Evaluation of Treatment Pathways in Oncology: Modeling Approaches

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Objectives

- Rationale for modeling treatment pathways
- Treatment pathway simulation model framework
- Model approach
- Clinical data needs and statistical analysis
Why Do We Model Oncology Treatment Pathways?

- Lack of clinical trials to compare treatment pathway options
  - Most trials focus on the efficacy and safety of individual drugs.
- Models provide a framework that can:
  - Bring together relevant evidence and synthesize it appropriately to predict clinical and economic outcomes
  - Test scenarios that may not be observed in clinical trials
  - Test new treatment options in the treatment pathway to account for the changing dynamics of oncology treatments
  - Compare multiple treatment sequence options
Simulating Treatment Pathways: Model Framework

- Treatment pathway models follow patients’ treatment status over the course of the disease.

BSC: best supportive care
## Considerations for Selecting Model Approaches

| Modeling Objectives | • Comparing treatment options in the same line of treatment  
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<th>• Comparing treatment pathway options over the course of disease</th>
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| Events of Interest/Outcome Measures | • OS directly from trials/observational study  
|                     | • Surrogate endpoints: e.g., PFS, response, duration of treatment |
| Subsequent Treatment | • Cross-over observed in the trial  
|                     | • Subsequent treatments significantly prolong survival. |
| Heterogeneity of Patients | • Patients’ experiences with treatment and disease progression similar enough?  
|                        | • Number of subgroups |
| Data Availability     | • Discrete event simulation (DES) and Markov models require more detailed data than do survival partition models. |
Review of Oncology Modeling Approaches

- Survival partition model
- Markov transition model
- DES
Modeling Approaches In Oncology: Survival Partition Models

- Commonly used approach in advanced oncology indications
- Usually separate patient disease pathways into 3 health states: PFS, post-progression, and death
- Use area under the survival curves (both PFS and OS) to calculate the proportion of patients at given time point in each health state.
- Does not require explicit transitions between the health states.
- Simple, straightforward, directly modeling OS using trial/observational study results
Modeling Approaches: Markov Models

- **Markov cohort models:**
  - Structured around a set of mutually exclusive health states
  - Captures features present in the course of a disease or clinical practice
  - Main advantage is that it is relatively simple to develop, debug, communicate, and analyze using user-friendly software such as Microsoft Excel.
  - Main disadvantage is the underlying assumption that the transition probability from one state to another does not depend on past history.
    - This Markovian property can be very limiting in oncology where time in a given state is strongly determined by previous history.

- **Individual simulation Markov models:**
  - Has the same structure as a Markov cohort model; however, simulates individuals, allowing for tracking of each simulated individual’s history
  - Converting time-to-event data (e.g., survival data) into time-dependent transition probabilities is needed.
Modeling Approaches: Discrete Event Simulations

- Increasingly used in oncology models
- Conceptualizes the course of disease and its management in terms of the events that can happen to individuals and the effect these events have over time on their current and future health
- Individual time-to-event simulations:
  - Events are the central component of DES and are defined as anything that can happen to an entity during the simulation.
  - Time is at the core of DES and is continuous rather than in discrete intervals.
- Compared to individual simulation Markov approach, DES is less complex and easier to develop, debug, communicate, and analyze.
Simulating Treatment Pathway: Model Approach

- DES is the most suitable approach for modeling treatment pathways in most cases.
  - Survival partition models cannot track patients through multiple treatments and require OS data.
  - Markov cohort models assume that the transition probability from one state to another does not depend on past history, which is not true in oncology: Time spent in post-progression is strongly correlated with previous history.

- Individual simulation with Markov approach may be suitable for treatment pathway models but is less transparent and more complicated than DES:
  - When multiple health states are required
  - When long-term follow-up is needed with a relatively short model cycle
  - Converting time-to-event data (e.g., survival data) into time-dependent transition probabilities is needed.
Steps in Discrete Event Simulation

1. Assign estimated risks for each individual.
2. Estimate times to events.
   - e.g., age, gender, medical history

Assign characteristics

Create a group of patients

Determine time to next event (e.g., death, tx disc, tx start)

Die or Model End?

Exit

Y

N

Process the event

Update Risks and Event Times
Clinical Data Required for the Pathway Model

- Clinical data at each phase of treatment over the pathway are needed, such as disease progression, treatment discontinuation, response, and mortality.

- Prediction equations are used in the model to predict time to events and the disease status at the end of each phase of treatment.
  - e.g., time to first-line treatment discontinuation, time to death while treated with first-line treatment, time from first-line end to second-line start, Eastern Cooperative Oncology Group (ECOG) status at the end of treatment

- Parametric survival analysis techniques are used to identify an appropriate distribution that captures the shape of the hazard of event and incorporate predictors that can increase or decrease these hazards.

- Patient-level data are preferred when deriving prediction equations.
  - Patient characteristics and disease status could be used as predictors for events, which would help synthesize data from different sources.