Using multi-state modelling to facilitate informed personalised treatment planning in Follicular Lymphoma

Stuart E. Lacy

25th April, 2018

Epidemiology and Cancer Statistics Group, University of York

Aims

- Demonstrate an application of multi-state modelling to a clinically motivated problem
- Discuss design considerations for multi-state models
- Identify appropriate ways to communicate the findings from such models

Background

Haematological Malignancy Research Network

Clinical Network

14 hospitals organised into 5 adult MDTs &
a network-wide paediatric oncology service

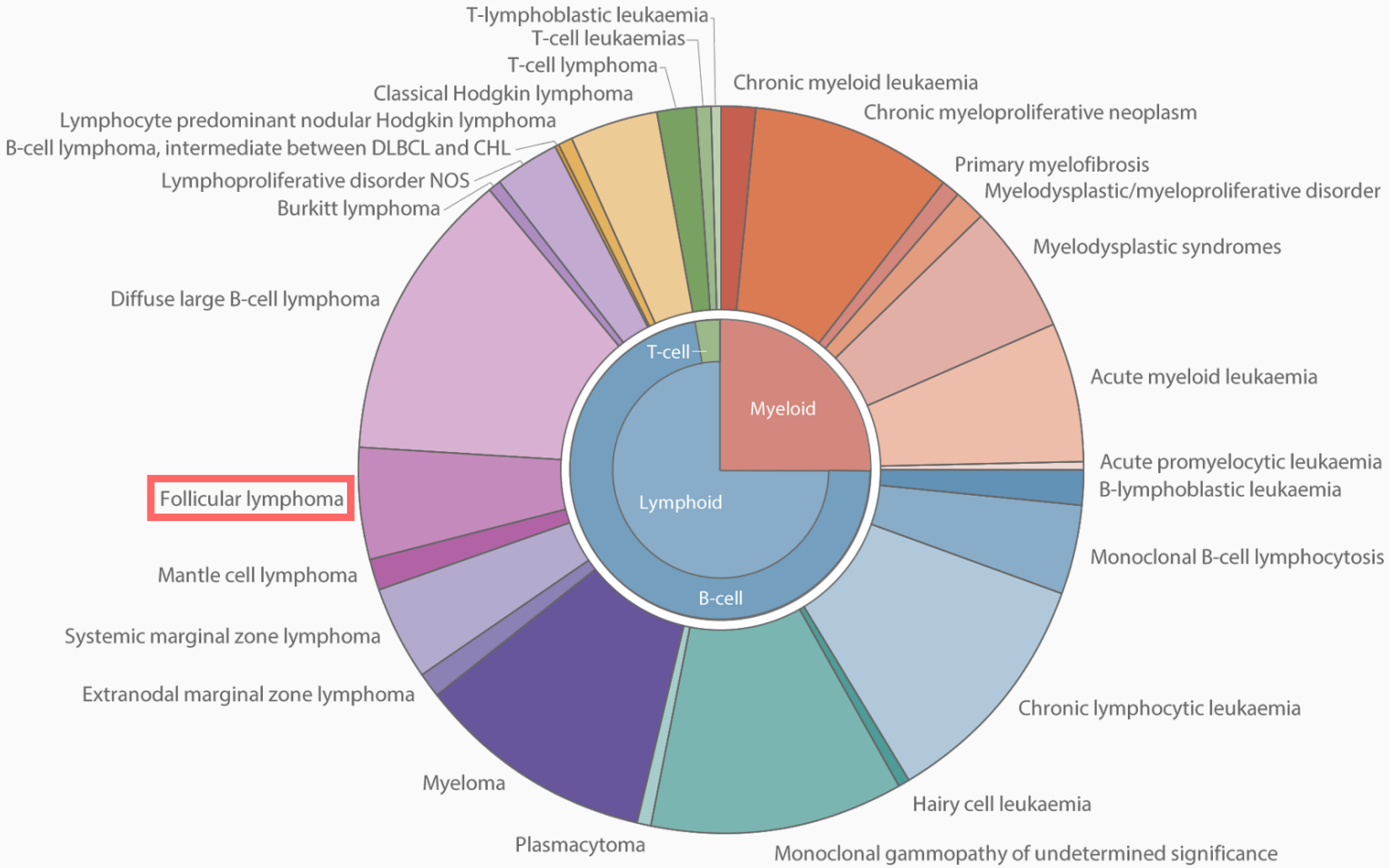
Diagnostics

Haematological Malignancy
Diagnostic Service

Data management & analysis

Epidemiology & Cancer Statistics Group
(ECSG)

HMRN Diseases

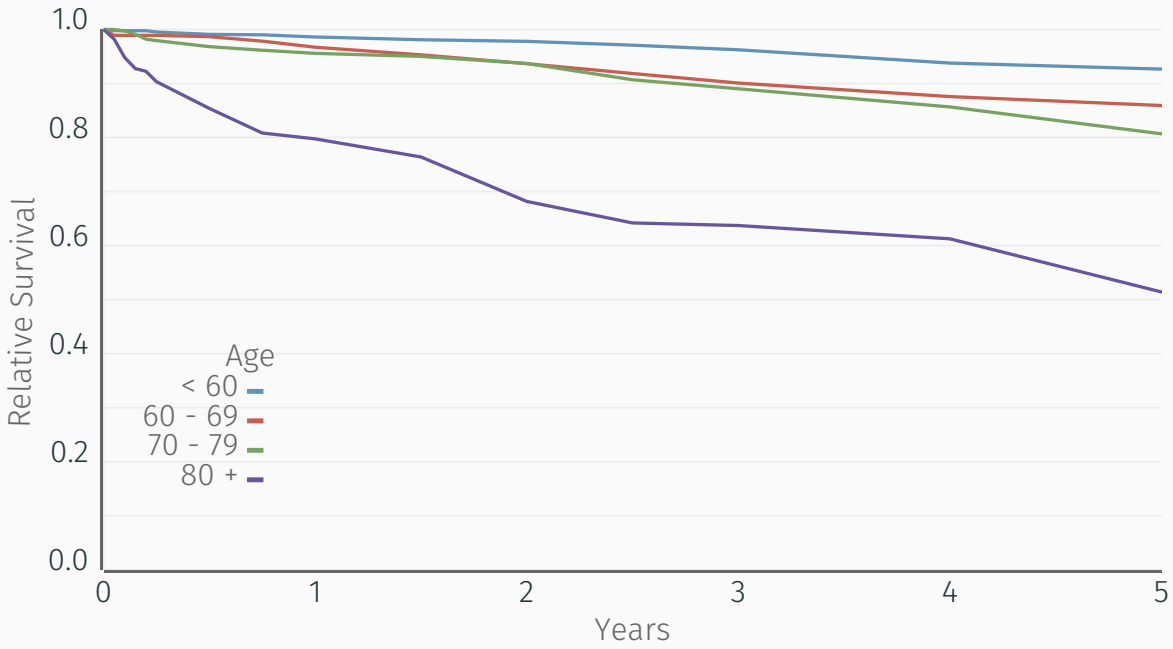


[1]Data taken from https://www.hmrn.org/

Decision making in chronic haematological malignancies

- Project: *Facilitating informed decision making in haemato-oncology*
- Chronic haematological malignancies: follicular lymphoma, myeloma, and chronic lymphocytic leukaemia
- These diseases comprise very heterogeneous treatment pathways - Multi-State models are inherently well suited
- Aim to provide patient-specific prognostic forecasts to aid clinical decision making
- Collaborative project undertaken with qualitative analysts, health economists, epidemiologists, all with direct feedback from clinicians and patients themselves

Follicular Lymphoma



- Most common indolent non-Hodgkin's lymphoma
- Many patients put onto watch-and-wait or have multiple treatment lines
- Can progress onto the more aggressive *Diffuse large b-cell lymphoma*

- Annual incidence rate of 3 per 100,000 (1,900 expected cases in UK, 510 in NL)
- 971 patients for whom we have diagnostic, treatment, and mortality data

Modelling treatment pathways

Design considerations

- State structure - feedback from clinicians useful here
- Managing the trade-off between realistic models of treatment pathways and having sufficient number of events in each transition
- Which covariates to include, and where?

Design considerations

- State structure - feedback from clinicians useful here
- Managing the trade-off between realistic models of treatment pathways and having sufficient number of events in each transition
- Which covariates to include, and where?
- Parametric vs semi-parametric

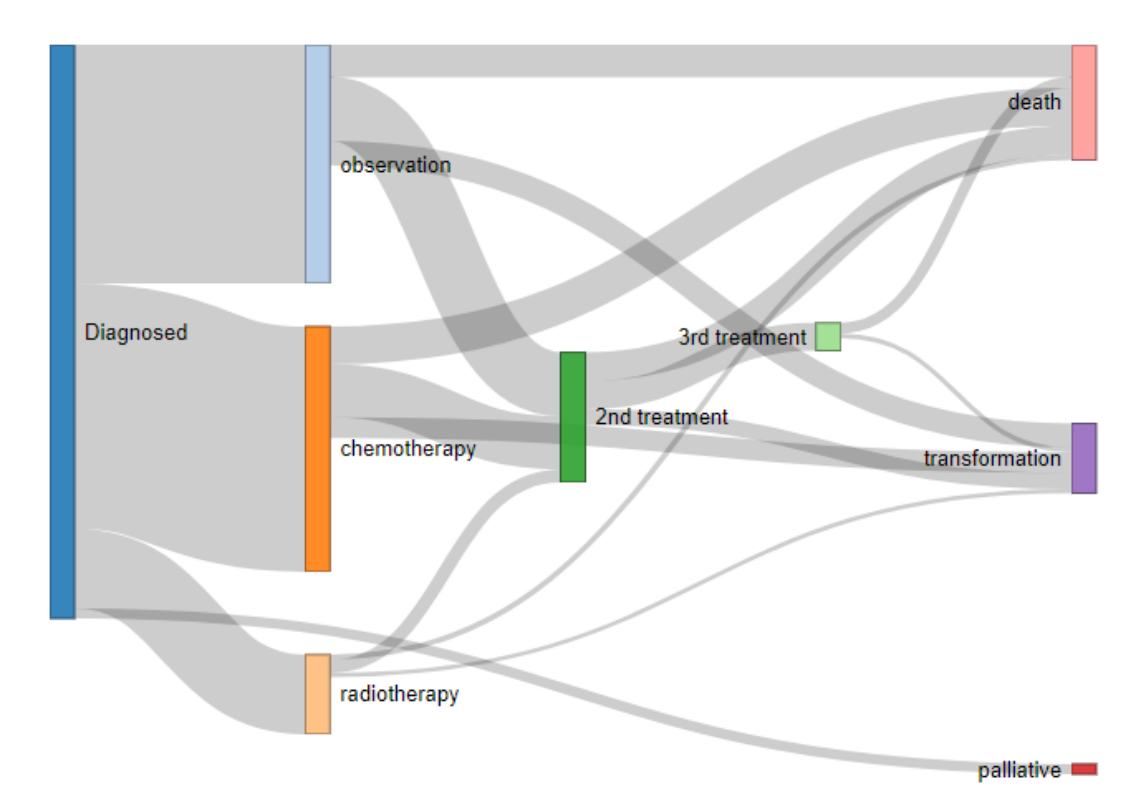
Design considerations

- State structure - feedback from clinicians useful here
- Managing the trade-off between realistic models of treatment pathways and having sufficient number of events in each transition
- Which covariates to include, and where?
- Parametric vs semi-parametric
- Time-scale - clock forward or reset?

Design considerations

- State structure - feedback from clinicians useful here
- Managing the trade-off between realistic models of treatment pathways and having sufficient number of events in each transition
- Which covariates to include, and where?
- Parametric vs semi-parametric
- Time-scale - clock forward or reset?
- Incorporate state arrival times (so called extended-state semi-Markov)

Chosen state structure



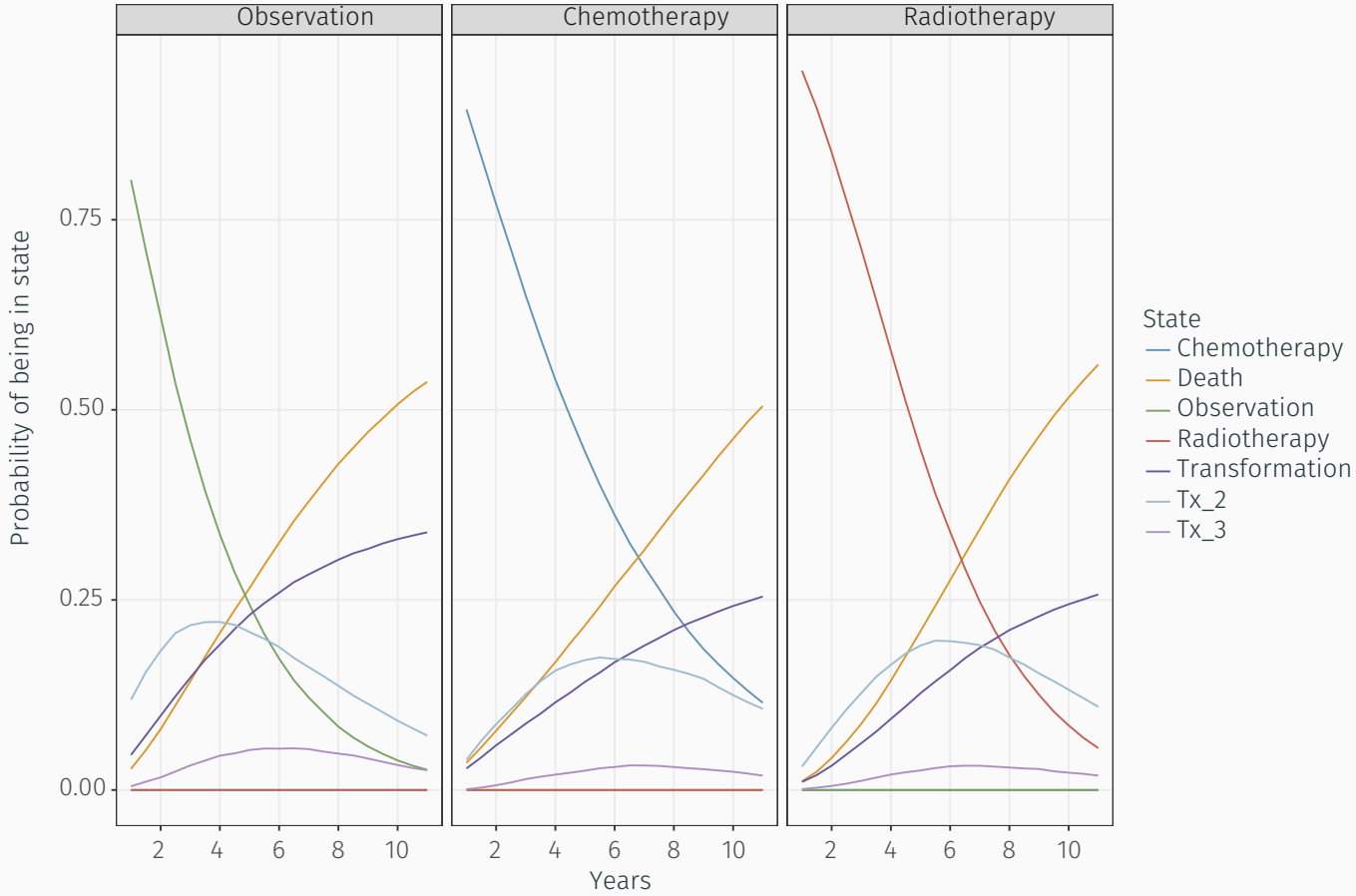
- Want to keep model as parsimonious as possible due to 'small' sample size ($n = 971$)
- Main area of interest is difference between initial treatment decision

Final model

- Investigated using a variety of covariates, but hampered by missingness. The only factors we have without any missing values are age at diagnosis and sex
- Found that other factors, such as disease stage, are correlated with initial treatment state, and so do not need to be incorporated
- Ended up with just age at state entry time acting on all transitions to death, and from observation $\rightarrow$ second-line treatment
- Using parametric models, as prediction is the overall goal

Model application

Simulating transition probabilities



- Estimate transition probabilities using simulation (as semi-Markov)
- Custom simulation that is faster and more flexible than `flexsurv`[2]

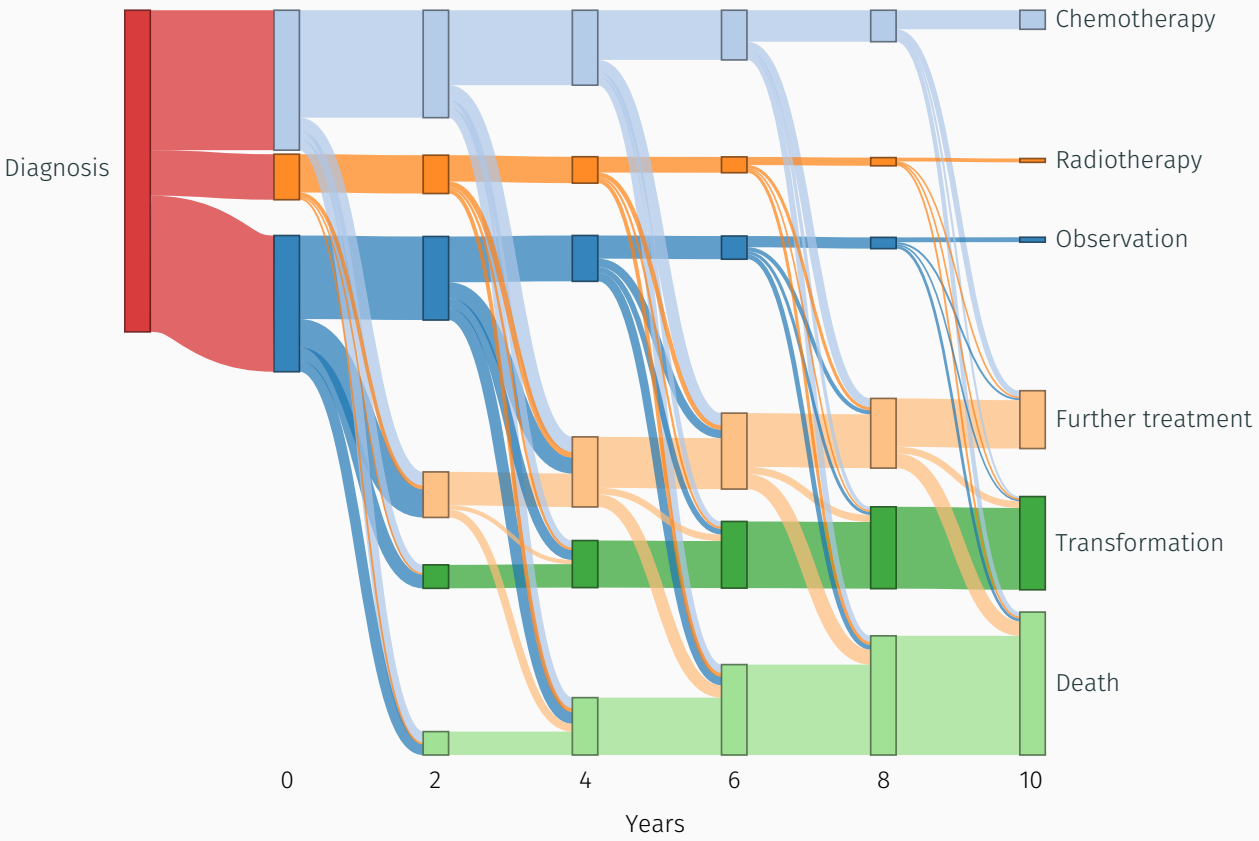
[2] Available at `www.github.com/stulacy/RDES`

Communicating prognosis

- How to communicate predictions from a complex multi-faceted model? Intend to deploy this model in a clinical tool eventually
- This will be informed by qualitative research
- Can emphasize different aspects of the model for target audience
- Can have interactive plots, or animations[3]

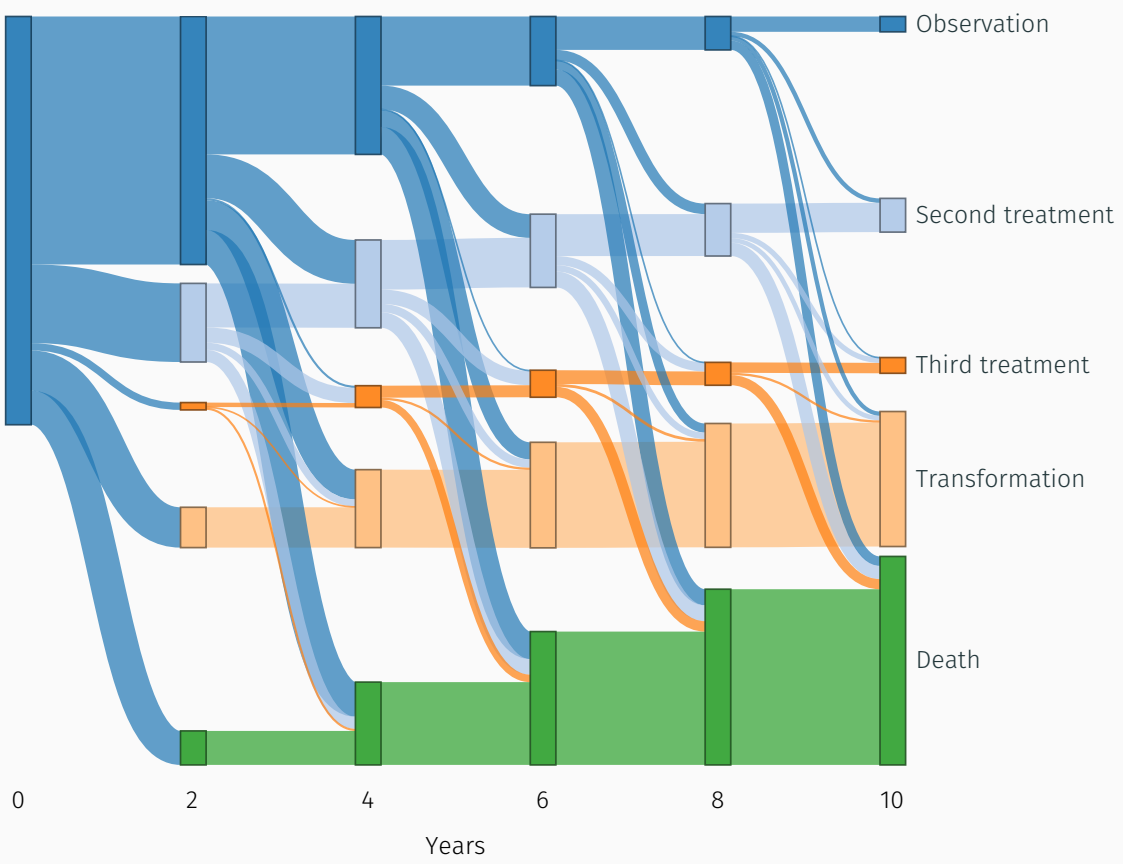
[3] See previous app `stulacy.shinyapps.io/msm-shiny/`

Treatment flow diagram



- View treatment pathways using dynamic predictions
- Shown above for median age individual

Treatment flow diagram for a given initial treatment



- When a patient has been assigned a first treatment (observation above) their expected pathway can be visualised

Further Work

- Externally validate model
- Identify statistics for evaluating prognostic value of multi-state models
- Look at other ways of modelling these three time-scales: time since diagnosis, age, and state arrival time (Iacobelli & Carstensen 2013)
- Incorporate genomic data
- Develop means of applying the model for clinical use

Thank you for listening!