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Health Policy Analysis

Predicting the Population Health Economic Impact of Current and New Cancer Treatments for Colorectal Cancer: A Data-Driven Whole Disease Simulation Model for Predicting the Number of Patients with Colorectal Cancer by Stage and Treatment Line in Australia

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ABSTRACT

Objectives: Effective healthcare planning, resource allocation, and budgeting require accurate predictions of the number of patients needing treatment at specific cancer stages and treatment lines. The Predicting the Population Health Economic Impact of Current and New Cancer Treatments (PRIMCAT) for Colorectal Cancer (CRC) simulation model (PRIMCAT-CRC) was developed to meet this requirement for all CRC stages and relevant molecular profiles in Australia.

Methods: Real-world data were used to estimate treatment utilization and time-to-event distributions. This populated a discrete-event simulation, projecting the number of patients receiving treatment across all disease stages and treatment lines for CRC and forecasting the number of patients likely to utilize future treatments. Illustrative analyses were undertaken, estimating treatments across disease stages and treatment lines over a 5-year period (2022-2026). We demonstrated the model's applicability through a case study introducing pembrolizumab as a first-line treatment for mismatch-repair-deficient stage IV.

Results: Clinical registry data from 7163 patients informed the model. The model forecasts 15 738 incident and 2821 prevalent cases requiring treatment in 2022, rising to 15 921 and 2871, respectively, by 2026. Projections show that over 2022 to 2026, there will be a total of 116 752 treatments initiated, with 43% intended for stage IV disease. The introduction of pembrolizumab is projected for 706 patients annually, totaling 3530 individuals starting treatment with pembrolizumab over the forecasted period, without significantly altering downstream utilization of subsequent treatments.

Conclusions: PRIMCAT-CRC is a versatile tool that can be used to estimate the eligible patient populations for novel cancer therapies, thereby reducing uncertainty for policymakers in decisions to publicly reimburse new treatments.

Keywords: colorectal cancer, disease projection, health technology assessment, real-world data, treatment utilization, whole-disease model.

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Highlights

- Accurate forecasting of patient numbers at specific cancer stages and treatment lines is vital for efficient healthcare planning and resource distribution. However, current predictions are typically limited to overall and stage-specific incidence forecasting. To ensure effective healthcare planning, novel tools are needed for Australia's colorectal cancer (CRC) landscape.
- The Predicting the Population Health Economic Impact of Current and New Cancer Treatments-CRC model, grounded in real-world Australian data, offers unparalleled granularity in predicting CRC patient counts segmented by disease stage, cancer type, and treatment utilization. The model's ability to simulate the introduction of new treatments, exemplified through the pembrolizumab case study, demonstrates its adaptability and relevance for both present and future healthcare scenarios.
- The Predicting the Population Health Economic Impact of Current and New Cancer Treatments-CRC model sheds light on Australia's current CRC treatment trajectory. As a dynamic tool, it may assist policymakers in assessing the impact of introducing new cancer treatments by forecasting potential patient populations. Its adaptability ensures proactive healthcare planning, for various interventions throughout the patient pathway.

Introduction

Cancer is one of the most prevalent and deadly diseases worldwide, and its treatment involves complex and expensive procedures driving up global healthcare spending.[1,2] Cancer care expenses include direct costs, such as hospitalization, surgery, radiation therapy, and anti-neoplastic medicines, as well as indirect costs, such as lost productivity, reduced quality of life, and caregiver burden.[2,3] In the United States, direct cancer care expenses constitute around 7% of the overall healthcare expenses, which is a substantial proportion.[4] Costs associated with cancer care in the United States were projected to approximately US$208.9 billion in 2020, reflecting the high cost of cancer treatment in the country.[2] This cost burden can have significant impacts on patients, families, and the healthcare system as a whole.[5-8] Similarly, in Australia, the estimated costs of cancer care are approximately AU$10.1 billion annually, which makes up about 8.3% of overall health expenditure.[9] The management of cancer care expenses and the provision of effective and affordable cancer care services are crucial for

improving patient outcomes and making the healthcare system more economically sustainable.[10]

Colorectal cancer (CRC), cancers arising in the colon or rectum, is a significant health concern worldwide. According to the World Cancer Research Fund, CRC is the third most common cancer worldwide, with an estimated 1.9 million new cases and 935 173 deaths in 2020.[11] In Australia, CRC is the fourth most commonly diagnosed cancer, with an estimated 15 713 new cases in 2022,[12] and the second leading cause of cancer-related deaths, with an estimated 5326 deaths in 2022.[12] The incidence rates of CRC are increasing in Australia and several other countries,[11,13] particularly in younger age groups.[14,15] The management of CRC is complex and expensive, potentially including surgery, radiation therapy, chemotherapy, targeted therapies, and immunotherapies, which contributes to a significant healthcare expenditure in the country[9,16] and worldwide, making this cancer the second most expensive overall.[1]

Globally, the forecasted increase in cancer care expenditure is attributed to various factors, such as the rising cancer incidence rates, the development of costly and personalized treatments, and better survival rates prolonging care needs.[2] When novel treatments are considered for reimbursement, many health technology assessment agencies consider incremental costs and outcomes compared with standard of care. In addition to incremental outcomes on individual level, the total budget impact of new listings is critical and thus accurate forecasting of the number of patients who may be treated in the future is essential for effective healthcare planning, resource allocation, and budgeting. However, predicting the number of patients who will require cancer care in the future is a challenging task for decision makers because of the complexity of the disease and the multiple factors that can influence cancer risk and outcomes.[7] Moreover, the lack of real-world data on the global treatment landscape increases the uncertainty around the eligible number of individuals with CRC, across different stages and treatment lines.[17,18] Therefore, forecasting methods that consider multiple factors, including real-world data analyses, appropriate modeling techniques, and input from various stakeholders and especially consumers, can support decision making related to the introduction of new therapies.[19] High-level models are commonly used for budget impact analyses because of their simplicity and broad applicability. However, these often fail to capture detailed patient care pathways and the financial implications of evolving treatment standards. Furthermore, they do not appropriately account for relevant downstream consequences and conditionalities, resulting in potentially biased estimates.[20] Such granular insight is essential for precise economic evaluations, facilitating more accurate budget planning and resource allocation. That depth of analysis is required to support policymakers in making informed decisions regarding the adoption and funding of new therapies in today's complex clinical pathways, ensuring that healthcare systems are prepared for real-world demands. The objective of the Predicting the Population Health Economic Impact of Current and New Cancer Treatments (PRIMCAT) project is to improve the prediction of the eligible patient population for novel CRC systemic therapies, through the development of data-driven simulation models. A model was developed to estimate the number of patients receiving treatment across all disease stages and treatment lines for CRC in Australia. To forecast the utilization of novel therapies, the model was built flexibly, allowing scenario analyses, to be able to integrate new treatments at different stages of the treatment journey. The model was tested by forecasting the number of patients who will require treatment with pembrolizumab in the first-line setting of metastatic mismatch-repair-deficient (dMMR) CRC in Australia. By providing granular predictions of patient counts and treatment utilizations, our model provides essential data for economic evaluations, offering a novel tool for budget impact analyses. This approach not only aids in precise healthcare budgeting but also supports policymakers in making informed decisions regarding the public reimbursement of new cancer therapies.

Methods

Data Sources

The Australian Comprehensive Cancer Outcomes and Research Database

Established in 2008, The Australian Comprehensive Cancer Outcomes and Research Database (ACCORD) is an Australian clinical quality registry that aims to improve cancer care and outcomes nationally. ACCORD collects data from more than 80 hospitals across Australia and covers a range of cancer types, including CRC.[21] It includes information on patient demographics, cancer diagnosis and stage, treatments received, and clinical outcomes, such as overall survival and quality of life.

The Treatment of Recurrent and Advanced CRC registry

Treatment of Recurrent and Advanced Colorectal Cancer (TRACC) registry was established to collect real-world data of patients with recurrent and advanced CRC to help improve their treatment outcomes at multiple public and private hospitals across and outside Australia. To date, more than 4000 patients have been enrolled in TRACC, and detailed patient and disease characteristics, treatment history of primary disease, and metastatic treatment motivation and outcomes across multiple treatment lines have been collected prospectively.[22]

Data Cleaning and Classification

Within ACCORD and TRACC, data tables corresponding to patient status, care episodes, and recurrence status were used. Within each, date and type of events were extracted, including diagnosis, surgical procedures, radiotherapy, systemic treatments, recurrence, progression, last visit, and death. Each event was classified into 3 levels, from broader to more detailed information. For example, in ACCORD, the event "diagnosis" is the upper level and "diagnosis stage II" the intermediate level, whereas the more detailed level is "diagnosis stage II, right colon." Both registries contain treatment lines, which are curated by clinicians. For each treatment line, systemic treatments were categorized according to the most intensive chemotherapy, that is, singlet, doublet, or triplet chemotherapy (1, 2, or 3 chemotherapy drugs given in combination), and the biological agent according to the first exposed biological. Biologicals considered are epidermal growth factor receptor and vascular endothelial growth factor inhibitors, with prescription of either being dependent on Rat Sarcoma (RAS) mutation status. For example, the event "chemotherapy" would be further subclassified as "doublet" as intermediate level, and folinic acid, fluorouracil, and irinotecan as the most detailed level.

All included variables were evaluated for potential data coding errors through visualizations and inspection of value distributions. When errors were encountered for individual records, custodians were informed, and data entries corrected. Particular attention was given to event dates, such as ensuring treatment start occurred at or after initial diagnosis.

Patient Inclusion

All individuals with CRC diagnosed with stages I to III between October 01, 2005 to December 31, 2019 from ACCORD were included. All individuals diagnosed at stage IV between June 01, 2015 to December 31, 2019 identified from TRACC were included. The time frame of diagnoses was chosen to capture the introduction of targeted therapies in Australia, such as the public reimbursement of cetuximab for RAS wild-type (RASwt) metastatic disease in June 2015, and to allow for a reasonable follow-up period to capture events and outcomes. Both ACCORD and TRACC share unique identifiers for patients across their data sets, although the 2 registries are independent in that they collect different types of data corresponding to the treatments related to the different stages (stages I-III in ACCORD and stage IV in TRACC). This consistency allows us to track the progression of patients from early-stage diagnoses in ACCORD to later stages in TRACC, thereby ensuring a continuous observational scope for each patient's journey through different cancer stages. Therefore, if patients were initially diagnosed with stage I to III disease and later progressed to metastatic (stage IV) disease, data recorded in ACCORD was used in estimating parameters for stages I to III and for locoregional recurrence where applicable, and data recorded in TRACC was used for treatments and outcomes related to their progression to stage IV.

Modeling Framework for Stage- and Molecular Subtype-Specific Clinical Pathways

For all patients included, we constructed chronological timelines from diagnosis to detail treatment and outcome trajectories. Sankey diagrams were used to analyze treatment utilization patterns for each stage and treatment line. These patterns were mapped to stage-specific treatment algorithms developed by CRC clinicians (Y.H.T. and P.G.), based on consensus guidelines, Pharmaceutical Benefits Scheme listed therapies, and Medicare Benefits Schedule services in Australia, and validated by an international panel of clinical experts. The purpose was to provide a comprehensive overview of the treatment options available in 2021, integrating them with real-world treatment data to develop the PRIMCAT-CRC model framework. This integration aimed to capture contemporary real-world treatment patterns alongside the guideline-based pathways. During this process, we identified small treatment deviations from "best practice" guidelines, which were included in the model if they were reimbursed and occurred in >1% of patients to reflect realistic clinical practices. This exclusion was guided by clinical expert advice and ensured that our model remained accurate and reflective of contemporary practices in Australian healthcare. This structured approach allowed us to populate the parameters of the simulation model with data that are both current and relevant, ensuring the model's applicability in policymaking and healthcare planning.

This integration captured both contemporary real-world treatment patterns and guideline-based pathways. We included deviations from "best practice" guidelines that were reimbursed and occurred in more than 1% of patients, reflecting realistic clinical practices. This approach, guided by clinical expertise, ensured our model's accuracy and relevance to contemporary Australian healthcare practices. The treatment algorithms and real-world data integration established a robust model framework aligned with best practice,[23] demonstrating the events a patient may encounter post-diagnosis. In early-stage disease (stages I-III), colon and rectal cancers were considered separately because of different treatment options. In contrast, advanced disease (stage IV) treated both cancers similarly, varying by RAS status, either RASwt or mutated (RASmt). The model also accommodates potential new therapies across all stages for scenario analysis.

The full model is displayed in Appendix 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.06.006. After diagnosis, we evaluated whether patients received treatment, and if so, which type. For example, in stage I colon cancer, the sole option was surgery, whereas in stage I rectal cancer, 4 options were available: surgery, neoadjuvant therapy and surgery, surgery and adjuvant therapy, or a combination of all 3 (Fig. 1A). We then assessed recurrence, distinguishing between local-regional and distant metastatic diseases. The subsequent events, depending on the type of recurrence, are outlined in a separate model structure (Fig. 1B).

Time-to-Event Analyses, Treatment Utilization, and Progression Rates

For time-to-event data, we used Gompertz and Weibull distributions in proportional specifications to evaluate alternative scenarios via hazard ratios. In scenarios without competing events, these were applied as individual or mixed distributions. For competing events, the event-specific probabilities and distributions (ESPD) approach was used, which samples the event type first and time-to-event second.[24,25] Parameters for these distributions were estimated using Flexsurv v2.0,[26] whereas mixture models and ESPD methods were implemented with custom functions[25] and optimized using maxLik v1.4-6.[27] All analyses were performed in RStudio.[28] This method aligns with clinical expert recommendations and facilitates specifying scenarios with relative risks and hazard ratios for event-specific outcomes required for scenario analyses based on a parallel horizon scanning effort.[29]

For each disease stage, the time-to-treatment post-diagnosis was first modeled using standard parametric approaches. The time-to-outcome, considering competing events of cancer recurrence/progression and death without recurrence/progression, was then modeled using the ESPD method to include treatment effects.[25] Treatment utilization for surgical, radiotherapy, and systemic interventions was calculated separately for each stage and line of therapy. Detailed analytical steps and results for stage I colon cancer are documented in Appendix 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.06.006.

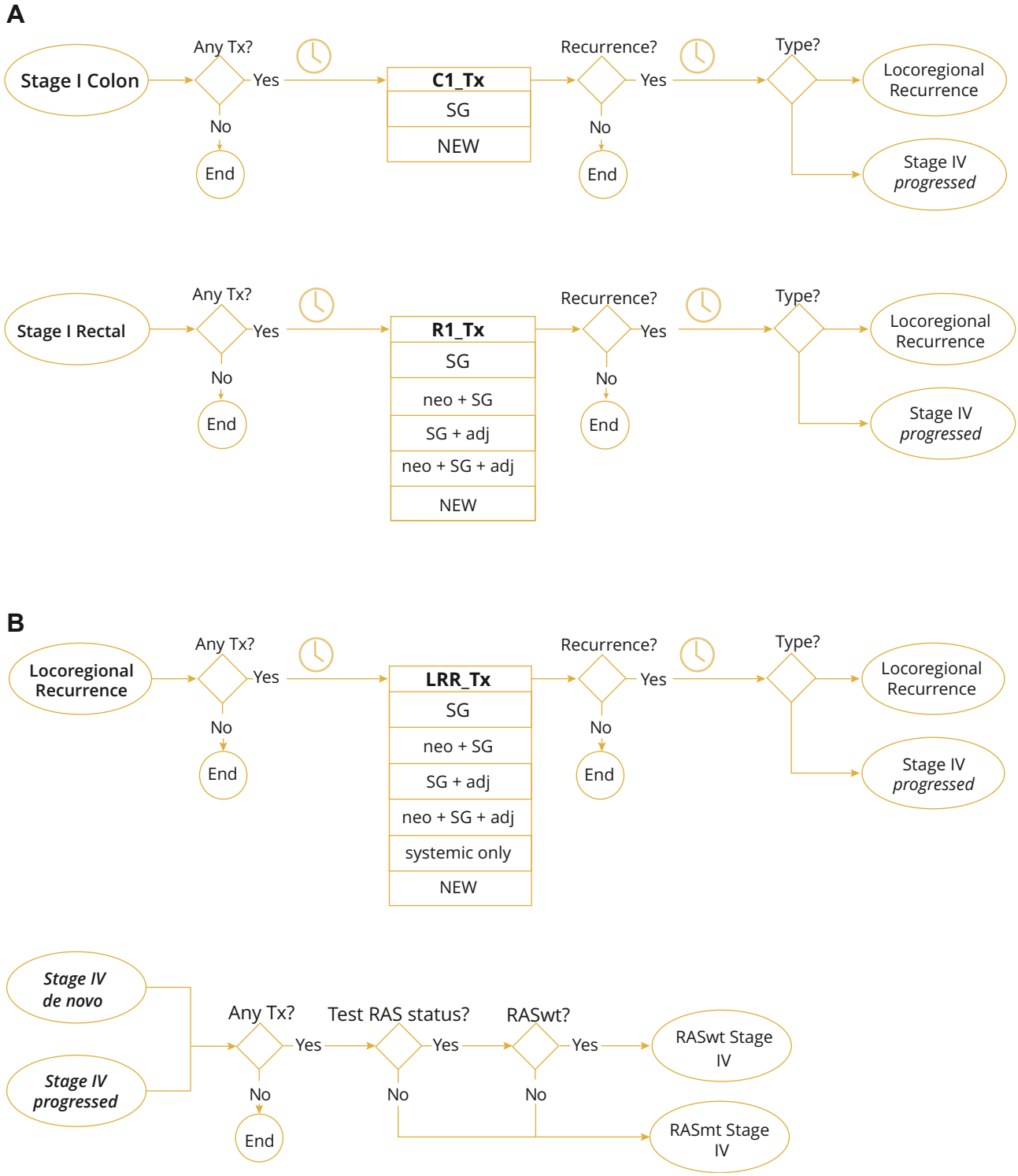
CRC Incidence and Stage Distribution

To estimate the number of incident CRC cases by disease stage over the years, we utilized incidence data from the Australian Institute of Health and Welfare (AIHW) for colon and rectal cancers. Linear regression models for each cancer type predicted incident cases for years without AIHW data.[12] Similarly, the reported stage at diagnosis for both colon and rectal cancers by the Victorian Cancer Registry annual reports[30] from 2010 to 2019 were used to define the stage distribution. Changes in the stage distribution were extrapolated using a linear regression model for the years beyond 2019. The parameters used for the incidence and stage distribution are fully detailed in Appendix 1, Appendix Tables 1-1 to 1-4 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.06.006.

Discrete-Event Simulation Model

The established modeling framework (Appendix 1, Appendix Fig. 1-3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.06.006), established parameters and distributions, and incidence information were used to define and parameterize a discrete-event simulation model in R software v4.0.3.[31] Specifically, the PRIMCAT-CRC model has 4 modules that integrate

Figure 1. Model structure of PRIMCAT-CRC detailing treatment options and type of recurrence depending on stage at diagnosis and progression type. (A) Model structure for colon and rectal cancers diagnosed at stage I and (B) for loal-regional recurrence and progression to stage IV.



PRIMCAT-CRC indicates The Predicting the Population Health Economic Impact of Current and New Cancer Treatments for Colorectal Cancer.

information on colon and rectal cancer incidence over the years, disease stage distribution at diagnosis, treatment utilization rates, and all the different time-to-events (Appendix 1, Appendix Fig. 1-1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.06.006). PRIMCAT-CRC accounts for colon versus rectal disease for stages I to III and considers CRC for stage IV, with distinction made based on RAS mutation status. PRIMCAT-CRC is open-source, and a description of its structure, functions,

implementation, validation, and the 239 parameters generated to populate the modeling framework are available on the GitHub repository.

Using the default setting and parameter values, a simulation with PRIMCAT-CRC starts in the year 2010. The base-case scenario used the default model parameters informed by ACCORD and TRACC to reflect the current treatment pathways, (ie, standard of care in Australia). To define alternative scenarios, parameters can be updated at any point in time throughout the simulation to incorporate changes, for example, in treatment utilization over time.

Model Validation

The PRIMCAT-CRC model underwent extensive testing and independent verification to assure its robustness and accuracy. This process included structured walkthroughs, extreme value testing to evaluate the model's logic under atypical conditions, and a comprehensive independent review of the R code, including assessment of the algorithms and implementation by a team member (F.F.).

For internal validation, multiple simulation runs were executed based on yearly incidence rates from 2010 to 2023. To ensure reliable outcomes, we averaged results from 50 runs, each including 262 346 simulated individuals. This robust simulation framework allowed for the precise validation of model outputs against clinical expectations and predefined parameters.

Key aspects of the model were validated, specific events were analyzed within the simulation to confirm their alignment with expected clinical pathways, and detailed records of treatment utilization and outcomes were evaluated. We compared the density and distribution of times to events against expected survival curves informed by clinical knowledge and expertise (Y.H.T. and P.G.) to confirm the model's predictive accuracy. Additionally, the simulation's ability to estimate recurrence probabilities was validated by aligning simulated data with empirical probabilities and clinical expertise (Y.H.T. and P.G.).

We assessed the model's accuracy by comparisons of simulated events, treatment outcomes, and utilization rates with data from the ACCORD and TRACC registries. Finally, the forecasted incidence rates were compared with existing models (Appendix 1, Appendix Table 1-5 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.06.006).

Case Study on Pembrolizumab

To demonstrate the use of PRIMCAT-CRC, the 5-year impact (2022-2026) of introducing pembrolizumab as first-line treatment for dMMR metastatic CRC in Australia was estimated. For context, pembrolizumab received taxpayer reimbursement approval in August 2021, post our study's data cut-off. The dMMR prevalence among patients diagnosed with stage IV was estimated from the literature and the TRACC registry, yielding estimates of 15%[32] and 6.9%, respectively. The uptake rate of dMMR testing was modeled on historical RAS testing trends from the TRACC registry, which initially rose from 42% to 82%. Anticipating a similar pattern for dMMR, we project an increase from 42% in 2022 to 82% by 2023. André et al[32] provided key evidence on pembrolizumab's outcomes, with a hazard ratio of 0.6 and a 19% mortality reduction. We used these data to calculate relative risks (RRs) for disease progression in the context of RAS status, comparing with standard chemotherapy and biological regimens. The derived RRs were 1.07 for RASwt and 1.11 for RASmt, leading to 4 forecasting scenarios:

- Scenario-1 (S1): dMMR prevalence 15%, testing uptake 100%.
- Scenario-2 (S2): as per S1, considering HR 0.6 and RR progression of 1.07 (RASwt) and 1.11 (RASmt).
- Scenario-3 (S3): dMMR prevalence 6.9%, testing uptake 42% (2022), 84% from 2023.
- Scenario-4 (S4): as per S3, considering HR 0.6 and RR progression of 1.07 (RASwt) and 1.11 (RASmt).

Results

Demographics

A total of 7163 individuals with CRC for whom data were captured in ACCORD or TRACC were included for analyses (Table 1). Colon cancer represented 73% of diagnosed stages I to III disease (n = 4242), of which stage II was the most prevalent (42.4%), whereas rectal cancer (n = 1563) was most diagnosed at stage I disease (36.5%). Overall, the mean and median age of diagnosis was 67, with stage IV diagnosed at earlier age (63.8 and 65.1 years, respectively) compared with stages I to III disease.

Base-Case Analysis

The base-case analysis forecasts the number of CRC patients treated under current standard care in Australia from 2022 to 2026, serving as a baseline for evaluating the impact of new treatments. Fig. 2 shows patient counts by disease type and stage from 2010 to 2026, updated quarterly. The red vertical line in the figure represents the end of the "warm-up" period to account for prevalent cases (locoregional/distant recurrences) in the period of interest that result from patients who were initially diagnosed at stages I to III disease but experienced disease recurrence/progression. This warm-up period incorporates data from patients diagnosed before 2022 to ensure that ongoing treatments and disease progressions are accurately reflected in the model during the 5-year period of interest, representing the prevalent patient population. The forecasts begin at the end of this warm-up period, transitioning into our primary study period for which outcomes are captured, which extends until 2026. The results indicate that trends stabilize post the warm-up period, providing a reliable basis for projecting patient outcomes and treatment utilization during the 5-year period of interest.

The PRIMCAT-CRC model forecasts the total number of patients expected to start treatments, accounting for both incident and prevalent cases, by incorporating local-regional recurrences and progression to stage IV. This methodology enables a thorough analysis of treatment utilization and patient volumes. The model outputs detailed tables of treatment numbers and frequencies by forecast year, cancer type, stage, and treatment line (Appendix 3, Appendix Table 3-1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.06.006). Appendix Fig. 3-1 (Appendix 3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.06.006), summarizes treatment projections from 2022 to 2026, with chemotherapy as the predominant systemic treatment in stage IV and surgery as the primary treatment in stages I to III.

Table 2 presents the PRIMCAT-CRC's overall forecast of the number of treatments that will be provided to patients in Australia for CRC from 2022 to 2026 and the associated frequency by year of forecast. The numbers for colon and rectal cancers represent treatments for stages I to III disease, whereas the colorectal category corresponds to stage IV disease. The overall column represents the sum and frequency of initiated treatments for a given disease stage across the 5-years, whereas the total row provides the sum and frequency of treatments initiated across all stages for a given year. Our forecast highlight that a total number of 116 752 treatments will be initiated over the 2022 to 2026

Table 1. Overview of age, stage, and year of diagnosis for colon, rectal, and CRC patients included for analysis from ACCORD (colon and rectal) and TRACC (colorectal) registries.

Clinical characteristics	ACCORD registry		TRACC registry	Overall (N = 7163)
	Colon (n = 4242)	Rectal (n = 1563)	Colorectal (n = 1358)	
Age at diagnosis				
Mean (SD)	68.8 (12.8)	65.1 (12.8)	63.8 (14.1)	67.0 (13.3)
Median [min, max]	70.1 [14.9, 101]	65.9 [22.1, 102]	65.1 [14.5, 95.7]	68.3 [14.5, 102]
Disease stage				
Stage I	931 (21.9)	570 (36.5)	0 (0)	1501 (21.0)
Stage II	1797 (42.4)	490 (31.4)	0 (0)	2287 (31.9)
Stage III	1514 (35.7)	503 (32.2)	0 (0)	2017 (28.2)
Stage IV	0 (0)	0 (0)	1358 (100)	1358 (19.0)
Year of diagnosis				
2005-2009	1025 (24.2)	446 (28.5)	0 (0)	1471 (20.5)
2010-2014	1560 (36.8)	577 (36.9)	0 (0)	2137 (29.8)
2015-2019	1657 (39.1)	540 (34.5)	1358 (100)	3555 (49.6)

Note. All values are n (%) unless otherwise specified.
ACCORD indicates The Australian Comprehensive Cancer Outcomes and Research Database; TRACC, The Treatment of Recurrent and Advanced Colorectal Cancer.

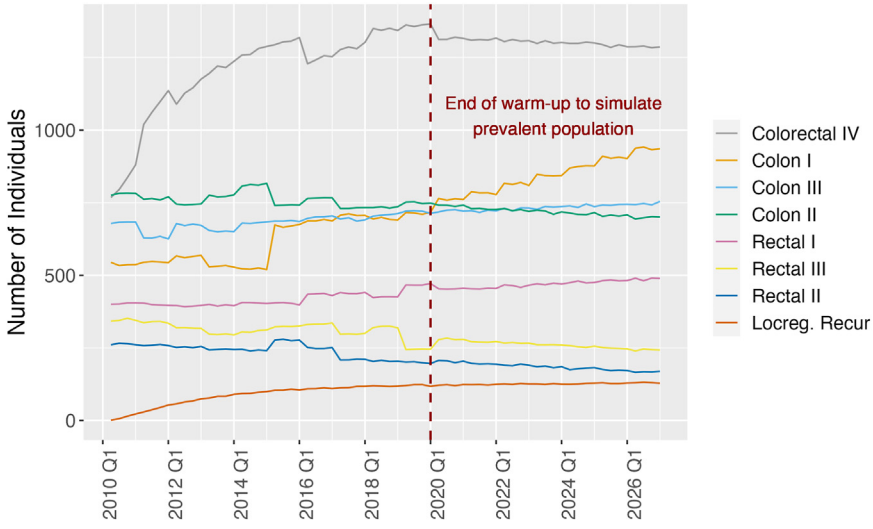
period, with 43% of these treatments used for stage IV disease (Table 2). In stage IV, these treatments are systemic therapies, excluding local surgeries and radiotherapies often provided palliatively. Including these, local therapies account for 20 265 treatments, with 39.7% radiotherapies, 31.8% surgeries of metastasis, and 28.5% surgeries of primary tumors (Appendix 3, Appendix Table 3-3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.06.006).

The evolution of treatment utilization for stages I to III colon and rectal specifically is illustrated in Fig. 3. The chart breaks down the number of patients per quarter receiving each type of treatment across the 3 stages (A). Similarly, the systemic treatment lines for stage IV from 2022 to 2026 is provided (B). The plot breaks down the patient counts across the 4 treatment lines and maps out the number of individuals receiving each type of treatment per quarter.

Forecasting Case Study: Pembrolizumab

In addition to its comprehensive forecasting capabilities, the PRIMCAT-CRC model is specifically designed to integrate novel treatments into its framework, enabling the provision of detailed scenario analyses. To demonstrate this feature, we incorporated the introduction of pembrolizumab into our model, conducting 4 distinct scenario analyses. Similar to the base-case scenario, PRIMCAT-CRC generates an extensive output table that details the total number of various treatment types, by RAS status and line of therapy. The overall result table is segmented by forecast year, cancer type, disease stage, and treatment line and is provided in Appendix 3, Appendix Table 3-6 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.06.006. Moreover, given that eligible patients with stage IV disease include both incident and prevalent cases, the model distinctly categorizes these groups to

Figure 2. Number of patients per disease type and stage, considering incident and prevalent cases (right of dashed line is actual estimate).



Locreg. Recur indicates locoregional recurrence.

Table 2. Number of patients treated for CRC over the forecast period 2022-2026.

Disease stage	2022, n (%)	2023, n (%)	2024, n (%)	2025, n (%)	2026, n (%)	Overall, n (%)
Colon						
Stage I	3251 (14.01)	3361 (14.46)	3484 (14.91)	3610 (15.40)	3734 (15.89)	17 440 (14.94)
Stage II	2898 (12.49)	2874 (12.36)	2850 (12.20)	2825 (12.05)	2797 (11.91)	14 244 (12.20)
Stage III	2918 (12.58)	2934 (12.62)	2952 (12.63)	2970 (12.67)	2983 (12.70)	14 757 (12.64)
Rectal						
Stage I	1851 (7.98)	1879 (8.08)	1899 (8.13)	1928 (8.22)	1947 (8.29)	9504 (8.14)
Stage II	766 (3.30)	744 (3.20)	717 (3.07)	695 (2.96)	671 (2.86)	3593 (3.08)
Stage III	1069 (4.61)	1046 (4.50)	1021 (4.37)	1001 (4.27)	972 (4.14)	5109 (4.38)
Locoregional recurrence	371 (1.60)	373 (1.60)	372 (1.59)	379 (1.62)	386 (1.64)	1881 (1.61)
Colorectal, stage IV	10 073 (43.42)	10 036 (43.17)	10 071 (43.10)	10 041 (42.82)	10 003 (42.58)	50 224 (43.02)
Total, n (% overall)	23 197 (19.87)	23 247 (19.91)	23 366 (20.01)	23 449 (20.08)	23 493 (20.12)	116 752 (100)

enhance understanding of treatment dynamics under different scenarios, as shown in Appendix 3, Appendix Table 3-5 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.06.006.

Based on 15% dMMR prevalence and a full uptake (S1), it was estimated that an average of 706 patients per year would receive pembrolizumab as first-line treatment in Australia, totaling 3530 patients over 2022 to 2026. Using Australian dMMR prevalence and testing uptake estimates from the RWD (S3, 6.9% prevalence), a total of 138 patients would receive pembrolizumab in 2022 and on average 273 per year for the period 2023 to 2026, amounting to approximately 1230 patients overall. In scenarios 2 and 4, the model additionally accounted for the time to progression and the RR for progression to the next treatment line. This allowed for analyzing the effect of introducing pembrolizumab on the distribution of patients across later treatment lines, together with downstream treatment utilization (Fig. 4), compared with the base-case scenario (no pembrolizumab).

Discussion

PRIMCAT-CRC is a data-driven whole-disease simulation model designed to estimate the number of CRC patients in Australia requiring treatment across specific disease stages and treatment phases over time. Our model is built on the integration of real-world data from Australian clinical registries, rather than relying solely on results from published clinical trials, to ensure that the PRIMCAT-CRC model accurately mirrors the current oncology practice within Australia. This approach not only enhances the robustness of our forecasts but also ensures they are context-specific and highly relevant for health policymaking and healthcare planning.

The base-case scenario provided a detailed projection of the CRC patient population receiving standard of care treatment, segmented by disease stage, cancer type, and treatment type and utilization. Our model's incidence estimates for 2022 to 2026 align with those from subsequent published projections from AIHW[12] and those by Cancer Patient Population Projections (Cancer-PPP),[33] underscoring the ongoing prevalence of colon cancer. Beyond these foundational epidemiological insights, the strength of our model lies in its ability to deliver nuanced aspects of treatment pathways.

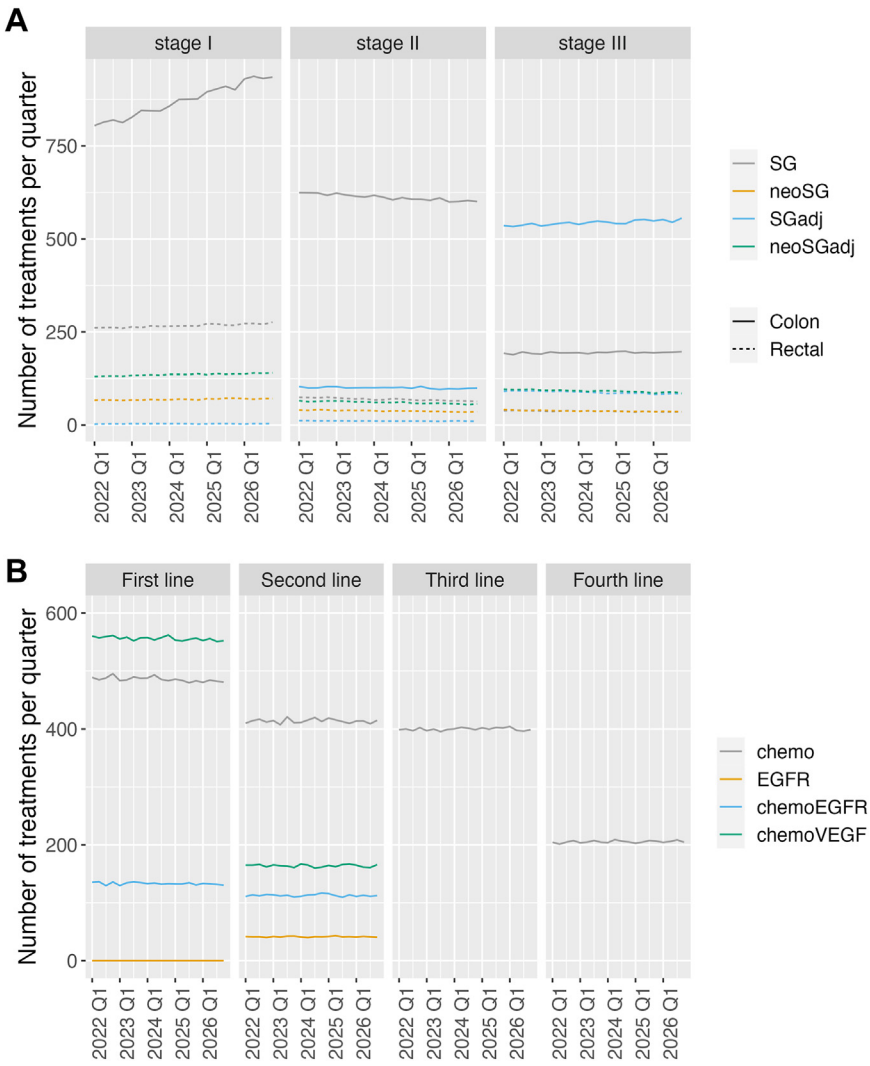
Our model provides novel insights into treatment utilizations across all CRC stages and lines, expanding beyond traditional incidence and diagnosis trends. This depth enhances the strategic value of our forecasts, enabling precise and informed decision making. We showed that over the period 2022 to 2026, it is expected that 50 224 treatments will be provided for stage IV disease, with first-line treatments representing 47% of all stage IV treatments, whereas second, third, and fourth lines represent, respectively, 29%, 16%, and 8%. Furthermore, PRIMCAT-CRC provides granular understanding of treatment regimens. For example, across all lines, chemotherapy regimens represent 41.3% of all treatments, whereas in the first-line setting, anti-vascular endothelial growth factor combined with chemotherapy regimens represent 47.3% of treatments provided.

The case study findings on pembrolizumab as a first-line treatment for dMMR stage IV reveal that, despite longer times to progression and subsequent rise in patients progressing to subsequent treatment lines, the total downstream treatment use over the 5-year period remained comparable. This suggests pembrolizumab can offer tangible benefits to patients without significantly escalating healthcare resource utilization in the short term. The case study not only provides a positive outlook for metastatic dMMR CRC treatment but also exemplifies the flexibility and adaptability of the PRIMCAT-CRC model in accommodating and evaluating novel treatments.

Model Validation and Comparison

The PRIMCAT-CRC model underwent rigorous validation, including extensive simulation runs to ensure stability and reliability, confirming that the model accurately mirrors real-world conditions by comparing simulated outcomes with data from the ACCORD and TRACC registries. Considering PRIMCAT-CRC's unique framework as the first model of its kind, comparing its projections with similar benchmarks within Australia presents certain challenges. The closest available comparison would be Cancer-PPP[33] projections, based on the established Policy1-Bowel[34] platform. Each model serves important yet distinct forecasting functions: PRIMCAT-CRC offers detailed, whole-disease projections and all treatment regimens utilization, providing granular insights over a 5-year horizon, whereas Cancer-PPP delivers epidemiological forecasts of incidence and prevalence for 2023 to 2043, including by age-categories, and it recently expanded to include treatment projections for surgery only, combined surgery and chemotherapy/radiotherapy, and other. Both models are inherently different, making direct comparisons complex. We conducted a descriptive analysis to enhance

Figure 3. Forecasted number of patients starting treatments over time, based on the type of treatment received, and considering the current standard of care (base-case scenario). (A) Treatment utilization by patients with either colon or rectal cancer, stages I to III, and (B) treatment utilization per line of treatment of CRC stage IV.



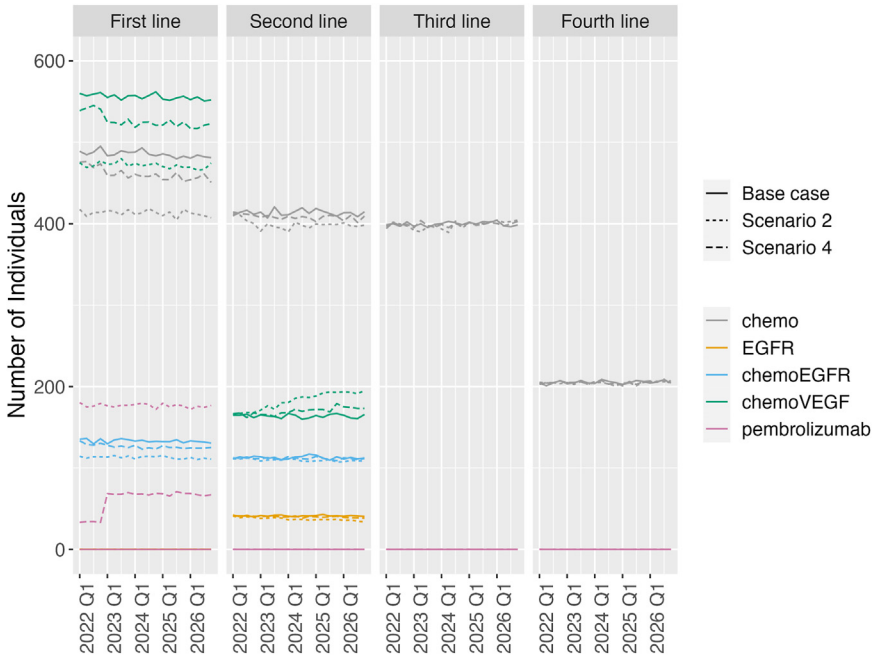
Chemo indicates chemotherapy; chemoEGFR, chemotherapy and epidermal growth factor receptor targeted therapy; chemoVEGF, chemotherapy and vascular endothelial growth factor targeted therapy; EGFR, epidermal growth factor receptor targeted therapy; neoSG, neoadjuvant chemotherapy and surgery; neoSGadj, neoadjuvant chemotherapy, surgery, and adjuvant chemotherapy; SG, surgery; SGadj, adjuvant chemotherapy and surgery.

understanding of each model's capabilities for their shared forecasted years 2023 to 2026, highlighting key similarities and differences that inform their respective impacts on healthcare forecasting.

For instance, although incident case projections from both models align reasonably well (Appendix Table 3-3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.06.006), with total number of incident cases ranging from 15 738 in 2023 to 15 921 in 2026 for PRIMCAT-CRC and 16 210 to 16 518 for the same period by Cancer-PPP, prevalent case estimates diverge substantially. PRIMCAT-CRC estimates a total of 2821 prevalent cases for 2023 to 2871 in 2026, whereas Cancer-PPP's prevalent cases range from 56 664 to 56 986. This discrepancy may stem from PRIMCAT-CRC's specific focus on patients expected to start treatment as opposed to Cancer-PPP's broader prevalence data, which may include patients who are no longer in active treatment, which is particularly relevant for prevalent cases.

Additionally, there were some similarities and major differences in the treatment utilization projections. Comparisons could only be made for stages I to III and for broad regimens of surgery only versus combination of surgery and chemotherapy/radiotherapy (Appendix Table 3-4 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2024.06.006). The total counts of surgery-only treatment were roughly aligned between the models, with PRIMCAT-CRC forecasting between 8100 to 8412 treatments, compared with 7438 to 7497 for Cancer-PPP. However, when broken down by stage, the surgery-only regimen in stage I colon and rectal represented, respectively, 41.5% and 13.0% of all stages considered but were 28.2% for colon and 5.3% for rectal in Cancer-PPP estimates for the same regimen in 2023. Finally, the utilization of the combined surgery and chemotherapy/

Figure 4. Forecasted number of patients starting a particular treatment line over time, considering the base-case scenario (no new introduction) and the introduction of pembrolizumab as first-line treatment for dMMR stage IV CRC.



Chemo indicates chemotherapy; chemoEGFR, chemotherapy and epidermal growth factor receptor targeted therapy; chemoVEGF, chemotherapy and vascular endothelial growth factor targeted therapy; EGFR, epidermal growth factor receptor targeted therapy.

radiotherapy regimen revealed greater discrepancies, with PRIMCAT-CRC forecasting approximately 1.6 times the annual utilization compared with Cancer-PPP.

To validate the PRIMCAT-CRC projections, we plan to analyze retrospective population-level linked data comprehensively. This will enable us to validate the total number of patients undergoing various treatments and align these figures with our forecasts. Such validation will help confirm the accuracy of our model against actual healthcare delivery data.

Model Adaptability and Future Applications

The insights derived from the PRIMCAT-CRC model are pivotal for healthcare policymakers, especially given the rapidly evolving landscape of CRC treatments. By forecasting changes in treatment utilization and patient volumes, the model plays a crucial role in strategic healthcare planning and resource allocation. It supports informed decision making, ensuring that healthcare systems are prepared to integrate new therapies efficiently. For instance, the scenario analysis involving pembrolizumab highlights how changes in treatment guidelines can shift treatment patterns and resource allocation. By forecasting the potential increase in patient volumes requiring this novel therapy, policymakers can better prepare for its budgetary impact and ensure that the necessary funding and infrastructure are in place.

Beyond incorporating new therapies for forecasting, the model supports diverse scenario analyses by adapting to changes in incidence data and stage distributions over time. For example, this adaptability would allow to simulate the effects of enhanced CRC screening efforts that could lead to earlier diagnoses through a stage-shift model. By adjusting parameters to reflect changes in screening practices, the model projects how these shifts impact treatment pathways and healthcare resource utilization. Additionally, it offers insights into how enhanced screening could change the patient population needing treatment, providing crucial information for healthcare planning and policymaking.

Future expansions of this work will include detailed scenario analyses to model the impact of varying screening rates on cancer stage distribution, healthcare utilization, and outcomes. Moreover, although the current model is structured to categorize various costs associated with cancer care treatments, including systemic, surgical, radiotherapy, diagnostics, and consultations, a comprehensive cost analysis using population-level data is anticipated in the model's expansion.

This study has several limitations. Because of its retrospective nature, the model depends heavily on the accuracy and timeliness of the data used. Updated data are essential to align the model's predictions with current trends in cancer care, ensuring that the base-case scenario accurately reflects the standard of care in Australia. Significant changes in the treatment landscape would require revisions to maintain the model's relevance.

Additionally, although our model simulates changes in screening and diagnosis rates, it does not account for unforeseen shifts in societal behaviors unrelated to screening policies. Finally, because of registry data limitations, we could not estimate the proportion of untreated stage IV patients, which may vary up to 20% because of factors such as age or comorbidities. This might lead to an overestimation of the total number of patients receiving metastatic disease treatment.

In conclusion, the PRIMCAT-CRC model offers a novel and innovative approach to forecast the number of patients needing treatment at specific cancer stages and treatment lines. Designed to be flexible and adaptable to the healthcare landscape, the model can be updated as new data become available and treatment paradigms shift, ensuring its ongoing relevance and utility. This adaptability is crucial for maintaining accurate forecasts in oncology, which is characterized by the frequent emergence of

new treatments and diagnostic tools. Through detailed simulations of potential patient populations under various scenarios, the model provides critical insights that directly inform healthcare planning and decision making, supporting effective health policy and resource allocation.

Author Disclosures

Author disclosure forms can be accessed below in the Supplemental Material.

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REFERENCES

1. Chen S, Cao Z, Prettner K, et al. Estimates and projections of the global economic cost of 29 cancers in 204 countries and territories from 2020 to 2050. *JAMA Oncol*. 2023;9(4):465–472.
2. Mariotto AB, Enewold L, Zhao J, Zeruto CA, Yabroff KR. Medical care costs associated with cancer survivorship in the United States. *Cancer Epidemiol Biomarkers Prev*. 2020;29(7):1304–1312.
3. Iragorri N, de Oliveira C, Fitzgerald N, Essue B. The out-of-pocket cost burden of cancer care-A systematic literature review. *Curr Oncol*. 2021;28(2):1216–1248.
4. Laviana AA, Luckenbaugh AN, Resnick MJ. Trends in the cost of cancer care: beyond drugs. *J Clin Oncol*. 2020;38(4):316–322.
5. Dowling EC, Chawla N, Forsythe LP, et al. Lost productivity and burden of illness in cancer survivors with and without other chronic conditions. *Cancer*. 2013;119(18):3393–3401.
6. Altice CK, Banegas MP, Tucker-Seeley RD, Yabroff KR. Financial hardships experienced by cancer survivors: a systematic review. *J Natl Cancer Inst*. 2017;109(2):djw205.
7. Ouwens M, Mukhopadhyay P, Zhang Y, Huang M, Latimer N, Briggs A. Estimating lifetime benefits associated with immuno-oncology therapies: challenges and approaches for overall survival extrapolations. *Pharmacoeconomics*. 2019;37(9):1129–1138.
8. Henderson RH, French D, Maughan T, et al. The economic burden of colorectal cancer across Europe: a population-based cost-of-illness study. *Lancet Gastroenterol Hepatol*. 2021;6(9):709–722.
9. Health system expenditure on cancer and other neoplasms in Australia, 2015-16. Australian Institute of Health and Welfare. https://www.aihw.gov.au/reports/cancer/health-system-expenditure-cancer-other-neoplasms. Accessed July 2021.
10. Smith TJ, Hillner BE. Bending the cost curve in cancer care. *N Engl J Med*. 2011;364(21):2060–2065.
11. Colorectal cancer global statistics. World Cancer Research Fund International. https://www.wcrf.org/cancer-trends/colorectal-cancer-statistics/. Accessed April 2023.
12. Cancer data in Australia. Australian Institute of Health and Welfare. https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia. Accessed July 2022.
13. GLOBOCAN. New global cancer data. Union for International Cancer Control, UICC. https://www.uicc.org/news/globocan-2020-new-global-cancer-data. Accessed April 2023.
14. Sifaki-Pistolla D, Poimenaki V, Fotopoulou I, et al. Significant Rise of Colorectal Cancer Incidence in Younger Adults and Strong Determinants: 30 years Longitudinal Differences between under and over 50s. *Cancers (Basel)*. 2022;14(19):4799.
15. Sinicrope FA. Increasing incidence of early-onset colorectal cancer. *N Engl J Med*. 2022;386(16):1547–1558.
16. Goldsbury DE, Yap S, Weber MF, et al. Health services costs for cancer care in Australia: estimates from the 45 and Up Study. *PLoS One*. 2018;13(7):e0201552.
17. Griesinger F, Cox O, Sammon C, Ramagopalan SV, Popat S. Health technology assessments and real-world evidence: tell us what you want, what you really, really want. *J Comp Eff Res*. 2022;11(5):297–299.
18. Akehurst R, Murphy LA, Solà-Morales O, Cunningham D, Mestre-Ferrandiz J, de Pouvourville G. Using real-world data in the health technology assessment of pharmaceuticals: strengths, difficulties, and a pragmatic way forward. *Value Health*. 2023;26(4):11–19.
19. Wale JL, Thomas S, Hamerlijnck D, Hollander R. Patients and public are important stakeholders in health technology assessment but the level of involvement is low – a call to action. *Res Involvement Engagement*. 2021;7(1):1.
20. Degeling K, Franken MD, May AM, et al. Matching the model with the evidence: comparing discrete event simulation and state-transition modeling for time-to-event predictions in a cost-effectiveness analysis of treatment in metastatic colorectal cancer patients. *Cancer Epidemiol*. 2018;57:60–67.

21. Australian comprehensive cancer outcomes and research database. BioGrid. http://www.biogrid.org.au/page/110/cancer-data-collection-software. Accessed May 2022.
22. Field K, Wong HL, Shapiro J, et al. Developing a national database for metastatic colorectal cancer management: perspectives and challenges. *Int Med J*. 2013;43(11):1224–1231.
23. Karnon J, Stahl J, Brennan A, et al. Modeling using discrete event simulation: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force–4. *Value Health*. 2012;15(6):821–827.
24. Degeling K, Koffijberg H, Franken MD, Koopman M, IJzerman MJ. Comparing strategies for modeling competing risks in discrete-event simulations: a simulation study and illustration in colorectal cancer. *Med Decis Making*. 2019;39(1):57–73.
25. Franchini F, Fedyashov V, IJzerman MJ, Degeling K. Implementing competing risks in discrete event simulation: the event-specific probabilities and distributions approach. *Front Pharmacol*. 2023;14:1255021.
26. Jackson C. flexsurv: a platform for parametric survival modeling in R. *J Stat Softw*. 2016;70(8):1–33.
27. Henningsen A, Toomet O. maxLik: a package for maximum likelihood estimation in R. *Comp Stat*. 2011;26(3):443–458.
28. RStudio: integrated development for R. RStudio Team. http://www.rstudio.com/. Accessed July 2022.
29. Soon JA, To YH, Alexander M, et al. A tailored approach to horizon scanning for cancer medicines. *J Cancer Policy*. 2023;38:100441.
30. Latest VCR annual statistics & trends report. Victorian Cancer Registry. https://www.cancervic.org.au/research/vcr/fact-sheets-and-annual-reports. Accessed July 2022.
31. R Core Team. R: a language and environment for statistical computing. R Foundation for Statistical Computing. https://www.R-project.org. Accessed July 2022.
32. André T, Shiu KK, Kim TW, et al. Pembrolizumab in microsatellite-instability-high advanced colorectal cancer. *N Engl J Med*. 2020;383(23):2207–2218.
33. Cancer patient population projections: colorectal cancer in Australia. Sydney, Australia. The Daffodil Centre. daffodilcentre.org/results/cancer-patient-population-projections-dashboard/. Accessed July 2023.
34. Lew JB, Greuter MJE, Caruana M, et al. Validation of microsimulation models against alternative model predictions and long-term colorectal cancer incidence and mortality outcomes of randomized controlled trials. *Med Decis Making*. 2020;40(6):815–829.