Estimating the treatment cost of colon cancer at Groote Schuur Hospital

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Dedication

To my beloved family (Obi, Amamife, Onaedo and Onyinye), thank you for your constant support and encouragement. I am forever grateful for each of you.

Thesis Abstract

Background: Due to the high mortality-to-incidence ratio of colon cancer in South Africa, urgent public health measures are needed to improve treatment outcomes. Costing studies can be leveraged to understand the treatment cost burden for colon cancer, providing crucial insights for allocating resources to finance such measures. This study aims to assess treatment options and costs for colon cancer treatment from the perspective of healthcare providers at a public healthcare facility in South Africa.

Method: The study used an ingredient-based approach to assess colon cancer treatment costs by stage at the colorectal clinic and combined colorectal oncology unit at Groote Schuur Hospital. The costing process involved two steps: first, treatment options were defined according to facility guidelines and verified through expert interviews; then, these options were linked to relevant cost items for each cancer stage based on expert input. Second, a bottom-up costing method was used to estimate and aggregate per-patient costs across treatment components for each stage. One-way sensitivity analysis addressed uncertainties in post-surgical inpatient admissions and staff categories. All costs are presented in 2024 South African Rands (ZAR) and United States Dollars (USD).

Results: Colon cancer treatment components include staging and risk assessment investigations, clinical consultations, surgery and chemotherapy. The estimated guideline-based per-patient costs for treatment are R60,156 ($3,216) for stages I and II (low-risk); R75,132 ($4,017) for high-risk stage II and stage III; and R171,935 ($9,193) for stage IV. Surgical treatment represents a major cost driver, with additional expenses from inpatient admissions following surgery. Sensitivity analysis indicates that reducing postoperative inpatient stay by 25% lowers the treatment cost by approximately 5% across all stages.

Conclusion: Colon cancer treatment costs are significant, increasing with each colon cancer stage. To manage these escalating costs and reduce the overall healthcare burden, policies should prioritise early detection and invest in accessible, stage-appropriate interventions to improve patient outcomes.

Acknowledgement

My sincere gratitude goes to Dr.Lucy Cunnama, Prof. Jennifer Moodley, Prof John Ataguba, the African Awareness of CANcer and Early Diagnosis (AWACAN-ED) program, and the Health Economics Unit, University of Cape Town for their unwavering support during this study.

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Acronyms

ASIR Age-Standardized Incidence Rate

ASMR Age-Standardized Mortality Rate

AWACAN-ED African aWAreness of CANcer and Early Diagnosis

CRC Colorectal Cancer

DALYs Disease Adjusted Life Years

ERAS Enhanced Recovery After Surgery

GDP Gross Domestic Product

GSH Groote Schuur Hospital

HDI Human Development Index

LMICs Low-to Middle-Income Countries

MDT Multi Disciplinary Team

NHLS National Health Laboratory Service

SSA Sub-Shaharan Africa

UHC Universal Health Coverage

UPFS Uniform Patient Fee Schedule

USD United States Dollar

WCDoH Western Cape Department of Health

yCRC Young-onset Colorectal Cancer

Part A

Structured literature review

1 Objectives of the literature review

This section aims to critically appraise the theoretical, methodological, and empirical literature on estimating the treatment cost of colon cancer. The review presents a theoretical background on the burden and treatment of colon cancer, followed by a conceptual and methodological analysis of the micro-costing framework and healthcare costs estimation. Finally, it offers an empirical review of previous peer-reviewed studies on colon cancer treatment costs, both globally and within South Africa. The review also identified the current gaps in the literature regarding the study theme.

2 Literature search strategy

The literature included in this section was obtained from electronic database searches and book chapters. The advanced search option was used to identify the relevant literature on PUBMED, ECONLIT and Cochrane databases. Other databases used included Google Scholar, ACCESS, EBSCO, and Web of Science. The search terms used include colorectal OR colon OR rectum AND cancer OR metastatic disease OR malignancy OR neoplasms AND cost OR costing OR cost analysis OR estimating the cost OR quantifying the cost AND Treatment OR care OR management. Other search terms include epidemiology of colon cancer, disease-specific costing, and cost of illness analysis. A manual search of the references from the included articles (using a backwards snowballing technique) was also done to complement the review. The empirical review was limited to English-language publications and focused on studies published between 2013 and 2024 to capture the most current evidence and reflect recent developments in colon cancer clinical guidelines and treatment costs.

3 Theoretical background on Colon Cancer

This section explores the epidemiologic burden of colon cancer, emphasising the economic challenges related to its treatment. It also offers an introductory description of the clinical features and treatment approaches for colon cancer. Finally, the section places the disease burden in the context of South Africa, providing insights into how colon cancer is treated at Groote Schuur Hospital (GSH).

3.1 The burden of colon cancer

Globally, Colorectal Cancer (CRC) ranks fourth in terms of incidence and third in terms of cancer-related mortality in both men and women of all ages with an estimated Age-Standardized Incidence Rate (ASIR) and Age-Standardized Mortality Rate (ASMR) of 18.4 and 8.1 per 100,000, respectively (Ferlay et al., 2024). In 2022, over 1.9 million new cases and 900,000 deaths attributed to CRC were recorded, accounting for approximately 9.6 and 9.3 per cent of global cancer incidence and mortality, respectively (Ferlay et al., 2024). Figure 1 depicts the global number of new cases and deaths from CRC, illustrating the contributions of colon, rectal and anal cancers. The value is shown in percentage on top of each column and is calculated against the total CRC number in 2022 for both sexes and all ages.

Colon cancer constitutes the most substantial portion of the burden related to CRC, both in terms of incidence and mortality. In 2022, colon cancer exhibited a global ASIR of 10.7 per 100,000 ranking fifth in terms of cancer incidence (Bray et al., 2024; Ferlay et al., 2024). The estimated incidence rate of colon cancer demonstrates marked regional variations with the highest ASIR in the Oceania region (19.8 per 100,000) and least rates in Africa (4.3 per 100,000) (Ferlay et al., 2024). The number of new colon cancer cases is positively correlated with increase in the Human Development Index (HDI) (Ferlay et al., 2024). The incidence rate in countries with high HDI is approximately four times greater than in low HDI countries, and a continuous rise in the number of new colon cancer cases has been reported in countries with medium to high HDI (Sung et al., 2021; M. C. S. Wong et al., 2021). This has led to the recognition of colon cancer as a marker of socioeconomic development (Fidler, Soerjomataram and Bray, 2016; Bray et al., 2024). Over time, an increase in the incidence rate of

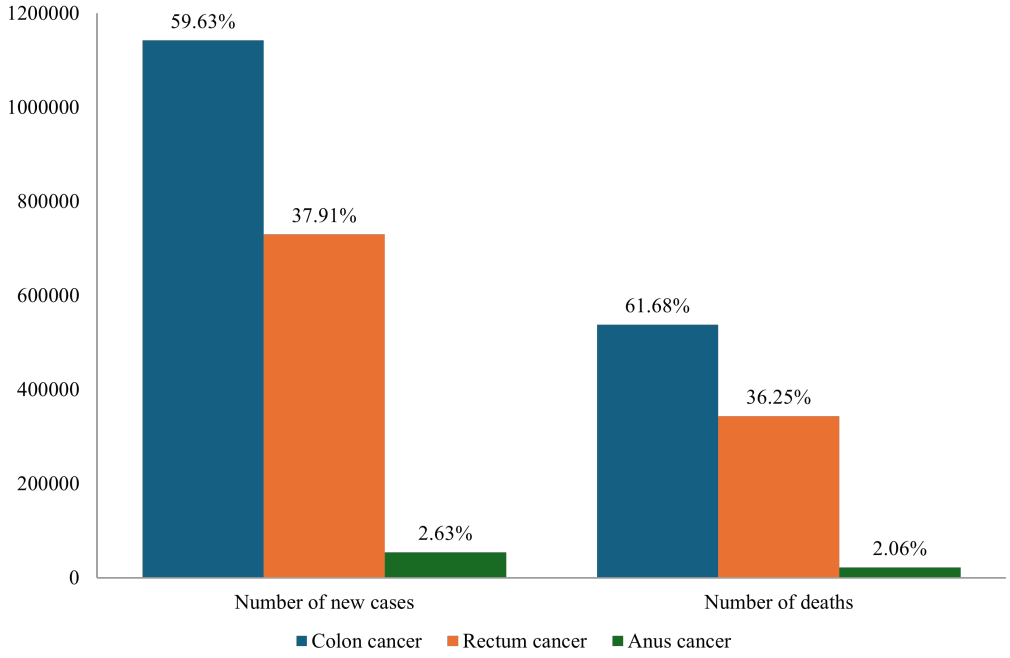

Figure 1: Global new cases and deaths of colon cancer, rectum cancer, and anus cancer in 2022.
Source: Data from Ferlay et al., 2024

both colon and rectal cancers has been reported in many countries within Eastern Europe, Asia, and South America (Arnold, Abnet et al., 2020; Arnold, Sierra et al., 2017). This increase in regions formerly considered low-risk is likely a result of shifts towards the lifestyle and dietary risk factors of colon cancer (Arnold, Sierra et al., 2017). While declines in the incidence of colon cancer in some high-risk countries mainly since the early 2000s have been attributed to population-level shifts toward healthier lifestyles, and to colonoscopy screening and removal of precursor lesions (Arnold, Abnet et al., 2020). The global incidence of CRC is projected to exceed three million by 2040 (Xi and P. Xu, 2021) and over the past decades, a global surge in the incidence of Young-onset Colorectal Cancer (yCRC) has been reported (Vuik et al., 2019). This signifies increased CRC occurrence in regions with a significant youth population once considered low risk. This trend has both epidemiologic and economic implications, especially for healthcare systems as they face an increasing number of colon cancer patients.

On the other hand, colon cancer ranks seventh in terms of caner mortality with an ASMR of 4.7 per 100,000 (Ferlay et al., 2024). Compared to its incidence, the estimated mortality rates of colon cancer

is relatively less diverse across geographical regions, ranging from 7.7 per 100,000 in Europe to 2.9 per 100,000 in Africa (Ferlay et al., 2024). Notably, while Africa has the lowest estimated ASMR for colon cancer, it also exhibits the highest mortality-to-incidence ratio in the world. This ratio signifies poor outcomes relative to the incidence rate, indicating the need for improved strategies for colon cancer management in the region.

3.2 The global economic burden of colon cancer

Colon cancer is associated with increased economic expenditure worldwide (Chen et al., 2023; Bhimani, G. Y. M. Wong et al., 2022). With the rise in colon cancer incidence due to population ageing (Arnold, Sierra et al., 2017), this global economic burden is expected to increase in the future. The costs related to the diagnosis, treatment, and management of colon cancer, along with the economic burden of lost productivity and life years, contribute to the overall economic impact of the disease. The economic burden associated with colon cancer encompasses both direct and indirect costs, as discussed by Orangio, 2018. Direct costs pertain to the expenses incurred for resources used in diagnosing and treating colon cancer; the healthcare system usually bears these costs. Indirect costs are associated with productivity losses related to colon cancer treatment both for patients and their caregivers (family). Together, these costs contribute significantly to the societal burden of colon cancer, including losses in productivity and broader economic impact.

Chen et al., 2023 reports that out of twenty-nine cancers studied, CRC is among the top five cancers contributing 50% of the total global economic burden of cancer. CRC alone is estimated to yield total macroeconomic cost of INT $2012 to 3749 billion (International Dollars) between 2020 and 2050 in 204 countries (Chen et al., 2023). The economic burden of colon cancer is unevenly distributed across world regions and income levels, while high-resource countries bear the largest macroeconomic costs, the Low-to Middle-Income Countries (LMICs) experience the greatest human toll (Chen et al., 2023). This highlights the need for health system strengthening and implementation of relevant public health policies. Without such, as the incidence of colon cancer continues to rise in the LMICs, the growing economic costs will add to the already substantial human burden they face.

3.3 Clinical description and treatment of colon cancer

CRC is a cancerous growth in the large bowel, including the colon and rectum.The colon and rectum are anatomically related as two separate regions of a single continuous organ (large intestine). Therefore, colon and rectal cancers are considered the same disease, generally called CRC. However, colon and rectal cancers can be differentiated based on clinical features and tumour anatomical sites (Hong, Clark and Haigis, 2012). In most cases of CRC, the colon is affected twice as often as the rectum (Arnold, Sierra et al., 2017). Colon malignancies can start anywhere in the proximal (ascending and transverse) or distal (descending and sigmoid) colon. This malignant neoplasm mainly arises from adenomatous polyps; usually, these polyps are premalignant, with a few maturing into cancer (Mayer, 2022). The progression of a polyp to cancer is a long process of several steps involving oncogenic activation and the loss of genes responsible for tumorigenesis suppression (Mayer, 2022; Jass, 2007). The risk factors of colon cancer include age, hereditary factors, a family history of CRC or adenomatous ploys, inflammatory bowel disease, consumption of diets rich in fats and red meat, physical inactivity, cigarette smoking, alcohol use and obesity (Papadakis and McPhee, 2023; Mayer, 2022). Colon cancers are adenocarcinomas that grow slowly and can be asymptomatic. However, once symptomatic, the presenting symptoms vary based on the anatomic location of the tumour (Mayer, 2022). Symptoms may include a change in bowel habits, chronic and insidious bleeding, blood-streaked stool, abdominal pain, intestinal perforation, fatigue and weakness indicative of iron deficiency (Mayer, 2022; Papadakis and McPhee, 2023). Screening is a strategy for the secondary prevention of cancer, aiming to detect the disease at an early, more treatable stage (WHO, 2017; WHO, 2020). The rationale behind colon cancer screening is to reduce its occurrence by detecting and removing adenomatous polyps before they develop into cancer (Mayer, 2022). This early detection of localised colon tumours in asymptomatic individuals can improve the chances of successful colon cancer treatment interventions. Some screening strategies utilised over the past decades and currently include digital rectal examinations, stool testing such as occult blood and faecal DNA, imaging procedures such as contrast barium enemas and computed tomography colonography, and endoscopy (flexible sigmoidoscopy and colonoscopy) (Mayer, 2022). Several laboratory and imaging investigations are used to diagnose colon cancer. A complete blood count could be used to identify anaemia, elevated liver biochemicals are useful to inform possible metastasis, faecal DNA and immunochemical tests, and carcinoembryonic antigen (CEA) levels to

monitor for recurrence (M. A. Smith, 2019; Papadakis and McPhee, 2023). Imaging procedures such as computed tomography (CT scan) and magnetic resonance imaging (MRI) are best used to identify distant metastasis, while X-rays are helpful for perioperative staging (M. A. Smith, 2019). According to Mayer, 2022, the staging and patient prognosis for colon cancer depends on the depth of tumour penetration into the intestinal wall (T), regional lymph node involvement (N) and distant metastasis (M); these three variables are incorporated into a TNM classification system. Lesions involving regional lymph nodes that have not penetrated through the submucosa or the muscularis are designated as stage I disease. In contrast, tumours that penetrate through the muscularis but have not spread to lymph nodes are stage II disease. The involvement of regional lymph nodes defines stage III disease, while the tumour spread to other sites or organs indicates stage IV. Figure 2 describes the staging of colorectal malignancies using the TNM classification system.

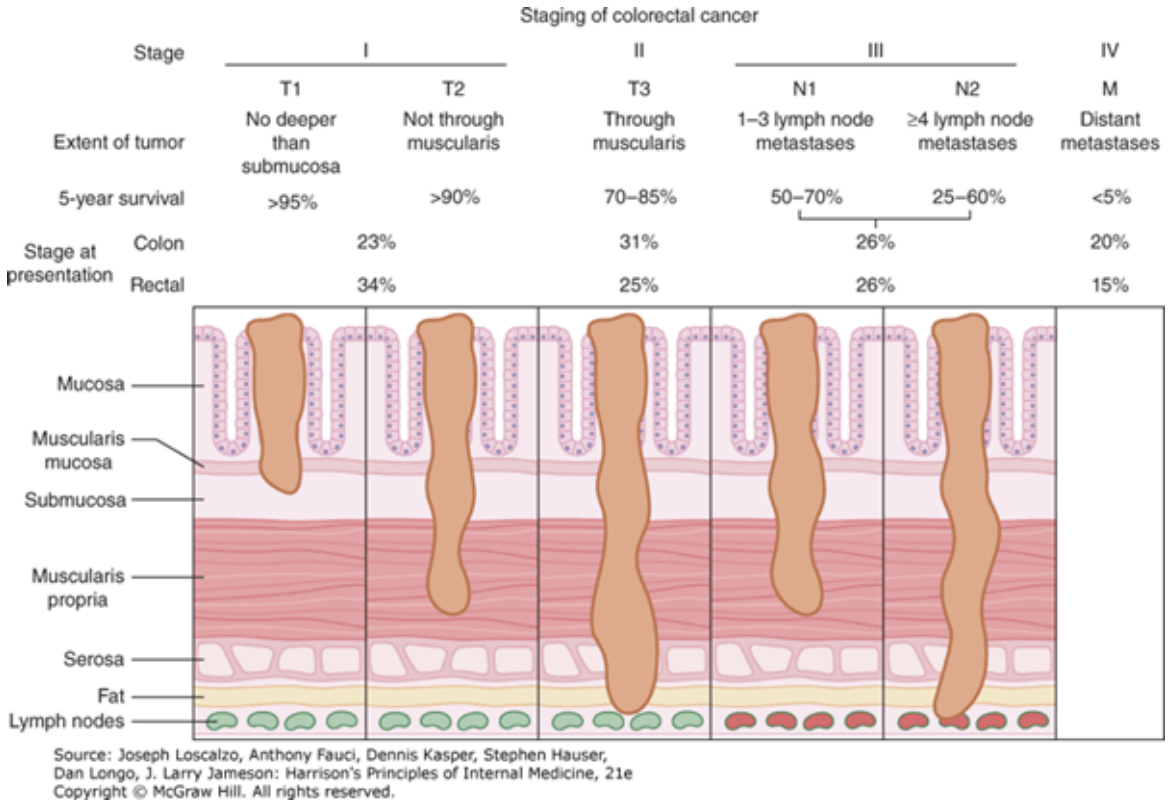

Figure 2: TNM staging of colorectal cancer
Source: Adapted directly from Mayer, 2022

3.3.1 A Global perspective on colon cancer treatment

The treatment of colon cancer is based on the TNM stage described above. The prevailing global approach to treating non-metastasized (stage I -III) colon cancer involves the removal of the primary tumour and selected lymph nodes, typically followed by adjuvant chemotherapy for a subset of patients (Chakrabarti et al., 2020; Labianca et al., 2013; Costas-Chavarri, Temin and Shah, 2019). The resected lymph nodes are useful for the pathological staging of the disease, and a minimum of twelve lymph nodes is recommended for accurate staging and improved survival (levoyer 2003). Tumour resection alone effectively cures most stage I colon cancer cases while adjuvant chemotherapy is recommended for high-risk stage II patients identified through a risk classification based on clinical and pathological features, and all stage III patients (Labianca et al., 2013; Osterman and Glimelius, 2018; Costas-Chavarri, Temin and Shah, 2019). Currently, this combined approach of surgery and adjuvant chemotherapy offers the possibility of long-term survival for approximately two-thirds of colon cancer patients with lymph node involvement (Chakrabarti et al., 2020). The principal aim of surgical treatment in early-stage colon cancer is to remove the visible malignant tumour, the affected portions of the colon, and the corresponding draining lymph nodes while maintaining mesocolon integrity (Lorenzon et al., 2018; Mayer, 2022). Surgical resection can be performed using either open or minimally intrusive techniques. Adjuvant chemotherapy is to eliminate any remaining minimal disease post-tumour removal to ensure a complete cure. A fluoropyrimidine, 5-Fluorouracil (5-FU), remains the cornerstone cytotoxic agent for colon cancer treatment; it is usually administered intravenously but can also be used orally as capecitabine (Mayer, 2022). Other chemotherapeutic agents used in colon cancer chemotherapy alongside the 5-FU and leucovorin (LU) backbone are irinotecan and oxaliplatin (Mayer, 2022). Clinical trials have demonstrated improved overall survival with oxaliplatin based regimens (FOLFOX and CAPOX) compared to the 5-FU/LV regimen (André et al., 2015; Haller et al., 2011).

For metastatic (stage IV) colon cancer, the timing of the metastatic process, the anatomical site of metastasis and other patient-specific factors hold significance in terms of treatment options (Sugarbaker, 2013; Kanthan et al., 2012). Metastasis from colon cancer typically manifests in the liver and peritoneal surfaces and may occur concurrently with disease detection or later during follow-up. The primary

treatment aims are to extend overall survival and maintain quality of life for as long as feasible or achieve a cure in the case of localised metastasis (Kanthan et al., 2012). Stage IV Patients with resectable liver metastasis receive surgical treatment immediately or after perioperative chemotherapy, while those with unresectable tumours receive palliative chemotherapy (Kanthan et al., 2012). Surgical procedures can be conducted to achieve cure, as in the resection of isolated organ metastasis or to provide symptomatic relief and palliation for abdominal obstruction or bleeding (Papadakis and McPhee, 2023). Currently, stage IV colon cancer is managed with chemotherapy and biological agents. Such biological agents include monoclonal antibodies, cetuximab, panitumumab and bevacizumab (Mayer, 2022). Targeted therapy is also employed in the treatment of late-stage colon cancer, as utilising systemic chemotherapy plans for all sites of colorectal metastatic disease does not align with the highest standards of care (Kanthan et al., 2012).

3.4 The South Africa context

3.4.1 The burden of colon cancer in South Africa

In Africa, colon cancer ranks among the top 10 leading cancers both in terms of incidence and mortality, with ASIR and ASMR of 4.3 and 3.0 per 100,000 persons respectively (Ferlay et al., 2024). Despite the relatively low burden of colon cancer in Africa, there is minimal investment in CRC control evidenced by the high age-standardised mortality-to-incidence ratio (0.69) and increasing Disease Adjusted Life Years (DALYs) (Ferlay et al., 2024; Fitzmauric et al., 2019). This indicates there has been limited progress in the standard care, diagnosis and treatment of the disease, as well as the implementation of primary and secondary prevention strategies in Africa (Awedew, Asefa and Belay, 2022). Admittedly, it is difficult to assess the burden of CRC in Sub-Shaharan Africa (SSA) due to the absence of formal cancer registries, unavailability of quality data and limited national coverage (Williams et al., 2016). The global estimates indicate a greater colon cancer incidence than the local South African registries, which mainly report pathologically-diagnosed cases (Ferlay et al., 2024; Health and Service, 2012). The incidence of colon cancer in South Africa aligns with global trends as it remains one of the most frequently diagnosed cancers. It is the sixth leading cause of cancer-related deaths in both men and women, with an ASIR of 6.8 per 100,000 and ASMR of 6.3 per 100,000 (Ferlay et al., 2024). Alarmingly, these estimates indicate that over half of the individuals diagnosed with this cancer in South Africa

do not survive, underscoring the severity of the condition. A Preliminary analysis of both colon and rectal cancer patients in South Africa showed that there is a predominance of left-sided colon tumours, and a significant majority of these patients seek medical care at public health facilities (L. M. Prodehl et al., 2017). Brand, Gaylard and Ramos, 2018 reports that CRC patients treated in the South African private healthcare sector exhibit disease presentation patterns similar to those found internationally and experience comparable outcomes following various treatment pathways. Considering that government expenditure primarily funds healthcare in South Africa (Edet-Utan and Gooyabadi, 2021; Ekenze, 2019), it is crucial to guarantee that resources are utilised appropriately and that equitable healthcare is provided, irrespective of the patient's treatment location. Assessing the resource requirement for delivering healthcare services is a valuable tool for informing and planning healthcare delivery, ensuring that the healthcare needs of the more significant portion of the population are adequately addressed and resources are allocated efficiently.

3.4.2 The economic burden of colon cancer on the South Africa healthcare system

South Africa is classified as an upper middle-income country, with a Gross Domestic Product (GDP) per capita of $6,022(2015) (World Bank Group, 2024). The nation houses a population of approximately 60 million in 2022 and over 12 million residents living below the poverty line at $2 per day (Stats SA, 2024). This poverty level already indicates a significant burden of healthcare expenditure on the government, aiming to prevent further impoverishment of patients and their families due to healthcare payments. Moreover, income inequality remains a significant issue, with a summary measure (Gini index) surpassing 60% (World Bank Group, 2024). This exacerbates the socioeconomic divide in South Africa and places a disproportionate healthcare financing burden on the government of South Africa (Ataguba, 2021). Unlike many African countries where out-of-pocket payments are a major source of healthcare financing, South Africa relies on only 8% of such payments (Edet-Utan and Gooyabadi, 2021), while government health spending exceeds 5% of GDP (World Bank Group, 2024). Typically, cancer patients in low-resource settings bear a disproportionate burden of out-of-pocket fee payments due to the limited healthcare services and government funding, and access to treatment is often more favourable for patients who can afford medical insurance (Siddiqui and Rajkumar, 2012). However, given the income inequality in South Africa, healthcare access, provision, and funding

pose significant challenges, with most patients relying on publicly funded government healthcare services (Ataguba, 2021). While there is notable prioritisation of the health sector relative to other public sectors in South Africa, reflected in a domestic general government health expenditure of approximately 15% of general government expenditure (World Bank Group, 2024), this allocation has not translated into adequate resources for funding health services in the public sector (Jobson, 2018). In contrast to findings regarding colon cancer patients in the private sector (Brand, Gaylard and Ramos, 2018), a constrained availability of CRC chemotherapy options within the South African public health sector and the need to refine clinical pathways to improve the management of colon cancer has been established (Herbst, Miot et al., 2018). As South Africa moves toward Universal Health Coverage (UHC), calling for increased government spending on healthcare is questionable if existing funds are not used efficiently and equitably. Understanding the financial burden of colon cancer treatment on the healthcare system is crucial for making the best use of available resources, and this understanding can be achieved through costing analysis.

3.4.3 Colon cancer treatment at Groote Schuur Hospital (GSH)

The treatment of colon tumours follows a structured process as outlined in the GSH protocol for colon cancer treatment (Groote Schuur Hospital, 2022). Treatment commences with pre-surgical staging and moves on to the initial management which involves assessments for resection and surgical treatment. Subsequently, post-operative management ensues, including patient risk assessment and the consideration of adjuvant chemotherapy. Lastly, follow-up management includes routine visits, telephonic consultations, and diagnostic investigations. Table 1 provides a summary of the standard treatment for colon cancer based on Groote Schuur Hospital, 2022.

In contrast to the global approach for managing metastatic disease, the availability of targeted agents is limited due to resource constraints. Additionally, chemotherapy is not administered continuously until toxicity or disease progression in this context.

Treatments for stage I and low-risk stage II colon cancer are identical, as are treatments for stage III and high-risk stage II; thus, guideline cost results have been presented accordingly.

Table 1: Adenocarcinoma colon TNM staging and management summary

Stage (TNM)	**Initial Management**	**Post-operative Management**	**Follow-up**
Non-metastatic colon cancer			
Stage I (T1 or T2, N0, M0)	Surgery	No adjuvant chemotherapy	Annual surgical clinic assessment with carcinoembryonic antigen testing.
Low-risk stage II (T3 or T4 or T4b, N0, M0)	Surgery	No adjuvant chemotherapy	same as stage I
High-risk stage II	Surgery	Adjuvant chemotherapy	Surgical clinical assessment every nine months for thirty-six months following surgery or completion of adjuvant chemotherapy, then annual visits for two years with carcinoembryonic antigen testing. Repeat CT scan and colonoscopy three years post-surgery.
Stage III (T1-4, N1-2b, M0)	Surgery	Adjuvant chemotherapy	same as high-risk stage II
Metastatic colon cancer			
Resectable	Surgery immediately or after perioperative chemotherapy	Adjuvant chemotherapy if no perioperative or conversion chemotherapy	same as stage III
Unresectable:			
Performance status 0-2	No surgery	Palliative chemotherapy	
Performance status ≥ 3	No surgery	Supportive management	

Source: Adapted from Groote Schuur Hospital, 2022
"High-risk" and "low-risk" are distinguished based on tumour characteristics and patient health.

Abbreviations:
T, primary tumour (T1, tumour invades submucosa; T2, tumour invades muscularis propria; T3, tumour invades into peri colorectal tissues; T4a, tumour penetrates to surface of visceral peritoneum; T4b, tumour invades or is adherent to other organs or structures). N, regional lymph nodes (N1, metastases in 1–3 regional lymph nodes; N1c, tumour deposit(s) in subserosa, mesentery, or nonperitonealzed pericolic or perirectal tissues without regional nodal metastasis; N2a, metastases in 4–6 lymph nodes; N2b, metastases in 7 or more regional lymph nodes). M, distant metastasis (M1a, metastases confined to one organ or site; M1b, metastases in more than one organ or peritoneum).

4 Methodological review of estimating healthcare costs

This section introduces the concept of cost and healthcare costing, providing an overview of the micro-costing framework and the methodological principles for evaluating healthcare costs.

4.1 Costs and costing

The concept of cost is a fundamental notion in economics. A cost represents the value of resources, materials, risks, time, and utilities expended in procuring goods and services (Samuels and Schmid, 1997). There are two main types of cost: financial and economic cost, each relevant for different purposes. Financial costs represent the monetary value of resources that are paid for, while the economic cost aims to encompass the highest value of the forgone alternative, the opportunity cost (Vassall et al., 2017). The standard cost measures include total cost, which refers to the overall cost of producing an output, and it can encompass fixed and variable costs or capital and recurrent costs. Unit costs are the average costs for each unit of production. Marginal costs, on the other hand, represent the cost of producing one additional unit of output, usually used to capture additional cost change as service levels increase (Drummond et al., 2015). Generally, cost estimates are utilised in economic evaluations and other economic assessments for various purposes. Estimating these costs, known as costing, is applicable in multiple contexts. In the health system, economic evaluation plays a crucial role in guiding various healthcare decisions due to the limited availability of resources and the necessity of making

choices regarding their allocation (Drummond et al., 2015). Economic evaluation approaches include, cost-effectiveness analyses, cost-utility analysis, cost-benefit analysis, cost-minimization analysis, and distributional cost-effectiveness (Cunningham, 2000; Drummond et al., 2015; Meunier et al., 2023). Each approach uses a different technique but entails the comparative assessment of varying alternatives, considering both the costs and outcomes associated with these alternatives, except the cost-minimization analysis, which considers only the costs where the effects are found to be equal. The distributional cost-effectiveness analysis is a recent approach that incorporates equity and is used as part of a health technology assessment approach (Meunier et al., 2023). Health system costing entails the assessment of resources involved in delivering a health service, program or intervention (Drummond et al., 2015; Vassall et al., 2017). It can be considered a form of partial economic evaluation with a primary emphasis on cost evaluation, excluding the incorporation of effectiveness. The advantages of costing are its ability to generate easily interpretable cost estimates that facilitate direct cost comparisons among various health interventions or programs, and its practical use in decision-making processes. According to Vassall et al., 2017, costing in healthcare serves various purposes. Firstly, it plays a crucial role in economic evaluation and the prioritisation of resources. Cost estimates are used to analyse allocative efficiency, which informs decision-making processes. Analytical methods such as cost-effectiveness analysis, cost-utility analysis, cost-benefit analysis, distributive cost-effectiveness analysis and health technology assessment processes consider cost outcomes. Secondly, costing is essential for exploring the cost differences and identifying cost drivers among different resource users or for comparing to establish standards. Without cost information, assessing technical efficiency is not feasible. Additionally, cost estimates are valuable for budgeting and price setting. They are used to predict expenditure, which, in turn, informs budget allocation and price-setting decisions. Costing provides essential cost data for financial planning and the evaluation of resource use; this serves as evidence to make an investment case, supports national healthcare planning (such as national strategic plans), and guides efficient resource allocation.

4.2 The ingredient or micro-costing concept

Ingredient or micro-costing is a method in health economics used to measure and evaluate the costs of specific health interventions or services by identifying and quantifying each resource

consumed (Drummond et al., 2015). Unlike macro-costing, which aggregates costs at a higher level, micro-costing provides a granular approach, focusing on individual cost components to offer a more accurate estimation. Micro-costing involves direct enumeration and valuation of every input consumed in patient treatment (X. Xu, Lazar and Ruger, 2021). The assessment of health service costs using the a micro-costing approach typically involves three primary steps: identification, measurement, and valuation (Fox-Rushby and Cairns, 2005). Once the applicable range of resources used in the provision of the healthcare service has been identified, the individual resource inputs must be measured and assigned a monetary value to obtain a unit costs (Drummond et al., 2015). Micro-costing is particularly useful in economic evaluations, clinical trials, and budget impact analyses because it provides more precise cost estimates than macro-costing, which relies on averages or aggregated data. It allows for customization of cost estimates to local contexts, making it highly relevant for regional health policy decisions. However, micro-costing is resource-intensive, requiring detailed data collection and accurate measurement of all resources. Due to variability in data availability, micro-costing can also result in variations in cost estimates (X. Xu, Lazar and Ruger, 2021).

4.3 Methods of estimating healthcare costs

Healthcare cost estimation is approached from different perspectives. The choice of perspective and other methodological considerations in costing are primarily determined by the specific purpose of the healthcare cost estimation (Vassall et al., 2017; Mogyorosy and P. Smith, 2005). After establishing the purpose, several principles and methodological considerations become pivotal in healthcare cost estimation (Drummond et al., 2015; Vassall et al., 2017; Mogyorosy and P. Smith, 2005; Fox-Rushby and Cairns, 2005). These include:

1. Perspective selection: the choice of a perspective defines the viewpoint for costing, which significantly influences the resources included in the costing process. This perspective can be from the healthcare providers, payer (patient or third party), or societal angle. A ~~health~~ healthcare provider's angle is adopted when analysing the cost incurred per patient by the health facility. Conversely, the societal perspective becomes necessary if a policymaker aims to assess the cost-effectiveness of a particular national health intervention. Nevertheless, factors like data availability can impact the selection of the perspective (Mogyorosy and P. Smith, 2005), often

leading to the adoption of a perspective for which data sources are readily accessible, such as the third-party perspective. Table 2 presents the Inclusion of cost elements for different costing perspectives.

2. Defining the type of cost: The cost under estimation should be explicitly defined in terms of economic or financial cost, normative or empirical cost, and full or incremental cost. It is essential to specify the type of cost estimates needed because different types of costs are suitable for different purposes (Vassall et al., 2017). For example, economic evaluation necessitates incremental economic cost, whereas real-world or normative financial costs are used for financial planning. These various cost types demand distinct measurement and valuation approaches. Therefore, to ensure proper study design, it is crucial to begin the cost estimation process with a well-defined specification of the type of cost being considered.

3. Resource identification, measurement, and valuation: Accurately identifying the cost items/inputs. Once the relevant cost inputs have been outlined, they must be measured and valued appropriately.

4. Time horizon specification: Clearly define the time frame during which the costs will be assessed, accounting for potential variations over time due to various influencing factors.

5. Data quality and consistency: Ensure that data quality and consistency are maintained, facilitating comparability and minimising errors in the estimation process. Table 2 shows the inclusion of cost elements for different costing perspectives.

The basic idea in costing is to determine the quantities (Q) of services utilised and the individual prices (P) of such services; the full cost of each service unit is then obtained by multiplying (Q) and (P) (Drummond et al., 2015). Before determining the quantities, we must first identify the services to be included in the costing. The number of these services, known as the 'cost inputs/item', is determined by the desired details or data availability level (Hendriks et al., 2014). The gross-costing or micro or ingredient-costing approaches can be used for this initial identification. Gross costing is a more aggregate approach requiring fewer resources and considers costing the relatively large resources used. In contrast, the ingredient approach provides a high level of detail, considers every resource component used, and estimates a unit cost for each identified input (Drummond et al., 2015). Creating

Table 2: Cost elements from different perspectives

Cost Elements	Health Provider	Patient	Third-Party (Insurer)	Societal
Health service costs	All resource cost	All paid for	All covered	All included
User fees	Excluded	Any paid for	Any paid for	All included
Transportation	Excluded	All paid for	Any paid for	All included
Informal carers	Excluded	All paid for	Excluded	All included
Other non-health costs	Excluded	Any paid for	Any paid for	All included
Productivity cost	Excluded	All	Any paid for	Included
Sick leave	Excluded	None	All paid + admin cost	Admin costs only
Disability benefits	Excluded	None	All paid + admin cost	Admin costs only

Source: Adapted from Mogyorosy and P. Smith, 2005

a comprehensive description of a clinical management pathway or flowchart can be instrumental in identifying these items (Mogyorosy and P. Smith, 2005). Hendriks et al., 2014, in comparing the ingredient approach to the gross method, suggest that the ingredient costing approach is likely to produce more precise and accurate cost estimates. The measurement of cost items refers to measuring the volume or quantities (Q) of utilisation for each identified resource/cost item. The measurement approach for each cost item varies depending on the availability and precision of utilisation data. Typically, this process involves gathering data from diverse sources, including expert opinion and patient registries. In cases where utilisation data is lacking, data collection tools like activity review logs and time sheets can be employed to acquire the necessary information. Generally, resource utilisation can be measured prospectively, retrospectively, or by modelling (Mogyorosy and P. Smith, 2005). The valuation of cost items can be done using two approaches: the top-down (step-down) or bottom-up method. While the step-down approach uses formulae that allocate overall expenditure to each input to determine unit costs, the bottom-up approach uses detailed action such as input utilisation data from records (or observed utilisation) to estimate unit costs (Drummond et al., 2015; Batura et al., 2014). In contrast to the bottom-up method, which considers individual measures and utilisation, the step-down method assigns equal weights to identical resources, irrespective of variations in individual utilisation, timeframes, or settings, making it a less accurate approach (Drummond et al., 2015). The bottom-up method is capital and time-intensive but provides more accurate cost

estimates. At the same time, the step-down approach, which is more straightforward, is usually based on several assumptions that easily compromise the accuracy of the cost estimates (Mogyorosy and P. Smith, 2005). Cost estimates are inherently uncertain due to assumptions and variable factors involved in the costing process. Addressing the impact of parameter uncertainty is crucial; one effective method is through univariate or multivariate sensitivity analyses (Drummond et al., 2015). In univariate sensitivity analyses, individual parameters are altered while keeping others constant. This allows for an independent assessment of the impact of each parameter's uncertainty. Parameters can be varied at a fixed percentage (e.g., a 10% change) or by utilising uncertainty ranges such as standard deviations. Multivariate sensitivity analyses, on the other hand, involve simultaneously varying multiple parameters. This approach provides a more comprehensive understanding of how changes in various factors collectively influence the cost estimate. Beyond parameter uncertainty, other vital levels of uncertainty include model uncertainty and generalizability uncertainty (Edejer, 2003).

Differences in methodology often stem from the level of accuracy determined by the identification of cost inputs (gross or ingredient-costing) and the valuation of these inputs (bottom-up or top-down) (Tan et al., 2009). The combination of various costing approaches influences the accuracy of the obtained cost estimates. A top-down gross or ingredient approach results in moderately accurate cost estimates, compared to a bottom-up gross or ingredient costing approach, which yields more accurate estimates. The methodological consideration of time in measuring cost items also introduces variations in cost estimates (Mogyorosy and P. Smith, 2005). Prospective studies provide more accurate measurements than retrospective studies, as the reliability and validity of retrospective studies depend on the accuracy and quality of the original data recording system. The top-down method is retrospective in practice as it relies on financial records and databases, while the bottom-up approach can either be prospective or retrospective. The integration of the bottom-up valuation method with the ingredient approach (bottom-up ingredient-costing) is widely regarded as the method that produces the most precise cost estimates for healthcare activity, as it identifies and values all relevant cost items at the finest level of detail (Drummond et al., 2015; Mogyorosy and P. Smith, 2005; Tan et al., 2009). However, this more precise costing approach can be resource-intensive, making it impractical in some cases, particularly where data collection is not feasible. Therefore, a mixed costing methodology is often

suggested (Shepard, Hodgkin and Anthony, 2000). Here, activities that represent a significant portion of total costs or resources where data collection is feasible are costed using the bottom-up method, and the less critical resources are costed using the less accurate step-down method. In resource-limited settings, a mixed costing methodology is recommended for facility-based costing studies (Guerre, Hayes and Bertaux, 2018). This approach is considered efficient, especially in LMICs, where resource constraints and data limitations are typical (Hendriks et al., 2014). Furthermore, in response to the limitations of the hospital setting, hospital economists have integrated both micro and gross costing approaches (Guerre, Hayes and Bertaux, 2018).

4.4 Disease-specific ingredient costing from the health providers perspective

Disease-specific costing offers cost data that guide the decision-making of healthcare providers, funders, and policymakers regarding the disease in focus. These studies highlight the resources necessary for delivering specific services or healthcare interventions, helping identify areas of inefficiency and cost-driving factors (Mogyorosy and P. Smith, 2005; Drummond et al., 2015). Based on findings from Hodgson and Meiners, 1982, healthcare costs originating from illness can be categorised as direct, indirect, and psychosocial. Direct costs encompass medical care expenses (direct medical cost) and non-medical expenses (direct non-medical cost). Direct medical costs cover hospitalisation, diagnosis, counselling, rehabilitation, medication, and more. Direct non-medical costs involve expenses related to training, research, administrative functions, transportation, caregiving for patients, and property losses due to illness. Indirect costs arise from productivity and time losses due to morbidity and mortality. Another category of costs from the patient's perspective are intangible costs, or psychosocial costs, which encompass factors like deterioration in quality of life and other personal catastrophes such as marked changes in personality and suffering that cannot be quantified in monetary terms. Disease-specific costs can be categorised as prevalence-based or incidence-based, depending on the chosen approach for estimation. The more common prevalence approach focuses on the total cost associated with the disease in a specific period, usually a year. In contrast, the incidence approach takes a long-term perspective, calculating the lifetime cost burden of the diseases for individuals diagnosed within a specified period (Tarricone, 2006). Choosing between these approaches depends on your specific goals and available data, but both offer valuable insights into the economic impact of a

disease.

When assessing disease-specific cost from the health provider's perspective, the focus is on medical resource costs. These resource costs are categorized as capital or recurrent based on their estimated lifespan and value (Drummond et al., 2015). Capital costs encompass resources primarily composed of fixed assets with a useful lifetime frame exceeding one year and a value greater than 100 USD, such as buildings, equipment and land. Recurrent costs mainly refer to resources procured regularly and estimated to have a lifetime use of less than one year, such as medications, diagnostic consumables, and personnel salaries (Hansen et al., 2017; Drummond et al., 2015). Capital costs are distinct from operating costs as they signify an investment in an asset utilised over time. To incorporate both the depreciation and opportunity cost aspects, the best approach to quantifying capital costs is to spread the initial capital equivalent over the asset's expected useful lifespan, i.e., computing its equivalent annual cost (Drummond et al., 2015). Clinical pathways based on guidelines or daily clinical practice in a hospital can be used to support disease-specific costing (Hendriks et al., 2014).

5 Empirical review of estimating the treatment cost of colon cancer

This section provides a comprehensive review of the literature on estimating the treatment cost of colon cancer. It aims to identify gaps in the existing literature, discuss the implications of current findings for the present study, and highlight the importance of further research in this field. After an extensive literature review, it was noted that most articles focused on the cost of treating CRC, encompassing both colon and rectal cancers. These findings have been integrated into the review.

An international systematic review by Kriza et al., 2013 described the development of CRC-related costs and highlighted important cost drivers. Most of the studies analysed in the review adopted a third-party (health insurance) perspective and stratified costs by treatment phase. The treatment phase, as outlined in various articles, encompasses three distinct stages of cancer care: the initial phase, the continuing phase, and the terminal phase. Long-term costs for CRC of up to $50,175 per-patient (2008 values) were estimated. The use of biological agents such as cetuximab and bevacizumab was

identified as a cost driver in treating CRC. In summary, the findings from Kriza et al., 2013 suggest that the treatment of colon and rectal cancers is associated with heightened economic expenditure.

A more recent systematic review Bhimani, G. Y. M. Wong et al., 2022 analysed seventeen studies examining the lifetime direct medical costs of CRC. The review considered advancements in the medical management of colon and rectal tumours over the past two decades and the need to focus on direct healthcare costs. Out of the seventeen studies examined in Bhimani, G. Y. M. Wong et al., 2022, nine adopted the health insurer's perspective, six took on the viewpoint of the healthcare providers, and one considered the societal standpoint. Overall, Bhimani, G. Y. M. Wong et al., 2022 reported that the initial phase lifetime cost ranged from $7,893 to $60,289, while the continuing phase costed from $2,323 to $15,744, and the terminal phase from $15,916 to $99,687. Retrospective case-control and cohort study designs were used to estimate the real-life direct costs of CRC. However, differences in the cost estimates were observed based on the differences in study methodology. The initial and terminal phase costs estimated from case-control studies were more significant than those from the cohort studies; while the cohort studies estimated higher costs for the continuing phase than the case-control studies. Given the overall heterogeneity of the different studies, Bhimani, G. Y. M. Wong et al., 2022 concluded that it was impossible to accurately determine the global estimates of the CRC phase-specific direct healthcare costs. However, the differences in costs across various countries also imply that certain nations might be more inclined to allocate greater resources for the treatment of patients with colon and rectal cancers than others.

Laudicella et al. (2016) estimated the lifetime cost of care for four significant cancers, including CRC in England, by matching cost of care data to population-based patient-level data. Cost estimates were determined separately for patients between 18 and 64 years and those above 65 years due to the limited evidence on the costs of care for the former age group both nationally and internationally. The cost estimates were differentiated based on the cancer stage and juxtaposed with a population without cancer. Laudicella et al., 2016 reported an average per patient incidence cost of £38,098 and £37,948 for the younger and older patient cohorts, respectively. The average per-patient incidence costs for the earlier stage (I-II) were £33,728 and £38,876 for the younger and older cohorts, respectively.

Meanwhile, for the late stage (III-IV), it was £46,306 for the younger cohort and £43,170 for the older cohort. A 5-year prevalence cost of £195,198 for the 18 to 64-years old cohort and £329,249 for the older cohort was also reported. In conclusion, Laudicella et al., 2016 suggest that the younger patient group consumed fewer CRC treatment resources up to three years post-diagnosis compared to the older patients and that a lower stage at diagnosis is associated with more significant cost savings across both age groups.

Alefan, Malhees and Mhaidat, 2017 conducted a retrospective analysis to estimate the annual direct medical costs associated with colon and rectal cancer in North Jordan. The study employed the prevalence-based bottom-up costing approach from the healthcare provider's perspective. The treatment cost was categorised based on disease stage. Aligning with findings from Laudicella et al., 2016, a correlation between increasing disease stage and higher direct medical costs for CRC was indicated. The annual direct medical costs were estimated at 1,159 Jordanian Dinar (JD) for stage I, JD1,835 for stage II, JD3,132 for stage III and JD5,147 for stage IV.

Focusing on the health insurers' perspective, Haug et al., 2014 reported the mean total and incremental cost of treating CRC by treatment phase in Germany using a retrospective review of patient information from 2005 to 2010. The cost estimates were stratified by the tumour site (colon, rectosigmoid junction and rectum) and treatment phase. The cost of treatment was compared with a control group of patients with a non-cancer diagnosis to obtain incremental cost. The total mean cost of treating colon tumours was reported as €27,735 for the initial treatment phase, €5,145 for the intermediate phase and €68,947 for the end-of-life phase. The total mean incremental cost for treating colon tumours was €24,351 for the initial phase, €1,317 for the intermediate phase and €56,127 for the end-of-life phase. Findings from Haug et al., 2014 reveal that the initial and intermediate phase cost of treating CRC tumours located in the colon is lower than that of rectosigmoid and rectal tumours.

Färkkilä et al., 2015 estimated the resource use and associated costs among CRC patients in Finland at five different disease states. These states were identified as primary treatment, rehabilitation, remission, metastatic disease, and palliative care. Patients were assigned to these disease states

based on their time from diagnosis and metastatic status. A cross-sectional study design was used to estimate the prevalent direct medical, productivity and informal care costs occurring in 6 months. Direct healthcare costs varied significantly between the disease states, with an estimated cost of €16,244 for primary treatment, €1,601 for rehabilitation, €1,450 for remission, €14,277 for metastatic disease and €10,004 for palliative care. These findings indicate a significant drop in direct medical costs after the primary disease state, particularly if treatment resulted in a good prognosis and no recurrence. Färkkilä et al., 2015 concludes that the primary disease state was the most resource-intense disease state, followed by the metastatic, palliative, remission, and rehabilitation states with estimated total costs of €22,200, €21,460, €20,540, €2,812, and €2,106 accordingly.

In a retrospective analysis involving six hundred and fifty-seven CRC patients in Iran receiving post-surgical chemotherapy, Nejati et al., 2021 reported a total direct medical cost of $21,407 per patient solely for the initial treatment phase (first 12 months), considering the healthcare providers' perspective. The estimated direct medical cost per patient, at $17.017, surpassed the direct non-medical cost by more than twofold, standing at $4,389. In-patient hospitalisation, surgery and chemotherapy were identified as the significant direct medical cost drivers of treating colon cancer.

Sougklakos et al., 2022; Shen et al., 2020 published direct medical cost evidence and treatment pathways of metastatic CRC in Greece and China, respectively. Both studies adopted the third-party (insurers' perspective) and differentiated the direct treatment cost by the line of treatment. The weighted annual cost of drugs and resource use in 1st line per patient was calculated at €28,407, in 2nd line, €33,568, and in 3rd line, €25,550 by Sougklakos et al., 2022, while Shen et al., 2020 reported mean direct medical costs per patient per cycle increasing from $2,514 to $2,678 to $5121 for the 1st, 2nd and 3rd lines of chemotherapy accordingly. In consideration of the differences in methodology, while Shen et al., 2020 used a retrospective costing analysis to determine the treatment cost per cycle of chemotherapy, Sougklakos et al., 2022 was based on a two-step costing methodology as adopted for the costing approach discussed in this thesis. First, the treatment pathways and associated resource use were identified through expert interviews. Secondly, the total annual cost for each pathway was estimated using activity-based costing.

It is pertinent to note that most of the studies considered thus far have been done in high-resource settings. Both international systematic reviews on the cost of treating CRC discussed above included no studies from the LMICs (Bhimani, G. Y. M. Wong et al., 2022; Kriza et al., 2013), highlighting the need for more CRC cost information in these regions. In this regard, two studies Herbst, Miot et al., 2018; Herbst, Lee et al., 2020 exploring the cost of chemotherapy for colon and rectal malignancies in South Africa were reviewed. Both studies focused on the direct treatment cost of chemotherapy in CRC using the third-party (Insurers) perspective. Herbst, Miot et al., 2018 developed and costed the clinical treatment pathways for early and advanced CRC chemotherapy in the public healthcare sector and compared the theoretical cost of receiving treatment to the actual cost for a patient cohort. Theoretical cost of adjuvant chemotherapy for colon tumours of €3087, €1390, €7963, and €2807 were estimated for 5FU+LV, Capecitabine, FOLFOX and CAPOX regimens, respectively, while the patient cohort estimated costs were €2932, €602, and €2239 for 5FU+LV, Capecitabine and CAPOX regimens respectively. Theoretically, metastatic chemotherapy cost €3087, €2807, €3981, and €1390 for the 5FU+LV, Capecitabine, FOLFOX and CAPOX regimens respectively, while the actual cohort cost were €2957, €453, €4411, and €2528 for 5FU+LV, Capecitabine, FOLFOX and CAPOX regimens respectively. Although a total pathway cost comparison was not possible, the actual treatment costs for adjuvant chemotherapy appeared to be lower than the theoretical costs. Findings from Herbst, Miot et al., 2018, demonstrated the complexity of CRC chemotherapy treatment, the limited chemotherapy options available in the South African public health sector, and the need to refine the clinical pathways to enhance colon cancer care.

Herbst, Lee et al., 2020, compared the findings from Herbst, Miot et al., 2018, to a private-sector CRC patient cohort for the same period. The comparative study estimated the average cost per cycle of each chemotherapy regimen using previously developed treatment guidelines and reported that more patients in the private sector cohort received second (13% vs 19%) and third-line treatments (0% vs 5%) compared to the public sector cohort. This was mainly due to the absence of third-line therapies in South Africa's public sector. The average cost per cycle was similar between the stages for the same regimens in the private sector, while the early-stage chemotherapy cost was less than

the late-stage in the public sector cohort. Comparing chemotherapy costs in the early CRC subgroup was not feasible due to the lack of access to regimens like FOLFIRI or FOLFOX in the public sector patient cohort. Similarly, newer therapies, including cetuximab and bevacizumab, were not comparable as they are unavailable in the public sector. However, when comparing the CAPOX regimen for both early and late-stage CRC, a higher cost per cycle was estimated for the private patient cohort. In summary, Herbst, Lee et al., 2020 concludes that CRC patients in the private sector have access to more approved chemotherapy regimens at higher costs than their counterparts receiving treatment in public facilities. A table summarizing the studies discussed in this empirical review is provided in Appendix 4. The table includes details such as the authors' names, publication year, country of focus, methods employed, and key findings.

6 Identification of gaps and need for further research

In South Africa, colon cancer stands as the sixth most common cause of cancer-related death in both men and women (Ferlay et al., 2024). The situation is worsened by an increased mortality-to-incidence, which signifies poor colon cancer outcomes relative to incidence. Given the current and increasing pressure to limit healthcare expenditure in many countries and the need for public health measures to control colon cancer in South Africa, a better understanding of the cost burden of colon cancer, as well as specified determinants and drivers of expenditure, is needed. Several studies, particularly in high-income countries, have explored the direct cost of colon cancer treatment and concluded that it contributes a significant economic burden on the healthcare system (Bhimani, G. Y. M. Wong et al., 2022; Kriza et al., 2013; Heisser et al., 2022). However, such cost evidence from studies in the LMICs is limited. Furthermore, many of these studies in high-resource settings have highlighted the role of the newer biological agents (Kriza et al., 2013), and in-patient hospitalisation (Laudicella et al., 2016) as the primary drivers of treatment cost. Considering the restricted availability of these biological agents in the South African public sector (Herbst, Lee et al., 2020), it becomes crucial to identify the specific cost influencers of colon cancer treatment in this setting. This underscores the primary gap identified in this review: the necessity for additional colon cancer treatment costing studies focused on identifying cost drivers specifically within the LMICs, including South Africa.

The treatment cost of colon cancer has commonly been stratified by various factors, including one or more of the following: the phases of treatment (Bhimani, G. Y. M. Wong et al., 2022; Laudicella et al., 2016; Haug et al., 2014), the disease stage (Alefan, Malhees and Mhaidat, 2017; Laudicella et al., 2016), tumour site (Haug et al., 2014; Herbst, Miot et al., 2018), and different states of the disease (Färkkilä et al., 2015). Colon tumour cases accounted for the majority (over 60%) of patients in the studies that stratified patient disease information by primary tumour site (Alefan, Malhees and Mhaidat, 2017; Haug et al., 2014), and the treatment of patients with a higher cancer stage was identified to be more cost intensive in the studies that differentiated treatment costs by stage of the disease (Alefan, Malhees and Mhaidat, 2017; Laudicella et al., 2016). This highlights the need for by-stage cost data for the treatment of colon cancer if aspects of cost saving due to early diagnosis and implementation of screening must be considered. This has influenced the decision to stratify the current study's cost estimates by cancer stage. Conversely, other studies have estimated the cost associated with a single treatment phase (Nejati et al., 2021), individual cancer stage (Sougklakos et al., 2022; Shen et al., 2020) and specific treatment components such as chemotherapy (Herbst, Miot et al., 2018; Herbst, Lee et al., 2020; Shen et al., 2020; Sougklakos et al., 2022). Two such studies; Herbst, Miot et al., 2018; Herbst, Lee et al., 2020, conducted in South Africa, have examined the cost associated with adjuvant and metastatic chemotherapy in both the public and private sector from the health insurers perspective. While these studies offer valuable insights into chemotherapy delivery within the studied context, there remains a need for broader cost data encompassing other components of colon cancert treatment from the healthcare providers' viewpoint.

Due to the differences in costing methodologies, Bhimani, G. Y. M. Wong et al., 2022 was unable to establish a standardised cost estimate for CRC treatment. This methodological diversity impacts the reliability, duplicability, and comparability of cost outcomes. Consequently, comparing the results in Haug et al., 2014 with other available cost estimates from Germany proved challenging. Similarly, Alefan, Malhees and Mhaidat, 2017 encountered the same difficulty as some studies employed a prevalence-based approach, while others were relied on expert opinion, resulting in disparate treatment cost estimates. However, this diversity can also be seen as advantageous, as it enables the

estimation of treatment costs across various settings, albeit with certain limitations associated with specific methods.

In conclusion, the literature review highlights the need for more comprehensive cost estimation as a foundation for economic evaluations (EE) in colon cancer treatment, particularly in South Africa. The existing studies reveal significant gaps in CRC treatment cost data and resource utilisation. This is particularly pertinent for LMICs, where resource constraints demand efficient allocation to maximise healthcare outcomes (Drummond et al., 2015). In the context of UHC, the integration of routine data collection and electronic health records could significantly enhance the accuracy of costing. Understanding the detailed costs associated with colon cancer treatments can lead to comprehensive economic evaluation, health technology assessment and, in turn, the development of healthcare benefits packages. Such information can be useful for budget impact analyses, which are essential for developing investment cases and national strategic plans for healthcare. By understanding the economic implications of different treatment options, policymakers can allocate resources more efficiently to improve access to essential treatments and enhance overall healthcare quality. This approach not only supports the achievement of UHC but also contributes to sustainable and equitable healthcare systems that can adapt to evolving healthcare challenges. Therefore, the findings from this literature review advocate for a systematic approach to costing and economic evaluation in colon cancer treatment, starting with detailed and accurate cost assessments as the cornerstone of effective healthcare planning and policy formulation.

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Part B

Journal manuscript

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Estimating the treatment cost of colon cancer at Groote Schuur Hospital

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1 Abstract

Background: Due to the high mortality-to-incidence ratio of colon cancer in South Africa, urgent public health measures are needed to improve treatment outcomes. Costing studies can be leveraged to understand the treatment cost burden for colon cancer, providing crucial insights for allocating resources to finance such measures. This study aims to assess treatment options and the cost of colon cancer treatment from the perspective of healthcare providers at a public healthcare facility in South Africa.

Method: The study used an ingredient-based approach to assess stage-specific colon cancer treatment costs at the colorectal clinic and combined oncology unit in Groote Schuur Hospital (GSH). The costing process involved two steps: first, treatment components were defined based on facility guidelines and verified through expert interviews, linking these components to relevant cost items for each cancer stage. Second, a bottom-up costing method was used to estimate and aggregate per-patient direct costs across treatment components for each stage. All capital items where annuitised using a rate of 3% and sensitivity analyses were conducted. All costs are reported in 2024 South African Rands (ZAR) and United States Dollars (USD).

Results: Identified colon cancer treatment components at the tertiary hospital include staging and risk assessment investigations, clinical consultations, surgery and chemotherapy. The estimated guideline-based per-patient costs for treatment are R60,156 ($3,216) for stages I and II (low-risk); R75,132 ($4,017) for high-risk stage II and stage III; and R171,935 ($9,193) for stage IV(resectable cases). Surgery represents a major treatment cost driver, with additional expenses from post-operative inpatient admissions.

Conclusion: The treatment costs for colon cancer are substantial and increase with each advancing stage. To mitigate these rising costs and reduce the healthcare burden, policies should prioritize early detection and invest in accessible, stage-appropriate interventions that can improve patient outcomes and reduce overall morbidity.

Keywords: Colon cancer, Colorectal cancer, Treatment cost, Cost estimation, Resource utilisation.

2 Background

Despite the availability of reliable screening methods and effective treatment options, colon cancer remains a significant contributor to morbidity, mortality, and economic costs worldwide (Ferlay et al., 2024; Chen et al., 2023; Institute for Health Metrics and Evaluation (IHME), 2024). With global Age-Standardised Incidence Rate (ASIR) and Age-Standardized Mortality Rate (ASMR) of 7.9 and 4.6 per 100,000, respectively, colon cancer ranks fifth in terms of incidence and seventh in terms of cancer-related mortality for both men and women of all ages (Bray et al., 2024). The global incidence of both colon and rectal cancer is expected to surpass three million cases annually by 2040 (Gunter et al., 2019; Xi and P. Xu, 2021); however, colon cancer cases are projected to be significantly higher, as the colon is affected twice as often as the rectum in colorectal cancer (CRC) cases (Arnold, Sierra et al., 2017). This rising incidence may be attributed to various factors, including population ageing, dietary changes, improved diagnostic methods, and enhanced survival rates (Brenner et al., 2011). Colon cancer incidence varies significantly across the continents, with the highest ASIR in Oceania, Europe, and Northern America, and the lowest in Africa and Asia. While Africa, despite its low incidence, experiences relatively high ASMR compared to regions with higher incidence (Ferlay et al., 2024; Bray et al., 2024). In South Africa, colon cancer ranks among the top ten most common causes of cancer-related death in both men and women of all ages, with an estimated 3,603 new cases and 3,235 deaths due to colon cancer in 2022 (Ferlay et al., 2024). With an ASIR of 6.8 and ASMR of 6.3 per 100,000, South Africa's estimated mortality-to-incidence ratio for colon cancer exceeds 0.9 (Ferlay et al., 2024), highlighting alarmingly poor colon cancer outcomes relative to incidence. Therefore, public health measures to manage colon cancer in South Africa are increasingly essential. However, the resources required to finance such measures cannot be determined without understanding the treatment cost burden of colon cancer.

South Africa, an upper middle-income country with a population of approximately 60 million in 2022, operates a large resource-constrained public sector and a smaller well-resourced private sector (Stats SA, 2024). Despite notable prioritisation of health reflected in public health expenditure exceeding 5% of GDP and accounting for around 15% of total government expenditure (World Bank Group, 2024),

inequitable access persists, driven by deep income inequality (Gini index above 60%) and widespread poverty (World Bank Group, 2024; Stats SA, 2024). Although out-of-pocket payments contribute only 8% to healthcare financing (Edet-Utan and Gooyabadi, 2021), the majority of South Africans depend on the public sector, where resource limitations affect service delivery (Ataguba, 2021). These disparities are especially evident in cancer care, where access to treatment, including chemotherapy for colorectal cancer, is more favourable in the private sector compared to the public sector (Brand, Gaylard and Ramos, 2018; Herbst, Miot et al., 2018). As the country advances toward universal health coverage, improving the efficiency and equity of resource use is essential.

Costing studies can be leveraged to estimate the cost burden associated with diseases and health interventions (Drummond et al., 2015; Vassall et al., 2017). Several studies, particularly in high-resource settings, have shown that the direct cost of treating colon and rectal cancers contributes a significant economic burden on the healthcare system (Kriza et al., 2013; Bhimani, G. Y. M. Wong et al., 2022; Bhimani, G. Y. Wong et al., 2022). In CRC costing studies that stratified patients by primary tumour site, the majority (over 60%) had colon tumours (Haug et al., 2014; Alefan, Malhees and Mhaidat, 2017). The treatment of patients with advanced cancer has been identified as more cost-intensive in studies that differentiated treatment costs by cancer stage (Alefan, Malhees and Mhaidat, 2017; Laudicella et al., 2016). This highlights the need for by-stage cost data for colon cancer treatment if aspects of cost saving due to early diagnosis and screening implementation are to be considered. The role of biological agents such as bevacizumab and cetuximab, and inpatient hospitalisation has been identified as the primary drivers of colon cancer treatment costs (Kriza et al., 2013; Bhimani, G. Y. M. Wong et al., 2022; Laudicella et al., 2016). However, considering the unavailability of these biological agents in the South African public sector as reported by Herbst, Lee et al., 2020, it becomes crucial to identify the available treatment options and specific cost drivers of colon cancer treatment in this setting. The access to and cost associated with adjuvant and metastatic chemotherapy in South Africa have been estimated from the health insurers' viewpoint using a public sector patient cohort; adjuvant chemotherapy costs were estimated at €2932 for 5FU+LV, €602 for Capecitabine, and €2239 for CAPOX (Herbst, Miot et al., 2018). Metastatic chemotherapy costs were €2957 for 5FU+LV, €453 for Capecitabine, €4411 for FOLFOX, and €2528 for CAPOX (Herbst, Miot et al., 2018).

These estimates were compared to theoretical costs from a developed chemotherapy pathway. This comparison highlighted the complexity of colon cancer chemotherapy, the limited options in the South African public health sector, and the need to refine clinical pathways to improve care (Herbst, Miot et al., 2018). More patients in the private sector receive second (13% vs 19%) and third-line treatments (0% vs 5%) compared to the public sector, mainly due to the absence of third-line therapies in South Africa's public sector (Herbst, Lee et al., 2020). Although these studies provide valuable insights into chemotherapy delivery within the specific context, there is still a need for more comprehensive cost data covering other components of colon cancer treatment.

The existing studies reveal significant gaps in colon cancer treatment resource utilisation information in South Africa. This cost evidence is particularly relevant for Low-to Middle-Income Countries (LMICs), where resource constraints demand efficient allocation to maximise healthcare outcomes (Drummond et al., 2015). Therefore, to understand the treatment options and resource requirements for colon cancer treatment in South African public healthcare, this study outlines the treatment components and associated resource use for colon cancer at a South African tertiary hospital and estimates the per-patient direct costs per cancer stage from the healthcare provider's perspective. Outlining the colon cancer treatment components and linking the relevant cost inputs by cancer stage will help inform future costing studies in the South African public health sector and other LMICs. Understanding the costs associated with the different colon cancer treatment options and the context-specific treatment cost drivers can lead to comprehensive economic evaluation, health technology assessment (HTA) and, in turn, the development of healthcare benefits packages in the context of the South African National Health Insurance. Such cost information can be helpful in budget impact analyses, which are essential for developing investment cases and national strategic plans for healthcare.

3 Methods

This study estimated the direct cost of treating a colon cancer patient at the colorectal clinic and combined oncology unit in GSH, considering each of the four cancer stages from the healthcare providers' perspective. A two-step methodology was applied: first, local experts identified treatment

components and resource use based on the facility's guidelines; second, unit costs were assigned to each item to calculate per-patient costs for each treatment component. These costs were then summed by cancer stage to determine the overall per-patient cost at each stage. All costs were estimated in 2024 South African Rands and converted to U.S. Dollars using the 2024 average annual exchange rate of \$1=R18.70 (SARS, 2024).

3.1 Identifying treatment components and resource-use

Three clinicians at the colorectal clinic and combined oncology unit, specializing in surgery and oncology, completed a researcher-administered questionnaire outlining colon cancer treatment components and healthcare resource use at GSH. Each clinician manages a weekly patient pool of about 20 CRC cases. Findings from Hendriks et al., 2014 show that clinical pathways whether based on established guidelines or daily hospital practices combined with expert opinions support disease-specific costing, especially in low-resource settings. Accordingly, a questionnaire was designed to gather data on colon cancer treatment components, associate each component with relevant cost inputs, and quantify the cost items by cancer stage. The questionnaire was structured around the facility's current *adenocarcinoma of the colon treatment protocol* (Groote Schuur Hospital, 2022). A public health physician reviewed the initial draft, and their feedback was incorporated to refine the questions. The questionnaire was piloted by interviewing a general surgeon before a final version (Appendix 2) was administered to the clinicians. Additional details, especially for identifying and measuring relevant cost items, were gathered through further discussions with other healthcare personnel and facility staff. To avoid redundancies, colon cancer stages were grouped as follows based on similarities in treatment: all stage I and low-risk stage II; high-risk stage II and all stage III (since treatment for stage II varied based on tumour and patient characteristics); and stage IV further divided into resectable, unresectable, and unfit cases based on patient fitness or surgical resectability. A split questionnaire design was used to ensure comprehensive information was obtained across all sections of the questionnaire. The surgeons focused on surgical treatments and consults, while the oncologist addressed chemotherapy and supportive management. Mixed elicitation methods improved data accuracy and richness: dichotomous and multiple-choice questions were used to confirm guideline details and provide structured data, respectively, while open-ended questions gathered information

on resource use and provided deeper insights. The information collected from the questionnaire was entered into a Microsoft Excel document, which served as the basis for developing the cost model template. To estimate per-patient guideline treatment costs, the study assumed no progression between cancer stages, considering only baseline treatment as per the protocol without accounting for disease recurrence or management of treatment-related complications.

3.2 Cost per identified treatment component

Prices for the identified cost inputs were obtained from publicly available sources, independent medical suppliers, published literature and internet searches. An ingredient/micro-costing approach was used to determine the cost inputs for each treatment component. The cost estimation included resource inputs such as personnel directly involved in patient care, building space used, equipment and procedure costs, relevant consumables, and pharmaceuticals specific to each treatment component. The overall cost per treatment component was determined by summing the costs of individual resource inputs.

The costs of equipment and furniture were determined using annualised replacement costs. The annuity function for determining the annualised replacement value considered the equipment's replacement cost and expected lifespan (in years) using a 3% rate. Replacement costs (present purchasing value) were sourced from independent medical equipment suppliers and internet searches. A lifespan of 5 to 10 years was applied, depending on the specific item. In accordance with World Health Organization (WHO) recommendations, these capital items were annualised using a 3% rate (Drummond et al., 2015; Shepard, Hodgkin and Anthony, 2000). The cost per treatment was calculated by determining the annualised cost per minute of functional use for each item and then multiplying it by the treatment duration in minutes. Similarly, the building cost for each treatment option was calculated based on the replacement value of the hospital calculated for the duration of each treatment. Replacement costs per square meter were sourced from estimates for new hospitals (Council for Scientific and Industrial Research, 2012). The original building costs were adjusted for inflation to reflect the current ZAR 2024 values using the relevant consumer price index (Statistics South Africa, 2024).

To estimate personnel costs for each treatment component, mean annual salaries were sourced from

the facility's salary notch/ total cost of employment 2023/2024 data (DPSA, 2023). Personnel costs per minute were calculated by dividing these annual salaries by the total productive working time per year. Productive working time was determined based on an average of 8 working hours per day and a total of 235 working days per year, accounting for official leave days. The personnel cost per treatment component was then calculated by multiplying the personnel cost per minute of productive work by the duration of personnel involvement in various activities related to each treatment, as obtained through the questionnaire. The bottom-up micro-costing approach was also employed to assess the costs of pharmaceuticals and consumables, requiring unit prices and patient utilisation data. Unit prices for medications were sourced from the current master health product list (National Department of Health, 2024), while prices for consumables were obtained from health equipment suppliers and internet searches. Average patient utilisation and medication doses were gathered from expert interviews and chemotherapy record sheets. The cost for each consumable and medication was calculated by multiplying its unit price by the average utilisation quantity. Given that most colon cancer chemotherapy regimens consist of multiple drug combinations, the cost per regimen was determined by summing the costs of the individual medications. The total regimen cost was then calculated by multiplying the cost of each cycle by the number of prescribed chemotherapy cycles. The costs of staging and risk assessment procedures were sourced from the National Health Laboratory Service (NHLS) price list for 2023/24 (NHLS, 2023), the Uniform Patient Fee Schedule (UPFS) (Western Cape Health Department, 2022), published literature (Johnson et al., 2023), and internet searches. The costs for inpatient post-surgical admission were obtained from the UPFS for level 3 hospitals (Western Cape Health Department, 2022). These costs were then adjusted for inflation using the relevant consumer price index to reflect current values (ssa, 2024). Table 1 summaries the methodologies, data requirements, and calculations to value each cost input.

Table 1: Methods, data requirements, and calculations to value each cost component

Cost Items	**Costing Approach**	**Data Collected**	**Calculation**
Building	Micro bottom-up	Building cost per m^2 per treatment, Expected Life years (ELY), Interest rate, Total yearly utilisation (Minutes), Building utilisation per patient per treatment component (Minutes)	Cost per m^2 × annuity function (interest rate and ELY) × building space (m^2) per treatment = Annuitised building cost per treatment. Annuitised building cost / the yearly use duration (minutes) = building cost per minute. Building cost per minute × treatment duration per patient.

Equipment	Micro bottom-up	Replacement prices per equipment, Expected Life years (ELY), Interest rate, Equipment total yearly duration of use (Minutes), Treatment duration per patient (Minutes)	Multiply replacement price by annuity function (interest rate and ELY) to obtain annuitised cost. Then, divide the annuitised cost by the yearly use duration (minutes) to obtain equipment cost per work minute. Multiply equipment cost per work minute by relevant treatment duration per patient.
Personnel	Micro bottom-up	Annual total cost of employment (TCE) to GSH, Total productive work duration (minutes per year), Treatment duration per patient	Annual TCE is divided by the yearly productive work minutes to obtain personnel cost per minute. Then, multiply the personnel cost per minute by the relevant treatment duration per patient.
Medication	Micro bottom-up	Unit prices per drug, Medication list and dose per patient	Unit prices per drug multiplied by per patient dose.

Consumables	Micro bottom-up	Unit prices per consumable, Average consumable quantities per patient	Unit prices per consumable multiplied by average quantity per patient.
Procedure/Services **Diagnostics** **Post-surgical inpatient day**	NA	Price of procedure	Individual price multiplied by average patient utilisation.

3.3 Per-patient cost for each cancer stage

To estimate the per-patient treatment cost for each colon cancer stage, the costs of each identified treatment component—such as staging investigations, pre-operative and post-operative consultations, surgery, and chemotherapy—were summed for each cancer stage. Additionally, the guideline costs for five years of follow-up care were estimated.

3.4 Identification of local treatment cost drivers

By analysing the estimated costs associated with each treatment component per cancer stage, we identified the most cost-intensive colon cancer treatment component. These components were recognized as the primary cost drivers for colon cancer treatment specific to the healthcare facility. Understanding these cost drivers is crucial for developing strategies to improve resource allocation and optimize treatment efficiencies within the healthcare system.

3.5 Sensitivity analysis

To evaluate how changes in cost model variables affect final cost estimates, sensitivity analyses were conducted. Two key cost model inputs were adjusted: (1) a 25% reduction in post-surgical inpatient days, to reflect potential efficiency gains from enhanced recovery protocols or shorter hospital stays; and (2) variations in the nursing staff cadre based on the mean annual cost of employment, to account

for differences in staffing levels and task shifting. These adjustments were made to assess their impact on the estimated treatment costs across different cancer stages.

4 Results

4.1 Treatment components and resource use

The identified treatment components for colon cancer at the facility include clinical consultations, surgery, chemotherapy, and staging/risk profiling investigations. It was found that the Multi Disciplinary Team (MDT) discussions were integrated into clinical consultations and thus considered part of the consultation costs. Interviewed experts indicated that each colon cancer case is reviewed by the MDT at least twice, regardless of stage, though higher cancer stages require more clinic visits both before and after surgery. The identified resource inputs for consultations included personnel, building, and equipment costs, with personnel costs being the primary contributor to the overall consultation and MDT costs per cancer stage.

Colon cancer patients with stages I, II, III, and those with resectable stage IV metastasis receive surgical treatment at the health facility under study. The choice of surgical procedure depends on case-specific factors and surgeon preference. Generally, a less invasive procedure is preferred for lower-stage cases, while open colectomy procedures are more commonly used for advanced stages. To ensure reproducibility, costs have been estimated for both single-sided laparoscopic and open colectomy procedures. The risk of complications following both open and minimally invasive procedures was relatively similar; however, it varied by cancer stage. Experts agreed that patients with more advanced cancer stages faced a higher risk of post-surgical complications, often requiring slightly longer inpatient admissions. For metastatic cases, the specific organ site of metastasis could not be determined through the questionnaire, as metastasis could involve the lungs, liver, or other nearby organs. However, a liver resection procedure was included in the costing, as the liver was identified as the most common site of metastasis by the interviewed experts. The identified resource inputs for the surgical treatment component included personnel, equipment, operating theatre space, medications (such as anaesthesia), necessary consumables, and post-operative inpatient admission days.

It was found that the application of chemotherapeutics was recognized for various treatment modalities, including adjuvant therapy, perioperative or conversion therapy, neoadjuvant therapy, and palliative therapy. Adjuvant chemotherapy, which is administered after surgical treatment, is recommended for all stage III cases and for stage II patients classified as 'high-risk.' This typically consists of a single-line, four-cycle treatment with capecitabine and oxaliplatin (CAPOX), given over twelve weeks. For patients with resectable stage IV cancer, the same single-line chemotherapy may be provided as neoadjuvant or adjuvant therapy, depending on specific case factors. Up to eight cycles can be administered in this context, with a computed tomography (CT) scan performed after the fourth cycle to assess the need for the additional four cycles. Palliative chemotherapy is also an option for stage IV cases that are fit for treatment but have unresectable cancer. On average, the same CAPOX regimen is used as first-line chemotherapy; if no progression is observed after the first four cycles, a second-line chemotherapy (CAPIRI) is administered for an additional four cycles. To estimate the cost of chemotherapy, resources such as personnel, chemotherapy drugs, supportive medications, equipment, consumables, and building were considered. Table 2 details the treatment options, resource components, and average per-patient utilisation quantities for each stage of colon cancer, as identified through expert interviews and included in this cost estimation.

The colon cancer risk profiling and staging investigations outlined in Groote Schuur Hospital, 2022 were confirmed by the experts as the necessary diagnostic and radiological procedures and were included in the cost analysis. Table 2 outlines the expert reported by-stage colon cancer treatment components, average per-patient utilisation and relevant cost inputs at the facility.

Table 2: Treatment components, average utilisation, and identified cost items by cancer stage

Cancer Stage	**Treatment Components**	**Average Utilisation (Quantities)**	**Relevant Cost Items per Component**
All Stage I and Low-Risk Stage II	Staging Investigations	1 each	Cost of individual procedure
	Clinical consultations	3 visits and at least 2 MDT	Building, Equipment, Personnel
	Surgery (Laparoscopic single-sided colectomy)	1 procedure	Theatre space, Equipment, Personnel, Pharmaceuticals and consumables
	Post-surgical inpatient days	6 days	Inpatient daily fees
All Stage III and High-Risk Stage II	Staging Investigations	1 each	Cost of individual procedure
	Clinical consultations	5 visits and at least 2 MDT	Building, Equipment, Personnel
	Surgery (Laparoscopic single-sided colectomy)	1 procedure	Theatre space, Equipment, Personnel, Pharmaceuticals and consumables
	Post-surgical inpatient days	6 days	Inpatient daily fees
	Adjuvant chemotherapy (CAPOX)	4 cycles	Building, Equipment, Personnel, Chemotherapy, supportive drugs, and consumables

Continued on next page

Cancer Stage	Treatment Components	Average Utilisation (Quantities)	Relevant Cost Items per Component
Stage IV	Staging Investigations	1 each	Cost of individual procedure
	Clinical consultations	6 visits and at least 2 MDT	Building, Equipment, Personnel cost
	Surgery(Open colectomy and Liver resection)	2 procedures	Theatre space, Equipment, Personnel, Pharmaceuticals and consumables
	Post-surgical inpatient days	10 days	Inpatient daily fees
	Neoadjuvant OR Adjuvant chemotherapy	6 to 8 cycles	Building, Equipment, Personnel, Chemotherapy, supportive drugs, and consumables cost
	Palliative chemotherapy (CAPOX and CAPIRI)	8 cycles	Building, Equipment, Personnel, Chemotherapy, supportive drugs, and consumables

4.2 Unit cost per treatment component

Table 3 contains the unit cost per treatment component, including consultations, surgical procedures, chemotherapy regimens, staging investigations, and post-surgical inpatient admissions. Unit costs are presented in both South African Rand (R) and US Dollars ($). A supplementary table (Appendix 5) provides a detailed breakdown and explanation of the unit cost estimations, along with the individual cost components used in the analysis. Consultation costs are presented as preoperative/postoperative and MDT costs. Surgical procedures include costs for single-sided laparoscopic and open colectomies,

as well as liver resection, relevant for patients with resectable metastasis. Chemotherapy costs are presented by regimen type, specifically CAPOX and CAPIRI. Calculation for chemotherapy medications presented are based on a 1.5kg/m2 body surface area. Unit cost per staging investigation, are detailed to include specific procedures such as colonoscopy, CT scans, and primovist MRI. Diagnostic tests such as lesion biopsy, full blood count, carcinoembryonic antigen tests renal and liver function tests , integral for staging and risk profiling, were also included.

Table 3: Unit costs for treatment components

Treatment Component	**Unit Cost (R)**	**Unit Cost (USD)**
Consultation (cost per visit)		
Preoperative/Postoperative	397	23
MDT	679	39
Surgery (cost per procedure)		
Single-sided Laparoscopic Colectomy	31,082	1,662
Open Colectomy	36,254	1,938
Liver Resection	36,261	1,939
Post-surgical Inpatient Admission (cost per day)	2198	118
Chemotherapy (cost per cycle)		
CAPOX	3,744	213
CAPIRI	1,259	71
Staging Investigations (cost per procedure)		
Colonoscopy	4,865	260
CT Scans of the Chest, Abdomen, and Pelvis	7,000	398
Full Blood Count	69	4
Lesion Biopsy	133	8
Renal Function Tests and Electrolytes	145	8
Liver Function Tests	368	21
Carcinoembryonic Antigen (CEA)	360	20
Primovist MRI	8,800	500

4.3 Per-patient cost per cancer stage

Overall guideline per-patient treatment costs of R60,156 ($3216), R75,132 ($4017) and R171,935 ($9,193) were estimated for stage I and low-risk stage II, high-risk stage II and stage III, and stage

IV(resectable cancer) cases respectively. An estimated R47,497 ($2,539) was calculated for patients with stage IV colon cancer who are fit but have unresectable tumours. These patients receive palliative chemotherapy without surgical resection of the cancer, although surgery may be performed to alleviate distressing symptoms. However, the costs presented here do not include expenses related to such palliative surgeries. Table 4 provides a summary of these calculated costs, including the estimated total treatment cost and projected 5-year follow-up costs, according to clinical guidelines, for each stage of colon cancer.

Table 4: Total per-patient treatment and follow-Up costs by cancer Stage

Cancer Stage	**Treatment Cost (R)**	**Treatment Cost (USD)**	**Follow-Up Cost (R)**	**Follow-Up Cost (USD)**
Stage I / II Low Risk	60,156	3,216	17,785	951
Stage II High Risk / Stage III	75,132	4,017	23,407	1,252
Stage IV (resectable)	171,936	9,193	51,406	2,749
Stage IV (fit but unresectable)	47,497	2,539		

4.4 Identified local treatment cost drivers

To identify the local treatment cost drivers, the percentage contribution of each treatment component to the total per-patient treatment costs was estimated and compared across different cancer stages. Surgical treatment costs, including surgery and post-operative inpatient admission, accounted for 74%, 59%, and 68% of the total per-patient costs for Stage I/II low-risk, Stage III/II high-risk, and Stage IV (resectable), respectively.

The cost of surgery was further increased by expenses associated with post-operative inpatient admission days. As illustrated by Figure 1, surgical treatment contributed over 50% of the total per-patient treatment costs for all colon cancer stages that required surgery.

4.5 Sensitivity Analysis

Figure 2 presents results for the one-way sensitivity analyses conducted. The three scenarios were compared for each cancer stage:

1. **Base case:** This represents the estimated per-patient treatment cost without any modifications.

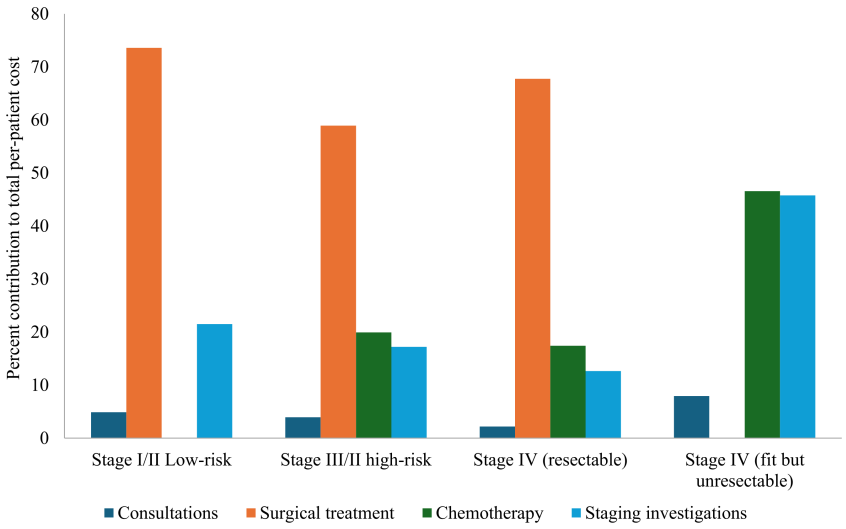

Figure 1: Percent contribution of treatment components to total per-patient costs by cancer stage

2. **Reduction in post-operative inpatient days**: This scenario models a 25% decrease in post-operative inpatient days to reflect the impact of reducing the length of hospital stay on treatment cost. A 25% reduction in post-surgical hospital days reduced per-patient costs by R3,297 ($176) for Stage I/II low-risk and Stage II high-risk/III cases, and R10,990 ($588) for Stage IV resectable cases.

3. **Lowest nursing staff grade**: This scenario assumes that the lowest grade of nursing staff are utilised to examine the effects of task shifting on the estimated guideline costs. Lowering nursing staff grade resulted in cost savings, though the effect is less pronounced compared to the reduction of post-surgical inpatient days. However, the potential effects of using lower-level nursing staff on overall treatment quality and health outcomes remain uncertain.

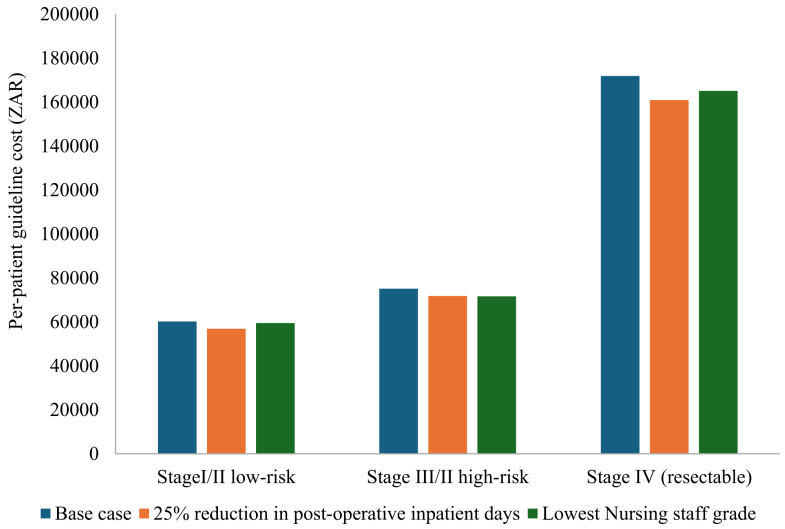

Figure 2: Sensitivity analysis

5 Discussion

This cost analysis identified the components of colon cancer treatment and, based on facility guidelines, estimated the per-patient costs for each cancer stage from the healthcare provider's perspective at a tertiary hospital in the Western Cape, South Africa. The identified treatment components for colon cancer, includes surgery, chemotherapy, clinical consultations, and various investigations for staging and risk profiling. The estimated total per-patient treatment costs for each cancer stage were as follows: R60,156($3,216) for stage I and stage II low-risk cases; R75,132 ($4,017) for high risk stage II and stage III cases; and R171,935 ($9,193) for stage IV resectable cases. A significant portion of these costs was attributed to surgery and inpatient stay post-surgery.

The findings on treatment components align with globally recognized approaches for colon cancer management. Surgery is recommended as the primary treatment modality for early-stage colon cancer (stages I and II), where the goal is often curative resection of localized tumors (Benson et al., 2021; Chakrabarti et al., 2020). In advanced stages (III and IV), our results further support the global practice of combining surgery with systemic chemotherapy to manage the heightened risk of metastatic spread (Kanthan et al., 2012; Van Cutsem et al., 2016). In resectable stage IV cases, resection of

both the primary tumor and metastatic lesions, combined with chemotherapy, may improve survival outcomes. For stage IV cases where surgical resection is not feasible, palliative chemotherapy serves as a primary treatment option, aiming to prolong life and alleviate symptoms (Van Cutsem et al., 2016). A key finding of this study is the absence of targeted therapies, which are typically used to treat late-stage colon cancer, likely due to resource constraints. Instead, systemic chemotherapy is relied upon exclusively for all metastatic sites, representing a deviation from the highest standards of care (Kanthan et al., 2012). This highlights the importance of treatment planning and efficient resource allocation to maximize outcomes within limited resources, underscoring the relevance of this study.

The total per-patient cost estimates show that the expense of providing colon cancer treatment rises significantly with advancing cancer stage. This trend, where treatment costs escalate as cancer progresses, is theoretically expected due to the increased need for advanced surgeries, extended hospital stays, more frequent consultations, and additional rounds of chemotherapy, as reflected in our findings. However, similar results have been observed in studies from high-resource settings using patient-level data (Alefan, Malhees and Mhaidat, 2017; Laudicella et al., 2016; Haug et al., 2014), which consistently show that early-stage colon cancer patients generally incur lower treatment costs compared to those in advanced stages. Although targeted therapies are typically unavailable due to limited resources (Groote Schuur Hospital, 2022), reliance on conventional surgery and chemotherapy at GSH still leads to a substantial cost increase as the cancer advances. Understanding this cost gradient has significant implications for health system planning in resource-limited environments. In South Africa, a large proportion of CRC patients present at advanced stages (Brand, Gaylard and Ramos, 2018). This trend places a significant financial strain on the government, which predominantly funds these public healthcare services (Edet-Utan and Gooyabadi, 2021; Ataguba, 2021). However, earlier colon cancer detection, achievable through efficient screening programs (WHO, 2020; WHO, 2017), could lead to substantial cost savings by reducing the number of patients requiring intensive, high-cost treatments.

Surgical treatment was identified as the most cost-intensive aspect of colon cancer management, with the high cost exacerbated by post-operative inpatient admissions. Another study conducted in

Jordan (Alefan, Malhees and Mhaidat, 2017) reported the annual direct medical costs of CRC using a retrospective cohort cost analysis. While the per-patient cost of surgery for colon cancer was higher than that of drugs and laboratory tests, the total annual cost of surgery was the lowest. This was attributed to the limited number of patients who underwent surgery, as more than 50% of the cohort was diagnosed with advanced stage IV disease, which significantly increased overall drug-related costs. In line with the findings, inpatient admission has also been identified as a major driver of colon cancer treatment costs (Nejati et al., 2021; Bhimani, G. Y. M. Wong et al., 2022). One potential solution to reduce these costs is the Enhanced Recovery After Surgery (ERAS) program. ERAS was developed in 2001 by a group of European academic surgeons, it focuses on improving the quality of recovery rather than simply accelerating it. This multidisciplinary, evidence-based approach involves optimizing outcomes through collaborative care, addressing recovery delays and complications, continuously auditing and refining management protocols (Ljungqvist, Scott and Fearon, 2017). Widely adopted in high-income countries, ERAS has substantial evidence supporting its effectiveness in improving patient outcomes, reducing hospital stay and healthcare costs (Ljungqvist, Scott and Fearon, 2017). However, the implementation of ERAS in Sub-Saharan Africa is limited, with few studies on its feasibility and efficacy in resource-poor settings (Kifle et al., 2024). Recent research in South Africa has shown promising results, indicating that successful implementation of ERAS protocols can reduce hospital stays, minimize post-operative complications (Oodit et al., 2024), and ultimately lower treatment costs. Supporting this, our sensitivity analysis results reveal that a 25% reduction in post-surgical inpatient days decreased overall treatment costs across all stages of colon cancer. The cost of surgery and inpatient days post-surgery accounted for over 50% of the overall treatment cost per cancer stage. Although the use of biological agents has been identified as a significant cost driver in treating colon malignancy (Haug et al., 2014; Kriza et al., 2013; Bhimani, G. Y. Wong et al., 2022), this factor does not apply in the current study facility. Biological agents, often used for targeted therapy, are not available within the study's healthcare setting, due to limited resources and unaffordable pharmaceutical prices. As a result, costs associated with colon cancer treatment in this context are driven by other factors, such as surgical procedures and extended hospital admissions, rather than by high-cost biological therapies.

To our knowledge, this study is the first to examine the costs associated with colon cancer treatment at a tertiary facility such as GSH in South Africa. A recent review revealed no prior studies focusing on the detailed cost structure of colon cancer treatment at this facility. However, two studies have explored CRC chemotherapy options and their associated costs across both public and private healthcare settings in South Africa (Herbst, Miot et al., 2018; Herbst, Lee et al., 2020). Consistent with findings from Herbst, Lee et al., 2020, this study confirms the absence of third-line chemotherapy options within the South African public health sector. When comparing the costs of adjuvant CAPOX for colon cancer, this study estimated a per-patient, per-cycle cost of $213, whereas Herbst, Miot et al., 2018 reported theoretical and cohort-based total costs of €2807.01 and €2239.59, respectively. For ease of comparison, these costs were converted to Rands (ZAR) using the applicable 2018 rates stated in Herbst, Miot et al., 2018, adjusted for inflation to reflect 2024 values, and then reconverted to U.S dollars using the 2024 average annual exchange rate (SARS, 2024). This resulted in theoretical and cohort-based total costs of $2852 and $2204, and per-patient costs of $17.6 and $13.6 respectively. A direct comparison between these costs is challenging due to methodological differences. For instance, comparing per-cycle costs to overall chemotherapy costs is problematic without knowing the number of cycles included in the total estimates. Additionally, the two analyses may differ in the cost components they include, further complicating a straightforward comparison.

The findings from this tertiary-level academic facility reflect the resource availability typical of tertiary hospitals in the Western Cape. Comparing these results with data from other tertiary centres and lower-tier hospitals in different provinces would offer a more comprehensive view of cost variations across the health system. Future research should prioritise cross-tier and cross-provincial analyses to support more equitable resource allocation and budgeting.

Limitations

CRC generally includes malignancies of both the colon and rectum, but this study focuses solely on the costs associated with colon tumours. While this narrower scope does not capture the complete cost burden of CRC treatment, it offers valuable cost estimates specific to colon cancer. These insights can aid in resource planning, budgeting, and policy development for managing colon cancer specifically,

which may share some treatment components with rectal cancer. Cost estimation based solely on expert opinion and guidelines, without patient-level data, is sometimes criticized for not fully capturing real-world treatment costs. However, this approach of relying on expert-driven opinion and guidelines has distinct advantages. It addresses inconsistencies commonly found in patient-level data, such as variations in data quality, incomplete records, and subjective interpretations (Drummond et al., 2015). This method is especially valuable in settings where patient-level data may be difficult to access and interpret. However, other methodological limitations and assumptions inherent in this guideline-based cost estimation can affect the comparability of reported costs with those from studies that account for colon cancer treatment variations, such as managing recurrences and complications. Assessing staff time, productive working hours and time spent per patient are ideally observed through time-and-motion studies, which involve direct observation of both staff and patients or the use of staff activity logs (Tan et al., 2009), rather than getting verbal estimates from experts. Given the ingredient-based approach used in this study, another limitation is that cost estimates rely on single-unit prices instead of bulk purchasing rates. In reality, healthcare facilities often purchase supplies in bulk, leading to significant cost savings. Therefore, using unit prices may either overestimate or underestimate actual expenses, especially if the tender price is higher than the actual cost. For more accurate cost estimates, it would be preferable to obtain direct supplier quotes based on specific product versions and bulk order volumes. Another limitation of this cost analysis is the exclusion of certain components of cancer treatment, such as palliative care, the ERAS, and the management of recurrence and treatment complications. These elements were not explicitly detailed in the facility's colon cancer treatment guidelines, nor were they sufficiently addressed in expert interviews to allow for accurate cost estimation. The omission of these cost components impacts the comparability of this study's cost estimates with other analyses that include such elements. Additionally, these components play a significant role in budgeting, resource allocation, and treatment planning. Future research should address these areas to provide a more comprehensive understanding of the full costs associated with colon cancer treatment.

6 Conclusion

The findings of this study reveal that per-patient treatment costs for colon cancer at GSH are substantial, increasing with disease progression. Surgery and inpatient admissions were identified as the most cost-intensive components of treatment. This analysis offers valuable insights into specific cost drivers for colon cancer treatment and identifies potential areas for cost-saving measures in resource-limited settings. Policymakers could consider commissioning a cost-effectiveness analysis of investing in early detection and prevention initiatives compared to the status quo, as these programs not only improve patient outcomes but also help manage overall treatment costs. By reducing the incidence of late-stage cases, an early detection strategy could alleviate the financial burden on the healthcare system, providing a sustainable approach to managing colon cancer care in resource-constrained environments.

List of Abbreviations

ASIR	Age Standardised Incidence Rate
ASMR	Age Standardised Mortality Rate
CAPOX	Capecitabine, Oxaliplatin
CAPIRI	Capecitabine, Irinotecan
CRC	Colorectal Cancer
CT	Computed Tomography
ERAS	Enhanced Recovery After Surgery
GSH	Groote Schuur Hospital
HTA	Health Technology Assessment
LMIC	Low-to Middle-Income Country
MDT	Multi-Disciplinary Team
MRI	Magnetic Resonance Imaging
NHLS	National Health Laboratory Service
UPFS	Uniform Patient Fee Schedule

WCDoH Western Cape Department of Health

Author contributions

Nnene, K.A designed the study, wrote the paper, analysed results, reviewed the paper and submitted it for publication.

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Data availability

The datasets generated and/or analysed during the current study are available from the corresponding author on request.

Ethics approval

Ethical approval was obtained from the University of Cape Town Human Research Ethics Committee (UCT_HREC Ref: 744/2023) and the Western Cape Department of Health (WCDoH). Institutional approval was also secured from GSH prior to the commencement of the study. During the expert

interviews, clinicians' privacy was maintained, and no identifying information, such as names or identity numbers, was collected.

Consent to participate

Informed consent was obtained from the interviewed experts before interviews.

Consent for publication

"Not applicable"

Competing interests

No competing interests.

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Part C

Policy brief

INVESTING IN EARLY DETECTION AND EFFICIENT RESOURCE ALLOCATION: A COST ANALYSIS OF COLON CANCER TREATMENT IN A SOUTH AFRICAN PUBLIC HEALTHCARE FACILITY

Health Economics Unit, School of Public Health
University of Cape Town

by Kelechi Nnene

KEY MESSAGES

- The high mortality-to-incidence ratio for colon cancer in South Africa signals poor outcomes, underscoring an urgent need for public health measures.
- Cost assessments for colon cancer treatment are essential to inform effective resource allocation for these measures.
- Per-patient guideline costs indicate that colon cancer treatment expenses increase significantly with advancing cancer stage.
- Surgical treatment accounts for over 50% of total per-patient costs across all colon cancer stages, with additional costs from post-operative inpatient stays.

The need for cost insights: setting the context

Despite reliable screening and effective treatments, colon cancer remains a major cause of morbidity, mortality, and economic burden worldwide. (Ferlay et al., 2024; Chen et al., 2023).

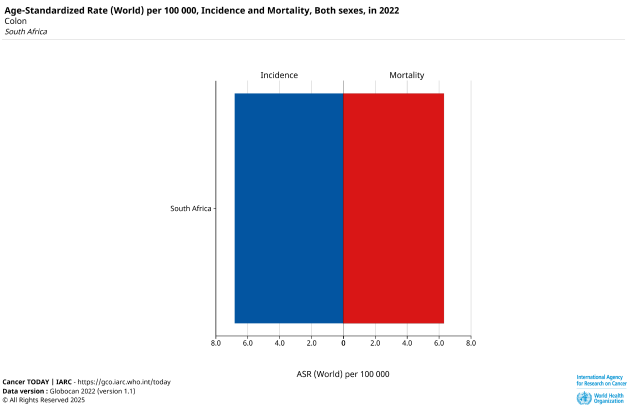

Figure 1: Colon cancer incidence vs mortality for South Africa

With the high number of deaths compared to new cases of colon cancer, it is crucial to implement public health measures to manage colon cancer in South Africa. However, the lack of reliable cost data hinders understanding the resources required to fund these measures. This policy brief summaries a costing study that was conducted at a tertiary facility in Western Cape, South Africa.

Research approach and findings

The study determined the costs of treating colon cancer at different stages by breaking down each part of the treatment. The research used a two-step plan: First, clinical experts defined the colon cancer treatment components and linked each component to the relevant cost items. Next, we estimated the cost of each item required to treat one patient and summed them up to find out how much the overall treatment would cost.

- Estimated per-patient costs are: R60, 156 ($3,216) for stages I/II(low-risk); R75, 132 ($4,017) for stage III/II (high-risk); R171,935 ($9,193) for stage IV (resectable); and R47,497 ($2,539) for stage IV(unresectable).
- Surgery and inpatient admissions contributed the largest share of the overall treatment costs.

Figure 2 show a breakdown of the treatment cost by cancer stages and the various identified treatment components. While figure 3 presents the percentage share of per-stage cost in the cumulative total.

Insights and recommendations

Findings from the study indicate that the per-patient treatment cost of colon cancer is

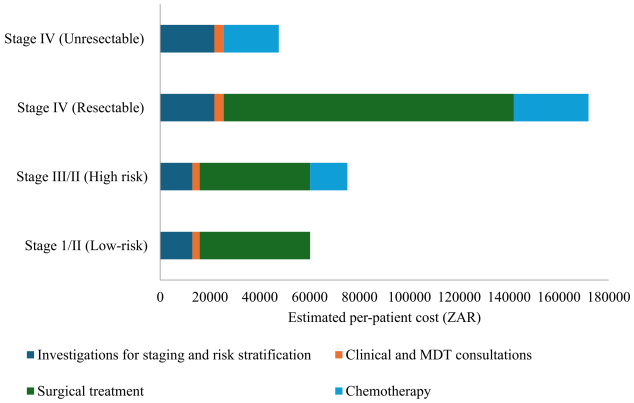

Figure 2: Breakdown of total per-patient costs by cancer stage and treatment component Source: Author's computation

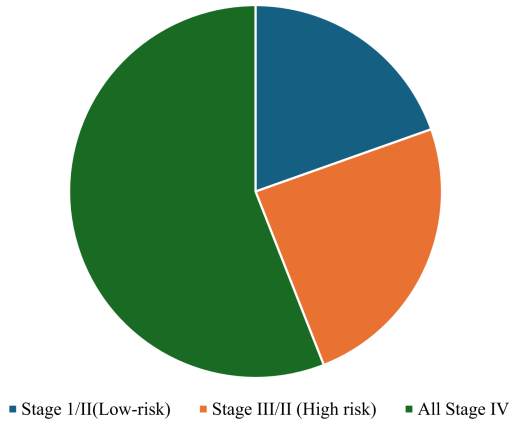

Figure 3: Percentage share of per-stage costs in the cumulative total
Source: Author's computation

significant and increases as the disease progresses. Advanced-stage cases require more cost intensive treatment, leading to increased expenses for the healthcare system. Surgery and the associated inpatient stay emerged as major cost drivers, accounting for over 50% of the total treatment expenses.

Recommendations to support cost-saving measures and enhance patient outcomes

- Policymakers should prioritize early detection and prevention programs to minimise the high per-patient treatment costs that increases with colon cancer progression. These initiatives improve patient outcomes and help lower the number of late-stage cases (WHO, 2017), thereby reducing the overall cost burden on the healthcare system.

- Given that surgery and inpatient admissions are the most cost-intensive aspects of colon cancer treatment, efforts to optimise these areas could yield significant savings. This may include enhancing surgical efficiency, and implementing clinical protocols proven to minimize inpatient stay post-surgery such as the Enhanced Recovery After Surgery (ERAS) program.

- The development of clinical guidelines that emphasize cost-effective treatment strategies will manage expenditure while maintaining patient outcomes. Achieving this calls for strengthened research and capacity-building initiatives to support more comprehensive economic evaluations.

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1 Appendix 1: Research Protocol

1.1 Background

Cancer remains a leading cause of death worldwide, and in 2018 it was responsible for one out of six deaths (World Health Organization, 2020). In 2020, over 19 million new cases and almost 10 million deaths from cancer were estimated to have occurred, with a predicted increase of 47% by 2040 (Ferlay et al., 2024). Globally, colorectal cancer CRC ranks fourth in terms of incidence and third in terms of cancer-related mortality in both men and women of all ages (Ferlay et al., 2024). With estimated age-standardised incidence rate ASIR and age-standardised mortality rate ASMR rates of 18.4 and 8.1 per 100,000, respectively (Ferlay et al., 2024). In 2022, over 1.9 million new cases and 900,000 deaths attributed to CRC were recorded, accounting for approximately 9.6 and 9.3 per cent of global cancer incidence and mortality, respectively (Ferlay et al., 2024). In 2022, colon cancer exhibited a global ASIR of 10.7 per 100,000 ranking fifth in terms of cancer incidence (Re). The incidence rate in high-resource countries is approximately four times higher than in lower-resource countries (Sung et al., 2021). This has led to the recognition of colon cancer as a marker of socioeconomic development (Fidler, Soerjomataram and Bray, 2016; Bray et al., 2024). Over time, an increase in the incidence rate of both colon and rectal cancers has been reported in many countries within Eastern Europe, Asia, and South America (Arnold, Sierra et al., 2017; Arnold, Abnet et al., 2020). This increase in regions formerly considered low-risk is likely a result of shifts towards the lifestyle and dietary risk factors of colon cancer (Arnold, Sierra et al., 2017; Arnold, Abnet et al., 2020). On the other hand, declines in the incidence of colon cancer in some high-risk countries mainly since the early 2000s have been attributed to population-level shifts toward healthier lifestyles, and to colonoscopy screening and removal of precursor lesions (Arnold, Abnet et al., 2020). Over the past decades, a global surge in the incidence of young-onset colorectal cancer yCRC has been noted (Vuik et al., 2019). This signifies increased CRC occurrence in regions with a significant youth population once considered low risk. This trend carries both epidemiologic and economic implications, leading to an increased burden on the healthcare systems as they contend with a rising number of colon cancer patients. On the other hand, colon cancer ranks seventh in terms of cancer-related mortality with an ASMR of 4.7 per 100,000 (Ferlay et al., 2024). Unlike the incidence, the estimated mortality rates of colon cancer is relatively less diverse

across geographical regions, ranging from 7.7 per 100,000 in Europe to 2.9 per 100,000 in Africa (Ferlay et al., 2024). Notably, while Africa has the lowest estimated ASIR and ASMR for colon cancer, it also exhibits the highest mortality-to-incidence ratio in the world (Ferlay et al., 2024). This ratio signifies poor outcomes relative to the incidence rate, indicating the need for improved strategies for colon cancer treatment in the region. Therefore, Public Health efforts to control colon cancer are increasingly important and will require necessary resource provision. However, as the health systems expand due to the need to provide treatment for an increasing population of patients, understanding the resource requirement for colon cancer treatment and management is essential.

The Southern African region bears the most significant burden of colon cancer in Africa; both colon and rectal cancers accounted for 147,780 DALYs in the southern sub-Saharan African region in 2019 (Sharma et al., 2022). The incidence of CRC in South Africa follows an international trend as one of the most diagnosed cancers, and colon cancer stands as the sixth most common cause of cancer-related death in both men and women, with an ASIR of 6.8 per 100,000 and ASMR of 6.3 per 100,000 (Ferlay et al., 2024). Worryingly, more than half of the individuals diagnosed with this disease within South Africa succumb to it, highlighting the severity of the condition. In a study describing the presentation of colon cancer patients in a privately insured population in SA, Brand, Gaylard and Ramos, 2018 reported that one- third of the patients presented with liver or pulmonary metastasis. Another study, L. Prodehl et al., 2020, in the public sector in Gauteng discovered that 38.9% of participants had distant metastatic disease at the time of presentation. Late presentation increases the likelihood of tumour recurrence even after surgical treatment (Guraya, 2019), placing a greater demand on the healthcare system. Considering the increasing burden of colon cancer and trends of late presentation among these patients in South Africa, there is a need for information on the health system costs of colon cancer treatment. This cost can be determined through costing studies. The results from costing studies are an essential tool for further health economic evaluations and can inform decision-making and planning of healthcare services. The treatment of Colon cancer differs from that of rectal cancers and usually involves surgery, chemotherapy, and other targeted therapies, usually depending on the stage at presentation and tumour site. The treatment cost varies depending on the type and duration of treatment, availability and affordability of medications and clinical services (brand). In the United States (US), the cost of treating CRC in 2018 was estimated to be US $16.6 billion (Bhimani, G. Y. M. Wong et al., 2022), this shows

that the treatment of colon cancer is costly and places a tangible financial burden on governments, healthcare systems, patients, and their families. Therefore, colon cancer places a significant burden on the South African health system. It becomes essential to understand the economic burden and, specifically, the healthcare costs from the provider's perspective, which include the costs directly related to the medical treatment for patients. This cost reflects the economic impact of colon cancer treatment on the health system and is relevant for CRC treatment planning. Groote Schuur Hospital (GSH) is a tertiary care academic health facility in Cape Town, in the Western Cape Province of South Africa which provides specialised services for patients with colon and rectal malignancies. However, there is a dearth of relevant information on the treatment cost of colon cancer in GSH.

1.2 Study rationale

The background above indicates the global burden of colon cancer regarding incidence and mortality. It also highlights the increasing incidence of yCRC. Additionally, the incidence of colon cancer has been observed to be rising in countries where incidence was once low due to changes in population structure, behavioural lifestyle, and dietary habits (Arnold, Sierra et al., 2017; Arnold, Abnet et al., 2020). South Africa is an upper middle-income country which bears an appreciable burden of colon cancer in Africa (Ferlay et al., 2024). Understanding the cost of treatment for colon cancer in South Africa is important due to its increasing incidence and the conflicting budgetary constraints within the health system. With the advent of National Health Insurance in South Africa as a means to achieve Universal Health Coverage (Ataguba and McIntyre, 2018), knowing the cost of healthcare for specific diseases becomes relevant to guide budget allocation as understanding the cost of healthcare delivery is a prerequisite for allocating health resources (Drummond et al., 2015). Despite this, relevant data on the cost of treating colon cancer in South Africa still needs to be explored, with limited information on the treatment cost drivers and differences in the treatment cost by stage at diagnosis at Groote Schuur Hospital GSH. A review of the relevant literature shows that there is no existing study that has estimated the cost of colon cancer treatment from the provider's perspective at GSH. Two Previous studies on the cost of CRC in South Africa Herbst, Miot et al., 2018; Herbst, Lee et al., 2020 have focused on the cost of chemotherapy from the health insurer's perspective.Therefore, this study seeks to estimate the cost of treatment for colon cancer at GSH from the healthcare provider's perspective

using an ingredient-based costing approach. Adopting the health systems perspective is rational as this perspective will estimate the resource inputs required by the public healthcare system to provide colon cancer treatment at the health facility under study. A majority of the existing literature on the cost of colon cancer treatment report that the health facility cost comprised a large share of the direct treatment cost (Kriza et al., 2013; Bhimani, G. Y. M. Wong et al., 2022). Considering the greater demand for public healthcare financing in South Africa (Ataguba, 2021), understanding the resource requirement for treating colon cancer at a public healthcare facility will provide cost data that guides planning and efficient resource allocation. Furthermore, studying the cost from the healthcare perspective will aid the identification of specific treatment components of colon cancer that are exceptionally costly, thereby focusing attention on how to adopt more cost- effective approaches in the future. A better understanding of the health system's cost burden and the specific drivers of colon cancer treatment cost is needed to inform health service planning and to improve colon cancer healthcare delivery.

1.3 Mini literature review

This brief review presents a summarised introduction to the epidemiologic and economic burden of colon caner. A short background on the costing concepts, an assessment of previous empirical studies estimating the cost of colon cancer treatment is also presented.

1.3.1 The burden of colon cancer

Colon cancer constitutes the most substantial portion of the burden related to CRC, both in terms of incidence and mortality. In 2022, colon cancer exhibited a global ASIR of 10.7 per 100,000 ranking fifth in terms of cancer incidence (Ferlay et al., 2024). The estimated incidence of colon cancer demonstrates a marked regional variation, with the highest ASIR in the Oceania region (19.8 per 100,000) and least estimated rates in Africa (4.3 per 100,000) (Ferlay et al., 2024). Based on data from Ferlay et al., 2024, the number of new colon cancer cases positively correlates with an increase in the Human Development Index HDI. Colon cancer has been recognized as a marker of socioeconomic development (Fidler, Soerjomataram and Bray, 2016), with incidence rates in developed countries approximately four times higher than in developing countries (Sung et al., 2021). A continuous rise in the number of new colon

cancer cases has been reported in countries with medium to high HDI by M. C. S. Wong et al., 2021. On the other hand, colon cancer ranks seventh in terms of caner mortality with an ASMR of 4.7 per 100,000 (Ferlay et al., 2024). Compared to its incidence, the estimated mortality rates of colon cancer is relatively less diverse across geographical regions, ranging from 7.7 per 100,000 in Europe to 2.9 per 100,000 in Africa (Ferlay et al., 2024). In South Africa, colon cancer is among the top ten leading cancers in terms of incidence and mortality, with an ASIR of 6.8 per 100,000 and ASMR of 6.3 per 100,000 (Ferlay et al., 2024).

Colon cancer is associated with increased economic expenditure worldwide (Chen et al., 2023; Bhimani, G. Y. M. Wong et al., 2022). With the rise in colon cancer incidence due to population ageing (Arnold, Sierra et al., 2017), this global economic burden is expected to increase in the future. The costs related to the diagnosis, treatment, and management of colon cancer, along with the economic burden of lost productivity and life years, contribute to the overall economic impact of the disease. The economic burden associated with colon cancer encompasses both direct and indirect medical costs, as discussed by Orangio, 2018. Direct costs pertain to the expenses incurred for resources used in diagnosing and treating colon cancer; the healthcare system usually bears these costs. On the other hand, indirect costs are associated with productivity losses related to colon cancer treatment both for patients and their caregivers (family) and contribute to the societal burden of colon cancer. Chen et al., 2023 reports that out of twenty-nine cancers studied, CRC is among the top five cancers contributing 50% of the total global economic burden of cancer. CRC alone is estimated to yield total macroeconomic cost of INT $2012 to 3749 billion (International Dollars) between 2020 and 2050 in 204 countries (Chen et al., 2023).The economic burden of colon cancer is unevenly distributed across world regions and income levels, while high-resource countries bear the largest macroeconomic costs, the LMICs experience the greatest human toll (Chen et al., 2023). This highlights the need for health system strengthening and implementation of relevant public health policies. Without such advancements, as the incidence of colon cancer continues to rise in the LMICs, the growing economic costs will add to the already substantial human burden they face.

1.3.2 Background on costing

According to Vassall et al., 2017, costing refers to estimating the cost of a health intervention or service in a specific context. As the definition clearly states, many issues concerning costing are context-specific (Drummond et al., 2015), therefore, the methods adopted for costing differ. Costs can be economic or financial, be derived normatively or empirically using a micro or gross costing approach. Different aspects of healthcare costs can be assessed depending on the perspective of the costing. A perspective defines the costing point of view and could be the healthcare provider, payer (patient or third-party) or societal perspective. However, defining the purpose of the cost estimation is a critical determinant of this perspective and other methodological choices of costing (Drummond et al., 2015; Vassall et al., 2017). Costing is done for several purposes including economic evaluation or priority-setting processes. This involves using cost estimates in the analytical determination of allocative efficiency that informs decision-making usually through cost-utility analyses. Secondly, results from costing studies are used to assess technical efficiency usually through cost-effectiveness analyses. Using cost figures to predict expenditure informs budgetary allocation and price setting. Finally, costing provides cost-helpful information for financial planning and the assessment of resource utilisation. This supports national planning, provides evidence for making an investment case and guides efficient resource distribution (Drummond et al., 2015). Disease-specific costing gives an idea of the resources required to provide specific health interventions and aid in identifying areas of inefficiency and aspects that drive cost (Mogyorosy and P. Smith, 2005). When performing disease-specific costing, cost items can be valued using bottom-up and top-down approaches. The approach to use is a vital decision that affects the costs and the resources required to conduct the cost study (Cunnama et al., 2016). While the step-down approach uses formulae that allocate overall expenditure to each input to determine unit costs, the bottom-up approach uses detailed action such as input utilisation data from records (or observed utilisation) to estimate unit cost (Batura et al., 2014; Cunnama et al., 2016).

1.3.3 Estimating the treatment cost of colon cancer

An international systematic review Kriza et al., 2013 on the CRC cost of illness described the development of CRC-related costs and highlighted important cost drivers. Most of the studies analysed by Kriza et al., 2013 adopted a third-party (health insurance) perspective and long-term costs for

CRC of up to $50,175 per patient (2008 values) were estimated. The cost burden estimates were stratified by phase of treatment, and most of the studies reported that the initial and terminal phases of treatment were the most expensive, while the continuing treatment phase was found to be the least costly. Kriza et al., 2013 reported the use of biological agents such as cetuximab and bevacizumab as identified cost drivers in CRC treatment. With advancements in the medical management of colon cancer over the past two decades and the need to focus on the direct healthcare costs, another study, Bhimani, G. Y. M. Wong et al., 2022, that systematically analysed seventeen studies examining the lifetime direct medical costs of treating CRC by phase of care was reviewed. All the seventeen studies analysed were from high-income countries; this highlights the need for more cost information on the management of colon cancer in LMICs. Again, most studies adopted the health insurer's perspective. Both retrospective case-control and retrospective-cohort study designs were used to estimate the real-life direct costs of treating CRC. Overall, Bhimani, G. Y. M. Wong et al., 2022, reported that the initial phase cost ranged from $7,893 to $60,289, the continuing phase from $2,323 to $15,744, and the terminal phase from $15,916 to $99,687. In agreement with Kriza et al., 2013, the continuing treatment phase cost the least. However, there were differences in the cost estimates based on the type of study; while the initial and terminal phase costs estimated from case-control studies were greater than those from the cohort studies, the cohort studies estimated higher costs for the continuing phase compared to the case-control studies. Laudicella et al., 2016 estimated the cost of care for CRC in England separately for patients between 18 and 65 years and those above 65 years through the health provider's viewpoint. The cost estimates were compared by disease stage and to a population without cancer. Laudicella et al., 2016, reported that hospital care due to CRC cost the health system 542 million pounds in 2010 and that a lower-stage diagnosis is associated with more significant cost savings across both age groups. Cost evidence has also been published on the direct treatment cost of metastatic CRC (Bhimani, G. Y. Wong et al., 2022). Sougklakos et al., 2022 presents the cost of pharmaceutical drug use and associated medical resources utilised in the management of metastatic disease in Greece. Shen et al., 2020 reported the cost of chemotherapy by line of treatment for patients with metastatic colorectal cancer in China. The costing done in Sougklakos et al., 2022 was based on a two-step approach methodology which has been adopted for the current study. First, a panel of experts identified the metastatic CRC treatment pathways and associated resource use.

Secondly, the total cost for each pathway was estimated, using an ingredient-based method. Studies have estimated the cost of chemotherapy for CRC in South Africa (Herbst, Miot et al., 2018; Herbst, Lee et al., 2020). Herbst, Miot et al., 2018 developed and costed the clinical treatment pathways for CRC chemotherapy in the South African public healthcare facility and compared this theoretical cost to the empirical cost for a patient cohort. Findings from Herbst, Miot et al., 2018 demonstrated the complexity of CRC chemotherapy and the need to refine the clinical pathways. Herbst, Lee et al., 2020 compared the findings from Herbst, Miot et al., 2018 to a private-sector CRC patient cohort for the same period. The average cost per cycle of each chemotherapy regimen was estimated using already-developed treatment guidelines. Herbst, Lee et al., 2020 reported that more patients in the private sector cohort received second (13% vs 19%) and third line treatments (0% vs 5%) compared to the public sector cohort. This was mainly due to the absence of third line treatments in South Africa's public sector. The average cost per cycle was similar between the stages for the same regimens in the private sector, while the early-stage chemotherapy cost was less than the late-stage in the public sector cohort. However, both studies focused on the direct treatment cost of chemotherapy for CRC using the third-party (Insurers) perspective. Therefore, there is a need to estimate the overall cost of care for CRC from other relevant perspectives in South Africa. Although this analysis focuses on direct healthcare system costs, incorporating additional perspectives—such as patient out-of-pocket expenses and broader social care costs—would provide a more comprehensive estimate of the overall cost of care for colorectal cancer. This is particularly important for informing policies aimed at financial risk protection and equitable access to care.

1.4 Study aim and objectives

1.4.1 Study aim

The overreaching aim of this study is to identify the colon cancer treatment options and estimate the direct cost of colon cancer treatment at GSH from the healthcare providers' perspective using an ingredient-based costing approach.

1.4.2 Specific objectives of the study

1. To outline the treatment components and relevant direct treatment cost inputs of colon cancer per disease stage through expert interviews based on the GSH colon cancer treatment guideline.
2. Estimate the total per-patient direct medical cost of colon cancer per disease stage.
3. Identify the cost drivers of colon cancer treatment at GSH.

1.5 Conceptual framework

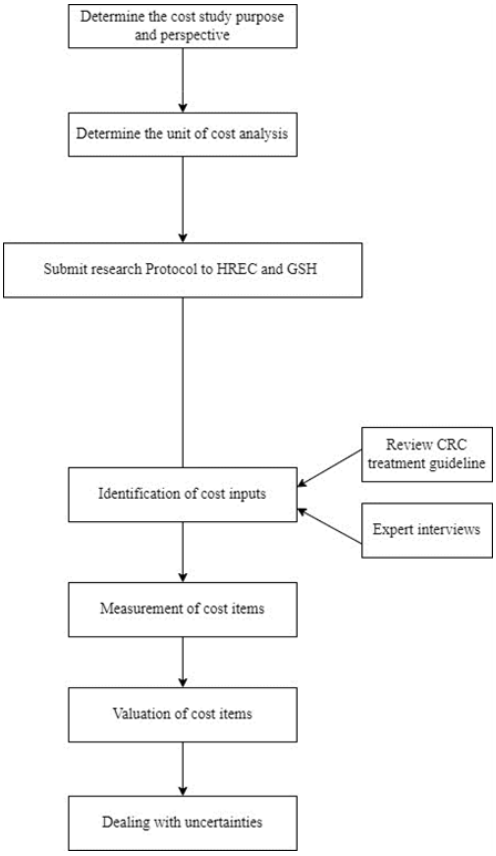
The costing study will use a micro/ingredient-costing framework. This costing framework provides a detailed and accurate approach to estimating the costs of healthcare interventions by examining the specific resources utilized in the provision of the healthcare service under consideration. Unlike gross-costing, which relies on broader, aggregated estimates, micro-costing focuses on the cost of individual services, treatments, and procedures by itemizing each resource involved (Drummond et al., 2015; Tan et al., 2009). Ingredient-costing involves three key steps: identifying the resources used in the intervention or treatment, measuring the quantity of each resource, and assigning a monetary value to them. A proposed workflow for the study based on the micro-costing framework is presented in Figure (4).

1.6 Methods

1.6.1 Study design and setting

This will be an expert based real-life costing study to determine the total per-patient treatment cost of colon cancer from the healthcare provider's perspective. All costs will be estimated in 2024 South African Rands (ZAR) and converted to United States DollarUnited States Dollar (USD) using the average exchange rate for the year. The study site will be the CRC clinic and combined colorectal oncology unit in GSH.

Figure 4: Proposed Micro-costing workflow



Source: Adapted from Hendriks et al., 2014

1.6.2 Costing approach

The study methodology will follow a two-step approach. First, the colon cancer treatment components and associated resource inputs per cancer stage will be identified through a structured expert interview based on the health facility's colon cancer treatment guidelines. According to Hendriks et al., 2014, clinical pathways based on guidelines, expert opinion or daily clinical practice in a hospital can support disease-specific costing. Secondly, using mainly a micro-bottom-up costing technique, the per-patient cost for each identified input per treatment component will be estimated by assigning unit costs to each input, and aggregated across all treatment components per stage to give the total per-patient cost of each colon cancer stage.

Following a review of the GSH colon cancer treatment guideline (Groote Schuur Hospital, 2022), a questionnaire will be designed and administered to the relevant local clinical experts. These interviews will outline the available treatment options, link them with relevant cost items, and provide measurements for the identified cost items.

Using a mix of micro bottom-up and top-down costing approaches, the unit cost for each direct cost item per cancer stage will be estimated and summed up to give the total cost for each treatment option per cancer stage. The total cost for each treatment component per cancer stage will then be summed up to give the total treatment cost per stage of colon cancer.Although the study adopts a micro costing approach for the identification of cost items, the constrained hospital and resource environment warrants a mixed-method valuation approach as has been recommended for facility-based costing studies especially in LMICs (Guerre, Hayes and Bertaux, 2018; Hendriks et al., 2014; Cunnama et al., 2016). The bottom-up valaution method will be used to estimates costs for direct cost items to be considered in the study, which include personnel involved in direct patient care, equipment and procedures that could be assigned to a specific treatment, consumables for specific therapies, and medications. While the step-down costing method will be used to account for overhead cost and cost of procedures where applicable. Table (1) outlines the potential treatment components, identified cost components, proposed valuation method and source of data. It's important to note that following expert interviews and design of a costing pathway, some variables identified in the table may undergo adjustments to better reflect the specific context and requirements of the study.

Expected treatment component	**Cost component**	**Anticipated valuation method**	**Data source**
Consultations	Building and Equipment cost Personnel cost	Bottom-up	Centre for scientific and Industrial Research. GSH finance and Human Resources.
Diagnostics	Cost of procedure	Top-down	NHLS Price-list.

Surgery	Building and Equipment cost Personnel cost Medication cost Post-surgical inpatient cost	Bottom-up	Centre for scientific and Industrial Research. GSH finance and Human Resources. Essential medicines list.
Chemotherapy	Building and Equipment cost Personnel cost Medication cost Relevant consumables	Bottom-up	Centre for scientific and Industrial Research. GSH finance and Human Resources. Essential medicines list.

Table 1: Anticipated treatment components, cost components, proposed valuation method and source of data

1.6.3 Identification of treatment cost drivers

Looking through the total cost for each treatment component per cancer stage , the most cost-intensive treatment components were identified as the GSH-specific colon cancer treatment cost drivers.

1.6.4 Sensitivity analysis

Due to some uncertainties that may influence the cost estimates, a simple one-way sensitivity analysis will be done to determine the robustness of cost estimates. Sensitivity analyses will be conducted to assess the impact of varying the measured or observed utilisation data.

1.6.5 Data analysis and handling

The utilisation, financial and expenditure information will be collected using appropriately designed data collection instruments. The instruments will be reviewed and checked for errors at the throughout the data collection period. The data will be entered into Microsoft Excel (Microsoft Corporation, USA) for quality evaluation and analysis.

1.7 Expected results and implication of the study

At the end of the study, each identified colon cancer treatment component will be connected to the relevant cost inputs. This will be a potential framework for future colon cancer costing studies in GSH and the South African public health sector. Estimating the total per-patient treatment cost for the four disease stages will provide an idea of the financial burden of colon cancer on the health facility. This will be useful for planning and budgeting to inform colon cancer healthcare delivery and serve as evidence for further research to strengthen the implementation of relevant colon cancer control programmes. Finally, identifying the GSH-specific cost drivers of colon cancer treatment will inform the need for further economic evaluation analysis to guide policy decision-making.

1.8 Possible difficulties and solutions

The lack of similar studies in the same setting will make the validation/comparability of the findings against other studies difficult. The finding will be discussed in line with empirical evidence from other available settings as a solution to this challenge. The availability and access to the relevant clinical experts, financial data and expenditure information is another possible challenge. Appropriate permissions will be obtained to enable access to required financial and expenditure data. Secondary cost data will also be used if necessary.

1.9 Ethical consideration

A research protocol will be completed and submitted to the Human Research Ethics Committee of the faculty of Health Sciences at the University of Cape Town and the school of Public Health Department Research Committee. Permission to execute the study in GSH will also be obtained before the study. The study involves interviewing a few medical experts and collecting necessary cost data.

1.9.1 Voluntary participation

Clinical experts who wish to participate in the study will be given an informed consent form (Appendix 2). The decision to participate in this study is voluntary. If you decide not to participate in this study, you may withdraw from your participation at no cost.

1.9.2 Potential risks and benefits

This study poses no known potential harm or risk, and the final findings will be communicated to the health facility if requested.

1.9.3 Privacy and confidentiality

Data will be collected in a de-identified manner, and no personal or identifiable records of the health professionals will be obtained. All obtained information will remain private and confidential and will be used only for the study.

1.10 Proposed timelines

Events	**Aug 2023**	**Sept 2023**	**Oct 2023**	**Nov 2023**	**Dec 2023**	**Jan 2024**
Finalise protocol and submit to DRC and HREC	X					
DRC and HREC approvals		X				
Write up structured literature review		X	X			
Data collection and analysis			X	X		
Write up journal manuscript and policy brief				X	X	
Submit first draft of thesis write up					X	
Submit dissertation						X

Table 2: Gantt chart

1.11 Budget

The study will be self-funded for the master of Public Health Dissertation specialising in Health Economics. The African Awareness of Cancer and Early Diagnosis African aWAreness of CANcer and Early Diagnosis (AWACAN-ED) project supports the research. AWACAN-ED is a UK Government's National Institute for Health and Care Research funded project advancing early cancer diagnosis in Southern Africa.

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2 Appendix 2: Expert questionnaire

Expert questionnaire

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Not shared

Stage I and Low-risk stage II

In your opinion, what percentage of colon cancer patients treated at GSH are diagnosed with stage I cancer, on average

Your answer

In your opinion, what percentage of colon cancer patients treated at GSH are diagnosed with low-risk stage II cancer, on average

Your answer

Diagnostic investigations

On average, can you confirm that lesion biopsy, colonoscopy, CT scans of the chest, abdomen and pelvis, full blood count, electrolytes, renal function tests, liver function tests and carcinoembryonic antigen (CEA) are required investigations for the diagnosis, staging and risk profiling for treating stage I and low-risk stage II colon cancer at GSH?

Choose

If false or others, please specify

Your answer

Treatment components

On average, can you confirm that the treatment for stage I and low-risk stage II colon cancer at GSH primarily involves clinical consultations and surgery?

Choose

If false or others, please specify

Your answer

Identify and measure relevant cost inputs for clinical consultations.
On Average, will you let me know the following about the pre-operative consultations for the treatment of stage I and low-risk stage II colon cancer at GSH.

Estimated number of consultations (or frequency):

Your answer

Estimated duration of each consultation (in minutes):

Your answer

Personnel required for each consultation (Cadre and quantity):

Your answer

Consultation space/room:

Your answer

Relevant medical supplies (consumables):

Your answer

Relevant medical equipment (note shared equipment):

Your answer

In your opinion, on average, would the pre-operative clinical consultation described above be similar for the treatment of other cancer stages (i.e. stage III and IV colon cancer)?

Choose

Identify and measure relevant cost inputs for post-operative clinical consultations.
On Average, will you let me know the following about the post-operative consultations for the treatment of stage I and low-risk stage II colon cancer at GSH.

Estimated number of consultations (or frequency):

Your answer

Estimated duration of each consultation (in minutes):

Your answer

Personnel required for each consultation (Cadre and quantity):

Your answer

Consultation space/room:

Your answer

Relevant medical supplies (consumables):

Your answer

Relevant medical equipment (note shared equipment):

Your answer

In your opinion, on average would the post-operative clinical consultation described above be similar for the treatment of other cancer stages (i.e. stage III and IV)?

Choose

Identify and measure relevant cost inputs for Surgery
Please inform me about the surgical treatment for stage I and low-risk stage II colon cancer at GSH, on average.

What is the standard surgical procedure for stage I and low-risk stage II colon cancer at GSH:

Your answer

Who are the personnel required for the surgery? (Note cadre and quantity)

Your answer

Estimated duration of surgical procedure:

Your answer

Which operating room/theatre is used?

Your answer

Operative equipment :

Your answer

Operative medication:

Your answer

Relevant consumables:

Your answer

Is there anyone you think I can talk to to find out more about the surgical procedure?

Choose

If yes, please specify

Your answer

Briefly describe the in-hospital post-surgical management

Your answer

How would you rate the probability of surgical complications

Choose

Follow-up treatment

Could you provide me with information regarding follow-up management for stage I and low-risk stage II colon cancer at GSH, on average?

Kindly confirm that annual post-surgical clinical assessment and CEA tests for five years is the follow-up treatment for patients with stage 1 and low-risk stage II colon cancer not requiring adjuvant chemotherapy and without recurrence.

Choose

If false or others, please specify

Your answer

Back Next Clear form

Expert questionnaire

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Not shared

Stage III and High-risk stage II

In your opinion, what percentage of colon cancer patients treated at GSH are diagnosed with high-risk stage II cancer, on average

Your answer

In your opinion, what percentage of colon cancer patients treated at GSH are diagnosed with stage III cancer, on average

Your answer

Diagnostic Investigations

On average, can you confirm that lesion biopsy, colonoscopy, CT scans of the chest, abdomen and pelvis, full blood count, electrolytes, renal function tests, liver function tests and carcinoembryonic antigen (CEA) are required investigations for the diagnosis, staging and risk profiling for treating stage III and high-risk stage II colon cancer at GSH?

Choose

If false or others, please specify

Your answer

Treatment components
Can you confirm the treatment components for high-risk stage II and stage III colon cancer at GSH on average?

On average, can you confirm that the treatment for stage III and high-risk stage II colon cancer at GSH primarily involves clinical consultations, surgery and adjuvant chemotherapy?

Choose

If false or others, please specify

Your answer

Identify and measure relevant cost inputs for clinical consultations.
On Average, will you let me know the following about the pre-operative consultations for the treatment of stage III and high-risk stage II colon cancer at GSH (or would you say it would be the same as for stage I and low-risk stage II above)

Estimated number of consultations (or frequency)

Your answer

Estimated duration of each consultation (in minutes)

Your answer

Personnel required for each consultation (cadre and quantity):

Your answer

Consultation space/room:

Your answer

Medical supplies (consumables):

Your answer

Medical equipment (Note shared equipment):

Your answer

***Identify and measure relevant cost inputs for clinical consultations*.**
On Average, will you let me know the following about the post-operative consultations for the treatment of stage III and high-risk stage II colon cancer at GSH.

Estimated number of visits (or frequency):

Your answer

Estimated duration of each consultation (in minutes):

Your answer

Personnel required for each consultation (cadre and quantity):

Your answer

Consultation space/room:

Your answer

Medical supplies (consumables):

Your answer

Medical equipment:

Your answer

Identify and measure relevant cost inputs for Surgery

Will you provide me with information on average about the surgical treatment for stage III and high-risk stage II colon cancer at GSH?

What is the standard surgical procedure for stage I and low-risk stage II colon cancer at GSH

Your answer

Who are the personnel required? (Note cadre and quantity)

Your answer

Estimated duration of surgical procedure:

Your answer

Operating room/Theatre is used?

Your answer

Operative equipment :

Your answer

Operative medication:

Your answer

Briefly describe the in-hospital post-surgical management

Your answer

How would you rate the probability of surgical complications

Choose

Is there someone i can talk to to find out more about this surgical treatment?

Choose

If yes or others, please specify

Your answer

Identify and measure relevant cost inputs for adjuvant chemotherapy
On Average, will you confirm the following about the adjuvant chemotherapy regimen and cycles for high-risk stage II and stage III colon cancer

CAPOX (Oxaliplatin 130mg/m2 IV over 2 hours D1 and Capecitabine 1000mg/m2 PO bd D1-14) is given as a 3-week cycle for four cycles and eight cycles for high-risk stage III.

If oxaliplatin is contraindicated, 5FU and Leucovorin (Leucovorin 20mg/m2 IV D1-5 and 5fluorauracil 425mg/m2 IV D1-5) are given as a 4-week cycle for four cycles.

(Capecitabine 1250mg/m2 PO bd D1-14) is given as a 3-week cycle for eight cycles with clinical assessment at each cycle for patients who live far away.

Choose

If False, please specify

Your answer

Which is the usually prescribed regimen at GSH?

Your answer

Identify and measure relevant cost inputs for adjuvant chemotherapy

On Average, will you let me know the following about the adjuvant chemotherapy supportive medication and administration

Is supportive medication prescribed per adjuvant chemotherapy cycle

Choose

5. If yes, please specify the supportive medicines for each adjuvant chemotherapy regimen (Note medication name and dose given per cycle)

Your answer

What personnel are required for chemotherapy administration:

Your answer

Chemotherapy preparation duration:

Your answer

Where is chemotherapy administered

Your answer

Medical supplies (consumables):

Your answer

Medical equipment:

Your answer

Is there anyone you think I can talk to to learn more about the administration of adjuvant chemotherapy?

Choose

If yes, please specify

Your answer

Follow-up treatment

On average, would you confirm the following about follow-up management in the treatment of stage III and high-risk stage II colon cancer at GSH

On average can you confirm that post-surgical clinical assessments and CEA tests every nine months with CT scans of the chest, abdomen and pelvis at 18 months for 36 months. Followed by annual clinical assessment and CEA tests till five years, and a five-year colonoscopy until 75 years old is the follow-up treatment for patients with stage III colon cancer at risk of possible recurrence.

Choose

If false or others, please specify:

Your answer

Back Next Clear form

Expert questionnaire

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Not shared

Stage IV (Metastatic colon cancer)

In your opinion, what percentage of colon cancer patients treated at GSH are diagnosed with stage IV cancer, on average

Your answer

Staging investigation

On average, would you confirm the staging investigations in the treatment of stage IV colon cancer at GSH

On average, can you confirm that lesion biopsy, colonoscopy, CT scans of the chest, abdomen and pelvis, full blood count, electrolytes, renal function tests, liver function tests and carcinoembryonic antigen (CEA) are required investigations for the diagnosis, staging and risk profiling for treating stage IV colon cancer at GSH?

Choose

If false or others, please specify

Your answer

Treatment components

Will you confirm the following statements about the classification and treatment components of stage IV colon cancer at GSH

Can you confirm that to treat stage IV colon cancer at GSH, cases are classified based on patients' fitness and possibility of tumor resection?

Choose

If false or others, please specify

Your answer

Can you confirm that for cases where resection is possible and patient is fit, either of the following is the primary treatment option;
1. clinical consultations, immediate surgery followed by adjuvant chemotherapy
OR
2. clinical consultations, pre-operative chemotherapy followed by surgery are the primary treatment options

Choose

If false or others, please specify:

Your answer

Can you confirm that palliative chemotherapy and supportive management are the treatment components for cases of unresectable disease in patients with performance status 0-2 and ≥3, respectively

Choose

If false or others, please specify

Your answer

Identify and measure relevant cost inputs for clinical consultations.
On Average, will you let me know the following about the peri-operative consultations for the treatment of any stage IV colon cancer at GSH.

Estimated number of consultations (or frequency):

Your answer

Estimated duration of each consultation (in minutes):

Your answer

Personnel required for each consultation (cadre and quantity):

Your answer

Consultation space/room:

Your answer

Relevant medical supplies (consumables):

Your answer

Medical equipment:

Your answer

Identify and measure relevant cost inputs for clinical consultations.
On Average, will you let me know the following about the post-operative consultations for the treatment of stage IV colon cancer at GSH.

Estimated number of consultations (or frequency):

Your answer

Estimated duration of consultation (Minutes):

Your answer

Personnel required for each consultation (cadre and quantity):

Your answer

Consultation space/room:

Your answer

Relevant medical supplies (consumables):

Your answer

Medical equipment:

Your answer

Identify and measure relevant cost inputs for Surgery
Can you provide me with information about the surgical treatment for stage IV colon cancer with possible resection at GSH?

Type (name) of procedure:

Your answer

Who are the personnel required? (Note cadre and quantity)

Your answer

Estimated duration of surgical procedure:

Your answer

Which operating room/Theatre is used?

Your answer

Operative equipment :

Your answer

Operative medication:

Your answer

Relevant consumables:

Your answer

What is the post-surgical management

Your answer

Kindly estimate the probability of surgical complications

Choose

Is there someone i can talk to to know more about this surgical treatment?

Choose

If yes or others, please specify:

Your answer

Identify and measure relevant cost inputs for neoadjuvant or adjuvant chemotherapy

On Average, will you confirm the following about the neoadjuvant and adjuvant chemotherapy regimen and cycles for stage IV colon cancer with possible resection.

All patients with resectable disease will receive CAPOX (Oxaliplatin 130mg/m2 IV over 2 hours D1 and Capecitabine 1000mg/m2 PO bd D1-14 given as a 3-week cycle for eight cycles) either as conversion, neoadjuvant or adjuvant chemotherapy

Choose

If false, please specify

Your answer

Identify and measure relevant cost inputs for neoadjuvant or adjuvant chemotherapy

On Average, will you let me know the following about the neoadjuvant or adjuvant chemotherapy supportive medication and administration in stage IV colon cancer with possible resection.

Is supportive medication prescribed per adjuvant chemotherapy cycle

Choose

5. If yes, please specify the supportive medicines for each adjuvant chemotherapy regimen (Note medication name and dose given per cycle)

Your answer

What personnel are required for chemotherapy administration:

Your answer

Chemotherapy preparation duration:

Your answer

Where is chemotherapy administered

Your answer

Medical supplies:

Your answer

Medical equipment:

Your answer

Identify and measure relevant cost inputs for palliative chemotherapy

On average, please provide details about the palliative chemotherapy regimen, including the number of cycles and supportive medication, for unresectable cases in patients with performance status 0-2.

What regimen is commonly prescribed

Your answer

What support medication is commonly prescribed per cycle of chemotherapy (Note medicines and dose)

Your answer

Identify and measure relevant cost inputs for supportive management
On Average, will you provide details on the supportive management for unresectable stage IV cases with performance status greater than or equal to 3

Kindly let me know what constitutes this supportive management

Your answer

Is this management case dependent?

Choose

If yes, provide details on the the standard supportive management commonly provided in GSH

Your answer

Follow-up Management
On average, would you confirm the following about follow-up management in the treatment of any stage IV colon cancer at GSH

Nine monthly post-surgical clinical assessments and CEA tests with CT scans of the chest, abdomen and pelvis at 18 months for 36 months. Followed by annual clinical assessment and CEA tests till five years, and a five-year colonoscopy until 75 years old is the follow-up treatment for patients with stage III colon cancer

Choose

If false or others, please specify:

Your answer

Back Submit Clear form

3 Appendix 3: Ethics consent form

Participant information and consent form

Title of study: Estimating the treatment cost of Colon cancer at Groote Schuur Hospital.
Principal investigator: Dr. Lucy Cunnama (Lucy.cunnama@uct.ac.za) Institutional contact: Health Economics Unit, Department of Public Health and family medicine, faculty of health sciences University of Cape Town, Rondebosch, Cape Town,7700

Introduction and purpose of the study: The overreaching aim of this study is to estimate the direct financial cost of treatment for colon cancer at Groote Schuur Hospital from the health providers' perspective using an ingredient-based normative approach.
Research description: When you consent to this study, you will participate in a structured interview to help develop and outline the colon cancer treatment components at GrooteSchuur Hospital by disease stage. This pathway will outline the cost items and required quantities for each identified colon cancer treatment component. This will form the basis for the costing study.
Potential risks and benefits: There are no known risks or harm to you for participating in this study.
Privacy and confidentiality: Your responses are completely anonymous. No personal identifying information or addresses will be collected. Every answer given will be used only for this study.
Cost: There is no cost to you for participating in this study.
Participation and authorisation: Your decision to participate in this study is voluntary. If you decide not to participate in this study, you may withdraw from your participation at any time without penalty.

I voluntarily agree to participate in this research program
(Tick as appropriate)[ ] Yes [ ] No

Signature: ..... Date: .....
Lucy Cunnama (Principal investigator)

4 Appendix 4: Summary empirical review table

Authors (Year)	Title	Country	Method	Cost element	Cost stratified by	Unit cost	Costs
Kriza et al. (2013)	Cost of Illness in Colorectal Cancer: An International Review	France, USA, Ireland	Systematic review of 10 publications on CRC cost of illness between 2002 and 2012	Mixed	Mixed	Mixed	Long-term costs range from 14,461 to 50,175 per patient. Annual prevalence-based costs range from 8,415 to 175,020.

Continued on next page

Authors (Year)	Title	Country	Method	Cost element	Cost stratified by	Unit cost	Costs
Haug et al. (2014)	Estimating Colorectal Cancer Treatment Costs: A Pragmatic Approach Exemplified by Health Insurance Data from Germany	Germany / Euros (€)	Perspective: Third-party (Insurer); Design: Retrospective review of 21,851 CRC patients from 2005 to 2010	In-patient, outpatient, and drug costs	Tumour site and treatment phase	N/A	The total costs for initial, intermediate, and end-of-life phases are 29,400, 6,100, and 64,600 respectively. Total mean increment costs for these phases are 25,900, 2,300, and 51,700.

Continued on next page

Authors (Year)	Title	Country	Method	Cost element	Cost stratified by	Unit cost	Costs
Färkkilä et al. (2015)	Cost of Colorectal Cancer in Different Stages of the Disease	Finland/ Euros (€)	Perspective: Societal; Design: Cross-sectional survey of 508 CRC patients in the Helsinki and Uusimaa Hospital District between September 2009 and April 2011	Direct medical, productivity, and informal care costs	Five Disease States	Cost per patient	Six months' direct medical costs: 16,244 for primary, 1,601 for rehabilitation, 1,450 for remission, 1,4277 for metastatic, and 10,004 for palliative stages.

Continued on next page

Authors (Year)	Title	Country	Method	Cost element	Cost stratified by	Unit cost	Costs
Laudicella et al. (2016)	Cost of Care for Cancer Patients in England: Evidence from Population-Based Patient-Level Data	England/ Euros (€)	Perspective: Health provider's; Design: Retrospective cohort study of 275,985 CRC, 359,771 Breast cancer, 286,426 Prostate cancer, and 283,940 lung cancer adult patients in England from 2001 to 2010	General healthcare services	Patient age, phases of care, and disease stage	Cost per patient	Average incidence cost for patients aged 16-64 is 38,098, and 37,948 for those above 65.

Continued on next page

Authors (Year)	Title	Country	Method	Cost element	Cost stratified by	Unit cost	Costs
Alefan et al. (2017)	The Direct Medical Cost Associated with Colorectal Cancer in North Jordan	Jordan / JD	Perspective: Healthcare providers; Design: Retrospective analysis using a prevalence-based bottom-up costing approach for 97 CRC patients at King Abdullah University Hospital, 2014	Direct medical cost	Primary tumour site, disease stage, and cost category	N/A	Total annual direct medical costs of 695,608.

Continued on next page

Authors (Year)	Title	Country	Method	Cost element	Cost stratified by	Unit cost	Costs
Herbst et al. (2018)	Access to Colorectal Cancer Chemotherapy and Associated Costs in a South African Public Healthcare Patient Cohort	South Africa/ Euros (€)	Perspective: Third-party (Insurers'); Design: Retrospective review of chemotherapy utilisation of 162 patients, 2012-2014	Drugs, supportive medications, administration and admin expenses for adjuvant/metastatic chemotherapy	Type of chemotherapy, tumour site, treatment line for metastatic chemotherapy	Cost per chemotherapy regimen	Theoretical cost of adjuvant chemotherapy for colon tumours: 3,087 (5FU+LV), 1,390 (Capecitabine), etc.
Herbst et al. (2020)	Colorectal Cancer Treatment Costs in Public vs. Private Sectors in Johannesburg, South Africa	South Africa/ Euros (€)	Perspective: Third-party (Insurers'); Design: Retrospective cohort claims analysis of 1,296 CRC patients, 2014-2015	Chemotherapy drugs, related medication, and admin costs for outpatient services	Disease stage and line of treatment	Cost per chemotherapy cycle	

Continued on next page

Authors (Year)	Title	Country	Method	Cost element	Cost stratified by	Unit cost	Costs
Shen et al. (2020)	Treatment Patterns and Direct Medical Costs of Metastatic Colorectal Cancer Patients: A Retrospective Study in Urban China	China / USD ($)	Perspective: Third-party (Insurer); Design: Retrospective review of 404 patients from 12 hospitals, 2011-2016	Direct medical costs of wards, diagnostic tests, surgery, etc.	Line of treatment	Cost per patient per chemotherapy cycle	Mean cost: 2,514 for 1st line, 2,678 for 2nd, 5,121 for 3rd.
Nejati et al. (2021)	Resource Use and Costs Associated with Initial Treatment for CRC Patients in Iran	Iran / USD ($)	Perspective: Health providers'; Design: Retrospective patient review of 657 CRC patients from 5 regions, March 2016-2017	Both direct medical and non-medical costs		Cost per patient	Total direct cost of 21,407

Continued on next page

Authors (Year)	Title	Country	Method	Cost element	Cost stratified by	Unit cost	Costs
Sougklakos et al. (2022)	Treatment Pathways and Associated Costs of Metastatic CRC in Greece	Greece / Euros (€)	Perspective: Third-party (Health Insurer); Design: Two-step approach with local treatment pathway identification and resource use assignment	Direct medical costs of chemotherapy drugs and associated services	Line of treatment	Cost per patient	Annual costs: 28,407 (1st line), 33,568 (2nd line), 25,550 (3rd line).
Bhimani et al. (2022)	Lifetime Direct Healthcare Costs of Treating CRC: A Systematic Review	USA, Spain, England, Italy, Germany, Canada, Taiwan, Australia / USD ($)	Systematic review of 17 studies on CRC direct costs	Mixed	Treatment phase	Mixed	Costs for initial phase: 7,893 to 60,289, continuing phase: 2,322 to 15,744, end-of-life: 15,916 to 99,687.

Continued on next page

Authors (Year)	Title	Country	Method	Cost element	Cost stratified by	Unit cost	Costs

5 Appendix 5: Unit cost per cost item for each treatment component per cancer stage

Treatment components	**Identified cost ingredients**	**Unit cost (R)**	**Unit cost (USD)**
Consultation			
Preoperative / Post-operative Visits	Building	3.23	0.17
	Equipment	0.16	0.01
	Personnel	393.58	21.04
		396.96	**21.22**
MDT	Building	2.58	0.14
	Equipment	0.41	0.02
	Personnel	676.49	36.17
		679.49	**36.33**
Surgery			
Single-sided Laparoscopic colectomy	Building	64.10	3.43
	Equipment	88.48	4.73
	Personnel	8417.41	450.04
	Medication	355.41	19.00
	Relevant consumables	22156.54	1184.60
		31,081.94	**1,661.79**
Open colectomy including post-surgical inpatient admission	Building	96.14	5.14

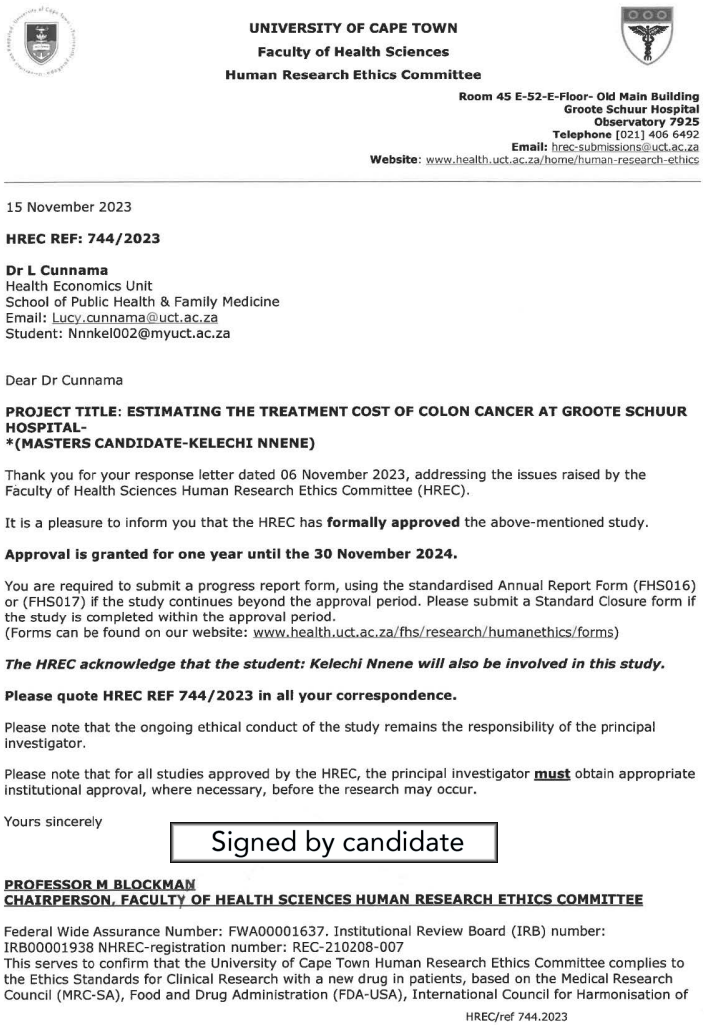
Table continued on next page

Treatment components	**Identified cost ingredients**	**Unit cost (R)**	**Unit cost (USD)**
	Equipment	129.74	6.94
	Personnel	12626.12	675.05
	Medication	355.41	19.00
	Relevant consumables	23046.70	1232.19
		36,254.10	**1,938.32**
Liver resection	Building	96.14	5.14
	Equipment	136.92	7.32
	Personnel	12626.12	675.05
	Medication	355.41	19.00
	Relevant consumables	23046.70	1232.19
		36,261.29	**1,938.71**
Chemotherapy (cost per cycle)			
CAPOX (1st line)	Building	12.91	0.69
	Equipment	7.01	0.37
	Personnel	2,902.65	155.19
	Medication (Chemo and supportive)	737.75	39.44
	Relevant consumables	83.46	4.46
		3,743.79	**200.16**
CAPIRI (2nd line)	Building	4.84	0.26
	Equipment	2.63	0.14

Table continued on next page

Treatment components	**Identified cost ingredients**	**Unit cost (R)**	**Unit cost (USD)**
	Personnel	698.40	37.34
	Medication (Chemo and supportive)	469.37	25.09
	Relevant consumables	83.46	4.46
		1,258.70	**67.30**
Staging investigations (cost per procedure)			
Colonoscopy	Procedure cost	4,865.14	260.11
CT scans of the chest abdomen and pelvis	Procedure cost	7,000.00	374.25
Full blood count	Procedure cost	69.31	3.71
Lesion biopsy	Procedure cost	132.90	7.11
Renal function tests and electrolytes	Procedure cost	145.00	7.75
Liver function tests	Procedure cost	367.96	19.67
Carcinoembryonic antigen (CEA)	Procedure cost	360.00	19.25
Primovist MRI	Procedure cost	8,800.00	470.49
Inpatient admission (cost per day)	Facility fees	2,198.00	117.52

6 Appendix 6: University of Cape Town Human Research Ethics Committee approval



UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

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Telephone [021] 406 6492
Email: hrec-submissions@uct.ac.za
Website: www.health.uct.ac.za/home/human-research-ethics

15 November 2023

HREC REF: 744/2023

Dr L Cunnama
Health Economics Unit
School of Public Health & Family Medicine
Email: Lucy.cunnama@uct.ac.za
Student: Nnnkel002@myuct.ac.za

Dear Dr Cunnama

PROJECT TITLE: ESTIMATING THE TREATMENT COST OF COLON CANCER AT GROOTE SCHUUR HOSPITAL-
***(MASTERS CANDIDATE-KELECHI NNENE)**

Thank you for your response letter dated 06 November 2023, addressing the issues raised by the Faculty of Health Sciences Human Research Ethics Committee (HREC).

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 November 2024.

You are required to submit a progress report form, using the standardised Annual Report Form (FHS016) or (FHS017) if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledge that the student: Kelechi Nnene will also be involved in this study.

Please quote HREC REF 744/2023 in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

Signed by candidate

PROFESSOR M BLOCKMAN
CHAIRPERSON, FACULTY OF HEALTH SCIENCES HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637. Institutional Review Board (IRB) number: IRB00001938 NHREC-registration number: REC-210208-007
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for Harmonisation of

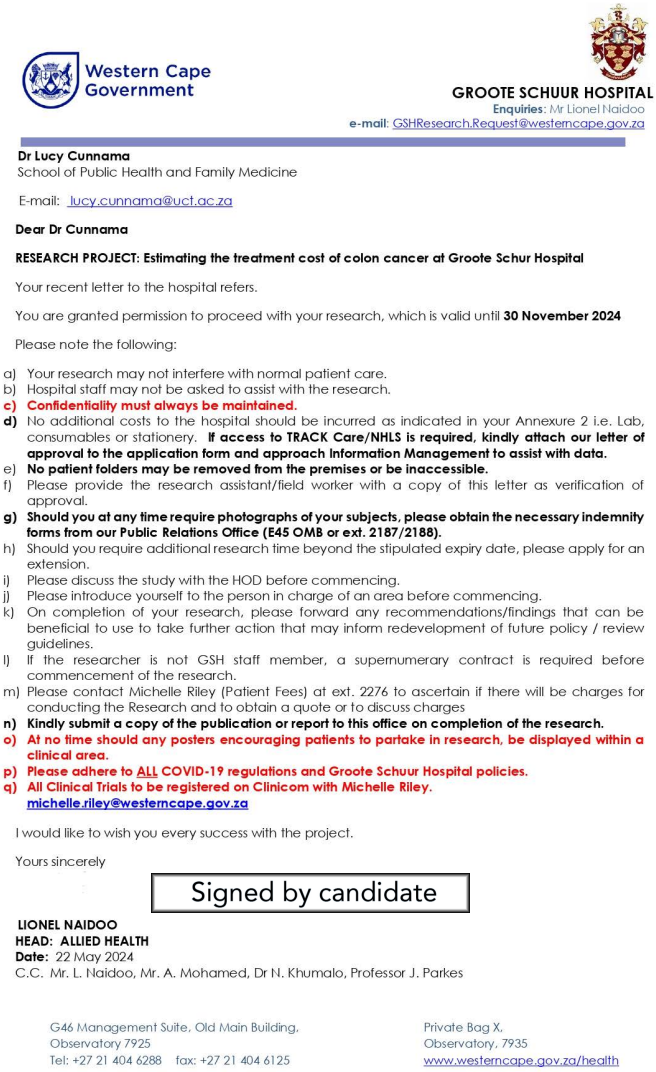
Figure 5: UCT HREC Approval

Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2020), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

HREC/ref 744.2023

Figure 6: UCT HREC Approval page 2

7 Appendix 7: Groote Schuur Hospital Research Approval Letter



Western Cape Government

GROOTE SCHUUR HOSPITAL
Enquiries: Mr Lionel Naidoo
e-mail: GSHResearch.Request@westerncape.gov.za

Dr Lucy Cunnama
School of Public Health and Family Medicine

E-mail: lucy.cunnama@uct.ac.za

Dear Dr Cunnama

RESEARCH PROJECT: Estimating the treatment cost of colon cancer at Groote Schur Hospital

Your recent letter to the hospital refers.

You are granted permission to proceed with your research, which is valid until **30 November 2024**

Please note the following:

a) Your research may not interfere with normal patient care.
b) Hospital staff may not be asked to assist with the research.
c) Confidentiality must always be maintained.
d) No additional costs to the hospital should be incurred as indicated in your Annexure 2 i.e. Lab, consumables or stationery. **If access to TRACK Care/NHLS is required, kindly attach our letter of approval to the application form and approach Information Management to assist with data.**
e) **No patient folders may be removed from the premises or be inaccessible.**
f) Please provide the research assistant/field worker with a copy of this letter as verification of approval.
g) Should you at any time require photographs of your subjects, please obtain the necessary indemnity forms from our Public Relations Office (E45 OMB or ext. 2187/2188).
h) Should you require additional research time beyond the stipulated expiry date, please apply for an extension.
i) Please discuss the study with the HOD before commencing.
j) Please introduce yourself to the person in charge of an area before commencing.
k) On completion of your research, please forward any recommendations/findings that can be beneficial to use to take further action that may inform redevelopment of future policy / review guidelines.
l) If the researcher is not GSH staff member, a supernumerary contract is required before commencement of the research.
m) Please contact Michelle Riley (Patient Fees) at ext. 2276 to ascertain if there will be charges for conducting the Research and to obtain a quote or to discuss charges
n) Kindly submit a copy of the publication or report to this office on completion of the research.
o) At no time should any posters encouraging patients to partake in research, be displayed within a clinical area.
p) Please adhere to ALL COVID-19 regulations and Groote Schuur Hospital policies.
q) All Clinical Trials to be registered on Clinicom with Michelle Riley.
michelle.riley@westerncape.gov.za

I would like to wish you every success with the project.

Yours sincerely

Signed by candidate

LIONEL NAIDOO
HEAD: ALLIED HEALTH
Date: 22 May 2024
C.C. Mr. L. Naidoo, Mr. A. Mohamed, Dr N. Khumalo, Professor J. Parkes

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Figure 7: Groote Schuur Hospital Research Approval Letter

8 Appendix 8: The instructions for the authors for the target journal

8.1 Submission Guidelines

1. Criteria

Research articles should report on original primary research or new experimental or computational methods, tests or procedures. Manuscripts reporting results of a clinical trial must conform to CONSORT 2010 guidelines. Authors of randomized controlled trials should submit a complete CONSORT checklist alongside their manuscript, available at www.consort-statement.org. Research articles may also report on systematic reviews of published research provided they adhere to the appropriate reporting guidelines which are detailed in our editorial policies. Please note that non-commissioned pooled analyses of selected published research and bibliometric analyses will not be considered. Studies reporting descriptive results from a single institution or region will only be considered if analogous data have not been previously published in a peer reviewed journal and the conclusions provide distinct insights that are of relevance to a regional or international audience.

Data sharing

BMC Health Service Research strongly supports open research, including transparency and openness in reporting. Further details of our Data availability policy can be found on the journal's About page. Professionally produced Visual Abstracts BMC Health service research will consider visual abstracts. As an author submitting to the journal, you may wish to make use of services provided at Springer Nature for high quality and affordable visual abstracts where you are entitled to a 20% discount.

2. Preparing your manuscript

The information below details the section headings that you should include in your manuscript and what information should be within each section. Please note that your manuscript must include a 'Declarations' section including all of the subheadings (please see below for more information).

3. Title page The title page should:

A. Present a title that includes, if appropriate, the study design e.g.: "A versus B in the treatment of C: a randomized controlled trial", "X is a risk factor for Y: a case control study", "What is the impact

of factor X on subject Y: A systematic review" or for non-clinical or non-research studies a description of what the article reports.

B. List the full names and institutional addresses for all authors if a collaboration group should be listed as an author, please list the Group name as an author. If you would like the names of the individual members of the Group to be searchable through their individual PubMed records, please include this information in the "Acknowledgements" section in accordance with the instructions below. Large Language Models (LLMs), such as ChatGPT, do not currently satisfy our authorship criteria. Notably an attribution of authorship carries with it accountability for the work, which cannot be effectively applied to LLMs. Use of an LLM should be properly documented in the Methods section (and if a Methods section is not available, in a suitable alternative part) of the manuscript.

C. Indicate the corresponding author

4. Abstract

The Abstract should not exceed 350 words. Please minimize the use of abbreviations and do not cite references in the abstract. Reports of randomized controlled trials should follow the CONSORT extension for abstracts. The abstract must include the following separate sections:

a. Background: the context and purpose of the study

b. Methods: how the study was performed and statistical tests used

c. Results: the main findings

d. Conclusions: brief summary and potential implications

e. Trial registration: If your article reports the results of a health care intervention on human participants, it must be registered in an appropriate registry and the registration number and date of registration should be stated in this section. If it was not registered prospectively (before enrollment of the first participant), you should include the words 'retrospectively registered'. See our editorial policies for more information on trial registration.

5. Keywords

Three to ten keywords representing the main content of the article.

6. Background

The Background section should explain the background to the study, its aims, a summary of the existing literature and why this study was necessary or its contribution to the field.

7. Methods

The methods section should include:

a. The aim, design and setting of the study

b. The characteristics of participants or description of materials

c. A clear description of all processes, interventions and comparisons. Generic drug names should generally be used. When proprietary brands are used in research, include the brand names in parentheses

d. The type of statistical analysis used, including a power calculation if appropriate.

8. Results

This should include the findings of the study including, if appropriate, results of statistical analysis which must be included either in the text or as tables and figures.

9. Discussion

This section should discuss the implications of the findings in context of existing research and highlight limitations of the study.

10. Conclusions This should state clearly the main conclusions and provide an explanation of the importance and relevance of the study reported.

11. List of abbreviations If abbreviations are used in the text they should be defined in the text at first use, and a list of abbreviations should be provided.

12. Declarations

All manuscripts must contain the following sections under the heading
Declarations:

a. Ethics approval and consent to participate

b. Consent for publication

c. Availability of data and materials

d. Competing interests

e. Funding

f. Authors' contributions

g. Acknowledgements

h. Authors' information (optional)

Please see below for details on the information to be included in these sections.
If any of the sections are not relevant to your manuscript, please include the heading and write 'Not applicable' for that section.

13. Ethics approval and consent to participate

Manuscripts reporting studies involving human participants, human data or human tissue must:

a. include a statement on ethics approval and consent (even where the need for approval was waived)

b. include the name of the ethics committee that approved the study and the committee's reference number if appropriate.

Studies involving animals must include a statement on ethics approval and for experimental studies involving client-owned animals, authors must also include a statement on informed consent from the client or owner. See our editorial policies for more information. If your manuscript does not report on or involve the use of any animal or human data or tissue, please state "Not applicable" in this section.

14. Consent for publication

If your manuscript contains any individual person's data in any form (including any individual details, images or videos), consent for publication must be obtained from that person, or in the case of children, their parent or legal guardian. All presentations of case reports must have consent for publication. You can use your institutional consent form or our consent form if you prefer. You should not send the form to us on submission, but we may request to see a copy at any stage (including after publication). See our editorial policies for more information on consent for publication. If your manuscript does not contain data from any individual person, please state "Not applicable" in this section.

15. Availability of data and materials

All manuscripts must include an 'Availability of data and materials' statement. Data availability statements should include information on where data supporting the results reported in the article can be found including, where applicable, hyperlinks to publicly archived datasets analysed or generated during the study. By data we mean the minimal dataset that would be necessary to interpret, replicate and build upon the findings reported in the article. We recognise it is not always possible to share research data publicly, for instance when individual privacy could be compromised, and in such instances data availability should still be stated in the manuscript along with any conditions for access. Authors are also encouraged to preserve search strings on searchRxiv, an archive to support researchers to report, store and share their searches consistently and to enable them to review and re-use existing searches. searchRxiv enables researchers to obtain a digital object identifier (DOI) for their search, allowing it to be cited.

Data availability statements can take one of the following forms (or a combination of more than one if required for multiple datasets):

a. The datasets generated and/or analysed during the current study are available in the [NAME]

repository, [PERSISTENT WEB LINK TO DATASETS]

b. The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

c. All data generated or analysed during this study are included in this published article [and its supplementary information files].

d. The datasets generated and/or analysed during the current study are not publicly available due [REASON WHY DATA ARE NOT PUBLIC] but are available from the corresponding author on reasonable request.

e. Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

f. The data that support the findings of this study are available from [third party name] but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of [third party name].

g. Not applicable. If your manuscript does not contain any data, please state 'Not applicable' in this section.

More examples of template data availability statements, which include examples of openly available and restricted access datasets, are available here. BioMed Central strongly encourages the citation of any publicly available data on which the conclusions of the paper rely in the manuscript. Data citations should include a persistent identifier (such as a DOI) and should ideally be included in the reference list. Citations of datasets, when they appear in the reference list, should include the minimum information recommended by DataCite and follow journal style. Dataset identifiers including DOIs should be expressed as full URLs. For example:
Hao Z, AghaKouchak A, Nakhjiri N, Farahmand A. Global integrated drought monitoring and prediction system (GIDMaPS) data sets. figshare. 2014. http://dx.doi.org/10.6084/m9.figshare.853801 With the corresponding text in the Availability of data and materials statement:

The datasets generated during and/or analysed during the current study are available in the [NAME] repository, [PERSISTENT WEB LINK TO DATASETS].[Reference number]
If you wish to co-submit a data note describing your data to be published in BMC Research Notes, you can do so by visiting our submission portal. Data notes support open data and help authors to comply with funder policies on data sharing. Co-published data notes will be linked to the research article the data support (example).

16. Competing interests

All financial and non-financial competing interests must be declared in this section. See our editorial policies for a full explanation of competing interests. If you are unsure whether you or any of your co-authors have a competing interest please contact the editorial office. Please use the authors initials to refer to each authors' competing interests in this section. If you do not have any competing interests, please state "The authors declare that they have no competing interests" in this section.

17. Funding

All sources of funding for the research reported should be declared. The role of the funding body in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript should be declared.

18. Authors' contributions

The individual contributions of authors to the manuscript should be specified in this section. Guidance and criteria for authorship can be found in our editorial policies. Please use initials to refer to each author's contribution in this section, for example: "FC analyzed and interpreted the patient data regarding the hematological disease and the transplant. RH performed the histological examination of the kidney, and was a major contributor in writing the manuscript. All authors read and approved the final manuscript".

19. Acknowledgements

Please acknowledge anyone who contributed towards the article who does not meet the criteria for

authorship including anyone who provided professional writing services or materials. Authors should obtain permission to acknowledge from all those mentioned in the Acknowledgements section. See our editorial policies for a full explanation of acknowledgements and authorship criteria. If you do not have anyone to acknowledge, please write "Not applicable" in this section. Group authorship (for manuscripts involving a collaboration group): if you would like the names of the individual members of a collaboration Group to be searchable through their individual PubMed records, please ensure that the title of the collaboration Group is included on the title page and in the submission system and also include collaborating author names as the last paragraph of the “Acknowledgements” section. Please add authors in the format First Name, Middle initial(s) (optional), Last Name. You can add institution or country information for each author if you wish, but this should be consistent across all authors. Please note that individual names may not be present in the PubMed record at the time a published article is initially included in PubMed as it takes PubMed additional time to code this information.

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21. Footnotes

Footnotes can be used to give additional information, which may include the citation of a reference included in the reference list. They should not consist solely of a reference citation, and they should never include the bibliographic details of a reference. They should also not contain any figures or tables. Footnotes to the text are numbered consecutively; those to tables should be indicated by superscript lower-case letters (or asterisks for significance values and other statistical data). Footnotes to the title or the authors of the article are not given reference symbols. Always use footnotes instead of endnotes.