

Prognostic impact of post-prostatectomy PSA slope determined with a novel, Nucleic Acid Detection Immunoassay (NADiA® ProsVue™) for total PSA

J. W. Moul,¹ O. J. Semmes,² R. L. Vessella,³ J. E. McDermed,⁴ H. Lilja⁵

¹Duke University Medical Center, Durham, NC; ²Eastern Virginia Medical School, Norfolk, VA; ³University of Washington, Seattle, WA; ⁴Iris Molecular Diagnostics, Carlsbad, CA;

⁵Memorial Sloan-Kettering Cancer Center, New York, NY

ABSTRACT

Background: ProsVue is an investigational 2-site immunometric PSA assay where the reporter anti-PSA antibody is labeled with an assay-specific synthetic DNA sequence. Real-time PCR is used to detect the DNA signal indicating the PSA concentration. Pilot studies demonstrated that ProsVue slope (the least-squares linear slope of 3 post-RP PSA values) correctly classified prostate cancer (PC) patients (pts) with no evidence of disease (NED) and clinical progression (CP) using a 2 pg/mL/month (mo) ProsVue decision threshold. In a retrospective, multicenter clinical trial, we evaluated the potential prognostic value of ProsVue slope at this decision threshold.

Methods: 392 PC pts having RPs 11/1991 to 8/2001 were studied. Eligibility required first post-RP PSA <100 pg/mL, full pathologic and radiographic data and 3 frozen banked serum samples drawn 6 weeks to 19.4 mo post-RP. Adjuvant radiotherapy (RT) and/or androgen deprivation therapy (ADT) was not allowed. CP was documented by positive imaging, biopsy results or PC-related death. Efficacy of ProsVue slope as a prognostic test for NED/CP at a 2 pg/mL/month decision threshold was determined and also examined with regards to Gleason score (GS), pre-RP PSA and final pathology stage.

Results: Median (range) of pre-RP PSA was 6.3 (0-60.6) ng/mL and post-RP GS was 7.0 (4-10). 73 pts received neoadjuvant therapy. Final pathology stage was pT0-2 (228), pT3 (147), pT4 (17); 116 pts had positive surgical margins and 8 had positive lymph nodes. The 3 PSA values were drawn after a median of 4.9, 8.6 and 12.8 mo and showed median values of 10.7, 23.0 and 50.7 pg/mL, respectively. Calculated sensitivity, specificity, PPV and NPV for a 2 pg/mL/mo ProsVue slope were 75.0%, 96.6%, 81.4% and 95.2%, respectively. Median follow-up (f/u) was 10.5 years. There were 40 deaths (14 from PC).

Conclusions: ProsVue provides information previously unknown in post-RP pts. ProsVue slope \leq 2 pg/mL/mo in the first year is highly associated with NED over long-term follow-up. Potential clinical utility may include predicting pts not requiring long-term oncologic follow-up and predicting a need for post-RP adjuvant RT. ProsVue slope may become a new paradigm for identifying those patients at reduced risk for recurrence of prostate cancer post-RP. Further studies are planned to address these questions.

Background: RP is an effective treatment modality for localized prostate cancer, however disease recurrence occurs in 30-40% of men. While recurrence is more likely to occur when risk factors associated with higher recurrence risk are present, disease does not progress in all "high-risk" men. Level I evidence shows that immediate adjuvant RT improves metastasis-free progression and survival.¹ However 12 patients must be treated to improve survival in 1 patient, therefore this approach can result in substantial overtreatment. Clearly, a personalized test is needed to identify men judged to be at high risk for recurrence that may be at lower risk for clinical recurrence.

NADiA® ProsVue™ is a highly sensitive investigational total PSA assay based on immuno-PCR technology. This method can precisely and accurately quantitate PSA in serum samples at low picogram (pg) per mL levels. Pilot studies showed that the least-squares linear slope of PSA determined from 3 serum samples obtained post-RP might serve as a prognostic indicator for assessing risk of prostate cancer progression. This study was done to verify the performance of a ProsVue slope cutpoint of 2.0 pg/mL/month to identify men at low risk for clinical progression following RP.

STUDY DETAILS

- ▶ 392 men with prostate cancer were studied
- ▶ RPs done at 4 clinical sites between November 1991 and August 2001
- ▶ First post-RP PSA was <100 pg/mL using each site's current assay
- ▶ Complete pathologic and radiographic data was required
- ▶ 3 frozen banked serum samples drawn 6 weeks to 19.4 mo post-RP
- ▶ 73 men received neoadjuvant treatment (ADT, RT and/or chemotherapy)
- ▶ Adjuvant/salvage RT was not allowed during the first year post-RP
- ▶ Adjuvant/salvage ADT was not allowed until \geq 20 months post-RP
- ▶ Progression documented by positive imaging, biopsy or PC related death
- ▶ Prognostic efficacy of ProsVue slope tested at a 2 pg/mL/month cutpoint
- ▶ Covariates included GS, pre-RP PSA and pathologic stage

Definitions of stable and recurrent disease

- ▶ **Recurrence:** positive imaging, biopsy or death due to prostate cancer BCR **was not** considered evidence of clinical recurrence
- ▶ **Stable:** negative imaging, biopsy and death not due to cancer

Methods:

- ▶ 3 PSA calibrators (5, 25 and 100 pg/mL) assayed in triplicate on each run
- ▶ AB 7500 Fast Dx used for DNA amplification
- ▶ Threshold cycles converted to pg/mL using standard curve
- ▶ Least-squares linear slope calculation employed

Patient characteristics		
Age (years)	Median	61.0
	IQR	56.2-65.8
Clinical stage	T1c	24
	T2a-b	253
	T3	115
Pre-RP PSA (ng/mL)	<4.0	86
	4.1 – 9.9	221
	10.0 – 19.9	68
	>20	17
	Median	6.31
Follow-up (years)	IQR	4.31 – 9.61
	Median	10.5
	IQR	8.6 – 12.2

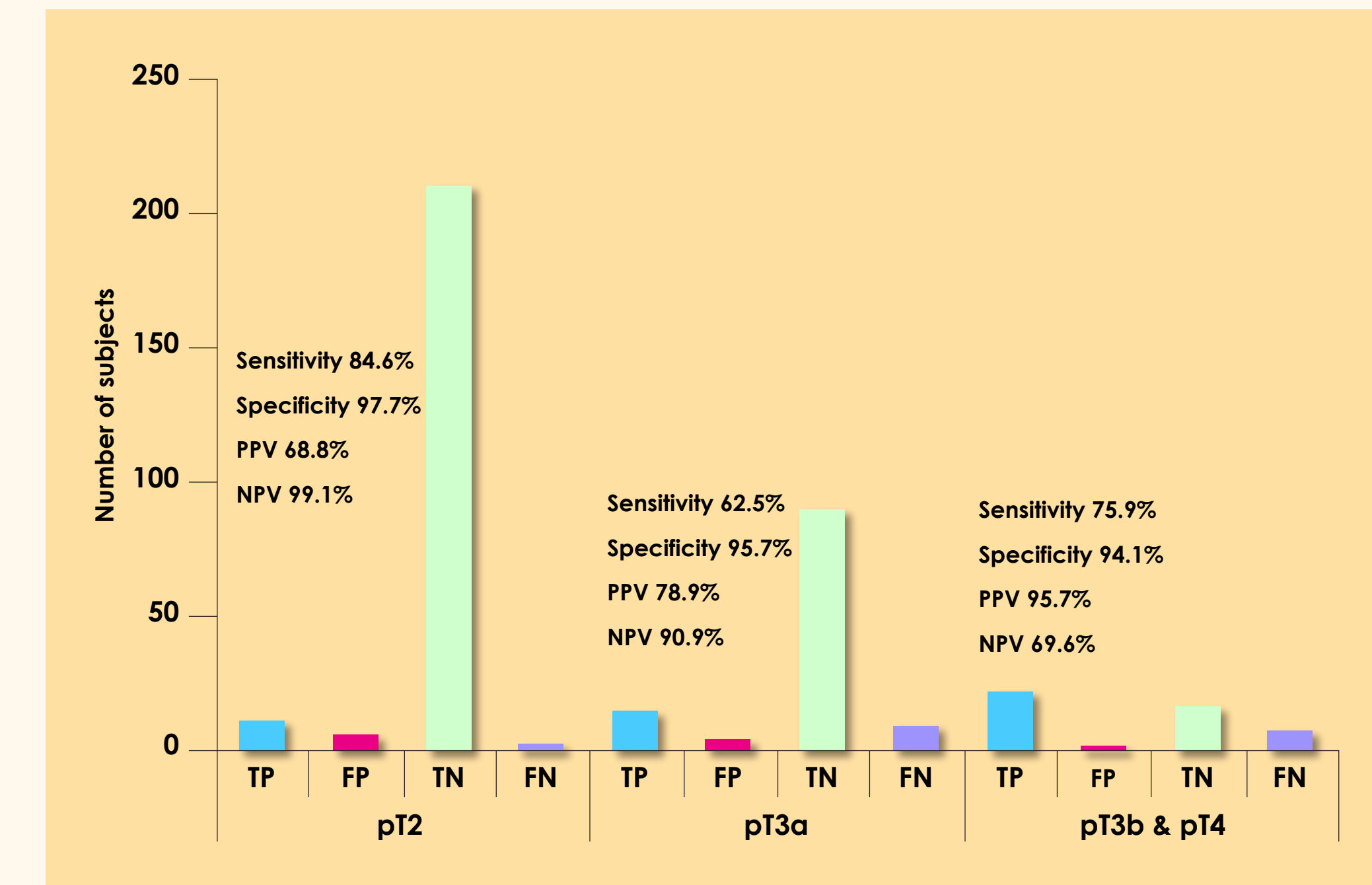
Patient characteristics		
Gleason score	4 & 5	55
	6	137
	7	154
	8 – 10	46
Pathology stage	T2	228
	T3a	118
	T3b	29
	T4	17
	N+	8
	Margins +	116
	Margins -	276
Cancer related deaths		14

RESULTS

Clinical endpoint		Stable (N=304)	BCR ¹ (N=24)	CP ² (N=64)
ProsVue nadir (pg/mL)	Median	2.71	5.90	14.1
	IQR	1.58 – 4.98	2.13 – 15.1	4.06 – 48.0
P value versus stable subset ³		–	0.0088	<0.0001
ProsVue slope (pg/mL/month)	Median	0.036	0.478	6.003
	IQR	-0.045 – 0.214	0.080 – 2.352	1.990 – 22.986
P value versus stable subset ³		–	<0.0001	<0.0001

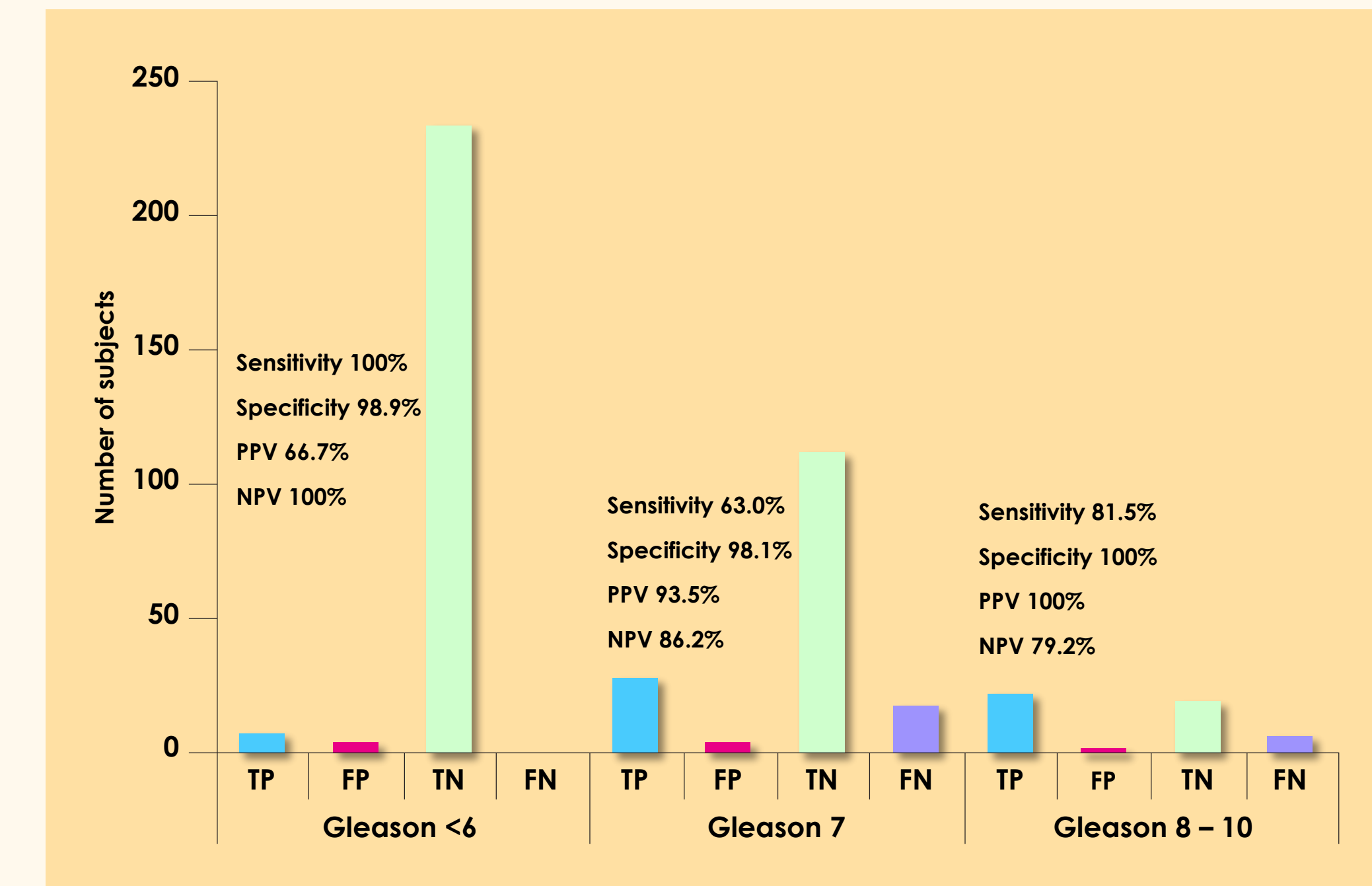
¹ BCR = biochemical recurrence; ² CP = clinical progression; ³ Mann-Whitney test

2.0 pg/mL/month ProsVue slope cutpoints vs. pathological stage



TP = true positive; FP = false positive; TN = true negative; FN = false negative

2.0 pg/mL/month ProsVue slope cutpoint vs. Gleason score



TP = true positive; FP = false positive; TN = true negative; FN = false negative

SUMMARY

ProsVue provides a means to quantify serum PSA in the post-RP period. Expressing ProsVue as a linear slope of PSA vs. time may provide improved prognostic utility compared to single nadir measurement. The accuracy of ProsVue slope appears to be primarily driven by better classification of true negatives.

This large, retrospective trial studied the performance of linear slope of PSA using 3 serum samples taken over 1.5 to 19.4 months post-RP. Results suggest that a ProsVue slope cutpoint of 2.0 pg/mL/month may be a suitable candidate for identifying post-RP patients at low risk of clinically recurrent prostate cancer. Calculated sensitivity, specificity, PPV and NPV using this slope cutpoint were 75.0%, 96.6%, 81.4% and 95.2%, respectively. The incidence of clinically stable patients having a false positive slope was low.

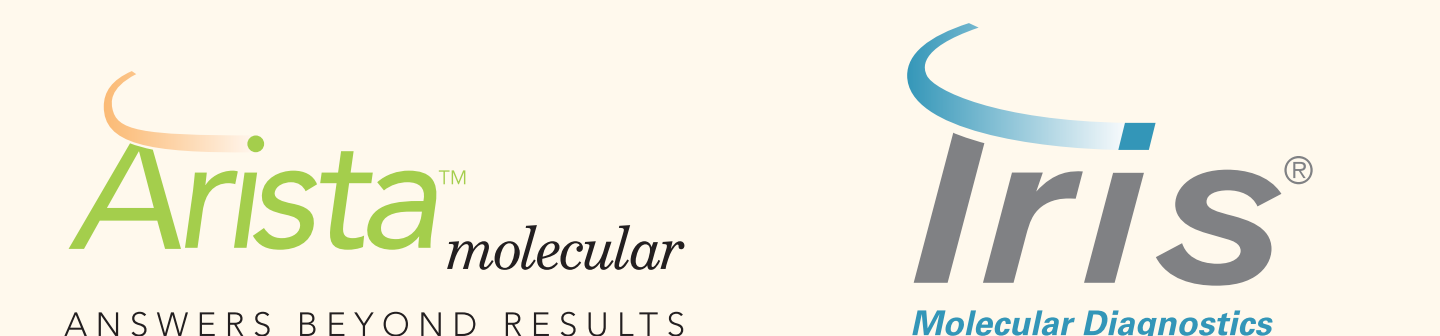
Subgroup analysis according to pathological stage and surgical Gleason score shows that the specificity and NPV of ProsVue linear slope were minimally attenuated. This suggests that ProsVue slope may potentially be useful as an aid to physicians in their assessment of post-RP patients when used in conjunction with traditional risk factors.

Precision studies performed in accordance with CLSI EP5-A guidelines preliminarily demonstrate that ProsVue values are sufficiently precise to calculate post-RP PSA linear slope.

Conclusions:

- ▶ ProsVue provides information previously unknown in post-RP pts.
- ▶ ProsVue slope \leq 2.0 pg/mL/month in the first year post-RP is highly associated with NED over long-term follow-up.
- ▶ Potential clinical utility may include predicting patients that will not require long-term oncologic follow-up and possibly predicting a need for post-RP adjuvant RT.
- ▶ ProsVue slope may become a new paradigm for identifying those patients at reduced risk for clinical recurrence of prostate cancer post-RP.
- ▶ Case-cohort studies statistically modeled and powered are underway to establish if ProsVue slope may be capable of serving as a prognostic indicator for identifying post-RP patients at low risk for cancer recurrence.
- ▶ Future studies are planned to investigate the possible utility of ProsVue linear slope for other potential clinical applications.

Pending 510(k) review, not available in the United States



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