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Web-based Supplementary Materials for A Bayesian Screening Approach for Hepatocellular Carcinoma using Multiple Longitudinal Biomarkers

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Web Appendix A. HALT-C Trial

Web Appendix A.1 *Analysis data description*

HCV cirrhosis patients are at high risk for HCC and are recommended to undergo regular surveillance. Within the HALT-C Trial, 427 patients were diagnosed with cirrhosis at the baseline biopsy. We excluded 18 patients not diagnosed with HCC but with less than 12 months of follow-up. Our analysis dataset consists of 361 control patients who were not diagnosed with HCC during a median follow-up period of 78 months (range 15-109 months) and 48 confirmed HCC cases. In Web Figure 1, we illustrate the subsets of patients in the HALT-C Trial and the biomarkers measured during follow-up. We have local laboratory tests for AFP at all the patient visits. DCP was measured at a central laboratory as part of an ancillary study, which used stored samples collected during the first 42 months post-randomization as per the trial protocol. We excluded biomarker data from visits that took place during the last 12 months of follow-up in the controls to ensure that they did not have HCC when biomarker data was collected.

[Web Figure 1 about here.]

In Web Figure 2 and 3 we plot the individual trajectories of AFP and DCP, respectively, for all 48 HCC cases in the analysis cohort. In Web Figure 4 and 5 we plot the individual trajectories of AFP and DCP, respectively, in 48 randomly selected patients that have at least 12 months of follow-up and do not develop HCC during the study.

[Web Figure 2 about here.]

[Web Figure 3 about here.]

[Web Figure 4 about here.]

[Web Figure 5 about here.]

Web Appendix A.2 *Exploratory data analysis*

The structure of our proposed model was based on initial exploratory data analysis of AFP and DCP in cases and controls from the HALT-C Trial. In Web Figure 6, we plot the histograms of the distribution of AFP and DCP before and after logarithmic transfromations in control patients from the HALT-C Trial. In our model we assume that these transformed markers have a normal distribution.

[Web Figure 6 about here.]

Next we evaluated whether the patient specific mean biomarker levels in the absence of disease, θ_{ik}, were correlated. For each control patient in the HALT-C Trial we calculated their average log(AFP) and log(DCP+1) values. In Web Figure 7, we observe that there is minimal correlation between the mean log(AFP) and log(DCP+1) levels in control patients. Therefore we conclude that a simpler model that does not specify a joint prior for θ_{ik} is suitable for our analysis.

[Web Figure 7 about here.]

Next we considered the biomarker levels within two years of clinical diagnosis in HCC cases in the HALT-C Trial. For each patient we fitted a simple linear model for both log(AFP) and log(DCP+1) when patients had two or more observations within the two years prior to clinical diagnosis. The subject specific slope is a rough estimate of γ_{ik} for each biomarker. In Web Figure 8, we observe that there is minimal correlation between the slopes log(AFP) and log(DCP+1) levels in case patients with sufficient data. Therefore we conclude that a simpler model that does not specify a joint prior for γ_{ik} is suitable for our analysis.

[Web Figure 8 about here.]

In the HALT-C analysis, we chose the values of the hyperparameters in the prior distributions for the biomarker specific parameters during exploratory analysis and they are listed in Web Table 1.

The hyperparameters for $\mu_{\theta 1}$ and $\mu_{\theta 2}$ were chosen after fitting a linear mixed model for AFP and DCP respectively in control patients from the HALT-C Trial. The hyperparameters for $\mu_{\gamma 1}$ and $\mu_{\gamma 2}$ were chosen by examining the trajectories of AFP in HALT-C HCC cases within two-years prior to clinical diagnosis (see Web Figure 8). The hyperparameters for $\mu_{\tau 1}$ and $\mu_{\tau 2}$ were chosen to reflect prior knowledge that HCC is a fast growing cancer and therefore on average we expect mean onset to be within 1 year prior to clinical diagnosis. For $\sigma_{\tau 1}$ and $\sigma_{\tau 2}$, we set the hyperparameters to have the prior expected value of 0.75 such that all the values in the support (2 years prior to clinical diagnosis) of the changepoint parameter τ have non-negligible prior probability. For $\sigma_{\theta k}$ and $\sigma_{\gamma k}$ $(k = 1, 2)$, the hyperparameters we have chosen encourage similar values for slope and intercepts across subjects (note that these priors concentrate on very small values). We note that in Web Figure 18, the posterior distribution for most of these parameters are not concentrated around values that have high prior probability overall highlighting the weak influence of the hyperparameters on the posterior inference.

[Web Table 1 about here.]

Web Appendix A.3 *MCMC Convergence*

[Web Figure 9 about here.]

[Web Figure 10 about here.]

Web Appendix A.4 *Model assessment*

[Web Figure 11 about here.]

[Web Figure 12 about here.]

[Web Figure 13 about here.]

Web Appendix A.5 *Prior sensitivity*

The sensitivity of the results to the prior distributions was assessed by evaluating how the mean posterior probability of an AFP and DCP changepoint varied in the 48 HCC cases as the prior distributions for the parameters η_I, μ_I, μ_γ and μ_τ were changed. The posterior probability of a changepoint is an important component of the model fit that affects the performance of the screening algorithm. In Figures 3-6, we plot the posterior probability of an AFP and DCP changepoint under three different prior distributions for each parameter.

For the MRF parameter η_I, our assumed prior is a Beta distribution with mean of 0.1. In Web Figure 14, we consider Beta priors for η_I where the mean is 0.5 and 0.8 while keeping the standard deviation similar to that of the assumed prior (SD=0.042). As we increase the mean of the prior for η_I, there is little effect on the posterior probability of a changepoint for those patients with a very low posterior probability of a changepoint to start with. For those with a high posterior probability of a changepoint for one marker, increasing parameter η_I increases the posterior probability of a changepoint for the other marker. This is expected since we are increasing the strength of the connection between the markers. For those with borderline values, a higher prior mean for η_I pulls both posterior probabilities of a changepoints upwards.

For the other MRF parameter μ_I, we evaluated how the posterior probabilities of a changepoint varied when the mean of the Beta prior of the logistic transformation of μ_I was decreased to 0.4 or increased to 0.6, while keeping the standard deviation of the Beta prior similar. In Web Figure 15 we see that for μ_I, there is more sensitivity in the posterior probability of changepoints to the changes but the rankings of the patients are mostly preserved. Spearman's rank correlation was 0.994-0.997 for the posterior probability of an AFP changepoint and 0.945-0.967 for the posterior probability of a DCP changepoint.

In Web Figure 16 we observe that the posterior probability of changepoints are highly sensitive to the prior of μ_γ. When we decreased the mean of the prior to 2 the posterior probability of changepoints for AFP and DCP increased and conversely when we increased the mean of the prior to 3.5 the posterior probability of changepoints for AFP and DCP decreased. The inverse relationship is expected since a flatter slope would potentially apply to more HCC cases. The choice of prior for the slope parameters in most studies of this type is very important since it is rare to have sufficient data on cases to estimate these well. The rankings of the patients for the posterior probability of an AFP changepoint are preserved (Spearman's rank correlation: 0.990-0.995) but that is not the case for the posterior probability of an DCP changepoint (Spearman's rank correlation: 0.618-0.845). Since we have reduced follow-up for DCP, we expect that the prior selection is even more important for this marker.

For μ_τ (Web Figure 17), we decreased the mean of the prior to 0.5 and increased it to 1.5. In most patients we observed minimal sensitivity of the posterior probability of changepoints to these changes.

[Web Figure 14 about here.]

[Web Figure 15 about here.]

[Web Figure 16 about here.]

[Web Figure 17 about here.]

[Web Figure 18 about here.]

Web Appendix A.6 *Cross-validated analysis*

[Web Figure 19 about here.]

For each method, we calculate the time of the first positive screen during the entire screening period, within two years of clinical diagnosis and within one year of clinical

diagnosis. In Web Table 2-4, the $(i,j)^{th}$ entry corresponds to the empirical mean percentage of times the i^{th} method has a positive screen first and the $(j,i)^{th}$ entry to the empirical mean percentage of times the j^{th} method has a positive screen first. The empirical mean percentage of times where the i^{th} and the j^{th} methods have a positive screen at the same time is 100 - $(i,j)^{th}$ entry - $(j,i)^{th}$ entry. For each comparison, we have highlighted (bold text) the higher percentage.

[Web Table 2 about here.]

[Web Table 3 about here.]

[Web Table 4 about here.]

Web Appendix B. Methods

Web Appendix B.1 *Markov Chain Monte Carlo Procedure: Computational Algorithm*

Step 0: Initialize parameters:

(1) $\boldsymbol{\theta}_k^{(0)} = \{\theta_{ik}^{(0)},\, i = 1,\ldots,N\},\, k = 1,\ldots,K$

(2) $\mu_{\theta k}^{(0)},\, k = 1,\ldots,K$

(3) $\sigma_{\theta k}^{2(0)},\, k = 1,\ldots,K$

(4) $\sigma_{k}^{2(0)},\, k = 1,\ldots,K$

(5) $\mathbf{I}_k^{(0)} = \{I_{ik}^{(0)},\, i = n_0+1,\ldots,N\},\, k = 1,\ldots,K$

(6) $\mu_I^{(0)}$

(7) $\eta_I^{(0)}$

(8) $\boldsymbol{\gamma}_k^{(0)} = \{\gamma_{ik}^{(0)}, i = n_0+1,\ldots,N : I_{ik} = 1\},\, k = 1,\ldots,K$

(9) $\mu_{\gamma k},\, k = 1,\ldots,K$

(10) $\sigma_{\gamma k}^2,\, k = 1,\ldots,K$

(11) $\boldsymbol{\tau}_k^{(0)} = \{\tau_{ik}^{(0)}, i = n_0+1,\ldots,N : I_{ik} = 1\},\, k = 1,\ldots,K$

Step 1-S: Update parameters for $s \in \{1, \ldots, S\}$ and $s^* = 1 + 3(s-1)$.

(1) Update $\mu_{\theta k}$, $k = 1, \ldots, K$: Sample $\mu_{\theta k}^{(s)}$ from $N(\mu_{0k^*}, \sigma_{0k^*}^2)$, where $\mu_{0k^*} = \frac{\sigma_{\theta k}^{2(s-1)}}{\sigma_{\theta k}^{2(s-1)} + N\sigma_{0k}^2}\mu_{0k} + \frac{\sigma_{0k}^2}{\sigma_{\theta k}^{2(s-1)} + N\sigma_{0k}^2}\sum_{i=1}^N \theta_{ik}^{(s-1)}$ and $\sigma_{0k^*}^2 = \frac{\sigma_{\theta k}^{2(s-1)}\sigma_{0k}^2}{\sigma_{\theta k}^{2(s-1)} + N\sigma_{0k}^2}$.

(2) Update $\sigma_{\theta k}^2$, $k = 1, \ldots, K$: Sample $\sigma_{\theta k}^{2(s)}$ from $IG(a_{\theta_k^*}, b_{\theta_k^*})$, where $a_{\theta_k^*} = a_{\theta k} + N/2$ and $b_{\theta_k^*} = b_{\theta k} + \frac{1}{2}\sum_{i=1}^N (\theta_{ik}^{(s-1)} - \mu_{\theta k}^{(s)})^2$.

(3) Update σ_k^2, $k = 1, \ldots, K$: Sample $\sigma_k^{2(s)}$ from $IG(a_{\sigma_k}, b_{\sigma_k})$, where $a_{\sigma k} = \frac{1}{2}\sum_{i=1}^N J_i$, $b_{\sigma k} = \frac{1}{2}\sum_{i=1}^N \sum_{j=1}^{J_i} (Y_{ijk} - \theta_{ijk}^*)^2$ and

$$\theta_{ijk}^* = \begin{cases} \theta_{ik}^{(s-1)} & \text{if } D_i = 0 \text{ or } (D_i = 1 \text{ and } I_{ik}^{(s^*-1)} = 0) \\ \theta_{ik}^{(s-1)} + \gamma_{ik}^{(s^*-1)}(t_{ij} - \tau_{ik}^{(s^*-1)})^+ & \text{if } D_i = 1 \text{ and } I_{ik}^{(s^*-1)} = 1 \end{cases}$$

(4) Update μ_I:

(a) Generate μ_I^* from its proposal distribution $J_{\mu_I}(\mu_I | \mu_I^{(s-1)}) = N(\mu_I^{(s-1)}, \delta_{\mu_I}^2)$.

(b) Compute acceptance ratio

$$\log(r) = \min\left[\log\left\{\frac{P(\mathbf{I}^{(s^*-1)}|\mu_I^*, \eta_I^{(s-1)})P(\mu_I^*|p_1,p_2)}{P(\mathbf{I}^{(s^*-1)}|\mu_I^{(s-1)}, \eta_I^{(s-1)})P(\mu_I^{(s-1)}|p_1,p_2)}\right\}, 0\right]$$
$$= \min[\log\{P(\mathbf{I}^{(s^*-1)}|\mu_I^*, \eta_I^{(s-1)})\} + \log\{P(\mu_I^*|p_1,p_2)\} - \log\{P(\mathbf{I}^{(s^*-1)}|\mu_I^{(s-1)}, \eta_I^{(s-1)})\}$$
$$- \log\{P(\mu_I^{(s-1)}|p_1,p_2)\}, 0]$$

$$\text{where } P(\mathbf{I}|\mu_I, \eta_I) = \prod_{i=n_0+1}^n \exp\left\{\mu_I\left(\sum_{k=1}^K I_{ik}\right) + \eta_I\left(\sum_{k=1}^{K-1}\sum_{k'=k+1}^K I_{ik}I_{ik'}\right)\right\} \times c$$
$$\text{and } c^{-1} = \sum_{\tilde{I}\in\mathscr{I}} \exp\left\{\mu_I\left(\sum_{k=1}^K \tilde{I}_k\right) + \eta_I\left(\sum_{k=1}^{K-1}\sum_{k'=k+1}^K \tilde{I}_k\tilde{I}_{k'}\right)\right\}$$
$$\text{for } \mathscr{I} = \text{All possible combinations of vector } \tilde{I} \text{ with binary } \tilde{I}_k$$
$$\text{and } P(\mu_I|p_1,p_2) = P_{\text{Beta}}\left\{\frac{\exp(\mu_I)}{1+\exp(\mu_I)}\middle| p_1,p_2\right\}\left|\frac{d}{d\mu_I}\frac{\exp(\mu_I)}{1+\exp(\mu_I)}\right|$$
$$= P_{\text{Beta}}\left\{\frac{\exp(\mu_I)}{1+\exp(\mu_I)}\middle| p_1,p_2\right\}\frac{\exp(\mu_I)}{\{1+\exp(\mu_I)\}^2}$$

(c) Generate $u \sim \text{Uniform}(0,1)$. If $\log(u) < \log(r)$ set $\mu_I^{(s)} = \mu_I^*$; otherwise set $\mu_I^{(s)} = \mu_I^{(s-1)}$

(5) Update η_I:

(a) Generate η_I^* from its proposal distribution $J_{\eta_I}(\eta_I|\eta_I^{(s-1)}) = \text{Beta}(\tilde{a}, \tilde{b})$, where $\tilde{a}$ and $\tilde{b}$ are chosen so that the mean and variance of the Beta distribution are $\eta_I^{(s-1)}$ and $\delta_{\eta_I}^2$ respectively.

(b) Compute acceptance ratio

$$\log(r) = \min\left[\log\left\{\frac{P(\mathbf{I}^{(s^*-1)}|\mu_I^{(s)}, \eta_I^*)P(\eta_I^*|p_3,p_4)}{P(\mathbf{I}^{(s^*-1)}|\mu_I^{(s)}, \eta_I^{(s-1)})P(\eta_I^{(s-1)}|p_3,p_4)}\frac{J_{\eta_I}(\eta_I^{(s-1)}|\eta_I^*)}{J_{\eta_I}(\eta_I^*|\eta_I^{(s-1)})}\right\}, 0\right]$$
$$= \min[\log\{P(\mathbf{I}^{(s^*-1)}|\mu_I^{(s)}, \eta_I^*)\} + \log\{P(\eta_I^*|p_3,p_4)\} - \log\{P(\mathbf{I}^{(s^*-1)}|\mu_I^{(s)}, \eta_I^{(s-1)})\}$$
$$- \log\{P(\eta_I^{(s-1)}|p_3,p_4)\} + \log\{J_{\eta_I}(\eta_I^{(s-1)}|\eta_I^*)\} - \log\{J_{\eta_I}(\eta_I^*|\eta_I^{(s-1)})\}, 0]$$

(c) Generate $u \sim \text{Uniform}(0,1)$. If $\log(u) < \log(r)$ set $\eta_I^{(s)} = \eta_I^*$; otherwise set $\eta_I^{(s)} = \eta_I^{(s-1)}$

(6) Update $\mu_{\gamma k}, k = 1, \ldots, K$: Sample $\mu_{\gamma k}^{(s)}$ from $N(\mu_{1k^*}, \sigma_{1k^*}^2)$, where $\mu_{1k^*} = \frac{\sigma_{\gamma k}^{2(s-1)}}{\sigma_{\gamma k}^{2(s-1)} + n_{Ik}\sigma_{1k}^2}\mu_{1k} + \frac{\sigma_{1k}^2}{\sigma_{\gamma k}^{2(s-1)} + n_{Ik}\sigma_{1k}^2}\sum_{i=1}^{n_{Ik}}\log(\gamma_{ik}^{(s^*-1)})$, $\sigma_{1k^*}^2 = \frac{\sigma_{\gamma k}^{2(s-1)}\sigma_{1k}^2}{\sigma_{\gamma k}^{2(s-1)} + n_{Ik}\sigma_{1k}^2}$ and $n_{Ik} = \sum_{i=n_0+1}^{N} I_{ik}^{(s^*-1)}$.

(7) Update $\sigma_{\gamma k}^2$, $k = 1, \ldots, K$: Sample $\sigma_{\gamma k}^{2(s)}$ from $IG(a_{\gamma_k^*}, b_{\gamma_k^*})$, where $a_{\gamma_k^*} = a_{\gamma k} + n_{Ik}/2$, $b_{\gamma_k^*} = b_{\gamma k} + \frac{1}{2}\sum_{i=1}^{n_{Ik}}\{\log(\gamma_{ik}^{(s^*-1)}) - \mu_{\gamma k}^{(s)}\}^2$ and $n_{Ik} = \sum_{i=n_0+1}^{N} I_{ik}^{(s^*-1)}$.

(8) Update $\mu_{\tau k}$, $k = 1, \ldots, K$:

(a) Generate $\mu_{\tau k}^*$ from its proposal distribution $J_{\mu_{\tau k}}(\mu_{\tau k}|\mu_{\tau k}^{(s-1)}) = N(\mu_{\tau k}^{(s-1)}, \delta_{\mu_{\tau k}}^2)$.

(b) Compute acceptance ratio

$$\log(r) = \min\left[\log\left\{\frac{P(\boldsymbol{\tau}_k^{(s^*-1)}|\mu_{\tau k}^*, \sigma_{\tau k}^{2(s-1)})P(\mu_{\tau k}^*|\mu_{2k}, \sigma_{2k}^2)}{P(\boldsymbol{\tau}_k^{(s^*-1)}|\mu_{\tau k}^{(s-1)}, \sigma_{\tau k}^{2(s-1)})P(\mu_{\tau k}^{(s-1)}|\mu_{2k}, \sigma_{2k}^2)}\right\}, 0\right]$$
$$= \min[\log\{P(\boldsymbol{\tau}_k^{(s^*-1)}|\mu_{\tau k}^*, \sigma_{\tau k}^{2(s-1)})\} + \log\{P(\mu_{\tau k}^*|\mu_{2k}, \sigma_{2k}^2)\}$$
$$- \log\{P(\boldsymbol{\tau}_k^{(s^*-1)}|\mu_{\tau k}^{(s-1)}, \sigma_{\tau k}^{2(s-1)})\} - \log\{P(\mu_{\tau k}^{(s-1)}|\mu_{2k}, \sigma_{2k}^2)\}, 0]$$

(c) Generate $u \sim \text{Uniform}(0,1)$. If $\log(u) < \log(r)$ set $\mu_{\tau k}^{(s)} = \mu_{\tau k}^*$; otherwise set $\mu_{\tau k}^{(s)} = \mu_{\tau k}^{(s-1)}$

(9) Update $\sigma_{\tau k}^2$, $k = 1, \ldots, K$:

(a) Generate $\sigma_{\tau k}^{2*}$ from its proposal distribution $J_{\sigma_{\tau k}^2}(\sigma_{\tau k}^2|\sigma_{\tau k}^{2(s-1)}) = TN_{[0,\infty]}(\sigma_{\tau k}^{2(s-1)}, \delta_{\sigma_{\tau k}}^2)$.

(b) Compute acceptance ratio

$$\log(r) = \min\left[\log\left\{\frac{P(\boldsymbol{\tau}_k^{(s^*-1)}|\mu_{\tau k}^{(s)}, \sigma_{\tau k}^{2*})P(\sigma_{\tau k}^{2*}|a_{\tau k}, b_{\tau k})}{P(\boldsymbol{\tau}_k^{(s^*-1)}|\mu_{\tau k}^{(s)}, \sigma_{\tau k}^{2(s-1)})P(\sigma_{\tau k}^{2(s-1)}|a_{\tau k}, b_{\tau k})}\frac{J_{\sigma_{\tau k}^2}(\sigma_{\tau k}^{2(s-1)}|\sigma_{\tau k}^{2*})}{J_{\sigma_{\tau k}^2}(\sigma_{\tau k}^{2*}|\sigma_{\tau k}^{2(s-1)})}\right\}, 0\right]$$
$$= \min[\log\{P(\boldsymbol{\tau}_k^{(s^*-1)}|\mu_{\tau k}^{(s)}, \sigma_{\tau k}^{2*})\} + \log\{P(\sigma_{\tau k}^{2*}|a_{\tau k}, b_{\tau k})\} - \log\{P(\boldsymbol{\tau}_k^{(s^*-1)}|\mu_{\tau k}^{(s)}, \sigma_{\tau k}^{2(s-1)})\}$$
$$- \log\{P(\sigma_{\tau k}^{2(s-1)}|a_{\tau k}, b_{\tau k})\} + \log\{J_{\sigma_{\tau k}^2}(\sigma_{\tau k}^{2(s-1)}|\sigma_{\tau k}^{2*})\} - \log\{J_{\sigma_{\tau k}^2}(\sigma_{\tau k}^{2*}|\sigma_{\tau k}^{2(s-1)})\}, 0]$$

(c) Generate $u \sim \text{Uniform}(0, 1)$. If $\log(u) < \log(r)$ set $\sigma_{\tau k}^{2(s)} = \sigma_{\tau k}^{2*}$; otherwise set $\sigma_{\tau k}^{2(s)} = \sigma_{\tau k}^{2(s-1)}$

(10) Update each θ_{ik}, $i = 1, \ldots, N$ and $k = 1, \ldots, K$:

- If $D_i = 0$, sample $\theta_{ik}^{(s)}$ from $N(\mu_{\theta k^*}, \sigma_{\theta k^*}^2)$, where $\mu_{\theta_k^*} = \frac{\sigma_k^{2(s)}}{\sigma_k^{2(s)}+J_i\sigma_{\theta k}^{2(s)}}\mu_{\theta k}^{(s)} + \frac{\sigma_{\theta k}^{2(s)}}{\sigma_k^{2(s)}+J_i\sigma_{\theta k}^{2(s)}}\sum_{j=1}^{J_i} Y_{ijk}$ and $\sigma_{\theta_k^*} = \frac{\sigma_k^{2(s)}\sigma_{\theta k}^{2(s)}}{\sigma_k^{2(s)}+J_i\sigma_{\theta k}^{2(s)}}$.
- If $D_i = 1$ and $I_{ik}^{(s^*-1)} = 0$, sample $\theta_{ik}^{(s)}$ from $N(\mu_{\theta k^*}, \sigma_{\theta k^*}^2)$, where $\mu_{\theta_k^*} = \frac{\sigma_k^{2(s)}}{\sigma_k^{2(s)}+J_i\sigma_{\theta k}^{2(s)}}\mu_{\theta k}^{(s)} + \frac{\sigma_{\theta k}^{2(s)}}{\sigma_k^{2(s)}+J_i\sigma_{\theta k}^{2(s)}}\sum_{j=1}^{J_i} Y_{ijk}$ and $\sigma_{\theta_k^*}^2 = \frac{\sigma_k^{2(s)}\sigma_{\theta k}^{2(s)}}{\sigma_k^{2(s)}+J_i\sigma_{\theta k}^{2(s)}}$.
- If $D_i = 1$ and $I_{ik}^{(s^*-1)} = 1$, sample $\theta_{ik}^{(s)}$ from $N(\mu_{\theta k^*}, \sigma_{\theta k^*}^2)$, where $\mu_{\theta_k^*} = \frac{\sigma_k^{2(s)}}{\sigma_k^{2(s)}+J_i\sigma_{\theta k}^{2(s)}}\mu_{\theta k}^{(s)} + \frac{\sigma_{\theta k}^{2(s)}}{\sigma_k^{2(s)}+J_i\sigma_{\theta k}^{2(s)}}\sum_{j=1}^{J_i}\{Y_{ijk} - \gamma_{ik}^{(s^*-1)}(t_{ij} - \tau_{ik}^{(s^*-1)})^+\}$ and $\sigma_{\theta_k^*}^2 = \frac{\sigma_k^{2(s)}\sigma_\theta^{2(s)}}{\sigma_k^{2(s)}+J_i\sigma_\theta^{2(s)}}$.

(11) Update $\mathbf{I}$, $\boldsymbol{\gamma}$ and $\boldsymbol{\tau}$.

(a) Update each I_{ik}, $i = n_0 + 1, \ldots, N$ and $k = 1, \ldots, K$:

If $I_{ik}^{(s^*-1)} = 0$,

(1) Generate γ_{ik}^* from its prior $\log(\gamma_{ik}) \sim N(\mu_{\gamma k}^{(s)}, \sigma_{\gamma k}^{2(s)})$

(2) Generate τ_{ik}^* from its prior $\tau_{ik} \sim TN_{[d_i-\tau_k^*, d_i]}(d_i - \mu_{\tau k}^{(s)}, \sigma_{\tau k}^{2(s)})$

(3) Compute acceptance ratio

$$\log(r) = \min\left[\log\left\{\frac{P(\mathbf{Y}_{ik}|I_{ik}=1,\theta_{ik}^{(s)},\sigma_k^{2(s)},\gamma_{ik}^*,\tau_{ik}^*)}{P(\mathbf{Y}_{ik}|I_{ik}=0,\theta_{ik}^{(s)},\sigma_k^{2(s)})}\frac{\pi_{ik}}{1-\pi_{ik}}\right\},0\right]$$
$$= \min[\log\{P(\mathbf{Y}_{ik}|I_i=1,\theta_{ik}^{(s)},\sigma_k^{2(s)},\gamma_{ik}^*,\tau_{ik}^*)\}$$
$$-\log\{P(\mathbf{Y}_{ik}|I_{ik}=0,\theta_{ik}^{(s)},\sigma_k^{2(s)})\}+\log\{\pi_{ik}\}-\log\{1-\pi_{ik}\},0]$$
$$\text{where } \pi_{ik} = \frac{\exp\left\{\mu_I^{(s)}+\eta_I^{(s)}\left(\sum_{k'<k}I_{ik'}^{(s^*)}+\sum_{k'>k}I_{ik'}^{(s^*-1)}\right)\right\}}{1+\exp\left\{\mu_I^{(s)}+\eta_I^{(s)}\left(\sum_{k'<k}I_{ik'}^{(s^*)}+\sum_{k'>k}I_{ik'}^{(s^*-1)}\right)\right\}}$$

(4) Generate $u \sim \text{Uniform}(0,1)$. If $\log(u) < \log(r)$ set $I_{ik}^{(s^*)} = 1$, $\gamma_{ik}^{(s^*)} = \gamma_{ik}^*$, and $\tau_{ik}^{(s^*)} = \tau_{ik}^*$; otherwise set $I_{ik}^{(s^*)} = 0$.

If $I_{ik}^{(s^*-1)} = 1$,

(1) Compute acceptance ratio

$$\log(r) = \min\left[\log\left\{\frac{P(\mathbf{Y}_{ik}|I_{ik}=0,\theta_{ik}^{(s)},\sigma_k^{2(s)})}{P(\mathbf{Y}_{ik}|I_{ik}=1,\theta_{ik}^{(s)},\sigma_k^{2(s)},\gamma_{ik}^{(s^*-1)},\tau_{ik}^{(s^*-1)})}\frac{1-\pi_{ik}}{\pi_{ik}}\right\},0\right]$$
$$= \min[\log\{P(\mathbf{Y}_{ik}|I_{ik}=0,\theta_{ik}^{(s)},\sigma_k^{2(s)})\}$$
$$-\log\{P(\mathbf{Y}_{ik}|I_{ik}=1,\theta_{ik}^{(s)},\sigma_k^{2(s)},\gamma_{ik}^{(s^*-1)},\tau_{ik}^{(s^*-1)})\}$$
$$+\log\{1-\pi_{ik}\}-\log\{\pi_{ik}\},0]$$
$$\text{where } \pi_{ik} = \frac{\exp\left\{\mu_I^{(s)}+\eta_I^{(s)}\left(\sum_{k'<k}I_{ik'}^{(s^*)}+\sum_{k'>k}I_{ik'}^{(s^*-1)}\right)\right\}}{1+\exp\left\{\mu_I^{(s)}+\eta_I^{(s)}\left(\sum_{k'<k}I_{ik'}^{(s^*)}+\sum_{k'>k}I_{ik'}^{(s^*-1)}\right)\right\}}$$

(2) Generate $u \sim \text{Uniform}(0,1)$. If $\log(u) < \log(r)$ set $I_{ik}^{(s^*)} = 0$, otherwise set $I_{ik}^{(s^*)} = 1$, $\gamma_{ik}^{(s^*)} = \gamma_{ik}^{(s^*-1)}$, and $\tau_{ik}^{(s^*)} = \tau_{ik}^{(s^*-1)}$.

(b) Update each γ_{ik}, $i \in \{i = n_0+1,\ldots,N : I_{ik}^{(s^*)} = 1\}$ and $k = 1,\ldots,K$:

(1) Generate $\log(\gamma_{ik}^*)$ from its proposal distribution

$$J_{\gamma_{ik}}(\gamma_{ik}|\gamma_{ik}^{(s^*)}) = N(\log(\gamma_{ik}^{(s^*)}),\delta_{\gamma k}^2).$$

(2) Compute acceptance ratio

$$\log(r) = \min\left[\log\left\{\frac{P(\mathbf{Y}_{ik}|I_{ik}^{(s^*)}=1,\theta_{ik}^{(s)},\sigma_k^{2(s)},\gamma_{ik}^*,\tau_{ik}^{(s^*)})}{P(\mathbf{Y}_{ik}|I_{ik}^{(s^*)}=1,\theta_{ik}^{(s)},\sigma_k^{2(s)},\gamma_{ik}^{(s^*)},\tau_{ik}^{(s^*)})}\right.\right.$$
$$\left.\left.\frac{P(\gamma_{ik}^*|\mu_{\gamma k}^{(s)},\sigma_{\gamma k}^{2(s)})}{P(\gamma_{ik}^{(s^*)}|\mu_{\gamma k}^{(s)},\sigma_{\gamma k}^{2(s)})}\frac{J_{\gamma_{ik}}(\gamma_{ik}^{(s^*)}|\gamma_{ik}^*)}{J_{\gamma_{ik}}(\gamma_{ik}^*|\gamma_{ik}^{(s^*)})}\right\},0\right]$$
$$= \min[\log\{P(\mathbf{Y}_{ik}|I_{ik}^{(s^*)}=1,\theta_{ik}^{(s)},\sigma_k^{2(s)},\gamma_{ik}^*,\tau_{ik}^{(s^*)})\}$$
$$-\log\{P(\mathbf{Y}_{ik}|I_{ik}^{(s^*)}=1,\theta_{ik}^{(s)},\sigma_k^{2(s)},\gamma_{ik}^{(s^*)},\tau_{ik}^{(s^*)})\}$$
$$+\log\{P(\gamma_{ik}^*|\mu_{\gamma k}^{(s)},\sigma_{\gamma k}^{2(s)})\}-\log\{P(\gamma_{ik}^{(s^*)}|\mu_{\gamma k}^{(s)},\sigma_{\gamma k}^{2(s)})\}$$
$$+\log\{J_{\gamma_{ik}}(\gamma_{ik}^{(s^*)}|\gamma_{ik}^*)\}-\log\{J_{\gamma_{ik}}(\gamma_{ik}^*|\gamma_{ik}^{(s^*)})\},0]$$

(3) Generate $u \sim \text{Uniform}(0,1)$. If $\log(u) < \log(r)$ set $\gamma_{ik}^{(s^*+1)} = \gamma_{ik}^*$, $I_{ik}^{(s^*+1)} = 1$ and $\tau_{ik}^{(s^*+1)} = \tau_{ik}^{(s^*+1)}$; otherwise set $\gamma_{ik}^{(s^*+1)} = \gamma_{ik}^{(s^*)}$, $I_{ik}^{(s^*+1)} = 1$ and $\tau_{ik}^{(s^*+1)} = \tau_{ik}^{(s^*)}$.

(c) Update each τ_{ik}, $i \in \{i = n_0+1,\ldots,N : I_{ik}^{(s^*+1)} = 1\}$ and $k = 1,\ldots,K$

(1) Generate τ_{ik}^* from its proposal distribution $J_{\tau_{ik}}(\tau_{ik}|\tau_{ik}^{(s^*+1)}) = TN_{[d_i-\tau_k^*,d_i]}(\tau_{ik}^{(s^*+1)},\delta_{\tau k}^2)$.

(2) Compute acceptance ratio

$$\log(r) = \min\left[\log\left\{\frac{P(\mathbf{Y}_{ik}|I_{ik}^{(s^*+1)}=1,\theta_{ik}^{(s)},\sigma_k^{2(s)},\gamma_{ik}^{(s^*+1)},\tau_{ik}^*)}{P(\mathbf{Y}_{ik}|I_{ik}^{(s^*+1)}=1,\theta_{ik}^{(s)},\sigma_k^{2(s)},\gamma_{ik}^{(s^*+1)},\tau_{ik}^{(s^*+1)})}\right.\right.$$
$$\left.\left.\frac{P(\tau_{ik}^*|\mu_{\tau k}^{(s)},\sigma_{\tau k}^{2(s)})}{P(\tau_{ik}^{(s^*+1)}|\mu_{\tau k}^{(s)},\sigma_{\tau k}^{2(s)})}\frac{J_{\tau_{ik}}(\tau_{ik}^{(s^*+1)}|\tau_{ik}^*)}{J_{\tau_{ik}}(\tau_{ik}^*|\tau_{ik}^{(s^*+1)})}\right\},0\right]$$
$$= \min[\log\{P(\mathbf{Y}_{ik}|I_{ik}^{(s^*+1)}=1,\theta_{ik}^{(s)},\sigma_k^{2(s)},\gamma_{ik}^{(s^*+1)},\tau_{ik}^*)\}$$
$$-\log\{P(\mathbf{Y}_{ik}|I_{ik}^{(s^*+1)}=1,\theta_{ik}^{(s)},\sigma_k^{2(s)},\gamma_{ik}^{(s^*+1)},\tau_{ik}^{(s^*+1)})\}$$
$$+\log\{P(\tau_{ik}^*|\mu_{\tau k}^{(s)},\sigma_{\tau k}^{2(s)})\}-\log\{P(\tau_{ik}^{(s^*+1)}|\mu_{\tau k}^{(s)},\sigma_{\tau k}^{2(s)})\}$$
$$+\log\{J_{\tau_{ik}}(\tau_{ik}^{(s^*+1)}|\tau_{ik}^*)\}-\log\{J_{\tau_{ik}}(\tau_{ik}^*|\tau_{ik}^{(s^*+1)})\},0]$$

(3) Generate $u \sim \text{Uniform}(0,1)$. If $\log(u) < \log(r)$ set $\tau_{ik}^{(s^*+2)} = \tau_{ik}^*$, $\gamma_{ik}^{(s^*+2)} = \gamma_{ik}^{(s^*+1)}$ and $I_{ik}^{(s^*+2)} = 1$; otherwise set $\tau_{ik}^{(s^*+2)} = \tau_{ik}^{(s^*+1)}$, $\gamma_{ik}^{(s^*+2)} = \gamma_{ik}^{(s^*+1)}$ and $I_{ik}^{(s^*+2)} = 1$.

Web Appendix B.2 *Posterior risk calculations*

For the $(N+1)^{th}$ patient at screening time t_{ij}, the posterior risk of disease given their screening history is:

$$\begin{aligned}\frac{P(D_{N+1}=1|\mathbf{Y}_{N+1})}{P(D_{N+1}=0|\mathbf{Y}_{N+1})} &= \frac{P(\mathbf{Y}_{N+1}|D_{N+1}=1)}{P(\mathbf{Y}_{N+1}|D_{N+1}=0)} \times \frac{P(D_{N+1}=1)}{1-P(D_{N+1}=1)} \\ &= \frac{\prod_{k=1}^{K} P(\mathbf{Y}_{N+1,k}|D_{N+1}=1)}{\prod_{k=1}^{K} P(\mathbf{Y}_{N+1,k}|D_{N+1}=0)} \times \frac{P(D_{N+1}=1)}{1-P(D_{N+1}=1)}\end{aligned}$$

where $\mathbf{Y}_{N+1,k} = \{Y_{(N+1)j'k}, j' = 1, \ldots, j\}$ and $\mathbf{Y}_{N+1} = \{\mathbf{Y}_{N+1,k}, k = 1, \ldots, K\}$. Each of the components is calculated in the following algorithm:

Draw S samples from posterior distribution of the biomarker specific and Markov random field parameters: σ_k^2, $\mu_{\theta k}$, $\sigma_{\theta k}^2$, $\mu_{\gamma k}$, $\sigma_{\gamma k}^2$, $\mu_{\tau k}$, $\sigma_{\tau k}^2$, for $k = 1, \ldots, K$ and μ_I and η_I. For each patient i, at each time t_{ij}

- Calculate $P\{(Y_{i1k}, \ldots, Y_{ijk})|D_i = 0\}$ for each $k = 1, \ldots, K$.
  - For each of the S posterior samples, draw θ_{ik} from its predictive distribution $N(\mu_{\theta k}, \sigma_{\theta k}^2)$.
  - For each of the S samples, calculate the joint probability of $(Y_{i1k}, \ldots, Y_{ijk})$ given θ_{ik} and σ_k^2: $\prod_{j'=1}^{j} \phi\left(\frac{Y_{ij'k}-\theta_{ik}}{\sigma_k}\right)$.
  - Average the joint probabilities over the S samples to get an estimate of $P\{(Y_{i1k}, \ldots, Y_{ijk})|D_i = 0\}$.
- For each of the S posterior samples, draw $\mathbf{I}_i$ from its predictive distribution $MRF(\mu_I, \eta_I)$.
- For each of the S posterior samples, draw an imputation of the unknown clinical diagnosis time d_i from it's empirical distribution in the study data.
- Calculate $P\{(Y_{i1k}, \ldots, Y_{ijk})|D_i = 1\}$ for each $k = 1, \ldots, K$.
  - For each of the S posterior samples, draw θ_{ik} from its predictive distribution $N(\mu_{\theta k}, \sigma_{\theta k}^2)$.
  - Extract the S posterior samples of I_{ik}.
  - For each of the S samples, if $I_{ik} = 0$
    - Calculate the joint probability of $(Y_{i1k}, \ldots, Y_{ijk})$ given θ_{ik} and σ_k^2: $\prod_{j'=1}^{j} \phi\left(\frac{Y_{ij'k}-\theta_{ik}}{\sigma_k}\right)$.

– Or if $I_{ik} = 1$

· Draw $\log(\gamma_{ik})$ from its predictive distribution $N(\mu_{\gamma k}, \sigma^2_{\gamma k})$.

· Draw τ_{ik} from its predictive distribution $TN_{[d_i-\tau^*_k, d_i]}(d_i - \mu_{\tau k}, \sigma^2_{\tau k})$.

· Calculate the joint probability of $(Y_{i1k}, \ldots, Y_{ijk})$ given θ_{ik}, γ_{ik}, τ_{ik} and σ^2_k: $\prod_{j'=1}^{j} \phi\left(\frac{Y_{ij'k} - \theta_{ik} - \gamma_{ik}(t_{ij} - \tau_{ik})^+}{\sigma_k}\right)$.

– Average the joint probabilities over the S samples to get an estimate of $P\{(Y_{i1k}, \ldots, Y_{ijk}) | D_i = 1\}$.

Web Appendix C. Simulations

[Web Table 5 about here.]

[Web Table 6 about here.]

Web Appendix C.1 *Alternative methods under consideration*

Univariate fully Bayesian screening algorithm

The univariate fully Bayesian (uFB) screening algorithm proposed by Skates et al. (2001) assumes that a single biomarker levels vary randomly around a constant mean in the absence of disease and after disease onset, the biomarker may or may not change over time. Our proposed methodology reduces to that of Skates et al. (2001) when there is only a single marker (i.e. K=1). For completeness we include the uFB model here.

For control patients, with $D_i = 0$, the biomarker level is assumed to randomly fluctuate around a constant mean θ_{i1} and follows the model

$$Y_{ij1} = \theta_{i1} + \varepsilon_{ij1},$$

where $\varepsilon_{ij1} \sim N(0, \sigma^2_1)$. For cases, with $D_i = 1$, we define an unobserved indicator I_{i1} to distinguish between the two possible models for the marker. If $I_{i1} = 0$, then we assume

that the marker level does not increase after disease onset and follows the same model as control patients, i.e $Y_{ij1} = \theta_{i1} + \varepsilon_{ij1}$. If $I_{i1} = 1$, then we assume the marker level randomly fluctuates around a constant mean θ_{i1} until an unobserved change-point time τ_{i1}, after which the biomarker level increases linearly at a rate of γ_{i1} with model

$$Y_{ij1} = \theta_{i1} + \gamma_{i1}(t_{ij} - \tau_{i1})^+ + \varepsilon_{ij1},$$

where $(.)^+$ indicates the positive part of the expression.

We assume the uninformative Jeffreys' prior, $1/\sigma_1^2$, for the variability of the biomarker. The constant mean biomarker level θ_{i1} is assumed to be normally distributed with mean $\mu_{\theta 1}$ and variance $\sigma_{\theta 1}^2$. The case-specific random effect for the rate γ_{i1} is assumed to be log-normally distributed, i.e. $\log(\gamma_{i1}) \sim N(\mu_{\gamma 1}, \sigma_{\gamma 1}^2)$. The change-point time τ_{i1} is assumed to occur within τ_1^* years prior to diagnosis d_i. The parameter τ_1^* is fixed and reflects the known preclinical behavior of the disease. In the case of HCC, which is a fast growing cancer, τ_1^* is set to be 2 years and the onset of HCC is assumed to be at most 2 years prior to clinical diagnosis of HCC. Therefore the change-point time τ_{i1} is assumed to follow a truncated normal (TN) distribution with lower bound $d_i - \tau_1^*$, upper bound d_i, mean $d_i - \mu_{\tau 1}$ and variance $\sigma_{\tau 1}^2$. I_{i1} is assumed to follow a Bernoulli distribution with parameter π_1. Note that the Markov Random Field prior that we use in the proposed joint model reduces to a Bernoulli distribution with parameter $\pi_1 = \exp(\mu_I)/\{1 + \exp(\mu_I)\}$ when $K = 1$.

Univariate parametric empirical Bayes screening algorithm

The univariate parametric empirical Bayes (uEB) screening algorithm proposed by McIntosh and Urban (2003) defines a patient and screen specific threshold that incorporates both the prior screening history of the patient and a model for the biomarker behavior in control patients. In control patients, with $D_i = 0$, the biomarker level is assumed to randomly fluctuate around a constant mean θ_{i1} and follows a hierarchical distribution:

$$Y_{ij1}|\theta_{i1} \sim N(\theta_{i1}, \sigma_1^2)$$

$$\theta_{i1} \sim N(\mu_{\theta 1}, \sigma_{\theta 1}^2)$$

I.e. given the patient-specific mean θ_{i1}, the transformed biomarker levels Y_{ij1} are independent and identically distributed with mean θ_{i1} and variance σ_1^2 and θ_{i1} itself is normally distributed with mean $\mu_{\theta 1}$ and variance $\sigma_{\theta 1}^2$. The within-subject variance σ_1^2 and between-subject variance $\sigma_{\theta 1}^2$ are key measures that effect the performance of the PEB algorithm. Y_{ij} can be centered and rescaled to simply the derivation. Let $Z_{ij} = (Y_{ij1} - \mu_{\theta 1})/\sqrt{\sigma_1^2 + \sigma_{\theta 1}^2}$. Then

$$Z_{ij}|\mu_i \sim N(\mu_i, 1 - B_1)$$

$$\mu_i \sim N(0, B_1)$$

$$\text{where } B_1 = \frac{\sigma_{\theta 1}^2}{\sigma_1^2 + \sigma_{\theta 1}^2}.$$

Note that a simple calculation verifies that the marginal distribution of Z_{ij} is the standard normal distribution.

The standard threshold (ST) approach ignores prior screening history of the patient and instead uses the same threshold for all patients. One possible approach for determining this threshold is to use the above model, which describes the transformed biomarker distribution in the control population, to specify a threshold that controls the population-wide false positive rate (FPR). Since Z_{ij} is assumed to follow a standard normal distribution, then $Pr(Z_{ij} > z_{1-f_0}) = f_0$ where z_{1-f_0} is the $100(1 - f_0)$ percentile of the standard normal distribution. Therefore, using the standard threshold screening rule, patient i has a positive screen at the j^{th} screening visit if $Z_{ij} > z_{1-f_0}$.

If the patient's mean biomarker level (μ_i) were known, we could define an individually tailored screening rule that still ensures the population-wide FPR is not more than f_0 since given μ_i, $(Z_{ij} - \mu_i)/\sqrt{1 - B_1}$ follows a standard normal distribution. Therefore $Pr\{(Z_{ij} -$

$\mu_i)/\sqrt{1-B_1} > z_{1-f_0}|\mu_i\} = f_0$ and patient i has a positive screen at the j^{th} screening visit if $Z_{ij} > \mu_i + z_{1-f_0}\sqrt{1-B_1}$.

However μ_i is not known, so instead we use the parametric empirical Bayes (PEB) estimate of this parameter. This estimate, denoted by $\hat{\mu}_{ij}$, is a weighted average of the population mean (which is 0 in this case) and the sample average of the patients screening history. The PEB screening rule then indicates a positive screen for patient i at the j^{th} screening visit if

$$Z_{ij} > \hat{\mu}_{ij} + z_{1-f_0}\sqrt{1-B_1B_j}, \tag{1}$$

where $\hat{\mu}_{ij} = 0 * (1-B_j) + \bar{Z}_{ij} * B_j$, $\bar{Z}_{ij} = \frac{1}{j-1}\sum_{j'=1}^{j-1} Z_{ij'}$ and $B_j = \frac{\sigma^2_{\theta 1}}{\sigma^2_1/(j-1)+\sigma^2_{\theta 1}}$.

To implement the PEB screening algorithm, we require estimates for the parameters $\mu_{\theta 1}$, σ^2_1 and $\sigma^2_{\theta 1}$. These can be obtained by fitting a linear mixed model with a random intercept in the control patients from the training data. We then apply the PEB screening rule to all the screenings conducted in the validation data.

Independent multivariate fully Bayesian screening algorithm

The independent multivariate fully Bayesian (mFB-I) screening algorithm incorporates all K biomarkers into the model but assumes the markers are independent (i.e. there is no MRF prior to connect the biomarkers). Instead the priors for each indicator I_{ik} are assumed to be independent Bernoulli distributions with parameter π_k, for $k = 1, \ldots, K$. The rest of the model remains the same (see Section 3 of the main manuscript).

Web Appendix C.2 *Additional Simulation Results*

[Web Table 7 about here.]

[Web Table 8 about here.]

[Web Table 9 about here.]

The patient-level sensitivity is defined to be the percentage of detectable cases with a positive screen after disease onset (italicized diagonal of Web Table 10 contains the empirical

mean ROC(0.1) based on this definition of sensitivity). For each method, we calculate the time of the first positive screen after disease onset. In Web Table 10, the $(i,j)^{th}$ entry corresponds to the empirical mean percentage of times the i^{th} method has a positive screen first and the $(j,i)^{th}$ entry to the empirical mean percentage of times the j^{th} method has a positive screen first among the detectable cases. The empirical mean percentage of times where the i^{th} and the j^{th} methods have a positive screen at the same time is 100 - $(i,j)^{th}$ entry - $(j,i)^{th}$ entry. For each comparison, we have highlighted (bold text) the higher percentage.

[Web Table 10 about here.]

In our model, we assume that the variance of each biomarker (σ_k^2, $k = 1,..,K$) is constant and not subject to change. We evaluated the impact of this assumption in a series of simulation studies where we generated data that included increasing variability in the biomarker after the changepoint in HCC cases but left our model (as described in Section 3) unchanged. The simulation study adapted Scenario A to generate the data and assumed that in controls and HCC cases with no changepoint, σ_k^2, $k = 1,..,K$ is constant. In HCC cases with a changepoint, we assumed the standard deviation of each marker increases linearly with rate δ_k, $k = 1,..,K$. The results for Scenario A ($\delta_k = 0$, $k = 1,..,3$), Scenario E ($\delta_k = 0.1$, $k = 1,..,3$), Scenario F ($\delta_k = 0.1$, $k = 1,..,3$), and Scenario G ($\delta_k = 0.1$, $k = 1,..,3$) are presented in Table 11. The increasing variability has minimal impact on the performance of the joint multivariate fully Bayesian screening approach which assumes constant variance. Therefore while it may be important to consider a model that allows for a corresponding changepoint in the variance of the biomarker in other scenarios, it is beyond the scope of our current project and simulation studies show that our results are robust to our assumption in biomarker trajectories that mimic those observed in the HALT-C Trial.

[Web Table 11 about here.]

References

McIntosh, M. W. and Urban, N. (2003). A parametric empirical bayes method for cancer screening using longitudinal observations of a biomarker. *Biostatistics* **4,** 27–40.

Skates, S. J., Pauler, D. K., and Jacobs, I. J. (2001). Screening based on the risk of cancer calculation from bayesian hierarchical changepoint and mixture models of longitudinal markers. *JASA* **96,** 429–439.

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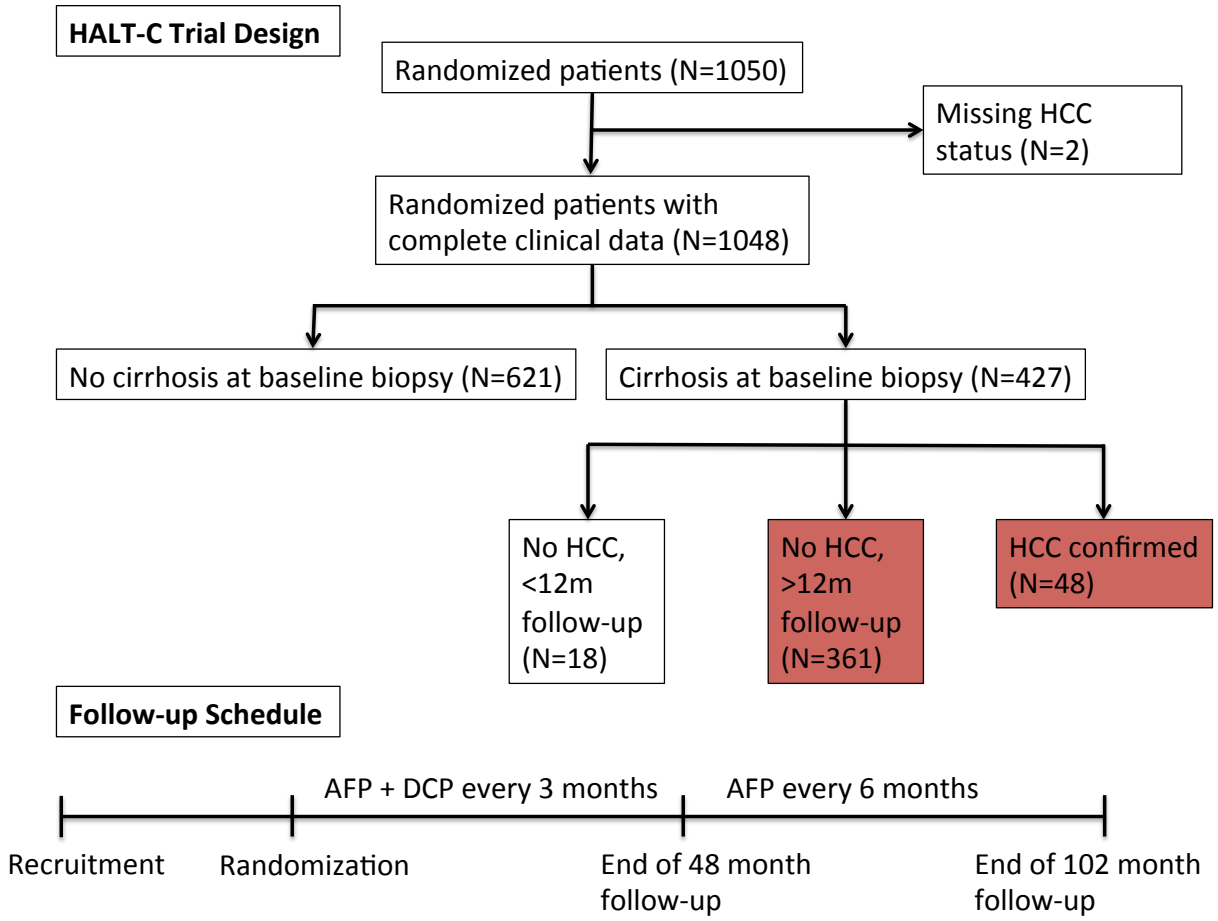
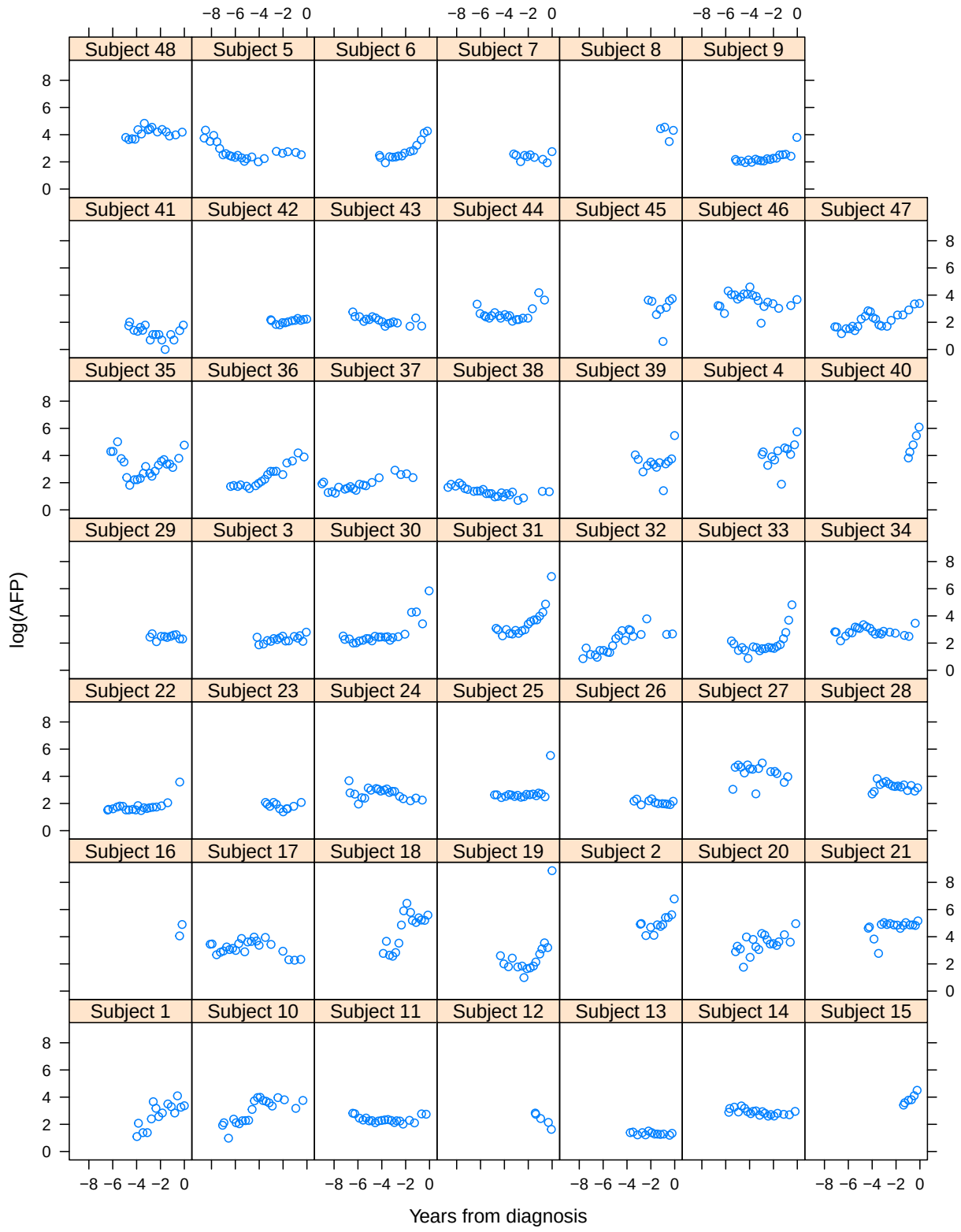
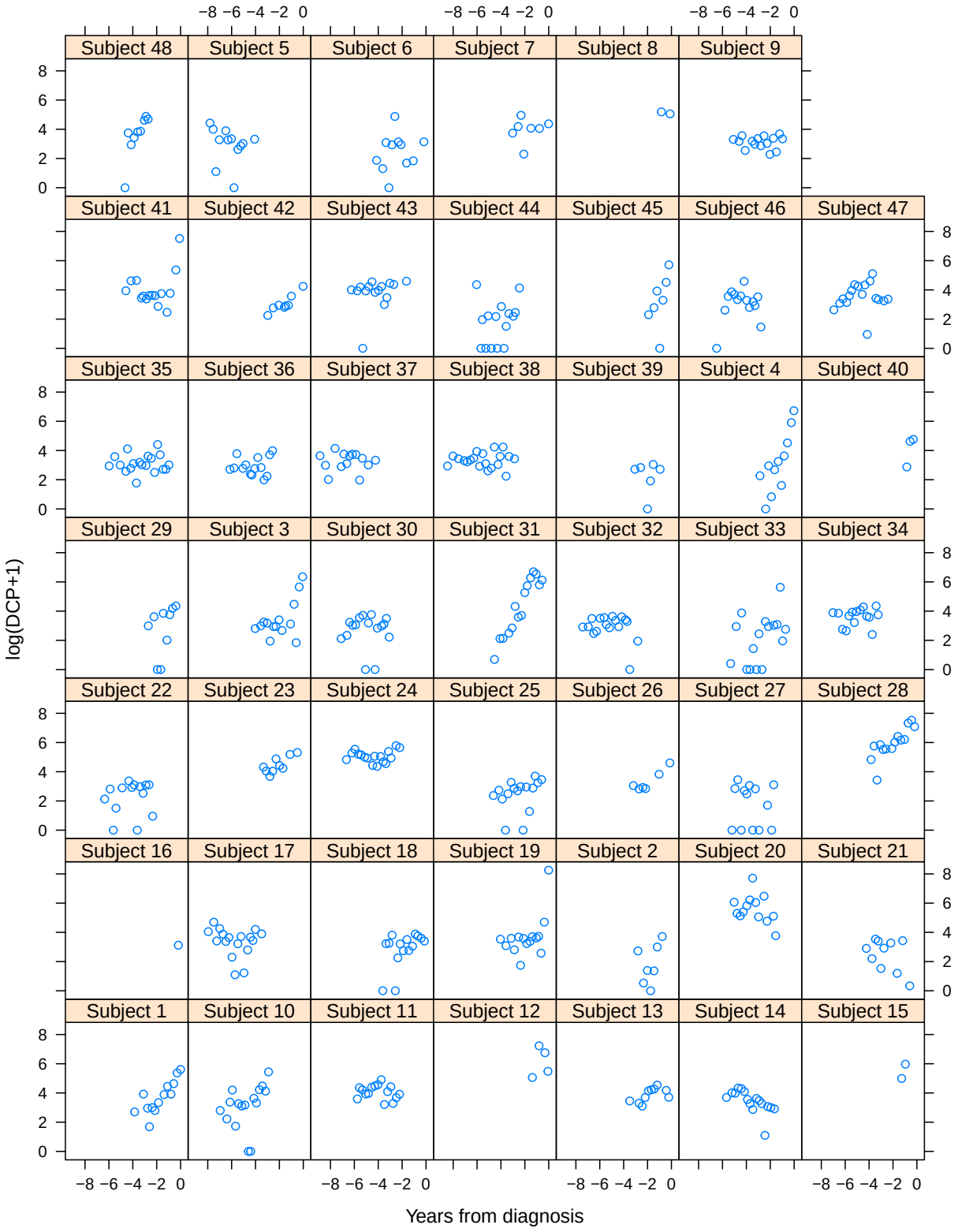


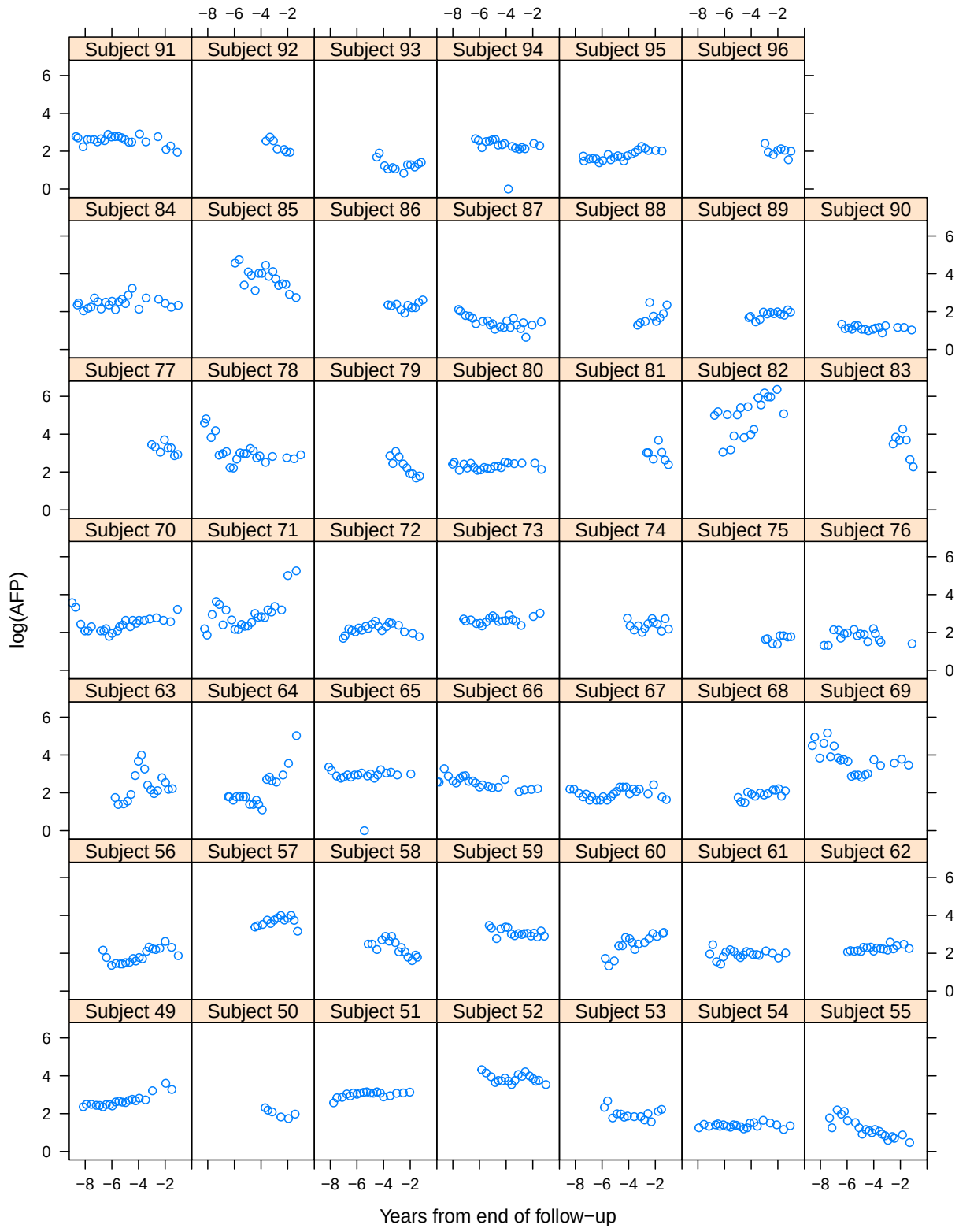
Web Figure 1. Standards for Reporting of Diagnostic accuracy (STARD) flow diagram and follow-up schedule in the HALT-C Trial. In our analysis dataset (highlighted in red), we have 361 patients with no HCC and 48 confirmed HCC datasets.



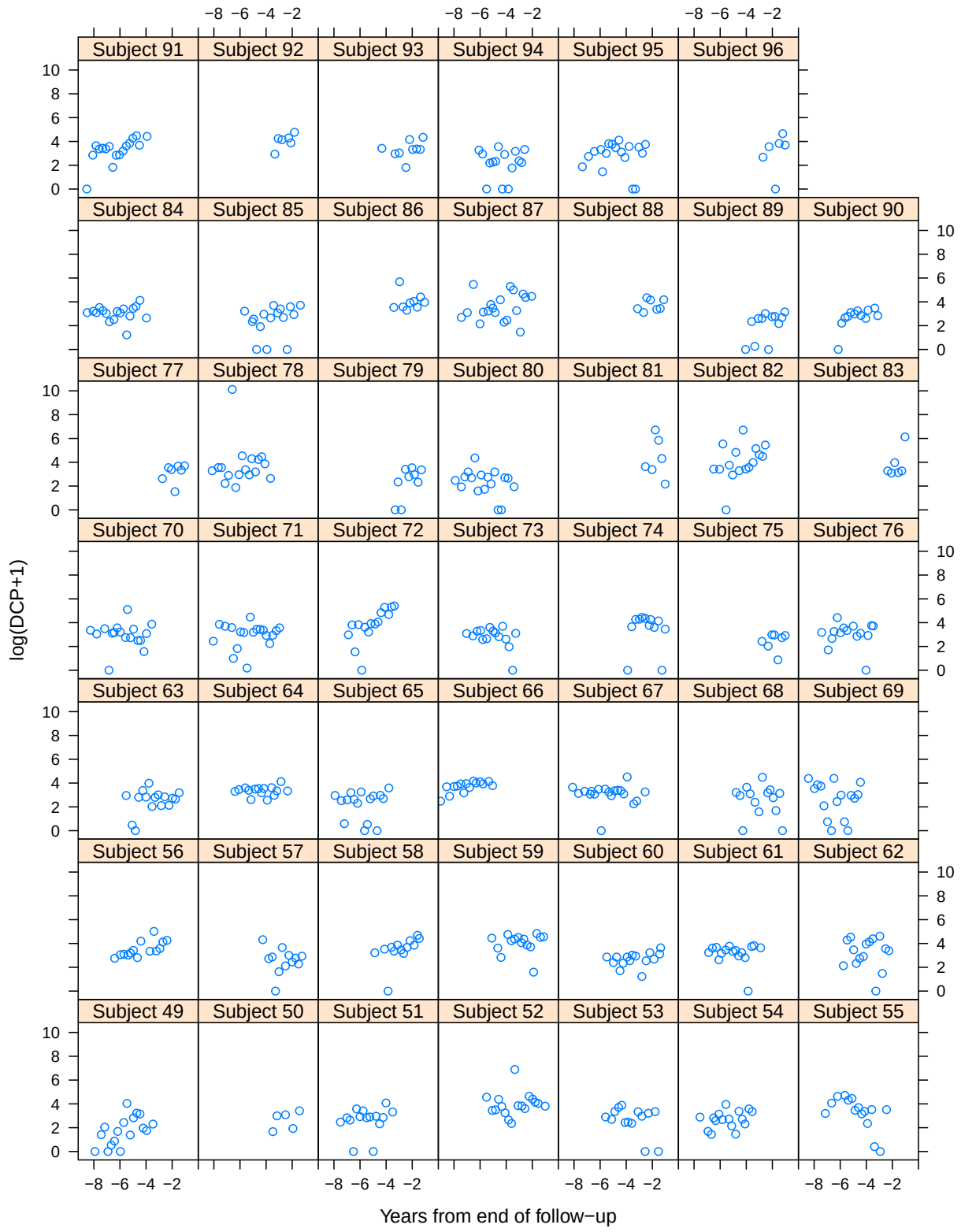
Web Figure 2. AFP trajectories for all 48 HCC cases in our analysis cohort.



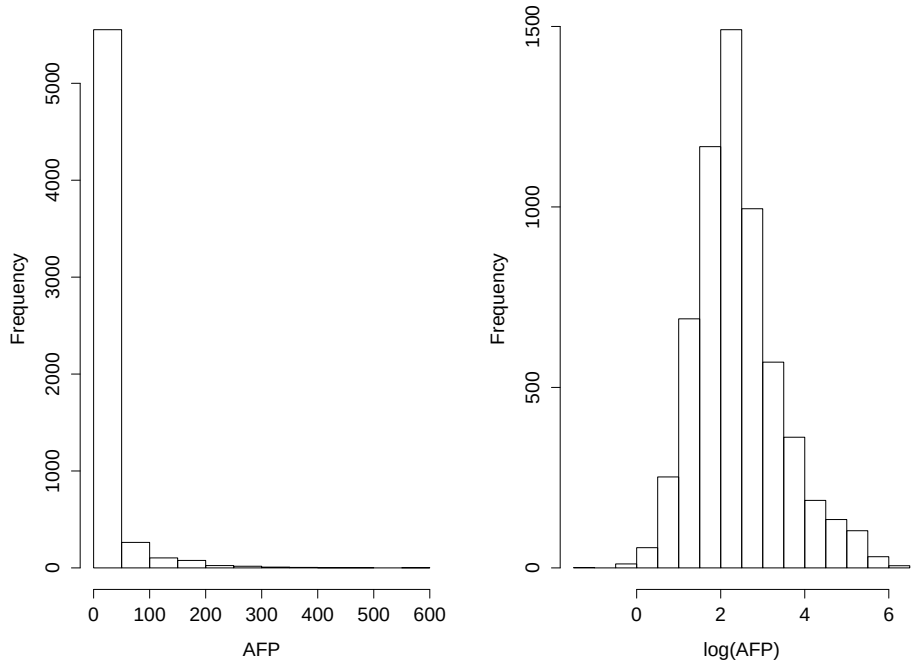
Web Figure 3. DCP trajectories for all 48 HCC cases in our analysis cohort.



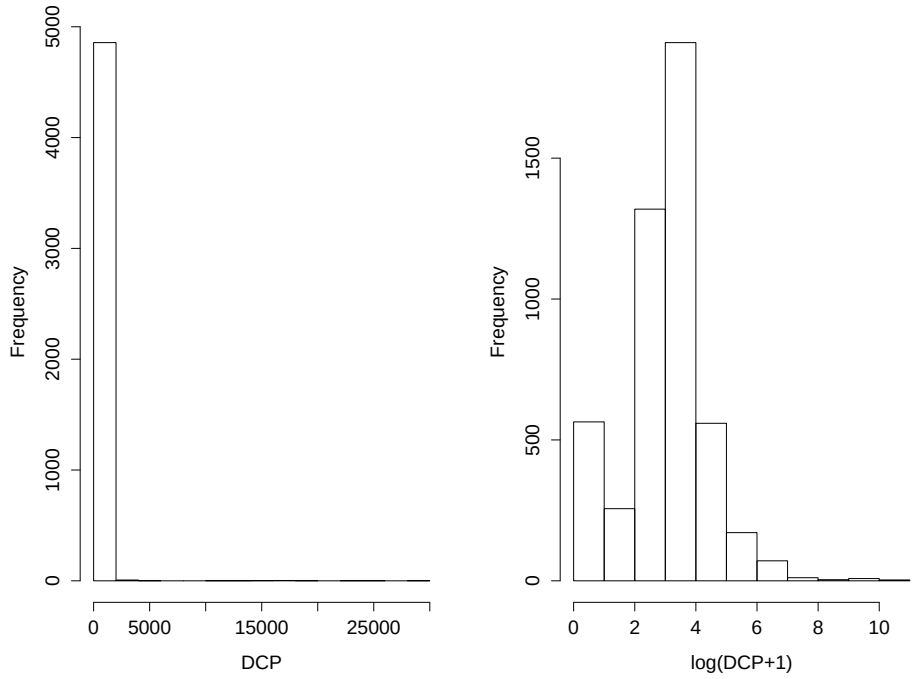
Web Figure 4. AFP trajectories for 48 randomly selected patients with no HCC from our analysis cohort.



Web Figure 5. DCP trajectories for 48 randomly selected patients with no HCC from our analysis cohort.

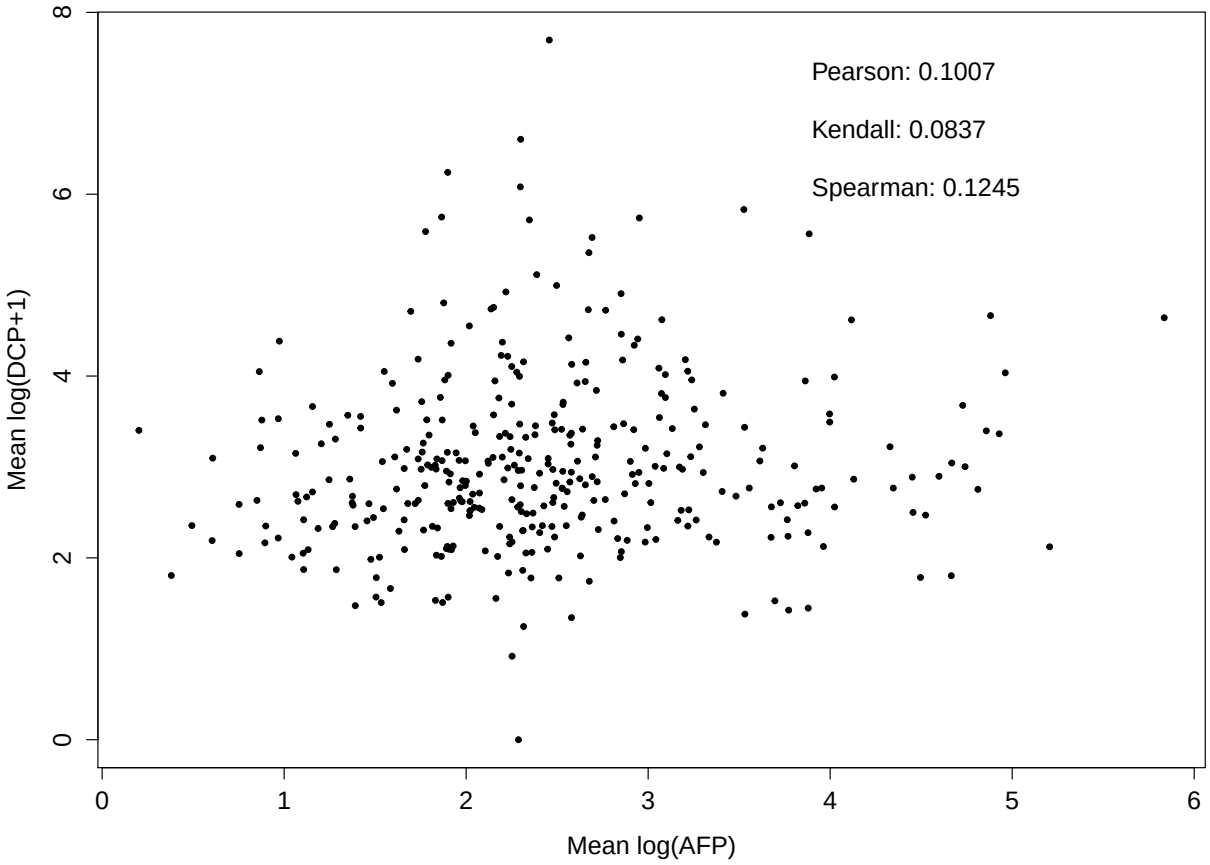


(a) AFP

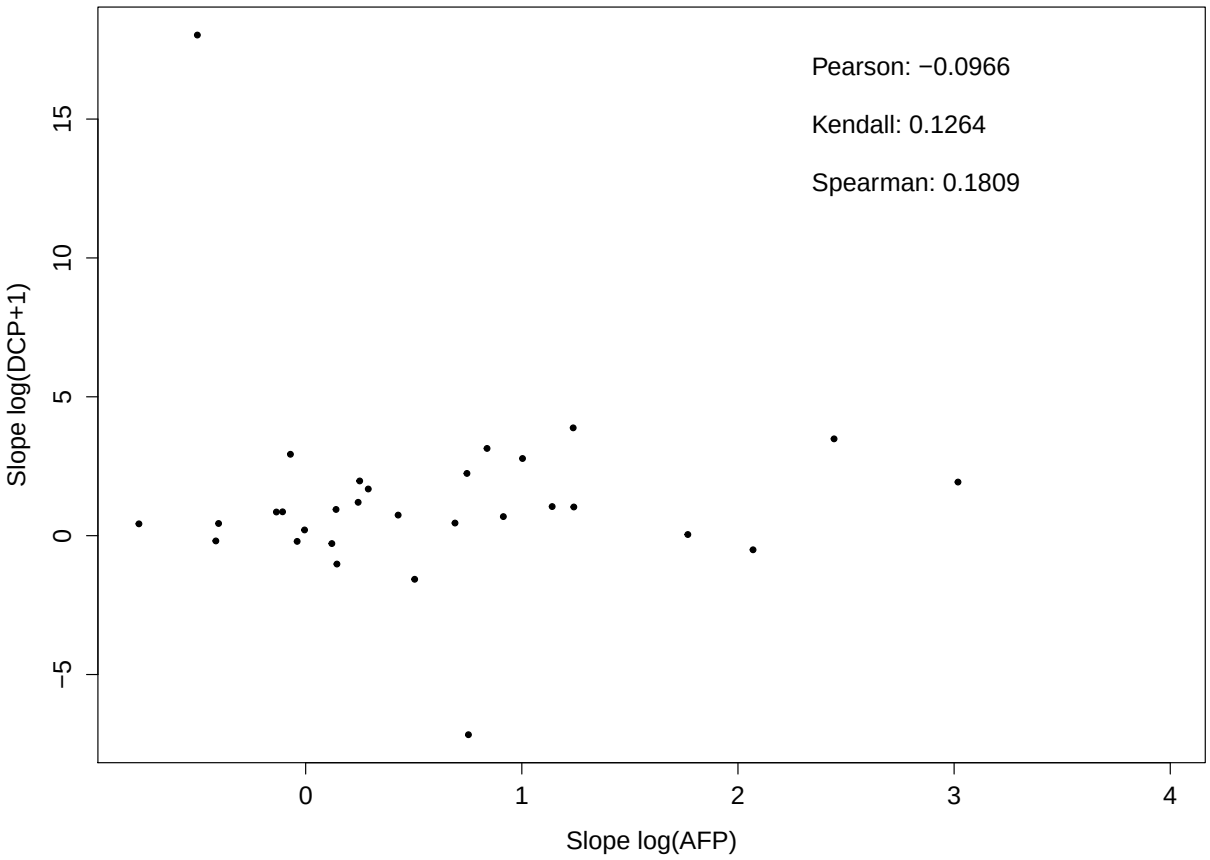


(b) DCP

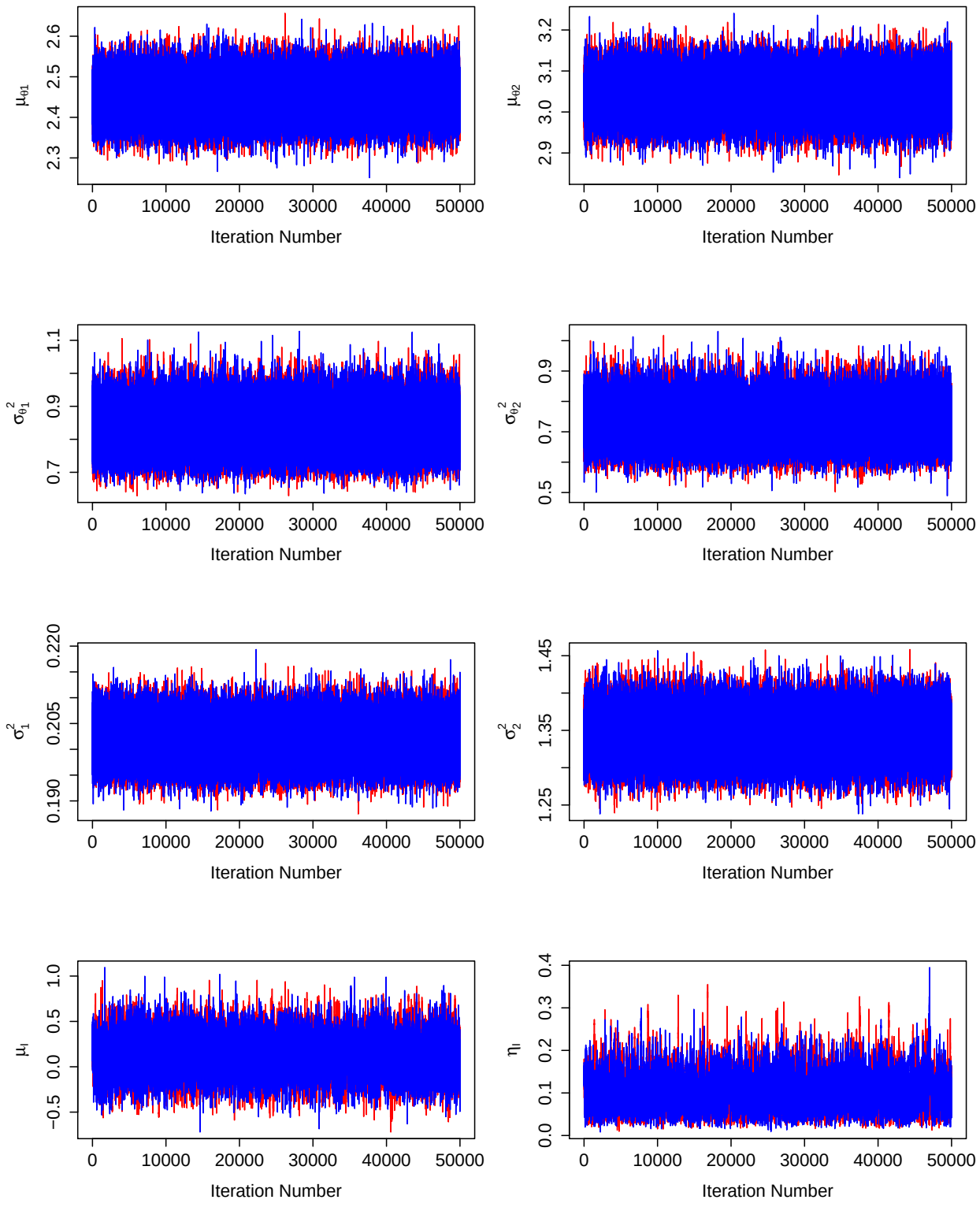
Web Figure 6. Distribution of AFP and DCP before and after logarithmic transformations in control patients from the HALT-C Trial.



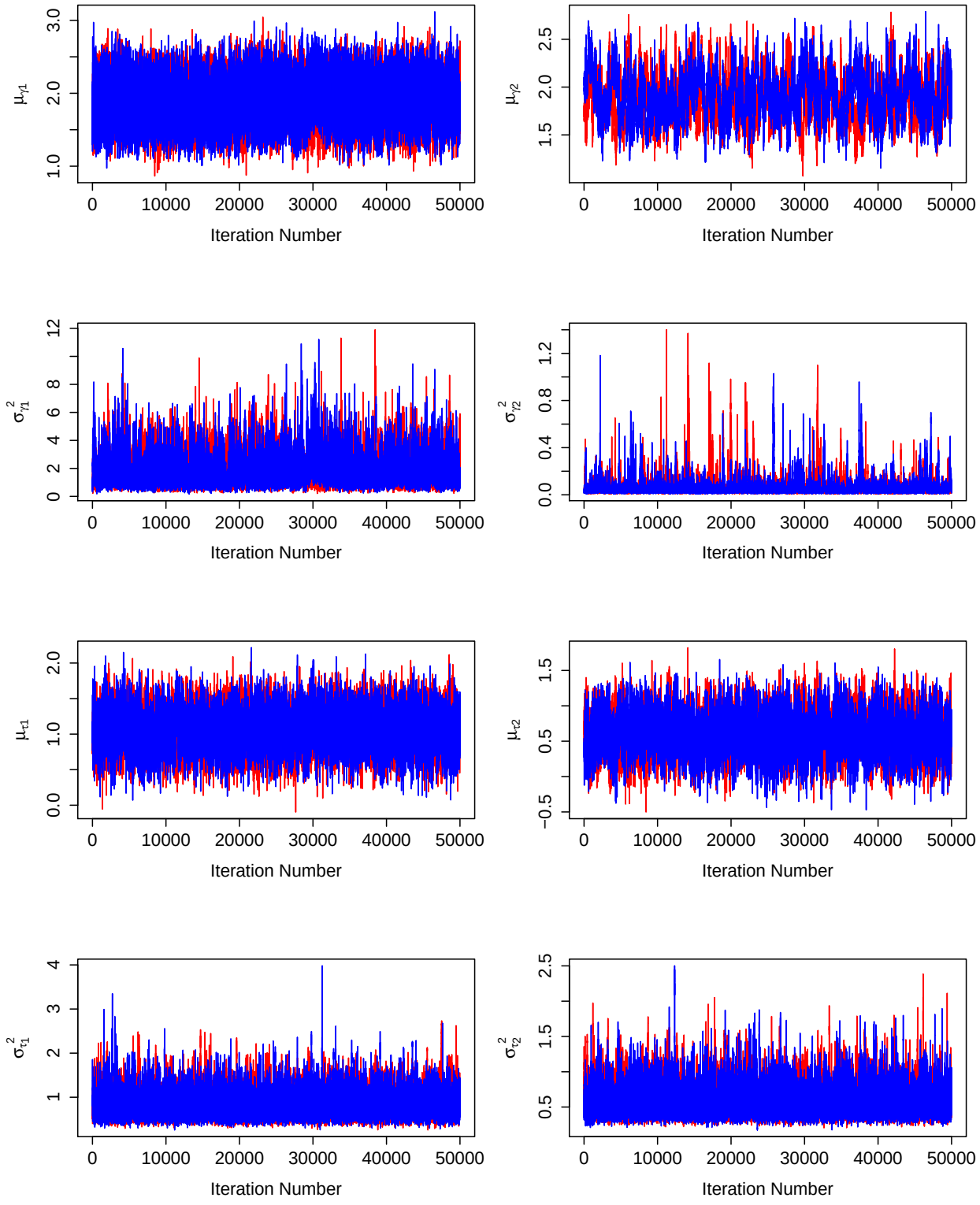
Web Figure 7. Examining correlation between average log(AFP) and log(DCP+1) values in controls from the HALT-C Trial.



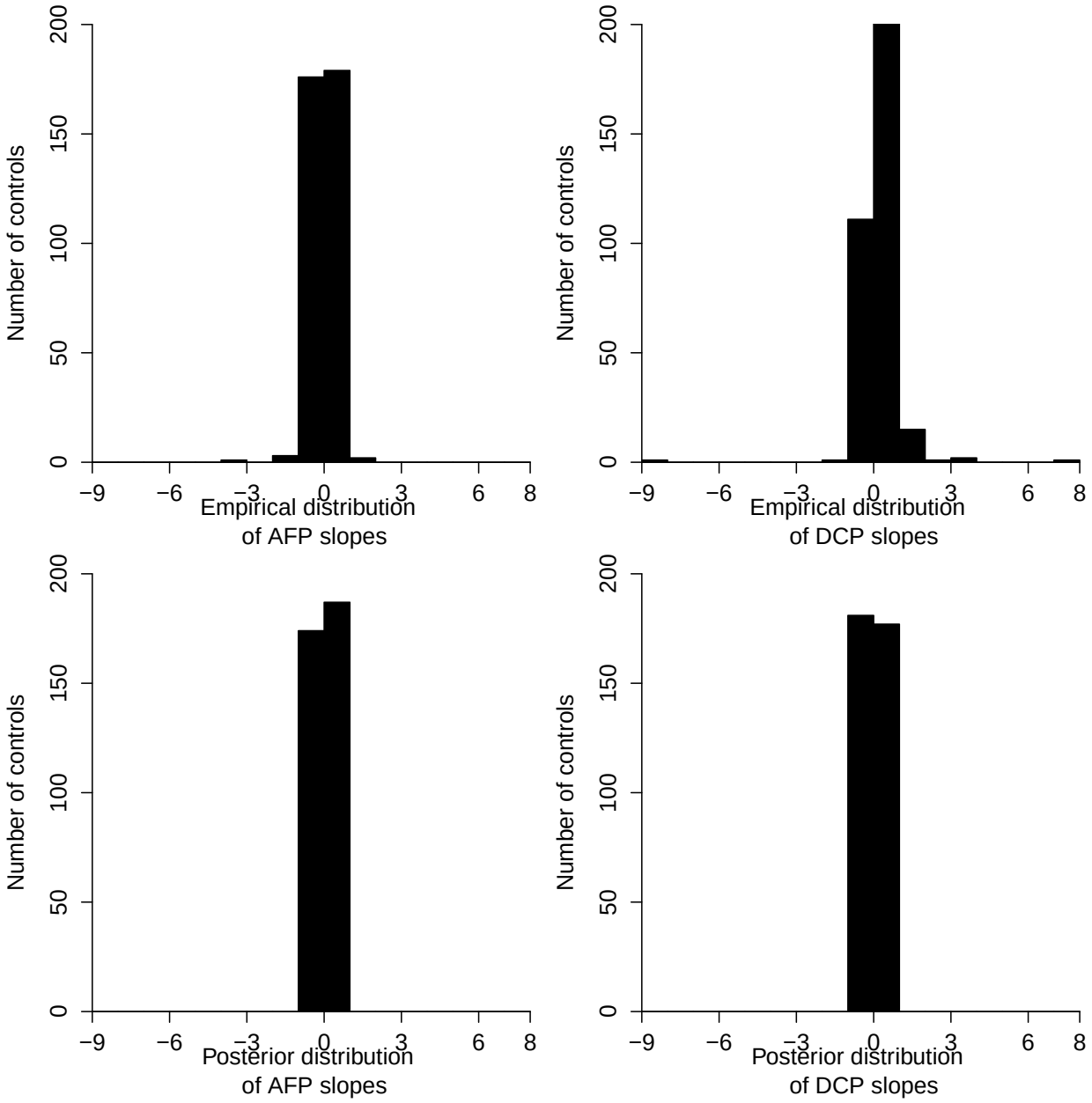
Web Figure 8. Examining correlation between log(AFP) trajectory and log(DCP+1) trajectory within two years of clinical diagnosis of HCC in cases from the HALT-C Trial.



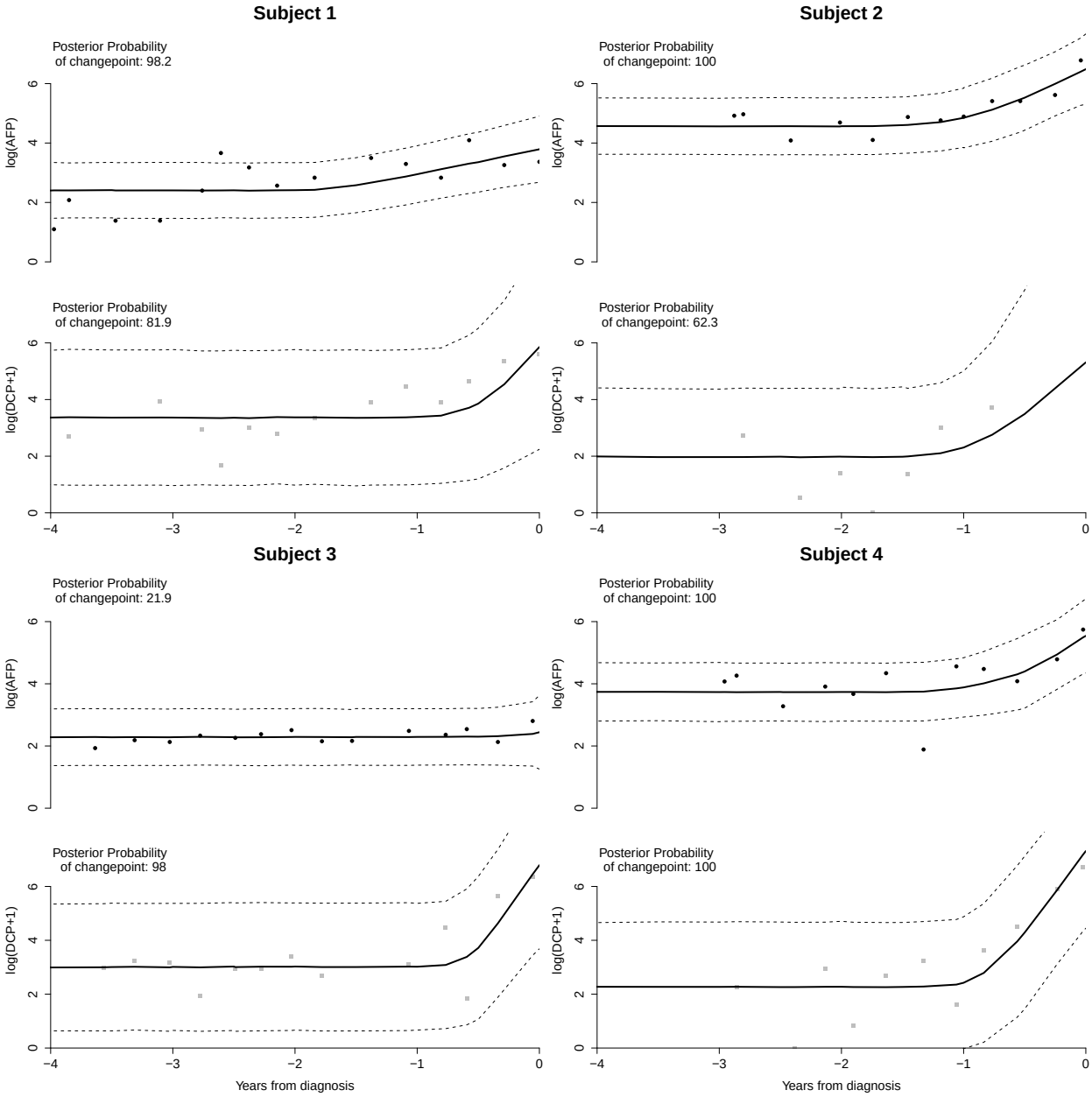
Web Figure 9. Traceplots of model parameters ($\mu_{\theta 1}$, $\mu_{\theta 2}$, $\sigma^2_{\theta 1}$, $\sigma^2_{\theta 2}$, σ^2_1, σ^2_2, μ_I, η_I) for chain 1 (red) and chain 2 (blue) from the HALT-C Trial.



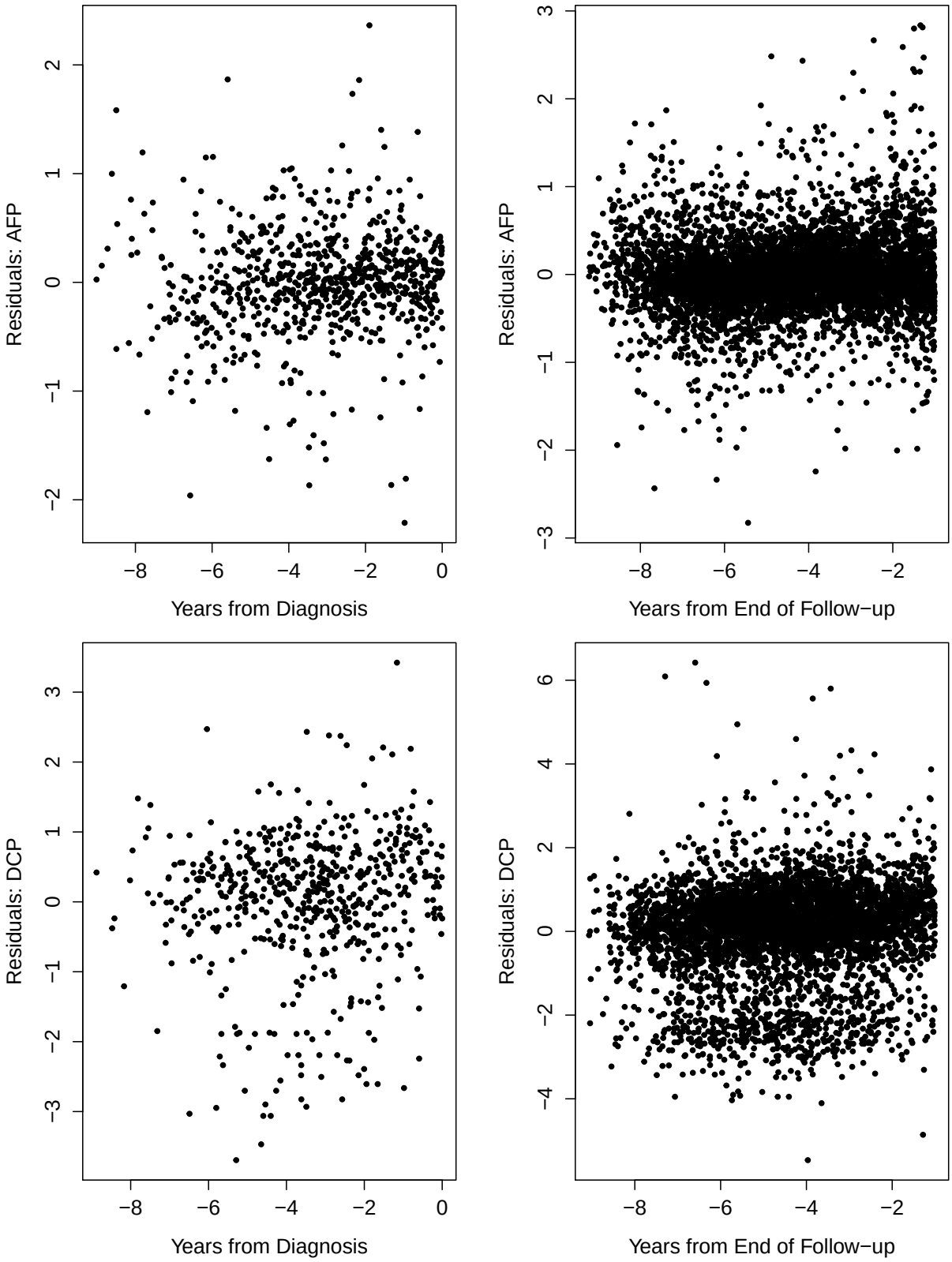
Web Figure 10. Traceplots of model parameters ($\mu_{\gamma 1}$, $\mu_{\gamma 2}$, $\sigma^2_{\gamma 1}$, $\sigma^2_{\gamma 2}$, $\mu_{\tau 1}$, $\mu_{\tau 2}$, $\sigma^2_{\tau 1}$, $\sigma^2_{\tau 2}$) for chain 1 (red) and chain 2 (blue) from the HALT-C Trial.



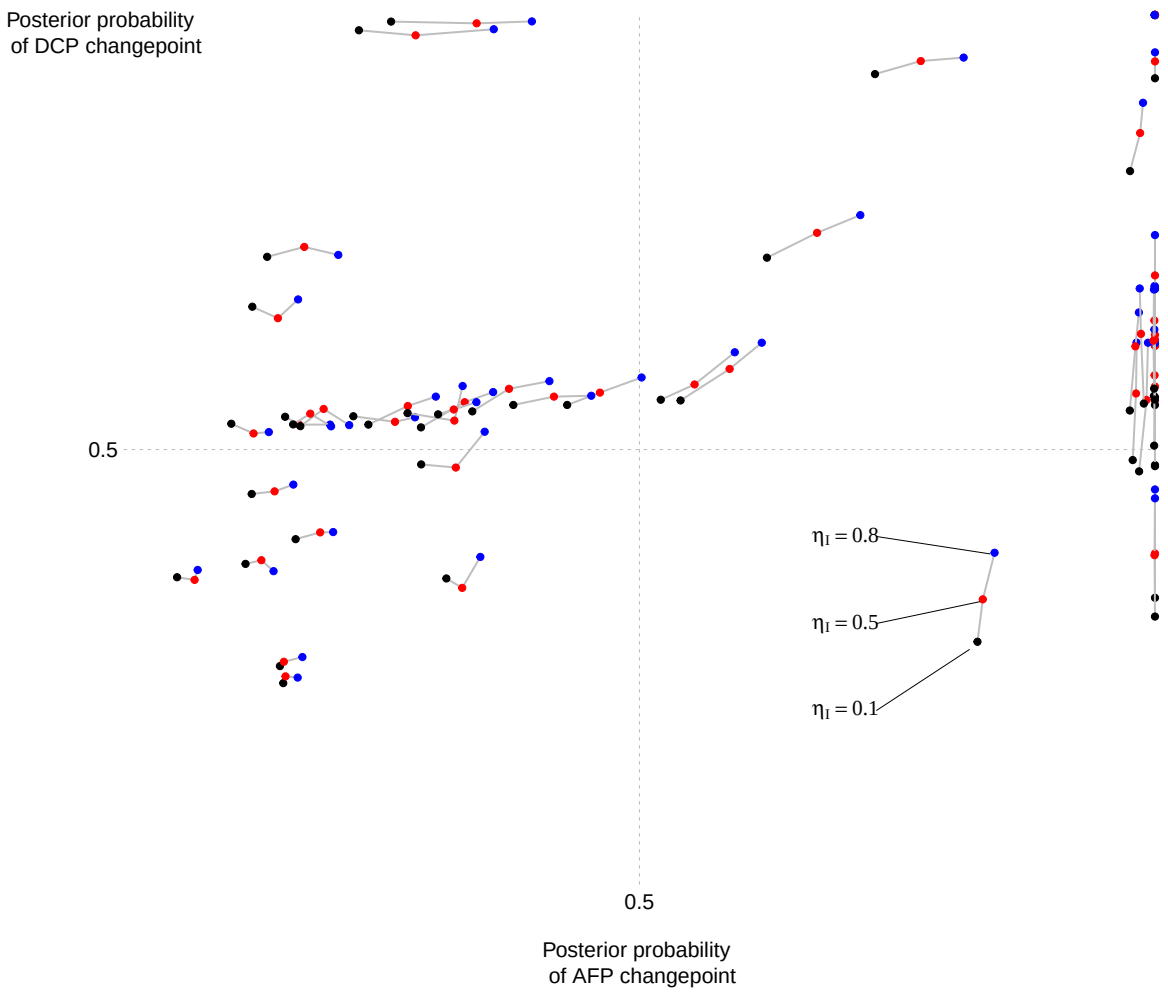
Web Figure 11. Model goodness of fit for AFP and DCP slopes in controls from the HALT-C Trial



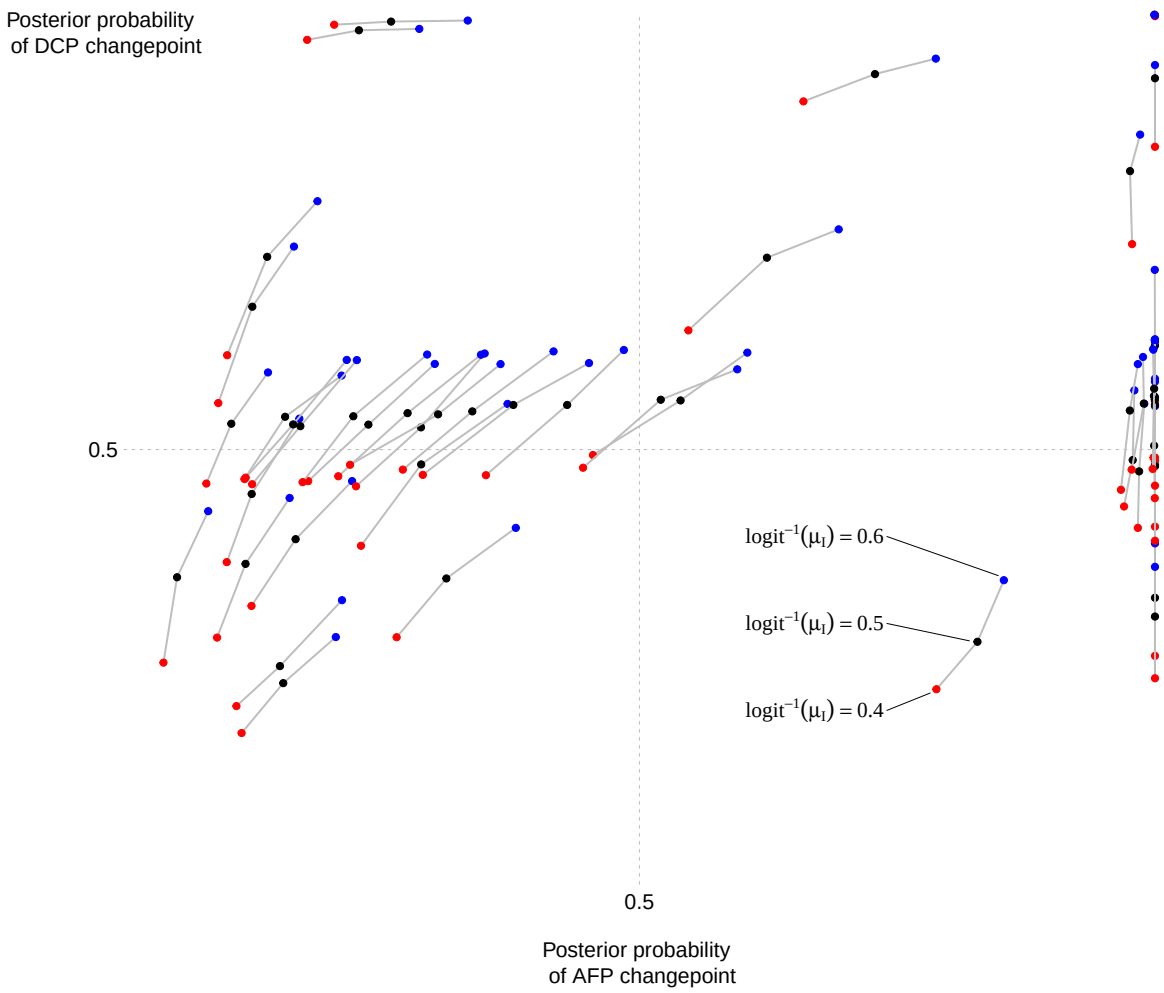
Web Figure 12. Model goodness of fit for AFP and DCP trajectories in four HCC cases from the HALT-C Trial.



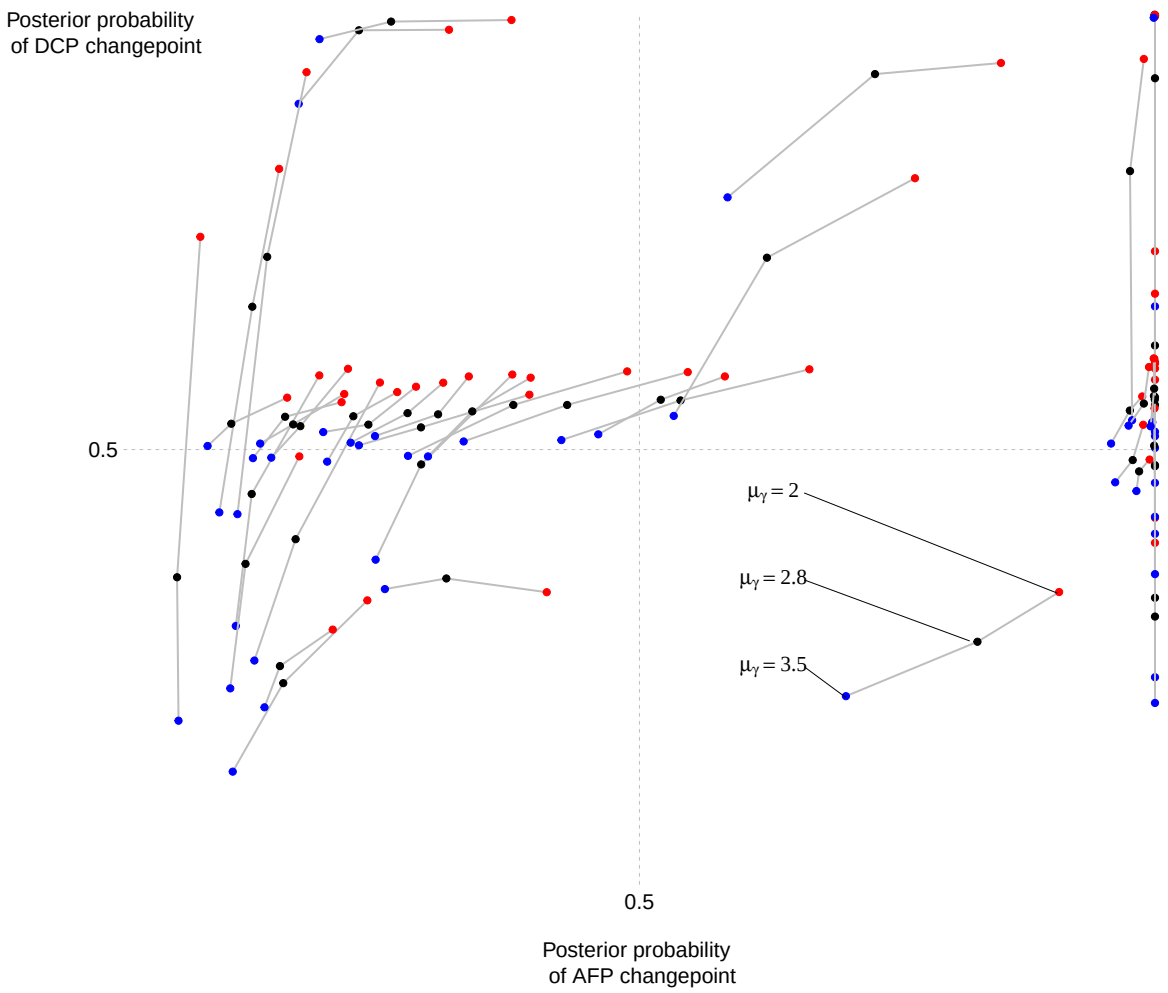
Web Figure 13. Examining the residuals (ε_{ijk}) for AFP and DCP in HCC cases (left column) and controls (right column) from the HALT-C Trial. There is no evidence of a time trend in the residuals.



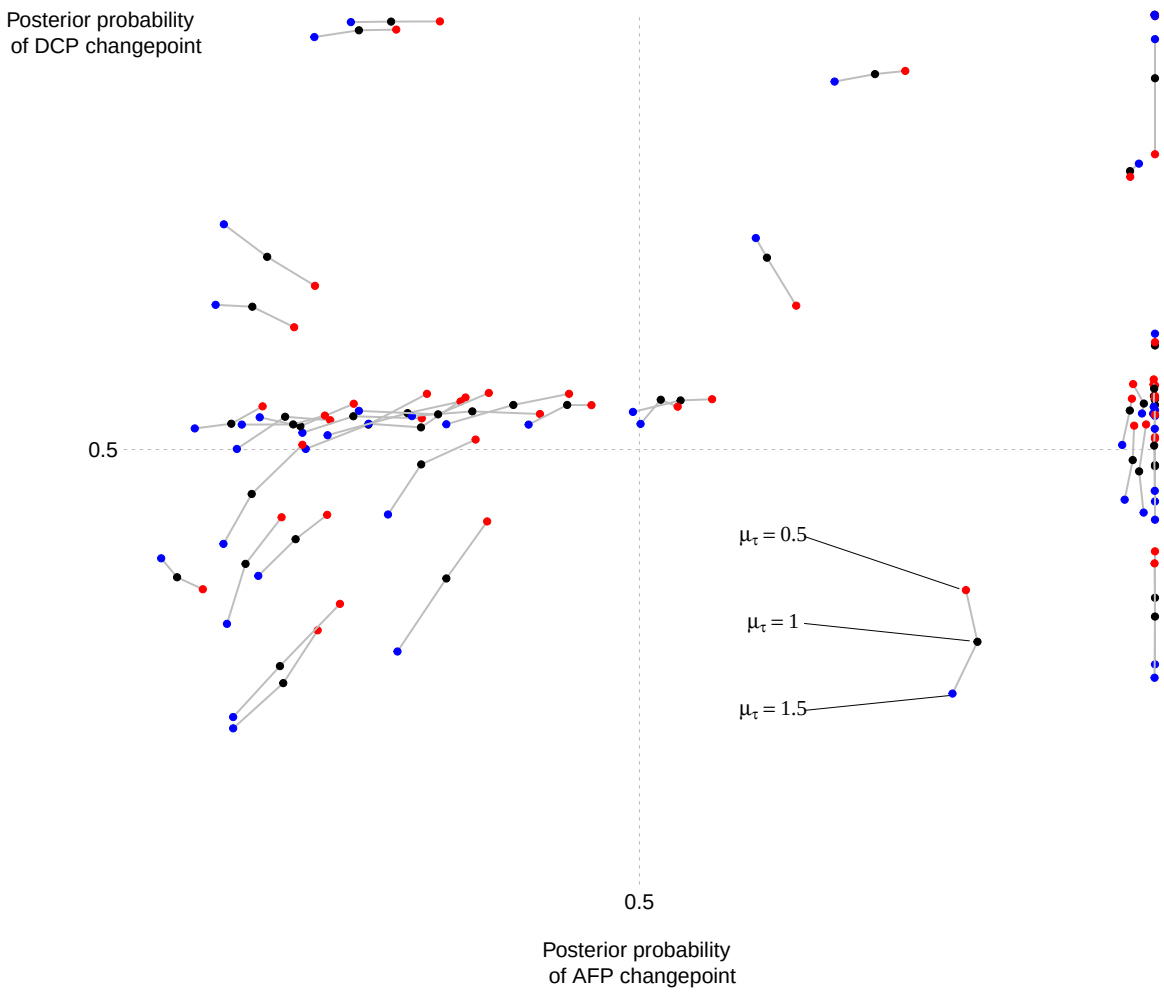
Web Figure 14. Sensitivity Analysis: η_I. The posterior probabilities for each HCC case are connected with gray line.



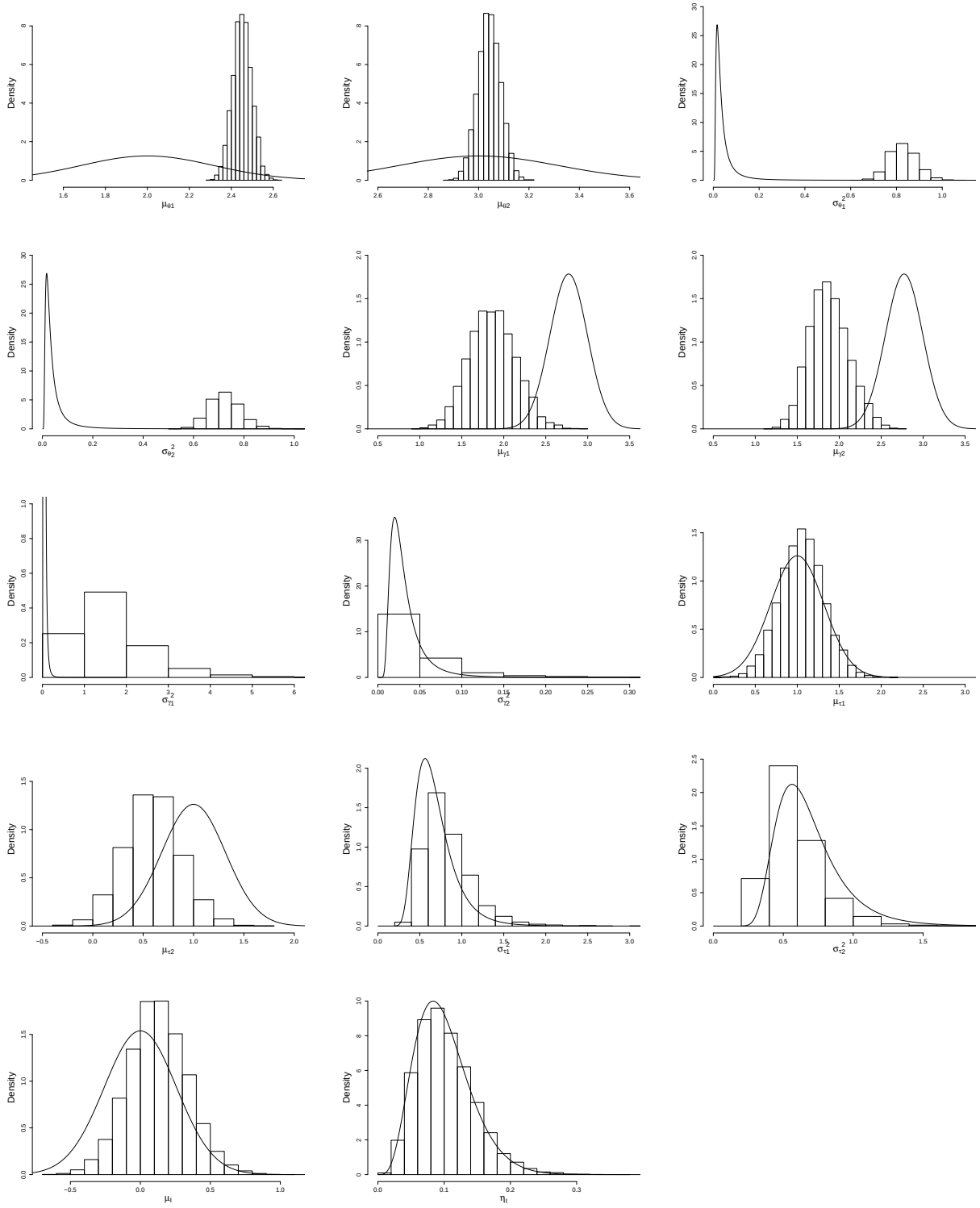
Web Figure 15. Sensitivity Analysis: μ_I. The posterior probabilities for each HCC case are connected with gray line.



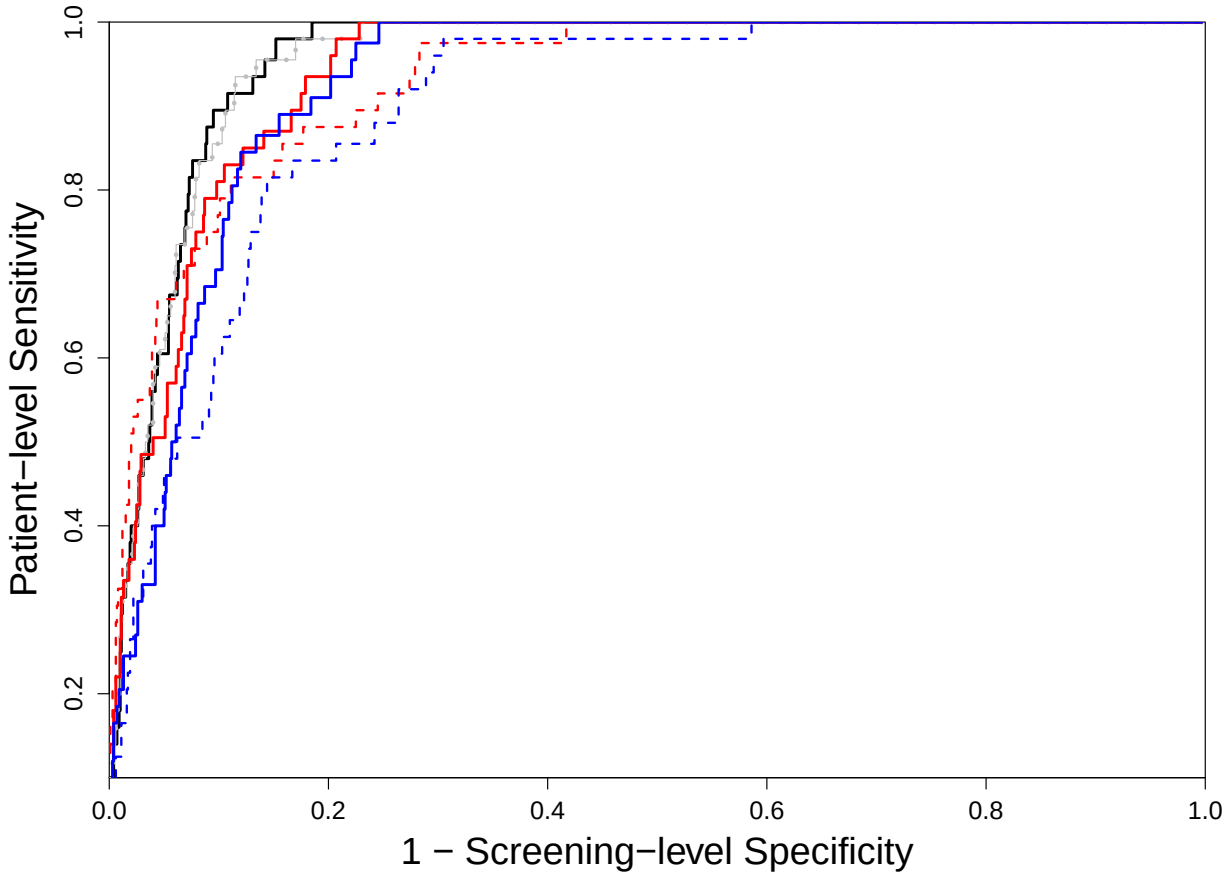
Web Figure 16. Sensitivity Analysis: μ_γ. The posterior probabilities for each HCC case are connected with gray line.



Web Figure 17. Sensitivity Analysis: μ_τ. The posterior probabilities for each HCC case are connected with gray line.



Web Figure 18. Posterior distribution for each parameter in the model. The prior distributions are overlayed (solid line).



Web Figure 19. Cross-valiated ROC curve for mFB-J: joint multivariate fully bayesian (solid black line), mFB-I: independent multivariate fully bayesian (grey line), uFB: univariate fully bayesian (solid red line for AFP and solid blue line for DCP) and uEB: parametric empirical bayes (dashed red line for AFP and dashed blue line for DCP).

	AFP (k=1)	DCP (k=2)		AFP (k=1)	DCP (k=2)
$\mu_{\theta k}$	$N(2, 0.1)$	$N(3, 0.1)$	$\sigma^2_{\theta k}$	$IG(2, 0.05)$	$IG(2, 0.05)$
	[1.380, 2.620]	[2.380, 3.620]		[0.009, 0.206]	[0.009, 0.206]
$\mu_{\gamma k}$	$N(\log(16), 0.05)$	$N(\log(16), 0.05)$	$\sigma^2_{\gamma k}$	$IG(4, 0.1)$	$IG(4, 0.1)$
	[2.332, 3.208]	[2.332, 3.208]		[0.011, 0.092]	[0.011, 0.092]
$\mu_{\tau k}$	$N(1, 0.1)$	$N(1, 0.1)$	$\sigma^2_{\tau k}$	$IG(10, 6.19)$	$IG(10, 6.19)$
	[0.380, 1.620]	[0.380, 1.620]		[0.362, 1.291]	[0.362, 1.291]

Web Table 1

Prior distributions of AFP and DCP specific parameters in the joint model. The 2.5^{th} and 97.5^{th} percentiles for each distribution is given below in brackets.

	mFB-J	mFB-I	uFB AFP	uFB DCP	uEB AFP	uEB DCP
mFB-J	·	**25.00**	**33.00**	**52.00**	**29.00**	**68.00**
mFB-I	24.50	·	**35.50**	**49.00**	23.50	**59.00**
uFB AFP	20.00	31.00	·	**48.00**	24.00	**62.00**
uFB DCP	36.50	29.00	41.50	·	45.50	**44.50**
uEB AFP	26.50	**29.00**	**28.50**	**48.00**	·	**60.00**
uEB DCP	19.00	19.00	29.50	16.50	27.50	·

Web Table 2

Percentage of times each method has a positive screen first in the HALT-C Trial. The $(i, j)^{th}$ entry corresponds to the cross-validated percentage of times the i^{th} method has a positive screen first. mFB-J: joint multivariate fully Bayesian, mFB-I: independent multivariate fully Bayesian, uFB: univariate fully Bayesian and uEB: parametric empirical Bayes

	mFB-J	mFB-I	uFB AFP	uFB DCP	uEB AFP	uEB DCP
mFB-J	·	4.50	**16.50**	**46.30**	4.50	**40.74**
mFB-I	**6.00**	·	**16.50**	**45.37**	6.50	**39.81**
uFB AFP	8.00	10.50	·	**47.22**	8.00	**41.67**
uFB DCP	12.04	9.26	25.00	·	8.33	2.78
uEB AFP	**29.00**	**29.50**	**33.00**	**52.78**	·	**47.22**
uEB DCP	34.26	31.48	36.11	**37.96**	25.00	·

Web Table 3

Percentage of times each method has a positive screen first within 2-years of clinical diagnosis in the HALT-C Trial. The $(i, j)^{th}$ entry corresponds to the cross-validated percentage of times the i^{th} method has a positive screen first. mFB-J: joint multivariate fully Bayesian, mFB-I: independent multivariate fully Bayesian, uFB: univariate fully Bayesian and uEB: parametric empirical Bayes

	mFB-J	mFB-I	uFB AFP	uFB DCP	uEB AFP	uEB DCP
mFB-J	·	**4.50**	**10.50**	**50.93**	12.50	**44.44**
mFB-I	4.00	·	**10.50**	**42.59**	12.50	**36.11**
uFB AFP	6.00	6.50	·	**47.22**	10.00	**43.52**
uFB DCP	13.89	10.19	23.15	·	16.67	0.00
uEB AFP	**18.50**	**21.00**	**20.50**	**55.56**	·	**39.81**
uEB DCP	29.63	25.93	29.63	**34.26**	25.93	·

Web Table 4

Percentage of times each method has a positive screen first within 1-years of clinical diagnosis in the HALT-C Trial. The $(i, j)^{th}$ entry corresponds to the cross-validated percentage of times the i^{th} method has a positive screen first. mFB-J: joint multivariate fully Bayesian, mFB-I: independent multivariate fully Bayesian, uFB: univariate fully Bayesian and uEB: parametric empirical Bayes

Parameter	Scenario A	Scenario B	Scenario C
σ_1^2	0.23	0.23	0.23
$\mu_{\theta 1}$	2.43	2.43	2.43
$\sigma_{\theta 1}^2$	0.79	0.79	0.79
$\mu_{\gamma 1}$	1.87	0.87	1.87
$\sigma_{\gamma 1}^2$	1.61	0.3	0.3
$\mu_{\tau 1}$	1.05	1.05	1.05
$\sigma_{\tau 1}^2$	0.82	0.82	0.82
σ_2^2	1.35	1.35	1.35
$\mu_{\theta 2}$	3.10	3.10	3.10
$\sigma_{\theta 2}^2$	0.80	0.80	0.80
$\mu_{\gamma 2}$	1.92	0.92	0.92
$\sigma_{\gamma 2}^2$	0.05	0.05	0.05
$\mu_{\tau 2}$	0.56	0.56	0.56
$\sigma_{\tau 2}^2$	0.58	0.58	0.58
σ_3^2	0.80	0.80	0.80
$\mu_{\theta 3}$	2.75	2.75	2.75
$\sigma_{\theta 3}^2$	0.79	0.79	0.79
$\mu_{\gamma 3}$	1.00	0.65	0.65
$\sigma_{\gamma 3}^2$	0.20	0.10	0.10
$\mu_{\tau 3}$	0.75	0.75	0.75
$\sigma_{\tau 3}^2$	0.70	0.70	0.70
μ_I	0.15	0.15	0.15
η_I	0.1	0.1	0.1

Web Table 5
Fixed parameter values used in simulation study to generate data.

	Marker (1) (k=1)	Marker (2) (k=2)	Marker (3) (k=3)
$\mu_{\theta k}$	$N(2, 0.1)$	$N(3, 0.1)$	$N(2, 0.1)$
$\sigma^2_{\theta k}$	$IG(2, 0.05)$	$IG(2, 0.05)$	$IG(2, 0.05)$
$\mu_{\gamma k}$	$N(\log(16), 0.05)$	$N(\log(16), 0.05)$	$N(\log(16), 0.05)$
$\sigma^2_{\gamma k}$	$IG(4, 0.1)$	$IG(4, 0.1)$	$IG(4, 0.1)$
$\mu_{\tau k}$	$N(1, 0.1)$	$N(1, 0.1)$	$N(1, 0.1)$
$\sigma^2_{\tau k}$	$IG(10, 6.19)$	$IG(10, 6.19)$	$IG(10, 6.19)$
		$\frac{\exp(\mu_I)}{1+\exp(\mu_I)} \sim Beta(30, 30)$	
		$\eta_I \sim Beta(5, 45)$	

Web Table 6

Prior distributions for the joint model parameters that were used in all scenarios of the simulations.

Scenario D					
Biomarker	mFB-J	mFB-I	uFB	uEB	ST
(1)			63.43 (0.49)	62.90 (0.50)	49.33 (0.52)
(2)	78.38 (0.46)	78.77 (0.42)	60.18 (0.54)	59.48 (0.54)	53.07 (0.53)
(3)			54.79 (0.54)	54.79 (0.52)	44.34 (0.53)

Web Table 7

Summary of simulation results in 200 studies: empirical mean ROC(0.1) (empirical standard error of the mean). mFB-J: joint multivariate fully Bayesian, mFB-I: independent multivariate fully Bayesian, uFB: univariate fully Bayesian, uEB: parametric empirical Bayes and ST: single threshold

Scenario A					
Biomarker	mFB-J	mFB-I	uFB	uEB	ST
(1)			67.75 (0.49)	66.61 (0.50)	51.28 (0.56)
(2)	81.75 (0.41)	81.67 (0.41)	64.20 (0.56)	63.03 (0.51)	55.48 (0.52)
(3)			58.58 (0.52)	58.41 (0.49)	46.88 (0.50)
Scenario B					
Biomarker	mFB-J	mFB-I	uFB	uEB	ST
(1)			63.97 (0.48)	64.18 (0.47)	45.01 (0.53)
(2)	72.21 (0.46)	71.75 (0.47)	54.52 (0.54)	54.56 (0.55)	44.81 (0.49)
(3)			55.83 (0.54)	54.82 (0.52)	41.97 (0.55)
Scenario C					
Biomarker	mFB-J	mFB-I	uFB	uEB	ST
(1)			70.91 (0.47)	69.35 (0.47)	55.91 (0.49)
(2)	77.96 (0.43)	77.63 (0.42)	54.55 (0.51)	55.08 (0.55)	45.20 (0.51)
(3)			56.18 (0.54)	54.71 (0.46)	42.22 (0.50)
Scenario D					
Biomarker	mFB-J	mFB-I	uFB	uEB	ST
(1)			63.67 (0.48)	62.99 (0.50)	49.36 (0.52)
(2)	78.62 (0.44)	78.82 (0.42)	60.26 (0.52)	59.39 (0.52)	52.92 (0.51)
(3)			54.77 (0.53)	54.67 (0.51)	44.28 (0.51)

Web Table 8

Summary of simulation results in 200 studies: empirical mean sensitivity corresponding to threshold established in training data (empirical standard error of the mean). mFB-J: joint multivariate fully Bayesian, mFB-I: independent multivariate fully Bayesian, uFB: univariate fully Bayesian, uEB: parametric empirical Bayes and ST: single threshold.

Scenario A					
Biomarker	mFB-J	mFB-I	uFB	uEB	ST
(1)			88.46 (0.07)	88.36 (0.07)	88.55 (0.13)
(2)	87.40 (0.08)	87.48 (0.08)	88.71 (0.07)	88.65 (0.07)	88.64 (0.10)
(3)			89.13 (0.07)	89.03 (0.07)	89.04 (0.10)
Scenario B					
Biomarker	mFB-J	mFB-I	uFB	uEB	ST
(1)			88.69 (0.08)	88.61 (0.07)	88.91 (0.13)
(2)	88.32 (0.08)	88.36 (0.07)	89.47 (0.07)	89.31 (0.07)	89.30 (0.10)
(3)			89.36 (0.07)	89.34 (0.07)	89.25 (0.11)
Scenario C					
Biomarker	mFB-J	mFB-I	uFB	uEB	ST
(1)			88.30 (0.07)	88.16 (0.07)	88.21 (0.13)
(2)	87.78 (0.08)	87.81 (0.08)	89.49 (0.07)	89.24 (0.07)	89.30 (0.09)
(3)			89.41 (0.07)	89.36 (0.07)	89.30 (0.10)
Scenario D					
Biomarker	mFB-J	mFB-I	uFB	uEB	ST
(1)			88.40 (0.07)	88.32 (0.08)	88.43 (0.13)
(2)	87.46 (0.08)	87.36 (0.08)	88.86 (0.07)	88.74 (0.07)	88.74 (0.10)
(3)			89.19 (0.07)	89.06 (0.07)	89.07 (0.11)

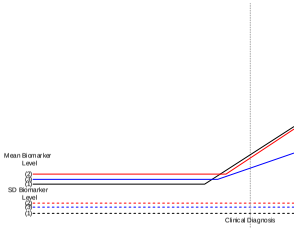
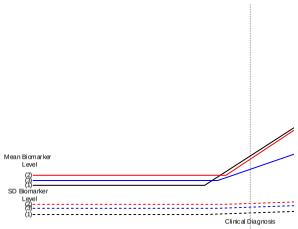
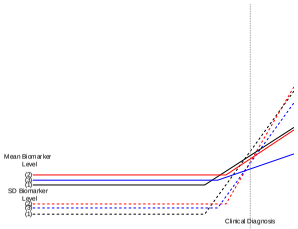
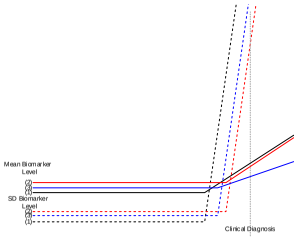
Web Table 9

Summary of simulation results in 200 studies: empirical mean specificity corresponding to threshold established in training data (empirical standard error of the mean). mFB-J: joint multivariate fully Bayesian, mFB-I: independent multivariate fully Bayesian, uFB: univariate fully Bayesian, uEB: parametric empirical Bayes and ST: single threshold.

	mFB-J	mFB-I	uFB (1)	uFB (2)	uFB (3)	uEB (1)	uEB (2)	uEB (3)
mFB-J	*77.49*	**2.30**	**31.32**	**41.17**	**48.32**	**29.85**	**40.04**	**47.00**
mFB-I	2.24	*77.48*	**31.06**	**41.15**	**48.05**	**29.89**	**40.08**	**46.89**
uFB (1)	5.82	5.38	*53.15*	**35.46**	**37.96**	5.37	**34.66**	**37.80**
uFB (2)	6.87	6.77	26.17	*46.98*	**32.04**	25.42	4.79	**31.07**
uFB (3)	6.72	6.56	21.43	24.40	*39.87*	20.78	24.06	5.28
uEB (1)	13.75	13.86	**15.14**	**40.98**	**43.57**	*59.19*	**38.69**	**41.52**
uEB (2)	13.77	13.71	31.18	**14.72**	**38.22**	28.84	*53.78*	**35.54**
uEB (3)	13.37	13.38	27.18	30.50	**16.00**	24.81	28.14	*47.20*

Web Table 10

Percentage of times each method has a positive screen first after disease onset in Scenario A of the simulation study. The $(i, j)^{th}$ entry corresponds to the empirical mean percentage of times the i^{th} method has a positive screen first. The $(i, i)^{th}$ corresponds to the empirical mean ROC(0.1) of the i^{th} method after disease onset. mFB-J: joint multivariate fully Bayesian, mFB-I: independent multivariate fully Bayesian, uFB: univariate fully Bayesian and uEB: parametric empirical Bayes.

	Entire screening period	2-year prior to clinical diagnosis	1-year prior to clinical diagnosis
	**Scenario A**		
	81.52 (0.41)	72.21 (0.49)	68.52 (0.51)
	**Scenario E**		
	81.72 (0.42)	72.96 (0.50)	69.21 (0.53)
	**Scenario F**		
	81.78 (0.41)	72.07 (0.45)	67.97 (0.48)
	**Scenario G**		
	82.95 (0.40)	71.05 (0.46)	65.83 (0.49)

Web Table 11

Summary of simulation results in 200 studies: empirical mean ROC(0.1) (empirical standard error of the mean) of the proposed joint multivariate fully Bayesian approach. The mean and standard deviation of the biomarker trajectories assumed for each scenario are shown in column 1. We consider three time periods to evaluate the impact of increasing variability in the biomarkers in the time periods close to diagnosis.