# A Multistate Model Incorporating a Relative Survival Framework and Mixed Time Scales

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#### About me

- Born and raised in Taipei, Taiwan
- Came to Sweden for my exchange studies at Lund University in 2018
- 2018-2020: MSc in Epidemiology at KI
- 2021-current: PhD student in Biostatistics at KI
- PhD project title: Extrapolating Survival with Applications to Health Technology Assessment
- Supervisors: Paul Dickman, Mark Clements, Magnus Björkholm, Shuang Hao, Torsten Dahlén

This presentation is based on the paper co-authored with Paul Dickman and Mark Clements, published in *PharmacoEconomics*.

PharmacoEconomics https://doi.org/10.1007/s40273-024-01457-w

**ORIGINAL RESEARCH ARTICLE** 

#### A Multistate Model Incorporating Relative Survival Extrapolation and Mixed Time Scales for Health Technology Assessment

Enoch Yi-Tung Chen<sup>1</sup> · Paul W. Dickman<sup>1</sup> · Mark S. Clements<sup>1</sup>

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# Research question

Title:

A Multistate Model Incorporating a Relative Survival Framework and Mixed Time Scales

#### Key question to answer

How can we incorporate relative survival extrapolation<sup>1</sup> into multistate models to improve long-term predictions?

- We introduce a multistate model that integrates long-term projections of general population mortality rates.
- To implement this, we need to address survival predictions from mix timescales in a competing risks setting.

Andersson et al, Stat in Med, 2013.

## Multistate models

- Mutually exclusive disease/health states
- A set of transition-specific survival models<sup>2</sup>
- Each state is associated with costs and length of stay



Figure: An illness-death model.

Crowther and Lambert, Stat in Med, 2017. Briggs and Sculpher, PharmEcon, 1998.

## Relative survival framework

• Relative survival ratio

$$R(t)=\frac{S(t)}{S^*(t)},$$

where S(t) is all-cause survival, and  $S^*(t)$  is expected survival.

## Relative survival framework

Relative survival ratio

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• The analogue on a hazard scale is

$$\lambda(t)=h(t)-h^*(t),$$

 $\lambda(t)$ : excess hazard; h(t): all-cause hazard from the patient survival data;  $h^{*}(t)$ : expected hazard from the general population mortality rates.

$$h(t) = h^*(t) + \lambda(t)$$

$$S(t)=S^*(t)^*R(t),$$

where S(t): all-cause survival;  $S^*(t)$ : expected survival; R(t): relative survival Enoch Yi-Tung Chen

# Multistate model incorporating relative survival framework



- Time scales:
- t: Time since study entry
- a: Age at study entry
- c: Calendar year at study entry
- u: Time at progression

Figure: An illness-death model incorporating a relative survival framework and mixed time scales.

## Motivating example: CLL-8 trial

• A clinical trial of chronic lymphocytic leukemia treatments (CLL-8 trial<sup>3</sup>) compared the new treatment (RFC) vs. the traditional treatment (FC). The median age at study entry was 61 years.



Figure: Figure retrieved from the CLL-8 trial by Hallek et al.<sup>3</sup> Chemoimmunotherapy: RFC; chemotherapy: FC.

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# Motivating example: CLL-8 trial

- 1. Prepare a population mortality file
- 2. Fit flexible parametric (relative survival<sup>4</sup>) models<sup>5</sup> for the transitions h(t) or  $\lambda(t)$ , with treatment as a covariate and df=2, dftvc=2.
- 3. Simulate 1 million individuals from the fitted survival models (microsimulation package)



Figure: An illness-death model incorporating a relative survival framework and mixed time scales.

## Motivating example: CLL-8 trial: Hazard functions



Figure: Prog: progression; PFS: progression-free survival; ExpD: expected death; ExcD: excess death. \*We only show the RFC arm here.

# Motivating example: CLL-8 trial: Probabilities of being at states



# Survival extrapolation

#### Drummond et al., BMC Health Services Research, 2023<sup>6</sup>

..the length of the available clinical studies may be short at the time that the health technology assessment is conducted, and hence **extrapolation** to long term endpoints will be required...

# Survival extrapolation within an all-cause survival framework



Figure: Example of poor survival extrapolation.

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# Survival extrapolation within a relative survival framework



Figure: Ideal survival extrapolation can be achieved by relative survival extrapolation<sup>1</sup>(Andersson, Stat in Med, 2013).

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# Survival extrapolation within a relative survival framework



Figure: Illustrating hazard functions for survival extrapolation using a relative survival framework.

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- Williams et al.<sup>7</sup> applied a (semi-Markov) multistate model to extrapolate survival of 4 years to 15 years for the CLL-8 trial<sup>3</sup>.
- The transitions were modelled with the standard parametric models within an all cause survival framework (h<sub>1</sub>(t) and h<sub>3</sub>(t) with Gompertz, and h<sub>2</sub>(t) with generalized-gamma distributions).



Figure: An illness-death model.

Williams, Med Dis Mak, 2017.

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Figure: Compare survival extrapolation for the RFC arm with the observed OS. SPMs, standard parametric models; FPMs, flexible parametric models; ASF, all-cause survival framework; RSF, relative survival framework. \*We only show the RFC arm here.

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Figure: Prog: progression; PFS: progression-free survival; ExpD: expected death; ExcD: excess death.\*We only show the RFC arm here.



Figure: Prog: progression; PFS: progression-free survival; ExpD: expected death; ExcD: excess death.\*We only show the RFC arm here.

# Discussion: Summary

- 1. We introduce a multistate model incorporating a relative survival framework and mixed time scales. (Implemented in the microsimulation and rstpm2 packages on CRAN.)
- 2. This model serves as a parametric approach to integrate relative survival in multistate models<sup>8</sup>.
- 3. It allows relative survival extrapolation to be carried out in a multistate setting.

Manevski, Stat Methods in Med Res, 2022.

## Discussion: Is the extrapolation reasonable?



Figure: Compare survival extrapolation for the RFC arm with the observed OS. SPMs, standard parametric models; FPMs, flexible parametric models; ASF, all-cause survival framework; RSF, relative survival framework. \*We only show the RFC arm here.

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## Discussion: Extrapolate transition to progression



Figure: Prog: progression; PFS: progression-free survival; ExpD: expected death; ExcD: excess death. \*We only show the RFC arm here.

## Discussion: Extrapolate transition to progression



Figure: Prog: progression; PFS: progression-free survival; ExpD: expected death; ExcD: excess death. \*We only show the RFC arm here.

# Discussion: Extrapolate transition to progression

#### Question

Any suitable approach to extrapolate progression rate in an illness-death model?

- 1. In an oncological RCT, the intermediate state is typically defined as disease progression to a more advanced stage, such as metastasis, relapse, etc.
- 2. Impose constraint on parameters during model fitting, e.g., change knot position in a spline model. Domain experts' opinions matter.
- 3. Select other parametric distributions which are clinically plausible.
- 4. Use long-term data, for example, cancer register data, to aid survival extrapolation for short-term data like RCTs.

## Conclusions

PharmacoEconomics https://doi.org/10.1007/s40273-024-01457-w

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The slides can be found @ https://enochytchen.com/talks/2024-microsim/2024-microsim.pdf LinkedIn: Enoch Yi-Tung Chen Email: enoch.yitung.chen@ki.se

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## Extrapolate transition to progression

LIFE



Figure: Adapted from Verdecchia, Stat in Med, 1989<sup>9</sup>. Estimating incidence of lung cancer with other known parameters:  $\alpha(x)$ ,  $\beta(x, y)$ ,  $\delta(x, y)$ ,  $\gamma(x)$ .

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## Extrapolate transition to progression

LIFE



Figure: Estimating progression rate of lung cancer with other known parameters:  $\alpha(x)$ ,  $\beta(x, y)$ ,  $\delta(x, y)$ ,  $\gamma(x)$ .

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