A Clinical Decision and Economic Analysis Model of Cancer Pain Management

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Objective: To design a model that educates clinical decision makers and healthcare professionals about the burden of cancer pain in their individual populations, and that assists them in weighing the effectiveness and cost of different cancer pain management strategies.

Study Design: Tailored cost-effectiveness analysis using an evidence-based decision analytic model.

Methods: The spreadsheet-based model compares 3 strategies: (1) guideline-based care (GBC), (2) oncology-based care (OBC), and (3) usual care (UC). The model calculates the likelihood of cancer pain in a healthcare population, how effectively that pain is managed, and the average monthly cost of medications plus procedural interventions. Model inputs were derived from published US population demographics, cancer registry data, high-quality studies of cancer pain management, standard reimbursement schedules, and expert opinion. The model permits users to tailor population demographics, strategy effectiveness, and resource costs.

Results: Of 100 000 patients with typical US demographics, approximately 508 (0.51%) will have cancer and 205 (0.20%) will suffer from cancer pain. After 1 month, the percentage of cancer pain patients with effective pain management and the cost of each strategy were estimated as follows: (1) GBC, 80% and $579; (2) OBC, 55% and $466; and (3) UC, 30% and $315. Compared with OBC, GBC had an incremental cost-effectiveness ratio of $452 per additional patient relieved of cancer pain. Compared with UC, OBC had an incremental cost-effectiveness ratio of $601 per additional patient relieved of cancer pain.

Conclusion: Guideline-based cancer pain management leads to improved pain control with modest increases in resource use.

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Pain plagues patients with cancer. Notably, 40% of patients with localized cancer and more than 70% of patients with advanced cancer will complain of pain.[1,2] It is a source of physical and psychological distress, and is the most commonly feared symptom of cancer.[1,3,4]

Despite a growing body of evidence about the prevalence of pain and the importance of its management, there are gross inconsistencies in the recognition of the problem and approach to care, ranging from little intervention to excessive use of costly medications and procedural interventions. Physician and patient barriers hamper recognition of cancer pain as an important issue. Physician-related barriers include inadequate pain assessment, inadequate knowledge of medication and intervention options, fear of tolerance, and fear of addiction.[4-7] Patient-related barriers include concerns about analgesics, fear of addiction, concerns about side effects, fear of the implication of pain, and reluctance to complain.[4,8,9] Systemwide barriers such as governmental regulation of opioids and limited access to medications, interventions, and specialists also exist.[6] Such barriers contribute to haphazard and inadequate management, and characterize the usual state of care outside of the specialist arena.

In response to this inadequate management, the World Health Organization (WHO) identified cancer pain relief as one of its top priorities. Central to this program was the development and distribution of a guideline for cancer pain management advocating the "WHO Analgesic Ladder."[10] In 1994, the US Agency for Health Care Policy and Research (AHCPR; now the Agency for Healthcare Research and Quality [AHRQ]) published its evidence-based clinical practice guideline, *Management of Cancer Pain,* which also advocated care based on the WHO Analgesic Ladder.[11] The distribution of these guidelines has led to the increased awareness of cancer pain as a problem and increased uptake of rational management strategies, especially among target providers such as oncologists.[10,12-15]

The application of such guidelines can lead to improved patient outcomes.[16,17] Du Pen and colleagues randomized cancer pain patients to pain management

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according to a multistep algorithm based on the AHCPR guideline administered by study clinicians versus usual pain management by community oncologists. Patients in the algorithm arm achieved a significant reduction in pain intensity, and there was a significant difference in the profile of medications prescribed in the 2 groups.[16,18]

Consistent with previous reports, oncology specialists in the Du Pen et al study prescribed pain medications more frequently than nonspecialists (according to previous reports), with the probable result of better pain outcomes.[18-21] However, patients cared for by oncologists also were more likely to receive costly medications when lower-cost options were available.[18] The integration of newer and more costly medications, surgical and anesthesiology procedures, radiotherapy, psychotherapy, and other interventions is likely to increase—hopefully with the result of improved cancer pain control.[22] Indeed, newer guidelines such as the proposed National Comprehensive Cancer Network Cancer Pain Management Guideline will likely include recommendations for such interventions.[23]

Different pain management strategies such as guideline-based care (GBC), oncology-based care (OBC), and community-based care provide different degrees of pain control and integrate different pain management practices. Because the literature lacks synthesized data about the relative effectiveness or cost of the various approaches, it has been difficult to compare strategies of cancer pain management and advocate one over another.[24] Hence, this evidence-based clinical decision and economic analytic model was designed to educate clinicians and healthcare policy decision makers about the problem of cancer-related pain, highlight the burden of cancer pain in their population, and assist them in comparing the clinical effectiveness and economic impact of 3 different strategies of cancer pain management—(1) GBC, (2) OBC, and (3) usual care (UC).[25-27] To increase functionality, the model incorporates a dynamic, spreadsheet-based design that can be tailored to fit individual healthcare populations, allowing the user to compare individualized, real-world outcomes for clinical benefit and resource consumption.

METHODS

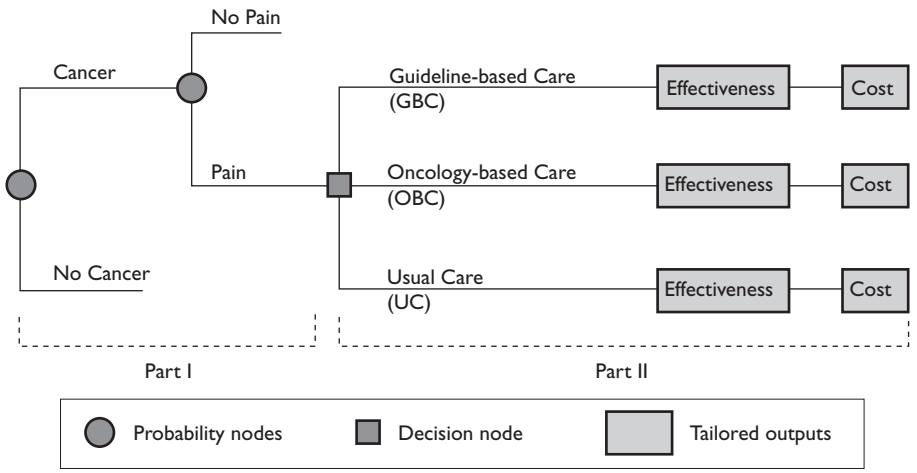
Model Design

The objectives of the model are to (1) summarize the evidence for the prevalence of cancer pain and for different cancer pain management strategies to date, (2) project the burden of cancer in a large user-specified cohort, (3) project the burden of cancer pain in a large user-specified cohort, and (4) estimate the cost-effectiveness of using different pain management strategies in the user-specified cohort. The target audience includes healthcare policy decision makers, managers of healthcare organizations, pharmacy and therapeutics committees, and active clinicians; the model perspective is that of the healthcare organization (eg, a clinical practice setting, a health insurer).

A decision analytic model was constructed in 2 parts (**Figure 1**). The first part facilitates estimates of cancer pain prevalence based on demographics and the epidemiology of cancer and cancer pain. The second part evaluates the impact of cancer pain and its management in a default or user-defined healthcare population. Results are modeled over a 1-month time frame with a steady-state assumption.

This project was performed in accordance with the recommendations for industry-sponsored health economics research.[28] The complete spreadsheet for the model is available at: http://diseasemodels.duhs.duke.edu.

Figure 1. Structure of the Decision Analytic Model



Cancer pain prevalence is calculated in part I based on the probability of cancer and cancer pain. The impact of the 3 cancer pain management strategies is calculated in part II.

Table 1. Cancer Pain Probabilities

Variable	Base Model (Range)	Reference(s)
All sites, in situ	0.00 (0.00-0.10)	1, 2, 41
All sites, locoregional	0.40 (0.11-0.75)	1, 2, 41
All sites, distant	0.71 (0.47-0.96)	1, 2, 41
All sites, unstaged	0.50 (0.11-0.75)	1
Bladder, locoregional	0.40 (0.28-0.57)	1, 2, 38, 41 (data from colorectal)
Bladder, distant	0.69 (0.47-0.95)	1, 2, 38, 41 (data from colorectal)
Breast, locoregional	0.40 (0.34-0.56)	1, 2, 41
Breast, distant	0.72 (0.56-0.94)	1, 2, 41
Central nervous system, locoregional	0.40 (0.28-0.57)	1, 2, 38, 41 (data from colorectal)
Central nervous system, distant	0.69 (0.47-0.95)	1, 2, 38, 41 (data from colorectal)
Cervix, locoregional	0.35 (0.24-0.60)	1, 2, 41
Cervix, distant	0.75 (0.40-1.00)	1, 2, 41
Colorectal, locoregional	0.40 (0.28-0.57)	1, 2, 38, 41
Colorectal, distant	0.69 (0.47-0.95)	1, 2, 38, 41
Esophagus, locoregional	0.45 (0.40-0.46)	1, 2, 41 (data from stomach)
Esophagus, distant	0.75 (0.67-0.77)	1, 2, 41 (data from stomach)
Head and neck, locoregional	0.43 (0.35-0.51)	1, 2, 38, 41 (data from lung)
Head and neck, distant	0.72 (0.58-0.85)	1, 2, 38, 41 (data from lung)
Kidney, locoregional	0.30 (0.20-0.54)	1, 2, 41 (data from prostate)
Kidney, distant	0.75 (0.55-0.80)	1, 2, 41 (data from prostate)
Leukemia	0.52 (0.05-0.58)	1, 2, 41
Liver, locoregional	0.40 (0.28-0.57)	1, 2, 38, 41 (data from colorectal)
Liver, distant	0.69 (0.47-0.95)	1, 2, 38, 41 (data from colorectal)
Lung, locoregional	0.43 (0.35-0.51)	1, 2, 38, 41
Lung, distant	0.72 (0.58-0.85)	1, 2, 38, 41
Lymphoma, locoregional	0.31 (0.12-0.41)	1, 2, 41
Lymphoma, distant	0.58 (0.20-0.59)	1, 2, 41
Multiple myeloma	0.75 (0.55-0.80)	1, 2, 41 (data from prostate)
Other, locoregional	0.40 (0.11-0.75)	1, 2, 41 (data from all sites)
Other, distant	0.71 (0.47-0.96)	1, 2, 41 (data from all sites)
Ovary, locoregional	0.39 (0.24-0.60)	1, 2, 41 (data from cervix for range)
Ovary, distant	0.59 (0.40-1.00)	1, 2, 41 (data from cervix for range)
Pancreas, locoregional	0.46 (0.43-0.60)	1, 2, 41
Pancreas, distant	0.79 (0.72-1.00)	1, 2, 41
Prostate, locoregional	0.30 (0.20-0.54)	1, 2, 41
Prostate, distant	0.75 (0.55-0.80)	1, 2, 41
Sarcoma, locoregional	0.45 (0.40-0.46)	1, 2, 41 (data from stomach)
Sarcoma, distant	0.75 (0.67-0.77)	1, 2, 41 (data from stomach)
Skin (malignant), locoregional	0.45 (0.40-0.46)	1, 2, 41 (data from stomach)
Skin (malignant), distant	0.75 (0.67-0.77)	1, 2, 41 (data from stomach)
Stomach, locoregional	0.45 (0.40-0.46)	1, 2, 41
Stomach, distant	0.75 (0.67-0.77)	1, 2, 41
Testis, locoregional	0.39 (0.24-0.60)	1, 2, 41 (data from ovary)
Testis, distant	0.59 (0.40-1.00)	1, 2, 41 (data from ovary)
Thyroid, locoregional	0.30 (0.20-0.54)	1, 2, 41 (data from prostate)
Thyroid, distant	0.75 (0.55-0.80)	1, 2, 41 (data from prostate)
Uterus, locoregional	0.20 (0.14-0.60)	1, 2, 41
Uterus, distant	0.75 (0.40-1.00)	1, 2, 41

Data Sources

Model inputs are summarized in **Tables 1-4.** Data sources and the processing required to calculate model inputs are detailed below.

Population Demographics. The default population is a cohort of 100 000 American patients with the age, sex, and racial distribution of the US population based on the May 1999 US census estimate.[29]

Probability of Cancer. The probability of cancer was calculated by using the 1999 estimated US cancer prevalence counts published by the National Cancer Institute.[30] The Connecticut Tumor Registry has infor-

Table 2. Probabilities of Pharmaceutical and Nonpharmaceutical Interventions

	Probability of a Cancer Pain Patient Requiring an Intervention (A)			Probability of a Cancer Pain Patient Receiving an Intervention if it is Required (B)			Probability That a Cancer Pain Patient Will Both Require and Receive an Intervention (A ¥ B)		
Intervention	**GBC**	**OBC**	**UC**	**GBC**	**OBC**	**UC**	**GBC**	**OBC**	**UC**
Long-acting opioids	0.84	0.84	0.84	0.95	0.53	0.13	0.80	0.45	0.11
Short-acting opioids	0.92	0.92	0.92	0.95	0.63	0.38	0.87	0.58	0.35
NSAIDs/acetaminophen	1.00	1.00	1.00	1.00	0.63	0.53	1.00	0.63	0.53
Neuropathic pain coanalgesics	0.69	0.69	0.69	0.72	0.19	0.08	0.50	0.13	0.05
Parenteral opioids	0.05	0.05	0.05	0.95	0.53	0.13	0.05	0.03	0.01
Medications for side effects									
Nausea and vomiting	0.72	0.82	0.23	0.50	0.60	0.90	0.36	0.49	0.21
Constipation	0.97	0.93	0.40	1.00	1.00	0.90	0.97	0.93	0.36
Sedation	0.44	0.27	0.14	0.20	0.10	0.01	0.09	0.03	0.00
Delirium	0.08	0.09	0.04	1.00	1.00	1.00	0.08	0.09	0.04
NSAID-related GI distress	0.42	0.29	0.24	0.80	0.80	0.95	0.34	0.23	0.23
Myoclonus	0.06	0.11	0.03	0.02	0.10	0.01	0.01	0.01	0.00
Dry mouth	0.64	0.69	0.21	0.00	0.00	0.00	0.00	0.00	0.00
Blocks	0.03	0.03	0.03	1.00	1.00	0.80	0.03	0.03	0.02
Surgery	0.02	0.02	0.02	1.00	1.00	0.80	0.02	0.02	0.01
Radiation	0.03	0.03	0.03	1.00	1.00	0.80	0.03	0.03	0.02
Psychosocial modalities	0.02	0.02	0.02	1.00	1.00	0.80	0.02	0.02	0.01
Physical modalities	0.02	0.02	0.02	1.00	1.00	0.80	0.02	0.02	0.01

GBC indicates guideline-based care; GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug; OBC, oncology-based care; UC, usual care.

mation on cancer cases as early as 1935 and is the only registry in the United States with sufficient follow-up data to directly estimate cancer prevalence.[31] The 1999 estimated US cancer prevalence counts were generated by applying 1994 historical Connecticut prevalence rates to the 1999 estimated US population in the standard method described by Feldman and colleagues.[32] In the model, cancer prevalence rates are integrated with default or user-defined inputs on population size and sex, age, and racial distributions. The burden of cancer is represented as the total number of cancer cases by tumor type and stage. Users can modify the tumor type and stage outputs to fit their organization.

Probability of Cancer Pain. The MEDLINE database was searched for English-language articles on cancer pain prevalence by using the MESH key words neoplasms, pain, probability, prevalence, and epidemiology; bibliographies of selected articles were reviewed. All evidence was graded according to the evidence-based medicine guidelines of Sackett and others.[33]

Because the highest quality studies separated patients into 2 groups—locoregional (stages I-III) versus advanced disease (stage IV or metastatic)—only patients in these staging groups were regarded as having pain. Patients with in situ disease were assumed not to have pain. In cases in which data were unavailable or uncertain, prevalence was estimated by using tumor types with similar invasion patterns likely to cause similar degrees of pain. The cumulative probabilities broken down by tumor type were compared with the overall cancer pain probabilities for all sites reported in the literature and little discrepancy was found; estimates by tumor type are used in the model (Table 1).[1,2,34-42] The cancer pain probabilities are integrated with the number of cancer cases in the population by tumor type and stage to generate the number of patients in the population with cancer-related pain.

Efficacy of Cancer Pain Management Strategies. The MEDLINE database was searched for English-language articles on cancer pain management using the MESH key words neoplasms, pain, therapy, analgesics, practice guidelines, algorithms, longitudinal studies, treatment outcome, and decision making; bibliographies of selected articles were reviewed. All evidence was graded according the evidence-based medicine guidelines of Sackett and others.[33]

Table 3. Example of the Cost Accounting for Surgical Interventions

Treatment Scenario	Component CPT/DRG Description and Code	Cost per Component	No. of Components per Scenario	Component Subtotal and Total Scenario Cost	Probability of Treatment Scenario	Weighted Scenario Cost
Percutaneous cordotomy	Office consultation (99244)	$120.87	1	$120.87		
	Remove spinal cord lesion (63600)	$913.44	1	$913.44		
	Spinal procedures (DRG 004)	$12 378.08	1	$12 378.08		
				$13 412.39	0.65	**$8718.05**
Intrathecal pump with morphine	Test admission (3 days) (DRG 004)	$4951.23	1	$4951.23		
	Injection of diagnostic anesthetic (62277)	$116.35	1	$116.35		
	External disposable pump (E0781)	$214.74	1	$214.74		
	Implant spinal catheter (62350)	$396.29	0.6	$237.77		
	Implant spine infusion pump (62362)	$407.75	0.6	$244.65		
	Programmable infusion pump (E0783)	$4483.84	0.6	$2690.30		
	Refills	$350.00	4.20	$1470.00		
				$9925.04	0.30	**$2977.51**
Midbrain tractotomy	Incise skull/brain surgery (61735)	$1231.23	1	$1231.23		
	Craniotomy age >17 y except for trauma (DRG 001)	$16 704.18	1	$16 704.18		
Total cost				**$17 935.41**	0.05	**$896.77**
Total cost for a typical surgical intervention						**$12 592.33**

CPT indicates Current Procedural Terminology; DRG, diagnosis-related group.

One randomized, controlled trial of different strategies in cancer pain management was identified. The study by Du Pen and colleagues randomized 81 patients to care according to a cancer pain management algorithm versus standard care according to the treating oncologist.[16] The algorithm was developed in 1995 and based on the 1994 AHCPR guideline.[11,16] Study physicians and nurses prescribed analgesics for intervention patients according to a rigorous multilevel algorithm. The patient's oncologist prescribed control arm (standard therapy) analgesics. The oncologist was unblinded to the algorithm medications prescribed only on a need-to-know basis. The primary outcome measure was "change in usual pain" over the 3-month study period. Pain was measured on a visual analog scale with the Wisconsin Brief Pain Inventory.[43] The study demonstrated that patients randomized to the pain algorithm achieved a statistically significant reduction in usual pain intensity ($P < .02$).[16] Study nurses also collected data on medications required, medications prescribed, side effects, and medical encounters. Because such specific information was not presented in the original manuscript, the authors were contacted and they generously provided the original dataset. This dataset was independently reanalyzed to confirm the

Table 4. Summary of the Resource Use Calculations, Including Ranges for the Sensitivity Analysis

	GBC			OBC			UC		
Intervention	**Probability of Use (A) (Range)**	**Intervention Cost (B) (Range)**	**Cost per Cancer Pain Patient (A × B)**	**Probability of Use (A) (Range)**	**Intervention Cost (B) (Range)**	**Cost per Cancer Pain Patient (A × B)**	**Probability of Use (A) (Range)**	**Intervention Cost (B) (Range)**	**Cost per Cancer Pain Patient (A × B)**
Long-acting opioids	0.797 (0.70-0.89)	$122.10 ($98-$147)	$97.28	0.447 (0.39-0.50)	$110.68 ($89-$133)	$49.52	0.107 (0.09-0.12)	$114.87 ($92-$138)	$12.31
Short-acting opioids	0.873 (0.78-0.95)	$75.95 ($61-$91)	$66.27	0.582 (0.52-0.63)	$87.47 ($70-$105)	$50.91	0.347 (0.31-0.38)	$93.57 ($75-$112)	$32.50
NSAIDs and acetaminophen	1.000 (0.80-1.00)	$36.02 ($29-$43)	$36.02	0.633 (0.51-0.63)	$36.02 ($29-$43)	$22.79	0.531 (0.42-0.53)	$37.11 ($30-$55)	$19.69
Neuropathic pain coanalgesics	0.500 (0.39-0.61)	$63.73 ($51-$76)	$31.87	0.134 (0.11-0.16)	$110.55 ($88-$133)	$14.80	0.051 (0.04-0.06)	$129.27 ($103-$155)	$6.66
Parenteral opioids	0.047 (0.01-0.10)	$440.14 ($352-$528)	$20.87	0.027 (0.01-0.05)	$440.14 ($352-$528)	$11.72	0.006 (0.001-0.013)	$434.04 ($347-$521)	$2.77
Medications for side effects		$63.74 ($51-$76)	$63.74		$53.28 ($43-$64)	$53.28		$31.34 ($25-$38)	$31.34
Blocks	0.030 (0.01-0.10)	$331.62 ($265-$398)	$9.95	0.030 (0.01-0.10)	$331.62 ($265-$398)	$9.95	0.024 (0.01-0.08)	$331.62 ($265-$398)	$7.96
Surgery	0.015 (0.01-0.08)	$12 592 ($10 074-$15 111)	$188.89	0.015 (0.01-0.08)	$12 592 ($10 074-$15 111)	$188.89	0.012 (0.01-0.06)	$12 592 ($10 074-$15 111)	$151.11
Radiation	0.030 (0.01-0.10)	$1957 ($1565-$2348)	$58.70	0.030 (0.01-0.10)	$1957 ($1565-$2348)	$58.70	0.024 (0.01-0.08)	$1957 ($1565-$2348)	$46.96
Psychosocial modality	0.015 (0.01-0.08)	$270.30 ($216-$324)	$4.05	0.015 (0.01-0.08)	$270.30 ($216-$324)	$4.05	0.012 (0.01-0.06)	$270.30 ($216-$324)	$3.24
Physical therapy	0.015 (0.01-0.08)	$62.52 ($50-$75)	$0.94	0.015 (0.01-0.08)	$62.52 ($50-$75)	$0.94	0.012 (0.01-0.06)	$62.52 ($50-$75)	$0.75
Cost per cancer pain patient			**$578.58**			**$465.55**			**$315.29**

GBC indicates guideline-based care; OBC, oncology-based care; UC, usual care.

original findings and generate the necessary calculations for the model.[18]

In the model, the algorithm arm in the study by Du Pen et al is represented as GBC, and the standard-therapy arm is represented as OBC. In the GBC paradigm, clinicians recognize, assess, and treat cancer pain in a manner consistent with the 1994 AHCPR guideline. Assessment is made at baseline and after each intervention, and neuropathic pain is identified in approximately two thirds of cases (Table 2). Round-the-clock long-acting opioids with breakthrough doses of short-acting opioids are standard; all patients receive nonsteroidal or acetaminophen coanalgesics. Opioid side effects are recognized and treated appropriately. Oncology-based care resembles GBC except that long-acting opioids are prescribed half as often, short-acting opioids are prescribed two thirds as often, nonopioid analgesics are prescribed two thirds as often, and neuropathic pain is recognized one third as often. Because no data exist to support a difference in the prescribing patterns of nonpharmaceutical interventions, patterns of usage are similar for GBC and OBC. Usual care is based on the well-described suboptimal care that many cancer pain patients receive, especially outside of the pain specialist or oncology setting.[7,20,44] Pain management practices in this setting have not been systematically studied. It was assumed with UC that pain is sporadically assessed and that round-the-clock dosing

with long-acting opioids, prescription of short-acting opioids, and treatment of neuropathic pain problems are infrequent. Further, it was assumed that UC providers prescribe nonpharmaceutical interventions at least 20% less often because of inadequate assessment and knowledge. All relative assumptions for GBC, OBC, and UC are clearly evident in the model and can be tailored to mimic the individual situation.

"Effectiveness" was defined as successful cancer pain relief as demonstrated by the reduction of the usual pain level to less than or equal to 3 on a 0-10 visual analog scale. Effectiveness for GBC and OBC was based directly on the dataset of Du Pen et al and was calculated as the percentage of patients in each arm that meet the effectiveness criteria. Because standard therapy is approximately 25% less effective than the algorithm in the Du Pen et al study, the effectiveness of UC was assumed to be 25% less than OBC.[7,20,44]

Intervention Costs. Costs were calculated from direct medical resource utilization (pharmaceutical and nonpharmaceutical) and unit costs. Direct nonmedical and indirect costs were not included. Pharmaceutical utilization was divided into medications for pain (long-acting opioids, short-acting opioids, nonsteroidal anti-inflammatory medications [NSAIDs] or acetaminophen, neuropathic pain coanalgesics, parenteral opioids, and intrathecal opioids) and medications for side effects. Nonpharmaceutical utilization was divided into anesthesiology procedures, surgical procedures, radiotherapy, psychosocial modalities, and physical therapy. All costs are in US dollars.

PHARMACEUTICAL UTILIZATION AND UNIT COSTS. The likelihood that a medication would be used was derived from the product of the probability that the medication would be required and the probability that a medication would be prescribed if it were required. The probability of patient compliance with a prescribed medication was not included, as it was assumed that a medication that is prescribed would be purchased within the system. Also, it was assumed that patients who did not require an intervention did not receive it.

Medications were defined as required if the patient had pain that would have dictated such intervention according to the algorithm. Side effects experienced were based on patient reports collected by Du Pen et al study nurses using the Memorial Symptom Assessment Scale; side effect medications were defined as required if the patient had a side effect that would have dictated such intervention according to the algorithm.[45] The probability that a medication category would be required in the GBC and OBC strategies was calculated from the percentage of patients needing medication in that category in each arm of the study by Du Pen et al. The probability that a medication category would be required in the UC arm was modeled by using the known differences between GBC and OBC, the expectation that UC physicians are less likely to prescribe opioids and more likely to choose nonopioid medications, evidence of poor understanding and treatment of neuropathic pain, and evidence-based plus expert-based input about the likelihood of a side effect given the likelihood of the medication profile.[7,11,20,44,46]

Medications prescribed in the Du Pen et al dataset were individually counted to determine the frequency of use within each pharmaceutical category for GBC and OBC. With UC, the following assumptions were made: (1) nearly all of the long-acting opioids prescribed are long-acting morphine, as UC physicians have little experience with fentanyl and long-acting oxycodone and they generally regard methadone as outside of their prescribing authority; (2) most short-acting opioid prescriptions are combination products that can be prescribed over the telephone, like hydrocodone plus acetaminophen and codeine plus acetaminophen; (3) meperidine use is more common; (4) NSAID usage patterns are similar to those with OBC, except that UC physicians prescribe more ketorolac; and (5) neuropathic pain coanalgesic usage patterns are similar to those with OBC, except that UC physicians prescribe more gabapentin. Representative side effect medications were chosen based on the Du Pen et al dataset. Typical daily doses of each medication were calculated by using the mean number of morphine equivalents prescribed per day in the Du Pen et al study and expert guidance. Year 2000 Red Book values for average wholesale price were used for unit drug costs; generic costs were used if a generic product was available. For parenteral opioids, Medicare fee schedules were used for medical services and durable medical equipment (DME). Users can tailor the medications used and the cost based on the cost structure within their individual healthcare organization. Pharmaceutical intervention probabilities are presented in Table 2, and a resource cost summary is presented in Table 4.

NONPHARMACEUTICAL UTILIZATION AND COSTS. The likelihood that a nonpharmaceutical intervention would be used was derived from the product of the probability that the intervention would be required and the probability that the intervention would be performed if it were required. There is a paucity of information about intervention rates in the literature; other authors have noted this as well.[47] Du Pen et al collected some information about interventions, but the small sample size and low intervention frequencies diminished the usefulness of this data.

Published intervention rates and expert guidance were integrated to determine the probability that a can-

cer pain patient would require each intervention category. For example, data from Italy based on older strategies suggest that blocks and surgical interventions were required in fewer than 3% of pain patients with advanced cancer.[48] The same patient may have required multiple procedures. In the model, it was assumed that blocks and surgery combined are required in 3% of all cancer pain patients, that for any such intervention patient there is a 50% risk of needing 2 interventions, and that blocks are used twice as frequently as surgery. It was conservatively assumed that all patients in the GBC and OBC arms who required an intervention would receive it. Because UC physicians are less likely to recognize that their patient is having pain difficulties, the probability that a UC patient who required an intervention would receive it is 0.8.

Per patient cost by intervention category (eg, surgery) was based on the probability that a particular type of procedure (eg, percutaneous cordotomy) would be used in the intervention category and the summed cost of each of the procedure types. Judgments were solicited from pain, anesthesiology, surgery, radiotherapy, and psychology specialists at Duke University Medical Center (Durham, NC) about the 3-10 most common procedures that they perform and the relative frequency of each procedure. Generally, these results were generated from internal data tracked by the specialists. Specialists also described the service (in terms of Current Procedural Terminology [CPT] and/or diagnosis-related group [DRG] codes) and DME components that would be required to complete the procedure. Each procedure was built into a scenario based on the required components and the typical period of effectiveness, and then the total cost of the scenario was determined by using the US 2000 Medicare CPT or DRG reimbursement for each component. A weighted per patient cost was generated for each procedure scenario by multiplying the scenario cost by the relative frequency of the scenario; scenario costs were summed to generate the total per patient cost within each intervention category. Procedural probabilities used in the model are presented in Table 2, an example of a complete scenario calculation is provided in Table 3, and a resource cost summary is in Table 4. Users can tailor the likelihood that a nonpharmaceutical intervention will be prescribed and the cost of that intervention based on their individual healthcare organization.

Incremental Cost-Effectiveness Ratios

The incremental cost-effectiveness ratio (ICER) reflects the increased expense incurred to effectively treat 1 more patient when changing from a less effective cancer pain management strategy (strategy Y) to a more effective strategy (strategy X), and is calculated according to the following formula:

$$\text{ICER} = (\text{cost X} - \text{cost Y})/(\text{effectiveness X} - \text{effectiveness Y}).$$

Sensitivity Analyses

Sensitivity analyses were conducted to evaluate the effect of variations in clinical probabilities and cost estimates on the results. For the burden of cancer and cancer pain, these variations reflect the probability ranges reported in the literature. For pharmaceutical and nonpharmaceutical utilization parameters, these variations reflect the likely probability ranges and costs according to clinical experts in these areas. One to two inputs were varied at a time. Worst-case and best-case scenarios were examined by using cumulative changes in the likelihood that an intervention would be used and in the intervention cost. The ranges for the probability that a cancer patient would have pain are presented in Table 1. The ranges for the probability that an intervention would be used and the cost of each intervention type are presented in Table 4. The influences of various probabilities and cost inputs on model outputs were compared with each other by normalizing the results to a standard unit, according to the following formula:

$$\text{Influence of input} = (\text{percent change in model output})/(\text{percent change from baseline model input}).$$

RESULTS

Baseline Analysis

The baseline population consisted of 100 000 individuals with demographic assignments of sex, race, and age similar to those of the US population. In this population, 508 individuals would have cancer, including 21 patients with in situ disease, 418 patients with locoregional disease, and 69 patients with distant metastatic disease (**Table 5**). Of these cancer patients, 205 would have cancer-related pain. At the end of a month, effective pain management would be achieved in 80% of patients who receive GBC, 55% of patients who receive OBC, and 30% of patients who receive UC. Of the 205 cancer pain patients, 164 in the GBC group, 113 in the OBC group, and 61 in the UC group would be relieved of pain, leaving 41, 92, and 144 patients, respectively, still in pain.

The estimated treatment costs per cancer pain patient by strategy were as follows: (1) GBC $578.59,

(2) OBC $465.56, and (3) UC $315.29. These figures translate to the following baseline population costs and per member per month costs: (1) GBC $118 436 and $1.18, (2) OBC $95 300 and $0.95, and (3) UC $64 540 and $0.65 (Table 5 and **Figure 2**).

Because no strategy is 100% effective, not all patients will be relieved of pain. Compared with OBC, GBC has an ICER of $452.11 per additional patient relieved of cancer pain (Table 5). Compared with UC, OBC has an ICER of $601.07 per additional patient relieved of cancer pain. Compared with UC, GBC has an ICER of $526.59 per additional patient relieved of cancer pain. For example, if an organization changes from an OBC to a GBC strategy, 51 more patients will be relieved of pain with an additional cost of $23 136, leading to an ICER of $452 (actual $453; small difference due to rounding).

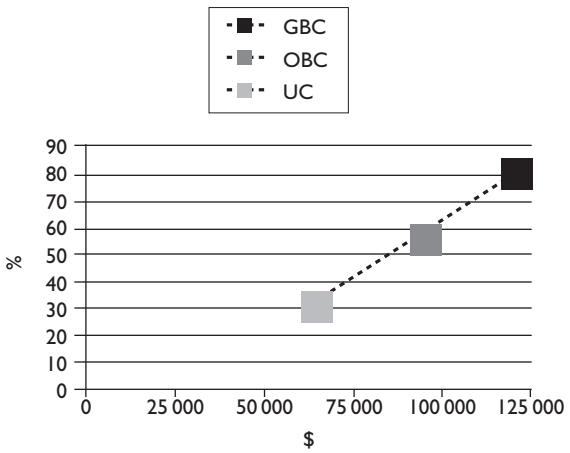
Table 5. Model Output Summary for the Baseline Population (n = 100 000)

Population Characteristic	GBC	OBC	UC
Number of cancer patients	508	508	508
% of total population with cancer	0.51	0.51	0.51
Number of cancer pain patients	205	205	205
% of total population with cancer pain	0.20	0.20	0.20
% of cancer patients with cancer pain	40.32	40.32	40.32
Strategy effectiveness	80%	55%	30%
Number of patients relieved of pain	164	113	61
Cost per cancer pain patient	$578.59	$465.56	$315.29
Population cost	$118 436	$95 300	$64 540
Cost per member per month	$1.18	$0.95	$0.65

Change	ICER (per cancer pain patient)
From OBC to GBC	$452.11
From UC to OBC	$601.07
From UC to GBC	$526.59

GBC indicates guideline-based care; ICER, incremental cost-effectiveness ratio; OBC, oncology-based care; UC, usual care.

Figure 2. Graphical Summary of the Effectiveness of Each of the 3 Strategies Versus the Total Population Cost for Treating Cancer Pain in the Baseline Population



GBC indicates guideline-based care; OBC, oncology-based care; UC, usual care.

Sample Custom Population

The model was tested with sample populations to ensure that all outputs responded to user-defined changes in the model inputs. For example, results were generated for a projected Veterans Administration (VA) population in Veterans Integrated Service Network 6 in fiscal year 2000.[49] This population of 1 305 761 is older (15% are ≥75 years old) and 94% male; there also is a high prevalence of smoking and comorbid diseases. Model outputs are presented in **Table 6.** The relative risk of having cancer in this population was 2.5 times higher than that in the baseline population; similarly, the per member per month cost for cancer pain management was 2.6 times higher for each of the strategies.

Sensitivity Analysis

Examination of clinical and cost inputs over broad ranges showed that the cost of each of the strategies was most sensitive to the prevalence of cancer pain in locoregional disease, the probability that surgical interventions would be required, and the cost of surgical interventions. When the prevalence of cancer pain in patients with locoregional disease was increased to 75% (87% increase from baseline), the population cost in the GBC group increased to $166 383 (40% increase from baseline). This reflects the predominance of cancer patients with locoregional disease in the baseline population (82%). When the probability that surgery would be performed for a cancer pain patient was

increased to 3% (100% increase from baseline), the population cost in the GBC group increased to $157 101 (33% increase from baseline). This increase reflects the high cost of surgery relative to the other types of interventions; for example, the cost of surgical pain interventions is 6.4 times higher than the cost of anesthesiology-based blocks in the model. Similarly, the other major influence on population cost in the model is the actual cost of the surgical interventions, such that increasing the cost of surgery by 20% increased the total population cost in the GBC group to $126 169 (7% increase from baseline). As expected, the sensitivity of total population cost to changes in the probability that various interventions would be prescribed or performed varies with the sensitivity to changes in the cost of the interventions themselves. **Figure 3** shows how changing each of the intervention probabilities influences the overall costs of the model. Long-acting opioids, short-acting opioids, and radiotherapy also played important roles in the overall costs of the cancer pain management strategies.

DISCUSSION

This is the first evidence-based clinical decision and economic analysis model on the substantial problem of cancer pain and its management. To assist healthcare policy decision makers and clinicians in comparing different strategies of cancer pain management, explicit, quantitative methods were used to synthesize data from high-quality studies, describing the burden of cancer pain in modeled populations and demonstrating the relative effectiveness and cost of GBC, OBC, and UC. Because the raw data from a methodologically sound, randomized, controlled trial of cancer pain management were used to derive the clinical inputs for GBC and OBC, model outputs for these 2 groups are well substantiated with a high level of documentation. The third group, UC, is more speculative and based on historical trends from cohort studies; UC gives healthcare decision makers the opportunity to model their own organization.

The model demonstrates that cancer pain is common and undertreated. Cancer pain afflicts 0.20% of the baseline population. As expected, the number of cancer pain patients is related to the number of cancer patients and particularly the number with metastatic disease. When a projected VA cohort was modeled—an older population with 2.5 times the number of cancer patients—0.61% of the population had cancer pain. As a population ages, more patients are likely to have cancer and aggressive solid tumors, and the percentage with cancer pain that needs treatment increases.

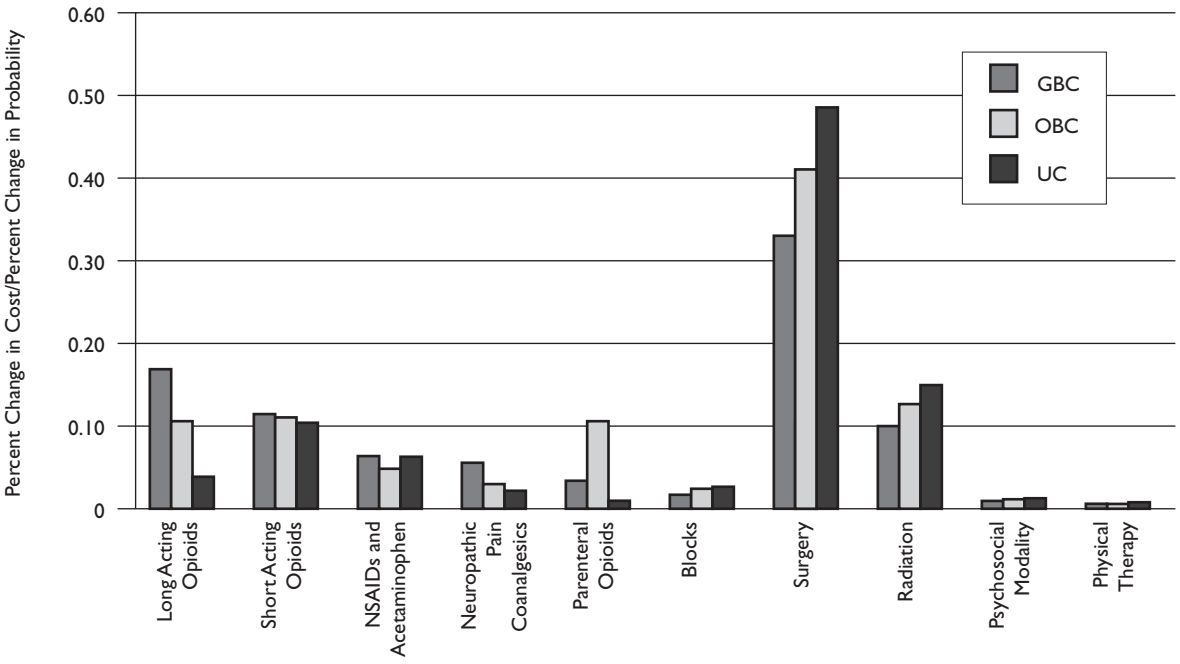
More patients are pain free when a guideline-based strategy is used. At the end of 1 month, 80% of GBC patients have effective pain control, whereas only 55% of OBC and 30% of UC patients have such effective management. Increased pain control results in modestly increased costs for the organization. The costs to care for a cancer pain patient in the GBC, OBC and UC groups are $578.59, $465.56, and $315.29 per month, respectively. But when ICERs are compared, it is evident that changing to a more efficacious strategy results in only a small increase in cost. For example, if an organization that relies on its oncologists to manage most cancer pain patients (OBC) institutes practices that reflect guideline-based management, the cost will increase only $452.11 for each additional cancer pain patient effectively treated. Because improved pain control leads to improved satisfaction, this is a small price for increased patient satisfaction within the organization. Further, this small increased cost may lead to fewer hospital-

Table 6. Model Output Summary for a Sample User-Defined Population (n = 1 305 761)

Population Characteristic	GBC	OBC	UC
Number of cancer patients	16 590	16 590	16 590
% of total population with cancer	1.27	1.27	1.27
Number of cancer pain patients	6878	6878	6878
% of total population with cancer pain	0.53	0.53	0.53
% of cancer patients with cancer pain	41.46	41.46	41.46
Strategy effectiveness	80%	55%	30%
Number of patients relieved of pain	5502	3783	2063
Cost per cancer pain patient	$578.59	$465.56	$315.29
Population cost	$3 979 707	$3 202 263	$2 168 677
Cost per member per month	$3.05	$2.45	$1.66

GBC indicates guideline-based care; OBC, oncology-based care; UC, usual care.

Figure 3. Influence on the Total Strategy Cost of Changing the Probability That an Intervention Will Be Prescribed or Performed



This influence is demonstrated by normalizing the results of the sensitivity analysis. It was calculated as follows: percent change in total population cost/percent change in probability input.
GBC indicates guideline-based care; NSAIDs, nonsteroidal anti-inflammatory drugs; OBC, oncology-based care; UC, usual care.

izations for pain control, fewer pain specialist visits, increased likelihood of maintaining a health plan, and an increased sense that the health system is committed to quality cancer care.

In a graph of the cost versus the effectiveness of each of the strategies, OBC falls slightly below and to the right of a line drawn from GBC to UC (Figure 2). Hence, by extended dominance OBC is less preferred. This may suggest that an organization can develop a mix of GBC and UC that would, on average, be better than ever using OBC. However, this model is not an exercise in the rational allocation of resources, but rather is intended to assist users in comparing gross differences in 3 different strategies of cancer pain management. The numbers are not precise; it would not be appropriate to interpret the extended dominance as a reason to reject OBC.

The sensitivity analysis indicates what is driving the overall costs and the relative differences between the groups. Clearly, surgical interventions have the most impact, despite the fact that the probability of the use of surgery is very low (1.5% for GBC). Other influential interventions include long-acting opioids, short-acting opioids, and radiotherapy. Figure 3 demonstrates that UC is more sensitive to the cost of surgical interventions than GBC, but GBC is more sensitive to the cost of long-acting opioids. Hence, the sensitivity analysis identifies important places where decision makers can impact their overall costs. The institution of strategies that reserve surgery for difficult cases, the preferential use of anesthesiology procedures like nerve blocks instead of surgery, and control of surgical costs all can lead to cost savings—especially for the UC group. Contracts that control the costs of opioids may lead to expenditure reductions—especially for the GBC group. Recognition of these influential forces is important, especially as utilization of newer and more costly procedures for the management of cancer pain is likely to increase.[22,23]

The cost estimates consider only interventions historically used to manage cancer pain and direct medical costs to the healthcare system. The cost of medication side effects is included, although the cost of iatrogenic complications of nonpharmaceutical interventions is not included. Although very infrequent, iatrogenic complications can be very costly and influence the analysis; users of the model can incorporate such concerns as appropriate for the given organization. Other costs of caring for a cancer pain population (eg, societal con-

cerns like patient adherence and indirect costs) are not included. Overall, the model output appears to be a conservative estimate that may understate the cost because it does not include the costs of untreated pain such as hospitalization and lost wages. Economic reports highlight the significant hospital costs for unscheduled admissions for unrelieved pain. During the evaluation period, patients with unscheduled cancer pain admissions had longer lengths of stay than the hospital average, and each reporting hospital estimated an annual cost of about $5 million.[47,50] There are high family costs for unrelieved pain as well, primarily due to lost time for medical treatment after failed initial therapy. In 1993, Stommel and colleagues estimated that family costs were $12 532 per year to care for a cancer patient with pain.[51]

Particular strengths of the model include its rigorous methodology, its transparency, and the ability to customize the model for user-defined populations. Background data were based on a prescribed and systematic search of the literature, detailed critical appraisal of identified information, and judicious application of methodologically sound research. When the published literature did not provide appropriate clinical inputs for the model, study authors were contacted and, with their gracious permission, their original dataset was reanalyzed to derive useful estimates for the model. Assumptions and expert input are clearly identified in the background spreadsheets and this manuscript. The spreadsheets are available for public review on the center Web site: http://diseasemodels.duhs.duke.edu.

The model has several limitations. First, the level of evidence about cancer pain and various cancer pain management strategies limits the model. Cancer pain prevalence was estimated by summing the probability of cancer pain for each tumor type broken down by extent of the disease. Data about the prevalence of cancer pain in some tumor types were lacking, and estimates had to be applied based on similar tumor spread patterns. Some reported prevalence estimates were based on very small cohorts (eg, prostate). It was assumed that patients with in situ cancers did not have pain, and the possibility of treatment-related pain was ignored because no data were available. Nonetheless, the estimated composite pain prevalence rates for all cancer patients derived from large cohort studies corresponds remarkably well to a summation of the model estimate by tumor type and extent of disease.[1] The individual prevalence estimates are used in the model because they allowed more accurate predictions of the number of pain patients in user-defined populations.

Further, strategy effectiveness and cost were calculated by applying estimates of effective management, the probability of interventions, and intervention costs. These estimates were based on reanalysis of a single randomized, controlled trial with only 81 participants. Although incorporation of the Du Pen et al dataset provided solid estimates of the effectiveness and the probabilities of pharmaceutical interventions, these data were limited to 1 small population. Also, the dataset did not include the probabilities of nonpharmaceutical interventions or intervention costs. Historical Italian data and expert advice were used to derive the probabilities of the nonpharmaceutical interventions, including the various components that make up each intervention scenario. Because there was no evidence that GBC and OBC differ with respect to nonpharmaceutical interventions, it was conservatively assumed that the probability of use in these 2 groups is the same. Because the model is particularly sensitive to the cost of surgical interventions, errors in these assumptions may significantly skew the cost estimates. If nonpharmaceutical interventions are decidedly more prevalent than estimated, the model's cost estimates will be erroneously low—although the relative differences between the groups will likely remain similar.

A second limitation of the model is its scope. Some users may want to utilize the model to relate practice patterns to outcome at the micro level, but this model was not designed for such micro-level analysis. The model was designed to estimate the cost and cost-effectiveness of 3 different practice patterns, assuming that effectiveness and patterns of care are fixed at plausible values derived from trial data (for GBC and OBC) and extrapolation from other data sources (for UC). Limitations in the background data and assumptions make it impractical to use this model to test the exact result of a particular organizational decision. To the extent that effectiveness and practice patterns are generally similar in other healthcare settings to what is presented in the analysis, the model permits plausible and useful estimates of the magnitude of the problem of cancer pain and the potential impact of changing practice strategy.

The third limitation of the model is the use of CPT, DRG, and DME Medicare payment rates to derive the costs. Different organizations have individualized costs based on contractual agreements, utilization volumes, and policies. The Medicare rates allow normalization of the costs for the basic US population. The goal of the model is to demonstrate a general scenario and then allow users to tailor the model inputs to fit their individual organizations, including their organizations' costs for the various interventions. Hence, customized

model outputs will reflect organizational costs rather than Medicare norms.

A final imperative of the model is its ability to highlight research directions and areas for more intense clinical analysis and audit. Immediate areas of interest include nonpharmaceutical intervention uptake rates and their relative variability and impact. Similarly, parenteral opioid usage and effect are inadequately described. Pharmaceutical research efforts should include attention to neuropathic pain, nonopioid analgesics, relative effectiveness of opioid preparations, and side effect regimens. A controlled trial of GBC in the UC environment is a natural next step, especially as more primary care providers are asked to participate in the routine care of cancer patients. Robust evaluation of new cancer pain management guidelines also will be important, especially guidelines that include both pharmaceutical and nonpharmaceutical interventions. The model was designed for easy modification as new data become available.

CONCLUSION

The clinical and economic analysis of cancer pain management offers healthcare policy decision makers and clinicians a rational and comprehensive approach to evaluating various strategies of cancer pain management. More cancer patients are pain free when a guideline-based strategy is used, with a small increase in cost to the healthcare organization. This evidence-based approach can assist decision makers in advocating strategies that include coordinated cancer pain management.

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