

# 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

- 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

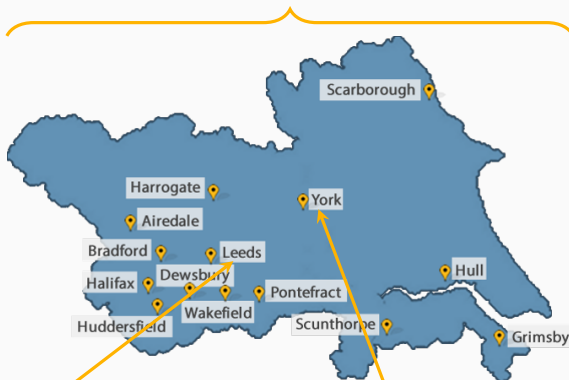
# Background

---

# Haematological Malignancy Research Network

## Clinical Network

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



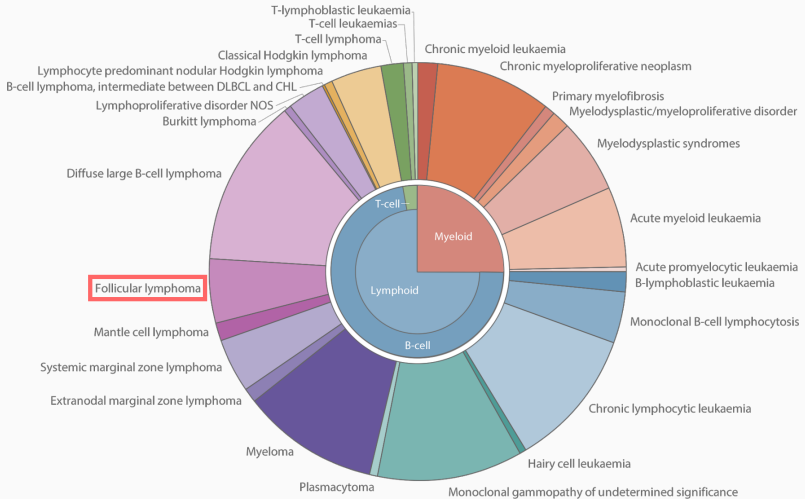
## Diagnostics

Haematological Malignancy  
Diagnostic Service

## Data management & analysis

Epidemiology & Cancer Statistics Group<sub>3</sub>  
(ECSG)

# HMRN Diseases

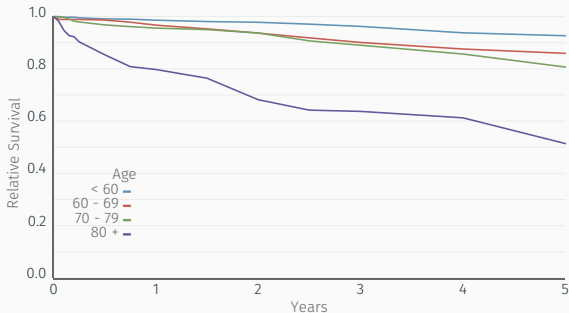


<sup>1</sup>Data taken from <https://www.hmrn.org/>

# 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

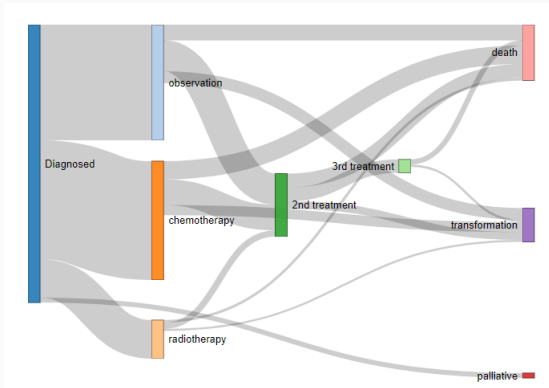
# Design considerations

- **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



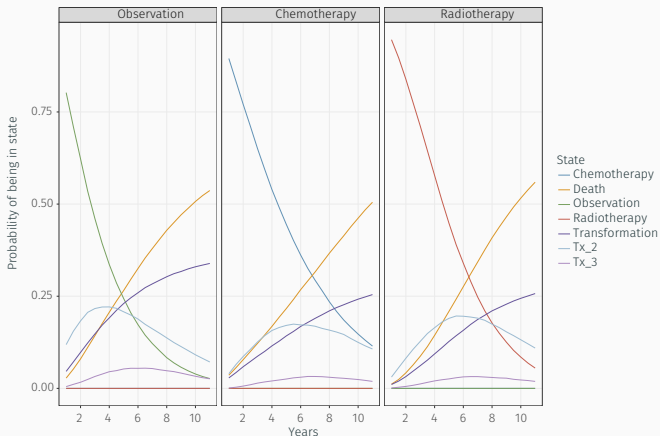
- Want to keep model as **parsimonious** as possible due to 'small' sample size ( $n = 971$ )
- Main area of interest is difference between initial treatment decision

- 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<sup>2</sup>**

<sup>2</sup>Available at [www.github.com/stulacy/RDES](http://www.github.com/stulacy/RDES)



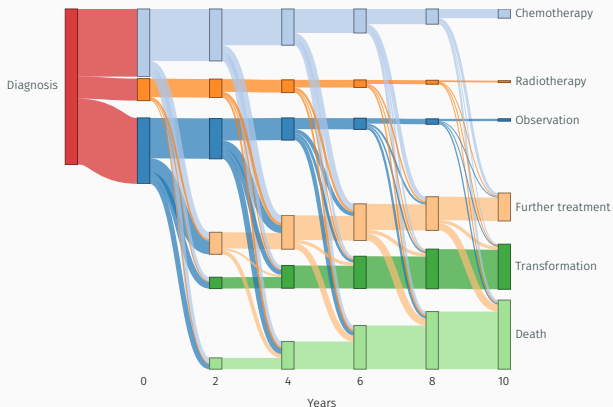
# Communicating prognosis

- 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<sup>3</sup>

---

<sup>3</sup>See previous app [stulacy.shinyapps.io/msm-shiny/](http://stulacy.shinyapps.io/msm-shiny/)

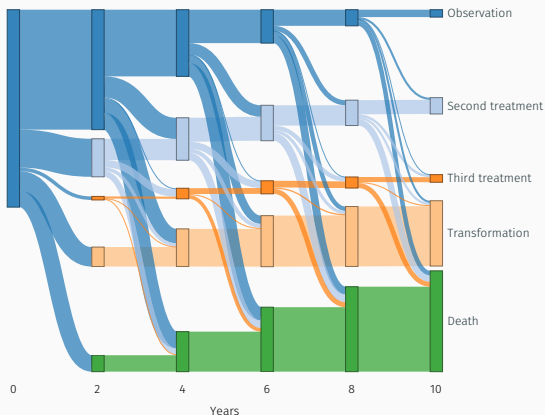
# Treatment flow diagram



- 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!

hmrn