Oncology Treatment Sequence Models in Health Technology Assessment – A Literature Review

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BACKGROUND

- Novel anticancer treatments significantly improve patient outcomes through delayed progression and improved overall survival (OS)
- With numerous novel oncology treatments approved each year, the treatment decisions become more complex
- Patients often receive multiple lines of treatments over time. But the question concerning which treatment sequence achieves optimal disease control and maximum cumulative survival remains unaddressed
- From a health technology assessment (HTA) agency's perspective, reimbursement decisions are not only whether the treatment should be included in the treatment pathway, but also where the novel treatment should be placed in the sequence
- Therefore, developing a rigorous oncology treatment sequence model to identify the more efficacious and cost-effective treatment sequence is relevant to both clinical and payers' decision-making
- While previous studies have reviewed economic models of treatment sequences for chronic diseases such as rheumatoid arthritis, literature reviews of oncology sequence models are limited
- Zheng et al[1] identified 40 treatment sequence models (13 related to oncology) based on a review of the National Institute for Health and Care Excellence (NICE) technology appraisals (TAs) prior to October 24, 2014, and summarized the rationale and approaches for treatment sequence models in general
- However, that review did not summarize specific considerations for oncology treatment sequence models

OBJECTIVE

- To review oncology sequence models in NICE submissions and to assess the methodological approaches and challenges

METHODS

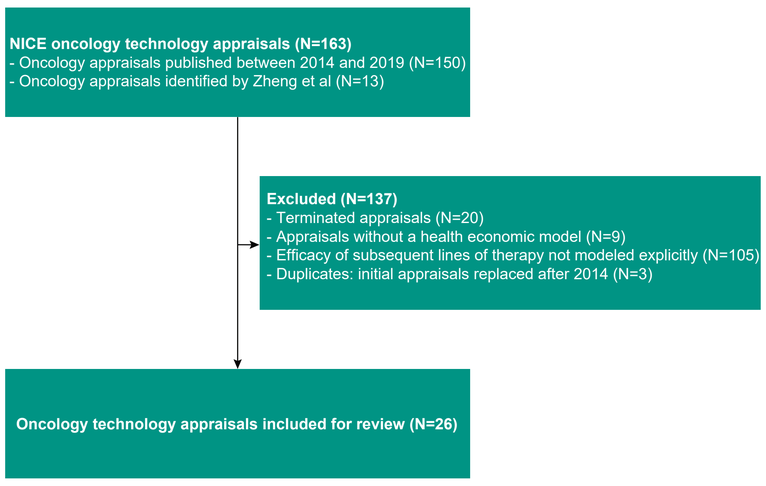
Literature Search Strategy

- Data source for literature search
  - We retrieved NICE oncology TAs identified by Zheng et al and obtained additional NICE oncology appraisal recommendations published between 2014 and 2019
  - Models developed by manufacturers (for single technology appraisals) and evidence review group (for multiple technology appraisals) were retrieved
- Eligibility criteria
  - Cost-effectiveness models that explicitly modeled efficacy of subsequent lines of therapy were included in the review
  - There was no restriction to population, intervention, and outcomes
- Extracted information
  - Objectives, model structure, data sources, and techniques for modeling treatment sequences were summarized

RESULTS

- A total of 163 oncology TAs published before September 2019 were assessed for eligibility (**Figure 1**)
- 26 oncology sequence models were included in the final review, with 58% published after 2015

Figure 1. Study Selection

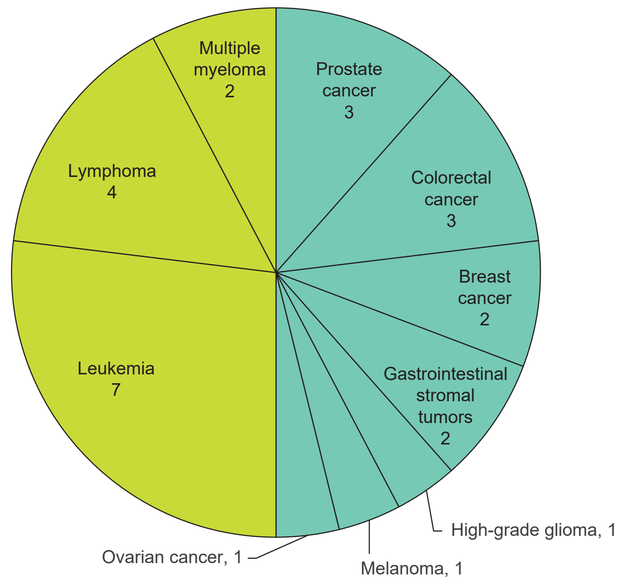


Study Characteristics

- The majority of the oncology sequence models intended to assess a new treatment in the treatment pathways recommended by the clinical guidelines or commonly used in clinical practice
- 2-8 relevant sequences were evaluated in each model
- 13 models focused on solid tumors and the other 13 models focused on hematology indications (**Figure 2**)

Figure 2. Study by Cancer Type

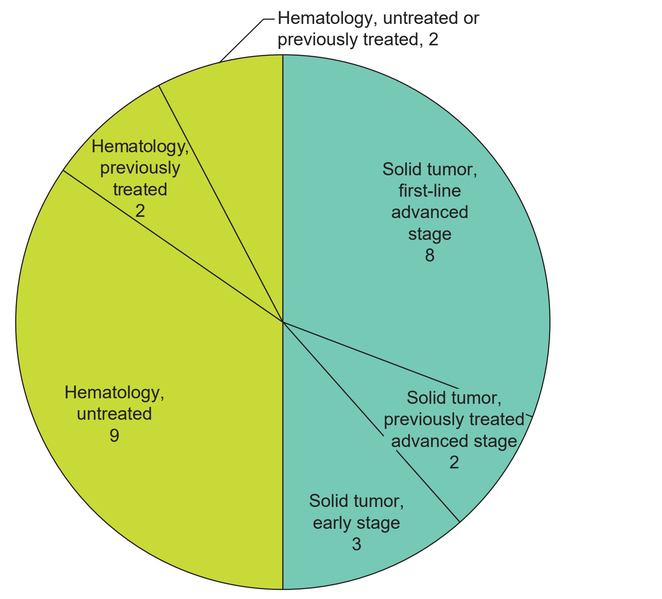
Study by cancer type (N=26)



- Majority of the sequence models were developed for untreated populations in hematology indications (N=9) or first-line advanced stage solid tumor (N=8) (**Figure 3**)

Figure 3. Study by Treatment Setting

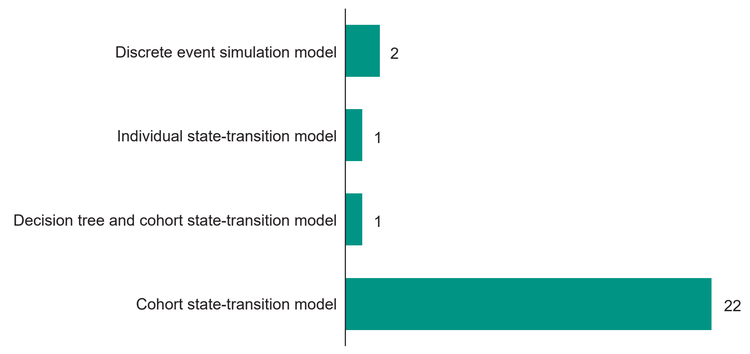
Study by treatment setting (N=26)



- The most common model structure was cohort state-transition model (N=22) (**Figure 4**)

Figure 4. Model Structure

Study by model structure (N=26)



Key Methodological Issues in the Existing Oncology Sequence Models

- The following methodological issues were summarized. Limitations and potential approaches to improve the methodologies were discussed
  - Modeling efficacy of treatment sequences
  - Incorporating indirect treatment comparison (ITC)
  - Modeling treatment-free intervals (TFIs)

Modeling Efficacy of Treatment Sequences

- Summary of methodologies in the existing models
  - Most studies (N=25) used data from clinical trials in different lines of therapy to model the efficacy of a treatment sequence without adjusting for patient characteristics in the trials in later lines
    - OS for an entire treatment sequence was modeled by combining progression-free survival (PFS) from the trials in previous lines and OS from the trials in later lines
    - Survival data for each line was obtained directly from the corresponding line of trials
  - One study modeled OS for an entire treatment sequence based on the first-line trial
    - Inverse probability of censoring weighted (IPCW) analysis was used to adjust the distribution of subsequent treatment when estimating patients' survival from the trial data in TA 377
- General limitations
  - Patients enrolled in subsequent line trials (eg, 2L) may be healthier than those who initiated the same treatment as a subsequent therapy in 1L trials or in the real world due to the specific inclusion/exclusion criteria
    - Failing to adjust for the differences in disease characteristics is likely to overestimate the efficacy for the treatment sequence
  - Using 2L trial data for patients' progression on 1L treatment in the model assumes that patients entering 2L trials are representative of patients progressing on 1L treatment, though patient characteristics are likely to be associated with the subsequent treatment choices
    - Failing to adjust for patient characteristics when modeling patients receiving a specific subsequent line of therapy is likely to lead to selection bias
- Potential approaches to improve the methodologies
  - If a clinical trial provides sufficient sample size and follow-up time to estimate OS for a specific treatment sequence, data from this trial may be used to model the survival of patients who receive this treatment sequence. Adjustment for non-randomization of switching to a specific subsequent treatment should be included in the model
  - Due to the scarcity of clinical trials that capture long-term impacts of sequences, combining trial data from different lines is often necessary to model a treatment sequence. Patients' characteristics in the later line trials need to be adjusted based on those initiating a subsequent treatment in the previous line trial. The extent of adjustment depends on the available data in the previous line trial (ie, patient characteristics at the time of subsequent treatment initiation). Patient characteristics at the time of initiating a later line treatment may also be obtained from real-world data and used for adjustment in efficacy estimation

Incorporating Indirect Treatment Comparison

- Summary of methodologies in the existing models
  - The majority of the models (N=19) did not explicitly consider ITC
  - Among the models applying ITC
    - 6 models did it within a specific line of treatment sequence (TA326, TA370, TA426, TA429, TA439, and TA491)
    - Only one applied ITC to every line (ie, 1L and 2L) in the treatment sequence (TA563)
- General limitations
  - Naïve comparison introduces bias due to potential cross-trial differences
- Potential approaches to improve the methodologies
  - ITC within each line should be conducted and applied to estimate the comparative efficacy between two treatment sequences
  - Depending on the data availability, ITC may further adjust for patient characteristics at the time of subsequent treatment initiation

Modeling Treatment-free Intervals

- Summary of methodologies in the existing models
  - The majority of the models (N=24) did not explicitly consider TFIs
  - Only 2 TAs estimated TFIs between 1L and 2L treatments (ie, TA370 and TA380)
    - Standard parametric models were fitted to the trial-based TFI data, and the best fitted curve was selected to derive the transition probability from progression on 1L treatment to progression-free on 2L
- General limitations
  - Failing to consider TFI results leads to inaccurate estimate of subsequent treatment initiation time, which may
    - Generate bias in the OS estimate
    - Overestimate the discounted treatment costs
- Potential approaches to improve the methodologies
  - Estimate the TFI using IPD from the previous line trial if the timing of subsequent treatment initiation is recoded or uses real-world data
  - Use TFI to estimate transition probabilities from the previous line progressed disease to subsequent line progression-free disease

CONCLUSIONS

- The scarcity of clinical data and the limitations of current modeling approaches have been found to be common challenges for modeling oncology sequences
- Future research is required to bridge data gaps and to develop a comprehensive modeling framework for evaluation of treatment pathways in oncology and potentially generalizable for other disease areas
- Ideal model framework should accommodate different objectives, eg, maximizing survival or quality-adjusted life-years of the treatment sequence, maximizing efficiency (ie, cost-effectiveness), or minimizing costs

Reference:

1. Zheng Y, Pan F, Sorensen S. Modeling treatment sequences in pharmacoeconomic models. *Pharmacoeconomics*. 2017 Jan 1;35(1):15-24.

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