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Individual dynamic predictions: predicting the occurrence of an event based on individual longitudinal information

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Individual Dynamic Predictions:

Predicting the occurrence of an event based on individual longitudinal information

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Context of individualized prediction

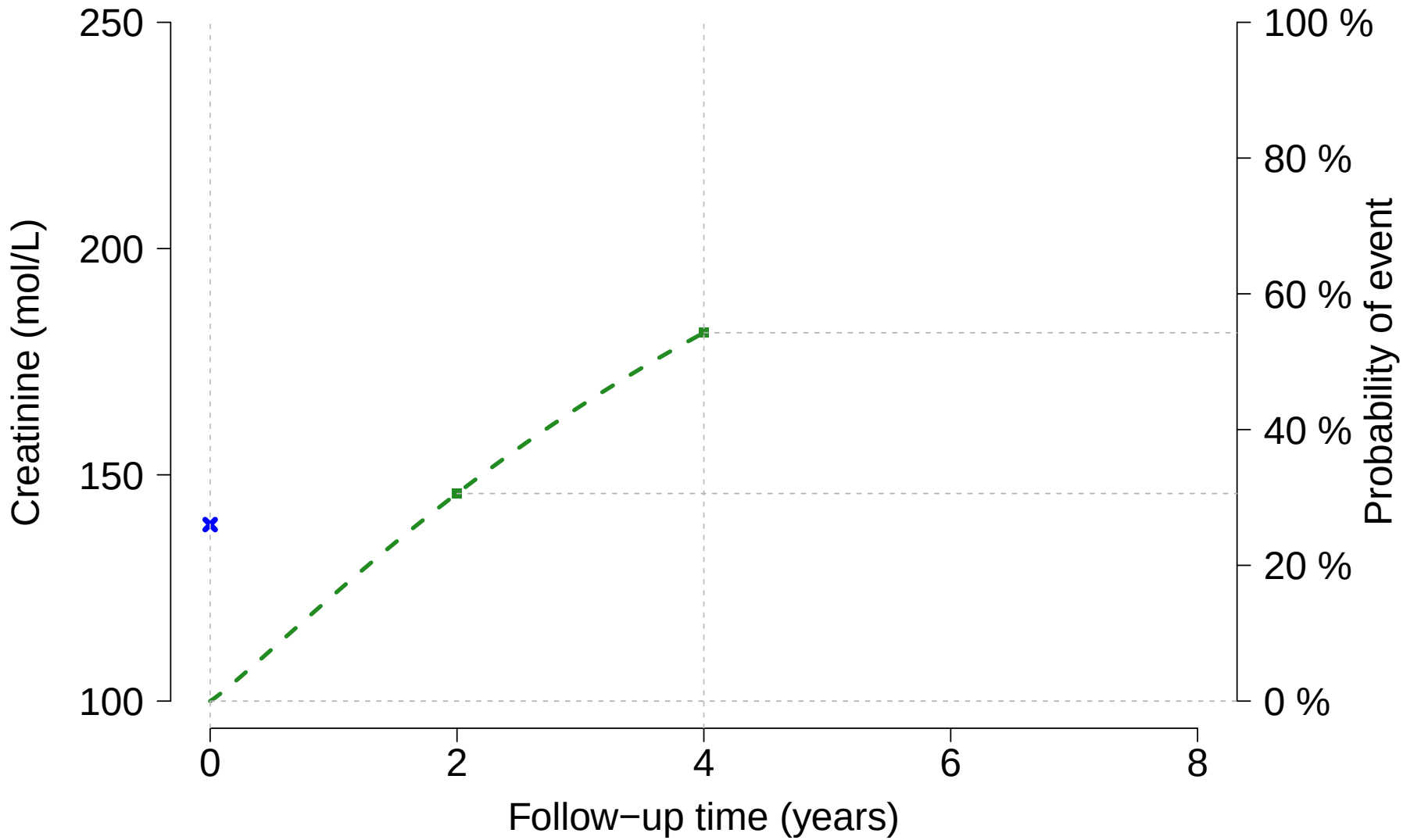
- Predicting the risk of an event has become central :
  - for monitoring, screening and managing chronic diseases
  - for early diagnosing and initiating therapies
  - for targeting ”at high risk” individuals in clinical trials
- Examples of questions after a diagnosis of cancer
  - what is my risk of dying ?
  - what is my risk of experiencing a recurrence ?
  - what is my prognosis ?
- Idea of using the individual information to provide individualized risk predictions
  - individualized medicine

Principle of individual predictions

Predict what will happen to a patient based on available information

- Mostly occurrence of an event
  - complication, reccurence, death, diagnosis, etc.
- Prediction in terms of :
  - probability of having the event
  - probability of not having the event (”event-free survival”)
  - score (linear combination of prognostic variables)
  - at risk group (probability $>$ threshold)
- Nature of the available information
  - information collected at baseline
    $\rightarrow$ age, gender, biomarkers at diagnosis, etc
  - information collected during a follow-up
    $\rightarrow$ most often biomarkers

Principle of individual predictions from baseline information



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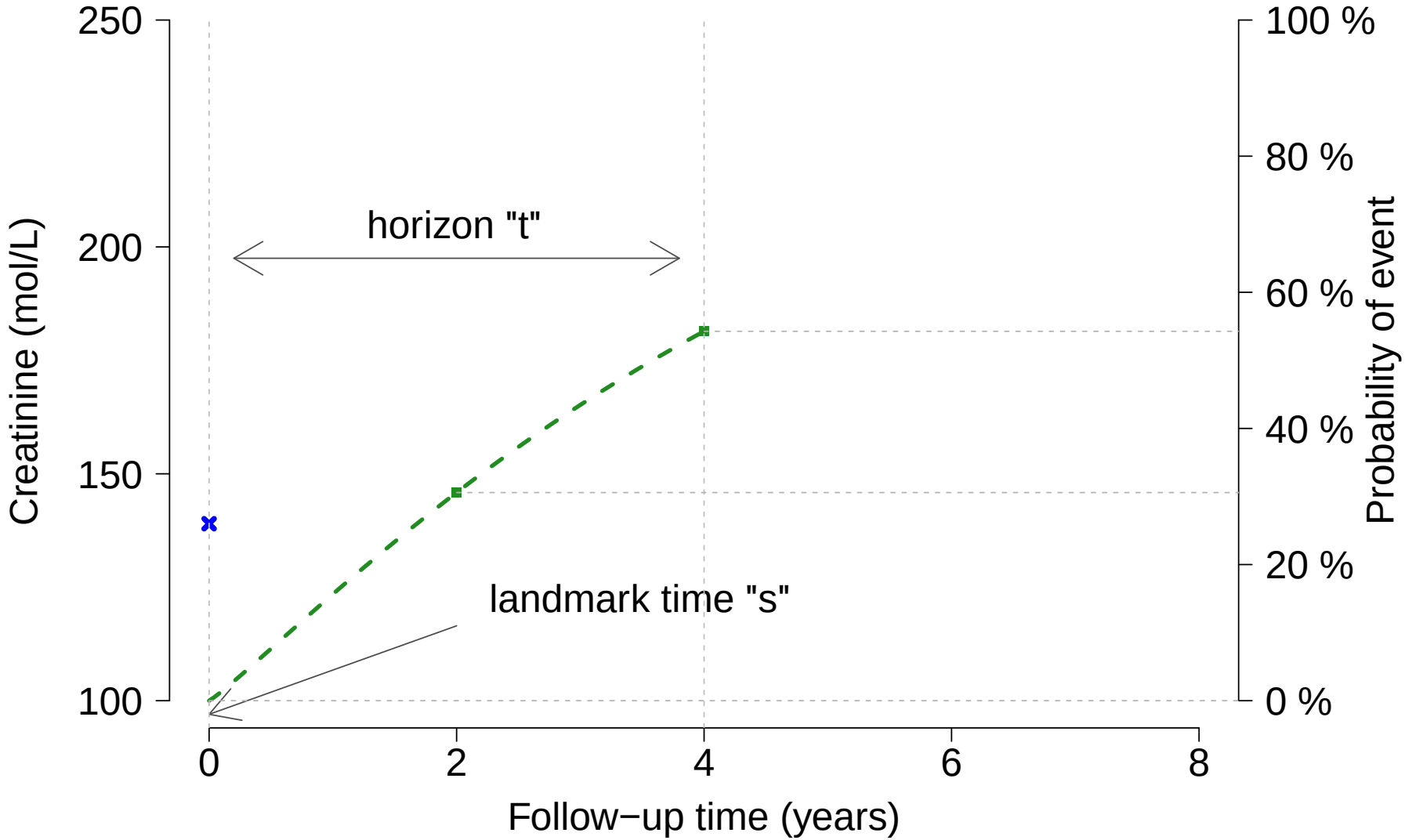

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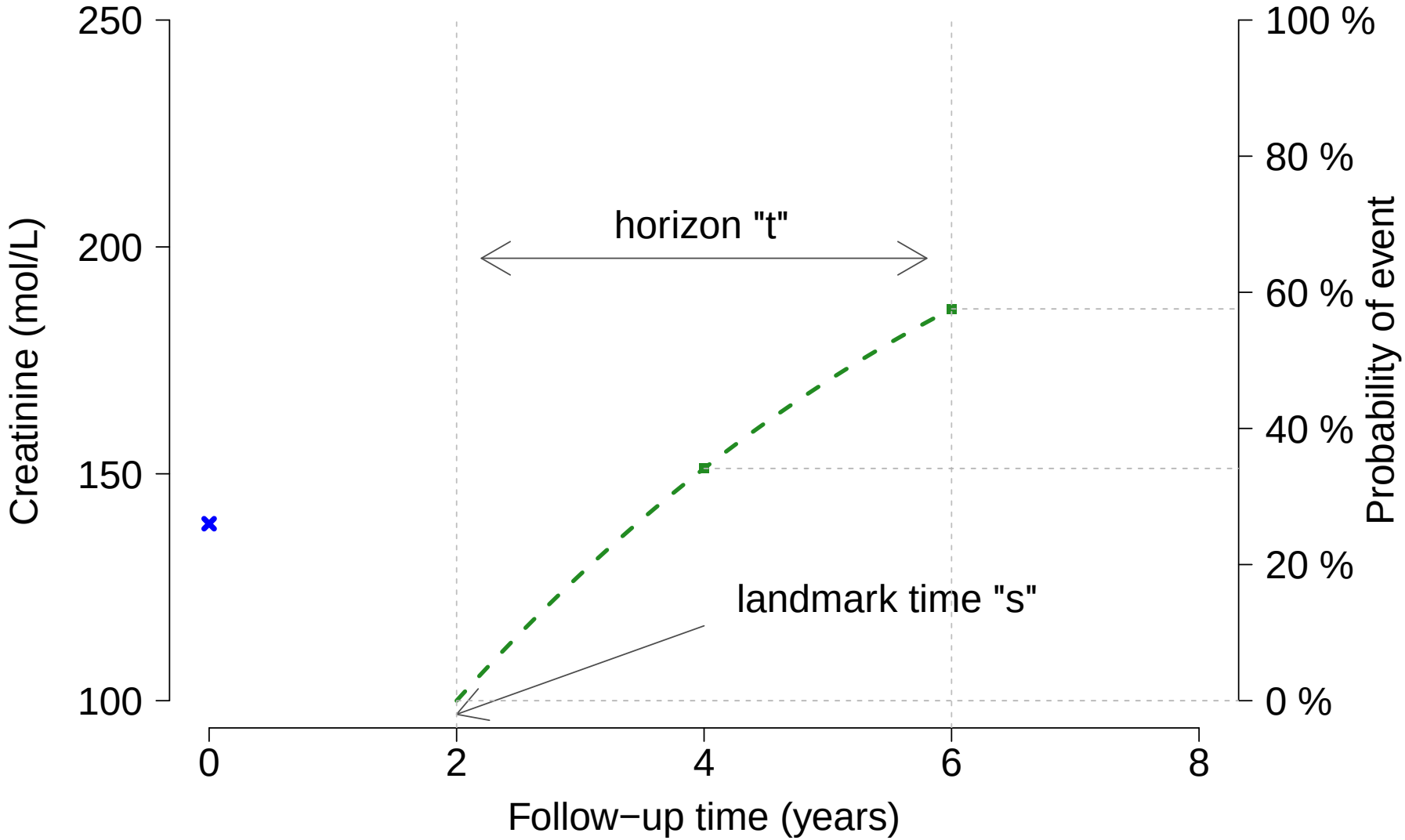
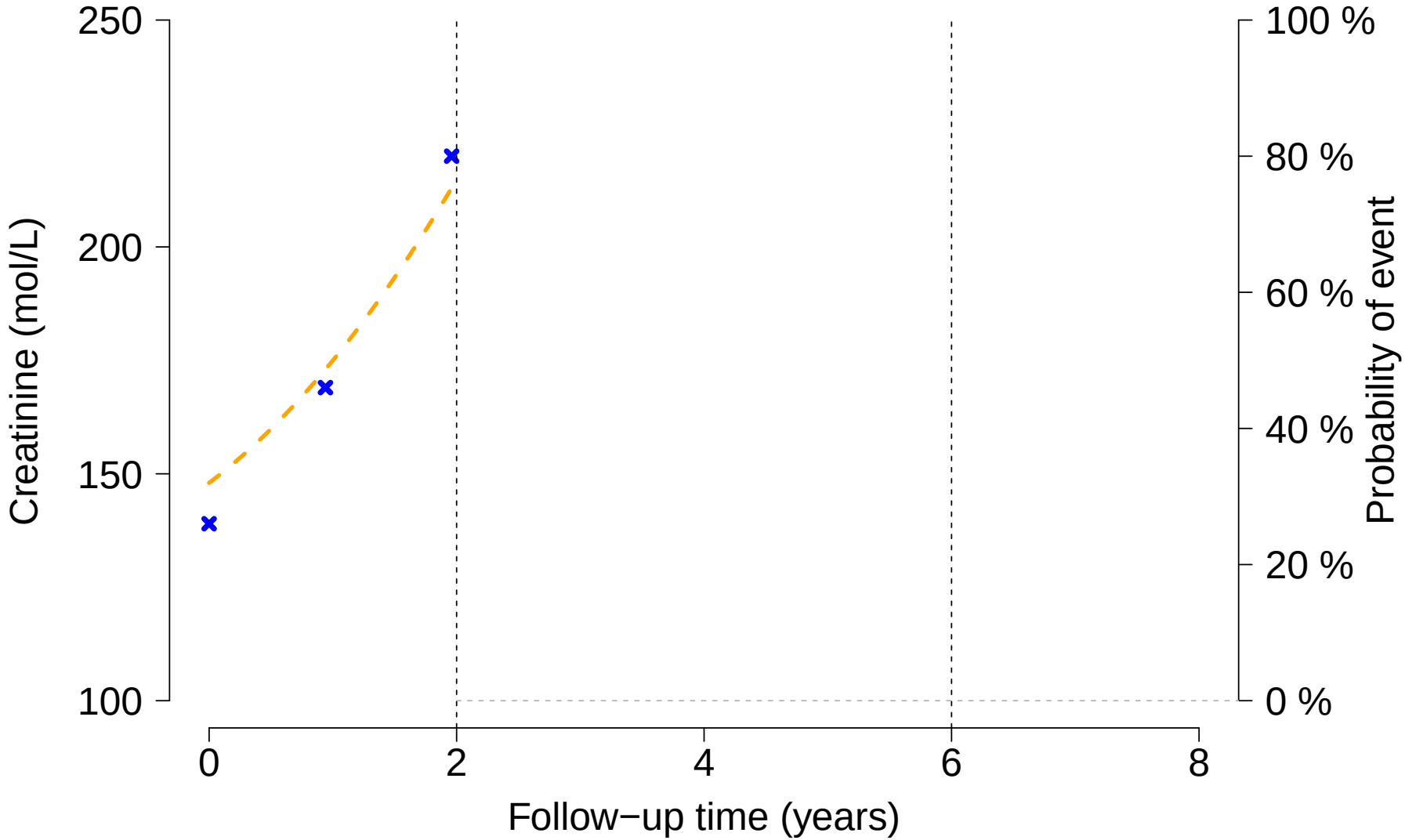


Principle of individual predictions from repeated information (Proust-Lima 2015)



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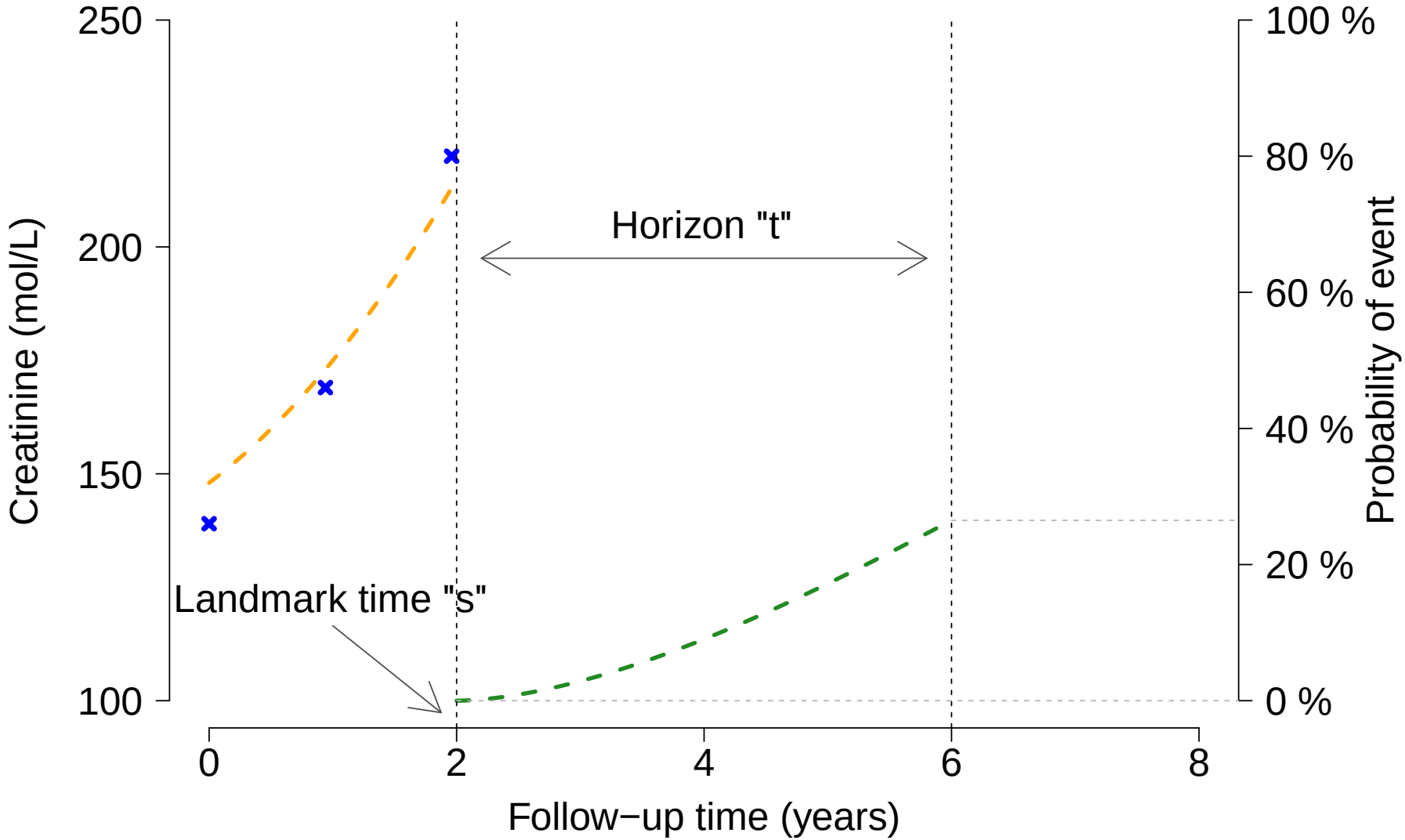

Examples of applications

- Renal disease :
  - concentration of creatinine and graft failure
- Prostate Cancer :
  - Prostate Specific Antigen (PSA) and recurrence of cancer
- HIV :
  - CD4 counts and AIDS-defining diseases
- Hepatitis C :
  - hepatic fibrosis stage and complication of cirrhosis

How to compute dynamic predictions ?

- Predicted probability of event given information collected until s :

$$P_i(s,t) = P(T_i \leq s+t \mid T_i \geq s, \mathcal{H}_i(s), X_i)$$

  - baseline covariates X_i and biomarker measures until s : $\mathcal{H}_i(s) = \{Y_i(u), u \leq s)\}$

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- Two main statistical approaches in the presence of repeated information
  - Landmark model (van Houwelingen, 2011)
    - focus on the subjects still at risk at the landmark time s
    - classical survival model according to information at baseline X_i and repeated information collected until s, $\mathcal{H}_i(s)$

    $\rightarrow$ estimated parameters $\hat{\theta}$

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  - Joint model (Rizopoulos 2012)
    - focus on all the information simultaneously
    - joint model for the longitudinal process and the time to event
    $\rightarrow$ estimated parameters $\hat{\theta}$

How to obtain a prediction tool from the models ?

- Estimations of $\hat{\theta}$ and $\hat{V(\hat{\theta})}$ on a certain population
- For a new subject, we know :
  - baseline covariates : X_i
  - information collected until s : $\mathcal{H}_i(s) = \{Y_i(u), u \leq s)\}$
- Two strategies (Ferrer 2017) :
  1. Plug-in estimate :
     individual prediction of event $P_i(s,t)$ computed in $\hat{\theta}$
  2. Approximation of the posterior distribution of $P_i(s,t)$:
     D draws $\theta_d \sim \mathcal{N}\left(\hat{\theta}, \hat{V(\hat{\theta})}\right)$ or combined with a permutation technique
     individual prediction of event $P_i(s,t)$ computed in θ_d
     $\rightarrow$ median + 95% confidence interval

Example in Prostate cancer (models estimated on 459 men)

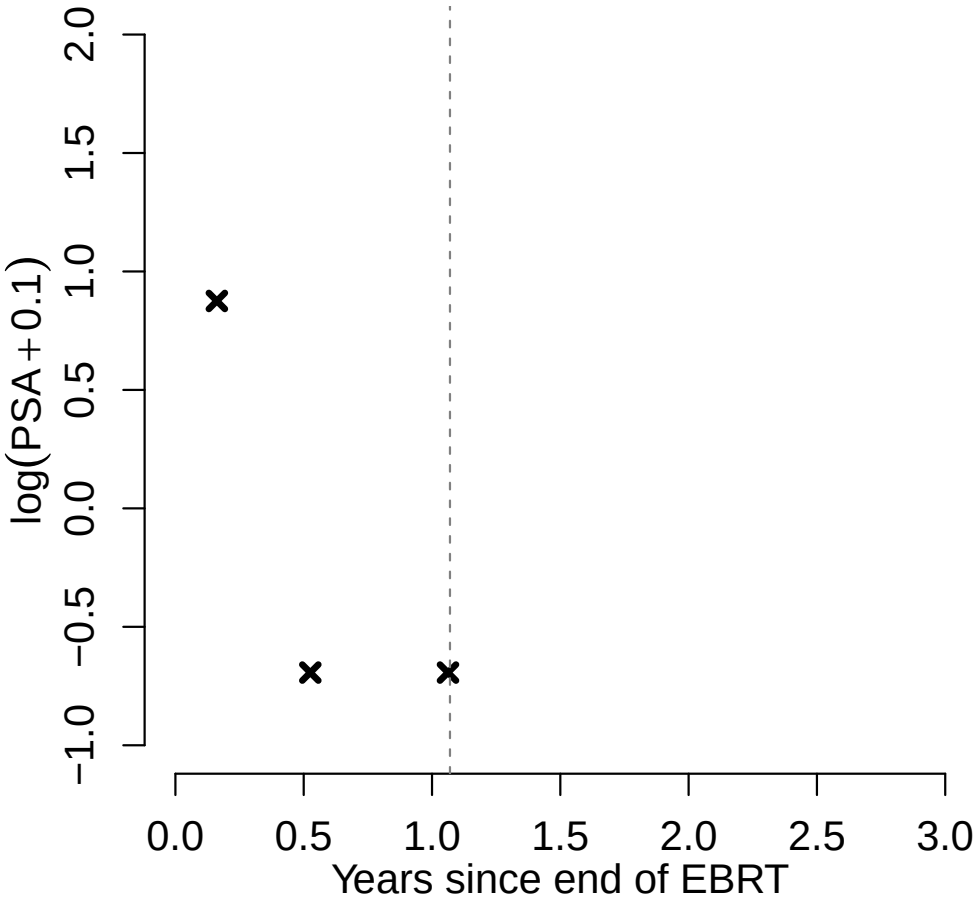
For a man with a recurrence at 3.8 years

x PSA measures

Predicted probability
of recurrence
in the next 3 years
with 95%CI :

▲ with joint model
(JLCM, 4 classes)

• with survival model
(no PSA information)



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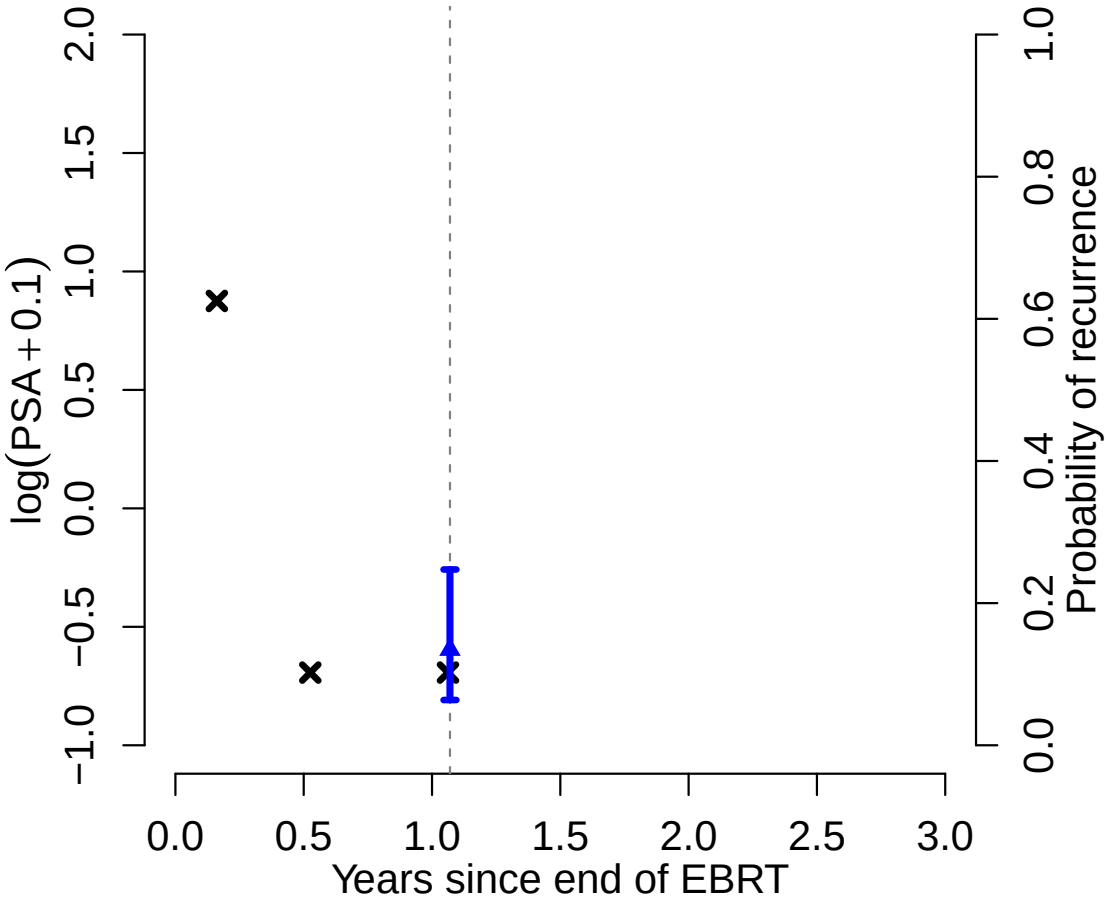

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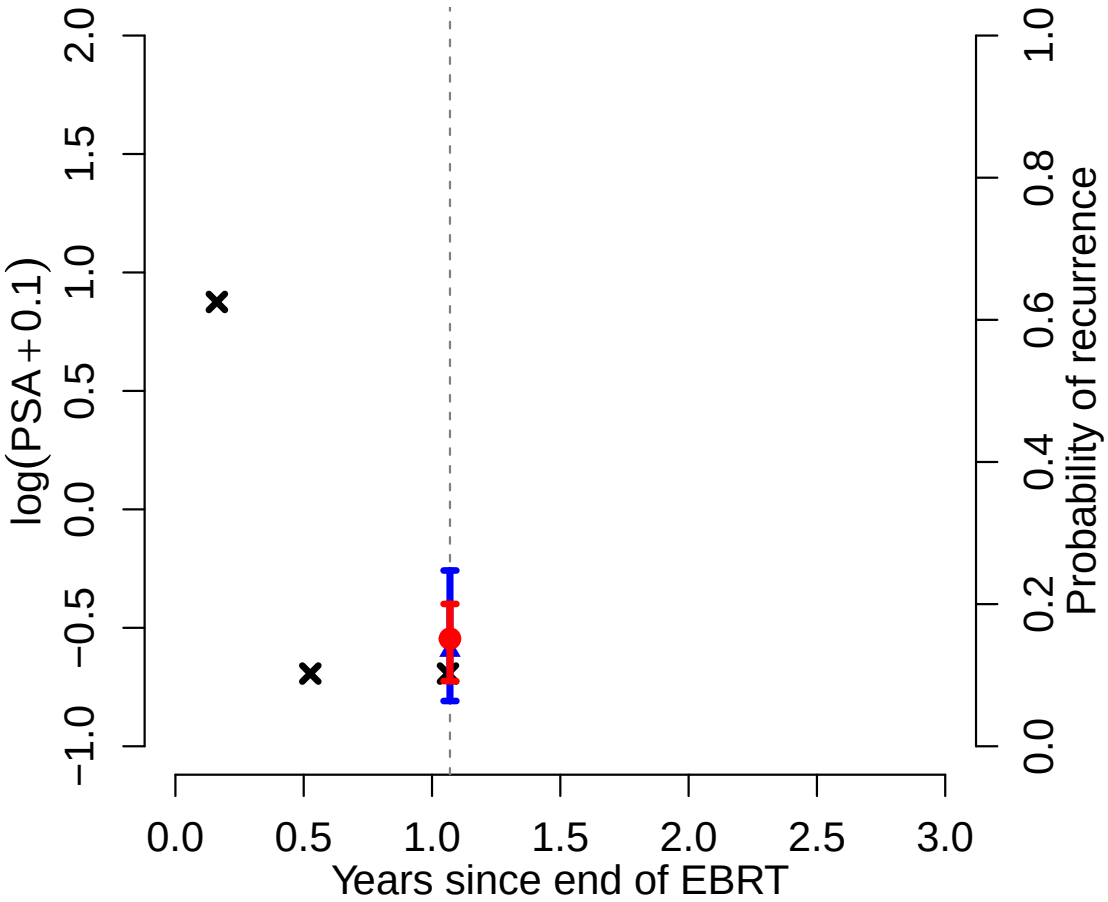

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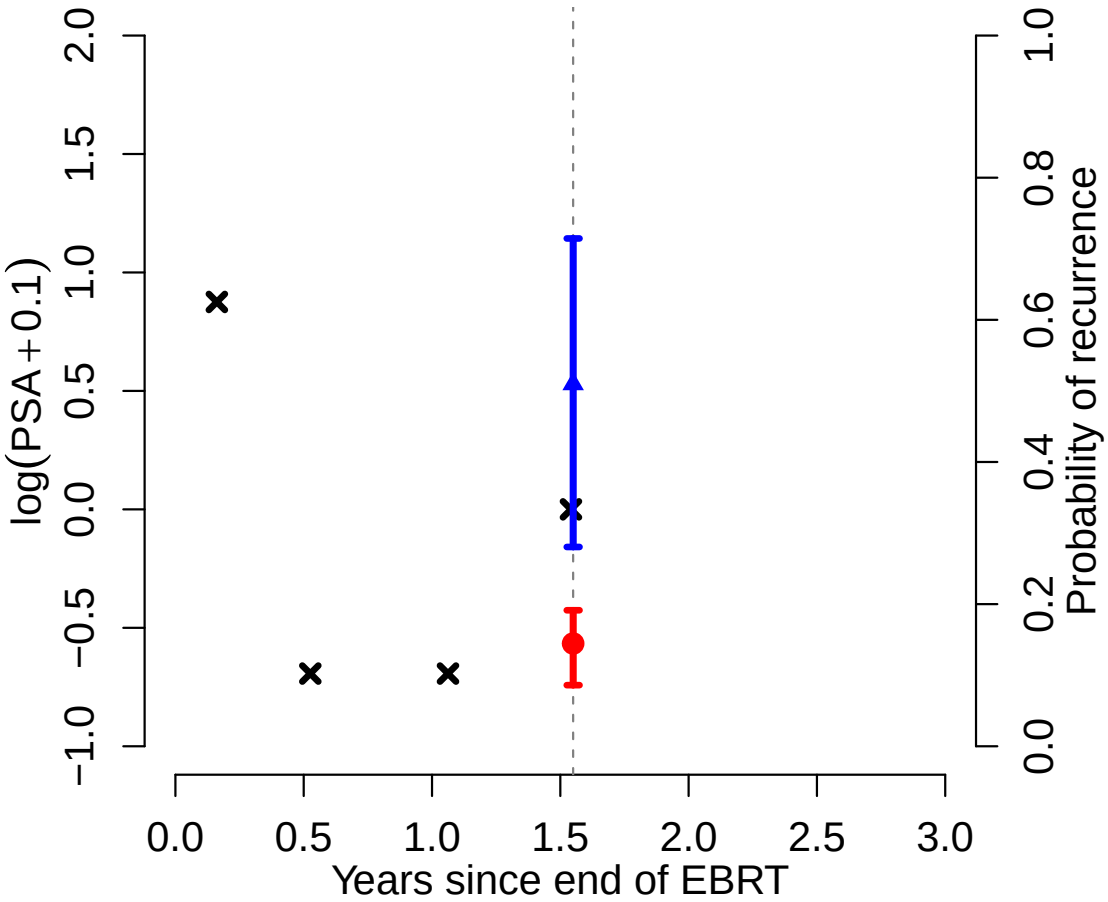

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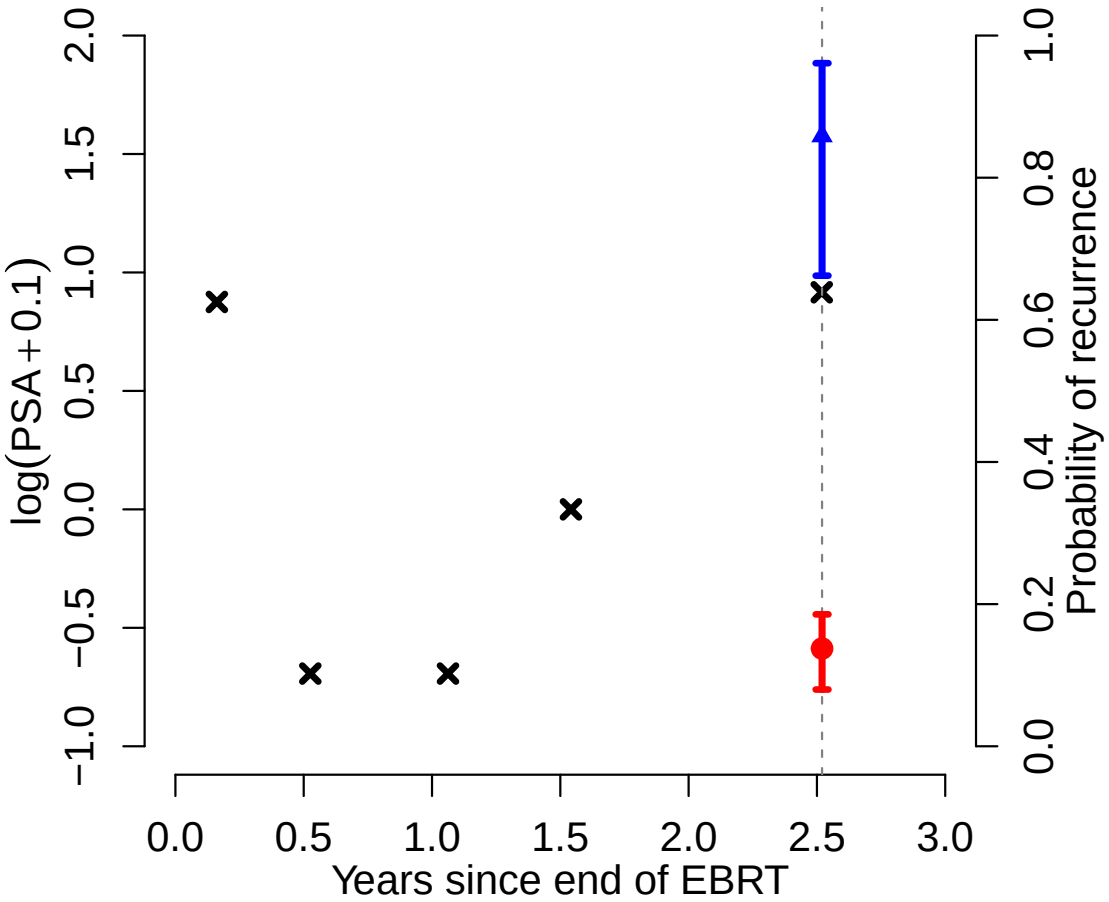

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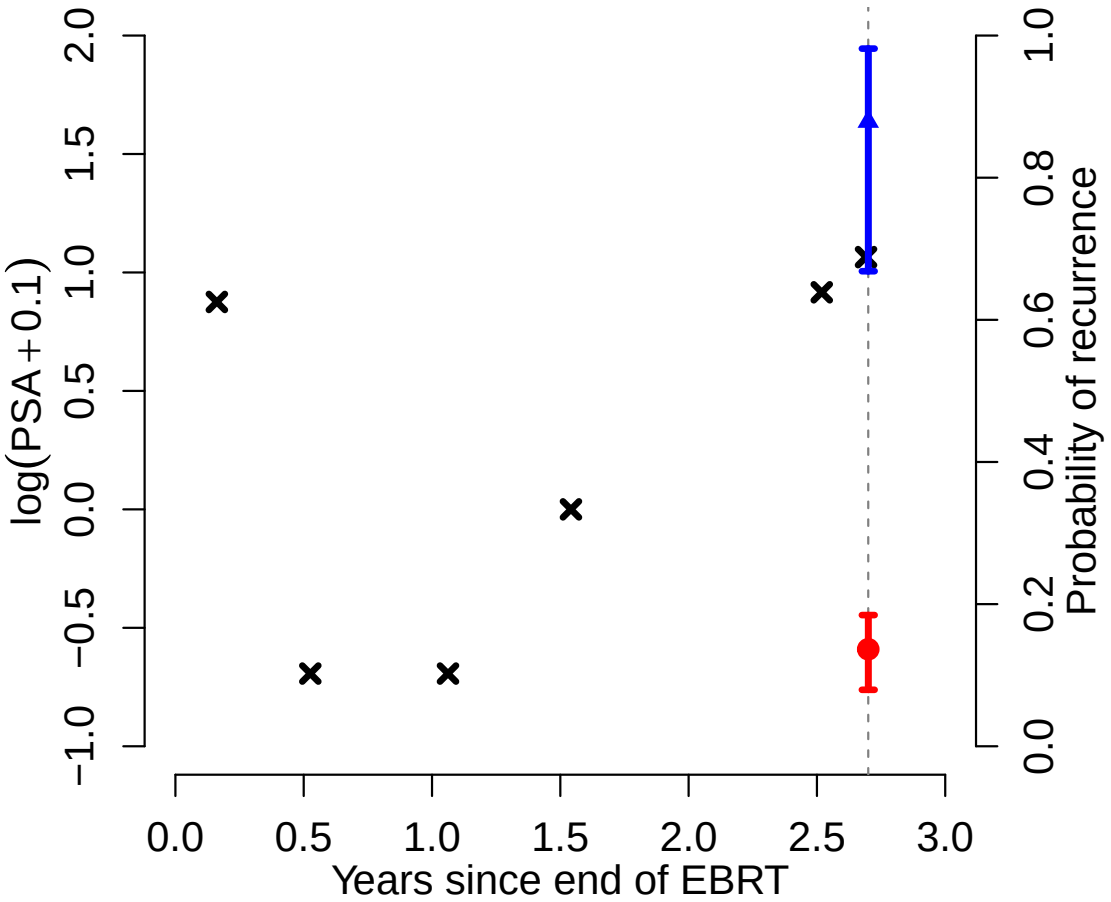


How to assess dynamic predictions ? The methods

- Two major notions :
  - calibration : x events expected among 100 individuals with a predicted risk of x%
  - discrimination : subjects with higher predicted risk are more likely to experience the event

- Main methods :
  - AUC (ROC curve methodology) for discriminative power
    evaluates the concordance of $\hat{p}_i(s,t)$ *with the observations*
    (Blanche 2013,2015)

  - Brier score for error of predictions
    compares directly $\hat{p}_i(s,t)$ *with the event status* $\Upsilon_i(s+t)$
    (Schoop 2008 ; Proust-Lima 2014 ; Blanche 2015)

  - prognostic cross-entropy (EPOCE) for prognostic information criterion
    evaluates the conditional log-density of the event given the biomarker history
    (Commenges 2012 ; Proust-Lima 2014 ; Sène 2016)

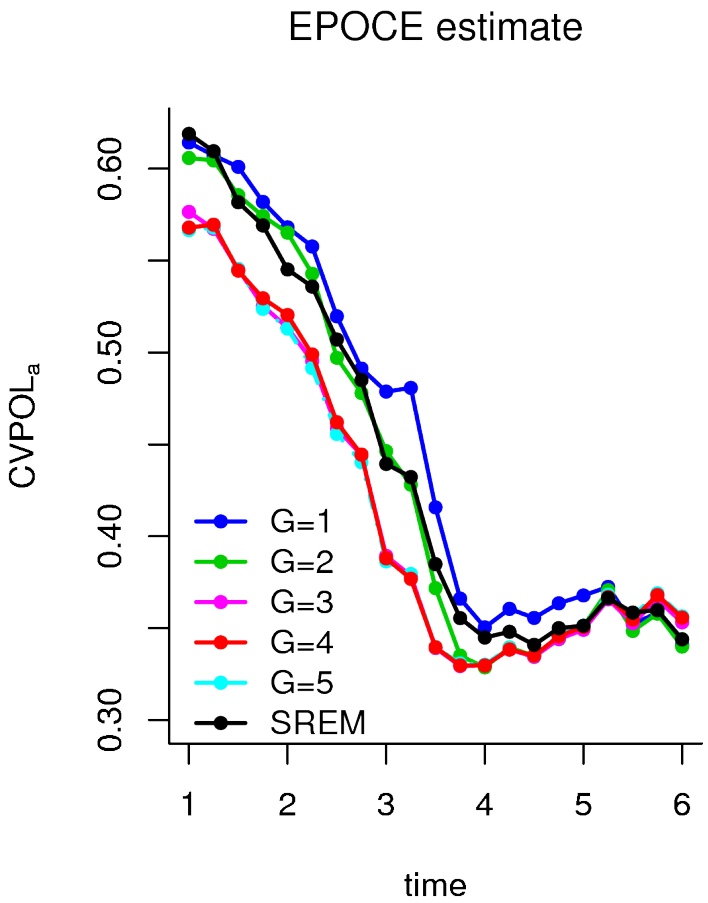
How to assess dynamic predictions ? The estimators

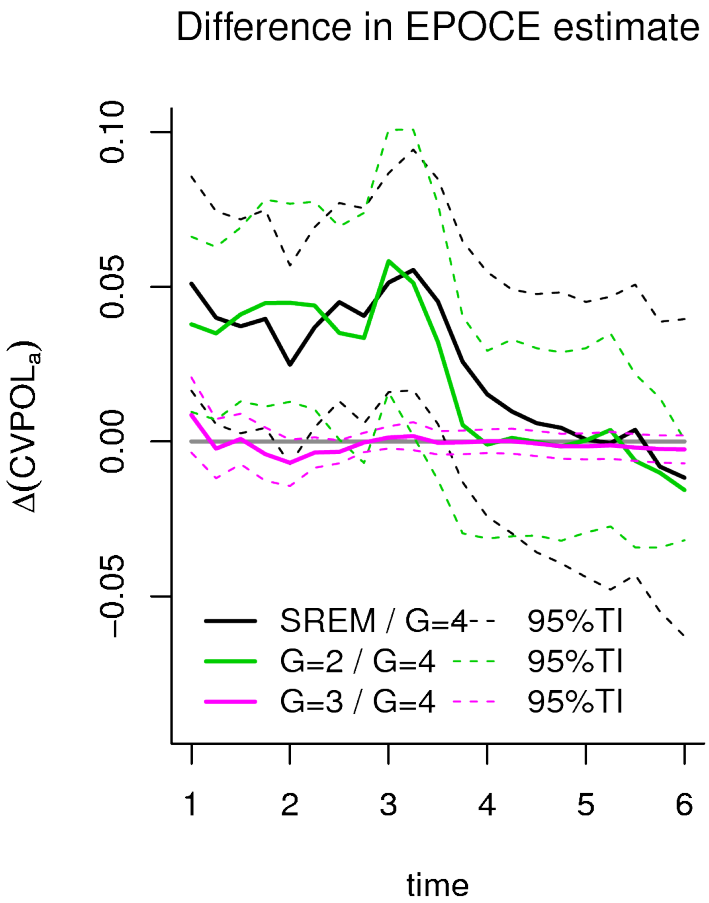
- Estimation of measures presents two main difficulties :
  - Censoring
    Usually done by Inverse Censoring Probability Weighting (IPCW)
  - The summary of the evaluation for each couple (s,t)
    for AUC and BS, integrated /average versions on a horizon $[0, \tau]$
    for EPOCE, directly on an horizon $[0, \tau]$

How to assess dynamic predictions ? The populations

- Training data (used for the estimation)
  - Apparent measures over evaluate the predictiveness of the model (overoptimism)
    $\rightarrow$ especially important with complex models
  - Correction by cross-validation (Gerds 2007)
    $\rightarrow$ very long with complex models
  - Correction by approximated cross-validation
    $\rightarrow$ direct computation - available for EPOCE (Commenges 2012) and BS (Sène 2016)
- Validation (external) data
  - Apparent measures OK

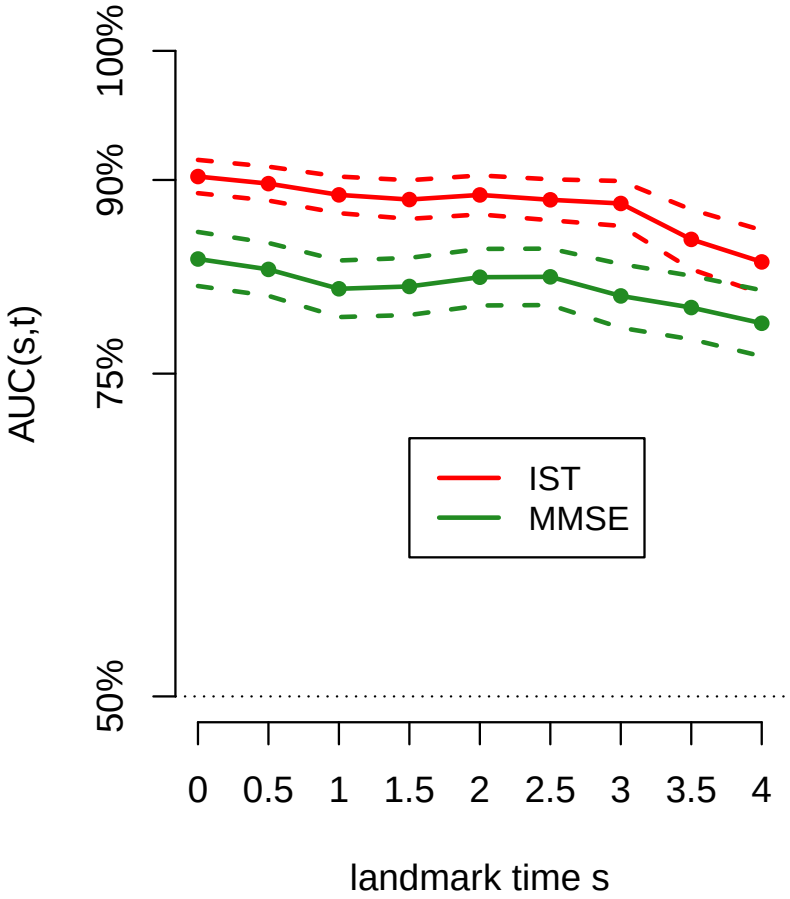
Example : EPOCE in Prostate cancer recurrence from different joint models (Proust-Lima 2014)

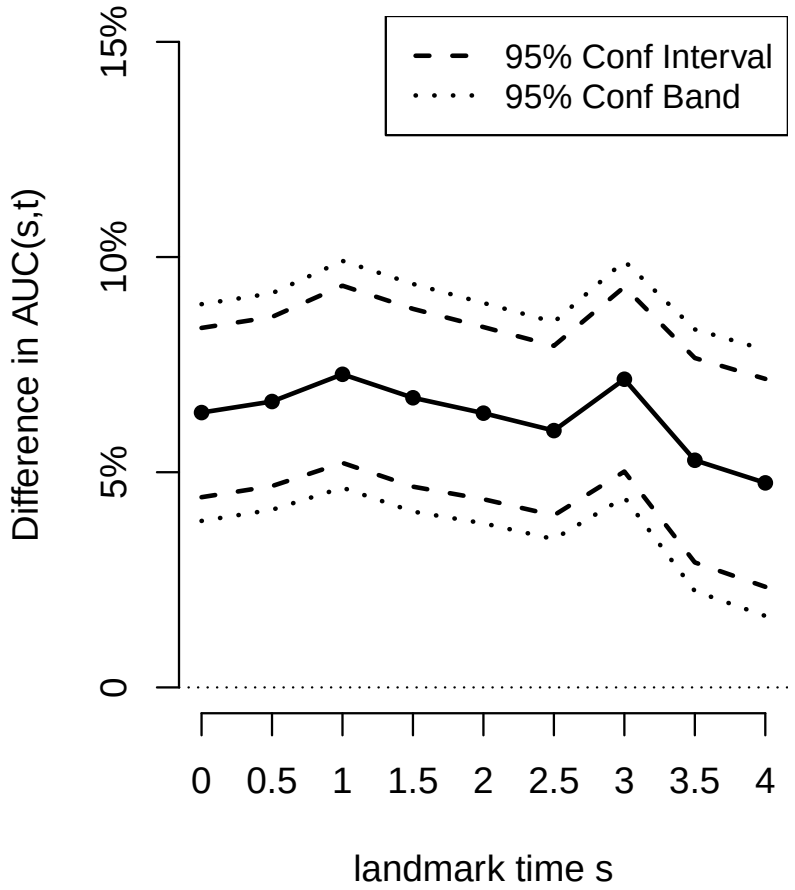




On training data with correction by cross validation

Example : AUC and BS in joint models for dementia comparing two longitudinal cognitive measures (Blanche 2015)





On validation data

→ MMSE = global functioning ; IST = verbal fluency (with speed component)

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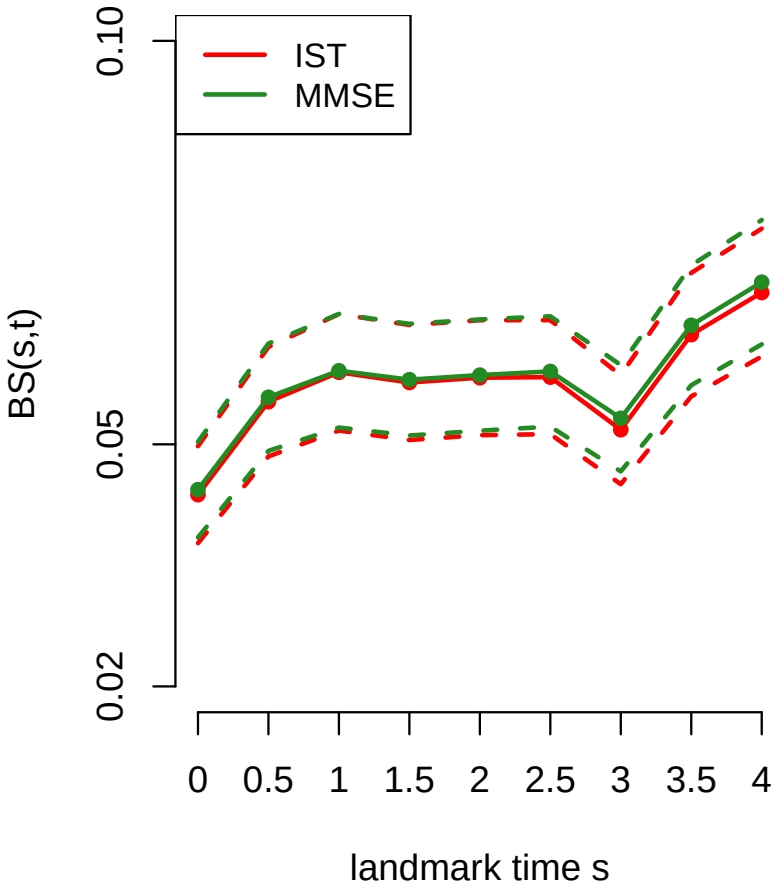

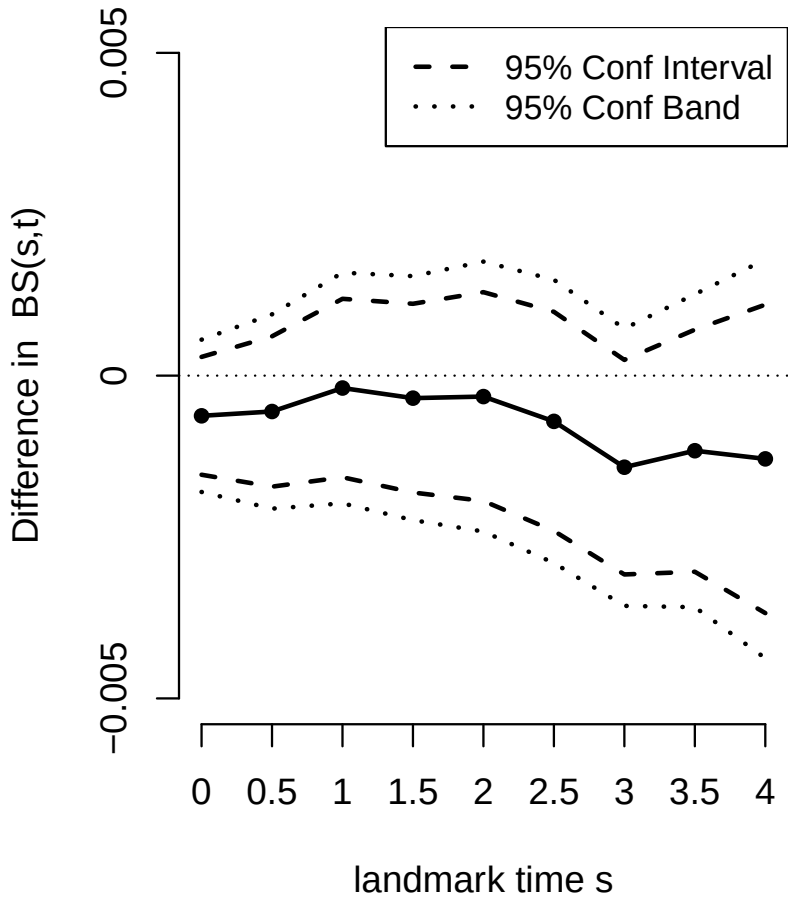

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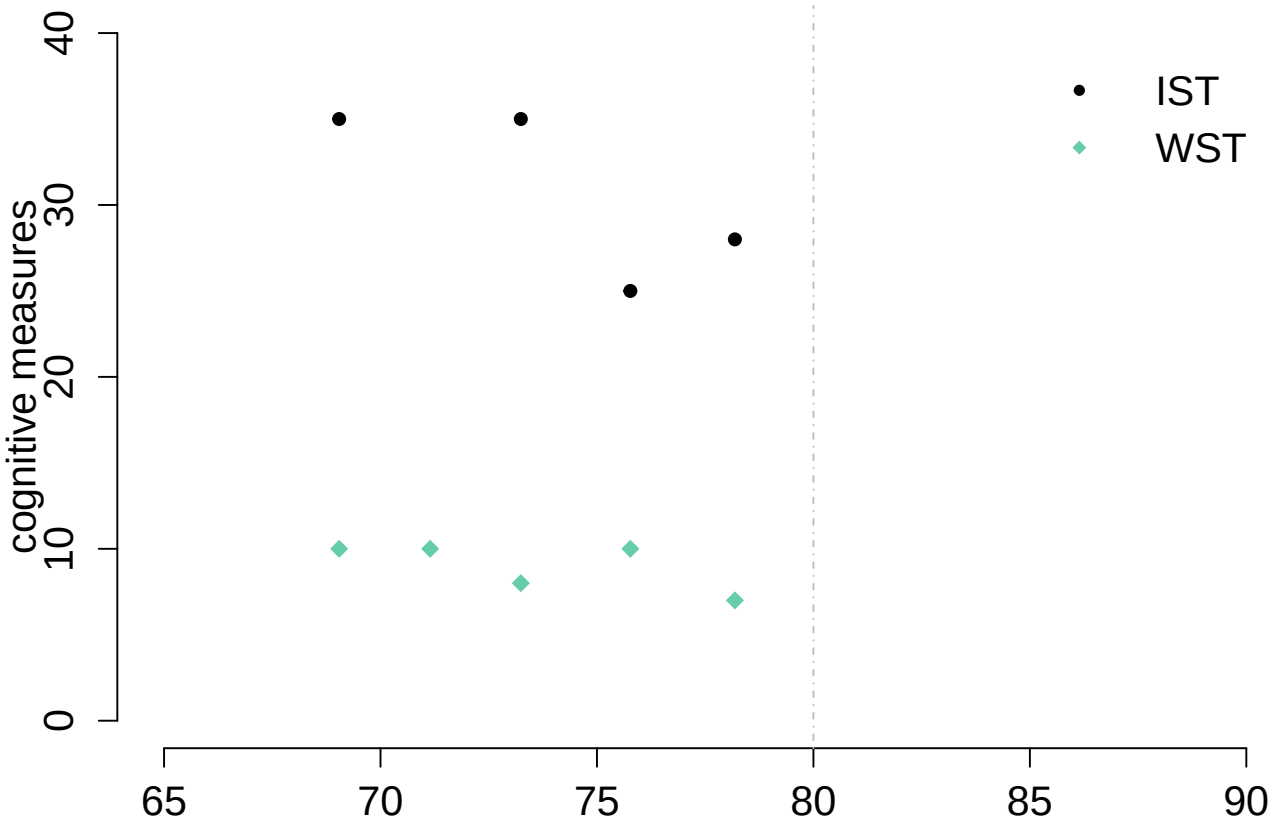
What about competing risks ?

- A unique cause of event is very rare in practice
  - Other causes have to be taken into account for proper estimation of predictions
- Solutions
  - Use of statistical models dealing with competing risks (joint or landmark approaches)
  - Use of estimators of predictive accuracy dealing with competing risks (Blanche 2015)
- Example
  - joint model for multiple longitudinal measures of cognition, dementia and death (Proust-Lima 2016)

What about competing risks ? prediction of dementia and dementia-free death from a joint latent class model



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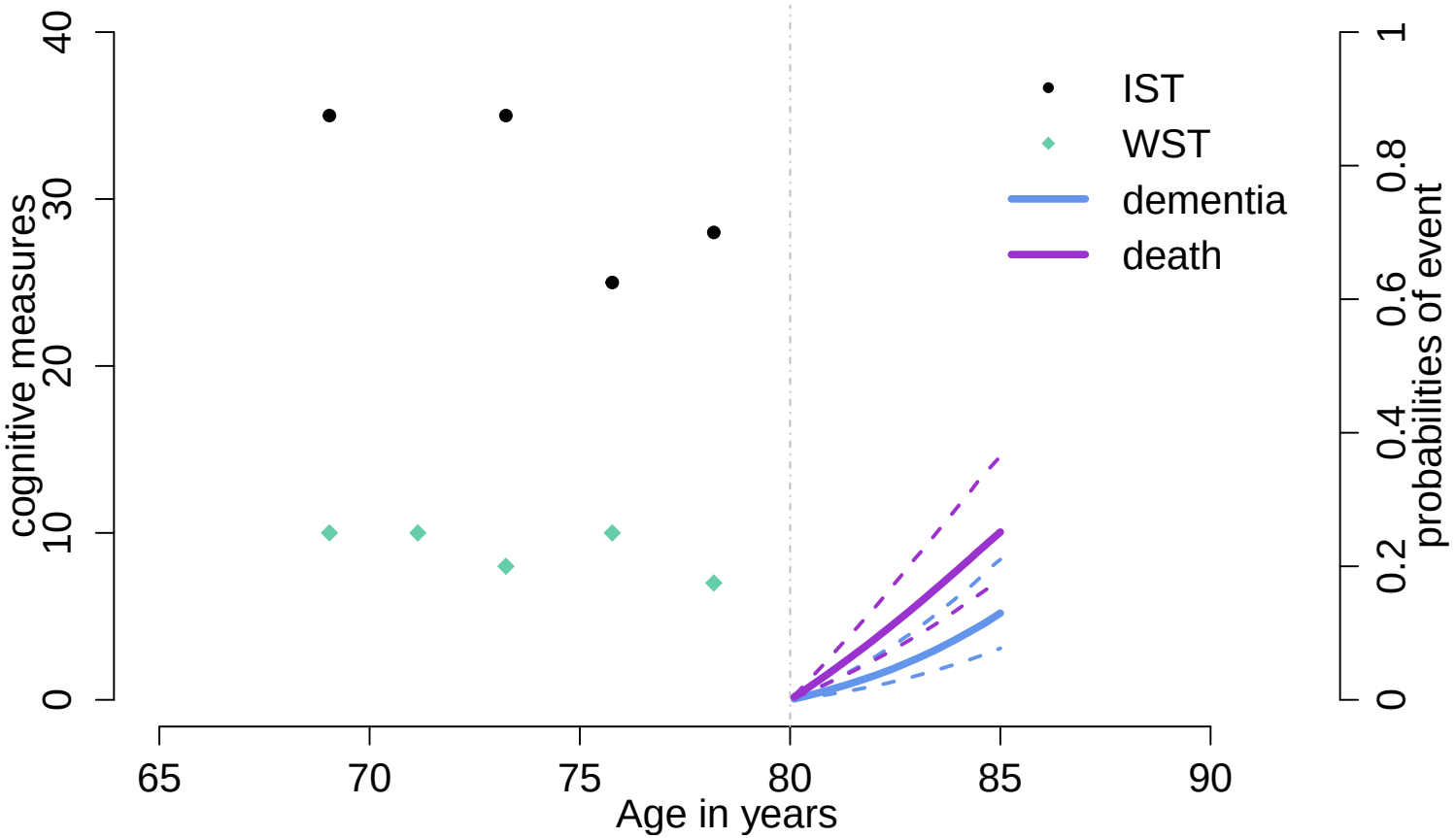

	at 80 years old
5-year probability of dementia (%) :	13.0 [7.7,21.0]
5-year probability of death (%) :	25.1 [18.1,36.5]

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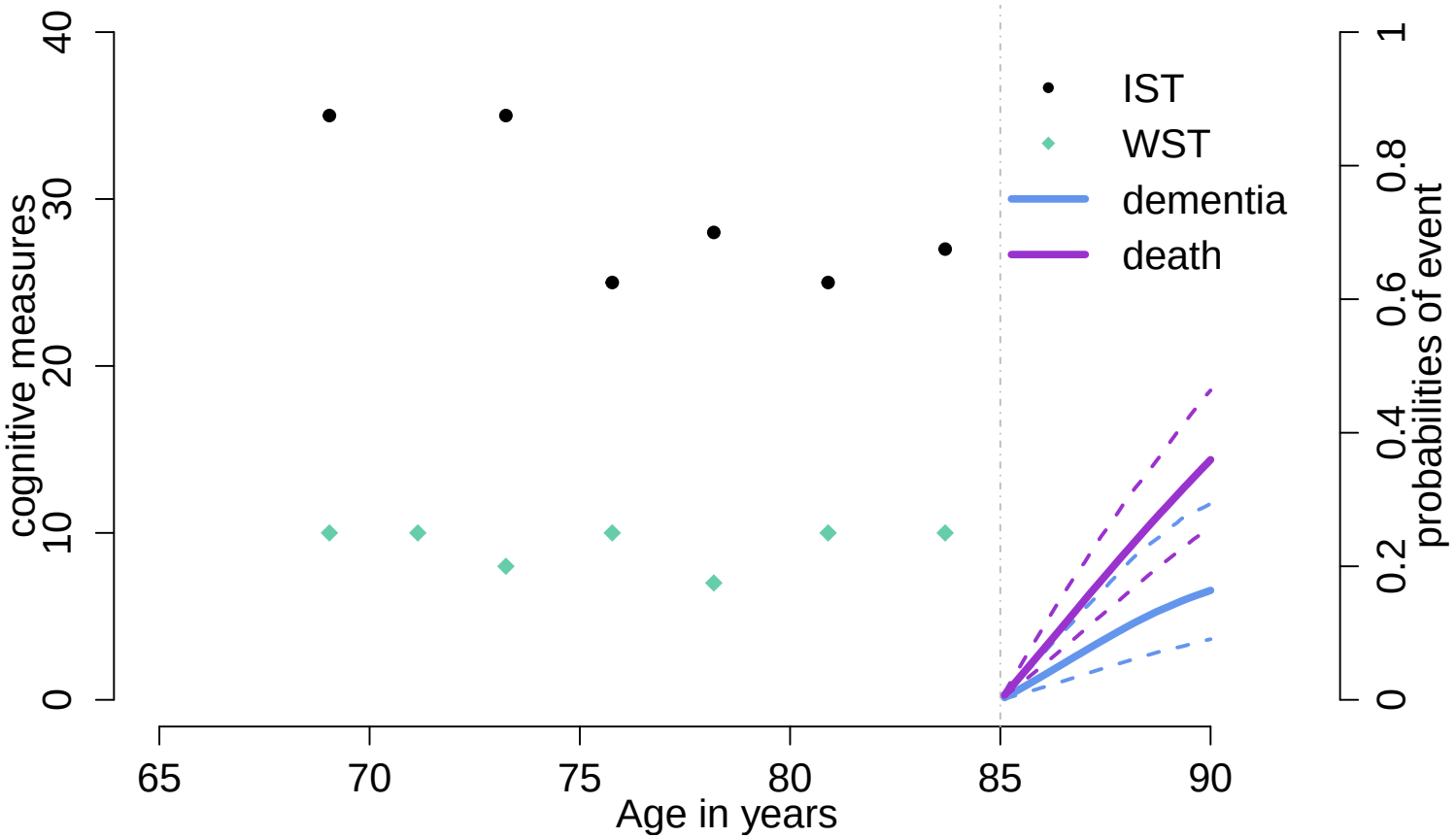


	at 80 years old	at 85 years old
5-year probability of dementia (%) :	13.0 [7.7,21.0]	16.4 [9.1,29.4]
5-year probability of death (%) :	25.1 [18.1,36.5]	36.0 [25.9,46.3]

Change in treatment in the monitoring of patients after a cancer (Sène, 2016)

Dynamic predictions assume an absence of change in the follow-up

In practice, frequent initiation of second treatments :

hormonal therapy (HT) in prostate cancer

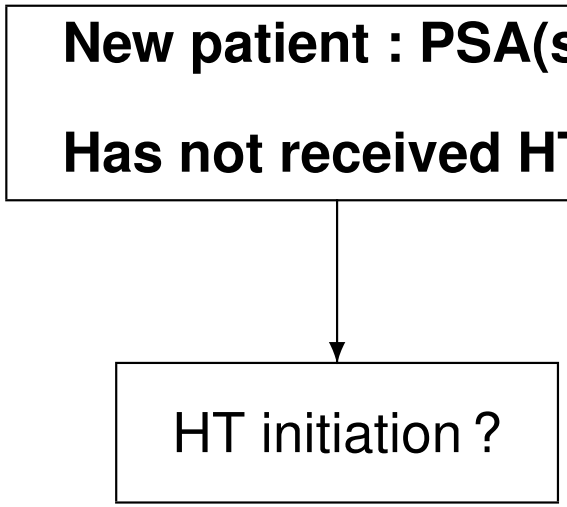
$\rightarrow$ changes the dynamics of the biomarker

$\rightarrow$ changes the risk of event

Solution :

- model the initiation of second treatment (ST)
- define differential dynamic predictions according to the initiation of ST

Differential individual dynamic predictions in patients free of HT (Sène 2016)



PSA(s)= collected PSA until today
X= available covariates at diagnosis
τ = time of initiation of hormonal therapy

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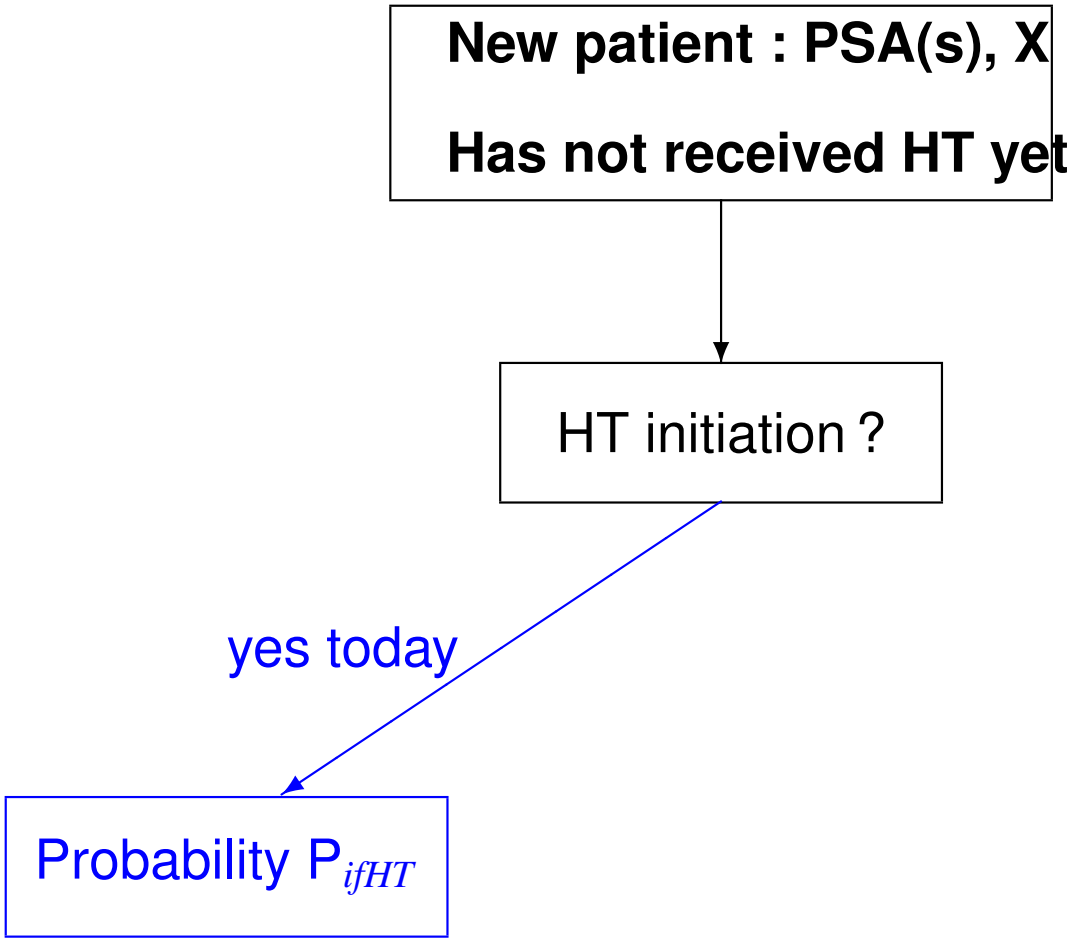

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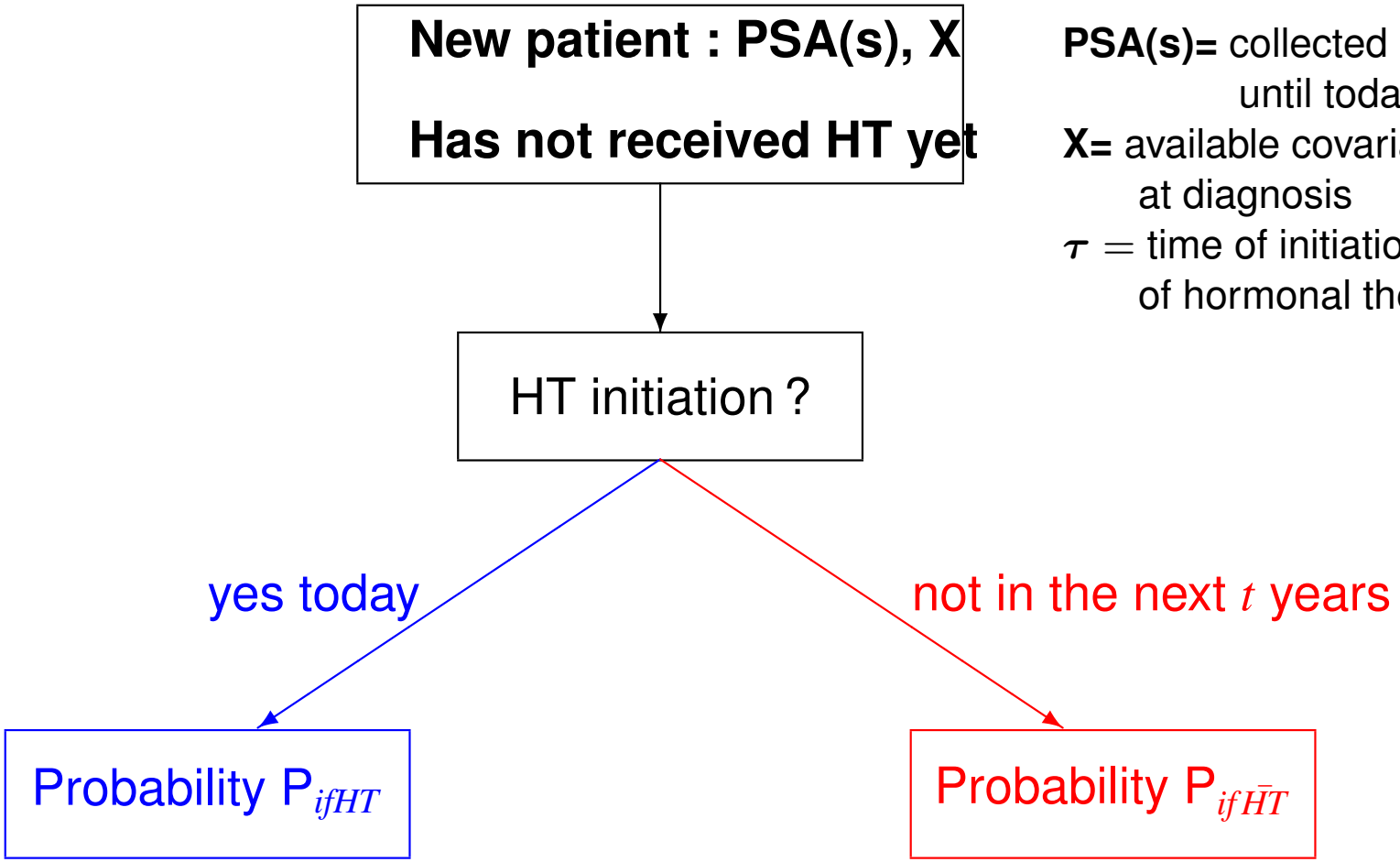

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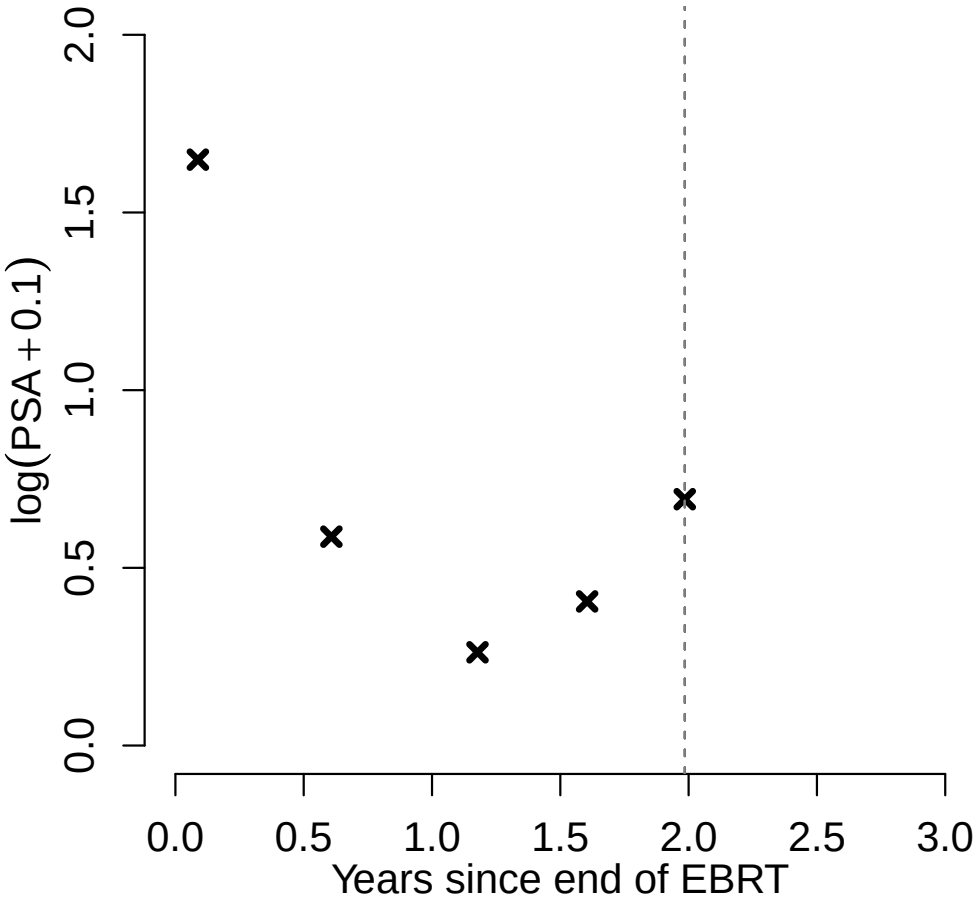
$$P(T_i \leq s+t \mid T_i \geq s, \tau_i = s, Y_i^{(s)}, X_i) \qquad P(T_i \leq s+t \mid T_i \geq s, \tau_i > \min(T_i, s+t), Y_i^{(}$$

Example of differential dynamic predictions (model estimated on 2386 men treated by radiation therapy)

For a man with a recurrence at 2.7 years

x PSA measures



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Predicted probability
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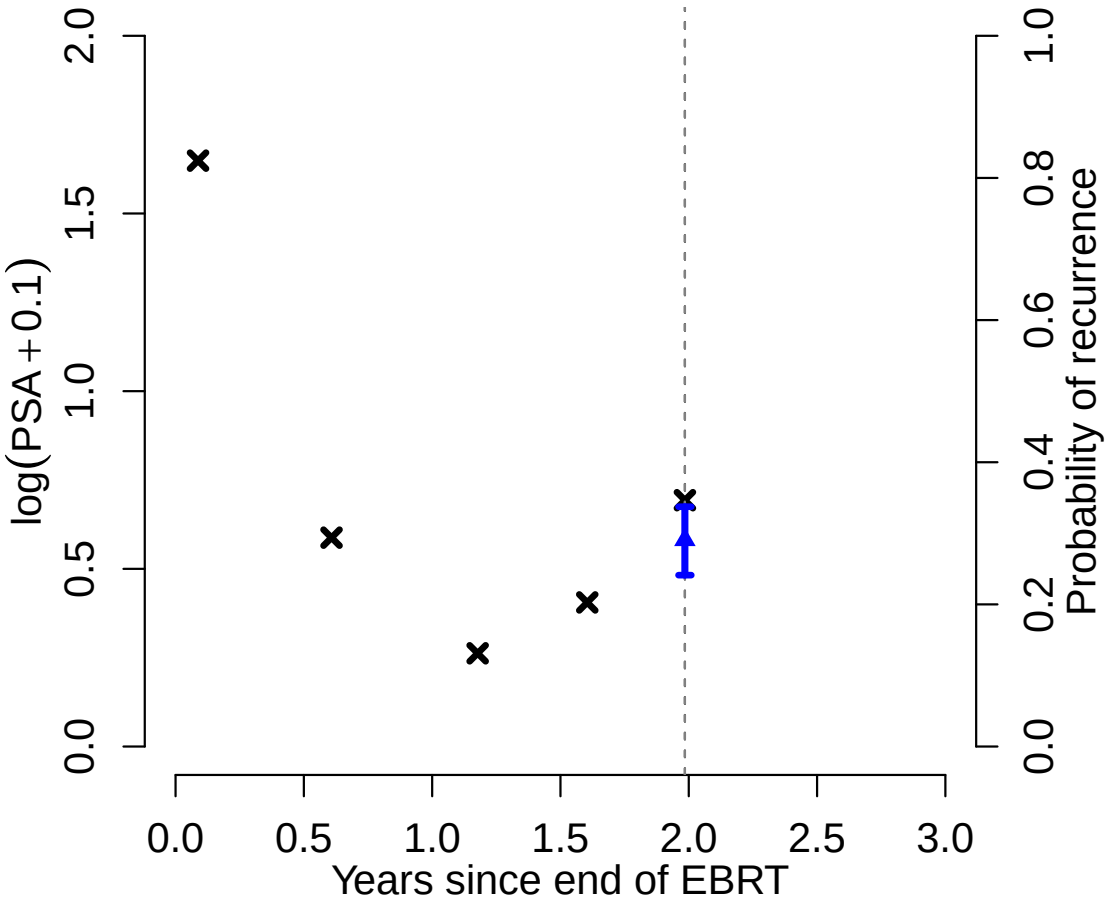
▲ in absence of HT



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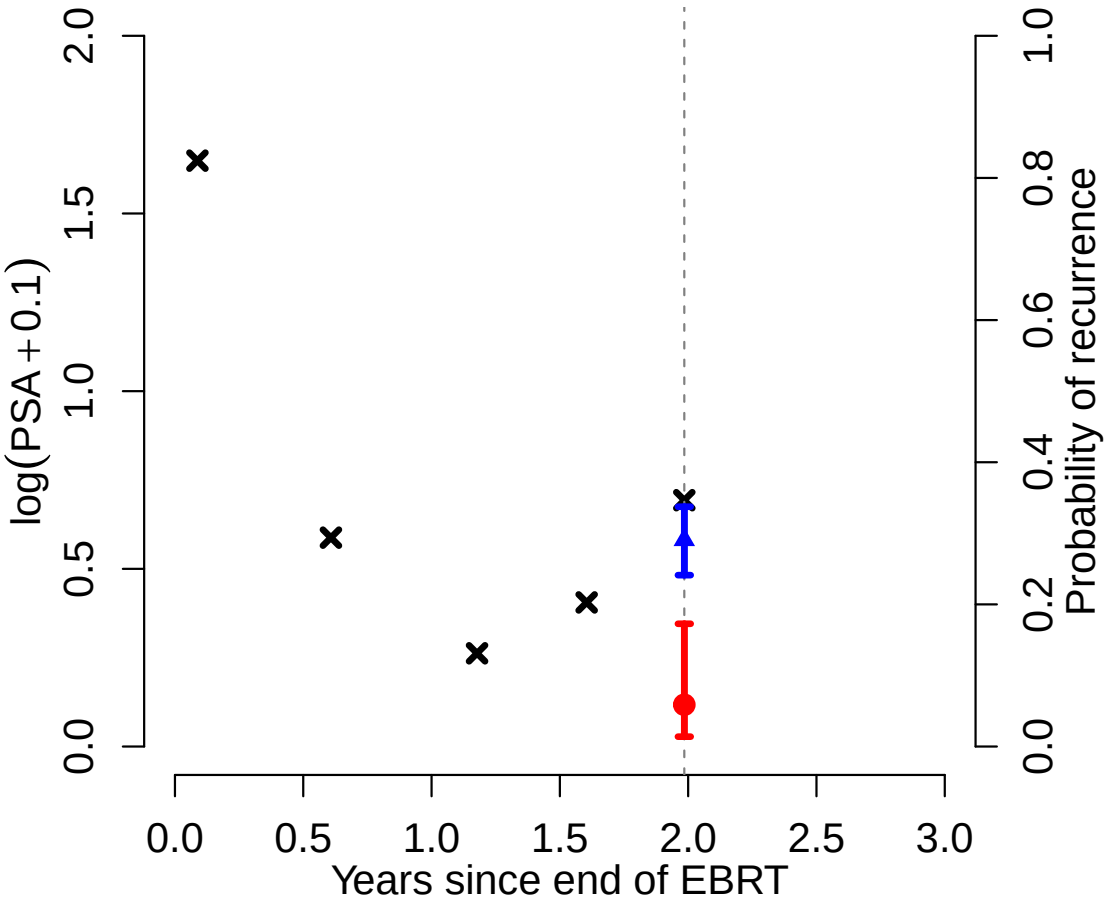

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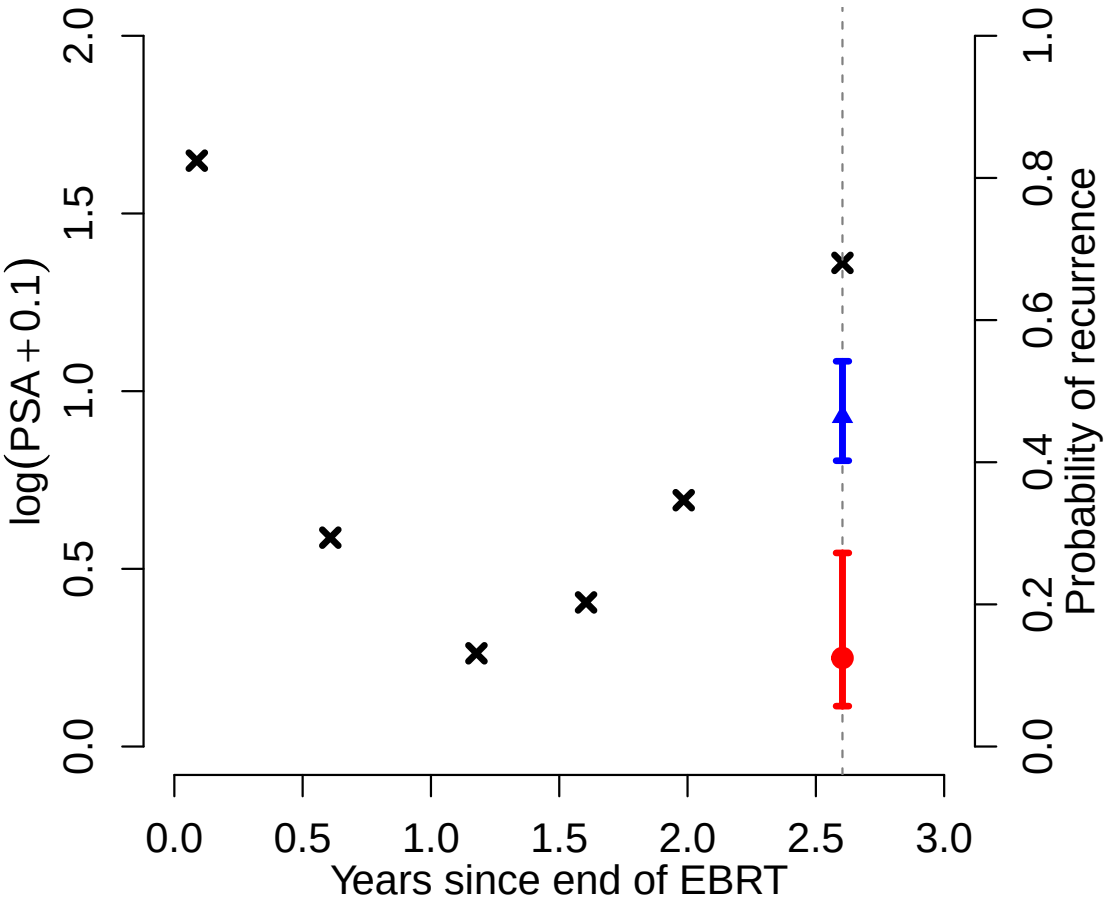

Conclusion

- Individual dynamic predictions :
  - usually more accurate and powerful due to the updated information
  - can be computed from joint models (but careful with the assumptions)
  - can be computed from landmark models (but careful with the efficiency)

- Cautions :
  - better fit does not mean better predictive accuracy
  - a good model for etiology is rarely a good model for prediction (van Houwelingen 2011)
  - don't forget the problems of competing risks, censoring and selection at the landmark time
  - external validation should always be favored
  - prognostic tools need large populations for their development and validation

- Software (R packages only + non exhaustive) :
  - dynpred, JM, JMBayes, lcmm, frailtypack for computations of dynamic predictions
  - pec, timeROC for evaluation

References

Blanche et al. (2013). Estimating and comparing time-dependent areas under receiver operating characteristic curves for censored event times with competing risks. Statistics in Medicine, 32(30), 5381-5397.

Blanche et al. (2015). Quantifying and comparing dynamic predictive accuracy of joint models for longitudinal marker and time-to-event in presence of censoring and competing risks. Biometrics, 71(1), 102-113.

Commenges et al. (2012). Choice of prognostic estimators in joint models by estimating differences of expected conditional Kullback-Leibler risks. Biometrics, 68(2), 380-387.

Gerds & Schumacher (2007). Efron-type measures of prediction error for survival analysis. Biometrics, 63(4), 1283-7.

Ferrer et al. (2017). Individual dynamic predictions : estimator validation and robustness to models hypotheses. Technical Report.

Proust-Lima & Blanche (2015). Dynamic Predictions. In Wiley StatsRef : Statistics Reference Online. John Wiley & Sons, Ltd

Proust-Lima et al. (2016). Joint modeling of repeated multivariate cognitive measures and competing risks of dementia and death : a latent process and latent class approach. Statistics in Medicine, 35(3), 382-398.

Proust-Lima et al. (2014). Joint latent class models for longitudinal and time-to-event data : A review. Statistical Methods in Medical Research, 23(1), 74-90.

Rizopoulos (2012). Joint Models for Longitudinal and Time-to-Event Data : With Applications in R. Chapman & Hall/CRC Biostatistics Series.

Schoop et al. (2008). Quantifying the predictive performance of prognostic models for censored survival data with time-dependent covariates. Biometrics, 64(2), 603-10.

Sène et al. (2016). Individualized dynamic prediction of prostate cancer recurrence with and without the initiation of a second treatment : Development and validation. Statistical Methods in Medical Research, 25(6), 2972-2991.

van Houwelingen and Putter (2011). Dynamic Prediction in Clinical Survival Analysis. Monographs on Statistics & Applied Probab 123. Chapman & Hall/CRC, Lon- don.

van Houwelingen (2014). From model building to validation and back : a plea for robustness. Statistics in Medicine, 33(30), 5223-5238.

Vickers & Cronin (2010). Everything you always wanted to know about evaluating prediction models (but were too afraid to ask). Urology, 76(6), 1298-1301.