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

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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

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?
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- Parametric vs semi-parametric
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- Which **covariates** to include, and where?

- Parametric vs semi-parametric

- Time-scale - clock forward or reset?
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- 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 → 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

\(^2\)Available at [www.github.com/stulacy/RDES](http://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

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3See previous app stulacy.shinyapps.io/msm-shiny/
Treatment flow diagram

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