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The Prostate Health Index in predicting initial prostate biopsy outcomes in Asian men with prostate-specific antigen levels of 4–10 ng/mL

C. F. Ng · Peter K. F. Chiu · N. Y. Lam · H. C. Lam · Kim W. M. Lee · Simon S. M. Hou

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Abstract
Purpose To investigate the role of the Prostate Health Index (*phi*) in prostate cancer (PCa) detection in patients with a prostate-specific antigen (PSA) level of 4–10 ng/mL receiving their first prostatic biopsy in an Asian population.
Methods This was a retrospective study of archived serum samples from patients enlisted in our tissue bank. Patients over 50 years old, with PSA level of 4–10 ng/mL, a negative digital rectal examination, and received their first prostatic biopsy between April 2008 and April 2013, were recruited. The serum sample collected before biopsy was retrieved for the measurement of various PSA derivatives and the *phi* value was calculated for each patient. The performance of these parameters in predicting the prostatic biopsy results was assessed.
Results Two hundred and thirty consecutive patients, with 21 (9.13 %) diagnosed with PCa, were recruited for this study. Statistically significant differences between PCa patients and non-PCa patients were found for total PSA, PSA density, [-2]proPSA (p2PSA), free-to-total PSA ratio (%fPSA), p2PSA-to-free PSA ratio (%p2PSA), and *phi*. The areas under the curve of the receiver operating characteristic curve for total PSA, PSA density, %fPSA, %p2PSA, and *phi* were 0.547, 0.634, 0.654, 0.768, and 0.781, respectively. The *phi* was the best predictor of the prostatic biopsies results. At a sensitivity of 90 %, the use of the *phi* could have avoided unnecessary biopsies in 104 (45.2 %) patients.
Conclusions Use of the *phi* could improve the accuracy of PCa detection in patients with an elevated PSA level and thus avoid unnecessary prostatic biopsies.

Keywords Prostate cancer · Biomarkers · Screening · Prostate-specific antigen · PSA density · PSA isoform

C. F. Ng (✉) · P. K. F. Chiu · N. Y. Lam · H. C. Lam · K. W. M. Lee · S. S. M. Hou
Division of Urology, Department of Surgery, The Chinese University of Hong Kong, Shatin, Hong Kong SAR, China
e-mail: ngcf@surgery.cuhk.edu.hk

Introduction

Prostate cancer (PCa) is the second most common cancer in the world, and its incidence in the Asia–Pacific region is increasing [1]. Fortunately, the use of serum levels of prostate-specific antigen (PSA) as a diagnostic tool has increased the detection rate of PCa at an earlier stage, when management with various therapies can adequately control the disease [2]. Unfortunately, the level of PSA in serum is not an ideal cancer biomarker, because it can be elevated due to many other conditions (such as benign prostatic hyperplasia and prostatitis), and is therefore not cancer-specific. Thus, due to the false-positive results obtained by the PSA test during screening, many patients are subjected to an unnecessary transrectal ultrasound-guided prostatic biopsy (TRUSPB), which is an invasive procedure that can lead to significant morbidity, and even mortality [3, 4].

Many approaches have been explored to improve the performance of PSA in the detection of PCa, such as correlating the PSA level with the prostate volume (PSA density), the rate of change in PSA over time (PSA velocity), and the ratio of different non-complexed forms of PSA in the serum [5]. One of the most recent approaches has been to measure the PSA isoform, [-2]proPSA (p2PSA) and its derivatives and calculate the Beckman Coulter Prostate Health Index (*phi*) [6–8]. In 2012, the US Food and Drug Administration approved the use of the *phi* for

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the detection of PCa in men over 50 years of age with a serum PSA level of 2–10 ng/mL and negative digital rectal examination (DRE) findings. The initial clinical validation of this new marker to improve the detection of PCa compared with PSA was performed mainly on Caucasian populations [9]. To confirm the clinical efficiency of the *phi* in an Asian population, we compared the performance of the *phi* with that of other PSA derivatives in the detection of PCa in patients with a serum level of PSA between 4 and 10 ng/mL, who had been selected for an initial TRUSPB.

Methods

Study design

This was a retrospective study on archived serum samples from patients enlisted in our prostate tissue bank. Patients with a total serum PSA level of 4–10 ng/mL (measured using a Roche Cobas e601 system with standardization against the WHO 96/670 reference standard) and negative DRE findings who received their first TRUSPB between April 2008 and April 2013 were recruited. As in most of the centers in our area, patients who are suspected of having PCa, because of either an elevated level of serum PSA $>$ 4 ng/mL or an abnormal DRE, are recommended to have a TRUSPB for further assessment. In our center, immediately before each patient undergoes a TRUSPB, additional informed consent is obtained for blood collection to establish a prostate disease tissue bank, which has been approved by our local institutional ethics committee. All of the studies were conducted according to the Declaration of Helsinki. If the patient agreed to participate in the study, then the blood was collected immediately before the biopsy. These archived sera are the basis of our study.

Men aged 50 years or older with a serum PSA level in the range of 4–10 ng/mL and negative DRE findings were included in the study. A previous history of TRUSPB was an exclusion criterion and all men who were included had been scheduled for an initial biopsy. At least 10 systematic prostatic biopsy cores were taken during the TRUSPB, and all of the clinical data were available for review. The 10 cores of prostatic biopsy were based on the classical sextant biopsy with two additional lateral biopsies on each side. We used this 10-core extended biopsy template for all our patients receiving their first TRUSPB. This template would be adequate for detecting PCa in men for their first biopsy, without excessive increases in complication rate [10, 11]. Patients with a known history of PCa or a history of past prostatic surgery for any prostatic condition would be excluded. And patients with history of urinary tract infection, acute urinary retention, bladder stone, and prostatic massage within 3 months before blood taking would be excluded. Patients had a history of use of a 5-α reductase inhibitor or any other drugs that have anti-androgenic properties (such as androgen receptor blockers, ketoconazole) at any time before blood collection were also excluded. Finally, patients whose serum samples had been archived for more than 3 years were not included.

After identifying the eligible subjects, their clinical data, serum samples collected before biopsy, and biopsy results were retrieved for the study.

Specimens and laboratory analysis

Blood samples collected from consenting patients were immediately stored at 0 °C and then processed (centrifuged and refrigerated) within 3 h of blood collection. The sera were then frozen at −70 °C or below for future research.

The measurement of serum PSA and its derivatives was performed with an Access2 automated immunoassay analyzer system (Beckman Coulter, Brea, CA, USA). The research staffs who operated the system were blinded to the clinical information of the patients. The assay used was a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of p2PSA. The levels of total PSA (tPSA), free PSA (fPSA), and p2PSA were determined by calibration to the Hybritech standard. All assays were performed using the same batch of calibrators, and all results were obtained by a single determination.

The free-to-total PSA ratio (%fPSA) and p2PSA-to-free PSA ratio (%p2PSA) were calculated. The Beckman Coulter Prostate Health Index (*phi*) was determined by the formula $phi = (\text{p2PSA/fPSA}) \times (\text{square root of tPSA})$. The levels of these parameters were then compared between patients diagnosed with PCa (PCa patients) and those with no evidence of PCa (non-PCa patients). The receiver operating characteristic (ROC) curves of these parameters were also constructed and compared.

Statistical methods

The PSA density was calculated by dividing the serum level of tPSA (measured by the Hybritech-calibrated Assess2 system) by the prostate volume (determined by transrectal ultrasound during the biopsy). The differences in mean age, prostate volume, and levels of various PSA derivatives between the PCa and non-PCa patients were assessed using the Student's *t* test for normal data and the Mann–Whitney U test for skewed data. All of the descriptive statistics and comparisons were performed using the SPSS v.20.0 software package (SPSS, Chicago, IL, USA). The areas under the ROC curves (AUCs) and the sensitivity and specificity were calculated to assess the diagnostic performance of the various assays in terms of

Table 1 Patient characteristics of the study population

Mean (range)	Overall $N = 230$	Non-cancer patients $N = 209$	Cancer patients $N = 21$	p value
Age (years)	65.9 (50–79)	65.7 (50–84)	69.2 (57–76)	0.172
Total PSA (ng/ml)[a]	6.285 (4–9.5)	6.260 (4–9.5)	7.424 (4.6–9.4)	0.378
Prostate volume (ml)	46.2 (11–163)	46.8 (11–163)	39.6 (16.3–97.4)	0.061
Total PSA[b]	6.745 (3.18–9.98)	6.721 (3.18–9.98)	6.985 (4.75–9.11)	0.451
PSA density (ng/ml2)	0.175 (0.044–0.513)	0.171 (0.044–0.513)	0.213 (0.073–0.414)	0.043
Free PSA (ng/ml)	1.31 (0.39–4.09)	1.32 (0.39–4.09)	1.24 (0.50–2.36)	0.566
Free to total PSA ratio (%fPSA, %)	19.688 (6.227–47.379)	19.839 (6.297–47.379)	18.188 (6.227–31.307)	0.275
p2PSA level (pg/ml)	14.42 (4.29–67.33)	14.02 (4.29–67.33)	18.42 (6.27–35.82)	0.020
p2PSA to free PSA ratio (%p2PSA, %)	1.141 (0.393–2.572)	1.105 (0.393–2.528)	1.493 (0.629–2.572)	<0.001
phi	29.30 (9.58–78.08)	28.20 (9.58–78.08)	39.45 (13.89–77.63)	<0.001

[a] Measured by a Roche Cobas e601 system calibrated with the WHO 96/670 reference standard

[b] Measured by a Hybritech-calibrated Beckman Coulter Assess2 System

PCa detection. The AUCs of the ROC curves and the multivariable analysis were derived using MedCalc (Version 12.6.1.0-64 bit). A two-sided p value of <0.05 was considered to be significant in all of the analyses.

Results

Between April 2008 and March 2013, 1,766 patients received an initial TRUSPB in our center, and 930 consented to give blood samples. Of these, 230 consecutive patients fulfilled the inclusion criteria, and their clinical data and sera were retrieved for the study. Twenty-one patients (9.13 %) were diagnosed as having PCa from the results of the initial biopsy. The baseline information of these patients is given in Table 1.

The values of the various PSA parameters are also summarized in Table 1. Patients with PCa had a smaller prostate than the non-PCa patients. Statistically significant differences between the PCa patients and non-PCa patients were noted for PSA density, p2PSA, %p2PSA, and *phi*. However, the tPSA, fPSA, and %fPSA levels of the two groups were not statistically significantly different (Table 1).

The AUCs of the ROC of tPSA, PSA density, %fPSA, %p2PSA, and *phi* were 0.547, 0.634, 0.654, 0.768, and 0.781, respectively (Fig. 1). Of the various parameters, the *phi* showed the best performance in predicting the results of the initial prostatic biopsy in our population.

To assess the performance of the various parameters further, we set the sensitivity level at 90 %, which eliminated two of the 21 cancer cases. The *phi* had the best specificity of 49.76 % (95 % confidence interval: 42.8–56.7) (Table 2). If we had applied the *phi* to the cohort during the initial assessment, 104 (45.2 %) patients with no evidence of PCa after their initial TRUSPB would have avoided undergoing a biopsy. The two PCa cases that were eliminated from the analysis were both clinically T1c disease, with only one positive core (out of 10 biopsy cores) that was assessed as Gleason 3 + 3. Both of these were therefore considered to be low-risk cases [12].

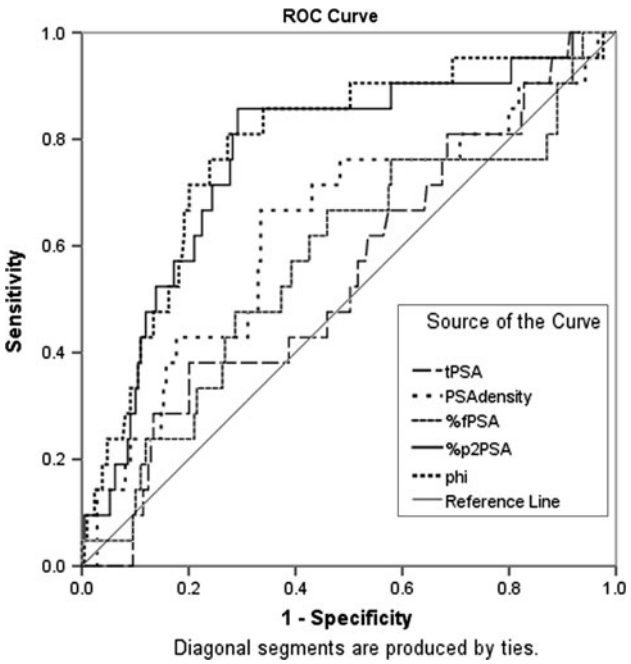

Fig. 1 Receiver operating characteristic (ROC) *curves* of the various prostate-specific antigen (PSA) derivatives

Multivariate analysis was used to assess the value of %p2PSA and *phi* in the diagnosis of PCa at TRUSPB, as suggested by Guazzoni et al. [7]. Age, tPSA, prostate volume, and %fPSA were put into the multivariate analysis as base prediction model (Table 3). The p2PSA level free PSA and PSA density were omitted from the base model to avoid problems of multicollinearity. Both %p2PSA and the *phi* improved the AUC of the base multivariate model from

Table 2 Performance characteristics at a preset sensitivity of 90 % or not missing any Gleason 7–10 cancer

	Cutoff for needing biopsy	Specificity at 90 % sensitivity (%, 95 % CI)	Number of patients with no evidence of cancer that could have avoided a biopsy (total 209)
Total PSA (ng/ml)	>5.251	17.22 (12.4–23.0)	36
PSA density (ng/ml^2)	>0.102	18.18 (13.2–24.1)	38
Free to total PSA ratio (%)	<27.978	11.0 (7.1–16.1)	23
p2PSA (pg/ml)	>9.269	22.97 (17.4–29.3)	48
p2PSA to free PSA ratio (%)	>0.995	42.11 (35.3–49.1)	88
phi	>26.54	49.76 (42.8–56.7)	104

Table 3 Multivariate analyses of the predictive value of each of the parameters in the diagnosis of prostate cancer

	AUC 95 % CI of AUC	Univariate analysis OR (95 %CI); *p* value	Multivariable analysis		
			Base model OR (95 %CI); *p* value	With %p2PSA OR (95 %CI); *p* value	With *phi* OR (95 %CI); *p* value
Age	0.589 (0.476–0.702)	1.052 (0.978–1.133); 0.174	1.068/(0.987–1.155); 0.101	1.076 (0.988–1.172); 0.093	1.076 (0.988–1.172); 0.093
tPSA	0.547 (0.421–0.674)	1.119 (0.836–1.499); 0.450	1.103 (0.814–1.494); 0.528	1.075 (0.791–1.461); 0.644	0.859 (0.607–1.215); 0.390
Free PSA[a]	0.538 (0.413–0.663)	0.736 (0.300–1.804); 0.503	–	–	–
%fPSA	0.572 (0.437–0.708)	0.965 (0.901–1.034); 0.311	0.974 (0.902–1.052); 0.507	0.982 (0.908–1.063); 0.658	0.982 (0.908–1.062); 0.651
Prostate volume	0.624 (0.501–0.747)	0.980 (0.954–1.006); 0.129	0.978 (0.950–1.007); 0.141	0.993 (0.964–1.023); 0.640	0.994 (0.965–1.023); 0.684
PSAD[a]	0.634 (0.501–0.768)	82.032 (1.113–6,046.391); 0.045	–	–	–
p2PSA[a]	0.654 (0.523–0.786)	1.059 (1.009–1.111); 0.020	–	–	–
%p2PSA	0.768 (0.660–0.876)	8.497 (2.899–24.900); <0.001	–	8.153 (2.529–26.287); <0.001	–
Phi	0.781 (0.675–0.887)	1.078 (1.038-1.119); <0.001	–	–	1.082 (1.035–1.132); 0.001
AUC of the multivariable models (95 %CI)			0.668 (0.540–0.795)	0.786 (0.677–0.894)	0.792 (0.668–0.895)

[a] These parameters were excluded from the multivariabale analysis to avoid multi-collinearity problems

0.668 to 0.786 and 0.792, respectively. Because not every patient would have had a transrectal ultrasound for prostate volume before TRUSPB, we tested an additional base model using only clinical parameters: patient age, tPSA, and %fPSA. We then tested the effect of adding %p2PSA and the *phi* on the accuracy of diagnosis (Table 4). Both %p2PSA and the *phi* improved the AUC of this second base multivariate model from 0.623 to 0.783 and 0.787, respectively. Comparing the first and second base models after the inclusion of the *phi*, no significant difference in

Table 4 Multivariate analyses of the predictive value of each of the parameters in the diagnosis of prostate cancer, with patient age, tPSA, %fPSA, %p2PSA, and phi only

	AUC 95 % CI of AUC	Univariable analysis OR (95 %CI); *p* value	Multivariable analysis		
			Base model (Age + tPSA) OR (95 %CI); *p* value	With %p2PSA OR (95 %CI); *p* value	With *phi* OR (95 %CI); *p* value
Age	0.594 (0.487–0.702)	1.057 (0.986–1.132); 0.119	1.068 (0.987–1.156); 0.100	1.062 (0.785–1.436); 0.091	1.076 (0.988–1.172); 0.092
tPSA	0.582 (0.459–0.704)	1.195 (0.934–1.529); 0.156	1.044 (0.780–1.398); 0.774	1.062 (0.785–1.436); 0.697	0.844 (0.603–1.179); 0.319
%fPSA	0.572 (0.437–0.708)	0.965 (0.901–1.034); 0.311	0.951 (0.884–1.022); 0.169	0.974 (0.908–1.044); 0.455	0.975 (0.909–1.045); 0.473
%p2PSA	0.784 (0.686–0.881)	9.705 (3.519–26.762); <0.001	–	8.856 (2.874–27.289); <0.001	–
phi	0.803 (0.706–0.899)	1.086 (1.047–1.126); <0.001	–		1.085 (1.039–1.133); <0.001
AUC of the Multivariable models (95 % CI)			0.623 (0.493–0.752)	0.783 (0.676–0.890)	0.787 (0.683–0.891)

the AUC with or without prostate volume was observed (0.792 vs. 0.787). Therefore, the measurement of prostate volume (for the determination of PSA density) may not improve the performance of %p2PSA and the *phi* in the diagnosis of PCa further.

We also compared the *phi* value between PCa patients with a Gleason score of 3 + 3 and those with Grade 4 or 5 components (i.e., Gleason sum = 7 or above). The mean *phi* levels for Gleason 6 and Gleason 7 or above were 35.28 (standard deviation = 10.12) and 52.77 (standard deviation = 14.81) ($p = 0.007$).

Discussion

Despite its beneficial role in the detection of early stage PCa, several issues related to the use of PSA in the diagnosis of PCa remain unsettled. One is its lack of cancer specificity, which leads to a large number of patients with elevated PSA levels undergoing unnecessary TRUSPBs. The *phi* has been shown to give better results than tPSA and %fPSA in the diagnosis of PCa in patients with serum PSA levels ranging from 2 to 10 ng/mL. In a recent meta-analysis, at a sensitivity of 90 %, the specificity of the *phi* was 32 % (range 26–43 %) and the AUCs obtained by ROC analysis were between 0.703 and 0.77 [9]. Most of the current data on the *phi* were based on studies in Caucasian populations, which have a higher incidence of PCa. According to Filella and Giménez [9], the positive biopsy rate for patients with a PSA level of 2–10 ng/mL ranged from 39.9 to 57.2 %. However, data on the application of the *phi* in Asian populations, which have a lower incidence of PCa, were sparse. Ito et al. [13] reported the application of p2PSA and the *phi* in a Japanese population with levels of tPSA that ranged from 2 to 10 ng/mL, with or without abnormal DRE findings. The results showed that the performance of the *phi* in diagnosing PCa was superior to that of tPSA and %fPSA at all levels of sensitivity.

Our results showed that the *phi* also performed better than the other parameters, even with a positive biopsy rate of around 10 %. The AUC of the ROC analysis of *phi* was 0.781, which was comparable with that reported in the literature [9]. Compared with the report from Ito et al., our population had a lower positive biopsy rate (9.13 vs. 18.3 % in patients with normal DRE findings) [13]. Nevertheless, both studies support the use of *phi* in Asian populations to improve the accuracy of PCa diagnosis.

In addition to its role in the diagnosis of PCa, the use of *phi* might also help to predict the pathology and tumor aggressiveness of PCa [6, 14]. In our study, a significant difference was observed between the *phi* level in patients with a Gleason score of 3 + 3 and those with Gleason 4 or 5 components. However, because of the small sample size (only 21 cases of PCa, five of which had Gleason 4 or 5 components), more meaningful analysis of the correlation with pathology was difficult. Therefore, further studies of the role of the *phi* in predicting pathology results in Asian populations are needed.

First introduced by Benson et al. in 1992, PSA density is another simple approach that improves the diagnostic and prognostic value of PSA [5]. While ultrasound prostate size assessment was routinely used in some part of the world, unfortunately, it was not a routine procedure during either PCa screening or the assessment of lower urinary tract symptoms in our local hospitals. Thus, the determination of PSA density implies an additional procedure in our centers. Moreover, from our results, *phi* alone had a better performance than PSA density in diagnosis prostate cancer in our study population. Furthermore, when we compared the use of two different base models for multivariate analysis using the *phi*, the inclusion of PSA density or a measurement of prostate volume produced minimal further improvements in the AUC in the multivariate model. Therefore, use of the *phi* would provide a more accurate prediction of prostate cancer and also might help to save the need of prostate size measurement during the initial assessment of patients in some centers.

During assessment of the effect of the *phi* on the diagnosis of PCa, it might be prudent to assess its financial impact on the healthcare system in addition to its diagnostic performance. From our results, the use of the *phi* could have avoided a large proportion of unnecessary TRUSPBs (45 %), even when the sensitivity level was set at 90 %. The financial savings on unnecessary TRUSPBs would need to be set against the additional cost of testing each patient. Nichol et al. [15] used a mathematical model to calculate the cost-effectiveness of an additional *phi* measurement over a 25-year cycle of annual screening in the US healthcare system and concluded that the addition of a *phi* measurement to routine PSA screening was more cost-effective than PSA testing alone. However, this conclusion might not be applicable to other healthcare systems or non-annual screening situations. Moreover, as many different tests are available to improve the diagnostic yield of TRUSPB, a comparison of the various approaches, such as the *phi*, PSAD, and even prostate cancer antigen 3 [16, 17], would be helpful to determine the most cost-effective approach in clinical management.

One of the drawbacks of our study is its retrospective nature and the use of stored blood samples. In this study, all patients' data and blood were collected prospectively for prostate tissue bank, and we hoped this would minimize potential bias. Moreover, our standard practice ensured that all of the blood samples were handled immediately after collection (within 3 h) and stored at − 70 °C until further use [18]. We also limited the study to samples that had been in storage for less than 3 years, and thus, the use of stored samples hopefully did not affect the assessment of the PSA derivatives. However, further prospective studies may be needed to verify our results.

Another problem is the difference in the assays used to measure serum levels of tPSA. The initial PSA measurement (which was an inclusion criteria) was made with our own hospital laboratory system, which is calibrated according to the WHO 96/670 reference standard. However, in the subsequent study, the measurement of PSA and its derivatives was performed with a Beckman Coulter Access2 system that was calibrated to a Hybritech Tandem-R calibrator. This may have led to some discrepancy in the two tPSA levels [19]. Thus, although the inclusion criterion was set as patients with a tPSA level of 4–10 ng/mL, the tPSA range measured by the Access2 system was 3.18–9.98 ng/mL. We understood that there were many different commercial assays used for PSA measurement available, and they may differ slightly in their calibration and also measured PSA values. In real-life clinical practice, different centers may use different PSA measuring systems. Therefore, our main study objective was to assess the role of *phi* as a separate tool in PCa diagnosis among patients with PSA level between 4 to 10 ng/mL in our current practice. However, in order to ensure that measurements were comparable in all of the analyses (including PSA density), those parameters obtained from the Access2 system were used for comparison alone. The PSA level measured by the Roche Cobas e601 system was only used in the inclusion criteria. Nevertheless, our data showed a promising role for *phi* in improving the accuracy of the need for TRUSPB in our population.

Conclusion

As demonstrated in other studies, the use of p2PSA and its derivatives improves the accuracy of the detection of PCa in patients with an elevated level of PSA among an Asian population that has a lower incidence of this tumor. Among the various parameters, the *phi* showed the best performance, and its use could significantly decrease the number of patients who are selected to undergo a prostatic biopsy.

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Conflict of interest None.

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