Product Lifecycle Services (PLS), NBS

A Semi-parametric Bayesian Model for Personalized Medicine

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Introduction

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Personalized Medicine

Preventative and predictive way to manage a better healthcare

- Utilizes patient's virtual cloud of data points – genetics, medical history, demographics, environment, disease type, etc.
- Demystify disease and population subtype characteristics
- Potentially predict risk factors, and treatment outcomes
- Help clinicians to make right decisions about patients

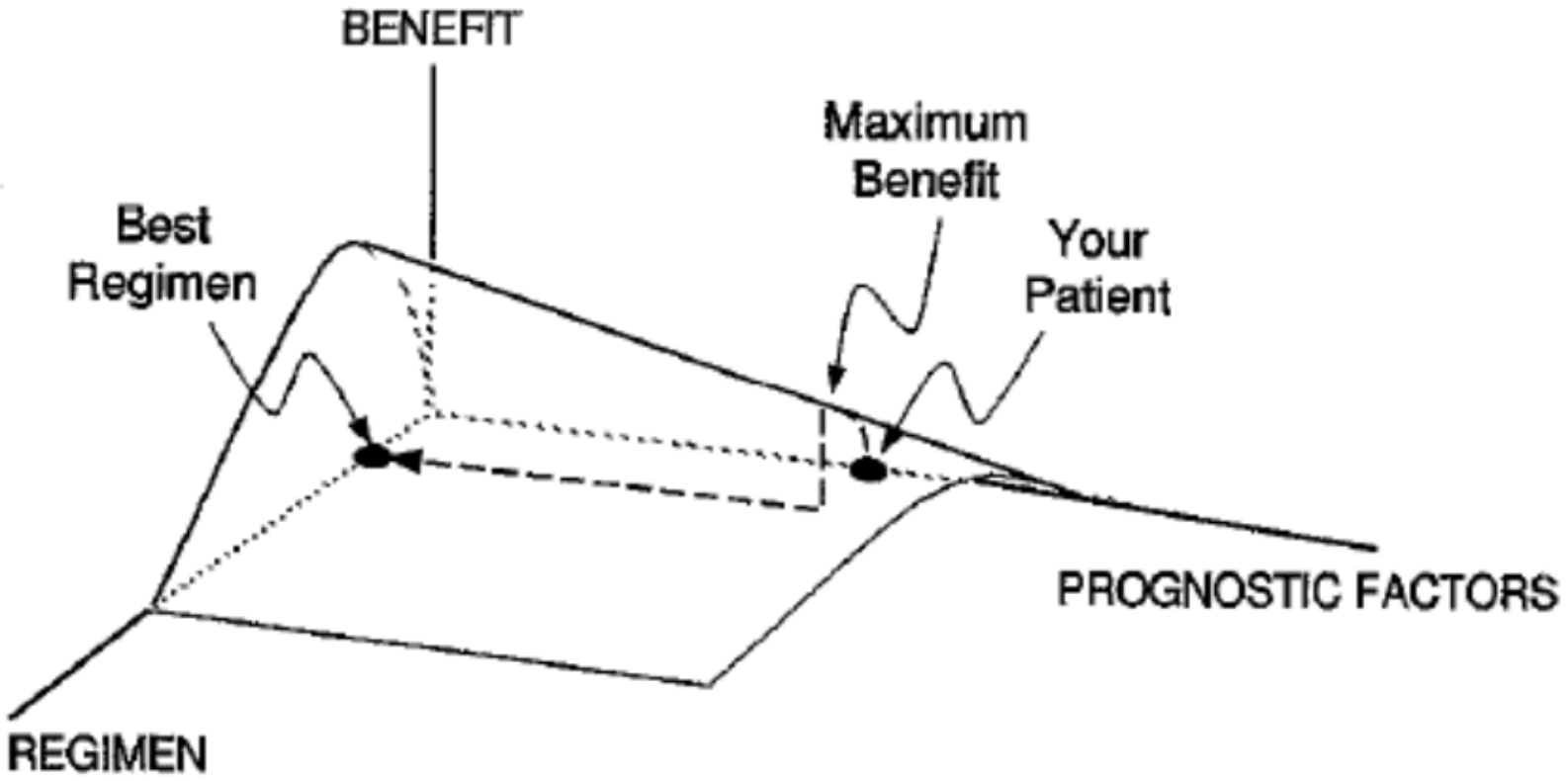
Adaptive Trial Designs for Personalized Therapy

- Adaptive trial designs which consider many therapies in the same trial, and using accruing data and **Bayesian techniques** to gradually matching patient subtypes with their most appropriate therapies.
- *"Improved utilization of adaptive and Bayesian methods" could help resolve low success rate of and expense of phase 3 clinical trials* - Janet Woodcock, Director CDER FDA
- FDA's Critical Path Opportunities Report (2006) – *"Uncovered a consensus that the two most important areas for improving medical product development are biomarker development and streamlining clinical trials."*

Innovations in Trial Designs - Use of Bayesian Techniques

- **I-SPY 2 –** In 2010, the Biomarkers Consortium initiated a groundbreaking adaptive biomarker-driven trial in neo-adjuvant breast cancer
  - Identify improved treatment regimens for subsets on the basis of molecular characteristics (biomarker signatures) of their disease
  - Uses Bayesian predictive probability to 'graduate' or 'drop-off' any therapy from the trial with their corresponding biomarker signature(s)
- **ADAPT- IT** – Funded jointly by the NIH and FDA to bring innovative trial design to the NETT (Neurological Emergencies Treatment Trials) network.
  - The ADAPT-IT teams explored and developed confirmatory adaptive clinical trial designs with the individual trial teams of NETT (five teams).

Therapeutic Response Surface – An Example (Clin Pharmacol Ther 1997)



Role of Bayesian Techniques in Personalized Medicine

- Efficiently *utilizes* the information to *provide* the disease sub populations with the ‘best possible’ regimen thereby *protecting* patients from getting over-treated with ineffective and excessively toxic regimen.
- To develop innovative clinical trial **designs**
  – Monitoring strategies, improved dose-finding strategies, adaptive randomization, and improved screening designs
- To develop innovative **methods** to analyze data from collaborative research studies
  – Data mining, adaptive learning, and integrating information across multiple platforms

Objective

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Objectives

➢ Our Objective

- To build a semi-parametric Bayesian model for personalized medicine

➢Ultimate Clinical Objective

- Guide clinicians to recommend the most effective treatment to patients of certain age and belonging to distinctly different disease subtypes
- Monitor patient's response over the years and utilizing it for dynamic decisions

Data Description

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Description of the data

➢The data comprises of:

- Response
  – **Treatment Response** – '*y*' (continuous, lower the better)
- Predictors
  – **Age** – '*x*' (in years)
  – **Treatment** – 0 => Standard Treatment, 1 => New Treatment
  – **Population/ Disease Subtype** – 0, 1 and 2

➢We used *simulated* data for our problem, although real data from various historical clinical trials, comprises of similar predictors, may also be analyzed.

Data Simulation

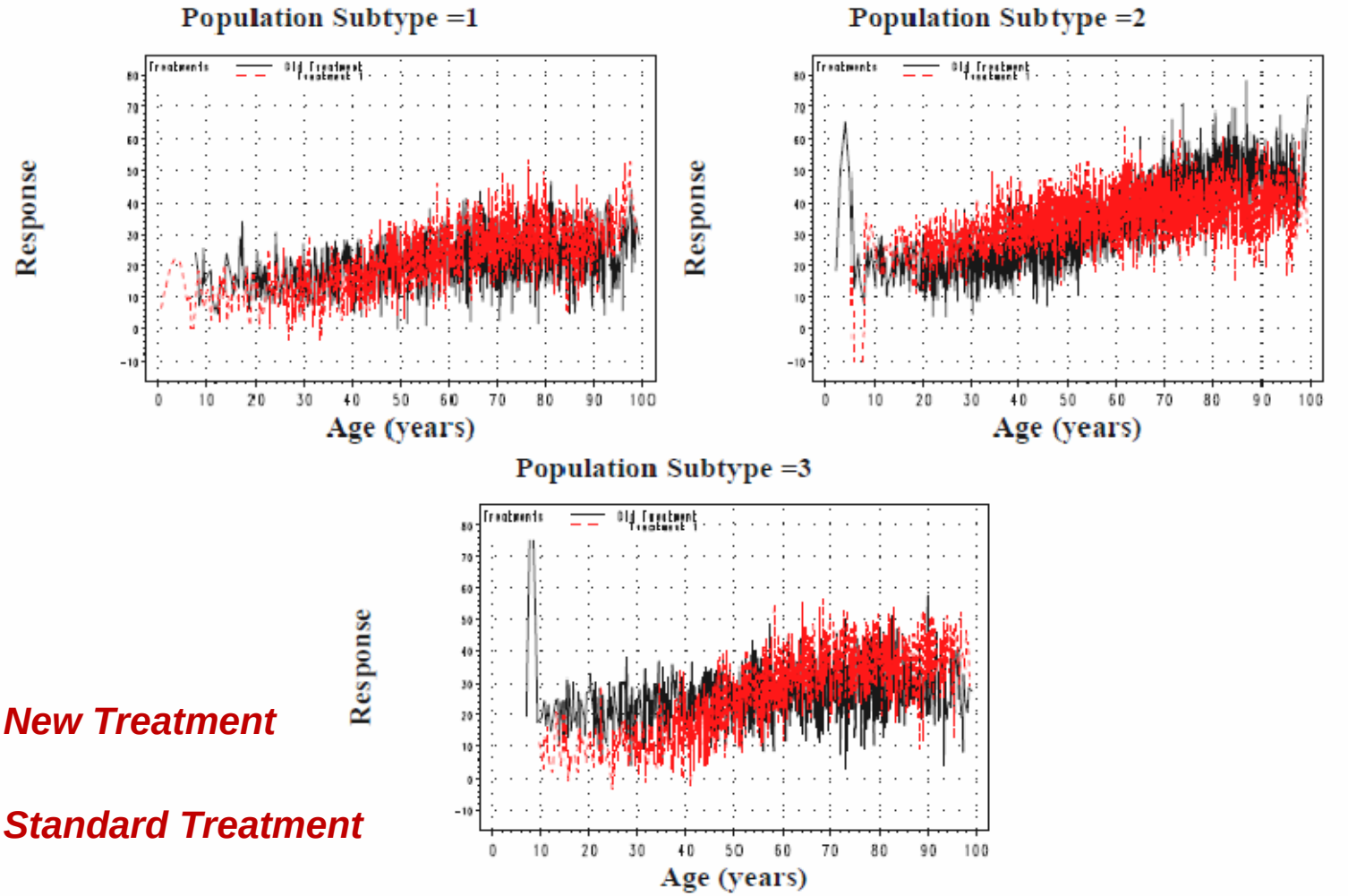
- The data were split into a ***training*** set (n_1 =10,000) and a ***test*** set (n_2 =1,000).
- The response and predictor variables for each sample dataset are generated as follows
  - $Treatment_k \sim Bernoulli\ (p_{trt})$ *and* $Type_k \sim Binomial\ (2, p_{type})$, where the subscript *k* denotes each sample unit in the dataset.
- Both the *success probabilities* are considered to be 0.5, which necessitates approx. 1:1 sample proportion for treatments and 1:2:1 sample proportion for population subtypes
  - $Age_k \sim 100 * Beta\ (3, 2)$
  - $Response_k \sim Normal\ (\mu, 5 + Age/25)$
  - $Mean\ respone\ \mu \sim f(Age, Type, Treatment)$

Data Simulation (continued)

- For each choices of *(Type=i, Treatment=j)*, the mean response ***μ*** has the logistic form $\mu = a_{ij} + b_{ij} * logit\{(Age - c_{ij})/d_{ij}\}$, where $logit\ (x) = e^x/(1+e^x)$
- The choices of constants *a, b, c,* and *d*, are chosen such that there exist **different treatment behaviours** over **different population subtypes**.

(Type, Treatment)	(a, b)	(c, d)
(0, 0)	(15, 10)	(50, 10)
(0, 1)	(10, 20)	(50, 10)
(1, 0)	(20, 30)	(60, 10)
(1, 1)	(25, 15)	(60, 10)
(2, 0)	(20, 10)	(50, 10)
(2, 1)	(8, 30)	(50, 10)

Figure I: Comparison of True Response over Subtypes – Training data



Methodology

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Statistical model (parametric)

- A general form of the semi-parametric model is considered

$$Y = f_{param}(age, type, treatment; \beta_k) + f_{semiparam}(age, \gamma_j) + \varepsilon$$

where ε is the unexplained (random error) component of the model

- Two linear choices of the ***parametric*** part of the functional form, depending on ***with*** or ***without*** interaction terms with ***age***, are considered as follows:

$$f_{param}(age, type, treatment; \beta_k) = \beta_0 + \beta_1 * treatment + \beta_2 * type + \beta_3 * treatment * type + \beta_4 * age * type + \beta_5 * treatment * age + \beta_6 * treatment * type * age \ldots\ldots\ldots (1)$$

$$f_{param}(age, type, treatment; \beta_k) = \beta_0 + \beta_1 * treatment + \beta_2 * type + \beta_3 * treatment * type \ldots\ldots\ldots (2)$$

Statistical model (semi-parametric)

- The unknown, ***semi-parametric*** functional form can be approximated either by a *cubic B-spline* (with varying number of knots) or by a higher order *polynomial*

- Cubic B-Spline Approximation: The following model is selected, with varied number of knots 'j' ϵ {5, 10, 15, 20, 25, etc}

$$f_{semiparam}(age;\ \gamma_j) = \sum_{j=1}^{J} B_j(age) * \gamma_j \ldots\ldots (3)$$

- Polynomial Approximation: The following (cubic and quadratic) models are selected

$$f_{semiparam}(age;\ \gamma_j) = \gamma_1 * age + \gamma_2 * age^2 + \gamma_3 * age^3 \ldots . (4)$$

$$f_{semiparam}(age;\ \gamma_j) = \gamma_1 * age + \gamma_2 * age^2 \ldots . (5)$$

Statistical model (continued)

- Based on the judgment on performances of predicting the test data set, the following models are shortlisted

Parametric part	Semi-parametric part	Number of Knots	Acronym Used
With Interactions of Age	Cubic B-Spline Model	5, 10, 15, 20, and 25	Spline-5, Spline-10, etc.
	Cubic polynomial Model	N.A.	Cubic
	Quadratic polynomial Model	N.A.	Quad
Without Interactions of Age	Cubic B-Spline Model	5, and 10	Spline-5A, Spline-10A
	Cubic polynomial Model	N.A.	Cubic-A
	Quadratic polynomial Model	N.A.	Quad-A

Prior Selection

- Flat priors for intercept term β_0 and Gaussian prior on random error component $\varepsilon \sim Normal\ (0, 1/\tau_e)$
- Independent Cauchy (t with ν=1) priors for β_k and γ_j, which is of the form $t_\nu(0, 1/\lambda)$, where λ is the scaling parameter
- In hierarchical terms, the above Cauchy priors can be reduced to

$$\beta_k \sim N\left(0, \frac{1}{\tau_{\beta_k}}\right) where\ \tau_{\beta_k} \sim G\left\{\frac{\nu}{2}, \left(\frac{\nu * \lambda}{2}\right)\right\}$$

$$\gamma_j \sim N\left(0, \frac{1}{\tau_{\gamma_j}}\right) where\ \tau_{\gamma_j} \sim G\left\{\frac{\nu}{2}, \left(\frac{\nu * \lambda}{2}\right)\right\}$$

- The hyper priors for λ and τ_e are taken as G (a_1, b_1) and G (a_2, b_2) respectively
- Small values of a_1, b_1, a_2, and b_2 (= 0.01) are chosen, for non-informative choices

Model fit

- The final shortlisted models are fitted to the training data and validated on the test set using posterior predicted response
- Models are compared using Mean Squared Prediction Error (MSPE) and coverage of prediction intervals (based on HPD)
- The model which provides the least MSPE and better coverage (95% prediction interval) is declared to be the ‘best’ under our set-up
- Based on the analyses, Figure II, and Figure III, the **cubic B-Spline model with 5 knots under ‘presence of interaction terms’** is selected
- A detailed prior sensitivity result proves the robustness and supports the finding

Figure II: Mean Squared Prediction Error (MSPE) for various models

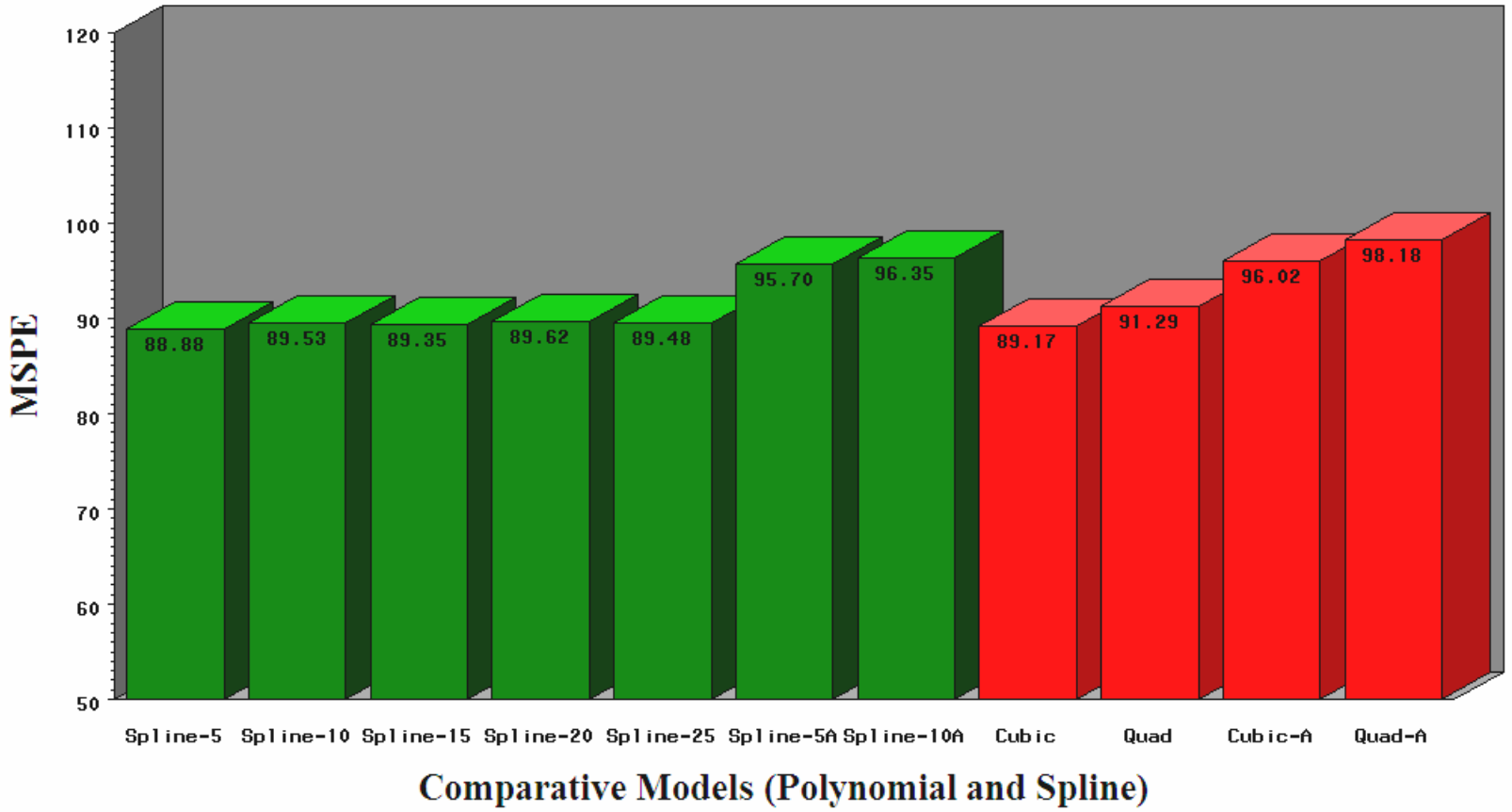

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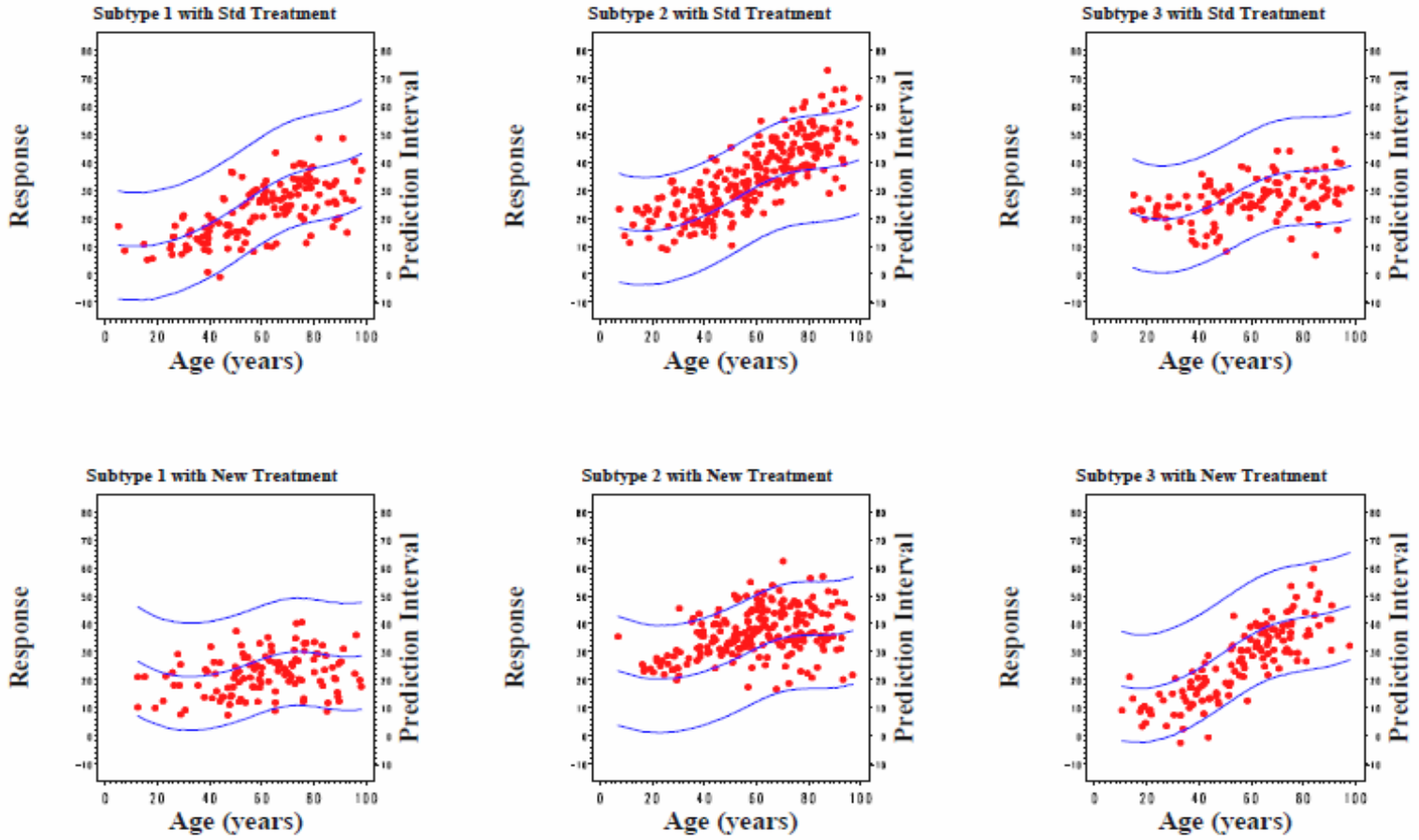
Figure III: 95% Prediction interval over cohorts – B Spline (5 knots)



Computational Details

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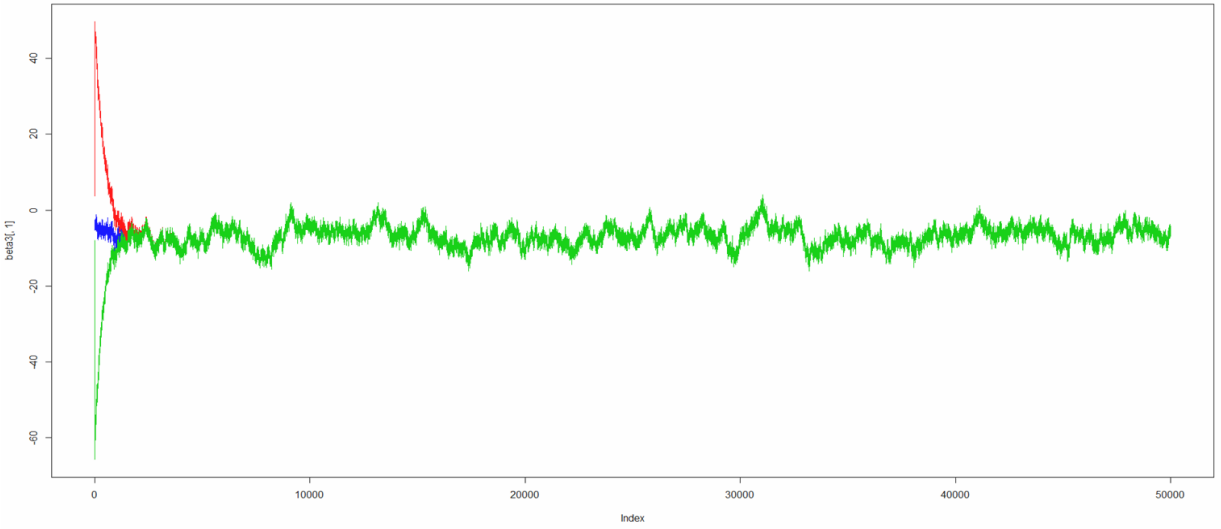
Computational details

- Random samples from posterior distributions were drawn using MCMC algorithm
- *Blocked Gibbs* sampler was applied, with β_0, coefficient vector, τ_e, and λ as four blocks
- Posterior statistics were estimated with **50,000** iterations and **1,000** burn-in samples
- The different chains are found to converge, proving the effectiveness of the algorithm
- The trace plot for β_3, using three independent chains with different initial values is shown below



Results

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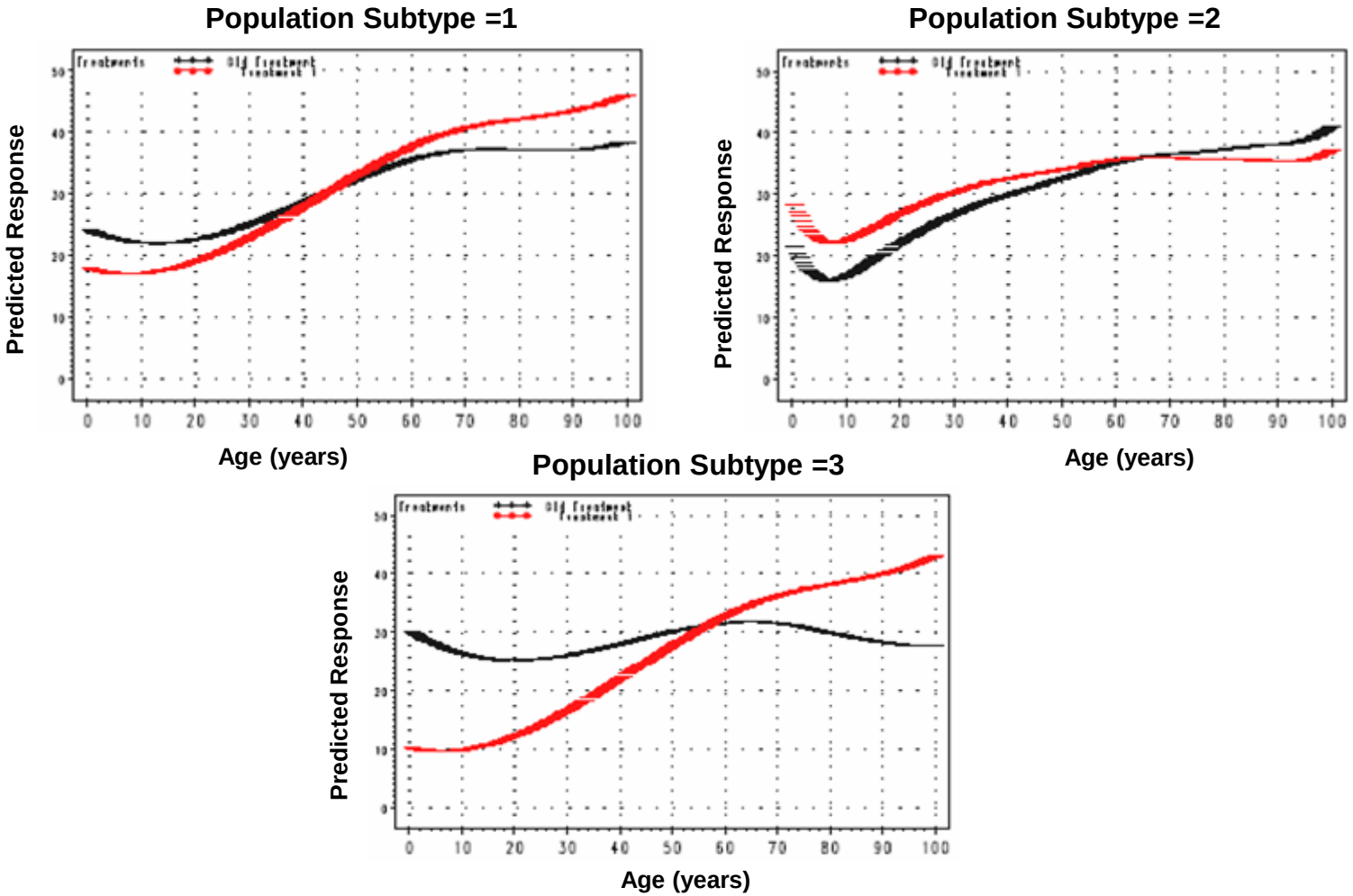
Posterior Summaries of Model Parameters

Parameters	Mean (s.d.)	Parameters	Mean (s.d.)
Intercept	10.58 (1.773)	Treatment*Age*Type	0.25 (0.013)
Treatment	19.97 (1.040)	Basis Spline parameter	-2.62 (2.588)
Type	7.00 (0.597)	Basis Spline parameter	6.59 (1.562)
Treatment*Type	-13.15 (0.852)	Basis Spline parameter	28.62 (2.022)
Age*Type	-0.09 (0.010)	Basis Spline parameter	27.82 (1.900)
Treatment*Age	-0.35 (0.016)	Basis Spline parameter	32.48 (2.239)
Error precision	0.01 (0.001)	Lamda λ	45.78 (40.861)

- Posterior estimate of the scale parameter λ is high – also sensitive to choices of priors and ν
- ***General Rule***: The effect of a model parameter can be considered to be insignificant if the posterior estimate is close to zero and with very high precision

Figure IV: Comparison of predicted response over population subtypes



Results aimed for medics

- The clinical behaviors in **Subtype I** are moderately different
  - New treatment promises to target younger patients (< 40 years), very less effective otherwise
  - Standard treatment is more effective for older patients, consistent performance for this group
- On the contrary, the clinical behaviors in **Subtype II** is almost similar!
  - New treatment fails to be more efficacious, except for very older patients (> 70 years)
  - Existing standard treatment over-performs the new one, though marginally
- The clinical behaviors of the two treatments in **Subtype III** is entirely different!
  - New treatment works exceedingly well, but only for patients less than 50 years of age
  - Performance of the standard treatment is consistent over age, recommended for older patients
- Overall, the new treatment fails to show consistent performance in older patients
- *The performance plots would highly benefit clinicians – helps to follow-up patients*

Prediction Intervals of Response for Treatment and Treatment Difference

➢ We consider *nine* individuals (young, middle, old) belonging to three different subtypes (I, II, and III)

Population Subtype	*Age*	*Standard Treatment*	*New Treatment*	*Difference (New – Std)*
Subtype I	20	(4.63, 36.38)	(1.08, 32.80)	(-4.74, -2.14)
Subtype I	50	(16.78, 48.30)	(17.43, 49.02)	(0.07, 1.39)
Subtype I	80	(26.37, 57.83)	(31.28, 62.77)	(4.14, 5.77)
Subtype II	20	(-0.33, 31.38)	(4.36, 36.11)	(4.03, 5.51)
Subtype II	50	(14.59, 45.80)	(16.10, 47.32)	(1.19, 1.93)
Subtype II	80	(26.91, 58.54)	(25.24, 56.84)	(-2.09, -1.14)
Subtype III	20	(7.26, 39.24)	(-5.70, 26.24)	(-14.15, -11.58)
Subtype III	50	(14.52, 45.96)	(12.09, 43.57)	(-2.98, -1.69)
Subtype III	80	(19.19, 50.67)	(27.37, 58.91)	(7.43, 9.07)

Prior Sensitivity

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Prior Sensitivity

- To check any variations in model performance and posterior estimators
- *Three* choices of ν are considered, choices indicate the distributions – *Cauchy, t,* and *Normal*
- For each such choices of ν, *three* choices of $\mathbf{a_1}$, $\mathbf{b_1}$, $\mathbf{a_2}$, and $\mathbf{b_2}$ are chosen
- The choices on hyper priors indicate weak informative to non informative behaviours

Choices of (a_1, b_1) and (a_2, b_2)	***Degrees of freedom (v)***	***Prior Index***	***Remarks***
(0.1, 0.1) (0.1, 0.1)	1, 10, and 100	1, 2, and 3	Weakly Informative
(0.01, 0.01) (0.01, 0.01)	1, 10, and 100	*4*, 5, and 6	Non Informative
(0.001, 0.001) (0.001, 0.001)	1, 10, and 100	7, 8, and 9	Most Non Informative

Figure V: Prior Sensitivity plot of Model parameters

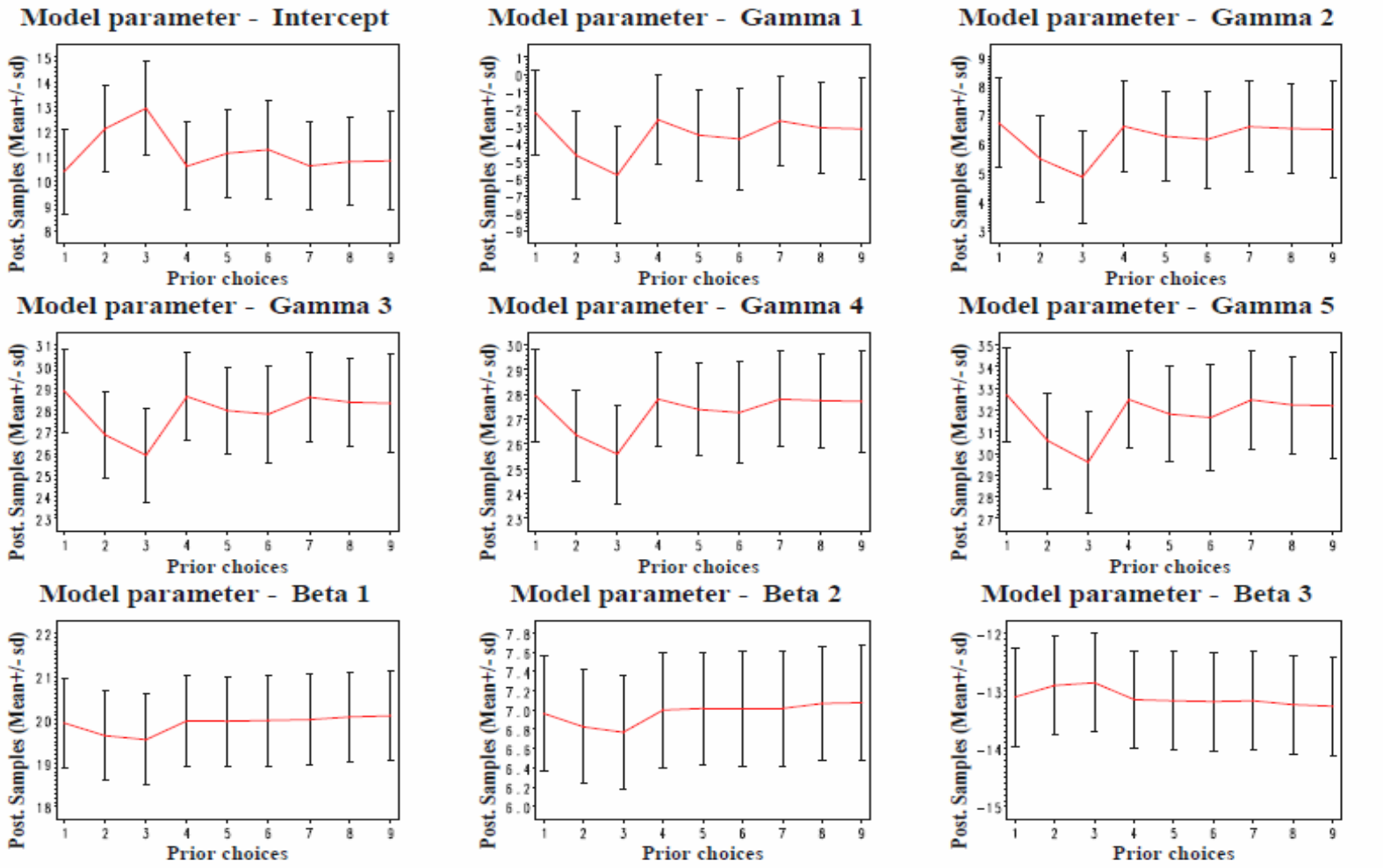

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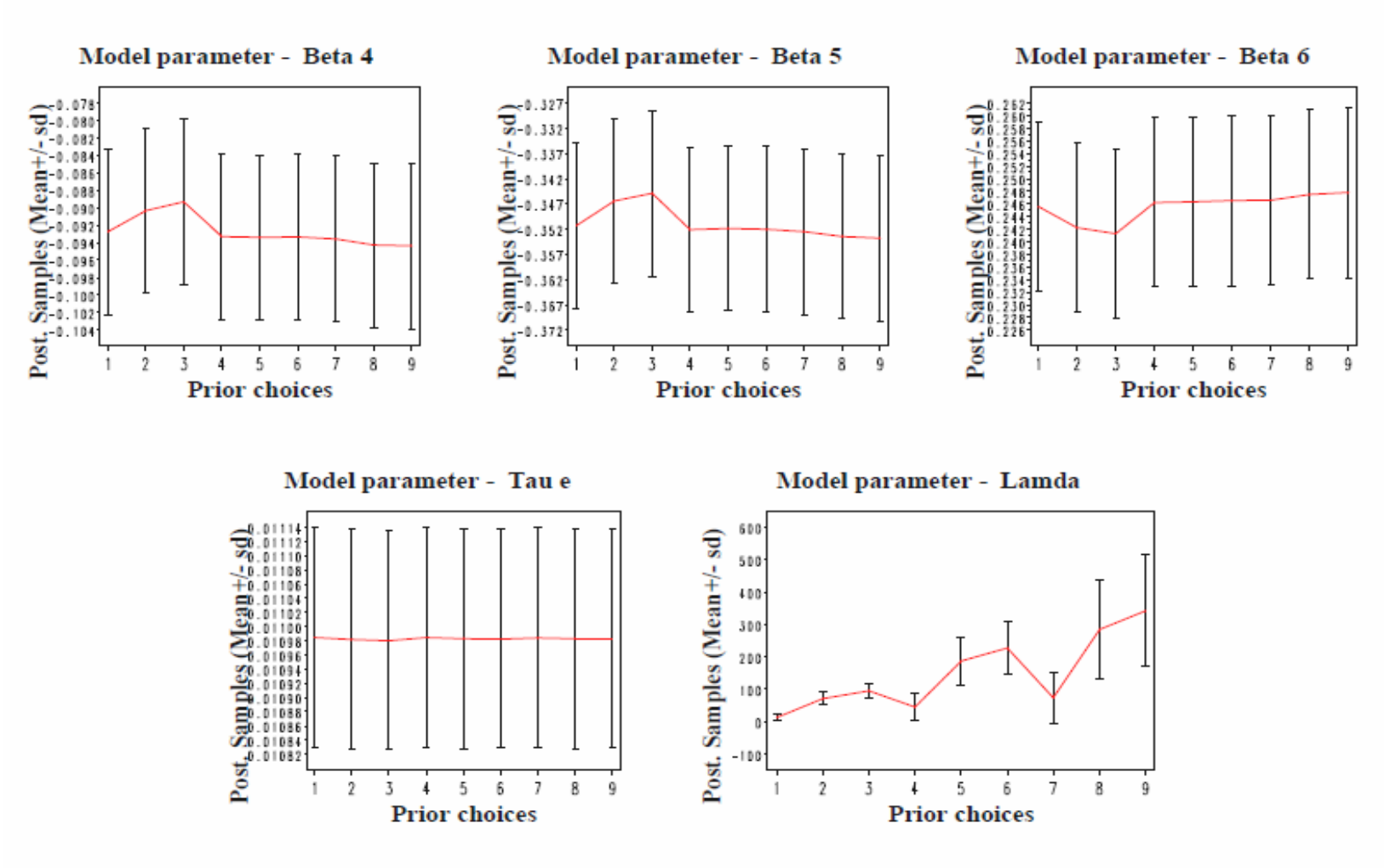
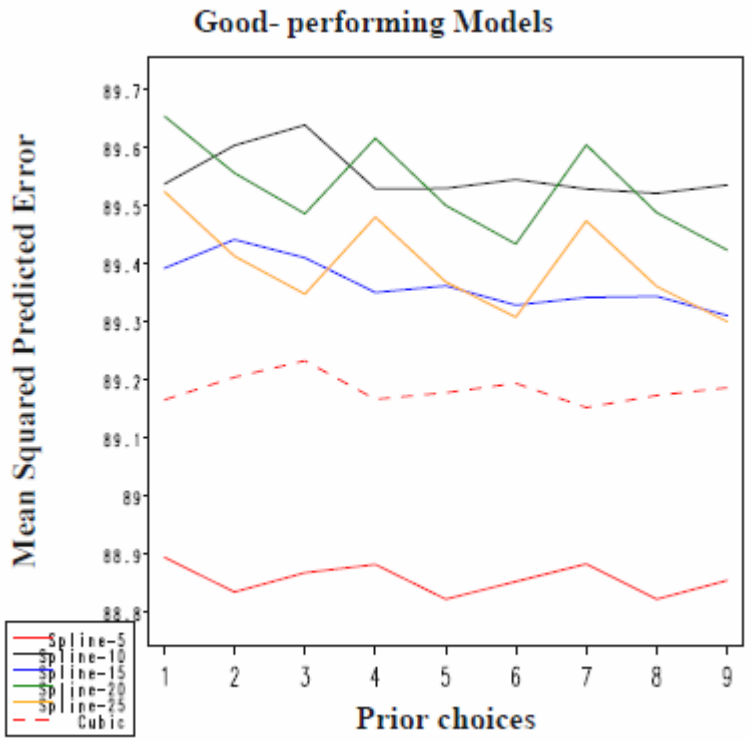
Figure VI: Prior Sensitivity plot of Model parameters

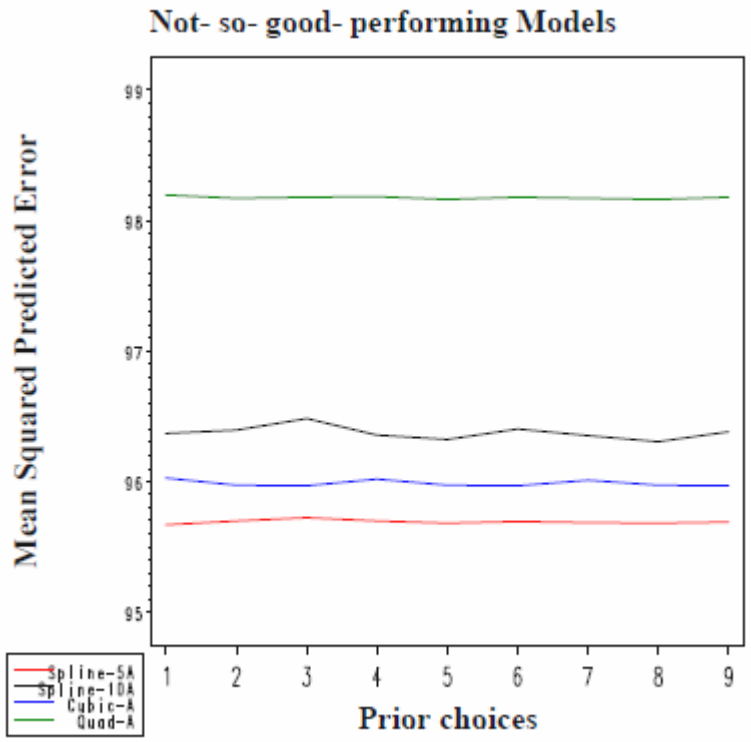


Prior Sensitivity

- The error precision remains unaffected
- The spline parameters show the same pattern and stabilizes with ‘Prior – 4’ onwards
- The ‘non-spline’ model parameters also stabilizes with ‘Prior – 4’ onwards
- The estimate (and variability) of scale parameter λ
  - Increases with increase in $\boldsymbol{\nu}$, with non-informative index ($\mathbf{a_1}$, $\mathbf{b_1}$) kept constant
  - Increases rapidly with increase in non-informative index, with $\boldsymbol{\nu}$ kept constant
- Justified to consider ‘Prior – 4’ in our model analyses

Figure VII: Prior Sensitivity plot of Model Diagnostics





- *The MSPE of the model 'Quad' is around **91.2**, which is between 'good' and 'not-so-good' models*
- The performance of the 'Spline-5' model is ***strongly robust*** under prior variations

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Conclusion

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Conclusion

- The Bayesian semi-parametric model, uses prior information about response/ factors, demystifies patient characteristics data, and helps clinicians to
  - Prevent patients by predicting risks and responses
  - Take right decisions to match individuals/ subtypes with best treatment regimens
  - Helps to monitor patients by dynamically varying treatments
- Protect patients getting over-treated with non-efficacious and more toxic drugs
- Helps to provide and maintain a better healthcare

Extensions

- In scenarios where more factors (genetics, safety, demographics, etc) are to be utilized, non-parametric Bayesian approaches like Dirichlet Process Mixture (DPM) models can be applied and compared with the semi-parametric cubic B-Spline models

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Thank you

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