ORIGINAL ARTICLE

Cost analysis of prostate cancer detection including the prostate health index (phi)

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Abstract

Objective To assess the economic impact of introducing the prostate health index (phi) for prostate cancer (PCa) detection.
Methods A total of 177 patients who presented in an academic institution with a tPSA between 2 and 10 ng/ml and underwent prostate biopsies within the 3 months were enrolled. With phi and tPSA thresholds of 43 and 4 ng/ml, respectively, probability for each branch of a decision tree model for PCa diagnosis and corresponding mean cost were estimated with "Monte Carlo" simulations. A sensitivity analysis was performed.
Results With a similar sensitivity, phi strategy increased positive predictive value by 13.9 points and negative predictive value by 31.6 points in comparison to tPSA strategy. Mean costs per patient with tPSA and phi strategies were €514 and €528, respectively, for a phi test price at 50€. One-way sensitivity analysis showed that phi strategy was less expensive (508€/patient) than tPSA strategy with a phi test price below 30€. In multi-criteria sensitivity analysis, PPV and the rates of positive phi and tPSA were the parameters with the largest impact on the final cost as opposed to the cost of the biopsy or imaging which have less influence. With an expected rate of positive phi test < 60%, tPSA strategy was more expensive than phi strategy.
Conclusions The introduction of phi index in PCa detection would result in a significant clinical benefit compared to tPSA strategy. In our economic model, the phi strategy was equivalent or slightly more expensive than the current tPSA strategy.

Keywords Prostate-specific antigen (PSA) · Prostate health index (phi) · Prostatic neoplasm · Diagnosis · Cost analysis

Introduction

The European randomized study of screening for prostate cancer (ERSPC) recently showed that screening based on total prostate-specific antigen (tPSA) reduces prostate cancer (PCa) mortality [1]. However, the use of tPSA remains debated because of many inherent limitations as a biomarker. Recent randomized studies suggest that tPSA screening leads to a significant level of overdiagnosis and overtreatment of indolent PCa [1, 2]. Due to its relatively low specificity, tPSA strategy may be responsible for delay in the diagnosis of some clinically aggressive cancers [3].

Novel biomarkers that capture the biological and clinical potential of PCa cells hold the promise of improving the early detection of clinically significant PCa. Prostate health index (phi), that integrates the [−2]proPSA component, has been proposed to improve clinical specificity of tPSA for the early detection of PCa [4]. This biomarker has been suggested to improve diagnostic accuracy and avoid

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unnecessary biopsies [5]. Phi has been also discussed to improve PCa detection of clinically significant disease in men eligible for active surveillance and, therefore, may be useful in the selection and monitoring of these patients [6, 7]. Nevertheless, a biomarker needs to be cost efficient to add maximum value to our current diagnostic and treatment pathways [8]. Routine use of phi for PCa detection may be associated with an increased cost that may be offset by the reduction in unnecessary biopsies. Cost analyses with phi diagnostic strategy are limited and its relevance may be questionable according to disease prevalence and reimbursement schemes [9, 10].

Therefore, our objective was to evaluate the economic impact of introducing the phi index in the clinical practice of a French University hospital for PCa detection compared to a standard strategy using tPSA.

Materials and methods

Population and data collection

The study included 177 patients who were prospectively identified between June 2009 and October 2010 at a single academic institution. Patient inclusion criteria were male > 50 years old, who underwent trans-rectal ultrasound guided prostate biopsies within 6 months after being referred to a urologist because of a tPSA between 2 and 10 ng/ml. Patients with a past history of PCa, use of five alpha-reductase inhibitors or prior prostate biopsies were excluded. Biopsy protocol included 12 systematic prostatic cores. Serum samples were collected at initial evaluation; phi and tPSA were determined using access reagents on a Beckman Coulter DxI instrument (Beckman Coulter, Brea, California, USA). A WHO calibration for PSA and free PSA was used. Patients were followed for at least 6 months after the initial evaluation. All diagnostic tests and diagnostic related events (imaging, transport, and antibiotic prophylaxis), from the first visit with the urologist to the therapeutic decision, were collected.

Economic analysis

Study type

The economic analysis adopted the healthcare payer's perspective and only considered direct medical costs (i.e., healthcare resource consumption). Indirect costs (e.g., lost income) and intangible costs (e.g., pain and suffering) were not assessed. The direct costs of PCa diagnosis included hospitalization, medical, and consultation costs. Hospitalization costs included nursing, care, pharmacy, diagnostic tests, laboratory tests, staff, general equipment, administration,

security, central supply, dietetics, and social services. The time horizon of the study was defined from the day of the first visit with the urologist to the day where the therapeutic option was chosen in the case of prostate cancer detection.

The objective of this study was to assess the economic impact of introducing a new diagnostic test on the management of the detection of prostate cancer and a cost-minimization study was designed. The cost-minimization analysis is an economic study in which two or more therapeutic alternatives with the same effectiveness (in terms of mortality) are compared in terms of net costs to establish the cheapest alternative indeed, in this study, no difference was expected in terms of quantity and quality of life and thus in terms of quality-adjusted life-years (QALYs).

Cost assessment

The cost of outpatient care, i.e., care not requiring hospitalization, as well as any other procedures, was valued according to French government health insurance rates at the time. Hospitalizations were valued using the French diagnosis-related groups corresponding to inpatient care. All prices were recorded as €2012.

Model structure

The decision tree methodology used in this study is a decision support tool that uses a tree-like graph or model of decisions and their possible consequences, including chance event outcomes and/or resource costs. Decision trees are commonly used in operations research, specifically in decision analysis, to help identify a strategy that is most likely to reach a goal [11]. Another use of decision trees is as a descriptive means for calculating conditional probabilities and associated mean costs.

A decision tree modeling was used to describe the patient's diagnostic pathway with the tPSA or phi strategies (Fig. 1). A tPSA value ≥ 4 ng/ml and a phi value ≥ 43 were used to define respective test positivity and derived the corresponding positive and negative predictive values. Using these thresholds, phi and tPSA have a similar sensitivity of 69% [3].

Cost and sensitivity analysis

For each branch of the decision tree, a probability and a cost were estimated from population study. A determinist analysis was performed, i.e., the mean cost was assessed with Monte Carlo simulations. Monte Carlo methods are a broad class of computational algorithms that rely on repeated random sampling to obtain numerical results. Their essential idea is using randomness to solve problems that might be deterministic in principle.
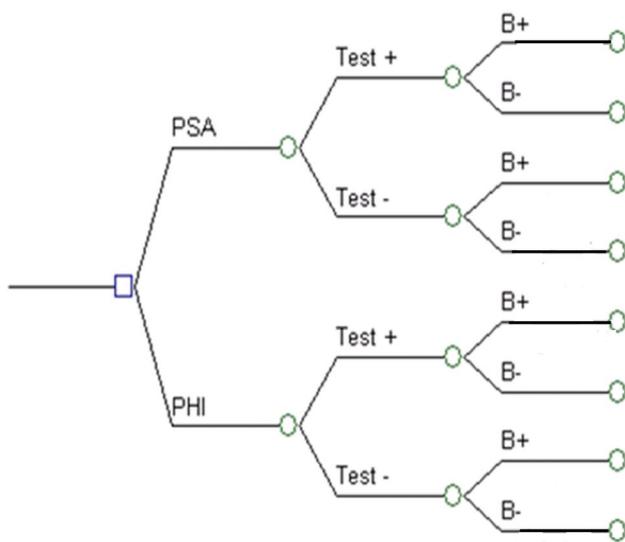
Fig. 1 Global decision tree. B+ positive biopsy, B− negative biopsy, Test+ positive test, Test− negative test

10,000 simulations were performed. The variance and the *p* value were not deduced, but the sensitivity analyses were performed to validate the robustness of the results by varying parameters and cost values. The variation of each parameter was determined according the literature review when available and according experts otherwise.

Results

Patients, tumors, and care management characteristics

Patients' characteristics and data regarding PCa detection management are presented in Table 1. Median age was 62 years. Median tPSA and phi at the initial evaluation were 4.5 ng/ml (range 1.7–7.7) and 63.3 (14.3–2722.1), respectively. Overall, 154 (87%) and 119 (67.2%) patients had a tPSA ≥ 4 ng/ml and a phi ≥ 43, respectively. Two hundred and three TRUS-guided prostate biopsies were performed; 21 and two patients underwent second and third biopsies, respectively. 95.5% of the biopsies were performed as an outpatient procedure. 19 patients had complications related to the biopsies, but only four required urological evaluation or re-admission. PCa was identified in 110 patients: 100 were diagnosed at the initial biopsy and 10 at repeated biopsy. Imaging was performed in 62 patients, including 59 multiparametric magnetic resonance imaging (mp-MRI), 3 abdominal CT scan, and 12 bone scans.

Table 1 Patient, tumor, and management characteristics

Characteristics	L
Number of patients (*n*)	177
Median age, years (range)	62 (50–78)
PSA, median (range)	4.5 (2–10)[a]
PSA ≥ 4, *n* (%)	154 (87)
Phi, median (range)	63.3 (14.3–2722.1)
Phi ≥ 43 *n* (%)	119 (67.2)
Biopsy rounds	
1, *n* (%)	154 (87)
2, *n* (%)	21 (11.9)
3, *n* (%)	2 (1.1)
Biopsy status	
First biopsy (*n*)	177
Negative, *n* (%)	77 (43.5)
Positive, *n* (%)	100 (56.5)
Second biopsy (*n*)	23
Negative *n* (%)	13 (56.5)
Positive, *n* (%)	10 (43.5)
Complications	
No, *n* (%)	181 (89.3)
Yes, *n* (%)	19 (9.4)
PCa	
No (*n*, %)	67 (37.9)
Yes (*n*, %)	110 (62.1)
Gleason 6 (3 + 3), *n* (%)	77 (37.9)
Gleason 7 (3 + 4), *n* (%)	19 (9.4)
Gleason 7 (4 + 3), *n* (%)	8 (3.9)
Gleason 8 (4 + 4), *n* (%)	6 (3)
Imaging	
Abdominal and pelvic MRI *n* (%)	59 (33.3)
Abdominal and pelvic CT scan *n* (%)	3 (1.7)
Pet–CT *n* (%)	12 (6.8)

PCa prostate cancer, *PSA* prostate-specific antigen, *Phi* prostate health index

[a]The actual value measured was between 1.7 and 7.7 ng/ml due to the calibration against the WHO standard but corresponds to a 2–10 ng/ml range in Hybritech calibration

Cost analysis

The price of tPSA assay was 20.52€, while a non-fixed price from 30€ of to 90 € was allocated to the phi test. All corresponding French prices are presented in Table 2. As compared to tPSA strategy and with a similar sensitivity, the phi strategy increased the positive predictive value (PPV) by 13.9 points (from 55.8 to 69.7%) and the negative predictive value (NPV) by 31.6 points (from 39.1 to 70.7%). The mean cost of the phi strategy was €528, while the tPSA strategy was expected to cost €514 for a cost of the phi index set at €50.
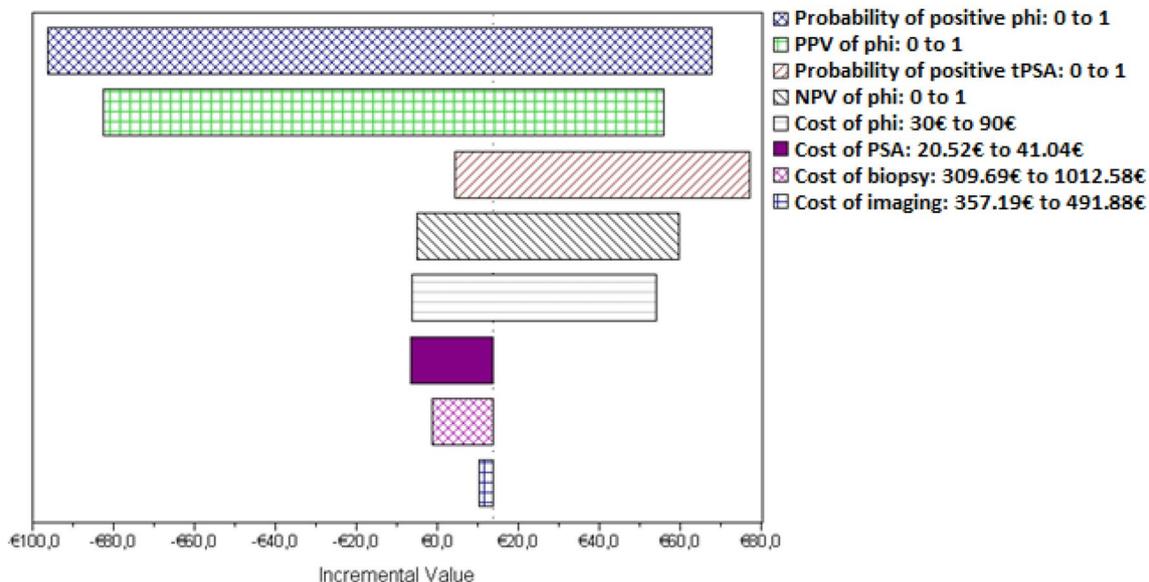
Table 2 Model input for costs

Cost component	Unit cost (€)
Urologist visit	18.40
PSA blood test	20.52
Phi blood test	30–90
Urine analysis	14.04
Hemostasis blood test	8.64
Platelets blood test	3.24
Cleansing enema	2.96
Hemogram	6.7
Anesthesiologist visit	18.4
Cardiologist visit	18.4
TRUS-guided prostate biopsy (outpatient care)	91.68
Pathologist examination (positive biopsies)	71.68
Pathologist examination (negative biopsies)	60.48
Immunohistochemistry	44.8
Antibioprophylaxis	7.48
Total cost of biopsy in outpatient care	217.63
Biopsy hospitalization cost	1354.29
Abdominal and pelvic MRI	309.75
Abdominal and pelvic CT scan	117.39
Pet–CT	144.35
Individual transport	7.42
Ambulance transport	142.23
Transport by taxi	47.80

Sensitivity analysis

Tornado diagram (Fig. 2) represents the influence of various parameters on the model prediction in one-way sensitivity analysis. The model was mostly sensitive to changes of the rate of positive phi test and of phi PPV. Modification of the phi PPV from 0 to 1 showed that, for a PPV above 0.6 (Fig. 3a), the phi strategy was more expensive than the tPSA strategy. Modification of the phi NPV showed that the phi strategy was more expensive at nearly all levels except for an NPV above 0.9 (Fig. 3b). Modification of phi pricing from 30 to 90€ resulted in a differential cost from −6 to 53.8€ (Fig. 3c). In the model, sensitivity analysis showed that the use of several tPSA test (cost > 41€) compared to one phi test made the tPSA strategy more expensive. With a rate of positive phi test < 0.60, tPSA strategy was also more expensive (from −67.5 to +96.2€) (Fig. 3d). The cost variation of prostate biopsy or PCa staging showed no benefit of one model over the other. Figure 4 represents multivariable sensitivity analysis with NPV and PPV. For various combinations of NPV and PPV, phi strategy was cheaper than the tPSA strategy.

Discussion

PCa screening is a subject of ongoing debate, since it is mostly based on tPSA, a biomarker with limited specificity and low predictive value. New urinary and blood tests

Probability of positive phi: 0 to 1
PPV of phi: 0 to 1
Probability of positive tPSA: 0 to 1
NPV of phi: 0 to 1
Cost of phi: 30€ to 90€
Cost of PSA: 20.52€ to 41.04€
Cost of biopsy: 309.69€ to 1012.58€
**Cost of imaging: 357.19€ to 491.88€**

Incremental Value

Fig. 2 Tornado diagram (phi vs PSA) from one-way sensitivity analysis; Tornado diagram (phi vs PSA) represents the influence of various parameters on the model prediction in one-way sensitivity analysis. It represents cost differential between phi and PSA strategy for the lower and upper limits of each parameter value. In this study, the most sensitive parameter is the probability of positive phi, meaning that this variable has the most influence in variation of cost
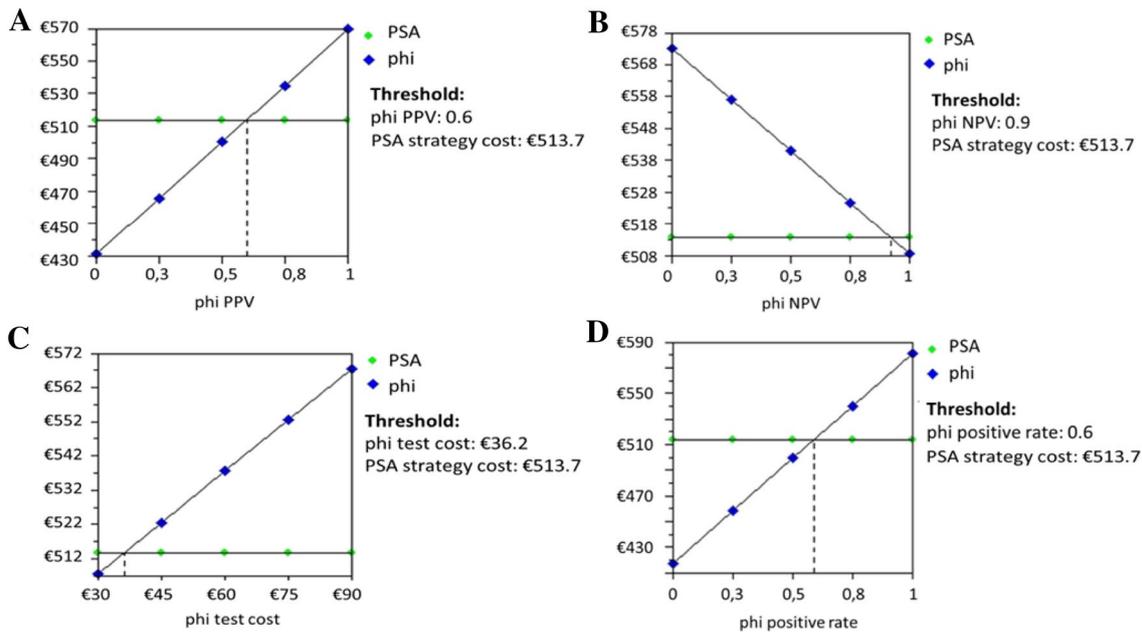
Fig. 3 One-way sensitivity analyses: In these analyses, the impact of the variation of four variables on the total cost of each strategy was tested. **a** One-way sensitivity analysis for the phi PPV, **b** one-way sensitivity analysis for the phi NVP, **c** one-way sensitivity analysis for the cost of phi, and **d** one-way sensitivity analysis for the positive rate of phi. *PPV* positive predictive value, *NPV* negative predictive value
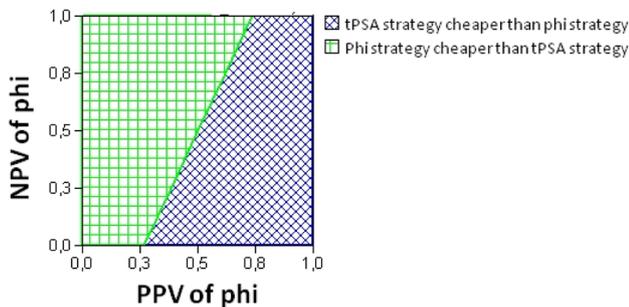
Fig. 4 Multivariable analysis according to negative and positive predictive values of phi (with a fixed price of 30€). *PPV* positive predictive value, *NPV* negative predictive value

have been discussed to improve PCa detection of clinically significant disease. A molecular isoform of free PSA, [− 2] proPSA has been identified in immunohistochemistry analysis to be more specifically expressed in cancerous tissue of the prostate. The Prostate Health Index (phi), is an index resulting from a mathematical algorithm, that combined the serum concentrations of tPSA, fPSA, and [−2]proPSA [12]. Several clinical studies have shown that the phi index improved the clinical specificity and sensitivity for the detection of PCa in patients with intermediate values of tPSA from 2 to 10 ng/ml [13]. One benefit of phi seems to be a decrease in unnecessary biopsies resulting in cost savings for healthcare system.

In this study, we analyzed the economic impact of introducing the phi index in clinical practice for the early detection of PCa. In this cost analysis, we first investigated the performance of phi for PCa detection in our patient population. At a similar sensitivity of 69%, the use of phi increased PPV by 13.9% and NPV by 31.6% as compared to tPSA. These results are concordant with the previous studies [3, 5, 14–18]. In a multi-institutional study, Lazzeri et al. evaluated the performance of phi and tPSA in a cohort of 1026 patients [5]. ROC analysis showed that phi had a higher predictive value than tPSA. A phi threshold of 40 was considered optimal regarding sensitivity and specificity (64.8 and 71.3%, respectively). Stephan et al. evaluated phi in a cohort of 1362 patients: 668 with biopsy confirmed PCa and 694 with no evidence of malignancy [3]. The initial tPSA values ranged from 1.6 to 8.0 μg/l. Phi was significantly higher in patients with PCa and had the largest area under the ROC curve, specifically in patients with PCa pathological Gleason score ≥ 7. In this cohort, 84% patients with a PCa ≥ 7 (4 + 3) had a phi threshold > 40. According to these results and to achieve a comparable sensitivity of 0.69 with tPSA (PSA threshold = 4 ng/ml), a phi threshold of 43 was considered in our study.

In our study, with a cost of €50 for a phi test, the use of tPSA was €14 cheaper than phi. Two previous studies by Nichol et al. investigated potential cost savings with the introduction of phi in PCa screening [9, 10]. Estimated additional cost to calculate phi (freePSA + [− 2] proPSA) was

approximately $100 (2009 US dollars) [9]. However, additional costs of the blood test were offset by the cost savings associated with the reduction of unnecessary biopsies. In a health plan model with 100,000 men aged 50–74 years, the expected 1-year costs for PCa detection with an additional phi test were $356 647 and $94 219 lower than using a tPSA threshold of ≥ 2 and ≥ 4 ng/ml, respectively [10]. With an annual screening cycles over 25 years, combination of phi and tPSA test resulted in a cost saving of $1199 or $443 and an expected gain of 0.08 or 0.03 QUALYs per person, considering tPSA thresholds of ≥ 2 and ≥ 4 ng/ml for prostate biopsy, respectively [9]. Recently, Heijnsdijk et al. presented a simulation model based on the ERSPC data including phi as part of tPSA screening in a European population [19]. With a predicted 23% reduction of negative biopsies, use of phi resulted in 1% reduction in total costs related to PCa healthcare and 17% reduction in costs for diagnostics. The estimated gained Qualys were similar in both tPSA and phi strategies. Cost-effectiveness was €126,426/QALY and €112,979/QALY, respectively, using a 3.5% discount rate.

In contrast with previously published studies that evaluated the potential cost saving of phi in a PCa screening setting, we analyzed the cost implications of introducing phi in an opportunistic case finding situation in a cohort from a tertiary center. We demonstrated that the cost impact of introducing phi for PCa detection in the clinical practice varied widely according to different parameters. Modification of phi PPV suggests that, for a PPV above 0.6, the phi strategy is more expensive than the tPSA strategy. This means that, above this threshold, the cost related to additional true positive PCa cases is exceeding the savings due to the number of negative biopsy that phi avoids. We further reported that below 60% of positive phi test, tPSA strategy is more expensive. These results confirm the observations of previous cost analysis studies in the context of PCa screening [9, 10, 19]. In a screening population, rates of positive tests are usually lower than this threshold and our results indicate that the phi strategy may be less costly than the tPSA strategy in this setting. These findings may also help to define the cutoff that should be used to propose the first biopsies. In our study, the decision to perform a biopsy was based on a single tPSA test. In our one-way sensitivity analysis, we demonstrated that considering two tPSA tests for one phi test makes the phi strategy cheaper. Finally, our study analyzed the influence of the phi test price on the overall cost of the phi strategy for PCa detection. The introduction of phi test with a price of €30 would result in a cheaper strategy as compared to the current clinical practice with tPSA. These findings are of the utmost importance to maximize the economic benefit of a PCa detection strategy that includes the new phi index.

Although prospective, our study has some limitations. First, the cohort of patients recruited is relatively small.

Second, only PCa detection and related events until treatment decision were considered and long-time effects were not assessed. The model did not discriminate "aggressive" from "indolent" PCa and, therefore, did not consider the implications of the corresponding treatment modalities. Such discrimination using phi and tPSA strategies would be interesting. Indeed, best accuracy of phi to detect a significant PCa could avoid unnecessary "indolent" PCa diagnosis and corresponding expensive treatment [20]. More favorable cost results could be expected if the phi index would have been evaluated at repeat biopsy. However, in our study, Phi was only offered at the initial biopsy and only 23 patients underwent repeat biopsy. Therefore, no conclusions can be drawn in this sub-population and further investigations in this setting would be of utmost interest. Favorable cost results could also be expected in patients with tPSA > 10 ng/ml, as the performance of phi has been also reported in this population [21]. However, our study did not include patients with tPSA > 10 ng/ml and cost–benefit remains to demonstrate. The performance of novel biomarkers should also be discussed regarding the widespread use of mp-MRI before first-line and repeated biopsies [22–24]. Our study did not address the cost–benefit of combining phi and mp-MRI results in PCa detection as most of the mp-MRI were performed after the first round of biopsies. Our results are only based on costs associated with PCa detection in a French academic institution with related healthcare specificities. Cost-effectiveness variations in the private practice could be anticipated, due to biopsy and medical imaging cost difference. However, in our sensitivity analysis, these parameters had no significant influence on the model. Finally, in this preliminary study, a minimization cost regarding management of PCa diagnosis was proposed. Therefore, we did not investigated differences in terms of quantity QALY between both strategies and validation of cost-effectiveness with phi strategy warrants further investigations.

Conclusion

The introduction of the phi index for PCa detection in the clinical practice of a tertiary center could lead to significant clinical benefits at equivalent or slightly more expensive cost than the current tPSA strategy. Further cost-effectiveness analyses that consider patient quality of life are necessary to explore the potential cost-effectiveness of the phi index in the early detection of PCa.

Compliance with ethical standards

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