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Platinum Priority – Bladder Cancer

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Outcomes of a Bladder Cancer Screening Program Using Home Hematuria Testing and Molecular Markers

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Abstract

Background: We previously reported the preliminary findings from a feasibility study of bladder cancer (BCa) screening with urinary molecular markers (Bladder Cancer Urine Marker Project [BLU-P]) that has now been terminated.
Objective: To report the final results from BLU-P to determine whether mass screening for BCa is feasible and useful.
Design, setting, and participants: BLU-P was a Dutch population-based study initiated in 2008 to evaluate BCa screening. A total of 6500 men were invited to participate in the study, 1984 (30.5%) agreed, and 1747 (88.1%) men completed the protocol and were followed for 2 yr.
Intervention: The screening protocol included home hematuria testing followed by molecular markers—nuclear matrix protein 22 (NMP22), microsatellite analysis (MA), fibroblast growth factor receptor 3 (FGFR3) mutation snapshot assay, and a custom methylation-specific (MLPA) test—to determine the need for cystoscopy.
Outcome measurements and statistical analysis: Outcomes included the number of cystoscopies and the cancer detection rate within and outside the protocol, as determined by linkage to national registries.
Results and limitations: Overall, 409 men (23.4%) tested positive for hematuria and underwent molecular testing. Current smokers ($n = 295$ [17%]) and past smokers ($n = 998$ [58%]) were significantly more likely to test positive for hematuria than nonsmokers. Seventy-one of 75 men (94.6%) with positive molecular markers underwent the recommended cystoscopy. Four BCas and one kidney tumor were detected through this sequential protocol, whereas one BCa and one kidney tumor were missed through the screening program. Limitations include the possibility of healthy subject bias.
Conclusions: For BCa screening, use of a sequential protocol with home hematuria testing followed by molecular markers substantially reduced the number of cystoscopy recommendations compared with dipstick testing alone. A sequential screening approach may help minimize unnecessary invasive follow-up testing, with very few missed cancers. Nevertheless, this mass screening program had a very low diagnostic yield in an unselected asymptomatic European male population.

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1. Introduction

In 2012 bladder cancer (BCa) accounted for 7% of new cancer diagnoses and 3% of cancer deaths in US men [1]. Due to the high costs of monitoring and treatment, it was among the most expensive cancers in the United States and accounted for approximately $3.7 billion in 2001 [2]. BCa is also a major problem worldwide. According to data from GLOBOCAN 2008, there were 133 696 new BCa cases and 51 056 deaths in Europe [3].

Approximately one-fourth of BCas are muscle invasive at the time of diagnosis, with high rates of treatment-related morbidity as well as metastatic progression. Accordingly, there has been investigation into BCa screening, with the goal of identifying the disease at an earlier stage.

Initial studies of home dipstick testing for microhematuria found lower cancer-specific mortality among screen-detected cases compared to registry data [4,5]. However, the positive predictive value (PPV) of home microhematuria testing as a trigger for further evaluation was 8% for urothelial carcinoma and 12.3% for any genitourinary malignancy. Traditional screening tools (eg, cystoscopy) are not adequate for population-based screening because they are invasive and are not cost-efficient [2]. In addition, the procedure may be associated with some pain or discomfort in a third of cases [6]. To reduce the number of unnecessary cystoscopies required to diagnose a single cancer, the authors suggested future studies to evaluate a sequential screening approach with dipstick testing and molecular markers [7].

Such a study, called the Bladder Cancer Urine Marker Project [BLU-P], was initiated in the Netherlands [8]. This study analyzed the feasibility and performance characteristics of BCa screening with newly developed molecular tools in an asymptomatic Dutch population. The purpose of this report is to present the final results of the BLU-P study, which has been completed.

2. Patients and methods

2.1. Subjects, recruitment, and underlying risk factors

BLU-P was designed as a feasibility study to assess the feasibility of population-based screening for BCa on the basis of consecutive (14-d) home-based hematuria testing.

In addition, we aimed to assess the performance characteristics and feasibility of applying four urine-based molecular tests with the goal of reducing unnecessary cystoscopies; Messing et al. [4] found that up to 92% were unnecessary if positive hematuria was the only indication for cystoscopy.

At the beginning in February 2008, we identified 22 500 men aged 50–75 yr using the population registry of the city of Rotterdam. We excluded men with a prior history of BCa. A letter of invitation was sent in batches of 500 invitations to the remainder to participate in a BCa screening protocol [8]. As in prior studies [5,9], only men were included in this feasibility study because the incidence of BCa in the Netherlands is four times higher in men and thus fewer participants would be required to test the proposed algorithm.

At baseline, all participants completed a detailed questionnaire regarding their demographics, diet, medication, family history of BCa, occupation (eg, exposure to heavy metals, dry cleaning chemicals), and specific exposures that have been associated with BCa risk (eg, smoking, artificial sweeteners). Men who returned the signed informed consent and the completed questionnaire were included in the study and received by mail the hematuria dip sticks, an instruction letter, and a form to record the test results (Fig. 1).

2.2. Screening tests

The screening protocol involved a two-tiered approach beginning with home hematuria testing using 14 dipsticks for 14 consecutive days (Siemens Health Care Diagnostics, Breda, The Netherlands). After completing the 14-d testing, men returned the test results by mail. Men with one positive home hematuria test or more were recommended to undergo the second tier of screening with four molecular biomarkers: nuclear matrix protein 22 (NMP22), microsatellite analysis (MA), fibroblast growth factor receptor 3 (FGFR3) mutation snapshot assay, and a custom methylation-specific multiplex ligation-dependent probe amplification (MLPA) test.

For the molecular testing, men were asked to collect four urine samples of approximately 50 ml, which were mixed with Copan preservative (Copan Italia SpA, Brescia, Italy). At the screening visit, the samples were tested for leukocytes to avoid confounding of the results from a urinary tract infection. Men with positive leukocyte tests were referred to their general practitioners, and repeated molecular testing was performed after 6 wk with a negative dipstick leukocyte test.

2.2.1. Nuclear matrix protein 22

NMP22 is a point-of-care urine test for nuclear matrix proteins that was previously shown to have greater sensitivity than urine cytology for BCa detection. The NMP22 point-of-care test was performed at our screening center using four drops of fresh voided urine, as previously described [11]. The result becomes available after 30 min. Our personnel were trained by Matritech. It was anticipated that sensitivity and specificity for NMP22 would be 75% and 80%, respectively.

2.2.2. Microsatellite analysis

Microsatellites are repetitive sequences within the genome, and prior studies have shown that loss of heterozygosity (LOH) is a frequent event in urothelial carcinoma [12]. MA was performed at the molecular section of the pathology department of Erasmus University Medical Center (Rotterdam, The Netherlands). The test uses 10–12 microsatellite markers and is considered positive in cases of LOH of one marker or more. LOH is scored if the allelic imbalance ratio is <0.70 [13]. For MA, it was anticipated that sensitivity and specificity would be approximately 90% and 95%, respectively.

2.2.3. Fibroblast growth factor receptor 3

Mutations in the *FGFR3* gene may also be measured in urine and have been associated with detection of noninvasive urothelial carcinoma [12]. FGFR3-mutation detection was performed using the Snapshot analysis, as described by Van Oers et al. [14]. A mutation is detected as an additional and differentially labeled peak in the electropherogram. When no mutation is present, only the peaks for the wild type nucleotides are visible. For the FGFR3-mutation Snapshot assay, the expected sensitivity and specificity were 62% and 89%, respectively.

2.2.4. Multiplex ligation-dependent probe amplification

Finally, the MLPA test has been previously reported by our group and is based on previous data showing aberrant methylation in BCa [15]. The MLPA assay tests 25 possible methylation sites in the genome. The results are displayed as peaks in an electropherogram that appear only when the site is methylated. When one of these peaks is present (eg, CH3), the gene is considered to be methylated. For the methylation MLPA assay, the anticipated sensitivity and specificity were 82% and 96%, respectively.

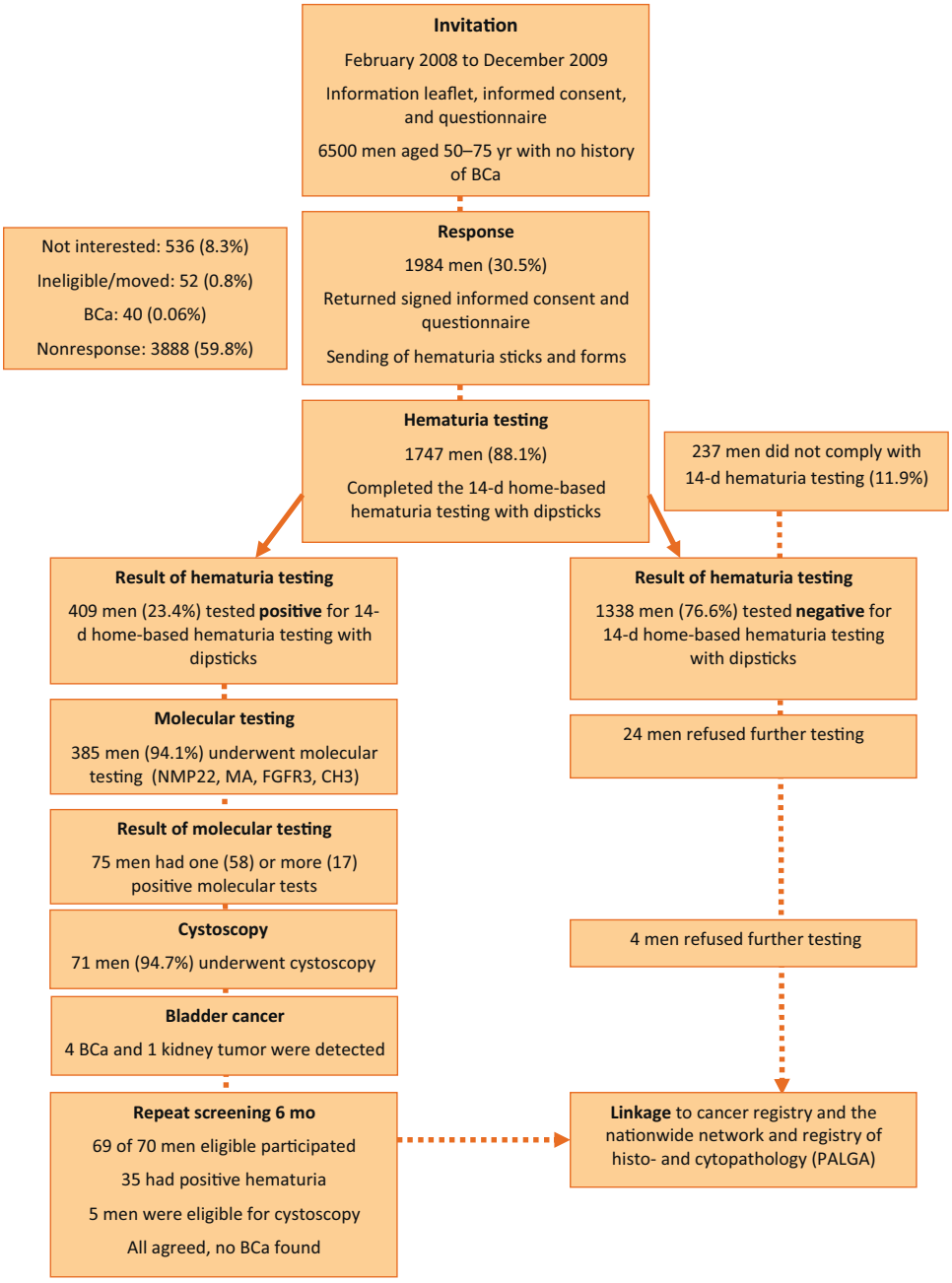

Fig. 1 – Bladder Cancer Urine Marker Project (BLU-P) flow chart. BCa = bladder cancer; CH3 = methyl group CH3; FGFR3 = fibroblast growth factor receptor 3; MA = microsatellite analysis; NMP22 = nuclear matrix protein 22.

2.3. *Disease ascertainment*

Men with one positive molecular test or more were recommended to undergo outpatient flexible cystoscopy, which was performed at the urology department at Erasmus University Medical Center. Urologists performing the cystoscopy were aware of a positive test but were not aware which test was positive. Participants with macroscopic intravesical or intraurethral abnormalities on flexible cystoscopy were referred for transurethral endoscopic biopsy or resection, whereas those with bloody efflux from the ureteral orifice were referred for further work-up. Participants with positive markers and a negative cystoscopy were asked to undergo rescreening with microhematuria home testing at 6 mo. A positive marker result without positive cystoscopy findings during the *second* screening resulted in advice for upper tract evaluation by contrast computed tomography scan in collaboration with the urologist. Due to the low incidence of upper urinary tract urothelial cell tumors, it was estimated that not more than one or two cases would be found.

All data were prospectively recorded, including all BCa and other genitourinary malignancies identified through the study. Medical records were reviewed to obtain information on stage and grade for tumors diagnosed through the screening protocol. For individuals who provided informed consent, linkage was also performed with the nationwide network and registry of histo- and cytopathology (ie, PALGA) and the regional cancer registry to identify urologic cancers diagnosed outside the study protocol during a 2-yr period (Fig. 1).

2.4. Statistical analysis

The primary objective of the study was to assess the feasibility of home-based hematuria testing as well as the feasibility of including urine-based molecular markers as a method of BCa screening in an asymptomatic population of men without prior history of BCa. In addition, we wanted to assess performance characteristics of the additional molecular markers with regard to their potential to reduce unnecessary cystoscopies.

To assess the test performance characteristics, we hypothesized that the detection of 140–150 BCa cases would allow reliable statistical testing. Based on available literature, we estimated that 20% of participants would have microhematuria on home testing and that approximately 7–8% of BCa cases would be detected in the hematuria-positive group (55% low-grade and 45% high-grade cancers) [4,5,9]. Based on prior data from BCa screening studies elsewhere and compliance data from the European Randomized Study of Screening for Prostate Cancer [10], approximately 45% of men invited to participate in the screening study would accept the invitation. These estimates led us to estimate that we needed approximately 2000 men testing positive for hematuria, 10 000 men actively participating, and 22 500 invitations.

All statistical analysis was performed using Stata, and $p < 0.05$ was considered statistically significant. Descriptive statistics were used to characterize the frequency of positive dipstick and molecular tests. For each marker, the following performance characteristics were calculated: sensitivity, specificity, PPV, and negative predictive value (NPV). We also calculated odds ratios (ORs) for positive dipstick and molecular tests based on smoking status (defined as *current smoker, past smoker*, or *nonsmoker*).

2.5. Trial registry and monitoring

The trial was approved by the Health Council of the Netherlands (2007/01WBO. ISBN: 978-90-5549-634-1). A data monitoring committee (DMC) was established to check data entry. The DMC delivered data every 6 mo to M.J. Roobol for statistical analysis. A quality control committee was established for supervision of histology and marker assays.

3. Results

3.1. Outcomes of the screening program

From a total of 6500 men invited to the study up to December 2009, 1984 (30.5%) responded that they would participate in the study and 536 responded that they would not participate. An additional 23 invitations were returned because the addressee had moved away from the area and 19 had died. An additional 50 responded that they were ineligible to participate due to a prior history of BCa ($n = 40$) or because they were too old ($n = 10$).

Of the 1984 men who agreed to participate, 1747 (88.1%) actually underwent hematuria testing. Of these, 1338 (76.6%) were negative for hematuria and 409 (23.4%) tested positive for hematuria, including 203 (49.6%) with trace hematuria and 206 (50.4%) with more significant hematuria.

Of the 409 patients who tested positive for hematuria, 385 (94.1%) underwent molecular testing according to the study protocol, and 18 men tested positive for leukocytes, 3 of whom had a positive NMP22 test. These men were retested 6 wk later with a negative leukocyte dipstick and again tested positive for NMP22. Considering each test separately, 14 (3.6%) tested positive for NMP22, 33 (8.6%) tested positive for MA, 6 (1.6%) tested positive for FGFR3, and 40 (10.4%) tested positive for CH3. Of the men with significant (nontrace) microhematuria, NMP22, MA, FGFR3, and CH3 were positive in 7 (3.4%), 16 (7.8%), 4 (1.9%), and 16 (7.8%) participants, respectively. Overall, 58 participants had one positive molecular test, 16 had two positive molecular tests, and 1 had three positive molecular tests.

On the basis of positive hematuria and molecular testing, cystoscopy was recommended for 75 individuals, and 71 (94.6%) actually underwent cystoscopy. Four BCas (one pTa grade 1 and three pTa grade 2) and one kidney urothelial tumor were detected through the screening. Repeat screening at 6 mo did not result in additional BCa diagnoses (Fig. 1). At this point, it was decided to stop further inclusion and evaluate the outcomes of the screening trial with the available data.

Based on the study design, all four participants diagnosed with BCa in the study had positive hematuria and molecular tests (sensitivity and NPV 100% by design). For significant hematuria by dipstick, the specificity was 88.4% and PPV was 1.9% for a diagnosis of BCa in the study.

For any positive molecular test, the specificity was 95.9% and PPV was 5.3% for a diagnosis of BCa within the study. For the individual tests, NMP22 had a sensitivity of 25%, specificity of 99.3%, PPV of 7.7%, and NPV of 99.8%. MA had a sensitivity of 50%, specificity of 98.2%, PPV of 6.1%, and NPV of 99.9%. FGFR3 had a sensitivity of 25%, specificity of 99.7%, PPV of 20%, and NPV of 99.8%. Finally, CH3 had a sensitivity of 25%, specificity of 97.8%, PPV of 2.5%, and NPV of 99.8%.

3.2. Cancer registry linkages

Using linkages to the Dutch cancer registry and PALGA during 2-yr follow-up, we identified one participant from the screening program with negative hematuria testing who had a prior history of BCa in 2007. In addition, we identified one BCa and one kidney cancer diagnosed among compliant participants within a year of the screening program; therefore, these were deemed to have been missed by the protocol. Finally, two BCas were diagnosed in men who signed informed consent to participate but did not follow through with the hematuria testing. Considering only participants without a prior diagnosis of BCa, Table 1 shows the performance characteristics of sequential hematuria and molecular testing, incorporating the registry data.

3.3. Risk factor analysis

A history of smoking was reported by 1721 (98.5%) of the 1747 men who underwent hematuria testing. A total of 428 men (24.9%) never smoked, 998 men had smoked in the past (58%), and 295 men still smoked (17.1%). Table 2 shows the percentages of positive hematuria tests and outcomes of molecular testing by smoking status. Current smokers (OR: 1.90 [95% confidence interval [CI], 1.20–3.00) and past smokers (OR: 1.43 [95% CI, 0.97–2.11) were more likely to have true positive hematuria than nonsmokers. Similar

Table 1 – Performance characteristics of sequential microhematuria and molecular marker testing for incident bladder cancer for participants in the Bladder Cancer Urine Marker Project (BLU-P) with no prior history of bladder cancer (including registry data)

	Sensitivity, %	95% CI	Specificity, %	95% CI	PPV, %	95% CI	NPV, %	95% CI
Any microhematuria	80	28.4–99.5	76.7	74.7–78.7	0.98	0.3–2.5	99.9	99.6–100.0
Nontrace microhematuria	80	28.4–99.5	88.4	86.8–89.9	1.9	0.5–4.9	99.9	99.6–100.0
Any positive molecular marker*	80	28.4–99.5	95.9	94.9–96.8	5.3	1.5–13.1	99.9	99.7–100.0
+ NMP22*	25	0.63–80.6	96.6	94.2–98.2	7.1	0.18–33.9	99.2	97.7–99.8
+ MA*	50	6.8–93.2	91.9	88.7–94.4	6.1	0.74–20.2	99.4	98.0–99.9
+ FGFR*	25	0.63–80.6	98.7	97.0–99.6	16.7	0.42–64.1	99.2	97.7–99.8
+ CH3*	25	0.63–80.6	89.8	86.3–92.6	2.5	0.06–13.2	99.1	97.5–99.8

CH3 = methyl group; CI = confidence interval; FGFR3 = fibroblast growth factor receptor 3; MA = microsatellite analysis; NPV = negative predictive value; NMP22 = nuclear matrix protein 22; PPV = positive predictive value.
* Only performed in 385 patients with positive microhematuria testing.

Table 2 – Percentages of positive home-based hematuria testing and molecular testing per smoker status (never, past, and current smoker)

	Never smoked, %	Past smoker, %	Current smoker, %	*p* value**
Any microhematuria	19.6	23.4	27.5	0.047
Nontrace microhematuria	8.6	11.9	15.3	0.023
Any positive molecular marker*				
+ NMP22*	2.4	3.8	3.7	0.817
+ MA*	10.7	5.6	13.6	0.051
+ FGFR*	1.2	2.1	–	0.382
+ CH3*	13.1	9.0	8.6	0.512

CH3 = methyl group; FGFR3 = fibroblast growth factor receptor 3; MA = microsatellite analysis; NMP22 = nuclear matrix protein 22.
* Only performed in 385 patients with positive microhematuria testing.
** Chi-square test.

results for molecular testing showed no significant differences with ORs >1 comparing current and past smokers with nonsmokers for MA, NMP22, and FGFR3 and an OR <1 for CH3. Interestingly, three of the four BCas found in the study were in nonsmokers. With regard to occupational exposures, 36% of men answered positively to one of these options. Industrial cleaning agents (eg, dry cleaning; 15%), paint/glue/solvents (17%), and heavy metals (6.8%) were the most commonly reported exposures. There were no significant differences in positive hematuria or positive molecular tests based on these occupational exposures.

4. Discussion

BCa screening has been studied as a possible way to decrease the frequency, morbidity, and mortality of advanced disease. Our results from the BLU-P screening study suggest that sequential screening for BCa using home dipstick testing and molecular markers is feasible but has a low diagnostic yield in an asymptomatic European population. Although the use of molecular markers reduced the number of cystoscopies performed for microhematuria evaluation, very few urothelial tumors were diagnosed in this protocol (0.23%).

For comparison, prior international studies evaluated BCa screening using dipstick testing alone. In the United States, Messing et al. performed two sequential studies of hematuria home screening for average-risk men age ≥50 yr [4,5]. In the first phase, participants performed daily home hematuria testing for 5 d, then weekly testing for 1 yr. In the second phase, participants performed daily testing for 2 wk, and if all tests were negative, this was repeated 9 mo later. Any positive result led to referral for laboratory studies, upper tract imaging, and cystoscopy. Of 3515 men invited, 1575 completed the study (44.8%). A total of 21 BCas were diagnosed (1.3%) through screening, and no screening participant was diagnosed with BCa outside of the protocol within 18 mo of completion.

Compared to unscreened men from the Wisconsin Tumor Registry, screening detected a similar amount of low-grade superficial tumors [4]. However, high-grade tumors were more likely to be diagnosed at a muscle-invasive stage in unscreened registry men compared with screening participants. Furthermore, with long-term follow-up, the authors reported lower disease-specific mortality among BCa cases diagnosed through the screening program compared with registry data [5,16]. Despite these positive findings, potential harms are associated with screening for BCa, including the costs of the screening program. Another harm is false-positive dipstick results, leading to unnecessary imaging and/or cystoscopic procedures with associated cost and potential morbidity [2,6].

Another study of home dipstick testing was performed by Britton et al. in the United Kingdom, including 2356 average-risk men age >60 yr [9]. Of 474 men with hematuria on dipstick, 319 agreed to further investigation. Overall, 17 men had bladder tumors, of which 10 had abnormal urine cytology. The authors concluded that routine population-based screening with dipsticks would lead to a large number of men requiring further urologic

work-up but that combining dipsticks with cytology might provide an alternate strategy.

Due to these concerns about the number of unnecessary diagnostic evaluations triggered by home dipstick testing alone, our study sought to examine the results of a sequential approach with molecular markers. An increasing number of new BCa markers have been recently identified, and there is a great need for additional data on the integration of these markers into clinical paradigms [7]. Our study did not find utility in population-based BCa screening through home dipstick testing and molecular markers. These findings are in line with the recently updated US Preventive Services Task Force recommendation statement on BCa screening [17]. Following a systematic review of the published data, the task force determined that there was insufficient evidence to assess the balance of benefits and harms of screening in asymptomatic adults.

It should be noted that screening for BCa may have different performance characteristics in selected high-risk populations, such as those with aristolochic acid nephropathy or occupational exposures [18,19]. Indeed, the proportion of smokers in our study population (17.1%) is lower than the 27% reported prevalence of smoking in the overall Dutch population [20]. In previous studies, smoking status affected the performance characteristics of molecular tests [21]. Because smoking is one of the most important independent risk factors for BCa [22], the lower proportion of smokers in this study may help to explain the lower-than-expected yield of screening in this population.

Several limitations of our study deserve mention. Of the 6500 men invited to participate in the study, only 1747 ultimately followed through with home dipstick testing. This reduced the sample size to look at the influence of potential risk factors and may have led to bias in the results if there were systematic differences between participants and nonparticipants. Similar to prior studies, this was not a randomized trial, and it is also possible that the results would have differed using an alternate set of markers. There was no method to verify compliance with home testing; however, it must be noted that in earlier screening studies, compliance with home-based hematuria testing was 97.7%, and 88.7% used the correct techniques [4].

Cystoscopy was performed only in patients with positive sequential tests, and verification bias is possible. Although registry data were used to assess for BCa diagnosed outside the screening protocol during the 2 yr of follow-up, it was possible to perform this linkage only for individuals who provided informed consent. In addition, the participants in our study were mostly white men from the Netherlands, so the results may not be generalizable to other populations with different genetic and environmental risk factors. Moreover, women were not included in the study because of the lower incidence of BCa and the worse performance characteristics of dipstick hematuria and molecular testing in women [21]. Finally, the economic impact of screening programs is an important consideration [23]; however, we did not assess costs in this study because the program was not considered an effective intervention for use in the general population.

5. Conclusions

A sequential BCa screening protocol of home dipstick testing followed by molecular markers substantially reduced the number of cystoscopy recommendations compared with dipstick testing alone and had very few missed cancers. However, this mass screening program was not useful in an unselected asymptomatic European male population. This finding might be explained in part by a lower frequency of risk factors in our population. Additional study is warranted to evaluate the performance of a two-tier screening protocol in selected high-risk cohorts.

Author contributions: Monique J. Roobol had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Bangma, Loeb, Zwarthoff, Roobol.
Acquisition of data: Bangma, El Bouazzaoui, Refos, Van Der Keur, Tjin, Franken, Busstra.
Analysis and interpretation of data: Loeb, Zhu, Roobol.
Drafting of the manuscript: Loeb, Zhu, Roobol.
Critical revision of the manuscript for important intellectual content: Bangma, Loeb, Busstra, Zhu, El Bouazzaoui, Refos, Van Der Keur, Tjin, Franken, van Leenders, Zwarthoff, Roobol.
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Supervision: Bangma, Zwarthoff, Roobol.
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