Use of the Prostate Health Index in Predicting Adverse Oncologic Outcomes on Active Surveillance

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Background:
While the majority of active surveillance (AS) patients have very favorable oncologic outcomes, a fraction will experience adverse oncologic outcomes such as extreme grade reclassification to Gleason grade (GG) group ≥3, recurrence after treatment, non-organ confined disease at prostatectomy or metastases. Biomarkers are needed to identify early which patients might benefit from an early confirmatory biopsy or upfront treatment. We sought to determine if a baseline prostate health index (PHI) test obtained at the start of AS can predict adverse oncologic outcomes for favorable-risk prostate cancers.

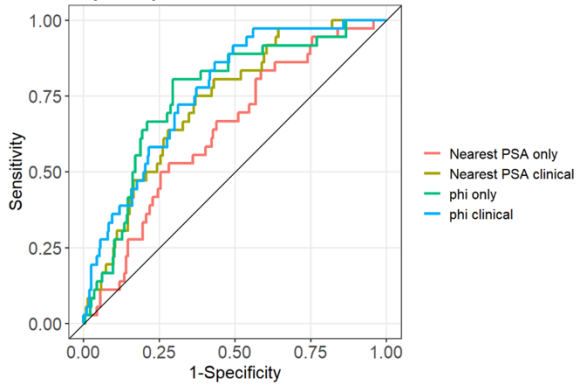
Methods:
We identified N=1,102 AS patients with prospectively banked serum, obtained prior to confirmatory biopsy. Primary endpoint was a composite of adverse AS outcomes including GG≥3 at biopsy or surgery, non-organ confined disease (seminal vesicle invasion or node-positive), recurrence after treatment or metastasis. The cohort was randomly divided into a training set (N=690) and test set (N=412). In the training set, multivariable Cox proportional hazard regression models adjusted for age, body mass index, GG and prostate size were performed to evaluate the association between baseline PHI versus the closest clinical PSA and the adverse outcomes. In the test set, model ability to predict either outcome at 1- and 5-years after diagnosis was compared using areas under the curve (AUC). PSA and PHI levels were converted to a natural logarithmic scale.

Results:
In the training set, on multivariable Cox regression model PSA was associated with the adverse outcomes (HR 2.30 (95% CI 1.66, 3.20), $p<0.001$). In a separate model PHI was also associated with the adverse outcomes (HR 2.49 (95% CI 1.85, 3.34, $p<0.001$). In the test set, PHI was significantly better than PSA at predicting adverse outcomes at 1-year (AUC 0.760 for PHI versus 0.638 for PSA) and 5-years (0.662 versus 0.575) (Figure 1). At 1-year PHI alone performed marginally better than the PSA combined with the same clinical variables used in the regression models (AUC 0.728 for PSA + clinical variables, however the difference in AUCs was not significant). At 5-years, PHI still performed significantly better than PSA, but with the addition of clinical variables both biomarkers performed similarly (Figure 1). Probabilities of the adverse outcomes at 1- vs 5-years, per the commercial PHI thresholds are listed in Table 1.

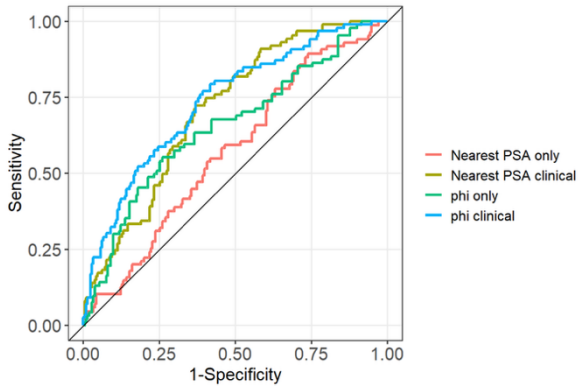
Conclusions:
A baseline PHI is independently associated with adverse oncologic outcomes on AS and is a better predictor than baseline PSA, especially for the early events at 1-year. PHI thresholds can provide individualized risk of having adverse oncologic outcomes which can be helpful for patient counseling.

Figure 1: Receiver operating curves (ROC) and areas under the curves (AUC) for one- and five- year predictions of the adverse outcomes in test set (N=412)

A: One-year prediction



B: Five-year prediction



Biomarker	1-year AUC (95% CI)	5-year AUC (95% CI)
PSA	0.638 (0.552, 0.725)	0.575 (0.505, 0.644)
PHI	0.760 (0.684, 0.837)	0.662 (0.593, 0.732)
PSA + Clinical Model	0.728 (0.653, 0.803)	0.710 (0.650, 0.770)
PHI + Clinical Model	0.766 (0.696, 0.837)	0.735 (0.673, 0.797)
Model difference (PHI-PSA)	0.122 (0.019, 0.225)	0.087 (0.010, 0.164)
Model difference (PHI – (PSA+ Clinical Model))	0.032 (-0.062, 0.126)	-0.048 (-0.120, 0.024)
Model difference ((PHI + Clinical Model) – (PSA+ Clinical Model))	0.038 (-0.020, 0.096)	0.025 (-0.024, 0.074)

AUC: area under the curve; CI: confidence interval; PSA: prostate specific antigen; PHI: prostate health index.
Note: Models adjusted for age, body mass index, grade group and prostate size.

Table 1: Probabilities of the adverse outcomes at 1- vs 5-years by commercial PHI thresholds in the overall cohort (N=1,102)

PHI threshold Hybritech Calibration	**N (%)**	**Probability of adverse outcome by year 1 % (95 CI)**	**Probability of adverse outcome by year 5 % (95 CI)**
0-26.9	232 (21)	1.7% (0, 3.4)	10.3% (6.1, 14.3)
27.0-35.9	258 (23)	5.5% (2.7, 8.3)	19.8% (14.4, 24.9)
36.0-54.9	384 (35)	9.0% (6.0, 11.8)	21.1% (16.7, 25.2)
55+	228 (21)	24.0% (18.2, 29.4)	42.4% (35.0, 48.9)

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