC)	£1043		11.59			21	18	16	16	16
CTL_PDD (CTL_WLC)	£1090	£47	11.60	0.01	£3301	11	10	9	9	9
FISH_PDD (FISH_WLC)	£1227	£136	11.64	0.04	£3650	20	18	18	18	17
IMM_PDD (IMM_WLC)	£1451	£224	11.65	0.01	£28,840	16	15	15	15	15
CSC_FISH_PDD (FISH_WLC)	£1999	£548	11.66	0.01	£60,008	18	20	20	21	21
CSC_PDD (CSC_WLC)	£2080	£81	11.63	–0.03	Dominated	3	4	5	5	6
CSC_IMM_PDD (IMM_WLC)	£2190	£191	11.66	<0.01	Extendedly dominated	11	14	15	15	15
CSC_IMM_PDD (CSC_WLC)	£2367	£368	11.66	<0.01	£277,574	0	1	1	2	2

Strategy	Deterministic result					Probability of cost-effectiveness for different threshold values for society's willingness to pay for a life-year (%)				
	Average cost	Incremental cost	Average life-years	Incremental life-years	Incremental cost/life-year	£10,000	£20,000	£30,000	£40,000	£50,000
RR_R = 0.8										
CTL_WLC (CTL_WLC)	£1043		11.59			17	13	12	12	12
CTL_PDD (CTL_WLC)	£1084	£41	11.60	0.01	£2773	13	11	10	9	9
FISH_PDD (FISH_WLC)	£1215	£131	11.64	0.04	£3469	23	21	19	18	18
IMM_PDD (IMM_WLC)	£1439	£224	11.65	0.01	£28,553	15	16	16	15	15
CSC_FISH_PDD (FISH_WLC)	£1986	£547	11.66	0.01	£59,527	16	18	19	19	19
CSC_PDD (CSC_WLC)	£2071	£85	11.63	–0.03	Dominated	4	5	7	8	8
CSC_IMM_PDD (IMM_WLC)	£2177	£191	11.66	<0.01	£267,929	11	14	15	16	17
CSC_IMM_PDD (CSC_WLC)	£2357	£180	11.66	<0.01	£304,531	1	2	3	3	3
RR_R = 0.64										
CTL_WLC (CTL_WLC)	£1043		11.59			18	14	13	12	12
CTL_PDD (CTL_WLC)	£1075	£31	11.61	0.02	£2005	13	12	12	12	11
FISH_PDD (FISH_WLC)	£1197	£122	11.64	0.04	£3181	21	19	18	18	18
IMM_PDD (IMM_WLC)	£1420	£223	11.65	0.01	£28,083	18	18	17	17	17
CSC_FISH_PDD (FISH_WLC)	£1965	£545	11.66	0.01	£58,791	15	17	18	18	18
CSC_PDD (CSC_WLC)	£2058	£93	11.63	–0.03	Dominated	3	4	5	6	6
CSC_IMM_PDD (IMM_WLC)	£2156	£190	11.66	<0.01	£239,084	11	15	16	16	17
CSC_IMM_PDD (CSC_WLC)	£2341	£185	11.66	<0.01	£395,494	1	1	2	2	2

TABLE 47 *Sensitivity analysis associated with relative risk for progression comparing PDD with WLC*

	Deterministic result					Probability of cost-effectiveness for different threshold values for society's willingness to pay for a life-year (%)				
Strategy	**Average cost**	**Incremental cost**	**Average life-years**	**Incremental life-years**	**Incremental cost/life-year**	**£10,000**	**£20,000**	**£30,000**	**£40,000**	**£50,000**
Base case (RR_P = 1.0)										
CTL_WLC (CTL_WLC)	£1043		11.59			21	18	17	16	15
CTL_PDD (CTL_WLC)	£1094	£51	11.60	0.01	£3423	11	10	9	9	9
FISH_PDD (FISH_WLC)	£1235	£141	11.64	0.04	£3806	20	17	16	17	17
IMM_PDD (IMM_WLC)	£1458	£223	11.65	0.01	£28,864	18	18	17	17	17
CSC_FISH_PDD (FISH_WLC)	£2005	£547	11.66	0.01	£60,284	17	18	18	18	18
CSC_PDD (CSC_WLC)	£2082	£77	11.63	–0.03	Dominated	2	4	5	5	6
CSC_IMM_PDD (IMM_WLC)	£2195	£190	11.66	< 0.01	Extendedly dominated	9	14	15	15	16
CSC_IMM_PDD (CSC_WLC)	£2370	£365	11.66	< 0.01	£270,375	1	3	3	3	3
RR_P = 0.9										
CTL_WLC (CTL_WLC)	£1043		11.59			20	16	15	14	14
CTL_PDD (CTL_WLC)	£1095	£51	11.60	0.01	£3697	12	10	9	9	9
FISH_PDD (FISH_WLC)	£1236	£141	11.64	0.04	£3797	21	19	19	19	19
IMM_PDD (IMM_WLC)	£1460	£225	11.65	0.01	£29,123	15	16	15	15	14
CSC_FISH_PDD (FISH_WLC)	£2009	£549	11.66	0.01	£60,273	15	17	18	18	19
CSC_PDD (CSC_WLC)	£2086	£77	11.63	–0.03	Dominated	4	6	7	7	8
CSC_IMM_PDD (IMM_WLC)	£2200	£191	11.66	< 0.01	Extendedly dominated	11	14	15	15	16
CSC_IMM_PDD (CSC_WLC)	£2376	£366	11.66	< 0.01	£272,285	2	2	2	3	3

Strategy	Deterministic result					Probability of cost-effectiveness for different threshold values for society's willingness to pay for a life-year (%)				
	Average cost	Incremental cost	Average life-years	Incremental life-years	Incremental cost/life-year	£10,000	£20,000	£30,000	£40,000	£50,000
RR_P=0.8										
CTL_WLC (CTL_WLC)	£1043		11.59			19	16	15	14	14
CTL_PDD (CTL_WLC)	£1093	£50	11.60	0.01	£3529	11	9	9	9	9
FISH_PDD (FISH_WLC)	£1233	£140	11.64	0.04	£3760	25	22	21	20	20
IMM_PDD (IMM_WLC)	£1458	£225	11.65	0.01	£29,122	16	16	15	15	15
CSC_FISH_PDD (FISH_WLC)	£2006	£548	11.66	0.01	£60,046	16	18	19	19	20
CSC_PDD (CSC_WLC)	£2085	£78	11.63	–0.03	Dominated	3	5	6	6	6
CSC_IMM_PDD (IMM_WLC)	£2197	£191	11.66	<0.01	Extendedly dominated	11	12	13	14	15
CSC_IMM_PDD (CSC_WLC)	£2374	£367	11.66	<0.01	£273,525	1	2	2	2	2
RR_P=0.56										
CTL_WLC (CTL_WLC)	£1043		11.59			22	18	17	17	17
CTL_PDD (CTL_WLC)	£1089	£46	11.60	0.01	£3148	10	9	9	9	8
FISH_PDD (FISH_WLC)	£1227	£137	11.64	0.04	£3671	21	19	18	17	17
IMM_PDD (IMM_WLC)	£1452	£225	11.65	0.01	£29,110	15	15	15	14	14
CSC_FISH_PDD (FISH_WLC)	£1999	£547	11.66	0.01	£59,522	16	18	18	19	19
CSC_PDD (CSC_WLC)	£2080	£81	11.63	–0.03	Dominated	4	6	6	7	7
CSC_IMM_PDD (IMM_WLC)	£2191	£192	11.66	<0.01	Extendedly dominated	10	13	15	15	15
CSC_IMM_PDD (CSC_WLC)	£2369	£370	11.66	<0.01	£276,805	2	3	3	3	3

Discount rate

Another sensitivity analysis was conducted by changing the discount rate. The cost-effectiveness of the different strategies did not markedly change when the discount rate was changed between 0% and 6% (*Table 48*). The CEACs for these sensitivity analyses are shown in Appendix 25.

Proportions in each prognostic risk group for non-muscle-invasive disease

Changes to the proportions in each prognostic risk group for non-muscle-invasive disease were also considered (note that as the proportion in the low-risk group was increased, the proportion in the high-risk group decreased). The likelihood that CTL_WLC (CTL_WLC), IMM_PDD (IMM_WLC), FISH_PDD (FISH_WLC) or CSC_FISH_PDD (FISH_WLC) would be considered cost-effective did not change although some non-dominated or non-extendedly dominated strategies in the base-case analysis became dominated or extendedly dominated (*Table 49*). The CEACs for these sensitivity analyses are shown in Appendix 26.

Starting age of population and time horizon

Sensitivity analysis was used to investigate the effects of changing the starting age of the patient population or changing the number of years that the model was performed. None of these sensitivity analyses altered the likelihood of a given strategy being considered cost-effective (*Table 50*). However, as the time horizon was reduced, the incremental cost per life-year gained for each non-dominated strategy increased. This is because the majority of costs are incurred in earlier years but of course as the time horizon increases it is possible to gain more life-years. The CEACs for the sensitivity analyses are shown in Appendix 27.

Strategy used in follow-up and quality of life measures

The final sensitivity analyses performed involved including the use of PDD in follow-up and conducting cost–utility analysis using the values reported in *Table 38*. The CEACs for these two sensitivity analyses are shown in Appendices 28 and 29 respectively. These results did not change much and there was no strategy that was likely to be considered the most cost-effective as shown in *Table 51*. It was noted that the strategies associated with flexible cystoscopy were dominated by others when using QoL measures.

Subgroup analyses

No subgroup analyses were conducted because of lack of relevant data.

Summary of results

The economic model presented in this chapter considered some strategies involving PDD, WLC, biomarkers, cytology and flexible cystoscopy that are potentially relevant for the diagnosis and follow-up of bladder cancer patients. The effectiveness data for diagnostic tests came from the effectiveness review. However, there were no data available on the performance of flexible cystoscopy alone or combined with cytology or biomarkers. Therefore, the sensitivity and specificity of flexible cystoscopy were assumed to be the same as those of WLC as it was likely that flexible and rigid cystoscopies would identify similar types of cancer at the same rate. Plausible changes in this rate did not change the results to any extent. For the strategies relating to combined tests it was assumed that flexible cystoscopy was combined with cytology and/or biomarkers and then followed by WLC or PDD if any one of the previous tests performed was positive.

The base-case analysis model suggests that, for a prevalence rate of 5% in a population with suspected bladder cancer, the diagnostic strategy that would be cost-effective depends upon the value that society would be willing to pay to obtain an additional unit of outcome. Broadly speaking the results based on cases detected were similar to those based upon life-years. The strategy of flexible cystoscopy and ImmunoCyt followed by PDD in initial diagnosis and flexible cystoscopy followed by WLC in follow-up [CSC_IMM_PDD(CSC_WLC)], which produced 11.66 life-years and had a mean cost of £2370 per patient, was the most costly among the diagnostic strategies in the base-case analysis. The CTL_WLC (CTL_WLC) strategy was the least costly (£1043) and least effective (11.59 life-years). Although the differences between strategies in terms of costs and effects appear to be small, the important issue is the results of the willingness to pay for additional gain. CTL_WLC (CTL_WLC) had a greater chance of being cost-effective when the willingness to pay was less than £20,000 per life-year. IMM_PDD (IMM_WLC), FISH_PDD (FISH_WLC) and CSC_FISH_PDD (FISH_WLC) had a greater probability of being cost-effective when the willingness to pay was

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TABLE 48 *Sensitivity analysis associated with discount rate*

Strategy	Deterministic result					Probability of cost-effectiveness for different threshold values for society's willingness to pay for a life-year (%)				
	Average cost	Incremental cost	Average life-years	Incremental life-years	Incremental cost/life-year	£10,000	£20,000	£30,000	£40,000	£50,000
Base case (discount rate = 3.5%)										
CTL_WLC (CTL_WLC)	£1043		11.59			21	18	17	16	15
CTL_PDD (CTL_WLC)	£1094	£51	11.60	0.01	£3423	11	10	9	9	9
FISH_PDD (FISH_WLC)	£1235	£141	11.64	0.04	£3806	20	17	16	17	17
IMM_PDD (IMM_WLC)	£1458	£223	11.65	0.01	£28,864	18	18	17	17	17
CSC_FISH_PDD (FISH_WLC)	£2005	£547	11.66	0.01	£60,284	17	18	18	18	18
CSC_PDD (CSC_WLC)	£2082	£77	11.63	–0.03	Dominated	2	4	5	5	6
CSC_IMM_PDD (IMM_WLC)	£2195	£190	11.66	< 0.01	Extendedly dominated	9	14	15	15	16
CSC_IMM_PDD (CSC_WLC)	£2370	£365	11.66	< 0.01	£270,375	1	3	3	3	3
Discount rate = 6%										
CTL_WLC (CTL_WLC)	£978		9.84			21	17	15	15	14
CTL_PDD (CTL_WLC)	£1031	£53	9.85	0.01	£4364	12	10	9	9	9
FISH_PDD (FISH_WLC)	£1166	£134	9.88	0.03	£4509	23	20	19	18	17
IMM_PDD (IMM_WLC)	£1382	£217	9.88	0.01	£36,596	16	14	14	14	14
CSC_FISH_PDD (FISH_WLC)	£1940	£558	9.89	0.01	£80,682	16	21	21	21	22
CSC_PDD (CSC_WLC)	£1987	£46	9.87	–0.03	Dominated	2	4	5	5	6
CSC_IMM_PDD (IMM_WLC)	£2122	£181	9.89	< 0.01	Extendedly dominated	10	13	15	15	16
CSC_IMM_PDD (CSC_WLC)	£2278	£337	9.89	< 0.01	£408,489	1	2	2	3	3

continued

TABLE 48 *Sensitivity analysis associated with discount rate (continued)*

Strategy	Deterministic result					Probability of cost-effectiveness for different threshold values for society's willingness to pay for a life-year (%)				
	Average cost	Incremental cost	Average life-years	Incremental life-years	Incremental cost/life-year	£10,000	£20,000	£30,000	£40,000	£50,000
Discount rate = 1%										
CTL_WLC (CTL_WLC)	£1124		13.95			19	17	16	15	15
CTL_PDD (CTL_WLC)	£1172	£48	13.97	0.02	£2607	10	9	8	8	8
FISH_PDD (FISH_WLC)	£1323	£151	14.02	0.05	£3215	20	17	16	15	15
IMM_PDD (IMM_WLC)	£1554	£231	14.03	0.01	£22,648	17	16	16	16	15
CSC_FISH_PDD (FISH_WLC)	£2088	£533	14.04	0.01	£44,272	18	20	21	21	21
CSC_PDD (CSC_WLC)	£2203	£115	14.00	–0.04	Dominated	4	5	7	7	8
CSC_IMM_PDD (IMM_WLC)	£2289	£201	14.04	< 0.01	Extendedly dominated	12	15	16	16	16
CSC_IMM_PDD (CSC_WLC)	£2487	£399	14.04	< 0.01	£190,983	1	2	2	3	3
Discount rate = 0%										
CTL_WLC (CTL_WLC)	£1162		15.13			17	15	14	14	14
CTL_PDD (CTL_WLC)	£1209	£47	15.15	0.02	£2316	9	8	8	8	8
FISH_PDD (FISH_WLC)	£1365	£156	15.20	0.05	£3009	21	19	17	17	17
IMM_PDD (IMM_WLC)	£1600	£235	15.21	0.01	£20,526	17	17	16	16	16
CSC_FISH_PDD (FISH_WLC)	£2127	£527	15.23	0.01	£38,899	17	18	18	18	18
CSC_PDD (CSC_WLC)	£2261	£134	15.18	–0.04	Dominated	4	6	7	7	7
CSC_IMM_PDD (IMM_WLC)	£2334	£207	15.23	< 0.01	£162,110	13	15	17	17	17
CSC_IMM_PDD (CSC_WLC)	£2543	£209	15.23	< 0.01	£174,776	2	3	3	3	4

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TABLE 49 *Sensitivity analysis associated with proportions in prognostic risk groups*

Strategy	Deterministic results					Probability of cost-effectiveness for different threshold values for society's willingness to pay for a life-year (%)				
	Average cost	Incremental cost	Average life-years	Incremental life-years	Incremental cost/life-year	£10,000	£20,000	£30,000	£40,000	£50,000
Base case, low = 0.1, high = 0.45										
CTL_WLC (CTL_WLC)	£1043		11.59			21	18	17	16	15
CTL_PDD (CTL_WLC)	£1094	£51	11.60	0.01	£3423	11	10	9	9	9
FISH_PDD (FISH_WLC)	£1235	£141	11.64	0.04	£3806	20	17	16	17	17
IMM_PDD (IMM_WLC)	£1458	£223	11.65	0.01	£28,864	18	18	17	17	17
CSC_FISH_PDD (FISH_WLC)	£2005	£547	11.66	0.01	£60,284	17	18	18	18	18
CSC_PDD (CSC_WLC)	£2082	£77	11.63	–0.03	Dominated	2	4	5	5	6
CSC_IMM_PDD (IMM_WLC)	£2195	£190	11.66	< 0.01	Extendedly dominated	9	14	15	15	16
CSC_IMM_PDD (CSC_WLC)	£2370	£365	11.66	< 0.01	£270,375	1	3	3	3	3
Low = 0.3, high = 0.3										
CTL_WLC (CTL_WLC)	£1020		11.60			21	17	15	15	15
CTL_PDD (CTL_WLC)	£1071	£51	11.61	0.01	Extendedly dominated	9	9	8	8	8
FISH_PDD (FISH_WLC)	£1190	£170	11.65	0.05	£3254	22	20	19	19	18
IMM_PDD (IMM_WLC)	£1400	£210	11.66	0.01	£27,170	16	16	15	15	15
CSC_FISH_PDD (FISH_WLC)	£1957	£557	11.67	0.01	£58,259	18	19	20	20	21
CSC_PDD (CSC_WLC)	£2011	£54	11.64	–0.03	Dominated	4	6	7	7	7
CSC_IMM_PDD (IMM_WLC)	£2132	£175	11.67	< 0.01	£224,407	9	12	13	13	14
CSC_IMM_PDD (CSC_WLC)	£2283	£151	11.67	< 0.01	£389,886	2	2	3	3	3

continued

TABLE 49 *Sensitivity analysis associated with proportions in prognostic risk groups (continued)*

Strategy	Deterministic results					Probability of cost-effectiveness for different threshold values for society's willingness to pay for a life-year (%)				
	Average cost	Incremental cost	Average life-years	Incremental life-years	Incremental cost/life-year	£10,000	£20,000	£30,000	£40,000	£50,000
Low = 0.6, high = 0.1										
CTL_WLC (CTL_WLC)	£979		11.61			18	16	14	14	13
CTL_PDD (CTL_WLC)	£1029	£49	11.63	0.01	Extendedly dominated	10	9	8	8	8
FISH_PDD (FISH_WLC)	£1111	£132	11.67	0.05	£2487	23	21	20	18	18
IMM_PDD (IMM_WLC)	£1302	£190	11.67	0.01	£28,973	17	17	16	16	16
CSC_FISH_PDD (FISH_WLC)	£1867	£565	11.68	0.01	£51,823	19	20	20	21	21
CSC_PDD (CSC_WLC)	£1883	£17	11.65	–0.03	Dominated	2	5	6	7	7
CSC_IMM_PDD (IMM_WLC)	£2036	£170	11.68	< 0.01	£296,812	8	11	12	12	12
CSC_IMM_PDD (CSC_WLC)	£2117	£80	11.68	< 0.01	£420,138	3	4	4	4	4

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TABLE 50 *Sensitivity analysis associated with starting age and time horizon*

Strategy	Deterministic results					Probability of cost-effectiveness for different threshold values for society's willingness to pay for a life-year (%)				
	Average cost	Incremental cost	Average life-years	Incremental life-years	Incremental cost/life-year	£10,000	£20,000	£30,000	£40,000	£50,000
Base case, starting age 67 years										
CTL_WLC (CTL_WLC)	£1043		11.59			21	18	17	16	15
CTL_PDD (CTL_WLC)	£1094	£51	11.60	0.01	£3423	11	10	9	9	9
FISH_PDD (FISH_WLC)	£1235	£141	11.64	0.04	£3806	20	17	16	17	17
IMM_PDD (IMM_WLC)	£1458	£223	11.65	0.01	£28,864	18	18	17	17	17
CSC_FISH_PDD (FISH_WLC)	£2005	£547	11.66	0.01	£60,284	17	18	18	18	18
CSC_PDD (CSC_WLC)	£2082	£77	11.63	–0.03	Dominated	2	4	5	5	6
CSC_IMM_PDD (IMM_WLC)	£2195	£190	11.66	<0.01	Extendedly dominated	9	14	15	15	16
CSC_IMM_PDD (CSC_WLC)	£2370	£365	11.66	<0.01	£270,375	1	3	3	3	3
Starting age 57 years										
CTL_WLC (CTL_WLC)	£1095		13.34			21	18	16	16	15
CTL_PDD (CTL_WLC)	£1145	£50	13.35	0.02	£2821	10	9	9	8	8
FISH_PDD (FISH_WLC)	£1294	£149	13.40	0.04	£3376	25	22	21	20	20
IMM_PDD (IMM_WLC)	£1522	£228	13.41	0.01	£23,832	16	16	16	16	16
CSC_FISH_PDD (FISH_WLC)	£2061	£539	13.42	0.01	£47,517	17	19	21	21	21
CSC_PDD (CSC_WLC)	£2162	£101	13.38	–0.04	(Dominated)	2	3	4	5	5
CSC_IMM_PDD (IMM_WLC)	£2258	£197	13.42	<0.01	Extendedly dominated	8	11	12	13	14
CSC_IMM_PDD (CSC_WLC)	£2447	£386	13.42	<0.01	£197,884	1	1	2	2	2

continued

TABLE 50 *Sensitivity analysis associated with starting age and time horizon (continued)*

Strategy	Deterministic results					Probability of cost-effectiveness for different threshold values for society's willingness to pay for a life-year (%)				
	Average cost	Incremental cost	Average life-years	Incremental life-years	Incremental cost/life-year	£10,000	£20,000	£30,000	£40,000	£50,000
Starting age 77 years										
CTL_WLC (CTL_WLC)	£951		8.84			23	19	18	18	18
CTL_PDD (CTL_WLC)	£1005	£54	8.85	0.01	Extendedly dominated	11	10	9	9	9
FISH_PDD (FISH_WLC)	£1135	£184	8.87	0.04	£5041	20	17	16	16	15
IMM_PDD (IMM_WLC)	£1349	£214	8.88	0	£44,105	13	12	12	11	11
CSC_FISH_PDD (FISH_WLC)	£1911	£562	8.88	0.01	£100,340	17	18	18	19	19
CSC_PDD (CSC_WLC)	£1946	£35	8.86	–0.02	Dominated	3	6	6	7	8
CSC_IMM_PDD (IMM_WLC)	£2089	£178	8.88	<0.01	Extendedly dominated	12	16	17	18	18
CSC_IMM_PDD (CSC_WLC)	£2239	£328	8.89	<0.01	£709,968	2	3	3	3	3
Time horizon 10 years										
CTL_WLC (CTL_WLC)	£983		8.37			25	19	16	15	14
CTL_PDD (CTL_WLC)	£1034	£51	8.38	0.01	Extendedly dominated	11	11	10	10	10
FISH_PDD (FISH_WLC)	£1155	£121	8.40	0.02	£5255	26	21	21	20	19
IMM_PDD (IMM_WLC)	£1369	£213	8.40	<0.01	£54,101	17	17	17	16	16
CSC_FISH_PDD (FISH_WLC)	£1926	£557	8.41	<0.01	£121,083	13	18	19	20	21
CSC_PDD (CSC_WLC)	£1972	£46	8.39	–0.02	Dominated	2	4	6	6	7
CSC_IMM_PDD (IMM_WLC)	£2105	£179	8.41	0	Dominated	6	9	10	11	12
CSC_IMM_PDD (CSC_WLC)	£2259	£333	8.41	<0.01	£4,183,060	0	1	1	1	2

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TABLE 51 *Sensitivity analysis associated with strategy and quality of life measures*

Strategy	Deterministic results					Probability of cost-effectiveness for different threshold values for society's willingness to pay for a life-year (%)				
	Average cost	Incremental cost	Average life-years	Incremental life-years	Incremental cost/life-year	£10,000	£20,000	£30,000	£40,000	£50,000
Base case, second test in follow-up is WLC										
CTL_WLC (CTL_WLC)	£1043		11.59			21	18	17	16	15
CTL_PDD (CTL_WLC)	£1094	£51	11.60	0.01	£3423	11	10	9	9	9
FISH_PDD (FISH_WLC)	£1235	£141	11.64	0.04	£3806	20	17	16	17	17
IMM_PDD (IMM_WLC)	£1458	£223	11.65	0.01	£28,864	18	18	17	17	17
CSC_FISH_PDD (FISH_WLC)	£2005	£547	11.66	0.01	£60,284	17	18	18	18	18
CSC_PDD (CSC_WLC)	£2082	£77	11.63	–0.03	Dominated	2	4	5	5	6
CSC_IMM_PDD (IMM_WLC)	£2195	£190	11.66	<0.01	Extendedly dominated	9	14	15	15	16
CSC_IMM_PDD (CSC_WLC)	£2370	£365	11.66	<0.01	£270,375	1	3	3	3	3
Second test in follow-up is PDD										
CTL_WLC (CTL_PDD)	£1069		11.59			20	17	15	15	14
CTL_PDD (CTL_PDD)	£1119	£50	11.60	0.01	£3372	11	9	9	8	8
FISH_PDD (FISH_WLC)	£1279	£160	11.64	0.04	£4314	20	18	17	17	17
IMM_PDD (IMM_PDD)	£1517	£238	11.65	0.01	£30,839	15	15	15	15	15
CSC_FISH_PDD (FISH_PDD)	£2051	£533	11.66	0.01	£58,765	18	20	21	21	21
CSC_PDD (CSC_PDD)	£2140	£90	11.63	–0.03	Dominated	4	5	6	6	6
CSC_IMM_PDD (IMM_PDD)	£2257	£207	11.66	<0.01	Extendedly dominated	10	13	15	15	15
CSC_IMM_PDD (CSC_PDD)	£2433	£383	11.66	<0.01	£284,001	2	3	3	3	4

continued

TABLE 51 *Sensitivity analysis associated with strategy and quality of life measures (continued)*

	Deterministic results					Probability of cost-effectiveness for different threshold values for society's willingness to pay for a life-year (%)				
Strategy	**Average cost**	**Incremental cost**	**Average life-years**	**Incremental life-years**	**Incremental cost/life-year**	**£10,000**	**£20,000**	**£30,000**	**£40,000**	**£50,000**
Cost–utility analysis										
CTL_WLC (CTL_WLC)	£1043		9.00			25	20	18	18	18
CTL_PDD (CTL_WLC)	£1094	£51	9.01	0.01	£4678	11	9	9	8	8
FISH_PDD (FISH_WLC)	£1235	£141	9.04	0.03	£5051	22	20	19	18	17
IMM_PDD (IMM_WLC)	£1458	£223	9.04	<0.01	Extendedly dominated	16	16	15	15	15
CSC_FISH_PDD (FISH_WLC)	£2005	£770	9.05	0.01	£66,905	16	19	19	19	19
CSC_PDD (CSC_WLC)	£2082	£77	9.01	–0.04	Dominated	2	3	4	4	4
CSC_IMM_PDD (IMM_WLC)	£2195	£190	9.05	0	Dominated	8	12	14	15	16
CSC_IMM_PDD (CSC_WLC)	£2370	£365	9.05	0	Dominated	1	2	2	3	3

increased to £30,000. Nevertheless, over most of the range of willingness to pay values there appeared to be no strategy that would have a likelihood of being cost-effective more than 50% of the time. For example, when the willingness to pay was over £10,000 per life-year the cost-effectiveness of FISH_PDD ranged from 16% to 20%. It should be noted, however, that four out of the eight strategies considered in the sensitivity analyses each had a probability of being considered cost-effective of approximately 20%. Three of these four strategies involved a biomarker and PDD.

The results of probabilistic sensitivity analyses performed to handle the uncertainty around the parameters within the model were broadly consistent with the point estimates in the base-case analysis and did not change the order of strategies in terms of cost. The likelihood that different strategies might be considered cost-effective, however, did change in some sensitivity analyses. For example, the CSC_FISH_PDD (FISH_WLC) strategy had a 31% chance of being considered cost-effective when the prevalence rate was increased to 20% and society's willingness to pay for a life-year was £20,000. Furthermore, CSC_IMM_PDD (IMM_WLC) and CSC_FISH_PDD (FISH_WLC) had an increased chance of being cost-effective in the situation in which the sensitivity and specificity of flexible cystoscopy were increased. This is important because in the base-case analysis it was assumed that the sensitivity and specificity of flexible cystoscopy would be the same as those of WLC. Both methods of cystoscopy use white light so it might be appropriate to assume that they would identify (and miss) similar types of cancer at the same rates. However, flexible cystoscopy may be able to visualise more of the bladder than rigid cystoscopy. This means that it may be possible for flexible cystoscopy to detect more cancers. Whether this is true and, if it is true, to what extent it improves sensitivity and specificity is unclear. Overall, a potentially plausible 5% gain in performance would not greatly alter the conclusions drawn on the basis of the cost-effectiveness results.

In sensitivity analyses the results did not change greatly when the QoL estimates were used to determine QALYs. The strategies associated with flexible cystoscopy were dominated and there was a decreased chance of them being considered cost-effective. This is because flexible cystoscopy, being an invasive surgical procedure, is more likely to reduce QoL than cytology or biomarkers.

In the model WLC was considered the second test in follow-up in each strategy if the result of the first test in follow-up was positive. Sensitivity analysis suggested that the non-dominated or non-extendedly dominated strategies had slightly improved life-years with higher costs compared with the base case when WLC in follow-up was replaced by PDD. However, strategies did not markedly change in how likely they were to be cost-effective.

Chapter 7

Assessment of factors relevant to the NHS and other parties

Factors relevant to the NHS

Should strategies that involve PDD be adopted by the NHS then costs to the NHS would increase and new capital equipment would be required. It is likely, however, that learning to use PDD should be straightforward for an experienced cystoscopist and hence the training period should be short. Replacing WLC with PDD should increase the number of cancers detected but this comes at the price of an increasing number of false positives. These false positives lead to an increased workload as unnecessary tests and investigations are performed and, because these tests are unlikely to be without risk, a potential increase in complications.

The results of the economic evaluation suggest that the use of cytology as part of a diagnostic strategy might be reduced. Furthermore, the results suggest that there may be merit in the increased use of biomarkers. Changes in the use of such tests would have resource implications for the NHS and would suggest transfers of resources between those parts of the NHS involved in the conduct, analysis and interpretation of these tests.

The adoption of less invasive tests in place of more invasive tests may also allow shifts in the balance of care between secondary and primary care, at least for initial diagnosis and potentially also for follow-up. Whether such changes are desirable would of course depend upon a host of other factors in addition to feasibility, such as a desire to maintain continuity of care amongst those who have been treated for bladder cancer.

One consequence of any adoption of a more effective diagnostic test is that it may result in greater survival (as estimated in the economic evaluation). Although this outcome is desirable it is important to remember that these patients will require continuing care and follow-up over a longer period. Therefore, it is possible that workload will increase for those specialties involved in follow-up. Other longer-term effects, for example the effect on palliative services, are less easy to predict.

The results of the cost-effectiveness analysis suggest that the strategies involving PDD were likely to detect more true positive cases and produce more life-years at higher costs.

Factors relevant to other parties

Quality of life for patients

The use of strategies involving PDD, ImmunoCyt and FISH could provide advantages to patients in terms of early detection of disease and (for strategies that replace an invasive procedure with a biomarker) provide a reduction in the number of invasive procedures that they may have to undergo. These strategies are also likely to decrease the number of false negatives, which will reduce the risks from false reassurance and the psychological distress following a subsequent correct diagnosis. However, there is a price to pay for this in that strategies involving these tests are also associated with an increased chance of a false-positive diagnosis. Such a diagnosis may have health effects as further tests and investigations performed are not without risk. The false-positive diagnosis may also cause considerable anxiety and distress, not only for the patients but also for their families.

Patients and their families may also have views about which diagnostic strategy they prefer that go beyond preferences over different aspects of diagnostic performance or longer-term health effects. In particular, there may be preferences about the process of care. All things being equal patients would prefer the use of non-invasive biomarker tests to the use of unpleasant, less convenient and potentially risky invasive tests. Nevertheless, all things are not equal and there are choices and trade-offs to be made between process, short-term outcomes and long-term outcomes. Currently there are no data with which to inform decision-makers about how these different outcomes might be traded off against each other.

Chapter 8
Discussion

Statement of principal findings

Photodynamic diagnosis

Diagnostic accuracy

The included diagnostic accuracy studies reported true and false positive and negative results or provided information that allowed these data to be calculated, thereby allowing further calculation of sensitivity, specificity, positive and negative likelihood ratios, DORs and positive and negative predictive values. Most studies compared PDD with WLC. Studies comparing PDD with WLC were included in the pooled estimates (meta-analyses) using a HSROC curve model. This method takes into account the inherent trade-off between sensitivity and specificity and also allows for differences in accuracy between studies. Summary pooled estimates of the sensitivity and the specificity were calculated. Meta-analyses were performed on two levels:

- patient
- biopsy.

In addition to the meta-analysis models of the diagnostic accuracy of PDD and WLC individually, two HSROC models were run for patient- and biopsy-level analysis that simultaneously modelled PDD and WLC diagnostic accuracy from all of the studies included in the pooled estimates. Analysis was also undertaken on the sensitivity of PDD and WLC for the detection of stage and grade of bladder cancer, which was considered in two broad categories:

- less aggressive, lower risk tumours (pTa, G1, G2)
- more aggressive, higher risk tumours (pT1, G3, CIS).

The sensitivity of PDD and WLC for the detection of CIS alone was also considered. Stage and grade analysis was undertaken for both patient- and biopsy-level detection of bladder cancer. An analysis of the sensitivity of PDD according to the type of photosensitising agent used (5-ALA, HAL or hypericin) was also undertaken. Information on stage and grade analysis and type of agent used was presented as median and range across studies.

In terms of methodological quality, in all studies the spectrum of patients who received the tests was considered to be representative of those who would receive the tests in practice, partial verification bias was avoided in that all patients who underwent PDD also received a reference standard test, and test review bias was avoided in that the PDD results were considered to have been interpreted without knowledge of the results of the reference standard test. However, in only 55% (15/27) of studies were patients considered to have received the same reference standard regardless of the index test result. All of the studies were judged to have suffered from incorporation bias in that PDD was not considered to be independent of the reference standard test as the biopsies used for the reference standard were obtained via the PDD procedure.

Although biopsy-level analysis of the accuracy of the test is more commonly reported, patient-level data are more useful in determining management. Most studies took multiple biopsies from participants, leading to clustering within participants. We were unable to account for this clustering in the biopsy-level analysis and therefore estimates from the biopsy-level analysis will be to some degree artificially precise. In the pooled estimates for patient-level analysis, based on direct evidence, PDD had higher sensitivity than WLC [92% (95% CI 80% to 100%) versus 71% (95% CI 49% to 93%)] but lower specificity [57% (95% CI 36% to 79%) versus 72% (95% CI 47% to 96%)]. As for patient-level analysis, in the pooled estimates for biopsy-level analysis, based on direct evidence, PDD also had higher sensitivity than WLC [93% (95% CI 90% to 96%) versus 65% (95% CI 55% to 74%)] but lower specificity [60% (95% CI 49% to 71%) versus 81% (95% CI 73% to 90%)]. In terms of sensitivity the upper CI for WLC did not overlap with the lower CI for PDD, supporting evidence of a difference in sensitivity in favour of PDD, and for specificity the upper CI for PDD did not overlap with the lower CI for WLC, supporting evidence of a difference in specificity in favour of WLC. The corresponding CIs for the patient-level analysis were wider because of the reduced number

of studies although the direction was consistent. Although at least four of the five studies included for patient-level analysis and at least nine of the 14 studies included for biopsy-level analysis in the pooled estimates contained a mixture of patients with a suspicion of bladder cancer and those with previously diagnosed non-muscle-invasive disease, test performance in these groups was not reported separately. The formal comparison of PDD and WLC in patient- and biopsy-based analysis supported strong evidence of a difference in sensitivity in favour of PDD and in specificity in favour of WLC.

The consequence of underdiagnosis at a patient level would mean that a patient's treatment path may be detrimentally affected (e.g. discharged from follow-up or chanelled to an inappropriately low-risk follow-up pathway). The consequence of underdiagnosis at a biopsy level is that a patient may have suboptimal treatment of their known bladder cancer, for example by failure to remove an occult lesion or failure to institute a therapy because of underestimating the patient's risk category (e.g. by failing to diagnose concomitant CIS).

Across studies the median sensitivities (range) of PDD and WLC for detecting lower risk, less aggressive tumours were broadly similar for patient-level detection [92% (20% to 95%) versus 95% (8% to 100%)], but sensitivity was higher for PDD for biopsy-level detection [96% (88% to 100%) versus 88% (74% to 100%)]. However, for the detection of more aggressive, higher risk tumours the median sensitivities of PDD for both patient-level [89% (6% to 100%)] and biopsy-level [99% (54% to 100%)] detection were much higher than those of WLC [56% (0% to 100%) and 67% (0% to 100%) respectively]. The superior sensitivity of PDD was also reflected in the detection of CIS alone, both for patient-level [83% (41% to 100%) versus 32% (0% to 83%)] and biopsy-level [86% (54% to 100%) versus 50% (0% to 68%)] detection. However, these results should be interpreted with caution as, other than for PDD biopsy-based detection of lower risk disease, the range of sensitivities for both tests was very wide. [It may also be useful to note that, although not meeting the inclusion criteria for this review as information was not provided on false positives and true negatives, Schmidbauer and colleagues,[207] in a European multicentre study (19 centres), reported that, of 83 patients with CIS lesions, CIS was detected in 80 (96%) by PDD (HAL) compared with 64 (77%) by WLC.]

In terms of the relative sensitivities of the photosensitising agents used, for patient-level detection of bladder cancer, the median sensitivity (range) of 5-ALA was slightly higher than that of HAL [96% (64% to 100%) versus 90% (53% to 96%)] whereas HAL had higher specificity than 5-ALA [81% (43% to 100%) versus 52% (33% to 67%)]. This situation was also reflected in biopsy-based detection, with 5-ALA associated with higher sensitivity [95% (87% to 98%) versus 85% (76% to 94%)] but lower specificity [57% (32 to 67%) versus 80% (58 to 100%)] than HAL. One study, by Sim and colleagues,[76] reporting biopsy-based detection of bladder cancer, used hypericin, reporting sensitivity of 82% and specificity of 91%. These results suggest that 5-ALA may be associated with slightly higher sensitivity than HAL and that HAL has higher specificity than 5-ALA, but this should be interpreted with caution as a number of factors other than the photosensitising agent used may have contributed to the sensitivity and specificity values reported by the studies.

Twelve studies[51–53,61–63,65,71–73,78,81] involving 1543 patients reported that there were no side effects or no serious side effects associated with the photosensitising agent used. Seven studies[50,57,66,67,71,76,77] involving 746 patients reported 41 side effects associated with the agent (5-ALA, 19; HAL, 21; hypericin, 1), none of which was considered to be serious.

No other systematic reviews of PDD for detecting bladder cancer or reporting effectiveness outcomes such as tumour recurrence were identified.

In summary, compared with WLC, PDD has higher sensitivity (fewer false negatives) and so will detect cases of bladder cancer that are missed by WLC. However, compared with WLC, PDD's lower specificity (more false positives) will result in additional, unnecessary biopsies of non-cancerous tissue being taken and sent for analysis. Reasons cited in the literature for PDD false-positive results include: (1) inexperience in using PDD, in which the application of tangential fluorescence light may cause fluorescence in normal urothelium, (2) simple hyperplasia, (3) lesions with inflammation or scarring after previous TURBT when PDD was carried out within 6 weeks of the previous procedure and (4) previous instillation therapy within 3–6 months of PDD.[208,209] De Dominicis and colleagues[53] noted that a greater number of false-positive lesions were detected during the period when the authors were still not sufficiently trained in the PDD procedure, particularly in the first 15

patients. In terms of the detection of stage and grade of tumour, the results suggest that PDD is much more sensitive than WLC in the detection of more aggressive, higher risk tumours, and the superior performance of PDD is also reflected in the detection of CIS alone. From a clinical point of view, compared with WLC, the advantages of PDD's higher overall sensitivity in detecting bladder cancer and also its higher sensitivity in detecting more aggressive, higher risk tumours have to be weighed against the disadvantages of a higher false-positive rate leading to additional, unnecessary biopsies of normal tissue being taken and potentially additional unnecessary investigations being carried out and the resulting anxiety caused to patients and their families.

Recurrence/progression of disease

Jain and Kockelbergh[210] noted that the high recurrence rate of superficial bladder cancer, up to 70% at 5 years, was responsible for a huge workload for urologists and much inconvenience for patients. They stated that the recurrence rate at the first check cystoscopy varied enormously, suggesting that incomplete resection or failure to detect small additional tumours may be a risk factor.[210] The evidence from the diagnostic accuracy part of this review suggests that PDD has a higher sensitivity for the detection of bladder cancer than WLC. Therefore, compared with WLC, the use of PDD during initial TURBT may be expected to result in lower recurrence and progression rates, given that some tumours, including more aggressive, higher risk tumours such as CIS, that might be missed by WLC will be detected by PDD.

For the assessment of PDD-assisted TURBT compared with WLC in terms of effectiveness outcomes such as recurrence and progression, this review focused on RCTs. Four RCTs (reported in eight papers) involving 544 participants met the inclusion criteria. In terms of methodological quality, in all four studies the groups were considered to be similar at baseline in terms of prognostic factors, eligibility criteria for the studies were specified and the length of follow-up was considered adequate in relation to the outcomes of interest. However, in all studies it was unclear whether the sequence generation was really random or whether treatment allocation was adequately concealed.

When meta-analysis was undertaken, the results were reported using RR as the effect measure and a fixed-effect model in the absence of statistical heterogeneity, otherwise a random-effects model was used. Two studies[86,89] reported recurrence-free survival at 12 and 24 months. In pooled estimates the direction of effect for both time points favoured PDD, although the difference was statistically significant only at the 24-month time point (RR 1.37, 95% CI 1.18 to 1.59).

Four studies[86,88,89,92] reported residual tumour rate at first cystoscopy following TURBT. In pooled estimates PDD was associated with both statistically significantly fewer residual pTa tumours (RR 0.32, 95% CI 0.15 to 0.70) and fewer residual pT1 tumours (RR 0.26, 95% CI 0.12 to 0.57) than WLC (overall pooled estimate RR 0.37, 95% CI 0.20 to 0.69). Two of the studies[86,88] also reported residual tumour according to grade (G1, G2 and G3). Pooled estimates for G1 (RR 0.13, 95% CI 0.03 to 0.71) and G2 (RR 0.32, 95% CI 0.16 to 0.64) were statistically significant in favour of PDD, with the direction of effect for G3 favouring PDD without reaching statistical significance (RR 0.57, 95% CI 0.21 to 1.56), and the overall pooled estimate was statistically significant in favour of PDD (RR 0.31, 95% CI 0.18 to 0.53).

Two studies[88,89] reported tumour recurrence rate during follow-up (5 years and 8 years respectively). In pooled estimates the direction of effect favoured PDD without reaching statistical significance (RR 0.64, 95% CI 0.39 to 1.06). Both studies[88,89] also reported tumour progression during their respective follow-up periods and again in the pooled estimates the direction of effect favoured PDD without reaching statistical significance (RR 0.57, 95% CI 0.22 to 1.46).

Two studies[86,88] reported time to recurrence, both favouring PDD. Babjuk and colleagues[86] reported a median time to recurrence of 17.05 months for the PDD group and 8.05 months for the WLC group, whereas Daniltchenko and colleagues[88] reported a median (range) time to recurrence of 12 (2 to 58) months for the PDD group and 5 (2 to 52) months for the WLC group.

In summary, the evidence from the RCTs[86,88,89,92] suggests that, compared with WLC, the use of PDD during TURBT results in a statistically significant and large reduction in residual pTa and pT1 tumours, longer recurrence-free survival of patients at 2 years following surgery and a longer interval between TURBT and tumour recurrence. However, these results should be interpreted with caution as they are based on data from only four small studies. Based on the limited evidence it is unclear whether PDD compared with WLC is associated with lower

tumour recurrence and progression rates in the longer term. Also, as discussed in the section on uncertainties, the administration of adjuvant intravesical therapy varied across the studies, making it difficult to assess what the true added value of PDD might be in reducing recurrence rates in routine clinical practice.

Biomarkers and cytology

The included diagnostic accuracy studies reported true and false positive and negative results or provided information that allowed these data to be calculated, thereby allowing the further calculation of sensitivity and specificity, positive and negative likelihood ratios, DORs and positive and negative predictive values for the three included urine biomarkers (FISH, ImmunoCyt and NMP22) and cytology. Meta-analyses were undertaken for each of the individual biomarkers and cytology for patient-based detection of bladder cancer using the HSROC model. Additional meta-analyses were also undertaken on the subset of studies included in the pooled estimates that directly compared biomarkers with cytology. Analysis was also undertaken on the sensitivity of the biomarkers and cytology for the detection of stage and grade of bladder cancer, which was considered in the two broad categories previously referred to (less aggressive/lower risk tumours and more aggressive/higher risk tumours), and also for detection of CIS alone.

For each biomarker only those studies that were considered to have a similar ('common') cut-off, which was generally taken to be the most frequently used cut-off across studies, were included in the meta-analyses. The common cut-off was also used when studies reported results using a number of different cut-offs. The following common cut-offs were used: FISH, gains of two or more chromosomes or five or more cells with polysomy or four or more aneusomic of 25 counted cells; ImmunoCyt, at least one green or one red fluorescent cell; NMP22, 10 U/ml; urine cytology, cytologist subjective assessment.

In terms of methodological quality, in all 71 studies the reference standard (cystoscopy with histological assessment of biopsied tissue) was considered likely to correctly classify bladder cancer. In 99% (70/71) of studies the spectrum of patients receiving the tests was considered to be representative of those who would receive the test in practice, and incorporation bias was avoided in that the reference standard was independent of the biomarker/cytology test. In 96% (68/71) of studies partial verification bias was avoided in that all patients who received a biomarker/cytology test also received a reference standard test, and in 87% (62/71) of studies differential verification bias was avoided in that all patients received the same reference standard regardless of the index test result. However, only 69% (49/71) of studies were considered to have given a clear definition of what constituted a positive result.

Table 52 shows the pooled estimates (sensitivity, specificity, DORs) as well as the median (range) positive and negative predictive values across studies for the biomarkers and cytology for patient-based detection of bladder cancer. In the pooled estimates, based on indirect evidence, sensitivity was highest for ImmunoCyt at 84% (95% CI 77% to 91%) and lowest for cytology at 44% (95% CI 38% to 51%). ImmunoCyt (84%, 95% CI 77% to 91%) had higher sensitivity than NMP22 (68%, 95% CI 62% to 74%), with the lack of overlap between the CIs supporting evidence of a difference in sensitivity in favour of ImmunoCyt over NMP22. FISH (76%, 95% CI 65% to 84%), ImmunoCyt (84%, 95% CI 77% to 91%) and NMP22 (68%, 95% CI 62% to 74%) all had higher sensitivity than cytology (44%, 95% CI 38% to 51%), and again the lack of overlap of the CIs between the three biomarkers and cytology supported evidence of a difference in sensitivity in favour of the three biomarkers over cytology. This situation was reversed for specificity, which was highest for cytology at 96% (95% CI 94% to 98%) and lowest for ImmunoCyt at 75% (68% to 83%). Cytology (96%, 95% CI 94% to 98%) had higher specificity than FISH (85%, 95% CI 78% to 92%), ImmunoCyt (75%, 95% CI 68% to 83%) or NMP22 (79%, 95% CI 74% to 84%), with the lack of overlap of the CIs between cytology and the three biomarkers supporting evidence of a difference in specificity in favour of cytology over the biomarkers.

DORs (95% CI) ranged from 8 (5 to 11) to 19 (6 to 26), with higher DORs indicating a better ability of the test to differentiate between those with and those without bladder cancer. Based on the DOR values, FISH and cytology performed similarly well [18 (3 to 32) and 19 (11 to 27) respectively], ImmunoCyt slightly less so [16 (6 to 26)] and NMP22 relatively poorly [8 (5 to 11)]. However, as the DOR confidence intervals for each of the tests all overlapped these results should be interpreted with caution.

TABLE 52 *Summary of pooled estimate results and predictive values for biomarkers and cytology for patient-based detection of bladder cancer*

Test	Number of studies	Number analysed	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	DOR (95% CI)	PPV (%), median (range)	NPV (%), median (range)
FISH	12	2535	76 (65 to 84)	85 (78 to 92)	18 (3 to 32)	78 (27 to 99)	88 (36 to 97)
ImmunoCyt	8	2896	84 (77 to 91)	75 (68 to 83)	16 (6 to 26)	54 (26 to 70)	93 (86 to 100)
NMP22	28	10,119	68 (62 to 74)	79 (74 to 84)	8 (5 to 11)	52 (13 to 94)	82 (44 to 100)
Cytology	36	14,260	44 (38 to 51)	96 (94 to 98)	19 (11 to 27)	80 (27 to 100)	80 (38 to 100)

Across studies the median (range) PPVs were 80% (27% to 100%) for cytology (36 studies), 78% (27% to 99%) for FISH (12 studies), 54% (26% to 70%) for ImmunoCyt (eight studies) and 52% (13% to 94%) for NMP22 (28 studies). NPVs were 93% (86% to 100%) for ImmunoCyt, 88% (36% to 97%) for FISH, 82% (44% to 100%) for NMP22 and 80% (38% to 100%) for cytology. However, it should be noted that predictive values are affected by disease prevalence, which is rarely constant across studies.

Five studies[80,126,127,131,150] reporting NMP22 used the BladderChek point of care test. Across these studies, using a cut-off of 10 U/ml for a positive test result, the median (range) sensitivity and specificity for patient-based detection of bladder cancer were 65% (50% to 85%) and 81% (40% to 87%) respectively. This is broadly similar to the 68% (95% CI 62% to 74%) sensitivity and 79% (95% CI 74% to 84%) specificity for the 28 studies included in the pooled estimates.

In terms of the detection of stage/grade of tumour, ImmunoCyt had the highest median sensitivity across studies (81%) for the detection of less aggressive/lower risk tumours whereas FISH had the highest median sensitivity across studies (95%) for the detection of more aggressive/higher risk tumours. For detection of CIS the median sensitivity across studies for both FISH and ImmunoCyt was 100%. Cytology had the lowest sensitivity across studies for detecting less aggressive/lower risk tumours (27%), more aggressive/higher risk tumours (69%) and also CIS (78%). For each of the tests, the median sensitivity across studies was consistently higher for the detection of more aggressive/higher risk tumours than for the detection of less aggressive, lower risk tumours. The results for the stage/grade analysis should be interpreted with caution, however, as they are based on a relatively small number of studies for ImmunoCyt ($n = 6$) and FISH ($n = 10$), as are the results for the detection of CIS (ImmunoCyt, $n = 6$; FISH, $n = 8$; NMP22, $n = 11$). Additionally, for all of the tests the range of sensitivities across the studies for detecting stage/grade (both lower and higher risk) and CIS was very wide.

Some studies included in the pooled estimates for the individual tests also directly compared tests, comparing FISH with cytology (five studies), ImmunoCyt with cytology (six studies) and NMP22 with cytology (16 studies). In each set of comparisons cytology had lower sensitivity but higher specificity than the biomarker with which it was being compared. ImmunoCyt had higher sensitivity (82%, 95% CI 76% to 89%) than cytology (44%, 95% CI 35% to 54%), whereas cytology had higher specificity (94%, 95% CI 91% to 97%) than ImmunoCyt (85%, 95% CI 71% to 85%), with the lack of overlap of the CIs supporting evidence of differences in sensitivity in favour of ImmunoCyt and in specificity in favour of cytology. Similarly, NMP22 had higher sensitivity (70%, 95% CI 59% to 80%) than cytology (40%, 95% CI 31% to 49%), whereas cytology had higher specificity (97%, 95% CI 95% to 99%) than NMP22 (81%, 95% CI 74% to 88%), with the lack of overlap of the CIs supporting evidence of differences in sensitivity in favour of NMP22 and in specificity in favour of cytology. The pooled estimates for the sensitivity and specificity of the tests in the direct comparison studies were broadly similar to those reported for the individual tests. The formal comparison for a difference between tests supported a difference between both ImmunoCyt and NMP22, and cytology, but there was no evidence for a difference between FISH and cytology. The latter finding was based upon a small number of studies and therefore a real difference may exist as implied by the results for the individual tests, which were based upon a larger number of studies.

In studies reporting the sensitivity and specificity of tests used in combination, sensitivity was generally

higher but specificity lower for the combined tests compared with the higher value of the two individual tests. Most combinations of tests were reported by only one or two studies apart from the combination of ImmunoCyt and cytology, which was reported by eight studies.

In studies specifically reporting unevaluable tests, rates were 6.1% (65/1059, five studies) for FISH, 5% (279/5292, 10 studies) for ImmunoCyt and 2% (54/2566, six studies) for cytology. None of the NMP22 studies specifically reported unevaluable tests.

A few other systematic reviews have reported the sensitivity and specificity of biomarkers and cytology for detecting bladder cancer (*Table 53*). In a systematic review and meta-analysis of biomarkers for the surveillance monitoring of previously diagnosed bladder cancer Lotan and Roehrborn[211] reported, amongst other biomarkers, ImmunoCyt, NMP22 and cytology. A systematic review by Glas and colleagues[212] of tumour markers in the diagnosis of primary bladder cancer reported, amongst others, NMP22 and cytology. A systematic review by van Rhijn and colleagues[213] of urine markers for bladder cancer surveillance reported, amongst others, FISH, ImmunoCyt, NMP22 and cytology. Our results for the sensitivity and specificity of FISH, ImmunoCyt, NMP22 and cytology were mostly similar to those reported by the other reviews, other than we reported higher specificity for FISH (85% compared with 70%), higher sensitivity for ImmunoCyt (84% compared with 67%) and slightly higher specificity for NMP22 (79% compared with 73%) than van Rhijn and colleagues,[213] respectively, and, for cytology, higher sensitivity than Lotan and Roehrborn[211] and van Rhijn and colleagues[213] (44% compared with 34% and 35% respectively) but lower sensitivity than Glas and colleagues (44% compared with 55% respectively).[212]

Strengths and limitations of the assessment

Diagnostic accuracy/ effectiveness

In terms of strengths, for PDD/WLC effectiveness outcomes such as recurrence we focused only on RCTs. In biomarker/cytology case–control studies in which the control group contained a proportion of completely healthy controls, the control group was reanalysed minus the healthy controls to try to make it more representative of the types of people who would receive the tests in practice. If this was not possible the study was excluded. Case–control studies in which the whole control group consisted of healthy volunteers were excluded.

In terms of limitations, non-English language studies were excluded, as were biomarker studies with fewer than 100 patients included in the analysis. Cytology studies whose publication year predated the publication year of the earliest included biomarker study were excluded. Although most studies contained a mixture of patients with a suspicion of bladder cancer and those with a history of previously diagnosed bladder cancer, few studies reported results for these groups separately. Only five of the 41 included NMP22 studies used the BladderChek point of care test.

Uncertainties

Diagnostic accuracy/ effectiveness

PDD in the clinical pathway

PDD could potentially be used in conjunction with rigid WLC at different stages in the clinical pathway, including initial diagnosis and treatment and surveillance monitoring. As with rigid WLC, PDD is not only a diagnostic test but also involves treatment in that during the procedure suspicious lesions are not only identified but also removed. Although most of the studies included in the pooled estimates for both patient- and biopsy-level analysis contained a mixture of patients with a suspicion of bladder cancer and those with previously diagnosed non-muscle-invasive disease, test performance in these groups was not reported separately. In the pooled estimates for both patient- and biopsy-level analysis, PDD had higher sensitivity than WLC but lower specificity. Across studies the median sensitivities (range) of PDD and WLC for detecting lower risk, less aggressive tumours were broadly similar for patient-level detection but the sensitivity of PDD was higher than that of WLC for biopsy-level detection. However, for the detection of more aggressive, higher risk tumours the median sensitivities of PDD for both patient- and biopsy-level detection were much higher than those of WLC and this superior sensitivity of PDD was also reflected in the detection of CIS alone. This suggests that the appropriate point in the clinical pathway for PDD to be used is in conjunction with rigid WLC during the initial TURBT, and possibly also in conjunction with rigid WLC during surveillance monitoring of some high-risk patients.

TABLE 53 *Systematic reviews/meta-analyses reporting sensitivity and specificity of biomarkers included in the present review*

	FISH			ImmunoCyt			NMP22			Cytology		
	No. of studies	**Sensitivity (%)**	**Specificity (%)**	**No. of studies**	**Sensitivity (%)**	**Specificity (%)**	**No. of studies**	**Sensitivity (%)**	**Specificity (%)**	**No. of studies**	**Sensitivity (%)**	**Specificity (%)**
Present review	12	76 (65 to 84)	85 (78 to 92)	8	84 (77 to 91)	75 (68 to 83)	28	68 (62 to 74)	79 (74 to 84)	36	44 (38 to 51)	96 (94 to 98)
Glas 2003[212]	–	–	–	–	–	–	14	67 (60 to 73)	78 (72 to 83)	26	55 (48 to 62)	94 (90 to 96)
Lotan 2003[211]	–	–	–	1	86	79	15	73 (47 to 87)	80 (58 to 91)	18	34 (20 to 53)	99 (83 to 99)
van Rhijn 2005[213]	4	79 (70 to 86)	70 (66 to 93)	6	67 (52 to 100)	75 (62 to 82)	15	71 (47 to 100)	73 (55 to 98)	26	35 (13 to 75)	94 (85 to 100)

Figures in parentheses are 95% CIs apart from the study by van Rhijn and colleagues, which reported medians and ranges.

In the four studies reporting effectiveness outcomes, PDD was used during the initial TURBT. Patients were randomised to WLC- or WLC- and PDD-assisted TURBT,[86,89,92] or WLC- or PDD-assisted TURBT.[88] In the studies by Babjuk and colleagues,[86] Denzinger and colleagues[89] and Kriegmair and colleagues[92] residual tumour in both groups was evaluated by WLC-assisted resection. However, in the study by Daniltchenko and colleagues[88] residual tumour in both groups was evaluated by PDD-assisted resection. In three studies the patients were followed up using WLC and urinary cytology.[86,88,89] (As the aim of the study by Kriegmair and colleagues[92] was to assess residual tumour 10–14 days following TURBT there was no longer-term follow-up).

Adjuvant chemotherapy

Adjuvant single-dose chemotherapy administered within the first 24 hours and ideally within the first 6 hours following TURBT is standard practice in the UK and much of Europe and can reduce recurrence rates by up to 50% in the first 2 years. However, the administration of adjuvant intravesical therapy varied across the four studies reporting effectiveness outcomes. The study by Kriegmair and colleagues[92] did not state whether intravesical therapy was given. The study by Daniltchenko and colleagues[88] reported that none of the patients received adjuvant intravesical therapy. In the study by Babjuk and colleagues[86] none of the patients with grade 1 or grade 2 tumours received intravesical therapy, whereas all those with grade 3 tumours received intravesical BCG immunotherapy. In the study by Denzinger and colleagues[89] patients with a solitary primary tumour staged pTaG1–G2 (low-risk group) did not receive intravesical therapy, whereas those with multifocal tumours staged pTaG1–G2 or pT1G1–G2 (intermediate-risk group) underwent mitomycin therapy and those with primary stage pT1G3, CIS or treatment failure with mitomycin (high-risk group) received BCG therapy. In this study, although there were consistently fewer recurrences for PDD compared with WLC across all risk groups, the difference in recurrence rates between PDD and WLC was smaller in the intermediate- and high-risk groups, both of which received adjuvant intravesical therapy, than it was in the low-risk group.[89] The fact that adjuvant intravesical therapy was not given to all of the patients in all of the studies makes it difficult to assess what the true added value of PDD might be in reducing bladder tumour recurrence rates in routine practice.

Biomarker/cytology test performance in patients with a suspicion of bladder cancer and those with a history of non-muscle-invasive disease

It is possible that the diagnostic accuracy of urine biomarkers/cytology may differ in patients newly presenting with a suspicion of bladder cancer compared with those with a previous history of non-muscle-invasive disease. Most of the included studies contained a mixture of patients with a suspicion of bladder cancer and those with previously diagnosed disease but did not report results for these groups separately. However, in a few of the studies included in the pooled estimates that reported patient-level analysis the whole patient population consisted either of one or other of these groups. *Table 54* shows, for each test, the median (range) sensitivity and specificity across studies containing those newly presenting with symptoms of bladder cancer and those with previously diagnosed non-muscle-invasive disease. For each test, both sensitivity and specificity were slightly higher for the studies containing patients newly presenting with symptoms of bladder cancer, although these results should be interpreted with caution as they are based on limited evidence, especially for FISH and ImmunoCyt.

Biomarkers as a replacement for cytology

In the pooled estimates the lack of overlap of the CIs between the three biomarkers and cytology supported evidence of the biomarkers' superior sensitivity over cytology. ImmunoCyt had the highest sensitivity (84%, 95% CI 77% to 91%), followed by FISH (76%, 95% CI 65% to 84%) and NMP22 (68%, 95% CI 62% to 74%), with cytology having the lowest sensitivity (44%, 95% CI 38% to 51%). This situation was reversed for specificity, with the lack of overlap of the CIs between cytology and the three biomarkers supporting evidence of cytology's superior specificity over all three biomarkers. The specificity of cytology was 96% (95% CI 94% to 98%), compared with 85% (95% CI 78% to 92%) for FISH, 79% (95% CI 74% to 84%) for NMP22 and 75% (95% CI 68% to 73%) for ImmunoCyt. The question of whether biomarkers might replace cytology depends on the relative importance of higher sensitivity (fewer false-negative results) compared with higher specificity (fewer false-positive results). If the sensitivity of the test was seen as being more important than its specificity then a test such as ImmunoCyt could be regarded as a potential candidate for replacing cytology. However, if the specificity of the test

TABLE 54 *Biomarker/cytology test performance in patients with a suspicion of bladder cancer and those with previously diagnosed disease*

Test	Suspicion/previous history of BC	Number of studies	Number analysed	Sensitivity (%), median (range)	Specificity (%), median (range)
FISH	Suspicion of BC	1	497	69	78
	Previous history of BC	1	250	64	73
ImmunoCyt	Suspicion of BC	1	280	85	88
	Previous history of BC	1	326	81	75
NMP22	Suspicion of BC	4	1893	71 (56 to 100)	86 (80 to 87)
	Previous history of BC	7	4284	69 (50 to 85)	81 (46 to 93)
Cytology	Suspicion of BC	7	3331	44 (16 to 100)	99 (87 to 100)
	Previous history of BC	6	4195	38 (12 to 47)	94 (83 to 97)

BC, bladder cancer.
Values for sensitivity and specificity are medians and ranges across studies.

was seen as being more important then cytology would remain the test of choice, given its superior specificity over all three biomarkers. A highly sensitive test will have few false negatives, whereas a highly specific test will have few false positives. In the case of high-risk bladder cancer, for example, the consequences of a false-negative test result are potentially great, whereas those of a false-positive test result are relatively low, inasmuch as these patients are unlikely to progress to a significantly morbid treatment without a further diagnostic test.

Biomarkers as a replacement for flexible cystoscopy in monitoring patients with a history of low-risk bladder cancer

There have been suggestions that, given appropriate sensitivity, a biomarker might replace the use of some flexible cystoscopy for monitoring patients with a history of low-risk bladder cancer. In the pooled estimates the median (95% CI) sensitivity was 84% (77% to 91%) for ImmunoCyt, 76% (65% to 84%) for FISH and 68% (62% to 74%) for NMP22. ImmunoCyt at 84% had the highest sensitivity but this may still be regarded as too low for its consideration as a replacement for flexible cystoscopy. Messing and colleagues[111] stated that for all biomarkers the lowest sensitivity was for detecting low-grade tumours, which would be of concern if these tests were used to replace some cystoscopic examinations for monitoring patients with a history of low-risk bladder cancer. Also, a study by Yossepowitch and colleagues[214] interviewed 200 consecutive patients previously diagnosed with non-muscle-invasive bladder cancer who were undergoing outpatient flexible cystoscopy at follow-up. The authors reported that, of the 200 patients, 75% would accept the results of a urine test as a replacement for cystoscopy only if it was capable of detecting more than 95% of recurrent bladder tumours. Anxiety associated with the possibility of missing cancer was given as the major determinant of the minimal accepted accuracy.[214] However, these findings may not take account of the fact that cystoscopy itself may not have perfect sensitivity.

Random biopsies

There appears to be no general consensus on whether random biopsies of normal-appearing areas of the bladder should be undertaken during cystoscopy. Some authors[54,68] argue that flat lesions such as dysplasias and CIS may be difficult to visualise and therefore random biopsies should be undertaken. Kiemeney and colleagues,[215] in a study involving 854 patients with superficial bladder cancer, noted that random biopsies from normal-appearing areas revealed important histological findings that were of high prognostic value. However, Witjes and colleagues,[194] in a study of 1026 patients, claimed that random biopsies were of little value in determining patients' prognosis. In a study by van der Meijden and colleagues,[216] the authors stated that in approximately 90% of patients the biopsies of normal-appearing urothelium in patients with stage Ta or T1 bladder cancer showed no abnormalities and therefore did not contribute to staging or to the correct choice of adjuvant therapy following TURBT. Jichlinski and colleagues[65] stated that random biopsies of normal urothelium remained a subject of controversy and did not recommend their use in the general

population of patients with non-muscle-invasive bladder cancer.

Cost-effectiveness analysis

Statement of principal findings

The base-case analysis was based on a 5% prevalence rate of bladder cancer regardless of whether the cost-effectiveness measure was presented in terms of either cost per true positive case detected or cost per life-year. Flexible cystoscopy and ImmunoCyt followed by PDD in initial diagnosis and flexible cystoscopy followed by WLC in follow-up [CSC_IMM_PDD (CSC_WLC)], which produced on average 11.66 life-years and had a mean cost of £2370 per patient, was the most costly among the diagnostic strategies considered in this study. The CTL_WLC strategy was the least costly (£1043) and least effective (11.59 life-years). There were six 'non-dominated' or non-extendedly dominated strategies in the base-case model when outcomes were measured in terms of incremental cost per life-year: CTL_WLC (CTL_WLC), CTL_PDD (CTL_WLC), FISH_PDD (FISH_WLC), IMM_PDD (IMM_WLC), CSC_FISH_PDD (FISH_WLC) and CSC_IMM_PDD (CSC_WLC). Although the differences between these appear to be small in terms of cost and effects, it is important to remember that in only 5% of patients in the base-case analysis would testing provide any gain. The important issue is what society would be willing to pay for additional gain. The base-case results of the economic model indicated that the diagnostic strategy that would be cost-effective depends upon the value that society would be willing to pay to obtain an additional life-year. Cytology followed by WLC as the initial diagnosis and follow-up using the same interventions [CTL_WLC (CTL_WLC)] had a greater chance of being cost-effective when the willingness to pay was less than £20,000 per life-year. However, when the willingness to pay was increased to £30,000 per life-year IMM_PDD (IMM_WLC), FISH_PDD (FISH_WLC) and CSC_FISH_PDD (FISH_PDD) also had a greater probability of being cost-effective. Nevertheless, over most of the range of willingness to pay values there appeared to be no strategy that would have a likelihood of being cost-effective more than 50% of the time. For example, when the willingness to pay was over £10,000 per life-year the cost-effectiveness of FISH_PDD (FISH_WLC) ranged from 16% to 20%. Of note, however, is that four of the eight strategies considered in the probabilistic analysis were each associated with a 20% probability of being considered cost-effective at a range of values that society might be willing to pay. Three of these four strategies involved the use of a biomarker and PDD.

Results of probabilistic sensitivity analyses performed to handle the uncertainty around the parameters within the model were broadly consistent with the point estimates in the base-case analysis and did not change the order of strategies in terms of cost. However, the likelihood that different strategies might be considered cost-effective changed when some of the parameters were varied. For example, the CSC_FISH_PDD (FISH_WLC) strategy had a 25% chance of being considered cost-effective when the prevalence rate was increased to 20% and society's willingness to pay for a life-year was £20,000. There was some concern that, because of lack of data, the performance of flexible cystoscopy might be underestimated. Sensitivity analyses suggest that plausible (but contentious) increases in diagnostic performance would not alter the conclusions drawn.

In the cost–consequence analysis presented as part of the economic evaluation it was shown that the different strategies were likely to vary not only in terms of long-term performance but also in terms of short-term diagnostic performance. It is likely that patients will have preferences about these different short-term outcomes that would not be reflected in estimates of life-years or indeed in QALYs based upon standard generic instruments such as the EQ-5D. Furthermore, as indicated in Chapter 7 patients may also have preferences about the process of care (including the use of non-invasive tests). The net impact of including these other potential benefits is unclear at present and might be considered as an area for further research.

Strengths and limitations

This work is important as it is the first study to evaluate the cost-effectiveness of the diagnostic and follow-up strategies in patients with bladder cancer. The analysis considered the use of PDD, biomarkers and cytology, in a variety of combinations, using a decision tree and a Markov model.

A structured literature search was performed to identify existing economic analyses of the diagnosis and management of patients with bladder cancer. No studies were identified that directly compared the interventions under consideration. The approach adopted in this study provides an explicit, reproducible methodology with which to

consider the interventions under consideration. Based on the relevant guidelines and detailed discussion with clinical experts involved in this study, the care pathways were developed to build up the structure of an economic model. The methods used to estimate the parameters used in the model were explicit and systematic and sought to identify the best available evidence.

Although the methods adopted to obtain the parameter estimates sought to identify the best evidence available, the results should be interpreted with caution as there are uncertainties and assumptions made in the economic model. For example, there was no evidence of what happens to patients who have false-negative results. It is likely that bladder cancers missed in initial diagnosis would not be treated until later, resulting in the risk of faster progression of disease. It was also difficult to identify suitable data on how quickly untreated bladder cancer progresses compared with treated bladder cancer. In the model a RR of progression or mortality comparing no treatment (false-negative results) with treatment (treatment of true positives) was used. In the base-case analysis it was assumed that the rate of RRs for progression (to muscle-invasive disease) and mortality for patients who did not receive treatment (i.e. those falsely diagnosed as negative) compared with those who did receive treatment (i.e. those correctly diagnosed as positive) was 2.56. It should be noted, however, that the sensitivity analysis that addressed this assumption had very little impact on the results because there were small differences in false-negative cases (or proportions) between strategies at the level of prevalence (5%) of bladder cancer considered in the base-case analysis, indicating that this variable might not be that important as a determinant of cost-effectiveness.

The model structure focused on the diagnosis and management of bladder cancer. The costs and benefits of identifying and treating other causes of the symptoms (e.g. upper urinary tract problems, etc.) that patients presented with have not been included. The net effect of not including this in a model is uncertain.

Besides the uncertainties surrounding the parameter estimates there were several other limitations to the report. One of the limitations of the economic evaluation was that it was not possible to perform analysis on the impact of diagnosis and treatment of bladder cancer on QoL as there were no data based on a generic economic tool. Although QoL data for other urological cancers were available, after discussion with clinical experts they were deemed not to be generalisable to this group of patients. A simple sensitivity analysis suggested that the inclusion of QoL estimates may not greatly change the results. However, further research to elicit relevant health rate utilities would be useful.

Another challenge was that it was not possible to conduct subgroup analysis because of a lack of data relating to subgroups. The subgroups considered in this study were number of tumours on first cystoscopic examination; type of tumour; tumour recurrence at the first 3-month cystoscopic examination following TURBT; and diagnostic performance of the different PDD photosensitising agents. Also considered were types of tumour and tumour recurrence on diagnostic performance of the different categories of urine biomarker; and whether the urine sample for urine biomarkers was voided or obtained by bladder wash. More data are needed to perform these subgroup analyses.

Another limitation was the lack of evidence on the performance of flexible cystoscopy, although it is the most commonly used test in current UK practice. The reasons for lack of evidence for flexible cystoscopy may be attributable to the fact that it is an invasive procedure purely based on the judgement of the person performing it, making it difficult to evaluate the subjective outcome. Sensitivity analysis showed that potentially plausible improvements in the performance of flexible cystoscopy may not be meaningful.

Another limitation was the determination of the most appropriate value for the prevalence rate of bladder cancer in the population that presents with various symptoms of bladder cancer. There is evidence that the prevalence rate may vary depending on the symptoms that the patients present with. Ideally the population in the model should have been based on patients who had primary bladder cancer without a cancer history. However, it was difficult to establish relevant numbers from the review of effectiveness as the results were based on both first-time presentations as well as repeat patients. It can be argued that the prevalence rate considered in the model may either overestimate or underestimate the number of people with primary bladder cancer. Sensitivity analysis results indicated that the prevalence rate has a big impact on the cost-effectiveness results. At a low level of prevalence (e.g. 1%) it is most likely that the least costly strategy [CTL_WLC (CTL_WLC)] would be cost-effective over most of the

strategy range for a cost per life-year that society might be willing to pay. At higher prevalences (e.g. 20%) it is more likely that the more costly but more effective strategies would be considered worthwhile. One implication of the sensitivity of the model to prevalence rates is that it suggests that should a subgroup of the population be identified that has a higher expected prevalence rate then it is possible that more effective (but more costly) strategies would be worthwhile for such patients. Further research could consider whether such subgroups could be identified.

The economic evaluation may suffer from other limitations in addition to those related to the evidence base. A number of assumptions were made with respect to the way that the decision tree and the Markov model were constructed. These assumptions were mostly made because of the lack of data to populate the model. As mentioned in Chapter 6, it was assumed that the cycle lengths for risk groups were the same during follow-up. Given the different intensities of follow-up for different types of bladder cancer, in practice there would be more than one opportunity per cycle for recurrent cancer to be diagnosed for some risk groups.

A further assumption was made regarding the management of patients following recurrent disease. During follow-up following treatment for bladder cancer, individuals could be incorrectly identified as still clear of cancer at a follow-up visit (i.e. be a false-negative). There were no data to help model the impact of missing a cancer on follow-up on mortality and progression. However, in our model all patients would have relatively frequent repeat testing during follow-up so the impact of this limitation is debatable.

Uncertainty in cost-effectiveness

Although cost-effectiveness analysis was performed using the best available data there was some uncertainty surrounding some of the parameters used in the model. One of these parameters was the risk group categorisation of non-muscle-invasive disease. The ideal categorisation would need to be based on all six prognostic risk factors and include long-term survival and disease-free information. As mentioned in Chapter 1, although the EORTC classification was the most recently recommended version and may have been the ideal one to be adopted in the model, it was not possible to use because of its complexity. Also, there were no reliable data associated with the risk groups. In addition, the diagnostic technology for follow-up of bladder cancer may depend on the risk level for progression and recurrence, for example T1G3 and CIS will always be followed up using rigid cystoscopy. It is acknowledged that the definition of risk groups may affect the judgement of cost-effectiveness in the model. However, the sensitivity analysis suggested that there is only a slight impact on base-case analysis when the proportions of risk group are changed.

There was also uncertainty relating to survival and recurrence-free and progression-free survival data as they were only available up to 5 years post initial diagnosis. These data were extrapolated to predict cost-effectiveness up to 20 years. Data at 5 years suggested little difference in terms of survival and recurrence- and progression-free survival. However, results would be greatly strengthened if longer-term randomised data were available. For the purposes of the model the mortality, progression and recurrence rates were assumed to be constant over time. Given that data were extrapolated for 20 years in total, this assumption is perhaps unrealistic. However, it is unlikely that the effect of holding the recurrence, progression and mortality rates constant would have any impact on the direction of results.

The cost data used were also imprecise because the costs of diagnosis and treatments were mainly identified from NHS reference costs. As mentioned there were very few studies that collected data on resource utilisation and, what published data there were, were not generalisable to the UK. A further issue regarding costs was that inflation was not taken into account. For the purposes of the analysis all prices were taken for the year 2007. However, the costs identified from NHS reference costs, the paper by Rodgers and colleagues[179] and the unpublished report for PDD were all 2006 costs. Normal practice within an economic evaluation would argue that such costs be inflated to the same base year allowing all costs to be comparable. The analyses conducted as part of this review, however, did not take into account inflation over time. However, it is anticipated that the failure to inflate the costs, given the similar price years of the data, may have little impact on the results.

One final point of uncertainty was the discount rate. The discount rates utilised followed published guidance relevant at the time that the technology assessment report was commissioned. Increases to the discount rate (mentioned in the methods

chapter) would not change the overall direction of effects but are likely to make the more effective strategies (in terms of life-years) less likely to be cost-effective. This is because these additional benefits accrue over time and hence are given less weight when the discount rate is increased.

Chapter 9
Conclusions

Implications for service provision

In terms of test performance, PDD has higher sensitivity than WLC [pooled estimates for biopsy-level analysis: 93% (95% CI 90% to 96%) versus 65% (95% CI 55% to 74%) respectively] in detecting bladder cancer in patients with symptoms such as haematuria and is better at detecting more aggressive, higher risk tumours, including CIS [median (range) sensitivity across studies for biopsy-level analysis: 99% (54% to 100%) versus 67% (0% to 100%) respectively]. However, PDD has lower specificity than WLC [pooled estimates for biopsy-level analysis: 60% (95% CI 49% to 71%) versus 81% (95% CI 73% to 90%) respectively]. The advantages of higher sensitivity (fewer false-negative results, better detection of higher risk tumours) have to be weighed against the disadvantages of lower specificity (more false-positive results, leading to additional unnecessary biopsies and potentially additional unnecessary investigations and the resulting anxiety caused to patients and their families).

In terms of the photosensitising agents used, across studies the median (range) specificity reported for HAL was higher than that of 5-ALA for both patient-level [81% (43% to 100%) compared with 52% (33 to 67%)] and biopsy-level [80% (58% to 100%) compared with 57% (32% to 67%)] detection of bladder cancer, although the ranges were wide and factors other than the agent used may also have contributed to the specificity values reported.

Compared with WLC, the use of PDD at TURBT results in fewer residual tumours at check cystoscopy (pooled estimate RR 0.37, 95% CI 0.20 to 0.69) and longer recurrence-free survival (pooled estimate RR 1.37, 95% CI 1.18 to 1.59), although these results are based on limited evidence (three and two studies respectively) and should be interpreted with caution. The advantages of PDD at TURBT in reducing tumour recurrence (pooled estimate RR 0.64, 95% CI 0.39 to 1.06) and progression (pooled estimate RR 0.57, 95% CI 0.22 to 1.46) in the longer term were less clear (based on two studies, one with 5 years' and one with 8 years' follow-up). In addition, as adjuvant single-dose intravesical therapy following TURBT (standard practice in the UK and much of Europe) was not given to all of the patients in all of the studies it is difficult to assess what the true added value of PDD over WLC might be in routine clinical practice in terms of outcomes such as residual tumour at check cystoscopy, tumour recurrence and progression. However, single-dose intravesical chemotherapy is known to be ineffective against high-risk tumours, the types more likely to be detected by PDD.

All three biomarkers had higher sensitivity but lower specificity than cytology for detecting bladder cancer in patients with symptoms such as haematuria. In the pooled estimates (95% CI) ImmunoCyt had the highest sensitivity [84% (77% to 91%)], followed by FISH [76% (65% to 84%)], NMP22 [68% (62% to 74%)] and cytology [44% (38% to 51%)], whereas cytology had the highest specificity [96% (94% to 98%)], followed by FISH [85% (78% to 92%)], NMP22 [79% (74% to 84%)] and ImmunoCyt [75% (68% to 83%)]. ImmunoCyt [84% (95% CI 77% to 91%)] had higher sensitivity than NMP22 [68% (95% CI 62% to 74%)], with the lack of overlap between the CIs supporting evidence of a difference in sensitivity in favour of ImmunoCyt. FISH [76% (95% CI 65% to 84%)] also had higher sensitivity than NMP22 although the difference in sensitivity was more uncertain as the CIs overlapped. All three biomarkers and cytology were better at detecting more aggressive, higher risk tumours [median (range) sensitivity across studies: FISH 95% (50% to 100%), ImmunoCyt 90% (67% to 100%), NMP22 83% (0% to 100%), cytology 69% (0% to 100%)] than lower risk, less aggressive tumours [ImmunoCyt 81% (55% to 90%), FISH 65% (32% to 100%), NMP22 50% (0% to 86%), cytology 27% (0% to 93%)]. A urine biomarker test such as ImmunoCyt could potentially replace some cytology tests if higher sensitivity (fewer false negatives) was considered more important than higher specificity (fewer false positives). However, if higher specificity was considered to be more important then cytology would remain the test of choice.

The most cost-effective strategy for diagnosis and follow-up of bladder cancer patients amongst PDD,

WLC, biomarkers, cytology and flexible cystoscopy was evaluated. Based on currently available data and taking into account the assumptions made in the model, the strategy of flexible cystoscopy and ImmunoCyt followed by PDD in initial diagnosis and flexible cystoscopy followed by WLC in follow-up is likely to be the most costly and the most effective (£2370 per patient and 11.66 life-years). The strategy of cytology followed by WLC in initial diagnosis and follow-up is likely to be the least costly (£1043 per patient) and least effective in terms of life-years (11.59) per patient. Compared with WLC in each strategy, PDD is more likely to be cost-effective. However, it should be noted that the diagnostic strategy that would be cost-effective depends upon the value that society would be willing to pay to obtain an additional life-year. There appeared to be no strategy that would have a likelihood of being cost-effective more than 50% of the time over most of the range of willingness to pay values. Nevertheless, the four strategies involving PDD and biomarkers were cumulatively associated with over a 70% likelihood of being considered cost-effective. The strategies of ImmunoCyt or FISH followed by PDD in initial diagnosis and ImmunoCyt or FISH followed by WLC in follow-up may be considered to be the most cost-effective when the willingness to pay is over £20,000.

In summary, given the evidence presented a judgement needs to be made as to whether the current 'standard' strategies with regard to diagnosis and follow-up of bladder cancer should be altered. Currently, there is no standard strategy for the detection and follow-up of primary bladder cancer. The implications of the finding that diagnostic strategies involving ImmunoCyt or FISH and PDD appear to have potential long-term outcome benefits compared with current commonly used strategies involving cytology or flexible cystoscopy need to be considered. Diagnostic strategies involving ImmunoCyt or FISH and PDD may also have potential short-term benefits, such as more true-positive cases detected and less false-negative cases missed. However, any decision needs to take into account the extra costs associated with PDD and indeed whether the probable gains in QoL justify this increased cost.

In the sensitivity analyses no strategy was likely to have more than a 50% probability of being cost-effective. This suggests that either the evidence base is insufficient to warrant a change in practice or we are indifferent between several strategies in terms of cost-effectiveness, or more likely a combination of these two factors.

There were no data on the combination of flexible cystoscopy and cytology, the tests that are involved in current commonly used strategies. Also, as there were no data available with which to explicitly incorporate QoL within the model, a judgement needs to be made as to whether the expected gain in QoL is sufficient to offset any extra cost.

Currently, PDD is used in only a few centres in the UK and therefore the impact on the use of operating theatres arising from an increase in the use of PDD would need to be considered. Learning to use PDD should be straightforward for an experienced cystoscopist and the training period should be relatively short.

Suggested research priorities

Further research is required in the following areas:

- RCTs comparing PDD with rigid WLC plus adjuvant intravesical therapy at TURBT in patients presumed to have non-muscle-invasive bladder cancer. The design of such studies should take into account participant characteristic risk groups, for example smoking and age, and allow outcomes to be reported based on risk categories at randomisation. Clinical effectiveness outcomes should include residual tumour rates at first check cystoscopy, recurrence-free survival, tumour recurrence rates, time to first recurrence, and progression. Such studies should make provision for longer-term follow-up (up to 10 years) and as a matter of course include an economic evaluation and measurement of health state utilities for incorporation into a cost–utility analysis.
- Diagnostic cross-sectional studies comparing FISH with ImmunoCyt, NMP22 BladderChek point of care test and voided urine cytology, and also combinations of these tests, against a reference standard of cystoscopy with histological assessment of biopsied tissue in the same patient population. The patient population would be those newly presenting with symptoms suspicious for bladder cancer and those with previously diagnosed non-muscle-invasive bladder cancer. The studies should report true and false positives and negatives for a patient-level analysis of the whole patient group and also for the suspicion of bladder cancer/previously diagnosed disease subgroups. For each of these groups the studies should report the sensitivity of the tests in detecting stage (pTa, pT1, ≥ pT2, CIS)

and grade (G1, G2, G3) of tumour, and size (< 1 cm, 1–3 cm, > 3cm) and number (one, two to three, more than three) of tumours. Upper tract end points should also be considered. Observer variability in the interpretation of tests should also be reported. There should be formal follow-up of patients who are categorised as negative for bladder cancer to better understand the consequences of false-negative case ascertainment. The results of such studies should be incorporated into a refined economic model that fully reflects the pragmatic factors listed above.

- In addition, BAUS and the Renal Association have recently produced a new diagnostic algorithm for the diagnosis of patients with haematuria. This would be an appropriate setting for further evaluating novel urinary biomarkers such as ImmunoCyt and FISH and also for assessing their performance in specific populations with a higher prevalence of bladder cancer, such as men aged over 60 years who smoke.
- The level of QoL data suitable for incorporation into an economic model. Consideration should be given to the collection of data suitable to expand on economic evaluations from cost-effectiveness analyses. Such data may be derived from further prospective studies or stand-alone studies that seek to identify health state utilities relevant to a refined economic model.
- The different strategies differ in terms of longer-term outcomes and also in terms of the process of care and short-term outcomes. This suggests that consideration should be given to preference elicitation studies using recognised methodology that explore the trade-offs and valuations between processes and health outcomes. Such analysis should be conducted in such a way that it can be incorporated into future models based on trial-based analysis.
- False-negative results, either at diagnosis or at follow-up, will prevent or at least delay those patients from receiving potentially beneficial treatment. Further information is required as to what would happen to these patients in practice and the impact of an incorrect diagnosis on future survival, QoL and costs. Such information could be identified through follow-up of patients who are discharged following an initial negative result.

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Contribution of authors

Graham Mowatt (Research Fellow) screened the search results, assessed full-text studies for inclusion, undertook data extraction and quality assessment, drafted the chapters on photodynamic diagnosis and biomarkers, and coordinated the review. Shihua Zhu (TAR Training Fellow) and Mary Kilonzo (Research Fellow) drafted the chapter on cost-effectiveness, supervised by Luke Vale (Professor of Health Technology Assessment). Shihua Zhu, TR Leyshon Griffiths (Senior Lecturer and Honorary Consultant Urological Surgeon) and Ghulam Nabi (Clinical Lecturer in Urology) drafted the background chapter. Charles Boachie (Statistician) drafted the data analysis section of the review and conducted the statistical analysis, supervised by Jonathan Cook (Statistician). TR Leyshon Griffiths, James N'Dow (Professor of Urology) and Ghulam Nabi provided expert advice on clinical aspects of the review. Cynthia Fraser (Information Officer) developed and ran the search strategies, obtained papers and formatted the references. All authors assisted in preparing the manuscript, reading and commenting on drafts, and reading the final draft.

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Appendix 1
Search strategies

Clinical effectiveness
MEDLINE (1966 to March Week 3 2008), EMBASE (1980 to 2008 Week 13), Medline In-Process (31 March 2008)

Ovid Multifile Search
URL: http://gateway.ovid.com/athens

1. urinary bladder neoplasms/use mesz
2. exp bladder cancer/use emez
3. hematuria/
4. (bladder adj3 (cancer$or neoplasms$or carci$)).tw.
5. (hematuria or haematuria).tw.
6. or/1–5
7. *urinary bladder neoplasms/su use mesz
8. exp *bladder cancer/su use emez
9. cystectomy/
10. ((bladder adj3 resect$) or cystectomy or turbt).tw.
11. or/7–10
12. cystoscopy/
13. cystoscop$.tw.
14. (photo dynamic$or photodynamic$or fluorescence$).tw.
15. (12 or 13) and 14
16. hypericin.tw.
17. 548–04–9.rn.
18. hexvix.tw.
19. hexaminolevulinate.tw.
20. (hexyl$adj3 aminolevulinate).tw.
21. 106–60–5.rn.
22. 5-ALA.tw.
23. 5-aminolevulinic acid.tw.
24. 5-aminolevulinic acid hexyl ester.tw,rn.
25. or/15–24
26. (6 or 11) and 25
27. tumor markers,biological/use mesz
28. exp tumor marker/or biological marker/or disease marker/use emez
29. ((tumo?r or biological or molecular or histolog$or biochem$or genetic$or urine or disease) adj3 marker$).tw.
30. 6 and (27 or 28 or 29))
31. In Situ Hybridization, Fluorescence/
32. fluorescence in situ hybridization.tw.
33. urovysion.tw
34. or/31–33
35. 6 and 34
36. nuclear proteins/
37. (nuclear matrix protein 22 or nmp22).tw,rn.
38. or/36–37
39. 6 and 38
40. urine/cy
41. urine cytology/use emez
42. cytodiagnosis/use mesz
43. cancer cytodiagnosis/use emez
44. cell count/
45. immunocyt$or ucyt$.tw.
46. or/40–45
47. 6 and 46
48. 26 or 30 or 35 or 39 or 47
49. (animals/or nonhuman/) not humans/
50. 48 not 49
51. (editorial or letter or comment or case reports).pt.
52. editorial/or letter/or note/or case report/use emez
53. 50 not (51 or 52)
54. "sensitivity and specificity"/
55. roc curve/
56. receiver operating characteristic/use emez
57. predictive value of tests/
58. diagnostic errors/use emez
59. false positive reactions/use mesz
60. false negative reactions/use mesz
61. diagnostic accuracy/use emez
62. diagnostic value/use emez
63. du.fs. use mesz
64. sensitivity.tw.
65. distinguish$.tw.
66. differentiate.tw.
67. identif$.tw.
68. detect$.tw.
69. diagnos$.tw.
70. (predictive adj4 value$).tw.
71. accura$.tw.
72. comparison.tw.
73. or/54–72
74. 53 and 73
75. exp diagnostic errors/
76. reproducibility of results/
77. observer variation
78. exp reliability/
79. diagnosis, differential/
80. early diagnosis/
81. (reliab$or reproduc$).tw.
82. or/75–81
83. 53 and 82

84. prognosis/
85. (predict$or prognosis or prognostic).tw.
86. 84 or 85
87. 53 and 86
88. 26 or 74 or 83 or 87

Science Citation Index (1970 to 1 April 2006), BIOSIS (1985 to 3 April 2008)
Web of Knowledge
URL: http://wok.mimas.ac.uk/

#1 TS=(bladder SAME (cancer* or neoplasm* or carci*))
#2 TS=(hematuria OR haematuria)
#3 #1 or #2
#4 TS=((bladder SAME resect*) or cystectomy or turbt)
#5 #3 or #4
#6 TS=(cystoscop* AND (photo* dynamic* OR photodynamic* OR fluorescence*))
#7 #5 AND #6
#8 TS=(hypericin or hexvix or hexaminolevulin*or hexyl* aminolevulin* or 5-ala or 5-aminolevulin*)
#9 #5 and #8
#10 #7 or #9
#11 TS=(marker* SAME (tumor or tumour or biological or molecular or histolog* or biochem* or genetic* or urine or disease))
#12 #3 and #11
#13 TS=(immunocyt* or ucyt*)
#14 TS=cytolog*
#15 TS=(nmp22 or nuclear matrix protein 22)
#16 TS=urovysion
#17 TS=(fluorescence SAME hybridization)
#18 #13 or #14 or #15 or #16 or #17
#19 #3 and #18
#20 #10 or #12 or #19
#21 TS=((bladder or hemauturia or haematuria) SAME (predict* or prognosis or prognostic or reliab* or reproduc*))
#22 TS=((bladder or hemauturia or haematuria) SAME (sensitivity or specificity or roc))
#23 TS=((bladder or hemauturia or haematuria) SAME (identif* or accura* or compara*))
#24 TS=((bladder or hemauturia or haematuria) SAME detect*)
#25 TS=((bladder or hemauturia or haematuria) SAME diagnos*)
#26 #21 or #22 or #23 or #24 or #25
#27 #20 and #26
#28 #10 or #27

Health Management Information Consortium (1979 to March 2008)
Ovid Multifile Search
URL: http://gateway.ovid.com/athens

1. bladder cancer/
2. haematuria/
3. 1 or 2
4. (photo$dynamic$or photodynamic or fluorescence).tw. (17)
5. (hypericin or hexvix or hexyl$or 5-ala$or aminolevulonate).tw.
6. (marker$or biomarker$).tw.
7. (nmp22 or immunocyt$or ucyt$or urovysion or fish).tw. (
8. cytology/
9. or/4–8
10. 3 and 9

Cochrane Library (Issue 1 2008)
URL: http://www3.interscience.wiley.com/cgi-bin/mrwhome/106568753/HOME

#1 URINARY BLADDER NEOPLASMS single term (MeSH)
#2 HEMATURIA single term (MeSH)
#3 (#1 or #2)
#4 ((photo* next dynamic*) or photodynamic* or fluoresence*)
#5 (hypericin or hexvix or hexyl* or ala)
#6 (#4 or #5)
#7 (#3 and #6)
#8 marker*
#9 #9 nmp22 or immunocyt or urovysion or fish
#10 (#3 and (#8 or #9))
#11 (#7 or #10)

DARE and HTA databases (March 2008)
NHS Centre for Reviews and Dissemination
URL: http://nhscrd.york.ac.uk/welcome.htm

1 MeSH Bladder Neoplasms EXPLODE 1 2 3 4 49
2 MeSH Hematuria EXPLODE 1 2 15
4 nmp22 OR immunocyt OR ucyt OR urovysion OR fish 93
5 marker* or biomarker* 419
7 #1 or #2 63
8 #5 and #7 11
9 photo AND dynamic OR photodynamic 83
10 #7 and #9 2
12 fluorescence OR hexvix OR hexyl OR hypericin OR 5-ala 34
13 #1 or #2 or #4 or #8 or #10 or #12 171

Medion (March 2008)
URL: www.mediondatabase.nl/

Bladder or hematuria or haematuria

National Research Register Archive (September 2007)
URL: www.update-software.com/National/

#1 URINARY BLADDER NEOPLASMS single term (MeSH)
#2 HEMATURIA single term (MeSH)
#3 (#1 or #2)
#4 ((photo* next dynamic*) or photodynamic* or fluoresence*)
#5 (hypericin or hexvix or hexyl* or ala)
#6 (#4 or #5)
#7 (#3 and #6)
#8 marker*
#9 #9 nmp22 or immunocyt or urovysion or fish
#10 (#3 and (#8 or #9))
#11 (#7 or #10)

ClinicalTrials.gov (March 2008)
URL: http://clinicaltrials.gov/ct/gui/c/r

"bladder cancer":Topic AND (photodynamic OR fluoresence OR ALA OR hexvix OR hexyl OR hypericin or NMP22 or Immunocyt or urovysion or fish): Search terms

Current Controlled Trials (March 2008)
URL: www.controlled-trials.com/

bladder AND (marker% OR photo% OR fluoresence OR ALA OR hexvix OR hexyl OR hypericin or NMP22 or Immunocyt or urovysion or fish)

WHO ICTRP (March 2008)
URL: www.who.int/ictrp/en/

(photodynamic OR fluoresence OR ALA OR hexvix OR hexyl OR hypericin or NMP22 or Immunocyt or urovysion or fish):TI AND bladder cancer:Condition

Cost-effectiveness

MEDLINE (1966 to March Week 3 2008), EMBASE (1980 to 2008 Week 13), Medline In-Process (1 April 2008)

Ovid Multifile Search
URL: http://gateway.ovid.com/athens

1. urinary bladder neoplasms/use mesz
2. exp bladder cancer/use emez
3. hematuria/
4. (bladder adj3 (cancer$or neoplasm$or carci$)).tw.
5. (hematuria or haematuria).tw.
6. or/1–5
7. *urinary bladder neoplasms/su use mesz
8. exp *bladder cancer/su use emez
9. cystectomy/
10. ((bladder adj3 resect$) or cystectomy or turbt).tw.
11. or/7–10
12. cystoscopy/
13. cystoscop$.tw.
14. (photo dynamic$or photodynamic$or fluorescence$).tw.
15. (12 or 13) and 14
16. hypericin.tw.
17. 548–04–9.rn.
18. hexvix.tw.
19. hexaminolevulinate.tw.
20. (hexyl$adj3 aminolevulinate).tw.
21. 106–60–5.rn.
22. 5-ALA.tw.
23. 5-aminolevulinic acid.tw.
24. 5-aminolevulinic acid hexyl ester.tw,rn.
25. or/15–24
26. (6 or 11) and 25
27. tumor markers,biological/use mesz
28. exp tumor marker/or biological marker/or disease marker/use emez
29. ((tumo?r or biological or molecular or histolog$or biochem$or genetic$or urine or disease) adj3 marker$).tw.
30. 6 and (27 or 28 or 29)
31. In Situ Hybridization, Fluorescence/
32. fluorescence in situ hybridization.tw.
33. urovysion.tw.
34. or/31–33
35. 6 and 34
36. nuclear proteins/
37. (nuclear matrix protein 22 or nmp22).tw,rn.
38. or/36–37
39. 6 and 38
40. urine/cy
41. urine cytology/use emez
42. cytodiagnosis/use mesz
43. cancer cytodiagnosis/use emez
44. cell count/
45. immunocyt$.tw.
46. or/40–45
47. 6 and 46
48. 26 or 30 or 35 or 39 or 47
49. exp "costs and cost analysis"/
50. economics/
51. exp economics,hospital/
52. exp economics,medical/
53. economics,pharmaceutical/
54. exp budgets/
55. exp models, economic/

56. exp decision theory/
57. ec.fs. use mesz
58. monte carlo method/
59. markov chains/
60. exp health status indicators/
61. cost$.ti.
62. (cost$adj2 (effective$or utilit$or benefit$or minimis$)).ab.
63. economic$model$.tw.
64. (economics$or pharmacoeconomic$or pharmo-economic$).ti.
65. (price$or pricing$).tw.
66. (financial or finance or finances or financed).tw.
67. (value adj2 (money or monetary)).tw.
68. markov$.tw.
69. monte carlo.tw.
70. (decision$adj2 (tree? or analy$or model$)).tw.
71. (standard adj1 gamble).tw.
72. trade off.tw.
73. or/49–72
74. 48 and 73
75. remove duplicates from 74

Science Citation Index (1970 to 1 April 2008)
Web of Knowledge
URL: http://wok.mimas.ac.uk/

#1 TS=(bladder SAME (cancer* or neoplasm* or carci*))
#2 TS=(hematuria OR haematuria)
#3 #1 or #2
#4 TS=((bladder SAME resect*) or cystectomy or turbt)
#5 #3 or #4
#6 TS=(cystoscop* AND (photo* dynamic* OR photodynamic* OR fluorescence*))
#7 #5 AND #6
#8 TS=(hypericin or hexvix or hexaminolevulin*or hexyl aminolevulin* or 5-ala or 5-aminolevulin*)
#9 #5 and #8
#10 #7 or #9
#11 TS=(marker* SAME (tumor or tumour or biological or molecular or histolog* or biochem* or genetic* or urine or disease))
#12 #3 and #11
#13 45,591 TS=(immunocyt* or ucyt)
#14 35,989 TS=cytolog*
#15 221 TS=(nmp22 or nuclear matrix protein 22)
#16 33 TS=urovysion
#17 13,601 TS=(fluorescence SAME hybridization)
#18 #13 or #14 or #15 or #16 or #17
#19 #3 and #18
#20 #10 or #12 or #19
#21 TS=economic*
#22 TS=cost*
#23 TS=(price* OR pricing*)
#24 TS=(financial or finance*)
#25 TS=(decision* SAME (tree* OR analy* or model*))
#26 TS=markov*
#27 TS=monte carlo
#28 #21 or #22 or #23 or #24 or #25 or #26 or #27
#29 #20 and #28

NHS Economic Evaluation Database (March 2008)
NHS Centre for Reviews and Dissemination
URL:http://nhscrd.york.ac.uk/welcome.htm

1 MeSH Bladder Neoplasms EXPLODE 1 2 3 4 49
2 MeSH Hematuria EXPLODE 1 2 15
4 nmp22 OR immunocyt OR ucyt OR urovysion OR fish 93
5 marker* or biomarker* 419
7 #1 or #2 63
8 #5 and #7 11
9 photo AND dynamic OR photodynamic 83
10 #7 and #9 2
12 fluorescence OR hexvix OR hexyl OR hypericin OR 5-ala 34
13 #1 or #2 or #4 or #8 or #10 or #12 171

Health Management Information Consortium (1979 to March 2008)
Ovid Multifile Search
URL: http://gateway.ovid.com/athens

1. bladder cancer/
2. haematuria/
3. 1 or 2
4. (photo$dynamic$or photodynamic or fluorescence).tw. (17)
5. (hypericin or hexvix or hexyl$or 5-ala$or aminolevulonate).tw.
6. (marker$or biomarker$).tw.
7. (nmp22 or immunocyt$or ucyt$or urovysion or fish).tw. (
8. cytology/
9. or/4–8
10. 3 and 9

CEA Registry (March 2008)
Centre for the Evaluation of Value and Risk in Health
URL: https://research.tufts-nemc.org/cear/default.aspx

bladder or hemauria or haematuria

Quality of life and cost data for model

MEDLINE (1966 to March Week 3 2008), EMBASE (1980 to 2008 Week 13), Medline In-Process (1 April 2008)

Ovid Multifile Search
URL: http://gateway.ovid.com/athens

1. urinary bladder neoplasms/di, pc
2. exp bladder cancer/di, dm
3. *hematuria/
4. (hematuria or haematuria).ti.
5. (bladder adj1 (cancer$or neoplasm$or carci$)).ti.
6. *cystoscopy/
7. or/1–6
8. exp "costs and cost analysis"/
9. economics/
10. exp economics,hospital/
11. exp economics,medical/
12. economics,pharmaceutical/
13. exp budgets/
14. exp models, economic/
15. exp decision theory/
16. ec.fs. use mesz
17. monte carlo method/
18. markov chains/
19. exp health status indicators/
20. cost$.ti.
21. (cost$adj2 (effective$or utilit$or benefit$or minimis$)).ab.
22. economic$model$.tw.
23. (economics$or pharmacoeconomic$or pharmo-economic$).ti
24. (price$or pricing$).tw.
25. (financial or finance or finances or financed).tw.
26. (value adj2 (money or monetary)).tw.
27. markov$.tw.
28. monte carlo.tw.
29. (decision$adj2 (tree? or analy$or model$)).tw.
30. (standard adj1 gamble).tw.
31. trade off.tw.
32. or/8–31
33. 7 and 32
34. quality of life/
35. quality adjusted life year/
36. "Value of Life"/use mesz
37. health status indicators/use mesz
38. health status/use emez
39. sickness impact profile/use mesz
40. disability evaluation/use mesz
41. disability/use emez
42. activities of daily living/use mesz
43. exp daily life activity/use emez
44. cost utility analysis/use emez
45. rating scale/
46. questionnaires/
47. (quality adj1 life).tw.
48. quality adjusted life.tw.
49. disability adjusted life.tw.
50. (qaly? or qald? or qale? or qtime? or daly?).tw.
51. (euroqol or euro qol or eq5d or eq 5d).tw.
52. (hql or hqol or h qol or hrqol or hr qol).tw.
53. (hye or hyes).tw.
54. health$year$equivalent$.tw.
55. (hui or hui1 or hui2 or hui3).tw.
56. (health adj3 (utilit$or disutili$)).tw.
57. (health adj3 (state or status)).tw.
58. (sf36 or sf 36 or short form 36 or shortform 36).tw.
59. (sf6 or sf 6 or short form 6 or shortform 6).tw.
60. (sf12 or sf 12 or short form 12 or shortform 12).tw.
61. (sf16 or sf 16 or short form 16 or shortform 16).tw.
62. (sf20 or sf 20 or short form 20 or shortform 20).tw.
63. willingness to pay.tw.
64. standard gamble.tw.
65. or/34–64
66. 7 and 65
67. 33 or 66
68. (case report or editorial or letter).pt.
69. case report/
70. 67 not (68 or 69)
71. limit 70 to english language
72. remove duplicates from 71

IDEAS (March 2008)

RePeC
URL: http://ideas.repec.org/

Bladder or hematuria or haematuria

Websites consulted

Cancer Research UK –
URL: www.cancerresearchuk.org/

European Association of Urology –
URL: www.uroweb.org/

European Organisation for Research and Treatment of Cancer (EORTC) –
URL: www.eortc.be/

Hexvix, GE Healthcare Medical Diagnostics –
URL: www.hexvix.com/cont.shtml

National Cancer Institute, US National Institutes of Health –
URL: www.cancer.gov/

National Comprehensive Cancer Network –
URL: www.nccn.org/default.asp

National Insitute of Diabetes and Digestive and Kidney Diseases (NIDDK) –
URL: http://www2.niddk.nih.gov/Research/ScientificAreas/Urology/

NHS National Institute for Health and Clinical Excellence –
URL: www.nice.org.uk/

Scottish Intercollegiate Guidelines Network, NHS Quality Improvement Scotland –
URL: www.sign.ac.uk/

Appendix 2

PDD quality assessment checklist (QUADAS tool)

Study id: Assessor initials:

Date assessed:

Item		Yes	No	Unclear
1	Was the spectrum of patients representative of the patients who will receive the test in practice?			
2	Is the reference standard likely to correctly classify the target condition?			
3	Is the time period between the reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?			
4	Did the whole sample or a random selection of the sample receive verification using a reference standard of diagnosis?			
5	Did patients receive the same reference standard regardless of the index test result?			
6	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?			
7	Were the index test results interpreted without knowledge of the results of the reference standard?			
8	Were the reference standard results interpreted without knowledge of the results of the index test?			
9	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?			
10	Were uninterpretable/intermediate test results reported?			
11	Were withdrawals from the study explained?			
12	Did the study provide a clear definition of what was considered to be a 'positive' result?			
13	Were data on observer variation reported and within an acceptable range?			

Appendix 3

PDD quality assessment checklist (RCTs)

Study id: Assessor initials:

Date assessed:

Criteria		Yes	No	Unclear
1	Was the assignment to the treatment groups really random? (Adequate approaches to sequence generation: computer-generated random tables, random number tables; inadequate approaches to sequence generation: use of alternation, case record numbers, birth dates or week days)			
2	Was the treatment allocation concealed? [Adequate approaches to concealment of randomisation: centralised or pharmacy-controlled randomisation, serially numbered identical containers, on-site computer-based system with a randomisation sequence that is not readable until allocation, other approaches with robust methods to prevent foreknowledge of the allocation sequence to clinicians and patients; inadequate approaches to concealment of randomisation: use of alternation, case record numbers, birth dates or week days, open random numbers lists, serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)]			
3	Were the groups similar at baseline in terms of prognostic factors?			
4	Were the eligibility criteria specified?			
5	Was the intervention (and comparison) clearly defined?			
6	Were the groups treated in the same way apart from the intervention received?			
7	Was follow-up long enough to detect important effects on outcomes of interest?			
8	Was the outcome assessor blinded to the treatment allocation?			
9	Was the care provider blinded?			
10	Were the patients blinded?			
11	Were the point estimates and measures of variability presented for the primary outcome measures?			
12	Was the withdrawal/dropout rate likely to cause bias?			
13	Did the analyses include an intention to treat analysis?			
14	Was the operation undertaken by somebody experienced in performing the procedure?			

Appendix 4

Photodynamic diagnosis (PDD) included studies

Diagnostic accuracy

Cheng 2000

Cheng CW, Lau WK, Tan PH, Olivo M. Cystoscopic diagnosis of bladder cancer by intravesical instillation of 5-aminolevulinic acid induced porphyrin fluorescence – the Singapore experience. *Ann Acad Med Singapore* 2000;**29**:153–8.

Colombo 2007

Colombo R, Naspro R, Bellinzoni P, Fabbri F, Guazzoni G, Scattoni V, *et al*. Photodynamic diagnosis for follow-up of carcinoma in situ of the bladder. *Ther Clin Risk Manage* 2007;**3**:1003–7.

De Dominicis 2001

De Dominicis C, Liberti M, Perugia G, De Nunzio C, Sciobica F, Zuccala A, *et al*. Role of 5-aminolevulinic acid in the diagnosis and treatment of superficial bladder cancer: improvement in diagnostic sensitivity. *Urology* 2001;**57**:1059–62.

D'Hallewin 2000

D'Hallewin MA, De Witte PA, Waelkens E, Merlevede W, Baert L. Fluorescence detection of flat bladder carcinoma in situ after intravesical instillation of hypericin. *J Urol* 2000;**164**:349–51.

Ehsan 2001

Ehsan A, Sommer F, Haupt G, Engelmann U. Significance of fluorescence cystoscopy for diagnosis of superficial bladder cancer after intravesical instillation of delta aminolevulinic acid. *Urol Int* 2001;**67**:298–304.

Filbeck 1999

Primary reference

Filbeck T, Roessler W, Knuechel R, Straub M, Kiel HJ, Wieland WF. Clinical results of the transurethral resection and evaluation of superficial bladder carcinomas by means of fluorescence diagnosis after intravesical instillation of 5-aminolevulinic acid. *J Endourol* 1999;**13**:117–21.

Secondary reference

Filbeck T, Roessler W, Knuechel R, Straub M, Kiel HJ, Wieland WF. 5-aminolevulinic acid-induced fluorescence endoscopy applied at secondary transurethral resection after conventional resection of primary superficial bladder tumors. *Urology* 1999;**53**:77–81.

Fradet 2007

Fradet Y, Grossman HB, Gomella L, Lerner S, Cookson M, Albala D, *et al*. A comparison of hexaminolevulinate fluorescence cystoscopy and white light cystoscopy for the detection of carcinoma in situ in patients with bladder cancer: a phase III, multicenter study. *J Urol* 2007;**178**:68–73.

Frimberger 2001

Frimberger D, Zaak D, Stepp H, Knuchel R, Baumgartner R, Schneede P, *et al*. Autofluorescence imaging to optimize 5-ALA-induced fluorescence endoscopy of bladder carcinoma. *Urology* 2001;**58**:372–5.

Grimbergen 2003

Grimbergen MC, van Swol CF, Jonges TG, Boon TA, van Moorselaar RJ. Reduced specificity of 5-ALA induced fluorescence in photodynamic diagnosis of transitional cell carcinoma after previous intravesical therapy. *Eur Urol* 2003;**44**:51–6.

Hendricksen 2006

Hendricksen K, Moonen PM, der Heijden AG, Witjes JA. False-positive lesions detected by fluorescence cystoscopy: any association with p53 and p16 expression? *World J Urol* 2006;**24**:597–601.

Hungerhuber 2007

Primary reference

Hungerhuber E, Stepp H, Kriegmair M, Stief C, Hofstetter A, Hartmann A, *et al*. Seven years' experience with 5-aminolevulinic acid in detection of transitional cell carcinoma of the bladder. *Urology* 2007;**69**:260–4.

Secondary references

Zaak D, Kriegmair M, Stepp H, Stepp H, Baumgartner R, Oberneder R, *et al*. Endoscopic detection of transitional cell carcinoma with 5-aminolevulinic acid: results of 1012 fluorescence endoscopies. *Urology* 2001;**57**:690–4.

Zaak D, Hungerhuber E, Schneede P, Stepp H, Frimberger D, Corvin S, *et al*. Role of 5-aminolevulinic acid in the detection of urothelial premalignant lesions. *Cancer* 2002;**95**:1234–8.

Jeon 2001

Jeon SS, Kang I, Hong JH, Choi HY, Chai SE. Diagnostic efficacy of fluorescence cystoscopy for detection of urothelial neoplasms. *J Endourol* 2001;**15**:753–9.

Jichlinski 1997

Primary reference

Jichlinski P, Forrer M, Mizeret J, Glanzmann T, Braichotte D, Wagnieres G, *et al*. Clinical evaluation of a method for detecting superficial surgical transitional cell carcinoma of the bladder by light-induced fluorescence of protoporphyrin IX following the topical application of 5-aminolevulinic acid: preliminary results. *Lasers Surg Med* 1997;**20**:402–8.

Secondary reference

Jichlinski P, Wagnieres G, Forrer M, Mizeret J, Guillou L, Oswald M, *et al*. Clinical assessment of fluorescence cytoscopy during transurethral bladder resection in superficial bladder cancer. *Urol Res* 1997;**25**(Suppl. 1):S3–6.

Jichlinski 2003

Jichlinski P, Guillou L, Karlsen SJ, Malmstrom PU, Jocham D, Brennhovd B, *et al*. Hexyl aminolevulinate fluorescence cystoscopy: new diagnostic tool for photodiagnosis of superficial bladder cancer – a multicenter study. *J Urol* 2003;**170**:226–9.

Jocham 2005

Jocham D, Witjes F, Wagner S, Zeylemaker B, van Moorselaar J, Grimm MO, *et al*. Improved detection and treatment of bladder cancer using hexaminolevulinate imaging: a prospective, phase III multicenter study. *J Urol* 2005;**174**:862–6.

Koenig 1999

Koenig F, McGovern FJ, Larne R, Enquist H, Schomacker KT, Deutsch TF. Diagnosis of bladder carcinoma using protoporphyrin IX fluorescence induced by 5-aminolaevulinic acid. *BJU Int* 1999;**83**:129–35.

Kriegmair 1996

Primary reference

Kriegmair M, Baumgartner R, Knuchel R, Stepp H, Hofstadter F, Hofstetter A. Detection of early bladder cancer by 5-aminolevulinic acid induced porphyrin fluorescence. *J Urol* 1996;**155**:105–9.

Secondary references

Kriegmair M, Baumgartner R, Knuechel R, Steinbach P, Ehsan A, Lumper W, *et al*. Fluorescence photodetection of neoplastic urothelial lesions following intravesical instillation of 5-aminolevulinic acid. *Urology* 1994;**44**:836–41.

Kriegmair M, Stepp H, Steinbach P, Lumper W, Ehsan A, Stepp HG, *et al*. Fluorescence cystoscopy following intravesical instillation of 5-aminolevulinic acid: a new procedure with high sensitivity for detection of hardly visible urothelial neoplasias. *Urol Int* 1995;**55**:190–6.

Kriegmair 1999

Primary reference

Kriegmair M, Zaak D, Stepp H, Stepp H, Baumgartner R, Knuechel R, *et al*. Transurethral resection and surveillance of bladder cancer supported by 5-aminolevulinic acid-induced fluorescence endoscopy. *Eur Urol* 1999;**36**:386–92.

Secondary references

Schneeweiss S, Kriegmair M, Stepp H. Is everything all right if nothing seems wrong? A simple method of assessing the diagnostic value of endoscopic procedures when a gold standard is absent. *J Urol* 1999;**161**:1116–9.

Schneeweiss S. Sensitivity analysis of the diagnostic value of endoscopies in cross-sectional studies in the absence of a gold standard. *Int J Technol Assess Health Care* 2000;**16**:834–41.

Landry 2003

Landry JL, Gelet A, Bouvier R, Dubernard JM, Martin X, Colombel M. Detection of bladder dysplasia using 5-aminolaevulinic acid-induced porphyrin fluorescence. *BJU Int* 2003;**91**:623–6.

Riedl 1999

Riedl CR, Plas E, Pfluger H. Fluorescence detection of bladder tumors with 5-amino-levulinic acid. *J Endourol* 1999;**13**:755–9.

Sim 2005

Sim HG, Lau WK, Olivo M, Tan PH, Cheng CW. Is photodynamic diagnosis using hypericin better than white-light cystoscopy for detecting superficial bladder carcinoma? *BJU Int* 2005;**95**:1215–18.

Song 2007

Song X, Ye Z, Zhou S, Yang W, Zhang X, Liu J, *et al*. The application of 5-aminolevulinic acid-induced fluorescence for cystoscopic diagnosis and treatment of bladder carcinoma. *Photodiagnosis Photodyn Ther* 2007;**4**:39–43.

Szygula 2004

Primary reference

Szygula M, Wojciechowski B, Adamek M, Pietrusa A, Kawczyk-Krupka A, Cebula W, *et al*. Fluorescent diagnosis of urinary bladder cancer – a comparison of two diagnostic modalities. *Photodiagnosis Photodyn Ther* 2004;**1**:23–6.

Secondary reference

Szygula M, Wojciechowski B, Adamek M, Kawczyk-Krupka A, Cebula W, Zieleznik W, *et al*. Photodynamic vs autofluorescent diagnosis of urinary bladder using Xillix LIFE system. *Physica Medica* 2004;**20**(Suppl. 1):55–7.

Tritschler 2007
Tritschler S, Scharf S, Karl A, Tilki D, Knuechel R, Hartmann A, *et al*. Validation of the diagnostic value of NMP22 BladderChek test as a marker for bladder cancer by photodynamic diagnosis. *Eur Urol* 2007;**51**:403–7.

Witjes 2005
Witjes JA, Moonen PM, van der Heijden AG. Comparison of hexaminolevulinate based flexible and rigid fluorescence cystoscopy with rigid white light cystoscopy in bladder cancer: results of a prospective phase II study. *Eur Urol* 2005;**47**:319–22.

Zaak 2002
Zaak D, Stepp H, Baumgartner R, Schneede P, Waidelich R, Frimberger D, *et al*. Ultraviolet-excited (308 nm) autofluorescence for bladder cancer detection. *Urology* 2002;**60**:1029–33.

Zumbraegel 2003
Zumbraegel A, Bichler KH, Krause FS, Feil G, Nelde HJ. The photodynamic diagnosis (PDD) for early detection of carcinoma and dysplasia of the bladder. *Adv Exp Med Biol* 2003;**539**:61–6.

Effectiveness

Babjujk 2005
Babjuk M, Soukup V, Petrik R, Jirsa M, Dvoracek J. 5-aminolaevulinic acid-induced fluorescence cystoscopy during transurethral resection reduces the risk of recurrence in stage Ta/T1 bladder cancer. *BJU Int* 2005;**96**:798–802.

Daniltchenko 2005
Primary reference
Daniltchenko DI, Riedl CR, Sachs MD, Koenig F, Daha KL, Pflueger H, *et al*. Long-term benefit of 5-aminolevulinic acid fluorescence assisted transurethral resection of superficial bladder cancer: 5-year results of a prospective randomized study. *J Urol* 2005;**174**:2129–33.

Secondary reference
Riedl CR, Daniltchenko D, Koenig F, Simak R, Loening SA, Pflueger H. Fluorescence endoscopy with 5-aminolevulinic acid reduces early recurrence rate in superficial bladder cancer. *J Urol* 2001;**165**:1121–3.

Denzinger 2007
Primary reference
Denzinger S, Burger M, Walter B, Knuechel R, Roessler W, Wieland WF, *et al*. Clinically relevant reduction in risk of recurrence of superficial bladder cancer using 5-aminolevulinic acid-induced fluorescence diagnosis: 8-year results of prospective randomized study. *Urology* 2007;**69**:675–9.

Secondary references
Burger M, Zaak D, Stief CG, Filbeck T, Wieland WF, Roessler W, *et al*. Photodynamic diagnostics and noninvasive bladder cancer: is it cost-effective in long-term application? A Germany-based cost analysis. *Eur Urol* 2007;**52**:142–7.

Denzinger S, Wieland WF, Otto W, Filbeck T, Knuechel R, Burger M. Does photodynamic transurethral resection of bladder tumour improve the outcome of initial T1 high-grade bladder cancer? A long-term follow-up of a randomized study. *BJU Int* 2008;**101**:566–9.

Filbeck T, Pichlmeier U, Knuechel R, Wieland WF, Roessler W. Clinically relevant improvement of recurrence-free survival with 5-aminolevulinic acid induced fluorescence diagnosis in patients with superficial bladder tumors. *J Urol* 2002;**168**:67–71.

Kriegmair 2002
Kriegmair M, Zaak D, Rothenberger KH, Rassweiler J, Jocham D, Eisenberger F, *et al*. Transurethral resection for bladder cancer using 5-aminolevulinic acid induced fluorescence endoscopy versus white light endoscopy. *J Urol* 2002;**168**:475–8.

Appendix 5

Photodynamic diagnosis excluded studies

Required outcomes not reported (*n* = 12)

Chin WW, Ramaswamy B, Thong PSP, Heng PWS, Gan YY, Olivo M, *et al*. Preclinical and pilot clinical cancer studies using fluorescence-guided photodynamic therapy with chlorin e6-polyvinylpyrrolidone and hypericin. *Singapore Gen Hosp Proc* 2007;**16**:118–26.

D'Hallewin MA, Vanherzeele H, Baert L. Fluorescence detection of flat transitional cell carcinoma after intravesical instillation of aminolevulinic acid. *Am J Clin Oncol* 1998;**21**:223–5.

D'Hallewin MA, Kamuhabwa AR, Roskams T, De Witte PA, Baert L. Hypericin-based fluorescence diagnosis of bladder carcinoma. *BJU Int* 2002;**9**:760–3.

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Appendix 6

Characteristics of the PDD diagnostic studies

Study[a]	Participants	Tests	Outcomes summary
Cheng 2000[50] Time period: Jan 1997 to Dec 1998 Country: Singapore	Enrolled: 41; analysed: 41 No previous history of BC: NS; history of BC: NS Age (years): mean 66.8, range 42 to 89 Sex: M 24; F 17	Index test: PDD Agent: 5-ALA Comparator: WLC 'Random' biopsies of normal-appearing areas: yes for PDD	Unit of analysis: biopsy (*n* = 175) Sensitivity: PDD 89%, WLC 66% Specificity: PDD 65%, WLC 84%
Colombo 2007[51] Time period: Feb 2004 to Mar 2006 Country: Italy	Enrolled: 49; analysed: 49 No previous history of BC: 0; history of BC: 49 Age (years): mean 70, SD 12 Sex: NS Notes: All patients were suffering from CIS alone at inclusion and undergoing BCG therapy	Index test: PDD Agent: 5-ALA, HAL Comparator: WLC 'Random' biopsies of normal-appearing areas: yes (NS whether PDD or WLC or both)	Unit of analysis: patient (*n* = 49) Sensitivity: PDD 100%, WLC 0% Specificity: PDD 71%, WLC 97%
De Dominicis 2001[53] Time period: May 1997 to NS Country: Italy	Enrolled: 49; analysed: 49 No previous history of BC: 17; history of BC: 32 Age (years): mean 60, range 31 to 77 Sex: M 42; F 7	Index test: PDD Agent: 5-ALA Comparator: WLC 'Random' biopsies of normal-appearing areas: yes for both PDD and WLC	Unit of analysis: biopsy (*n* = 179) Sensitivity: PDD 87%, WLC 17% Specificity: PDD 63%, WLC 88%
D'Hallewin 2000[52] Time period: NS Country: Belgium	Enrolled: 40; analysed: 40 No previous history of BC: NS; history of BC: NS Age (years): NS Sex: NS	Index test: PDD Agent: hypericin Comparator: none 'Random' biopsies of normal-appearing areas: yes for PDD	Unit of analysis: biopsy (CIS) (*n* = 281) Sensitivity: PDD 93% Specificity: PDD 99%
Ehsan 2001[54] Time period: NS Country: Germany	Enrolled: 30; analysed: 30 No previous history of BC: NS; history of BC: NS Age (years): mean NS, range 55 to 85 Sex: M 19; F 11	Index test: PDD Agent: 5-ALA Comparator: WLC 'Random' biopsies of normal-appearing areas: yes for PDD and WLC	Unit of analysis: biopsy (*n* = 151) Sensitivity: PDD 59%, WLC 60% Specificity: PDD 98%, WLC 58%
Filbeck 1999[56] Time period: NS Country: Germany	Enrolled: 123; analysed: 120 No previous history of BC: NS; history of BC: NS Age (years): mean 64.5, range 28 to 86 Sex: NS Notes: 60 of the patients were having a secondary resection 6 weeks after primary tumour resection	Index test: PDD Agent: 5-ALA Comparator: WLC 'Random' biopsies of normal-appearing areas: no (except in cases of a resection in areas of a primary tumour)	Unit of analysis: biopsy (*n* = 347) Sensitivity: PDD 96% Specificity: PDD 35%

Study[a]	Participants	Tests	Outcomes summary
[Filbeck 1999[55]] Time period: Jan 1997 to Oct 1997 Country: Germany	Enrolled: 50; analysed: 50 No previous history of BC: NS; history of BC: NS Age (years): mean 63.4, range 32 to 88 Sex: M 36, F 14 Notes: Patients had undergone conventional TUR of primary tumour 6 weeks earlier	Index test: PDD Agent: 5-ALA Comparator: WLC 'Random' biopsies of normal-appearing areas: no for PDD and WLC	Unit of analysis: biopsy (n = 347) Sensitivity: WLC 69% Specificity: WLC 66% Unit of analysis: biopsy (n = 130) Sensitivity: PDD 78% Specificity: PDD 33% Unit of analysis: biopsy (n = 18) Sensitivity: WLC 64% Specificity: NS
Fradet 2007[57] Time period: NS Country: USA, Canada	Enrolled: 311; analysed: 196 (1 NS?) No previous history of BC: 62; history of BC: 133 Age (years): mean 67, SD 11 Sex: M 148, F 48 Notes: 49 patients received previous chemotherapy and 77 received previous BCG treatment	Index test: PDD Agent: HAL Comparator: WLC 'Random' biopsies of normal-appearing areas: yes for PDD and WLC	Unit of analysis: patient (n = 196) Sensitivity: PDD 87%, WLC 83% Specificity: PDD 82%, WLC 72% Unit of analysis: biopsy (n = NS, CIS 113) Sensitivity: PDD 92%, WLC 68% Specificity: NS
Frimberger 2001[58] Time period: NS Country: Germany	Enrolled: 25; analysed: 25 No previous history of BC: 0; history of BC: 25 Age (years): NS Sex: NS	Index test: PDD Agent: 5-ALA Comparator: WLC 'Random' biopsies of normal-appearing areas: yes for PDD and WLC	Unit of analysis: biopsy (n = 19) Sensitivity: PDD 95% Specificity: PDD 67% NS for WLC
Grimbergen 2003[59] Time period: Nov 1998 to Jun 2002 Country: Netherlands	Enrolled: 160; analysed: 160 No previous history of BC: 87?; history of BC: 73? Age (years): mean 67, range 30 to 91 Sex: NS Notes: 73 patients received previous BCG, mitomycin C or epirubicin treatment	Index test: PDD Agent: 5-ALA Comparator: WLC 'Random' biopsies of normal-appearing areas: yes for PDD and WLC	Unit of analysis: biopsy (n = 917) Sensitivity: PDD 97%, WLC 69% Specificity: PDD 49%, WLC 78%
Hendricksen 2006[60] Time period: Oct 2001 to Apr 2002 Country: Netherlands	Enrolled: 50; analysed: 50 No previous history of BC: 23; history of BC: 27 Age (years): mean 67, range 35 to 86 Sex: M 40, F 10 Notes: This study takes the patient data from the Radbound University Medical Centre, Nijmesen that contributed to Jocham 2005 and Schmidbauer 2004	Index test: PDD Agent: HAL Comparator: WLC 'Random' biopsies of normal-appearing areas: yes (NS whether PDD or WLC or both)	Unit of analysis: biopsy (PDD n = 217, WLC n = 123) Sensitivity: PDD 94%, WLC 88% Specificity: PDD 58%, WLC 86%

Study[a]	Participants	Tests	Outcomes summary
Hungerhuber 2007[61] Time period: Feb 1995 to Feb 2002 Country: Germany	Enrolled: 875; analysed: 875 No previous history of BC: 327; history of BC: 548 Age (years): mean 65.3, range 16 to 99 Sex: M 671, F 204 Notes: Patients with a history of recurrent disease had undergone multiple TURs (mean 3.6, range 1 to 22)	Index test: PDD Agent: 5-ALA Comparator: WLC 'Random' biopsies of normal-appearing areas: no for PDD and WLC	Unit of analysis: biopsy ($n = 4630$) Sensitivity: PDD 92%, WLC 76% Specificity: PDD 56%, WLC 86%
[Zaak 2002[83]] Time period: Jan 1995 to Dec 2000 Country: Germany, Austria	Enrolled: 713; analysed: 713 No previous history of BC: 270; history of BC: 443 Age (years): NS Sex: NS Notes: Patients previously treated for BC had a history of undergoing multiple TURs (mean 3.5, range 1 to 20)	Index test: PDD Agent: 5-ALA Comparator: WLC 'Random' biopsies of normal-appearing areas: no for PDD and WLC	Unit of analysis: biopsy (PDD $n = 3834$, WLC NS) Sensitivity: PDD 98%, WLC 47% Specificity: PDD 21%, WLC NS
[Zaak 2001[82]] Time period: 1995 to 1999 Country: Germany	Enrolled: 605; analysed: 605 No previous history of BC: 212; history of BC: 393 Age (years): mean 65.6, range 16 to 99 Sex: M 472, F 133 Notes: Patients previously treated for BC had a history of undergoing multiple TURs (mean 3.5, range 1 to 20)	Index test: PDD Agent: 5-ALA Comparator: WLC 'Random' biopsies of normal-appearing areas: no for PDD and WLC	Unit of analysis: biopsy (PDD $n = 1012$, WLC $n = 552$) Sensitivity: PDD 86%, WLC 66% Specificity: PDD 23%, WLC NS
Jeon 2001[62] Time period: Dec 1997 to Aug 1999 Country: South Korea	Enrolled: 62; analysed: 62 No previous history of BC: 36; history of BC: 26 Age (years): mean 61.9, range 32 to 80 Sex: M 57, F 5 Notes: Of the patients with a history of BC, five had nephrourterectomy performed with a bladder cuff resection for upper urinary tract carcinoma and six had BCG	Index test: PDD Agent: 5-ALA Comparator: WLC 'Random' biopsies of normal-appearing areas: no for PDD and WLC	Unit of analysis: biopsy ($n = 274$) Sensitivity: PDD 98%, WLC 61 Specificity: PDD 41%, WLC 92%
Jichlinski 1997[63] Time period: Feb 1994 to NS Country: Switzerland	Enrolled: 34; analysed: 34 No previous history of BC: 13; history of BC: 21 Age (years): mean 67.9, range 44 to 84 Sex: M 21, F 13	Index test: PDD Agent: 5-ALA Comparator: WLC 'Random' biopsies of normal-appearing areas: yes for PDD only	Unit of analysis: biopsy ($n = 215$) Sensitivity: PDD 89%, WLC 46%? Specificity: PDD 57% WLC 57%?

Study[a]	Participants	Tests	Outcomes summary
[Jichlinski 1997[64]] Time period: Jan 1995 to NS Country: Switzerland	Enrolled: 31; analysed: 31 No previous history of BC: 11; history of BC: 22 Age (years): mean 66.1, range 44 to 84 Sex: M 23, F 8 Notes: Topical chemotherapy or immunotherapy with BCG was added to the previous surgical treatments in 19 patients	Index test: PDD Agent: 5-ALA Comparator: WLC 'Random' biopsies of normal-appearing areas: biopsies of apparently normal mucosa under WLC	Unit of analysis: biopsy (n = 132) Sensitivity: PDD 83% Specificity: PDD 81%
Jichlinski 2003[65] Time period: Dec 2000 to Apr 2001 Country: Switzerland, Norway, Sweden, Germany	Enrolled: 52; analysed: 52 No previous history of BC: 18; history of BC: 34 Age (years): mean 72, SD 12 Sex: M 38, F 14	Index test: PDD Agent: HAL Comparator: WLC 'Random' biopsies of normal-appearing areas: yes for WLC	Unit of analysis: patient (n = 52) Sensitivity: PDD 96%, WLC 73% Specificity: PDD 43%, WLC 43% Unit of analysis: biopsy (PDD n = 421, WLC n = 414) Sensitivity: PDD 76%, WLC 80% Specificity: PDD 46%, WLC 93%
Jocham 2005[66] Time period: NS Country: Germany, Netherlands	Enrolled: 162; analysed: 146 No previous history of BC: 73; history of BC: 73 Age (years): mean 67, range 33 to 91 Sex: M 107, F 39 Notes: 18% received previous BCG immunotherapy and 18% received previous intravesical chemotherapy	Index test: PDD Agent: HAL Comparator: WLC 'Random' biopsies of normal-appearing areas: no for PDD and WLC	Unit of analysis: patient (n = 146) Sensitivity: PDD 53%, WLC 33% Specificity: PDD 81%, WLC 74%
Koenig 1999[67] Time period: NS Country: Germany, USA	Enrolled: 55; analysed: 49 No previous history of BC: NS; history of BC: NS Age (years): mean 66, range 31 to 87 Sex: M 44, F 11	Index test: PDD Agent: 5-ALA Comparator: WLC 'Random' biopsies of normal-appearing areas: yes (NS whether PDD or WLC or both)	Unit of analysis: biopsy (PDD n = 130, WLC n = 67) Sensitivity: PDD 87%, WLC 84% Specificity: PDD 59%, WLC NS

Study[a]	Participants	Tests	Outcomes summary
Kriegmair 1996[70] Time period: NS Country: Germany	Enrolled: 106; analysed: 106 No previous history of BC: 29; history of BC: 77 Age (years): mean 68, range 41 to 85 Sex: M 80, F 24	Index test: PDD Agent: 5-ALA Comparator: WLC 'Random' biopsies of normal-appearing areas: yes for PDD	Unit of analysis: biopsy ($n = 433$) Sensitivity: PDD 98%, WLC 73% Specificity: PDD 64%, WLC 69% Unit of analysis: patient ($n = 308$ – all patients) Sensitivity: PDD 93%, WLC 70% Specificity: PDD 53%, WLC 75% Unit of analysis: patient ($n = 165$ – history of BCG or chemotherapy) Sensitivity: PDD 96%, WLC 62% Specificity: PDD 72%, WLC 71%
[Kriegmair 1994[68]] Time period: NS Country: Germany	Enrolled: 68; analysed: 68 No previous history of BC: 6; history of BC: 62 Age (years): mean 66.2, range 43 to 83 Sex: M 51, F 17 Notes: 47 patients received previous intravesical chemotherapy or BCG	Index test: PDD Agent: 5-ALA Comparator: none 'Random' biopsies of normal-appearing areas: yes for PDD	Unit of analysis: biopsy ($n = 285$) Sensitivity: PDD 100% Specificity: PDD 76%
[Kriegmair 1995[69]] Time period: NS Country: Germany	Enrolled: 90; analysed: 90 No previous history of BC: 26; history of BC: 64 Age (years): mean 65, range 41 to 85 Sex: NS Notes: 64 patients with history of BC had received previous intravesical therapy with BCG or cytostatics	Index test: PDD Agent: 5-ALA Comparator: 'Random' biopsies of normal-appearing areas: yes for PDD	Unit of analysis: biopsy ($n = 294$) Sensitivity: PDD 98% Specificity: PDD 71%
Kriegmair 1999[71] Time period: NS Country: Germany	Enrolled: 208; analysed: 208 No previous history of BC: 72; history of BC: 136 Age (years): mean 64.8, range 16 to 89 Sex: M 170, F 38 Notes: Patients previously treated for BC had a history of multiple TURS (mean 3.5, range 1 to 20) and intravesical instillation with BCG ($n = 50$) or mitomycin C ($n = 49$)	Index test: PDD Agent: 5-ALA Comparator: WLC 'Random' biopsies of normal-appearing areas: no for PDD and WLC	Unit of analysis: biopsy (PDD $n = 328$, WLC $n = 163$) Sensitivity: PDD 98%, WLC 47% Specificity: PDD 41%, WLC NS

Study[a]	Participants	Tests	Outcomes summary
[Schneeweiss 1999[74]] Time period: Jan 1995 to Aug 1996 Country: Germany	Enrolled: 208; analysed: 208 No previous history of BC: 72; history of BC: 136 Age (years): mean 64.8, SD 12.4, range 16 to 89 Sex: M 170, F 38	Index test: PDD Agent: 5-ALA Comparator: WLC 'Random' biopsies of normal-appearing areas: no for PDD and WLC	Unit of analysis: biopsy ($n = 328$) Sensitivity: PDD 98%, WLC 47% Specificity: PDD 41%, WLC NS
[Schneeweiss 2000[75]] As above			
Landry 2003[72] Time period: NS Country: France	Enrolled: 50; analysed: 50 No previous history of BC: 50; history of BC: 0 Age (years): NS Sex: NS	Index test: PDD Agent: 5-ALA Comparator: 'Random' biopsies of normal-appearing areas: yes for WLC	Unit of analysis: patient ($n = 50$) Sensitivity: PDD 64%, WLC NS Specificity: PDD 67%, WLC NS
Riedl 1999[73] Time period: NS Country: Austria	Enrolled: 52; analysed: 52 No previous history of BC: NS; history of BC: NS Age (years): range 44 to 79 Sex: NS	Index test: PDD Agent: 5-ALA Comparator: WLC 'Random' biopsies of normal-appearing areas: yes (NS whether PDD or WLC or both)	Unit of analysis: patient ($n = 52$) Sensitivity: PDD 100%, WLC 76% Specificity: PDD 67%, WLC 100% Unit of analysis: biopsy ($n = 123$) Sensitivity: PDD 95%, WLC 76% Specificity: PDD 43%, WLC NS
Sim 2005[76] Time period: Jan 2001 to Oct 2004 Country: Singapore	Enrolled: 41; analysed: 41 No previous history of BC: NS; history of BC: NS Age (years): mean 66.1, SD 9.1, range 46 to 81 Sex: M 34, F 7	Index test: PDD Agent: hypericin Comparator: WLC 'Random' biopsies of normal-appearing areas: no for PDD and WLC	Unit of analysis: biopsy ($n = 179$) Sensitivity: PDD 82%, WLC 62% Specificity: PDD 91%, WLC 98%
Song 2007[77] Time period: Mar 2002 to Oct 2005 Country: China	Enrolled: 51; analysed: 51 No previous history of BC: 47; history of BC: 4 Age (years): mean 52 Sex: M 32, F 19 Notes: All patients had typical whole range anodynia gross haematuria	Index test: PDD Agent: 5-ALA Comparator: WLC 'Random' biopsies of normal-appearing areas: no for PDD and WLC	Unit of analysis: patient (PDD $n = 51$, WLC $n = 40$) Sensitivity: PDD 100%, WLC 53% Specificity: PDD 36%, WLC NS
Szygula 2004[78] Time period: NS Country: Poland	Enrolled: 52 (PDD group); analysed: 52 No previous history of BC: 52; history of BC: 0 Age (years): NS Sex: NS Notes: All patients received TURBT 3 months before investigative procedure. All patients received WLC	Index test: PDD Agent: 5-ALA Comparator: LIF 'Random' biopsies of normal-appearing areas: no Notes: unclear whether comparing PDD with LIF or PDD + WLC with LIF; no WLC only comparison	Unit of analysis: patient ($n = 52$) Sensitivity: PDD 91%, WLC NS Specificity: PDD 67%, WLC NS
[Szygula 2004[79]] As above			

Study[a]	Participants	Tests	Outcomes summary
Tritschler 2007[80] Time period: Sep 2004 to Apr 2005 Country: Germany	Enrolled: 100; analysed: 100 No previous history of BC: 30; history of BC: 70 Age (years): mean 67.9 Sex: M 71, F 29	Index test: PDD Agent: 5-ALA/HAL Comparator: WLC 'Random' biopsies of normal-appearing areas: no for PDD and WLC	Unit of analysis: patient (n = 100) Sensitivity: PDD 93%, WLC 88% Specificity: PDD 57%, WLC 55%
Witjes 2005[81] Time period: Jan 2004 to Mar 2004 Country: Netherlands	Enrolled: 20; analysed: 20 No previous history of BC: 10; history of BC: 10 Age (years): mean 71, range 49 to 89 Sex: M 17, F 3 Notes: Seven patients received previous intravesical chemotherapy or BCG for superficial papillary tumours	Index test: PDD Agent: HAL Comparator: WLC 'Random' biopsies of normal-appearing areas: no for PDD and WLC	Unit of analysis: patient (n = 20) Sensitivity: PDD 90%, WLC 79% Specificity: PDD 100%, WLC 100% Unit of analysis: biopsy (n = 28) Sensitivity: PDD 85%, WLC 74% Specificity: PDD 100%, WLC 100%
Zaak 2002[84] Time period: NS Country: Germany	Enrolled: 43; analysed: 43 No previous history of BC: 0; history of BC: 43 Age (years): mean 70, range 49 to 89 Sex: M 31, F 12	Index test: PDD Agent: 5-ALA Comparator: excimer laser-induced autofluorescence; no WLC comparison 'Random' biopsies of normal-appearing areas: yes for PDD	Unit of analysis: biopsy (n = 114) Sensitivity: PDD 90% Specificity: PDD 61%
Zumbraegel 2003[85] Time period: Jan 1997 to Jul 1999 Country: Germany	Enrolled: 108; analysed: 152 No previous history of BC: NS; history of BC: NS Age (years): NS Sex: NS	Index test: PDD Agent: 5-ALA Comparator: WLC 'Random' biopsies of normal-appearing areas: no for PDD or WLC	Unit of analysis: biopsy (n = 408) Sensitivity: PDD 94%, WLC 80% Specificity: PDD 32%, WLC 46%

BC, bladder cancer; BCG, bacillus Calmette–Guerin; LIF, laser-induced fluorescence; NS, not stated.
a Studies in square brackets, e.g. [Jichlinski 1997], are secondary reports.

Appendix 7

Quality assessment results for the individual PDD studies

Diagnostic studies

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13
Cheng 2000[50]	+	+	+	+	+	–	+	?	?	+	+	+	–
Colombo 2007[51]	–	+	+	+	+	–	+	+	?	+	+	–	–
De Dominicis 2001[53]	+	+	+	+	+	–	+	?	?	+	+	+	–
D'Hallewin 2000[52]	+	+	+	+	+	–	+	+	?	+	+	+	–
Ehsan 2001[54]	+	+	+	+	+	–	+	?	+	+	+	+	–
Filbeck 1999[56]	+	+	+	+	–	–	+	?	?	+	+	+	–
Fradet 2007[57]	+	+	+	+	+	–	+	+	?	+	+	–	–
Frimberger 2001[58]	+	+	+	+	+	–	+	?	?	+	+	+	–
Grimbergen 2003[59]	+	+	+	+	+	–	+	+	?	+	+	+	–
Hendricksen 2006[60]	+	+	+	+	+	–	+	?	?	+	+	+	–
Hungerhuber 2007[61]	+	+	+	+	–	–	+	+	?	+	+	+	–
Jeon 2001[62]	+	+	+	+	–	–	+	+	?	+	+	+	–
Jichlinski 1997[63]	+	+	+	+	+	–	+	+	?	+	+	+	–
Jichlinski 2003[65]	+	+	+	+	+	–	+	+	?	+	+	+	–
Jocham 2005[66]	+	+	+	+	–	–	+	+	?	+	+	+	–
Koenig 1999[67]	+	+	+	+	+	–	+	?	?	–	–	+	–
Kriegmair 1996[70]	+	+	+	+	+	–	+	?	?	+	+	+	–
Kriegmair 1999[71]	+	+	+	+	–	–	+	?	?	+	+	+	–
Landry 2003[72]	+	+	+	+	+	–	+	?	?	+	+	+	–
Riedl 1999[73]	+	+	+	+	?	–	+	?	?	+	+	+	–
Sim 2005[76]	+	+	+	+	–	–	+	+	?	+	+	+	–
Song 2007[77]	+	+	+	+	–	–	+	?	?	+	+	+	–
Szygula 2004[78]	+	+	+	+	–	–	+	?	?	+	+	+	–
Tritschler 2007[80]	+	+	+	+	–	–	+	+	?	+	+	–	–
Witjes 2005[81]	+	+	+	+	–	–	+	?	?	+	+	–	–
Zaak 2002[84]	+	+	+	+	+	–	+	?	?	+	+	+	–
Zumbraegel 2003[85]	+	+	+	+	–	–	+	?	?	+	+	–	–

+, yes to the question; –, no to the question; ?, unclear.

RCTs reporting recurrence/progression

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14
Babjuk 2005[86]	?	?	+	+	+	+	+	?	?	?	–	–	–	?
Daniltchenko 2005[88]	?	?	+	+	+	?	+	?	?	?	+	–	–	?
Denzinger 2007[89]	?	?	+	+	+	+	+	?	?	?	+	+	–	?
Kriegmair 2002[92]	?	?	+	+	+	?	+	?	?	?	–	+	+	?

+, yes to the question; –, no to the question; ?, unclear.

Appendix 8

Studies of PDD versus WLC included in pooled estimates for patient- and biopsy-level analysis and also those reporting stage/grade

	Patient	Biopsy	pTa	pTaG1	pTaG1–2	pTaG2	pTaG2–3	pTaG3	pTa–T1	G1–2
Cheng 2000[50]		✓							✓	
Colombo 2007[51]										
De Dominicis 2001[53]		✓					✓			
Ehsan 2001[54]		✓	✓							
Filbeck 1999[56]		✓			✓					
Fradet 2007[57]										
Grimbergen 2003[59]		✓								
Hendricksen 2006[60]		✓		✓		✓		✓		
Hungerhuber 2007[61]		✓		✓		✓		✓		
Jeon 2001[62]			✓							
Jichlinski 1997[63]		✓								
Jichlinski 2003[65]	✓	✓								
Jocham 2005[66]	✓		✓P							
Koenig 1999[67]				✓		✓		✓		
Kriegmair 1996[70]		✓							✓	
Riedl 1999[73]	✓									
Sim 2005[76]		✓								
Tritschler 2007[80]	✓		✓P							✓P
Witjes 2005[81]	✓	✓				✓P,B		✓P,B		
Zumbraegel 2003[85]		✓								

P, patient-level analysis; B, biopsy-level analysis.

pT1	pT1G1	pT1G1–2	pT1G2	pT1G3	>pT1	CIS	G3	pT2G2	pT2G3	≥ pT2	≥ pT2G3	pT4G3
						✓				✓		
						✓P						
						✓						
✓						✓						
		✓		✓	✓	✓						
						✓P,B						
			✓	✓		✓		✓	✓			✓
	✓		✓	✓		✓					✓	
✓						✓				✓		
						✓P,B						
✓P						✓P				✓P		
			✓	✓		✓			✓			
						✓						
✓P						✓P	✓P			✓P		
				✓P,B		✓P,B			✓P,B			
						✓						

Appendix 9

PDD and WLC test performance for detecting bladder cancer, results table with 2×2 data

Study[a,b,c]	Test	Unit of analysis	Number analysed	TP	FP	FN	TN	Sens (%)	Spec (%)	LR+	LR–
Cheng 2000[50]	PDD (5-ALA)	Biopsy	175	57	39	7	72	89	65	2.5	0.2
No. of patients 41, of whom primary NS, recurrent NS		Flat lesions	136	20	38	7	71	74	65	2.1	0.4
PDD 'random' biopsies		CIS lesions	7	5		2		71			
		pTa–T1 lesions	36	36		0		100			
		≥ pT2 lesions	5	5		0		100			
	WLC	Biopsy	175	42	18	22	93	66	84	4.0	0.4
		Flat lesions	136	5	16	22	93	23	85	1.5	0.9
		CIS lesions	7	1		6		14			
		pTa–T1 lesions	36	30		6		83			
		≥ pT2 lesions	5	5		0		100			
Colombo 2007[51]	PDD (5-ALA, HAL)	Patients with CIS	49	18	9	0	22	100	71	3.4	0.0
No. of patients 49, of whom primary 0, recurrent 49 (all being followed up for CIS)	WLC	Patients with CIS	49	0	1	18	30	0	97	0.0	0.0
'Random' biopsies (NS whether PDD or WLC or both)											
De Dominicis 2001[53]	PDD (5-ALA)	Biopsy	179	45	47	7	80	87	63	2.3	0.2
No. of patients 49, of whom primary 17, recurrent 32		Dysplasia	19	16		3		84			
PDD and WLC 'random' biopsies		CIS	13	10		3		77			
		SNA	2	1		1		50			
		pTaG2–3	10	10		0		100			
		pT1G3	0								
		pT1G2–3	8	8		0		100			
	WLC	Biopsy	179	9	15	43	112	17	88	1.5	0.9
		Dysplasia	19	6		13		32			
		CIS	13	3		10		23			
		SNA	2	0		2		0			
		pTaG2–3	10	0		10		0			
		pT1G3	8	0		8		0			
		pT1G2–3	0								

Study[a,b,c]	Test	Unit of analysis	Number analysed	TP	FP	FN	TN	Sens (%)	Spec (%)	LR+	LR–
D'Hallewin 2000[52]	PDD (hypericin)	Biopsy									
No. of patients 40, of whom primary NS, recurrent NS		CIS	281	132	2	10	137	93	99	93.0	0.1
PDD 'random' biopsies											
Ehsan 2001[54]	PDD (5-ALA)	Biopsy	151	59	32	1	59	98	65	2.8	0.0
No. of patients 30, of whom primary NS, recurrent NS		CIS	2	2		0		100			
		pTa	20	20		0		100			
PDD and WLC 'random' biopsies		pT1	28	28		0		100			
	WLC	Biopsy	151	36	38	24	53	60	58	1.4	0.7
		CIS	2	0		2		0			
		pTa	20	18		2		90			
		pT1	28	14		14		50			
Filbeck 1999[56]	PDD (5-ALA)	Biopsy (primary/recurrent/ secondary tumour resection)	347	119	145	5	78	96	35	1.5	0.1
No. of patients 120, of whom primary NS, recurrent NS (60 of the patients were having a secondary resection 6 weeks after primary tumour resection)		pTaG1–2	77	74		3		96			
		pT1G1–2	10	9		1		90			
		pT1G3	11	11		0		100			
		CIS	7	7		0		100			
		>pT1	6	6		0		100			
No 'random' biopsies (except in cases of a resection in areas of primary tumour)		Dysplasia	13	12?		1?		92?			
		Biopsy (primary/recurrent tumour resection)									
		pTaG1–2	64	64		0		100			
		pT1G1–2	8	8		0		100			
		pT1G3	10	10		0		100			
		CIS	5	5		0		100			
		>pT1	6	6		0		100			
		Dysplasia	6	6		0		100			

Study[a,b,c]	Test	Unit of analysis	Number analysed	TP	FP	FN	TN	Sens (%)	Spec (%)	LR+	LR–
		Biopsy (secondary tumour resection)									
		pTaG1–2	13	10		3		77			
		pT1G1–2	2	1		1		50			
		pT1G3	1	1		0		100			
		CIS	2	2		0		100			
		Dysplasia	7	6		1		86			
	WLC	Biopsy (primary/recurrent/ secondary tumour resection)	347	85	75	39	148	69	66	2.0	0.5
		pTaG1–2	77	57		20		74			
		pT1G1–2	10	8		2		80			
		pT1G3	11	8		3		73			
		CIS	7	4		3		57			
		>pT1	6	5		1		83			
		Dysplasia	13	3		10		30			
		Biopsy (primary/recurrent tumour resection)									
		pTaG1–2	64	54		10		84			
		pT1G1–2	8	7		1		88			
		pT1G3	10	8		2		80			
		CIS	5	4		1		80			
		>pT1	6	5		1		83			
		Dysplasia	6	2		4		33			
		Biopsy (secondary tumour resection)									
		pTaG1–2	13	3		10		23			
		pT1G1–2	2	1		1		50			
		pT1G3	1	0		1		0			
		CIS	2	0		2		0			
		Dysplasia	7	1		6		14			

Study[a,b,c]	Test	Unit of analysis	Number analysed	TP	FP	FN	TN	Sens (%)	Spec (%)	LR+	LR–
[Filbeck 1999[55]] (secondary TUR)	PDD (5-ALA)	Biopsy	130	14	75	4	37	78	33	1.2	0.7
No. of patients 50, all of whom were having a secondary TUR of the former resection area 6 weeks after conventional TUR	WLC	Biopsy	18	7?		11?		64?			
No 'random' biopsies											
Fradet 2007[57]	PDD (HAL)	Patient									
No. of patients 196, of whom primary 62, recurrent 133 (missing, 1)		CIS	196	50	25	8	113	87	82	4.8	0.2
		Biopsy									
PDD and WLC 'random' biopsies		CIS	113	104	223	9		92			
	WLC	Patient									
		CIS	196	48	39	10	99	83	72	3.0	0.2
		Biopsy									
		CIS	113	77	137	36		68			
Frimberger 2001[58]	PDD (5-ALA)	Biopsy	43	18	8	1	16	95	67	2.9	0.1
No. of patients 25, all of whom were recurrent		CIS	6	5		1		83			
		pTa	10	10		0		100			
PDD and WLC 'random' biopsies		pT2	3	3		0		100			
Grimbergen 2003[59]	PDD (5-ALA)	Biopsy	917	378	270	12	257	97	49	1.9	0.1
No. of patients 160, of whom primary 87?, recurrent 73?	WLC	Biopsy	917	270	115	120	412	69	78	3.2	0.4
PDD and WLC 'random' biopsies											

Study[a,b,c]	Test	Unit of analysis	Number analysed	TP	FP	FN	TN	Sens (%)	Spec (%)	LR+	LR–
Hendricksen 2006[60]	PDD (HAL)	Biopsy	217	88	52	6	71	94	58	2.2	0.1
No. of patients 50, of whom primary 23, recurrent 27		CIS	10	7		3		70			
'Random' biopsies (unclear whether PDD or WLC or both)		pTaG1	2	2		0		100			
		pTaG2	39	37		2		95			
		pTaG3	6	6		0		100			
		pT1G2	13	12		1		92			
		pT1G3	8	8		0		100			
		pT2G2	2	2		0		100			
		pT2G3	8	8		0		100			
		pT4G3	3	3		0		100			
	WLC	Biopsy	123	83	17	11	106	88	86	6.4	0.1
		CIS	10	3		7		30			
		pTaG1	2	2		0		100			
		pTaG2	39	39		0		100			
		pTaG3	6	6		0		100			
		pT1G2	13	12		1		92			
		pT1G3	8	7		1		88			
		pT2G2	2	2		0		100			
		pT2G3	8	8		0		100			
		pT4G3	3	3		0		100			

Study[a,b,c]	Test	Unit of analysis	Number analysed	TP	FP	FN	TN	Sens (%)	Spec (%)	LR+	LR–
Hungerhuber 2007[61]	PDD (5-ALA)	Biopsy	4630	1484	1339	129	1678	92	56	2.1	0.1
No. of patients 875, of whom primary 327, recurrent 548		pTxG1	47	42		5		89			
No 'random' biopsies		pTxG2	28	26		2		93			
		pTxG3	18	15		3		83			
		pTaG1	495	466		29		94			
		pTaG2	205	196		9		96			
		pTaG3	45	42		3		93			
		pT1G1	12	11		1		92			
		pT1G2	53	52		1		98			
		pT1G3	149	144		5		97			
		≥T2G3	101	90		11		89			
		CIS	274	254		20		93			
		Dysplasia grade 2	186	146		40		78			
	WLC	Biopsy	4630	1231	430	382	2587	76	86	5.4	0.3
		pTxG1	47	40		7		85			
		pTxG2	28	23		5		82			
		pTxG3	18	15		3		83			
		pTaG1	495	408		87		82			
		pTaG2	205	175		30		85			
		pTaG3	45	34		11		76			
		pT1G1	12	8		4		67			
		pT1G2	53	38		15		72			
		pT1G3	149	119		30		80			
		≥T2G3	101	87		14		86			
		CIS	274	155		119		57			
		Dysplasia grade 2	186	129		57		69			

Study[a,b,c]	Test	Unit of analysis	Number analysed	TP	FP	FN	TN	Sens (%)	Spec (%)	LR+	LR–
[Zaak 2002[83]]	PDD (5-ALA)	Lesion (same as biopsy)	3834	1222	2049	28	535	98	21	1.2	0.1
No. of patients 713, of whom primary 270, recurrent 443		CIS	159	145		14		91			
	WLC	Lesion (same as biopsy)									
No 'random' biopsies		CIS	159	75		84		47			
[Zaak 2001[82]]	PDD (5-ALA)	Endoscopy	1012	477	352	75	108	86	23	1.1	0.6
No. of patients 605, of whom primary 212, recurrent 393		Dysplasia grade 2	52	30		22		58			
		CIS	88	84		4		95			
No 'random' biopsies		pTxGx	1	1		0		100			
		pTxG1	13	11		2		85			
		pTxG2	5	5		0		100			
		pTxG3	6	6		0		100			
		pTaG1	178	146		32		82			
		pTaG2	80	69		11		86			
		pTaG3	11	11		0		100			
		pT1G1	9	8		1		89			
		pT1G2	26	26		0		100			
		pT1G3	46	43		3		93			
		>pT1G2–3	37	37		0		100			
	WLC	Endoscopy	552	363		189		66			
		Dysplasia grade 2	52	32		20		62			
		CIS	88	38		50		43			
		pTxGx	1	1		0		100			
		pTxG1	13	12		1		92			
		pTxG2	5	3		2		60			
		pTxG3	6	5		1		69			
		pTaG1	178	118		60		66			
		pTaG2	80	61		19		76			
		pTaG3	11	6		5		55			
		pT1G1	9	6		3		67			
		pT1G2	26	15		11		58			
		pT1G3	46	34		12		74			
		>pT1G2–3	37	32		5		86			

Study[a,b,c]	Test	Unit of analysis	Number analysed	TP	FP	FN	TN	Sens (%)	Spec (%)	LR+	LR–
Jeon 2001[62]	PDD (5-ALA)	Biopsy									
No. of patients 62, of whom primary 36, recurrent 26		CIS or more	274	140	77	3	54	98	41	1.7	0.0
		Dysplasia or more	274	145	72	3	54	98	43	1.7	0.0
No 'random' biopsies		Dysplasia	5	5		0		100			
		CIS	20	20		0		100			
		Ta	64	63		1		98			
		T1	42	40		2		95			
		≥T2	17	17		0		100			
	WLC	Biopsy									
		CIS or more	274	87	11	56	120	61	92	7.6	0.4
		Dysplasia or more	274	87	11	61	115	59	91	6.6	0.5
		Dysplasia	5	0		5		0			
		CIS	20	1		19		5			
		Ta	64	48		16		75			
		T1	42	25		17		60			
		≥T2	17	13		4		76			
Jichlinski 1997[63]	PDD (5-ALA)	Biopsy	215	97	46	12	60	89	57	2.1	0.2
No. of patients 34, of whom primary 13, recurrent 21	WLC	Biopsy	215	50?	46??	59?	60??	46?	57?	1.1	0.9
PDD 'random' biopsies											
[Jichlinski 1997[64]]	PDD (5-ALA)	Biopsies of apparently normal mucosa under WLC	132	34	17	7	74	83	81	4.4	0.2
No. of patients 31, of whom primary 11, recurrent 22 (data as reported)											
WLC 'random' biopsies											

Study[a,b,c]	Test	Unit of analysis	Number analysed	TP	FP	FN	TN	Sens (%)	Spec (%)	LR+	LR–
Jichlinski 2003[65]	PDD (HAL)	Patient	52	43	4	2	3	96	43	1.7	0.1
No. of patients 52, of whom primary 18, recurrent 34		CIS	13	12		1		92			
WLC 'random' biopsies		Biopsy	421	108	57	35	221	76	79	3.7	0.3
		CIS	57	31?		26?		54?			
	WLC	Patient	52	33	4	12	3	73	43	1.3	0.6
		CIS	13	3		10		30			
		Biopsy	414	65	19	75	255	46	93	6.7	0.6
		CIS	57	3		54		5			
Jocham 2005[66]	PDD (HAL)	Patient	146	61	6	54	25	53	81	2.7	0.6
No. of patients 146, of whom primary 73, recurrent 73		CIS	29	12		17		41			
No 'random' biopsies		pTa	66	13		53		20			
		pT1 (pT1a+pT1b)	16	1		15		6			
		pT2–4	22	3		19		14			
	WLC	Patient	146	38	8	77	23	33	74	1.3	0.9
		CIS	29	2		27		7			
		pTa	66	5		61		8			
		pT1 (pT1a+pT1b)	16	1		15		6			
		pT2–4	22	1		21		5			
Koenig 1999[67]	PDD (5-ALA)	Biopsy	130	58	26	9	37	87	59	2.1	0.2
No. of patients 55, of whom primary NS, recurrent NS		CIS	6	5		1		83			
'Random' biopsies (unclear whether PDD or WLC or both)		pTaG1	8	7		1		88			
		pTaG2	25	22		3		88			
		pTaG3	3	3		0		100			
		pT1G2	2	2		0		100			
		pT1G3	5	5		0		100			
		pT2G3	6	5		1		83			

Study[a,b,c]	Test	Unit of analysis	Number analysed	TP	FP	FN	TN	Sens (%)	Spec (%)	LR+	LR–
	WLC	Biopsy	67	56		11		84			
		CIS	6	4		2		67			
		pTaG1	8	6		2		75			
		pTaG2	25	24		1		96			
		pTaG3	0								
		pT1G2	0								
		pT1G3	0								
		pT2G3	6	5		1		83			
Kriegmair 1996[70]	PDD (5-ALA)	Biopsy	433	126	110	2	195	98	64	2.7	0.0
No. of patients 106, of whom primary 29, recurrent 77		Dysplasia grade 1 + CIS	329	23	110	1	195	96	64	2.7	0.1
PDD 'random' biopsies		Dysplasia grade 2 + CIS	221	13	12	0	196	100	94	17.2	0.0
		CIS	329	6	127	0	196	100	61	2.5	0.0
		pTa–T1	399	93	110	1	195	99	64	2.7	0.0
		Patients with dysplasia or TCC from normal bladder wall or bladder wall with non-specific inflammation – all patients	308	28	83	2	195	93	70	3.1	0.1
		Patients with dysplasia or TCC from normal bladder wall or bladder wall with non-specific inflammation – patients with a history of BCG instillation or chemotherapy	165	25	39	1	100	96	72	3.4	0.1

Study[a,b,c]	Test	Unit of analysis	Number analysed	TP	FP	FN	TN	Sens (%)	Spec (%)	LR+	LR–
	WLC	Biopsy	433	93	96	35	209	73	69	2.3	0.4
		Dysplasia grade 1 + CIS	329	10	96	14	209	42	69	1.3	0.9
		Dysplasia grade 2 + CIS	329	7	99	6	217	54	69	1.7	0.7
		CIS	329	4	102	2	221	67	68	2.1`	0.5
		pTa–T1	399	74	96	20	209	79	69	2.5	0.3
		Patients with dysplasia or TCC from normal bladder wall or bladder wall with non-specific inflammation – all patients	308	16	69	14	209	53	75	2.1	0.6
		Patients with dysplasia or TCC from normal bladder wall or bladder wall with non-specific inflammation – patients with a history of BCG instillation or chemotherapy	165	16	41	10	98	62	71	2.1	0.5
[Kriegmair 1994[68]] No. of patients 68, of whom primary 6, recurrent 62 PDD 'random' biopsies	PDD (5-ALA)	Biopsy	285	93	46	0	146	100	76	4.2	N/C
[Kriegmair 1995[69]] No. of patients 90, of whom primary 26, recurrent 64 PDD 'random' biopsies	PDD (5-ALA)	Biopsy	294	43	73	1	177	98	71	3.4	0.0
Kriegmair 1999[71,74,75] No. of patients 208, of whom primary 72, recurrent 136 No 'random' biopsies	PDD (5-ALA)	Biopsy	328	159	97	4	68	98	41	1.7	0.0
	WLC	Biopsy	163	77		86		47			
Landry 2003[72] No. of patients 50, of whom primary 50, recurrent 0 WLC 'random' biopsies	PDD (5-ALA)	Patient	50	9	12	5	24	64	67	1.9	0.5

Study[a,b,c]	Test	Unit of analysis	Number analysed	TP	FP	FN	TN	Sens (%)	Spec (%)	LR+	LR–
Riedl 1999[73]	PDD (5-ALA)	Patient	52	34	12	0	6	100	33	1.5	N/C
No. of patients 52, of whom primary NS, recurrent NS		Biopsy	123	50?	40?	3?	30?	95	43	1.7	0.1
	WLC	Patient	52	26	0	8	18	76	100	N/C	0.2
'Random' biopsies (unclear whether PDD or WLC or both)		Biopsy	70	53?		17?		76			
Sim 2005[76]	PDD (hypericin)	Biopsy	179	61	10	13	95	82	90	8.7	0.2
No. of patients 41, of whom primary NS, recurrent NS	WLC	Biopsy	179	46	2	28	103	62	98	32.7	0.4
No 'random' biopsies											
Song 2007[77]	PDD (5-ALA)	Patient	51	40	7	0	4	100	36	1.6	N/C
No. of patients 51, of whom primary 47, recurrent 4		Biopsy	103	68	21	2	12	97	36	1.5	0.1
	WLC	Patient	40	21		19		53			
No 'random' biopsies											
Szygula 2004[78,79]	PDD (5-ALA)	Patient	52	20	10	2	20	91	67	2.7	0.1
No. of patients 52, of whom primary 52?, recurrent 0?											
No 'random' biopsies											
Tritschler 2007[80]	PDD (5-ALA/ HAL)	Patient	100	37	26	3	34	93	57	2.1	0.1
No. of patients 100, of whom primary 30, recurrent 70		pTa	22?	21?		1?		95			
		CIS	9?	7?		2?		78			
No 'random' biopsies		pT1	4?	4?		0?		100?			
		≥ pT2	3?	3?		0?		100?			
		G1–2	22?	21?		1?		95?			
		G3	18?	16?		2?		89?			

Study[a,b,c]	Test	Unit of analysis	Number analysed	TP	FP	FN	TN	Sens (%)	Spec (%)	LR+	LR–
	WLC	Patient	100	35	27	5	33	88	55	1.9	0.2
		pTa	22?	21?		1?		95?			
		CIS	9?	5?		4?		56?			
		pT1	4?	4?		0?		100?			
		≥ pT2	3?	3?		0?		100?			
		G1–2	22?	21?		1?		95?			
		G3	18?	14?		4?		78?			
Witjes 2005[81]	PDD (HAL)	Patient	20	17	0	2	1	89	100	N/C	0.1
No. of patients 20, of whom primary 10, recurrent 10		pTaG2	8	7		1		88			
No 'random' biopsies		pTaG3	1	1		0		100			
		CIS	3	2		1		67			
		pT1G3	1	1		0		100			
		pT2G3	6	6		0		100			
		Lesion (same as biopsy)	28	23	0	4	1	85	100	N/C	0.1
		pTaG2	11	10		1		91			
		pTaG3	1	1		0		100			
		CIS	8	5		3		63			
		pT1G3	1	1		0		100			
		pT2G3	6	6		0		100			
	WLC	Patient	20	15	0	4	1	79	100	N/C	0.2
		pTaG2	8	8		0		100			
		pTaG3	1	1		0		100			
		CIS	3	1		2		33			
		pT1G3	1	1		0		100			
		pT2G3	6	4		2		67			
		Lesion	28	20	0	7	1	74	100	N/C	0.3
		pTaG2	1	10		1		91			
		pTaG3	1	1		0		100			
		CIS	8	4		4		50			
		pT1G3	1	1		0		100			
		pT2G3	6	4		2		67			

Study[a,b,c]	Test	Unit of analysis	Number analysed	TP	FP	FN	TN	Sens (%)	Spec (%)	LR+	LR–
Zaak 2002[84]	PDD (5-ALA)	Biopsy	114	19	36	2	57	90	61	2.3	0.2
No. of patients 43, of whom primary 0, recurrent 43											
PDD 'random' biopsies											
Zumbraegel 2003[85]	PDD (5-ALA)	Biopsy	408	125	186	8	89	94	32	1.4	0.1
No. of patients 108, of whom primary NS, recurrent NS		CIS	14	12		2		86			
		Dysplasia	48	43		5		90			
No 'random' biopsies	WLC	Biopsy	408	107	148	26	127	80	46	1.5	0.4
		CIS	14	9		5		64			
		Dysplasia	48	15		33		31			

FN, false negative; FP, false positive; LR+, positive likelihood ratio; LR–, negative likelihood ratio; NC, not calculable; NS, not stated; SNA, single nuclear atypia; TN, true negative; TP, true positive.

a Studies in square brackets, e.g. [Jichlinski 1997], are secondary reports.

b Blank cells: no data reported.

c No 'random' biopsies: study either stated that no random biopsies were carried out or did not state whether random biopsies were carried out. PDD 'random' biopsies: biopsies of normal-appearing areas on PDD. WLC 'random' biopsies: biopsies of normal-appearing areas on WLC.

Appendix 10

Biomarker/cytology included studies

Abbate 1998
Abbate I, D'Introno A, Cardo G, Marano A, Addabbo L, Musci MD, *et al*. Comparison of nuclear matrix protein 22 and bladder tumor antigen in urine of patients with bladder cancer. *Anticancer Res* 1998;**18**:3803–5.

Bastacky 1999
Bastacky S, Ibrahim S, Wilczynski SP, Murphy WM. The accuracy of urinary cytology in daily practice. *Cancer* 1999;**87**:118–28.

Bhuiyan 2003
Bhuiyan J, Akhter J, O'Kane DJ. Performance characteristics of multiple urinary tumor markers and sample collection techniques in the detection of transitional cell carcinoma of the bladder. *Clin Chim Acta* 2003;**331**:69–77.

Boman 2002
Boman H, Hedelin H, Holmang S. Four bladder tumor markers have a disappointingly low sensitivity for small size and low grade recurrence. *J Urol* 2002;**167**:80–3.

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Primary reference
Casella R, Huber P, Blochlinger A, Stoffel F, Dalquen P, Gasser TC, *et al*. Urinary level of nuclear matrix protein 22 in the diagnosis of bladder cancer: experience with 130 patients with biopsy confirmed tumor. *J Urol* 2000;**164**:1926–8.

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Shariat SF, Casella R, Monoski MA, Sulser T, Gasser TC, Lerner SP. The addition of urinary urokinase-type plasminogen activator to urinary nuclear matrix protein 22 and cytology improves the detection of bladder cancer. *J Urol* 2003;**170**:2244–7.

Shariat SF, Casella R, Khoddami SM, Hernandez G, Sulser T, Gasser TC, *et al*. Urine detection of survivin is a sensitive marker for the noninvasive diagnosis of bladder cancer. *J Urol* 2004;**171**:626–30.

Casetta 2000
Casetta G, Gontero P, Zitella A, Pelucelli G, Formiconi A, Priolo G, *et al*. BTA quantitative assay and NMP22 testing compared with urine cytology in the detection of transitional cell carcinoma of the bladder. *Urol Int* 2000;**65**:100–5.

Chahal 2001a
Chahal R, Gogoi NK, Sundaram SK. Is it necessary to perform urine cytology in screening patients with haematuria? *Eur Urol* 2001;**39**:283–6.

Chahal 2001b
Chahal R, Darshane A, Browning AJ, Sundaram SK. Evaluation of the clinical value of urinary NMP22 as a marker in the screening and surveillance of transitional cell carcinoma of the urinary bladder. *Eur Urol* 2001;**40**:415–20.

Chang 2004
Chang YH, Wu CH, Lee YL, Huang PH, Kao YL, Shiau MY. Evaluation of nuclear matrix protein-22 as a clinical diagnostic marker for bladder cancer. *Urology* 2004;**64**:687–92.

Daniely 2007
Daniely M, Rona R, Kaplan T, Olsfanger S, Elboim L, Freiberger A, *et al*. Combined morphologic and fluorescence in situ hybridization analysis of voided urine samples for the detection and follow-up of bladder cancer in patients with benign urine cytology. *Cancer* 2007;**111**:517–24.

Del Nero 1999
Del Nero A, Esposito N, Curro A, Biasoni D, Montanari E, Mangiarotti B, *et al*. Evaluation of urinary level of NMP22 as a diagnostic marker for stage pTa-pT1 bladder cancer: comparison with urinary cytology and BTA test. *Eur Urol* 1999;**35**:93–7.

Friedrich 2003
Primary reference
Friedrich MG, Toma MI, Hellstern A, Pantel K, Weisenberger DJ, Noldus J, *et al*. Comparison of multitarget fluorescence in situ hybridization in urine with other noninvasive tests for detecting bladder cancer. *BJU Int* 2003;**92**:911–4.

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Friedrich MG, Hellstern A, Hautmann SH, Graefen M, Conrad S, Huland E, *et al*. Clinical use of urinary markers for the detection and prognosis of bladder carcinoma: a comparison of immunocytology with monoclonal antibodies against Lewis X and 486p3/12 with the BTA STAT and NMP22 tests. *J Urol* 2002;**168**:470–4.

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Garbar C, Mascaux C, Wespes E. Is urinary tract cytology still useful for diagnosis of bladder carcinomas? A large series of 592 bladder washings using a five-category classification of different cytological diagnoses. *Cytopathology* 2007;**18**:79–83.

Giannopoulos 2001
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Giannopoulos A, Manousakas T, Gounari A, Constantinides C, Choremi-Papadopoulou H, Dimopoulos C. Comparative evaluation of the diagnostic performance of the BTA stat test, NMP22 and urinary bladder cancer antigen for primary and recurrent bladder tumors [see comment]. *J Urol* 2001;**166**:470–5.

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Giannopoulos A, Manousakas T, Mitropoulos D, Botsoli-Stergiou E, Constantinides C, Giannopoulou M, *et al*. Comparative evaluation of the BTAstat test, NMP22, and voided urine cytology in the detection of primary and recurrent bladder tumors. *Urology* 2000;**55**:871–5.

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Hakenberg OW, Franke P, Froehner M, Manseck A, Wirth MP. The value of conventional urine cytology in the diagnosis of residual tumour after transurethral resection of bladder carcinomas. *Onkologie* 2000;**23**:252–7.

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Halling KC, King W, Sokolova IA, Meyer RG, Burkhardt HM, Halling AC, *et al*. A comparison of cytology and fluorescence in situ hybridization for the detection of urothelial carcinoma. *J Urol* 2000;**164**:1768–75.

Hughes 1999
Hughes JH, Katz RL, Rodriguez-Villanueva J, Kidd L, Dinney C, Grossman HB, *et al*. Urinary nuclear matrix protein 22 (NMP22): a diagnostic adjunct to urine cytologic examination for the detection of recurrent transitional-cell carcinoma of the bladder. *Diagn Cytopathol* 1999;**20**:285–90.

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Junker K, Fritsch T, Hartmann A, Schulze W, Schubert J. Multicolor fluorescence in situ hybridization (M-FISH) on cells from urine for the detection of bladder cancer. *Cytogenet Genome Res* 2006;**114**:279–83.

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Karakiewicz PI, Benayoun S, Zippe C, Ludecke G, Boman H, Sanchez-Carbayo M, *et al*. Institutional variability in the accuracy of urinary cytology for predicting recurrence of transitional cell carcinoma of the bladder. *BJU Int* 2006;**97**:997–1001.

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Kipp BR, Halling KC, Campion MB, Wendel AJ, Karnes RJ, Zhang J, *et al*. Assessing the value of reflex fluorescence in situ hybridization testing in the diagnosis of bladder cancer when routine urine cytological examination is equivocal. *J Urol* 2008;**179**:1296–301.

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Kowalska M, Kaminska J, Kotowicz B, Fuksiewicz M, Rysinska A, Demkow T, *et al*. Evaluation of the urinary nuclear matrix protein (NMP22) as a tumour marker in bladder cancer patients. *Nowotwory* 2005;**55**:300–2.

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Kumar A, Kumar R, Gupta NP. Comparison of NMP22 BladderChek test and urine cytology for the detection of recurrent bladder cancer. *Jpn J Clin Oncol* 2006;**36**:172–5.

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Lahme S, Bichler KH, Feil G, Krause S. Comparison of cytology and nuclear matrix protein 22 for the detection and follow-up of bladder cancer. *Urol Int* 2001;**66**:72–7.

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May M, Hakenberg OW, Gunia S, Pohling P, Helke C, Lubbe L, *et al*. Comparative diagnostic value of urine cytology, UBC-ELISA, and fluorescence in situ hybridization for detection of transitional cell carcinoma of urinary bladder in routine clinical practice. *Urology* 2007;**70**:449–53.

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Mian C, Pycha A, Wiener H, Haitel A, Lodde M, Marberger M. Immunocyt: a new tool for detecting transitional cell cancer of the urinary tract. *J Urol* 1999;**161**:1486–9.

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Moonen PM, Merkx GF, Peelen P, Karthaus HF, Smeets DF, Witjes JA. UroVysion compared with cytology and quantitative cytology in the surveillance of non-muscle-invasive bladder cancer. *Eur Urol* 2007;**51**:1275–80.

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Oge O, Atsu N, Kendi S, Ozen H. Evaluation of nuclear matrix protein 22 (NMP22) as a tumor marker in the detection of bladder cancer. *Int Urol Nephrol* 2001;**32**:367–70.

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Olsson H, Zackrisson B. ImmunoCyt a useful method in the follow-up protocol for patients with urinary bladder carcinoma. *Scand J Urol Nephrol* 2001;**35**:280–2.

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Oosterhuis JWA, Pauwels RPE, Schapers RFM, Van Pelt J, Smeets W, Newling DWW. Detection of recurrent transitional cell carcinoma of the bladder with nuclear matrix protein-22 in a follow-up setting. *UroOncology* 2002;**2**:137–42.

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Potter JM, Quigley M, Pengelly AW, Fawcett DP, Malone PR. The role of urine cytology in the assessment of lower urinary tract symptoms. *BJU Int* 1999;**84**:30–1.

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Poulakis V, Witzsch U, De Vries R, Altmannsberger HM, Manyak MJ, Becht E. A comparison of urinary nuclear matrix protein-22 and bladder tumour antigen tests with voided urinary cytology in detecting and following bladder cancer: the prognostic value of false-positive results. *BJU Int* 2001;**88**:692–701.

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Sanchez-Carbayo 1999
Primary reference
Sanchez-Carbayo M, Herrero E, Megias J, Mira A, Soria F. Comparative sensitivity of urinary CYFRA 21–1, urinary bladder cancer antigen, tissue polypeptide antigen, tissue polypeptide antigen and NMP22 to detect bladder cancer. *J Urol* 1999;**162**:1951–6.

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Sanchez-Carbayo M, Urrutia M, Silva JM, Romani R, De Buitrago JM, Navajo JA. Comparative predictive values of urinary cytology, urinary bladder cancer antigen, CYFRA 21–1 and NMP22 for evaluating symptomatic patients at risk for bladder cancer. *J Urol* 2001;**165**:1462–7.

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Sarosdy MF, Kahn PR, Ziffer MD, Love WR, Barkin J, Abara EO, *et al*. Use of a multitarget fluorescence in situ hybridization assay to diagnose bladder cancer in patients with hematuria. *J Urol* 2006;**176**:44–7.

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Schmitz-Drager BJ, Beiche B, Tirsar LA, Schmitz-Drager C, Bismarck E, Ebert T. Immunocytology in the assessment of patients with asymptomatic microhaematuria. *Eur Urol* 2007;**51**:1582–8.

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Primary reference
Serretta V, Pomara G, Rizzo I, Esposito E. Urinary BTA-stat, BTA-trak and NMP22 in surveillance after TUR of recurrent superficial transitional cell carcinoma of the bladder. *Eur Urol* 2000;**38**:419–25.

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Skacel M, Fahmy M, Brainard JA, Pettay JD, Biscotti CV, Liou LS, *et al*. Multitarget fluorescence in situ hybridization assay detects transitional cell carcinoma in the majority of patients with bladder cancer and atypical or negative urine cytology. *J Urol* 2003;**169**:2101–5.

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Stampfer DS, Carpinito GA, Rodriguez-Villanueva J, Willsey LW, Dinney CP, Grossman HB, *et al*. Evaluation of NMP22 in the detection of transitional cell carcinoma of the bladder. *J Urol* 1998;**159**:394–8.

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Talwar R, Sinha T, Karan SC, Doddamani D, Sandhu A, Sethi GS, *et al*. Voided urinary cytology in bladder cancer: is it time to review the indications? *Urology* 2007;**70**:267–71.

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Tritschler S, Scharf S, Karl A, Tilki D, Knuechel R, Hartmann A, *et al*. Validation of the diagnostic value of NMP22 BladderChek test as a marker for bladder cancer by photodynamic diagnosis. *Eur Urol* 2007;**51**:403–7.

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Zippe C, Pandrangi L, Potts JM, Kursh E, Novick A, Agarwal A. NMP22: a sensitive, cost-effective test in patients at risk for bladder cancer. *Anticancer Res* 1999;**19**:2621–3.

Appendix 11

Biomarker/cytology excluded studies

Less than 100 participants included in the analysis (*n* = 119)

Abd El Gawad IA, Moussa HS, Nasr MI, El Gemae EH, Masooud AM, Ibrahim IK, *et al*. Comparative study of NMP-22, telomerase, and BTA in the detection of bladder cancer. *J Egypt Natl Cancer Inst* 2005;**17**:193–202.

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Appendix 12

Characteristics of the biomarker and cytology studies

Study	Participants	Tests	Outcomes summary
Abbate 1998[154] Study design: case–control Time period: NS Country: Italy	Enrolled: 182; analysed: 135 No previous history of BC: NS; history of BC: NS Age (years): mean 63, range 41 to 89 Sex: NS	Tests and cut-off used: NMP22, 12 U/ml	Unit of analysis: patient (n = 135) Sensitivity: 54% Specificity: 87%
Bastacky 1999[165] Study design: CC-SD (three centres) Time period: 1990–4 Country: USA	Enrolled: 1672; analysed: 743 No previous history of BC: 752; history of BC: 485 Age (years): NS Sex: NS	Tests and cut-off used: cytology (VU or BW), subjective assessment	Unit of analysis: patient (n = 743) Sensitivity: 64% Specificity: 93%
Bhuiyan 2003[120] Study design: C-SD Time period: NS Country: Saudi Arabia/USA	Enrolled: 233; analysed: 231 NMP22, 125 cytology No previous history of BC: NS; history of BC: NS Age (years): NS Sex: NS	Tests and cut-off used: NMP22, 3.6 U/ml, ≥ 10 U/ml; cytology (VU), subjective assessment	Unit of analysis: specimen (n = 231, NMP22; n = 125, cytology) Sensitivity: 25% (NMP22 10 U/ml), 40% (cytology) Specificity: 94% (NMP22 10 U/ml), 95% (cytology)
Boman 2002[155a] Study design: case–control Time period: Jan 1998 to Nov 1999 Country: Sweden	Enrolled: 250; specimens analysed: 297 NMP22, 293 cytology No previous history of BC: NS; history of BC: 174 Age (years): NS Sex: NS	Tests and cut-off used: NMP22, ≥ 4 U/ml; cytology (BW), subjective assessment	Unit of analysis: specimen (n = 297, NMP22; n = 293, cytology) Sensitivity: 54% (NMP22), 40% (cytology) Specificity: 68 (NMP22), 93% (cytology)
Casella 2000[121,145,146] Study design: C-SD Time period: Jan 1997 to Jun 1999 Country: Switzerland	Enrolled: 235; analysed: 235 NMP22, 200 cytology No previous history of BC: NS; history of BC: NS Age (years): mean 72, range 37 to 97 (M); mean 69, range 23 to 96 (F) Sex: 164 M, 71 F	Tests and cut-off used: NMP22 ≥ 10 U/ml; cytology (BW), subjective assessment	Unit of analysis: patient (n = 235, NMP22; n = 200, cytology) Sensitivity: 52% (NMP22), 53% (cytology) Specificity: 84% (NMP22), 90% (cytology)
Casetta 2000[122] Study design: C-SD Time period: Jan 1997 to Dec 1998 Country: Italy	Enrolled: 196; analysed: 196 No previous history of BC: 94; history of BC: 102 Age (years): mean 68, no history BC; mean 69, history BC; range NS Sex: 170 M, 26 F	Tests and cut-off used: NMP22 ≥10 U/ml, 11 U/ml, 12 U/ml; cytology (VU), subjective assessment	Unit of analysis: patient (n = 196) Sensitivity: 64% (NMP22 10 U/ml), 73% (cytology) Specificity: 63% (NMP22 10 U/ml), 80% (cytology)

Study	Participants	Tests	Outcomes summary
Chahal 2001[166] Study design: C-SD Time period: Jan 1998 to Jan 2000 Country: UK	Enrolled: 285; analysed: 285 No previous history of BC: NS; history of BC: NS Age (years): mean 62, range NS Sex: 171 M, 114 F	Tests and cut-off used: cytology (VU), subjective assessment	Unit of analysis: patient (*n* = 285) Sensitivity: 49% Specificity: 94%
Chahal 2001[45] Study design: CC-SD Time period: NS Country: UK	Enrolled: 211; analysed: 211 No previous history of BC: 96; history of BC: 115 Age (years): NS Sex: NS	Tests and cut-off used: NMP22 ≥ 10 U/ml; cytology (VU), subjective assessment	Unit of analysis: patient (*n* = 211) Sensitivity: 33% (NMP22), 24% (cytology) Specificity: 92 (NMP22), 97% (cytology)
Chang 2004[156a] Study design: case–control (no history of disease) Time period: NS Country: China	Enrolled: 399; analysed: 314 No previous history of BC: NS; history of BC: NS Age (years): mean 53, range 3 to 91 Sex: 220 M, 111 F	Tests and cut-off used: NMP22 ≥ 7.5 U/ml	Unit of analysis: patient (*n* = 314) Sensitivity: 36% Specificity: 83%
Daniely 2007[94] Study design: C-SD Time period: 2003–4 Country: Israel	Enrolled: 115; analysed: 115 No previous history of BC: 49; history of BC: 66 Age (years): NS Sex: 73 M, 42 F	Tests and cut-off used: FISH, minimum of four cells with gains of two or more chromosomes or 12 or more cells with homozygous loss of the 9p21 locus + cytology	Unit of analysis: patient (*n* = 115) Sensitivity: 100% Specificity: 50%
Del Nero 1999[123] Study design: C-SD Time period: NS Country: Italy	Enrolled: 105; analysed: 105 No previous history of BC: 0; history of BC: 105 Age (years): mean 54, range 42 to 73 Sex: 92 M, 13 F	Tests and cut-off used: NMP22 ≥ 5 U/ml, 6 U/ml, 10 U/ml; cytology (VU), subjective assessment	Unit of analysis: patient (*n* = 105) Sensitivity: 83% (NMP22 10 U/ml), 47% (cytology) Specificity: 87% (NMP22 10 U/ml), 83% (cytology)
Friedrich 2003[95,96a] Study design: C-SD Time period: NS Country: Germany	Enrolled: 103; analysed: 103 No previous history of BC: 55; history of BC: 48 Age (years): NS Sex: NS	Tests and cut-off used: NMP22 ≥ 10 U/ml; FISH, 20% of cells had a gain of two or more chromosomes (3, 7 or 17) or 40% of cells had a gain of one chromosome or 40% loss of 9p21 locus	Unit of analysis: patient (*n* = 103) Sensitivity: 70% (NMP22), 67% (FISH) Specificity: 65% (NMP22), 89% (FISH)
Garbar 2007[167] Study design: C-SD Time period: 2002–4 Country: Belgium	Enrolled: 139; analysed: 139 No previous history of BC: NS; history of BC: NS Age (years): mean 69 (men), range NS; mean 68 (female), range NS Sex: 90 M, 49 F	Tests and cut-off used: cytology (BW), subjective assessment	Unit of analysis: specimen (*n* = 592) Sensitivity: 60% Specificity: 95%
Giannopoulos 2001[124,125a] Study design: C-SD Time period: NS Country: Greece	Enrolled: 234; analysed: 213 No previous history of BC: 118; history of BC: 95 Age (years): mean 66, range 25 to 93 Sex: 200 M, 34 F	Tests and cut-off used: NMP22 ≥ 8 U/ml	Unit of analysis: patient (*n* = 213) Sensitivity: 64% Specificity: 72%

Study	Participants	Tests	Outcomes summary
Grossman 2005[126] Study design: CC-SD (23 centres) Time period: Sep 2001 to May 2002 Country: USA	Enrolled: 1331; analysed: 1331 No previous history of BC:1331; history of BC: 1331 Age (years): mean 59, range 18 to 96 Sex: 759 M, 572 F	Tests and cut-off used: NMP22 ≥ 10 U/ml; cytology (VU), subjective assessment	Unit of analysis: patient (*n* = 1331, NMP22; *n* = 1287, cytology) Sensitivity: 56% (NMP22), 16% (cytology) Specificity: 86% (NMP22), 99% (cytology)
Grossman 2006[127] Study design: CC-SD (23 centres) Time period: Sep 2001 to Feb 2002 Country: USA	Enrolled: 668; analysed: 668 No previous history of BC: 0; history of BC: 668 Age (years): mean 71, range 30 to 95 Sex: 503 M, 165 F	Tests and cut-off used: NMP22 ≥ 10 U/ml; cytology (VU), subjective assessment	Unit of analysis: patient (*n* = 668, NMP22; *n* = 650, cytology) Sensitivity: 50% (NMP22), 12% (cytology) Specificity: 87% (NMP22), 97% (cytology)
Guttierez Banos 2001[128] Study design: C-SD Time period: NS Country: Spain	Enrolled: 150; analysed: 150 No previous history of BC: 64; history of BC: 86 Age (years): mean 68, range 20 to 91 Sex: NS	Tests and cut-off used: NMP22 ≥ 6 U/ml, 10 U/ml; cytology (VU), subjective assessment; cystoscopy (rigid)	Unit of analysis: patient (*n* = 150) Sensitivity: 76% (NMP22 10 U/ml), 70% (cytology), 100% (cystoscopy) Specificity: 91% (NMP22 10 U/ml), 93% (cytology), 89% (cystoscopy)
Hakenberg 2000[168] Study design: C-SD Time period: Jun 1996 to Dec 1997 Country: Germany	Enrolled: 374; analysed: 374 No previous history of BC: 374; history of BC: 0 Age (years): mean 68 (men), 74 (female), range NS Sex: 276 M, 98 F	Tests and cut-off used: cytology (VU), subjective assessment	Unit of analysis: specimen (*n* = 417) Sensitivity: 76% Specificity: 80%
Halling 2000[97] Study design: C-SD Time period: NS Country: USA	Enrolled: 265; analysed: 118 No previous history of BC: 115; history of BC: 150 Age (years): mean 70, range 36 to 94 Sex: 200 M, 65 F	Tests and cut-off used: FISH five or more cells polysomy; cytology (VU), subjective assessment	Unit of analysis: patient (*n* = 151, FISH; *n* = 118, cytology) Sensitivity: 81% (FISH), 58% (cytology) Specificity: 96% (FISH), 98% (cytology)
Hughes 1999[129a] Study design: C-SD Time period: NS Country: USA	Enrolled: 107; analysed: 107 No previous history of BC: 0; history of BC: 107 Age (years): mean 66, range 33 to 86 Sex: 84 M, 23 F	Tests and cut-off used: NMP22 ≥ 6.4 U/ml; cytology (VU), subjective assessment	Unit of analysis: specimen (*n* = 128) Sensitivity: 47% (NMP22), 60% (cytology) Specificity: 79% (NMP22), 58% (cytology)
Junker 2006[98] Study design: C-SD Time period: NS Country: Germany	Enrolled: 141; analysed: 121 FISH, 109 cytology No previous history of BC: NS; history of BC: NS Age (years): NS Sex: NS	Tests and cut-off used: FISH, five or more cells showed gains of more than one chromosome (3, 7 or 17), or 10 or more cells showed gains of a single chromosome (3, 7 or 17) or 10 or more cells showed homozygous loss of 9p21 locus; cytology (NS)	Unit of analysis: patient (*n* = 121, FISH; *n* = 109, cytology) Sensitivity: 60% (FISH), 24% (cytology) Specificity: 81% (FISH), 91% (cytology)

Study	Participants	Tests	Outcomes summary
Karakiewicz 2006[169,170] Study design: C-SD (10 centres) Time period: NS Country: Austria	Enrolled: 2686; analysed: 2542 No previous history of BC: 0; history of BC: 2542 Age (years): mean 65, range 18 to 97 Sex: 1910 M, 632 F	Tests and cut-off used: cytology (VU), subjective assessment	Unit of analysis: patient (*n* = 2542) Sensitivity: 45% Specificity: 95%
Kipp 2008[99] Study design: C-SD Time period: Mar 2006 to Mar 2007 Country: USA	Enrolled: 124; analysed: 124 No previous history of BC: 41; history of BC: 81 Age (years): mean 72, range 45 to 89 Sex: 103 M, 21 F	Tests and cut-off used: FISH, four or more cells had polysomic signal patterns (gain of two or more of the four chromosomes in an individual cell), 10 or more cells demonstrated tetrasomy (four signal patterns for all four probes) or > 20% of the cells demonstrated 9p21 homozygous deletion (loss of two 9p21 signals)	Unit of analysis: patient (*n* = 124) Sensitivity: 62% Specificity: 87%
Kowalska 2005[130] Study design: C-SD Time period: NS Country: Poland	Enrolled: 98; analysed: 98 No previous history of BC: 0; history of BC: 98 Age (years): mean 67 (male), 64 (female), range 36 to 96 Sex: 84 M, 14 F	Tests and cut-off used: NMP22 ≥ 10 U/ml	Unit of analysis: patient (*n* = 98) Sensitivity: 53% Specificity: 46%
Kumar 2006[131] Study design: C-SD Time period: NS Country: India	Enrolled: 131; analysed: 131 No previous history of BC: 0; history of BC: 131 Age (years): mean 67, range 32 to 91 Sex: 117 M, 14 F	Tests and cut-off used: NMP22 ≥ 10 U/ml; cytology (VU), subjective assessment	Unit of analysis: patient (*n* = 131) Sensitivity: 85% (NMP22), 41% (cytology) Specificity: 78% (NMP22), 96% (cytology)
Lahme 2001[132,133] Study design: C-SD Time period: NS Country: Germany	Enrolled: 169; analysed: 109 No previous history of BC: 40; history of BC: 44 Age (years): NS Sex: NS	Tests and cut-off used: NMP22 ≥ 10 U/ml; cytology (VU), subjective assessment	Unit of analysis: patient (*n* = 109) Sensitivity: 63% (NMP22), 45% (cytology) Specificity: 61% (NMP22), 93% (cytology)
Lee 2001[157a] Study design: case–control (nhd) Time period: NS Country: South Korea	Enrolled: 106; analysed: 106 No previous history of BC: NS; history of BC: NS Age (years): mean 60 (cases), 62 (control), range 30 to 78 Sex: NS	Tests and cut-off used: NMP22 7.7 U/ml; cytology (VU), subjective assessment	Unit of analysis: patient (*n* = 106) Sensitivity: 76% (NMP22), 56% (cytology) Specificity: 72% (NMP22), 89% (cytology)
Lodde 2003[109] Study design: CC-SD Time period: NS Country: Austria, Italy	Enrolled: 235; analysed: 225 No previous history of BC: 98; history of BC: 137 Age (years): mean 72, range 32 to 86 Sex: NS	Tests and cut-off used: ImmunoCyt, at least one green or one red fluorescent cell; cytology (VU), subjective assessment; ImmunoCyt + cytology (VU)	Unit of analysis: patient (*n* = 225) Sensitivity: 87% (ImmunoCyt), 41% (cytology), 90% (ImmunoCyt + cytology) Specificity: 67% (ImmunoCyt), 94% (cytology), 68% (ImmunoCyt + cytology)

Study	Participants	Tests	Outcomes summary
Lodde 2006[110] Study design: CC-SD Time period: NS Country: Austria, Italy	Enrolled: 216; analysed: 195 No previous history of BC: 0; history of BC: 216 Age (years): NS Sex: NS	Tests and cut-off used: ImmunoCyt, at least one green or one red fluorescent cell; cytology (VU), subjective assessment; ImmunoCyt + cytology (VU)	Unit of analysis: tumour recurrence ($n = 334$, ImmunoCyt; $n = 277$, cytology; $n = 334$, ImmunoCyt + cytology) Sensitivity: 71% (ImmunoCyt), 49% (cytology), 86% (ImmunoCyt + cytology) Specificity: 78% (ImmunoCyt), 95% (cytology), 78% (ImmunoCyt + cytology)
May 2007[107] Study design: case–control (nhd) Time period: NS Country: Germany	Enrolled: 166; analysed: 166 No previous history of BC: 62; history of BC: 71 Age (years): mean 68, range 37 to 90 Sex: 139 M, 27 F	Tests and cut-off used: FISH, gain of two or more chromosomes in five or more cases per slide, or in cases of isolated gains of chromosome 3, 7 or 17 when the proportion of cells with such a gain was 10% or more of at least 100 cells evaluated, or when there were 10 or more cells with 9p21 loss; cytology (VU), subjective assessment	Unit of analysis: patient ($n = 166$) Sensitivity: 53% (FISH), 71% (cytology) Specificity: 74% (FISH), 84% (cytology)
Meiers 2007[100] Study design: C-SD Time period: NS Country: USA, Belgium	Enrolled: 624; analysed: 624 No previous history of BC: NS; history of BC: NS Age (years): NS Sex: NS	Tests and cut-off used: FISH, chromosomal gain of two or more chromosomes (+3, +7, +17) in four or more cells or deletion of 9p21 in 12 or more cells; cytology (VU), subjective assessment	Unit of analysis: patient ($n = 624$) Sensitivity: 93% (FISH), 73% (cytology) Specificity: 90% (FISH), 87% (cytology)
Messing 2005[111] Study design: C-SD (four centres) Time period: Nov 2000 to Nov 2003 Country: USA	Enrolled: 341; analysed: 326 No previous history of BC: 0; history of BC: 341 Age (years): NS Sex: NS	Tests and cut-off used: ImmunoCyt, one green or one red fluorescent cell; cytology (VU), subjective assessment; ImmunoCyt + cytology (VU)	Unit of analysis: patient ($n = 326$) Sensitivity: 81% (ImmunoCyt), 23% (cytology), 81% (ImmunoCyt + cytology) Specificity: 75% (ImmunoCyt), 93% (cytology), 73% (ImmunoCyt + cytology)
Mian 1999[112] Study design: CC-SD Time period: Nov 1997 to Mar 1998 Country: Austria	Enrolled: 264; analysed: 249 No previous history of BC: 114; history of BC: 150 Age (years): mean 66, range 21 to 93 Sex: 204 M, 60 F	Tests and cut-off used: ImmunoCyt, one green or one red fluorescent cell; cytology (VU), subjective assessment; ImmunoCyt + cytology (VU)	Unit of analysis: patient ($n = 249$) Sensitivity: 86% (ImmunoCyt), 47% (cytology), 90% (ImmunoCyt + cytology) Specificity: 79% (ImmunoCyt), 98% (cytology), 79% (ImmunoCyt + cytology)
Mian 2000[134] Study design: C-SD Time period: NS Country: Austria	Enrolled: 240; analysed: 240 No previous history of BC: 81; history of BC: 159 Age (years): mean 66, range 22 to 92 Sex: NS	Tests and cut-off used: NMP22 $\geq$ 10 U/ml	Unit of analysis: patient ($n = 240$) Sensitivity: 56% Specificity: 79%

Study	Participants	Tests	Outcomes summary
Mian 2003[101] Study design: CC-SD Time period: NS Country: Austria, Italy	Enrolled: 181; analysed: 181 ImmunoCyt, cytology; 57 FISH No previous history of BC: 81; history of BC: 100 Age (years): 67, range 32 to 83 Sex: NS	Tests and cut-off used: ImmunoCyt, one green or one red fluorescent cell; FISH, four or more aneusomic of 25 counted cells; cytology (VU), subjective assessment; ImmunoCyt + cytology (VU)	Unit of analysis: patient (n = 181, ImmunoCyt; n = 57, FISH; n = 181, cytology; n = 181, ImmunoCyt + cytology) Sensitivity: 86% (ImmunoCyt), 96% (FISH), 45% (cytology), 90% (ImmunoCyt + cytology) Specificity: 71% (ImmunoCyt), 45% (FISH), 94% (cytology), 66% (ImmunoCyt + cytology)
Mian 2006[113] Study design: C-SD Time period: Jan 2002 to Oct 2004 Country: Italy	Enrolled: 942; analysed: NS No previous history of BC: 0; history of BC: 942 Age (years): mean 73, range 32 to 87 Sex: NS	Tests and cut-off used: ImmunoCyt, one green or one red fluorescent cell; cytology (VU), subjective assessment; ImmunoCyt + cytology (VU)	Unit of analysis: specimen (n = 1886) Sensitivity: 85% (ImmunoCyt), 39% (cytology), 89% (ImmunoCyt + cytology) Specificity: 73% (ImmunoCyt), 99% (cytology), 73% (ImmunoCyt + cytology)
Miyanaga 1999[135a] Study design: C-SD (13 centres) Time period: Aug 1995 to Mar 1997 Country: Japan	Enrolled: 309; analysed: 309 No previous history of BC: 309; history of BC: 0 Age (years): NS Sex: 145 M, 164 F	Tests and cut-off used: NMP22 ≥ 12 U/ml; cytology (VU), subjective assessment	Unit of analysis: patient (n = 309) Sensitivity: 91% (NMP22), 55% (cytology) Specificity: 76% (NMP22), 100% (cytology)
Miyanaga 2003[136a] Study design: C-SD Time period: Jan 2000 to Mar 2002 Country: Japan	Enrolled: 156; analysed: 137 No previous history of BC: 99; history of BC: 57 Age (years): mean 69, range 37 to 91 Sex: 120 M, 36 F	Tests and cut-off used: NMP22 ≥ 5 U/ml, 12 U/ml; cytology (VU), subjective assessment	Unit of analysis: patient (n = 137) Sensitivity: 19% (NMP22 12 U/ml), 7% (cytology) Specificity: 85% (NMP22 12 U/ml), 98% (cytology)
Moonen 2007[102] Study design: C-SD Time period: Mar 2005 to Apr 2006 Country: the Netherlands	Enrolled: 105; analysed: 95 No previous history of BC: 0; history of BC: 105 Age (years): mean 70, range 44 to 93 Sex: 73 M, 22 F	Tests and cut-off used: FISH, four or more of the 25 morphologically abnormal cells showed gains of two or more chromosomes (3, 7 or 17) or 12 or more of the 25 cells had no 9p21 signals; cytology (VU), subjective assessment; FISH + cytology (VU)	Unit of analysis: specimen (n = 103, FISH; n = 108, cytology; n = 103, FISH + cytology) Sensitivity: 39% (FISH), 41% (cytology), 53% (FISH + cytology) Specificity: 90% (FISH), 90% (cytology), 79% (FISH + cytology)
Oge 2001[137] Study design: C-SD Time period: NS Country: Turkey	Enrolled: 114; analysed: 76 No previous history of BC: 37; history of BC: 39 Age (years): mean 59 (groups 1–3), range 26 to 87 Sex: 93 M, 21 F	Tests and cut-off used: NMP22 ≥ 10 U/ml	Unit of analysis: patient (n = 76) Sensitivity: 74% Specificity: 69%
Olsson 2001[114] Study design: C-SD Time period: Jun 1999 to Jul 2000 Country: Sweden	Enrolled: 121; analysed: 114 No previous history of BC: 60; history of BC: 61 Age (years): mean 68, range 15 to 93 Sex: 95 M, 26 F	Tests and cut-off used: ImmunoCyt, one green or one red fluorescent cell; cytology (BW), subjective assessment	Unit of analysis: patient (n = 114) Sensitivity: 100% (ImmunoCyt), 58% (cytology) Specificity: 69% (ImmunoCyt), NS (cytology)

Study	Participants	Tests	Outcomes summary
Oosterhuis 2002[138] Study design: C-SD Time period: NS Country: the Netherlands	Enrolled: 191; analysed: 191 No previous history of BC: 0; history of BC: 191 Age (years): mean 65, range 32 to 89 Sex: 146 M, 45 F	Tests and cut-off used: NMP22 ≥ 10 U/ml	Unit of analysis: specimen (n = 431) Sensitivity: 50% Specificity: 68%
Parekattil 2003[158a] Study design: case–control (nhd) Time period: Nov 1999 to Sep 2000 Country: USA	Enrolled: 253; analysed: 253 No previous history of BC: 155; history of BC: 98 Age (years): mean 63, range 16 to 89 Sex: 182 M, 71 F	Tests and cut-off used: NMP22 ≥ 2.5 U/ml; cytology (VU or BW), subjective assessment	Unit of analysis: patient (n = 252, NMP22; n = 253, cytology) Sensitivity: 70% (NMP22), 67% (cytology) Specificity: 45% (NMP22), 81% (cytology)
Piaton 2003[115,116] Study design: CC-SD (19 centres) Time period: NS Country: France	Enrolled: 694; analysed: 651 No previous history of BC: 236; history of BC: 458 Age (years): mean 66, range 32 to 92 Sex: 550 M, 144 F	Tests and cut-off used: ImmunoCyt, one green or one red fluorescent cell; cytology (VU), subjective assessment; ImmunoCyt + cytology (VU)	Unit of analysis: patient (n = 651, ImmunoCyt; n = 651, cytology; n = 146, ImmunoCyt + cytology) Sensitivity: 73% (ImmunoCyt), 62% (cytology), 82% (ImmunoCyt + cytology) Specificity: 82% (ImmunoCyt), 85% (cytology), NS (ImmunoCyt + cytology)
Planz 2005[171] Study design: C-SD Time period: NS Country: Germany	Enrolled: 626; analysed: 495 No previous history of BC: 353; history of BC: 273 Age (years): mean 62, range NS Sex: NS	Tests and cut-off used: cytology (VU), subjective assessment; cytology (BW), subjective assessment; cytology (VU + BW)	Unit of analysis: specimen (n = 346, cytology (VU); n = 191 cytology (BW); n = 535, cytology (VU) + cytology (BW)) Sensitivity: 38% (cytology (VU)), 38% (cytology (BW)), 39% (cytology (VU) + cytology (BW)) Specificity: 98% (cytology (VU)), 99% (cytology (BW)), 98% (cytology (VU) + cytology (BW))
Ponsky 2001[139] Study design: C-SD Time period: May 1996 to Dec 1998 Country: USA	Enrolled: 608; analysed: 608 No previous history of BC: 529; history of BC: 79 Age (years): mean 70 (malignant group), 61 (benign group), range NS Sex: 438 M, 170 F	Tests and cut-off used: NMP22 ≥ 10 U/ml; cytology (VU), subjective assessment	Unit of analysis: patient (n = 608) Sensitivity: 88% (NMP22), 62% (cytology) Specificity: 84% (NMP22), 85% (cytology)
Potter 1999[172] Study design: C-SD Time period: NS Country: UK	Enrolled: 336; analysed: 336 No previous history of BC: 336; history of BC: 0 Age (years): mean 64, range NS Sex: 336 M	Tests and cut-off used: cytology (VU), subjective assessment	Unit of analysis: patient (n = 336) Sensitivity: 100% Specificity: 99%
Poulakis 2001[140a] Study design: C-SD Time period: NS Country: Germany, USA	Enrolled: 739; analysed: 739 No previous history of BC: 353; history of BC: 386 Age (years): mean 67, range 37 to 90 Sex: 485 M, 254 F	Tests and cut-off used: NMP22 ≥ 8.25 U/ml; cytology (VU), subjective assessment	Unit of analysis: patient (n = 739) Sensitivity: 85% (NMP22), 62% (cytology) Specificity: 68% (NMP22), 96% (cytology)

Study	Participants	Tests	Outcomes summary
Raitanen 2002[173,174] Study design: CC-SD (18 centres) Time period: 1997–9 Country: Finland	Enrolled: 652; analysed: 570 No previous history of BC: 151; history of BC: 501 Age (years): mean 69, range 21 to 92 Sex: 449 M, 121 F	Tests and cut-off used: cytology (VU), subjective assessment	Unit of analysis: patient (*n* = 129 no history of BC; *n* = 441, previous BC history) Sensitivity: 57% (no history), 35% (BC history) Specificity: NS (no history), 90% (BC history)
Ramakumar 1999[159] Study design: case–control (nhd) Time period: Sep 1997 to Dec 1997 Country: USA	Enrolled: 196; analysed: 196 NMP22, 112 cytology No previous history of BC: 19; history of BC: 38 Age (years): mean 66, range 29 to 102 Sex: 152 M, 44 F	Tests and cut-off used: NMP22 ≥ 10 U/ml; cytology (VU), subjective assessment	Unit of analysis: patient (*n* = 196, NMP22; *n* = 112, cytology) Sensitivity: 53% (NMP22), 44% (cytology) Specificity: 60% (NMP22), 95% (cytology)
Saad 2002[141] Study design: C-SD Time period: NS Country: UK	Enrolled: 120; analysed: 120 No previous history of BC: 120; history of BC: 0 Age (years): mean 70, range 30 to 88 Sex: 100 M, 20 F	Tests and cut-off used: NMP22 ≥ 10 U/ml; cytology (VU), subjective assessment	Unit of analysis: patient (*n* = 120) Sensitivity: 81% (NMP22), 48% (cytology) Specificity: 87% (NMP22), 87% (cytology)
Sanchez-Carbayo 1999[161a] (primary report) Study design: case–control (nhd) Time period: NS Country: Spain	Enrolled: 267; analysed: 187 No previous history of BC: NS; history of BC: NS Age (years): NS Sex: NS	Tests and cut-off used: NMP22 ≥ 14.6 U/ml	Unit of analysis: patient (*n* = 187) Sensitivity: 76% Specificity: 95%
[Sanchez-Carbayo 1999[160]] (secondary report) Study design: case–control (nhd) Time period: NS Country: Spain	Enrolled: 267; analysed: 187 No previous history of BC: NS; history of BC: NS Age (years): NS Sex: NS	Tests and cut-off used: NMP22 ≥ 6.4, 7, 10, 12, 13.7 U/ml	Unit of analysis: patient (*n* = 187) Sensitivity: 81% (NMP22 10 U/ml) Specificity: 91% (NMP22 10 U/ml)
Sanchez-Carbayo 2001[142] Study design: C-SD Time period: NS Country: Spain	Enrolled: 232; analysed: 232 No previous history of BC: 0; history of BC: 232 Age (years): NS Sex: 201 M, 31 F	Tests and cut-off used: NMP22 ≥ 10 U/ml	Unit of analysis: patient (*n* = 232) Sensitivity: 69% Specificity: 93%
Sanchez-Carbayo 2001[162] Study design: case–control (nhd) Time period: Jan1999 to Jul 1999 Country: Spain	Enrolled: 187; analysed: 187 No previous history of BC: 112; history of BC: 0 Age (years): mean 66, range 24 to 89 Sex: 87 M, 25 F	Tests and cut-off used: NMP22 ≥ 10 U/ml; cytology (VU or catheterised)	Unit of analysis: patient (*n* = 187, NMP22; *n* = 112, cytology) Sensitivity: 61% (NMP22), 35% (cytology) Specificity: 80% (NMP22), 97% (cytology)
Sarosdy 2002[108] Study design: case–control (nhd) (21 centres) Time period: NS to Apr 2000 Country: USA	Enrolled: 451; analysed: 392 No previous history of BC: 0; history of BC: 176 Age (years): mean 71 (cases), 58 (control), range 25 to 98 Sex: NS	Tests and cut-off used: FISH, aneuploidy of chromosomes 3, 7 and 17 or loss of the 9p21 locus; cytology (VU), subjective assessment	Unit of analysis: patient (*n* = 392, FISH) Sensitivity: 71% (FISH) Specificity: 84% (FISH)

Study	Participants	Tests	Outcomes summary
Sarosdy 2006[103] Study design: C-SD (23 centres) Time period: NS to Apr 2003 Country: USA	Enrolled: 497; analysed: 473 No previous history of BC: 497; history of BC: 0 Age (years): mean 63, range 40 to 97 Sex: 298 M, 199 F	Tests and cut-off used: FISH, NS; cytology (VU), subjective assessment	Unit of analysis: patient ($n = 473$) Sensitivity: 69% (FISH), 38% (cytology) Specificity: 78% (FISH), NS (cytology)
Schmitz-Drager 2008[117,118] Study design: CC-SD Time period: Oct 2000 to Jul 2007 Country: Germany	Enrolled: 301; analysed: 280 No previous history of BC: 301; history of BC: 0 Age (years): mean 59 (gross hematuria group), 57 (microhematuria group), range 24 to 89 Sex: 227 M, 65 F	Tests and cut-off used: ImmunoCyt, more than one green or red urothelial cell; cytology (VU), subjective assessment; cystoscopy, NS; ImmunoCyt + cystoscopy; cystoscopy + cytology (VU)	Unit of analysis: patient ($n = 280$, ImmunoCyt; $n = 280$, cytology; $n = 278$, cystoscopy; $n = 280$, ImmunoCyt+ cystoscopy; $n = 280$, cystoscopy + cytology) Sensitivity: 85% (ImmunoCyt), 44% (cytology), 84% (cystoscopy), 100% (ImmunoCyt + cystoscopy), 88% (cystoscopy + cytology) Specificity: 88% (ImmunoCyt), 96% (cytology), 98% (cystoscopy), 87% (ImmunoCyt + cystoscopy), 95% (cystoscopy + cytology)
Serretta 2000[143,144] Study design: C-SD Time period: NS Country: Italy	Enrolled: 179; analysed: 179 No previous history of BC: 0; history of BC: 179 Age (years): mean 65, range 31 to 84 Sex: 151 M, 28 F	Tests and cut-off used: NMP22 ≥ 10 U/ml	Unit of analysis: patient ($n = 179$) Sensitivity: 75% Specificity: 55%
Shariat 2006[147] Study design: C-SD Time period: NS Country: Austria	Enrolled: 2951; analysed: 2871 No previous history of BC: 0; history of BC: 2871 Age (years): mean 68, range 21 to 97 Sex: 2166 M, 705 F	Tests and cut-off used: NMP22 ≥ 10 U/ml and 1–30 U/ml	Unit of analysis: patient ($n = 2871$) Sensitivity: 57% (NMP22 10 U/ml) Specificity: 81% (NMP22 10 U/ml)
Sharma 1999[148] Study design: C-SD Time period: NS Country: USA	Enrolled: 278; analysed: 278 No previous history of BC: 199; history of BC: 79 Age (years): NS Sex: NS	Tests and cut-off used: NMP22 ≥ 10 U/ml for patients with no previous history of BC, ≥ 6 U/ml for patients with previous history of BC; cytology (VU), subjective assessment	Unit of analysis: patient ($n = 199$, NMP22 10 U/ml; $n = 278$, cytology) Sensitivity: 67% (NMP22 10 U/ml), 56% (cytology) Specificity: 86% (NMP22 10 U/ml), 93% (cytology)
Skacel 2003[104] Study design: CC-SD Time period: 1996–2001 Country: USA	Enrolled: 120; analysed: 111 No previous history of BC: 26; history of BC: 94 Age (years): NS Sex: NS	Tests and cut-off used: FISH, chromosomal gain of two or more chromosomes in five or more cells per slide, or in cases of isolated gains of chromosome 3, 7 or 17 when the number of cells with such gain was ≥ 10%, or when 12 or more cells with 9p21 loss was the only abnormality	Unit of analysis: patient ($n = 111$) Sensitivity: 85% Specificity: 97%

Study	Participants	Tests	Outcomes summary
Sokolova 2000[105] Study design: C-SD Time period: NS Country: USA	Enrolled: 179; analysed: 179 No previous history of BC: 86; history of BC: 93 Age (years): NS Sex: NS	Tests and cut-off used: FISH, five or more cells with polysomy; cytology (VU), subjective assessment	Unit of analysis: patient (n = 179) Sensitivity: 85% Specificity: 92%
Sozen 1999[163] Study design: case–control (nhd) Time period: NS Country: Turkey	Enrolled: 140; analysed: 140 No previous history of BC: NS; history of BC: NS Age (years): mean 71 (cases), 62 (controls), range NS Sex: 127 M, 13 F	Tests and cut-off used: NMP22 ≥ 5, 6.4, 7, 10, 12, 15 U/ml; cytology (VU or catheterised), subjective assessment	Unit of analysis: patient (n = 140) Sensitivity: 73% (NMP22 10 U/ml), 35% (cytology) Specificity: 81% (NMP22 10 U/ml), 90% (cytology)
Stampfer 1998[149] Study design: C-SD (three centres) Time period: NS Country: USA	Enrolled: 231; analysed: 217 No previous history of BC: 0; history of BC: 231 Age (years): mean 68, range NS Sex: 166 M, 65 F	Tests and cut-off used: NMP22 ≥ 5, 6.4, 7, 10 U/ml; cytology (VU), subjective assessment	Unit of analysis: cystoscopy (n = 274, NMP22 10 U/ml; n = 200, cytology) Sensitivity: 49% (NMP22 10 U/ml), 43% (cytology) Specificity: 92% (NMP22 10 U/ml), 92% (cytology)
Takeuchi 2004[164a] Study design: case–control (nhd) Time period: Nov 1999 to May 2004 Country: Japan	Enrolled: 669; analysed: 669 No previous history of BC: 48; history of BC: 0 Age (years): NS Sex: NS	Tests and cut-off used: NMP22 ≥ 12 U/ml; cytology (VU), subjective assessment; NMP22 + cytology (VU)	Unit of analysis: patient (n = 669, NMP22; n = 699, cytology; n = 48, NMP22 + cytology) Sensitivity: 58% (NMP22), 44% (cytology), 60% (NMP22 + cytology) Specificity: 80% (NMP22), 100% (Cytology), NS (NMP22 + cytology)
Talwar 2007[150] Study design: C-SD Time period: Mar 2004 to Apr 2006 Country: India	Enrolled: 196; analysed: 196 No previous history of BC: 127; history of BC: 63 Age (years): mean 63, range 39 to 78 Sex: 142 M, 54 F	Tests and cut-off used: NMP22 ≥ 10 U/ml; cytology (VU), subjective assessment	Unit of analysis: patient (n = 196) Sensitivity: 67% (NMP22), 22% (cytology) Specificity: 81% (NMP22), 99% (cytology)
Tetu 2005[119] Study design: C-SD Time period: May 2000 to Jul 2002 Country: Canada	Enrolled: 904; analysed: 870 No previous history of BC: NS; history of BC: NS Age (years): NS Sex: NS	Tests and cut-off used: ImmunoCyt, one green or one red fluorescent cell; cytology (VU), subjective assessment; ImmunoCyt + cytology (VU)	Unit of analysis: patient (n = 870) Sensitivity: 74% (ImmunoCyt), 29% (Cytology), 84% (ImmunoCyt + cytology) Specificity: 62% (ImmunoCyt), 98% (cytology), 61% (Immunocyt + cytology)
Tritschler 2007[80] Study design: C-SD Time period: Sep 2004 to Apr 2005 Country: Germany	Enrolled: 100; analysed: 100 NMP22; 94 cytology No previous history of BC: 30; history of BC: 70 Age (years): mean 68, range NS Sex: 71 M, 29 F	Tests and cut-off used: NMP22 ≥ 10 U/ml; cytology (VU), subjective assessment; cytology (BW), subjective assessment	Unit of analysis: patient (n = 100, NMP22; n = 85, cytology (VU); n = 94, cytology (BW)) Sensitivity: 65% (NMP22), 44% (cytology (VU)), 76% (cytology (BW)) Specificity: 40% (NMP22), 78% (cytology (VU)), 62% (cytology (BW))

Study	Participants	Tests	Outcomes summary
Wiener 1998[151] Study design: C-SD Time period: Jan 1996 to Oct 1996 Country: Austria	Enrolled: 291; analysed: 291 No previous history of BC: 190; history of BC: 101 Age (years): mean 62, range 17 to 90 Sex: 199 M, 92 F	Tests and cut-off used: NMP22 ≥ 10 U/ml; cytology (VU), subjective assessment; cytology (BW), subjective assessment	Unit of analysis: patient (*n* = 291, NMP22; *n* = 291, cytology (VU); *n* = 200, cytology (BW)) Sensitivity: 48% (NMP22), 59% (cytology (VU)), 58% (cytology (BW)) Specificity: 69% (NMP22), 100% (cytology (VU)), 100% (cytology (BW))
Yoder 2007[106] Study design: C-SD Time period: Jun 2002 to Dec 2003 Country: USA	Enrolled: 250; analysed: 250 No previous history of BC: 0; history of BC: 250 Age (years): median 72, range NS Sex: 187 M, 63 F	Tests and cut-off used: FISH, more than two chromosomal gains of chromosomes 3, 7 or 17 in at least four analysed cells, or homozygous 9p21 deletion in at least 12 analysed cells, or isolated trisomy of chromosome 3, 7 or 17 in at least 10% of analysed cells	Unit of analysis: patient (*n* = 250) Sensitivity: 64% Specificity: 73%
Zippe 1999[152,153] Study design: C-SD Time period: Apr 1997 to Feb 1998 Country: USA	Enrolled: 330; analysed: 330 No previous history of BC: 330; history of BC: 0 Age (years): mean 63, range NS Sex: 254 M, 76 F	Tests and cut-off used: NMP22 ≥ 10 U/ml; cytology (VU), subjective assessment	Unit of analysis: patient (*n* = 330) Sensitivity: 100% (NMP22) 33% (cytology) Specificity: 86% (NMP22) 100% (cytology)

BW, bladder wash; C-SD, cross-sectional diagnostic study; CC-SD, consecutive cross-sectional diagnostic study; nhd, no completely healthy donors in control group; NS, not stated; VU, voided urine.
a Studies used non-standard cut-off.

Appendix 13

Quality assessment results for the biomarker and cytology studies

Study	Marker	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14
Abbate 1998[154]	N	+	+	+	+	?	+	?	+	?	+	+	+	+	–
Bastacky 1999[165]	C	+	+	?	+	+	+	?	?	?	+	+	+	+	–
Bhuiyan 2003[120]	N, C	+	+	+	+	+	+	?	?	?	+	+	–N, ?C	+N, –C	–
Boman 2002[155]	N, C	+	+	+	+	+	+	?	?	+	+	+	+	+	–
Casella 2000[121]	N,[a] C	+	+	+	+	+	+	?	?	?	+	+	+	+	–
Casetta 2000[122]	N,[a] C[a]	+	+	+	+	+	+	?	?	?	+	+	+C, –N	+	–
Chahal 2001[166]	C[a]	+	+	+	+	–	+	+	?	?	+	+	+	+	–
Chahal 2001[45]	N,[a] C[a]	+	+	+	+	?	+	+	+	?	+	+	+C, –N	+	–
Chang 2004[156]	N	+	+	?	?	?	+	?	?	?	+	+	–	+	–
Daniely 2007[94]	F+C	+	+	?	+	+	+	+	?	?	+	+	+	+	–
Del Nero 1999[123]	N,[a] C[a]	+	+	+	+	+	+	+	?	?	+	+	–N, ?C	+N, –C	–
Friedrich 2003[95]	N,[a] F[a]	+	+	+	+	+	+	?	?	?	+	+	+	+	–
Garbar 2007[167]	C	+	+	?	+	+	+	+	?	?	+	+	+	+	–
Giannopoulos 2001[125]	N	+	+	+	+	+	+	+	?	?	+	+	–	+	–
[Giannopoulos 2000[124]]	N, C[a]	+	+	+	+	+	+	+	?	?	+	+	–N, +C	+	–
Grossman 2005[126]	N,[a] C[a]	–	+	+	+	+	+	+	+	?	+	+	+	+	–
Grossman 2006[127]	N,[a] C[a]	+	+	+	+	+	+	+	+	?	+	+	+	+	–
Guttierez Banos 2001[128]	N,[a] C[a]	+	+	+	+	+	+	?	?	?	+	+	+N, ?C	+N, –C	–
Hakenberg 2000[168]	C	+	+	?	+	+	+	?	?	?	+	+	+	–	–
Halling 2000[97]	F,[a] C[a]	+	+	+	+	+	+	+	?	–	+	+	+	+	–
Hughes 1999[129]	N, C	+	+	–	+	+	+	?	?	?	+	+	+	+	+
Junker 2006[98]	F,[a] C	+	+	+	+	+	+	?	?	?	+	+	+	+	–
Karakiewicz 2006[170]	C[a]	+	+	+	+	+	+	?	?	–	+	+	+	+	–
Kipp 2008[99]	F[a]	+	+	–	+	+	+	+	?	+	+	+	+	–	–
Kowalska 2005[130]	N[a]	+	+	+	+	+	+	?	?	?	+	+	?	–	–
Kumar 2006[131]	N,[a] C,[a] N+C	+	+	+	+	+	+	+	+	?	+	+	+	+	–
Lahme 2001[132]	N,[a] C[a]	+	+	+	+	+	+	?	?	?	+	+	–N, ?C	+N, –C	–
Lee 2001[157]	N, C[a]	+	+	+	+	+	+	?	+	?	+	+	+	+	–
Lodde 2003[109]	I,[a] C,[a] I+C	+	+	+	+	+	+	?	?	?	+	+	+	+	–
Lodde 2006[110]	I, C, I+C	+	+	+	+	+	+	?	?	?	+	+	+	+	–
May 2007[107]	F,[a] C[a]	+	+	?	+	+	+	+	?	+	+	+	+	–	–

Study	Marker	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14
Meiers 2007[100]	F,[a] C[a]	+	+	?	+	+	+	?	?	?	+	+	+	+	–
Messing 2005[111]	I,[a] C,[a] I+C	+	+	+	+	+	+	+	?	?	+	+	+	+	+
Mian 1999[112]	I,[a] C,[a] I+C	+	+	+	+	+	+	?	?	?	+	+	+	+	–
Mian 2000[134]	N[a]	+	+	+	+	+	+	?	?	?	+	+	+	+	–
Mian 2003[101]	F,[a] I,[a] C,[a] I+C	+	+	+	+	+	+	?	?	+	+	+	+	–	–
Mian 2006[113]	I, C, I+C	+	+	?	+	–	+	?	?	?	+	+	+	+	–
Miyanaga 1999[135]	N, C[a]	+	+	+	+	+	+	?	?	?	+	+	+	+	–
Miyanaga 2003[136]	N, C[a]	+	+	+	+	+	+	?	+	?	+	+	+	+	–
Moonen 2007[102]	F, C, F+C	+	+	+	+	+	+	+	?	+	+	+	+F, ?C	+F, –C	–
Oge 2001[137]	N[a]	+	+	+	+	+	+	?	?	?	+	+	+	+	–
Olsson 2001[114]	I,[a] C	+	+	+	+	+	+	+	?	?	+	+	+I, ?C	+I, –C	–
Oosterhuis 2002[138]	N	+	+	+	+	+	+	?	?	?	+	+	–	+	–
Parekattil 2003[158]	N, C	+	+	?	+	+	+	+	+	?	+C, –N	+	+C, –N	+C, –N	–
Piaton 2003[116]	I,[a] C,[a] I+C	+	+	+	+	+	+	+C, ?I	?	?	+	+	+	+	–
Planz 2005[171]	C	+	+	+	+	+	+	?	+	?	+	+	+	–	–
Ponsky 2001[139]	N,[a] C[a]	+	+	?	+	?	?	?	?	?	+	+	+N, ?C	+N, –C	–
Potter 1999[172]	C[a]	+	+	?	–	–	+	+	?	?	+	+	?	–	–
Poulakis 2001[140]	N,[a] C[a]	+	+	+	+	+	+	+	?	?	+	+	+C, –N	+	–
Raitanen 2002[174b]	C[a]	+	+	+	+	+	+	+	?	–	+	+	+	+	–
Ramakumar 1999[159]	N,[a] C[a]	+	+	+	+	+	+	?	+	?	+	+	+C, –N	+	–
Saad 2002[141]	N,[a] C[a]	+	+	+	+	+	+	?	?	?	+	+	+N, ?C	+N, –C	–
Sanchez-Carbayo 1999[161] (primary report) [Sanchez-Carbayo 1999[160]] (secondary report)	N, [N[a]]	+	+	+	+	+	+	?	+	+	+	+	?	+	–
Sanchez-Carbayo 2001[142]	N[a]	+	+	+	+	+	+	?	?	?	+	+	–	+	–
Sanchez-Carbayo 2001[162]	N,[a] C	+	+	+	+	+	+	?	+	?	+	+	–N, ?C	+N, –C	–
Sarosdy 2002[108]	F,[a] C	+	+	+	+	+	+	+	+	?	+	+	+F, ?C	+F, –C	+C, –F
Sarosdy 2006[103]	F,[a] C	+	+	+	+	+	+	+	+	?	+	+	+F, ?C	–	–
Schmitz–Drager 2008[118]	I,[a] C[a]	+	+	?	+	?	+	+	?	?	+	–	+	+	–

Study	Marker	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14
Serretta 2000[144]	N[a]	+	+	?	+	+	+	?	?	?	+	+	+	+	–
Shariat 2006[147]	N[a]	+	+	+	+	+	+	?	+	?	+	+	+	+	–
Sharma 1999[148]	N,[a] C[a]	+	+	?	+	+	+	?	?	?	+	+	+N, ?C	+	–
Skacel 2003[104]	F[a]	+	+	+	+	+	+	+	+	?	+	+	+	+	–
Sokolova 2000[105]	F,[a] C	+	+	+	+	+	+	+	+	–	+	+	–F, ?C	+F, –C	–
Sozen 1999[163]	N,[a] C	+	+	?	?	?	+	+	+	?	+	+	–N, ?C	+N, –C	–
Stampfer 1998[149]	N, C	+	+	+	+	+	+	+	?	?	?	+	+C, –N	+	–
Takeuchi 2004[164]	N, C,[a] N+C	+	+	?	+	+	+	?	?	?	+	+	+	+	–
Talwar 2007[150]	N,[a] C[a]	+	+	+	+	+	+	?	+C, ?N	?	+	+	+N, ?C	+N, –C	–
Tetu 2005[119]	I,[a] C,[a] I+C	+	+	+	+	+	+	?	?	?	+	+	+	+	–
Tritschler 2007[80]	N,[a] C[a]	+	+	+	+	+	+	+N, ?C	+	?	+	+	+	+	–
Wiener 1998[151]	N,[a] C[a]	+	+	+	+	+	+	?	?	?	+	+	+	+	–
Yoder 2007[106]	F[a]	+	+	+	+	+	+	?	+	?	+	+	+	+	–
Zippe 1999[153]	N,[a] C[a]	+	+	?	+	+	+	+	?	?	+	+	+	+	–

C, cytology; F, FISH; I, Immunocyt; N, NMP22; +, yes to the question; –, no to the question; ?, unclear.
a Study included in the pooled estimates for this marker.
b Although Raitanen 2002[174] did not report observer variation, Raitanen 2002[173] did.

Appendix 14

Studies of biomarkers included in pooled estimates for patient-level analysis and also those reporting specimen and stage/grade

Study	Marker	Patient	Specimen	pTa	pTaG1	pTaG1–2	pTaG2	pTaG3	pTa, pT1	pTa, pT1, CIS	pTa, pT1G3	pTaG3–pT1	G1	G2	G1–2	G1 G3
Abbate 1998[154]	N	✓														
Bastacky 1999[165]	C	✓														
Bhuiyan 2003[120]	N, C		✓													
Boman 2002[155]	N, C		✓			✓						✓				
Casella 2000[121]	N,[a] C	✓											✓	✓		
Casetta 2000[122b]	N,[a] C[a]	✓														
Chahal 2001[166]	C[a]	✓			✓		✓	✓								
Chahal 2001[45]	N,[a] C[a]	✓		✓									✓	✓		
Chang 2004[156]	N	✓														
Daniely 2007[94]	F+C	✓														
Del Nero 1999[123]	N,[a] C[a]	✓		✓									✓	✓		
Friedrich 2003[95]	N,[a] F[a]	✓		✓									✓	✓		
[Friedrich 2002[96]]	N		✓	✓									✓	✓		
Garbar 2007[167]	C		✓													
Giannopoulos 2001[125]	N	✓		✓									✓	✓		
[Giannopoulos 2000[124]]	C[a]	✓		✓									✓	✓		
Grossman 2005[126]	N,[a] C[a]	✓		✓					✓				✓	✓		
Grossman 2006[127]	N,[a] C[a]	✓		✓									✓	✓		
Guttierez Banos 2001[128]	N,[a] C[a]	✓		✓									✓	✓		
Hakenberg 2000[168]	C		✓										✓	✓		
Halling 2000[97]	F,[a] C[a]	✓		✓									✓	✓		

Study	pT1	pT1G1	pT1G2	pT1G3	pT1G3 + CIS	pT1–4	CIS	G3	pT2	pT2, pT2a	pT2G2	pT2G3	pT2–3	pT2–4	≥pT2	pT3	pT3a, 3b	pT3G3	pT4
Abbate 1998[154]																			
Bastacky 1999[165]																			
Bhuiyan 2003[120]																			
Boman 2002[155]															✓				
Casella 2000[121]								✓											
Casetta 2000[122b]																			
Chahal 2001[166]		✓		✓	✓						✓	✓						✓	
Chahal 2001[45]	✓							✓	✓							✓			
Chang 2004[156]																			
Daniely 2007[94]																			
Del Nero 1999[123]	✓							✓											
Friedrich 2003[95]	✓						✓	✓							✓				
[Friedrich 2002[96]]	✓						✓	✓							✓				
Garbar 2007[167]							✓												
Giannopoulos 2001[125]	✓						✓	✓						✓					
[Giannopoulos 2000[124]]	✓						✓	✓						✓					
Grossman 2005[126]	✓						✓	✓		✓			✓				✓		
Grossman 2006[127]	✓						✓	✓	✓							✓			✓
Guttierez Banos 2001[128]	✓							✓						✓					
Hakenberg 2000[168]							✓	✓											
Halling 2000[97]						✓	✓	✓											

Study	Marker	Patient	Specimen	pTa	pTaG1	pTaG1–2	pTaG2	pTaG3	pTa, pT1	pTa, pT1, CIS	pTa, pT1G3	pTaG3–pT1	G1	G2	G1–2	G1 G3
Hughes 1999[129]	N, C		✓													
[Hutterer 2008[169]]	N, C	✓														
Junker 2006[98]	F,[a] C	✓														
Karakiewicz 2006[170]	C[a]	✓								✓					✓	
Kipp 2008[99]	F[a]	✓			✓		✓	✓								
Kowalska 2005[130]	N[a]	✓														
Kumar 2006[131]	N,[a] C,[a] N+C	✓		✓		✓						✓	✓	✓		
Lahme 2001[132]	N,[a] C[a]	✓		✓					✓				✓	✓		
Lee 2001[157]	N, C[a]	✓		✓									✓	✓		
Lodde 2003[109]	I,[a] C,[a] I+C	✓		✓									✓	✓		
Lodde 2006[110c]	I, C, I+C		✓													
May 2007[107]	F,[a] C[a]	✓		✓									✓	✓		
Meiers 2007[100]	F,[a] C[a]	✓											✓	✓		
Messing 2005[111]	I,[a] C,[a] I+C	✓		✓									✓	✓		
Mian 1999[112]	I,[a] C,[a] I+C	✓		✓									✓	✓		
Mian 2000[134]	N[a]	✓		✓									✓	✓		
Mian 2003[101]	F,[a] I,[a] C,[a] I+C	✓		✓									✓	✓		
Mian 2006[113]	I, C, I+C		✓	✓									✓	✓		
Miyanaga 1999[135]	N, C[a]	✓														
Miyanaga 2003[136]	N, C[a]	✓														
Moonen 2007[102]	F, C, F+C		✓	✓									✓	✓		
Oge 2001[137]	N[a]	✓			✓		✓									✓
Olsson 2001[114]	I,[a] C	✓														

Study	pT1	pT1G1	pT1G2	pT1G3	pT1G3 + CIS	pT1–4	CIS	G3	pT2	pT2, pT2a	pT2G2	pT2G3	pT2–3	pT2–4	≥pT2	pT3	pT3a, 3b	pT3G3	pT4
Hughes 1999[129]																			
[Hutterer 2008[169]]																			
Junker 2006[98]																			
Karakiewicz 2006[170]								✓							✓				
Kipp 2008[99]	✓						✓								✓				
Kowalska 2005[130]																			
Kumar 2006[131]	✓							✓							✓				
Lahme 2001[132]	✓							✓						✓					
Lee 2001[157]	✓							✓							✓				
Lodde 2003[109]	✓						✓	✓							✓				
Lodde 2006[110c]																			
May 2007[107]	✓						✓	✓	✓										
Meiers 2007[100]								✓											
Messing 2005[111]	✓						✓	✓	✓										
Mian 1999[112]	✓						✓	✓							✓				
Mian 2000[134]	✓						✓	✓							✓				
Mian 2003[101]	✓						✓	✓							✓				
Mian 2006[113]	✓						✓	✓							✓				
Miyanaga 1999[135]																			
Miyanaga 2003[136]																			
Moonen 2007[102]	✓							✓						✓					
Oge 2001[137]			✓				✓				✓								
Olsson 2001[114]																			

Study	Marker	Patient	Specimen	pTa	pTaG1	pTaG1–2	pTaG2	pTaG3	pTa, pT1	pTa, pT1, CIS	pTa, pT1G3	pTaG3–pT1	G1	G2	G1–2	G1 G3
Oosterhuis 2002[138]	N		✓	✓												
Parekattil 2003[158]	N, C	✓														
[d]Piaton 2003[116]	I,[a] C,[a] I+C	✓				✓					✓		✓	✓		
Planz 2005[171]	C		✓										✓	✓		
Ponsky 2001[139]	N,[a] C[a]	✓														
Potter 1999[172]	C[a]	✓														
Poulakis 2001[140]	N,[a] C[a]	✓		✓						✓			✓	✓		
[d]Raitanen 2002[174]	C[a]	✓		✓									✓	✓		
[d]Ramakumar 1999[159]	N,[a] C[a]	✓		✓									✓	✓		
Saad 2002[141]	N,[a] C[a]	✓		✓									✓	✓		
Sanchez-Carbayo 1999[161]	N	✓		✓									✓	✓		
[Sanchez-Carbayo 1999[160]]	N[a]	✓														
Sanchez-Carbayo 2001[142]	N[a]	✓											✓	✓		
Sanchez-Carbayo 2001[162e]	N,[a] C	✓		✓									✓	✓		
Sarosdy 2002[108]	F,[a] C	✓				✓		✓					✓	✓		
Sarosdy 2006[103]	F,[a] C	✓			✓		✓	✓					✓	✓		
Schmitz-Drager 2008[118]	I,[a] C[a]	✓														
Serretta 2000[144]	N[a]	✓		✓									✓	✓		

Study	pT1	pT1G1	pT1G2	pT1G3	pT1G3+ CIS	pT1–4	CIS	G3	pT2	pT2, pT2a	pT2G2	pT2G3	pT2–3	pT2–4	≥pT2	pT3	pT3a, 3b	pT3G3	pT4
Oosterhuis 2002[138]	✓						✓								✓				
Parekattil 2003[158]																			
[d]Piaton 2003[116]							✓	✓							✓				
Planz 2005[171]								✓											
Ponsky 2001[139]																			
Potter 1999[172]																			
Poulakis 2001[140]	✓						✓	✓	✓					✓		✓			✓
[d]Raitanen 2002[174]	✓						✓	✓						✓					
[d]Ramakumar 1999[159]							✓	✓											
Saad 2002[141]	✓						✓	✓	✓										
Sanchez-Carbayo 1999[161]	✓						✓	✓	✓							✓			✓
[Sanchez-Carbayo 1999[160]]							✓	✓											
Sanchez-Carbayo 2001[142]							✓	✓	✓							✓			
Sanchez-Carbayo 2001[162e]	✓		✓		✓		✓	✓	✓										
Sarosdy 2002[108]								✓	✓										
Sarosdy 2006[103]	✓						✓	✓											
Schmitz-Drager 2008[118]													✓						
Serretta 2000[144]	✓							✓							✓				

Study	Marker	Patient	Specimen	pTa	pTaG1	pTaG1–2	pTaG2	pTaG3	pTa, pT1	pTa, pT1, CIS	pTa, pT1G3	pTaG3–pT1	G1	G2	G1–2	G1 G3
Shariat 2006[147]	N[a]	✓														
Sharma 1999[148]	N,[a] C[a]	✓														
Skacel 2003[104f]	F[a]	✓		✓									✓	✓		
Sokolova 2000[105]	F,[a] C	✓		✓										✓		
Sozen 1999[163]	N,[a] C	✓														
Stampfer 1998[149g]	N, C			✓		✓						✓	✓	✓		
[d]Takeuchi 2004[164]	N, C,[a] N+C	✓											✓	✓		
Talwar 2007[150]	N,[a] C[a]	✓	✓	✓												
Tetu 2005[119]	I,[a] C,[a] I+C	✓		✓												
Tritschler 2007[80h]	N,[a] C[a]	✓		✓											✓	
Wiener 1998[151]	N,[a] C[a]	✓		✓									✓	✓		
Yoder 2007[106]	F[a]	✓														
Zippe 1999[153]	N,[a] C[a]	✓														

Study	pT1	pT1G1	pT1G2	pT1G3	pT1G3+ CIS	pT1–4	CIS	G3	pT2	pT2, pT2a	pT2G2	pT2G3	pT2–3	pT2–4	≥pT2	pT3	pT3a, 3b	pT3G3	pT4
Shariat 2006[147]																			
Sharma 1999[148]							✓	✓	✓										✓
Skacel 2003[104f]	✓					✓	✓	✓											
Sokolova 2000[105]																			
Sozen 1999[163]							✓	✓						✓	✓				
Stampfer 1998[149g]	✓							✓						✓					
[d]Takeuchi 2004[164]							✓		✓							✓			
Talwar 2007[150]	✓						✓								✓				
Tetu 2005[119]	✓						✓	✓							✓				
Tritschler 2007[80h]	✓							✓							✓				
Wiener 1998[151]	✓																		
Yoder 2007[106]																			
Zippe 1999[153]																			

a Included in the meta-analysis models for that biomarker.
b Casetta 2000[122] – NMP22 (cut-off 10 U/ml) 2×2 data reported only for the subgroup of patients with a history of bladder cancer.
c Lodde 2006[110] – unit of analysis was tumour.
d Stage/grade categories not on grid because of insufficient space: pT1G1–2;[116] ≥pTa + CIS;[116] G2–3;[174] pT1–T3b;[159] CIS–pT1.[164]
e Sanchez-Carbayo 2001[162] – stage and grade information reported only for NMP22 (not cytology).
f Skacel 2003[104] – stage and grade information reported only for FISH (not cytology).
g Stampfer 1998[149] – stage and grade information reported only for NMP22 at cut-off of ≥6.4 U/ml (not cytology) with cystoscopy (not patient or specimen) as the unit of analysis.
h Tritschler 2007[80] – stage and grade information reported only for NMP22 at cut-off 10 U/ml and bladder wash cytology (not voided urine cytology), with tumour as the unit of analysis (not patient).

Appendix 15

Biomarker and cytology test performance for detecting bladder cancer, results table with 2×2 data

Study	Test	Cut-off	Unit of analysis	Number analysed	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)
Abbate 1998[154] No. of patients 109, of whom no previous history of BC NS, history of BC NS, plus benign genitourinary disorders 26	NMP22 (Matritech test kit) Laboratory analysis	12 U/ml	Patient	135	59	4	50	22	54	85
Bastacky 1999[165] No. of patients 1672, of whom no previous history of BC 752, history of BC 485, other 435	Cytology (VU or BW)		Patient	743	115	39	65	524	64	93
Bhuiyan 2003[120] No. of patients 233, of whom no previous history of BC NS, history of BC NS	NMP22 (Matritech) Laboratory analysis	≥ 10 U/ml	Specimen						25	94
	NMP22 (voided)	3.6 U/ml	Specimen	231	42	66	27	96	61	59
	NMP22 (cystoscopically collected)	3.6 U/ml	Specimen						54	61
	Cytology (VU)		Specimen	125	27	3	40	55	40	95
	Cytology (cystoscopically collected)		Specimen						62	83
Boman 2002[155] No. of patients 250, of whom no previous history of BC NS, history of BC 174	NMP22 (Matritech) Laboratory analysis	≥ 4 U/ml	Specimen?	297	83	46	71	97	54	68
			No previous history of BC	127	42	16	23	46	65	74
			pTaG1–2	39	23		16		59	
			pTaG3–pT1	20	13		7		65	
			≥ pT2	6	6		0		100	
			≤ 10 mm	17	11		6		65	
			11–20 mm	24	13		11		54	
			21–30 mm	15	11		4		73	
			> 30 mm	9	8		1		89	

Study	Test	Cut-off	Unit of analysis	Number analysed	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)
			Previous history of BC	170	41	30	48	51	46	63
			pTaG1–2	68	25		43		37	
			pTaG3–pT1	13	10		3		77	
			≥ pT2	8	6		2		75	
			≤ 10 mm	73	30		43		41	
			11–20 mm	12	8		4		67	
			> 21 mm	5	3		2		60	
	Cytology (BW)		Specimen?	293	60	12	90	131	40	93
			No previous history of BC	125	26	4	37	58	41	94
			pTaG1–2	38	8		30		21	
			pTaG3–pT1	19	13		6		68	
			≥ pT2	6	5		1		83	
			≤ 10 mm	17	6		11		35	
			11–20 mm	24	8		16		33	
			21–30 mm	9	5		4		55	
			> 30 mm	8	7		1		87	
			Previous history of BC	168	34	8	53	73	39	92
			pTaG1–2	67	20		47		30	
			pTaG3–pT1	12	9		3		75	
			≥ pT2	8	5		3		63	
			≤ 10 mm	74	22		52		30	
			11–20 mm	11	10		1		91	
			> 21 mm	5	5		0		100	

Study	Test	Cut-off	Unit of analysis	Number analysed	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)
Casella 2000[121]	NMP22 (Matritech) Laboratory analysis	10 U/ml	Patient	235	67	17	63	88	52	84
No. of patients 235, of whom no previous history of BC NS, history of BC NS			Superficial (non-invasive)	77	28		49		36	
			G1	42	13		29		31	
			G2	50	28		22		56	
			G3	38	26		12		68	
	Cytology (BW)		Patient	200	50	11	45	94	53	90
			Superficial (non-invasive)	65	25		40		38	
			G1	30	9		21		30	
			G2	38	19		19		50	
			G3	24	22		2		92	
[Shariat 2003[145]]	NMP22 (Matritech) Laboratory analysis	≥ 10 U/ml	Patient	229	85	25	37	82	70	77
No. of patients 229, of whom no previous history of BC NS, history of BC NS	Cytology (BW)	Only high-grade atypia was considered positive	Patient	191	50	10	43	88	54	90
[Shariat 2004[146]]	NMP22	≥ 10 U/ml	Patient	209	58	14	59	78	50	85
No. of patients 209, of whom no previous history of BC NS, history of BC NS, controls 92			pTa	65	23		42		35	
			pT1	31	23		8		74	
			≥ pT2	17	12		5		71	
			CIS	4	0		4		0	
			G1	41	12		29		29	
			G2	41	22		19		54	
			G3	35	24		11		69	

Study	Test	Cut-off	Unit of analysis	Number analysed	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)
	Cytology (BW)	Only high-grade atypia was considered positive	Patient	174	46	8	43	77	52	91
			pTa	65	23		42		35	
			pT1	31	25		6		81	
			≥ pT2	17	16		1		92	
			CIS	4	3		1		75	
			G1	41	12		29		29	
			G2	41	18		23		45	
			G3	35	33		2		95	
Casetta 2000[122]	NMP22	11 U/ml	Patient	196	84	20	66	26	56	57
No. of patients 196, of whom no previous history of BC 94, history of BC 102	NMP22	12 U/ml	No previous history of BC	94	35	8	45	6	44	43
	NMP22	10 U/ml	History of BC	102	45	12	25	20	64	63
	Cytology (VU)	Dubious cases considered positive	Patient	196	110	9	40	37	73	80
			No previous history of BC	94	61	1	19	13	76	93
			History of BC	102	49	8	21	24	70	75
	Cytology (VU)	Dubious cases considered negative	Patient	196	88	5	62	41	59	89
			No previous history of BC	94	48	1	32	13	60	93
			History of BC	102	40	4	30	28	58	88
Chahal 2001[166]	Cytology (VU)	Suspicious classed with positive	Patient	285	23	14	24	224	49	94
No. of patients 285, of whom no previous history of BC NS, history of BC NS			pTaG1	11	3		8		27	
			pTaG2	12	3		9		25	
			pTaG3	3	2		1		67	
			pT1G1	1	0		1		0	
			pT1G2	5	4		1		80	
			pT1G3	6	4		2		67	
			pT1G3 and CIS	1	1		0		100	
			pT2G2	1	1		0		100	
			pT2G3	5	3		2		60	
			pT3G3	2	2		0		100	

Study	Test	Cut-off	Unit of analysis	Number analysed	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)
Chahal 2001[45] No. of patients 211, of whom no previous history of BC 96, history of BC 115	NMP22 (test kit) Laboratory analysis	10 U/ml	Patient	211	11	14	22	164	33	92
			pTa	22	2		20		9	
			pT1	7	3		4		43	
			pT2	3	1		2		33	
			pT3	1	1		0		100	
			G1	19	1		18		5	
			G2	6	2		4		33	
			G3	8	4		4		50	
			No previous history of BC	96	7	7	9	73	44	91
			Previous history of BC	115	4	8	13	90	24	92
	Cytology (VU) (these patients already included for cytology in Chahal 2001[166]?)		Patient	211	8	5	25	173	24	97
			pTa	22	4		18		18	
			pT1	7	5		2		72	
			pT2	3	1		2		33	
			pT3	1	1		0		100	
			G1	19	3		16		16	
			G2	6	2		4		33	
			G3	8	6		2		67	
			No previous history of BC	96	5	4	11	76	31	95
			Previous history of BC	115	2	1	15	97	13	99
Chang 2004[156] No. of patients 399, of whom benign urothelial disease or urogenital cancer 331 (11 BC), no previous history of BC NS, history of BC NS	NMP22 (Sancordon) Laboratory analysis	≥ 7.5 U/ml	Patient	314	4	52	7	251	36	83

Study	Test	Cut-off	Unit of analysis	Number analysed	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)
Daniely 2007[94] No. of patients 115, of whom no previous history of BC 49, history of BC 66	FISH (UroVysion) + cytology (VU)	FISH: minimum of four cells with gains of two or more chromosomes or ≥ 12 cells with homozygous loss of the 9p21 locus	Patient	115	12	51	0	52	100	50
Del Nero 1999[123] No. of patients 105, of whom no previous history of BC 0, history of BC 105	NMP22 Laboratory analysis	10 U/ml	Patient	105	62	4	13	26	83	87
			pTa	30	20		10		67	
			pT1	45	42		3		93	
			G1	29	20		9		69	
			G2	36	34		2		94	
			G3	10	8		2		80	
		6 U/ml	Patient	105	69	7	6	23	92	76
			pTa	30	25		5		83	
			pT1	45	44		1		98	
			G1	29	25		4		86	
			G2	36	35		1		97	
			G3	10	9		1		90	
		5 U/ml	Patient	105	70	11	5	19	94	63
	Cytology (VU)		Patient	105	35	5	40	25	47	83
			pTa	30	6		24		20	
			pT1	45	29		16		64	
			G1	29	11		18		38	
			G2	36	16		20		44	
			G3	10	8		2		80	

Study	Test	Cut-off	Unit of analysis	Number analysed	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)
Friedrich 2003[95]	NMP22 (Matritech) Laboratory analysis	≥ 10 U/ml	Patient	103	32	20	14	37	70	65
No. of patients 103, of whom no previous history of BC 55, history of BC 48			pTa	21	11		10		52	
			pT1	18	17		1		94	
			≥ pT2	6	5		1		83	
			CIS	1	1		0		100	
			G1	7	3		4		43	
			G2	28	20		8		70	
			G3	11	9		2		83	
	FISH (UroVysion)	If 20% of the cells had a gain of two or more chromosomes (3, 7 or 17) or 40% of the cells had a gain of one chromosome or 40% loss of 9p21 locus	Patient	103	31	6	15	51	67	89
			pTa	21	13		8		62	
			pT1	18	12		6		67	
			≥ pT2	6	5		1		83	
			CIS	1	1		0		100	
			G1	7	4		3		57	
			G2	28	18		10		63	
			G3	11	9		2		83	
[Friedrich 2002[96]]	NMP22	10 U/ml	Specimen	146	37	32	17	60	69	65
No. of patients 115, of whom no previous history of BC 70, history of BC 45			pTa	25	13		12		52	
			pT1	20	18		2		90	
			≥ pT2	8	6		2		75	
			CIS	1	0		1		0	
			G1	7	3		4		43	
			G2	31	22		9		71	
			G3	16	12		4		75	
Garbar 2007[167]	Cytology (BW)	Suspicious classed as positive	Specimen	592	98	22	65	407	60	95
No. of patients 139, of whom no previous history of BC NS (82 BW), history of BC NS (510 BW)			CIS	50	38		12		76	
			Low-grade atypia	59	22		37		37	
			High-grade atypia	14	3		11		21	

Study	Test	Cut-off	Unit of analysis	Number analysed	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)
Giannopoulos 2001[125] No. of patients 234, of whom no previous history of BC 118, history of BC 95, healthy volunteers 21	NMP22 (Matritech) Laboratory analysis	>8 U/ml	Patient (excluding healthy volunteers)	213	75	27	43	68	64	72
			pTa	57	30		27		53	
			pT1	32	21		11		66	
			pT2–4	20	18		2		90	
			CIS	6	5		1		83	
			G1	30	15		15		50	
			G2	45	25		20		56	
			G3	43	35		8		81	
			No previous history of BC	68	50		18		74	
			History of BC	50	28		22		56	
			Healthy volunteers	21		2		19		90
			Urological disease	50		16		34		68
			No evidence of disease	45		11		34		76
			Excluding stones, urinary tract infection and urological malignancies other than BC	211	75	18	43	75	64	81
[Giannopoulos 2000[124]] No. of patients 168, of whom no previous history of BC 85, history of BC 62, healthy volunteers 21	NMP22	>8 U/ml	Patient	168	62	18	37	51	63	74
			pTa	49	26		23		53	
			pT1	26	17		9		65	
			pT2–T4	16	14		2		88	
			CIS	5	4		1		80	
			G1	26	14		12		54	
			G2	39	21		18		54	
			G3	34	27		7		79	
			No evidence of disease	25		7		18		72
			Urological disease	23		9		14		72

Study	Test	Cut-off	Unit of analysis	Number analysed	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)
	Cytology (VU)		Patient (excluding 21 healthy volunteers)	147	38	4	61	44	38	92
			pTa	49	8		41		16	
			pT1	26	12		14		46	
			pT2–T4	16	11		5		69	
			CIS	5	5		0		100	
			G1	26	2		24		8	
			G2	39	10		29		26	
			G3	34	26		8		77	
			No evidence of disease	25		4		21		84
			Urological disease	9		0		9		100
Grossman 2005[126] No. of patients 1331, of whom no previous history of BC 1331, history of BC 0	NMP22 (Matritech) BladderChek	10 U/ml	Patient	1331	44	179	35	1073	56	86
			pTa	30	14		16		47	
			pT1	27	13		14		48	
			pTa, T1	62	31		31		50	
			pT2, T2a	6	6		0		100	
			pT3a, T3b	4	3		1		75	
			pT2–T3	10	9		1		90	
			CIS	5	4		1		80	
			pTx	7	4		3		57	
			G1	27	13		14		48	
			G2	18	9		9		50	
			G3	25	18		7		72	
			Gx (grade unknown)	9	4		5		44	
			No urinary tract disease	567		55		512		90
			Benign prostatic hypertrophy/prostatitis	280		49		231		83
			Cystitis/inflammation/ trigonitis/urinary tract infection	125		28		97		78
			Erythema	51		9		42		82

Study	Test	Cut-off	Unit of analysis	Number analysed	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)
			Hyperplasia/squamous metaplasia/cysts and polyps	53		12		41		77
			Calculi	40		11		29		73
			Trabeculations	217		42		175		81
			Other benign diseases, kidney and genitourinary	220		41		179		81
			Other cancer history, non-bladder	8		1		7		88
			Other active cancer, non-bladder	38		5		33		87
	Cytology (VU)		Patient	1287	12	10	64	1201	16	99
			pTa	28	2		26		7	
			pT1	27	5		22		19	
			pTa, T1	60	10		50		17	
			pT2, T2a	6	2		4		33	
			pT3a, T3b	3	0		3		0	
			pT2–T3	9	2		7		22	
			CIS	5	3		2		60	
			pTx	7	0		7		0	
			G1	25	0		25		0	
			G2	18	3		15		17	
			G3	24	9		15		38	
			Gx (grade unknown)	9	0		9		0	
	Cystoscopy (NS)		Patient	79	70		9		89	
	NMP22 + cystoscopy		Patient	79	74		5		94	

Study	Test	Cut-off	Unit of analysis	Number analysed	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)
Grossman 2006[127] No. of patients 668, of whom no previous history of BC 0, history of BC 668	NMP22 (Matritech) BladderChek	≥ 10 U/ml	Patient	668	51	72	52	493	50	87
			pTa	50	18		32		36	
			pT1	17	11		6		65	
			pT2	8	7		1		88	
			pT3	1	1		0		100	
			pT4	2	2		0		100	
			CIS	8	4		4		50	
			pTx	17	8		9		47	
			pTa, pT1, CIS	75	33		42		44	
			pTa, pT1, CIS, G1	53	19		34		36	
			pT2–T4	11	10		1		91	
			G1	38	12		26		32	
			G2	16	7		9		44	
			G3	32	24		8		75	
			All grades	86	43		43		50	
			Poorly differentiated muscle-invasive G3,T2–T4	33	24		9		73	
			No evidence of urinary tract disease	264		28		236		89
			Benign prostatic hyperplasia/prostatitis	120		17		103		86
			Erythema/cystitis/ inflammation	82		12		70		85
			Urinary tract infection	3		3		0		0
			Hyperplasia/squamous metaplasia/cyst/polyp/ carbuncle	23		2		21		91
			Calculi	6		1		5		83
			Trabeculations	49		6		43		88
			Diverticulum/pouch/ cellule	18		3		15		83

Study	Test	Cut-off	Unit of analysis	Number analysed	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)
	Cytology (VU)		Patient	650	12	17	86	535	12	97
			pTa	48	3		45		6	
			pT1	16	2		14		13	
			pT2	7	0		7		0	
			pT3	1	0		1		0	
			pT4	2	0		2		0	
			CIS	8	3		5		38	
			pTx	16	4		12		25	
			pTa, pT1, CIS	72	8		64		11	
			pTa, pT1, CIS, G1	50	2		48		4	
			pT2–T4	10	0		10		0	
			G1	37	2		35		5	
			G2	14	0		14		0	
			G3	31	6		25		19	
			All grades	82	8		74		10	
			Poorly differentiated muscle-invasive G3, T2–T4	32	6		26		19	
	Cystoscopy (NS)		Patient	103	94		9		91	
			G3	32	24		8		75	
	NMP22 + cystoscopy		Patient	103	102		1		99	
			G3	32	31		1		97	
	Cytology + cystoscopy		Patient	103	97		6		94	

Study	Test	Cut-off	Unit of analysis	Number analysed	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)
Gutierrez Banos 2001[128] No. of patients 150, of whom no previous history of BC 64, history of BC 86	NMP22 Laboratory analysis	10 U/ml	Patient	150	58	7	18	67	76	91
			pTa	16	8		8		50	
			pT1	46	39		7		80	
			pT2–T4	14	13		1		93	
			G1	16	8		8		50	
			G2	29	20		9		69	
			G3	31	30		1		97	
	NMP22 Laboratory analysis	6 U/ml	Patient	150	64	10	12	64	84	87
			pTa	16	11		5		69	
			pT1	46	39		7		85	
			pT2–T4	14	14		0		100	
			G1	16	11		5		69	
			G2	29	22		7		76	
			G3	31	31		0		100	
	Cytology (VU)		Patient	150	53	5	23	69	70	93
			pTa	16	6		10		38	
			pT1	46	35		1		76	
			pT2–T4	14	12		2		86	
			G1	16	7		9		44	
			G2	29	18		11		62	
			G3	31	28		3		90	
	Cystoscopy (R)		Patient	150	76	8	0	66	100	89

Study	Test	Cut-off	Unit of analysis	Number analysed	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)
Hakenberg 2000[168]	Cytology (VU)		Specimen	417	257	16	80	64	76	80
No. of patients 374, of whom no previous history of BC 374, history of BC 0			CIS	16	13		3		81	
			G1	57	27		30		47	
			G2	166	130		36		78	
			G3	98	87		11		89	
			Undergoing primary TUR	326	213	11	65	37	77	77
			CIS	11	8		3		73	
			G1	48	26		22		54	
			G2	136	106		30		78	
			G3	83	73		10		88	
			Undergoing secondary TUR	91	44	5	15	27	75	84
			CIS	5	5		0		100	
			G1	9	1		8		11	
			G2	30	24		6		80	
			G3	15	14		1		93	
Halling 2000[97]	FISH (UroVysion)	Five or more cells with polysomy	Patient	151	59	3	14	75	81	96
No. of patients 265, of whom no previous history of BC 115, previous history of BC 150			pTa	37	24		13		65	
			pT1–T4	19	18		1		95	
			CIS	17	17		0		100	
			G1	11	4		7		36	
			G2	25	19		6		76	
			G3	37	36		1		97	
	Cytology (VU)	Suspicious classed with positive	Patient	118	40	1	29	48	58	98
			pTa	36	17		19		47	
			pT1–T4	15	9		6		60	
			CIS	18	14		4		78	
			G1	11	3		8		27	
			G2	24	13		11		54	
			G3	34	24		10		71	

Study	Test	Cut-off	Unit of analysis	Number analysed	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)
Hughes 1999[129] No. of patients 107, of whom no previous history of BC 0, history of BC 107	NMP22 (Matritech) Laboratory analysis	≥ 6.4 U/ml	Specimen	128	25	16	28	59	47	79
	Cytology (VU)	Indeterminate results were classed as negative	Specimen	128	32	31	21	44	60	58
Junker 2006[98] No. of patients 141, of whom no previous history of BC NS, history of BC NS	FISH (UroVysion)	Five or more cells showed gains of more than one chromosome (3, 7 or 17), or ≥ 10 cells showed gains of a single chromosome (3, 7 or 17), or ≥ 10 cells showed homozygous loss of 9p21 locus	Patient	121	57	5	38	21	60	81
	Cytology (NS)		Patient	109	21	2	66	20	24	91
Karakiewicz 2006[170] No. of patients 2686, of whom no previous history of BC 0, history of BC 2686	Cytology (VU)		Patient	2542	404	87	494	1557	45	95
			pTa–T1, CIS	2542	284	92	408	1758	41	95
			≥ pT2	2542	122	117	84	2219	59	95
			G1–G2	2542	211	97	393	1841	35	95
			G3	2542	197	112	97	2136	67	95
[Hutterer 2008[169]] No. of patients 1731, of whom no previous history of BC 0, history of BC 1731	NMP22 Laboratory analysis	10 U/ml	Patients with non-TCC recurrence	1731	62	301	18	1350	78	82
	Cytology (VU)		Patients with non-TCC recurrence	1731	16	86	64	1565	20	95

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Study	Test	Cut-off	Unit of analysis	Number analysed	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)
Kipp 2008[99]	FISH (UroVysion)	Four or more cells had polysomic signal patterns (gain of two or more of the four chromosomes in an individual cell), ≥ 10 cells demonstrated tetrasomy (four signal patterns for all four probes) or > 20% of the cells demonstrated 9p21 homozygous deletion (loss of the two 9p21 signals)	Patient	124	53	5	32	34	62	87
No. of patients 124, of whom no previous history of BC 41, history of BC 81, previous cancer of the upper urinary tract 2			pTaG1	22	7		15		32	
			pTaG2	11	7		4		64	
			pTaG3	4	3		1		75	
			pT1	10	8		2		80	
			≥ pT2	16	14		2		88	
			CIS	21	13		8		62	
			Small cell carcinoma	1	1		0		100	
			With muscle-invasive BC	17	15		2		88	
	Cystoscopy (NS)	Suspicious classed with positive	Patient	124	57	6	28	33	67	85
			pTaG1	22	21		1		96	
			pTaG2	11	9		2		82	
			pTaG3	4	3		1		75	
			pT1	10	10		0		100	
			≥ pT2	16	13		3		81	
			CIS	21	16		5		76	
			Small cell carcinoma	1	1		0		100	
			With muscle-invasive BC	17	10		7		59	
	FISH (UroVysion) + cystoscopy		Patient	124	74	8	11	31	87	79
			With muscle-invasive BC	17	16		1		94	
Kowalska 2005[130]	NMP22 Laboratory analysis	10 U/ml?	Patient	98	10	43	9	36	53	46
No. of patients 98, of whom no previous history of BC 0, history of BC 98										

Study	Test	Cut-off	Unit of analysis	Number analysed	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)
Kumar 2006[131] No. of patients 131, of whom no previous history of BC 0, history of BC 131	NMP22 (Matritech) BladderChek	10 U/ml	Patient	131	39	19	7	66	85	78
			pTa	21	16		5		76	
			pT1	17	15		2		88	
			≥ pT2	8	8		0		100	
			G1	11	9		2		82	
			G2	22	18		4		81	
			G3	13	12		1		92	
			Low risk (pTaG1–G2)	18	15		3		83	
			High risk (pTaG3, T1)	20	16		4		80	
			≥ invasive pT2	8	8		0		100	
	Cytology (VU)		Patient	131	19	3	27	82	41	96
			pTa	21	3		18		14	
			pT1	17	8		9		47	
			≥ pT2	8	8		0		100	
			G1	11	2		9		19	
			G2	22	6		16		27	
			G3	13	11		2		85	
			Low risk (pTaG1–G2)	18	2		16		11	
			High risk (pTaG3, T1)	20	9		11		45	
			≥ invasive pT2	8	8		0		100	
	NMP22 + cytology (VU)		Patient	46	42		4		91	

Study	Test	Cut-off	Unit of analysis	Number analysed	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)
Lahme 2001[132] No. of patients 169, of whom no previous history of BC 40, history of BC 44, other 25, healthy controls 60	NMP22 (Matritech) Laboratory analysis	10 U/ml	Patient (excluding healthy controls)	109	25	27	15	42	63	61
			With BC or being followed up	84	25	15	15	29	63	66
			Ta	22	9		13		41	
			T1	8	5		3		63	
			Ta-T1	30	14		16		47	
			T2–4	10	9		1		90	
			G1						25	
			G2						68	
			G3						100	
			Healthy controls	60		4		56		93
			With benign lesions	25		12		13		51
	Cytology (VU)		Patient (excluding healthy controls)	109	18	5	22	64	45	93
			With BC or being followed up	84	18	5	22	39	45	89
			Ta	22	6		16		27	
			T1	8	5		3		63	
			Ta-T1	30	11		19		37	
			T2–4	10	7		3		70	
			G1						20	
			G2						59	
			G3						67	
			Healthy controls	60		0		60		100
			With benign lesions	25		0		25		100

Study	Test	Cut-off	Unit of analysis	Number analysed	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)
Lee 2001[157]	NMP22 (Matritech) Laboratory analysis	7.7 U/ml	Patient	106	53	10	17	26	76	72
No. of patients 106, of whom no previous history of BC NS, history of BC NS (cases 70; controls 36 with history of BC)			pTa	23	13		10		57	
			pT1	23	18		5		78	
			p ≥ T2	24	22		2		92	
			G1	19	11		8		58	
			G2	34	27		7		79	
			G3	17	15		2		88	
	Cytology (VU)		Patient	106	39	4	31	32	56	89
			pTa	23	8		15		35	
			pT1	23	13		10		57	
			p ≥ T2	24	18		6		75	
			G1	19	4		15		21	
			G2	34	22		12		65	
			G3	17	13		4		77	
Lodde 2003[109]	ImmunoCyt	At least one green or one red fluorescent cell	Patient	225	89	40	13	83	87	67
No. of patients 235, of whom no previous history of BC 98, history of BC 137			pTa	62	50		12		81	
			pT1	16	15		1		94	
			≥ pT2	11	10		1		91	
			CIS	13	13		0		100	
			G1	43	35		8		81	
			G2	28	25		3		89	
			G3	31	29		2		94	
			No previous history of BC	91	47	10	4	30	92	75
			pTa	29	25		4		86	
			pT1	13	13		0		100	
			≥ pT2	6	5		1		83	
			CIS	3	3		0		100	
			G1	20	17		3		85	
			G2	18	18		0		100	
			G3	13	12		1		92	

Study	Test	Cut-off	Unit of analysis	Number analysed	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)
			History of BC	134	42	30	9	53	82	64
			pTa	33	25		8		76	
			pT1	3	2		1		67	
			≥ pT2	5	5		0		100	
			CIS	10	10		0		100	
			G1	23	18		5		78	
			G2	10	7		3		70	
			G3	18	17		1		94	
	Cytology (VU)		Patient	225	42	7	60	116	41	94
			pTa	62	7		55		11	
			pT1	16	14		2		88	
			≥ pT2	11	10		1		91	
			CIS	13	12		1		92	
			G1	43	2		41		5	
			G2	28	12		16		43	
			G3	31	28		3		90	
			No previous history of BC	91	22	2	29	38	43	95
			pTa	29	4		25		14	
			pT1	13	11		2		85	
			≥ pT2	6	5		1		83	
			CIS	3	3		0		100	
			G1	20	1		19		5	
			G2	18	10		8		56	
			G3	13	11		2		85	
			History of BC	134	20	5	31	78	39	94
			pTa	33	3		30		9	
			pT1	3	3		0		100	
			≥ pT2	5	5		0		100	
			CIS	10	9		1		90	
			G1	23	1		22		4	
			G2	10	2		8		20	
			G3	18	17		1		94	

Study	Test	Cut-off	Unit of analysis	Number analysed	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)
	ImmunoCyt + cytology (VU)		Patient	225	92	40	10	83	90	68
			pTa	62	52		10		84	
			pT1	16	16		0		100	
			≥ pT2	11	11		0		100	
			CIS	13	13		0		100	
			G1	43	35		8		81	
			G2	28	27		1		55	
			G3	31	31		0		100	
			No previous history of BC	91	48	10	3	94	75	
			pTa	29	25		4		86	
			pT1	13	13		0		100	
			≥ pT2	6	6		0		100	
			CIS	3	3		0		100	
			G1	20	17		3		85	
			G2	18	18		0		100	
			G3	13	13		0		100	
			History of BC	134	44	30	7	53	86	64
			pTa	33	27		6		82	
			pT1	3	3		0		100	
			≥ pT2	5	5		0		100	
			CIS	10	10		0		100	
			G1	23	18		5		78	
			G2	10	9		1		90	
			G3	18	18		0		100	

Study	Test	Cut-off	Unit of analysis	Number analysed	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)
Lodde 2006[110]	ImmunoCyt	At least one green or one red fluorescent cell	Specimen	334	85	51	16	182	71	78
No. of patients 216, of whom no previous history of BC 0, history of BC 216			Low-risk group	132	26	21	4	81	87	79
			Intermediate-risk group	124	35	19	8	62	81	77
			High-risk group	78	24	11	4	39	86	78
	Cytology (VU)		Specimen	277	49	9	52	167	49	95
			Low-risk group	132	5	1	25	101	17	99
			Intermediate-risk group	67	20	4	23	20	47	83
			High-risk group	78	24	4	4	46	86	92
	ImmunoCyt + cytology (VU)		Specimen	334	87	52	14	181	86	78
			Low-risk group	132	26	21	4	81	87	79
			Intermediate-risk group	124	36	20	7	61	84	75
			High-risk group	78	25	11	3	39	89	78
May 2007[107]	FISH (UroVysion)	Gain of two or more chromosomes in five or more cells per slide, or in cases of isolated gains of chromosome 3, 7, or 17 when the proportion of cells with such a gain was 10% or more of at least 100 cells evaluated, or when there were ≥ 10 cells with 9p21 loss	Patient	166	33	27	29	77	53	74
No. of patients 166, of whom no previous history of BC 62, history of BC 71 and other 33			pTa	38	16		22		42	
			pT1	10	8		2		80	
			pT2	12	8		4		67	
			CIS	2	1		1		50	
			G1	33	14		19		42	
			G2	14	5		9		36	
			G3	15	14		1		93	
			No previous history of BC group	58	32		26		55	
			History of BC group	4	1		3		25	

Study	Test	Cut-off	Unit of analysis	Number analysed	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)
	Cytology (VU)		Patient	166	44	17	18	87	71	84
			pTa	38	16		22		58	
			pT1	10	10		0		100	
			pT2	12	10		2		83	
			CIS	2	2		0		100	
			G1	33	17		16		52	
			G2	14	13		1		93	
			G3	15	14		1		93	
			No previous history of BC group	58	41		17		71	
			History of BC group	4	3		1		75	
Meiers 2007[100] No. of patients 624, of whom no previous history of BC NS, history of BC NS	FISH (UroVysion)	Chromosomal gain of two or more chromosomes (+3, +7, +17) in four or more cells or deletion of 9p21 in 12 or more cells	Patient	624	158	44	12	410	93	90
			G1	42	36		6		42	
			G2	48	45		3		94	
			G3	80	77		3		96	
	Cytology (VU)		Patient	624	124	59	46	395	73	87
			G1	42	21		21		50	
			G2	48	38		10		79	
			G3	80	65		15		81	

Study	Test	Cut-off	Unit of analysis	Number analysed	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)
Messing 2005[111]	ImmunoCyt	One confirmed red or green fluorescent cell	Patient	326	42	68	10	206	81	75
No. of patients 341, of whom no previous history of BC 0, history of BC 341			pTa	35	29		6		83	
			pT1	8	6		2		75	
			pT2	2	2		0		100	
			CIS	5	5		0		100	
			G1	28	22		6		79	
			G2	10	9		1		90	
			G3	6	4		2		67	
			Tumour							
			< 1 cm	17	12		5		71	
			1–3 cm	19	16		3		84	
			> 3 cm	5	3		2		60	
	Cytology (VU)		Patient	326	12	19	40	255	23	93
			pTa	35	2		33		6	
			pT1	8	4		4		50	
			pT2	2	0		2		0	
			CIS	5	5		0		100	
			G1	28	2		26		7	
			G2	10	1		9		10	
			G3	6	4		2		67	
			Tumour							
			< 1 cm	17	3		14		18	
			1–3 cm	19	5		14		26	
			> 3 cm	5	1		4		20	
	ImmunoCyt + cytology (VU)		Patient	326	42	73	10	201	81	73
			pTa	35	29		6		83	
			pT1	8	6		2		75	
			pT2	2	2		0		100	
			CIS	5	5		0		100	
			G1	28	22		6		79	
			G2	10	9		1		90	
			G3	6	4		2		67	

Study	Test	Cut-off	Unit of analysis	Number analysed	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)
Mian 1999[112]	ImmunoCyt	At least one green or one red fluorescent cell	Patient	249	68	35	11	135	86	79
No. of patients 264, of whom no previous history of BC 114, history of BC 150			pTa	43	37		6		86	
			pT1	20	17		3		85	
			≥ pT2	12	10		2		83	
			CIS	4	4		0		100	
			G1	25	21		4		84	
			G2	25	21		4		84	
			G3	29	26		3		90	
	Cytology (VU)		Patient	249	37	3	42	167	47	98
			pTa	43	9		34		21	
			pT1	20	14		6		70	
			≥ pT2	12	10		2		83	
			CIS	4	4		0		100	
			G1	25	1		24		4	
			G2	25	13		12		52	
			G3	29	23		6		79	
	ImmunoCyt + cytology (VU)		Patient	249	71	35	8	135	90	79
			pTa	43	38		5		88	
			pT1	20	18		2		90	
			≥ pT2	12	11		1		92	
			CIS	4	4		0		100	
			G1	25	21		4		84	
			G2	25	22		3		88	
			G3	29	28		1		97	

Study	Test	Cut-off	Unit of analysis	Number analysed	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)
Mian 2000[134]	NMP22 (Matritech) Laboratory analysis	≥ 10 U/ml	Patient	240	30	39	24	147	56	79
No. of patients 240, of whom no previous history of BC 81, history of BC 159			pTa	29	15		14		52	
			pT1	13	6		7		46	
			≥ pT2	10	7		3		70	
			CIS	2	2		0		100	
			G1	18	9		9		50	
			G2	20	10		10		50	
			G3	16	11		5		69	
Mian 2003[101]	ImmunoCyt	At least one green or one red fluorescent cell	Patient	181	69	29	11	72	86	71
No. of patients 181, of whom no previous history of BC 81, history of BC 100			pTa	47	38		9		81	
			pT1	13	12		1		92	
			≥ pT2	10	9		1		90	
			CIS	10	10		0		100	
			G1	31	25		6		81	
			G2	24	21		3		88	
			G3	25	23		2		92	
	FISH (UroVysion)	Four or more aneusomic of 25 counted cells	Patient	57	27	16	1	13	96	45
			pTa	26	25		1		96	
			pT1	1	1		0		100	
			CIS	1	1		0		100	
			G1	8	7		1		88	
			G2	19	19		0		100	
			G3	1	1		0		100	

Study	Test	Cut-off	Unit of analysis	Number analysed	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)
	Cytology (VU)		Patient	181	36	6	44	95	45	94
			pTa	47	6		41		13	
			pT1	13	12		1		92	
			≥ pT2	10	9		1		90	
			CIS	10	9		1		90	
			G1	31	2		29		6	
			G2	24	11		13		46	
			G3	25	23		2		92	
	ImmunoCyt+ cytology (VU)		Patient	181	72	34	8	67	90	66
			pTa	47	39		8		83	
			pT1	13	13		0		100	
			≥ pT2	10	10		0		100	
			CIS	10	10		0		100	
			G1	31	26		5		84	
			G2	24	22		2		92	
			G3	25	24		1		96	
Mian 2006[113] No. of patients 942, of whom no previous history of BC 0, history of BC 942	ImmunoCyt	At least one green or one red fluorescent cell	Specimen	1886	253	436	45	1152	85	73
			pTa	202	165		37		82	
			pT1	47	42		5		89	
			≥ pT2	19	16		3		84	
			CIS	28	28		0		100	
			G1	121	96		25		79	
			G2	88	74		14		84	
			G3	89	82		7		92	
	Cytology (VU)		Specimen	1886	116	10	182	1578	39	99
			pTa	202	41		161		20	
			pT1	47	31		16		68	
			≥ pT2	19	17		2		90	
			CIS	28	26		2		93	
			G1	121	10		111		8	

Study	Test	Cut-off	Unit of analysis	Number analysed	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)
			G2	88	39		49		43	
			G3	89	67		22		75	
	ImmunoCyt + cytology (VU)		Specimen	1886	266	436	32	1152	89	73
			pTa	202	172		30		85	
			pT1	47	46		1		98	
			≥ pT2	19	17		2		90	
			CIS	28	28		0		100	
			G1	121	96		25		79	
			G2	88	80		8		91	
			G3	89	88		1		99	
Miyanaga 1999[135] No. of patients 309, of whom no previous history of BC 309, history of BC 0	NMP22 (Konica-Matritech) Laboratory analysis	12 U/ml	Patient (urothelial cancer, not just BC)	309	20	68	2	219	91	76
	Cytology (VU)		Patient (urothelial cancer, not just BC)	309	12	1	10	286	55	100
Miyanaga 2003[136] No. of patients 156, of whom no previous history of BC 99, history of BC 57	NMP22 (Matritech) Laboratory analysis	≥ 12 U/ml	Patient	137	8	14	35	80	19	85
		≥ 5 U/ml	Patient	137	21	32	22	62	49	66
	Cytology (VU)		Patient	137	3	2	40	92	7	98
Moonen 2007[102] No. of patients 105, of whom no previous history of BC 0, history of BC 105	FISH (UroVysion)	Four or more of the 25 morphologically abnormal cells showed gains of two or more chromosomes (3, 7 or 17) or ≥ 12 of the 25 cells had no 9p21 signals	Specimen	103	25	4	39	35	39	90
			pTa	44	12		32		27	
			pT1	10	6		4		60	
			pT2–4	4	2		2		50	
			G1	27	6		21		22	
			G2	19	7		12		37	
			G3	18	12		6		67	

Study	Test	Cut-off	Unit of analysis	Number analysed	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)
	Cytology (VU)		Specimen	108	26	4	38	40	41	90
			pTa	44	12		32		27	
			pT1	10	7		3		70	
			pT2–4	4	3		1		75	
			G1	27	6		21		22	
			G2	19	5		14		26	
			G3	18	15		3		83	
	FISH (UroVysion) + cytology (VU)		Specimen	103	34	8	30	31	53	79
			pTa	44	18		26		40	
			pT1	10	8		2		80	
			pT2–4	4	3		1		75	
			G1	27	8		19		30	
			G2	19	10		9		53	
			G3	18	16		2		89	
Oge 2001[137] No. of patients 114, of whom no previous history of BC 37, history of BC 39, benign urological conditions 18, healthy subjects 20	NMP22 (Matritech) Laboratory analysis	10 U/ml (study also reports sensitivity and specificity at 5 and 20 U/ml)	Patient (excluding those with benign urological disease and healthy volunteers)	76	37	8	13	18	74	69
			pTaG1	12	5		7		42	
			pTaG2	8	6		2		75	
			pT1G2	6	5		1		83	
			G1 G3	2	2		0		100	
			pT2G2	4	4		0		100	
			CIS G3	18	15		3		83	
Olsson 2001[114] No. of patients 121, of whom no previous history of BC 60, history of BC 61	ImmunoCyt	At least one green or one red cell	Patient	114	31	26	0	57	100	69
	Cytology (BW)		Patient	114	18		13		58	

Study	Test	Cut-off	Unit of analysis	Number analysed	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)
Oosterhuis 2002[138]	NMP22 (Matritech) Laboratory analysis	10 U/ml	Specimen	431	32	116	32	251	50	68
No. of patients 191, of whom no previous history of BC 0, history of BC 191			pTa	39	13		26		33	
			Low grade	32	7		25		22	
			High grade	7	6		1		86	
			pT1	17	14		3		82	
			Low grade	1	0		1		0	
			High grade	16	14		2		88	
			≥ pT2	2	2		0		100	
			CIS	4	1		3		25	
Parekattil 2003[158]	NMP22 Laboratory analysis	2.5 U/ml	Patient	252	19	123	8	102	70	45
No. of patients 253, of whom no previous history of BC 155, history of BC 98	Cytology (VU or BW)	Atypia classed with positive	Patient	253	18	43	9	183	67	81
Piaton 2003[116]	ImmunoCyt	At least one green or one red fluorescent cell	Patient	651	106	89	40	416	73	82
No. of patients 694, of whom no previous history of BC 236, history of BC 458			With no previous history of BC	215	44	26	15	130	75	83
			pTaG1–G2	22	15		7		68	
			pTa–1 G3	14	11		3		79	
			pT1G1–G2	4	3		1		75	
			≥ pT2	11	8		3		73	
			CIS	1	1		0		100	
			≥ pTa + CIS	5	4		1		80	
			pTxGx (bladder)	1	1		0		100	
			pTxGx (UUT)	1	1		0		100	
			G1	10	4		6		40	
			G2	17	15		2		88	
			G3	30	23		7		77	
			Gx	2	2		0		100	
			With previous history of BC	436	62	63	25	286	71	82

Study	Test	Cut-off	Unit of analysis	Number analysed	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)
			pTaG1–G2	42	27		15		64	
			pTa–1 G3	18	16		2		89	
			pT1G1–G2	3	2		1		67	
			≥ pT2	16	10		6		63	
			CIS	2	1		1		50	
			≥ pTa + CIS	3	3		0		100	
			pTxGx (bladder)	1	1		0		100	
			pTxGx (UUT)	2	2		0		100	
			G1	21	13		8		62	
			G2	24	16		8		67	
			G3	39	30		9		77	
			Gx	3	3		0		100	
	Cytology (VU)		Patient	651	90	74	56	431	62	85
			With no previous history of BC	215	42	26	17	130	71	83
			pTaG1–G2	22	10		12		45	
			pTa–1 G3	14	13		1		93	
			pT1G1–G2	4	4		0		100	
			≥ pT2	11	9		2		82	
			CIS	1	0		1		0	
			≥ pTa + CIS	5	4		1		80	
			pTxGx (bladder)	1	1		0		100	
			pTxGx (UUT)	1	1		0		100	
			G1	10	3		7		30	
			G2	17	12		5		71	
			G3	30	25		5		83	
			Gx	2	2		0		100	
			With previous history of BC	436	48	48	39	301	55	86

Study	Test	Cut-off	Unit of analysis	Number analysed	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)
			pTaG1–G2	42	19		23		45	
			pTa–1 G3	18	14		4		78	
			pT1G1–G2	3	3		0		100	
			≥ pT2	16	9		7		56	
			CIS	2	2		0		100	
			≥ pTa + CIS	3	0		3		0	
			pTxGx (bladder)	1	N/S					
			pTxGx (UUT)	2	1		1		50	
			G1	21	8		13		38	
			G2	24	14		10		58	
			G3	39	25		14		64	
			Gx	3	1		2		33	
	ImmunoCyt + cytology (VU)		Patient	146	120		26		82	
			With no previous history of BC	59	51		8		86	
			pTaG1–G2	22	16		6		73	
			pTa–1 G3	14	14		0		100	
			pT1G1–G2	4	4		0		100	
			≥ pT2	11	9		2		82	
			CIS	1	1		0		100	
			≥ pTa + CIS	5	5		0		100	
			pTxGx (bladder)	1	1		0		100	
			pTxGx (UUT)	1	1		0		100	
			G1	10	5		5		50	
			G2	17	16		1		94	
			G3	30	28		2		93	
			Gx	2	2		0		100	
			With previous history of BC	87	69		18		79	
			pTaG1–G2	42	30		10		71	
			pTa–1 G3	18	16		2		89	

Study	Test	Cut-off	Unit of analysis	Number analysed	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)
			pT1G1–G2	3	3		0		100	
			≥ pT2	16	13		3		81	
			CIS	2	2		0		100	
			≥ pTa + CIS	3	3		0		100	
			pTxGx (bladder)	1	1		0		100	
			pTxGx (UUT)	2	2		0		100	
			G1	21	13		8		62	
			G2	24	19		5		79	
			G3	39	34		5		87	
			Gx	3	3		0		100	
[Pfister 2003[115]] No. of patients 694, of whom no previous history of BC 236, history of BC 458	ImmunoCyt	At least one green or one red fluorescent cell	Patient	691	102	87	41	461	71	84
			pTa	75	52		23		75	
			pT1	28	19		9		67	
			≥ pT2	28	20		8		73	
			CIS	8	8		0		100	
			G1	31	19		12		61	
			G2	40	30		10		76	
			G3	68	52		16		77	
			No previous history of BC	58	42		16		72	
			History of BC	85	60		25		71	
	Cystoscopy		Patient	691	141	79	2	469	99	86
			No previous history of BC	58	58		0		100	

Study	Test	Cut-off	Unit of analysis	Number analysed	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)
	Cytology (VU)		Patient	691	70	30	73	518	49	95
			pTa	75	27		48		36	
			pT1	28	17		11		59	
			≥ pT2	28	25		3		91	
			CIS	8	3		5		33	
			G1	31	6		25		18	
			G2	40	19		21		46	
			G3	68	43		25		64	
			No previous history of BC	58	37		21		64	
			History of BC	85	33		52		39	
	ImmunoCyt + cytology (VU)		Patient	691	113	106	30	442	79	81
			pTa	75	56		19		75	
			pT1	28	22		6		78	
			≥ pT2	28	25		3		91	
			CIS	8	8		0		100	
			G1	31	21		10		67	
			G2	40	31		9		78	
			G3	68	59		9		87	
			No previous history of BC	58	49		9		84	
			History of BC	85	64		21		75	
Planz 2005[171]	Cytology (VU)		Specimen	346	54	4	88	200	38	98
No. of patients 626, of whom no previous history of BC 353, history of BC 273			One specimen	142	25	1	32	84	44	99
			Two specimens	142	32	1	25	84	56	99
			Three specimens	142	38	3	44	82	67	97

Study	Test	Cut-off	Unit of analysis	Number analysed	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)
	Cytology (BW)		Specimen	191	16	2	26	147	38	99
			One specimen	20	4	0	6	10	40	100
			Two specimens	20	5	0	5	10	50	100
			Three specimens	20	6	0	4	10	60	100
	Cytology (VU + BW)		Specimen	535	70	6	112	347	39	98
			G1	42	5		37		12	
			One specimen	13	2		11		15	
			Two specimens	13	2		11		15	
			Three specimens	13	2		11		15	
			G2	55	23		32		42	
			One specimen	27	13		14		48	
			Two specimens	27	16		11		59	
			Three specimens	27	20		7		74	
			G3	45	26		19		58	
			One specimen	23	12		11		52	
			Two specimens	23	15		8		65	
			Three specimens	23	18		5		78	
Ponsky 2001[139] No. of patients 608, of whom no previous history of BC 529, history of BC 79	NMP22 Laboratory analysis	> 10 U/ml	Patient	608	46	89	6	467	88	84
	Cytology (VU)		Patient	608	32	85	20	471	62	85
Potter 1999[172] No. of patients 336, of whom no previous history of BC 336, history of BC 0	Cytology (VU)		Patient	336	2	3	0	331	100	99

Study	Test	Cut-off	Unit of analysis	Number analysed	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)
Poulakis 2001[140]	NMP22 (Matritech) Laboratory analysis	≥ 8.25 U/ml (study also gives sensitivity and specificity from 6.4 to 20 U/ml)	Patient	739	347	107	59	226	85	68
No. of patients 739, of whom no previous history of BC 353, history of BC 386			pTa	210	174		36		83	
			pT1	47	40		7		85	
			pT2	58	55		3		95	
			pT3	45	43		2		96	
			pT4	9	9		0		100	
			CIS	31	23		8		74	
			Superficial invasive (pTa, pT1, CIS)	286	237		49		83	
			Superficial invasive (pT2–T4)	111	107		4		96	
			G1	129	106		23		82	
			G2	167	149		18		89	
			G3	70	66		4		94	
			With one tumour	208	165		43		79	
			With two to three tumours	92	83		9		90	
			With more than three tumours	99	96		3		97	
			With no history of BC	179	154		25		86	
			With history of BC	220	190		30		86	
		≥ 10 U/ml	Patient	739	321	101	85	232	79	70
	Cytology (VU)		Patient	739	253	14	153	319	62	96
			pTa	211	93		118		44	
			pT1	47	33		14		70	
			pT2	58	45		13		78	
			pT3	45	42		3		93	
			pT4	9	8		1		89	
			CIS	31	26		5		84	
			Superficial invasive (pTa, pT1, CIS)	287	152		135		53	

Study	Test	Cut-off	Unit of analysis	Number analysed	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)
			Superficial invasive (pT2–T4)	112	95		17		85	
			G1	129	49		80		38	
			G2	160	109		51		68	
			G3	70	63		7		90	
			With one tumour	208	99		109		48	
			With two to three tumours	92	63		29		68	
			With more than three tumours	99	85		14		86	
			With no history of BC	179	140		39		78	
			With history of BC	220	107		113		49	
Raitanen 2002[173] No. of patients 652, of whom no previous history of BC 151, history of BC 501	Cytology (VU)	Papanicolaou I–II classed as negative and III–V classed as positive (suspicious classed as positive)	Patient							
			With no previous history of BC	129	73		56		57	
			pTa	51	16		35		35	
			pT1	49	33		16		67	
			pT2–T4	22	19		3		86	
			pTx	3	3		0		100	
			CIS (no suspicious)	4	2		2		50	
			G1	44	10		34		23	
			G2	45	28		17		62	
			G3	39	34		5		87	
			Gx (only suspicious)	1	1		0		100	
			One tumour	86	49		37		57	
			Two tumours	26	14		12		54	
			More than three tumours	14	10		4		71	

Study	Test	Cut-off	Unit of analysis	Number analysed	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)
			With previous history of BC	441	41	32	77	291	35	90
			pTa	54	9		45		16	
			pT1	20	6		14		30	
			>pT2	3	2		1		67	
			pTx	33	13		20		39	
			CIS	8	6		2		75	
			G1	48	10		38		21	
			G2	35	16		19		46	
			G3 (no suspicious)	3	3		0		100	
			Gx	32	12		20		38	
		Papanicolaou I–III classed as negative and IV–V classed as positive (suspicious classed as negative)	Patient							
			With no previous history of BC	129	40		89		31	
			pTa	51	6		45		12	
			pT1	49	19		30		39	
			pT2-T4	22	11		11		50	
			pTx	3	2		1		67	
			CIS (no suspicious)	4	2		2		50	
			G1	44	5		39		11	
			G2	45	12		33		27	
			G3	39	23		16		59	
			Gx (only suspicious)	1	0		1		0	
			One tumour	86	27		59		31	
			Two tumours	26	5		21		19	
			More than three tumours	14	8		6		57	

Study	Test	Cut-off	Unit of analysis	Number analysed	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)
			With previous history of BC	441	21	11	97	312	18	97
			pTa	54	8		46		15	
			pT1	20	4		16		20	
			>pT2	3	0		3		0	
			pTx	33	5		28		15	
			CIS	8	4		4		50	
			G1	48	6		42		13	
			G2	35	7		28		20	
			G3 (no suspicious)	3	3		0		100	
			Gx	32	5		27		16	
[Raitanen 2002[174]]	Cytology (VU)	Papanicolaou I–III classed as negative and IV–V classed as positive (suspicious classed as negative) (local analysis)	Patient	575	71	8	177	319	29	98
			With no previous history of BC	129	50		79		39	
			pTa–T1	100	32		68		32	
			G1	44	3		41		7	
			G2–3	84	47		37		56	
			With history of BC	446	21	8	98	319	18	98
		Papanicolaou I–III classed as negative and IV–V classed as positive (suspicious classed as negative) (review analysis)	Patient	575	61	11	187	316	25	97
			With no previous history of BC	129	40		89		31	
			pTa–T1	100	25		75		25	
			G1	44	5		39		11	
			G2–3	84	35		49		42	
			With history of BC	446	21	11	98	316	18	97

Study	Test	Cut-off	Unit of analysis	Number analysed	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)
Ramakumar 1999[159]	NMP22 (Matritech) Laboratory analysis	10 U/ml	Patient	196	30	56	27	83	53	60
No. of patients 196, of whom no previous history of BC 19, history of BC 38 and control (others undergoing cystoscopy who were negative for BC and with negative urine specimen) 139			pTa	25	12		13		48	
			pT1–T3b	14	11		3		79	
			CIS	11	5		6		45	
			G1	9	4		5		44	
			G2	26	16		10		62	
			G3	13	8		5		62	
			No previous history of BC tumour	19	14		5		74	
			History of BC tumour	38	16		22		42	
	Cytology (VU)		Patient	112	24	3	30	55	44	95
			pTa	24	7		17		29	
			pT1–T3b	12	8		4		67	
			CIS	11	8		3		73	
			G1	9	2		7		22	
			G2	24	9		15		38	
			G3	12	10		2		83	
			No previous history of BC tumour	17	10		7		59	
			History of BC tumour	37	14		23		38	
Saad 2002[141]	NMP22 Laboratory analysis	≥ 10 U/ml	Patient	120	42	9	10	59	81	87
No. of patients 120, of whom no previous history of BC 120, history of BC 0			pTa	23	16		7		70	
			pT1	20	18		2		90	
			pT2	8	8		0		100	
			CIS	6	6		0		100	
			G1	13	8		5		62	
			G2	22	19		3		86	
			G3	17	15		2		88	

Study	Test	Cut-off	Unit of analysis	Number analysed	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)
	Cytology (VU)		Patient	120	25	9	27	59	48	87
			pTa	23	7		16		30	
			pT1	20	10		10		50	
			pT2	8	7		1		88	
			CIS	6	5		1		83	
			G1	13	2		11		15	
			G2	22	9		13		41	
			G3	17	14		3		82	
Sanchez-Carbayo 1999[160] No. of patients 267, of whom no previous history of BC NS, history of BC NS, other urological diseases 25, malignancies of non-bladder origin 25, healthy volunteers 30	NMP22 (Matritech) Laboratory analysis	> 14.6 U/ml	Patient (from group 1: 111 with positive cystoscopy for TCC of the bladder; from group 2: 76 with previous BC and free of disease at time of study)	187	84	4	27	72	76	95
			Patient (from group 1)							
			pTa	24	15		9		63	
			pT1	53	42		11		79	
			pT2	11	9		2		82	
			pT3	13	13		0		100	
			pT4	3	3		0		100	
			CIS	3	2		1		67	
			G1	33	25		8		76	
			G2	33	27		6		82	
			G3	40	33		7		83	
			Single tumour	25	18		7		72	
			Multiple tumours	81	61		20		75	
			< 0.5 cm	23	19		4		83	
			0.5–3 cm	42	34		8		81	
			> 3 cm	41	38		3		93	
			Papillary tumour	78	63		15		81	
			Solid tumour	28	28		0		100	
			No previous history of BC	43	33		10		77	
			Previous history of BC	64	54		10		84	

Study	Test	Cut-off	Unit of analysis	Number analysed	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)
[Sanchez-Carbayo 1999[161]]	NMP22 (Matritech) Laboratory analysis	6.4 U/ml	Patient	187	95	15	16	61	85	80
No. of patients as for Sanchez-Carbayo 1999[160]		7 U/ml	Patient	187	95	13	16	63	85	83
		10 U/ml	Patient	187	90	7	21	69	81	91
		12 U/ml	Patient	187	87	6	24	70	78	92
		13.7 U/ml	Patient	187	87	3	24	73	78	96
Sanchez-Carbayo 2001[162]	NMP22 (Matritech) Laboratory analysis	≥ 10 U/ml	Patient	232	38	13	17	164	69	93
No. of patients 232, of whom no previous history of BC 0, history of BC 232			Not receiving intravesical instillations	106	25	5	6	70	81	93
			Receiving intravesical instillations	126	13	8	11	94	65	92
			CIS	4	1		3		25	
			G1	29	8		21		27	
			G2	37	21		16		58	
			G3	40	30		10		76	
Sanchez-Carbayo 2001[142]	NMP22 (Matritech) Laboratory analysis	≥ 10 U/ml	Patient	187	26	29	17	115	61	80
No. of patients 187, of whom no previous history of BC 112, history of BC 0, other 75			Patients with no previous history of BC	112	26	7	17	62	60	90
			pTa	5	0		5		0	
			pT1	28	16		12		57	
			CIS	1	0		1		0	
			pT2	7	6		1		86	
			pT3	2	2		0		100	
			G1	11	2		9		18	
			G2	15	9		6		60	
			G3	17	14		3		82	
	Cytology (VU or catheterised)		Patients with no previous history of BC	112	15	23	28	46	35	97

Study	Test	Cut-off	Unit of analysis	Number analysed	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)
Sarosdy 2002[108] No. of patients 451, of whom no previous history of BC 0, history of BC 176 and other 275	FISH (UroVysion)	Aneuploidy of chromosomes 3, 7 and 17 or loss of the 9p21 locus	Patient (whole group excluding 59 healthy donors)	392	44	54	18	276	71	84
			Patients with history of BC	176	44	39	18	75	71	66
			pTaG1–G2	26	16		10		62	
			pTaG3	6	5		1		83	
			pT1G2	2	2		0		100	
			pT1G3	3	3		1		75	
			pT2	7	7		0		100	
			CIS	7	7		0		100	
			G1	22	12		10		55	
			G2	9	7		2		78	
			G3	18	17		1		94	
			Control group	275		15		260		95
			Healthy donors	59		0		59		100
			Non-genitourinary benign disease	48		4		44		92
			Non-genitourinary cancer	3		1		2		67
			Benign prostatic hyperplasia	58		5		53		92
			Microhaematuria	15		2		13		87
			Infections, inflammation	28		1		27		96
			Prostate and renal cancer	61		5		56		92

Study	Test	Cut-off	Unit of analysis	Number analysed	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)
	Cytology (VU)		Patient							
			pTaG1–G2	26	6		20		23	
			pTaG3	6	2		4		33	
			pT1G2	2	2		0		100	
			pT1G3	4	2		2		50	
			pT2	3	1		2		33	
			CIS	6	2		4		33	
			G1	22	4		18		18	
			G2	9	4		5		44	
			G3	17	7		10		41	
Sarosdy 2006[105] No. of patients 497, of whom no previous history of BC 497, history of BC 0	FISH (UroVysion)	NS (assay was performed according to instructions on the product labelling)	Patient	473	35	94	16	328	69	78
			pTaG1	21	10		11		48	
			pTaG2	6	5		1		83	
			pTaG3	4	4		0		100	
			pT1	7	6		1		86	
			pT2	10	9		1		90	
			Unknown stage	2	1		1		50	
			G1	21	10		11		48	
			G2	10	7		3		70	
			G3	17	15		2		88	
	Cytology (VU)		Patient	473	19		32		38	
			pTaG1	21	5		16		24	
			pTaG2	6	3		3		50	
			pTaG3	4	2		2		50	
			pT1	7	3		4		43	
			pT2	10	6		4		60	
			Unknown stage	2	1		1		50	
			G1	21	5		16		24	
			G2	10	3		7		30	
			G3	17	9		8		53	

Study	Test	Cut-off	Unit of analysis	Number analysed	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)
Schmitz-Drager 2008[117,118] No. of patients 301, of whom no previous history of BC 301, history of BC 0	ImmunoCyt	More than one green or one red urothelial cell	Patient	280	23	31	4	222	85	88
			Gross haematuria	63	15	8	2	38	88	83
			High grade	11	9		2		82	
			Low grade	5	5		0		100	
			Microhaematuria	217	8	23	2	184	80	89
			High grade	4	4		0		100	
			Low grade	6	4		2		67	
	Cytology (VU)		Patient	280	12	11	15	242	44	96
			Gross haematuria	63	8	4	9	42	47	91
			High grade	11	6		5		55	
			Low grade	5	2		3		40	
			Microhaematuria	217	4	7	6	200	40	97
			High grade	4	2		2		50	
			Low grade	6	4		2		67	
	Cystoscopy (NS)		Patient	278	21	4	4	249	84	98
			Gross haematuria	61	13	2	2	44	87	96
			High grade	11	8		3		73	
			Low grade	5	4		1		80	
			Microhaematuria	217	8	2	2	205	80	99
	ImmunoCyt + cystoscopy		Patient	280	27	32	0	221	100	87
			Gross haematuria	63	17	9	0	37	100	80
			Microhaematuria	217	10	23	0	184	100	89
	Cystoscopy + cytology (VU)		Patient	280	22	13	5	240	88	95
			Gross haematuria	63	14	6	3	40	82	87
			Microhaematuria	217	8	7	2	200	80	97

Study	Test	Cut-off	Unit of analysis	Number analysed	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)
Serretta 2000[144]	NMP22 (Matritech) Laboratory analysis	10 U/ml	Patient	179	41	56	14	68	75	55
No. of patients 179, of whom no previous history of BC 0, history of BC 179			pTa	13	7		6		54	
			pT1	27	20		7		74	
			pT2–T3	12	10		2		83	
			CIS	3	3		0		100	
			G1	7	3		4		43	
			G2	19	12		7		63	
			G3	29	26		3		90	
[Serretta 1998[143]]	NMP22	≥ 10 U/ml	Patient	137	30	37	12	58	71	61
No. of patients 137, of whom no previous history of BC 0, history of BC 137		20 U/ml	Patient	137	24	18	18	77	57	81
Shariat 2006[147]	NMP22 Laboratory analysis	≥ 10 U/ml (study also gives sensitivity and specificity for cut-offs from 1 to 30 U/ml)	Patient	2871	596	347	449	1479	57	81
No. of patients 2871, of whom no previous history of BC 0, history of BC 2871			≥ pT2	220	183		37		83	
			G3	329	247		82		75	
Sharma 1999[148]	NMP22 (Matritech) Laboratory analysis	≥ 10 U/ml for patients with no previous history of BC, ≥ 6 U/ml for patients with history of BC	Patient	278	28	44	6	200	82	82
No. of patients 278, of whom no previous history of BC 199, history of BC 79		≥ 10 U/ml	With no previous history of BC	199	4	27	2	166	67	86
		≥ 6 U/ml	With previous history of BC	79	24	17	4	34	86	67
	Cytology (VU)	Atypical classed with positive	Patient	278	19	17	15	227	56	93
			With no previous history of BC	199	2	8	4	185	33	96
			With previous history of BC	79	17	9	11	42	61	82

Study	Test	Cut-off	Unit of analysis	Number analysed	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)
	Cytology (VU)	Atypical classed with negative	Patient	278	10	1	24	243	29	100
			With no previous history of BC	199	1	0	5	193	17	100
			With previous history of BC	79	9	1	19	50	32	98
Skacel 2003[104]	FISH (UroVysion)	Chromosomal gain of two or more chromosomes in five or more cells per slide, or in cases of isolated gain of chromosome 3, 7 or 17 when the number of cells with such gain was ≥ 10%, or when 9p21 loss was the only abnormality, ≥ 12 cells with such loss	Patient	111	70	1	12	28	85	97
No. of patients 120, of whom no previous history of BC 26, history of BC 94			pTa	64	53		11		83	
			pT1	6	5		1		83	
			pT2	6	6		0		100	
			pT4	3	3		0		100	
			CIS	3	3		0		100	
			G1	23	19		4		83	
			G2	35	28		7		80	
			G3	24	23		1		96	
Sokolova 2000[105]	FISH (UroVysion)	Five or more cells with polysomy	Patient (urothelial carcinoma)	179	39	11	7	122	85	92
No. of patients 179, of whom no previous history of BC 86, history of BC 93			pTa	22	14		8		65	
			pT1–T4	12	11		1		95	
			CIS	12	12		0		100	
			G2	14	11		3		76	
			G3	22	21		1		97	
		2.8% of cells with tetrasomy	CEP3	19	14		5		74	
		6.5% of cells with tetrasomy	CEP7	21	16		5		76	

Study	Test	Cut-off	Unit of analysis	Number analysed	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)
		7.1% of cells with tetrasomy	CEP8	19	11		8		58	
			CEP9	21	11		10		52	
			CEP11	19	10		9		53	
		6.2% of cells with tetrasomy	CEP17	21	13		8		62	
		7.0% of cells with tetrasomy	CEP18	19	8		11		42	
		16.9% of cells with homozygous deletion	9p21	21	6		15		29	
		Four or more cells with polysomy	Patient (urothelial carcinoma)	179	41	16	5	117	90	88
			CEP3, 7, 17 and 9p21	21	20		1		95	
	Cytology (VU)		Patient (urothelial carcinoma)							
			pTa	22	10		12		47	
			pT1–T4	12	7		5		60	
			CIS	12	9		3		78	
			G2	14	8		6		54	
			G3	22	16		6		71	
Sozen 1999[163]	NMP22 (Matritech) Laboratory analysis	5 U/ml	Patient	140	36	37	4	63	90	63
No. of patients 140, of whom no previous history of BC NS, history of BC NS, control group of 100 with benign urological disease or renal or prostate cancer		6.4 U/ml	Patient	140	35	31	5	69	88	69
		7 U/ml	Patient	140	34	28	6	72	85	72
		10 U/ml	Patient	140	29	19	11	81	73	81
		12 U/ml	Patient	140	29	15	11	85	73	85
		15 U/ml	Patient	140	28	13	12	87	70	87
	Cytology (VU or catheterised)		Patient	140	14	10	26	90	35	90

Study	Test	Cut-off	Unit of analysis	Number analysed	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)
Stampfer 1998[149]	NMP22 (Matritech) Laboratory analysis	>6.4 U/ml	Specimen	274	45	42	21	166	68	80
No. of patients 231, of whom no previous history of BC 0, history of BC 231			pTa	44	27		17		61	
			pT1	6	6		0		100	
			≥ pT2	6	5		1		83	
			CIS	10	7		3		70	
			G1	13	4		9		31	
			G2	27	20		7		74	
			G3	26	21		5		81	
			Low risk (pTaG1, pTaG2)	39	23		16		59	
			High risk (pTaG3, T1)	11	10		1		90	
			Invasive (pT2–T4)	6	5		1		83	
		5 U/ml	Specimen	274	48	59	18	149	73	72
		7 U/ml	Specimen	274	43	34	23	174	65	84
		10 U/ml	Specimen	274	32	17	34	191	49	92
	Cytology (VU)		Specimen	200	18	12	24	146	43	92
Takeuchi 2004[164]	NMP22 (Konica-Matritech) Laboratory analysis	12 U/ml	Patient	669	28	124	20	497	58	80
No. of patients 669, of whom no previous history of BC 48, history of BC 0, benign disease 621			CIS–pT1	39	19		20		49	
			pT2–T4	9	9		0		100	
			G1	4	2		2		50	
			G2	35	19		16		54	
			G3	9	7		2		78	
			<10 mm	19	6		13		32	
			10–30 mm	17	11		6		65	
			>30 mm	12	11		1		92	
			Single	27	12		15		44	
			Two to four	10	6		4		60	
			Five or more	11	10		1		91	

Study	Test	Cut-off	Unit of analysis	Number analysed	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)
	Cytology (VU)		Patient	669	21	0	27	621	44	100
			CIS–pT1	39	15		24		39	
			pT2–T4	9	6		3		67	
			G1	4	1		3		25	
			G2	35	13		22		37	
			G3	9	7		2		78	
			< 10 mm	19	4		15		21	
			10–30 mm	17	8		9		47	
			> 30 mm	12	9		3		75	
			Single	27	9		18		33	
			Two to four	10	3		7		30	
			Five or more	11	9		2		82	
	NMP22 + cytology (VU)		Patient	48	29		19		60	
			CIS–pT1	39	20		19		51	
			pT2–T4	9	9		0		100	
			G1	4	2		2		50	
			G2	35	20		15		57	
			G3	9	7		2		78	
			< 10 mm	19	7		12		37	
			10–30 mm	17	11		6		65	
			> 30 mm	12	11		1		92	
			Single	27	13		14		48	
			Two to four	10	6		4		60	
			Five or more	11	10		1		91	

Study	Test	Cut-off	Unit of analysis	Number analysed	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)
Talwar 2007[150] No. of patients 196, of whom no previous history of BC 69, history of BC 127	NMP22 (Matritech) BladderChek	≥ 10 U/ml	Patient	196	35	28	17	116	67	81
			pTa	24	14		10		58	
			pT1	14	10		4		71	
			pT2	8	6		2		75	
			pT3	3	3		0		100	
			CIS	1	1		0		100	
			With well-differentiated tumours	21	11		10		52	
			With poorly-differentiated tumours	7	6		1		86	
			With moderately-differentiated tumours	22	17		5		77	
			No previous history of BC	69	9	7	1	52	90	88
			History of BC	127	27	21	15	64	64	75
			Non-invasive	39	25		14		64	
			Muscle invasive	1	9		2		82	
			Cystitis, inflammation, UTI	58		17		41		71
			Benign prostatic hyperplasia	38		5		33		87
			Calculi	44		7		37		84
			Non-TCC malignancies	2		2		0		0
			No urinary tract disease	51		2		49		96

Study	Test	Cut-off	Unit of analysis	Number analysed	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)
	Cytology (VU)		Patient	196	11	2	41	142	21	99
			pTa	24	14		10		58	
			pT1	14	2		12		14	
			pT2	8	2		6		25	
			pT3	3	3		0		100	
			CIS	1	0		1		0	
			With well-differentiated tumours	21	2		19		10	
			With poorly-differentiated tumours	7	4		3		57	
			With moderately-differentiated tumours	22	4		18		18	
			No previous history of BC	69	1	0	9	59	10	100
			History of BC	127	9	0	33	85	21	100
			Non-invasive	39	5		34		13	
			Muscle invasive	11	5		6		45	
			Cystitis, inflammation, UTI	58		1		57		98
			Benign prostatic hyperplasia	38		0		38		100
			Calculi	44		0		44		100
			Non-TCC malignancies	2		1		1		50
			No urinary tract disease	51		0		51		100

Study	Test	Cut-off	Unit of analysis	Number analysed	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)
Tetu 2005[119]	ImmunoCyt	Presence of one green or one red fluorescent cell	Patient	870	100	281	36	453	74	62
No. of patients 904, of whom no previous history of BC NS, history of BC NS			pTa	65	51		14		79	
			pT1	6	5		1		83	
			≥ pT2	19	13		6		68	
			CIS	14	13		1		93	
	Cytology (VU)	(The study included cases with atypias suspicious for malignancy in the negative category)	Patient	870	39	17	97	814	29	98
			pTa	65	8		57		12	
			pT1	6	4		2		67	
			≥ pT2	19	9		10		47	
			CIS	14	7		7		50	
	ImmunoCyt + cytology (VU)		Patient	870	114	284	22	450	84	61
			pTa	65	51		14		79	
			pT1	6	5		1		83	
			≥ pT2	19	15		4		79	
			CIS	14	14		0		100	
Tritschler 2007[80]	NMP22 (Matritech) BladderChek	10 U/ml	Patient	100	26	36	14	24	65	40
No. of patients 100, of whom no previous history of BC 30, history of BC 70			Tumour							
			G1–2	22	12		10		55	
			G3	18	14		4		78	
			pTa	22	12		10		55	
			CIS	9	7		2		78	
			Invasive T1	4	2		2		50	
			Invasive ≥ T2	3	3		0		100	
	Cytology (VU)		Patient	85	15	11	19	40	44	78
	Cytology (BW)		Patient	94	26	23	8	37	76	62
			Tumour							
			G1–2	22	17		5		83	
			G3	18	15		3		83	
			pTa	22	18		4		82	
			CIS	9	7		2		78	
			T1	4	3		1		75	
			≥ T2	3	2		1		67	

Study	Test	Cut-off	Unit of analysis	Number analysed	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)
Wiener 1998[151]	NMP22 (Matritech) Laboratory analysis	10 U/ml	Patient	291	44	62	47	138	48	69
No. of patients 291, of whom no previous history of BC 190, history of BC 101			pTa	47	23		24		49	
			pT1	25	11		14		44	
			≥ pT2	19	10		9		53	
			G1	23	12		11		52	
			G2	38	17		21		45	
			G3	30	15		15		50	
	Cytology (VU)		Patient	291	54	0	37	200	59	100
			pTa	47	23		24		49	
			pT1	25	16		9		64	
			≥ pT2	19	15		4		79	
			G1	23	4		19		17	
			G2	38	23		15		61	
			G3	30	27		3		90	
	Cytology (BW)		Patient	200	48	0	35	117	58	100
			pTa	47	22		25		47	
			pT1	25	18		7		25	
			≥ pT2	19	15		4		79	
			G1	23	5		18		22	
			G2	38	21		17		55	
			G3	30	27		3		90	

Study	Test	Cut-off	Unit of analysis	Number analysed	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)
Yoder 2007[106] No. of patients 250, of whom no previous history of BC 0, history of BC 250	FISH (UroVysion)	More than two chromosomal gains of chromosomes 3, 7 or 17 in at least four analysed cells, or homozygous 9p21 deletion in at least 12 analysed cells, or isolated trisomy of chromosome 3, 7, or 17 in at least 10% of analysed cells	Patient	250	25	56	14	155	64	73
Zippe 1999[152] No. of patients 330, of whom no previous history of BC 330, history of BC 0	NMP22 (Matritech) Laboratory analysis	> 10 U/ml	Patient	330	18	45	0	267	100	86
	Cytology (VU)		Patient	330	6	0	12	312	33	100
[Zippe 1999[153]] No. of patients 146, of whom no previous history of BC 146, history of BC 0	NMP22	> 10 U/ml	Patient	146	8	14	0	124	100	90
	Cytology (VU)		Patient	146	2	0	6	138	25	100

BC, bladder cancer; BW, bladder wash; FN, false negative; FP, false positive; NS, not stated; R, rigid; TN, true negative; TP, true positive; UTI, urinary tract infections; UUT, upper urinary tract; VU, voided urine.

Appendix 16

Cut-offs for a positive test used in studies reporting FISH

Study	Cut-off
Daniely 2007[94]	Minimum of four cells with gains of two or more chromosomes, or 12 or more cells with homozygous loss of the 9p21 locus
Friedrich 2003[95]	If 20% of the cells had a gain of two or more chromosomes (3, 7 or 17), or 40% of the cells had a gain of one chromosome or 40% loss of 9p21 locus
Halling 2000[97]	Five or more cells with polysomy
Junker 2006[98]	Five or more cells showed gains of more than one chromosome (3, 7 or 17), or 10 or more cells showed gains of a single chromosome (3, 7 or 17), or 10 or more cells showed homozygous loss of the 9p21 locus
Kipp 2008[99]	Four or more cells had polysomic signal patterns (gain of two or more of the four chromosomes in an individual cell), 10 or more cells demonstrated tetrasomy (four signal patterns for all four probes), or >20% of the cells demonstrated 9p21 homozygous deletion (loss of the two 9p21 signals)
May 2007[107]	Gain of two or more chromosomes in five or more cells per slide, or in cases of isolated gains of chromosome 3, 7, or 17 when the proportion of cells with such a gain was 10% or more of at least 100 cells evaluated, or when there were 10 or more cells with 9p21 loss
Meiers 2007[100]	Chromosomal gain of two or more chromosomes (+3, +7, +17) in four or more cells, or deletion of 9p21 in 12 or more cells
Mian 2003[101]	Four or more aneusomic of 25 counted cells
Moonen 2007[102]	Four or more of the 25 morphologically abnormal cells showed gains of two or more chromosomes (3, 7 or 17), or 12 or more of the 25 cells had no 9p21 signals
Sarosdy 2002[108]	Aneuploidy of chromosomes 3, 7 and 17 or loss of the 9p21 locus
Sarosdy 2006[103]	Assay was performed according to product instructions [the UroVysion Bladder Cancer Kit (UroVysion Kit) is designed to detect aneuploidy for chromosomes 3, 7, 17, and loss of the 9p21 locus]
Skacel 2003[104]	Chromosomal gain of two or more chromosomes in five or more cells per slide, or in cases of isolated gain of chromosome 3, 7 or 17 when the number of cells with such gain was ≥ 10%, or when 9p21 loss was the only abnormality, 12 or more cells with such loss
Sokolova 2000[105]	Five or more cells with polysomy
Yoder 2007[106]	More than two chromosomal gains of chromosomes 3, 7 or 17 in at least four analysed cells, or homozygous 9p21 deletion in at least 12 analysed cells, or isolated trisomy of chromosome 3, 7, or 17 in at least 10% of analysed cells

Appendix 17
Model structure

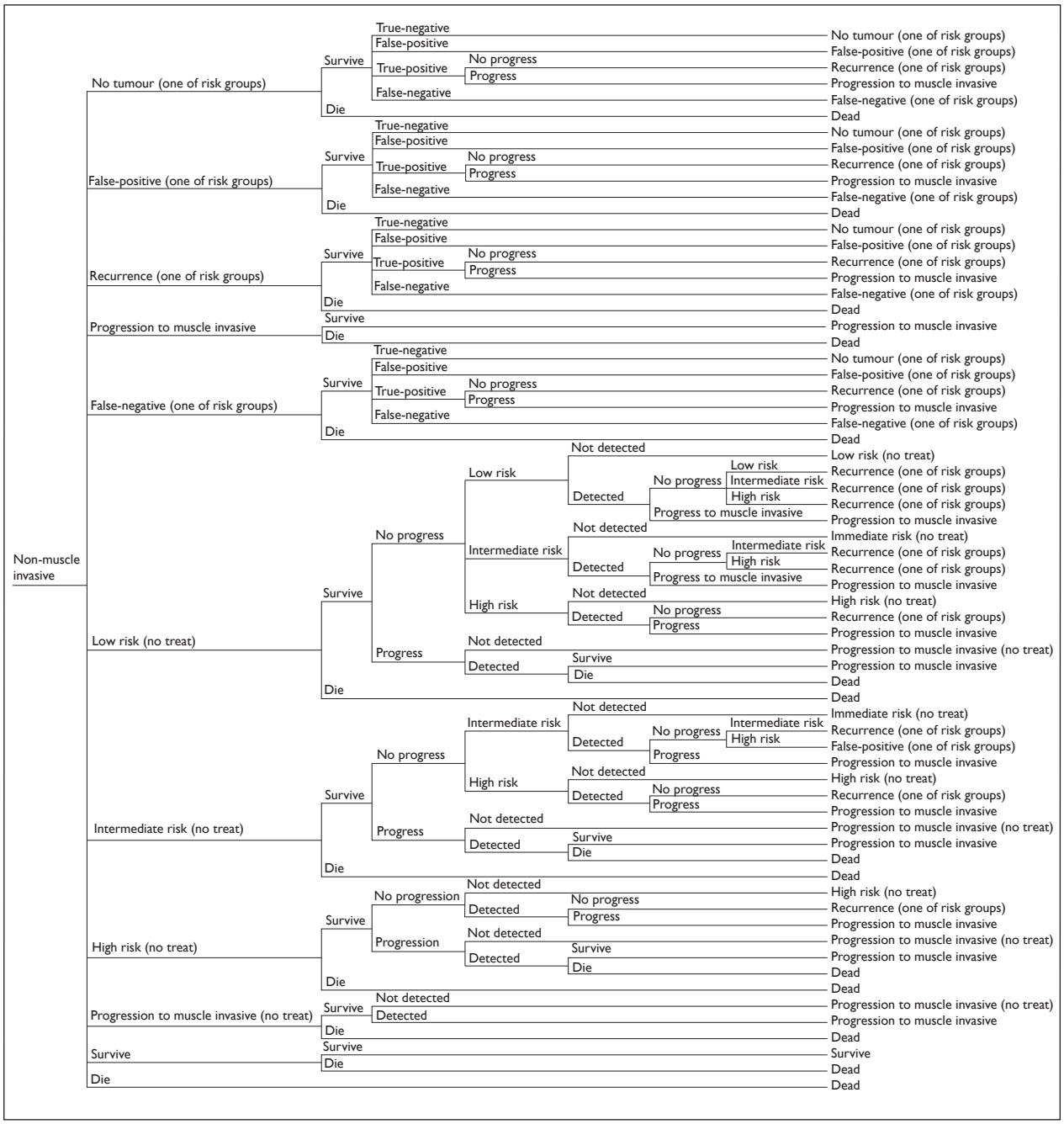


FIGURE 36 *Diagram of Markov model for non-muscle-invasive disease.*

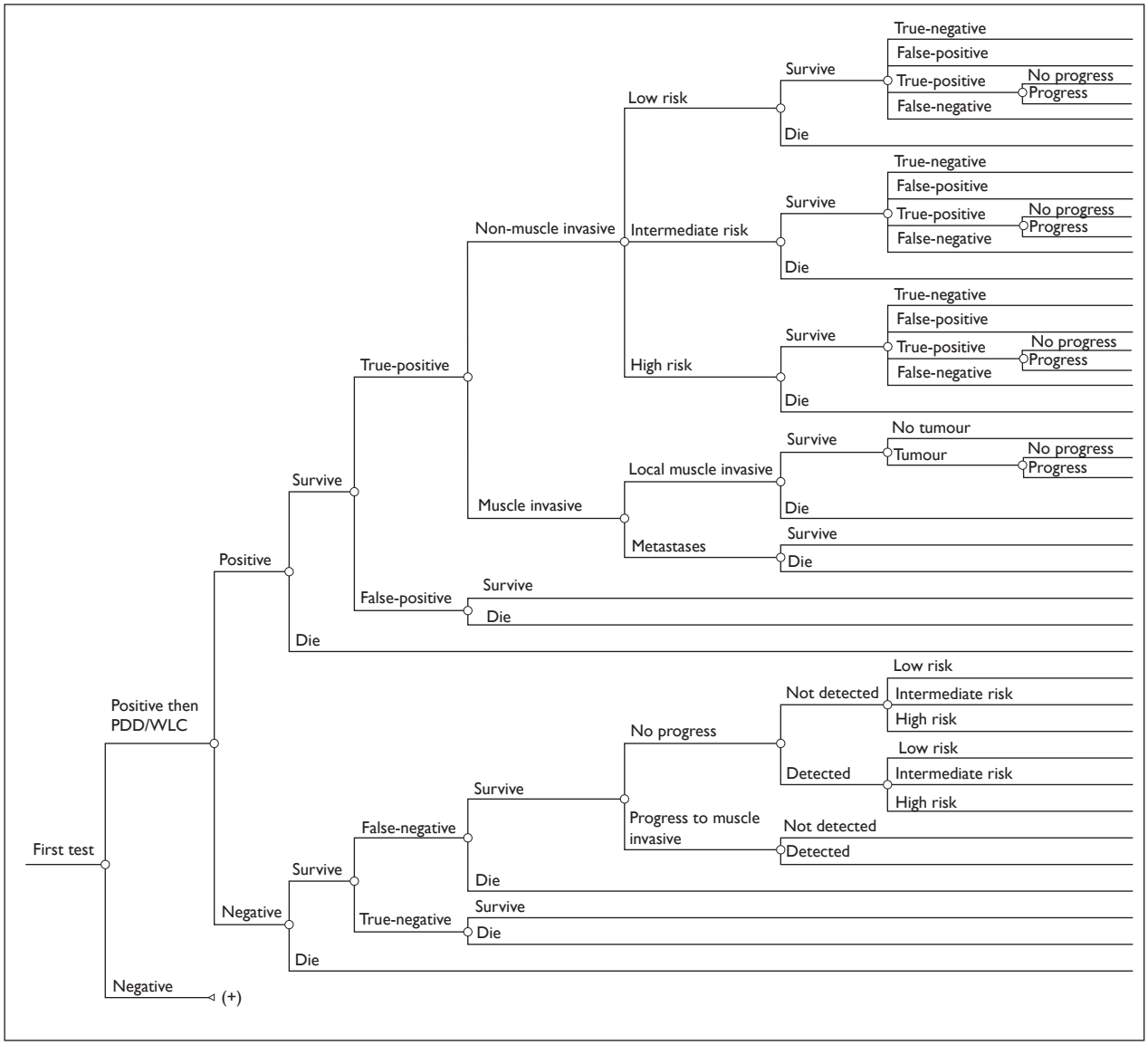


FIGURE 37 *Diagram of decision model.*

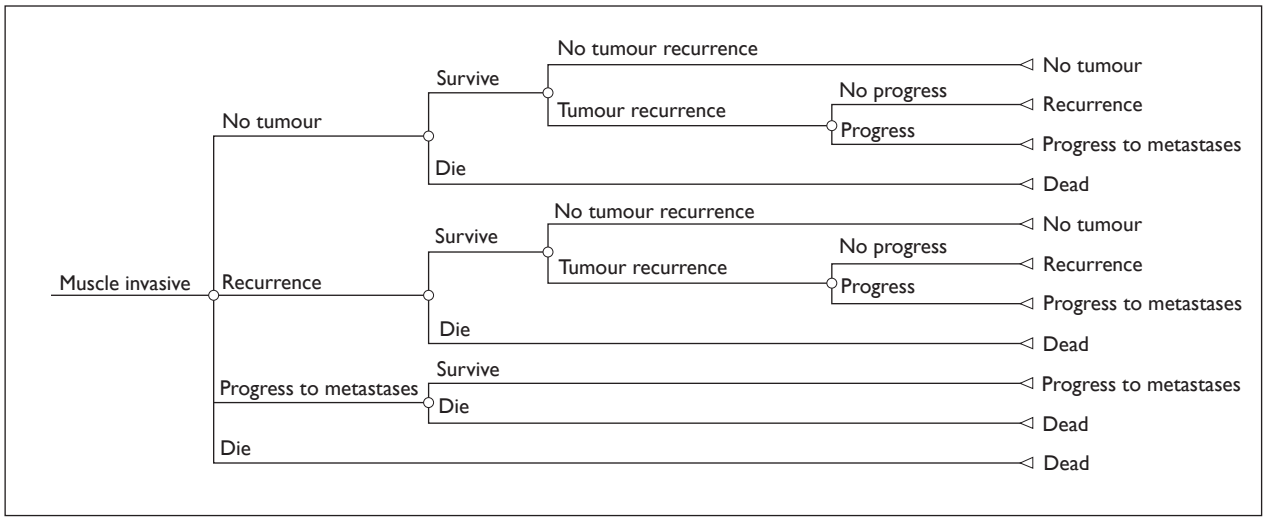


FIGURE 38 *Diagram of Markov model for muscle-invasive disease.*

Appendix 18

Summary of studies reporting prognosis and all-cause mortality rates for the UK

TABLE 55 *Summary of studies reporting prognostic factors for recurrence*

Study	Study type	Tumour status	No. of cases	Grade	T stage	CIS	Multiplicity	Tumour size	Intravesical instillations
Loening 1980[186]	Retrospective	Primary and recurrent	178	No	Yes	–	No	No	–
Narayana 1983[189]	Prospective	Primary and recurrent	468	No	Yes	Yes	No	Yes	–
				Yes	Yes	–	No	No	–
Dalesio 1983[182]	Prospective	Primary and recurrent	308	No	–	–	Yes	Yes	–
Parmar 1989[191]	Prospective	Primary	305	No	No	–	Yes	No	–
Witjes 1992[194]	Prospective	Primary	1026	No	Yes	No	No	–	Yes
Kiemeney 1993[184]	Prospective	Primary	1674	No	Yes	No	Yes	–	Yes
Kiemeney 1994[185]	Prospective	Primary	1674	Yes	Yes	No	–	–	Yes
Witjes 1994[195]	Prospective	Primary and recurrent	469	No	No	–	Yes	No	–
Mulders 1994[188]	Prospective	Primary and recurrent	371	No	No	–	Yes	No	–
Kurth 1995[181]	Retrospective	Primary and recurrent	576	Yes	No	–	Yes	No	–
Pawinski 1996[192]	Meta-analysis	Primary and recurrent	2535	–	–	–	–	–	Yes
Shinka 1997[193]	Prospective	Primary	141	No	Yes	No	No	Yes	–
Millán-Rodriguez 2000[187]	Retrospective	Primary	1529	No	No	Yes	Yes	Yes	Yes
Oosterlinck 2001[190]	Guideline	–	–	–	–	–	–	–	–
Sylvester 2006[20]	Retrospective	Primary and recurrent	2596	Yes	Yes	Yes	Yes	Yes	Yes
García 2006[183]	Retrospective	Primary and recurrent	473	Yes	No	No	Yes	No	Yes

TABLE 56 *Summary of studies reporting prognostic factors for progression*

Study	Study type	Tumour status	No. of cases	Grade	T stage	CIS	Multiplicity	Tumour size	Intravesical instillations
Herr 1997[196]	–	Primary and recurrent	221	–	Yes	–	–	–	–
Kiemeney 1993[184]	Prospective	Primary	1674	Yes	Yes	Yes	Yes	–	No
Kiemeney 1994[185]	Prospective	Primary and recurrent	1674	Yes	Yes	Yes	–	–	No
Kurth 1995[181]	Retrospective	Primary and recurrent	576	Yes	–	–	No	Yes	–
Pawinski 1996[192]	Meta-analysis	Primary and recurrent	2535	–	–	–	–	–	No
Millán-Rodriguez 2000[187]	Retrospective	Primary	1529	Yes	No	Yes	Yes	Yes	Yes
Sylvester 2006[20]	Retrospective	Primary and recurrent	2596	Yes	Yes	Yes	Yes	Yes	Yes
García 2006[183]	Retrospective	Primary and recurrent	473	Yes	Yes	Yes	Yes	No	Yes

TABLE 57 *All-cause mortality rates for the UK*

Age (years)	Female	Male	30% female/70% male
57	0.004643	0.007311	0.0065106
58	0.005050	0.007850	0.0070100
59	0.005639	0.008787	0.0078426
60	0.006160	0.010172	0.0089684
61	0.006807	0.011002	0.0097435
62	0.007443	0.012545	0.0110144
63	0.008116	0.013460	0.0118568
64	0.009152	0.015029	0.0132659
65	0.010041	0.016189	0.0143446
66	0.011114	0.017829	0.0158145
67	0.012173	0.019784	0.0175007
68	0.013430	0.021671	0.0191987
69	0.014893	0.024025	0.0212854
70	0.016138	0.026284	0.0232402
71	0.018145	0.029844	0.0263343
72	0.020737	0.032942	0.0292805
73	0.023061	0.036532	0.0324907
74	0.026217	0.041049	0.0365994
75	0.029660	0.045240	0.0405660
76	0.033232	0.050620	0.0454036
77	0.037046	0.056696	0.0508010
78	0.041599	0.062325	0.0561072
79	0.046364	0.069874	0.0628210
80	0.051959	0.076846	0.0693799
81	0.058465	0.085981	0.0777262
82	0.065710	0.094133	0.0856061
83	0.073339	0.103537	0.0944776
84	0.080283	0.111409	0.1020712
85	0.090944	0.121991	0.1126769
86	0.102260	0.136694	0.1263638
87	0.119838	0.159120	0.1473354
88	0.132897	0.174064	0.1617139
89	0.148659	0.192931	0.1796494
90	0.163740	0.201010	0.1898290
91	0.182212	0.220958	0.2093342
92	0.202965	0.243762	0.2315229
93	0.228008	0.269145	0.2568039
94	0.251579	0.281937	0.2728296
95	0.275949	0.319381	0.3063514
96	0.300473	0.342860	0.3301439
97	0.329979	0.371213	0.3588428

Appendix 19

Results of cost–consequence analysis

TABLE 58 *Ranking by diagnostic performance*

Ranking	True negative	True positive	False positive	False negative
1	CTL_WLC (CTL_WLC)	CSC_IMM_PDD (IMM_WLC)	CTL_WLC (CTL_WLC)	CSC_IMM_PDD (IMM_WLC)
2	CTL_PDD (CTL_WLC)	CSC_IMM_PDD (CSC_WLC)	CTL_PDD (CTL_WLC)	CSC_IMM_PDD (CSC_WLC)
3	FISH_WLC (FISH_WLC)	CSC_FISH_PDD (FISH_WLC)	FISH_WLC (FISH_WLC)	CSC_FISH_PDD (FISH_WLC)
4	NMP22_WLC (NMP22_WLC)	CSC_FISH_PDD (CSC_WLC)	NMP22_WLC (NMP22_WLC)	CSC_FISH_PDD (CSC_WLC)
5	FISH_PDD (FISH_WLC)	CSC_NMP22_PDD (NMP22_WLC)	FISH_PDD (FISH_WLC)	CSC_NMP22_PDD (NMP22_WLC)
6	IMM_WLC (IMM_WLC)	CSC_NMP22_PDD (CSC_WLC)	IMM_WLC (IMM_WLC)	CSC_NMP22_PDD (CSC_WLC)
7	CSC_WLC (CSC_WLC)	IMM_PDD (IMM_WLC)	CSC_WLC (CSC_WLC)	IMM_PDD (IMM_WLC)
8	CSC_CTL_WLC (CSC_WLC)	CSC_CTL_PDD (CSC_WLC)	CSC_CTL_WLC (CSC_WLC)	CSC_CTL_PDD (CSC_WLC)
9	CSC_CTL_WLC (CTL_WLC)	CSC_CTL_PDD (CTL_WLC)	CSC_CTL_WLC (CTL_WLC)	CSC_CTL_PDD (CTL_WLC)
10	NMP22_PDD (NMP22_WLC)	FISH_PDD (FISH_WLC)	NMP22_PDD (NMP22_WLC)	FISH_PDD (FISH_WLC)
11	CSC_FISH_WLC (FISH_WLC)	CSC_IMM_WLC (IMM_WLC)	CSC_FISH_WLC (FISH_WLC)	CSC_IMM_WLC (IMM_WLC)
12	CSC_FISH_WLC (CSC_WLC)	CSC_IMM_WLC (CSC_WLC)	CSC_FISH_WLC (CSC_WLC)	CSC_IMM_WLC (CSC_WLC)
13	IMM_PDD (IMM_WLC)	CSC_FISH_WLC (FISH_WLC)	IMM_PDD (IMM_WLC)	CSC_FISH_WLC (FISH_WLC)
14	CSC_NMP22_WLC (NMP22_WLC)	CSC_FISH_WLC (CSC_WLC)	CSC_NMP22_WLC (NMP22_WLC)	CSC_FISH_WLC (CSC_WLC)
15	CSC_NMP22_WLC (CSC_WLC)	CSC_PDD (CSC_WLC)	CSC_NMP22_WLC (CSC_WLC)	CSC_PDD (CSC_WLC)
16	CSC_PDD (CSC_WLC)	CSC_NMP22_WLC (NMP22_WLC)	CSC_PDD (CSC_WLC)	CSC_NMP22_WLC (NMP22_WLC)
17	CSC_IMM_WLC (IMM_WLC)	CSC_NMP22_WLC (CSC_WLC)	CSC_IMM_WLC (IMM_WLC)	CSC_NMP22_WLC (CSC_WLC)
18	CSC_IMM_WLC (CSC_WLC)	NMP22_PDD (NMP22_WLC)	CSC_IMM_WLC (CSC_WLC)	NMP22_PDD (NMP22_WLC)
19	CSC_CTL_PDD (CSC_WLC)	IMM_WLC(IMM_WLC)	CSC_CTL_PDD (CSC_WLC)	IMM_WLC (IMM_WLC)
20	CSC_CTL_PDD (CTL_WLC)	CSC_CTL_WLC (CSC_WLC)	CSC_CTL_PDD (CTL_WLC)	CSC_CTL_WLC (CSC_WLC)
21	CSC_FISH_PDD (FISH_WLC)	CSC_CTL_WLC (CTL_WLC)	CSC_FISH_PDD (FISH_WLC)	CSC_CTL_WLC (CTL_WLC)
22	CSC_FISH_PDD (CSC_WLC)	FISH_WLC (FISH_WLC)	CSC_FISH_PDD (CSC_WLC)	FISH_WLC (FISH_WLC)
23	CSC_NMP22_PDD (NMP22_WLC)	CSC_WLC (CSC_WLC)	CSC_NMP22_PDD (NMP22_WLC)	CSC_WLC (CSC_WLC)
24	CSC_NMP22_PDD (CSC_WLC)	NMP22_WLC (NMP22_WLC)	CSC_NMP22_PDD (CSC_WLC)	NMP22_WLC (NMP22_WLC)
25	CSC_IMM_PDD (IMM_WLC)	CTL_PDD (CTL_WLC)	CSC_IMM_PDD (IMM_WLC)	CTL_PDD (CTL_WLC)
26	CSC_IMM_PDD (CSC_WLC)	CTL_WLC (CTL_WLC)	CSC_IMM_PDD (CSC_WLC)	CTL_WLC (CTL_WLC)

For true results correct diagnosis and higher value life-years are better, and for false results incorrect diagnosis and lower value costs are better.

TABLE 59 *Ranking by diagnostic performance and life-year and cost*

Ranking	Correct diagnosis	Incorrect diagnosis	Life-years	Cost
1	CTL_WLC (CTL_WLC)	CTL_WLC (CTL_WLC)	CSC_IMM_PDD (CSC_WLC)	CTL_WLC (CTL_WLC)
2	CTL_PDD (CTL_WLC)	CTL_PDD (CTL_WLC)	CSC_IMM_PDD (IMM_WLC)	CTL_PDD (CTL_WLC)
3	FISH_WLC (FISH_WLC)	FISH_WLC (FISH_WLC)	CSC_FISH_PDD (CSC_WLC)	FISH_WLC (FISH_WLC)
4	FISH_PDD (FISH_WLC)	FISH_PDD (FISH_WLC)	CSC_FISH_PDD (FISH_WLC)	FISH_PDD (FISH_WLC)
5	NMP22_WLC (NMP22_WLC)	NMP22_WLC (NMP22_WLC)	CSC_NMP22_PDD (NMP22_WLC)	NMP22_WLC (NMP22_WLC)
6	IMM_WLC (IMM_WLC)	IMM_WLC (IMM_WLC)	CSC_NMP22_PDD (CSC_WLC)	NMP22_PDD (NMP22_WLC)
7	CSC_WLC (CSC_WLC)	CSC_WLC (CSC_WLC)	IMM_PDD (IMM_WLC)	IMM_WLC (IMM_WLC)
8	CSC_CTL_WLC (CSC_WLC)	CSC_CTL_WLC (CSC_WLC)	CSC_CTL_PDD (CTL_WLC)	IMM_PDD (IMM_WLC)
9	CSC_CTL_WLC (CTL_WLC)	CSC_CTL_WLC (CTL_WLC)	CSC_CTL_PDD (CSC_WLC)	CSC_CTL_WLC (CTL_WLC)
10	NMP22_PDD (NMP22_WLC)	NMP22_PDD (NMP22_WLC)	FISH_PDD (FISH_WLC)	CSC_FISH_WLC (FISH_WLC)
11	IMM_PDD (IMM_WLC)	IMM_PDD (IMM_WLC)	CSC_IMM_WLC (IMM_WLC)	CSC_NMP22_WLC (NMP22_WLC)
12	CSC_FISH_WLC (FISH_WLC)	CSC_FISH_WLC (FISH_WLC)	CSC_IMM_WLC (CSC_WLC)	CSC_CTL_PDD (CTL_WLC)
13	CSC_FISH_WLC (CSC_WLC)	CSC_FISH_WLC (CSC_WLC)	NMP22_PDD (NMP22_WLC)	CSC_WLC (CSC_WLC)
14	CSC_NMP22_WLC (NMP22_WLC)	CSC_NMP22_WLC (NMP22_WLC)	CSC_FISH_WLC (CSC_WLC)	CSC_IMM_WLC (IMM_WLC)
15	CSC_NMP22_WLC (CSC_WLC)	CSC_NMP22_WLC (CSC_WLC)	CSC_FISH_WLC (FISH_WLC)	CSC_CTL_WLC (CSC_WLC)
16	CSC_PDD (CSC_WLC)	CSC_PDD (CSC_WLC)	CSC_PDD (CSC_WLC)	CSC_FISH_WLC (CSC_WLC)
17	CSC_IMM_WLC (IMM_WLC)	CSC_IMM_WLC (IMM_WLC)	CSC_PDD (CSC_PDD)	CSC_FISH_PDD (FISH_WLC)
18	CSC_IMM_WLC (CSC_WLC)	CSC_IMM_WLC (CSC_WLC)	IMM_WLC (IMM_WLC)	CSC_NMP22_WLC (CSC_WLC)
19	CSC_CTL_PDD (CSC_WLC)	CSC_CTL_PDD (CSC_WLC)	CSC_NMP22_WLC (NMP22_WLC)	CSC_PDD (CSC_WLC)
20	CSC_CTL_PDD (CTL_WLC)	CSC_CTL_PDD (CTL_WLC)	CSC_NMP22_WLC (CSC_WLC)	CSC_IMM_WLC (CSC_WLC)
21	CSC_FISH_PDD (FISH_WLC)	CSC_FISH_PDD (FISH_WLC)	CSC_CTL_WLC (CTL_WLC)	CSC_NMP22_PDD (NMP22_WLC)
22	CSC_FISH_PDD (CSC_WLC)	CSC_FISH_PDD (CSC_WLC)	CSC_CTL_WLC (CSC_WLC)	CSC_CTL_PDD (CSC_WLC)
23	CSC_NMP22_PDD (NMP22_WLC)	CSC_NMP22_PDD (NMP22_WLC)	FISH_WLC (FISH_WLC)	CSC_IMM_PDD (IMM_WLC)
24	CSC_NMP22_PDD (CSC_WLC)	CSC_NMP22_PDD (CSC_WLC)	NMP22_WLC (NMP22_WLC)	CSC_FISH_PDD (CSC_WLC)
25	CSC_IMM_PDD (IMM_WLC)	CSC_IMM_PDD (IMM_WLC)	CSC_WLC (CSC_WLC)	CSC_NMP22_PDD (CSC_WLC)
26	CSC_IMM_PDD (CSC_WLC)	CSC_IMM_PDD (CSC_WLC)	CTL_PDD (CTL_WLC)	CSC_IMM_PDD (CSC_WLC)

Appendix 20

Cost-effectiveness acceptability curves for the eight strategies for changes in the incidence rate (base case = 5%)

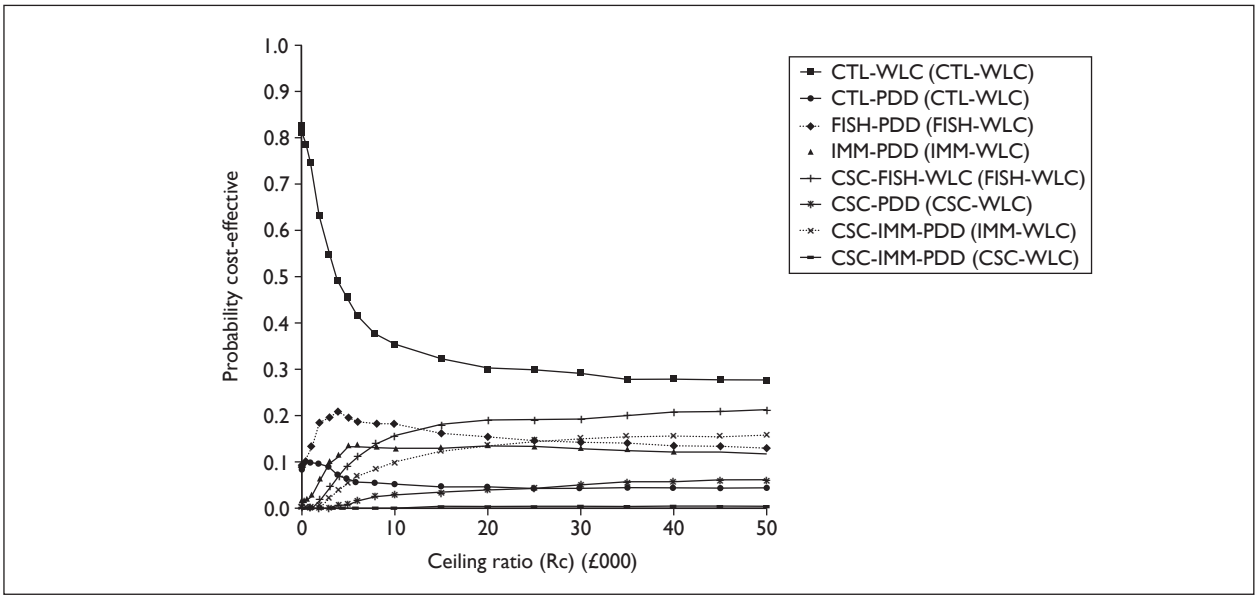


FIGURE 39 *Incidence rate is 1%.*

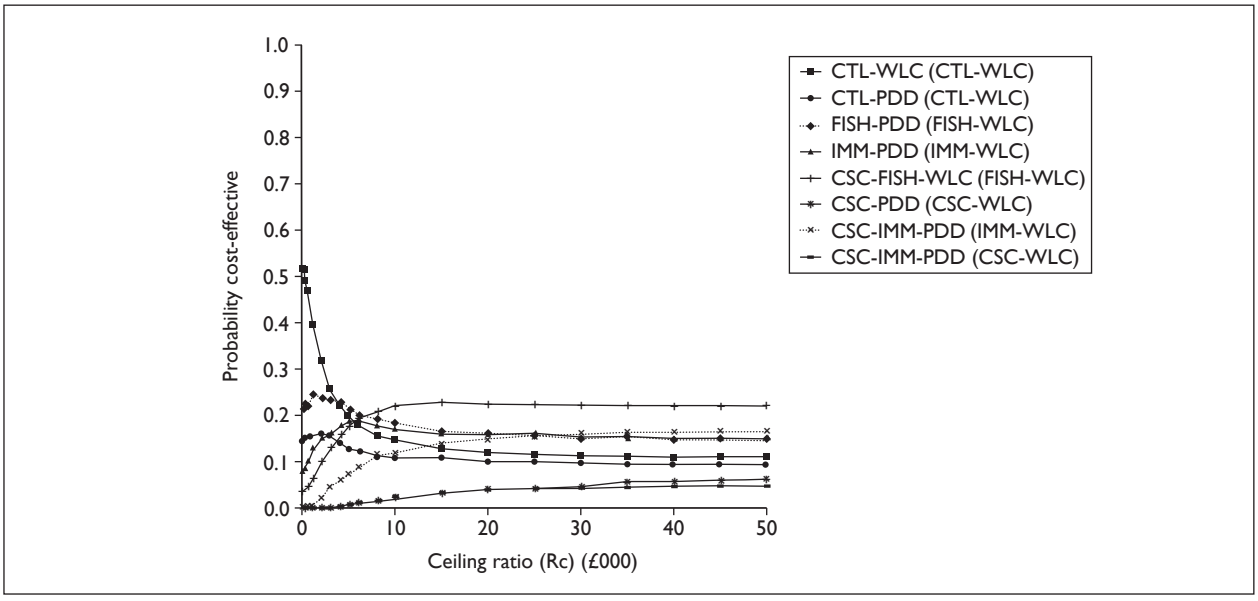


FIGURE 40 *Incidence rate is 10%.*

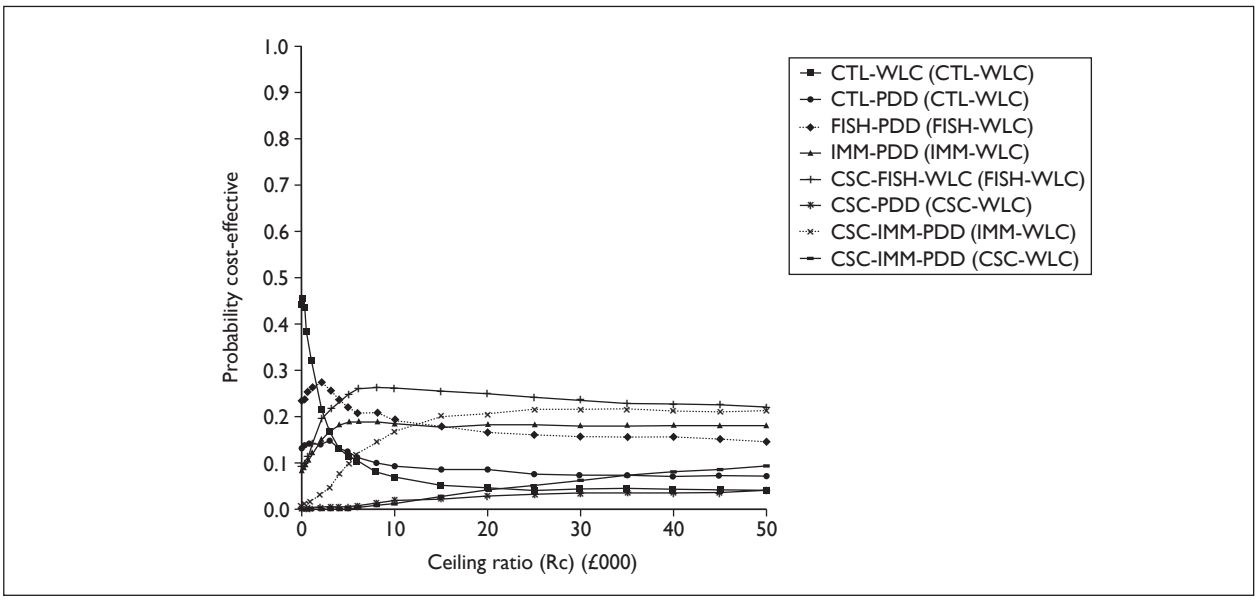


FIGURE 41 *Incidence rate is 20%.*

Appendix 21

Cost-effectiveness acceptability curves for changes to the performance of flexible cystoscopy (base-case flexible cystoscopy is the same as white light rigid cystoscopy)

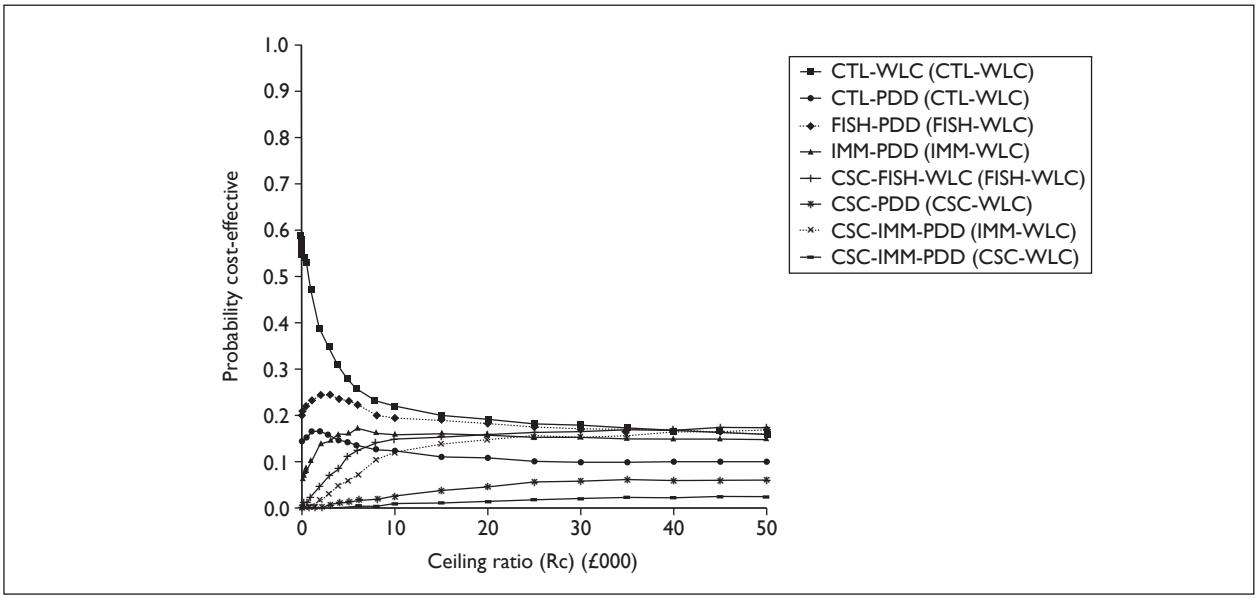


FIGURE 42 *Sensitivity and specificity of flexible cystoscopy are increased by 5% from base case.*

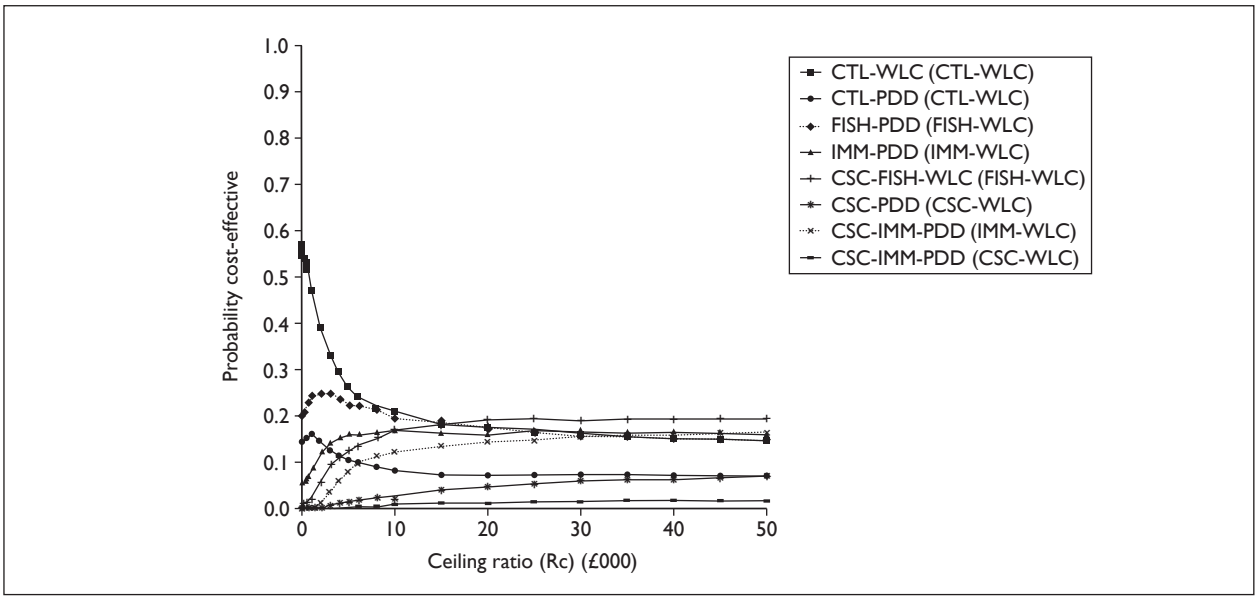


FIGURE 43 *Sensitivity and specificity of flexible cystoscopy are increased by 10% from base case.*

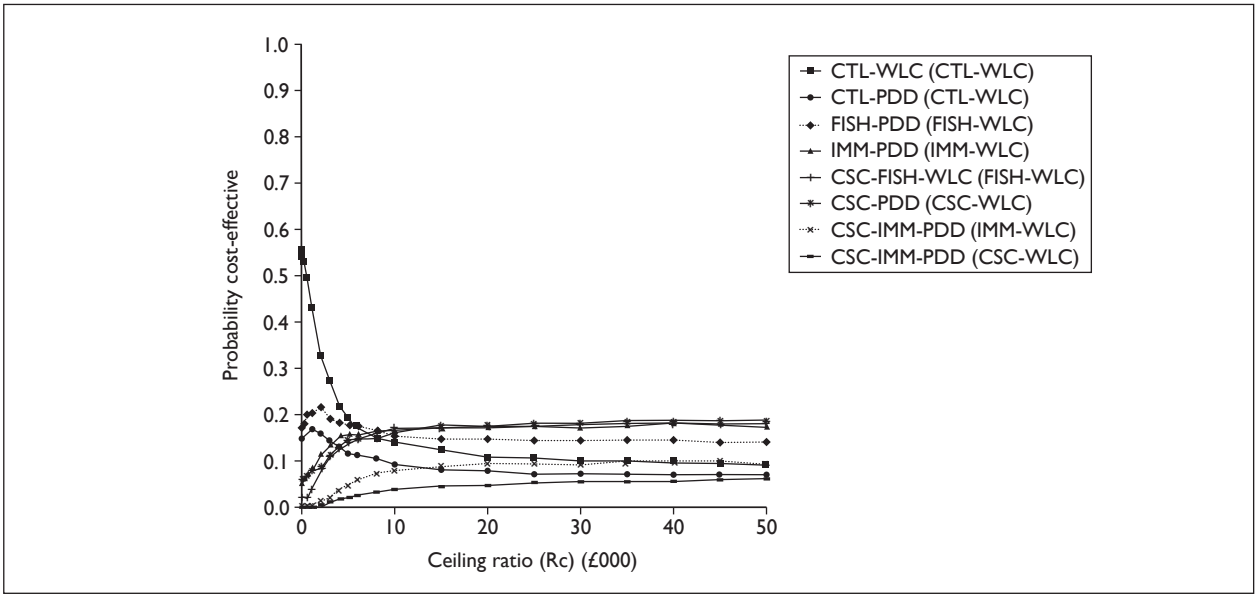


FIGURE 44 *Sensitivity and specificity of flexible cystoscopy are increased by 25% from base case.*

Appendix 22

Cost-effectiveness acceptability curves for changes to the relative risk (RR) of progression of bladder cancer for no treatment of bladder cancer compared with treatment of bladder cancer (base-case RR = 2.56)

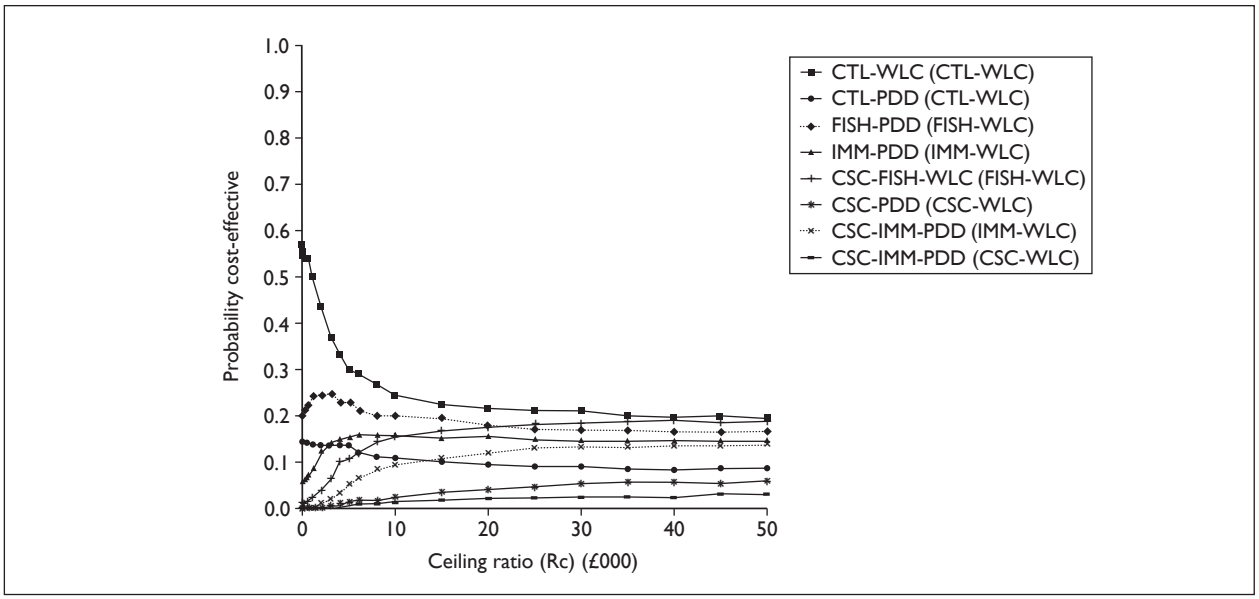


FIGURE 45 *The relative risk for progression comparing no treatment with treatment is decreased to 2.0.*

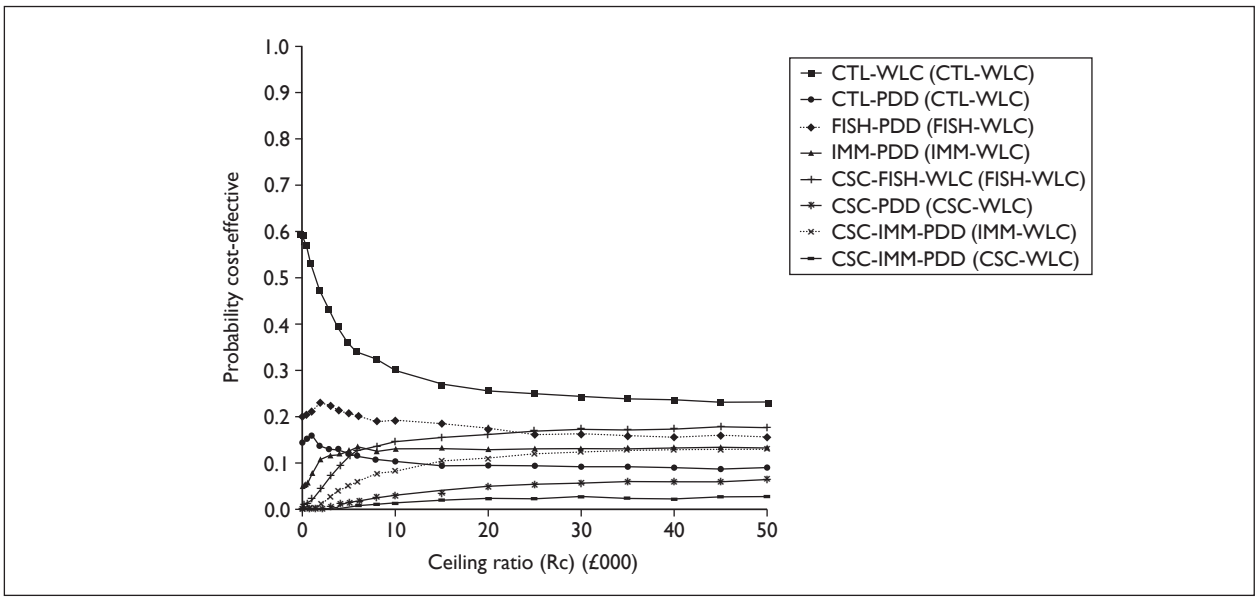


FIGURE 46 *The relative risk for progression comparing no treatment with treatment is decreased to 1.5.*

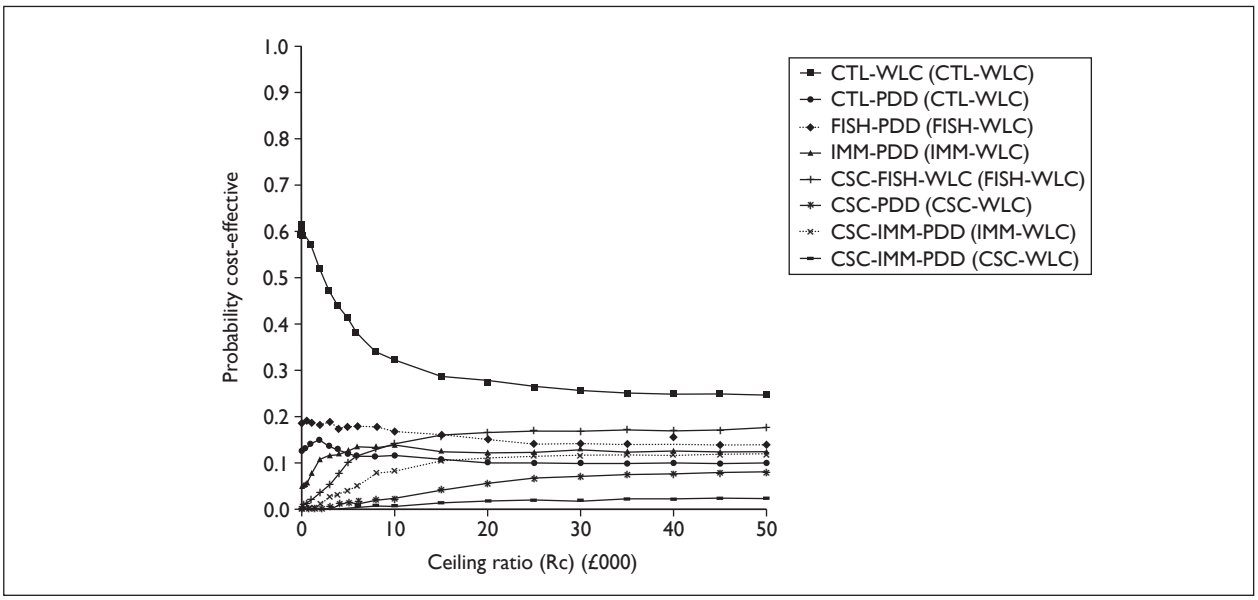


FIGURE 47 *The relative risk for progression comparing no treatment with treatment is decreased to 1.0.*

Appendix 23

Cost-effectiveness acceptability curves for the eight strategies for changes in the relative risk (RR) for recurrence comparing PDD with WLC (base-case RR = 1)

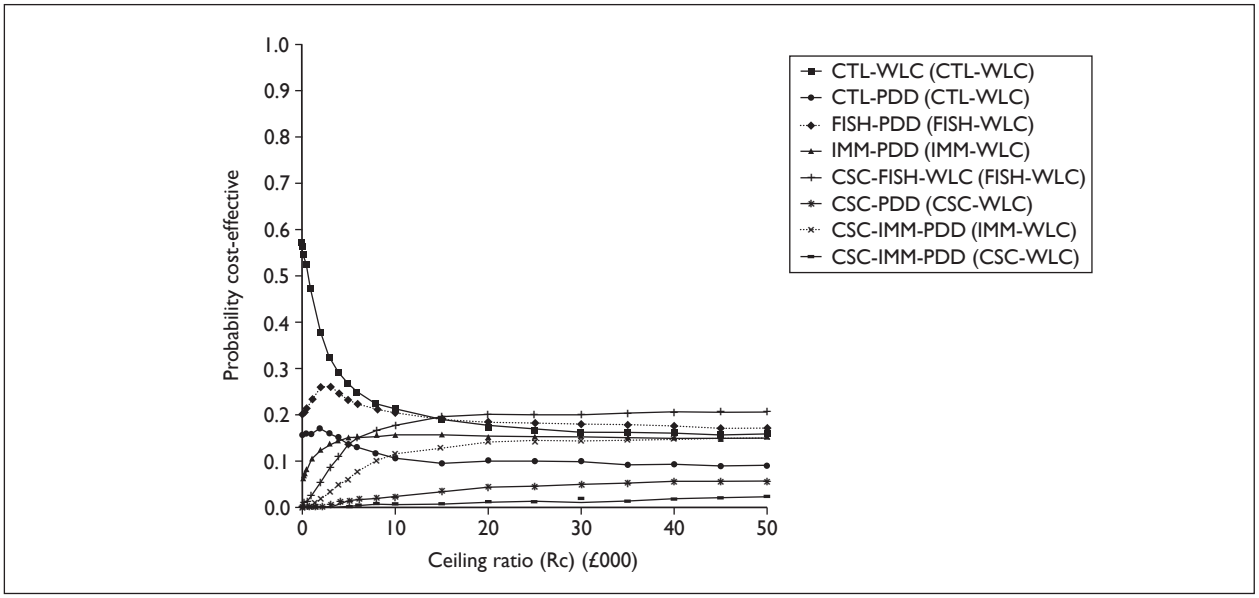


FIGURE 48 *The relative risk for recurrence for the comparison of PDD with WLC is 0.9.*

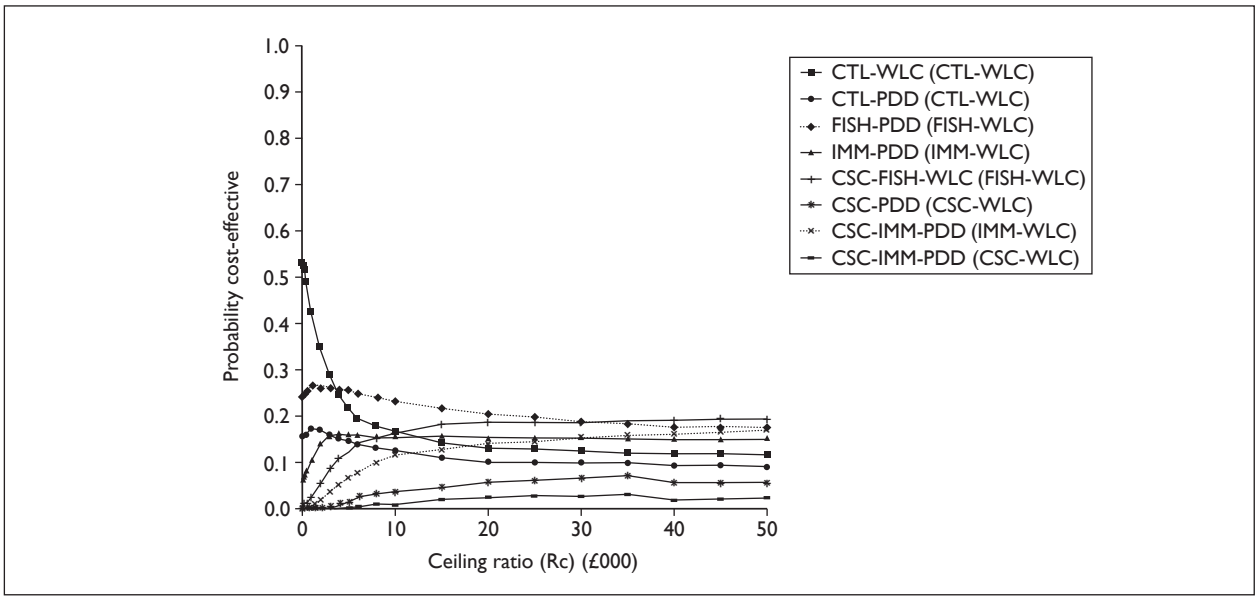


FIGURE 49 *The relative risk for recurrence for the comparison of PDD with WLC is 0.8.*

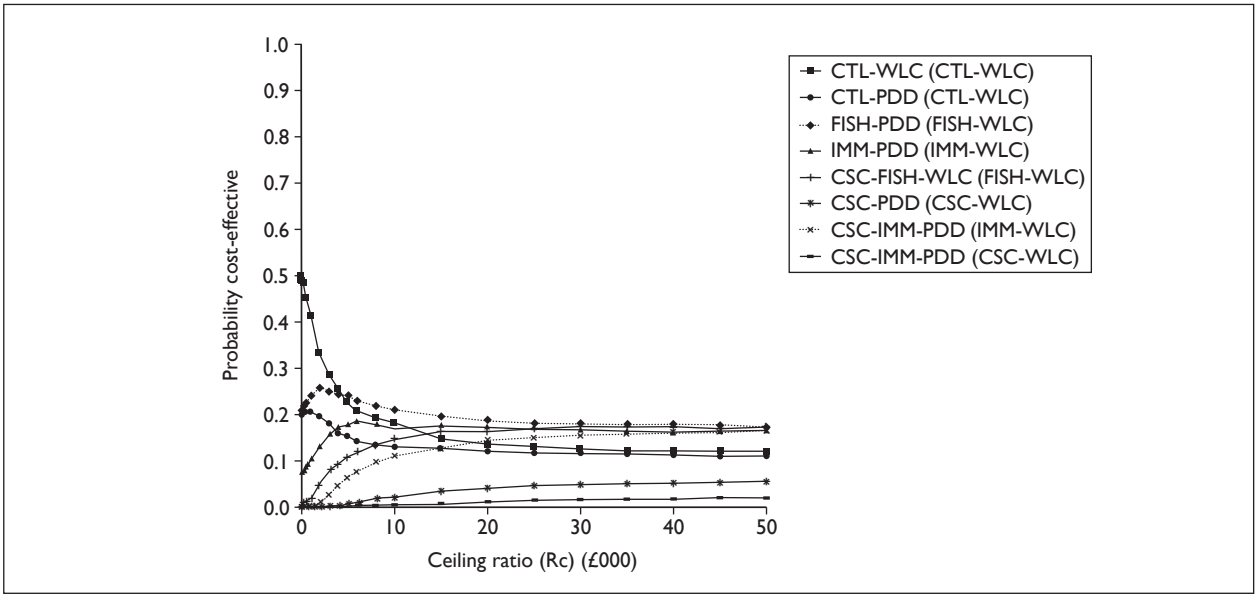


FIGURE 50 *The relative risk for recurrence for the comparison of PDD with WLC is 0.64.*

Appendix 24

Cost-effectiveness acceptability curves for the eight strategies for changes in the relative risk (RR) for progression comparing PDD with WLC (base-case RR = 1)

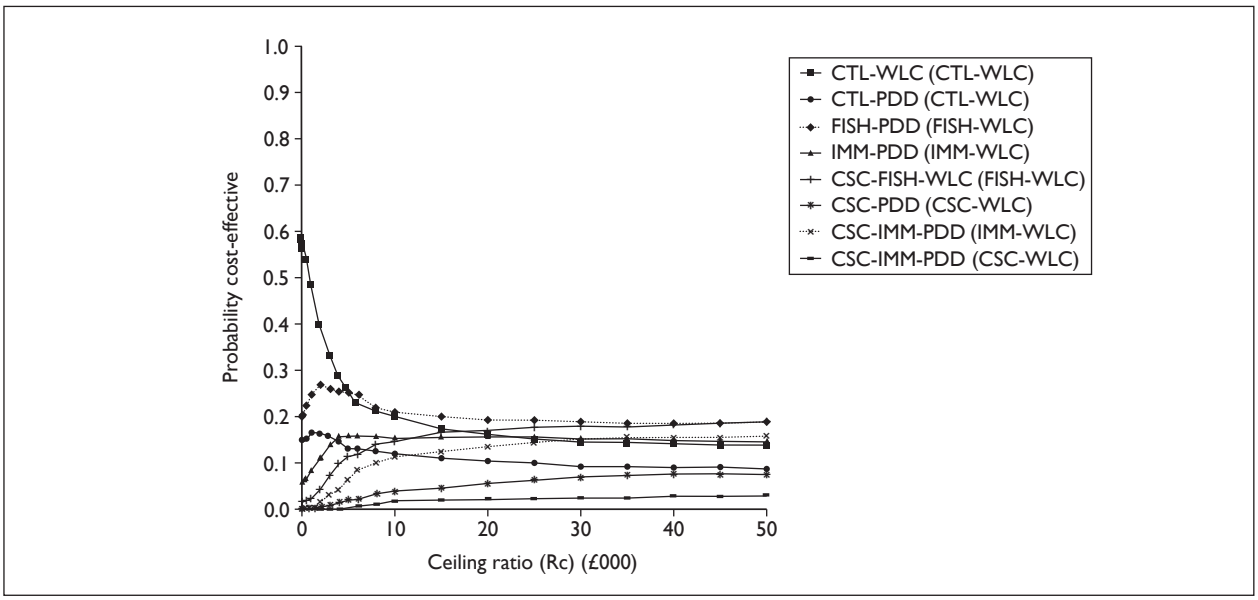


FIGURE 51 *The relative risk for progression for the comparison of PDD with WLC is 0.9.*

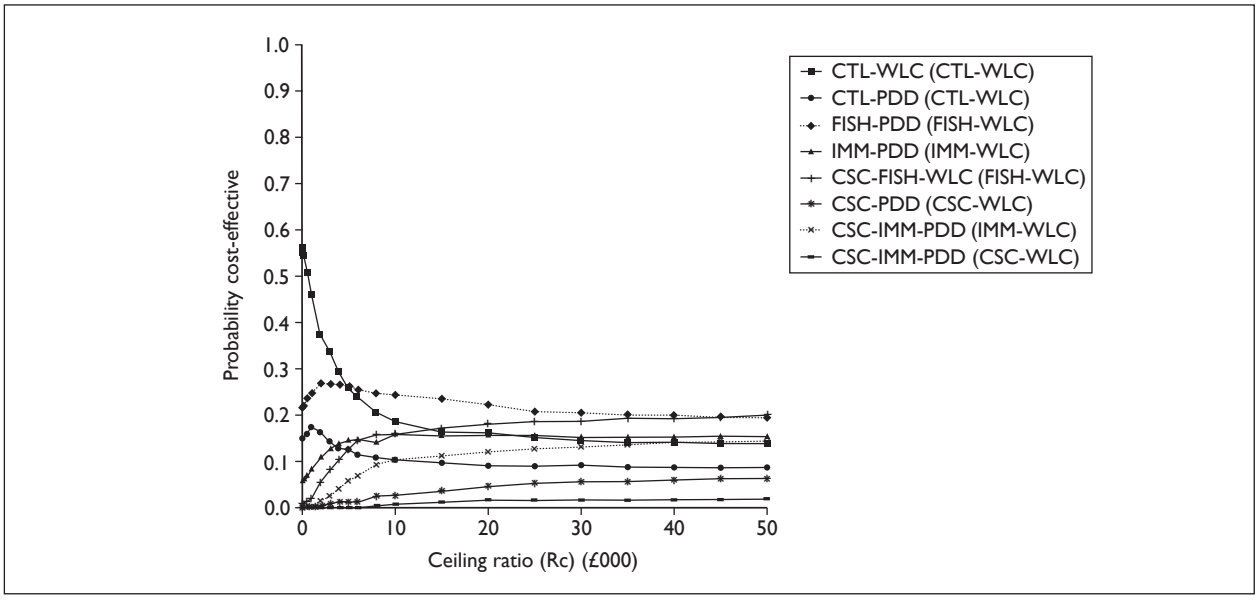


FIGURE 52 *The relative risk for progression for the comparison of PDD with WLC is 0.8.*

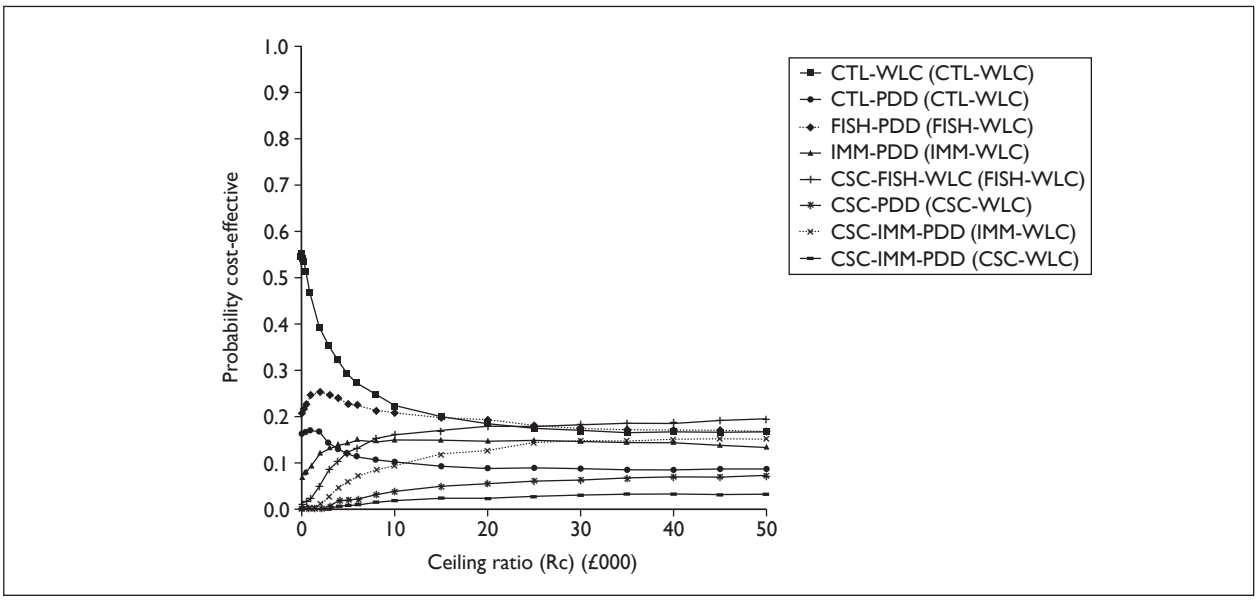


FIGURE 53 *The relative risk for progression for the comparison of PDD with WLC is 0.56.*

Appendix 25

Cost-effectiveness acceptability curves for the eight strategies for changes in the discount rate (base-case discount rate = 3.5%)

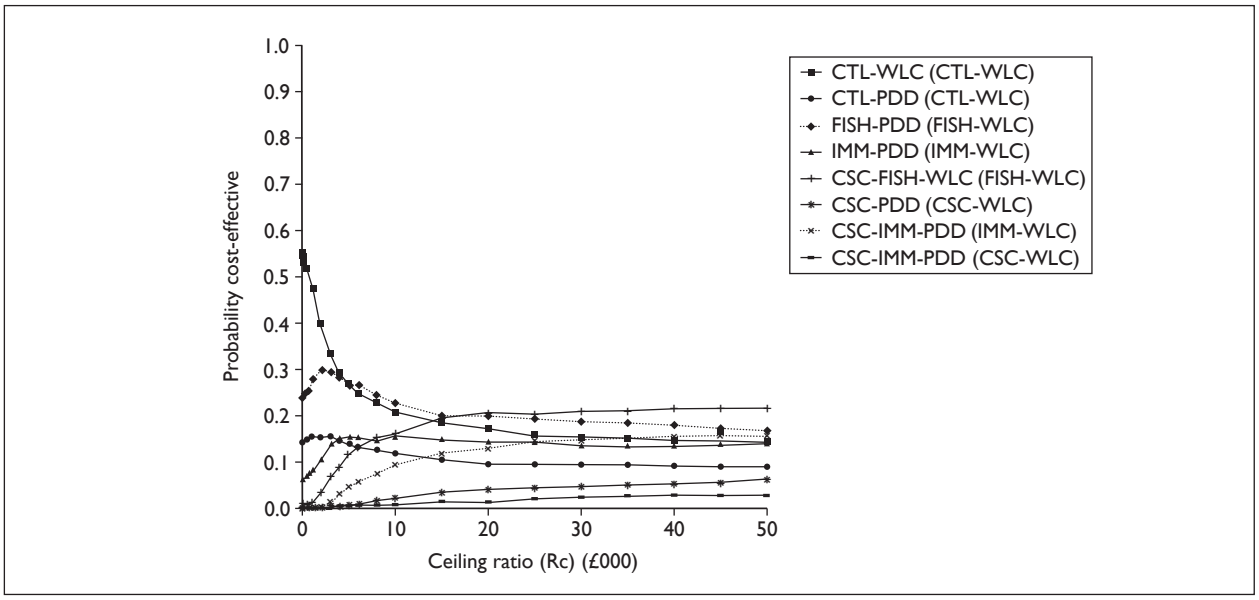


FIGURE 54 *The discount rate is 6%.*

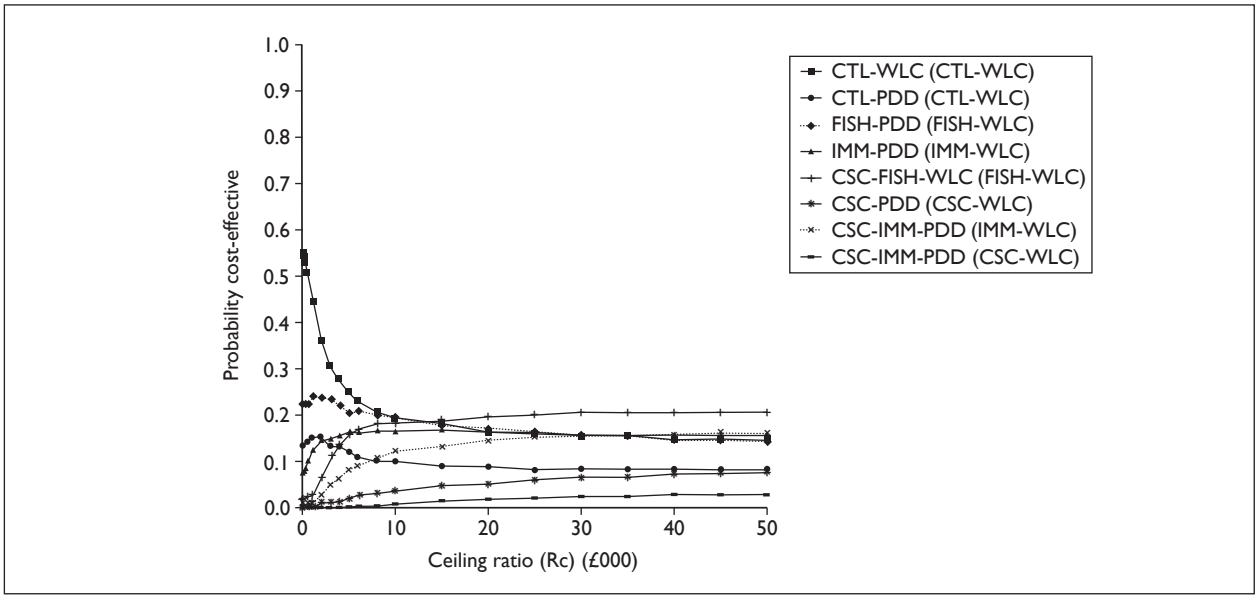


FIGURE 55 *The discount rate is 1%.*

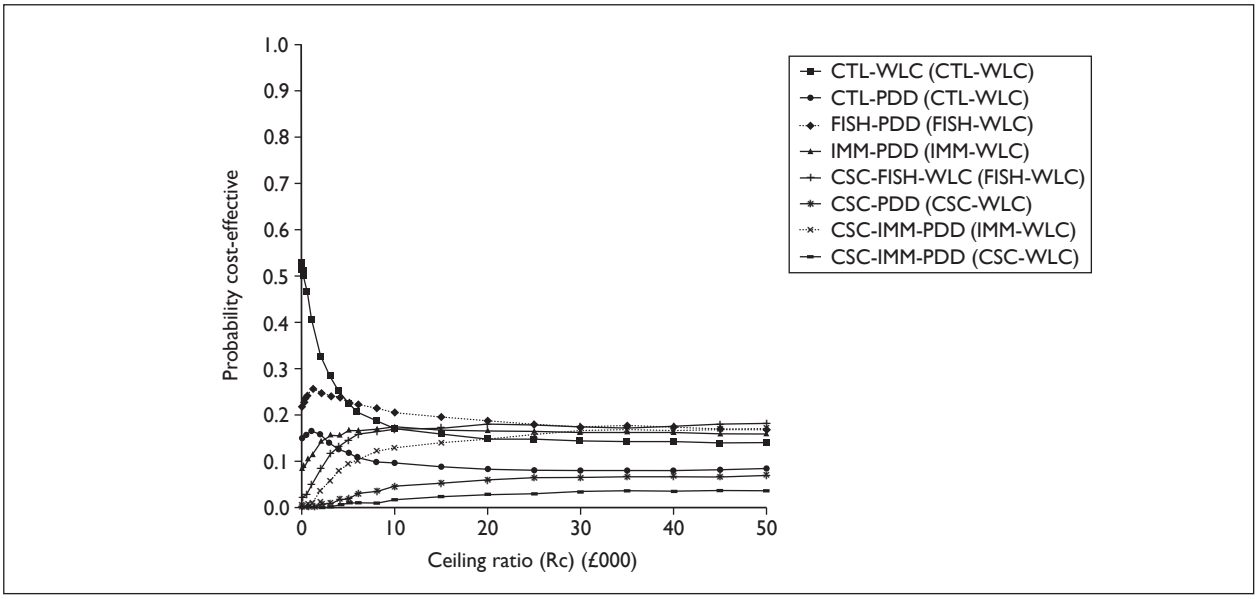


FIGURE 56 *The discount rate is 0%.*

Appendix 26

Cost-effectiveness acceptability curves for the eight strategies for changes in proportions in the risk groups for non-invasive disease (base case: proportion in low-risk group is 0.1 and proportion is high-risk group is 0.45)

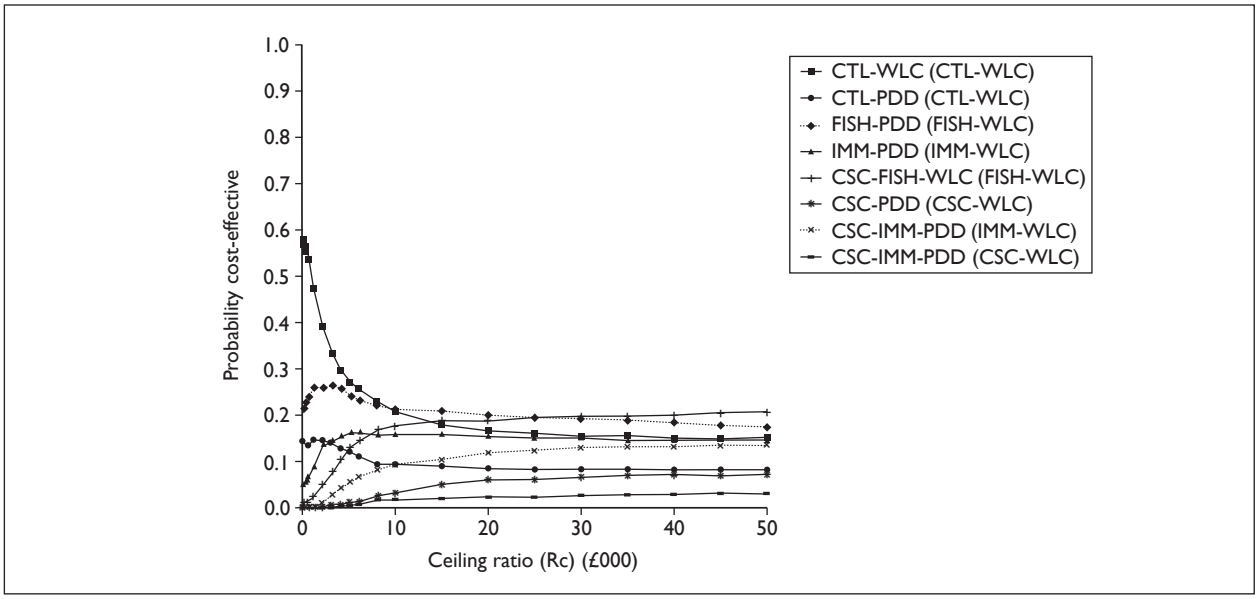


FIGURE 57 *Proportions in the high- and low-risk groups are 30%.*

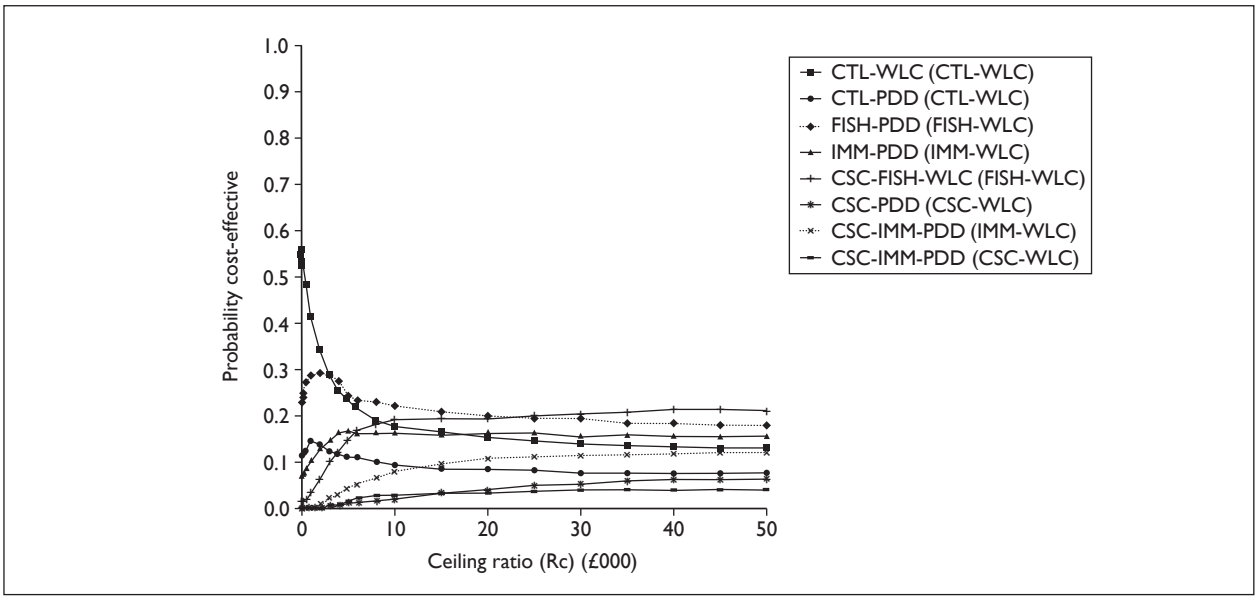


FIGURE 58 *Proportions in the high- and low-risk groups are 10% and 60% respectively.*

Appendix 27

Cost-effectiveness acceptability curves for the eight strategies for changes in the starting age and time horizon

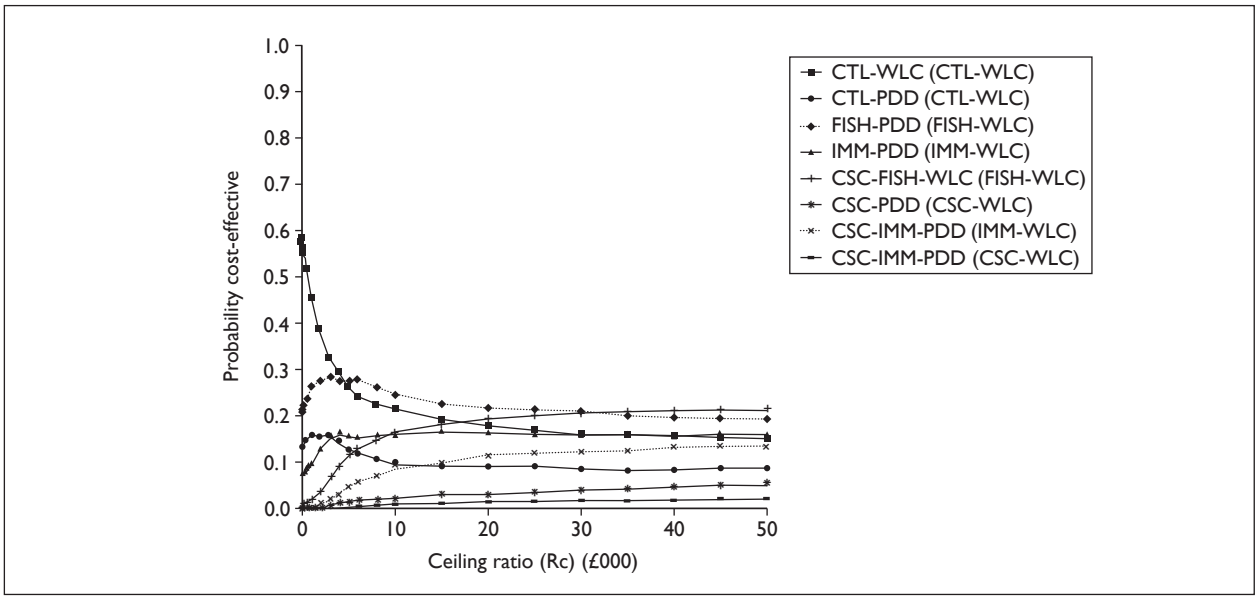


FIGURE 59 *Starting age is 57 years.*

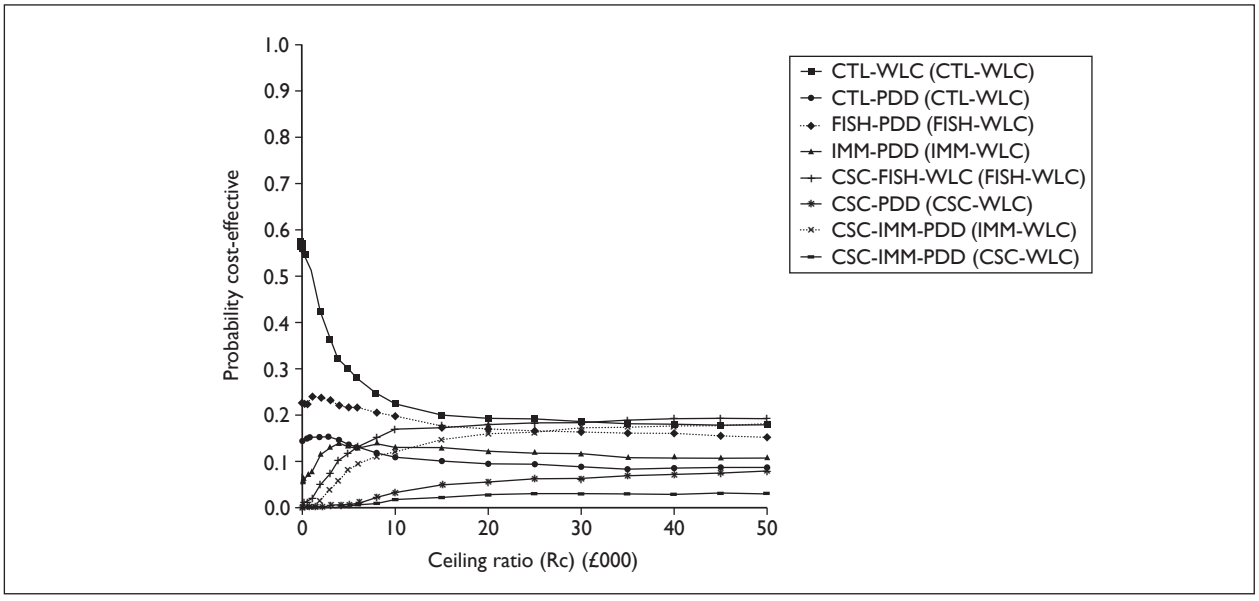


FIGURE 60 *Starting age is 77 years.*

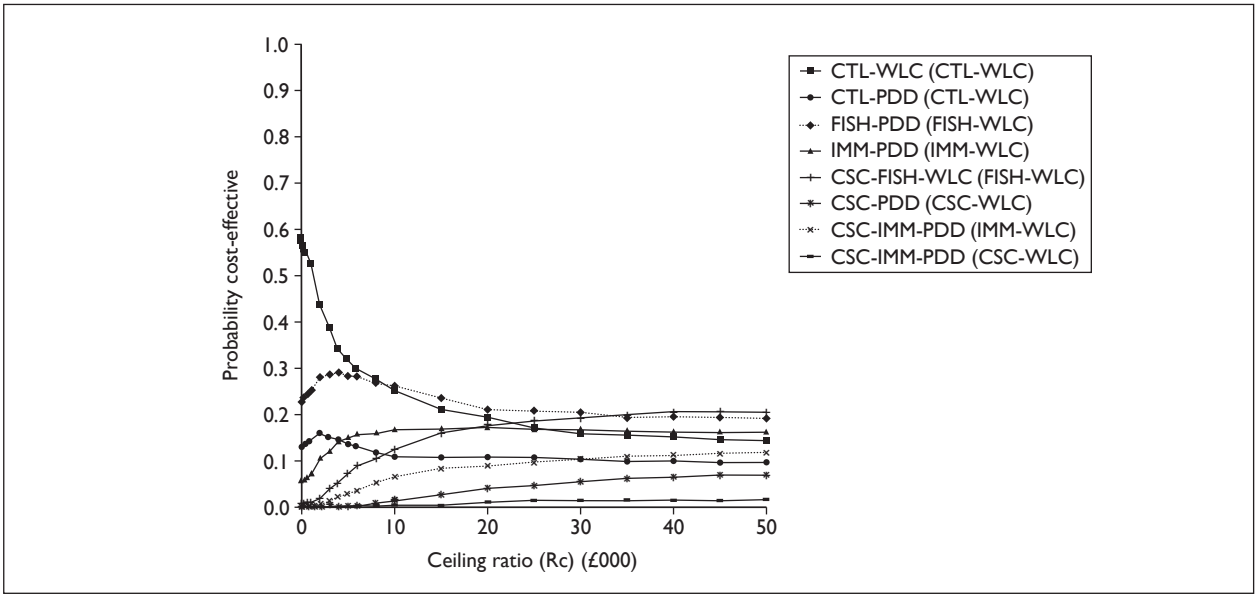
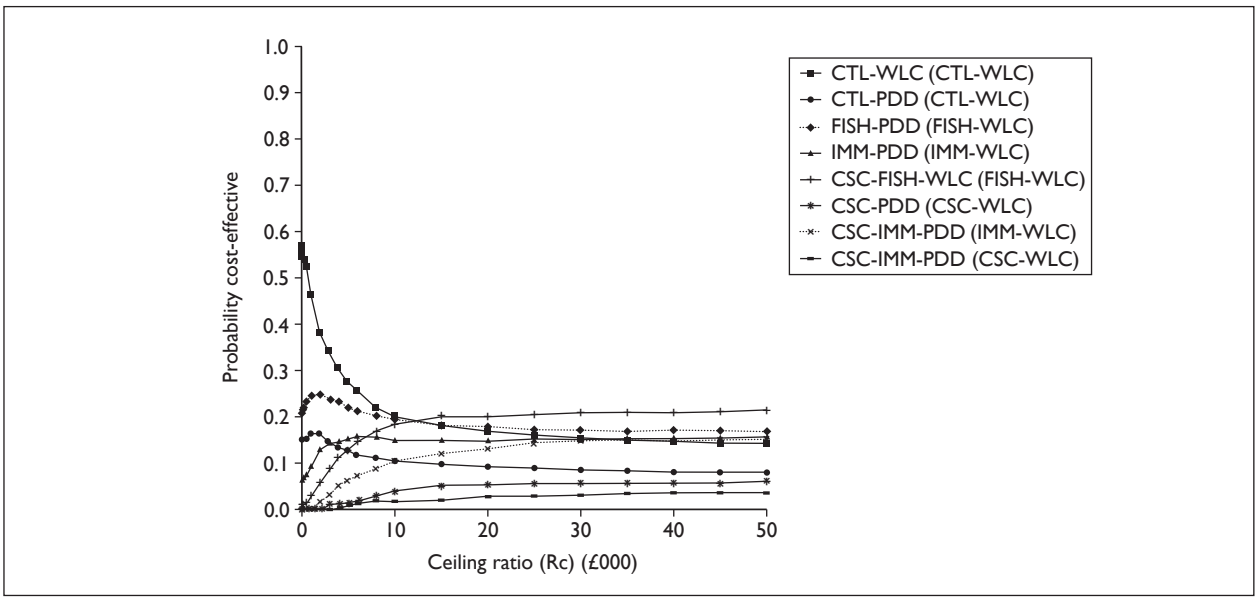


FIGURE 61 *Time horizon is 10 years.*

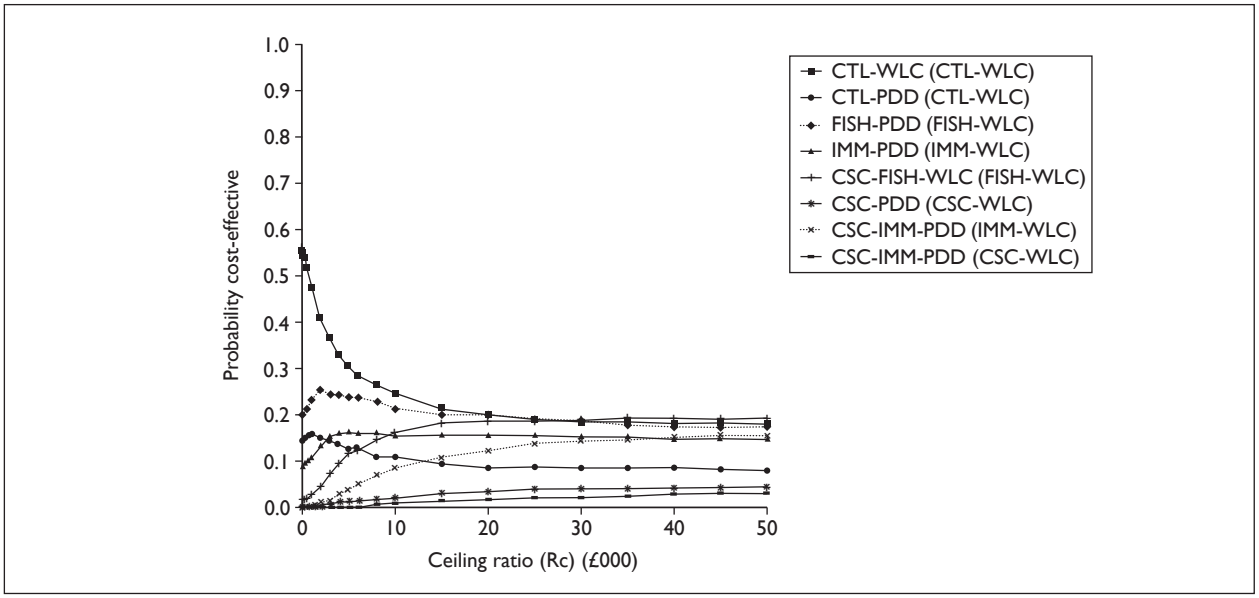
Appendix 28

Cost-effectiveness acceptability curves for the eight strategies when WLC is replaced by PDD in follow-up for each strategy



Appendix 29

Cost-effectiveness acceptability curves for the eight strategies when quality of life measures are incorporated to produce quality-adjusted life-years



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Health Technology Assessment programme

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The Correspondence Page on the HTA website (www.hta.ac.uk) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

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