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# Mixture Cure Models in HTA Submissions: A Comparative Review

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## INTRODUCTION

- Increased investment and rapid advancement in the development of transformative therapies have shown that the prospect of cure is becoming a reality in disease areas where treatments had previously focused on delaying progression and time to next therapy
- Survival outcomes from randomized controlled trials (RCTs) are often immature at the point of submitting evidence for reimbursement in health technology assessments (HTAs). Thus, extrapolation of survival outcomes is often required to estimate the long-term effects of new technologies[1]
- The most common source of uncertainty in HTAs is the choice of extrapolated curves. Parametric survival models are widely accepted across different disease areas, but in the case of transformative technologies with curative intent, they are often criticized for not reflecting the underlying hazards and anticipated survival trajectories[2]
- This may lead to uncertain estimates of the technology's cost-effectiveness, which may have downstream implications on patient access
- The use of alternative survival models such as mixture cure models (MCMs) has gained traction to more adequately capture these potentially curative, long-term outcomes. An MCM assumes that the cohort survival function consists of separate survival functions from two subgroups of patients: cured and uncured[3]
- However, MCMs are not yet commonly used in HTA submissions[4]

## OBJECTIVES

- To summarize the use of MCMs and their characteristics in technology appraisals (TAs) published by the UK's National Institute for Health and Care Excellence (NICE)
- To compare the detailed considerations related to MCMs between NICE and Canada's Drug Agency (CDA) and Pharmaceutical Benefits Advisory Committee (PBAC) in Australia, two HTA bodies with assessment frameworks similar to NICE

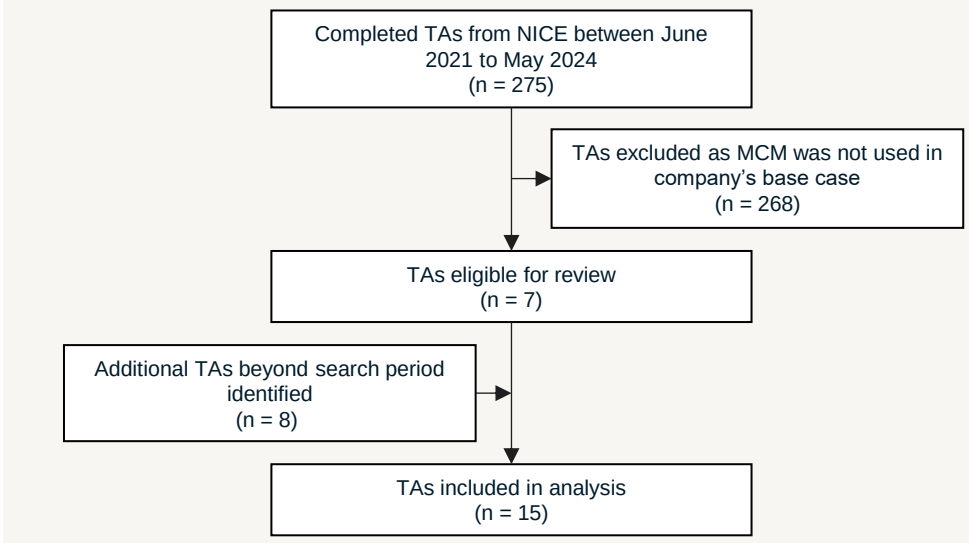
## METHODS

- A systematic review was conducted for NICE TAs that had final appraisal documents (FADs) that published online between June 2021 and May 2024
- All submissions that considered MCMs in the company's base case were included in the first review. Additional TAs that had also used a MCM in the company's base case before June 2021 were identified if they were referenced in the initial selection of TAs
- The following items were extracted for analysis: technology name, year of FAD publication, indication, model structure, rationale for using the MCM, endpoints that the MCM was used for, application of MCM and methodological critique by the HTA body
- Each NICE TA was then matched to their respective CDA and PBAC appraisal documents, where the above items were retrieved from the final publication document, where possible

## OVERVIEW OF RESULTS

- Among the 275 TAs identified within the search period, seven (2.6%) reported use of MCMs. Prior to 2021, eight additional TAs that had used MCMs were identified and included (Figure 1)

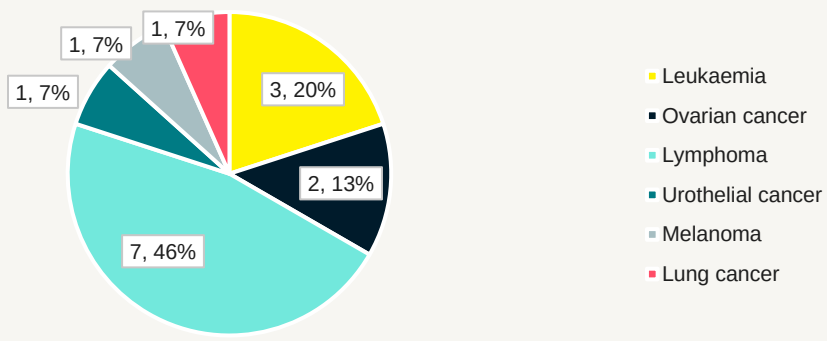
**Figure 1. PRISMA diagram**




**Key**: MCM, mixture cure model; NICE, National Institute for Health and Care Excellence; Preferred Reporting Items for Systematic reviews and Meta-Analyses; TA, technology appraisal.

- Of the 15 TAs included in the review, 10 (66.7%) were in haematological cancers; two (13.3%) were in gynaecological cancers; and one (6.7%) each was in urothelial cancer, non-small-cell lung cancer, and melanoma (Figure 2)

**Figure 2. Number of TAs with MCM used in company base-case, by indications**

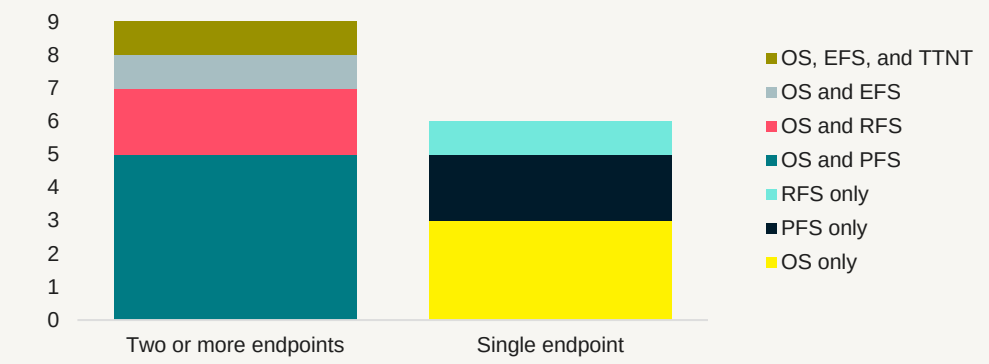



**Key**: MCM, mixture cure model; TA, technology appraisal.

## RESULTS

- MCMs were used mainly in partitioned survival models (13, 86.7%), with two (13.3%) being used in state transition models. The majority of the partitioned survival models (11, 84.6%) had three health states
  - Health states used were progression-free / progressed disease (PD) / dead (4, 36.3%), event-free / PD / dead (3, 27.2%), and one (9.1%) each for pre-progression / post-progression / dead, relapse-free / post-relapse / dead, event-free / post-event / dead, and on-treatment / off-treatment / dead.
- The main reasons for employing MCM were clinical plausibility for cure (TA963[5], TA874[6]), or clear plateau observed in the Kaplan–Meier curves indicative of a long-term response (TA946[7], TA478[8])
- The company's base case used MCMs for two or more endpoints in nine (60%) TAs, while the remaining TAs reported MCM use for a single endpoint (Figure 3)
  - Overall survival (OS) was modelled using MCM in most TAs (12, 80.0%)
  - Reasons for selecting a particular endpoint are not often stated explicitly. Even when acknowledged, there may be inconsistency in the rationale provided
    - In TA872[8] the company alluded that there has not been consensus in the application of MCM to progression-free survival (PFS), even though MCM had been used on PFS in previous TAs

**Figure 3. Number and types of endpoints MCMs were employed**




**Key**: EFS, event-free survival; MCM, mixture cure model; OS, overall survival; PFS, progression-free survival; RFS, relapse-free survival; TTNT, time to next treatment.

- The majority of TAs received critique on the use of MCMs as the base case:
  - Short trial follow-up and insufficient information supporting claims of cure or deep remission
  - Implausibly long survival exceeding that of general population
  - Differences in estimated cure fractions between OS and PFS/event-free survival (EFS)
- Eleven (73.3%) of the included TAs further assumed long-term cure for all patients
  - Various cure points ranging from 2 to 7 years were used, with no agreement between the companies and External Assessment Group (EAG) on the most appropriate choice
  - Seven (63.7%) TAs uplifted general population mortality with a standardized mortality ratio (SMR) to account for excess mortality compared with the general population due to the disease. There was also no consensus between the companies and EAGs on (a) application of SMR and (b) the most appropriate SMR value
- Out of the 15 NICE submissions that had incorporated MCMs in the company's base case, only four (26.7%) submissions with MCM use were identified from the final publication document published by the CDA and PBAC, respectively. It is noted that public reports from the CDA and PBAC are generally less detailed than NICE in terms of describing the conduct and critique of MCMs

**Table 1. NICE TAs that used MCMs and their respective use in CDA and PBAC**

| NICE TA | Technology | Therapeutic area | CDA | PBAC |
|---|---|---|---|---|
| TA975 | Tisagenlecleucel | Leukaemia | No | No |
| TA962 | Olaparib | Ovarian cancer | No | No |
| TA946 | Olaparib | Ovarian cancer | NA | NA |
| TA927 | Glofitamab | Lymphoma | No | NA |
| TA895 | Axicabtagene ciloleucel | Lymphoma | Yes | Yes |
| TA874 | Polatuzumab vedotin | Lymphoma | Yes | Yes |
| TA872 | Axicabtagene ciloleucel | Lymphoma | Yes | Yes |
| TA677 | Brexucabtagene autoleucel | Lymphoma | Yes | No |
| TA649 | Polatuzumab vedotin | Lymphoma | NR | No |
| TA589 | Blinatumomab | Leukaemia | No | No |
| TA545 | Gemtuzumab ozogamicin | Leukaemia | No | Yes |
| TA544 | Dabrafenib and trametinib | Melanoma | No | No |
| TA525 | Atezolizumab | Urothelial cancer | NA | NA |
| TA520 | Atezolizumab | Lung cancer | No | No |
| TA478 | Brentuximab vedotin | Lymphoma | No | No |

**Key**: CDA, Canada's Drug Agency; MCM, mixture cure model; NA, unable to locate respective submission; NICE, National Institute for Health and Care Excellence; NR, information about choice of model not available in report; PBAC, Pharmaceutical Benefits Advisory Committee; TA, technology appraisal.

## CONCLUSIONS

- The decision to use MCM was based largely on the hypothesis of cure and long-term remission, which may be corroborated with a plateau observed in the Kaplan–Meier curves
- There is heterogeneity in the methodological conduct of MCMs in terms of endpoints and assumptions. There is also a lack of consensus in the assessment of MCMs. Methodological guidance will be useful in the conduct and assessment of MCMs in the future
- MCMs appeared less frequently in submissions to the CDA and PBAC. This implies a lower appetite or acceptability for using MCMs, although it is not possible to distinguish potential reasons

## REFERENCES

[1]Latimer NR, Adler AI. *BMJ Med*. 2022; 1(1):e000094. [2]Felizzi F, et al. *Pharmacoecon Open*. 2021; 5(2):143-155. [3]Rutherford MJ, et al. *NICE DSU Technical Support Document 21*. [4]Latimer NR, Rutherford MJ. *Pharmacoeconomics*. 2024; 42(10):1073-1090. [5]NICE. TA963. Accessed Oct 2024. [6]NICE. TA874. Accessed Oct 2024. [7]NICE. TA946. Accessed Oct 2024. [8]NICE. TA478. Accessed Oct 2024.

An electronic version of the poster can be viewed by scanning the QR code.

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