Urinary Biomarkers in Bladder Cancer

Subjects: Oncology

Contributor: Manuel Castanheira de Oliveira , Hugo R. Caires , Maria J. Oliveira , Avelino Fraga , M. Helena Vasconcelos , Ricardo Ribeiro

Extracellular vesicles (EVs) are small membrane vesicles released by all cells and involved in intercellular communication. Importantly, EVs cargo includes nucleic acids, lipids, and proteins constantly transferred between different cell types, contributing to autocrine and paracrine signaling. In recent years, they have been shown to play vital roles, not only in normal biological functions, but also in pathological conditions, such as cancer. In the multistep process of cancer progression, EVs act at different levels, from stimulation of neoplastic transformation, proliferation, promotion of angiogenesis, migration, invasion, and formation of metastatic niches in distant organs, to immune escape and therapy resistance. Moreover, as products of their parental cells, reflecting their genetic signatures and phenotypes, EVs hold great promise as diagnostic and prognostic biomarkers. Importantly, their potential to overcome the current limitations or the present diagnostic procedures has created interest in bladder cancer (BCa). Indeed, cystoscopy is an invasive and costly technique, whereas cytology has poor sensitivity for early staged and low-grade disease. Several urine-based biomarkers for BCa were found to overcome these limitations.

extracellular vesicles   microvesicles   bladder cancer   urothelial cancer   biomarkers

liquid biopsy

1. Introduction: Bladder Cancer and Disease Management

Urological tumors represent approximately 25% of all human cancers [1]. Bladder cancer (BCa) is the 10th most common, and the 9th cause of death by malignancy worldwide [2]. Aging, ethnicity, and male gender are considered non-modifiable risk factors [2][3][4], but most tumors are derived from acquired environmental exposure to carcinogenic substances. Cigarette smoking is considered the main risk factor [5][6], with an estimated causal association for half of BCa in both genders [7][8][9], whereas occupational exposure accounts for 10–20% of all cases [10]. The worldwide incidence of BCa seems to reflect areas with higher exposure to risk factors [10], which explains why developed countries have a larger number of diagnosed cases [10]. As an example, *Schistosoma haematobium* infection, another known risk factor, is more prevalent in northern and sub-Saharan African countries, where there is a relatively higher incidence of BCa [10]. In addition, differences in healthcare systems also account for disparity of incidence rates, being better resources associated to an easier and faster diagnosis.

Urothelial cancer originates in the epithelial cells of the urothelium, extending from the renal pelvis to the urethra [11][12][13]. The majority of these tumors are located in the bladder, accounting for 90–95% of cases, while 5–10%

are located in the upper urinary tract (UUT) [14][15][16][17][18]. Tumor extension is classified according to the TNM (Tumor-Node-Metastasis) staging system. At diagnosis, approximately 75–80% of bladder tumors are non-muscle invasive (NMIBC), which includes mucosa (for stages Ta and Cis) and lamina propria (T1 stage) confined disease, while 20–25% are muscle-invasive (MIBC), when invading the muscle layer and beyond (T2–T4 stages) [1,4,14].

Although clinical presentation may be suggestive, the gold standard diagnostic procedures are cystoscopy and urinary cytology [19][20][21][22][23][24]. Nevertheless, cystoscopy is an invasive, operator-dependent procedure, with low sensitivity for small papillary or Cis tumors, which, if underdiagnosed and untreated, progress to muscle-invasive disease in approximately half of the patients [19][20][21][22][23][24]. The sensitivity and specificity of white light cystoscopy is 71% (95% CI: 0.49–0.93%) and 72% (95% CI: 47–96%), respectively [24]. However, due to its invasiveness, it is frequently associated with side effects such as dysuria (50%), hematuria (19%), or urinary tract infection (3%) [25][26].

As for urinary cytology, it has high diagnostic accuracy for high grade lesions and Cis, with a sensitivity of 80–90% and specificity between 98% and 100% [27]. However, it exhibits low sensitivity for low grade lesions, between 4% and 31% [28][29][30][31][32][33], and high rate of false positives, due to benign or inflammatory conditions produced by chemo or radiation therapy[34] [35]. To overcome these limitations, several urinary biomarkers were developed and are currently commercially available. Compared to cytology, they have higher sensitivity but lower specificity and are, unfortunately, less useful in low risk BCa [36][37][38]. Therefore, consensus among the different international societies on these biomarkers still do not recommend them as replacements of cytology in the current clinical practice [36][37][38].

The standard therapy for NMIBC is trans-urethral resection of the bladder (TURB), with both diagnostic and therapeutic purposes, complemented or not by intravesical adjuvant treatment [39][40]. However, even after complete endoscopic resection, there is a high recurrence rate, around 50–70%, and 10–30% will progress to MIBC [39][40]. This feature of BCa natural history elicits the need for a regular follow-up with cystoscopy and cytology at every 3 months interval, generally accompanied by repeated treatments due to recurrence, and which frequently result in high morbidity and economic burden [41][42].

Driven by the invasiveness and morbidity of cystoscopy, the lack of acceptable sensitivity of urinary cytology and of specificity of the commercially available urinary diagnostic biomarkers, urge the need for extensive research on the identification of novel and more effective biomarkers, to implement better tools for diagnosis, follow-up, and screening of at risk populations [42][43][44].

Extracellular vesicles (EVs) are small membrane vesicles which have emerged as a source of biomarkers in bladder cancer [45]. Their detection in liquid biopsies is feasible, due to their presence and stability in most human fluids, and may serve as biomarkers in bladder cancer early detection as they present similar cargo to their donor cancer cells [46]. Additionally, they have some advantages as a source of biomarkers since they are more abundant in liquid biopsies compared to circulating tumor cells (CTCs), protect their cargo against degradation and may carry molecular signatures associated with specific phenotypes [47][48][49]. The present review focus on the status of

urinary biomarkers in diagnosis and follow-up of bladder cancer, pinpointing the emerging potential role of urinary EVs on bladder cancer diagnosis and management.

2. Liquid Biopsy as a Source of Biomarkers for Bladder Cancer

The ideal biomarker would be cost-effective, objective, fast to process, and easy to interpret, with high sensitivity and specificity [50][51][52][53][54]. For urothelial cancer biomarkers, four goals have been proposed to be accomplished: (i) reduce the need for frequent invasive procedures; (ii) exclude recurrence; (iii) detect progression towards invasive disease; (iv) predict effective treatment response [43][44]. The close contact with urothelium makes urine an attractive approach to detect the presence of tumor cells, in a minimally invasive way. Importantly, this liquid biopsy approach would allow multiple longitudinal sampling of the tumor to identify presence of malignancy, grade, and genomic landscape for improved clinical follow-up. [53][54].

Following this line of thought, previous research for BCa biomarkers has been conducted using mostly proteins, nucleic acids, inflammatory and metabolite markers, within the concept of liquid biopsies [55][56]. Taking into consideration that such biopsies concern the detection of any kind of molecular or cellular biomarkers in patient bodily fluids (including urine, blood, saliva, pleural, peritoneal, or cerebrospinal fluids), a novel biomarkers array emerged. These include circulating tumor cells (CTCs), proteins, metabolites, circulating nucleic acids, namely cell-free tumor DNA (ctDNA), messenger RNA (mRNA), micro RNA (miRNA), or long non-coding RNA (lncRNA). Most of these biomarkers may be found free or within extracellular vesicles (EVs) shed by tumor cells or by other elements of the tumor microenvironment [56,57] (Figure 1). There is a growing interest on the liquid biopsy concept, since (i) the biomarkers found have extensive potential for diagnosis and monitoring of disease stage and recurrence; (ii) prediction of therapeutic response/resistance and disease prognosis, with minimally invasive procedures, and (iii) helping therapeutic clinical reasoning based on identified molecular changes [56][57][58].

Figure 1. Urine biomarkers for bladder cancer (BCa) diagnosis and follow up. Illustration of the distinct available approaches for the detection of urothelial cancer cells in patients' urine. The close interaction between the bladder tumor and the urine makes this body fluid a reliable source of cancer biomarkers. A plethora of non-invasive assays exploring distinct analytes (exfoliated tumor cells; proteins; genes; metabolites and extracellular vesicles) in patients' urine allows the longitudinal analysis of tumor progression. Some of the commercially-available tests includes FDA-approved (UroVysion™: aneuploidy of chromosomes 3; 7; 17 and the loss of 9p21 by FISH; ImmunoCyt™/uCyt+™ test: detection of carcinoembrionary antigen (CEA) and mucins by immunohistochemistry (IHC); bladder tumor antigen (BTA) TRAK/BTA Stat and NMP22 BC test kit); non-FDA approved (CxBladder™: IGFBP5, HOXA13, MDK, CDK1 and CXCR2 by RT-qPCR; Assure MDx™: FGFR3, TERT and HRAS (mutations), OTX1, ONECUT2 and TWIST1 (methylation); XPert Bladder Cancer Monitor™: UPK1B, IGF2, CRH, ANXA10 and ABL1 by RT-qPCR; and UBC™: cytokeratins 8 and 18 by ELISA) and the emerging extracellular vesicles (EV)-based biomarkers (not commercialized yet).

2.1. Commercially Available Urine Biomarkers in Bladder Cancer

Several interesting and promising biomarkers have been under clinical scrutiny during the past years, although only those approved by in vitro diagnostics (IVD) regulatory entities (e.g., FDA) became commercially available biomarkers, to be used as adjuncts to cystoscopy in primary diagnosis and follow-up of BCa. Taking into consideration the various reports on the subject, novel urinary biomarkers contributed to higher sensitivity but lower specificity than cytology, leaving them out of international guidelines recommendations [59][60][61][62]. Table 1 provides an overview of the biomarkers approved for clinical use and their reported diagnostic accuracy.

Table 1. Urine-based tests to aid bladder cancer clinical reasoning.[63][64][65][66][67][68][69][70][71][72][73][74][75][76][77][78]

Test	Sample	Biomarker	Assay	Purpose	Sensitivity	Specificity	References
BTA TRAK®	Protein	Complement factor H-related	CIA	Follow-Up	0.64 (0.58–0.69)	0.77 (0.73–0.81)	[63–65]
BTA Stat ®	Protein	Complement factor H-related	SIA	Follow-Up	0.65 (0.54–0.75)	0.74 (0.64–0.82)	[64–66]
NMP22 BC test®	Protein	NMP-22	SIA	Follow-Up	0.69 (0.62–0.75)	0.77 (0.70–0.83)	[67,68]
NMP22 BladderChek test®	Protein	NMP-22	SIA	Diagnosis	0.47 (0.33–0.61)	0.93 (0.81–0.97)	[67–69]
				Follow-Up	0.70 (0.40–0.89)	0.83 (0.75–0.89)	[67–69]
ImmunoCyt/uCyt+™	Sediment	Tumor associated cellular antigens	IF cytology	Diagnosis	0.85 (0.78–0.90)	0.83 (0.77–0.87)	[64,65,70]

		(M344; LDQ10; 19A11)		Follow-Up	0.75 (0.64–0.83)	0.76 (0.70–0.81)	[64,65,70]
UroVysion™	Sediment	Aneuploidy for chromosomes 3; 7; 17; and loss of 9p21 locus	FISH	Diagnosis	0.73 (0.50–0.88)	0.95 (0.87–0.98)	[71–73]
				Follow-Up	0.55 (0.36–0.72)	0.80 (0.66–0.89)	[71–73]
CxBladder Detect®	mRNA	IGFBP5; HOXA13; MDK; CDK1; CXCR2	RT-qPCR	Diagnosis	0.74 (0.65–0.81)	0.82 (0.79–0.84)	[74]
CxBladder Monitor®	mRNA	IGFBP5; HOXA13; MDK; CDK1; CXCR2	RT-qPCR	Follow-Up	0.91 (0.88–0.99)	0.96 (NPV)	[75]
AssureMDx™	DNA	FGFR3; TERT; HRAS; OTX1; ONECUT2; TWIST1	DNA methylat	Diagnosis	0.93	0.86	[76]
Xpert® Bladder Cancer	mRNA	UPK1B; IGF2; CRH; ANXA10; ABL1	RT-qPCR	Follow-Up	0.84 (0.69–0.93)	0.91 (0.83–0.96)	[77]
UBC®	Protein	Cytokeratin 8 and 18	SIA	Diagnosis	0.61–0;65	0.77–0.82	[78]

fragments

Abbreviations: BTA; bladder tumor antigen; CIA; colorimetric immunoassay; IF; immunofluorescence; NMP; nuclear matrix protein; UBC; urinary bladder cancer antigen; FISH; fluorescence in situ hybridization; RT-qPCR; reverse transcription-quantitative polymerase chain reaction; SIA; sandwich immunoassay

2.1.1. FDA-Approved Urine Biomarkers

The bladder tumor antigen (BTA) is a complement factor H related protein secreted by malignant cells, which confers them survival advantage, as it interferes in the complement cascade [79]. There are two approved versions of this test for BCa follow-up in concurrent use with cystoscopy, the BTA TRAK and the BTA Stat (Polymedco Inc., Cortlandt Manor, New York, USA) . In different reviews and meta-analysis, the BTA Stat has a sensitivity and specificity of 64% and 77%, respectively, whereas the BTA Trak has 65% and 74%, respectively. The sensitivity was higher in the diagnosis of symptomatic patients rather than in follow-up, but with similar specificity. Both tests demonstrated higher sensitivity than urinary cytology, despite the decreased specificity in conditions where the complement factor H related protein is present, such as in other genitourinary malignancies and benign conditions with hematuria, including lithiasis, inflammation, instrumentation, and intra-vesical therapies.[80]

The nuclear matrix has an important role on DNA replication and RNA transcription and splicing [81], with nuclear matrix proteins (NMP) being essential components of mitosis, with a role in tumoral proliferation. Numerous NMPs have been described in solid tumors, although NMP22 was shown to be specific for BCa [81][82]. It is released from apoptotic cells towards urine, with significantly higher release rate in cancer than in normal cells [83][84]. The NMP22 BC test kit (Matritech Inc.; Newton, MA, USA) is a quantitative test used for patient follow-up, whereas the NMP22 BladderChek test® (Matritech Inc.; Newton, MA, USA) is qualitative and used for both follow-up and initial diagnosis, in symptomatic patients [85][86][87]. Concerning sensitivity and specificity, the quantitative test has 69% and 77%, while the qualitative has 58% and 88%, respectively [88][89]. When compared to urinary cytology, the sensitivity of NMP22 was higher (70% versus 40%), albeit specificity was lower (81% versus 97%) [28]. Taken together, both NMP22 and cytology, resulted in sensitivity of 91% [89]. Notably, Grossman et al. studied approximately 2000 patients, to compare NMP22 Bladder Chek test® with cystoscopy, and observed decreased NMP22 sensitivity (50–56%) in comparison to cystoscopy (89–91%), although diagnostic accuracy was 94–99% if both tests were considered together [90]. Although NMP22 has higher sensitivity than urinary cytology, specificity is too low to replace it. The fact that it is released from apoptotic cells, which might also be seen in benign conditions, is responsible for the relatively high false positive rate [91]. However, if combined with cistoscopy, this significantly increases its diagnostic value.

The ImmunoCyt™/uCyt+™ test (Diagnocure Inc, Quebec, Canada) combines cytology with monoclonal antibody immunofluorescence labelling to detect three BCa antigens, M344, LDQ10, and 19A11, specifically found in malignant exfoliated urothelial cells [92]. To be positive, it requires many exfoliated cells (>500 per field). This test is expensive, with inter-observer variation and time-consuming analysis, but less prone to be influenced by benign

inflammatory conditions, comparatively to other tests [93][94]. It is recommended in BCa patients only for follow-up as adjunct test to urinary cytology [95]. Sensitivity varies between 83% and 85% and specificity between 75% and 87%. These are higher in primary diagnosis than follow-up . Mowatt et al. compared uCyt+™ with urinary cytology and showed that this test presented higher sensitivity (82% versus 44%) and lower specificity (85% versus 94%), respectively. Interestingly, the simultaneous use of both tests improved sensitivity without impacting on specificity (87% and 68%, respectively). Sensitivity and specificity, in the study of Schmitz-Dräger et al. [96], was 85% and 88% for immunocytology and 84% and 98% for cystoscopy. When combined, sensitivity increased to 100%, whereas specificity decreased to 87%. Although less prone to interference, immunoCyt™ has lower specificity than urinary cytology. Likewise, despite combination with cystoscopy increases sensitivity, the false positive rate remains elevated [96]. Pfister et al. [97] assert that due to its good sensitivity, the combined use of uCyt+™ with cytology might delay the time intervals between cystoscopies, particularly in lower risk patients. Currently, this test was approved only for patient follow-up .

UroVysion (Abbott Laboratories, Abbott Park, Illinois, USA) is a fluorescence in situ hybridization (FISH) probe set to detect bladder cancer cells [98]. It uses fluorescent labelled DNA probes to assess genetic changes in exfoliated cells, namely chromosomal aberrations suggestive of BCa, aneuploidy of chromosomes 3, 7, and 17, and loss of the 9p21 locus. It has been approved for primary diagnosis and follow-up of BCa patients [98]. The reported sensitivity is 63–72% and specificity 85–87% . Their diagnostic accuracy was superior in primary diagnosis than in follow-up, showing low sensitivity, similarly to urinary cytology, particularly for low grade tumors. Compared to cytology, UroVysion had better sensitivity (72% vs. 42%) and lower specificity (83% vs. 96%) . When used simultaneously, there was a significant improvement in sensitivity but still a low specificity of 50% . UroVysion™ is more expensive than cytology and requires specialized laboratory techniques. However, it could be useful in situations of atypical cytology and equivocal cystoscopy, identifying patients that may need further investigation. Two prospective studies found that UroVysion had high positive predictive value, supporting that patients with a positive test and negative cystoscopy are more likely to have disease recurrence within one year [99][100]. Thus, a FISH test that is positive may be used to anticipate BCa recurrence during follow-up, especially in low risk patients [100], and reduce the number of unnecessary bladder biopsies [101]. Therefore, these studies suggest that chromosomic aberrations precede the detection of malignant lesions by cystoscopy and other standard techniques [102].

Analyses comparing the above-mentioned biomarkers have been reported. No differences were found in terms of sensitivity and specificity between the NMP22 test kit (cut-off > 10 U/mL) and the BTA Stat, in different stages and tumor grades [103][104][105][106][107][108]. The ImmunoCyt™ has higher sensitivity for low stage (Ta, T1) and low-grade tumors, although lower specificity than the UroVysion™ test [109][110]. However, although these tests were FDA approved for diagnosis and follow-up of BCa, together with standard techniques, most of these studies are case–control ones in populations with high prevalence of the disease, giving them an unrealistically high positive predictive value. *On the other hand, the question remains how to interpret positive findings of these tests, when no significant findings are found on cystoscopy during follow-up. In fact, most positive results have not been submitted to confirmatory biopsy.* Moreover, there are few external validation studies to support their use in daily practice. In

summary, multicentric prospective studies are required to assess consequences from positive and negative tests in the long term, to increase the likelihood to be supported by international urology organizations.

2.1.2. Non-FDA Approved Urine Biomarkers

To overcome the limitations of approved diagnostics biomarkers, extensive research is ongoing to find more effective biomarkers for BCa diagnosis and follow-up. There are several commercially available tests, despite not being approved by regulatory institutions. The CxBladder (Pacific Edge Diagnostics, Dunedin, New Zeland) is a RTqPCR test in voided urine, that quantifies different mRNAs expressed in BCa, as *IGFBP5*, *HOXA13*, *MDK*, *CDK1,* and *CXCR2*, associated with non-malignant conditions, to reduce the number of false-positives results due to inflammation [111]. The Triage™, Detect™, and Monitor™ tests have specific population targets. The first was developed for screening of high-risk populations as a pre-test guiding the need for cystoscopy, the Cxbladder Detect™ was intended for aiding in diagnosis of symptomatic patients and the Monitor™ for BCa follow-up . Studies using Cxbladder Detect™ found higher sensitivity but lower specificity than cytology (73.6% sensitivity and 81.7% specificity) in one study , while another described 82% sensitivity and similar specificity [112]. There are reports for Cxbladder Monitor™ stating a sensitivity of 93% that increases to 95% in high risk patients . A large study comparing biomarkers performance for BCa detection in urine, found that the Cxbladder Monitor™ sensitivity (91%) overcomed cytology by 22%, NMP22 BC test kit® by 26% and NMP22 BladderChek® by 11%, with an estimated reduction in the number of cystoscopies needed in follow-up by 81.7% . Although prospective confirmatory trials are needed, some authors suggest its use as an auxiliary test to postpone the need of repeated cystoscopies in low risk patients . The Assure MDx™ (MDx Health, Irvine, CA, USA) is a test performed in urine to identify DNA mutations in three genes (*FGFR3*, *TERT,* and *HRAS*) and methylations in another three genes (*OTX1*, *ONECUT2,* and *TWIST1*)[113]. A multicentric study demonstrated a sensitivity of 93% and specificity of 86% for BCa diagnosis. It might be useful for screening low risk patients with symptomatic hematuria, reducing by an estimated 77% the number of unnecessary diagnostic cystoscopies. The XPert® Bladder Cancer (BC) Monitor (Cepheid, Sunnyvale, California, USA) is a RT-PCR test that measures the number of urinary transcripts in five genes, *UPK1B*, *IGF2*, *CRH*, *ANXA10,* and *ABL1*, and was designed for BCa patient follow-up . This test was superior to cytology on NMIBC during follow-up, in terms of sensitivity (84% versus 33%), while presenting similar specificity (91% versus 94%) , despite controversial findings from another study, that indicated 46.7% sensitivity and 77% specificity [114]. The heterogeneity between studies and the lack of external validation makes its present use unreliable. The UBC® (Urinary bladder cancer) is a test that detects the expression of cytokeratins 8 and 18 in urine, with presentation of quantitative, UBC®-ELISA, and qualitative UBC®-rapid procedures. The reported sensitivity for UBC®-rapid was 86.9% for detecting Cis, 30.4% for low grade NMIBC, 71.4% for high grade NMBC, and 60% for MIBC . Other studies reported sensitivities between 30% and 87% for Cis and specificity of 63–91% [115][116][117][118]. The UBC®-rapid is a test that provides results within 10 min, but in comparison with other tests has the lowest specificity [115].

2.2. Emerging Urine Biomarkers

Besides these commercially available diagnostic tools for BCa detection in the urine, extensive research is underway to find more effective biomarkers [119][120]. The insufficient number of patients in most studies, the lack of

external validation in large scale prospective studies, and absence of comparative trials between biomarkers, foster the need for both methodological improvement of existing biomarkers and uncover novel robust biomarkers. Moreover, the existing biomarkers, in general, perform poorly in low risk BCa or have low specificity, and are more accurate in the initial diagnosis of BCa than in follow-up . Taken together, these limitations preclude actual recommendations by most international clinical societies, and current literature suggests that single biomarkers are insufficient to overcome this problem. Therefore, the current trends of research are focusing on the combination of different biomarker signatures, to develop more accurate diagnostic and surveillance tools in BCa, as well as to predict its behavior in order to provide prognostic information [121].

References

1. Babjuk, M.; Böhle, A.; Burger, M.; Capoun, O.; Cohen, D.; Compérat, E.M.; Hernández, V.; Kaasinen, E.; Palou, J.; Rouprêt, M.; et al. EAU Guidelines on Non-Muscle-Invasive Urothelial Carcinoma of the Bladder. Uptdate 2016. Eur. Urol. 2017, 71, 447–461, doi:10.1016/j.eururo.2016.05.041.

2. Bray, F.; Ferlay, J.; Soerjomataram, I.; Siegelm, R.L.; Torre, L.A.; Jemal, A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J. Clin. 2018, 68, 394–424, doi:10.3322/caac.21492.

3. DeGeorge, K.C.; Holt, H.R.; Hodges, S.C. Bladder Cancer: Diagnosis and Treatment. Am. Fam. Physician 2017, 96, 507–514.

4. Bladder cancer: Diagnosis and management of bladder cancer: © NICE (2015) Bladder cancer: Diagnosis and management of bladder cancer. BJU Int. 2017, 120, 755–765, doi:10.1111/bju.14045.

5. Burger, M.; Catto, J.W.F.; Dalbagni, G.; Grossman, H.B.; Herr, H.; Karakiewicz, P.; Kassouf, W.; Kiemeney, L.A.; La Vecchia, C.; Shariat, S.; et al. Epidemiology and risk factors of urothelial bladder cancer. Eur. Urol. 2013, 63, 234–241, doi:10.1016/j.eururo.2012.07.033.

6. Cumberbatch, M.G.; Rota, M.; Catto, J.W.; La Vecchia, C. The role of tobacco smoke in bladder and kidney carcinogenesis. Eur. Urol. 2016, 70, 458–466, doi:10.1016/j.eururo.2015.06.042.

7. Park, S.; Jee, S.H.; Shin, H.R.; Park, E.H.; Shin, A.; Jung, K.W.; Hwang, S.S.; Cha, E.S.; Yun, Y.H.; Park, S.K.; et al. Attributable fraction of tobacco smoking on cancer using population-based nationwide cancer incidence and mortality data in Korea. BMC Cancer 2014, 14, 1–12, doi:10.1186/1471-2407-14-406.

8. Freedman, N.D.; Silverman, D.T.; Hollenbeck, A.R.; Schatzkin, A.; Abnet, C.C. Association Between Smoking and Risk of Bladder Cancer Among Men and Women. JAMA 2011, 306, 737–745, doi:10.1001/jama.2011.1142.

9. Agudo, A.; Bonet, C.; Travier, N.; González, C.A.; Vineis, P.; Bueno-de-Mesquita, H.B., Trichopoulos, D.; Boffetta, P.; Clavel-Chapelon, F.; Boutron-Ruault, M.C.; et al. Impact of cigarette smoking on cancer risk in the European prospective investigation into cancer and nutrition study. J. Clin. Oncol. 2012, 30, 4550–4557, doi:10.1200/JCO.2011.41.0183.

10. Antoni, S.; Ferlay, J.; Soerjomataram, I.; Znaor, A.; Jemal, A.; Bray, F. Bladder Cancer Incidence and Mortality: A Global Overview and Recent Trends. Eur. Urol. 2017, 71, 96–108, doi:10.1016/j.eururo.2016.06.010.

11. Miyazaki, J.; Nishiyama, H. Epidemiology of urothelial carcinoma. Int. J. Urol. 2017, 24, 730–734, doi:10.1111/iju.13376.

12. Czerniak, B.; Dinney, C.; McConkey, D. Origins of Bladder Cancer. Annu. Rev. Pathol. 2016, 11, 149–174, doi:10.1146/annurev-pathol-012513-104703.

13. Dinney, C.P.N.; McConkey, D.J.; Millikan, R.E.; Wu, X.; Bar-Eli, M.; Adam, L.; Kamat, A.M.; Siefker-Radtke, A.O.; Tuziak, T.; Sabichi, A.L.; et al. Focus on bladder cancer. Cancer Cell 2004, 6, 111–116, doi:10.1016/j.ccr.2004.08.002.

14. Maffezzini, M.; Campodonico, F. Bladder cancer. Bladder cancer in the senior patient. In ESMO Handbook of Cancer in the Senior Patient; Schrijvers, D., Aapro, M., Zakotnik, B., Audisio, R., van Halteren, H., Hurria, H., Eds.; Taylor & Francis Group: Boca Raton, FL, USA, 2010; pp. 121–127.

15. Siegel, R.L.; Miller, K.D.; Jemal, A. Cancer statistics, 2019. CA Cancer J. Clin. 2019, 69, 7–34, doi:10.3322/caac.21551.

16. Martin-Doyle, W.; Kwiatkowski, D.J. Molecular Biology of Bladder Cancer. Hematol. Oncol. Clin. N. Am. 2015, 29, 191–203, doi:10.1016/j.hoc.2014.10.002.

17. Goodison, S.; Rosser, C.J.; Urquidi, V. Bladder cancer detection and monitoring: Assessment of urine- and blood-based marker tests. Mol. Diagn. Ther. 2013, 17, 71–84, doi:10.1007/s40291-013-0023-x.

18. Knowles, M.A.; Hurst, C.D. Molecular biology of bladder cancer: New insights into pathogenesis and clinical diversity. Nat. Rev. Cancer 2015, 15, 25–41, doi:10.1038/nrc3817.

19. Raitanen, M.P.; Leppilahti, M.; Tuhkanen, K.; Forssel, T.; Nylund, P.; Tammela, T.; FinnBladder Group. Routine follow-up cystoscopy in detection of recurrence in patients being monitored for bladder cancer. Ann. Chir. Gynaecol. 2001, 90, 261–265.

20. Lam, T.; Nabi, G. Potential of urinary biomarkers in early bladder cancer diagnosis. Expert Rev. Anticancer Ther. 2007, 7, 1105–1115, doi:10.1586/14737140.7.8.1105.

21. Avritscher, E.B.; Cooksley, C.D.; Grossman, H.B.; Sabichi, A.L.; Hamblin, L.; Dinney, C.P.; Elting, L.S. Clinical model of lifetime cost of treating bladder cancer and associated complications. Urology 2006, 68, 549–553, doi:10.1016/j.urology.2006.03.062.

22. Lotan, Y.; Svatek, R.S.; Sagalowsky, A.I. Should we screen for bladder cancer in a high-risk population? A cost per life-year saved analysis. Cancer 2006, 107, 982–990, doi:10.1002/cncr.22084.

23. Svatek, R.S.; Sagalowsky, A.I.; Lotan, Y. Economic impact of screening for bladder cancer using bladder tumor markers: A decision analysis. Urol. Oncol. 2006, 24, 338–343, doi:10.1016/j.urolonc.2005.11.025.

24. Mowatt, G.; N'Dow, J.; Vale, L.; Nabi, G.; Boachie, C.; Cook, J.A.; Fraser, C.; Griffiths, T.R.; Aberdeen Technology Assessment Review (TAR) Group. Photodynamic diagnosis of bladder cancer compared with white light cystoscopy: Systematic review and meta-analysis. Int. J. Technol. Assess. Health Care 2011, 27, 3–10, doi:10.1017/S0266462310001364.

25. Biardeau, X.; Lam, O.; Ba, V.; Campeau, L.; Corcos, J. Prospective evaluation of anxiety; pain; and embarrassment associated with cystoscopy and urodynamic testing in clinical practice. J. Can. Urol. Assoc. 2017, 11, 104–110, doi:10.5489/cuaj.4127.

26. Burke, D.M.; Shackley, D.C.; O'Reilly, P.H. The community-based morbidity of flexible cystoscopy. BJU Int. 2002, 89, 347–349, doi:10.1046/j.1464-4096.2001.01899.x.

27. Grégoire, M.; Fradet, Y.; Meyer, F.; Têtu, B.; Bois, R.; Bédard, G.; Charrois, R.; Naud, A. Diagnostic accuracy of urinary cytology; and deoxyribonucleic acid flow cytometry and cytology on bladder washings during followup for bladder tumors. J. Urol. 1997, 157, 1660–1664.

28. Mowatt, G.; Zhu, S.; Kilonzo, M.; Boachie, C.; Fraser, C.; Griffiths, T.R.L.; N'Dow, J.; Nabi, J.; Cook, J.; Vale, L. 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. Health Technol. Assess. 2010, 14, 1–331, doi:10.3310/hta14040.

29. Clark, P.E.; Agarwal, N.; Biagioli, M.C.; Eisenberger, M.A.; Greenberg, R.E.; Herr, H.W.; Inman, B.A.; Kuban, D.A.; Kuzel, T.M.; Lele, S.M.; et al. National Comprehensive Cancer Network (NCCN). Bladder cancer: Clinical practice guidelines in oncology. J. Natl. Compr. Cancer Netw. 2013, 11, 446–475, doi:10.6004/jnccn.2013.0059.

30. Têtu, B. Diagnosis of urothelial carcinoma from urine. Mod. Pathol. 2009, 22, S53–S59, doi:10.1038/modpathol.2008.193.

31. Lotan, Y.; Roehrborn, C.G. Sensitivity and specificity of commonly available bladder tumor markers versus cytology: Results of a comprehensive literature review and meta-analyses. Urology 2003, 61, 109–118, doi:10.1016/s0090-4295(02)02136-2.

32. Karakiewicz, P.I.; Benayoun, S.; Zippe, C.; Lüdecke, G.; Boman, H.; Sanchez-Carbayo, M.; Casella, R.; Mian, C.; Friedrich, M.G.; Eissa, S.; 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, doi:10.1111/j.1464-410X.2006.06036.x.

33. Witjes, J.A.; Compérat, E.; Cowan, N.C.; De Santis, M.; Gakis, G.; Lebret, T.; Ribal, M.J.; Van der Heijden, A.G.; Sherif, A.; European Association of Urology. EAU guidelines on muscle-invasive and metastatic bladder cancer: Summary of the 2013 guidelines. Eur. Urol. 2014, 65, 778–792, doi:10.1016/j.eururo.2013.11.046. .

34. Burchardt, M.; Burchardt, T.; Shabsigh, A.; De La Taille, A.; Benson, M.C.; Sawczuk, I. Current concepts in biomarker technology for bladder cancers. Clin. Chem. 2000, 46, 595–605.

35. Chang, S.S.; Boorjian, S.A.; Chou, R.; Clark, P.E.; Daneshmand, S.; Konety, B.R.; Pruthi, R.; Quale, D.Z.; Ritch, C.R.; Seigne, J.D.; et al. Diagnosis and Treatment of Non-Muscle Invasive Bladder Cancer: AUA/SUO Guideline. J. Urol. 2016, 196, 1021–1029, doi:10.1016/j.juro.2016.06.049.

36. Flaig, T.W.; Spiess, P.E.; Agarwal, N.; Bangs, R.; Boorjian, S.A.; Buyyounouski, M.K.; Downs, T.M.; Efstathiou, J.A.; Friedlander, T.; Greenberg, R.E.; et al. NCCN Guidelines Insights: Bladder Cancer; Version 5.2018. J. Natl. Compr. Cancer Netw. 2018, 16, 1041–1053, doi:10.6004/jnccn.2018.0072.

37. National Institute for Health and Care Excellence. Bladder cancer: diagnosis and management, NICE guideline [NG2]. Available online: https://www.nice.org.uk/guidance/ng2 (accessed on 20 January 2020).

38. Lotan, Y.; O'Sullivan, P.; Raman, J.D.; Shariat, S.F.; Kavalieris, L.; Frampton, C.; Guilford, P.; Luxmanan, C.; Suttie, J.; Crist, H.; et al. Clinical comparison of noninvasive urine tests for ruling out recurrent urothelial carcinoma. Urol. Oncol. 2017, 35, 531.e15–531.e22, doi:10.1016/j.urolonc.2017.03.008.

39. Herr, H. Tumor progression and survival of patients with high grade; noninvasive papillary (TaG3) bladder tumors: 15-year outcome. J. Urol. 2000, 163, 60–62.

40. Sylvester, R.J.; van der Meijden, A.P.; Oosterlinck, W.; Witjes, J.A.; Bouffioux, C.; Denis, L.; Newling, D.W.; Kurth, K. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: A combined analysis of 2596 patients from seven EORTC trials. Eur. Urol. 2006, 49, 466–467, doi:10.1016/j.eururo.2005.12.031.

41. Leal, J.; Luengo-Fernandez, R.; Sullivan, R.; Witjes, J.A. Economic Burden of Bladder Cancer across the European Union. Eur. Urol. 2016, 69, 438–447, doi:10.1016/j.eururo.2015.10.024. .

42. Lee, D.J.; Chang, S.S. Cost Considerations in the Management of Bladder Cancer. Urol Times. Available online: https://www.urologytimes.com/bladder-cancer/cost-considerations-management-bladder-cancer (accessed on 02 February 2020).

43. Bellmunt, J.; Orsola, A.; Leow, J.J.; Wiegel, T.; De Santis, M.; Horwich, A.; ESMO Guidelines Working Group. Bladder cancer: ESMO Practice Guidelines for diagnosis; treatment and follow-up. Ann. Oncol. 2014, 25, iii40–8, doi:10.1093/annonc/mdu223.

44. Sapre, N.; Anderson, P.D.; Costello, A.J.; Hovens, C.; Corcoran, N.M. Gene-based urinary biomarkers for bladder cancer: An unfulfilled promise? Urol. Oncol. 2014, 32, 48.e9–48.e17, doi:10.1016/j.urolonc.2013.07.002.

45. Franzen, C.A.; Blackwell, R.H.; Foreman, K.E.; Kuo, P.C.; Flanigan, R.C.; Gupta, G.N. Urinary exosomes: The potential for biomarker utility; intercellular signaling and therapeutics in urological malignancy. J. Urol. 2016, 195, 1331–1339, doi:10.1016/j.juro.2015.08.115.

46. Soung, Y.H.; Ford, S.; Zhang, V.; Chung, J. Exosomes in cancer diagnostics. Cancers 2017, 9, 8, doi:10.3390/cancers9010008.

47. Valadi, H.; Ekstrom, K.; Bossios, A.; Sjöstrand, M.; Lee, J.J.; Lötvall, J.O. Exosome mediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells. Nat. Cell Biol. 2007, 9, 654–659, doi:10.1038/ncb1596.

48. Yanez-Mo, M.; Siljander, P.R.; Andreu, Z.; Zavec, A.B.; Borràs, F.E.; Buzas, E.I.; Buzas, K.; Casal, E.; Cappello, F.; Carvalho, J.; et al. Biological properties of extracellular vesicles and their physiological functions. J. Extracell. Vesicles 2015, 4, 27066, doi:10.3402/jev.v4.27066.

49. Stahl, P.D.; Raposo, G. Extracellular vesicles: Exosomes and microvesicles; integrators of homeostasis. Physiology 2019, 34, 169–177, doi:10.1152/physiol.00045.2018.

50. Soria, F.; Droller, M.J.; Lotan, Y.; Gontero, P.; D'Andrea, D.; Gust, K.M.; Rouprêt ,M.; Babjuk, M.; Palou, J.; Shariat, S.F. An up-to-date catalog of available urinary biomarkers for the surveillance of non-muscle invasive bladder cancer. World J. Urol. 2018, 36, 1981–1995, doi:10.1007/s00345-018-2380-x.

51. Califf, R.M. Biomarker definitions and their applications. Exp. Biol. Med. 2018, 243, 213–221, doi:10.1177/1535370217750088.

52. Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework. Clin. Pharmacol. Ther. 2001, 69, 89–95, doi:10.1067/mcp.2001.113989.

53. Noon, A.P.; Zlotta, A.R. Urothelial Bladder Cancer Urinary Biomarkers. EJIFCC 2014, 25, 99–114.

54. Urquidi, V.; Rosser, C.J.; Goodison, S. Molecular diagnostic trends in urological cancers. Curr. Med. Chem. 2013, 19, 3653–3663, doi:10.2174/092986712801661103.

55. Hegemann, M.; Stenzl, A.; Bedke, J.; Chi, K.N.; Black, P.C.; Todenhöfer, T. Liquid Biopsy: Ready to guide therapy in advanced prostate cancer? BJU Int. 2016, 118, 855–863, doi:10.1111/bju.13586.

56. Di Meo, A.; Bartlet, J.; Cheng, Y.; Pasic, M.D.; Yousef, G.M. Liquid Biopsy: A Step Forward towards Precision Medicine in Urologic Malignancies. Mol. Cancer 2017, 16, 80, doi:10.1186/s12943-017-0644-5.

57. Miake, M.; Owari, T.; Hori, S.; Yasushi, N.; Kiyohide, F. Emerging biomarkers for the diagnosis and monitoring of urothelial carcinoma. Res. Rep. Urol. 2018, 10, 251–261, doi:10.2147/RRU.S173027.

58. Siravegna, G.; Marsoni, S.; Siena, S.; Bardelli, A. Integrating liquid biopsies into the management of cancer. Nat. Rev. Clin. Oncol. 2017, 107, 223–238, doi:10.1038/nrclinonc.2017.14.

59. Budman, L.I.; Kassouf, W.; Steinberg, J.R. Biomarkers for detection and surveillance of bladder cancer. Can. Urol. Assoc. J. 2008, 2, 212–221, doi:10.5489/cuaj.600.

60. Shim, J.S.; Kang, S-G. Surveillance for Non-Muscle-Invasive Bladder Cancer. In Bladder Cancer, 1st ed.; Ku, J.H., Ed.; Academic Press: London, UK, 2018; pp. 541–551, ISBN 978-0-12-809939-1.

61. Leiblich, A. Recent Developments in the Search for Urinary Biomarkers in Bladder Cancer. Curr. Urol. Rep. 2017, 18, 100, doi:10.1007/s11934-017-0748-x.

62. Kamat, A.M.; Hegarty, P.K.; Gee, J.R.; Clark, P.E.; Svatek, R.S.; Hegarty, N.; Shariat, S.F.; Xylinas, E.; Schmitz-Dräger, B.J.; Lotan Y; et al. ICUD-EAU international consultation on bladder cancer 2012: Screening; diagnosis; and molecular markers. Eur. Urol. 2013, 63, 4–15, doi:10.1016/j.eururo.2012.09.057. .

63. Malkowcz, S.B. The application of human complement factor H-related protein (BTA TRAK) in monitoring patients with bladder cancer. Urol. Clin. N. Am. 2000, 27, 63–73, doi:10.1016/s0094-0143(05)70235-4.

64. Chou, R.; Gore, J.L.; Buckley, D.; Fu, R.; Gustafson, K.; Griffin, J.C.; Grusing, S.; Selph, S. Urinary biomarkers for diagnosis of bladder cancer: A Systematic Review and Meta-analysis. Ann. Intern. Med. 2015, 163, 922–931, doi:10.7326/M15-0997.

65. Sathianathen, N.J.; Butaney, M.; Weight, C.J.; Kumar, R.; Konety, B.R. Urinary Biomarkers in the Evaluation of Primary Hematuria: A Systematic Review and Meta-Analysis. Bladder Cancer 2018, 4, 353–363, doi:10.3233/BLC-180179.

66. Guo, A.; Wang, X.; Gao, L.; Shi, J.; Sun, C.; Wan, Z. Bladder tumour antigen (BTA stat) test compared to the urine cytology in the diagnosis of bladder cancer: A meta-analysis. J. Can. Urol. Assoc. 2014, 8, E347–352, doi:10.5489/cuaj.1668.

67. Liang, Q.; Zhang, G.; Li, W.; Wang, J.; Sheng, S. Comparison of the diagnostic performance of fluorescence in situ hybridization (Fish); nuclear matrix protein 22 (nmp22); and their combination model in bladder carcinoma detection: A systematic review and meta-analysis. Onco. Targets Ther. 2019, 12, 349–358, doi:10.2147/OTT.S186065.

68. Wang, Z.; Que, H.; Suo, C.; Han, Z.; Tao, J.; Huang, Z.; Ju, X.; Tan, R.; Gu, M. Evaluation of the NMP22 BladderChek test for detecting bladder cancer: A systematic review and meta-analysis. Oncotarget 2017, 8, 100648–100656, doi:10.18632/oncotarget.22065.

69. Kumar, A.; Kumar, R.; Gupta, N.P. Comparison of NMP22 BladderChek test and urine cytology for the detection of recurrent bladder cancer. Jpn. J. Clin. Oncol. 2006, 36, 172–175, doi:10.1093/jjco/hyi244.

70. He, H.; Han, C.; Hao, L.; Zang, G. ImmunoCyt test compared to cytology in the diagnosis of bladder cancer: A meta-analysis. Oncol. Lett. 2016, 12, 83–88, doi:10.3892/ol.2016.4556.

71. Hajdinjak, T. UroVysion FISH test for detecting urothelial cancers: Meta-analysis of diagnostic accuracy and comparison with urinary cytology testing. Urol. Oncol. 2008, 26, 646–651, doi:10.1016/j.urolonc.2007.06.002.

72. Dimashkieh, H.; Wolff, D.J.; Smith, T.M.; Houser, P.M.; Nietert, P.J.; Yang, J. Evaluation of urovysion and cytology for bladder cancer detection. Cancer Cytopathol. 2013, 121, 591–597, doi:10.1002/cncy.21327.

73. Daniely, M.; Rona, R.; Kaplan, T.; Olsfanger, S.; Elboim, L.; Freiberger, A.; Lew, S.; Leibovitch, I. 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, 517–524, doi:10.1002/cncr.23119.

74. Breen, V.; Kasabov, N.; Kamat, A.M.; Jacobson, E.; Suttie, J.M.; O'Sullivan, P.J.; Kavalieris, L.; Darling, D.G. A holistic comparative analysis of diagnostic tests for urothelial carcinoma: A study of Cxbladder Detect; UroVysion® FISH; NMP22® and cytology based on imputation of multiple datasets. BMC Med. Res. Methodol. 2015, 15, 45, doi:10.1186/s12874-015-0036-8.

75. Kavalieris, L.; O'Sullivan, P.; Frampton, C.; Guilford, P.; Darling, D.; Jacobson, E.; Suttie, J.; Raman, J.D.; Shariat, S.F.; Lotan, Y. Performance Characteristics of a Multigene Urine Biomarker Test for Monitoring for Recurrent Urothelial Carcinoma in a Multicenter Study. J. Urol. 2017, 197, 1419–1426, doi:10.1016/j.juro.2016.12.010.

76. van Kessel, K.E.M.; Beukers, W.; Lurkin, I.; Ziel-van der Made, A.; van der Keur, K.A.; Boormans, J.L.; Dyrskjøt, L.; Márquez, M.; Ørntoft, T.F.; Real, F.X.; et al. Validation of a DNA Methylation-Mutation Urine Assay to Select Patients with Hematuria for Cystoscopy. J. Urol. 2017, 197, 590–595, doi:10.1016/j.juro.2016.09.118.

77. Pichler, R.; Fritz, J.; Tulchiner, G.; Klinglmair, G.; Soleiman, A.; Horninger, W.; Klocker, H.; Heidegger, I. Increased accuracy of a novel mRNA-based urine test for bladder cancer surveillance. BJU Int. 2018, 121, 29–37, doi:10.1111/bju.14019.

78. Pichler, R.; Tulchiner, G.; Fritz, J.; Schaefer, G.; Horninger, W.; Heidegger, I. Urinary UBC rapid and NMP22 test for bladder cancer surveillance in comparison to urinary cytology: Results from a

prospective single-center study. Int. J. Med. Sci. 2017, 14, 811–919, doi:10.7150/ijms.19929

79. Cheng, Z.Z.; Corey, M.J.; Pärepalo, M.; Majno, S.; Hellwage, J.; Zipfel, P.F.; Kinders, R.J.; Raitanen, M.; Meri, S.; Jokiranta, T.S. Complement factor H as a marker for detection of bladder cancer. Clin. Chem. 2005, 51, 856–863, doi:10.1373/clinchem.2004.042192.

80. Lokeshwar, V.B.; Habuchi, T.; Grossman, H.B.; Murphy, W.M.; Hautmann, S.H.; Hemstreet, G.P., 3rd; Bono, A.V.; Getzenberg, R.H.; Goebell, P.; Schmitz-Dräger, B.J.; et al. Bladder tumor markers beyond cytology: International Consensus Panel on bladder tumor markers. Urology 2005, 66, 35–63, doi:10.1016/j.urology.2005.08.064.

81. He, D.; Zeng, C.; Brinkley, B.R. Nuclear Matrix Proteins as Structural and Functional Components of the Mitotic Apparatus. Int. Rev. Cytol. 1996, 162, 1–74.

82. Soloway, M.S.; Briggman, J.V.; Carpinito, G.A.; Chodak, G.W.; Church, P.A.; Lamm, D.L.; Lange, P.; Messing, E.; Pasciak, R.M.; Reservitz, G.B.; et al. Use of a new tumor marker; urinary NMP22; in the detection of occult or rapidly recurring transitional cell carcinoma of the urinary tract following surgical treatment. J. Urol. 1996, 156, 363–367, doi:10.1097/00005392-199608000-00008.

83. Jamshidian, H.; Kor, K.; Djalali, M. Urine concentration of nuclear matrix protein 22 for diagnosis of transitional cell carcinoma of bladder. Urol. J. 2008, 5, 243–247.

84. Miyanaga, N.; Akaza, H.; Tsukamoto, T.; Ishikawa, S.; Noguchi, R.; Ohtani, M.; Kawabe, K.; Kubota, Y.; Fujita, K.; Obata, K.; et al. Urinary nuclear matrix protein 22 as a new marker for the screening of urothelial cancer in patients with microscopic hematuria. Int. J. Urol. 1999, 6, 173–177, doi:10.1046/j.1442-2042.1999.06437.x.

85. Grossman, H.B.; Soloway, M.; Messing, E.; Katz, G.; Stein, B.; Kassabian, V.; Shen, Y. Surveillance for recurrent bladder cancer using a point-of-care proteomic assay. JAMA 2006, 295, 299–305, doi:10.1001/jama.295.3.299.

86. Tabayoyong, W.; Kamat, A.M. Current Use and Promise of Urinary Markers for Urothelial Cancer. Curr. Urol. Rep. 2018, 19, 96, doi:10.1007/s11934-018-0857-1.

87. Duquesne, I.; Weisbach, L.; Aziz, A.; luth, L.A.; Xylinas, E.; Young Academic Urologist Urothelial Carcinoma Group of the European Association of Urology. The contemporary role and impact of urine-based biomarkers in bladder cancer. Transl. Androl. Urol. 2017, 6, 1031–1042, doi:10.21037/tau.2017.11.29.

88. Schmitz-Dräger, B.J.; Droller, M.; Lokeshwar, V.B.; Lotan, Y.; Hudson, M.A.; van Rhijn, B.W.; Marberger, M.J.; Fradet, Y.; Hemstreet, G.P.; Malmstrom, P.U.; et al. Molecular markers for bladder cancer screening; early diagnosis; and surveillance: The WHO/ICUD consensus. Urol. Int. 2015, 94, 1–24, doi:10.1159/000369357.

89. Van Rhijn, B.W.G.; Van Der Poel, H.G.; Van Der Kwast, T.H. Urine markers for bladder cancer surveillance: A systematic review. Eur. Urol. 2005, 47, 736–748, doi:10.1016/j.eururo.2005.03.014.

90. Grossman, H.B.; Soloway, M.; Messing, E.; Soloway, M.; Tomera, K.; Katz, G.; Berger, Y.; Shen, Y. Detection of Bladder Cancer Using a Point-Of-Care Proteomic Assay. JAMA 2005, 293, 810–816, doi:10.1001/jama.293.7.810.

91. Sharma, S.; Zippe, C.D.; Pandrangi, L.; Nelson, D.; Agarwal, A. Exclusion criteria enhance the specificity and positive predictive value of NMP22 and BTA stat. J. Urol. 1999, 162, 53–57, doi:10.1097/00005392-199907000-00014.

92. Greene, K.L.; Berry, A.; Konety, B.R. ImmunoCyt/uCyt+Test in Bladder Cancer. Rev. Urol. 2006, 8, 190–197.

93. Hautmann, S.; Toma, M.; Gomez, M.F.L.; Friedrich, M.G.; Jaekel, T.; Michl, U.; Schroeder, G.L.; Huland, H.; Juenemann, K.P.; Lokeshwar, V.B. Immunocyt and the HA-HAase urine tests for the detection of bladder cancer: A side-by-side comparison. Eur. Urol. 2004, 46, 466–471, doi:10.1016/j.eururo.2004.06.006.

94. Todenhöfer, T.; Hennenlotter, J.; Tews, V.; Gakis, G.; Aufderklamm, S.; Kuehs, U.; Stenzl, A.; Schwentner, C. Impact of different grades of microscopic hematuria on the performance of urine-based markers for the detection of urothelial carcinoma. Urol. Oncol. 2013, 31, 1148–1154, doi:10.1016/j.urolonc.2011.10.011.

95. Darwiche, F.; Parekh, D.; Gonzalgo, M. Biomarkers for non-muscle invasive bladder cancer: Current tests and future promise. Indian J. Urol. 2015, 31, 273, doi:10.4103/0970-1591.166448.

96. Schmitz-Dräger, B.J.; Tirsar, L.A.; Schmitz-Dräger, C.; Dörsam, J.; Mellan, Z.; Bismarck, E.; Ebert, T. Immunocytology in the assessment of patients with asymptomatic hematuria. World J. Urol. 2008, 26, 31–37, doi:10.1007/s00345-007-0228-x.

97. Pfister, C.; Chautard, D.; Devonec, M.; Perrin, P.; Chopin, D.; Rischmann, P.; Bouchot, O.; Beurton, D.; Coulange, C.; Rambeaud, J.J. Immunocyt test improves the diagnostic accuracy of urinary cytology: Results of a French multicenter study. J. Urol. 2003, 169, 921–924, doi:10.1097/01.ju.0000048983.83079.4c.

98. Sokolova, I.A.; Halling, K.C.; Jenkins, R.B.; Burkhardt, H.M.; Meyer, R.G.; Seelig, S.A.; King, W. The development of a multitarget; multicolor fluorescence in situ hybridization assay for the detection of urothelial carcinoma in urine. J. Mol. Diagn. 2000, 2, 116–123, doi:10.1016/S1525-1578(10)60625-3.

99. Schlomer, B.J.; Ho, R.; Sagalowsky, A.; Ashfaq, R.; Lotan, Y. Prospective Validation of the Clinical Usefulness of Reflex Fluorescence In Situ Hybridization Assay in Patients With Atypical Cytology

for the Detection of Urothelial Carcinoma of the Bladder. J. Urol. 2010, 183, 62–67, doi:10.1016/j.juro.2009.08.157.

100. Seideman, C.; Canter, D.; Kim, P.; Cordon, B.; Weizer, A.; Oliva, I.; Rao, J.; Inman, B.A.; Posch, M.; Herr, H.; et al. Multicenter evaluation of the role of UroVysion FISH assay in surveillance of patients with bladder cancer: Does FISH positivity anticipate recurrence? World J. Urol. 2015, 33, 1309–1313, doi:10.1007/s00345-014-1452-9.

101. Kim, P.H.; Sukhu, R.; Cordon, B.H.; Sfakianos, J.P.; Sjoberg, D.D.; Hakimi, A.A.; Dalbagni, G.; Lin, O.; Herr, H.W. Reflex fluorescence in situ hybridization assay for suspicious urinary cytology in patients with bladder cancer with negative surveillance cystoscopy. BJU Int. 2014, 114, 354–359, doi:10.1111/bju.12516.

102. Moonen, P.M.J.; Merkx, G.F.M.; Peelen, P.; Karthaus, H.F.; Smeets, D.F.; Witjes, J.A. UroVysion Compared with Cytology and Quantitative Cytology in the Surveillance of Non-Muscle-Invasive Bladder Cancer. Eur. Urol. 2007, 51, 1275–1280, doi:10.1016/j.eururo.2006.10.044.

103. Friedrich, M.G.; Hellstern, A.; Hautmann, S.H.; Graefen, M.; Conrad, S.; Huland, E.; Huland, H. 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, 470–474, doi:10.1016/s0022-5347(05)64660-5.

104. Gutiérrez Baños, J.L.; Rebollo Rodrigo, M.H.; Antolín Juárez, F.M.; Martín García, B. BTA stat Test and Cytology in the Diagnosis of Bladder Cancer: A Comparative Study. Urol. Int. 2001, 66, 185–190, doi:10.1159/000056612.

105. Saad, A.; Hanbury, D.C.; McNicholas, T.A.; Boustead, G.B.; Morgan, S.; Woodman, A.C. A study comparing various noninvasive methods of detecting bladder cancer in urine. BJU Int. 2002, 89, 369–373, doi:10.1046/j.1464-4096.2001.01699.x.

106. 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, 419–425, doi:10.1159/000020318.

107. Toma, M.I.; Friedrich, M.G.; Hautmann, S.H.; Jäkel, K.T.; Erbersdobler, A.; Hellstern, A.; Huland, H. Comparison of the ImmunoCyt test and urinary cytology with other urine tests in the detection and surveillance of bladder cancer. World J. Urol. 2004, 22, 145–149, doi:10.1007/s00345-003-0390-8.

108. Wiener, H.G.; Mian, C.; Haitel, A.; Pycha, A.; Schatzl, G.; Marberger, M. Can urine bound diagnostic tests replace cystoscopy in the management of bladder cancer? J. Urol. 1998, 159, 1876–1880.

109. Horstmann, M.; Patschan, O.; Hennenlotter, J.; Senger, E.; Feil, G.; Stenzl, A. Combinations of urine-based tumour markers in bladder cancer surveillance. Scand. J. Urol. Nephrol. 2009, 43, 461–466, doi:10.3109/00365590903296837.

110. Sullivan, P.S.; Nooraie, F.; Sanchez, H.; Hirschowitz, S.; Levin, M.; Rao, P.N.; Rao, J. Comparison of ImmunoCyt; UroVysion; and urine cytology in detection of recurrent urothelial carcinoma. Cancer Cytopathol. 2009, 117, 167–173, doi:10.1002/cncy.20026.

111. Holyoake, A.; O'Sullivan, P.; Pollock, R.; Best, T.; Watanabe, J.; Kajita, Y.; Matsui, Y.; Ito, M.; Nishiyama, H.; Kerr, N.; et al. Development of a multiplex RNA urine test for the detection and stratification of transitional cell carcinoma of the bladder. Clin. Cancer Res. 2008, 14, 742–749, doi:10.1158/1078-0432.CCR-07-1672.

112. O'Sullivan, P.; Sharples, K.; Dalphin, M.; Davidson, P.; Gilling, P.; Cambridge, L.; Harvey, J.; Toro, T.; Giles, N.; Luxmanan, C.; et al. A multigene urine test for the detection and stratification of bladder cancer in patients presenting with hematuria. J. Urol. 2012, 188, 741–747, doi:10.1016/j.juro.2012.05.003.

113. van Kessel, K.E.M.; Van Neste, L.; Lurkin, I.; Zwarthoff, E.C.; Van Criekinge, W. Evaluation of an Epigenetic Profile for the Detection of Bladder Cancer in Patients with Hematuria. J. Urol. 2016, 195, 601–607, doi:10.1016/j.juro.2015.08.085.

114. Delia, C.; Pycha, A.; Folchini, D.M.; Mian, C.; Hanspeter, E.; Schwienbacher, C.; Vjaters, E.; Pycha, A.; Trenti, E. Diagnostic predictive value of Xpert Bladder Cancer Monitor in the follow-up of patients affected by non-muscle invasive bladder cancer. J. Clin. Pathol. 2019, 72, 140–144, doi:10.1136/jclinpath-2018-205393.

115. Ecke, T.H.; Arndt, C.; Stephan, C.; Hallmann, S.; Lux, O.; Otto, T.; Ruttloff, J.; Gerullis, H. Preliminary Results of a Multicentre Study of the UBC Rapid Test for Detection of Urinary Bladder Cancer. Anticancer Res. 2015, 35, 2651–2655.

116. Ecke, T.H.; Weiß, S.; Stephan, C.; Hallmann, S.; Barski, D.; Otto, T.; Gerullis, H. UBC® rapid test for detection of carcinoma in situ for bladder cancer. Tumor Biol. 2017, 39, 1010428317701624, doi:10.1177/1010428317701624.

117. Styrke, J.; Henriksson, H.; Ljungberg, B.; Hasan, M.; Silfverberg, I.; Einarsson, R.; Malmström, P.U.; Sherif, A. Evaluation of the diagnostic accuracy of UBC ® Rapid in bladder cancer: A Swedish multicentre study. Scand. J. Urol. 2017, 51, 293–300, doi:10.1080/21681805.2017.1313309.

118. Ritter, R.; Hennenlotter, J.; Kühs, U.; Hofmann, U.; Aufderklamm, S.; Blutbacher, P.; Deja, A.; Hohneder, A.; Gerber, V.; Gakis, G.; et al. Evaluation of a new quantitative point-of-care test platform for urine-based detection of bladder cancer. Urol. Oncol. 2014, 32, 337–344, doi:10.1016/j.urolonc.2013.09.024.

119. Leiblich, A. Recent developments in the search for urinary biomarkers in bladder cancer. Curr. Urol. Rep. 2017, 18, 100, doi:10.1007/s11934-017-0748-x.

120. Santoni, G.; Morelli, M.B.; Amantini, C.; Battelli, N. Urinary markers in bladder cancer: An update. Front. Oncol. 2018, 8, 362, doi:10.3389/fonc.2018.00362.

121. Nagata, M.; Muto, S.; Horie, S. Molecular biomarkers in bladder cancer: Novel potential indicators of prognosis and treatment outcomes. Dis. Markers 2016, 2016, 8205836, doi:10.1155/2016/8205836.

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