Figure 1: **Trade-off between the timing and number of biopsies (burden) and time delay in detecting Gleason upgrading (shorter is better):** The true time of Gleason upgrading (increase in Gleason grade group from group 1 to 2 or higher) for the patient in this Figure is July 2008. When biopsies are scheduled annually (**Panel A**), upgrading is detected in January 2009 with a time delay of six months, and a total of four biopsies are scheduled. When biopsies are scheduled biennially (**Panel B**), upgrading is detected in January 2010 with a time delay of 18 months, and a total of three biopsies are scheduled. Since biopsies are conducted periodically, the time of upgrading is observed as an interval. For example, between Jan 2008-Jan 2009 in **Panel A** and between Jan 2008-Jan 2010 in **Panel B**. The phrase `Gleason grade group' is shortened to ‘Gleason grade’ for brevity.

Figure 2: **Motivation for upgrading-risk based personalized biopsy decisions:** To utilize patients' complete longitudinal data and results from previous biopsies in making biopsy decisions. For this purpose, we first process data using a statistical model and then utilize the patient-specific predictions for risk of Gleason upgrading to schedule biopsies. For example, Patient A (**Panel A**) and B (**Panel B**) had their latest biopsy at year one of follow-up (green vertical line). Patient A's prostate-specific antigen (PSA) profile remained stable until his current visit at year two, whereas patient B's profile has shown a rise. Consequently, patient B's upgrading-risk at the current visit (year two) is higher than that of patient A. This makes patient B a more suitable candidate for biopsy than Patient A. Risk estimates in this figure are only illustrative.

Figure 3: **Illustration of the joint model on a real PRIAS patient. Panel A**: Observed PSA (blue dots) and fitted PSA (solid blue line), log-transformed from ng/mL. **Panel B:** Estimated instantaneous velocity of PSA (log-transformed). **Panel C:** Predicted cause-specific cumulative upgrading-risk (95% credible interval shaded). Upgrading is defined as an increase in the Gleason grade group from group 1 [2] to 2 or higher. This upgrading-risk is calculated starting from the time of the latest negative biopsy (vertical green line at year one of follow-up). The joint model estimated it by combining the fitted PSA (log scale) value and instantaneous velocity, and time of the latest negative biopsy. Black dashed line at year two denotes the time of current visit.

Figure 4: **Model Validation Results. Panel A:** time-dependent area under the receiver operating characteristic curve or AUC (measure of discrimination). AUC at year one is not shown because we do not intend to replace the confirmatory biopsy at year one. **Panel B:** calibration-at-large indicates model miscalibration. This is because solid lines depicting the non-parameteric estimate of the cause-specific cumulative upgrading-risk [24], and dashed lines showing the average cause-specific cumulative upgrading-risk obtained using the joint model fitted to the PRIAS dataset, are not overlapping. Recalibrating the baseline hazard of upgrading resolved this issue (Supplementary Figure 6). Full names of Cohorts are *PRIAS:* Prostate Cancer International Active Surveillance, *Toronto:* University of Toronto Active Surveillance, *Hopkins:* Johns Hopkins Active Surveillance, *MSKCC:* Memorial Sloan Kettering Cancer Center Active Surveillance, *KCL:* King's College London Active Surveillance, *MUSIC:* Michigan Urological Surgery Improvement Collaborative Active Surveillance, *UCSF:* University of California San Francisco AS.

Figure 5: **Illustration of personalized and fixed schedules of biopsies for patient from Figure 3**. **Panel A:** Predicted cumulative upgrading-risk (95% credible interval shaded). **Panel B:** Different biopsy schedules with a red `B' indicating a future biopsy. Risk: 5% and Risk: 10% are personalized schedules in which a biopsy is planned whenever the conditional cause-specific cumulative upgrading-risk is above 5% or 10% risk, respectively. Smaller risk thresholds lead to more frequently planned biopsies. Green vertical line at year one is the time of the latest negative biopsy. Black dashed line at year two denotes the time of the current visit. **Panel C:** Expected time delay in detecting upgrading (years) if patient progresses before year six. The maximum time delay with limited adverse consequences is three years [11]. A compulsory biopsy was scheduled at year six (maximum biopsy scheduling time in PRIAS, Supplementary C) in all schedules for a meaningful comparison between delays.