Detection of Clinically Significant Prostate Cancer by Systematic TRUS-Biopsies in a Population-Based Setting Over a 20 Year Period

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OBJECTIVE To assess the performance of systematic TRUS-biopsies in a population-based setting to detect clinically significant PCa (csPCa) in combination with age, clinical tumor category (cT), and prostate-specific antigen (PSA) in men referred for the first biopsy.

METHODS We identified all men referred for PCa work-up because of elevated PSA who underwent initial TRUS-biopsies in the nationwide Danish Prostate Cancer Registry (DaPCaR) between January 1st, 1995 and December 31st, 2016, in Denmark. Risk of histologic findings in initial TRUS-biopsies categorized as non−malignant, insignificant PCa, or significant PCa (csPCa). We defined csPCa as any biopsy containing Gleason score 3 + 4 or above as in the PRECISION trial. We assessed risk of csPCa with absolute risk, logistic regression model, and predicted risks.

RESULTS AND LIMITATIONS After exclusions, our cohort included 39,886 men. The diagnostic hit rate for csPCa was 40.8 %. Men with PSA > 20 ng/mL and ≥cT2 harbor a risk >75% for finding csPCa in the first TRUS biopsy-set. Men with cT1 tumors and PSA < 20 ng/mL have a risk of non−malignant histology of at least 58%. Limitations include the high number of exclusions based on missing information.

CONCLUSION The diagnostic accuracy of systematic TRUS-biopsies is high for men with palpable tumors and high PSA. Our data point to the fact that not all men need pre-biopsy MRI to find csPCa. UROLOGY 155: 20−25, 2021. © 2021 Elsevier Inc.

KEYWORDS Clinically significance, Pre-biopsy MRI, Prostate cancer, TRUS-biopsies

For decades, transrectal ultrasound-guided biopsies (TRUS-biopsies) have been the gold standard in prostate cancer (PCa) diagnostic work-up[1]. Standard sextant TRUS-biopsies were replaced by extended biopsies in the early 2000s to increase diagnostic accuracy.[2-5] However, even an extended biopsy scheme can result in false-negative TRUS-biopsies.[6-8]

Recently, magnetic resonance imaging (MRI) of the prostate has been introduced as an additional tool in the diagnostic work-up. Studies show a correlation between the assessment of the images and Gleason score (GS), and software enabling the fusion of MRI and ultrasound to target biopsies to areas of interest have been developed.[9-11] Initially, MRI studies of the prostate showed that many men with benign systematic TRUS-biopsies and elevated prostate-specific antigen (PSA) harbored clinically significant PCa (csPCa).[10,11] Later, pre-biopsy MRI studies have shown that an MRI-biopsy strategy can increase the number of csPCa and rule out significant disease.[9,12,13] This has questioned the validity of TRUS-biopsies to diagnose the patient correctly without MRI, and guidelines already advocate for pre-biopsy MRI in men referred for diagnostic work-up on the suspicion of PCa.[14] Studies investigating the performance of TRUS-biopsies to detect csPCa in combination with age, PSA-value, and clinical tumor category (cT) in an unselected population-based scale are lacking and could refine how we select men for

Abbreviations: *TRUS, transrectal ultrasound-guided; PCa, prostate cancer; csPCa, clinically significant prostate cancer; cT-category, clinical tumor category; PSA, prostate-specific antigen; MRI, magnetic resonance imaging; bpMRI, biparametric magnetic resonance imaging; DRE, digital rectal examination*

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pre-biopsy MRI in the future. We analyzed the results of the first systematic TRUS-biopsies in all Danish men referred for diagnostic work-up for suspicion of PCa in a 20-year period.

MATERIALS AND METHODS

Data Acquisition

The data were retrieved from The Danish Prostate Cancer Registry (DaPCaR), a population-based registry including all men with a histopathological assessment of prostatic tissue merged with clinical information including stage and PSA extracted from local laboratories across Denmark.[15] For the present study, PSA-values were included if taken within 6 months before the initial TRUS-biopsies. The DaPCaR is approved by the Danish Data Protection Agency (file number: 2012-41-0390), the Research Ethics Committee of the Capital Region of Denmark (local journal number: VD-2019-38), and the Danish Patient Safety Authority (3-3013-2814/1). We used data derived from all men who had TRUS-biopsies as their first specimen between January 1st, 1995 and December 31st, 2016. A full overview of the dataset including data for excluded men are available as Supplementary files. Due to missing data, some exclusions were performed before the final analysis of the cohort. Men who underwent MRI-guided biopsies were excluded. Men registered with cTx as TNM classification in the Danish Cancer Registry were excluded as this could represent different clinical scenarios such as unreachable prostate or registration error. We excluded men with PSA < 4 ng/mL as we do not know the exact reason for performing biopsies in the individual case. Lastly, men with missing PSA were excluded. The histologic findings were grouped into non−malignant, insignificant PCa, and significant PCa. We defined biopsies with GS 3 + 4 or above as csPCa according to the PRECISION trial.[12]

Statistics

For descriptive analysis, continuous variables were presented as medians with interquartile range (IQR) and categorical variables as total numbers. The absolute risk of the histologic findings in the first biopsy set was analyzed. The absolute risk was calculated as the number of men divided by the total number of men within the specific risk group based on age, PSA, and cT-category.

To demonstrate the absolute risk of csPCa, insignificant PCa, and non−malignant histology according to age, PSA, and cT-category, respectively, heatmaps were constructed. Risk categories and color gradings were classified into quartiles. In the heatmaps, PSA was categorized in 3 groups; 4-10 ng/mL, 10-20 ng/mL, >20 ng/mL. Age was categorized in 5-year intervals from younger than 60 years of age to older than 75 years of age. cT-categories were divided into cT1, cT2, or cT3 + T4. The number of men included for each risk group is also depicted in a heatmap to show the strength of this study. A logistic regression model to describe the risk of csPCa versus the other findings was computed using age, PSA, and cT as variables for univariate and multivariable analysis. In this model, age and PSA were analyzed as continuous variables with PSA on logarithmic base 2 scale and age as per ten-year increase. The model is graphically illustrated with knots from age 55 to 90 with 5-year intervals. We performed a sensitivity analysis for the year of biopsy to account for changes in referral patterns. Statistical analyses were performed with R version 4.0.2., *P*-values below .05 were considered statistically significant. The dataset is available upon request.

RESULTS

A total of 154,135 men were registered in DaPCaR, of whom 87,332 men had a first diagnostic systematic TRUS biopsy-set (Supplementary Table 1). The flow-chart is depicted in Figure 1.

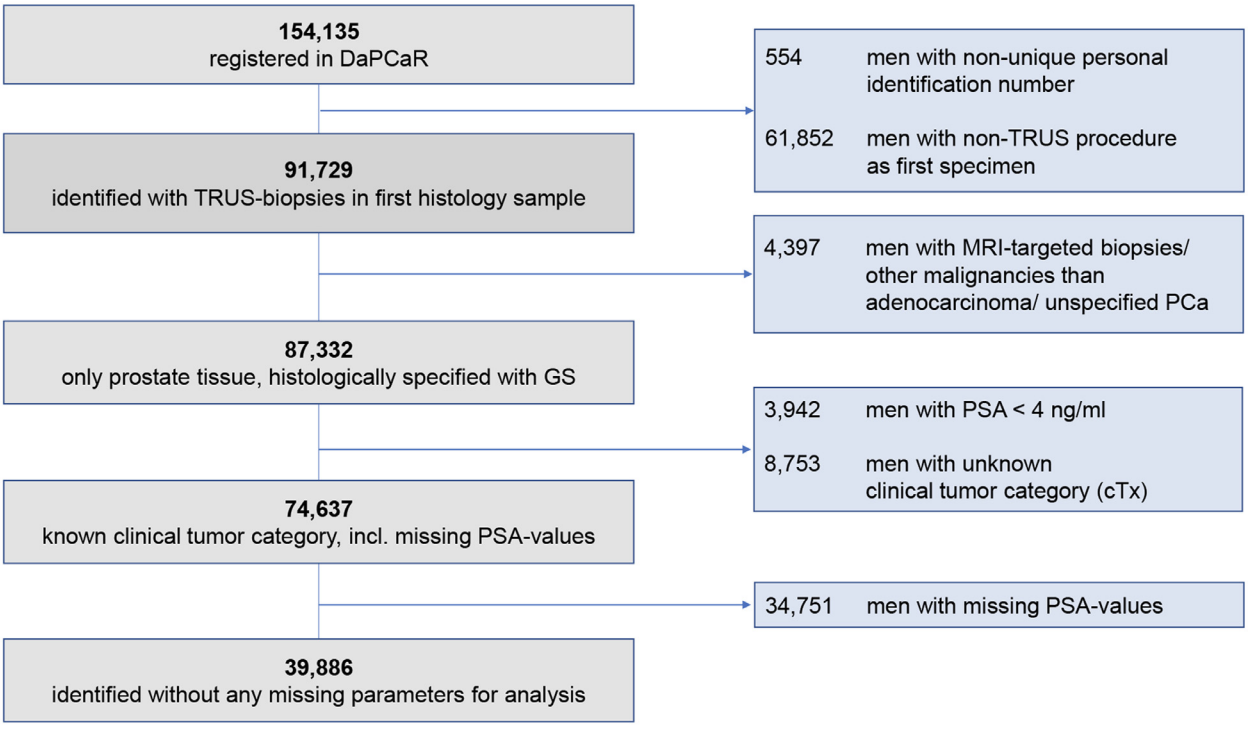

Figure 1. Flow-chart for the cohort (Color version of the figure is available online.).

Table 1. Characteristics of men with initial TRUS-biopsies with known PSA and cT-category

		N = 39,886
Age (Y), median (IQR)		68.1 (62.8-73.8)
PSA (ng/mL), median (IQR)		10 (6.6-23.1)
PSA grouping, N (%)	4-10 ng/mL	20,159 (50.5)
	10-20 ng/mL	8674 (21.7)
	>20 ng/mL	11,053 (27.7)
cT- category, N (%)	T1	25,731 (64.5)
	T2	7206 (18.1)
	T3 + 4	6949 (17.4)
Year of biopsy, N (%)	1995-2000	1104 (2.8)
	2001-2005	7077 (17.7)
	2006-2010	14,891 (37.3)
	2011-2016	16,814 (42.2)
TRUS-biopsy result, N (%)	Non−malignant	17,846 (44.7)
	Insignificant*	5760 (14.4)
	Significant†	16,280 (40.8)

* GS < 7.
† GS ≥ 7.

A total of 3942 had PSA lower than 4 ng/mL. Furthermore, 8753 men with unknown cT-category, and 34,751 men with missing PSA were excluded leaving a cohort of 39,886 men with full information on clinical parameters for analysis. Due to the high number of exclusions, we performed a series of analyses to demonstrate that the final cohort is representative of the total cohort. Firstly, the diagnostic hit rate including stratification per age in the total cohort is demonstrated in Supplementary Figure 1/Supplementary Table 1A. Secondly, a full heat-map depicting all the missing data in a separate column is shown in Supplementary Figure 2. Supplementary Tables 4 and 5 show the characteristics of men excluded based on PSA. We found that the missing PSAs were missing at random and that the analysis of the final cohort resembles the total cohort.

Patient characteristics for the final cohort at the first diagnostic biopsy are demonstrated in Table 1. The diagnostic hit rate for csPCa was 40.8 %. The median age and PSA were 68.1 years (IQR: 62.8-73.8) and 10 ng/mL (IQR: 6.6-23.1), respectively.

The heatmaps are shown in Figure 2. The heatmaps for the number of men in each of these risk groups are depicted in Supplementary Figure 4. As an example, the analyses

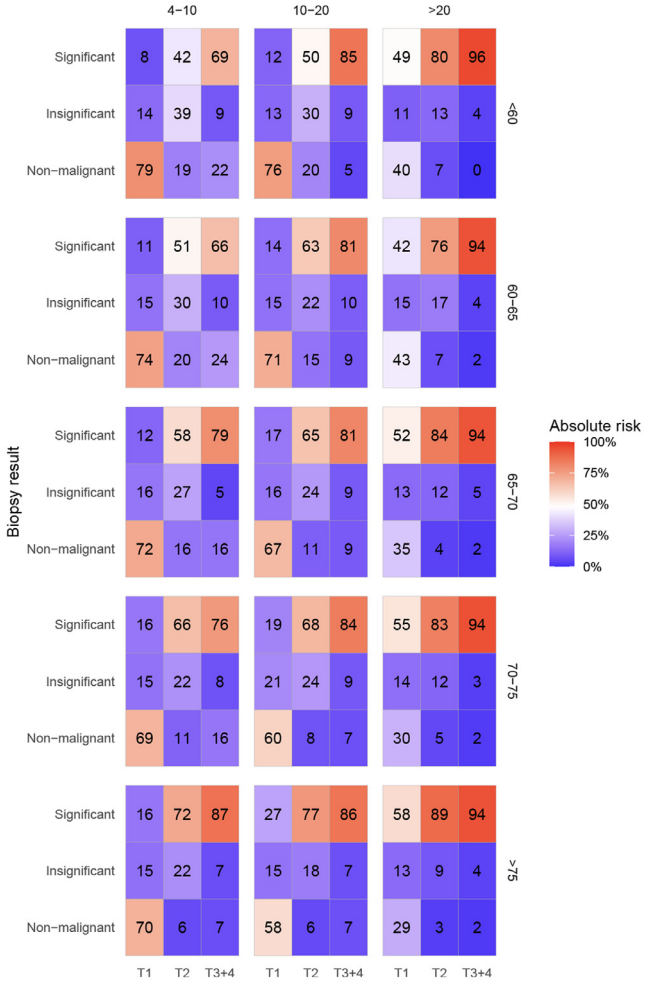

Figure 2. Heatmaps. The absolute risk of diagnosing clinically significant prostate cancer in the initial TRUS-biopsies based on the cohort (N = 39,886). The top of the columns are PSA-values, and the bottom of the columns are clinical tumor category. The left row is clinical significance, and the right row is the age in 5-year intervals. Biopsy containing GS 3 + 4 or above was defined as significant. Biopsies with dysplasia or high-grade prostatic intraepithelial neoplasia were considered non−malignant. Insignificant was the presence of adenocarcinoma with GS lower than 7 (Color version of the figure is available online.).

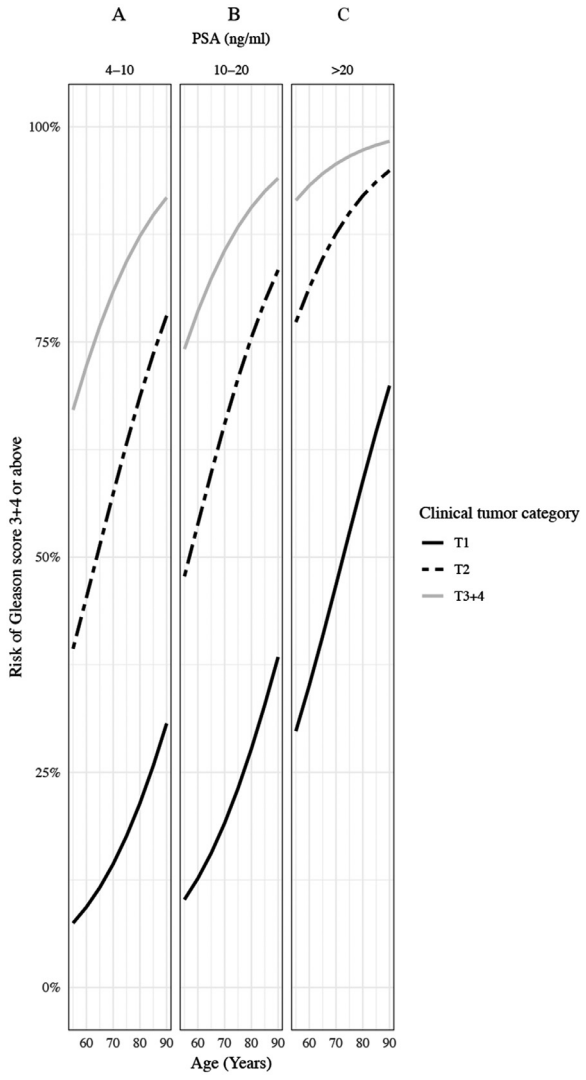

Figure 3. A-C: Predictive risk plots of diagnosing clinically significant prostate cancer in the first TRUS-biopsies for the cohort (N = 39,886). Biopsy containing GS 3 + 4 or above was defined as significant.

demonstrated that men with PSA > 20 ng/mL and ≥ cT2 all had a minimum 75% risk of csPCa in the first TRUS biopsy-set. On the other hand, it also showed that men with normal prostates (cT1) and PSA < 20 ng/mL had a risk of non−malignant histology of at least 58%.

The logistic regression analyses demonstrated that all included variables significantly affect the odds for csPCa in both univariate and multivariable analysis (Supplementary Table 2). Multivariable analysis of the cohort demonstrated that cT2 and cT3 + 4 are significantly associated with the risk of csPCa compared to cT1 (OR 8.42, 95% CI 7.91-8.96 and OR 18.43, 95% CI 16.89-20.11, respectively). A 10-year age increase increases the risk of csPCa (OR 1.41, 95% CI 1.36-1.46) and a doubling of PSA increases the risk of csPCa (OR 1.69, 95% 1.37-1.73). A graphical demonstration of the logistic regression is shown in Figure 3. Sensitivity analysis for the years of biopsy to account for changes in referral pattern did not find any impact on outcome (data not shown).

DISCUSSION

TRUS-biopsies have been standard procedure in diagnostic PCa work-up for decades.[1-5] Systematic TRUS-biopsies in combination with PSA have been criticized for the high risk of not finding cancer or overdetection of insignificant PCa, and the dilemma of overdiagnosis and overtreatment has persisted.[16] Moreover, diagnosing clinically irrelevant disease may cause harm to the patient both physically and mentally.[17,18] This problem and dilemma have fueled the interest in tools that can improve the prediction for estimating the individual risk of harboring PCa that needs treatment, also years before symptoms or metastatic disease.

Several biomarkers have been tested thoroughly during the past decades to improve sensitivity and specificity for the prediction of the biopsy result, but none has made it into clinical practice.[19] Recently, MRI of the prostate has been tested as an imaging biomarker to increase the diagnostic accuracy.[11,12] Studies show that pre-biopsy MRI can increase sensitivity and specificity to rule out significant disease.[9,12,13] As a result, international guidelines now recommend MRI before prostate biopsies for all men referred for suspicion of PCa.[14,20] However, the trials demonstrating a benefit from MRI applied the strategy to selected patients which may affect the generalizability of the results when transferred to men referred for biopsies in the general population.

The PRECISION trial included men with PSA ≤ 20 ng/mL and < cT3 but more than 75% of the included men had PSA < 10 ng/mL and most men (85%) had normal digital rectal examinations (DRE).[12] The mean age was 64.4 years and only 2.5% of the cohort were older than 72 years of age. In the trial, 28% of the men had no evidence of tumor on the MRI in which case biopsies were omitted. Therefore, we cannot derive the false-negative rate of MRI in the PRECISION trial which would have been clinically relevant. The trial was powered based on the assumption that csPCa would be found in 27% of biopsies in the TRUS-biopsy arm as demonstrated in a prior multi-practice community study.[21] This assumption was confirmed as 26% csPCa was found in the standard TRUS-biopsy arm. The percentage of men with csPCa in the PRECISION trial is lower than the overall percentage of men in our cohort; 26% versus 40.8%. If we only included men which would have been able to enter the PRECISION trial, we found a diagnostic hit rate for csPCa of 22%-30% (Supplementary Fig. 1/Table 1A). This confirms the selection bias in the PRECISION trial and the good argument for MRI in that clinical setting. It pinpoints that the optimal use of MRI may be selected to the group of men in which the risk of finding csPCa is low and where the negative predictive value (NPV) of a normal MRI results in avoidance of any biopsies to the prostate. This is also reflected in the BIDOC study which included 1020 men with a median PSA of 8 ng/mL (IQR: 5.7-13.0) and 37% with ≥cT2.[13] The aims were to test the diagnostic accuracy and the NPV of the biparametric

MRI (bpMRI) for detecting csPCa defined as either GS ≥4 + 3 or maximum cancerous core length >50% for GS = 3 + 4 and ruling out insignificant PCa, respectively. The BIDOC study found that 30% of men under suspicion of PCa could avoid prostate biopsies based on MRI results, and the NPV of a non−suspicious bpMRI was 97% (95% CI 95%-99%). The detection rate for csPCa was 47% for the targeted biopsies and 34% for the TRUS-biopsies. The study demonstrated that adding bpMRI to a model including PSA, cT-category, and age increased the likelihood of correctly predicting the presence of csPCa from 85% to 89%.[22] In our opinion, these results show that the largest benefit for the patient in the MRI pathway seems to be the NPV of a normal MRI and that patients should be selected based on the risk profile.

The definition of *clinically significant* PCa varies between MRI studies, and only a few studies follow the original definition proposed by Epstein *et al.* in 1994.[23] No clear international consensus exists although many studies define the presence of GS 3 + 4 or higher as csPCa.[12] Here, we chose the PRECISION definition for comparison. However, csPCa in this way refers to histopathological findings and not clinical endpoints. As discussed in an editorial in *European Urology*, MRI studies rely on the fact that csPCa detected on targeted biopsies have the same biological potential as the csPCa detected on systematic TRUS-biopsies which may not be the case.[24] We must continue to debate if 1 biopsy containing GS 3 + 4 is a disease that will become clinically important for the individual patient as observational data suggest that few patients with GS 3 + 4 will eventually progress to advanced disease.[25] The above-mentioned issues raise the debate whether all men before biopsies should undergo an MRI. This study shows that csPCa was detected with high probability in men with a clinically palpable tumor and high PSA.

Regardless of the age group, non−malignant histology is the most frequent biopsy result in men with cT1 and PSA < 20 ng/mL and this group of men seems to be an optimal candidate for pre-biopsy MRI which is in line with the selection criteria in the PRECISION trial. An important goal is still to reduce the number of unnecessary biopsies. Optimal selection for pre-biopsy MRI, based on data such as included here, could reduce the number of MRIs needed which may be a pertinent future problem as we switch biopsy strategy to an MRI pathway.

There are limitations to our study that must be addressed. It could be argued that the data are historical and do not represent a modern context. However, there are no previous population-based studies that have analyzed the diagnostic accuracy of the first TRUS biopsy-set. Although the European Randomized Study of Screening for Prostate Cancer (ERSPC) has shown data from the first biopsy round, the study only included men aged 55-70 years with a possible selection bias toward men suitable for and accepting entering a randomized trial.[26] That said, the data from the first biopsy results in ERSPC resemble the results demonstrated here regarding the risk of finding csPCa and demonstrate a close correlation with age, cT, and PSA. Unfortunately, most of the missing data here were PSA-values, which were missing at random. Over the 20-year inclusion period, a lot of laboratory databases have been closed or deleted and PSA-values could therefore not be retrieved. However, sensitivity analysis demonstrated that the final cohort was representative of the total cohort. It is recognized that ISUP 2005 reclassified the Gleason grading system and introduced a grade migration because of an upgrade of Gleason 3 to Gleason 4.[27] No ISUP-2005 re-evaluation of GS was done on histologic data before this reclassification which involves 20.5% of the total cohort. If regraded, the most likely effect would be a higher risk of csPCa in the cohort. Another limitation is the sparse variables in the prediction models. More factors such as PSA density, prostate volume, and a family history of PCa could improve the prediction of the risk of harboring csPCa in the first TRUS-biopsies. The data here included mainly men with European ancestry and the risk assessment may not be applicable among other ethnicities. The main strength of this study relates to the large population-based nature of the cohort that included all men referred for TRUS-biopsies in Denmark.

CONCLUSION

The likelihood of diagnosing csPCa on systematic TRUS-biopsies is high, especially in men with high PSA or clinically locally advanced PCa on DRE. Our data suggest that not all men need a pre-biopsy MRI and the optimal candidate should still be debated. According to this study, MRI seems optimal in men age <75 years, cT1, and PSA <20 ng/mL to reduce the number of unnecessary biopsies.

Acknowledgment. SMK, SBL, KB, and MAR contributed to the conception and design of the study. SMK, JTH, and BGT contributed to the acquisition of data. SMK, HVS, JTH, MAR participated in the collection and assembly of data. All authors participated in the draft of the manuscript, revised it critically, and gave final approval to submit for publication. SMK 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. MAR and KB report personal fees from Astellas Pharma A/S, Bayer a/s, Janssen-Cilag Nordic a/s, Amgen, Astra-Zeneca Nordic a/s, and Intuitive Surgical Systems, outside the submitted work. SMK, SBL, HVS, JTH, and BGT report nothing to declare.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urology.2021.06.007.

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