Technical notes for PSA calculator (June 2008)

The calculator in this website is derived from research undertaken at the University of Michigan by Professors Jeremy Taylor, Donna Ankerst and Howard Sandler and other colleagues and students. This research was supported by a grant from the National Cancer Institute, Grant number CA110518, Grant title "PSA based early detection of prostate cancer recurrence". Aspects of this research is published in the following articles

- Pauler, D.K. and Finkelstein, D.M. (2002). Predicting time to prostate cancer recurrence based on joint models for non-linear longitudinal biomarkers and event time outcomes. *Statistics in Medicine* **21**, 3897–3911.
- Pauler DK, Finkelstein DM. Bayesian Joint Models for Longitudinal Prostate-Specific Antigen and Time to Prostate-Cancer Recurrence, 2003, submitted.
- Law, N.J., Taylor, J.M.G., Sandler, H.: The Joint Modelling of a Longitudinal Disease Progression Marker and the Failure Time Process in the Presence of Cure. Biostatistics, 3: 547-563, 2002.
- Yu M., Law N.J. ,Taylor J.M.G. , Sandler H.M. Joint Longitudinal-Survival-Cure Models and Their Application to Prostate Cancer. Statistica Sinica, 14: 835-862, 2004.
- Yu, M, Taylor, JMG, Sandler, H: Individualized Prediction In Prostate Cancer Studies Using a Joint Longitudinal-Survival-Cure Model. Journal of the American Statistical Association, in press, 2008.
- Taylor, J.M.G., Yu, M., Sandler, H.: Individualized Predictions of Disease Progression Following Radiation Therapy for Prostate Cancer. Journal of Clinical Oncology, 23 (4): 816-825, 2005.
- Proust-Lima C, Taylor JMG, Williams SC, Ankerst DP, Liu N, Kestin LL, Bae K and Sandler HM. Determinants of change of prostate-specific antigen over time and its association with recurrence following external beam radiation therapy of prostate cancer in 5 large cohorts. International Journal of Radiation Oncology Biology Physics, 2008, In Press.

Underpining the calculator is a statistical model. The research has consisted of developing this statistical model, developing a method for fitting this model to data and fitting this model to different datasets. The datasets that have been available for developing and validating this model have been collected at different locations. All the datasets include information on patients who have been treated with radiation therapy for localized prostate cancer. They come from the following sources, University of Michigan, Ann Arbor, Michigan; William Beaumont Hospital, Detroit, Michigan; Vancouver; Royal Brisbane Hospital, Brisbane, Australia; Peter MacCallum Cancer Center, Melbourne, Australia; Massachusetts General Hospital, Boston, Massachusetts; Radiation Therapy Oncology Group clinical trials 9406, 9202 and 9413. The generosity of the investigators to make these data available is appreciated.

There are two components to the statistical models, a longitudinal model for the patterns of PSA after radiation therapy and a model for the hazard of recurrence of clinical disease (local, regional or distant) after radiation therapy. There are three calculators on this website.

1. Predicting PSA.

This is a calculator which takes as input a patient's pretreatment information and predicts the likely pattern of PSA after treatment. It is assumed that radiation therapy is the only treatment the patient

will receive. This calculator is designed to be helpful for patients who are about to receive or did recently receive radiation therapy. It is based exactly on the longitudinal model and results presented in Proust-Lima et al 2008. The model is a random effects model with 3 random terms consisting of an intercept, a short term decrease and a long term rise. The random effects allow for heterogeneity between people in the likely PSA pattern. Pretreament values of PSA, Gleason and T-stage and the radiation dose also contribute to the intercept, decrease and rise in post-treatment PSA as fixed effects in the model. The model was fit to multiple datasets to arrive at the specific parameter estimates that are used in the calculator using the SAS procedure PROC MIXED. The ouput from the calculator gives the most likely pattern of PSA after radiation and therapy and also the possible ranges of patterns. The most likely pattern is obtained from the fixed effects. The range of PSA patterns is obtained by including both the fixed and random effects, where the random effects are drawn from the estimated random effect distribution.

2. Predicting future progression, for patients who did not receive planned androgen deprivation therapy as part of their initial treatment.

This is a calculator which takes as input a patient's pretreatment information and available post-treatment PSA values and predicts the likely future pattern of PSA and the chance of clinical recurrence within the next three years. It is assumed that radiation therapy is the only treatment the patient received. This calculator is designed to be helpful for patients who received radiation therapy more than one year ago and are being monitored at regular intervals by looking at PSA measurements. The calculator is based on a joint longitudinal and hazard model. The two component of the model are as described in Proust-Lima et al 2008, but the estimation method is different. The random effects part of the model is as described above for predicting PSA. The hazard part of the model is a time-dependent proportional hazards model, the covariates in this hazard model are expected current value and slope of PSA (derived from longitudinal model), pretreatment PSA, Gleason, Stage and radiation dose. The model also includes a time-dependent term to account for salvage hormone therapy, which occurred in the datasets. The baseline hazard was assumed to be piece-wise constant with change points at 1, 2, 4 and 6 years after radiation therapy. This joint model was fit to available datasets using Bayesian methods. A Markov chain Monte Carlo approach was used. The exact details of the algorithm have not been published, but are very similar to those in Yu et al 2007 and Ankerst et al 2008. The results from fitting this model to the datasets is a set of draws from the posterior distribution of the population parameters and the random effects. Five hundred of the random draws for the population parameters are saved. When a patient enters data on the website, his data is combined with these 500 draws to calculate a prediction for the patient. For each of the 500 sets of saved population parameters a MCMC algorithm is run to obtain a draw from the conditional posterior distribution of the random effect for the patient. The enlarged set of 500 parameter values are used to give prediction of future PSA values and the probability of clinical recurrence for the patient. The most likely pattern of PSA is provided (using the median of the 500) together with a range (point-wise 5th and 95th percentile of the 500). The probability of clinical recurrence within three years is also shown graphically, the best estimate is the median of the 500 predicted probabilities and the range is the 5th and 95th percentile of the 500 predicted probabilities.

3. Predicting future progression, for patients who did receive planned androgen deprivation therapy as part of their initial treatment.

This calculator is not ready yet.