Joint Modeling of Tumor Kinetic and Overall Survival

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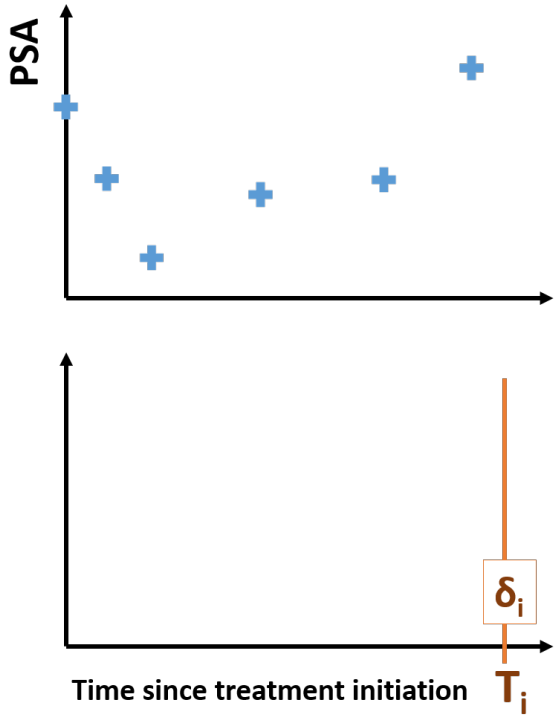
Time-to-event analysis

- Events are things that happen at a particular time
- Can be adverse (death, tumor recurrence) or positive (cure)
- Can be observed or non-observed (left-censoring)
- Known as "survival analysis" in Statistics
  - X_i = survival time for individual i
  - C_i = censoring time (last observation time)
  - $T_i = min(X_i, C_i)$
  - $\delta_i = I_{X_i \leq C_i}$: vital status indicator = $\begin{cases} 1 & if\ death \\ 0 & if\ censored \end{cases}$
  - $h_i(t) = lim_{dt \to 0} P(t < T_i \leq t + dt | T_i > t)$
  - $S_i(t) = P(T_i > t) = \exp(-\int_0^t h_i(u) du)$
- Proportional hazard model to assess the effect of a covariate Z:
  $h_i(t) = h_0(t) * \exp(\beta \times Z_i)$

Modeling longitudinal and survival data

Longitudinal data

- y_i: vector of longitudinal measurements
- can be described by a nonlinear model



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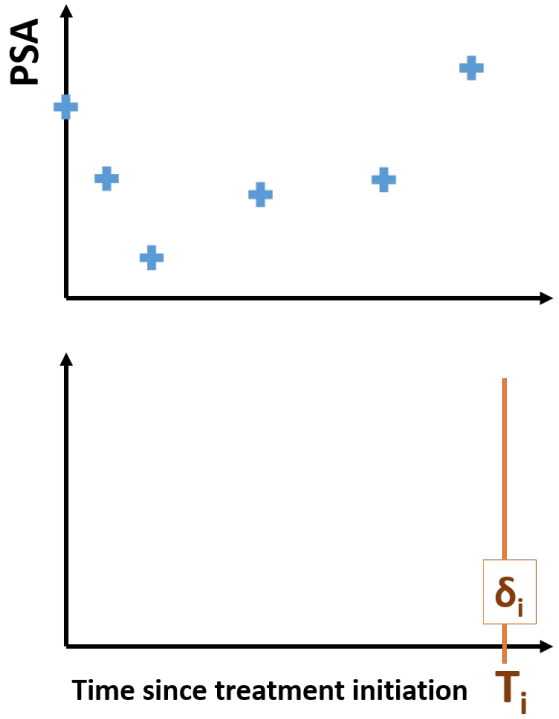
Time-to-event data

- T_i: observed event time
- δ_i: event indicator
$$= \begin{cases} 1 & \text{if event observed} \\ 0 & \text{if event not observed} \end{cases}$$



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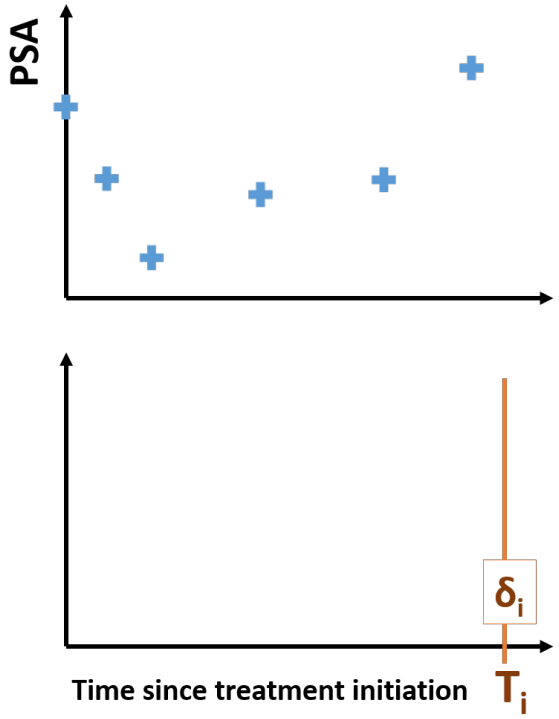
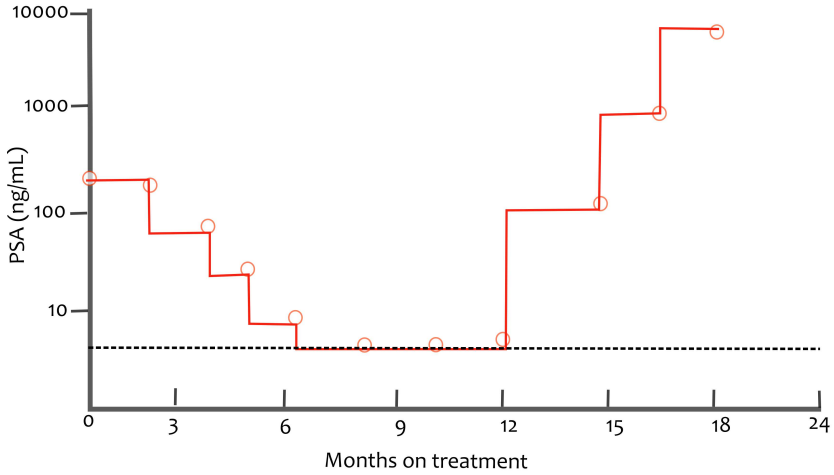


Two objectives

1. To characterize the (non-linear) kinetics of a biomarker in presence of a time-to-event
2. To characterize the impact of this kinetics on a time-to-event

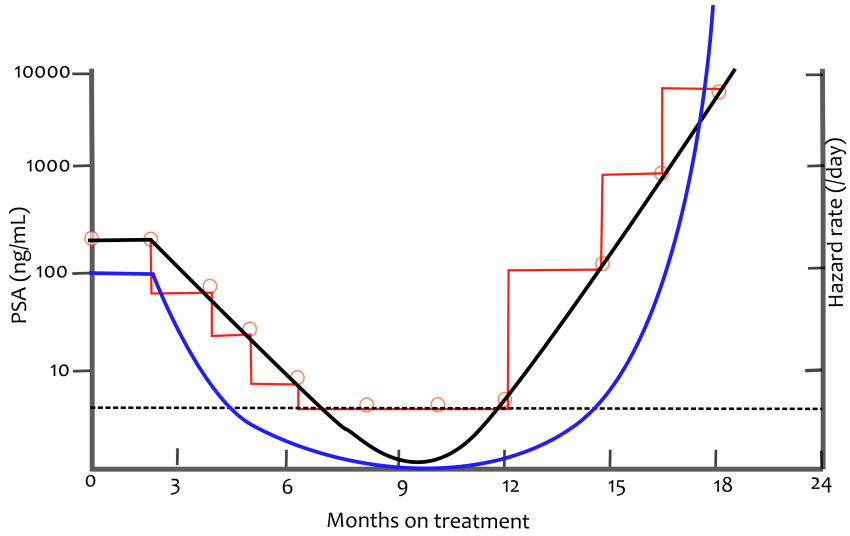
How to assess the impact of a kinetics on time-to-event ?

- Cox Model with a time-dependent covariate
  - Treat PSA as piecewise constant function $h_i(t) = h_0 * \exp(\beta \times PSA_i^{obs}(t))$
  - Is not valid for endogenous variables
  - Requires data at all event times
  - May cause spurious estimates (Prentice, Biometrika 1982)



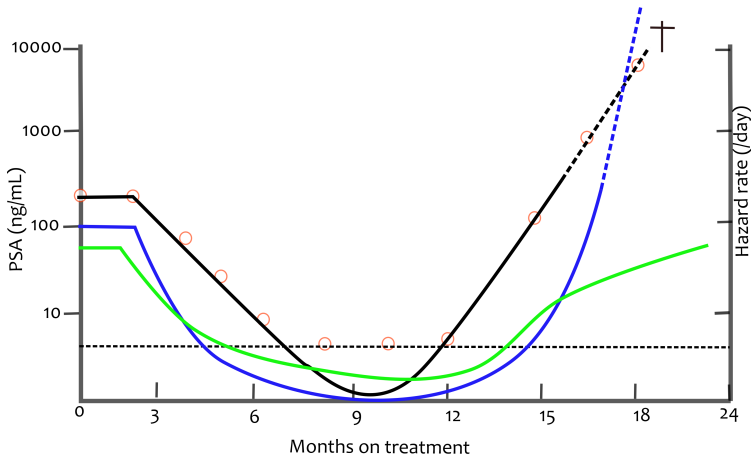
How to assess the impact of a kinetics on time-to-event ?

- Two stage approach
  - Fit the PSA kinetics and plug the predictions
  - $h(t) = h_0 * \exp(\beta \times PSA_i^{pred}(t))$
  - Reduces but does not eliminate all the bias (Dafni, Biometrics 1998)
  - Does not properly handle informative censoring



Informative censoring

The probability to not observe the biomarker depends on current (unobserved) biomarker value



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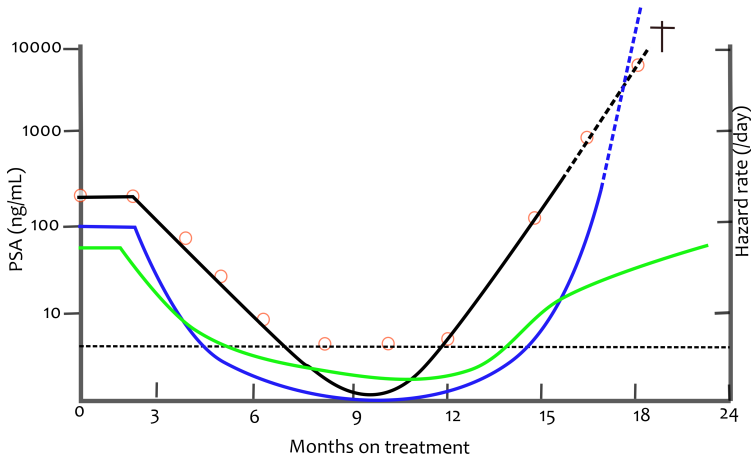
- "Poor responders" are more likely to drop out or to experience the event



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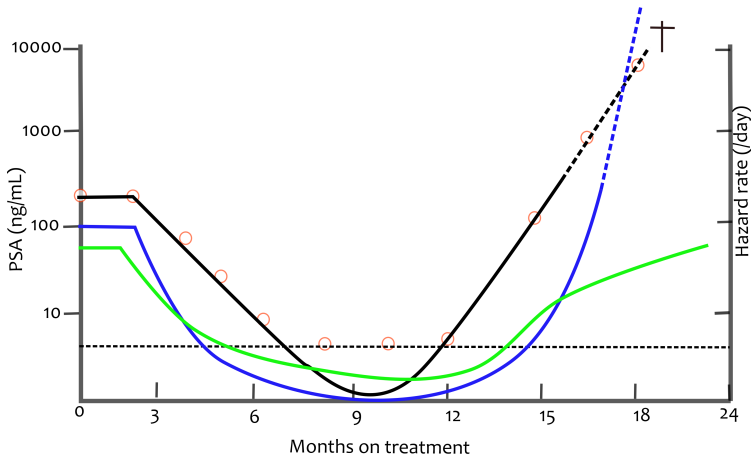

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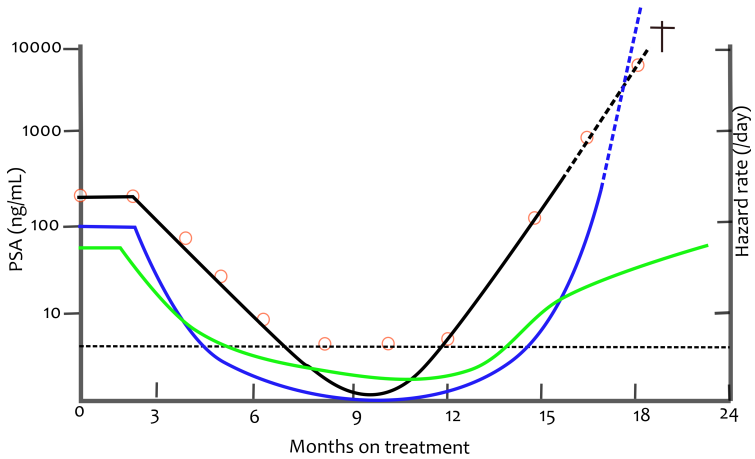

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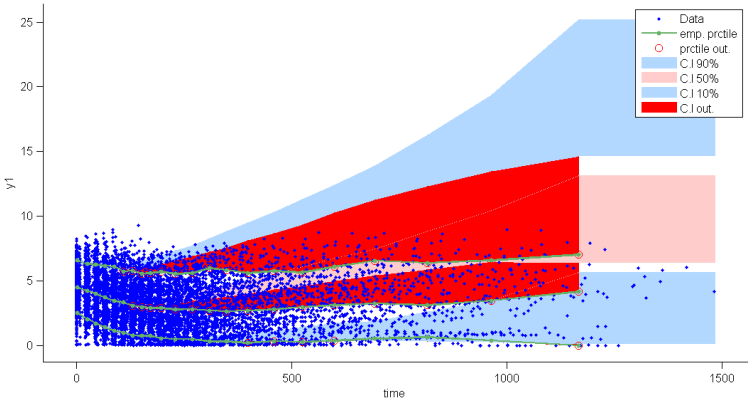


- Some parameters of kinetics will be identified only in survivors
  - → Bias on survival parameters
    - Tends to underestimate the impact of the dynamics on survival [1]
    - Underestimate standard error of the estimates
    - Immortality bias when using metrics derived [2]
  - → Bias on longitudinal parameters
    - Seems to be limited [3]
    - BUT unrealistic diagnostic plots and simulations, including VPC

[1] Desmée et al. (2017) Biometrics; Bjornsson et al. (2016) AAPS Journal

[3] Guedj et al (2010) Biometrics; Desmée et al. (2017) Biometrics; Bjornsson et al. (2016) AAPS Journal

Joint model

➔ 2 submodels:

Longitudinal part: Nonlinear mixed-effect models (NLMEM)

$$y_i(t) = \log(X(t, \psi_i) + 1) + \epsilon_i(t)$$

- X: process of interest (PSA) **possibly non-linear**
- ψ_i: individual longitudinal parameters
- $e_i(t)$: residual error

Survival part: Hazard function for patient i:

$$h_i(t|\psi_i) = h_0(t) \exp(\beta \times f(t, \psi_i)) \qquad \text{for } t \geq 0$$
$$S_i(t|\psi_i) = P(T_i \geq t) = \exp\left[-\int_0^t h_i(u|\psi_i) du\right]$$

- Link function f depends on ψ_i and longitudinal model (eg., $log[PSA(t, \psi_i)]$)

Parameter estimation

Simultaneous estimation of the longitudinal and survival parameters by maximization of the joint likelihood [4]

Joint log-likelihood for a patient i:

$$LL_i(\theta) = \log \int p(y_i|\eta_i;\theta)\{h_i(T_i|\eta_i;\theta)^{\delta_i} S_i(T_i|\eta_i;\theta)\}p(\eta_i;\theta)d\eta_i$$

where

- θ vector of longitudinal and survival parameters to estimate
- η_i vector of random effects
- p density function of the longitudinal processus
- **No closed-form for the LL_i if the process is nonlinear**
- **SAEM algorithm of Monolix extended to joint models** [5]

[4] Rizopoulos et al (2009) J. R. Stat. Soc.

[5] Mbogning et al (2015) JSCS

Data illustration

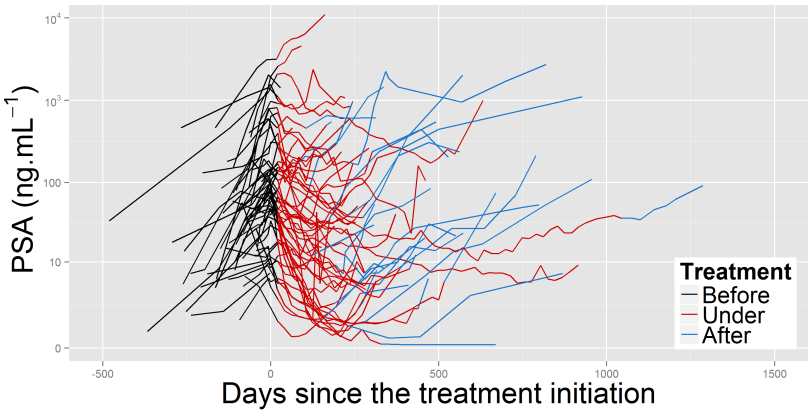
596 metastatic hormono resistant patients from the control arm of a phase 3 clinical trial treated with the standard first-line chemotherapy: docetaxel every 3 weeks and oral prednisone [6]

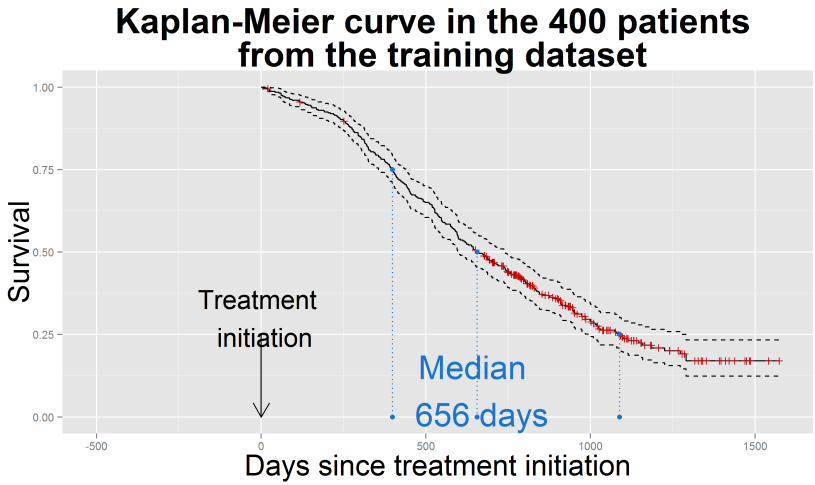
- A training dataset of 400 randomly selected patients

  ➔ Development of a mechanistic joint model

- A validation dataset of the 196 remaining patients

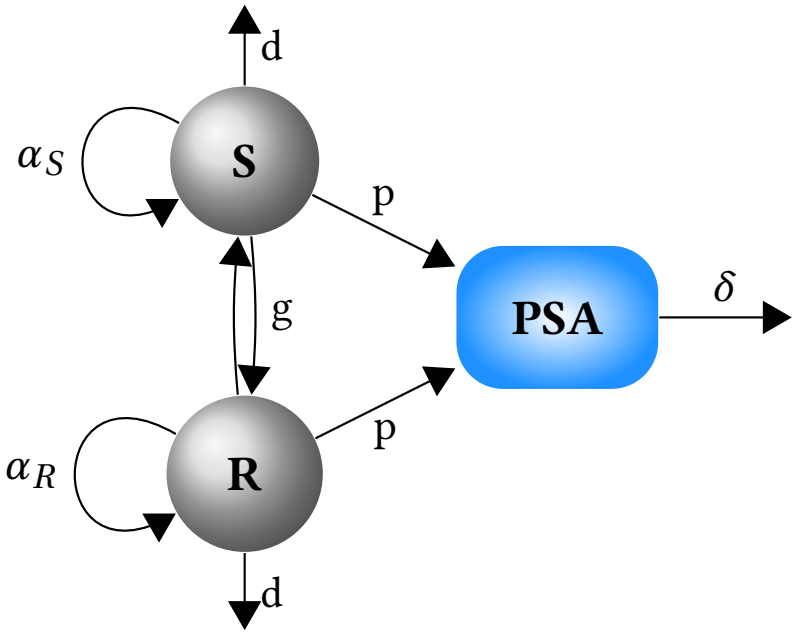
  ➔ Individual dynamic prediction





6 Tannock et al. (2013) Lancet Oncol.

Mechanistic model for PSA kinetics



PSA is produced by 2 types of cells [7]:

- Sensitive cells (S)
- Resistant cells (R)

$$\begin{cases} \frac{dS}{dt} = \alpha_S(1 - \frac{S+R}{N_{max}})S + g(R-S) - dS \\ \frac{dR}{dt} = \alpha_R(1 - \frac{S+R}{N_{max}})R + g(S-R) - dR \\ \frac{dPSA}{dt} = pS + pR - \delta PSA \end{cases}$$

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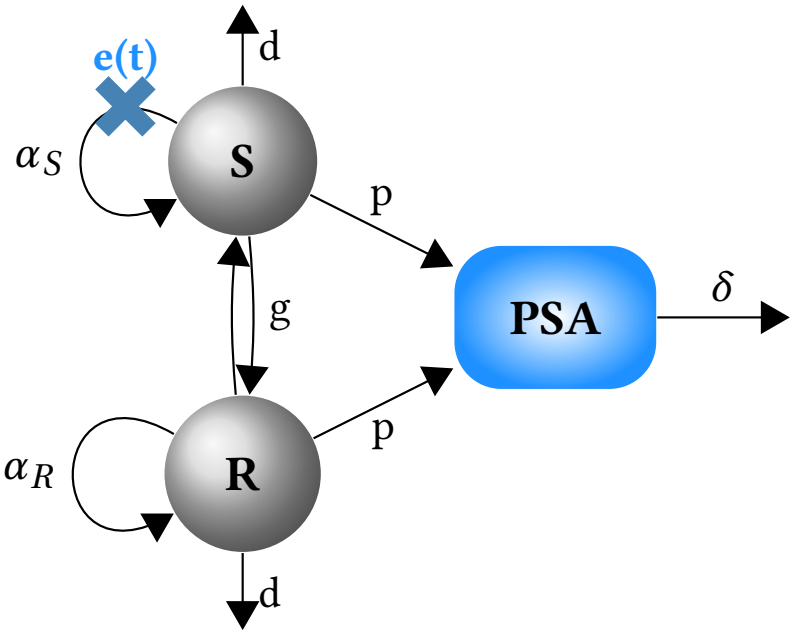

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Treatment initiation at time t=0

➔ Inhibition of the proliferation of S

$$e(t) = \begin{cases} 0 & if\ t \leqslant 0 \\ \varepsilon & if\ t > 0 \end{cases}$$

$$\begin{cases} \frac{dS}{dt} = \alpha_S(1-e(t))(1-\frac{S+R}{N_{max}})S + g(R-S) - dS \\ \frac{dR}{dt} = \alpha_R(1-\frac{S+R}{N_{max}})R + g(S-R) - dR \\ \frac{dPSA}{dt} = pS + pR - \delta PSA \end{cases}$$

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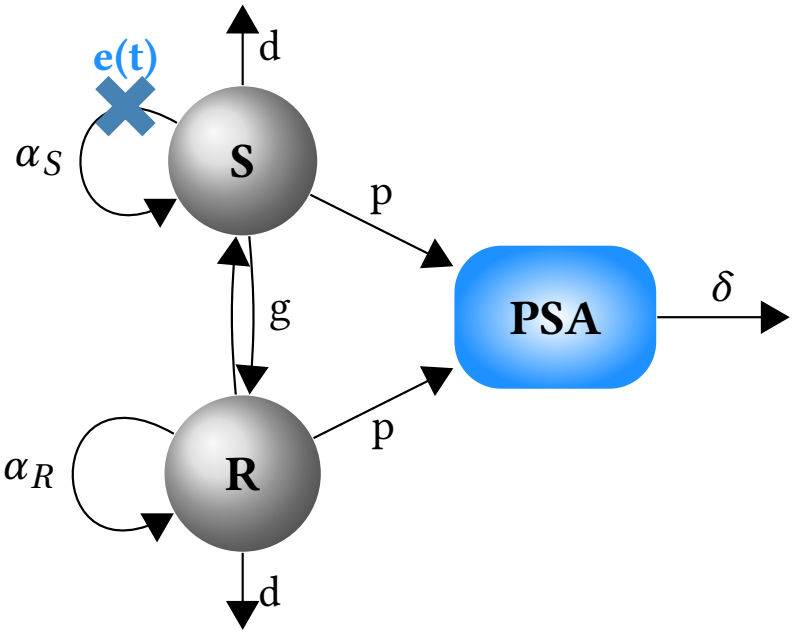

For the sake of identifiability

- δ, p and g fixed

Initial conditions:
At baseline = time of first PSA measurement

- PSA_b
- $S_b = \frac{\delta}{p} PSA_b$
- $R_b = \frac{g}{d - RF \times (g+d)} \times \frac{\delta}{p} PSA_b$

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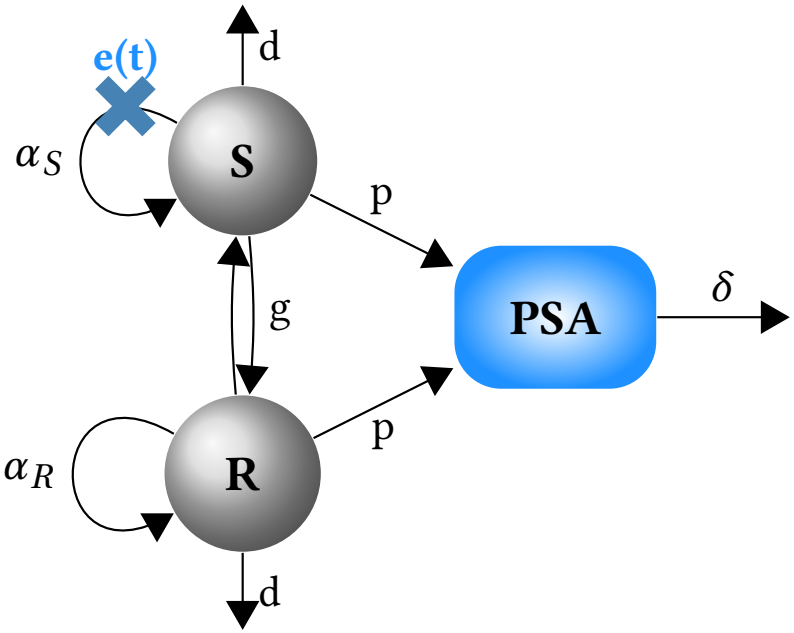

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→ 6 model parameters with random effects:

α_S, $RF = \frac{\alpha_R}{\alpha_S}$, $RE = \frac{d}{\alpha_R}$, ε, PSA_b, N_{max}

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Comparison of different link functions

Survival part: Hazard function for patient i:

$$h_i(t|PSA(t,\psi_i)) = h_0(t)\exp(f(t,\psi_i)) \qquad \text{for } t \geqslant 0$$

- Weibull baseline hazard function $h_0(t) = \frac{k}{\lambda}\left(\frac{t}{\lambda}\right)^{k-1}$
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➟ Selection by BIC

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  - PSA slope: $f = \beta \frac{d\log(PSA(t,\psi_i)+1)}{dt}$
  - Area under PSA: $f = \beta \int_0^t \log(PSA(u,\psi_i)+1)du$

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  - Area under PSA: $f = \beta \int_0^t \log(PSA(u,\psi_i)+1)du$
  - S+R: $f = \beta \log(S(t,\psi_i)) + \beta' \log(R(t,\psi_i))$

➠ Selection by BIC

Results: Model selection

BIC and parameters estimates (r.s.e.(%)) of PSA kinetics and survival in the 400 patients of the training dataset

	No link	Initial PSA	PSA	PSA slope	Area under PSA	S+R
BIC	14598	14582	14446	14581	14575	14421
α_S	0.066 (3)	0.060 (3)	0.078 (3)	0.078 (3)	0.061 (3)	0.067 (3)
RF	0.9997 (0)	0.9996 (0)	0.9998 (0)	0.9998 (0)	0.9997 (0)	0.9998 (0)
RE	0.81 (1)	0.79 (1)	0.84 (1)	0.84 (0)	0.79 (1)	0.82 (1)
ε	0.42 (4)	0.46 (4)	0.35 (4)	0.35 (5)	0.47 (4)	0.43 (3)
PSA_b	22.2 (8)	22.2 (8)	22.0 (8)	22.5 (8)	22.2 (8)	21.9 (8)
N_{max}	56 (4)	57 (4)	81 (4)	77 (4)	57 (4)	120 (4)
λ	885 (4)	1615 (8)	4259 (15)	920 (4)	1435 (7)	906 (7)
k	1.52 (5)	1.53 (3)	1.28 (2)	1.48 (2)	1.19 (2)	1 (-)
β	-	0.21 (12)	0.40 (7)	17 (17)	0.00023 (8)	0.00032 (21)
β'	-	-	-	-	-	0.39 (7)

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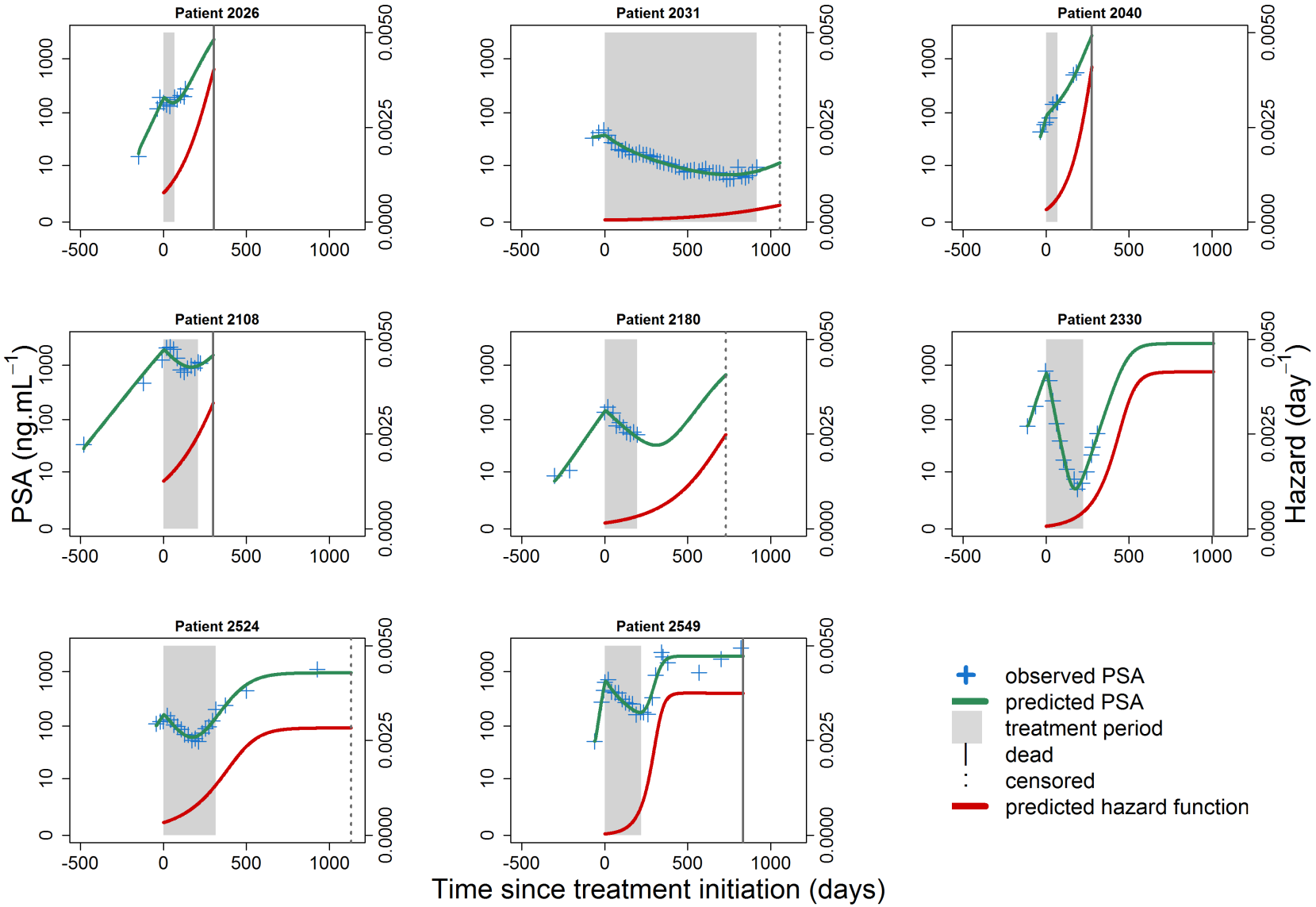
➠ **S+R model**: $f(t,\psi_i) = \beta \log(S(t,\psi_i)) + \beta' \log(R(t,\psi_i))$ with a constant baseline hazard function ($k = 1$) provided the smaller BIC

Individual fits of PSA and hazard functions



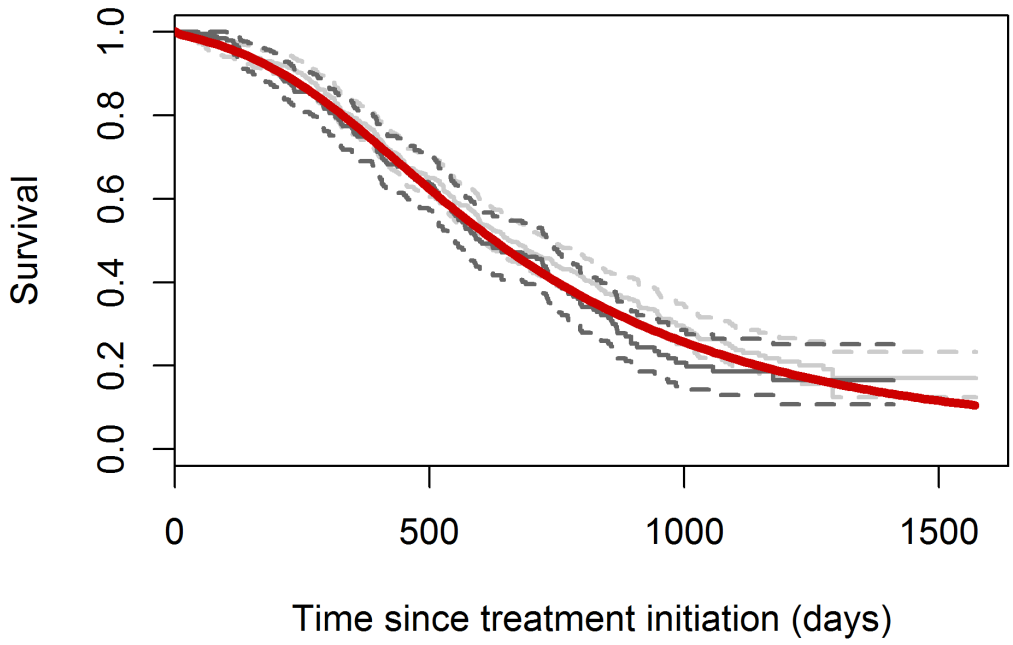
Prediction in the validation sample

Assumption: *true* joint model is known

➔ *Population parameters* θ *used as priors*

➔ *Individual EBEs* $\hat{\psi}_i$ *estimated using only the PSA measurements*

➔ *Mean survival function* $= \frac{1}{N}\sum_{i=1}^{N} S_i(t|\hat{\psi}_i, \hat{\theta})$



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Assumption: *true* joint model is known (simplified, no ODE)

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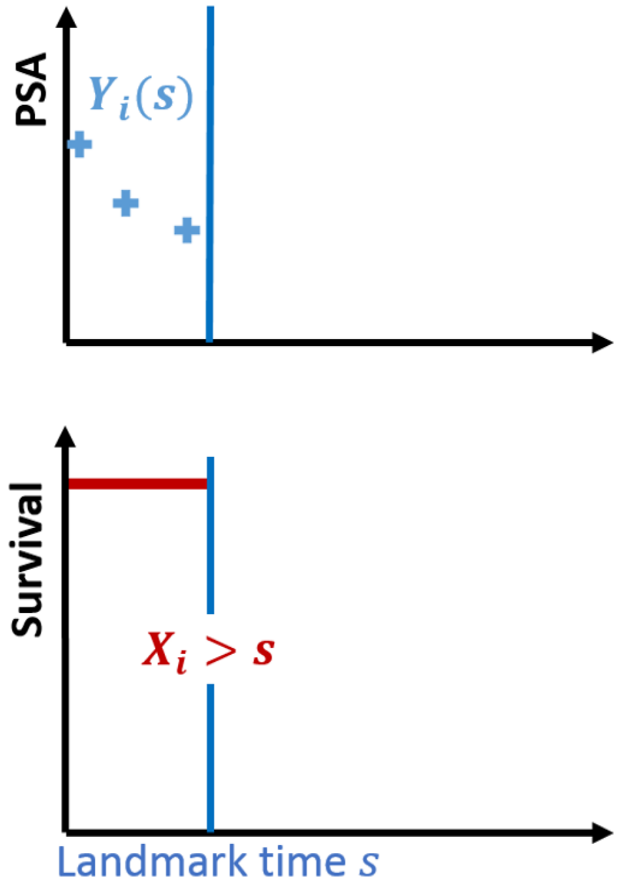

Dynamic predictions of a new individual

➔ Predict $S_i(s+t|s) = \mathbb{P}(X_i > s+t | X_i > s, \mathcal{Y}_i(s))$ the conditional survival probability up to the prediction horizon $s+t$ with $t > 0$

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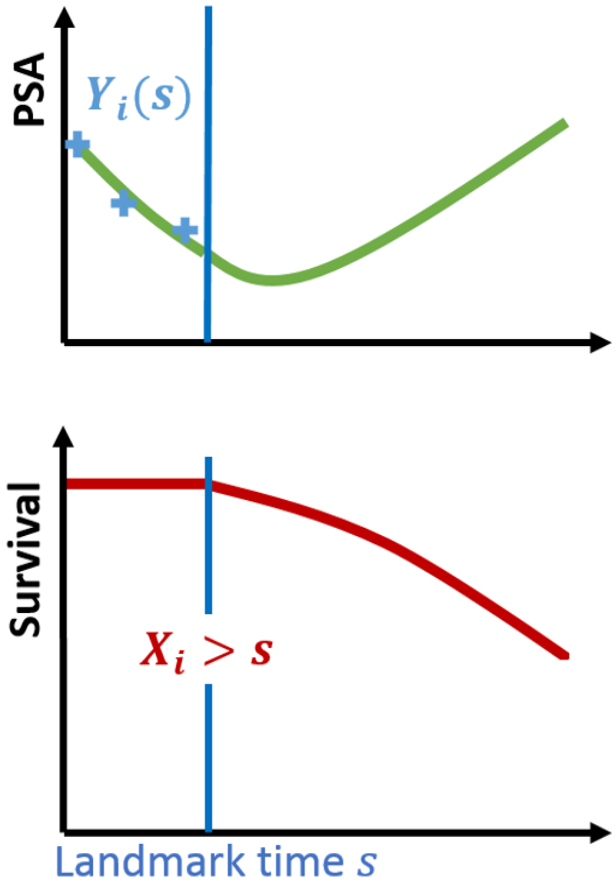

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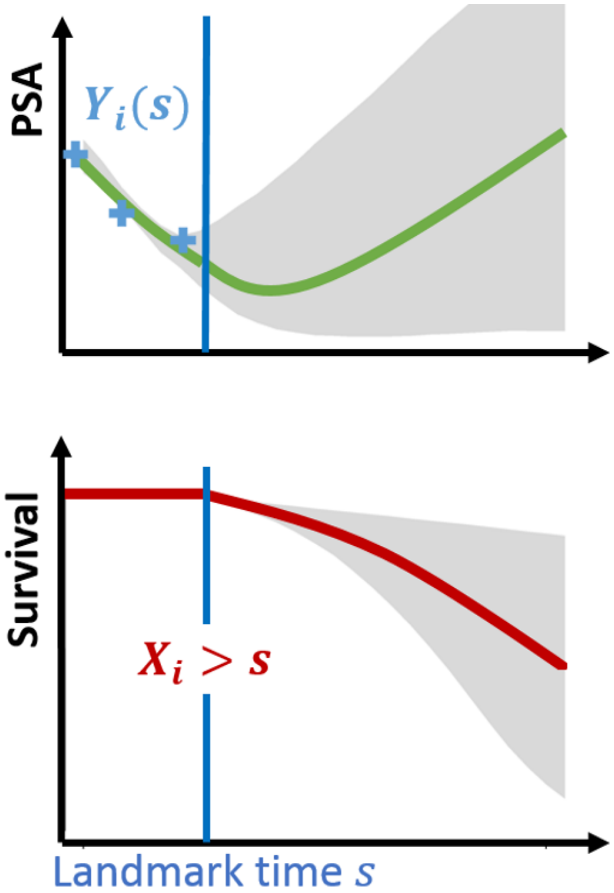
Assumption: *true* joint model is known (simplified, no ODE)

➔ *Population parameters* θ *used as priors*

For $\ell = 1, ..., L = 200$:

1. Draw in the *a posteriori* distribution of the individual parameters $\psi_i^{(\ell)} \sim \{\psi_i | X_i > s, \mathcal{Y}_i(s), \theta\}$ using Halmitonian Monte Carlo in Stan
2. Compute $S_i^{\ell}(s+t|s)$



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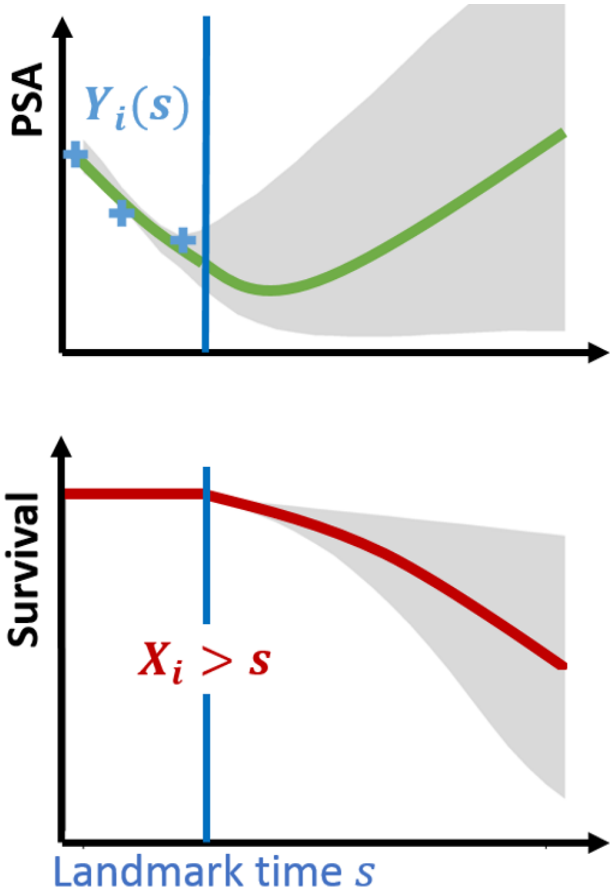
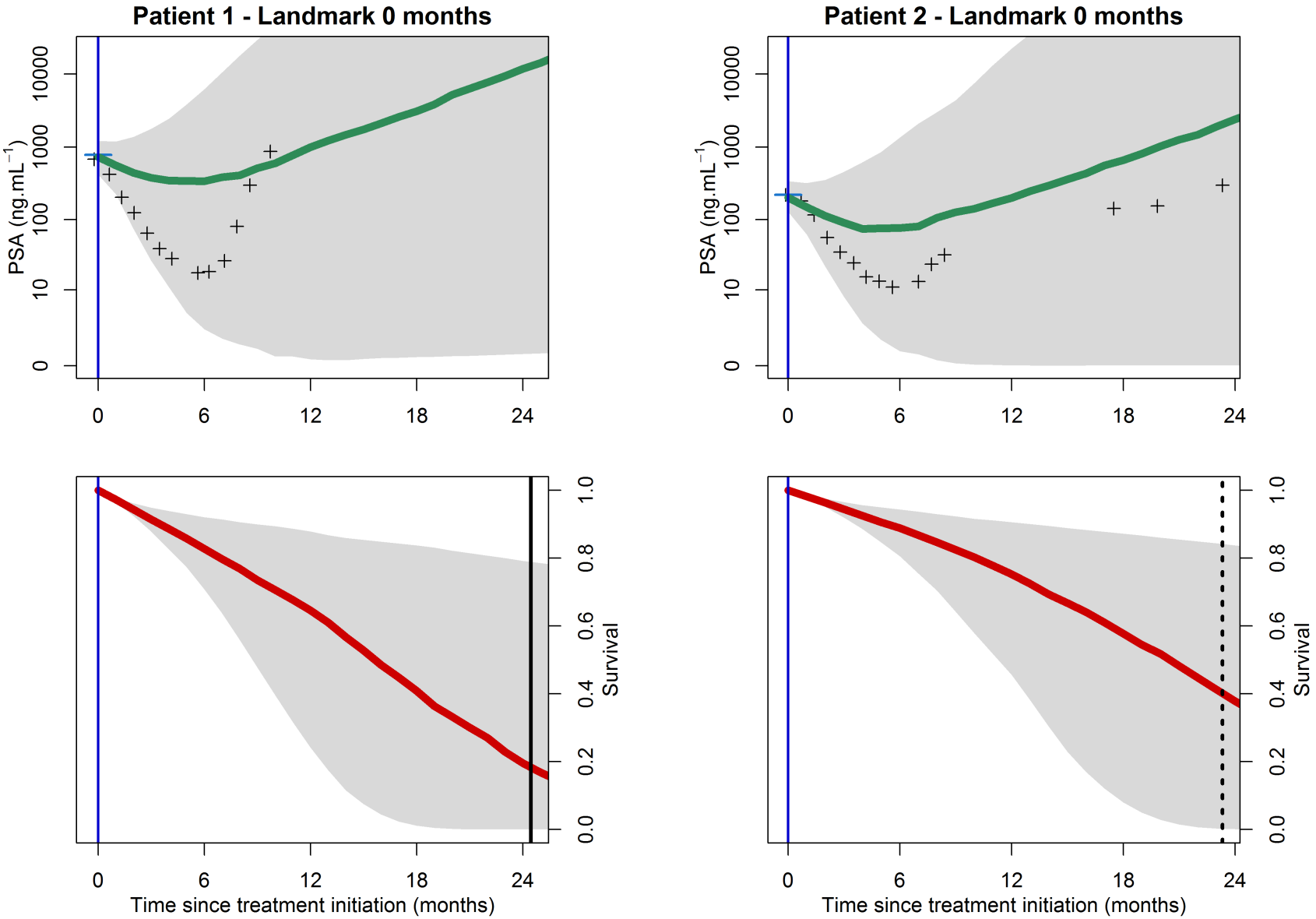
3. $\hat{S}_i(s+t|s) = median\{S_i^{(\ell)}(s+t|s)\}_{\ell=1,...,L}$ + 95% prediction interval



Dynamic predictions for 2 patients

Patient 1 died at 24 months - Patient 2 was censored at 24 months



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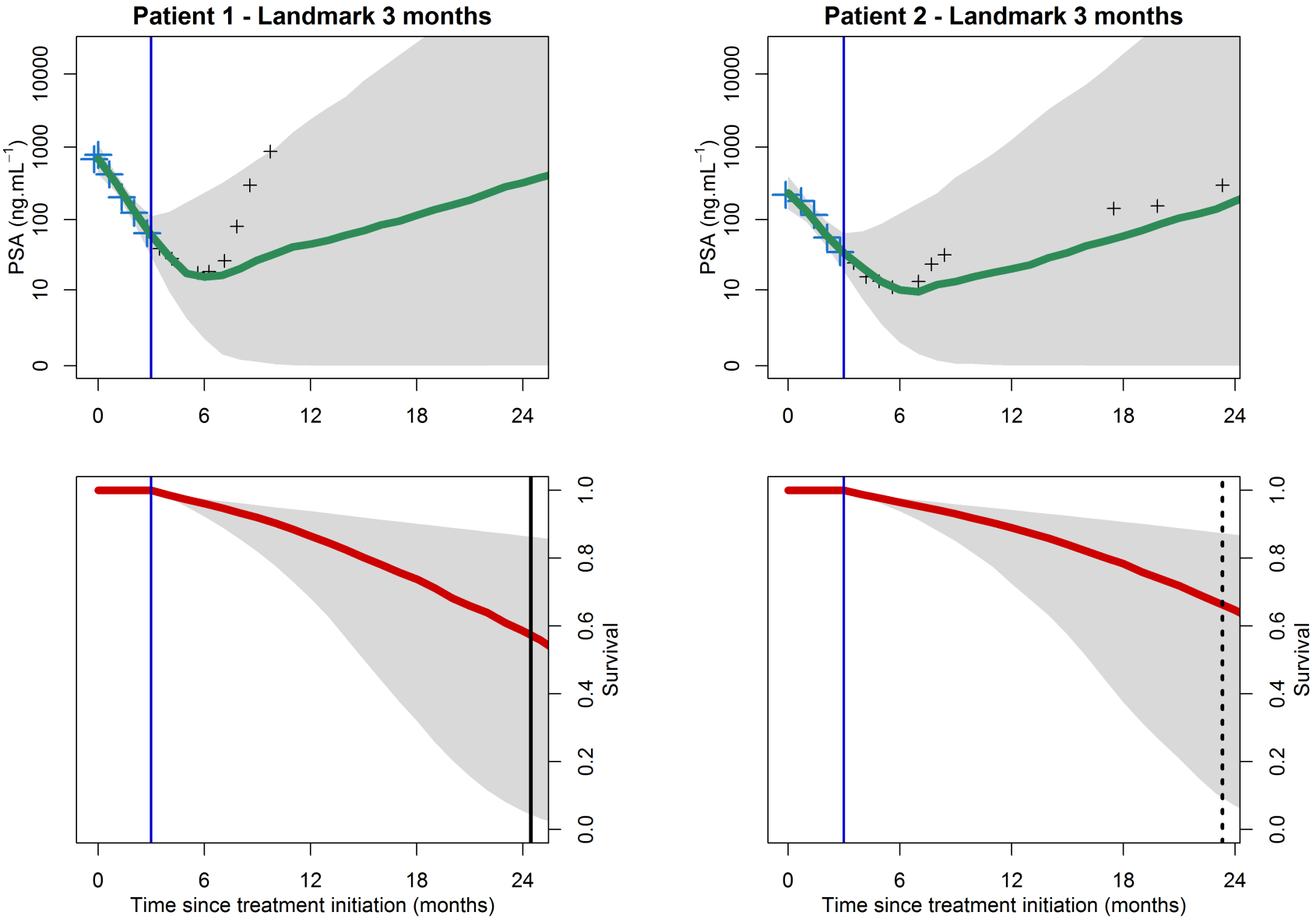

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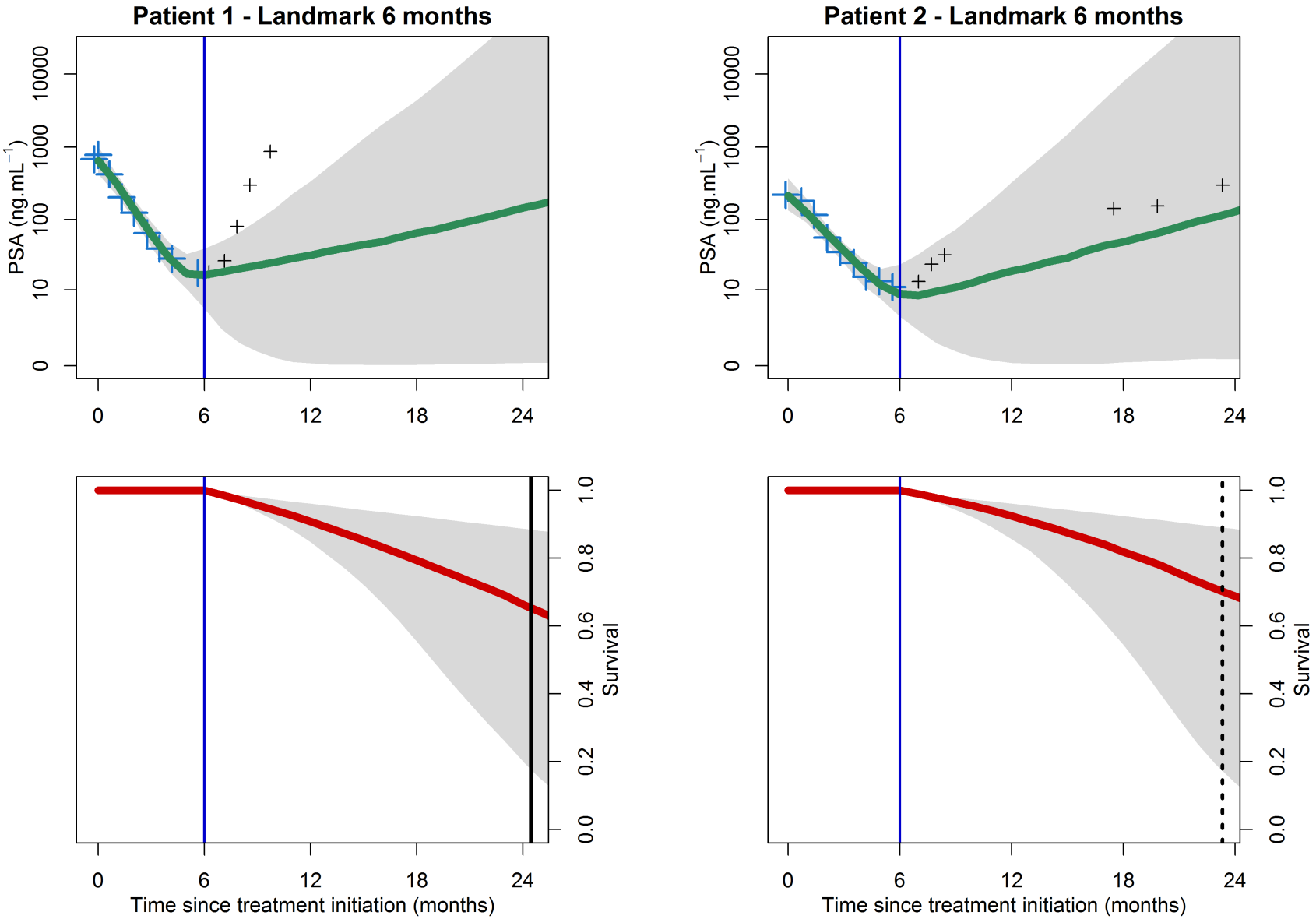

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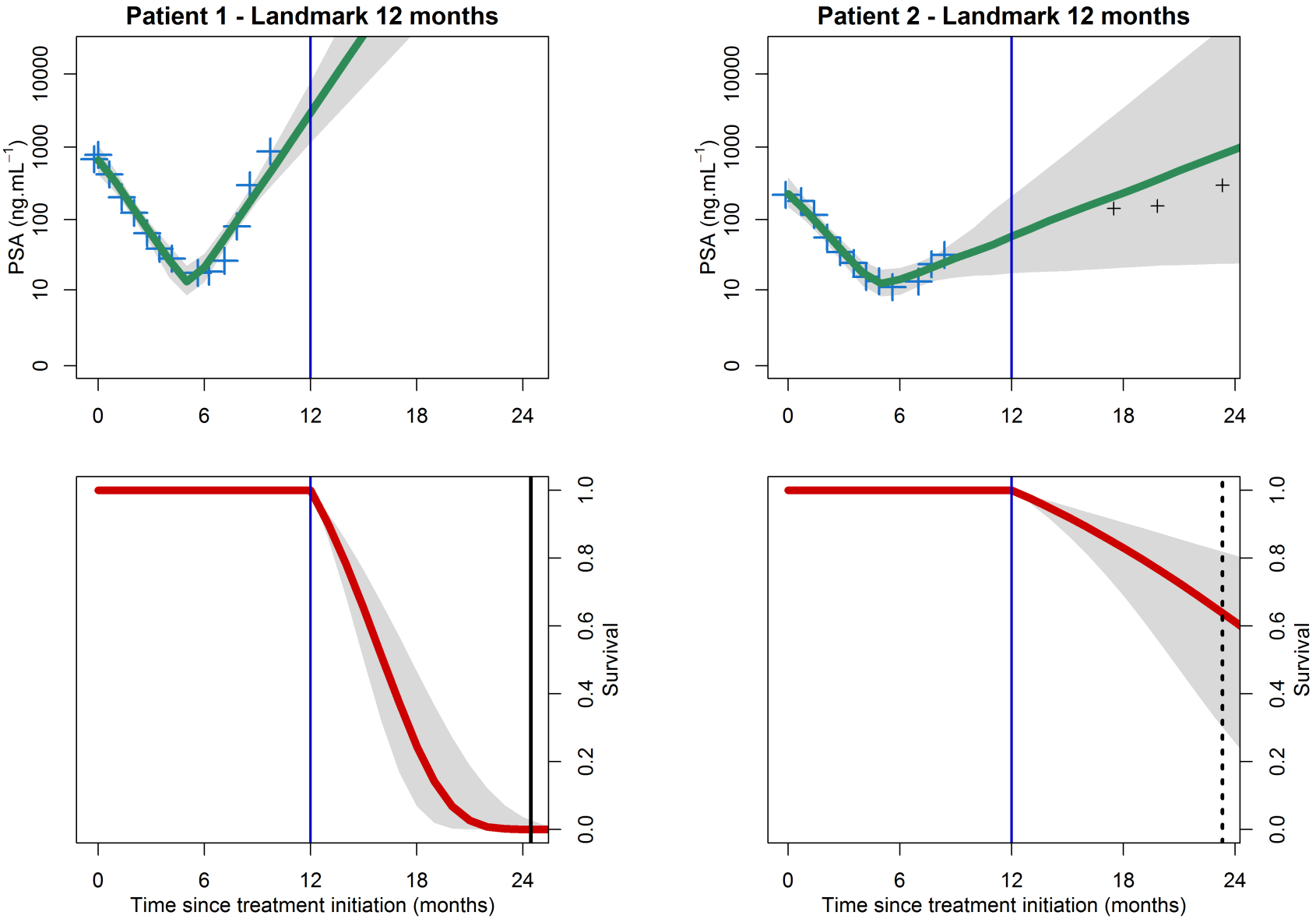

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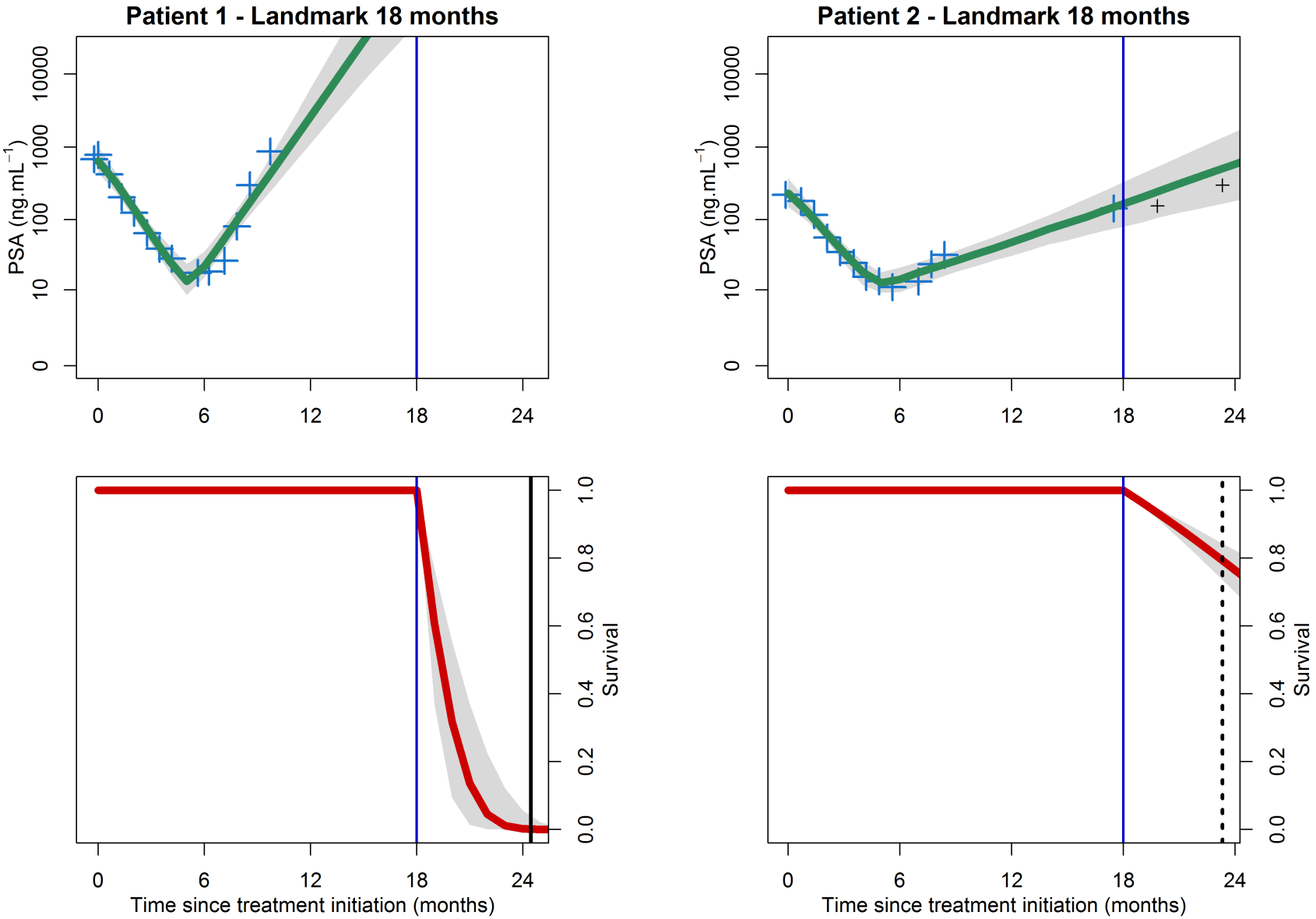

Discrimination and calibration metrics

Discrimination: ability of the model to distinguish patients of low and high risk of death

Calibration: ability of the model to predict future events

Discrimination and calibration metrics

Discrimination: ability of the model to distinguish patients of low and high risk of death

➟ **Area under the ROC curve** (AUC)

$$AUC(s,t) = \mathbb{P}(S_i(s+t|s) < S_j(s+t|s) | \mathbf{1}_{\{X_i<s+t\}} = 1, \mathbf{1}_{\{X_j<s+t\}} = 0, X_i > s, X_j > s)$$

The higher the better

Calibration: ability of the model to predict future events

Discrimination and calibration metrics

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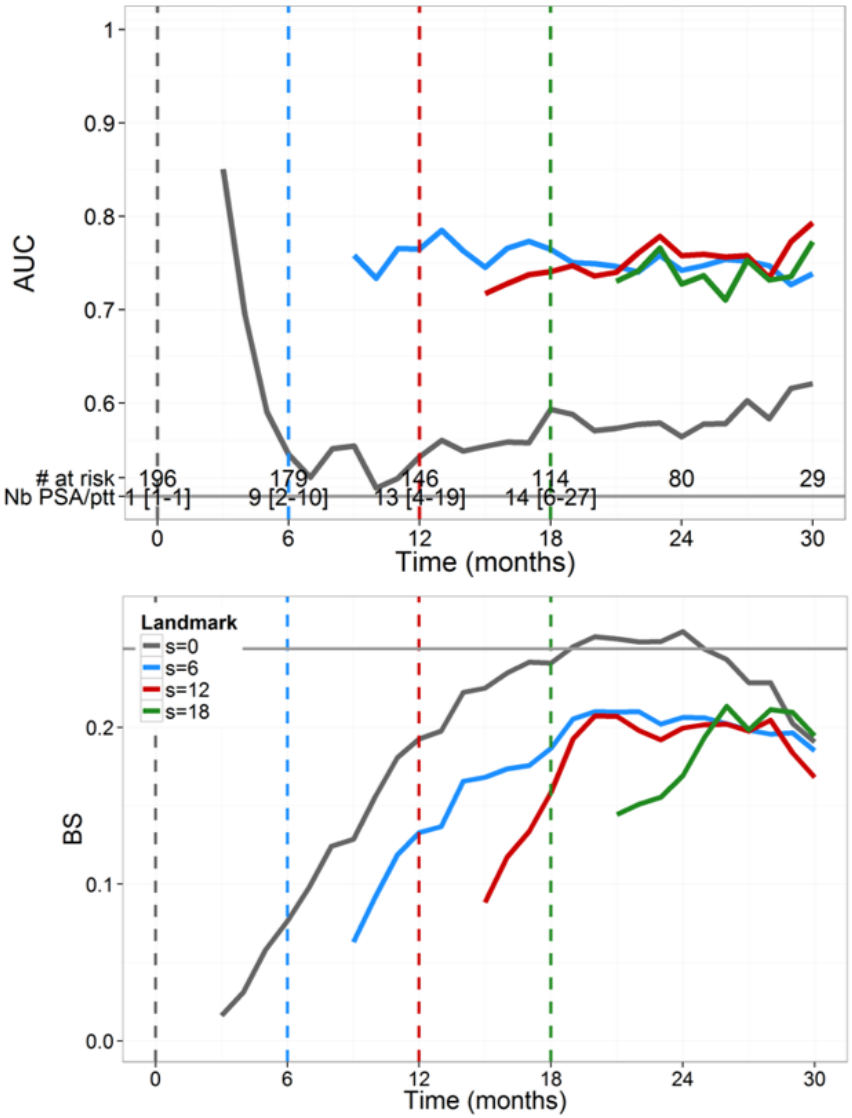
Calibration: ability of the model to predict future events

➟ **Brier score** (BS)

$$BS(s,t) = \mathbb{E}[(\mathbf{1}_{\{X>s+t\}} - S(s+t|s))^2 | X > s]$$

The lower the better

Time-dependent AUC and Brier score



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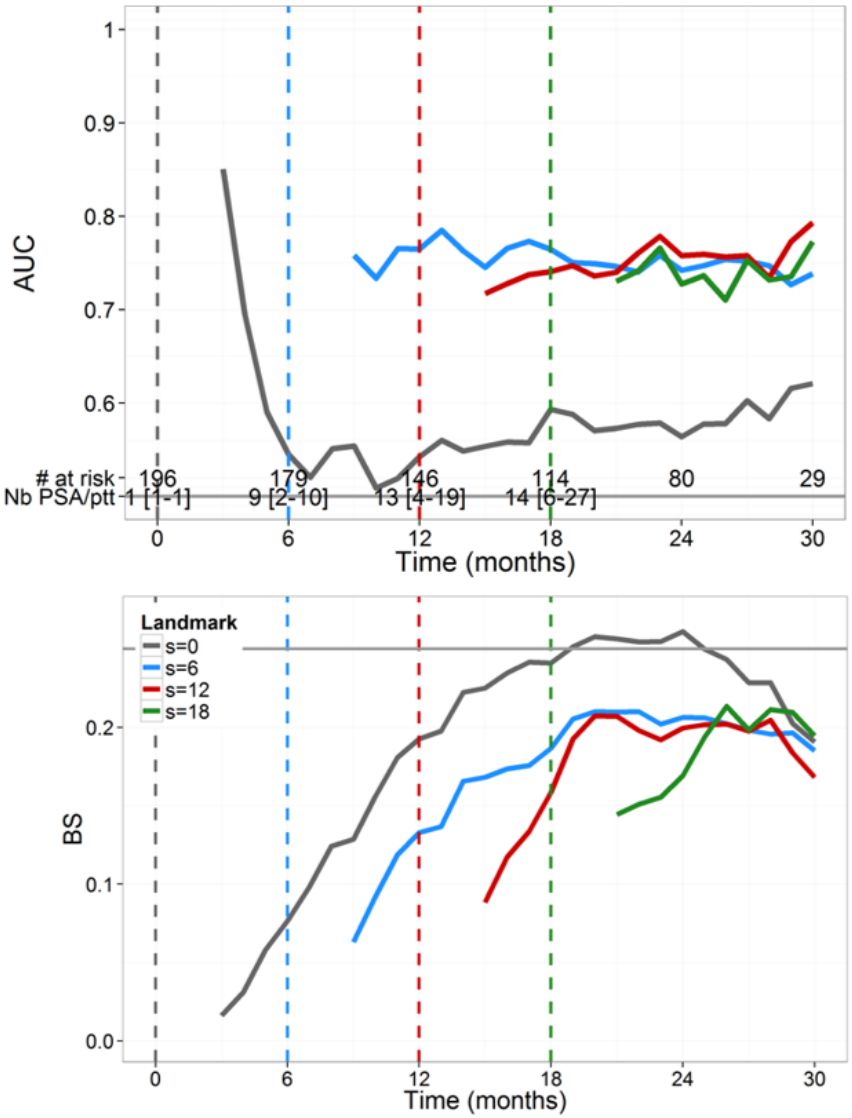

- s is the time of observation ("landmark")
- Metrics improve when s increase

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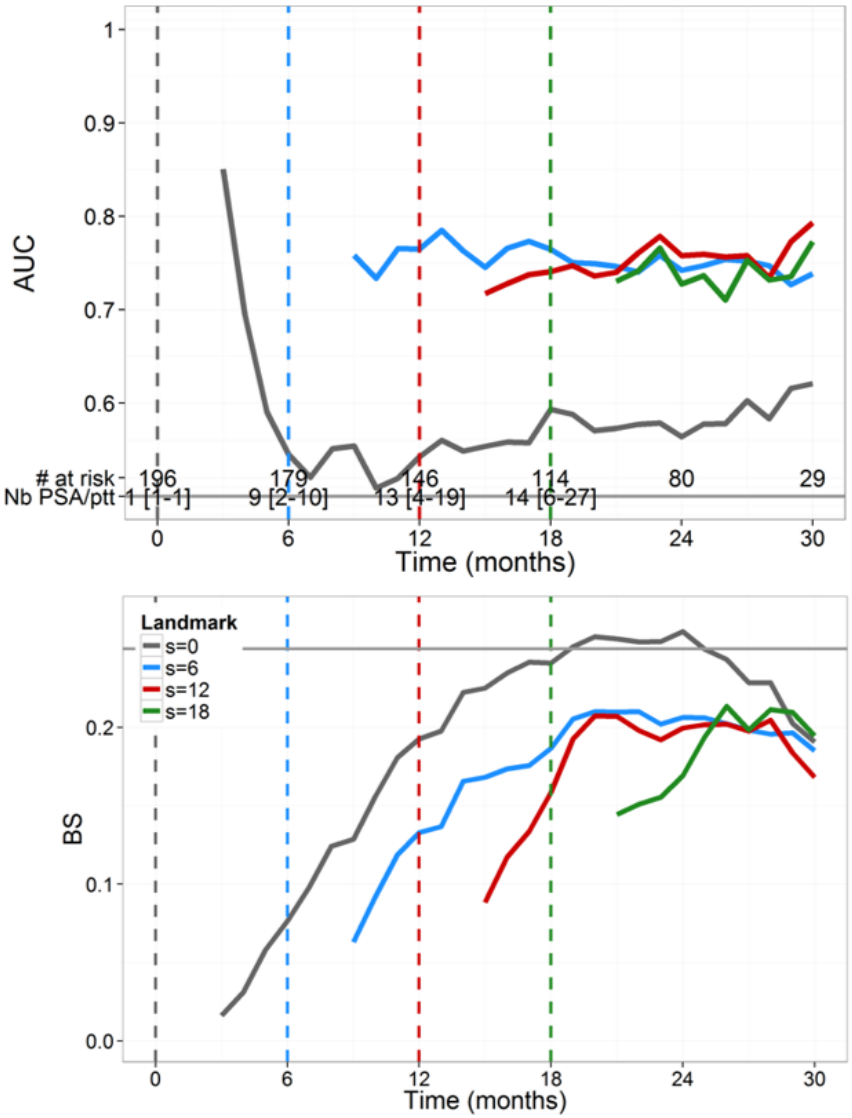

- s is the time of observation ("landmark")
- Metrics improve when s increase
- Here, $s = 12$ months provides the best tradeoff between
  - Follow-up duration
  - Prediction accuracy
    - $AUC(12, t) \simeq 0.75 \ \forall t$
    - $BS(12, t) \leqslant 0.21 \ \forall t$

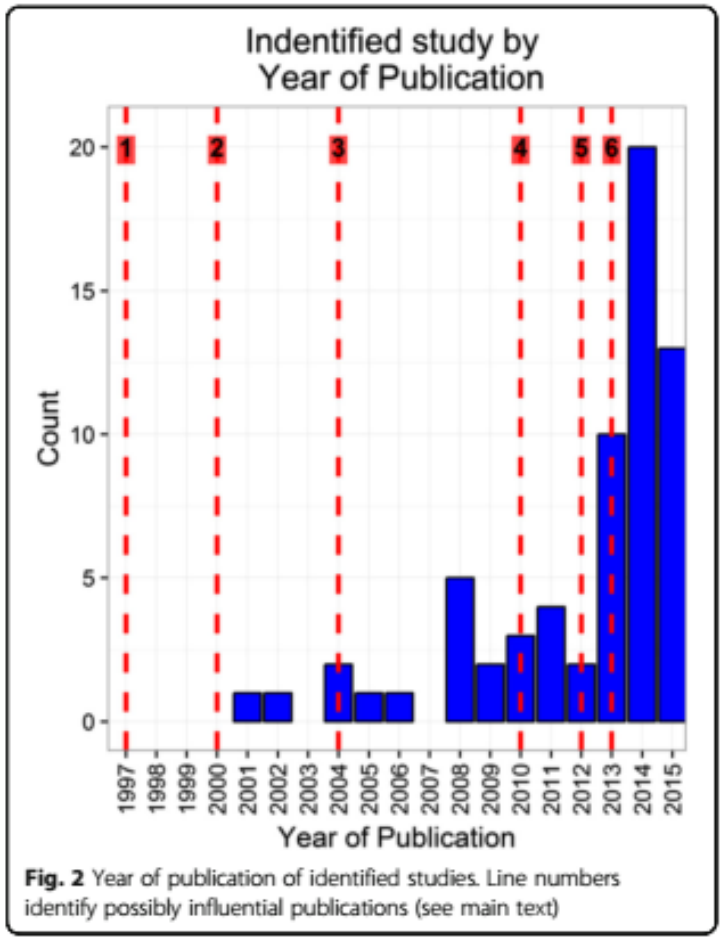

Fig. 2 Year of publication of identified studies. Line numbers identify possibly influential publications (see main text)

Sudell *et al. BMC Medical Research Methodology* (2016) 16:168
DOI 10.1186/s12874-016-0272-6

BMC Medical Research Methodology

RESEARCH ARTICLE Open Access

Joint models for longitudinal and time-to-event data: a review of reporting quality with a view to meta-analysis

Maria Sudell*, Ruwanthi Kolamunnage-Dona† and Catrin Tudur-Smith†

	N (%)
Full text or abstract available	
Full text	63 (96.9)
Abstract	2 (3.1)
Disease Area	
Cancer related data	10 (15.4)
HIV/AIDS	9 (13.8)
Patient status after transplants	8 (12.3)
Cognitive decline	7 (10.8)
Glaucoma	4 (6.2)
Renal disease	4 (6.2)
Disability in the elderly	3 (4.6)
Heart related data	3 (4.6)
Schizophrenia	3 (4.6)
Sclerosis	3 (4.6)
Other	11 (16.9)
Journal	
Statistics in Medicine	5 (7.7)
Journal of the Royal Statistical Society. Series C: Applied Statistics	4 (6.2)
Ophthalmology	3 (4.6)
Quality of Life Research	3 (4.6)
Journal of the American Geriatrics Society	2 (3.1)
Journal of the American Statistical Association	2 (3.1)
Journals of Gerontology - Series B Psychological Sciences and Social Sciences	2 (3.1)
Statistical Methods in Medical Research	2 (3.1)
Other (only one study per journal)	45 (64.6)
Reason for joint modelling use*	
To investigate the link between longitudinal and time-to-event outcomes	43 (66.2)
To account for dropout	22 (33.8)
To include longitudinally measured variable in time-to-event model	4 (6.2)
To increase efficiency	3 (4.6)
To reduce bias	2 (3.1)
Easier to interpret	1 (1.5)
To use of all available data	1 (1.5)

Conclusion

- Joint models are needed to:
  - characterize longitudinal processes in presence of informative dropout
  - assess the relationship between a longitudinal process and time-to-event data
- Has long been limited to linear models
- Still technical difficulties
  - Likelihood calculation burden
  - Intrinsic limitations of fully parametric models (baseline hazard, model for the association)
  - Landmarking, joint latent class models, Bayesian approaches ?
  - Model evaluation

Future of joint models

- Benefit for clinical decision making needs to be demonstrated
  - Clinical trial simulation, in particular from phase 2 to phase 3
  - Increase the power of studies BUT limitations due to a fully parametric model & issue of surrogacy
  - Competitive risks (new lesions, dropout) [10]
  - Improvement of early detection of phase 3 failure (underpowered, lack of efficacy on biomarker)
- Benefit for patient care
  - May improve treatment individualization
  - Inspired from what is proposed in pharmacokinetics
  - Early detection of most at risk's patient BUT assessment will require head to head evaluation through randomized clinical trial

10 Krol et al (2018) Stat in Med

Acknowledgements

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DOI: 10.1208/s12248-015-9745-5

Research Article

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

Solène Desmée,[1,2,4] France Mentré,[1,2] Christine Veyrat-Follet,[3] and Jérémie Guedj[1,2]

Biometrics

DOI: 10.1111/biom.12537

Using the SAEM Algorithm for Mechanistic Joint Models Characterizing the Relationship between Nonlinear PSA Kinetics and Survival in Prostate Cancer Patients

Solène Desmée,[1,2,*] France Mentré,[1,2] Christine Veyrat-Follet,[3] Bernard Sébastien,[4] and Jérémie Guedj[1,2]

Desmée *et al. BMC Medical Research Methodology* (2017) 17:105
DOI 10.1186/s12874-017-0382-9

BMC Medical Research Methodology

RESEARCH ARTICLE Open Access

Nonlinear joint models for individual dynamic prediction of risk of death using Hamiltonian Monte Carlo: application to metastatic prostate cancer

Solène Desmée[1*], France Mentré[1], Christine Veyrat-Follet[2], Bernard Sébastien[3] and Jérémie Guedj[1]