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A Joint Model Relating Changes in Prostate Specific Antigen to Survival in Castrate Resistant Prostate Cancer

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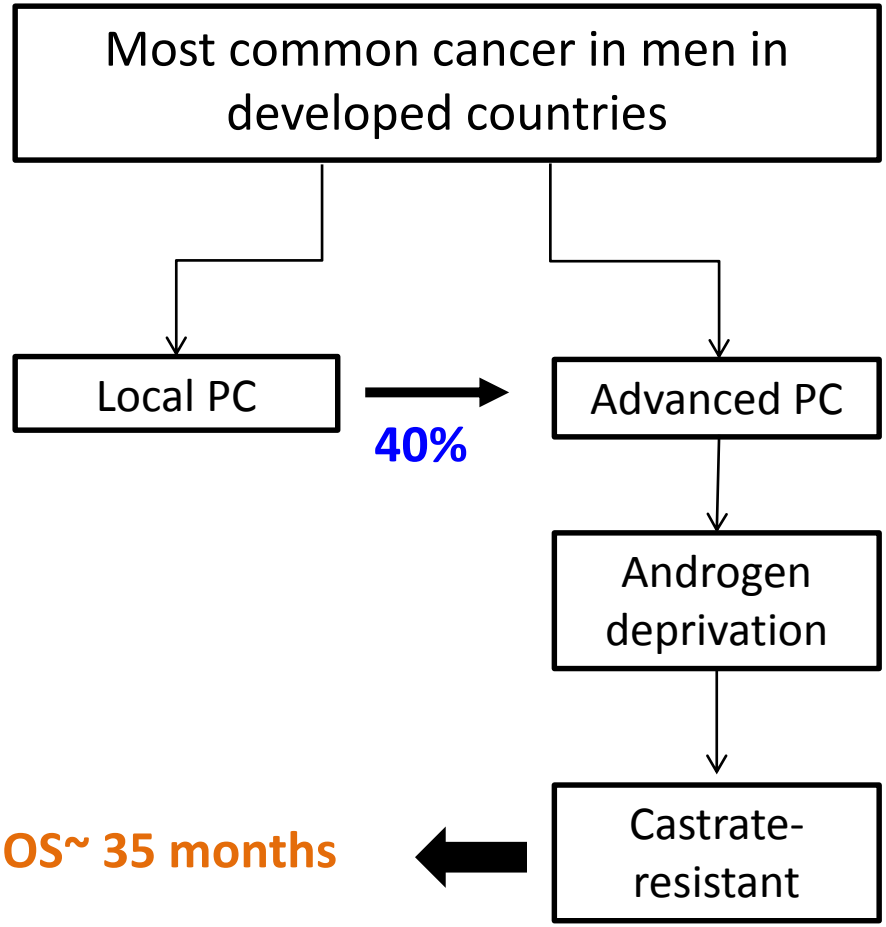
Conflict of Interest Statement

The authors have nothing to disclose

Background



No cure

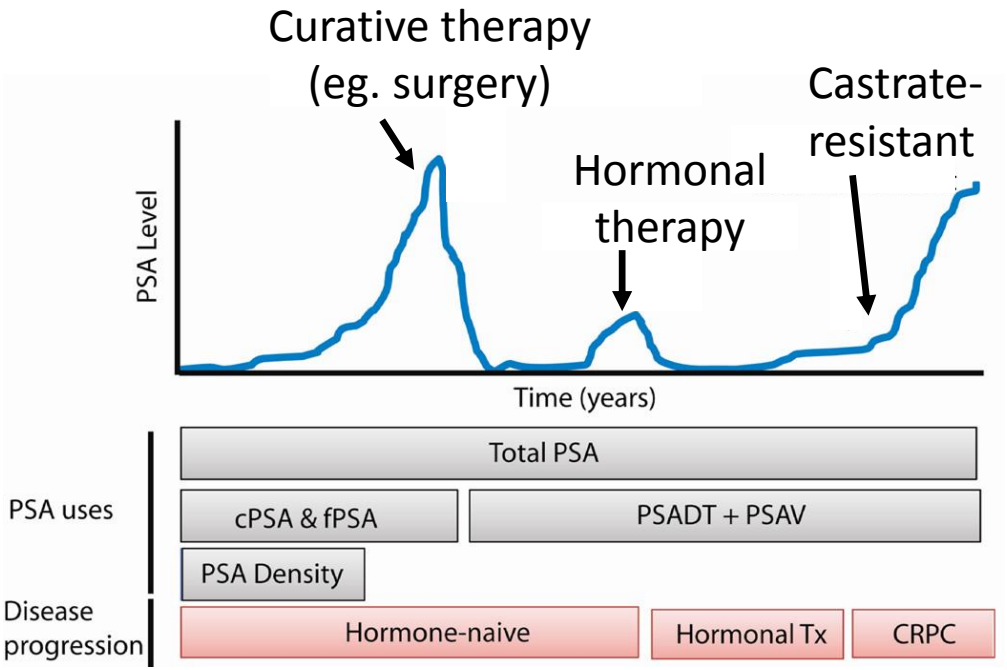
Drug development:

- **Time consuming (12-15 years)**
- **Costly ($1 billion)**

Evaluation of efficacy depends on overall survival (OS)

Goal: Determine an early endpoint that is predictive of OS benefit for clinical trial design using model-based approach

Prostate-Specific Antigen (PSA) as a Biomarker

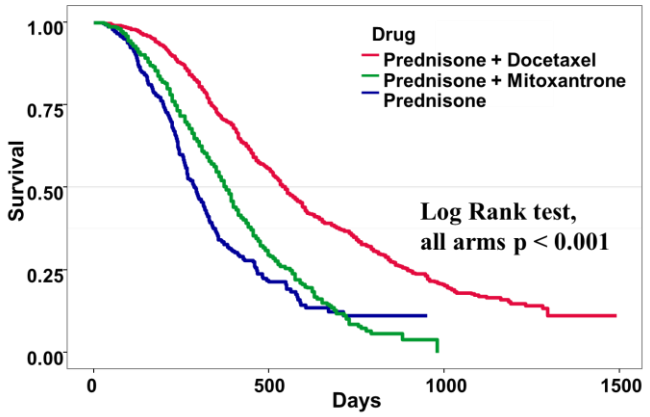


- PSA was recognized as a biomarker for monitoring the progression of patients with CRPC
- Easily measured in serum
- Accessible longitudinal data

Adapted from Prensner et al. *Sci Transl Med.* 2012 Mar 28; 4(127): 127rv3.

Phase III Clinical Trials

- Project Data Sphere allows access to control-arm data from phase III cancer clinical trials



ProjectDataSphere ID	N	Drugs	
1. Prostat_Pfizer_2008_81	201	Prednisone	+ Drug A
2. Prostat_Sanofi_2000_80	253	Prednisone + Mitoxantrone	+ Drug B
3. Prostat_Sanofi_2007_79	282	Prednisone + Mitoxantrone	+ Drug C
4. Prostat_Sanofi_2007_83	457	Prednisone + Docetaxel	+ Drug D
5. Prostat_CougarB_2008_101	253	Prednisone	+ Drug E
6. Prostat_Novacea_2006_89	312	Prednisone + Docetaxel	+ Drug F

Total: 1758 patients

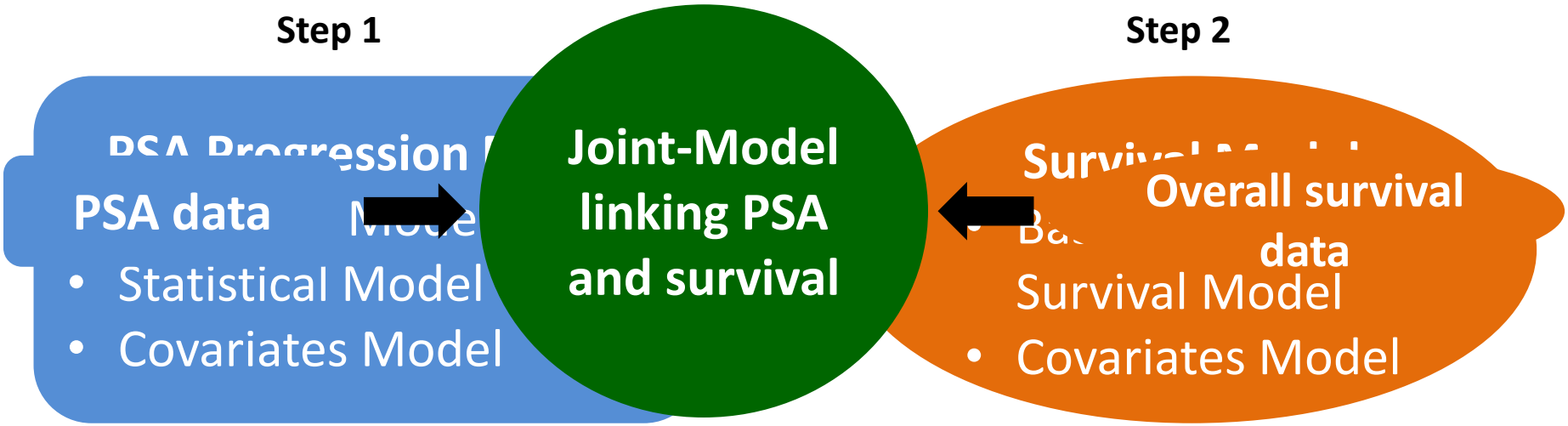
Modeling Strategies

$$PSA(t) = BSL * (e^{(-d*t)} + e^{(g*t)} - 1)$$ *

* Stein, W.D., et al.,. Clin Cancer Res, 2011. **17**(4): p. 907-17.

BSL: estimated baseline PSA
d: rate of decrease in PSA
g: PSA growth rate

Approach 1: Two-stage Model



Estimation of the Parameters

Approach 1: Two-stage model

Estimates of the PSA progression model

Population Parameters	Estimates	Units	BSV (%)
Baseline (BSL)	138	ng/mL	162
Growth	0.00069	1/day	138
Decay	0.0113	1/day	110
Baseline Hazard of dropout	0.0122		

Significant covariates in the Cox-regression survival model

PSA doubling time
Prior treatment with Docetaxel
Hemoglobin
Age
Performance status (ECOG)
Alkaline phosphatase
Diagnosis Day

Estimation of the Parameters

Approach 2: Joint-model

Population Parameters	Estimates	Units	BSV (%)
Baseline (BSL)	91.4	ng/mL	156
Growth	0.00058	1/day	140
Decay	0.0114	1/day	114
Baseline Hazard of Survival (BSHZ)	0.00087		
Beta	0.248		

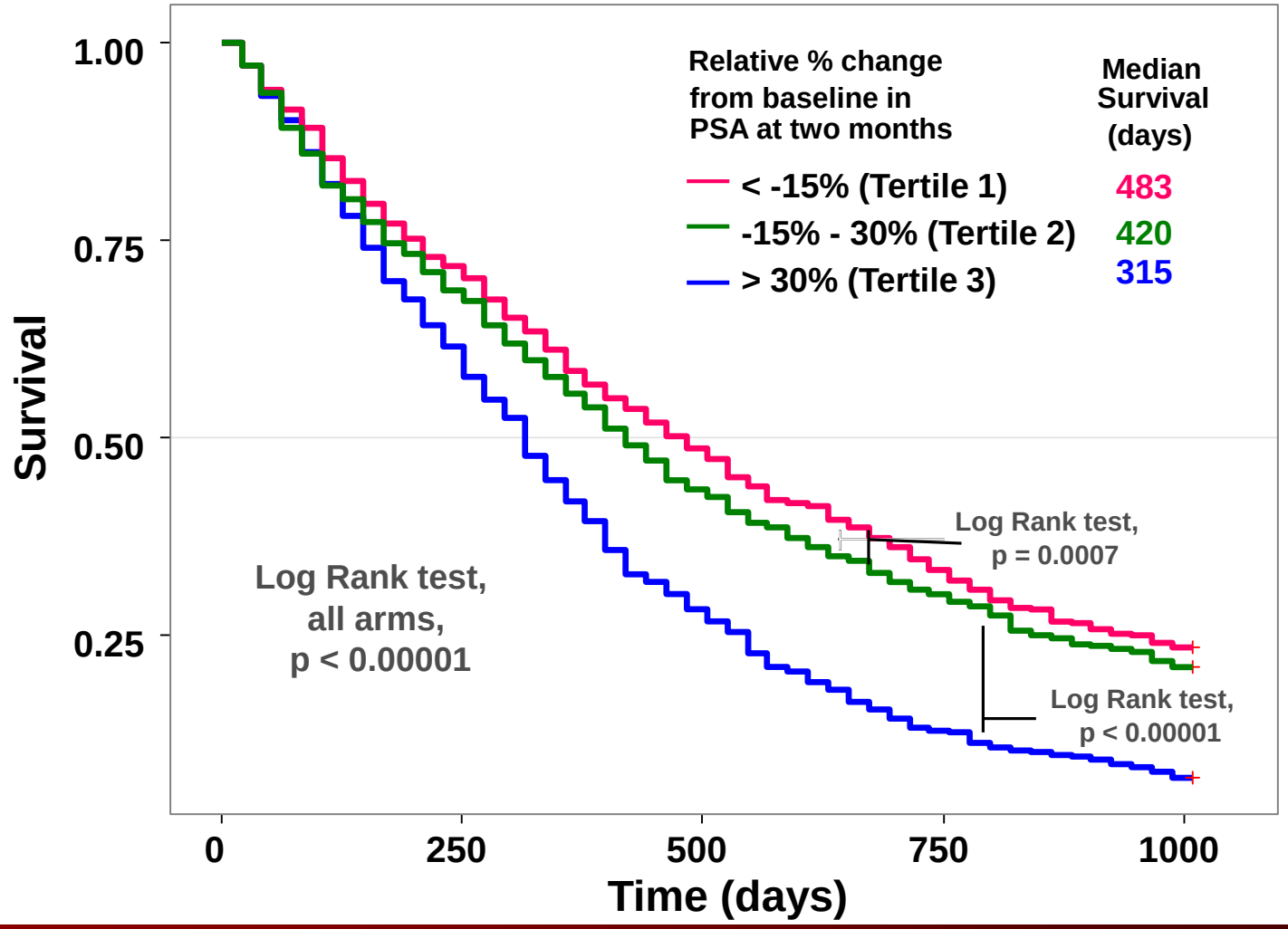
Significant Covariates	
Prior Docetaxel treatment Alkaline phosphatase Performance status	**Growth**
Drug Age Performance status	**Decay**
Prior Docetaxel treatment Alkaline phosphatase	**BSHZ**
Hemoglobin Performance status Drug Age	**Beta**
Hemoglobin Performance status Alkaline phosphatase	**BSL**

$$h_i(t|PSA(t)) = h_0(t) \exp(\beta PSA(t))$$

h_0:Weibull hazard function

$$h_0(t) = \frac{k}{\lambda}\left(\frac{t}{\lambda}\right)^{k-1}$$

Predicted Survival of Simulated Data by the Joint-Model



Summary & Future Directions

- CRPC disease progression models were developed with 2 approaches

	Two-stage Model	Joint-Model
PROS	• 2nd stage can be easily implemented by non-modelers	• Evaluate PSA kinetics and survival simultaneously
CONS	• Estimates of PSA kinetics are fixed in cox survival model • Requires 2 steps during development	• More difficult to implement for non-modelers

FUTURE DIRECTIONS:

- Simulations will be run to determine the superior model by VPC for survival
- Early PSA-based endpoints will be evaluated by simulations to be used in drug development

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Model Verification of PSA Values