

# Multi-timescale Multi-state Models

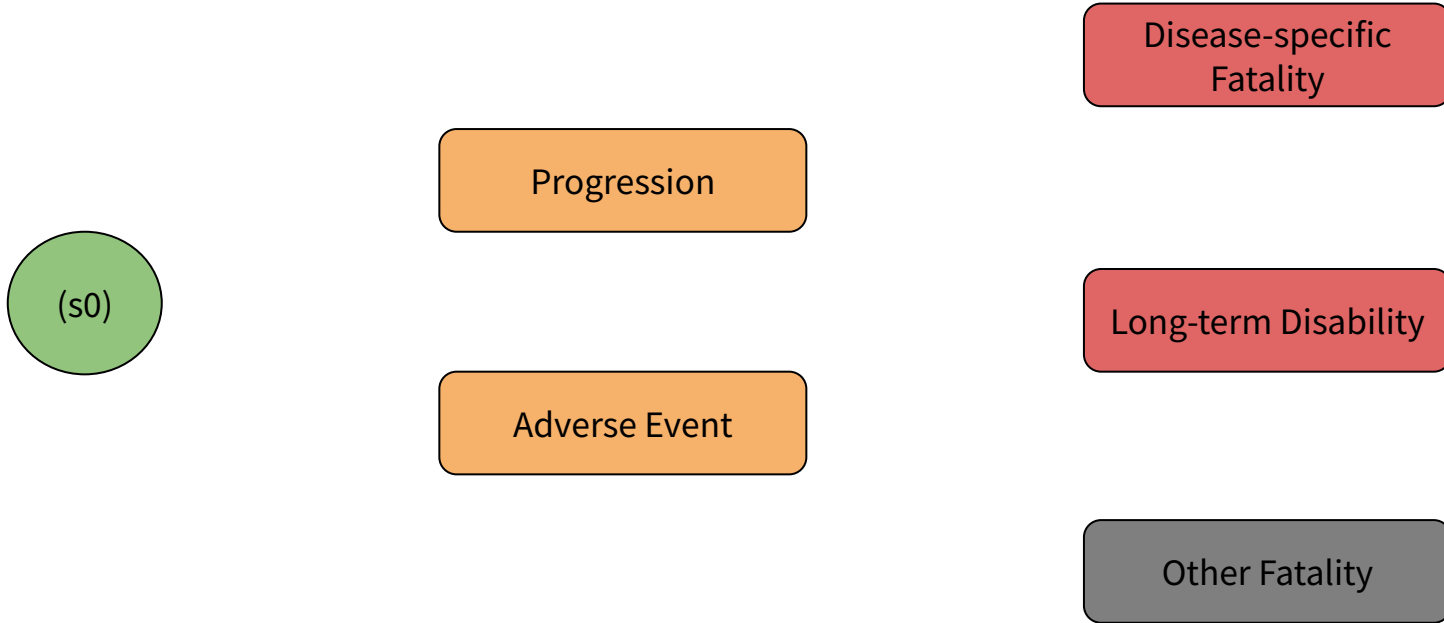
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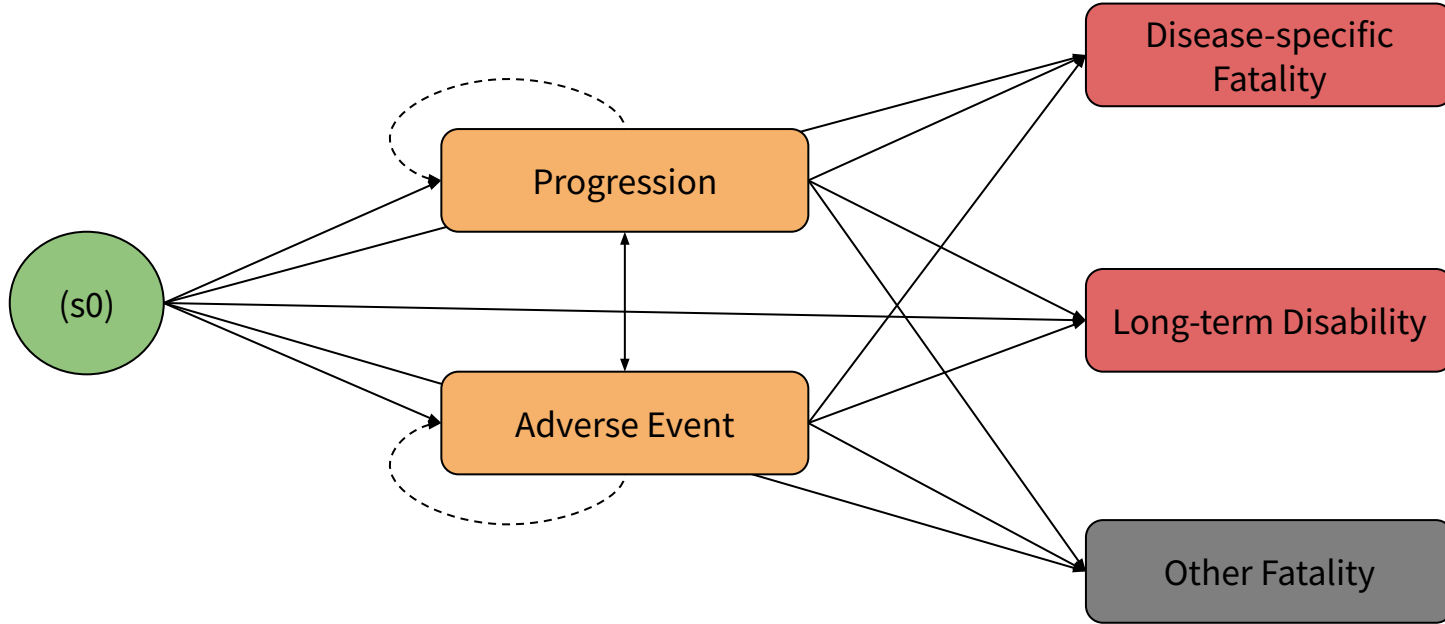
25 Oct 2024



# Anatomy of a Multi-state Model



# Anatomy of a Multi-state Model



# Why Multistate?

- Model event risk *jointly*
- Evaluate influence of previous events on future event risk
- Adjust for informative censoring
- Simulate likely clinical outcomes

# Likelihood

The model implemented here is inspired by that described in Kneib and Hennerfeind (2008).

For each possible transition  $h$  among all transitions  $1..H$  among the states, we estimate the probability of that transition  $\lambda_i^{(h)}(t)$  for each subject  $i$  at time  $t$ . Each transition probability is estimated using a hazard rate model analogous to a continuous-time hazard rate model used in a Cox survival analysis:

$$\lambda_i^{(h)}(t) = g^{(h)}(t) \exp(\eta_i^{(h)}(t))$$

where  $g^{(h)}(t)$  represents the baseline hazard for transition  $h$  and the relative log-hazard  $(\eta_i^{(h)}(t))$  for subject  $i$  is defined as follows:

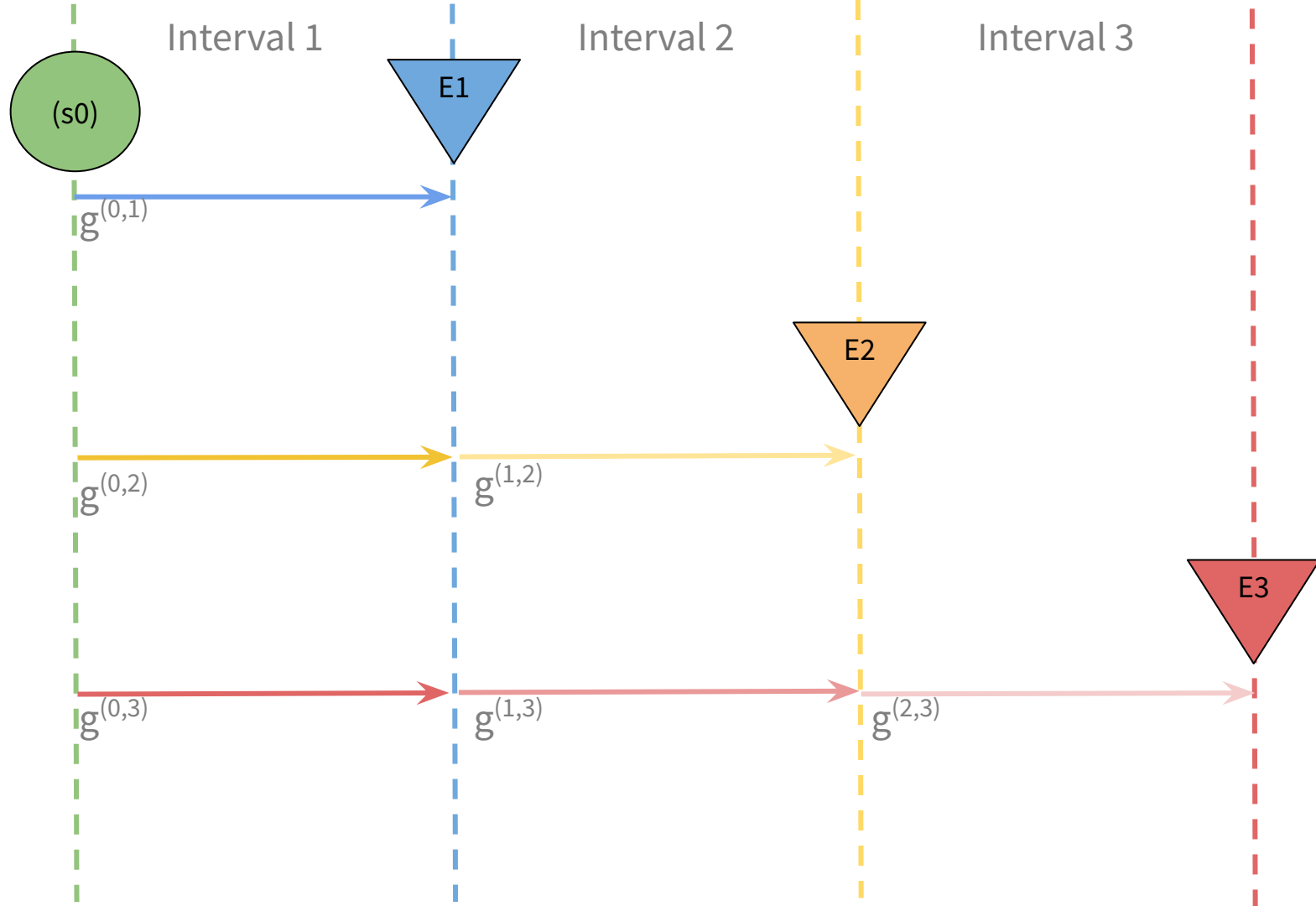
$$\eta_i^{(h)}(t) = \underbrace{x_i^{(h)} \beta^{(h)}}_{\text{covariates}} + \underbrace{\sum_{c=1}^{C^{(h)}} k^{(h)}(w_{ci}^{(h)}, \gamma^{(h)})}_{\text{nonlinear effects}} + \underbrace{\sum_{l=1}^L \nu_{li}(t) \xi_l^{(h)}}_{\text{exposure}} + \underbrace{\sum_{s=1}^S \mu_{si}(t) \phi_s^{(h)}}_{\text{event history}} + \underbrace{\alpha_i^{(h)}}_{\text{frailty}}$$

We need one more data point to define the subject-specific contribution to the likelihood: an at-risk indicator  $I_i^{(h)}(t)$  for each transition which takes values in 0, 1 to indicate whether a subject is at-risk for a transition  $h$  at time  $t$ . To connect this to the graph above, a subject in a state  $s$  is at risk for all transitions originating from  $s$ .

Given this and the estimated subject- and transition-specific hazard  $\lambda_i^{(h)}(t)$ , we define the likelihood contribution for each transition as a sum over possible transitions  $h$  in  $H$  and observed event times  $T_{ri}$  and event flags  $\delta_{ri}^{(h)}$  for each event  $r$  in  $m_i$ , where  $m_i$  represents the total number of events subject  $i$  experienced:

$$l_i = \sum_{r=1}^{m_i} \sum_{h=1}^H \left[ \underbrace{\delta_{r,i}^{(h)} \log(\lambda_i^{(h)}(T_{r,i}))}_{\text{likelihood of event}} - \underbrace{I_i^{(h)}(T_{r,i}) \int_{T_{(r-1),i}}^{T_{r,i}} \lambda_i^{(h)}(t) dt}_{\text{likelihood of survival}} \right]$$

```
for(h in 1:N_trans){  
  
  // Ragged array access  
  array[sum_risk[h]] int idx_atr = which_risk[h, 1:sum_risk[h]];  
  array[sum_trans[h]] int idx_occ = which_trans[h, 1:sum_trans[h]];  
  
  // Occurred transitions (log hazard at interval end time)  
  target += log_hazard(  
    log_C_haz[idx_occ, h], SBF[idx_occ,:], weights[h], log_w0[h]  
  );  
  
  // Transitions that were at risk (- integrated hazard over interval)  
  target += - integrate_hazard(  
    log_C_haz[idx_atr, h], SBFI[idx_atr,:], weights[h], log_w0[h]  
  );  
}
```

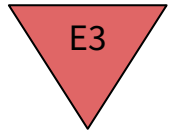
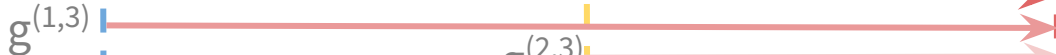
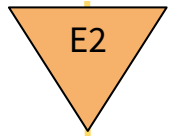
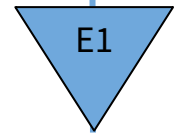
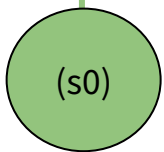




Interval 1

Interval 2

Interval 3





Save New Cohort    ↓ Biospecimen    ↓ Clinical    ↓ Manifest

|                              |                                   |
|------------------------------|-----------------------------------|
| <b>dbGaP Study Accession</b> | <a href="#">phs000178</a>         |
| <b>Project Name</b>          | Kidney Renal Clear Cell Carcinoma |

CASES AND FILE COUNTS BY DATA CATEGORY

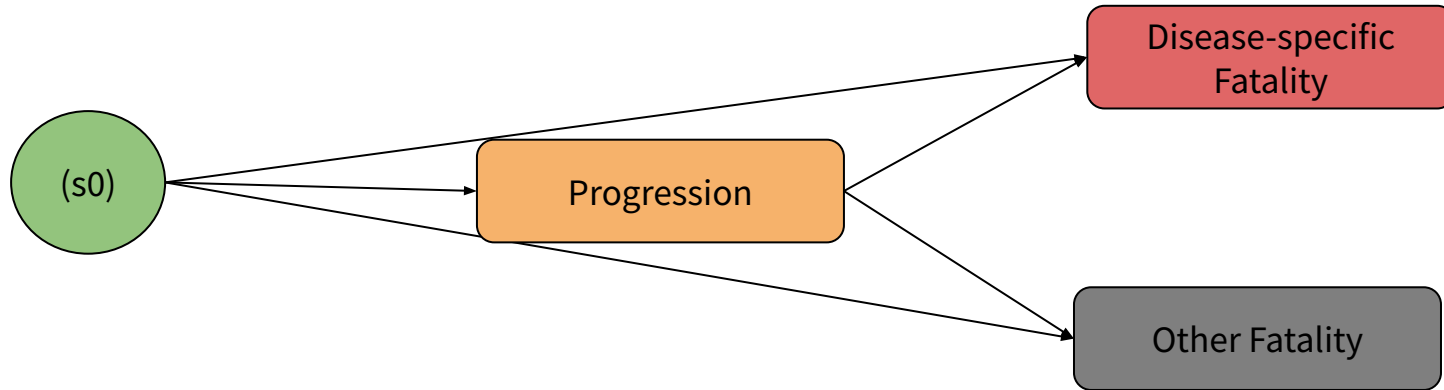
| Data Category                | Cases (n=537) | Files (n=29,352) |
|------------------------------|---------------|------------------|
| Biospecimen                  | 537 100.00%   | 3,257 11.10%     |
| Clinical                     | 537 100.00%   | 1,165 3.97%      |
| Copy Number Variation        | 534 99.44%    | 6,120 20.85%     |
| DNA Methylation              | 535 99.63%    | 2,709 9.23%      |
| Proteome Profiling           | 478 89.01%    | 478 1.63%        |
| Sequencing Reads             | 535 99.63%    | 3,603 12.28%     |
| Simple Nucleotide Variation  | 534 99.44%    | 7,082 24.13%     |
| Somatic Structural Variation | 11 2.05%      | 22 0.07%         |
| Structural Variation         | 533 99.26%    | 2,456 8.37%      |
| Transcriptome Profiling      | 534 99.44%    | 2,460 8.38%      |

# Example data

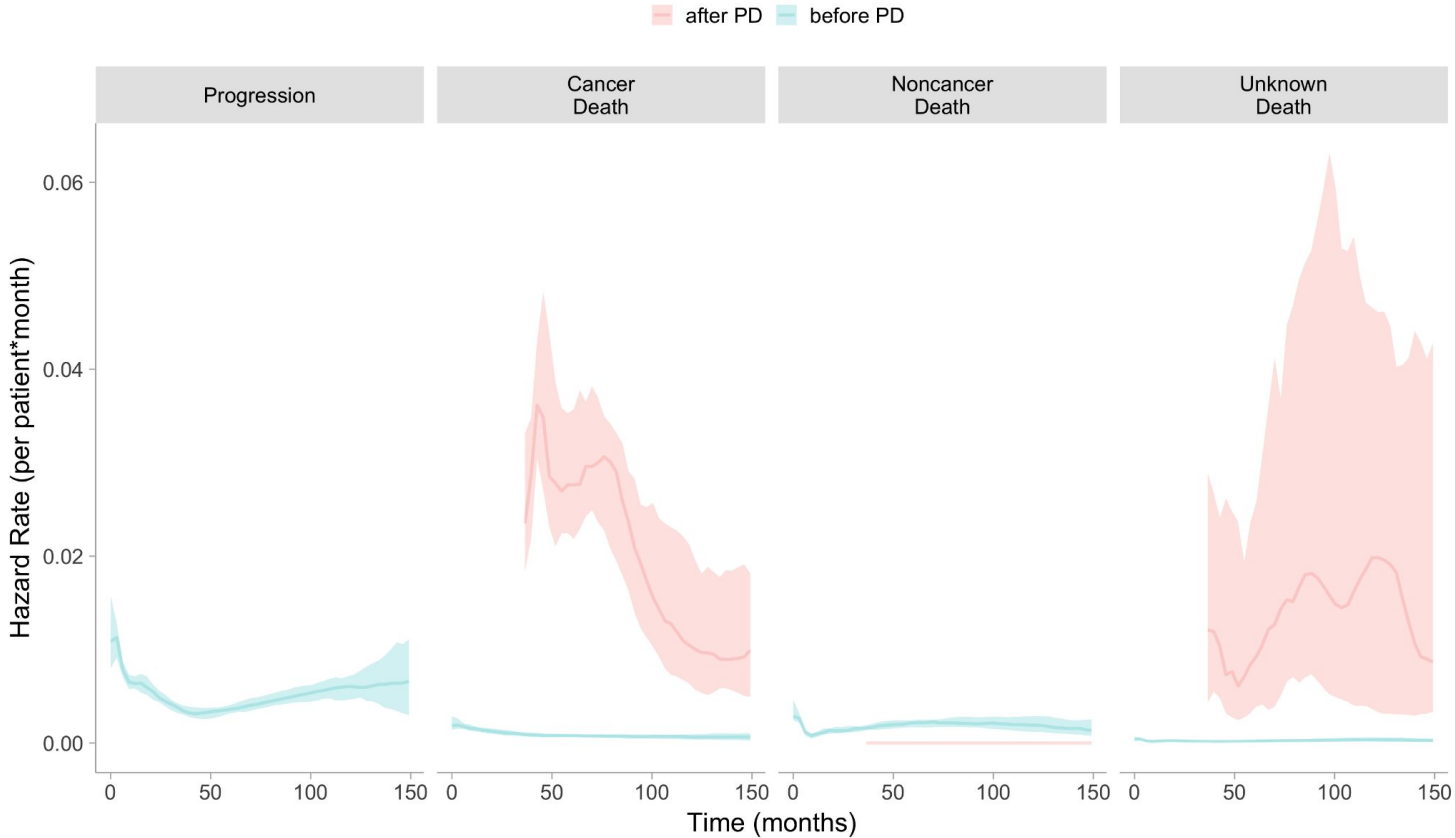
- Data for 509 subjects from The Cancer Genome Atlas (TCGA)
- These data are for patients with Renal Clear Cell Carcinoma (acronym: KIRC)

# Covariates & Events

- Tumor Stage at Diagnosis (I, II, III, IV)
- Age at Diagnosis

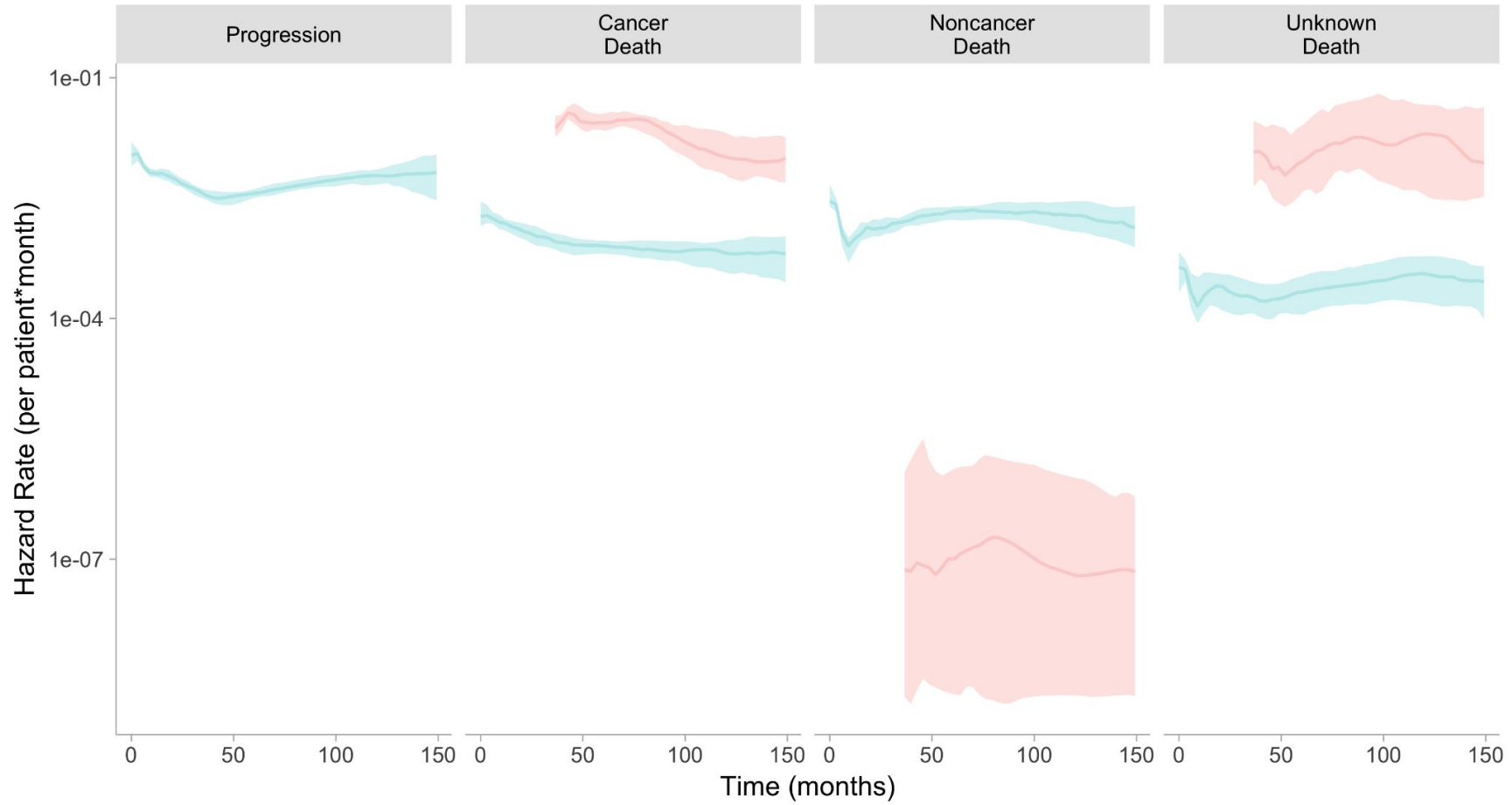


# Event Rate after PD event at 35 months

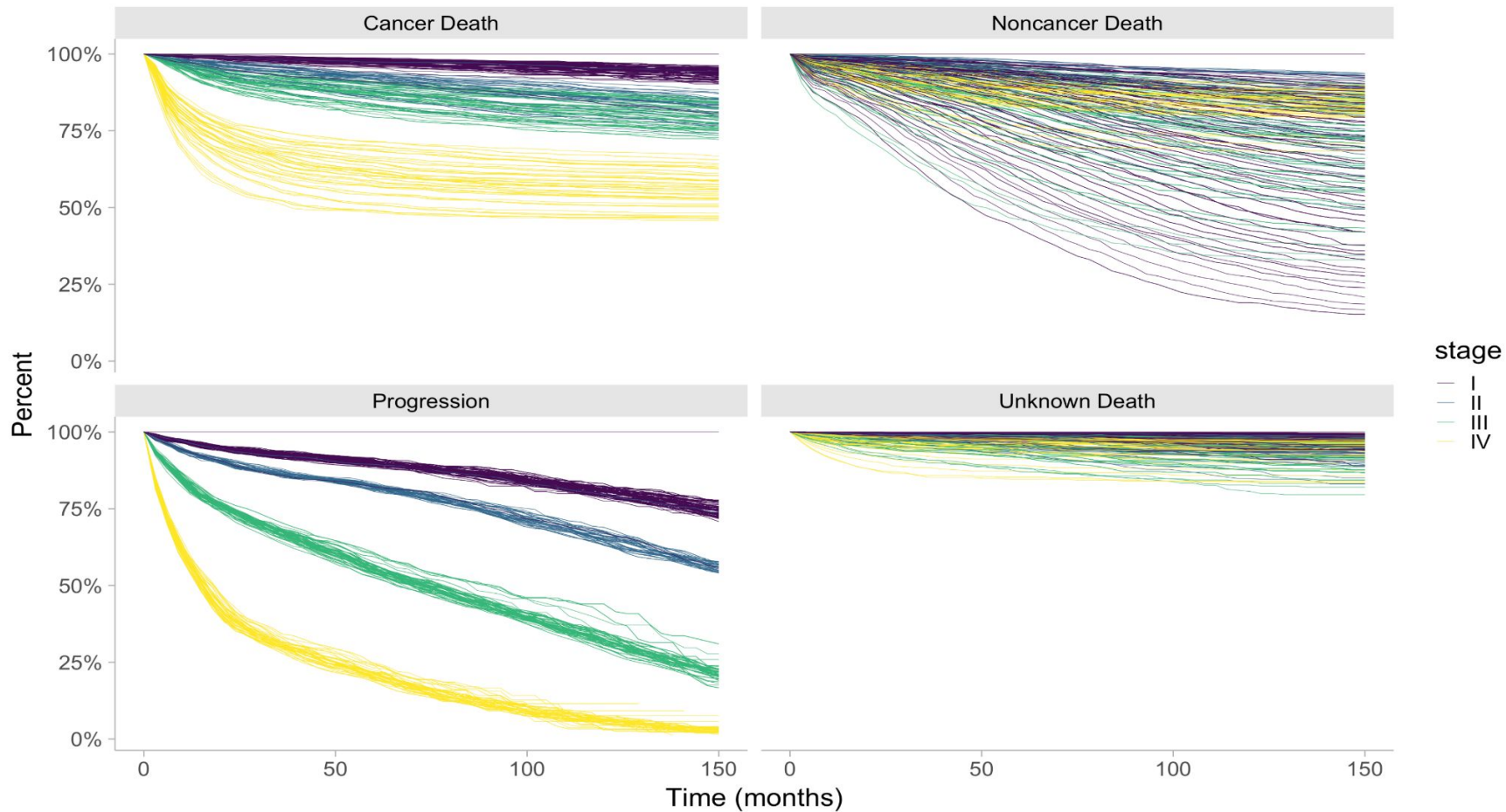


# Baseline hazard

after PD before PD



# Expected Event-Free Time per Subject



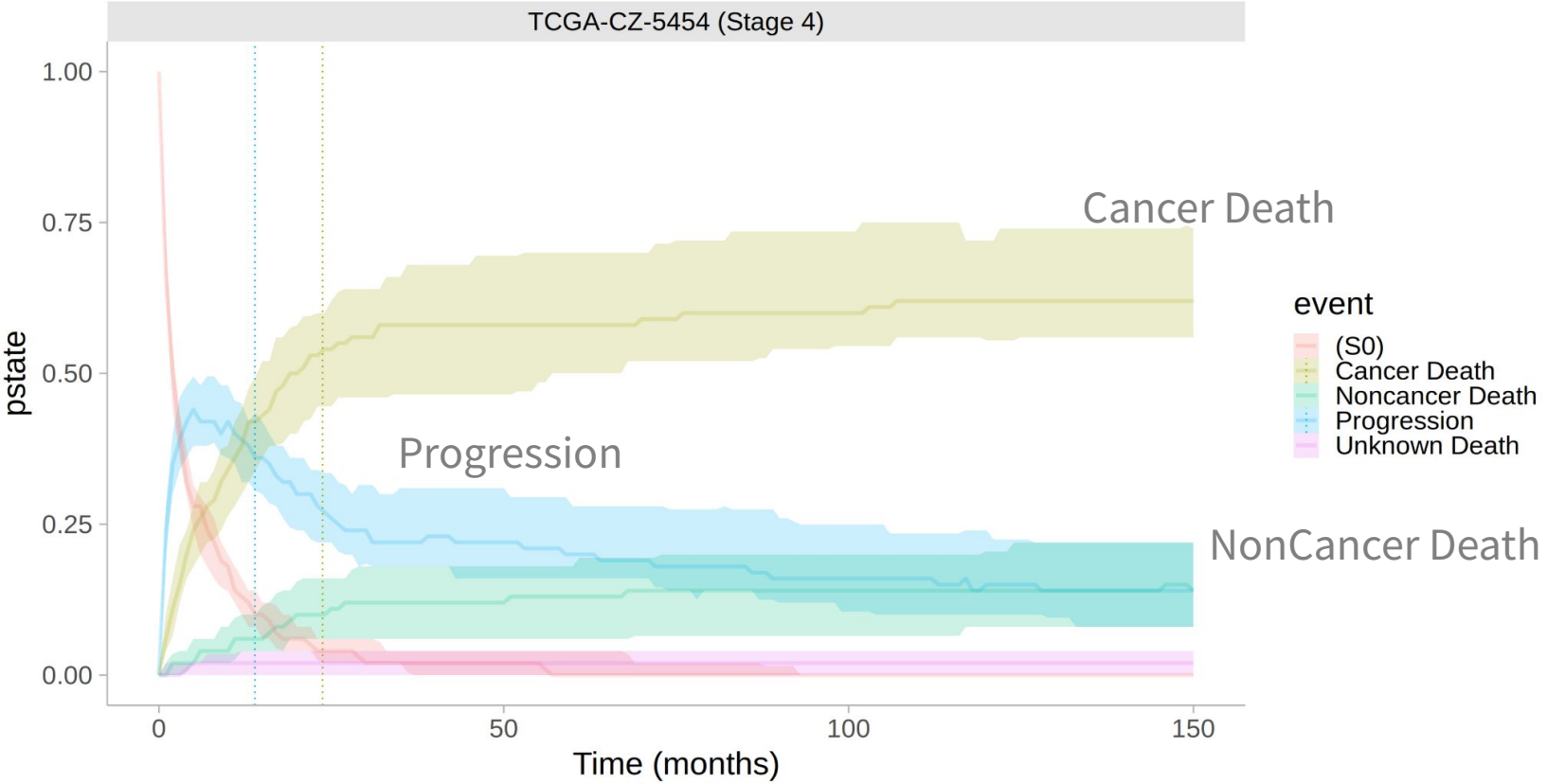
# Brier Scores

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| Event           | Integrated Brier Score |                   |             |
|-----------------|------------------------|-------------------|-------------|
|                 | Kaplan-Meier           | Multi-State Model | Improvement |
| Cancer Death    | 25.94                  | 22.56             | 13.01%      |
| Noncancer Death | 17.80                  | 15.80             | 11.26%      |
| Progression     | 25.96                  | 22.21             | 14.43%      |
| Unknown Death   | 5.11                   | 5.12              | -0.27%      |

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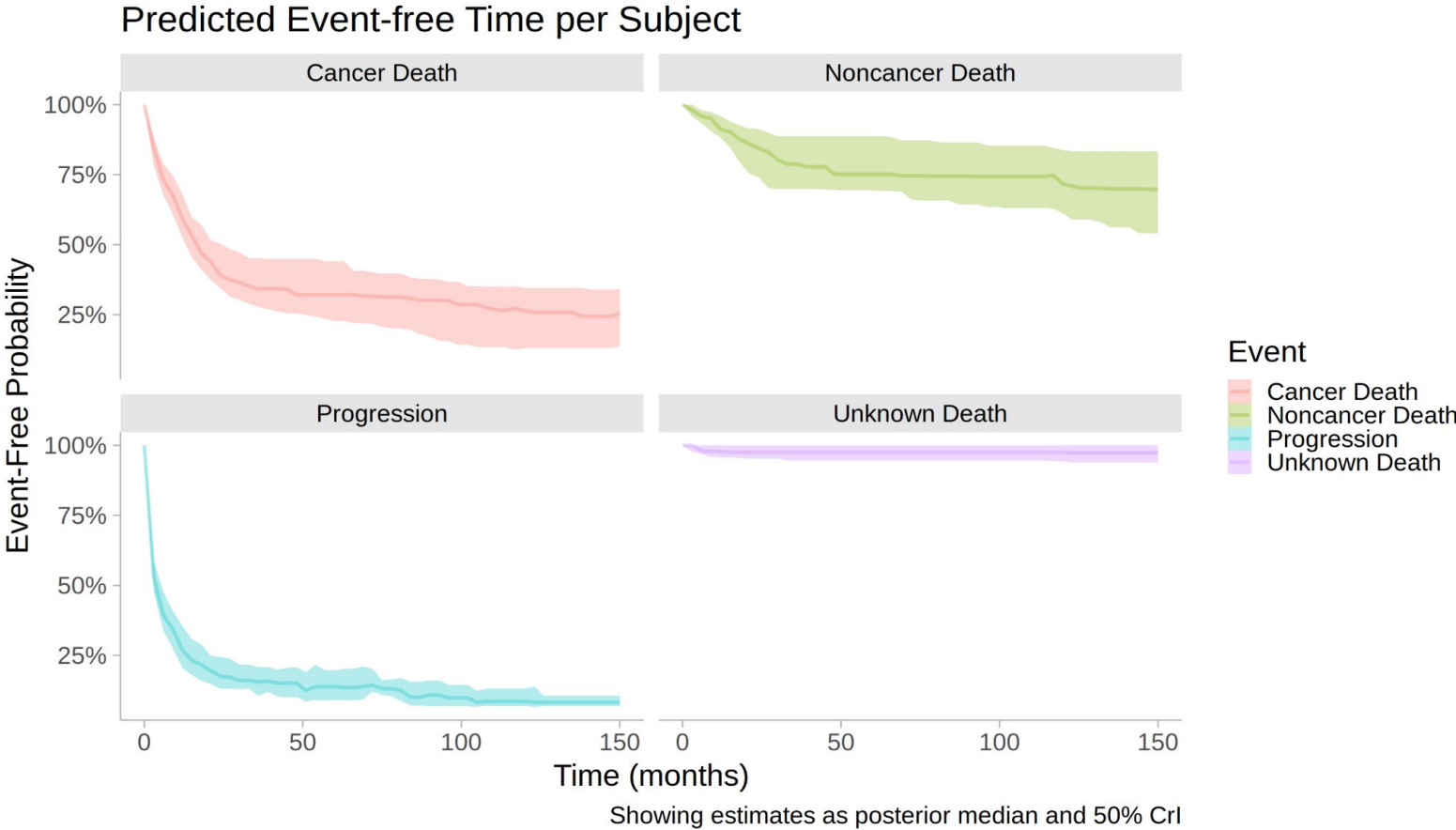
# Predicted States per Subject



Showing estimates as posterior median and 50% CrI



# Predicted Survival Probability per Subject



# Why Multistate?

- Model event risk *jointly*
- Evaluate influence of previous events on future event risk
- Adjust for informative censoring
- Simulate likely clinical outcomes

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- Summarize net impact of intervention on outcomes

# Thanks to the team at Generable



**Juho Timonen**  
jtimonen



**Bruna Wundervald**  
brunaw



**Eric Novik**  
ericnovik

*Generable*

# Thank you!!

Questions? Get in touch

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- [generable.com](https://generable.com)

Built with

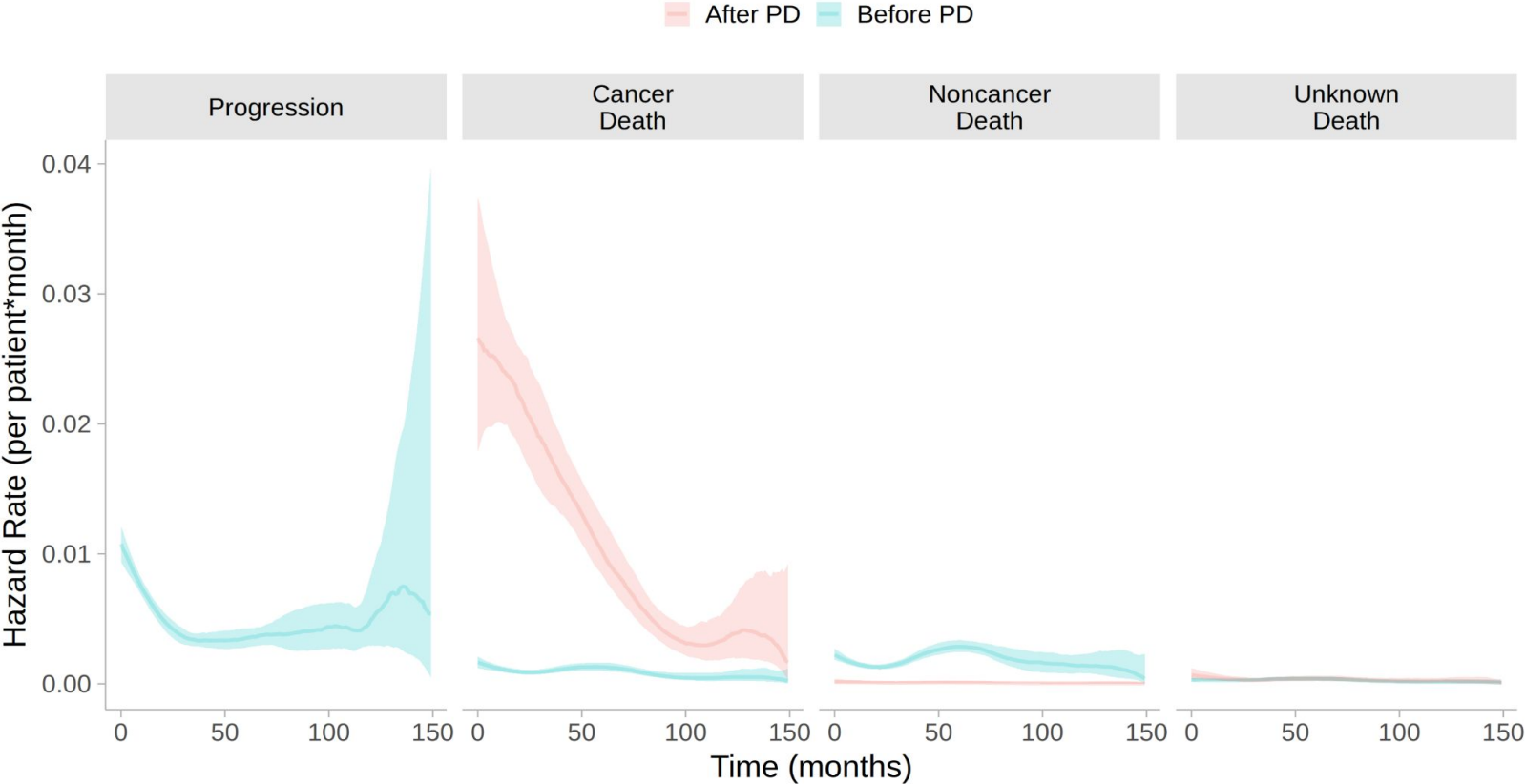


*Stan*

# Appendix



# Baseline Hazards



# Baseline Hazards

