Pre-treatment Prostate-specific Antigen Records in Risk Evaluation of Prostate Cancer

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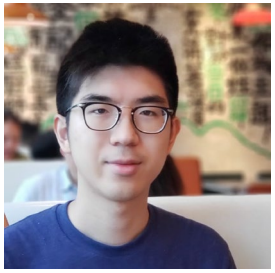

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Background

Prostate cancer

- 2nd most frequently diagnosed cancer of men, 5th leading cause of death from cancer in men[1]
- Primarily impacts older men – and as many prostate cancers are slow-growing, monitoring and observation can often suffice until mortality arrives via senescence.

Prostate-specific antigen (PSA)

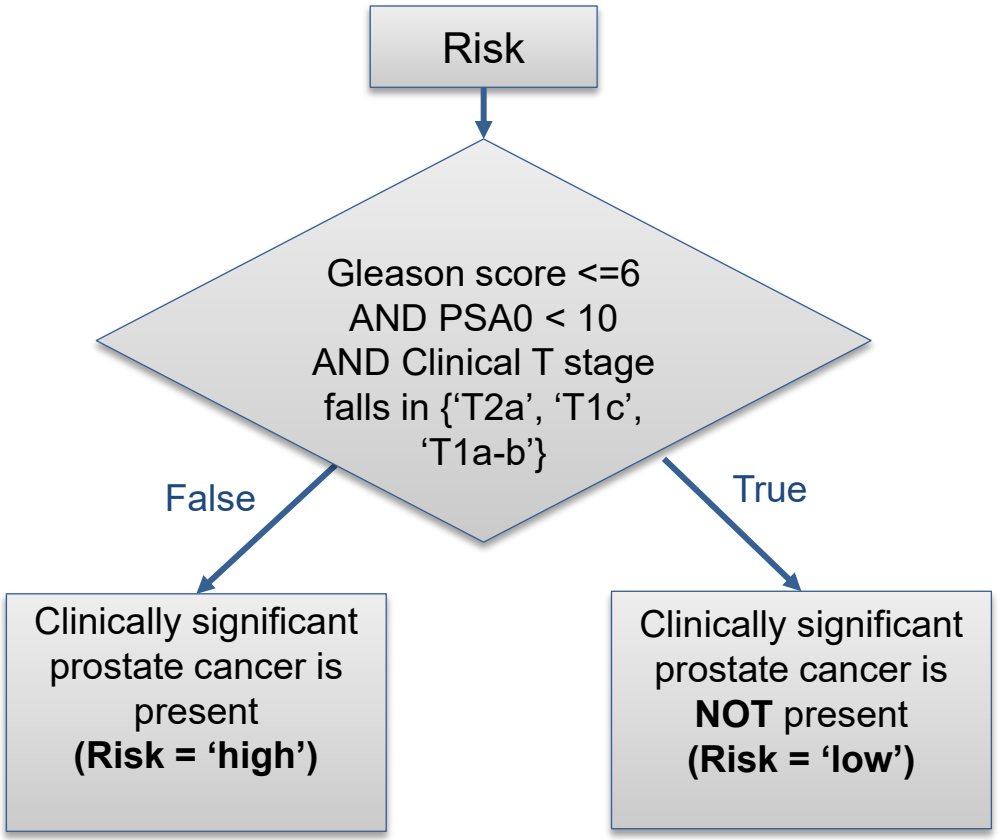
- A protein produced by normal and cancer cells of the prostate gland
- PSA level of healthy men is usually below 4 ng/ml
- Blood level of PSA is often elevated in men with prostate cancer
- A continuous rise in a man's PSA level over time may also be a sign of prostate cancer

1. *"Chapter 1.1". World Cancer Report. World Health Organization. 2014. ISBN 978-9283204299.*

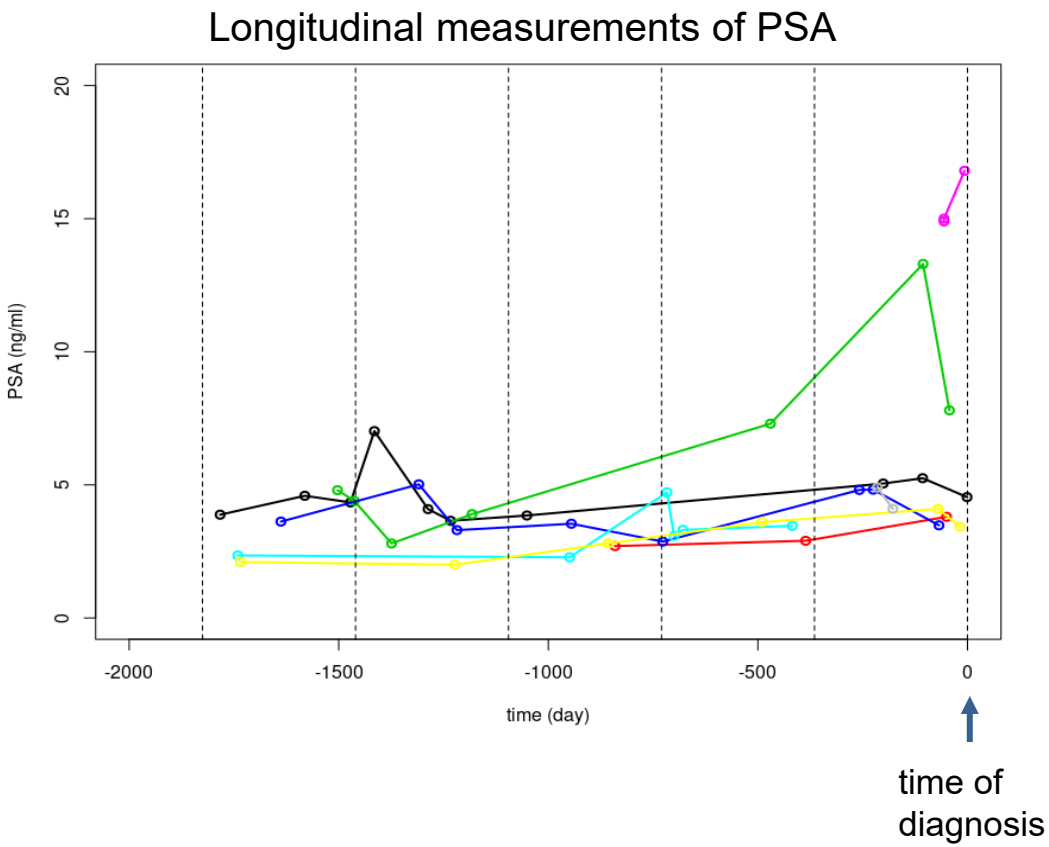
Data source

VA data: 48623 patients diagnosed with localized prostate cancer in the Veteran Health Administration from 2010-2018.

- PSA lab test dates and results in the five years prior to the diagnosis (PSA0: the most recent PSA measurement)
- Age at diagnosis
- Race
- Charlson index comorbidity score
- Clinical M, N, T stages
- Gleason score (cancer grade via biopsy sample)
- Treatment type
- End of follow-up (12/31/2018)



Objective

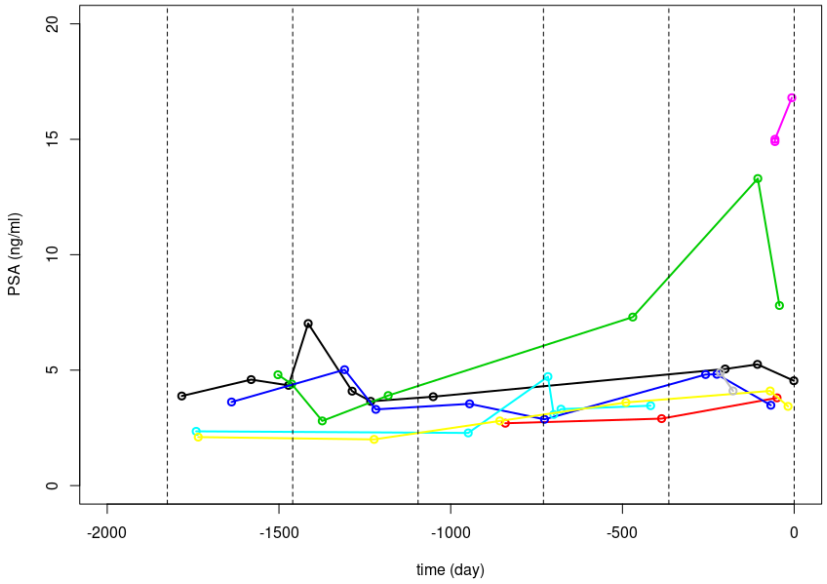


How can we make the best use of pre-diagnosis longitudinal PSA measurements to help risk evaluation?

- Currently, the absolute value of PSA is used in clinical practice
- PSA Velocity has been explored but recent studies have cast doubt on the value of it.[1, 2]
- Variation in PSA values over time has never been investigated yet

[1] Andrew J. Vickers and Simon F. Brewster. PSA Velocity and Doubling Time in Diagnosis and Prognosis of Prostate Cancer. Br J Med Surg Urol. 2012 Jul 1; 5(4): 162–168.
[2] Carter HB, Ferrucci L, Kettermann A, Landis P, Wright EJ, Epstein JI, et al. Detection of life-threatening prostate cancer with prostate-specific antigen velocity during a window of curability. *J Natl Cancer Inst.* 2006;98:1521–7.

Extract information from longitudinal PSA measurements



Interpretable features extracted from PSA measurements

- Velocity
  - Linear slope (b1): $\hat{b}_1$

  $x(t_i) = b_1 t_i + b_0 + \epsilon_i,\ \epsilon_i \sim N(0, \sigma^2)$

- Volatility
  - Average real variability (ARV):[1]

    $\frac{\sum|x(t_i) - x(t_{i-1})|}{n-1}$
  - Variance of residuals (VarResidual):

    $\frac{\sum[x(t_i) - \hat{b}_1 t_i - \hat{b}_0]^2}{n-1}$

[1] S. Park, et al. Intraoperative Arterial Pressure Variability and postoperative Acute Kidney Injury. CJASN, vol 15, 2020

Statistical analysis

- For each patient, extract velocity and volatility features from historical PSA
- Examine the association of volatility features with risk outcome, individually or jointly, via logistic regression
- Covariates AgeAtDiagnosis , CHARLSON and PSA0 are included in the regression

Cohort characteristics

Characteristic	N = 48,623[1]
AgeAtDiagnosis	66 (62, 70)
CHARLSON	3 (2, 5)
PSA0	5.94 (4.99, 7.32)
PSAVelocity	0.0021 (0.0014, 0.0031)
VarResidual	0.35 (0.14, 0.80)
ARV	0.98 (0.71, 1.41)
Risk	31,291 (64%)

[1]Median (IQR); n (%)

Association between ARV and risk

	PSAVelocity			ARV			PSAVelocity+ARV		
Characteristic	log(OR)[1]	95% CI[1]	p-value	log(OR)[1]	95% CI[1]	p-value	log(OR)[1]	95% CI[1]	p-value
age	0.02	0.02, 0.02	<0.001	0.02	0.01, 0.02	<0.001	0.02	0.01, 0.02	<0.001
CHARLSON	0.05	0.04, 0.06	<0.001	0.05	0.05, 0.06	<0.001	0.05	0.05, 0.06	<0.001
psa0	0.09	0.08, 0.11	<0.001	0.11	0.10, 0.12	<0.001	0.10	0.09, 0.11	<0.001
PSAVelocity	**16**	**11, 21**	**<0.001**				**16**	**12, 21**	**<0.001**
ARV				**-0.04**	**-0.06, -0.02**	**<0.001**	**-0.04**	**-0.06, -0.03**	**<0.001**
[1]OR = Odds Ratio, CI = Confidence Interval									

- Logistic regression model:
  - risk ~ age + CHARLSON + PSAVelocity and/or ARV
- Both PSAVelocity and ARV are significantly associated to risk outcome
- Intuitive interpretation:
  - PSA for patients at high risk -> monotonically increase
  - PSA for patients at lower risk -> (increase) with more fluctuation

Association between VarResidual and risk

	PSAVelocity			VarResidual			PSAVelocity+VarResidual		
Characteristic	log(OR)[1]	95% CI[1]	p-value	log(OR)[1]	95% CI[1]	p-value	log(OR)[1]	95% CI[1]	p-value
age	0.02	0.02, 0.02	<0.001	0.02	0.01, 0.02	<0.001	0.02	0.02, 0.02	<0.001
CHARLSON	0.05	0.04, 0.06	<0.001	0.05	0.05, 0.06	<0.001	0.05	0.04, 0.06	<0.001
psa0	0.09	0.08, 0.11	<0.001	0.10	0.09, 0.12	<0.001	0.09	0.08, 0.11	<0.001
PSAVelocity	**16**	**11, 21**	**<0.001**				**17**	**12, 22**	**<0.001**
VarResidual				**-0.004**	**-0.01, 0.00**	**<0.001**	**-0.004**	**-0.01, 0.00**	**<0.001**

[1]OR = Odds Ratio, CI = Confidence Interval

We get the same results for VarResidual.

Confirm the findings with sub cohort (#PSA >5)

- Reliability of b1, ARV and VarResidual are affected by the number of PSA measurements
- Refine the cohort to patients with more than five pre-diagnosis PSA measurements
- Check if the statistically significant association still exists

Sub cohort characteristics

Characteristic	N = 34,243[1]
AgeAtDiagnosis	66 (63, 70)
CHARLSON	4 (2, 5)
PSA0	5.93 (4.99, 7.30)
PSAVelocity	0.0020 (0.0014, 0.0028)
VarResidual	0.41 (0.19, 0.90)
ARV	0.92 (0.68, 1.27)
Risk	21,976 (64%)

[1]Median (IQR); n (%)

Association between ARV and risk (sub cohort)

	PSAVelocity			ARV			PSAVelocity+ARV		
Characteristic	log(OR)[1]	95% CI[1]	p-value	log(OR)[1]	95% CI[1]	p-value	log(OR)[1]	95% CI[1]	p-value
age	0.02	0.02, 0.03	<0.001	0.02	0.02, 0.02	<0.001	0.02	0.02, 0.03	<0.001
CHARLSON	0.05	0.04, 0.06	<0.001	0.05	0.04, 0.06	<0.001	0.05	0.04, 0.06	<0.001
psa0	0.04	0.03, 0.06	<0.001	0.11	0.09, 0.12	<0.001	0.06	0.04, 0.07	<0.001
PSAVelocity	**121**	**104, 139**	**<0.001**				**125**	**108, 142**	**<0.001**
arv				**-0.07**	**-0.10, -0.05**	**<0.001**	**-0.09**	**-0.12, -0.07**	**<0.001**

[1]OR = Odds Ratio, CI = Confidence Interval

- ARV and PSAVelocity are still significant
- PSAVelocity is still negatively correlated with risk

Association between VarResidual and risk (sub cohort)

	PSAVelocity			VarResidual			PSAVelocity+VarResidual		
Characteristic	log(OR)[1]	95% CI[1]	p-value	log(OR)[1]	95% CI[1]	p-value	log(OR)[1]	95% CI[1]	p-value
age	0.02	0.02, 0.03	<0.001	0.02	0.02, 0.02	<0.001	0.02	0.02, 0.03	<0.001
CHARLSON	0.05	0.04, 0.06	<0.001	0.05	0.04, 0.06	<0.001	0.05	0.04, 0.06	<0.001
psa0	0.04	0.03, 0.06	<0.001	0.10	0.08, 0.11	<0.001	0.04	0.03, 0.06	<0.001
PSAVelocity	**121**	**104, 139**	**<0.001**				**125**	**107, 142**	**<0.001**
VarResidual				**-0.003**	**-0.01, 0.00**	**<0.001**	**-0.005**	**-0.01, 0.00**	**<0.001**

[1]OR = Odds Ratio, CI = Confidence Interval

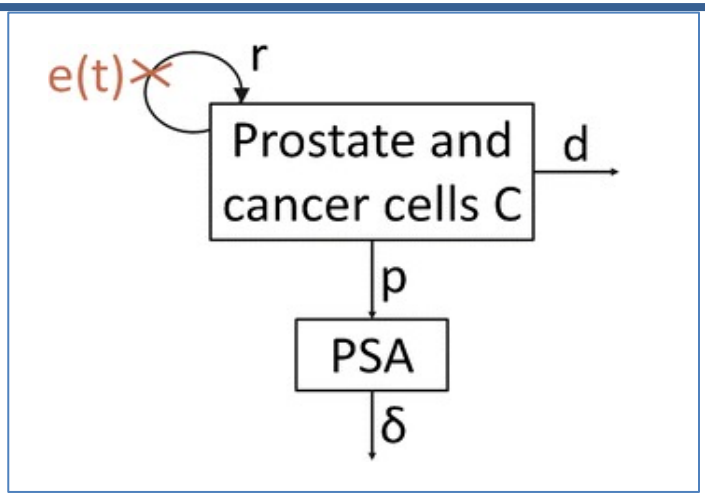
We get the same results for VarResidual.

Recent preliminary work: ODE for PSA kinetics

- Mechanistic Model for PSA kinetics[1]

$$\begin{cases} \frac{dC}{dt} = (r-d)C(t) \\ \frac{dPSA}{dt} = pC(t) - \delta PSA(t) \\ C_0 = \frac{\delta PSA_0}{p} \end{cases}$$

$$\rightarrow PSA(t) = \frac{\delta PSA_0}{r-d+\delta} e^{(r-d)t} + \left(PSA_0 - \frac{\delta PSA_0}{r-d+\delta} \right) e^{-\delta t}$$



- Individual parameters:

$$\theta = \{PSA_0, \delta, r-d\}$$

- Model PSA measurements of patient i

$$\log(y_{ij}+1) = \log\left(PSA\left(t_{ij}, \theta_i\right)+1\right) + \epsilon_{ij}, \qquad j = 1, \ldots, n_i$$

[1] Desmée, Solène & Mentré, France & Veyrat-Follet, Christine & Guedj, Jeremie. (2015). Nonlinear Mixed-Effect Models for Prostate-Specific Antigen Kinetics and Link with Survival in the Context of Metastatic Prostate Cancer: a Comparison by Simulation of Two-Stage and Joint Approaches. The AAPS journal. 17. 10.1208/s12248-015-9745-5.

Logistic regression for ODE extracted features

	ODE_PSA0			ODE_rmd			All ODE features		
Characteristic	OR[1]	95% CI[1]	p-value	OR[1]	95% CI[1]	p-value	OR[1]	95% CI[1]	p-value
age	1.02	1.01, 1.02	<0.001	1.02	1.01, 1.03	<0.001	1.02	1.01, 1.02	<0.001
CHARLSON	1.05	1.03, 1.07	<0.001	1.05	1.04, 1.07	<0.001	1.05	1.03, 1.07	<0.001
ode_psa0	**1.11**	**1.08, 1.13**	**<0.001**				**1.11**	**1.08, 1.14**	**<0.001**
ode_rmd				**1.62**	**1.31, 2.02**	**<0.001**	**1.55**	**1.25, 1.93**	**<0.001**
ode_res_var							**0.99**	**0.99, 1.00**	**0.004**

[1]OR = Odds Ratio, CI = Confidence Interval

$$PSA(t) = \frac{\delta PSA_0}{r - d + \delta} e^{(r-d)t} + \left(PSA_0 - \frac{\delta PSA_0}{r - d + \delta} \right) e^{-\delta t}$$

- Cohort: patients with five-year PSA measurements
- Features positively associated with risk:
  - ODE_psa0: PSA level at time 0 (blue)
  - ODE_rmd: reproduction rate of prostate cancer cells (red)
- Features negatively associated with risk :
  - ODE_res_var: variance of residuals, i.e., PSA variation not explained by ODE

Conclusion

- Confirmed the association between PSA velocity and risk: Higher velocity => higher risk
- Defined interpretable metrics to measure the variability of longitudinal PSA measurements
- For patients with localized prostate cancer, the volatility of pre-diagnosis PSA is significantly associated to risk (p-value < 0.05), adjusting for age, CHARLSON score and PSA0.
- Higher volatility => Lower risk
- ODE based models are in plan for future work

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