Title

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Replacing surveillance cystoscopy with urinary biomarkers in followup of patients with non-muscle-invasive bladder cancer: Patients' and urologic oncologists' perspectives

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Abstract

Introduction: Urinary biomarkers are being developed to detect bladder cancer recurrence/progression in patients with non-muscle-invasive bladder cancer (NMIBC). We conducted a questionnaire-based study to determine what diagnostic accuracy and cost would such test(s) need for both patients and urologic oncologists to comfortably forgo surveillance cystoscopy in favour of these tests.
Methods: Surveys were administered to NMIBC patients at followup cystoscopy visit and to physician members of the Society of Urologic Oncology. Participants were questioned about acceptable false-negative (FN) rates and costs for such alternatives, in addition to demographics that could influence chosen error rates and costs.
Results: A total of 137 patient and 51 urologic oncologist responses were obtained. Seventy-seven percent of patients were not comfortable with urinary biomarker(s) alternatives to repeat cystoscopy, with a further 14% willing to accept such alternatives only if the FN rate were 0.5% or lower. Seventy-five percent of urologic oncologists were comfortable with an alternative urinary biomarker test(s), with 37% and 33% willing to accept FN rates of 5% and 1%, respectively. Forty-seven percent of patients were not willing to pay out-of-pocket for such tests, while 61% of urologic oncologists felt that a price range of $100–500 would be reasonable.
Conclusions: This is the first survey evaluating patient and urologic oncologist perspectives on acceptable error rates and costs for urinary biomarker alternatives to surveillance cystoscopy for patients with NMIBC. Despite potential responder bias, this study suggests that urinary biomarker(s) will require sensitivity equivalent to that of cystoscopy in order to completely replace it in surveillance of patients with NMIBC.

Introduction

Patients with non-muscle-invasive bladder cancer (NMIBC) routinely undergo surveillance cystoscopy following primary treatment of their disease to identify tumour recurrence and prevent disease progression in a timely manner. Surveillance protocols for such patients can vary from one cystoscopy per year in low-risk patients to a more intense schedule of a cystoscopy every three months in high-risk patients.[1] However, adherence to such protocols is challenging and actual practice of surveillance varies significantly from the standards recommended in clinical guidelines.[2] There is also a rising concern regarding frequent cystoscopies, as this procedure has been shown to cause infection,[3] hematuria,[4] pain,[5] and anxiety.[6]

Over the past several decades, a number of urinary biomarkers have been developed and commercialized to aid in the followup of patients with NMIBC.[7] These tests can supplement surveillance cystoscopies by improving their diagnostic yield[8] and could potentially reduce the reliance on cystoscopies in the followup of such patients by replacing them partially or completely, leading to decreased patient morbidity and costs.[9] However, the diagnostic accuracy of such tests is still far from perfect, and any benefits obtained by forgoing cystoscopy in favour of such tests must be balanced against their reduced sensitivity and specificity.[7] Thus, the choice of whether to reduce the number of surveillance cystoscopies in favour of these biomarkers remains challenging. In an attempt to address this issue, we decided to perform a questionnaire-based study that aims to gauge what diagnostic accuracy and cost would a urinary biomarker(s) need to attain in order for both NMIBC patients and their treating urologic oncologists to comfortably forgo surveillance cystoscopy in favour of these non-invasive tests.

Methods

Study design

After receiving institutional internal review board ethics approval, survey responses were collected from consecutively consenting bladder cancer patients with histologically confirmed NMIBC at time of visit to the cystoscopy clinic at Toronto General Hospital between June 2016 and August 2016. Data from urologic oncologists worldwide was obtained in October 2016 by sending out an online survey via the Society of Urologic Oncology (SUO) using SurveyMonkey®. Survey participants were provided with an informational page prior to starting the survey, and electronic consent was required prior to completion of the survey. Repeat survey responses were not permitted to eliminate the possibility of repeat participants.

Survey instrument

The survey was modeled on a previously validated questionnaire administered to health professionals on acceptable levels of risk for major cardiac events following discharge from an emergency department.[10] The questionnaire was rigorously assessed for content validity and prior to administration, four urologists, two research staff, and three administrative personnel assessed the survey for ease of comprehension and language appropriateness. Two distinct, yet overlapping questionnaires were used for each of the populations. The patient questionnaire was comprised of seven questions and required approximately 15 minutes to complete. In addition to questions about age, highest level of education, annual income, marital status, and previous number of cystoscopies, patients were queried regarding what false negative (FN) rate, relative to the current gold standard, cystoscopy and out-of-pocket expense they would accept for such urinary biomarker(s) (Supplementary Fig. 1). The survey was administered in a separate room, immediately after undergoing flexible cystoscopy. Highly trained, experienced clinical research staff was responsible for administering the questionnaires in person and were available to provide any assistance or clarification necessary, particularly if the patient had any difficulty with understanding the concept of a FN rate. Patient comprehension of this concept was ascertained by the research staff prior to survey completion. Patient tumour grade and stage was ascertained via a thorough chart review of all available pathology reports and clinic notes. Urologists were asked about age, country of current practice, practice location (i.e., rural, suburban, urban, or metropolitan), practice setting, whether they completed fellowship training in urologic oncology, number of years since finishing residency training, tests currently used in the followup of patients with NMIBC, and acceptable FN rate and expense for urinary biomarker(s) in place of surveillance cystoscopy (Supplementary Fig. 2).

Statistical analyses

Descriptive statistics were summarized using frequencies and proportions for all categorical variables. The Chi-square test was used to determine whether patient sex, tumour grade, and/or tumour stage were associated with choice of FN rate and/or acceptable cost, and whether there were any significant differences between patient and urologic oncologist choices. Possible associations between the remaining baseline characteristics and FN rate and test(s) expense choices were also evaluated using the Chi-square test. Two-side statistical significance was set at α=0.05. Analyses were performed using R version 3.3.1.

Results

Study populations

One hundred and sixty-four consecutive NMIBC patients were approached with 137 responses obtained (response rate of 84%). One hundred and seven patients (78%) were male and 30 (22%) were female. One hundred and fifteen patients (84%) were older than 60 years. Our cohort's demographics were typical of that of patients with bladder carcinoma. Eighty-six (63%) patients continued their education beyond high school, 64 (59%) had a yearly income in excess of $50 000, and 106 (77%) were either married or in a committed long-term relationship. With regards to previous number of cystoscopies, 96 patients (70%) had undergone more than five cystoscopies prior to their study visit. Seventy-five patients (55%) had non-invasive papillary carcinoma, while 38 (28%) and 24 (18%) had invasive papillary disease and carcinoma in situ, respectively. As for tumour grade, 64 (47%) had low-grade disease, with the remaining 73 (53%) having high-grade disease (Table 1).

Six hundred and seventy urologic oncologists were surveyed and 51 responses were obtained (response rate of 8%). Thirty-six respondents (71%) were younger than 50 years, with 45 (88%) indicating that they currently work in the U.S. Most were working in a metropolitan area, with almost all in a group practice setting (including hospitals). Thirty-nine respondents (77%) had urologic oncology fellowship training, and 28 (55%) finished residency training less than 10 years ago. All respondents indicated that they always use cystoscopy in the followup of NMIBC patients, with other modalities including: urine cytology, computed tomography (CT) urography, magnetic resonance imaging (MRI), retrograde pyelography, and urine-based biomarkers (i.e., BTA STAT, BTA TRAK, NMP22, etc.) (Table 2).

Table 1. Patients' background information (n=137)

Characteristic	Frequency (percentage)
Sex	
Male	107 (78.1)
Female	30 (21.9)
Age (years)	
Under 50	7 (5.1)
50–59	15 (10.9)
60–69	40 (29.2)
70–79	46 (33.6)
80 and over	29 (21.2)
Highest level of education	
High school	51(37.2)
College degree or certificate	27 (19.7)
University undergraduate degree	27 (19.7)
Postgraduate (Master's, PhD, MD, law school)	32 (23.4)
Annual income	
<$25 000	24 (17.5)
$25 000–49 999	21 (15.3)
$50 000–74 999	22 (16.1)
≥$75 000	42 (30.7)
Prefer not to answer	28 (20.4)
Marital status	
Single	9 (6.6)
Married (or committed long-term relationship)	106 (77.4)
Separated/divorced	10 (7.3)
Widowed	12 (8.8)
Previous number of cystoscopies	
1	4 (2.9)
2–3	18 (13.1)
4–5	19 (13.9)
>5	96 (70.1)
Tumour stage	
Ta	75 (54.7%)
T1	38 (27.7%)
Tis	24 (17.5%)
Tumour grade	
Low	64 (46.7%)
High	73 (53.3%)

Table 2. Urologic oncologists' background information (n=51)

Characteristic	Frequency (percentage)
Age (years)	
Under 40	17 (33.3)
40–49	19 (37.3)
50–59	5 (9.8)
60–69	5 (9.8)
70 and over	5 (9.8)
Country of current practice	
U.S.	45 (88.2)
Canada	5 (9.8)
Other	1 (2.0)
Practice location	
Rural (population <1000)	0 (0)
Suburban (population 1000–29 999)	2 (3.9)
Urban (population 30 000–99 999)	4 (7.8)
Metropolitan (population ≥100 000)	45 (88.2)
Practice setting	
Solo practice	2 (3.9)
Group practice (including hospital setting)	49 (96.1)
Urology-oncology fellowship training	
Yes	39 (76.5)
No	12 (23.5)
Years since finished residency training	
Less than 5	13 (25.5)
5–9	15 (29.4)
10–14	4 (7.8)
15–19	5 (9.8)
20–24	4 (7.8)
25–29	3 (5.9)
30 or greater	7 (13.7)
Tests currently used in the followup of patients with non-muscle-invasive bladder cancer	
Cystoscopy	Always=51 (100)
Urine cytology	Always=29 (56.9) Sometimes=18 (35.3) Rarely=1 (2.0) Never=3 (5.9)
Computed tomography urography	Always=19 (37.3) Sometimes=27 (53.0) Rarely=4 (7.8) Never=1 (2.0)
Magnetic resonance imaging	Sometimes=14 (29.2) Rarely=27 (56.3) Never=8 (16.7)
Retrograde pyelography	Sometimes=25 (50) Rarely=23 (46.0) Never=3 (6.0)
Urine-based biomarkers (i.e., BTA STAT, BTA TRAK, NMP22, etc.)	Always=2 (3.9) Sometimes=10 (19.6) Rarely=23 (45.1) Never=16 (31.4)

Acceptable FN rates for urinary biomarker(s) in place of surveillance cystoscopy

Patient responses

One hundred and six (77%) of patients were not comfortable with urinary biomarker(s) in place of surveillance cystoscopy. A further 19 (14%) would only accept a urinary biomarker(s) if the FN rate was 0.5% or lower. Only six (8%) patients would be comfortable with an alternative test that has a FN rate of 5% or lower (Table 3). There was no association between choice of FN rate and patient sex, age, education

level, annual income, marital status, previous number of cystoscopies, tumour grade, and tumour stage.

Urologic oncologist responses

Thirteen (26%) urologic oncologists were not comfortable with a urinary biomarker(s) in place of surveillance cystoscopy. Seventeen (33%) would prefer a test(s) with a FN rate of 1% or lower, while 16 (37%) would accept a FN rate of 5% or lower (Table 3). There was no association between choice of FN rate and urologic oncologist age, country of practice, practice setting, completion of fellowship training or not, and years since finishing residency training. There were significant differences between patients' and urologic oncologists' choices ($p<0.01$), with physicians accepting of higher error rates compared to patients.

Acceptable costs for urinary biomarker(s) in place of surveillance cystoscopy

Patient responses

A total of 46.7% of patients would prefer a fully insured cystoscopy to any out-of-pocket expense; 27.7% of patients would only accept a cost less than $100, and 21.2% would find a $100–500 out-of-pocket expense reasonable (Table 4). There was an association between chosen out-of-pocket expense and age ($p=0.013$), highest education level ($p=0.007$), and marital status ($p<0.001$), whereby a fully insured cystoscopy was more likely to be requested by older patients, those with a high school diploma only, and those who are widowed or separated/divorced. There was no association between the remaining baseline characteristics and choice of acceptable out-of-pocket expense.

Urologic oncologist responses

A total of 11.8% of urologic oncologists responded that they do not believe the potential benefit warrants any expenditure; 60.8% indicated that $100–500 would a reasonable price range for urinary biomarker alternatives (Table 4). There was no association between choice of acceptable cost and urologic oncologists' baseline characteristics. There were significant differences between patients' and urologic oncologists' choices ($p<0.01$), with physicians accepting of higher expenses for these alternative tests.

Discussion

Although cystoscopy is well-established as the gold standard tool for surveillance in patients with NMIBC, the increased availability and improved performance of urinary biomarkers necessitates that we consider novel, alternate modes of surveillance. These biomarkers could potentially be used in a number of ways, with the options ranging from adjuncts to cystoscopies to direct replacements, with the ultimate goal being to decrease the number of invasive procedures and their associated complications.[3-6]

In conducting this survey, we felt it essential to elicit both patient and urologic oncologist perspectives on needed test characteristics for alternatives to repeat cystoscopy. NMIBC patients are a particularly suitable population of patients for studying alternatives to repeat cystoscopy, as such patients are familiar with this procedure (70% of patients had undergone more than five prior cystoscopies at time of survey administration) and will likely undergo many more as part of routine surveillance. Similarly, we felt it necessary to elicit the expert opinions of physician members of the SUO, as these are the physicians who manage bladder cancer patients on a regular basis and whose input in the shared decision-making process is invaluable to the patient.

Based on our results, the majority of patients (91%) are either not comfortable with a urinary biomarker(s) in place of surveillance cystoscopy or would only accept such an alternative if the FN rate were at most 0.5% (Table 3). This is markedly lower than the FN rates of currently available urinary biomarkers, which presently have FN rates in excess of 10%.[11] Furthermore, tumour grade/stage had no influence on choice of FN rate, despite patients being well-informed about their risks of disease recurrence/progression. These

Table 3. Patients' and urologic oncologists' acceptable false-negative rates for non-invasive test(s)

Rate	Patients			Urologic oncologists		
	Frequency	Percent	Cumulative percent	Frequency	Percent	Cumulative percent
20%	2	1.5%	1.5%	1	2.0%	2.0%
10%	3	2.2%	3.6%	2	3.9%	5.9%
5%	6	4.4%	8.0%	16	31.4%	37.3%
1%	1	0.7%	8.8%	17	33.3%	70.6%
0.5%	19	13.9%	22.6%	2	3.9%	74.5%
Not comfortable with a urinary biomarker(s) in place of surveillance cystoscopy	106	77.4%	100.0%	13	25.5%	100.0%
Total	137	100.0%	100.0%	51	100.0%	100.0%

Table 4. Patients' and urologic oncologist's choices for acceptable costs for non-invasive test(s)

Cost	Patients			Urologic oncologists		
	Frequency	Percent	Cumulative percent	Frequency	Percent	Cumulative percent
Less than $100	38	27.7%	27.7%	8	15.7%	15.7%
$100–499	29	21.2%	48.9%	31	60.8%	76.5%
$500–999	3	2.2%	51.1%	4	7.8%	84.3%
$1000–1999	1	0.7%	51.8%	2	3.9%	88.2%
$2000–4999	0	0.0%	51.8%	0	0.0%	88.2%
$5000 or greater	2	1.5%	53.3%	0	0.0%	88.2%
Do not believe benefit is enough to warrant any expenditure	64	46.7%	100.0%	6	11.8%	100.0%
Total	137	100.0%	100.0%	51	100.0%	100.0%

data suggest that NMIBC patients are comfortable with cystoscopy as the routine surveillance tool and any alternative testing modality will need to achieve accuracy equivalent to that of cystoscopy in order for patients to be willing to accept it. These results are not surprising, as previous studies have demonstrated that flexible cystoscopies are not associated with distressing levels of pain and that repeat procedures are less painful than the first ones, suggesting that patients adapt with increasing numbers of cystoscopies.[5]

Urologic oncologists, on the other hand, were significantly more comfortable with a urinary biomarker(s) as an alternative to surveillance cystoscopy ($p<0.01$). Only 25.5% were not comfortable with a urinary biomarker(s) alternative, whereas 37.3% and 70.6% would be comfortable with an alternative that has a FN rate of 5% and 1%, respectively (Table 3). These results indicate that urologic oncologists were more willing to accept urinary biomarker alternatives at the expense of a higher risk of missing disease recurrence/progression, compared to patients, who seemed reluctant to accept any degree of reduced diagnostic accuracy that could compromise their oncological outcomes.

Our results are consistent with findings from previous similar studies. Vriesema et al conducted a utility analysis of 85 patients evaluating their opinion regarding urinary tests versus flexible urethrocystoscopy in the followup examination for superficial bladder cancer. Sixty-eight percent of patients required a minimal accepted sensitivity of 99–100%. In contrast to our findings, a higher minimal accepted sensitivity was found in women, younger patients (67 years old or younger) and those who had undergone cystoscopy more frequently.[12] Yossepowitch et al similarly evaluated patient perspectives regarding use of urinary biomarkers for bladder cancer surveillance; 54% of patients requested an accuracy of 100%, thereby refusing to sacrifice any degree of diagnostic accuracy for the benefit of a non-invasive assay. A further 16% were only willing to accept a 1% decrease in diagnostic accuracy. The study determined that male gender and higher pain intensity at cystoscopy were associated with willingness to accept a small level of uncertainty on univariate and multivariate regression analyses.[13] Both studies are limited by their lack of evaluation of physician perspectives. Also, both studies did not investigate acceptable costs for such urinary biomarker(s). Often, novel diagnostic modalities are not insured initially, and thus, interested patients may be forced to pay out-of-pocket for such tests. It thus becomes necessary to determine how much patients are willing to pay for such tests.

The strengths of our study are our high patient response rate (84%) and face-to-face survey administration. Using the NMIBC patient cohort is also critical, as they have experienced prior cystoscopy and are the ultimate subjects we are suggesting to apply this paradigm on. This is the first study assessing urologic oncologist perspectives regarding accuracy and costs of urinary biomarker alternatives to surveillance cystoscopy.

Our study has several limitations. Even though our questionnaire was closely modeled after a previously validated survey addressing a very similar topic, it has not been previously validated for evaluating this question in NMIBC patients. Our questionnaire, which was administered post-cystoscopy, also did not query patients regarding acceptable waiting times for a urine test result[14] and post-cystoscopy symptoms, which are likely to have influenced patient FN rate choices.[13] Furthermore, our survey did not make a distinction between patients with low-risk vs. high-risk disease. Physicians were asked about non-invasive alternatives for any patient with NMIBC (Supplementary Fig. 2). Had a risk group been prespecified in the questionnaire, it is likely that physicians' responses would have differed for these two distinct populations.

We must note that more than half our patients had high-grade disease and almost all have had at least two previous cystoscopies. These patient characteristics are likely to have created a responder bias in favour of opting for cystoscopies. Studies that evaluate responses among patients with incident or "first-time" tumours may be needed to evaluate the impact of this potential bias. Our urologic oncologist response rate of 8% is low and the majority of responders were younger

than 50 (70.6%). These results are a significant source of responder bias. Younger urologic oncologists may have different perspectives regarding non-invasive alternatives compared to their older peers. It is likely that a different result would have emerged had a more complete, older urologist cohort been sampled. Our patient population may not be generalizable as well. They are patients who are essentially urban, educated, Canadian and Caucasian. Other cohorts with different demographic backgrounds may differ with regards to their choices and can be the subject of future research. We must also note that we have asked Canadian patients, who seldom pay out-of-pocket for healthcare services, to estimate acceptable costs for themselves and compared this to a group of mostly U.S.-based physicians.

Conclusion

This is the first survey evaluating both patients' and urologic oncologists' choices regarding acceptable error rates and costs for urinary biomarker(s) in lieu of cystoscopy for surveillance of patients with NMIBC. Ninety-one percent of patients were either not comfortable with biomarker alternatives or required a test with a FN rate of 0.5% or less. In light of these findings, it seems that any urinary biomarker alternative(s) will require sensitivity equivalent to that of cystoscopy in order to completely replace it in the surveillance of patients with NMIBC.

Competing interests: Dr. Finelli has attended advisory boards for Amgen, Astellas, and Janssen; and has received honoraria from AbbVie, AstraZeneca, and Ferring. Dr. Hamilton has attended advisory boards for AbbVie, Astellas, Bayer, and Janssen. Dr. Kulkarni has attended advisory boards for Amgen, Astellas, Bayer, Ferring, and Janssen; and has received educational grants from AbbVie and Sanofi. Dr. Zlotta has been an advisor for Ferring, LLC, Sanofi, and 3DBiopsy. Dr. Fleshner has attended advisory boards for AbbVie, Amgen, Astellas, Bayer, Ferring, Janssen, and Sanofi; has received grants from AbbVie, Amgen, Astellas, Bayer, the Canadian Cancer Research Institute, Ferring, Hybridyne Imaging Technologies, Janssen, and Sanofi; and has participated in clinical trials supported by Astellas, Bavarian Nordic, Bayer, Ferring, Janssen, Medivation, Nucleix, Progenics, Sanofi, and Spectracure AB. The remaining authors report no competing personal or financial interests.

This paper has been peer-reviewed.

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Supplementary Fig. 1. Patient version questionnaire

BLADDER CANCER OPINION SURVEY ___ ___ ___ ___ ___ ___

In order to optimize patient care, our urology staff is dedicated towards a better understanding of patient perspectives regarding bladder cancer treatment. As a patient currently being monitored for bladder cancer recurrence, your viewpoints are important to us. Currently, the followup of patients with a history of resected non-muscle-invasive bladder cancer includes a thorough history, urinalysis, urine cytology, and cystoscopy. In this survey, we will be asking questions regarding an alternate test or set of tests that could potentially replace repeat cystoscopy for your condition. Unlike a cystoscopy, this test would be non-invasive (i.e., like a urine test). Unfortunately, since no test is 100% accurate, we would like to know your level of tolerance for false negative or error rates (i.e., how often the test would miss a recurrence of your cancer and potentially delay the delivery of life-saving treatment?). Please circle the best answer to the following questions. All of your responses will be kept confidential.

1) Current age:
   a) Under 50
   b) 50–60
   c) 60–70
   d) 70–80
   e) Over 80

2) Highest level of education:
   a) High school
   b) College degree or certificate
   c) University undergraduate degree
   d) Postgraduate (Master's, PhD, law school, medical school)

3) Annual income:
   a) Less than $25 000
   b) $25 000–$50 000
   c) $50 000–$75 000
   d) More than $75 000
   e) Prefer not to answer

4) Marital status:
   a) Single
   b) Married (or committed long-term relationship)
   c) Separated/divorced
   d) Widowed

5) How many times in the past have you had a cystoscopy?
   a) 1
   b) 2–3
   c) 4–5
   d) Greater than 5

6) If you were to undergo a new non-invasive urinary test(s) that replaces cystoscopy in the detection of bladder cancer recurrence, what false negative rate (i.e., rate of the test failing to detect recurrence of disease and potentially delaying life-saving treatment) would you be comfortable with?
   a) It does not matter as long as it avoids cystoscopy
   b) 20% (i.e., 80 times out of 100, the cystoscopy could be safely omitted)
   c) 10% (i.e., 90 times out of 100, the cystoscopy could be safely omitted)
   d) 5% (i.e., 95 times out of 100, the cystoscopy could be safely omitted)
   e) 1% (i.e., 99 times out of 100, the cystoscopy could be safely omitted)
   f) 0.5% (i.e., 995 times out of 1000, the cystoscopy could be safely omitted)
   g) I am not comfortable with a non-invasive test in place of cystoscopy

7) If the government were to not cover the cost of the aforementioned test(s), how much money would you be willing to pay out-of-pocket for it?
   a) None, I do not believe the benefit is great enough to warrant this expenditure
   b) Less than $100
   c) $100–500
   d) $500–1000
   e) $1000–2000
   f) $2000–5000
   g) Greater than $5000

Thank you greatly for completing this survey. Results from your answers will provide invaluable insight on patient perspective concerning bladder cancer and new tests to diagnose advanced disease.

Supplementary Fig. 2. Physician version questionnaire

BLADDER CANCER OPINION SURVEY

Dear Physician,

In order to optimize patient care and guide appropriate therapeutic goals, our University Health Network Urology-Oncology research team is dedicated towards a better understanding of physician perspectives regarding bladder cancer treatment. As care providers for patients with bladder cancer, your viewpoints on potential new diagnostic tools are important to us. Currently, patients with resected, non-muscle-invasive bladder cancer are followed up with a thorough history, urinalysis, urine cytology, and cystoscopy. In this survey, we would like to gauge your opinion on urinary biomarker test(s) that aims to replace repeat cystoscopy in the followup of such patients. Recognizing that no test is 100% accurate, we would like to know your threshold for false negative rates (how often the test misses a progression of disease) in adopting such a test in your practice. Your opinion is invaluable for guiding future research and decision-making regarding bladder cancer diagnostics. With this in mind, we kindly ask that you choose the best answer to the following questions. We thank you greatly for completing this survey. Results from your answers will provide invaluable insight on patient perspective concerning bladder cancer and new tests to diagnose advanced disease.

1) Current age:
   a) Under 40
   b) 40–50
   c) 50–60
   d) 60–70
   e) Over 70
2) What is your country of current practice?
   a) U.S.
   b) Canada
   c) Other
3) What is your practice location?
   a) Rural (population <1000)
   b) Suburban (population >1000 but <30 000)
   c) Urban (population >30 000 but <100 000)
   d) Metropolitan (population >100 000)
4) What is your practice setting?
   a) Solo
   b) Group
   c) Other (please specify): _____
5) Have you completed fellowship training in urology-oncology?
   a) Yes b. No
6) How many years has it been since you finished residency training?
   a) Less than 5
   b) 5–10
   c) 10–15
   d) 15–20
   e) 20–25
   f) 25–30
   g) More than 30
7) What tests do you currently use in the follow up of patients with non-muscle-invasive bladder cancer?
   a) Cystoscopy
   b) Urine cytology
   c) CT urography
   d) MRI
   e) Retrograde pyelography
   f) Urine-based markers (i.e., bladder tumour antigen [BTA] STAT, BTA TRAK, Nuclear matrix protein (NMP) 22 and NMP22 BladderChek assays, ImmunoCyt test, FISH analysis…)
   g) Other (please comment): _____

Supplementary Fig. 2 (cont'd). Physician version questionnaire

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8) If you were offering a new urinary biomarker test(s) that replaces surveillance cystoscopy in the detection of recurrence/progression in patients with non-muscle-invasive bladder cancer, what false negative rate (i.e., rate of the test failing to detect progression of disease when there is one) are you comfortable with?

a) It does not matter as long as it avoids cystoscopy
b) 20%
c) 10%
d) 5%
e) 1%
f) 0.5%
g) I am not comfortable with a urinary biomarker test(s) in place of cystoscopy

9) If the test(s) were to be administered at a frequency similar to cystoscopies (i.e., every three months for the first two years, every six months for the following two years, and annually thereafter), what is a reasonable price for each administration of the test(s)?

a) None, I do not believe the benefit is enough to warrant this expenditure
b) Less than $100
c) $100–500
d) $500–1000
e) $1000–2000
f) $2000–5000
g) Greater than $5000