VALUE IN HEALTH 16 (2013) 542–553

Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.elsevier.com/locate/jval

Using Whole Disease Modeling to Inform Resource Allocation Decisions: Economic Evaluation of a Clinical Guideline for Colorectal Cancer Using a Single Model

Paul Tappenden, BA, MSc, PhD[1,*], *Jim Chilcott, BSc, MSc*[1], *Alan Brennan, BSc, MSc, PhD*[1], *Hazel Squires, BSc, MSc*[1], *Rob Glynne-Jones, FRCP, FRCR*[2], *Janine Tappenden, MBChB, MRCS, Surgical Registrar*[3]

[1]*Health Economics and Decision Science, School of Health and Related Research, University of Sheffield, Sheffield, UK;* [2]*East and North Hertfordshire NHS Trust, Northwood, UK;* [3]*Doncaster and Bassetlaw Hospitals, NHS Foundation Trust, Doncaster, UK*

ABSTRACT

Objective: To assess the feasibility and value of simulating whole disease and treatment pathways within a single model to provide a common economic basis for informing resource allocation decisions. **Methods:** A patient-level simulation model was developed with the intention of being capable of evaluating multiple topics within National Institute for Health and Clinical Excellence's colorectal cancer clinical guideline. The model simulates disease and treatment pathways from preclinical disease through to detection, diagnosis, adjuvant/neoadjuvant treatments, follow-up, curative/palliative treatments for metastases, supportive care, and eventual death. The model parameters were informed by meta-analyses, randomized trials, observational studies, health utility studies, audit data, costing sources, and expert opinion. Unobservable natural history parameters were calibrated against external data using Bayesian Markov chain Monte Carlo methods. Economic analysis was undertaken using conventional cost-utility decision rules within each guideline topic and constrained maximization rules across multiple topics. **Results:** Under usual processes for guideline development, piecewise economic modeling would have been used to evaluate between one and three topics. The Whole Disease Model was capable of evaluating 11 of 15 guideline topics, ranging from alternative diagnostic technologies through to treatments for metastatic disease. The constrained maximization analysis identified a configuration of colorectal services that is expected to maximize quality-adjusted life-year gains without exceeding current expenditure levels. **Conclusions:** This study indicates that Whole Disease Model development is feasible and can allow for the economic analysis of most interventions across a disease service within a consistent conceptual and mathematical infrastructure. This disease-level modeling approach may be of particular value in providing an economic basis to support other clinical guidelines.

Keywords: colorectal cancer, economic analysis, simulation models.

Introduction

This article concerns the development of Whole Disease Models, a system-level modeling approach that involves modeling events, costs, and outcomes across whole pathways from preclinical disease through to diagnosis and referral, adjuvant treatment, follow-up, potential recurrence, palliative treatment, end-of-life care, and eventual death within a single consistent model. This broader model boundary, together with a high level of depth in the representation of disease and treatment events, enables such models to provide a platform for the economic analysis of virtually any type of health intervention used at any point within the pathway. Recently, Tappenden et al. [1] set out a methodological framework for developing Whole Disease Models and outlined the circumstances under which the benefits of using such models may outweigh the costs of developing them. One such scenario is whereby a large set of decisions must be made across a disease pathway. In the United Kingdom, this is a common situation in the context of clinical guideline development.

Clinical guidelines are developed across the world with the intention of making recommendations for practice that will improve health outcomes for patients suffering from a particular disease or condition. Guideline development typically involves the prioritization of several discrete topics or research questions, and the formulation of clinical recommendations within each topic on consideration of the strengths and weaknesses of the available evidence. Clinical guidelines developed by the National Institute for Health and Clinical Excellence (NICE) in England and Wales differ from those produced elsewhere in that the recommendations of NICE's Guideline Development Groups (GDGs) are intended to be explicitly underpinned by considerations of cost-effectiveness [2]. The problems of formulating guidelines that adhere to a rigorous economic framework have been recognized for some time. Wailoo et al. [2] highlight a conflict between the responsibility of the GDG to promote the welfare of the individual

* *Address correspondence to:* Paul Tappenden, Health Economics and Decision Science, School of Health and Related Research, University of Sheffield, Regent Court, 30 Regent Street, Sheffield S1 4DA, UK.

E-mail: p.tappenden@sheffield.ac.uk.

1098-3015/$36.00 – see front matter

http://dx.doi.org/10.1016/j.jval.2013.02.012

Table 1 – Guideline topics, options, and methods for modifying the baseline model.

Topic	Clinical topic area	Option under assessment	Modification to the baseline Whole Disease Model
A	Diagnostic modalities for patients with symptoms of colorectal cancer	(A1) COL plus biopsy (baseline); (A2) CTC; (A3) FSIG + COL; (A4) FSIG followed by BE	Patients routed to alternative initial/secondary diagnostic test work centers, each of which differs in terms of operating characteristics, risks, and costs. No additional evidence required beyond that used to develop the baseline model
B	Tumor staging for colorectal cancer	Options include CT, CT/PET, MR, EUS, and DRE	Topic not evaluated using the Whole Disease Model
C	Curative treatment for patients with stage I or polyp cancer	(C1) radical resection (baseline); (C2) local resection including TEMS plus polypectomy; (C3) contact RT	DFS HR for TEMS vs. radical resection applied to baseline rectal cancer Dukes' A DFS curve. TEMS cost derived from Maslekar et al. [52]. No evidence was identified for contact RT
D	Treatment for patients presenting with emergency symptoms	(D1) CT scan (baseline); (D2) no CT scan; (D3) stenting as a bridge to surgery (baseline); (D4) immediate surgery	For options D2 and D4, stenting services and prior CT are not assumed to be available; hence, all patients with obstruction are routed to emergency surgery
E	The sequence of local and systemic treatments in patients presenting with locally advanced colorectal cancer	(E1) current local/systemic treatments (baseline); (E2) preop CRT (colon); (E3) surgery alone (colon); (E4) preop RT (rectal); (E5) preop CRT (rectal); (E6) preop chemotherapy (rectal); (E7) surgery alone (rectal)	For option E4, R0-predicted patients are routed to preop RT. For option E5, R0-predicted patients are routed to preop RT and a hazard ratio of 0.84 (95% CI 0.78–1.13) for preop CRT vs. RT was applied to the preop RT DFS curve for patients with Dukes' B/C cancer [53], and a cost of 2 × 5 d of 5-FU/FA was applied. For option E7, patients are routed to receive selective postop CRT. No evidence identified for options E2, E3, or E6.
F	Local/systemic treatment sequences in patients with synchronous metastases	(F1) staged resection (baseline); (F2) simultaneous resection; (F3) chemotherapy	Option F2 assumes shorter length of stay; hence, costs of surgery reduced by £2485 per patient with no difference in clinical outcomes. Option F3 was not evaluated because of a lack of evidence
G	Effectiveness of a) short course RT and b) CRT for rectal cancer	(G1) current mix of preop/postop treatments (baseline); (G2) preop RT; (G3) preop CRT	Option G2 routes R0-predicted patients to preop RT. Option G3 routes R0-predicted patients to preop RT and applies a hazard ratio of 0.84 for preop CRT vs. RT for Dukes B/C patients. Cost of 5-FU/FA for 10 days was also applied
H	Adjuvant chemotherapy after surgery for rectal cancer	(H1) current use of adjuvant chemotherapy (baseline); (H2) 5-FU/FA for all patients; (H3) no adjuvant chemotherapy	Option H2 DFS curves for preop RT and selective postop CRT adjusted by hazard ratio of 0.80 (95% CI 0.73–0.88). The probability that a Dukes' B/C rectal cancer patient receives adjuvant chemotherapy was set to 1.0. Option H3 was not run because it is confounded by the use of chemotherapy in the baseline time-to-event curves
I	Adjuvant chemotherapy for high-risk stage II colon cancer	(I1) 5-FU/FA-based chemotherapy (baseline); (I2) no adjuvant chemotherapy.	Option I2 assumes all patients with Dukes' B colon cancer routed to no chemotherapy, thereby assuming lower DFS and zero adjuvant chemo cost
J	Ablation, surgery, regional therapy, and systemic therapy for apparently incurable metastatic disease	(J1) palliative chemotherapy (baseline); (J2) HAI; (J3) best supportive care	Option J2 modeled by applying a hazard ratio from Mocellin et al. [54]. Cost estimates for HAI were drawn from Durand-Zeleski et al. [55]
K/L	Clinical indications for metastasectomy of the liver/lung	Competing options not defined	Topic not evaluated using the Whole Disease Model

Table 1 – *continued*

Topic	Clinical topic area	Option under assessment	Modification to the baseline Whole Disease Model
M	Chemotherapy for patients with advanced and metastatic disease	(M1) Current mix of palliative chemotherapies; (M2–M22) various chemotherapy sequences. A broader set of options was evaluated than those defined in the scope	Different OS and PFS hazard ratios applied to baseline model based on a network meta-analysis [56]. Costs applied according to treatment duration. Different downstaging success rates were applied according to each regimen
N	Follow-up after potentially curative treatment for colorectal cancer	(N1) Intensive follow-up; (N2) Relaxed follow-up	Follow-up test costs reduced by 62% based on a previous economic analysis [57]. The probability that a patient with metastatic recurrence is initially operable or potentially operable was multiplied by 0.50 based on Jeffery et al. [58]
O	Colorectal-specific support for diagnosed patients	Competing options not defined	Topic not evaluated using the Whole Disease Model

BE, barium enema; COL, colonoscopy; CRT, chemoradiation; CT, computed tomography; CTC, computed tomography colonography; DFS, disease-free survival; EUS, endoscopic ultrasound; 5-FU/FA, 5-fluorouracil plus folinic acid; FSIG, flexible sigmoidoscopy; HAI, hepatic arterial infusion; HR, hazard ratio; MR, magnetic resonance; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival; postop, postoperative; preop, preoperative; RT, radiotherapy; TEMS, transanal endoscopic microsurgery.

patient and their responsibility to other patients and society to promote cost-effectiveness within a resource-constrained health system. While each recommendation will have an impact on the allocation of scarce resources, these implications are not always formally considered.

Within each NICE clinical guideline, 15 to 20 topics are prioritized for review and the GDG makes best practice recommendations within each topic [3]. Owing to limited time and resource, the economic implications of between one and three topics are typically examined through the development of a *de novo* economic model. For the remaining topics, recommendations may be reliant on published analyses. Existing economic studies, however, tend to have limited applicability to the research questions addressed by the GDG, and sometimes no relevant published evidence is available. This results in a situation whereby the economic implications of service change are only partially addressed. Consequently, there remains a possibility that health improvements arising from the use of formal economic analysis within certain topics are negated by inefficiencies arising from other guideline recommendations that have not been subjected to a similar level of rigor.

The hypothesis underlying this study is that Whole Disease Modeling can provide a more coherent and useful platform for the economic evaluation of health technologies within a given disease area as compared against conventional piecewise economic evaluation. To test this hypothesis, this article details the development of a colorectal cancer Whole Disease Model to examine the potential value of the approach, using the NICE clinical guideline for the diagnosis and management of colorectal cancer [4] as a case study. From a methodological perspective, the model is simply intended to assess the feasibility and value of the approach, while from an applied viewpoint, it is intended to provide a comprehensive infrastructure for informing resource allocation decisions across the entire colorectal pathway. Because of the process constraints of the development of the colorectal cancer guideline, the Whole Disease Model was *not* used to inform guideline recommendations, and conventional economic analysis was undertaken by another academic center. This parallel model development activity thus creates a unique natural experiment whereby the value of Whole Disease Modeling can be directly compared against conventional piecewise economic evaluation.

Methods

The development of the colorectal cancer Whole Disease Model followed the methodological framework set out by Tappenden et al. [1] based on five main process elements: 1) understanding the decision problem, 2) model conceptualization and design, 3) implementation modeling, 4) model checking, and 5) engaging with the decision.

Decision Problem Scope

Fifteen topics were identified by stakeholders for consideration within the colorectal cancer guideline (see the left-hand columns in Table 1). These topics span most of the breadth of the colorectal pathway, ranging from the use of alternative diagnostic modalities to treatments of metastatic disease. Population screening and the management of increased-risk groups were excluded from the remit of the guideline. The presence of screening further upstream in the colorectal cancer service, however, may shift the case-mix of patients at diagnosis, thereby influencing the costs and outcomes of downstream services. Consequently, the scope of the Whole Disease Model is broader because it includes both a natural history model and a population screening component.

Conceptual Models of Disease and Service Pathways for Colorectal Cancer

Detailed problem-oriented conceptual models describing colorectal cancer disease progression and service pathways were developed by using methods described in Tappenden et al. [1] and Tappenden [5]. The first conceptual "disease logic" model describes the natural history of colorectal cancer and differential prognosis conditional on disease stage. The second conceptual "service pathways" model describes the main pathways for colorectal cancer services from detection and diagnosis through to treatments for early disease, follow-up, treatments for recurrence, and end-of-life care. These problem-oriented conceptual models were developed through the examination of cancer service guidance, local treatment protocols, NICE guidance, and considerable clinical input. These conceptual models

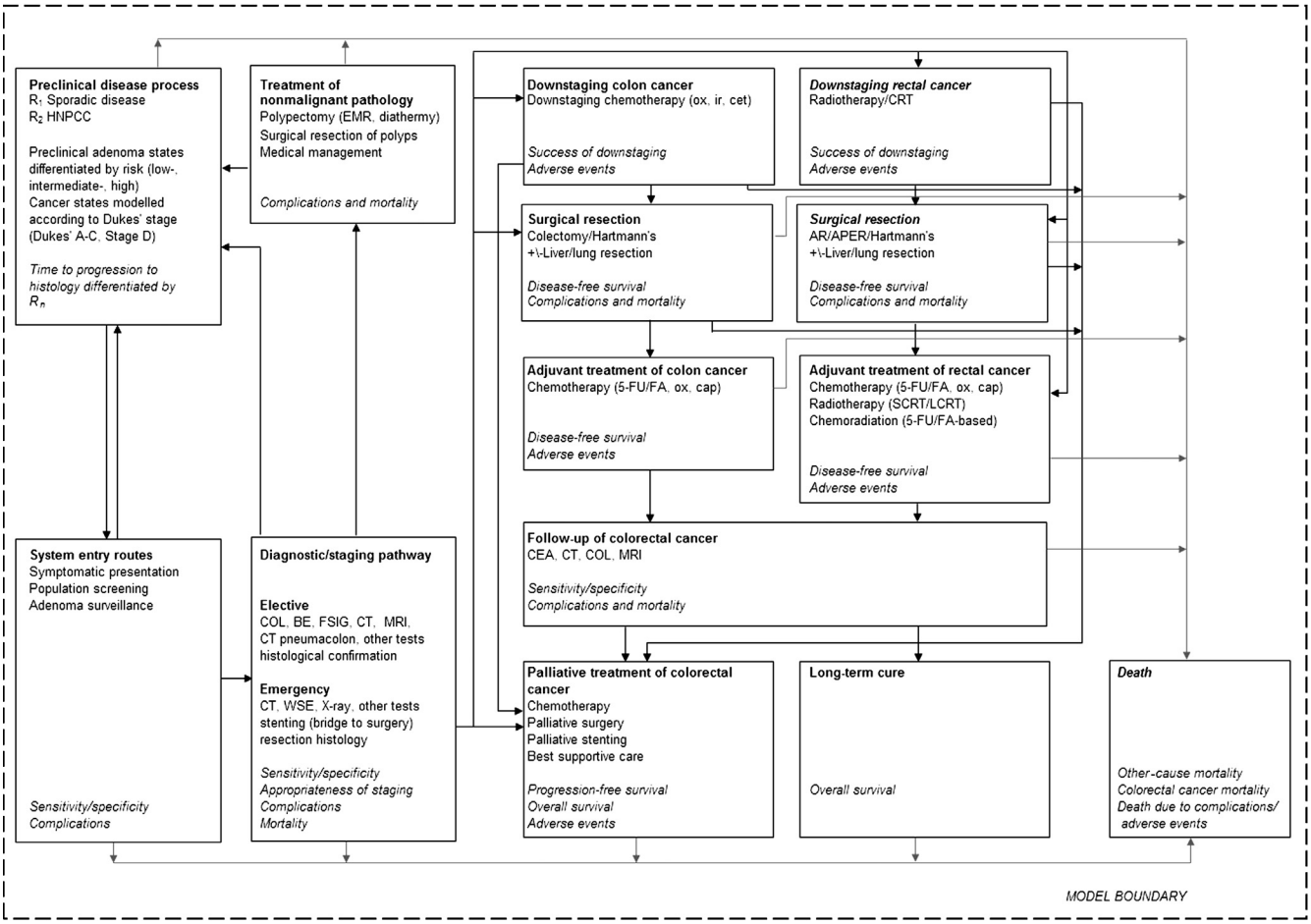

Fig. 1 – Structure of the colorectal cancer Whole Disease Model. Key disease events/clinical intent shown in italics. APER, abdominoperineal resection; AR, anterior resection; BE, barium enema; Cap, capecitabine; CEA, carcinoembryonic antigen; Cet, cetuximab; COL, colonoscopy; CRT, chemoradiation; CT, computed tomography; EMR, endoscopic mucosal resection; 5-FU/FA, 5-fluorouracil plus folinic acid; FSIG, flexible sigmoidoscopy; HNPCC, hereditary nonpolyposis colorectal cancer; Ir, irinotecan; LCRT, long course radiotherapy; MRI, magnetic resonance imaging; Ox, oxaliplatin; SCRT, short course radiotherapy; WSE, water-soluble enema.

reflect the complexity of the disease and current service pathways; they do not make assertions about the structure of the implemented model. Because of the complexity of these conceptual models, they are not presented here but are available in full elsewhere [6]. A third "design-oriented" conceptual model (Fig. 1) was developed to draw together interrelationships between the disease and service pathways. This latter model was used as a basis for considering alternative model designs, anticipated evidence requirements, and determining the appropriate level of depth within each part of the model.

The Implemented Colorectal Cancer Whole Disease Model

Economic perspective, costs, and health outcomes

The model was implemented as a probabilistic next-event patient-level simulation by using SIMUL8 based on the conceptual modeling exercise [6]. The economic analysis follows NICE's Reference Case [7] and includes those costs borne by the National Health Service (NHS) and Personal Social Services and benefits accrued by NHS patients. Costs are valued at 2011 prices. In line with current recommendations [7], costs and health outcomes are discounted at an annual rate of 3.5%. Discounting is applied from the earliest point at which a patient can enter the service in the model.

Model structure

The model simulates the experience of a hypothetical birth cohort from a normal epithelial state through to the development of adenomatous colorectal polyps, colorectal cancer, and eventual death. Discrete health states are modeled for low-, intermediate-, and high-risk patients [8]. Cancer states are modeled according to the Turnbull modification of Dukes' staging system (Dukes' A–C and stage D) [9,10]. Prior to diagnosis, the model simultaneously operates in two dimensions: 1) the patient's true underlying histological state, defined by the presence/absence of adenomas and/or cancer, and 2) what is known about the given patient's histology at any point of interaction with the colorectal service. Upon entry into the cancer service, patients remain notionally within the preclinical model until they undergo some change in clinical state (e.g., they receive a positive diagnosis of colorectal cancer, or are identified as having adenomas) or die. A proportion of the model population never develops adenomas or interacts with the cancer service during their lifetime. Preclinical natural history progression is characterized by using time-dependent Weibull distributions to describe dwell time in each histological state. At any point within the simulation, preclinical disease progression can be interrupted by patient presentation and intervention or other-cause mortality. With the exception of acute obstruction,

symptomatology is not directly modeled because of insufficient evidence concerning the joint relationship between symptoms, presentation rates, and diagnostic test operating characteristics.

Diagnosis, screening, and surveillance. The model simulates five possible entry routes into the colorectal cancer service: elective/emergency symptomatic presentation, referral from elsewhere in secondary care, follow-up for screen-positives, and surveillance for individuals in whom adenomas have previously been found. In each instance, patients follow rule-based diagnostic algorithms that are dependent on sampled test operating characteristics and probabilities of compliance, harm, and subsequent mortality. The initial test outcome determines whether the patient requires further investigation, immediate treatment (e.g., surgery for perforation), discharge (and whether their risk profile is subsequently modified), or referral into the colorectal cancer treatment model. Risks of complications and mortality are modeled for all investigations that involve bowel preparation and/or direct endoscopic visualization (colonoscopy [COL], flexible sigmoidoscopy, computed tomography colonography [CTC], and barium enema). COL, barium enema, and flexible sigmoidoscopy are assumed to be used only in patients younger than 85 years. Most patients referred for diagnostic investigation undergo COL; however, some undergo alternative tests because of the presence of certain symptoms (e.g., palpable abdominal mass), older age, or patient choice. Patients with acute symptoms are assumed to undergo preoperative imaging to identify the primary cause of the symptom secondary to the underlying tumor. A proportion of patients with underlying colon cancer who present with acute obstruction are assumed to undergo stenting as a bridge to elective surgery. If stenting is clinically successful, a lower operative mortality risk is modeled relative to those undergoing emergency surgery. Following diagnosis, patients who survive their emergency surgery are assumed to have the same prognosis as those who undergo elective surgery. Patients without obstruction are assumed to undergo elective surgery. Unfit patients presenting with emergency symptoms are assumed to receive supportive care and die imminently.

The model assumes the full rollout of biennial fecal occult blood screening for individuals aged 60 to 69 years. Some patients are assumed to never attend screening. Of those who participate on at least one occasion, a random proportion is assumed to participate during each screening round. Adenomas surveillance is modeled up to the age of 75 years [8]. While undergoing surveillance, patients are assumed to be ineligible for screening. Surveillance and diagnostic pathways for increased-risk groups (hereditary nonpolyposis colorectal cancer, familial adenomatous polyposis , ulcerative colitis, and Crohn's disease) are not explicitly modeled because of 1) an absence of evidence through which to directly parameterize or calibrate preclinical disease progression, 2) limited evidence regarding the epidemiology of these risk factors, and 3) the computational complexity associated with their inclusion. These patients are not excluded but are instead subsumed within the broader heterogeneous population.

Treatment and follow-up of nonmetastatic disease. The majority of patients with nonmetastatic colon cancer undergo active treatment, with the remainder receiving supportive care. Surgery is assumed for all fit individuals younger than 85 years; beyond this age, 50% of the patients are assumed to undergo surgery. Adjuvant and palliative chemotherapies are assumed to be available for patients below 80 years of age. All fit patients with Dukes' A colon cancer, and a proportion of those with Dukes' B/C disease, are assumed to undergo surgery alone and subsequently enter follow-up. The remainder receive surgery and adjuvant chemotherapy. Based on clinical advice and a lack of published evidence related to particular treatments, local relapse is not modeled for colon cancer patients. For rectal cancer, treatment options and prognosis are modeled principally according to magnetic resonance imaging–predicted circumferential resection margin involvement. Patients for whom an R0 resection is anticipated are assumed to undergo either short-course preoperative radiotherapy and surgery, or initial surgery alone with selective chemoradiation (CRT) for those with involved margins. Patients for whom an R1/R2 resection is predicted are assumed to undergo preoperative CRT; subsequent prognosis is modeled according to whether an R0 resection is achieved. The rectal cancer model operates by using the same general structure as the colon cancer model. Local relapse is included but is assumed to result only in additional surgery; possible relationships between local relapse incidence and distant relapse or death are not modeled because of a lack of data to differentiate between excess mortality resulting from local and distant relapse. A proportion of patients is assumed to receive a stoma, either permanent or temporary.

For all patients who survive surgery with curative intent, a disease-free survival (DFS) interval is sampled from stage-, treatment-, and location-specific parametric survival curves. From this point, other-cause mortality and relapse are modeled as competing risks. Patients who remain alive and disease-free 5 years following surgery are assumed to remain relapse-free indefinitely.

Management of metastatic colorectal cancer. Patients who present with synchronous metastatic disease and those who suffer metastatic relapse are allocated to one of three groups: 1) initially operable, 2) potentially operable, or 3) inoperable. Patients who are fit and have initially operable metastases may undergo curative surgery of the liver or lungs, assuming a staged resection of the primary tumor and metastases. Independent risks of perioperative mortality are assumed for each resection. DFS is modeled according to the metastatic site. Patients who remain relapse-free 5 years postsurgery are assumed to be cured. In the event of relapse, some patients with liver metastases may undergo re-resection and a second DFS interval is applied. Potentially operable patients are assumed to receive chemotherapy for up to 3 months. Patients whose tumors express the *KRAS* wild-type gene are assumed to receive cetuximab plus either 5-fluorouracil, folinic acid, and oxaliplatin (FOLFOX) or 5-fluorouracil, folinic acid, and irinotecan (FOLFIRI) [11]; treatment options for patients whose tumors express the mutated version of the KRAS gene are the same with the exclusion of cetuximab. The probability that chemotherapy renders the tumor operable is treatment-dependent. If downstaging is successful, metastasectomy is assumed to be attempted; thus, patients follow the pathway described above. A proportion of resections is assumed to be aborted open-close operations. Excluding those receiving cetuximab, patients for whom downstaging is unsuccessful and those for whom further surgery is unsuccessful continue receiving the same palliative chemotherapy regimen without the opportunity for subsequent resection (remaining overall survival [OS] and progression-free survival [PFS] are adjusted according to previous chemotherapy treatment time). Patients receiving cetuximab who are not successfully downstaged continue receiving the same regimen without cetuximab. Inoperable patients are assumed to receive active palliative chemotherapy if fit, or supportive care if unfit.

Palliative treatment of colorectal cancer and best supportive care. Fit patients with inoperable metastases are assumed to receive palliative chemotherapy and are assigned a time to other-cause mortality, time to cancer-specific mortality, PFS1 on first-line treatment, PFS2 on second-line treatment, and time receiving supportive care (calculated as OS − [PFS1 + PFS2]). These durations differ between chemotherapy sequences. Unfit

patients receiving supportive care are assigned a shorter OS time and zero PFS.

Evidence used to inform model parameters

Model parameters were informed by numerous evidence sources including systematic reviews, randomized controlled trials, meta-analyses, observational studies, screening pilot evaluations, resource use surveys, costing studies, health valuation studies, clinical audit, and expert opinion. Natural history parameters were estimated by using calibration methods. Evidence sources were identified from a previous systematic review [12], reviews produced within the colorectal cancer guideline development process, and additional searches. All parameter distributions are presented in Appendix 1 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2013.02.012.

Baseline characteristics. Patient-specific baseline characteristics include other-cause mortality based on life tables (http://www.ons.gov.uk/), fitness [13], location of neoplasia [14], and the presence of an abdominal mass [15].

Unobservable parameters relating to disease natural history and presentation behaviors. Several model parameters cannot be observed empirically. These include natural history progression rates, presentation rates given the patient's underlying histology, and the probability that an individual who presents symptomatically does so with obstructing cancer. These parameters were estimated by calibrating the model against data on age-specific incidence [14], Dukes' stage distribution at diagnosis [16], stage distribution of obstructing cancers [17], and preclinical adenoma prevalence [18]. A random walk variant of the Metropolis-Hastings algorithm [19] was programmed into the model and run until the chains appeared to have converged. The algorithm was then run for a further 17,000 iterations across two independent chains to approximate samples from the posterior distribution (see Fig. 2) for use in the probabilistic sensitivity analysis.

Diagnostic/screening test operating characteristics and harms. The operating characteristics of diagnostic tests and general practitioner consultation are modeled according to true test sensitivity and specificity given the patient's underlying histology based on systematic reviews, individual population-based studies, and observational data [20–25]. The probabilities of incomplete tests, perforation, and death were estimated from trials and observational studies [13,26–30].

Time-to-event estimates for DFS, OS, and PFS. DFS estimates for adjuvant/neoadjuvant treatments were estimated by fitting parametric survival curves to observe Kaplan-Meier curves derived from randomized controlled trials [31–33] and observational studies [34]. The Bucher method [35] for handling indirect comparisons was used where direct estimates were not available. For palliative treatments, a network meta-analysis [36] was used to estimate relative hazard ratios for different chemotherapy sequences, assuming baseline survival models for OS and PFS reported by Seymour et al. [37].

Probability of resectability. Modeling the comparative clinical effectiveness of alternative downstaging treatments is difficult because the available evidence base is largely composed of opportunistic findings reported within case series and underpowered phase I/II clinical trials. The probability that a patient with metastases is resectable, potentially respectable, or unresectable was taken from an observational study [38]. The model assumes that 10% of the patients are initially operable, 13% are potentially operable, and the remainder are inoperable. At the time of model development, there was no comparative evidence to suggest that the downstaging benefits of oxaliplatin are any lower than those of cetuximab; hence, the same rate is assumed for cetuximab-including regimens. The relative success of FOLFIRI compared with FOLFOX in downstaging tumors was estimated from one clinical trial [39]. It should be noted that these estimates are subject to considerable uncertainty.

Probabilities of receiving individual treatments. The probabilities that patients receive particular treatments were estimated from unpublished data from a survey [40] and expert opinion.

Health-related quality of life. The definition of different colorectal cancer health states was based on recent systematic reviews [12,41]. The model includes health-related quality-of-life (HRQOL) estimates for three general health states: no cancer, nonmetastatic/progression-free, and metastatic postprogression. The mean HRQOL without cancer was modeled by using the UK population EuroQol five-dimensional questionnaire tariff reported by Kind et al. [42]. A relative risk describing utility for nonmetastatic/progression-free cancer states was estimated from a longitudinal health utilities index study in long-term cancer survivors [43]. Lower HRQOL was assumed for patients following disease progression, based on a standard gamble study of hypothetical states of metastatic colorectal cancer [44].

Resource use and costs. Cost parameters were derived from NHS Reference Costs [45], the British National Formulary [46], Unit Costs for Health and Social Care [47], previous health technology assessment reports [48], and other literature [49–51].

Methods for using alternative economic decision rules

Table 1 shows the alternative options assessed within each guideline topic together with a description of how the baseline model was modified to incorporate the option. Three alternative decision rules were used: 1) piecewise cost-utility analysis [59], 2) Birch and Gafni's "step in the right direction" approach [60], and 3) disease-level constrained maximization [1].

Piecewise cost-utility analysis [59]. Total expected system costs and quality-adjusted life-years (QALYs) for each option within each topic were calculated over 1,500 probabilistic samples, each of which was composed of 300,000 simulated individuals. Incremental cost-effectiveness ratios (ICERs) were calculated by using conventional economic decision rules. Options that were subject to simple dominance or extended dominance were ruled out of the analysis.

Birch and Gafni's "step in the right direction" decision rule [60]. The results of the piecewise economic analysis were examined to identify 1) an option that increases system QALYs and costs compared with the current service (an investment option) and 2) an option within a different guideline topic that produces fewer QALYs at a lower cost than the current service (a disinvestment option). The investment option and the disinvestment option were jointly propagated through the probabilistic model to assess whether the total system QALYs are increased *and* total system costs are decreased compared against the current service.

***Disease-level constrained maximization** [1]*. The model was programmed such that all options within all topics could be evaluated simultaneously. Each guideline topic (topic A, topic B … topic N) was assigned a variable, and each topic option

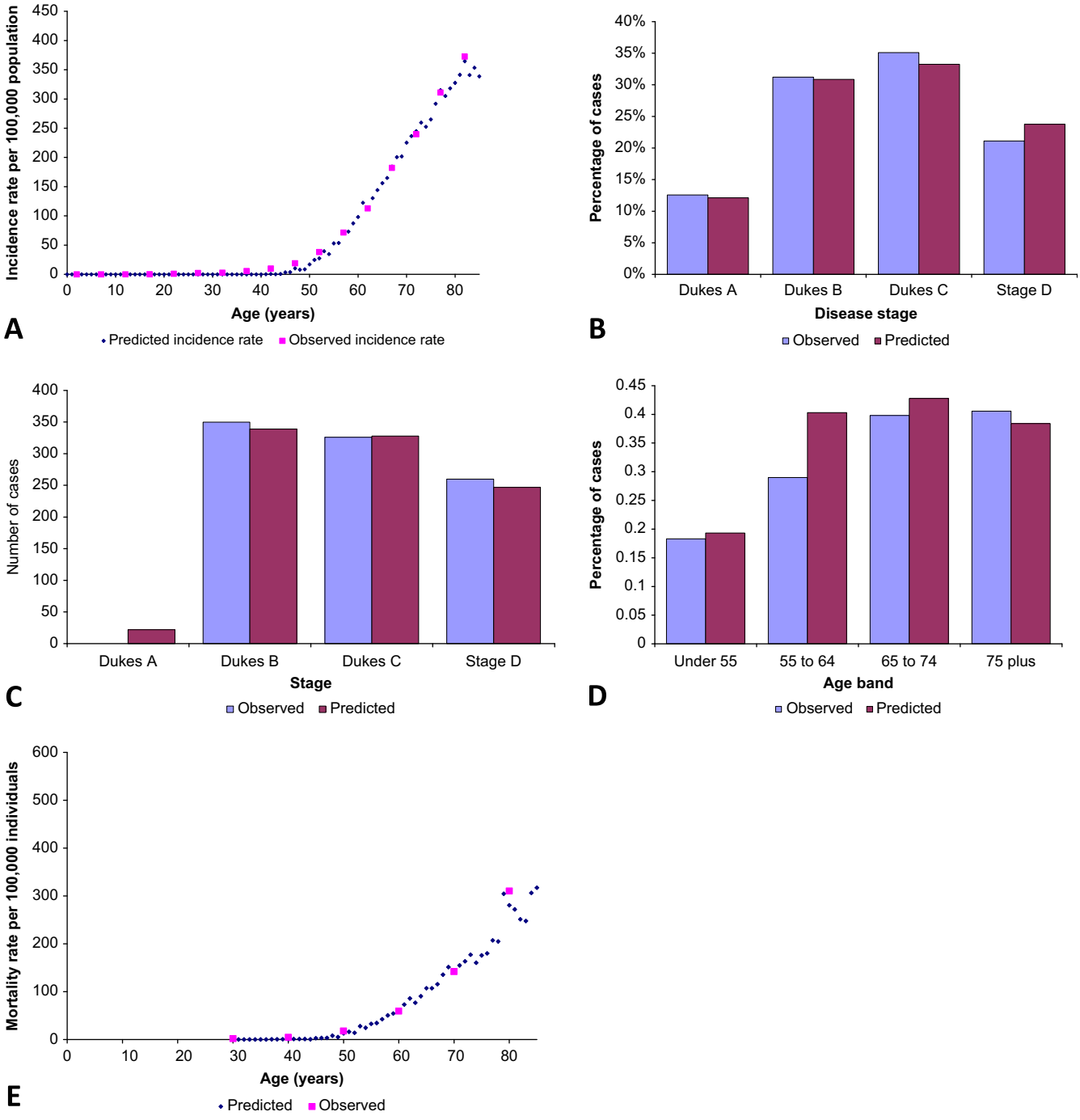

Fig. 2 – Maximum *a posteriori* estimates by using Metropolis-Hastings calibration. (A) Observed versus predicted colorectal cancer incidence by age. (B) Observed versus predicted stage distribution. (C) Observed versus predicted obstructed cases by stage. (D) Observed versus predicted adenoma prevalence by age. (E) Observed versus predicted mortality by age.

was assigned a unique number (baseline = 1, alternative 1 = 2, alternative 2 = 3, etc.) to allow the events, costs, and outcomes of multiple options to be evaluated simultaneously. For example, the current service is represented by chromosome (A1,C1,D1,D2,E1,F1, G1,H1,I1,J1,M1,N1), whereas a shift toward a service configuration that includes CTC, transanal endoscopic microsurgery, preoperative radiotherapy, and capecitabine followed by irinotecan is represented by chromosome (A2,C2,D11,D21,E4,F1,G1,H1,I1,J1, M14,N1). Sixteen thousand random service configurations were propagated through the model to identify the configuration that produces the greatest QALY gain with a system cost equal to or lower than that of the current service.

Results

Conventional Piecewise Cost-Effectiveness Analysis

The Whole Disease Model was capable of evaluating 11 of the 15 guideline topics (Table 2). Topic O was excluded because the

options were not fully defined. Topics B, K, and L related to staging/imaging technologies; these were excluded from the economic analysis because of insufficient evidence to characterize disease misclassification and the complexity associated with modeling counterfactual pathways, costs, and outcomes (note also that most "wrong" diagnostic classification decisions will already be embedded within randomized controlled trial evidence used to inform the model parameters).

The model suggests that CTC is expected to dominate the other diagnostic options. In practice, however, CTC is usually reserved for older, frail patients who cannot tolerate COL, and this technology is not available at all NHS trusts. The second most effective diagnostic option is flexible sigmoidoscopy→barium enema although this offers small benefits and considerable additional costs over the current baseline pathway.

With respect to topic C, transanal endoscopic microsurgery is expected to dominate radical resection because of its lower marginal cost and its expected improvement in both local and distant relapse.

The economic analyses of topics D1 and D2 produce exactly the same result, which is intuitively sensible, as CT is modeled as a precursor to allow for the use of stenting. The incremental cost-effectiveness ratio for stenting versus no stenting is expected to be around £1473 per QALY gained.

For topic E, preoperative CRT is expected to be the most effective option for resectable rectal cancer patients with an ICER of approximately £18,084 per QALY gained as compared against preoperative radiotherapy. Selective postoperative CRT and the current baseline service (a mixture of pre- and postoperative treatment) are expected to be dominated.

The analysis of topic F suggests that simultaneous resection in patients with operable metastases may offer considerable cost savings. There was insufficient evidence available to quantify the mortality risk associated with staged resections; hence, this topic was evaluated as a crude cost-minimization analysis. This is not ideal, and further clinical evidence should be sought when this becomes available.

Owing to overlap between guideline topics, the analysis of topic G is a more restrictive analysis of that presented for topic E with the exclusion of the selective postoperative CRT option. As this decision option was dominated, the results are otherwise identical to those for topic E.

The analysis of topic H suggests that adjuvant chemotherapy dominates no adjuvant chemotherapy in patients with stage II/III rectal cancer. Some caution is advised because of confounding in the evidence used to describe the baseline relapse hazard.

The analysis of topic I suggests that adjuvant chemotherapy for patients with Dukes' B colon cancer is expected to dominate no chemotherapy.

For topic J, hepatic arterial infusion is expected to be the most effective option for patients with liver-only metastases. Chemotherapy is expected to produce fewer QALYs than hepatic arterial infusion, although this difference is small. Supportive care alone is unsurprisingly the least effective and the least expensive option. The ICER for hepatic arterial infusion versus chemotherapy is expected to be around £110,932 per QALY gained, while the ICER for chemotherapy versus best supportive care is expected to be around £16,608 per QALY gained.

For topic M, the most effective option is expected to be capecitabine plus oxaliplatin followed on progression by capecitabine plus irinotecan. This is unlikely to be considered cost-effective under current acceptable thresholds, as the ICER is in excess of £134,000 per QALY gained. The ICER for capecitabine plus oxaliplatin followed on progression by irinotecan is expected to be around £19,160 per QALY gained as compared against first-line capecitabine followed by rechallenging with capecitabine. Based on the results for topics J and M, the indirect ICER for this chemotherapy option versus supportive care is expected to be around £11,867 per QALY gained. All other options are expected to be ruled out by simple or extended dominance.

For topic N, the current mix of intensive and relaxed follow-up is likely to yield an ICER of £15,551 per QALY gained compared against relaxed follow-up.

Sendi, Birch and Gafni Piecewise Investment-Disinvestment Decision Rule

Preoperative CRT for rectal cancer is expected to produce more QALYs at a greater cost than the current mix of adjuvant treatments. Disinvestment in the existing system could be used to fund this intervention. Joint investment in preoperative CRT and disinvestment in palliative chemotherapy to the less expensive and less effective capecitabine→irinotecan sequence is expected to produce a net improvement in system QALYs together with a reduction in the total system cost. It should be noted that this analysis is intended only to demonstrate the use of this decision rule, and other investment/disinvestment scenarios may produce more net QALYs gains and/or cost savings.

Disease-Level Constrained Maximization

Figure 3 shows the results of the constrained maximization analysis. Each plotted point represents the incremental costs and QALY gains for each unique service configuration compared against the current service. Assuming that system costs are constrained at their current level, the optimal service configuration is that which dominates the current service while also producing the greatest number of QALYs. This approach directly deals with technical efficiency and, to some degree, allocative efficiency, albeit within the confines of the direct health benefits generated by the colorectal cancer service. These constrained maximization results should however be interpreted with caution because this analysis is deterministic and does not account for the uncertainty surrounding the available evidence due to the considerable time constraints associated with model run time.

Discussion

This study demonstrates that Whole Disease Modeling is feasible and can provide a consistent and coherent platform for the economic evaluation of most interventions across a disease pathway. Within this case study, the Whole Disease Model was capable of evaluating 11 of 15 (73%) economic questions within the colorectal cancer guideline. Some analyses were crude; however, this reflects the uncertainty within the evidence base rather than a limitation of the modeling approach itself. The economic analysis of four topics was not attempted because of the vague definition of the research question or the absence of sufficient evidence to warrant formal evaluation. This analysis produced a considerably larger amount of economic information than that produced by piecewise economic analysis within the usual guideline process. Within the colorectal cancer guideline development process, just 1 of the 11 topics (topic M) was subjected to formal economic evaluation. The guideline document cites several reasons why other topics were not subjected to economic analysis including weak data, difficulties in capturing downstream events, costs and outcomes, and small populations reflected in the selected topics.

The factors captured within the analysis of topic M within this guideline analysis model and the Whole Disease Model were broadly similar, showing that the broader boundary of a Whole Disease Model does not restrict the level of depth possible within the model. Both the guideline model and the Whole Disease Model adopted similar structures: the same health states for

Table 2 – Probabilistic cost-effectiveness results for 300,000 simulated individuals.

Topic	Option	Cost (£)	QALY	Inc. cost (£)	Inc. QALY	ICER (QALY) (£)
Baseline service		103,857,495	14,636,083	–	–	Dominated
A	CT colonography	97,517,419	14,636,253	−1,297,809	2471.96	Dominating
	FSIG→BE	107,471,657	14,636,087	–	–	Dominated
	Baseline (COL)	103,857,495	14,636,083	–	–	Dominated
	FSIG→COL	98,815,228	14,633,781	–	–	–
C	TEMS	100,445,898	14,636,331	−3,411,597	248.55	Dominating
	Radical resection	103,857,495	14,636,083	–	–	–
D_1	Baseline	103,857,495	14,636,083	207,617	140.94	1,473
	No CT scan	103,649,878	14,635,942	–	–	–
D_2	Baseline	103,857,495	14,636,083	207,617	140.94	1,473
	No stenting	103,649,878	14,635,942	–	–	–
E	All preop CRT	104,494,625	14,636,396	1,197,601	66.22	18,084
	All preop RT	103,297,024	14,636,329	–	–	–
	Baseline	103,857,495	14,636,083	–	–	Dominated
	No preop adjuvant tx	104,333,702	14,635,990	–	–	Dominated
F	Simultaneous resection	103,757,024	14,636,083	−100,471	0.00	Dominating
	Baseline (staged)	103,857,495	14,636,083			
G	All preop CRT	104,494,625	14,636,396	1,197,601	66.22	18,084
	All preop RT	102,896,369	14,636,329	–	–	–
	Baseline	103,857,495	14,636,083	–	–	Dominated
H	Adjuvant chemotherapy	103,358,231	14,636,137	−499,264	53.58	Dominating
	Baseline	103,857,495	14,636,083	–	–	–
I	Baseline	103,857,495	14,636,083	−189,507	149.38	Dominating
	No adjuvant chemotherapy	104,047,002	14,635,934	–	–	–
J	HAI	106,308,256	14,636,105	2,450,761	22.09	110,932
	Baseline	103,857,495	14,636,083	13,111,810	789.47	16,608
	BSC only	90,745,685	14,635,293	–	–	–
M	XELOX→XELIRI	103,548,863	14,636,163	715,860	5.31	134,938.96
	XELOX→FOLFIRI	104,549,675	146,36,163	–	–	Dominated
	FOLFOX→XELIRI	106,494,974	14,636,163	–	–	Dominated
	FOLFOX→FOLFIRI	107,319,353	14,636,163	–	–	Dominated
	XELOX→IRI	102,833,003	14,636,158	4,812,554	251.18	19,159.98
	FOLFOX→IRI	105,779,115	14,636,158	–	–	Dominated
	Baseline	103,857,495	14,636,083	–	–	Dominated
	XELIRI→XELOX	105,324,882	14,636,055	–	–	Dominated
	XELIRI→FOLFOX	106,522,006	14,636,055	–	–	Dominated
	FOLFIRI→XELOX	108,144,085	14,636,055	–	–	Dominated
	FOLFIRI→FOLFOX	109,163,047	14,636,055	–	–	Dominated
	XELIRI→IRI	105,577,225	14,636,039	–	–	Dominated
	XELIRI→XEL	104,368,886	14,636,032	–	–	Dominated
	FOLFIRI→5-FU/FA	107,962,889	146,36,032	–	–	Dominated
	XEL→XELOX	99,033,548	14,635,931	–	–	Ext dom
	5-FU/FA→FOLFOX	102,913,909	14,635,930	–	–	Dominated
	XEL→XELIRI	100,025,257	14,635,920	–	–	Dominated
	5-FU/FA→FOLFIRI	103,711,773	14,635,919	–	–	Dominated
	XEL→IRI	99,239,714	14,635,913	–	–	Dominated
	5-FU/FA→IRI	102,141,844	14,635,913	–	–	Dominated
	XEL→XEL	98,020,449	14,635,906	–	–	–
	5-FU/FA→5-FU/FA	101,704,870	14,635,906	–	–	Dominated
N	Baseline	103,857,495	14,636,083	1,827,129	117.49	15,551
	Relaxed follow-up	102,030,367	14,635,965	–	–	–

BSC, best supportive care; COL, colonoscopy; CRT, chemoradiation; CT, computed tomography; ext dom, extendedly dominated; FOLFIRI, 5-FU/FA plus irinotecan; FOLFOX, 5-FU/FA plus oxaliplatin; FSIG, flexible sigmoidoscopy; 5-FU/FA, 5-fluorouracil plus folinic acid; HAI, hepatic arterial infusion; IRI, irinotecan; preop, preoperative; RT, radiotherapy; TEMS, transanal endoscopic microsurgery; tx, treatment; XELIRI, capecitabine plus irinotecan; XELOX, capecitabine plus oxaliplatin.

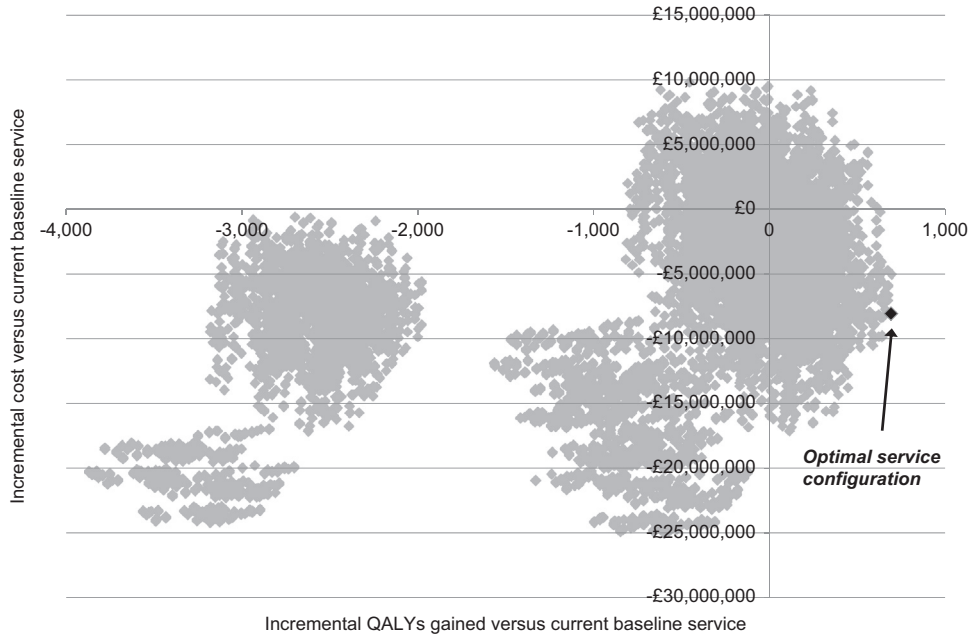

Fig. 3 – Results of the constrained maximization analysis. Optimal service configuration—topic A: CTC; topic C: TEMS; topic D_1: CT scan; topic D_2: stenting; topic E: preoperative chemoradiation; topic F: simultaneous resection; topic G: see topic E; topic H: adjuvant chemotherapy; topic I: adjuvant chemotherapy; topic J: palliative chemotherapy; topic M: XELOX→XELIRI; topic N: intensive follow-up. CT, computed tomography; CTC, computed tomography colonography; QALY, quality-adjusted life-year; TEMS, transanal endoscopic microsurgery.

metastatic patients were used in both models (alive and progression-free on first-line treatment, alive and progression-free on second-line treatment, alive with disease progression following first-line treatment, alive with disease progression following second-line treatment, and dead). Similarly, baseline and relative OS and PFS estimates were applied as mean sojourn times conditional on treatment sequence. In both models, these estimates were derived from network meta-analyses (a *de novo* analysis was undertaken in the guideline model while the Whole Disease Model instead relied on a published meta-analysis). The cost components included in each model were also similar, comprising drug acquisition, administration, and supportive care costs. Two key differences between the models are noteworthy. First, the guideline model includes utility adjustments for diarrhea, hand-foot syndrome, and febrile neutropenia for specific lines of chemotherapy using data from breast cancer as a proxy. In contrast, we did not include differential HRQOL impacts associated with specific chemotherapy sequences as the selective inclusion and valuation of some adverse events, but not others, would likely bias the model results. Our view is that the existing evidence base is simply too weak to include such health effects in a meaningful way. Second, we included a broader set of chemotherapy sequences than the guideline model. In both analyses, the majority of possible sequences were ruled out by simple or extended dominance. The preferred option in both analyses, assuming a threshold of £20,000 per QALY gained, involves first-line combination therapy using oxaliplatin followed by second-line irinotecan. The guideline model suggests that first-line treatment should include 5-FU/FA while the Whole Disease Model suggests that this combination should instead use capecitabine. This conflict is likely to be largely driven by different assumptions regarding the adverse event profiles for these two drugs.

While this article highlights that Whole Disease Models can provide considerably more useful economic information than the conventional piecewise analyses, other benefits should also be acknowledged. First, a broader value of Whole Disease Modeling is not just that it can evaluate a wealth of decision alternatives at various points in a disease pathway, but also that it does so within a single consistent set of assumptions about the disease and its management. Given the model scope, other economic questions beyond the remit of the guideline, for example, those questions posed within NICE's Technology Appraisal Programme, could also be addressed by using the same model infrastructure. As such, this modeling approach could be used as a means of bringing consistency between individual colorectal appraisals, clinical guidelines, and other policy decision problems. Furthermore, by placing decision nodes at various points in the simulated disease and treatment pathways, the model can also address questions about multiple changes to the entire pathway within a framework that explicitly considers the opportunity costs of service investment. This is essentially the question being asked within clinical guidelines, but remains one that conventional piecewise economic evaluation simply cannot answer. Further developmental work around operationalizing such decision approaches may be valuable.

These benefits carry several costs that in some circumstances may preclude the development of Whole Disease Models. First, model development requires a nontrivial investment of time and resource. The development and analysis of the colorectal cancer Whole Disease Model presented here required approximately 12 months. All model development was undertaken by one individual, although the authors did have access to evidence reviews undertaken by the NICE GDG. In addition, the need to capture the depth of the pathways and the presence of complicated feedback loops and differential prognoses for specific patient subgroups almost inevitably requires a simulation modeling approach, while the need to capture interactions between unobservable natural history and diagnostic/screening processes necessarily requires some form of model calibration. The combination of these two factors has significant implications for the time and technical complexity associated with model development. Despite these concerns, it is reasonable to argue that the time

and resource costs of undertaking 11 analyses by using a single Whole Disease Model are likely to be markedly less than those associated with developing 11 *de novo* piecewise models. Pragmatically, it may be possible to adopt some of the system-level ideas presented here within a more restrictive model boundary; however, this will infringe the range of economic questions that the model can be used to address.

So, what might this mean for the process of clinical guideline development? This case study suggests that Whole Disease Models could be considerably more useful than conventional piecewise economic evaluation. However, this represents a single example of a Whole Disease Model—in some clinical areas, Whole Disease Model development may require more time while others will require less. While Whole Disease Modeling is technically difficult, time-consuming, and resource-intensive, the benefits of producing economically informed guideline recommendations may far outweigh the costs of generating them by using this approach. There are other examples of system-level models available in the literature that in principle could be used in informing the economic basis of clinical guidelines; the most pertinent examples are the Coronary Heart Disease Policy model [61] and the Archimedes Diabetes model [62]. These models are also technically complex in nature and required considerable model development time. The alternative is however to continue to rely on a small number of *de novo* piecewise models developed within the guideline process, and, where possible, to fill in the gaps by using published economic analyses. In most disease areas, numerous gaps will likely remain whereby recommendations are formed on the basis of analyses that have a dubious applicability to the specified guideline question, or, in some instances, no economic evidence whatsoever. If we truly believe that the basis of resource allocation decisions should be an economic one, then this position is far from optimal. Whole Disease Modeling may represent a more useful basis for informing these decisions. Future research should focus on the feasibility of developing and using Whole Disease Models within live guideline development processes. This should be considered a priority for joint working between guideline developers, model developers, and other stakeholders to the clinical guideline development process.

Conclusions

This study demonstrates that Whole Disease Modeling can allow for the economic analysis of most interventions across a disease service within a consistent conceptual and mathematical infrastructure. The approach may be especially valuable in informing clinical guideline development.

Acknowledgments

The authors thank Dr. Andrew Champion of the National Collaborating Centre for Cancer and the members of the NICE Colorectal Cancer Guideline Development Group for enabling the author to observe the guideline development meetings.

Source of financial support: This study was funded by the National Institute for Health Research (NIHR) (study reference RDA/PAS03/2007/076). The views expressed here reflect those of the authors and do not necessarily reflect those of the NIHR or the National Institute for Health and Clinical Excellence. None of the authors have any conflicts of interest.

Supplemental Materials

Supplemental material accompanying this article can be found in the online version as a hyperlink at http://dx.doi.org/10.1016/j.jval.2013.02.012 or, if a hard copy of article, at www.valueinhealthjournal.com/issues (select volume, issue, and article).

REFERENCES

[1] Tappenden P, Chilcott J, Brennan A, Squires H, Stevenson M. Whole disease modeling to inform resource allocation decisions in cancer: a methodological framework. Value Health 2012;15:1127–36.
[2] Wailoo A, Roberts J, Brazier J, McCabe C. Efficiency, equity and NICE clinical guidelines. BMJ 2004;328:536–7.
[3] National Institute for Health and Clinical Excellence. The Guidelines Manual. London: National Institute for Health and Clinical Excellence, 2009.
[4] National Institute for Health and Clinical Excellence. Clinical Guideline – The Diagnosis and Management of Colorectal Cancer. London: National Institute for Health and Clinical Excellence, 2011.
[5] Tappenden P. Conceptual modelling for health economic model development. Health Economics and Decision Science Discussion Paper Series 12/05. 2012. Available from: http://www.shef.ac.uk/scharr/sections/heds/. [Accessed January 6, 2012].
[6] Tappenden P, Glynne-Jones, Shorthouse A, et al. Colorectal cancer and its detection, diagnosis, treatment and follow-up: disease and treatment pathways. Health Economics and Decision Science Discussion Paper Series 12/09. Available from: http://www.shef.ac.uk/scharr/sections/heds/. [Accessed January 6, 2012].
[7] National Institute for Health and Clinical Excellence. Guide to the Methods of Technology Appraisal. London: National Institute for Health and Clinical Excellence, 2008.
[8] Atkin WS, Saunders BP. Surveillance guidelines after removal of colorectal adenomatous polyps. Gut 2002;51(Suppl. 5):v6–9.
[9] Turnbull RB, Kyle K, Watson FR, Spratt J. Cancer of the colon: the influence of the no touch isolation technic on survival rates. Ann Surg 1967;166:421–5.
[10] Dukes CE. The classification of cancer of the rectum. J Pathol Bacteriol 1932;35:323–2.
[11] National Institute for Health and Clinical Excellence. Cetuximab for the First-Line Treatment of Metastatic Colorectal Cancer. Technology Appraisal No. 176. London: National Institute for Health and Clinical Excellence, 2009.
[12] Trueman P, Chilcott JB, Lowson K, et al. Bowel Cancer Services: Costs and Benefits. Report to the Department of Health. York: York Health Economics Consortium/University of Sheffield, 2010.
[13] Weller D, Moss S, Butler P, et al. English Pilot of Bowel Cancer Screening: An Evaluation of the Second Round. Report to the Department of Health. Edinburgh: The Institute of Cancer Research, 2006.
[14] Office for National Statistics. Registrations of cancer diagnosed in 2007. Series MB1 No. 38, 1–44. Available from: http://www.statistics.gov.uk/downloads. [Accessed May 4, 2010].
[15] Dunne JR, Gannon C, Osborn TM, et al. Perioperative anemia in colon cancer: assessment of risk factors. Am Surg 2002;68:582–7.
[16] Finan P, Smith J, Morris E, et al. National Bowel Cancer Audit 2009. Leeds: Association of Coloproctology of Great Britain and Ireland, 2011.
[17] Tekkis PP, Kinsman R, Thompson MR, et al. The Association of Coloproctology of Great Britain and Ireland study of large bowel obstruction caused by colorectal cancer. Ann Surg 2004;240:76–81.
[18] Williams AR. Polyps and cancer of the large bowel: a necropsy study in Liverpool. Gut 1982;23:835–42.
[19] Whyte S, Walsh C, Chilcott JB. Bayesian calibration of a natural history model with application to a population model for colorectal cancer. Med Decis Making 2011;31:625–41.
[20] Allison JE, Tekawa IS, Ransom LJ, Adrain AL. A comparison of fecal occult-blood tests for colorectal-cancer screening. N Engl J Med 1996;334:155–60.
[21] Allison JE, Feldman R, Tekawa IS. Hemoccult screening in detecting colorectal neoplasm: sensitivity, specificity, and predictive value. Ann Intern Med 1990;112:328–33.
[22] De Zwart IM, Griffioen G, Shaw MP, et al. Barium enema and colonoscopy for the detection of colorectal neoplasia: sensitivity, specificity, complications and its determinants. Clin Radiol 2001;56:401–9.
[23] Rex DK, Rahmani EY, Haseman JH, et al. Relative sensitivity of colonoscopy and barium enema for detection of colorectal cancer in clinical practice. Gastroenterology 1997;112:17–23.
[24] Halligan S, Altman DG, Taylor SA, et al. CT colonography in the detection of colorectal polyps and cancer: systematic review, meta-analysis, and proposed minimum data set for study level reporting. Radiology 2005;237:893–904.

[25] Graser A, Stieber P, Nagel D, et al. Comparison of CT colonography, colonoscopy, sigmoidoscopy and faecal occult blood tests for the detection of advanced adenoma in an average risk population. Gut 2009;58:241–8.
[26] Blakeborough A, Sheridan MB, Chapman AH. Complications of barium enema examinations: a survey of UK consultant radiologists 1992 to 1994. Clin Radiol 1997;52:142–8.
[27] Bowles CJA, Leicester R, Romaya C, et al. A prospective study of colonoscopy practice in the UK today: are we adequately prepared for national colorectal cancer screening tomorrow? Gut 2004;53:277–83.
[28] Burling D, Halligan S, Slater A, et al. Potentially serious adverse events at CT colonography in symptomatic patients: National Survey of the United Kingdom. Radiology 2006;239:464–71.
[29] UK Flexible Sigmoidoscopy Screening Trial Investigators. Single flexible sigmoidoscopy screening to prevent colorectal cancer: baseline findings of a UK multicentre randomised trial. Lancet 2002;359:1291–300.
[30] Gatto NM, Frucht H, Sundararajan V, et al. Risk of perforation after colonoscopy and sigmoidoscopy: a population-based study. J Natl Cancer Inst 2010;93:230–6.
[31] Sebag-Montefiore D, Stephens RJ, Steele R, et al. Preoperative radiotherapy versus selective postoperative chemoradiation in patients with rectal cancer (MRC CR07 and NCIC-CTG-C016): a multicentre, randomised trial. Lancet 2009;373:811–20.
[32] Clinical Outcomes of Surgical Therapy Study Group. A comparison of laparoscopically assisted and open colectomy for colon cancer. N Engl J Med 2004;350:2050–9.
[33] Andre T, Boni C, Mounedji-Boudiaf L, et al. Oxaliplatin, fluorouracil and leucovorin as adjuvant treatment for colon cancer. N Engl J Med 2004;350:2343–51.
[34] Mawdsley S, Glynne-Jones R, Grainger J, et al. Can histopathologic assessment of circumferential margin after preoperative pelvic chemoradiotherapy for T3-T4 rectal cancer predict for 3-year disease-free survival? Int J Radiat Oncol*Biol*Phys 2005;63:745–52.
[35] Bucher HC, Guyatt GH, Griffith LE, et al. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol 1997;50:683–91.
[36] Golfinopoulos V, Salanti G, Pavlidis N, et al. Survival and disease progression benefits with treatment regimens for advanced colorectal cancer: a meta-analysis. Lancet Oncol 2007;8:898–911.
[37] Seymour M, Maughan TS, Ledermann JA, et al. Different strategies of sequential and combination chemotherapy for patients with poor prognosis advanced colorectal cancer (MRC FOCUS): a randomised controlled trial. Lancet 2007;370:143–52.
[38] Adam R, Delvart V, Valeanu A, et al. Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. Ann Surg 2004;240:644–57.
[39] Tournigand C, André T, Achille E, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol 2004;22:229–37.
[40] Shabaruddin FH, Elliott RA, Valle JW, et al. Understanding chemotherapy treatment pathways of advanced colorectal cancer patients to inform an economic evaluation in the United Kingdom. Br J Cancer 2010;103:315–23.
[41] Cooper K, Pilgrim H, Carroll C, et al. Chemoprevention of colorectal cancer: a systematic review and economic model. Health Technol Assess 2010;14: i–203.
[42] Kind P, Hardman G, Macran S. UK Population Norms for EQ-5D. Centre for Health Economics Discussion Paper No. 172. York: University of York, 1999: 1–98.
[43] Ramsey SD, Anderson MR, Etzioni R, et al. Quality of life in survivors of colorectal carcinoma. Cancer 2000;88:1294–303.
[44] Petrou S, Campbell N. Stabilisation in colorectal cancer. Int J Palliat Nurs 1997;3:275–80.
[45] Department of Health. NHS Reference Costs 2010-11. Available from: http://www.dh.gov.uk/health/category/publications/reports-publications/. [Accessed April 5, 2012].
[46] Joint Formulary Committee. British National Formulary 61. London: B.M.J. Group and Pharmaceutical Press, 2012.
[47] Curtis L. Unit Costs of Health and Social Care. Kent: Personal Social Services Research Unit, 2011.
[48] Boland A, Haycox A, Bagust A, Fitzsimmons L. A randomised controlled trial to evaluate the clinical and cost-effectiveness of Hickman line insertions in adult cancer patients by nurses. Health Technol Assess 2003;7: i–112.
[49] Remák E, Brazil L. Cost of managing women presenting with stage IV breast cancer in the United Kingdom. Br J Cancer 2004;91:77–83.
[50] Osman HS, Rashid HI, Sathananthan N, Parker MC. The cost effectiveness of self-expanding metal stents in the management of malignant left-sided large bowel obstruction. Colorectal Dis 2000;2:233–7.
[51] Tappenden P, Chilcott JB, Eggington S, et al. Option appraisal of population-based colorectal cancer screening programmes in England. Gut 2007;56:677–84.
[52] Maslekar S, Pillinger SH, Sharma A, et al. Cost analysis of transanal endoscopic microsurgery for rectal tumours. Colorectal Dis 2007;9:229–34.
[53] Bosset JF, Collette L, Calais G, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. N Engl J Med 2006;355:1114–23.
[54] Mocellin S, Pasquali S, Nitti D. Fluoropyrimidine-HAI (hepatic arterial infusion) versus systemic chemotherapy (SCT) for unresectable liver metastases from colorectal cancer. Cochrane Database Syst Rev 2009:3.
[55] Durand-Zaleski I, Earlam S, Fordy C, et al. Cost-effectiveness of systemic and regional chemotherapy for the treatment of patients with unresectable colorectal liver metastases. Cancer 1998;83:882–8.
[56] Golfinopoulos V, Salanti G, Pavlidis N, Ioannidis JPA. Survival and disease-progression benefits with treatment regimens for advanced colorectal cancer: a meta-analysis. Lancet Oncol 2007;8:898–911.
[57] Tappenden P, Jones R, Paisley S, Carroll C. Systematic review and economic evaluation of bevacizumab and cetuximab for the treatment of metastatic colorectal cancer. Health Technol Assess 2007;11:i–128.
[58] Jeffery M, Hickey BE, Hilder PN. Follow-up strategies for patients treated for non-metastatic colorectal cancer. Cochrane Database Syst Rev 2008;4:i–35.
[59] Johannesson M, Weinstein MC. On the decision rules of cost-effectiveness analysis. J Health Econ 1993;12:459–67.
[60] Birch S, Gafni A. Cost-effectiveness/cost-utility analyses: do current decision rules lead us where we want to be? J Health Econ 1992;11:279–96.
[61] Weinstein MC, Coxson PG, Williams LW, et al. Forecasting coronary heart disease incidence, mortality and cost: the Coronary Heart Disease Policy Model. Am J Public Health 1987;77:1417–26.
[62] Eddy DM, Schlesinger L. Archimedes: a trial validation model of diabetes. Diabetes Care 2003;26:3093–101.