Clinical significance of the LacdiNAc-glycosylated Prostate-Specific Antigen Assay for prostate cancer detection

Tohru Yoneyama[1,2,], Yuki Tobisawa[2], Tomonori Kaneko[3], Takatoshi Kaya[3], Shingo Hatakeyama[2], Kazuyuki Mori[2], Mihoko Sutoh Yoneyama[4], Teppei Okubo[5], Koji Mitsuzuka[5], Wilhelmina Duivenvoorden[6], Jehonathan H. Pinthus[6], Yasuhiro Hashimoto[2], Akihiro Ito[5], Takuya Koie[7], Robert A. Gardiner[8], and Chikara Ohyama[1,2]*

[1]Department of Advanced Transplant and Regenerative Medicine, Hirosaki University Graduate School of Medicine,, Hirosaki, Japan.
[2]Department of Urology, Hirosaki University Graduate School of Medicine, Hirosaki, Japan.
[3]Corporate R&D Headquarters, Konica Minolta, Tokyo, Japan.
[4]Department of Cancer Immunology and Cell Biology, Oyokyo Kidney Research Institute, Hirosaki, Japan.
[5]Department of Urology, Tohoku University Graduate School of Medicine, Sendai, Japan.
[6]Department of Surgery, McMaster University, Hamilton, Canada.
[7]Department of Urology, Gifu University Graduate School of Medicine, Gifu, Japan.
[8]University of Queensland Centre for Clinical Research (UQCCR), Level 6, Building 71/918 Royal Brisbane Hospital, Herston, Australia,

Conflict of Interest Disclosure

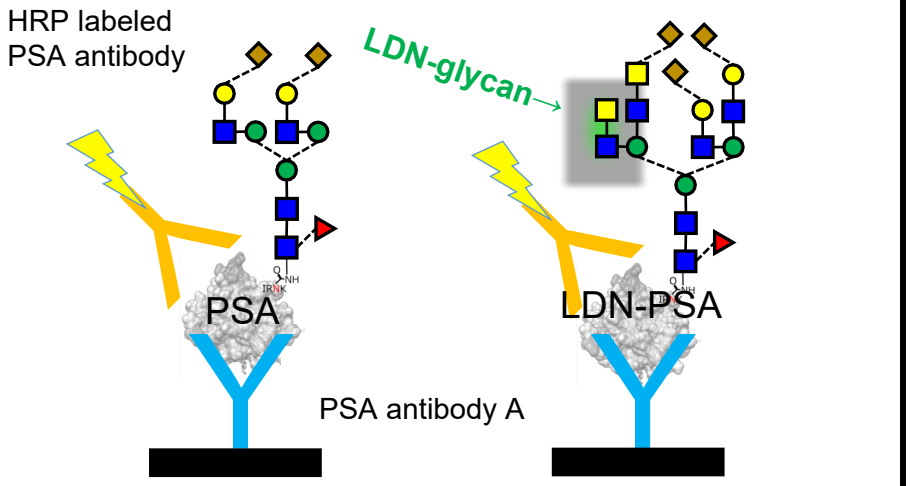
I have no potential conflict of interest to report

Background & Objective:

PSA test

vs

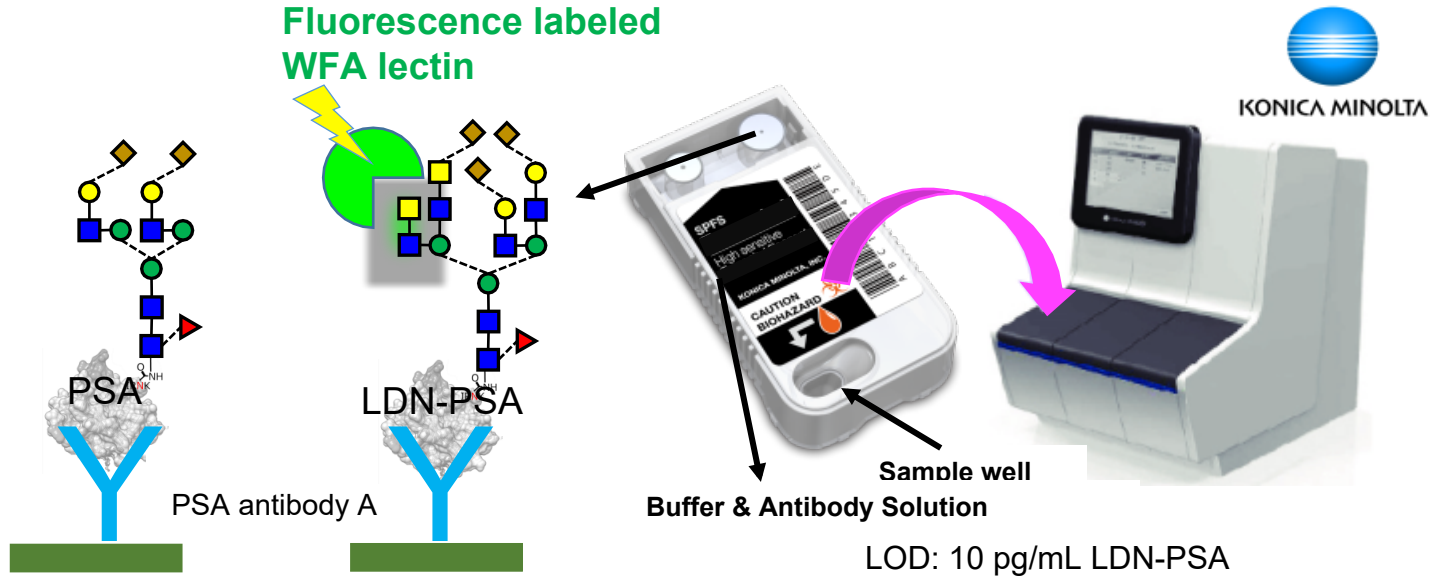
Quantitative analysis of PSA in serum
(prostate specific, but **not PC specific**)



LDN-PSA test

High-sensitive detection of LDN-PSA by SPFS

Quantitative analysis of PC specific glycan change of PSA (**PC specific**)



LOD: 10 pg/mL LDN-PSA

To reduce unnecessary prostate biopsies, better discrimination is needed.
We previously established a surface plasmon field-enhanced fluorescence spectroscopy (SPFS)-based immunoassay system to detect PC-associated terminal LacdiNAc-glycosylated PSA in serum[1, 2, 3].

Design, Setting, and participants of Pbx cohort:

Serum before Pbx (n=718)

Hirosaki U., Tohoku U., McMaster U.

Pbx negative (n=347)

Pbx positive

ASPC (n=38)

SigPC (n=333)

PSA, F/T PSA, PSAD, LDN-PSA & LDN-PSAD

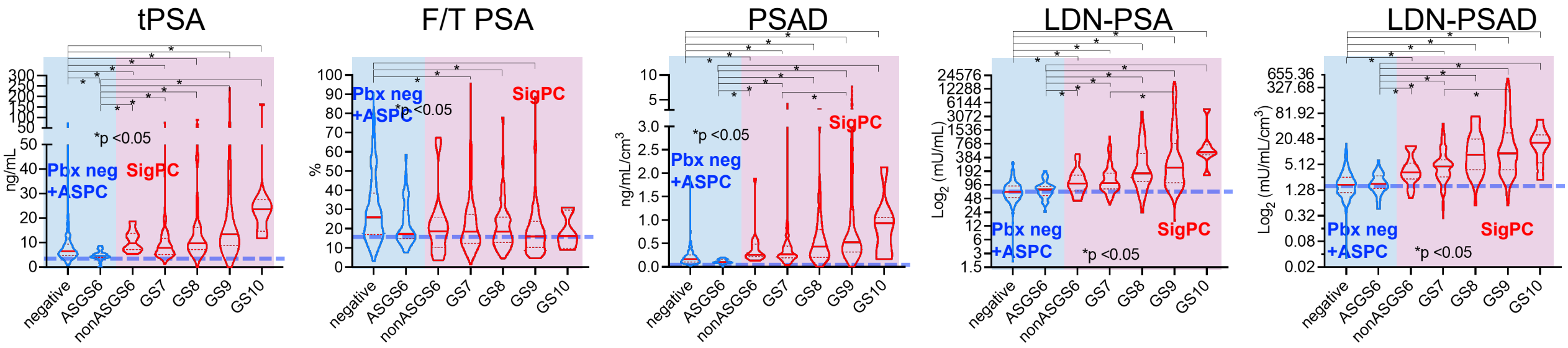
Diagnostic performance of overall, sigPC detection ROC & DCA analyses

Biopsy outcome	negative[a]	ASPC[b]	SigPC[c]		p Value	
All (n = 718)	(n = 347)	(n = 38)	(n = 333)	a vs b	a vs c	b vs c
Median age (IQR)	66 (61.0–72.0)	67 (64.5–73.3)	70 (65.0–74.0)	0.319	<0.0001	0.178
DRE status normal/abnormal	303/44	33/5	178/156	0.450	<0.0001	0.0001
Median P vol cm^3 (IQR)	40.1 (28.4–53.1)	41.8 (33.8–47.4)	27.1 (20.2–36.9)	0.306	<0.0001	<0.0001
Median tPSA ng/mL (IQR)	6.38 (4.67–9.31)	4.51 (4.67–9.31)	10 (6.42–15.59)	<0.0001	<0.0001	<0.0001
Median F/T PSA % (IQR)	25.9 (16.9–38.5)	17.3 (14.9–29.4)	17.7 (11.6–26.5)	0.009	<0.0001	0.301
Median PSAD ng/mL/cm3 (IQR)	0.17 (0.10–0.25)	0.11 (0.09–0.16)	0.36 (0.22–0.66)	<0.0001	<0.0001	<0.0001
Median LDN-PSA mU/mL (IQR)	67.2 (50.5–91.0)	76.7 (56.5–90.1)	150.7 (89.6–326.6)	0.361	<0.0001	<0.0001
Median LDN-PSAD mU/mL/cm3 (IQR)	1.70 (1.12–2.58)	1.78 (1.77–2.80)	5.58 (3.10–13.70)	0.800	<0.0001	<0.0001
Clinical T stage		n (%)	n (%)			
1c		32 (84.2)	172 (51.5)			
2a		5 (13.2)	47 (14.1)			
2b		1 (2.6)	36 (10.8)			
2c-3		0 (0)	73 (21.9)			
4		0 (0)	5 (1.5)			
prostate biopsy GS sum		n (%)	n (%)			
GS 6		38 (100)	19 (5.7)			
GS 7		0 (0)	145 (43.4)			
GS 8		0 (0)	45 (13.5)			
GS 9		0 (0)	117 (35.0)			
GS 10		0 (0)	7 (2.1)			

ASPC: Active surveillance eligible PC by PRIAS criteria
SigPC: non-ASPC

The assays were retrospectively evaluated using the AUC of ROC analysis and DCA analysis to discriminate overall PC, SigPC

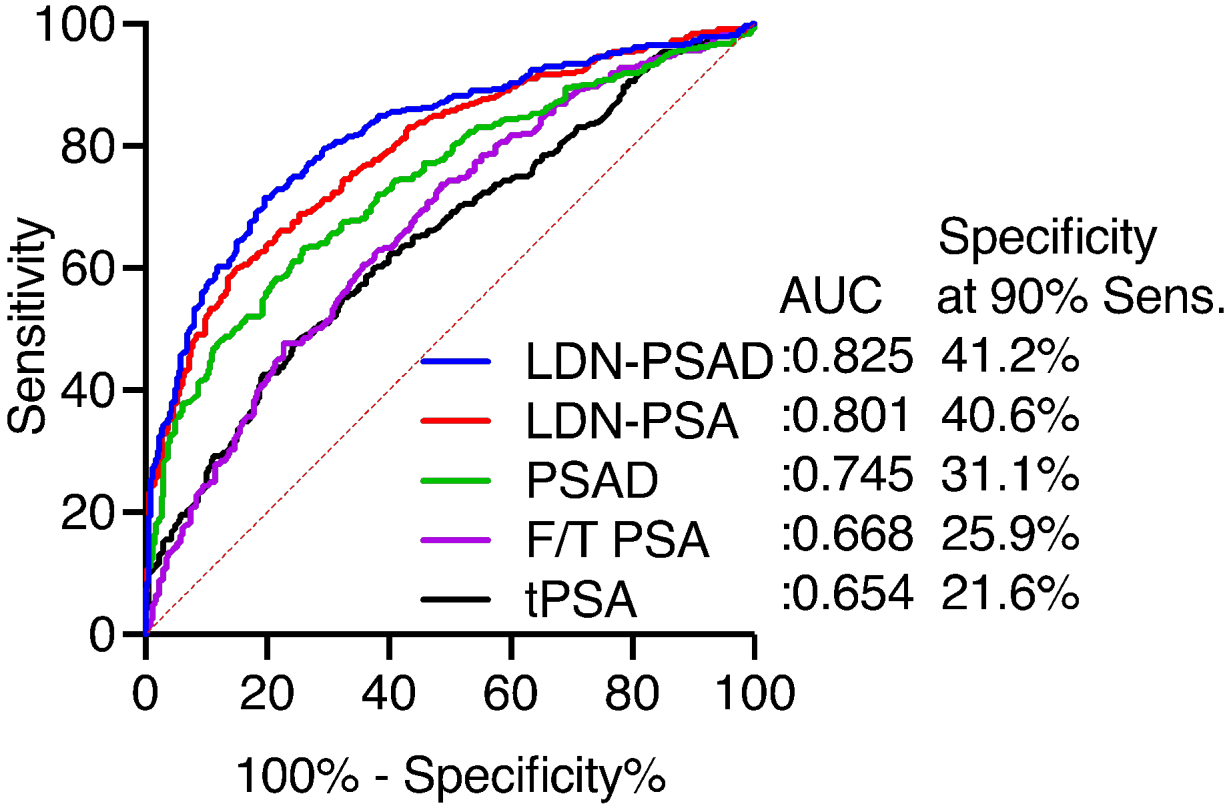
Violin plot in Pbx cohort



- **Serum level of LDN-PSA & LDN-PSAD** was **significantly increased in SigPC.**

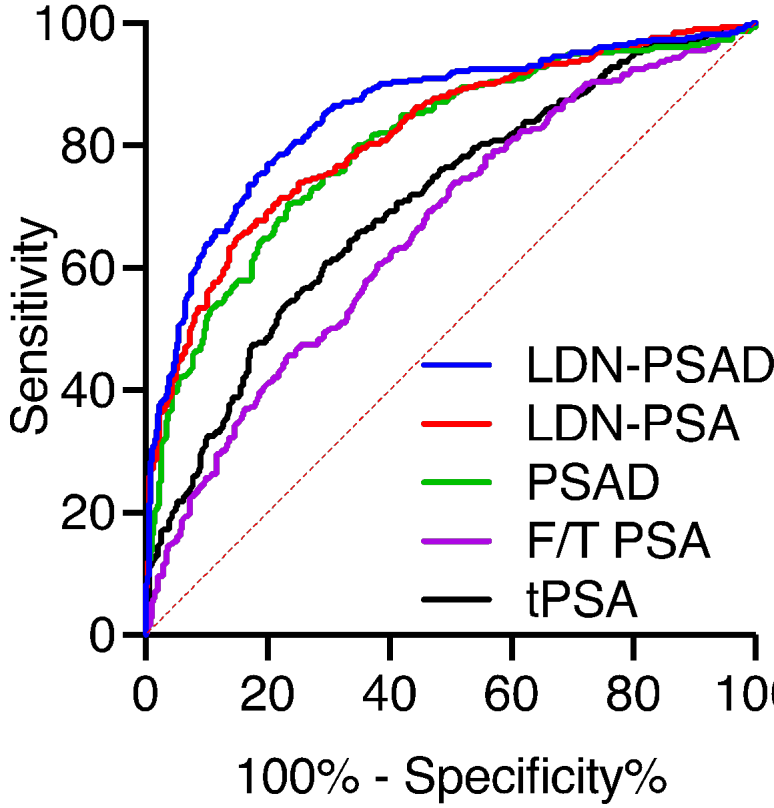
ROC analysis in Pbx cohort

Detection of overall PC



	AUC	Specificity at 90% Sens.
LDN-PSAD	:0.825	41.2%
LDN-PSA	:0.801	40.6%
PSAD	:0.745	31.1%
F/T PSA	:0.668	25.9%
tPSA	:0.654	21.6%

Detection of SigPC



	AUC	Specificity at 90% Sens.
LDN-PSAD	:0.860	62.9%
LDN-PSA	:0.827	48.6%
PSAD	:0.809	44.6%
F/T PSA	:0.661	28.3%
tPSA	:0.712	27.0%

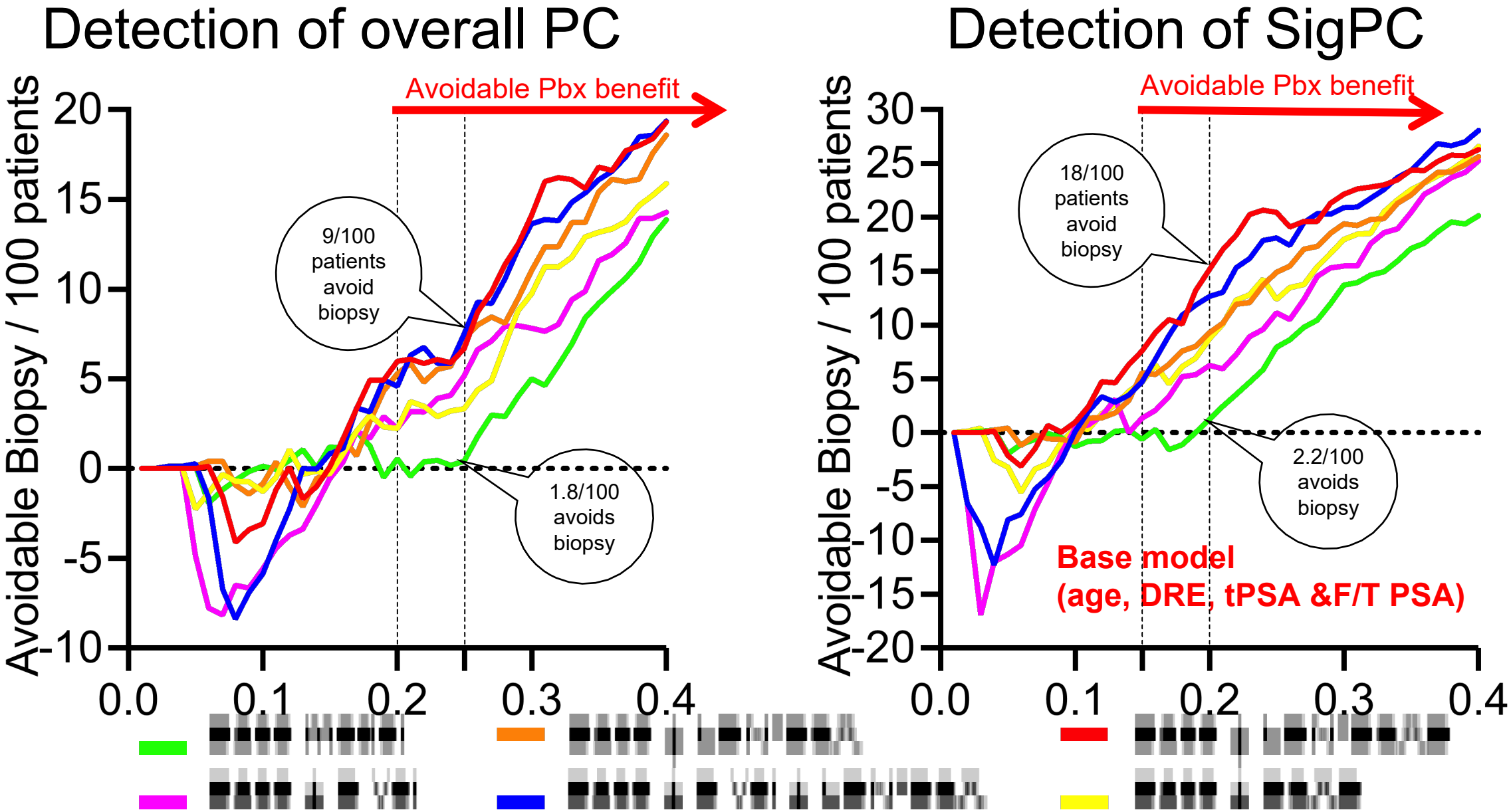
➢**LDN-PSAD had the largest AUC (0.825 for overall PC) (0.860 for SigPC)** and provided significantly better clinical performance for discriminating overall PC & SigPC compared with conventional test.

NPV, PPV & Specificity @ 90 sensitivity in Pbx cohort

Overall PC detection	tPSA	F/T PSA	PSAD	LDN-PSA	LDN-PSAD
Cut-off	4.3 ng/mL	37.90%	0.118 ng/mL/cm3	62.0 mU/mL	1.491 mU/mL/cm^3
AUC; p (vs LDN-PSAD)	0.654; p <0.0001	0.668; p <0.0001	0.745; p <0.0001	0.801; p = 0.0026	0.825
PPV, %	55.1	56.5	58.2	**61.9**	**62.1**
NPV, %	67	70.9	74.9	**79.2**	**79.4**
Specificity, %	21.6	25.9	31.1	**40.6**	**41.2**
SigPC detection	tPSA	F/T PSA	PSAD	LDN-PSA	LDN-PSAD
Cut-off	4.64 ng/mL	36.40%	0.153 ng/mL/cm3	66.8 mU/mL	2.060 mU/mL/cm^3
AUC; p (vs LDN-PSAD)	0.712; p <0.0001	0.661; p <0.0001	0.809; p <0.0001	0.827; p = 0.0024	0.860
PPV, %	51.6	52.1	60.3	**60.2**	**67.7**
NPV, %	75.9	76.8	84.7	**85.0**	**88.0**
Specificity, %	27.0	28.3	44.6	**48.6**	**62.9**

- **LDN-PSA(D)** provided significantly better **NPV and PPV** for discriminating overall PC & SigPC compared with conventional test.

Decision curve analysis in Pbx cohort



Decision curve analysis in Pbx cohort

	Risk threshold (%) of overall cohort					
Pbx avoided per 100 patients w/o missing overall PC	10	15	20	25	30	35
Base model	-9.7	1.1	-8.4	1.8	4.9	9.4
Base+ P vol.	-5.3	-2.8	2.4	6.3	7.2	11.0
Base+ PSAD	-1.3	-0.3	2.2	3.3	9.8	13.2
Base+ LDN-PSA	-5.6	**6.5**	**4.0**	**5.6**	**11.5**	**15.0**
Base+ P vol.+ LDN-PSA	-6.0	**2.2**	**3.8**	**8.2**	**11.8**	**16.1**
Base+ LDN-PSAD	-2.9	**2.0**	**4.5**	**9.3**	**14.2**	**16.4**
Pbx avoided per 100 patients w/o missing SigPC	10	15	20	25	30	35
Base model	-0.1	-0.5	2.2	9.1	12.8	17.2
Base+ P vol.	-0.8	2.5	6.1	11.8	16.4	21.4
Base+ PSAD	0.4	4.7	8.8	12.4	17.9	22.5
Base+ LDN-PSA	1.1	**5.3**	**9.9**	**14.5**	**17.2**	**22.1**
Base+ P vol.+ LDN-PSA	-0.8	**8.3**	**14.2**	**17.8**	**20.1**	**25.5**
Base+ LDN-PSAD	0.4	**8.9**	**18.1**	**16.7**	**20.8**	**23.7**

- **Base (age, DRE, tPSA, F/T) + LDN-PSAD** is the best option ≥ 15 % risk threshold.
- **Adding LDN-PSA & LDN-PSAD** to the base model permitted avoidance of even more biopsies w/o missing overall & SigPC.

Design, Setting, & participants of preop. PSA cohort:

Preop. PSA cohort

(n=174)

Queensland Univ.
Royal Brisbene Woman's Hospital

Radical prostatectomy

PC GS6 (n=8)

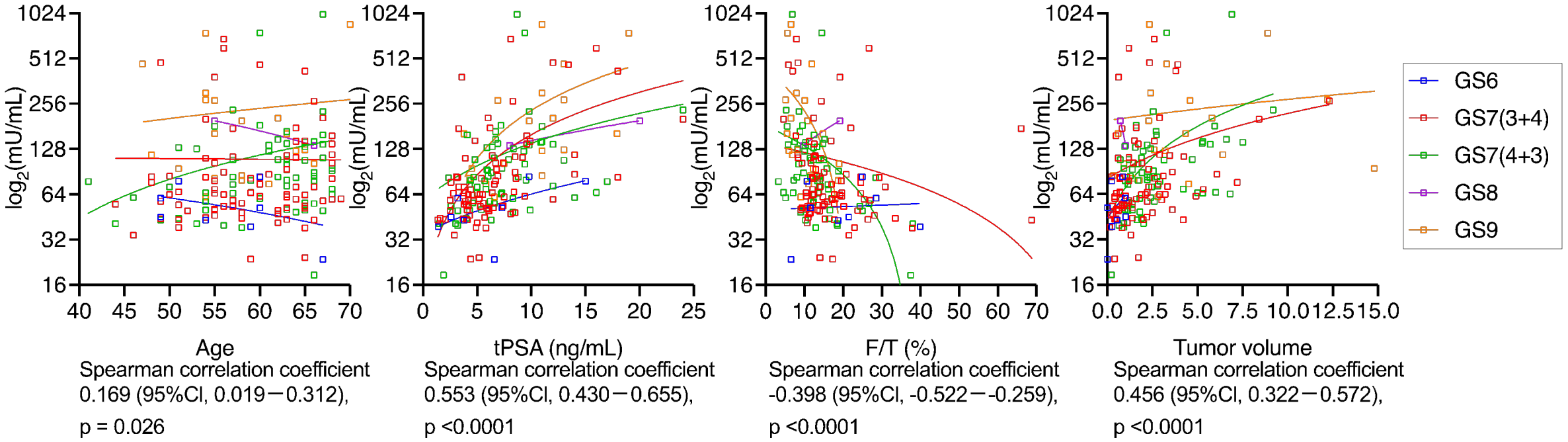
PC >GS7 (n=166)

PSA, F/T PSA, LDN-PSA test

Correlation analysis

Variables	median	(IQR)
Age	60	(55.0–65.0)
Tumor volume, cm^3	1.8	(0.91–2.92)
tPSA, ng/mL	6.4	(4.30–9.38)
F/T PSA, %	12.9	(10.1–17.8)
LDN-PSA, mU/mL	78.7	(54.6–128.0)
Pathological GS sum after RP	**n**	**(%)**
GS 6	8	4.6
GS 7 (3 + 4)	80	46.0
GS 7 (4 + 3)	64	36.8
GS 8	2	1.1
GS 9	20	11.5
Pathological stage	**n**	**(%)**
pT2a,b	59	33.9
pT2c	54	31.0
pT3	61	35.1
Perineural invasion (PNI)	**n**	**(%)**
Yes	144	82.8
No	30	17.2
Seminal vesicle invasion (SV)	**n**	**(%)**
Yes	8	4.6
No	166	95.4
Lymphovascular invasion (LVI)	**n**	**(%)**
Yes	44	25.3
No	130	74.7
Resection margin (RM)	**n**	**(%)**
Positive	23	13.2
Negative	151	86.8

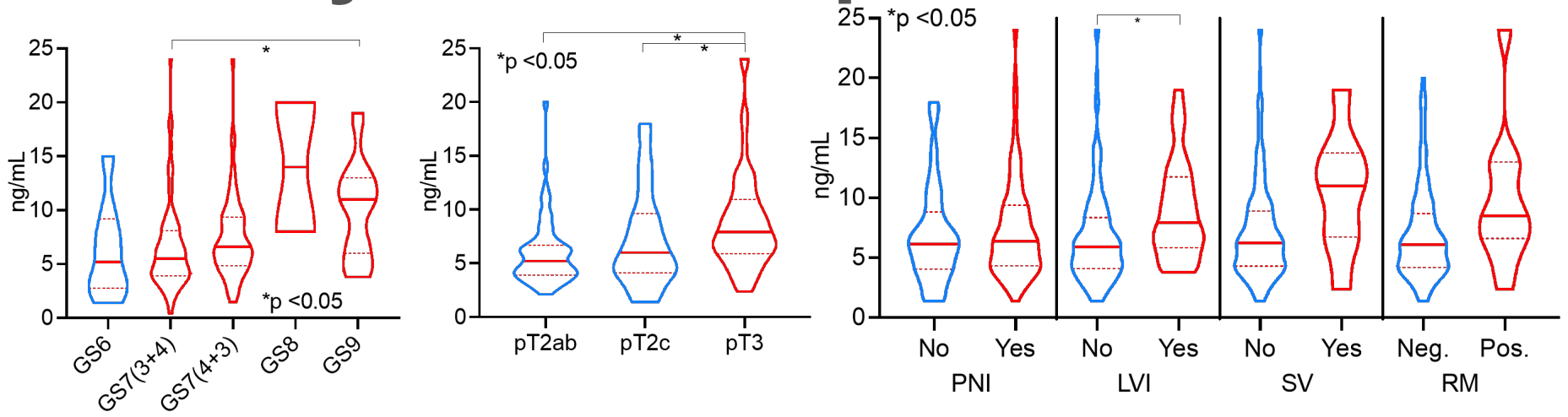
Correlation analysis in Preop-PSA cohort



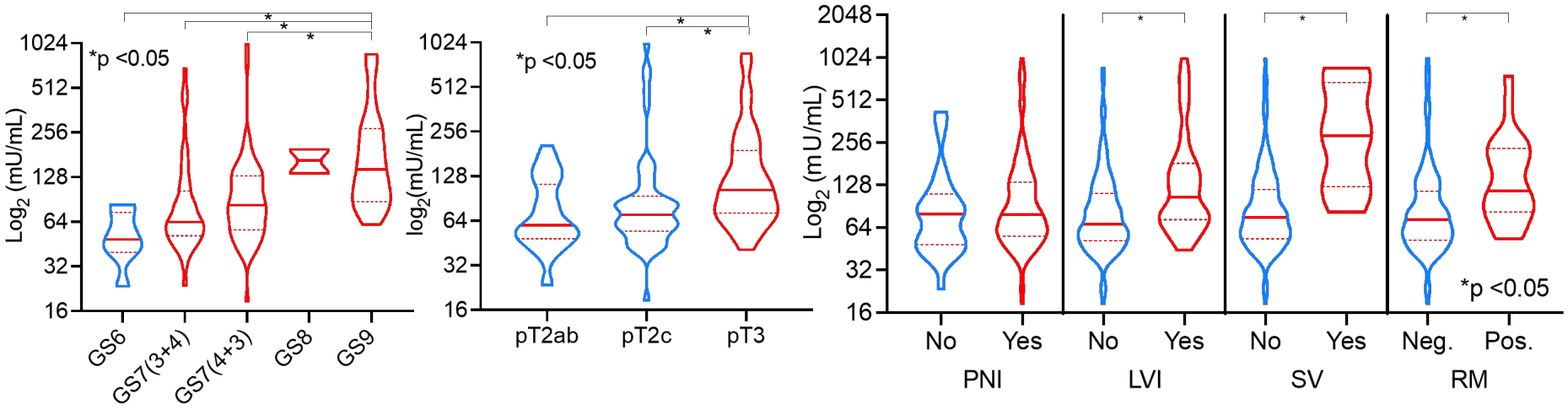
➢**preop-LDN-PSA value positively correlated with tumor volume and tPSA**

Correlation analysis in Preop-PSA cohort

tPSA



LDN-PSA



- **preop-LDN-PSA value** was significantly higher in **pT3**, pathological **GS ≥7, LVI+, SV+, & RM+**.

Conclusion:

- **The diagnostic performance of LDN-PSA(D)** is **significantly better than the PSA, FT/ PSA & PSAD test** in identifying patients with overall PC and sigPC.

- **Addition of LDN-PSA(D)** test to conventional diagnostic model **significantly improve avoidable biopsy effect** in identifying patients with overall PC and sigPC.

- **Preop. LDN-PSA level** positively correlated with **tPSA** and **tumor vol.**, **higher GS** & **pT3 case,** which might be reflect tumor malignancy.