# Do Treatment Sequencing / Pathways Models Have a Place in Health Technology Appraisal?

Moderator: **Dr Hugo Pedder**, BristolTAG, University of Bristol, UK

Panellists: **Dr Jeroen Jansen**, University of California, San Francisco, USA

**Professor Dawn Lee**, PenTAG, University of Exter, UK

**Mark Harries**, Ipsen, UK

# Overview

**Treatment sequence** or **treatment pathway models** estimate the cost-effectiveness of different sequences of treatments for a specific condition over multiple lines of therapy.

- Explain why these models might be useful/necessary
- Discuss challenges for their implementation – methodological and logistical

# Presenters

**Moderator**

**Hugo Pedder,**
Bristol Technology Assessment Group (BristolTAG), University of Bristol, UK

**Speaker 1**

**Jeroen Jansen,**
University of California, San Francisco, USA

**Speaker 2**

**Dawn Lee,**
Peninsula Technology Assessment Group (PenTAG), University of Exeter, UK

**Speaker 3**

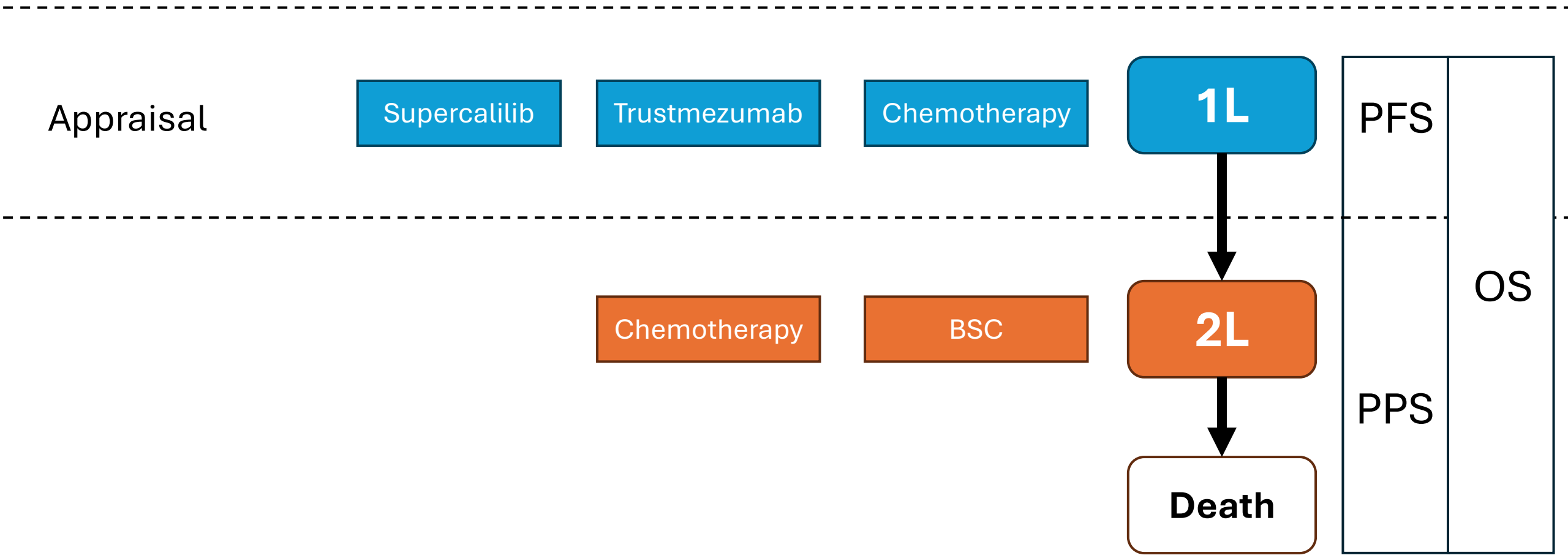
**Mark Harries,**
Ipsen Ltd, UK

# Declarations

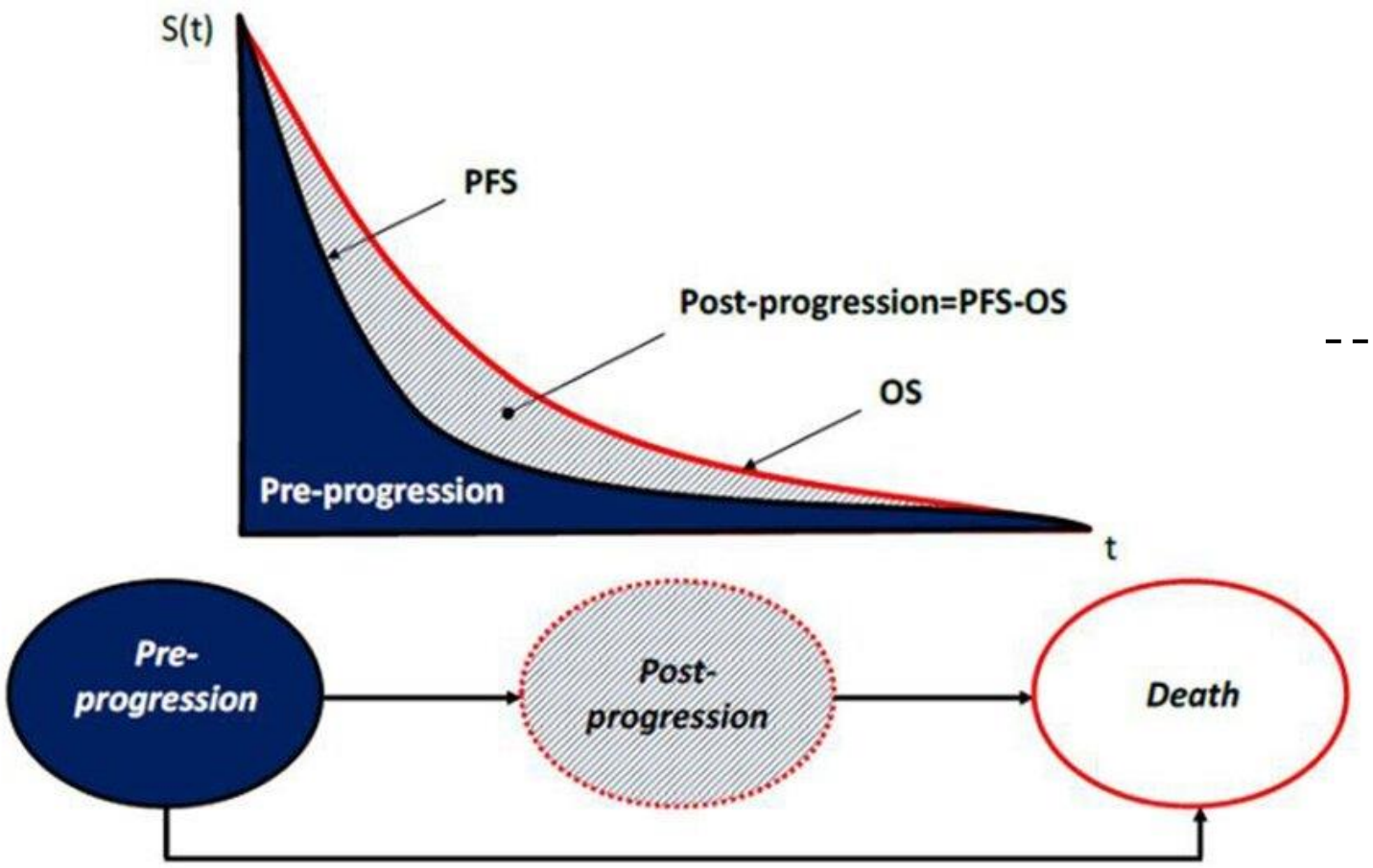
- HP is employed part-time by ConnectHEOR (started subsequently to work on NSCLC)

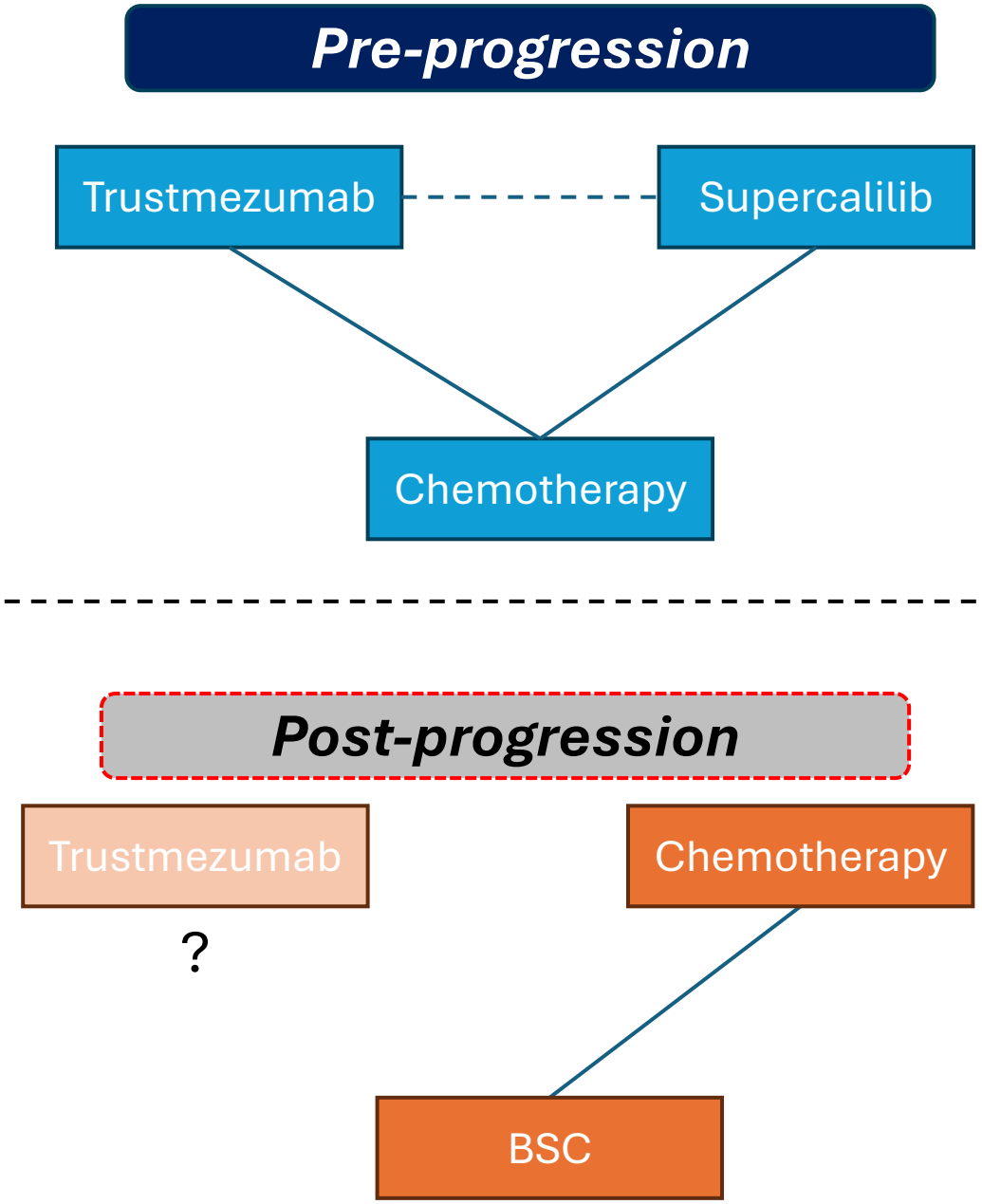
- The views and opinions expressed in this session are those of the presenters and do not necessarily reflect the organizations they represent.

# Clinical Pathway for Hypergnomatosis



# Data availability



Trustmezumab was recommended on a broad indication that allows its use *at any line of treatment* based on their trial in 1L patients. You now want to make a submission for Supercalilib. How would you approach this decision problem?

- Argue that Trustmezumab is not currently standard of care

  Try and ignore this issue as it sounds really complicated

- Send in a partitioned survival model based upon an indirect treatment comparison of 1L Supercalilib versus Trustmezumab for OS and PFS. Then adjust the costs of subsequent treatment to match the expected pathway in the local country.

  This is what I've always done, so it should be fine

- Send in a state transition model and assume that Trustmezumab has the same PFS at 2L as at 1L regardless of what treatment came before it.

  Without 2L data for Trustmezumab, that seems like a pretty conservative assumption

- I would do something else

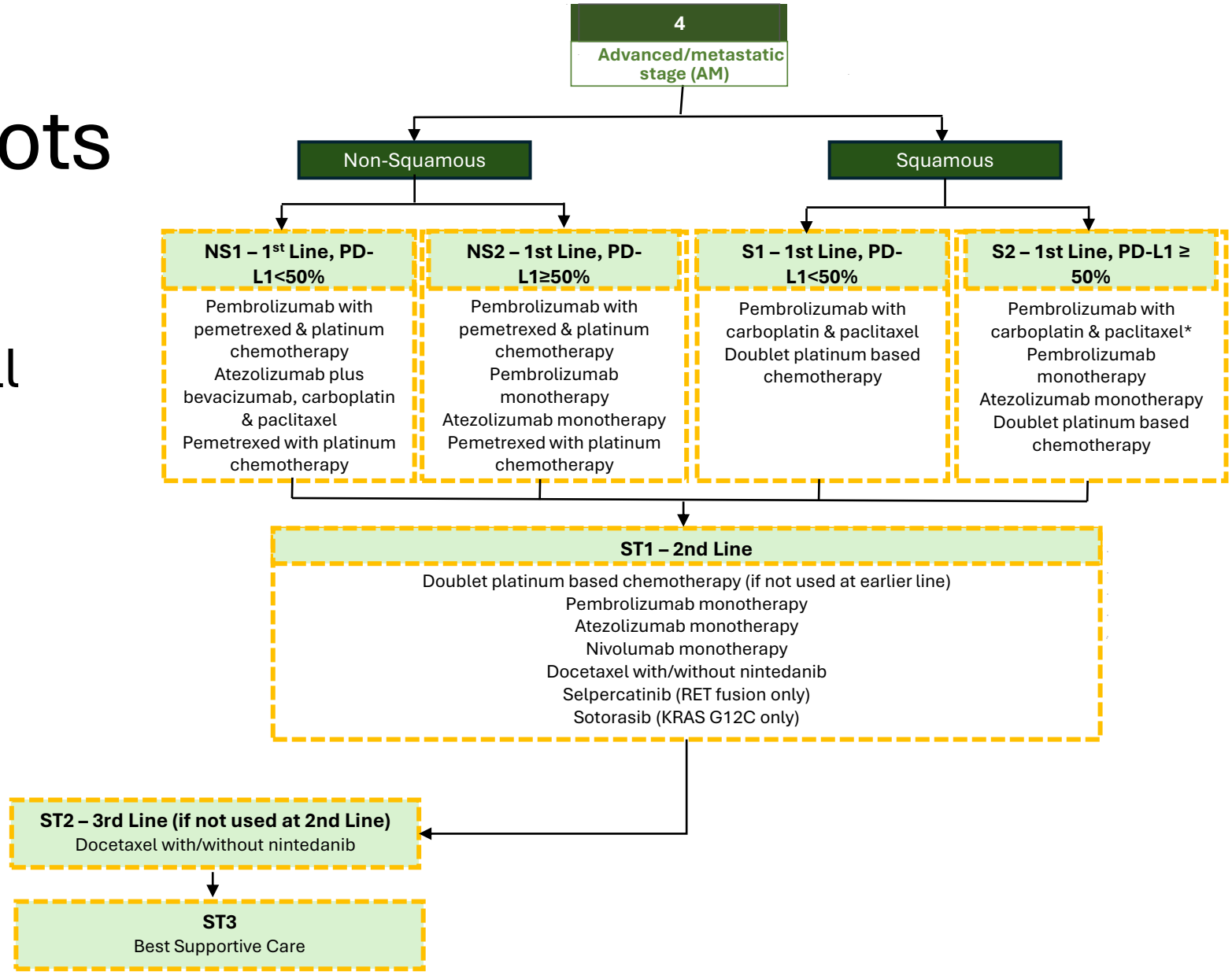
# Issues with current approach

- Inconsistencies in decision-making from performing multiple STAs
- Mismatch between costs and effectiveness in a single appraisal
- Differences in objectives & perspectives
  - RCTs designed for regulatory approval
  - HTAs want to know how a technology impacts the clinical pathway

**Is treatment sequence modelling the solution to this?**
**Can they have a role in HTAs?**

# NICE Pathways Pilots

- Renal cell carcinoma
- Advanced Non-Small Cell Lung Cancer



# What might the impact be?
## Renal Cell Carcinoma (at list prices)

| | State Transition Model ICER | Partitioned Survival Model ICER |
|---|---|---|
| Sunitinib | £251,374 | £279,035 |
| Nivolumab + Ipilimumab | £139,508 | £1,561,318 |
| Pembrolizumab + Lenvatinib | £396,657 | Dominant |

Impact on subsequent treatment options in the pathway is a key driver of difference

University of California
San Francisco

PRECISION AQ™

# What did we learn from developing open-source treatment sequence models

Jeroen P Jansen PhD

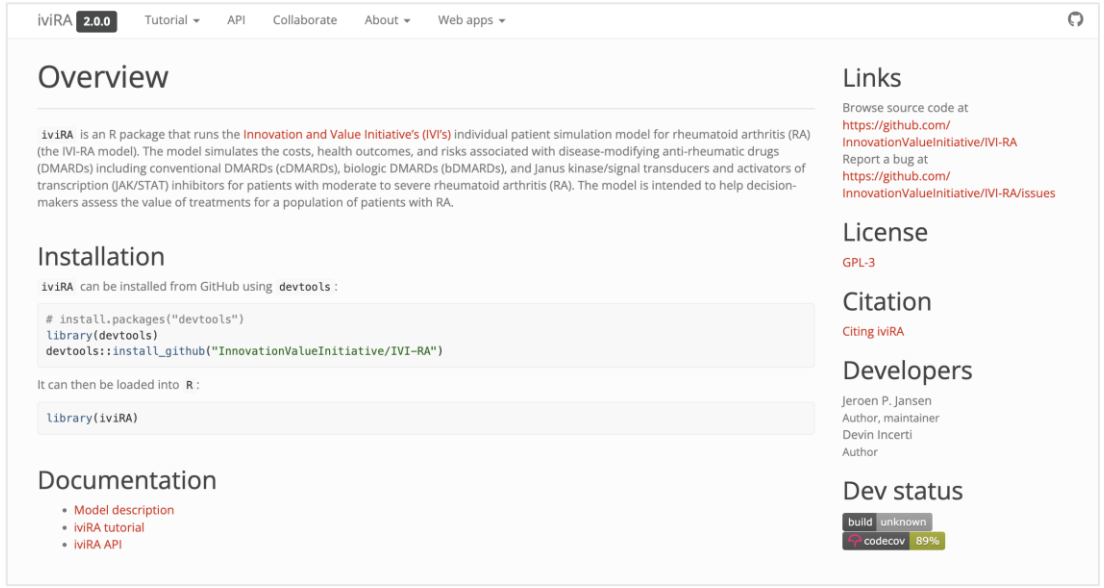
ISPOR Barcelona, 2024

# Treatment sequence models for the Innovation & Value Initiative (IVI)*

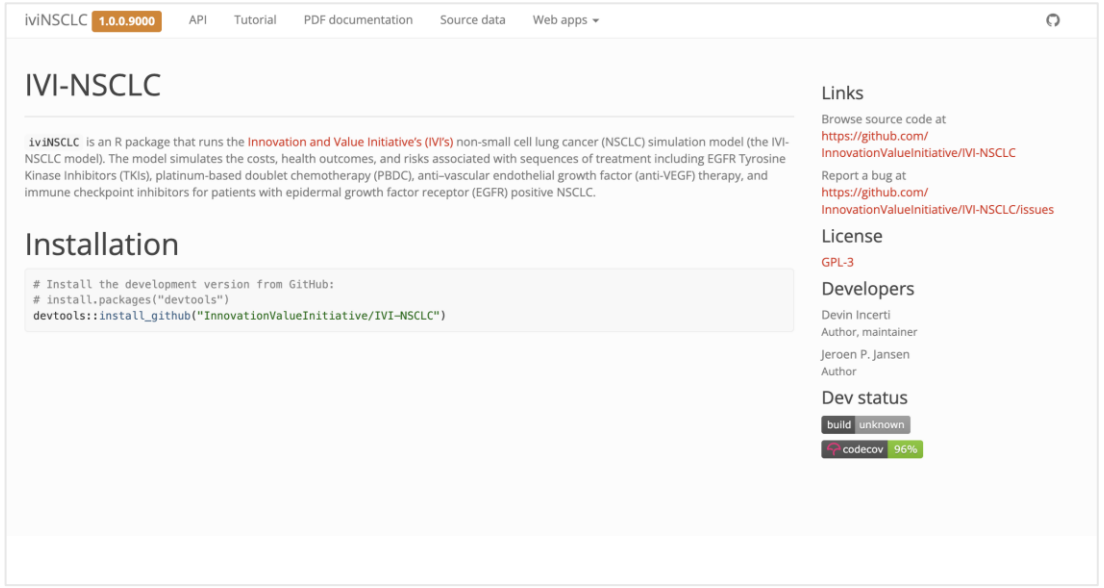
- Rheumatoid arthritis treatment sequence model
- Non-small cell lung cancer treatment sequence model

- Completely open source

https://innovationvalueinitiative.github.io/IVI-RA/

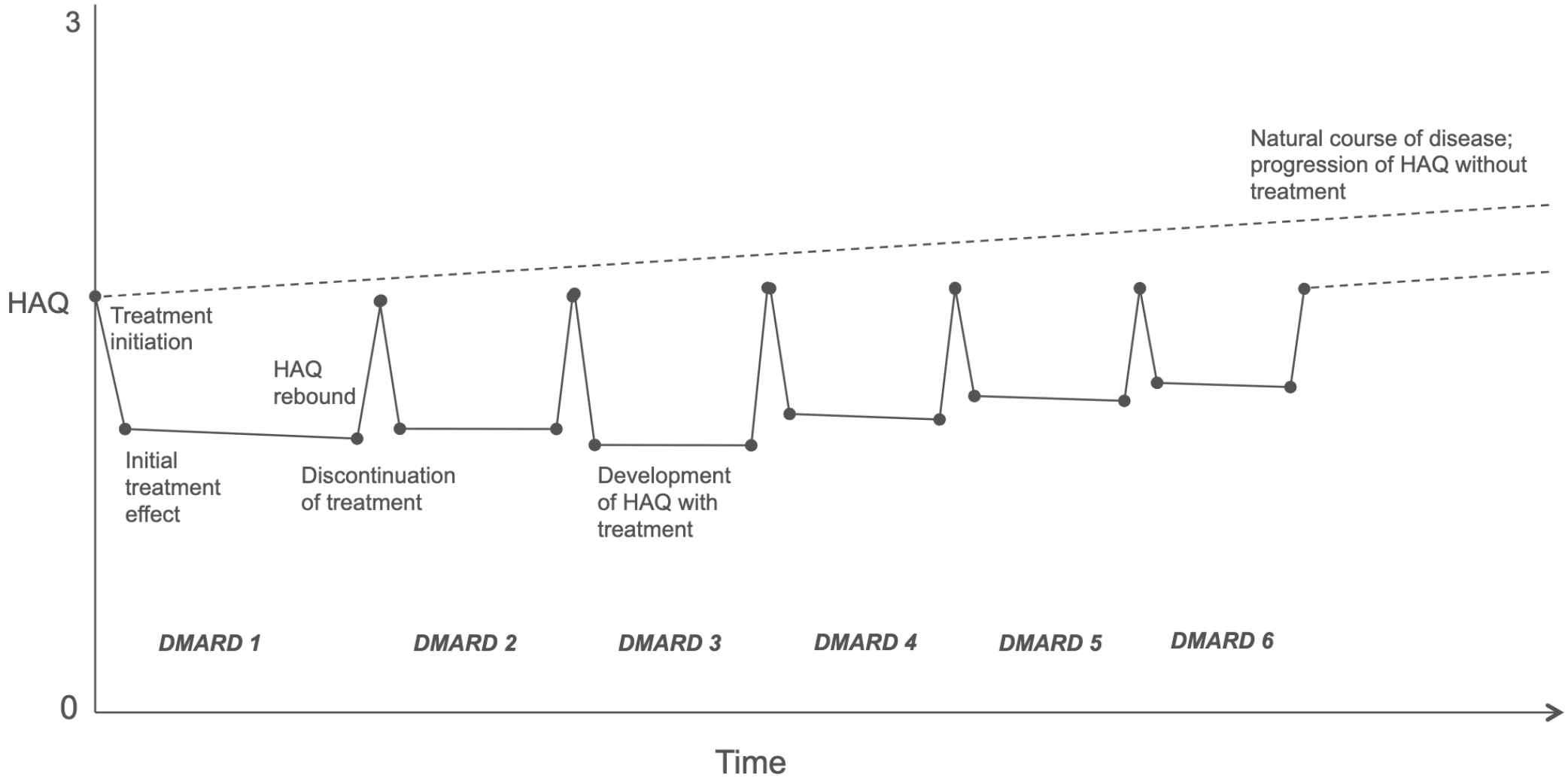



https://innovationvalueinitiative.github.io/IVI-NSCLC/

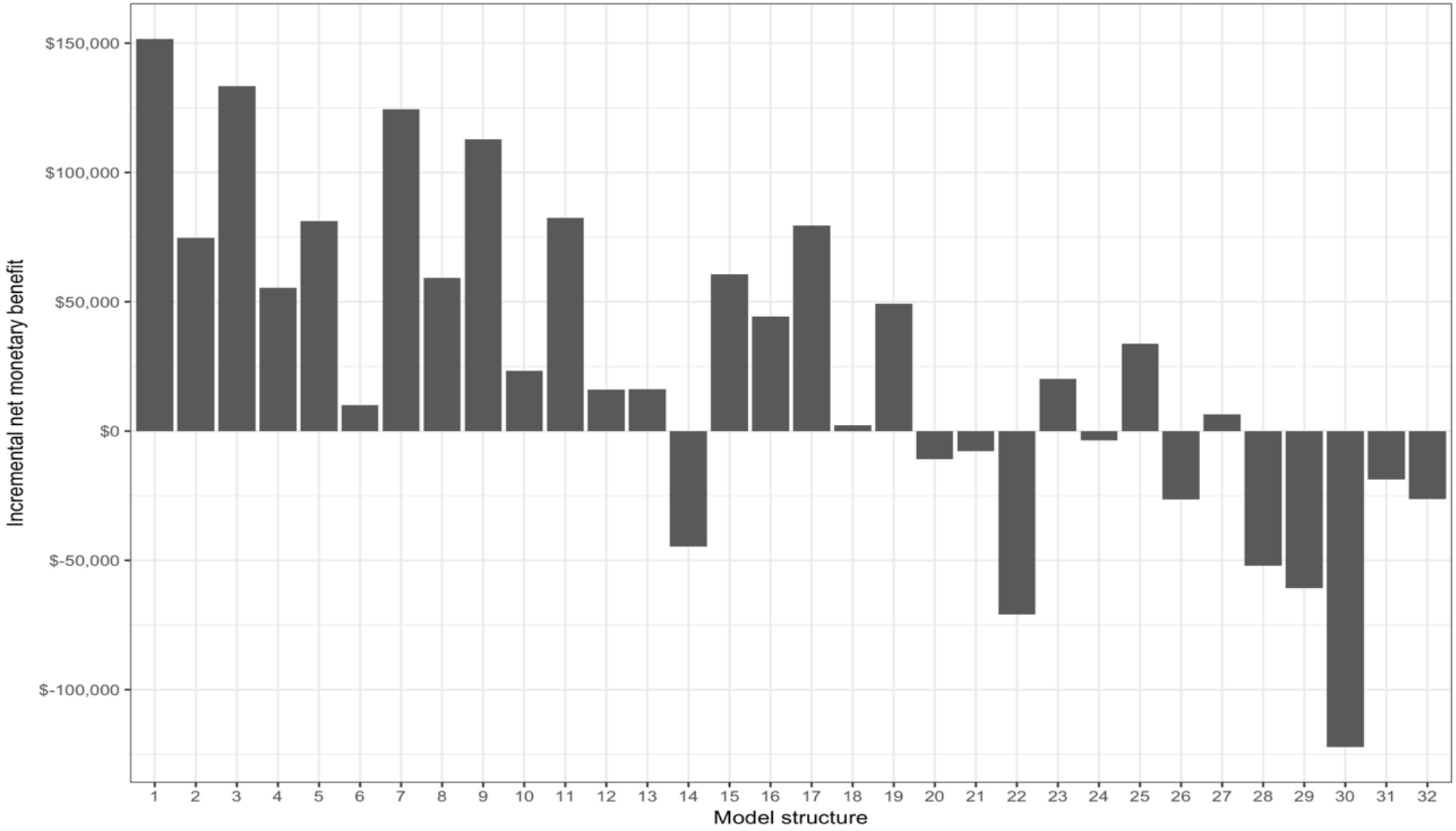



* Now renamed as Center for Innovation & Value Research

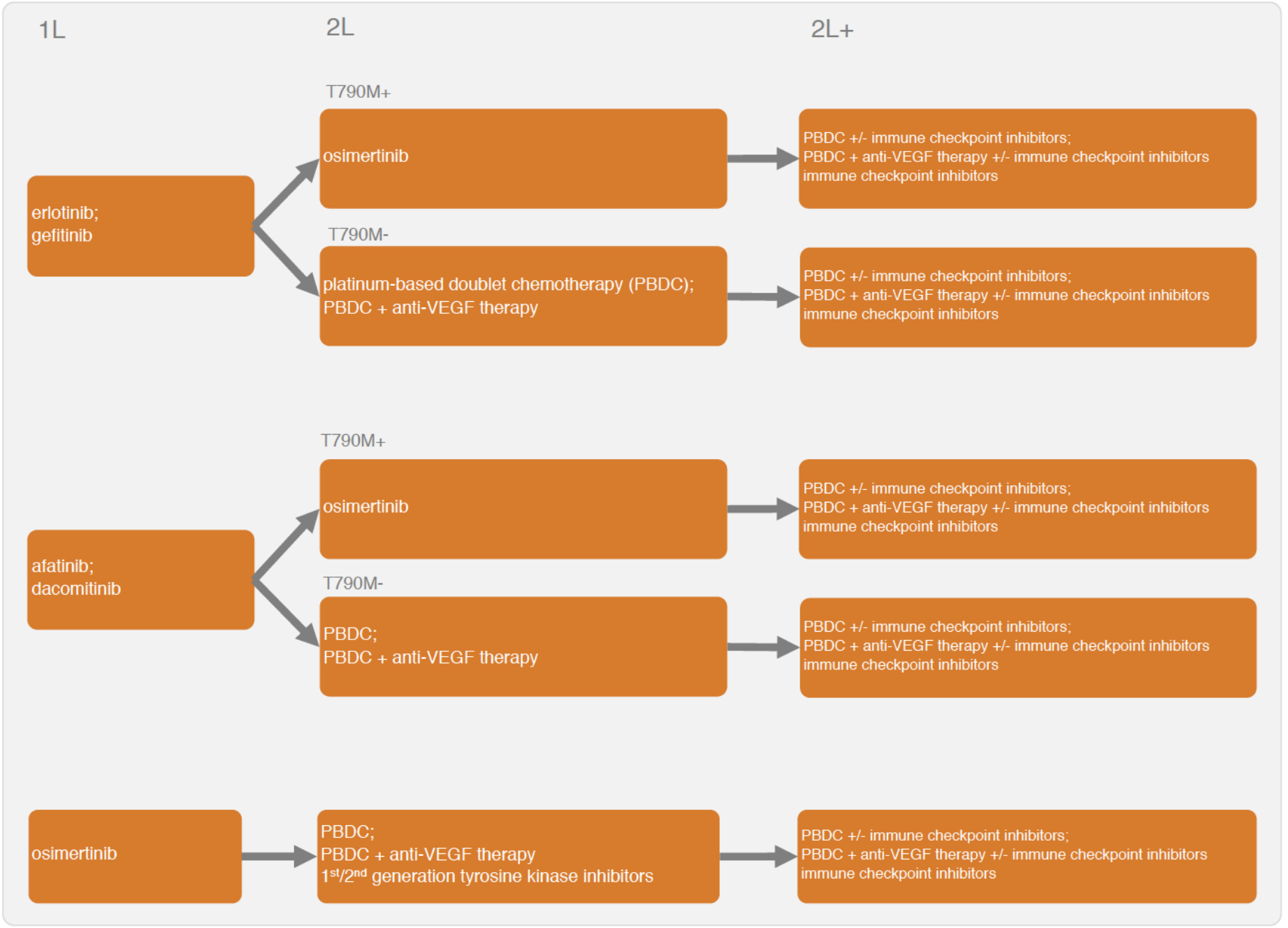
# RA model


3
HAQ
0
Natural course of disease; progression of HAQ without treatment
Treatment initiation
HAQ rebound
Initial treatment effect
Discontinuation of treatment
Development of HAQ with treatment
DMARD 1
DMARD 2
DMARD 3
DMARD 4
DMARD 5
DMARD 6
Time

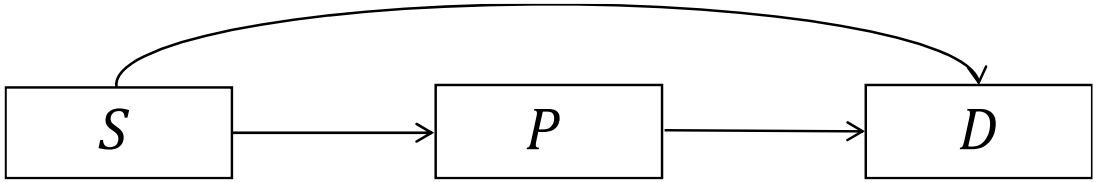
# Structural uncertainty



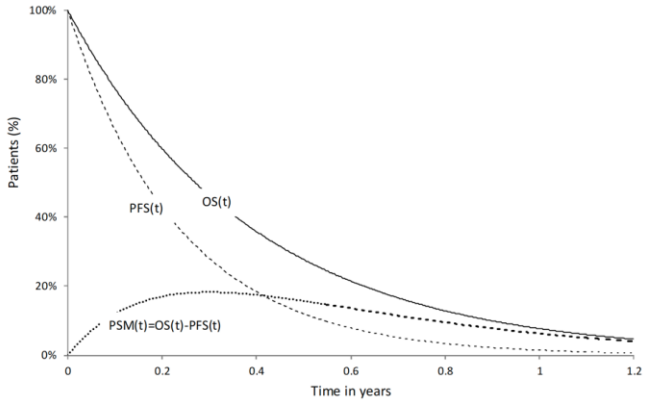
# NSCLC model

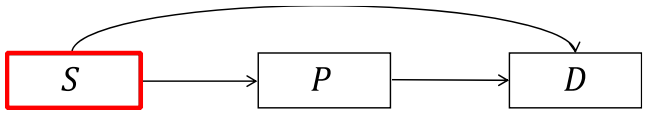

1L
2L
2L+
T790M+
osimertinib
PBDC +/- immune checkpoint inhibitors;
PBDC + anti-VEGF therapy +/- immune checkpoint inhibitors
immune checkpoint inhibitors
erlotinib;
gefitinib
T790M-
platinum-based doublet chemotherapy (PBDC);
PBDC + anti-VEGF therapy
PBDC +/- immune checkpoint inhibitors;
PBDC + anti-VEGF therapy +/- immune checkpoint inhibitors
immune checkpoint inhibitors
T790M+
osimertinib
PBDC +/- immune checkpoint inhibitors;
PBDC + anti-VEGF therapy +/- immune checkpoint inhibitors
immune checkpoint inhibitors
afatinib;
dacomitinib
T790M-
PBDC;
PBDC + anti-VEGF therapy
PBDC +/- immune checkpoint inhibitors;
PBDC + anti-VEGF therapy +/- immune checkpoint inhibitors
immune checkpoint inhibitors
osimertinib
PBDC;
PBDC + anti-VEGF therapy
1st/2nd generation tyrosine kinase inhibitors
PBDC +/- immune checkpoint inhibitors;
PBDC + anti-VEGF therapy +/- immune checkpoint inhibitors
immune checkpoint inhibitors

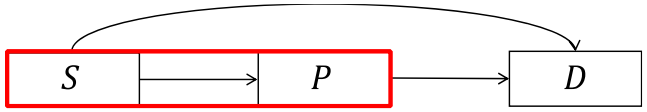
# Modeling options typically used in cancer




## Partitioned survival model

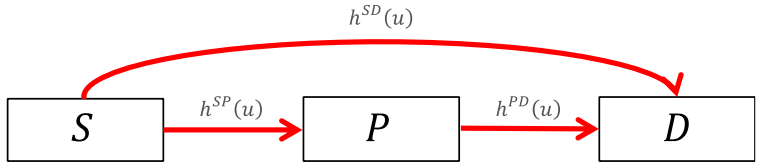



## Markov state-transition model

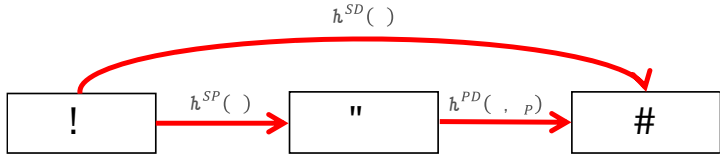
### Clock forward




*(time-varying) transition rates as a function of time in the model*

## Semi-Markov state-transition model

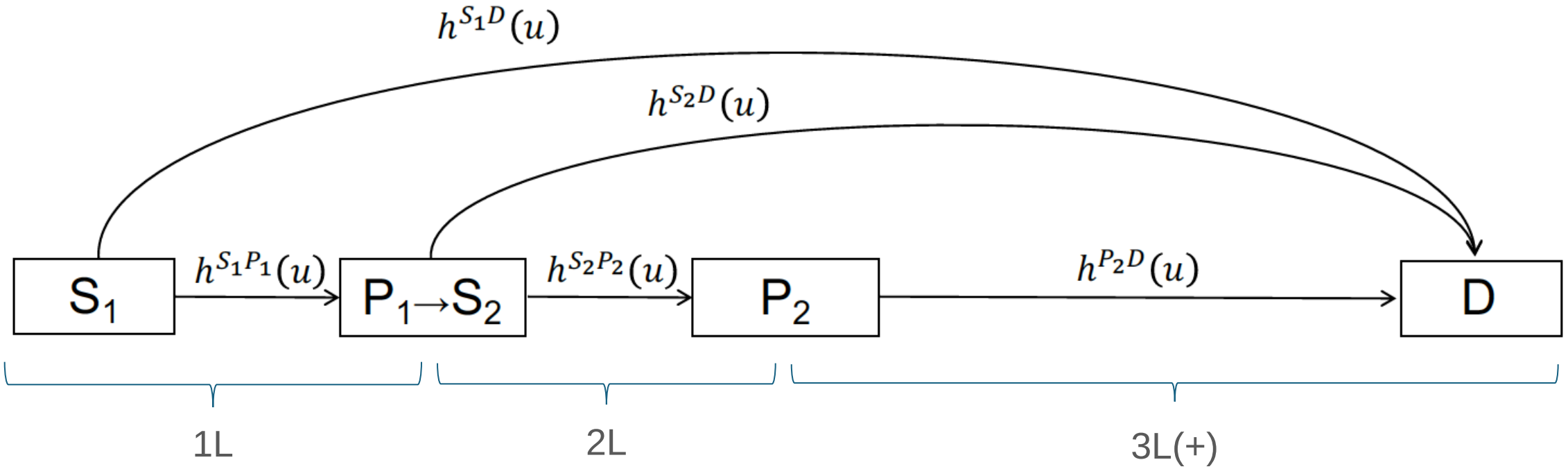
### Clock reset




*(time-varying) transition rates as a function of time in state*

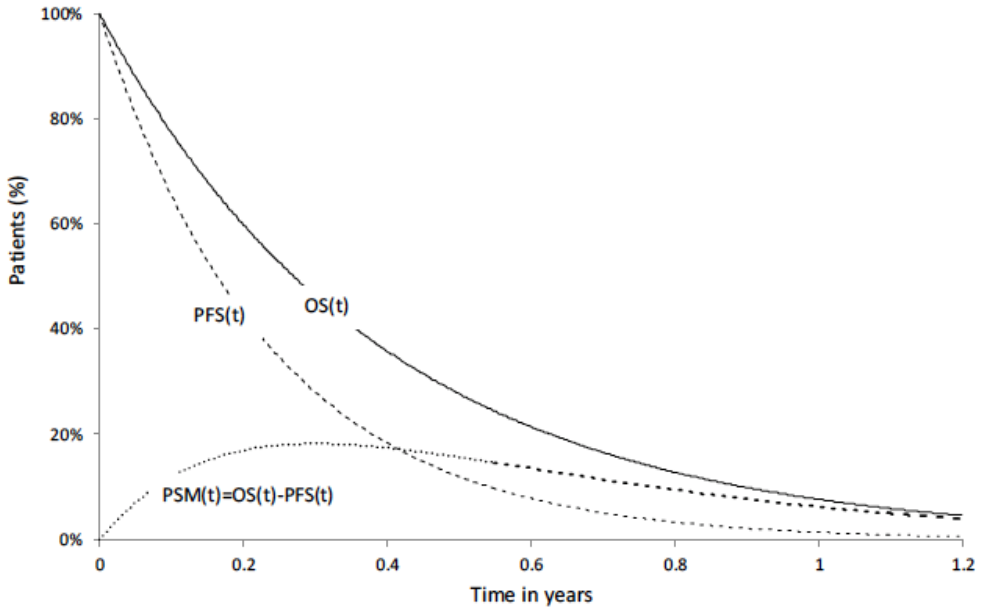
Source: Woods B, Sideris E, Palmer S, Latimer N, Soares M. NICE DSU Technical Support Document 19. Partitioned Survival Analysis for Decision Modelling in Health Care: A Critical Review. 2017 [Available from http://www.nicedsu.org.uk]

# NSCLC model –
# Individual-level continuous-time state transition model (CTSTM)




- Sequential treatment can be incorporated by expanding the number of health states according to the number of treatment lines.
- In general, one can define a health state for each treatment line, a health state after progression on the final line, and a death state. So, a model with *n* treatment lines will have *n+2* health states.

# Why multi-state and not partitioned survival?



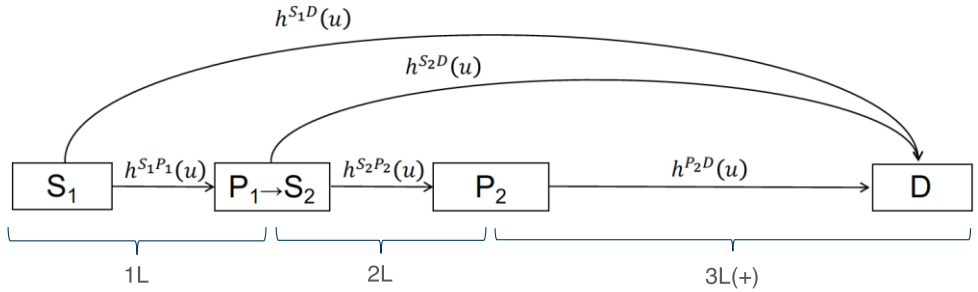

**Transition probabilities at time t in discrete time Markov cohort model**

| | Stable | Progressed | Death |
|---|---|---|---|
| Stable | $1 - [P^P(t) - P^D(t)] - P^D(t)$ | $P^P(t) - P^D(t)$ | $P^D(t)$ |
| Progressed | 0 | $1 - P^D(t)$ | $P^D(t)$ |
| Death | 0 | 0 | 0 |

- Assumption of same transition probability from stable -> death and progressed -> death is not innocuous, and implies that extrapolations are almost surely wrong.
- PFS and OS curves can cross during extrapolation or with probabilistic sensitivity analysis.
- Not straightforward to model sequential treatment (need cumulative survival functions).

# Evidence synthesis to estimate transition rates

- In principle, two potential time scales for multi-state models
  - Markov (i.e. “clock-forward”) implies hazard functions for the transitions based on time since initiating 1L treatment.
  - Semi-Markov (i.e., “clock-reset”) implies hazard functions for the transitions are based on time since entering each state.




- ***Challenge: Lack of clear evidence for P2->D transitions ...***

- Hence, we estimated 1L transitions and 2L/3L(+) transitions with two 3-state “clock-forward” multi-state (network) meta-analyses.
  - 1L (N)MA parameterizes transitions S1->P1 and S1->D
  - 2L (N)MA parameterized transitions S2-> P2, S2->D, and P2->D

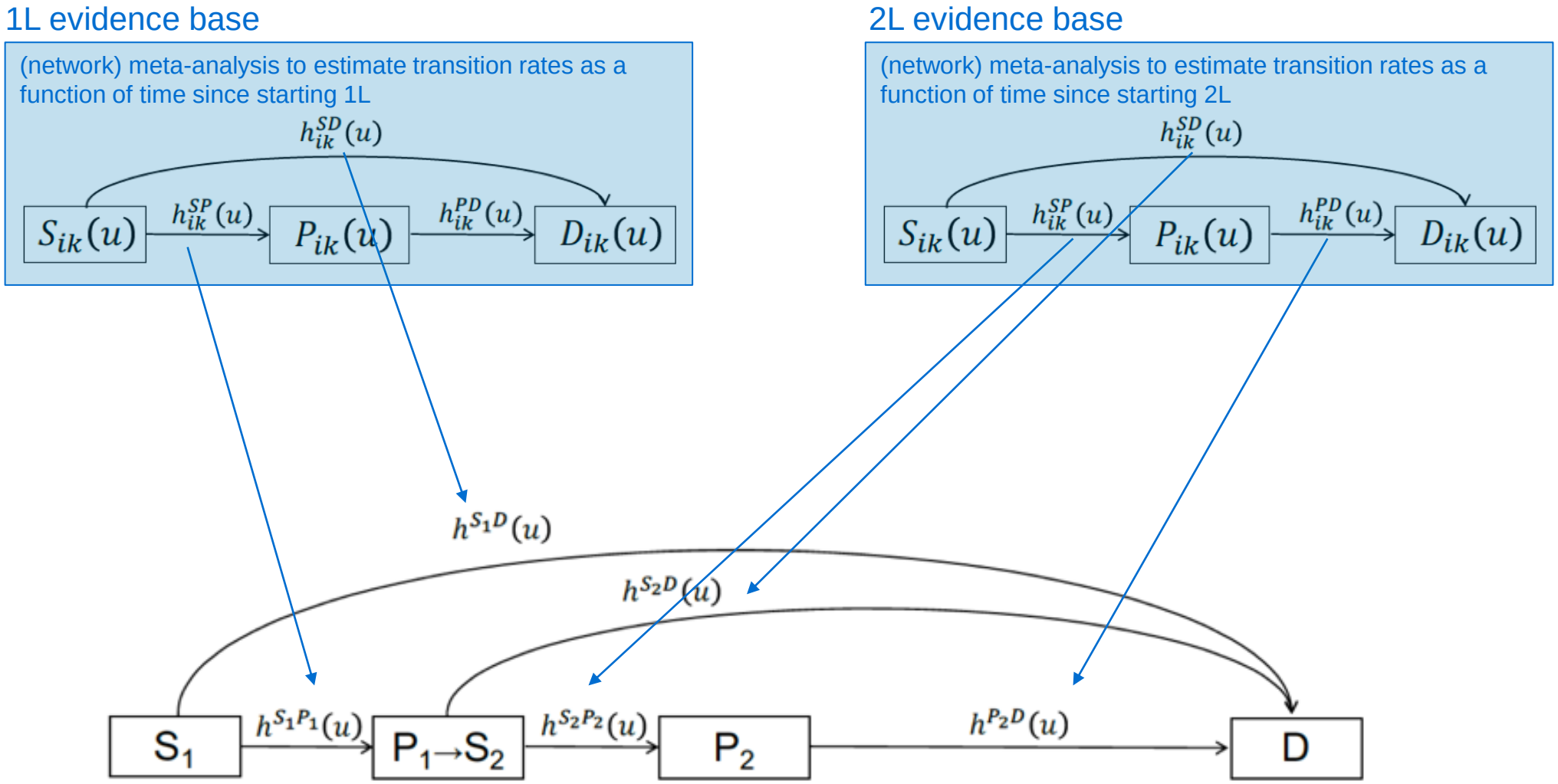
- As a result, we have a semi-Markov simulation model, but the P2->D transition is modeled according to time since entering S2.

# Novelty(?)

## Structure of evidence synthesis model = structure of simulation model

Evidence synthesis models

Simulation model



# Spin-off innovation: multi-state network meta-analysis method

Received: 29 September 2022 | Revised: 2 March 2023 | Accepted: 17 April 2023

DOI: 10.1002/sim.9810

RESEARCH ARTICLE

Statistics in Medicine WILEY

## Multi-state network meta-analysis of progression and survival data

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**Summary**

Multiple randomized controlled trials, each comparing a subset of competing interventions, can be synthesized by means of a network meta-analysis to estimate relative treatment effects between all interventions in the evidence base. Here we focus on estimating relative treatment effects for time-to-event outcomes. Cancer treatment effectiveness is frequently quantified by analyzing overall survival (OS) and progression-free survival (PFS). We introduce a method for the joint network meta-analysis of PFS and OS that is based on a time-inhomogeneous tri-state (stable, progression, and death) Markov model where time-varying transition rates and relative treatment effects are modeled with parametric survival functions or fractional polynomials. The data needed to run these analyses can be extracted directly from published survival curves. We demonstrate use by applying the methodology to a network of trials for the treatment of non-small-cell lung cancer. The proposed approach allows the joint synthesis of OS and PFS, relaxes the proportional hazards assumption, extends to a network of more than two treatments, and simplifies the parameterization of decision and cost-effectiveness analyses.

**KEYWORDS**

aggregate level data, multi-state models, network meta-analysis, non-proportional hazards, time-to-event data

# Evidence challenges

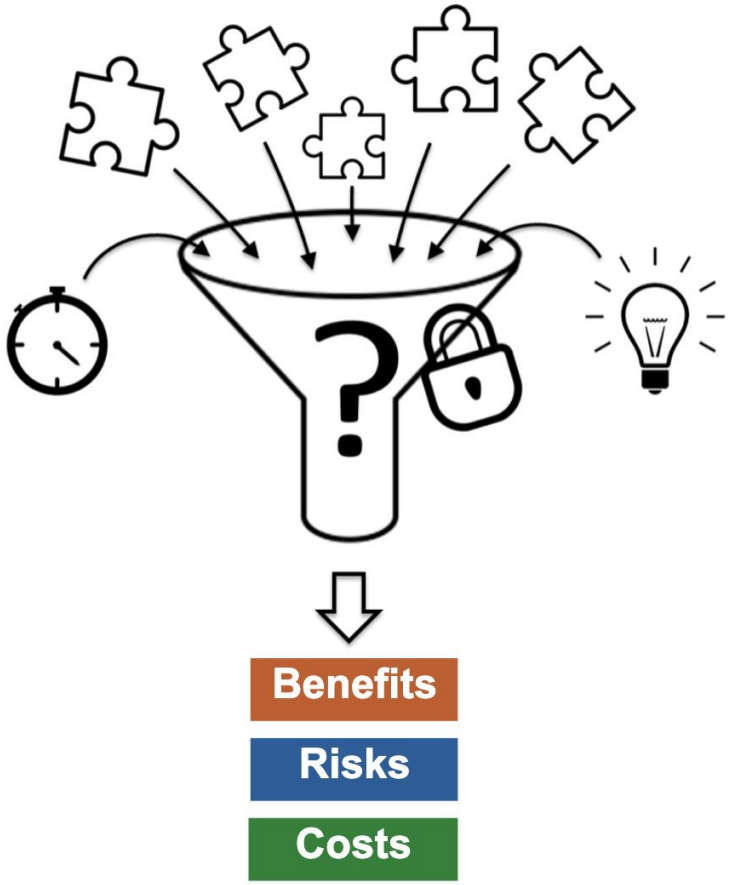
- Cancer trials providing evidence regarding treatment efficacy are often performed in later lines of therapy first and then move to earlier lines.
- As a result, depending on the treatment sequence of interest, the treatment history upon progression for the simulated population in the model may differ from the treatment history among the trial populations. If those differences in treatment history are (associated with factors that are) prognostic factors or effect-modifiers, the analysis will be biased.
- In the NSCLC model, survival distributions were modeled as a function of covariates. Unfortunately we did not have access to the data needed to parameterize covariate effects.

# Transparency

- Transparency ≠ open source
- Different stakeholders with different levels of expertise

- In an attempt to make the IVI-RA and IVI-NSCLC models transparent and accessible to multiple end users, both platforms consist of the following components:
  1. R and C++ **source code**
  2. **R-package** to run the model for custom CEA
  3. An **advanced web application** to allow full control over the model and perform custom analyses via a point and click interface;
  4. A **basic web application** that functions as a general audience educational tool regarding value assessment
  5. **Technical documentation**

- Key finding: developing truly open-source models tailored to different stakeholders takes a lot of time and resources



# Spin-off innovation: hesim

- A modular and computationally efficient R package for health economic simulation modeling and decision analysis that provides a general framework for integrating statistical analyses with economic evaluation.
  - Cohort discrete time state transition models (DTSTMs)
  - N-state partitioned survival models (PSMs)
  - Individual-level continuous time state transition models (CTSTMs), encompassing both Markov (time-homogeneous and time-inhomogeneous) and semi-Markov processes.
- Simulation code written in C++ making individual-level simulation, probabilistic sensitivity analysis (PSA), and incorporation of pati heterogeneity fast.
- **https://hesim-dev.github.io/hesim/dev/**
- **Course:** https://hesim-dev.github.io/rcea/

# Summary

- State-transition models are arguably preferred over partitioned survival models (for evaluating treatment sequences in cancer).

- Lesson learned:
  - Evaluation of structural uncertainty even more important
  - Frequently there are many evidence challenges
  - Open-source and transparency is not the same thing

- Spin-off innovations:
  - Multi-state network meta-analysis methodology
  - hesim R package

# Thank you

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University of Exeter

# Practical challenges

Learnings from the NICE RCC pathways pilot

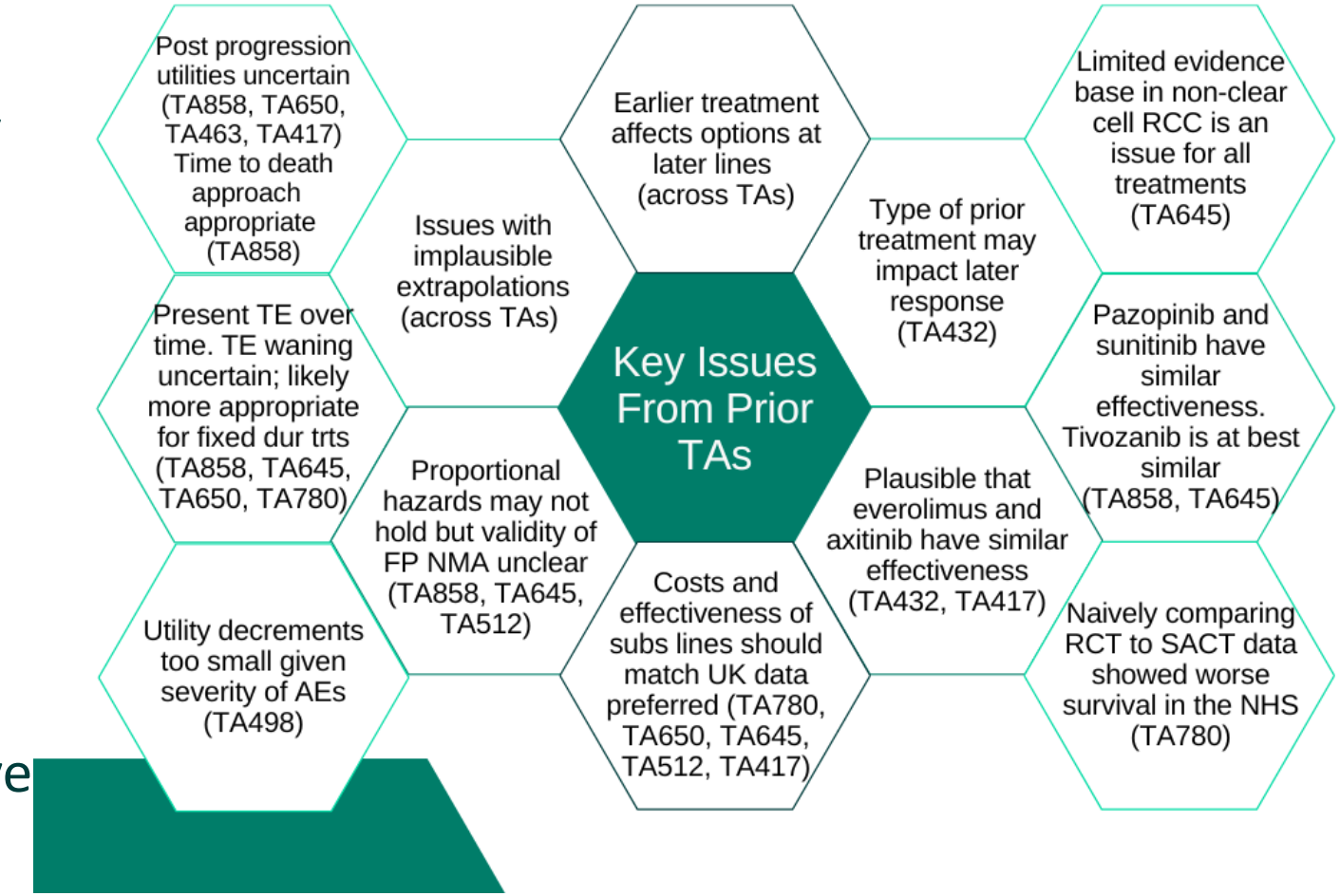
# Historical approach: duck the issue

"Treatments would likely be used in sequences, but cost-effectiveness analysis of sequences would be uncertain because of limited clinical data"

TA814 FAD, atopic dermatitis, 2022

# Why did we want a treatment sequence model for RCC?

- None of the previous TAs considered subsequent therapy appropriately
- Earlier treatment options affect options at later lines
- Recommendations and inputs inconsistent in previous TAs
- Treatments have been recommended which in hindsight were not cost-effective



# The NICE RCC Pathways Pilot Open-Source Model

- Developed on behalf of NICE to support a live appraisal (nivo+cabo)
- Ability to look at sequences
- 4 lines of treatment, 3 risk populations
- PartSA and state transition structures
- Time varying hazard-ratios and hazards
- Data provided by intervention company and comparators ranging from time to event data inputs to aggregate level data only
- Use of RWE for baseline risk which had to be sourced by the EAG

Lee, D., Burns, D. & Wilson, E. NICE's Pathways Pilot: Pursuing Good Decision Making in Difficult Circumstances. *PharmacoEconomics Open* (2024). https://doi.org/10.1007/s41669-024-00490-x

https://github.com/nice-digital/NICE-model-repo

# Practical challenges

## Complexity

744 sequences ~15,000 rows / columns of matrix multiplication

~90 minutes to run state transition model (< 5 mins for PartSA)

90 scenario analysis

Many stakeholders not familiar with R and redacting made it difficult for stakeholders to fully interact

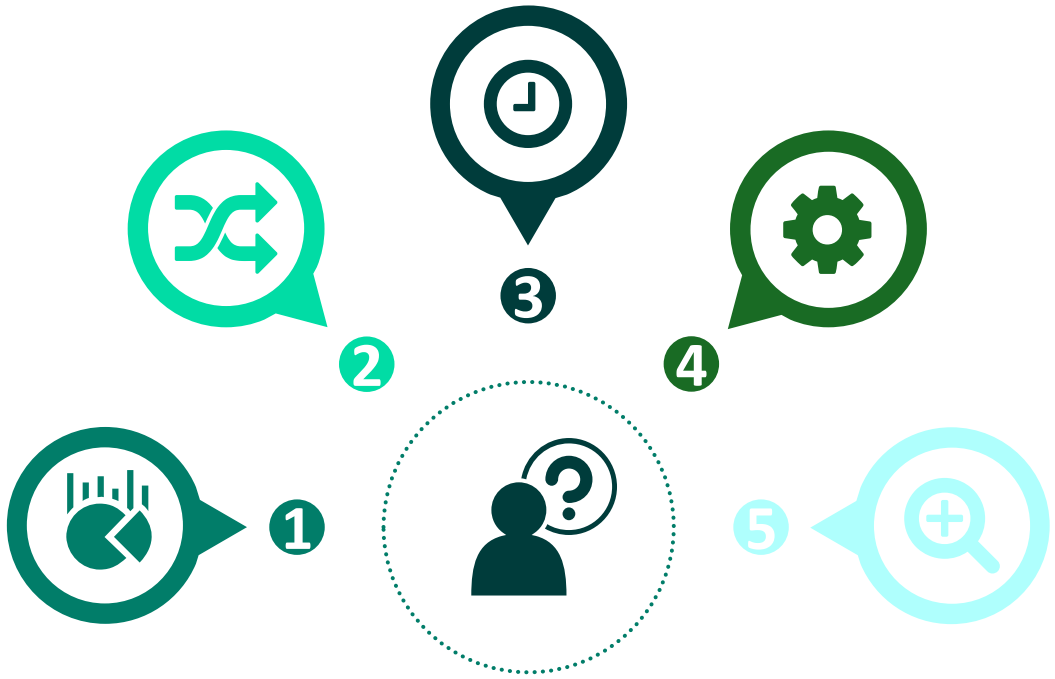
## What is the decision problem?

Real-world vs trial

Is Drug A cost-effective vs what is the most cost-effective sequence

## Data

Sequencing models often rely on heroic assumptions, such as independence of effects, or require access to patient-level data.




## HTA timelines

3 months for draft, 7 months for final vs 2 years for IVI model

Data not available at project start

Strict timelines for clarification and fact check steps

## Recommendation

No basis to recommend more than one option on the basis of similar cost-effectiveness

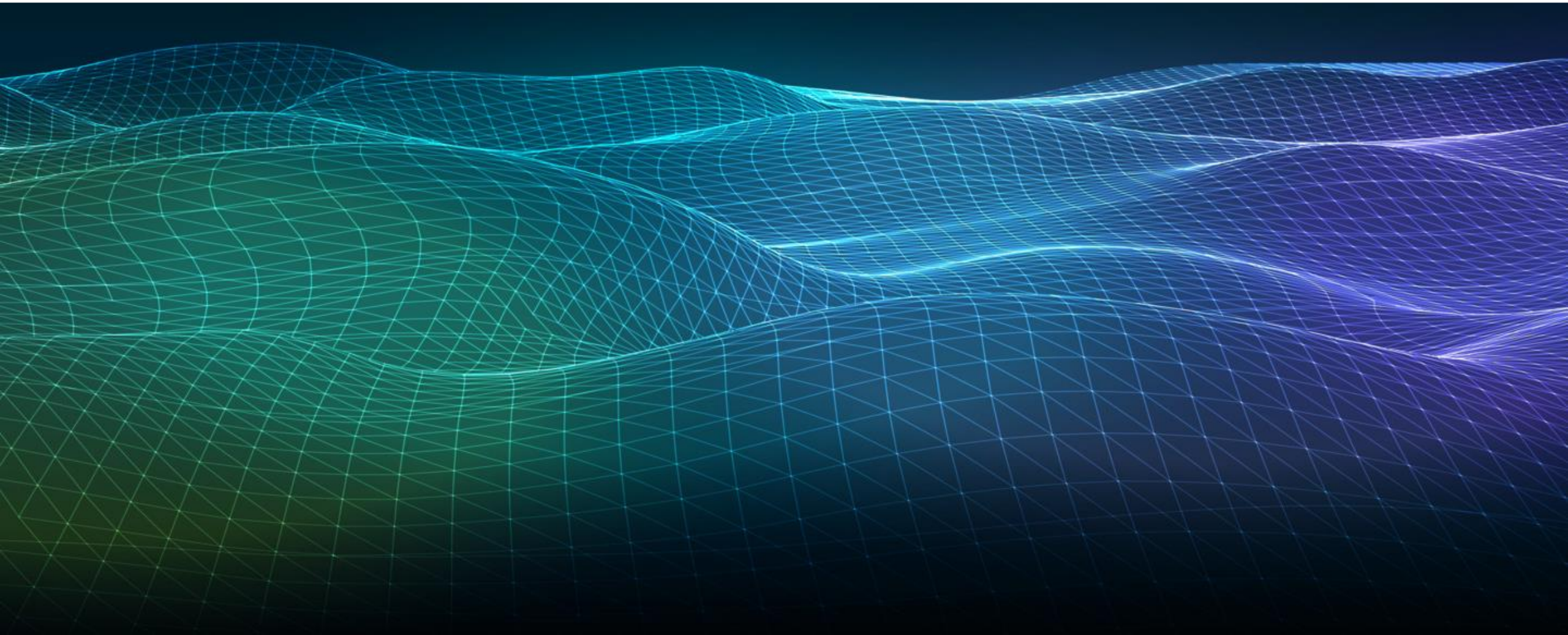
Cost changes, license changes, new treatments could all change what is most cost-effective


Additional open questions / topics for discussion

# What is the future for treatment sequence models?

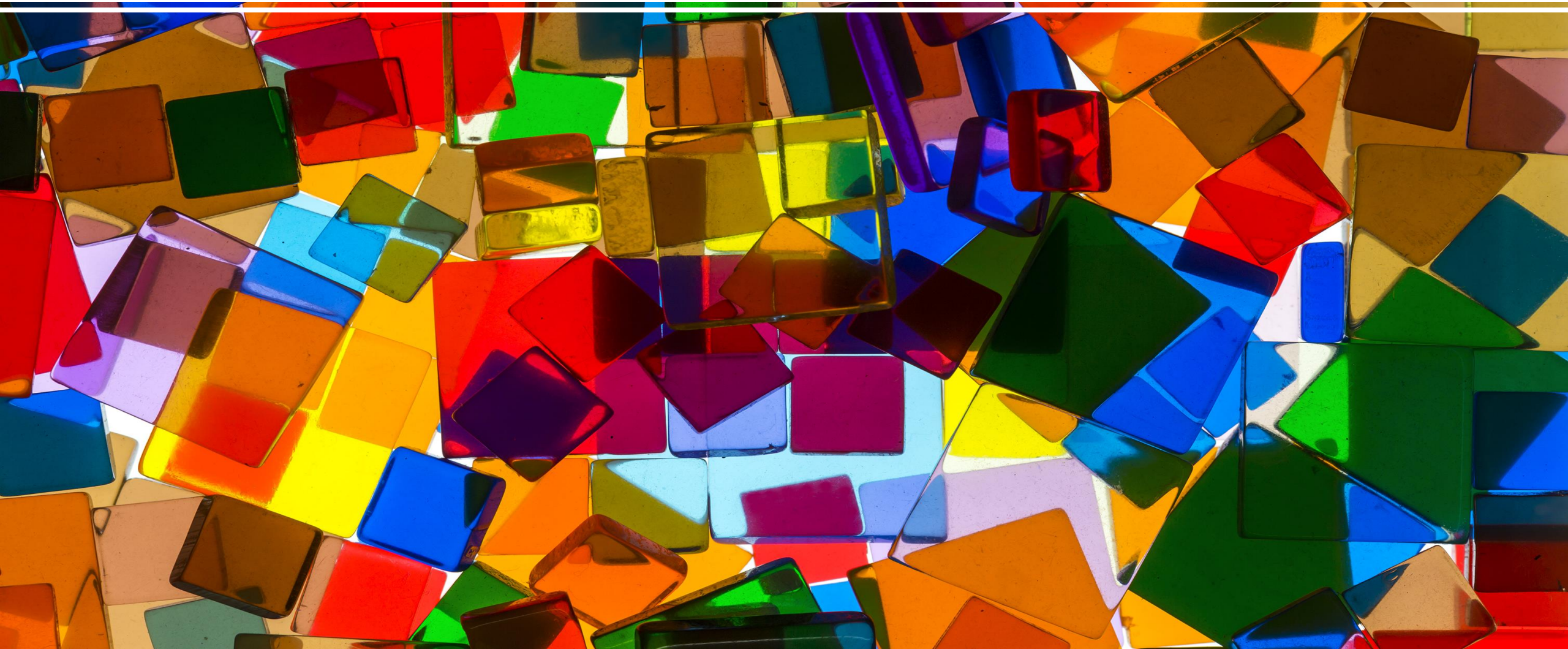
Does this mean the end of partitioned survival models in oncology?

# Where do we get hold of data to inform these models?



# What to do if a treatment stops being cost-effective when modelled within a sequence?

# How do we choose between a vast range of model structures?



How do we trade off accessibility versus efficiency when coding a treatment sequence model?