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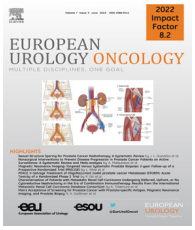

European Association of Urology

Effectiveness and Cost-effectiveness of Artificial Intelligence–assisted Pathology for Prostate Cancer Diagnosis in Sweden: A Microsimulation Study

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Abstract

Background and objective: Image-based artificial intelligence (AI) methods have shown high accuracy in prostate cancer (PCa) detection. Their impact on patient outcomes and cost effectiveness in comparison to human pathologists remains unknown. Our aim was to evaluate the effectiveness and cost-effectiveness of AI-assisted pathology for PCa diagnosis in Sweden.

Methods: We modeled quadrennial prostate-specific antigen (PSA) screening for men between the ages of 50 and 74 yr over a lifetime horizon using a health care perspective. Men with PSA $\geq$3 ng/ml were referred for standard biopsy (SBx), for which cores were either examined via AI followed by a pathologist for AI-labeled positive cores, or a pathologist alone. The AI performance characteristics were estimated using an internal STHLM3 validation data set. Outcome measures included the number of tests, PCa incidence and mortality, overdiagnosis, quality-adjusted life years (QALYs), and the potential reduction in pathologist-evaluated biopsy cores if AI were used. Cost-effectiveness was assessed using the incremental cost-effectiveness ratio.

Key findings and limitations: In comparison to a pathologist alone, the AI-assisted workflow increased the number of PSA tests, SBx procedures, and PCa deaths by $\leq$0.03%, and slightly reduced PCa incidence and overdiagnosis. AI would reduce the proportion of biopsy cores evaluated by a pathologist by 80%. At a cost of €10 per case, the AI-assisted workflow would cost less and result in <0.001% lower QALYs in comparison to a pathologist alone. The results were sensitive to the AI cost.

Conclusions and clinical implications: According to our model, AI-assisted pathology would significantly decrease the workload of pathologists, would not affect patient quality of life, and would yield cost savings in Sweden when compared to a human pathologist alone.

Patient summary: We compared outcomes for prostate cancer patients and relevant costs for two methods of assessing prostate biopsies in Sweden: (1) artificial intelligence (AI) technology and review of positive biopsies by a human pathologist; and (2) a human pathologist alone for all biopsies. We found that addition of AI would reduce the pathology workload and save money, and would not affect patient outcomes when compared

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to a human pathologist alone. The results suggest that adding AI to prostate pathology in Sweden would save costs.

1. Introduction

The diagnosis of prostate cancer (PCa) is typically determined via histopathological examination of needle biopsy samples from the prostate. A standard biopsy (SBx) following an elevated prostate-specific antigen (PSA) test result typically involves 10–12 needle cores sampled per patient. As PCa is the second most common cancer among men globally, a large number of cores need to be examined by pathologists [1]. This heavy workload is compounded by a shortage of pathologists worldwide, especially in low- and middle-income countries, where there is approximately one pathologist per 1 million population [2–4]. The scarcity of pathologists may lead to delayed diagnosis and treatment for patients, eventually affecting patients' survival and quality of life.

Image-based artificial intelligence (AI) methods to assist in pathology examinations have recently been developed and have shown very good discrimination for PCa diagnosis [5,6]. In Sweden, an AI prediction algorithm trained using biopsy slides from the population-based STHLM3 diagnostic study achieved excellent cancer detection performance, with an area under the receiver operating characteristic curve of 0.997 for an internal independent data set and 0.986 for an external validation data set [7]. Clinical validation studies have indicated that AI can improve on the sensitivity and specificity of pathologists and can reduce inter-pathologist variance when used as a parallel viewer [5,8,9]. This suggests that AI-assisted prostate pathology may be clinically implemented in different ways, for example, to improve sensitivity if there is high likelihood that pathologists have missed cancer in tissue samples, to improve inter-pathologist concordance, or to reduce the workload for pathologists.

The aim of this study was to evaluate the effectiveness and cost-effectiveness of implementing AI-assisted prostate pathology to reduce the workload for pathologists. The potential of AI to decrease the pathology workload needs to be assessed in terms of, for example, the reduction in the number of biopsy cores that need to be viewed by pathologists. When using AI as an alternative to pathologists, it is expected that patient outcomes might be affected because of false-negative cases missed by the AI; long-term outcomes for such cases have not yet been investigated. Moreover, an AI implementation requires additional costs related to the AI operation, which must be balanced against the potential reduction in pathology costs with an AI-assisted workflow. From a health economics perspective, it is critical to assess the overall impact of AI implementation on both long-term patient outcomes and costs.

2. Patients and methods

We used a microsimulation model for PCa screening to evaluate the effectiveness and cost-effectiveness of adding AI to a pathologist for prostate pathology in comparison to a pathologist alone in the Swedish health care setting.

2.1. Study population and screening strategy

We modeled men from the age of 50 yr over a lifetime horizon. The screening strategy was quadrennial PSA testing via general practitioners for men aged 50–74 yr (Fig. 1). Individuals with PSA ≥3 ng/ml were referred to a urologist for SBx.

The SBx cores would be examined using either the AI + a pathologist, or a pathologist alone (Fig. 2). In the AI-assisted workflow, the AI would examine all cores and filter out the cores that are highly likely to be benign. The pathologist would then examine the cores labeled positive by the AI. If cancer was detected in those cores, we assumed that the pathologist would not examine the AI-labeled negative cores.

2.2. Microsimulation model

We used an individual-level microsimulation model to simulate life histories that included cancer screening for all men, and PCa onset, progression, diagnosis, treatment and management, and death for PCa patients [10]. Health states were defined according to tumor T stage, International Society of Urological Pathology grade group (ISUP GG), and metastasis. This model has been well calibrated for the Swedish population using data from multiple registers and clinical trials [11–13]. A total of 10 million individuals were

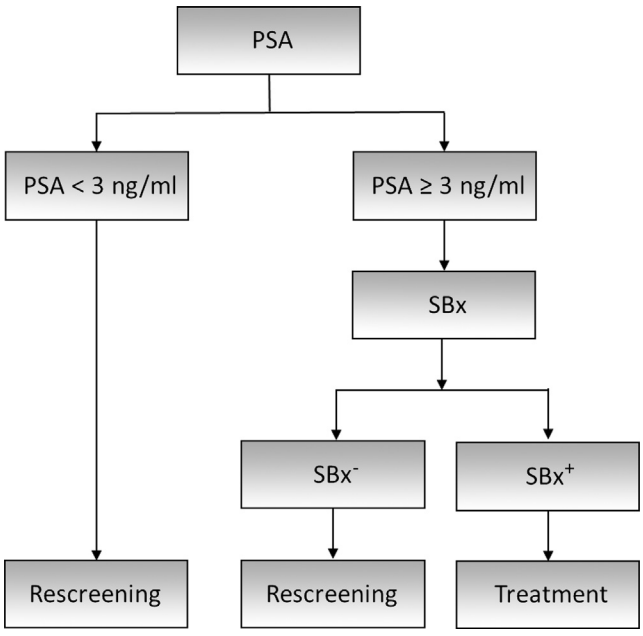

Fig. 1 – Schematic of the reference screening strategy. PSA = prostate-specific antigen; SBx = standard biopsy.

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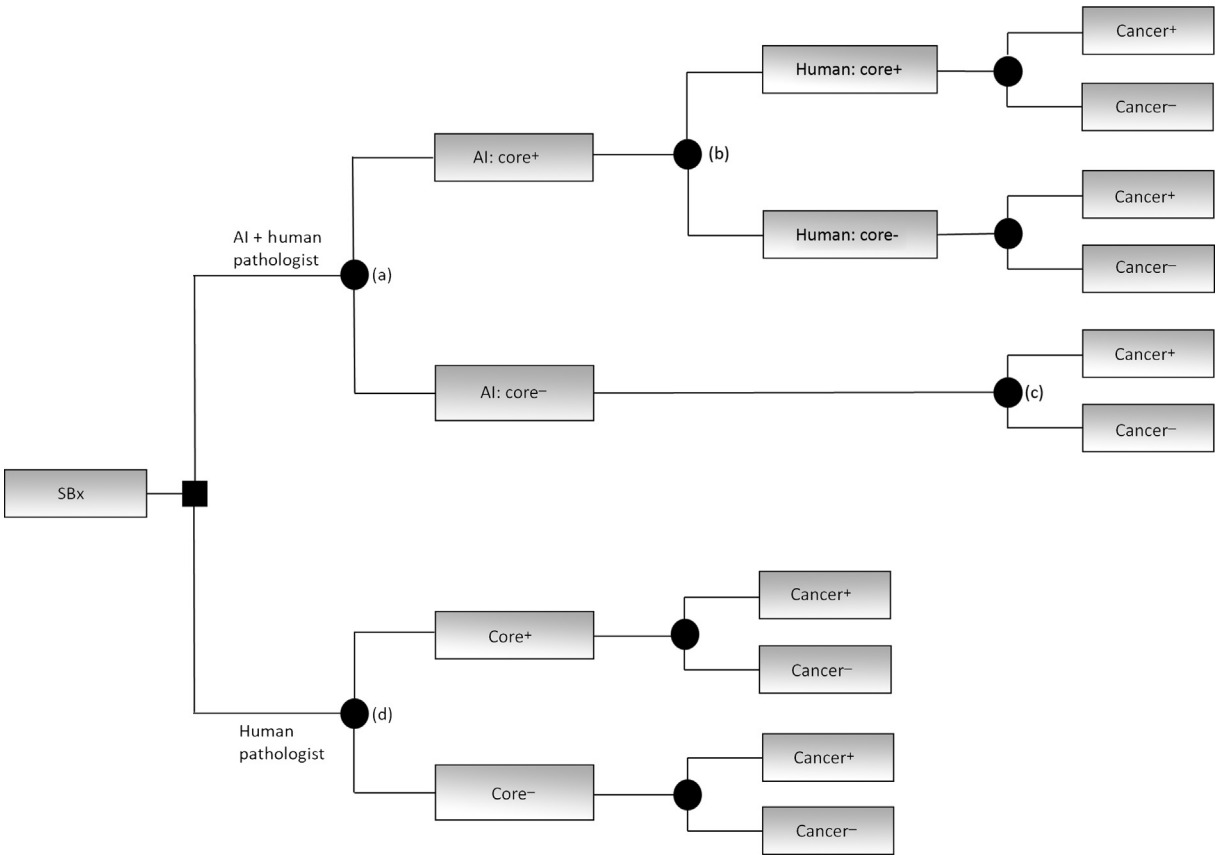

Fig. 2 – Decision tree comparing the AI + human pathologist and human pathologist alone workflows. A filled box denotes a decision node and filled circles denote chance nodes. For the AI + human pathologist workflow: (a) AI examines all the SBx tissue cores and labels them as either positive (suspicious for cancer; core$^+$) or negative (no suspicion of cancer; core$^-$); (b) a human pathologist then examines the cores labeled as positive by AI; and (c) for cores labeled as negative by AI, some men may have a delayed or missed diagnosis of cancer. For the human pathologist alone: (d) all cores are examined. Cancer$^+$ = patient with suspicion of cancer; Cancer$^-$ = patient with no suspicion of cancer. AI = artificial intelligence; SBx = standard biopsy.

simulated in the base case. Details of the microsimulation model have been described by Karlsson et al [10].

2.3. *Performance characteristics*

False-negative SBx rates stratified by ISUP GG are given in Table 1. We assumed that the true disease status was represented by SBx, and by combined targeted biopsy and SBx for men who had positive magnetic resonance imaging (MRI) results. These values were estimated using data from the STHLM3-MRI study and data on SBx for men who were MRI-negative from a multicenter clinical study (Supplementary material) [14–16].

AI performance characteristics in detecting cancer were estimated using data from the internal STHLM3 validation data set [7]. The sensitivity of AI at the per-patient level was calculated given the ISUP GG and prespecified sensitivity values at the per-core level (Table 1 and Supplementary material). Per-core sensitivity values of 97%, 98%, and 99% resulted in identical per-patient sensitivity for cancer detection. To balance the sensitivity of cancer detection and the reduction in biopsy cores, per-core sensitivity of 97% was selected for the base case. The pathologist was assumed to be 100% accurate for cancer detection in the base-case analysis.

Table 1 – SBx and AI performance characteristics used as input parameters in the cost-effectiveness analysis, stratified by grade group

Parameter	Value (95% CI)
SBx false-negative rate	
GG 1	0.057 (0.026–0.105)
GG 2–3	0.109 (0.073–0.156)
GG ≥4	0.109 (0.073–0.156)
Per-patient AI sensitivity [a]	
GG 1	0.992 (0.991–1.0)
GG 2–3	1.0 (0.985–1.0)
GG ≥4	1.0 (0.986–1.0)
Per-patient reduction in cores with AI [a]	
GG 0 (benign)	0.976 (0.912–1.0)
GG 1	0.577 (0.52–0.631)
GG 2-3	0.414 (0.315–0.515)
GG ≥4	0.249 (0.19–0.316)

AI = artificial intelligence; CI = confidence interval; GG = International Society of Urological Pathology grade group; SBx = standard biopsy
[a] Assuming per-core AI sensitivity of 97%.

2.4. *Outcomes reported*

For both workflows, we predicted mean lifetime estimates per 100 000 men followed from the age of 50 yr for biopsies,

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PCa incidence, clinically significant PCa (GG ≥2) incidence, overdiagnosis, mortality, and life expectancy. Overdiagnosis was defined as men who had screening-detected cancer but who would not have shown symptoms before dying from other causes. We also calculated the fraction of biopsy cores excluded by AI that would otherwise be examined by the pathologist.

2.5. Cost-effectiveness analysis

In accordance with Swedish guidelines, the base-case analysis was conducted from a health care perspective over a lifetime horizon [17]. Results are presented as the incremental cost-effectiveness ratio (ICER), calculated by dividing the difference in costs by the difference in quality-adjusted life years (QALYs) between the two workflows. An annual discount rate of 3% was applied. As there is no explicit cost-effectiveness threshold in Sweden, we used the cost-effectiveness categories suggested by the National Board of Health and Welfare. Low, moderate, high, and very high costs were defined as <100 000 Swedish Kronor (SEK; €9406), 100 000–499 999 SEK (€9406–€47 029), 500 000–1 million SEK (€47 029–€94 058), and >1 million SEK (€94 058) per QALY gained, respectively [18].

2.5.1. Resource use and costs

Direct costs related to screening, inpatient and outpatient care, pharmaceutical use, palliative care, and terminal illness were included in the base-case analysis. The resource use data and their unit costs were derived from previous health economics studies, with updates from more recent price lists where available (Supplementary Table 2) [14,19]. The base-case AI cost was assumed to be €10 per man (case). On the basis of expert opinion from Karolinska University Hospital, it was assumed that one-third of the total pathology costs in a laboratory can be attributed to the pathologists' time. The reduction in total pathology cost on addition of AI was calculated according to the proportional reduction in biopsy cores evaluated by a pathologist, stratified by ISUP GG, assuming per-core AI sensitivity of 97% (Table 1). All the unit costs were converted to calendar year 2022 using the Statistics Sweden consumer price index and are reported in Euro (€1 = 10.6317 SEK, 2022 rates) [20,21].

2.5.2. Health outcomes

QALYs were used as a measure of health outcomes. QALYs are the sum of health utility values in each health state multiplied by the duration of that health state. The health state values and respective durations were extracted from a previous cost-effectiveness study of PCa screening in Sweden (Supplementary Table 3) [14]. To adjust for age, we multiplied the health state values by age-specific general population health utility values in Sweden (Supplementary Table 4) [22].

2.5.3. Sensitivity analyses

One-way sensitivity analyses were conducted for the following scenarios: (1) AI costs of €100 and €200; (2) from a societal perspective; (3) referral for biopsy for PSA ≥4 ng/ml; (4) screening at ages between 55 and 69 yr, in accordance with the ERSPC study [23]; (5) use of AI for pathology in the postdiagnosis phase; (6) other prespecified per-core sensitivity values for AI; (7) assumption of the same sensitivity for the pathologist and AI; (8) health state values used in a cost-effectiveness analysis of the ERSPC study [23]; (9) 2-yearly and 6-yearly rescreening intervals; and (10) discount rates of 0% and 5%, as required by Swedish guidelines [17].

A probabilistic sensitivity analysis was conducted by allowing for the joint uncertainties for SBx and AI performance characteristics, costs, and health state values. Performance characteristics and health state values were assumed to follow a β distribution. Costs were assumed to follow a γ distribution with shape and scale of 100. We ran simulations for 1 million individuals and resampled the parameter sets 1000 times. Cost-effectiveness acceptability curves were plotted for the probability of one workflow being cost effective in comparison to the alternative at a certain cost-effectiveness threshold.

3. Results

3.1. Base-case analysis

In comparison to a pathologist alone, the AI-assisted workflow reduced the number of PCa cases detected (0.02%) and overdiagnosed (0.24%), with 12 more PSA screening tests (0.004%), 23 more biopsies (0.03%) and one more death (0.02%) per 100 000 men. The number of clinically significant PCa cases detected was the same in both workflows. The AI-assisted workflow reduced the number of biopsy cores to be viewed by a pathologist by 80% (Table 2).

Taking a health care perspective and assuming an AI cost of €10 per case, the AI-assisted workflow was predicted to have a 1.2% lower cost with a 0.0001% decrease in QALYs in comparison to the pathologist alone workflow. The ICER for comparison of the pathologist alone with the AI-assisted workflow was more than €7 million per QALY gained, which is considered a very high cost per QALY gained (Table 3).

3.2. Sensitivity analyses

The ICER was more than €1 million per QALY gained at an AI cost of €100 per case. The pathologist alone workflow was dominant at an AI cost of €200 per case (Table 3). When we assumed the same performance characteristics for the pathologist and AI, the QALYs were identical and the costs for the AI-assisted workflow were 1.5% lower (Supplementary Table 10). Our baseline findings were robust for the other deterministic sensitivity analyses. From the probabilistic sensitivity analysis, using a cost-effectiveness threshold of €47 029 (500 000 SEK) per QALY gained, the probability of the AI-assisted workflow being cost-effective was 100% (Supplementary Fig. 2).

4. Discussion

To the best of our knowledge, this is the first study to predict the long-term effectiveness and cost-effectiveness of

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Table 2 – Summary of lifetime predictions for outcomes and costs

Lifetime predictions	Human	AI [a] + human
Outcomes per 100 000 men		
Screening tests for men aged 50–74 yr	414 203	414 217
Biopsy procedures	76 031	76 054
PCa cases diagnosed	18 292	18 288
PCa GG ≥2 cases diagnosed	12 713	12 713
PCa cases diagnosed for men aged 50–74 yr	9381	9374
PCa GG ≥2 cases diagnosed for men aged 50–74 yr	5497	5497
Overdiagnosed PCa cases	1654	1650
PCa deaths	5170	5171
Reduction in biopsy cores viewed by a pathologist	–	80.40%
LY, undiscounted	3 219 088	3 219 081
QALYs, undiscounted	2 940 951	2 940 947
QALYs, discounted at 3%	1 850 841	1 850 840
QALYs, discounted at 5%	1 439 544	1 439 545
Costs per 100 000 men (million €)		
Health care perspective, undiscounted	490.13	484.48
Health care perspective, discounted at 3%	231.89	228.44
Health care perspective, discounted at 5%	150.05	147.52
Societal perspective, undiscounted	509.82	504.15
Societal perspective, discounted at 3%	245.59	242.13
Societal perspective, discounted at 5%	161.07	158.52

AI = artificial intelligence; GG = International Society of Urological Pathology grade group; LYs = life years; QALYs = quality-adjusted LYs; PCa = prostate cancer.
[a] Assuming per-core AI sensitivity of 97%.
[b] Assuming an AI cost of €10.

AI-assisted prostate pathology in reducing the pathologist workload via automated filtering of benign biopsies. The modelled impact of an AI-assisted workflow showed slight increases in the number of PSA tests (0.004%), SBx procedures (0.03%), and PCa deaths (0.02%) for 100 000 men over a lifetime horizon, while there were fewer PCa cases detected and overdiagnosed in comparison to a pathologist alone. Very small decrements in life years and QALYs gained were found for the AI-assisted workflow in comparison to a pathologist alone. These decrements may be explained by delayed diagnosis and treatment for the false-negative cases missed by AI. AI showed the same detection capability for GG ≥2 PCa as the pathologist alone, which suggests that the reductions in the number of PCa cases detected were mostly driven by benign and clinically insignificant cancers. These cases may have a limited impact on outcomes, as reflected in the clinically insignificant differences between the two workflows. AI reduced the number of biopsy cores to be examined by the pathologist by 80%.

From a health care perspective at a discount rate of 3%, the AI-assisted workflow had lower costs than the pathologist alone at an AI cost of €10 per case. Given that QALYs were practically the same for both workflows, AI-assisted pathology can be considered as cost-saving. The findings remained consistent in most sensitivity analyses but were sensitive to the AI cost. The pathologist alone workflow became dominant at an AI cost of €200 per case. The assumption of an AI cost of €10 was made on the basis of prices for similar products on the market. Higher costs could be expected when the market has grown and matured, and established AI software vendors start to prioritize covering their technology development costs.

Some limitations should be noted. First, the use of a SBx protocol was aligned with the STHLM3 study, from which the data were used to train the AI [24]. However, this strategy is now less clinically relevant because of its association with overdiagnosis and overtreatment [25]. Elevated PSA results are now more commonly followed by MRI and then possibly by a combined biopsy protocol [26,27]. Nevertheless, we posit that the patient outcomes when using AI in a screening pathway that includes MRI would be similarly safe: the number of GG ≥2 cancers would be similar for MRI, while adverse outcomes for GG 1 cancers would be expected to be few. Conversely, men with positive MRI findings may have a higher proportion of positive cores, for which the cost reduction associated with AI would be less. Second, the AI performance characteristics were derived from an internal held-out validation data set, for which the AI ability may be optimistic. The AI performance is expected to vary across laboratories, with images from diverse populations examined by different pathologists using different scanners. We did not perform analyses using data from the external validation data set because of undersampling of benign cores in this population. The AI performance in other settings should be assessed when more external data are available. A third concern relates to how AI will be implemented in clinical practice. For simplicity, we assumed that the pathologist would not re-examine cores labeled as benign by AI. Although AI has shown excellent diagnostic accuracy and did not affect patient quality of life, inherent algorithmic and statistical biases arising from AI training have been widely discussed [28,29]. To mitigate these biases, AI application should be based on the general principles for implementing any new test in clinical routine,

Table 3 – ICER base-case results from a health care perspective using a discount rate of 3% for costs and QALYs

AI cost	Strategy [a]	Costs per 100 000 men(million €)	QALYs per 100 000 men	ICER
€10	AI + human	228.4437	1 850 840	–
	Human	231.8864	1 850 841	7 392 007.86
€100	AI + human	231.3682	1 850 840	–
	Human	231.8864	1 850 841	1 112 693.72
€200	Human	231.8864	1 850 841	–
	AI + human	234.6176	1 850 840	Dominated

AI = artificial Intelligence; ICER = incremental cost-effectiveness ratio; QALYs = quality-adjusted life years.
[a] Assuming per-core AI sensitivity of 97%.

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meaning that the results from a new test need to be critically evaluated [29]. In practice, for legal and ethical reasons, a pathologist may prefer to re-examine cores labeled as benign by AI and may more rapidly analyze biopsy cores suspicious of having cancer. This raises challenges in the measurement of costs in economic evaluations. Fourth, we assumed that a pathologist would be 100% accurate, which is unlikely to be true in the real world. In a sensitivity analysis for which we assumed that an imperfect pathologist would have the same performance characteristics as AI, the AI-assisted workflow had identical outcomes and reduced costs. Finally, the estimate that one-third of pathology costs can be attributed to pathologists' time was based on expert opinion from a single laboratory. This assumption could be evaluated in other settings. Future evaluations could also consider other approaches to combining AI with human pathologists, including use of AI as a second rater for grading.

5. Conclusions

According to our model, AI could reduce the number of biopsy cores to be viewed by pathologists by 80%. In comparison to the pathologist alone workflow, the AI-assisted workflow would reduce costs with limited loss of QALYs at an AI cost was €10 per case. In conclusion, given the estimates available for AI performance characteristics in this setting, AI-assisted pathology for PCa diagnosis would be considered as cost-saving in comparison to a pathologist alone. These findings reflect a specific setting from an internal validation data set and should be assessed when more external data are available.

Author contributions: Xiaoyang Du 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: Du, Clements, Eklund, Kartasalo, Hao.
Acquisition of data: Eklund, Olsson, Du, Clements, Hao.
Analysis and interpretation of data: Du, Clements, Heintz, Hao.
Drafting of the manuscript: Du, Clements.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Du, Clements, Olsson.
Obtaining funding: Clements.
Administrative, technical, or material support: Clements.
Supervision: Clements, Heintz, Hao.
Other: None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euo.2024.05.004.

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