Supplementary materials: Development and validation of a dynamic prognostic tool for prostate cancer recurrence using repeated measures of post-treatment PSA: a joint modelling approach

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1. Directed graph of the joint latent class model

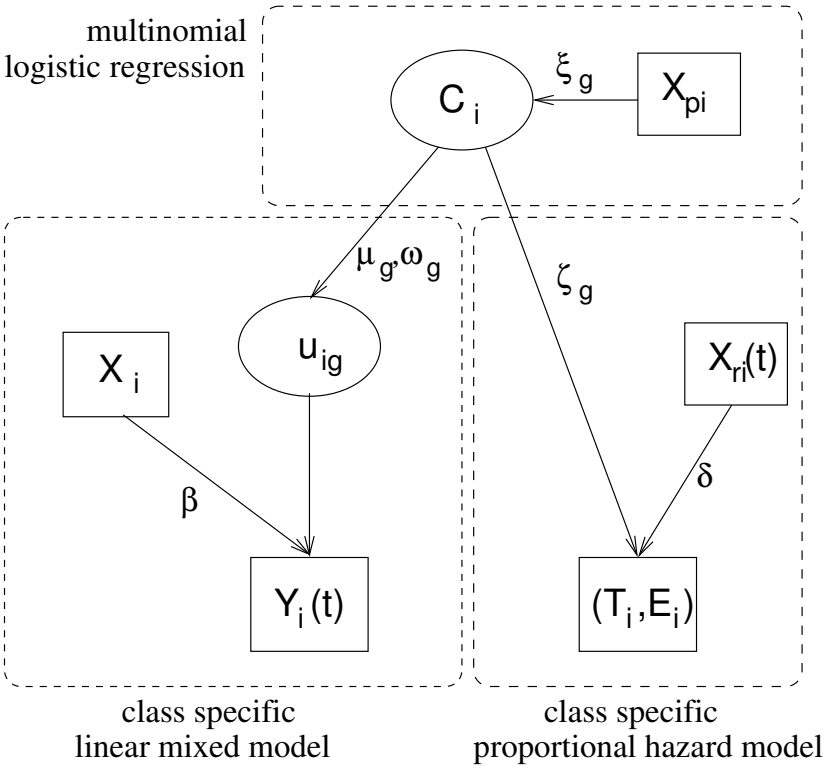

Figure S1. Directed graph of the joint latent class model at a time t. Boxes represent observed variables ($X_i = (X_{0i}, X_{1i}, X_{2i})$, $X_{ri}(t)$ and X_{pi} are the covariates vectors, $Y_i(t)$ the biomarker value at time t and (T_i, E_i) the time-to-event data). Circles represent latent variables (u_{ig} the class-specific vector of random-effects and C_i the latent class membership).

2. Illustration of the dynamic prognostic tools

We illustrate the use of the posterior probabilities of recurrence at time $s+t$ given the information collected until time s with six individual post-treatment PSA trajectories from UM cohort. For each, we computed the predicted cumulative risk of recurrence using the joint latent class model (noted 5LCM), the proportional

hazard model with baseline covariates (noted Baseline) and the two-stage landmark model (noted PSA(s)). Predicted probabilities using the naive landmark model with the latest PSA measure were very similar to the latter. We made predictions up to three years ahead, which is a reasonable time horizon in this clinical setting. The risk of recurrence was computed from 1 year after the end of the treatment to the time-to-recurrence with an update every 6 months for two patients with a relatively early recurrence (Rec 1 and Rec 2 in Figure S2) and every 1 year for the two patients with a later recurrence (Rec 3 and Rec 4 in Figure S3) and two patients who were censored before any recurrence (Cens 1 and Cens 2 in Figure S4). 95% confidence bands of each prediction are given using 2000 draws, as described in section 2.3.2 of the paper.

The shape of the PSA trajectory for patient Rec1 is characteristic of an early recurrence with a drop of PSA the first year after the end of treatment and a subsequent rise of PSA. However, levels of PSA are relatively low. The 5-LCM based prediction that accounts for the shape of the PSA evolution rather than the level of PSA captures the high risk of recurrence while the Last PSA level based prediction remains relatively low. Patient 2 has higher levels of PSA but the shape of the trajectory is more attenuated. However, the 5-LCM model still gives relatively high probabilities of recurrence while the Last PSA based prediction gives a high probability of recurrence only when the last PSA before the clinical recurrence becomes available. Patient Rec3 has the same kind of shape as patient Rec2 with a constant rise of PSA until recurrence. In this example, 5-LCM still predicts a recurrence earlier than other methods with relatively high probabilities after 4 years. Patient Rec4 in contrast does not exhibit any later rise of PSA after the end of treatment although he had a clinical recurrence of prostate cancer. As

a consequence, none of the methods based on PSA evolution manages to predict a higher probability of recurrence than the Baseline covariates based method. The PSA trajectory of censored patient Cens1 is similar to that of patient Rec4. As a consequence, predictions remain relatively similar with a moderate probability of event whatever the method used. Censored patient Cens2 has a characteristic PSA trajectory of a cured patients. However, as this patient has relatively bad prognostic factors (T-stage=3, Gleason=8 and iPSA=62.4 ng/mL) compared to patient Cens1 (T-stage=2, Gleason=7 and iPSA=15.2 ng/mL), the prediction based on baseline covariates predicts a very high probability of recurrence while the two dynamic prognostic tools update the risk of recurrence according to the PSA trajectory so that, as soon as 3 years after the end of the treatment, the probabilities of recurrence they provide become very low.

These individual predictions suggest that a dynamic prognostic tool that can adapt the probability of recurrence based on the PSA trajectory gives good results and that usually, the last PSA measurement is not as predictive as considering the whole PSA trajectory.

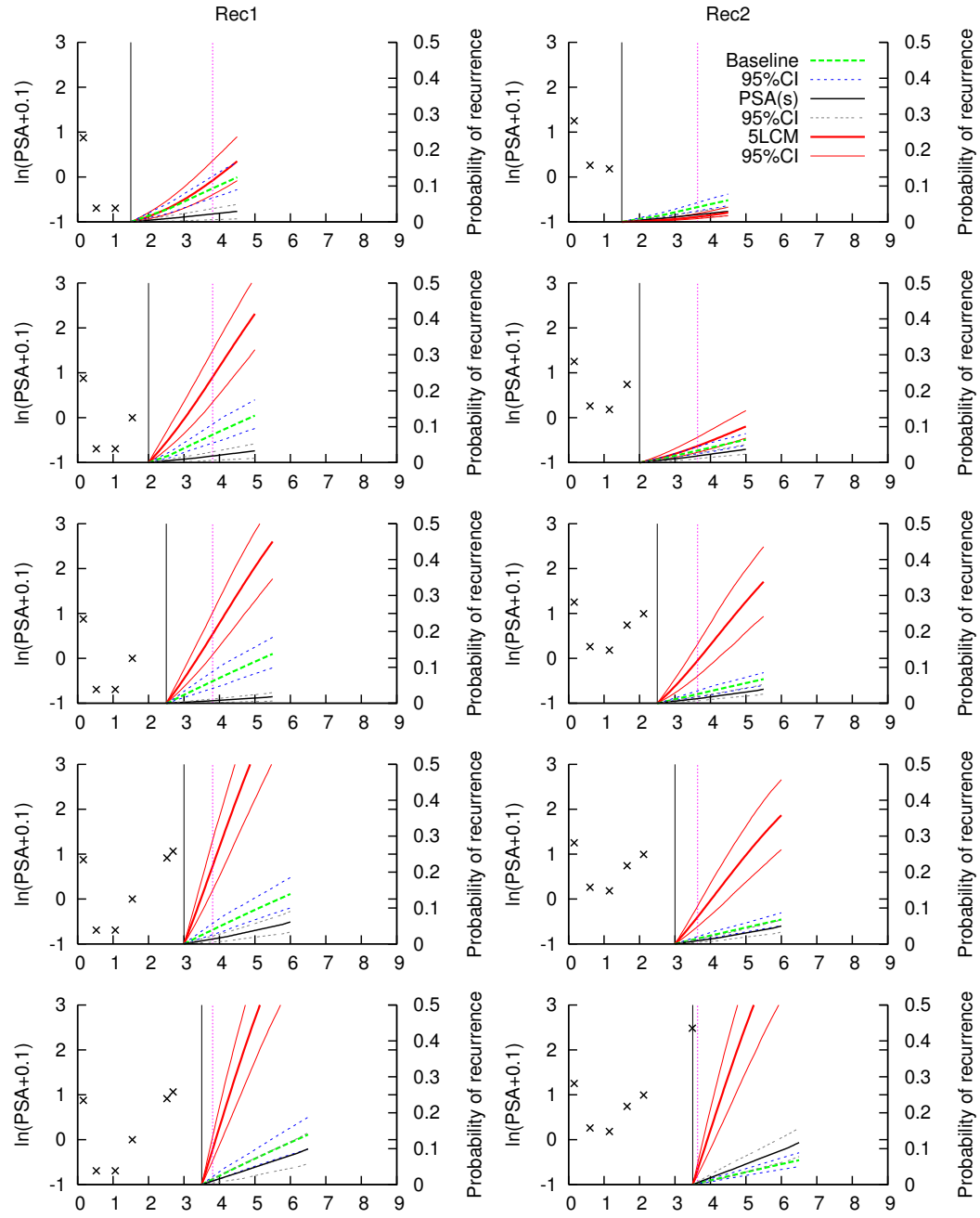

Figure S2. Individual prediction of prostate cancer recurrence for two patients from UM who had a recurrence in the first 4 years. Individual predictions are updated every 6 months from 1 year to 3.5 years. The $\mathbf{x}$ are the PSA measures used for the prediction, the vertical black solid line is the time s of prediction and the vertical pink dashed line is the time of recurrence.

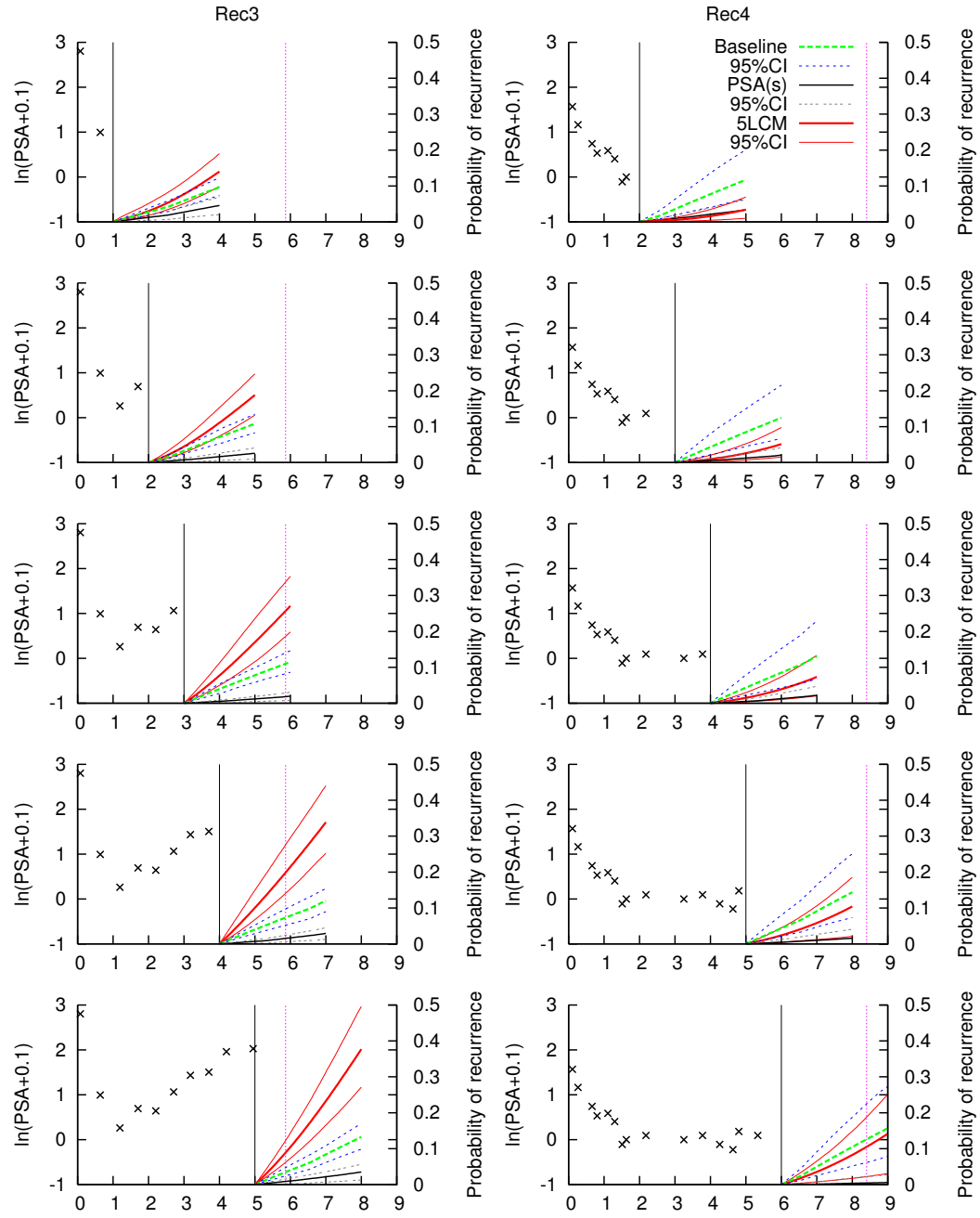

Figure S3. Individual prediction of prostate cancer recurrence for two patients from UM who had a recurrence after 4 years of follow-up. Individual predictions are updated every year from 1 or 2 years after end of EBRT until 5 years or 6 years. The **x** are the PSA measures used for the prediction, the vertical black solid line is the time s of prediction and the vertical pink dashed line is the time of recurrence.

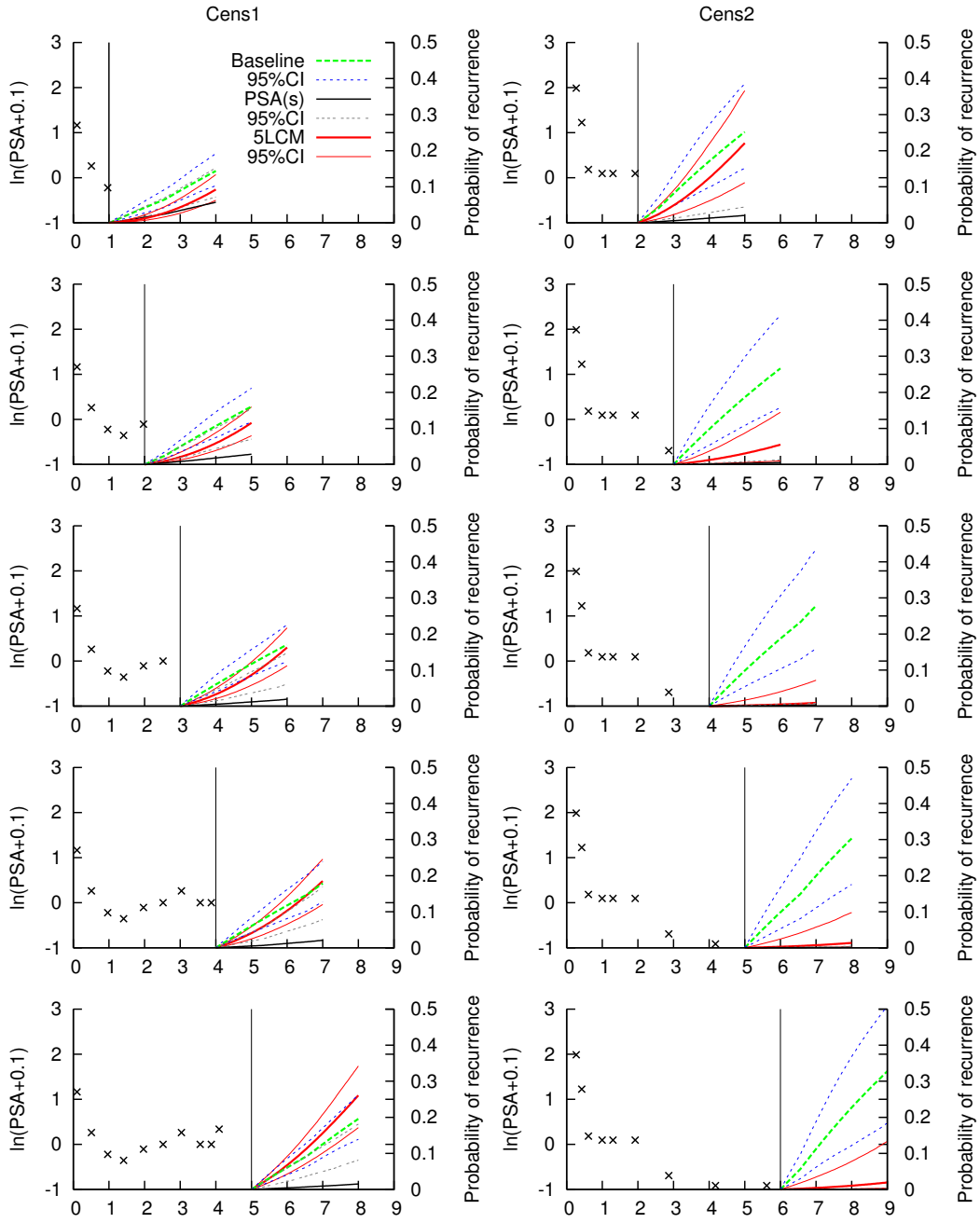

Figure S4. Individual prediction of prostate cancer recurrence for two patients from UM who were censored before any recurrence. Individual predictions are updated every year from 1 year after end of EBRT (or 2 for subject 6) until 5 years (or 6 years for subject 6). The $\mathbf{x}$ are the PSA measures used for the prediction and the vertical black solid line is the time s of prediction.