Comparison of Joint and Landmark Modeling for Predicting Cancer Progression in Men With Castration-Resistant Prostate Cancer
A Secondary Post Hoc Analysis of the PREVAIL Randomized Clinical Trial

Antonio Finelli, MD; Tomasz M. Beer, MD; Simon Chowdhury, PhD; Christopher P. Evans, MD; Karim Fizazi, MD, PhD; Celestia S. Higano, MD; Janet Kim, PhD; Lisa Martin, PhD; Fred Saad, MD; Olli Saarela, PhD

Abstract

IMPORTANCE Dynamic prediction models may help predict radiographic disease progression in advanced prostate cancer.

OBJECTIVE To assess whether dynamic prediction models aid prognosis of radiographic progression risk, using ongoing longitudinal prostate-specific antigen (PSA) assessments.

DESIGN, SETTING, AND PARTICIPANTS This prognostic study used data from the PREVAIL study to compare dynamic models for predicting disease progression. The PREVAIL study was a phase 3, multinational, double-blind, placebo-controlled randomized clinical trial of enzalutamide for prostate cancer conducted from September 2010 to September 2012. A total of 773 men with metastatic castration-resistant prostate cancer (CRPC) who had never received chemotherapy and had no baseline visceral disease were treated with enzalutamide. For illustration, 4 patients were selected based on PSA kinetics or PSA response in case studies. Data were analyzed from July 2018 to September 2019.

MAIN OUTCOMES AND MEASURES Landmark and joint models were applied to dynamically predict radiographic progression–freesurvival (PFS) using longitudinal PSA profile, baseline PSA, lactate dehydrogenase, and hemoglobin levels. The main outcome was radiographic PFS as predicted using landmark and joint models. Current PSA and PSA change were considered longitudinal biomarkers possibly associated with radiographic PFS. Predictive performance was evaluated using Brier score for overall prediction errors (PEs) and area under the curve (AUC) for model discriminative capability. Case studies were illustrated using dynamic prediction plots.

RESULTS A total of 763 men with metastatic CRPC treated with enzalutamide (mean [SD] age, 71.2 [8.5] years; mean [SD] body mass index [calculated as weight in kilograms divided by height in meters squared], 28.4 [4.6]) were included in the analysis. Current PSA and PSA change were associated with radiographic PFS in all models. Adding the PSA slope, compared with the landmark models using current PSA alone, improved the prediction of 5-month prospect of radiographic progression, with relative gains of 5.7% in prediction (PE [SE], 0.132 [0.008] vs 0.140 [0.008]) and 7.7% in discrimination (AUC [SE], 0.800 [0.018] vs 0.743 [0.018]) at month 10. In joint models with linear vs nonlinear PSA, prediction of 5-month risk of radiographic progression was improved when PSA trajectories were not assumed to be linear, with 8.0% relative gain in prediction (PE [SE], 0.150 [0.006] vs 0.138 [0.005]) and 19.4% relative gain in discrimination (AUC [SE], 0.653 [0.022] vs 0.780 [0.016]) at month 10. Predictions were affected by amount of marker information accumulated and prespecified assumptions. PSA changes affected progression risk more strongly at later vs earlier follow-up.

(continued)
CONCLUSIONS AND RELEVANCE This prognostic study found that prediction of radiographic PFS was improved when longitudinal PSA information was added to baseline variables. In a population of patients with metastatic CRPC, dynamic predictions using landmark or joint models may help identify patients at risk of progression.

Methods

The original PREVAIL trial (ClinicalTrials.gov identifier: NCT01212991) that served as a data source for this prognostic study was approved by independent review boards from participating sites in accordance with the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice. The abstract was presented at the annual meeting of the Society for Immunotherapy of Cancer, September 26-30, 2018, in Chicago, Illinois. The abstract was peer-reviewed and presented as a poster session at the annual meeting of the American Society for Radiation Oncology, September 1-5, 2018, in San Francisco, California.

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Clinical Practice Guideline. All patients provided written informed consent to participate in the PREVAIL study, which included consenting to future use of their study data for medical and pharmaceutical research, such as this post hoc analysis. This study was reported following the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) reporting guideline.

**Patient Data Set**

This prognostic study is a post hoc analysis using data from the PREVAIL study, a prospective, multinational phase 3, double-blind, placebo-controlled randomized clinical trial of 1717 men with chemotherapy-naïve metastatic castration-resistant prostate cancer (CRPC) conducted from September 2010 to September 2012. We included only patients without visceral disease who received enzalutamide (eTable 1 in the Supplement). The total sample included 773 patients (mean [SD] age at baseline, 71.2 [8.5] years; mean body mass index [BMI; calculated as weight in kilograms divided by height in meters squared], 28.4 [4.6]). At baseline, mean (SD) serum PSA was 137.9 (280.1) ng/mL (to convert to micrograms per liter, multiply by 1), mean (SD) lactate dehydrogenase was 204.7 (110.3) U/L (to convert to microkatal per liter, multiply by 0.0167), and mean hemoglobin was 12.98 (1.25) g/dL (to convert to grams per liter, multiply by 10) (eTable 1 in the Supplement).

Patient eligibility criteria for PREVAIL have been published elsewhere. Primary end points were radiographic progression-free survival (PFS), defined as the time from randomization to the first objective evidence of radiographic disease progression or death within 168 days after treatment discontinuation, and overall survival (OS). Radiographic PFS is described further in eAppendix 1 in the Supplement.

Selection for analysis included 763 patients and required the following conditions to be satisfied: for patients with radiographic progression, more than 1 marker history (ie, PSA level) was recorded before radiographic progression; for patients without radiographic progression, more than 1 marker history (ie, PSA level) was recorded until the last follow-up; and patients could not have any missing baseline PSA, lactate dehydrogenase, or hemoglobin data.

**Study Design**

Of 773 patients included, 763 were selected after data preprocessing steps required to fit the models. To avoid overfitting issues, the data from 763 patients were split into 2 parts for model development (training set, 610 patients) and to assess predictive performance (test set, 153 patients; reserved for new patients not used to train the models). This corresponds to model use in a clinical setting to identify patients with metastatic CRPC at greatest risk of progression and who may benefit most from imaging.

In the training set, 4349 PSA measurements were collected (median [range], 7 [1-187] assessments per patient), and 264 radiographic progressions occurred (43.3%), with median (interquartile range) survival of 22.0 (10.7-30.7) months. In the test set, 1092 PSA measurements were collected (median [range] 7 [1-14] assessments), and 63 radiographic progressions occurred (41.2%), with median (interquartile range) survival of 24.6 (11.0-not yet reached) months (eFigure 1 in the Supplement).

We selected 4 patients from the test set to represent distinct patterns of PSA change over time (Figure 1). Patients with radiographic progression toward study end without increasing PSA were considered to have good response; patients with radiographic progression early after study entry and increasing PSA were considered to have poor response. Typical case studies selected were: patient A (PSA decline followed by PSA increase), patient B (nonincreasing PSA), patient C (good response), and patient D (poor response). Dynamic predictions were calculated at different follow-up time points when PSA was measured.
Statistical Models

Model Specification and Variable Selection

Landmark and joint models were used to estimate the association structure between longitudinal biomarker (PSA) and event time (radiographic progression) and obtain dynamic predictions of patient outcomes (eTable 3 in the Supplement). To fit the models, baseline covariates were selected from candidate predictors of radiographic PFS by fitting a simple Cox proportional hazards model, with significance of associations determined at the α = .05 level (eTable 2 in the Supplement). The selected variables were baseline log transformed PSA, lactate dehydrogenase, and hemoglobin. The association of the longitudinal biomarker was included in outcome models using the current level and a measure of change or cumulative level.

To account for biomarker changes over time (eFigure 3 in the Supplement), individual-level PSA trajectories in joint modeling were assessed using linear mixed-effects (LME) and nonlinear mixed-effects (MEM-LQ) models, the latter including a quadratic time effect. Baseline hazard in joint models was approximated by B-spline basis functions or piecewise constant functions. The difference

Figure 1. Profiles of Typical Patient Cases Selected for Use in the Models

At baseline, patient A was aged in his 60s, with body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) 25.5; prostate-specific antigen 94.6 ng/mL (to convert to micrograms per liter, multiply by 1); lactate dehydrogenase, 272 U/L (to convert to microkatal per liter, multiply by 0.0167); hemoglobin, 12.9 g/dL (to convert to grams per liter, multiply by 10); Eastern Cooperative Oncology Group (ECOG) score, 0; total Gleason score, 7; and pain score (Brief Pain Inventory-Short Form item 3), 0. Patient B was aged in his 60s, with BMI, 31.3; PSA, 1.9 ng/mL; lactate dehydrogenase, 155 U/L; hemoglobin, 14.4 g/dL; ECOG score, 0; total Gleason score, 9; and pain score, 1. Patient C was aged in his 70s, with BMI, 27.2; PSA, 14.9 ng/mL; lactate dehydrogenase, 143 U/L; hemoglobin, 15.1 g/dL; ECOG score, 0; total Gleason score, 7; pain score, 0. Patient D was aged in his 60s, with BMI, 28.9; PSA, 73.5 ng/mL; lactate dehydrogenase, 170 U/L; hemoglobin, 14.0 g/dL; ECOG score, 1; total Gleason score, 8; and pain score, 0. Blue diamonds indicate observed PSA levels; vertical line, either the date a patient was reported to have a radiographic progression or the censored date. Patient A was censored at 18.60 months. Patient B was censored at 25.79 months. Patient C progressed at 24.64 months. Patient D progressed at 5.55 months.
between the 2 approximations was negligible, so dynamic predictions were calculated only for spline models. Overall model fit was assessed using log likelihood and Akaike information criterion.

Four models were selected to present case studies (eFigure 2 and eTable 4 in the Supplement): joint models with linear (JM2bs+LME) and nonlinear (JM2bs+MEM-LQ) longitudinal trajectories and landmark models with current PSA level (LMcurrent) and additional PSA change (LMslope). The final selection of these models was based on the values of log likelihood and Akaike information criterion, with a consideration of significance of the estimated parameters. Landmark models were fitted at landmark time points of 4, 7, and 10 months. Additional details about the model assumptions and prediction methods are given in eAppendix 2 in the Supplement.

**Statistical Analysis**

Predictive performance was evaluated using Brier score for overall prediction errors (PEs) (assessing the accuracy of radiographic PFS predictions) and area under the curve (AUC) for model discriminative capability between patients who would or would not experience radiographic progression within a specific time frame (eTable 5 and eTable 6 in the Supplement). Model performance was assessed by applying 5-fold cross-validation with 50 repetitions; additional details describing the 5-fold cross-validation are presented in eAppendix 2 in the Supplement.

For a comprehensive understanding of model performance, a percentage gain in landmark predictions was calculated as $100 \times \left( 1 - \frac{\text{LMslope PE}}{\text{LMcurrent PE}} \right)$, with a smaller value indicating better performance. Percentage gain in the measure of discriminative capability was calculated as $100 \times \left( \frac{\text{LMslope AUC}}{\text{LMcurrent AUC}} - 1 \right)$, with a larger value indicating better performance. The percentage gain in joint model predictions and the discriminative capability were assessed similarly.

Case studies reported predicted conditional probabilities $p_i(t | s)$ of radiographic PFS at time $t$ ($>s$) based on longitudinal marker information recorded to time $s$. Pointwise 95% prediction intervals (PIs) were obtained through simulation with 1000 Monte Carlo realizations of $p_i(t | s)$. The estimated effect of longitudinal marker process was illustrated using the percentage increase in a patient’s event risk, as calculated by

$$ (e^{\hat{y}_1} - 1) \times 100 $$

in which $\hat{y}_1$ is the estimated parameter associated with log PSA profile.

The fitting of landmark and joint models was implemented in the computing environment R version 3.4.3 (R Project for Statistical Computing) with function coxph(·) in the survival package for landmark models and function jointModel(·) in the JM package for joint models. The Monte Carlo simulation was performed using the built-in function survfitJM(·) in the JM package. Data were analyzed from July 2018 to September 2019.

**Results**

**Marker Associations**

The strength of associations between covariates and radiographic progression risk for joint (eTable 7 in the Supplement) and landmark (eTable 8 in the Supplement) models indicated that for both, hazard for radiographic progression was associated with both current value and slope of log PSA trajectories; for example, the estimated coefficient (SE) associated with the current value of log PSA was 0.395 (0.046) ($P < .001$) and slope of log PSA was 3.748 (0.504) ($P < .001$) when JM2bs+MEM-LQ was selected. With LMslope model and the landmark time point of 10 months, the estimated coefficient (SE) associated with the current value of log PSA was 0.254 (0.051) ($P < .001$) and slope of log PSA was 2.046 (0.382) ($P < .001$). Models incorporating time-dependent slopes provided larger likelihood and smaller Akaike information criterion values than their counterparts (eTable 7 and eTable 8 in the Supplement), suggesting that including extra slope parameters.
improved the model fit. In joint modeling, the effect of the longitudinal biomarker on event risk varied depending on how underlying PSA trajectories were modeled (MEM-LQ vs LME). Specifically, the association between the current log PSA and the risk for radiographic progression was 1.5-fold greater with the LME vs MEM-LQ model (eTable 7 in the Supplement). A unit increase in log PSA profile yielded a 48.4% increase in a patient’s event risk when data were fitted with JM2bs+MEM-LQ and an 83.7% increase in a patient’s event risk when data were fitted with JM2bs+LME.

In landmark models, strength of association between log PSA and event risk remained similar, irrespective of landmark times, particularly when LMcurrent model was considered. However, PSA changes were associated with the risk of radiographic progression more strongly at a later vs earlier follow-up, as indicated by an increased strength of associations between PSA slope and hazard for radiographic progression at 10 months vs 4 or 7 months (eTable 8 in the Supplement). Additional results obtained by fitting landmark models with different association structures are given in eTable 9 in the Supplement.

Predictive Performance of Models

Table 1 shows PE and AUC results for the 4 selected models. Other models are presented in eTable 5 and eTable 6 in the Supplement. Landmark models with PSA slope added to current PSA (LMslope) improved prediction of 5-month prospect of radiographic progression from 4-month follow-up; for example, there was a 5.7% relative gain in prediction (PE [SE], 0.132 [0.008] vs 0.140 [0.008]) and a 7.7% relative gain in discrimination (AUC [SE], 0.800 [0.018] vs 0.743 [0.018]) at month 10 (Table 1). Similarly, in joint models, when PSA trajectories were not assumed to be linear (ie, JM2bs+MEM-LQ model), compared with the linear joint model, predicting the 5-month prospect of radiographic progression was improved at 10-month follow-up by 8.0% in prediction (PE [SE], 0.150 [0.006] vs 0.138 [0.005]) and by 19.4% in discrimination (AUC [SE], 0.653 [0.022] vs 0.780 [0.016]) (Table 1). LMslope and JM2bs+MEM-LQ generally displayed smaller PEs and higher AUCs. In joint models, at less than 10 months follow-up, the 5-month progression prospect was predicted similarly, regardless of assuming linear vs nonlinear PSA, possibly owing to individual PSA trajectories showing a trend for PSA reduction to nadir and increase later in the follow-up period. Models did not have good discriminative ability at month 2 (Table 1), possibly because most patients had not yet experienced radiographic progression.

Case Studies: Survival Probabilities

We used 4 case studies to illustrate how changes in PSA profiles were reflected in changes in dynamic updates of radiographic PFS probabilities (Figure 1). Predicted conditional radiographic PFS

| Follow-up | JM2bs+LME | JM2bs+MEM-LQ | LMcurrent | LMslope |
|-----------|-----------|--------------|-----------|---------|
| 2-mo      | PE (SE)*  | 0.096 (0.005) | 0.095 (0.019) | 0.106 (0.008) | 0.107 (0.008) |
|           | AUC (SE)* | 0.626 (0.022) | 0.608 (0.025) | 0.614 (0.028) | 0.620 (0.028) |
| 4-mo      | PE (SE)*  | 0.128 (0.006) | 0.129 (0.021) | 0.125 (0.006) | 0.123 (0.007) |
|           | AUC (SE)* | 0.730 (0.017) | 0.751 (0.022) | 0.752 (0.020) | 0.769 (0.021) |
| 7-mo      | PE (SE)*  | 0.150 (0.006) | 0.150 (0.007) | 0.146 (0.005) | 0.144 (0.005) |
|           | AUC (SE)* | 0.706 (0.016) | 0.739 (0.014) | 0.751 (0.015) | 0.770 (0.014) |
| 10-mo     | PE (SE)*  | 0.150 (0.006) | 0.138 (0.005) | 0.140 (0.008) | 0.132 (0.008) |
|           | AUC (SE)* | 0.653 (0.022) | 0.780 (0.016) | 0.743 (0.018) | 0.800 (0.018) |

Abbreviations: AUC, area under the curve; JM2bs, joint model; LMcurrent, landmark model with current prostate-specific antigen level; LME, linear mixed effect; LMslope, landmark model with additional prostate-specific antigen change; MEM-LQ, nonlinear mixed effect; PE, prediction error.

* The PEs were calculated using the Brier score (range 0 to 1), which measures the discrepancy between the actual radiographic progression-free survival status (either 1 [not progressed] or 0 [progressed]) and the predicted conditional radiographic progression-free survival probability; with a score of 0 indicating the best prediction and a score of 1 indicating the failure of the model prediction.

* The values in the parenthesis are the estimated SEs across the 50 repetitions.
probability for clinically relevant windows of 2, 5, and 10 months at follow-up time points of 4 and 7 months are shown in Table 2; smaller probabilities indicate higher progression risk. Compared with patient B, whose PSA did not increase, patient A had a higher risk of radiographic progression. Similarly, patient D, who was classified as having poor response, had a higher risk of progression than patient C, who was classified as having good response. For both comparisons, predictions early after study entry seemed clinically less informative than at long-term follow-up.

In Figure 2 and eFigure 4 in the Supplement, we compare predictions of conditional survival probability at actual follow-up times using the estimation method of the selected models. Marker information and follow-up times for PSA measurement differed for each patient. For patient A, the rate of decrease in conditional survival probability became steeper in later vs early follow-up, irrespective of the model (Figure 2). For patient B, this rate was relatively consistent, regardless of follow-up and model, reflecting more stable serum PSA levels throughout the study (Figure 2).

Since patient C had good response, predicted probability of radiographic PFS toward study end was higher than for patient D, irrespective of follow-up stage (eFigure 4 in the Supplement). When marker information was limited owing to disease progression, the pattern of prediction was similar, irrespective of model selection. Predictions based on the standard Cox model are compared with the 4 selected models in eFigure 5 in the Supplement.

In joint modeling, another important factor for successfully predicting survival based on the time-dependent marker process is ensuring prediction of the longitudinal biomarker. In terms of model performance of mixed-effects models, MEM-LQ better captured the true evolution of marker information over time than LME. This could be corroborated by calculating mean squared PEs based on the training and test set (eTable 10 in the Supplement).

In Figure 3, using patient A as an example, for log PSA predicted by JM2bs-type models, the width of 95% pointwise PI, constructed based on Monte Carlo sample percentiles, becomes narrower as follow-up continues. This is because uncertainty in the prediction for later follow-up is reduced compared with the early phase, as more information was used. Also, MEM-LQ better captured the true dynamics of marker process. Predictions by JM2bs+MEM-LQ were relatively unstable vs JM2bs+LME, as indicated by the wider PI obtained from JM2bs+MEM-LQ.

### Table 2. Predicted Conditional Radiographic Progression–Free Survival Probability for Patients A, B, C, and D

| Model               | Patient A (PSA decline followed by PSA increase) | Patient B (nonincreasing PSA) | Patient C (good response) | Patient D (poor response) |
|---------------------|-----------------------------------------------|-------------------------------|---------------------------|---------------------------|
|                     | Prediction window, mo                         |                               |                           |                           |
|                     | 2      | 5     | 10   | 2      | 5      | 10   | 2      | 5      | 10   |
| 4-mo follow-up time | JM2bs+LME                                     | 0.919                         | 0.772                      | 0.547                      | 0.985 | 0.952 | 0.891 | 0.971 | 0.950 | 0.790 | 0.921 | 0.757 | 0.509 |
|                     | JM2bs+MEM-LQ                                  | 0.966                         | 0.898                      | 0.749                      | 0.995 | 0.987 | 0.969 | 0.982 | 0.954 | 0.885 | 0.922 | 0.789 | 0.557 |
|                     | LMcurrent                                     | 0.902                         | 0.801                      | 0.629                      | 0.981 | 0.955 | 0.905 | 0.964 | 0.918 | 0.828 | 0.888 | 0.758 | 0.544 |
|                     | LMslope                                       | 0.905                         | 0.806                      | 0.637                      | 0.980 | 0.953 | 0.900 | 0.965 | 0.919 | 0.828 | 0.892 | 0.765 | 0.549 |
| 7-mo follow-up time | JM2bs+LME                                     | 0.836                         | 0.692                      | 0.532                      | 0.966 | 0.932 | 0.891 | 0.928 | 0.858 | 0.767 | NA    | NA    | NA    |
|                     | JM2bs+MEM-LQ                                  | 0.925                         | 0.854                      | 0.661                      | 0.989 | 0.973 | 0.932 | 0.955 | 0.903 | 0.760 | NA    | NA    | NA    |
|                     | LMcurrent                                     | 0.867                         | 0.752                      | 0.606                      | 0.964 | 0.931 | 0.883 | 0.921 | 0.859 | 0.773 | NA    | NA    | NA    |
|                     | LMslope                                       | 0.873                         | 0.759                      | 0.613                      | 0.963 | 0.928 | 0.878 | 0.923 | 0.860 | 0.771 | NA    | NA    | NA    |

Abbreviations: JM2bs, joint model; LMcurrent, landmark model with current PSA level; LME, linear mixed effect; LMslope, landmark model with additional PSA change; MEM-LQ, nonlinear mixed effect; NA, not applicable; PSA, prostate-specific antigen.

* Smaller probabilities indicate higher progression risk.

† Predictions for Patient D were not implemented at the 7-month follow-up because the last follow-up for Patient D was at 5.5 months.
Discussion

The association between longitudinal biomarkers (eg, PSA profile) and outcomes has been established in multiple studies.²¹⁻²⁴ Despite such investigations, many models incorporate only a small portion of marker information or do not account for changes in underlying marker characteristics over time.²⁵⁻²⁷ A major statistical concern is analyzing both longitudinal and time-to-event data. This prognostic study applied landmark and joint models using patient data from the PREVAIL trial to identify associations between longitudinal PSA and time to radiographic progression of metastatic CRPC and showed that changes in individual PSA profile were associated with radiographic PFS. Specifically, we presented various types of dynamic predictions models that could be considered based on clinical interests, the selection and assessment of models, and interpretation of the estimated predictions using case studies.

In the joint and landmark models used in this study, radiographic progression risk was associated with the current value and slope of log PSA trajectories. Thus, we concluded that, in addition to absolute PSA, rate of PSA change also affects the prediction of radiographic progression, and corresponding terms should be included in models. Our results from joint modeling also indicated that full PSA trajectories could be better characterized by a MEM-LQ vs LME model. However, MEM-LQ increased variability in individual-level predictions, as indicated by the width of 95% PIs, perhaps reflecting the need for more longitudinal PSA data to produce reliable estimates of the quadratic effect of time.

Consistent with clinical observations, we found a higher risk of progression for a patient with a profile of PSA decline followed by PSA increase compared with a patient whose PSA did not increase and for a patient who had poor response vs one who had good response. While early PSA kinetics remain an important factor associated with progression from a clinical perspective, joint modeling

Figure 2. Individual Prostate-Specific Antigen (PSA) Evolution and Dynamic Predictions of Conditional Survival Probability for Patient A vs Patient B

JM2bs indicates joint model; LMcurrent, landmark model with current PSA level; LME, linear mixed effect; LMslope, landmark model with additional PSA change; and MEM-LQ, nonlinear mixed effect.
and landmarking predictions early after study entry may be less informative than at long-term follow-up because dynamic prediction is likely to be improved as marker information is accumulated. However, this also depends on collected data and sample size, underscoring the need to investigate a list of potentially meaningful models and assumptions before deriving a conclusion.

Figures 1-3 further demonstrated that predicting radiographic PFS in patients with metastatic CRPC could benefit from analysis of additional longitudinal PSA information, rather than baseline variables only, facilitating better determination of progression risk alongside the patients’ follow-up visits. This approach might provide clinicians with a useful evidence-based tool to better evaluate the impact of longitudinal PSA on prognosis, allowing a more optimized, and potentially more cost-effective, use of imaging and limiting the detrimental effects of more frequent imaging.2,3

Our work builds on studies from other areas, such as a cardiology study by Andrinopoulou et al,28 in which a joint model of longitudinal and time-to-event data were used for individualized dynamic event prediction in severe aortic stenosis. In that model, an increasing brain natriuretic peptide trend over time was a significant predictor of death, providing physicians with a potentially valuable evidence-based tool to evaluate the effect of this variable on prognosis.

Notably, a systematic review by Sudell et al29 of 65 studies using a range of joint models, software, and more than 10 disease areas (15.4% of which were cancer-related) noted an increased reporting of such models, but a lack of fully reported coefficients and precision estimates, highlighting that further work is needed.

**Limitations**

This study has some limitations, including examining only specific patient types; patient characteristics not included in dynamic prediction models may impact clinical decision-making. Also, the complexity of advanced statistical models requires clinician education. Moreover, larger data sets and longer follow-up may improve predictive capability. As models were trained in patients with metastatic CRPC who received enzalutamide treatment, results cannot be generalized to other populations. For example, aspects of postchemotherapy metastatic CRPC, such as PSA flares,30,31

**Figure 3. Dynamic Prediction of Conditional Survival Probability for Patient A**

**JM2bs + LME model: patient A, 2.8-mo follow-up**

**JM2bs + LME model: patient A, 4.6-mo follow-up**

**JM2bs + LME model: patient A, 16.7-mo follow-up**

**JM2bs + MEM-LQ model: patient A, 2.8-mo follow-up**

**JM2bs + MEM-LQ model: patient A, 4.6-mo follow-up**

**JM2bs + MEM-LQ model: patient A, 16.7-mo follow-up**

JM2bs indicates joint model; LME, linear mixed effect; MEM-LQ, nonlinear mixed effect; and PSA, prostate-specific antigen.
Conclusions

This prognostic study in a population with metastatic CRPC found that radiographic PFS predictions benefited from additional longitudinal PSA information compared with only baseline variables. While these models are not yet available in the clinic, dynamic predictions based on landmark or joint models could be used to improve identification of patients at risk of progression and help determine a personalized imaging schedule. This schedule could be based on the latest dynamic prediction and a prespecified decision threshold for radiographic PFS probability; for example, if the radiographic PFS probability was above a prespecified threshold, then imaging could be delayed and the decision reviewed when the prediction is updated at the next PSA measurement. However, the costs and benefits of adopting dynamic prediction-based personalized imaging schedules require further study.
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SUPPLEMENT.
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