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EE633

A Targeted Literature Review of the Modelling Approaches and Challenges in Early-Stage Oncology Treatment Sequence Models

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Overview

- The last few years have seen the emergence of promising targeted therapies in oncology leading to an increased potential number of total lines of therapy (LOT) in a sequence.
- Thus, It is important to develop economic models of treatment sequences, especially for the early-stage oncology indications to provide evidence for optimal treatment pathways.

Background:

- With an increasing number of targeted early-stage oncological interventions available for patients, the number of lines of therapy a patient can expect to receive is also increasing.
- Although clinical guidelines are available to inform clinical decision-making on patient treatment pathways, variations exist in treatment positioning based on country, disease progression and preceding line of therapy.
- Without real-world evidence, modelling treatment sequences in oncology has become increasingly important in order to provide evidence for optimal pathways in terms of clinical and cost effectiveness.
- The relevancy of modelling oncology treatment sequences is expected to rise, although current treatment sequence modelling techniques do pose some methodological challenges, thus it is important to highlight these challenges to aid the development of efficient treatment sequence models in this indication.

Aims:

- Summarize existing treatment sequence models in early oncology
- Highlight patterns regarding modelling approaches
- Point out key methodological challenges

Methods

- We conducted targeted literature searches in MEDLINE, Embase and Cochrane databases via the OVID platform, with no time limit, up to May 2022. No geographical limit was applied to the search. The relevant databases, the search strategy and PICOS criteria can be found adjacent.

Databases searched:

1) Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions(R) 1946 to May 2022
2) Embase 1974 to 2022 May
3) Cochrane library Databases
   i. Cochrane Central Register of Controlled Trials May 2022
   ii. Cochrane Database of Systematic Reviews 2005 to May 2022
   iii. Cochrane Clinical Answers May 2022
   iv. Cochrane Methodology Register 3rd Quarter 2012

Eligibility Criteria:

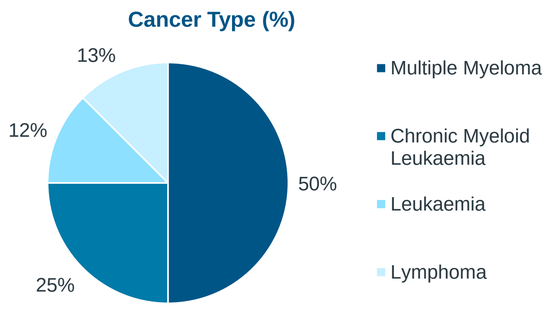
- Included articles were reviewed for relevance against the PICOS criteria listed in Table 2.
- English scientific articles published prior to May 2022 for which the full text was available and the study modelled sequential treatments in an early stage oncological population were included.
- Articles were excluded if they were abstract only, if they did not incorporate an sequential economic model or cost effectiveness outcome.

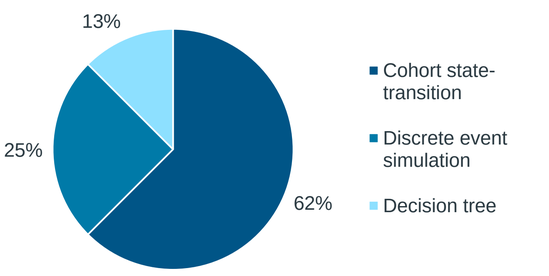
Table 1: PICOS criteria used for the TLR

PICOS	COMPONENT OF INTEREST
POPULATION	Patients with early-stage oncological disease
INTERVENTION	Any intervention
COMPARATOR	Any comparator
OUTCOMES	Modelling approaches, techniques, and challenges
STUDY DESIGN	Modelling studies incorporating a sequence of more than one therapy.

Results

- Of 538 identified articles, 8 were included and all of them conducted cost-effectiveness analysis in early-stage haematology.





Modelling technique

- 62.5% (5/8) of articles used a cohort state transition (Markov)
- 25% (2/8) used individual patient simulation
- 12.5% (1/8) applied a decision tree method

Efficacy outcomes used to define health state occupancy

- 50% (4/8) of models defined health states by disease progression status
- 25% (2/8) used time of treatment (ToT)
- 25% (2/8) used a combination of diseases progression and ToT

Data sources

- Clinical trials and real-world evidence were the primary sources of evidence in these studies
- 100% (8/8) derived efficacy data from multiple sources rather than one clinical trial or real-world data source

Efficacy adjustments

- Efficacy adjustments accounting for the sequence position of a LOT were not conducted in any of the studies
- Treatment-free intervals (TFIs) between treatment lines were not considered in any of the models
- 37.5% (3/8) studies incorporated indirect treatment comparisons

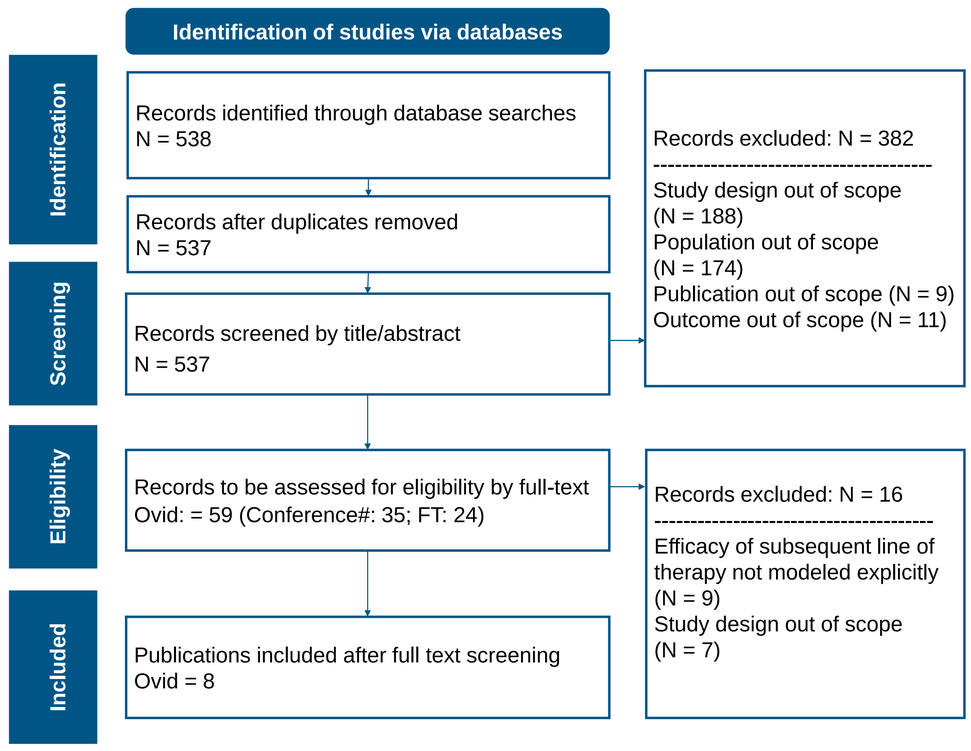


Figure 1: PRISMA flow diagram detailing the TLR process

- The search yielded 8 articles for which details can be found in **Table 2** below. The methodological challenges associated with each study are highlighted.

Table 2: Details of the identified articles returned in the TLR

Author, Year	Title	Challenges Highlighted
Blommestein et al, 2016	A cost-effectiveness analysis of real-world treatment for elderly patients with multiple myeloma using a full disease model.	TFI was not considered, however when health states are defined based on TOT instead of on progression, consideration of TFI as an extra health state before the next LOT may help capture the washout period associated with oncological interventions.
Whalen et al, 2016	Cost-effectiveness analysis of second-line tyrosine kinase inhibitor treatment for chronic myelogenous leukemia.	Data gaps exist, especially for response, progression, and mortality risks, and assumptions were used to derive these long-term model inputs.
Qerimi et al, 2018	Cost-effectiveness analysis of treating transplant-eligible multiple myeloma patients in Macedonia.	The results suggest that a substantial amount of uncertainty captured by the model is associated with some of the parameters used for the clinical trials and costs data – Querimi recommended to vary the uncertainty parameters within a Probabilistic Sensitivity Analysis (PSA) or Probabilistic One-way Sensitivity Analysis (POSA).
Rochau et al, 2015	Effectiveness and cost-effectiveness of sequential treatment of patients with chronic myeloid leukemia in the United States: A decision analysis.	Paucity of data leads to the inability to include all efficacy adjustments, treatment decisions, resource use etc. Rochau, where possible, ensured consistency across all treatment sequences so as to not bias results.
Soini et al, 2012	Economic Evaluation of Sequential Treatments for Follicular Non-Hodgkin Lymphoma.	Within a model structure in which a patient can move from both PF1 and PF2 to the PD state, it is difficult to assess the contribution of first-line therapy to overall survival.
Blommestein et al, 2021	Cost-effectiveness of Novel Treatment Sequences for Transplant-Ineligible Patients with Multiple Myeloma.	To make comparisons of treatments that are not head-to-head comparisons, assumptions need to be made. For example, assuming that the hazard ratio (HR) for PFS is representative of the HR for time to treatment discontinuation (TTD) in the Network Meta Analysis(NMA).
Rochau et al, 2015	Cost-effectiveness of the sequential application of tyrosine kinase inhibitors for the treatment of chronic myeloid leukemia.	Ensure all possible monitoring approaches and resistance testing processes that might influence treatment decisions for patients are taken into account in the model. Models populated with sparce and unreliable outcomes do not provide meaningful evidence.
Vukicevic et al, 2020	Long-Term Effectiveness and Cost Effectiveness of Multiple Myeloma Treatment Strategies for Elderly Transplant-Ineligible Patients in Serbia.	Assuming effectiveness of subsequent treatments to be independent of the type of prior treatment may result in bias as drugs with a common mechanism of action may also have similar resistance pathways. Care should be taken to account for differences or match patient characteristics.

Conclusion

Predominant model attributes:

- Early-stage oncology treatment sequence models are generally modelled using a Markov approach incorporating a cohort state transition structure with health states defined by disease progression.

- Owing to a paucity of clinical or real-world evidence, most models require a synthesis of data from multiple studies, and do not account for TFIs nor include indirect treatment comparisons or efficacy outcome adjustments relative to heterogeneity in baseline patient characteristics.

Limitations:

- A predominant limitation of sequence modelling is data availability. In the absence of clinical trials, data must be gathered from different sources or synthesised using ITCs. Use of this data does often necessitate the use of simplifying assumptions which can add bias to the models and conclusions generated.
- Treatment sequence models should mimic clinical practice, although structural discrepancies are often noted, driven by data source and perspective of analysis.
- Oncological treatment sequence modelling is a developing area and there is a lack of high-quality, robust published models. Due to the sample size, limited conclusions can be drawn from this review and caution is needed in interpreting the data.
- Our search drew publications from various relevant databases; to broaden the searches, a pragmatic search of additional literature sources such as conference abstracts or HTA websites could be done in future.

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