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ORIGINAL ARTICLE

Cost-effectiveness of using a gene expression profiling test to aid in identifying the primary tumour in patients with cancer of unknown primary

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We aimed to investigate the cost-effectiveness of a 2000-gene-expression profiling (GEP) test to help identify the primary tumor site when clinicopathological diagnostic evaluation was inconclusive in patients with cancer of unknown primary (CUP). We built a decision-analytic-model to project the lifetime clinical and economic consequences of different clinical management strategies for CUP. The model was parameterized using follow-up data from the Manitoba Cancer Registry, cost data from Manitoba Health administrative databases and secondary sources. The 2000-GEP-based strategy compared to current clinical practice resulted in an incremental cost-effectiveness ratio (ICER) of $44,151 per quality-adjusted life years (QALY) gained. The total annual-budget impact was $36.2 million per year. A value-of-information analysis revealed that the expected value of perfect information about the test's clinical impact was $4.2 million per year. The 2000-GEP test should be considered for adoption in CUP. Field evaluations of the test are associated with a large societal benefit.

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INTRODUCTION

The Canadian Cancer Society estimates that approximately 186,400 new cases of cancer will occur in Canada in 2014.[1] Approximately 4% are of metastatic cancer types not readily classified in the course of the initial diagnostic work up.[2] International and Canadian clinical guidelines recommend a further diagnostic work-up for these metastatic patients including immunohistochemical (IHC) analyses.[2] In the past decade, improvements in the number and accuracy of IHC stains have enabled pathologists and oncologists to make highly accurate tissue-of-origin diagnosis in many of these metastatic patients.[3,4] However, the current success rate of the diagnostic work-up, even after exhaustive clinical and pathologic investigation, varies from 20 to 25%.[3,4] Consequently, about 5000 new cancer cases are annually diagnosed with cancer of unknown primary (CUP) in Canada.

In the absence of a specific tumour diagnosis, there has been no consensus of defined treatment guidelines. Several broad-spectrum empiric chemotherapeutic regimens (not specific for any particular type of cancer) based on combination regimens of platinum or taxane drugs have generally been used.[5,6] However, patients have a poor prognosis with a median survival of 8-12 months from diagnosis and 1-year survival probabilities ranging from 15 to 35%.[3]

The ability to identify a primary tumour site is an important goal in the clinical management of any patient with metastatic cancer. When tumour origins are known, patient outcomes including survival may improve because oncologists have better information on which to base treatment strategies.[7,8] This allows patients to benefit from the increasing availability of specific chemotherapy regimens or therapies designed to target biologic characteristics of specific malignancies.[7,8] Patients may also find value in knowing where their cancer originated from, independent of effects on prognosis and treatment.

Prediction of the likely primary tumour site by testing the biopsy specimen of the metastatic tumour is improving through the use of gene expression profiling techniques.[9,10] To date, several gene expression-based tests have demonstrated the potential value of this approach in identifying the primary site.[4,11–24] One microarray-based test uses 2000-GEP to identify a tumour's primary site using formalin-fixed paraffin-embedded (FFPE) specimens (Tissue of Origin test, Response Genetics, Inc., Los Angeles, CA).[24] The test compares the RNA profile of a tumour FFPE specimen to established RNA profiles of 15 known tissues. Test results are presented as 15 similarity scores (SS) which are interpreted as probabilities, one for each of 15 different tissue types on the panel. The highest SS indicates the most likely tissue of origin. A maximum SS of 30 or less indicates indeterminate results which might occur if the specimen harbors less than 20% tumor content or if the tumour specimen is not represented by the 15 tissue types included in the test panel.[24] Specimen requirements include a minimum of 20% tumour content, a maximum of 20% necrosis and a minimum tumor area of 0.5 mm^2.

The 2000-GEP test was validated on 462 independent FFPE specimens derived from metastatic or poorly differentiated tumor

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specimens of known primary cancers and showed 89.3% sensitivity in identifying tumour's primary site.[24] Based on this analysis, the test was approved by the Food and Drug Administration in 2012[25] and has been available for clinical use in the United states. The 2000-GEP test results are intended for use in the context of the patient's clinicopathologic and radiologic history by a qualified oncologist and pathologist.[26–28] For instance, initial or additional clinical history, IHC analyses, and computed tomography (CT) scan images should be correlated and consistent with 2000-GEP tumour classification when suggesting a potential primary tumour site.

Although the test has been validated as a diagnostic tool, its impact on health and economic outcomes, if introduced into general practice for CUP patients, has not been determined. The 2000-GEP test has an official list price of $4400 CAD per patient.[29] As of September 2015, the test is not publically funded in any Canadian province. Current clinical management of CUP patients who are left without a primary tumour site diagnosis following clinical and pathological diagnostic workup undertaken according to current Canadian clinical practice has not been influenced by the availability of 2000-GEP testing. Generation of recommendations for Canadian clinical practice regarding the use of 2000-GEP test in CUP requires a comprehensive health economic evaluation of this approach in the Canadian setting.[30] In this project, we evaluated the incremental cost-effectiveness of using the 2000 GEP test to help identify the primary tumour when current clinical and pathological diagnostic evaluation fails to provide a diagnosis of primary tumour site for CUP patients.

METHODS

Model overview

We developed a decision analytic model[31] (Figure 1) to estimate the lifetime clinical and economic consequences of different clinical management strategies for patients diagnosed with CUP following their clinical and pathological diagnostic workup undertaken according to current Canadian clinical practice. The model begins with a decision to use the 2000-GEP test or to continue with current clinical practice (CCP) (Figure 1a). In the CCP strategy, we assumed that the primary tumour site stays undiagnosed and CUP patients are treated according to existing clinical practice (Figure 1b). In the 2000-GEP-based strategy, we classified patients according to their occult primary tumour sites (Figure 1c). For each occult primary tumour site, we assumed that the 2000-GEP test results would either be determinate (defined as classification of the tumour specimen to one of the 15 tissue types included in the test panel) or indeterminate (defined as highest SS is 30 or less) (Figure 1c). Determinate 2000-GEP test results could either be correct or incorrect tumour classification (Figure 1c). We assumed that determinate 2000-GEP test results would be used in the context of a patient's clinicopathologic and radiologic assessment (CRA) history by a qualified oncologist and pathologist when suggesting a primary tumour site (e.g., clinical history, immunohistochemistry analysis, and computer tomography scan images, etc).[26,28,32] When determinate 2000-GEP test classification (i.e., correct or incorrect) is found to be consistent with the CRA, we assumed that the test result will be considered to suggest a diagnosis of primary tumour which may be correct or incorrect and guide clinical management (Figure 1c). When determinate 2000-GEP test classification is found to be inconsistent with CRA, we assumed that the test result will not be considered and primary tumour stays undiagnosed (Figure 1c).

In the 2000-GEP-based strategy, other occult primary tumour sites represent tumour sites that are not covered by the 15 tissue types included in the test panel. For these occult primary tumour sites, we assumed that the 2000-GEP test results would either be indeterminate (defined as highest SS is 30 or less) or determinate but represent incorrect tumour classification (i.e., incorrect classification of the tumour specimen to one of the 15 tissue types included in the test panel).

CUP patients whose primary tumour stays undiagnosed in both strategies or those who have their primary tumour incorrectly diagnosed in the 2000-GEP-based strategy entered Markov model 'A' (Figure 1d). CUP patients whose primary tumour is correctly diagnosed in the 2000-GEP-based strategy entered Markov model 'B' (Figure 1e). Model 'A' differs from model 'B' in that it has an additional health state to account for the possibility that some CUP patients whose primary tumour site is undiagnosed or incorrectly diagnosed may have their true primary tumor site (i.e., diagnosis of latent primary tumour site) subsequently identified during the course of disease.[33]

Model 'A' simulated monthly transitions among the following five distinct health states: (1) Initial diagnosis of metastasis of unknown primary (IDMUP); (2) diagnosis of latent primary (LP); (3) diagnosis of second primary (i.e., defined as a new primary malignancy) (SP); (4) palliative care (PC); and (5) death. Model 'B' simulated monthly transitions among the following four distinct health states: (1) Initial diagnosis of metastasis of known primary (IDMKP); (2) SP; (3) PC; and (4) death.

The analysis was conducted from the Canadian health care payer's perspective. We applied a discount rate of 5% per annum to costs, life years (LY) and quality adjusted life years (QALYs) following Canadian guidelines.[34] We used a lifetime horizon and half cycle correction.[35] We used TreeAge Software (Tree-Age Software, Inc., Williamstown, MA, USA) to produce and evaluate the decision analytic model. Data collection and analysis involving Manitoba administrative databases were approved by the University of Manitoba Health Research Ethics Board, Manitoba Health Information Privacy Committee and University of Western Ontario Health Research Ethics Board.

Identification of the study cohort

We used the Manitoba Cancer Registry (MCR) to identify a study cohort consisting of all patients diagnosed initially with metastatic cancer who underwent clinical and pathological diagnostic workup in Manitoba during the period from January 1, 2002 to December 31, 2011. A minimum of two-year follow-up information from the time of initial diagnosis was available for each patient. We linked all patients with administrative data held by Manitoba Health including the Hospital Discharge Database, the Physician Claims Database and the Drug Program Information Network. We also used the MCR to identify patients in our study cohort who had a latent primary (LP) tumour site subsequently detected after their initial diagnosis with metastatic cancer during their life or through autopsy. Full details are given in Supplementary Appendix section A.

Distributions and transition probabilities

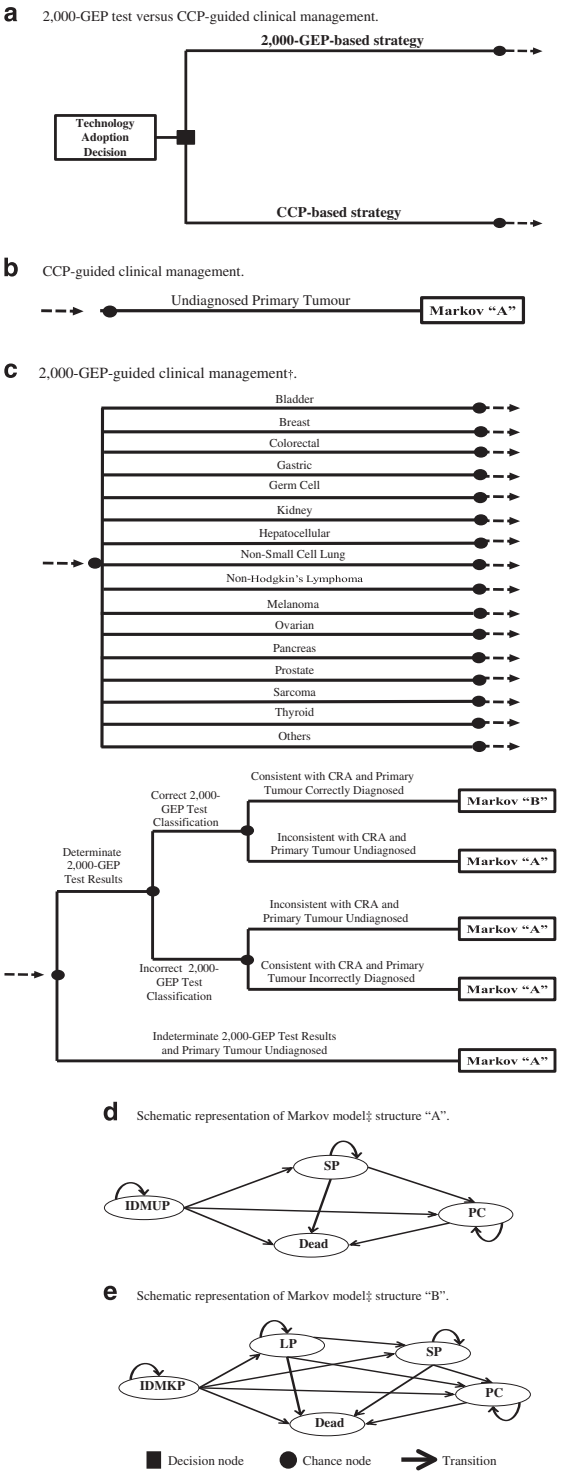
For each occult primary tumour site in the 2000-GEP model, we extracted the distribution of patients across 2000-GEP test results (i.e., determinate versus indeterminate 2000-GEP test results and correct versus incorrect 2000-GEP test classification) and across diagnostic results (i.e., correct diagnosis of primary tumour, incorrect diagnosis of primary tumour, and undiagnosed primary tumour) from a recent validation analysis[24] and clinical verification of the test performance[26] (Table 1). We estimated all other distributions in the decision tree and transition probabilities in the Markov models (Table 1) from the observed clinical management and survival outcomes in our study cohort. Full details are given in the Supplementary Appendix section B and Table A1.

Costs and utilities

The cost of 2000-GEP test is estimated at $4400 CAD per patient.[29] We used the costs of hospital stays, medical claims and prescription claims to estimate the cost per unit time in each Markov state (Table 2). We derived utility estimates from secondary sources (Table 3). Full details are given in the Supplementary Appendix section C and D.

Sensitivity analyses

In deterministic sensitivity analysis we focused on three groups of parameters: (1) Parameters related to the accuracy of 2000-GEP testing (akin sensitivity of the test) across occult primary sites (i.e., defined as the probability of correct 2000-GEP test classification given that the test result is determinate); (2) Parameters related to incorrect diagnostic results following determinate 2000-GEP test results (i.e., when the primary tumour stays undiagnosed following correct 2000-GEP test classification or when the primary tumour is incorrectly diagnosed following incorrect 2000-GEP test classification); and (3) Parameters related to survival following correct primary tumour diagnosis (i.e., the transition probabilities from IDM to PC, SP, or dead states in the 2000-GEP Markov models following the chance nodes when the primary is correctly diagnosed). We included the latter group of parameters in our sensitivity analyses to test the possibility that CUP patients may not respond as well as their counterparts



Patients entering Markov model "A" start the model and remain in the IDM state unless they develop LP or SP, start PC, or die. Patients who developed LP remain in the LP state or transition to SP, PC, or Dead states. Patients entering Markov model "B" start the model and remain in the IDM state unless they develop SP, start PC, or die. In both Markov models, patients who developed SP, remain in the SP state or make transition to PC or Dead states. Patients who started PC remain in the PC state or transition to Dead state.

* A decision analytic models are mathematical model used to combine data from several clinical trials or administrative databases as well as expert clinical and scientific opinion in order to project the impact of medical interventions and estimate their incremental cost-effectiveness ratios (see Inadomi 31 for an introduction). A decision tree is a common type of decision analytic model and used to simulate a sequence of decisions and uncertain events that may occur in a simple notion of time (i.e., one direction left to right chronologically). There are no shortcuts in a standard tree structure for representing events that recur over time (see Inadomi 31 for introduction).

† In the 2,000-GEP-based strategy, other occult primary tumour sites represent tumour sites that are not covered by the 15 tissue types included in the test panel. For these occult primary tumour sites, we assumed that the 2,000-GEP test results would either be indeterminate (defined as highest SS is 30 or less) or determinate but represent incorrect tumour classification (i.e., incorrect classification of the tumour specimen to one of the 15 tissue types included in the test panel) 26.

‡ A Markov model is a common type of decision analytic model and used to project scenarios that involve transitions between various states of health over a short or long period of time. The model allows movement back and forth between health states to represent events that recur over time (see Sonnenberg and Beck 35 for an introduction).

Abbreviations: CCP = Canadian clinical practice; GEP = Gene expression profiling; CRA = clinicopathologic and radiologic assessment; IDM = initial diagnosis of metastasis; LP = diagnosis of latent primary; SP = diagnosis of second primary; PC = palliative care.

Figure 1. Decision analytic model for CUP*.

Table 1. Base case probabilities and sources

Variables	*Base case value*	*Range tested in sensitivity analyses*	*Distribution used in PSA*[a]	*Data Source*
Probability distribution of occult primary tumour sites among CUP patients (%)				MCR
Bladder	0			
Breast	2.4		Dirichlet	
Colorectal	13		Dirichlet	
Gastric	1.1		Dirichlet	
Testicular germ cell	1.1		Dirichlet	
Kidney	3		Dirichlet	
Hepatocellular	0.6		Dirichlet	
Non-small cell lung	14.2		Dirichlet	
Non-Hodgkin's lymphoma	10		Dirichlet	
Melanoma	6.5		Dirichlet	
Ovarian	13.6		Dirichlet	
Pancreas	7.1		Dirichlet	
Prostate	3		Dirichlet	
Sarcoma	2		Dirichlet	
Thyroid	2		Dirichlet	
All other tumor sites not covered by the 2000-GEP test panel[b]	20.4		Dirichlet	
Distribution of these tumour sites				
Buccal cavity and pharynx	17.8			
Esophagus	1.2			
Small intestine	3.6			
Gallbladder	5.9			
Non-hepatocellular	3.6			
Other digestive system	14.3			
Other female genital system	4.8			
Other male genital system	1.2			
Small cell lung	8.3			
Other lung	26.2			
Ureter	2.4			
Other urinary system	1.2			
Multiple myeloma	8.3			
Other endocrine	1.2			
Probability of determinate 2000-GEP test result for each tumour site included in the 2000-GEP test panel[b] (%)	93	90–100		26
Probability of indeterminate 2000-GEP test results for each tumour site included in the 2000-GEP test panel[c] (%)	7	0–10	Beta	26
Probability of determinate 2000-GEP test result for other tumor sites not covered by the 2000-GEP test panel[b] (%)	67			26
Probability of indeterminate 2000-GEP test result for other tumor sites not covered by the 2000-GEP test panel[c] (%)	33	30–40	Beta	26
Accuracy of 2000-*GEP test by occult primary tumour site (%) given a determinate test result*				
Bladder				
Correct classification	79.3	60.3–92		24
Incorrect classification	20.7	8–39.7	Beta	24
Breast				
Correct classification	96.5	87.9–99.6		24
Incorrect classification	3.5	0.4–12.1	Beta	24
Colorectal				
Correct classification	91.7	77.5–98.2		24
Incorrect classification	8.3	1.8–22.5	Beta	24
Gastric				
Correct classification	72	50.6–87.9		24
Incorrect classification	28	12.1–49.4	Beta	24
Hepatocellular				
Correct classification	96	79.6–99.9		24
Incorrect classification	4	0.1–20.4	Beta	24
Germ cell				
Correct classification	84	63.9–95.5		24
Incorrect classification	16	4.5–36.1	Beta	24
Kidney				
Correct classification	89.3	71.8–97.7		24
Incorrect classification	10.7	0.3–28.2	Beta	24
Melanoma				
Correct classification	84	63.9–95.5		24
Incorrect classification	16	0.5–36.1	Beta	24
Non-Hodgkin's lymphoma				
Correct classification	89.7	72.6–97.8		24

Table 1. (Continued)

Variables	*Base case value*	*Range tested in sensitivity analyses*	*Distribution used in PSA*[a]	*Data Source*
Incorrect classification	10.3	2.2–27.4	Beta	[24]
Non-small cell lung				
Correct classification	85.2	66.3–95.8		[24]
Incorrect classification	14.8	4.2–33.7	Beta	[24]
Ovarian				
Correct classification	88.9	75.9–96.3		[24]
Incorrect classification	11.1	3.7–24.1	Beta	[24]
Pancreas				
Correct classification	85.7	67.3–96		[24]
Incorrect classification	14.3	4–32.7	Beta	[24]
Prostate				
Correct classification	96	79.6–99.9		[24]
Incorrect classification	4	0.1–20.4	Beta	[24]
Sarcoma				
Correct classification	88.9	70.8–97.6		[24]
Incorrect classification	11.1	2.4–29.2	Beta	[24]
Thyroid				
Correct classification	90.3	74.2–98		[24]
Incorrect classification	9.7	2–25.8	Beta	[24]
Others				
Correct classification	0			[26]
Incorrect classification	100			[26]
Probabilities of diagnostic results following the interpretation of determinate 2000-GEP test results in the context of CRA[d] *(%)*				
Following correct 2000-GEP test classification				
2000-GEP test classification is consistent with CRA and correct diagnosis of primary tumour is made	100	0 –100	Beta	[26,28,32]
2000-GEP test classification is inconsistent with CRA and primary tumour stays undiagnosed	0	0 –100		[26,28,32]
Following Incorrect 2000-GEP test classification				
2000-GEP test classification is inconsistent with CRA and primary tumour stays undiagnosed	100	0–100	Beta	[26,28,32]
2000-GEP test classification is consistent with CRA and incorrect diagnosis of primary tumour is made	0	0–100		[26,28,32]

Abbreviations: CRA, Clinicopathologic and radiologic assessment; CUP, Cancer of unknown primary; MCR, Manitoba Cancer Registry; PSA, probabilistic sensitivity analysis; SS, Similarity score. [a]The Dirichlet distribution is a multinomial extension of the beta distribution. The Dirichlet distribution was used in PSA for the probability estimates of occult primary tumour sites to provide probabilistic probabilities over multiple branches (i.e., represent occult primary tumour sites) that appropriately represent uncertainty while satisfying the requirement that mutually exclusive event probabilities should sum to 1.[36] Base-case probability estimates of 100% were assumed to be 99% in PSA. [b]The 2000-GEP test panel covers the following 15 tissue types: Hepatocellular, kidney, non-small cell lung, ovarian, pancreatic, prostate, and thyroid, melanoma, testicular germ cell, non-Hodgkins lymphoma, and sarcoma. [c]The 2000-GEP test result is classified as indeterminate when the highest SS is 30 or less due to unique specimens harboring less than 20% tumor content, or actual tissue of origin for a given tumour specimen is not covered by the 15 tissue types included in the test panel. [d]Determinate 2000-GEP test result (i.e., correct or incorrect 2000-GEP test classification) is assumed to be used in the context of the patient's clinicopathologic and radiologic history by a qualified oncologist and pathologist. For example, other available information such as clinical history, immunohistochemistry analysis, and computer tomography scan images are considered when suggesting a primary tumour site as by 2000-GEP test classification. When determinate 2000-GEP test classification is found to be inconsistent with CRA, the test result is not considered and primary tumour stays undiagnosed.

with metastatic of known primary cancers when their occult primary is identified and treated with current site-specific therapy.[56] We have separately performed additional deterministic sensitivity analyses on the cost of the test and probability of indeterminate test results across occult primary sites.

We conducted probabilistic sensitivity analysis using Monte Carlo simulation with 1000 iterations. Each iteration consisted of a random draw from an appropriate distribution for all model inputs (Tables 1, 2, 3) to produce a distribution of model outputs.

We also performed a value-of-information analysis[57] in which we estimated the expected monetary value of removing all statistical uncertainty about the clinical impact of the 2000-GEP test.[57,58] In particular, we compared results with and without uncertainty related to accuracy of the 2000-GEP test, diagnostic results following determinate 2000-GEP test results, and survival following correct primary tumour diagnosis.

RESULTS

Base-case scenario

There were 1,080 metastatic patients diagnosed with CUP who were left without a primary tumour site diagnosis following clinical and pathological diagnostic workup undertaken according to clinical practice in Manitoba from January 1, 2002 to December 31, 2011. Patient, tumour, and treatment characteristics of all the CUP patients are given in the Supplementary Appendix Table A2. Of those, 169 (15%) patients had their latent primary tumour site eventually detected during their life. During the same time period, there were 10 012 patients initially diagnosed with metastatic cancer of known primary. Of those, 202 (2%) patients had their cancer initially classified differently from their latent primary tumour identified later during life or at autopsy.

Our model predicted 1.13 LY, 0.63 QALY and $17,802 CAD for CUP (i.e., CCP-based strategy). By contrast, when the primary tumour is properly identified model outcomes ranged from 0.74 LY, 0.45 QALY, and $14,278 for metastatic cancer of hepatocellular primary tumour to 4.35 LY, 3.37 QALY, and $69,400 CAD for metastatic cancer of testicular germ cell primary tumour (Table 4). Overall, the model predicted 1.42 LY, 0.87 QALY and 28,609 CAD for the 2000-GEP-based strategy.

Table 2. Base case cost estimates and sources

Variables	*Base case value*	*Duration*	*Distribution used in PSA*[a]	*Data Source*
Cost associated with IDM (per month), $				
Breast				
First year after IDM				
Costs of inpatients and one day procedure stays	983	12 months	Log-logistic	HA
Physicians and other health care providers cost	257	12 months	Log-logistic	PC
Cost of prescription claims	73	12 months	Log-logistic	DPIN
After first year of IDM				
Costs of inpatients and one day procedure stays	490	Lifetime	Log-logistic	HA
Physicians and other health care providers cost	131	Lifetime	Log-logistic	PC
Cost of prescription claims	89	Lifetime	Log-logistic	DPIN
Colorectal				
First year after IDM				
Costs of inpatients and one day procedure stays	1273	12 months	Log-logistic	HA
Physicians and other health care providers cost	533	12 months	Log-logistic	PC
Cost of prescription claims	73	12 months	Log-logistic	DPIN
After first year of IDM				
Costs of inpatients and one day procedure stays	730	Lifetime	Log-logistic	HA
Physicians and other health care providers cost	284	Lifetime	Log-logistic	PC
Cost of prescription claims	89	Lifetime	Log-logistic	DPIN
Gastric				
First year after IDM				
Costs of inpatients and one day procedure stays	1425	12 months	Log-logistic	HA
Physicians and other health care providers cost	398	12 months	Log-logistic	PC
Cost of prescription claims	46	12 months	Log-logistic	DPIN
After first year of IDM				
Costs of inpatients and one day procedure stays	1372	Lifetime	Log-logistic	HA
Physicians and other health care providers cost	271	Lifetime	Log-logistic	PC
Cost of prescription claims	72	Lifetime	Log-logistic	DPIN
Hepatocellular				
First year after IDM				
Costs of inpatients and one day procedure stays	943	12 months	Log-logistic	HA
Physicians and other health care providers cost	185	12 months	Log-logistic	PC
Cost of prescription claims	42	12 months	Log-logistic	DPIN
After first year of IDM				
Costs of inpatients and one day procedure stays	737	Lifetime	Log-logistic	HA
Physicians and other health care providers cost	19	Lifetime	Log-logistic	PC
Cost of prescription claims	27	Lifetime	Log-logistic	DPIN
Kidney				
First year after IDM				
Costs of inpatients and one day procedure stays	1353	12 months	Log-logistic	HA
Physicians and other health care providers cost	373	12 months	Log-logistic	PC
Cost of prescription claims	78	12 months	Log-logistic	DPIN
After first year of IDM				
Costs of inpatients and one day procedure stays	1019	Lifetime	Log-logistic	HA
Physicians and other health care providers cost	224	Lifetime	Log-logistic	PC
Cost of prescription claims	93	Lifetime	Log-logistic	DPIN
Melanoma				
First year after IDM				
Costs of inpatients and one day procedure stays	508	12 months	Log-logistic	HA
Physicians and other health care providers cost	290	12 months	Log-logistic	PC
Cost of prescription claims	78	12 months	Log-logistic	DPIN
After first year of IDM				
Costs of inpatients and one day procedure stays	748	Lifetime	Log-logistic	HA
Physicians and other health care providers cost	164	Lifetime	Log-logistic	PC
Cost of prescription claims	85	Lifetime	Log-logistic	DPIN
Non-Hodgkin's lymphoma				
First year after IDM				
Costs of inpatients and one day procedure stays	1620	12 months	Log-logistic	HA
Physicians and other health care providers cost	346	12 months	Log-logistic	PC
Cost of prescription claims	123	12 months	Log-logistic	DPIN
After first year of IDM				
Costs of inpatients and one day procedure stays	1414	Lifetime	Log-logistic	HA
Physicians and other health care providers cost	183	Lifetime	Log-logistic	PC
Cost of prescription claims	77	Lifetime	Log-logistic	DPIN
Non-small lung				
First year after IDM				
Costs of inpatients and one day procedure stays	885	12 months	Log-logistic	HA
Physicians and other health care providers cost	241	12 months	Log-logistic	PC
Cost of prescription claims	33	12 months	Log-logistic	DPIN

Table 2. (Continued)

Variables	*Base case value*	*Duration*	*Distribution used in PSA*[a]	*Data Source*
After first year of IDM				
Costs of inpatients and one day procedure stays	773	Lifetime	Log-logistic	HA
Physicians and other health care providers cost	164	Lifetime	Log-logistic	PC
Cost of prescription claims	83	Lifetime	Log-logistic	DPIN
Ovarian				
First year after IDM				
Costs of inpatients and one day procedure stays	2618	12 months	Log-logistic	HA
Physicians and other health care providers cost	392	12 months	Log-logistic	PC
Cost of prescription claims	69	12 months	Log-logistic	DPIN
After first year of IDM				
Costs of inpatients and one day procedure stays	1144	Lifetime	Log-logistic	HA
Physicians and other health care providers cost	187	Lifetime	Log-logistic	PC
Cost of prescription claims	58	Lifetime	Log-logistic	DPIN
Pancreas				
First year after IDM				
Costs of inpatients and one day procedure stays	1164	12 months	Log-logistic	HA
Physicians and other health care providers cost	294	12 months	Log-logistic	PC
Cost of prescription claims	36	12 months	Log-logistic	DPIN
After first year of IDM				
Costs of inpatients and one day procedure stays	1345	Lifetime	Log-logistic	HA
Physicians and other health care providers cost	241	Lifetime	Log-logistic	PC
Cost of prescription claims	171	Lifetime	Log-logistic	DPIN
Prostate				
First year after IDM				
Costs of inpatients and one day procedure stays	961	12 months	Log-logistic	HA
Physicians and other health care providers cost	243	12 months	Log-logistic	PC
Cost of prescription claims	60	12 months	Log-logistic	DPIN
After first year of IDM				
Costs of inpatients and one day procedure stays	771	Lifetime	Log-logistic	HA
Physicians and other health care providers cost	119	Lifetime	Log-logistic	PC
Cost of prescription claims	64	Lifetime	Log-logistic	DPIN
Sarcoma				
First year after IDM				
Costs of inpatients and one day procedure stays	1451	12 months	Log-logistic	HA
Physicians and other health care providers cost	552	12 months	Log-logistic	PC
Cost of prescription claims	127	12 months	Log-logistic	DPIN
After first year of IDM				
Costs of inpatients and one day procedure stays	470	Lifetime	Log-logistic	HA
Physicians and other health care providers cost	119	Lifetime	Log-logistic	PC
Cost of prescription claims	176	Lifetime	Log-logistic	DPIN
Germ cell				
First year after IDM				
Costs of inpatients and one day procedure stays	1109	12 months	Log-logistic	HA
Physicians and other health care providers cost	606	12 months	Log-logistic	PC
Cost of prescription claims	129	12 months	Log-logistic	DPIN
After first year of IDM				
Costs of inpatients and one day procedure stays	903	Lifetime	Log-logistic	HA
Physicians and other health care providers cost	139	Lifetime	Log-logistic	PC
Cost of prescription claims	26	Lifetime	Log-logistic	DPIN
Thyroid				
First year after IDM				
Costs of inpatients and one day procedure stays	854	12 months	Log-logistic	HA
Physicians and other health care providers cost	417	12 months	Log-logistic	PC
Cost of prescription claims	39	12 months	Log-logistic	DPIN
After first year of IDM				
Costs of inpatients and one day procedure stays	484	Lifetime	Log-logistic	HA
Physicians and other health care providers cost	89	Lifetime	Log-logistic	PC
Cost of prescription claims	45	Lifetime	Log-logistic	DPIN
CUP				
First year after IDM				
Costs of inpatients and one day procedure stays	1145	12 months	Log-logistic	HA
Physicians and other health care providers cost	210	12 months	Log-logistic	PC
Cost of prescription claims	51	12 months	Log-logistic	DPIN
After first year of IDM				
Costs of inpatients and one day procedure stays	541	Lifetime	Log-logistic	HA
Physicians and other health care providers cost	90	Lifetime	Log-logistic	PC
Cost of prescription claims	100	Lifetime	Log-logistic	DPIN
Cost associated with latent primary (per month), $				
Patients initially diagnosed with CUP				
First year after latent primary				

Table 2. (Continued)

Variables	*Base case value*	*Duration*	*Distribution used in PSA*[a]	*Data Source*
Costs of inpatients and one day procedure stays	970	12 months	Log-logistic	HA
Physicians and other health care providers cost	191	12 months	Log-logistic	PC
Cost of prescription claims	88	12 months	Log-logistic	DPIN
After first year of latent primary				
Costs of inpatients and one day procedure stays	1724	Lifetime	Log-logistic	HA
Physicians and other health care providers cost	150	Lifetime	Log-logistic	PC
Cost of prescription claims	88	Lifetime	Log-logistic	DPIN
Cost associated with palliative care (per month), $				
Breast				
Costs of inpatients and one day procedure stays	1214	Lifetime	Log-logistic	HA
Physicians and other health care providers cost	236	Lifetime	Log-logistic	PC
Cost of prescription claims	98	Lifetime	Log-logistic	DPIN
Colorectal				
Costs of inpatients and one day procedure stays	1226	Lifetime	Log-logistic	HA
Physicians and other health care providers cost	204	Lifetime	Log-logistic	PC
Cost of prescription claims	77	Lifetime	Log-logistic	DPIN
Gastric				
Costs of inpatients and one day procedure stays	790	Lifetime	Log-logistic	HA
Physicians and other health care providers cost	149	Lifetime	Log-logistic	PC
Cost of prescription claims	56	Lifetime	Log-logistic	DPIN
Germ cell				
Costs of inpatients and one day procedure stays	594	Lifetime	Log-logistic	HA
Physicians and other health care providers cost	10	Lifetime	Log-logistic	PC
Cost of prescription claims	0	Lifetime	Log-logistic	DPIN
Kidney				
Costs of inpatients and one day procedure stays	1277	Lifetime	Log-logistic	HA
Physicians and other health care providers cost	259	Lifetime	Log-logistic	PC
Cost of prescription claims	184	Lifetime	Log-logistic	DPIN
Hepatocellular				
Costs of inpatients and one day procedure stays	544	Lifetime	Log-logistic	HA
Physicians and other health care providers cost	142	Lifetime	Log-logistic	PC
Cost of prescription claims	27	Lifetime	Log-logistic	DPIN
Non-small lung				
Costs of inpatients and one day procedure stays	1116	Lifetime	Log-logistic	HA
Physicians and other health care providers cost	175	Lifetime	Log-logistic	PC
Cost of prescription claims	67	Lifetime	Log-logistic	DPIN
Non-Hodgkin's lymphoma				
Costs of inpatients and one day procedure stays	1012	Lifetime	Log-logistic	HA
Physicians and other health care providers cost	242	Lifetime	Log-logistic	PC
Cost of prescription claims	268	Lifetime	Log-logistic	DPIN
Melanoma				
Costs of inpatients and one day procedure stays	853	Lifetime	Log-logistic	HA
Physicians and other health care providers cost	241	Lifetime	Log-logistic	PC
Cost of prescription claims	94	Lifetime	Log-logistic	DPIN
Ovarian				
Costs of inpatients and one day procedure stays	1182	Lifetime	Log-logistic	HA
Physicians and other health care providers cost	158	Lifetime	Log-logistic	PC
Cost of prescription claims	71	Lifetime	Log-logistic	DPIN
Pancreas				
Costs of inpatients and one day procedure stays	819	Lifetime	Log-logistic	HA
Physicians and other health care providers cost	144	Lifetime	Log-logistic	PC
Cost of prescription claims	55	Lifetime	Log-logistic	DPIN
Prostate				
Costs of inpatients and one day procedure stays	1358	Lifetime	Log-logistic	HA
Physicians and other health care providers cost	200	Lifetime	Log-logistic	PC
Cost of prescription claims	88	Lifetime	Log-logistic	DPIN
Sarcoma				
Costs of inpatients and one day procedure stays	1215	Lifetime	Log-logistic	HA
Physicians and other health care providers cost	197	Lifetime	Log-logistic	PC
Cost of prescription claims	112	Lifetime	Log-logistic	DPIN
Thyroid				
Costs of inpatients and one day procedure stays	463	Lifetime	Log-logistic	HA
Physicians and other health care providers cost	102	Lifetime	Log-logistic	PC
Cost of prescription claims	49	Lifetime	Log-logistic	DPIN
CUP				
Costs of inpatients and one day procedure stays	1233	Lifetime	Log-logistic	HA
Physicians and other health care providers cost	184	Lifetime	Log-logistic	PC
Cost of prescription claims	83	Lifetime	Log-logistic	DPIN

Table 2. (Continued)

Variables	*Base case value*	*Duration*	*Distribution used in PSA*[a]	*Data Source*
Cost associated with second primary[b]*(per month), $*				
Breast				
Costs of inpatients and one day procedure stays	527	Lifetime	Log-logistic	HA
Physicians and other health care providers cost	265	Lifetime	Log-logistic	PC
Cost of prescription claims	42	Lifetime	Log-logistic	DPIN
Colerectal				
Costs of inpatients and one day procedure stays	1283	Lifetime	Log-logistic	HA
Physicians and other health care providers cost	511	Lifetime	Log-logistic	PC
Cost of prescription claims	128	Lifetime	Log-logistic	DPIN
Gastric				
Costs of inpatients and one day procedure stays	464	Lifetime	Log-logistic	HA
Physicians and other health care providers cost	102	Lifetime	Log-logistic	PC
Cost of prescription claims	11	Lifetime	Log-logistic	DPIN
Germ cell				
Costs of inpatients and one day procedure stays	711	Lifetime	Log-logistic	HA
Physicians and other health care providers cost	1217	Lifetime	Log-logistic	PC
Cost of prescription claims	27	Lifetime	Log-logistic	DPIN
Kidney				
Costs of inpatients and one day procedure stays	2518	Lifetime	Log-logistic	HA
Physicians and other health care providers cost	285	Lifetime	Log-logistic	PC
Cost of prescription claims	164	Lifetime	Log-logistic	DPIN
Non-small lung				
Costs of inpatients and one day procedure stays	1147	Lifetime	Log-logistic	HA
Physicians and other health care providers cost	317	Lifetime	Log-logistic	PC
Cost of prescription claims	62	Lifetime	Log-logistic	DPIN
Non-Hodgkin's lymphoma				
Costs of inpatients and one day procedure stays	876	Lifetime	Log-logistic	HA
Physicians and other health care providers cost	343	Lifetime	Log-logistic	PC
Cost of prescription claims	138	Lifetime	Log-logistic	DPIN
Melanoma				
Costs of inpatients and one day procedure stays	1022	Lifetime	Log-logistic	HA
Physicians and other health care providers cost	437	Lifetime	Log-logistic	PC
Cost of prescription claims	166	Lifetime	Log-logistic	DPIN
Ovarian				
Costs of inpatients and one day procedure stays	600	Lifetime	Log-logistic	HA
Physicians and other health care providers cost	202	Lifetime	Log-logistic	PC
Cost of prescription claims	29	Lifetime	Log-logistic	DPIN
Prostate				
Costs of inpatients and one day procedure stays	1573	Lifetime	Log-logistic	HA
Physicians and other health care providers cost	254	Lifetime	Log-logistic	PC
Cost of prescription claims	83	Lifetime	Log-logistic	DPIN
Sarcoma				
Costs of inpatients and one day procedure stays	1246	Lifetime	Log-logistic	HA
Physicians and other health care providers cost	517	Lifetime	Log-logistic	PC
Cost of prescription claims	256	Lifetime	Log-logistic	DPIN
Thyroid				
Costs of inpatients and one day procedure stays	219	Lifetime	Log-logistic	HA
Physicians and other health care providers cost	142	Lifetime	Log-logistic	PC
Cost of prescription claims	48	Lifetime	Log-logistic	DPIN
CUP				
Costs of inpatients and one day procedure stays	910	Lifetime	Log-logistic	HA
Physicians and other health care providers cost	307	Lifetime	Log-logistic	PC
Cost of prescription claims	34	Lifetime	Log-logistic	DPIN

Abbreviations: CUP, Cancer of unknown primary ; DPIN, Drug Program Information Network records; IDM, Initial diagnosis of metastasis; HA, Hospital abstracts; MCR, Manitoba Cancer Registry; PC, physician claims; PSA, probabilistic sensitivity analysis. [a]Normal distributions were used for cost parameters in the PSA to simulate uncertainty at the population level. [b]Patients initially diagnosed with metastatic hepatocellular and pancreatic cancer did not have a second primary over the study follow up period and thus costs associated with second primary are not included for hepatocellular and pancreas. Full details on estimation procedures found in Supplementary Appendix section C.

Compared to CCP, the 2000-GEP-based strategy led to an increase of 0.28 LY and 0.24 QALY per person and an increase in cost of $10,807 CAD per person of which $4,400 is the cost of the test itself, resulting in an incremental cost effectiveness ratio (ICER) of $37,774 per LY gained and $44,151 per QALY. The clinical benefit of 0.28 LY is comparable to recently reported data showing an improved survival of 3.4 months for CUP patients received site-specific therapy based on a GEP diagnosis when compared to historical control patients.[8]

Budget impact analysis

We estimated the total expense of incorporating the 2000-GEP test into standard practice in Canada for CUP patients when current

Table 3. Utility values and sources

Health states	*Utility*[a]	*Duration*	*Range tested in sensitivity analyses*	*Distribution used in PSA*	*Data Source*[b]
Initial diagnosis of metastasis of known primary					
Breast	0.715	LT	-20% – +20%	Beta	38
Colorectal	0.730	LT	-20% – +20%	Beta	39
Gastric	0.729	LT	-20% – +20%	Beta	40
Hepatocellular	0.650	LT	-20% – +20%	Beta	41
Kidney	0.760	LT	-20% – +20%	Beta	42
Melanoma	0.580	LT	-20% – +20%	Beta	43
Non-Hodgkin's lymphoma	0.805	LT	-20% – +20%	Beta	44
Non-small Lung	0.530	LT	-20% – +20%	Beta	45
Ovarian	0.740	LT	-20% – +20%	Beta	46
Pancreas	0.600	LT	-20% – +20%	Beta	47
Prostate	0.740	LT	-20% – +20%	Beta	48
Sarcoma	0.690	LT	-20% – +20%	Beta	49
Testicular germ cell	0.776	LT	-20% – +20%	Beta	50,51
Thyroid	0.780	LT	-20% – +20%	Beta	51,52
Other primary tumour sites					
Buccal cavity and pharynx	0.670				53
Esophagus	0.670				53
Small intestine	0.730				39
Gallbladder	0.650				41
Non-hepatocellular	0.650				41
Other digestive system	0.730				39
Other female genital system	0.740				46
Other male genital system	0.740				48
Small cell lung	0.530				45
Other lung	0.530				45
Ureter	0.760				42
Other urinary system	0.760				42
Multiple myeloma	0.805				44
Other endocrine	0.800				51,52
Weighted average utility of other primary tumour sites[c]	0.649	LT	-20% – +20%	Beta	
Weighted average utility of metastasis of known primary[c]	0.645				
Initial diagnosis of metastasis of unknown primary [d]	0.560	LT	-20% – +20%	Beta	37
Diagnosis of latent primary tumour	Utility of metastasis of the corresponding primary tumour[e]	LT	-20% – +20%	Beta	
Diagnosis of Second primary tumour	7% reduction in the utility of the previous health state[f]	LT	-20% – +20%	Beta	54
Palliative care	0.4	LT	-20% – +20%	Beta	55
Death	0				

Abbreviations: CUP, cancer of unknown primary; LT, lifetime; PSA, Probabilistic sensitivity analysis. [a]All utility estimates were based on EuroQOL five dimensions questionnaire (EQ-5D). [b]When EQ-5D estimates are not available the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) utility estimates were converted to EQ-5D estimates according to mapping model described by Kim *et al.*[51] [c]Weighted average was based on the observed distribution of latent primary tumour sites in our CUP cohort (Table 1). [d]Utility with CUP was derived after applying 13% reduction on the weighted average utility of metastasis of known primary. [e]For example, if a latent primary tumour is detected in the course of metastatic disease for a CUP patient and found to be breast tumour, then this patient will transition to the 'diagnosis of latent primary tumour' state and receive the utility of metastasis of breast cancer (which is equal to 0.715) while remaining in this health state unless this patient transition to other health states. [f]For example, when a second primary tumour is detected in the course of metastatic disease of a CUP patient following Markov model 'A', this patient will transition from the 'initial diagnosis of metastasis of unknown primary' state (i.e., utility = 0.56) to the 'diagnosis of second primary tumour' state and receive 7% reduction in the utility of metastasis of unknown primary (i.e., 0.56 – (0.56*0.07) = 0.52) while remaining in this health state, unless this patient transitions to other health states. Full details on estimation procedures found in Supplementary Appendix Section D.

diagnostic evaluation fails to provide a diagnosis of primary tumour. In Manitoba, there were 120 patients diagnosed with CUP in 2010. Based on the population of Manitoba relative to the rest of Canada (1.2 million versus 33.5 million at the 2011 census), we anticipate approximately 3350 patients diagnosed with CUP annually could be eligible for the 2000-GEP test in Canada. The resulting total annual budget impact was $36.2 million CAD per year of which $14.7 million was due to 2000-GEP testing alone and $21.5 million was due to changes in the management of CUP following 2000-GEP testing.

Sensitivity analysis

The 2000-GEP-based strategy generated an ICER greater than $100,000 per QALY gained when the accuracy of the 2000-GEP test decreased by 50%, incorrect diagnostic results following 2000-GEP test classification increased by 20% and survival following correct primary diagnosis decreased by 30% (Figure 2). In separate analyses, the cost of the test and probability of indeterminate test results across occult primary sites did not substantially influence our baseline outcomes.

Table 4. Baseline outcomes of Markov models by decision model strategy, Markov model structure and primary tumour site

Strategy	*Markov model structure*	*Primary tumour site*	*Effectiveness*		*Cost*
			LY	*QALY*	
CCP- and 2000-GEP-based strategy[a]	'A'	Unknown primary	1.13	0.63	$17,802
2000-GEP-based strategy[b]	'B'	Breast	1.79	1.08	$30,874
		Colorectal	2.00	1.40	$38,978
		Gastric	1.09	0.73	$26,985
		Hepatocellular	0.74	0.45	$14,278
		Kidney	1.51	1.02	$34,157
		Melanoma	2.30	1.29	$33,056
		Non-Hodgkin's lymphoma	3.05	2.41	$68,662
		Non-small Lung	1.08	0.53	$20,165
		Ovarian	1.86	1.31	$50,000
		Pancreas	0.75	0.43	$18,157
		Prostate	2.62	1.78	$40,942
		Sarcoma	1.88	1.22	$36,015
		Testicular germ cell	4.35	3.37	$69,400
		Thyroid	3.77	2.97	$40,200

Abbreviations: LY, life year; QALY, quality adjusted life year. [a]Markov model structure 'A' was used in the CCP-based strategy and the 2000-GEP-based strategy when the primary tumour remains undiagnosed or is incorrectly diagnosed. [b]Markov models structure 'B' were only used in the 2000-GEP-based strategy when the primary tumour is correctly identified.

Using willingness to pay thresholds of $50,000 and $100,000 per QALY gained in probabilistic sensitivity analysis (Figure 3a), we found that the 2000-GEP-based strategy was the preferred strategy in 78.2 and 99.6% of simulations, respectively (Figure 3b).

Using our baseline ICER value of $44,151 per QALY gained as the willingness to pay, the opportunity cost associated with the choice of 2000-GEP-based strategy for guiding management of CUP resulted in a total expected value of partial perfect information (EVPPI) of $1266 per patient diagnosed with CUP of which $450 was due to uncertainty related to accuracy of the 2000-GEP test, $320 was due to uncertainty related to diagnostic results following determinate 2000-GEP test results, and $496 was due to uncertainty related to accuracy of survival following correct primary tumour diagnosis. The resulting total EVPPI for the entire CUP population that could be eligible for the 2000-GEP test in Canada was 3350 cases of CUP per year $\times$ $1266 per patient = $4.2 million CAD per year.

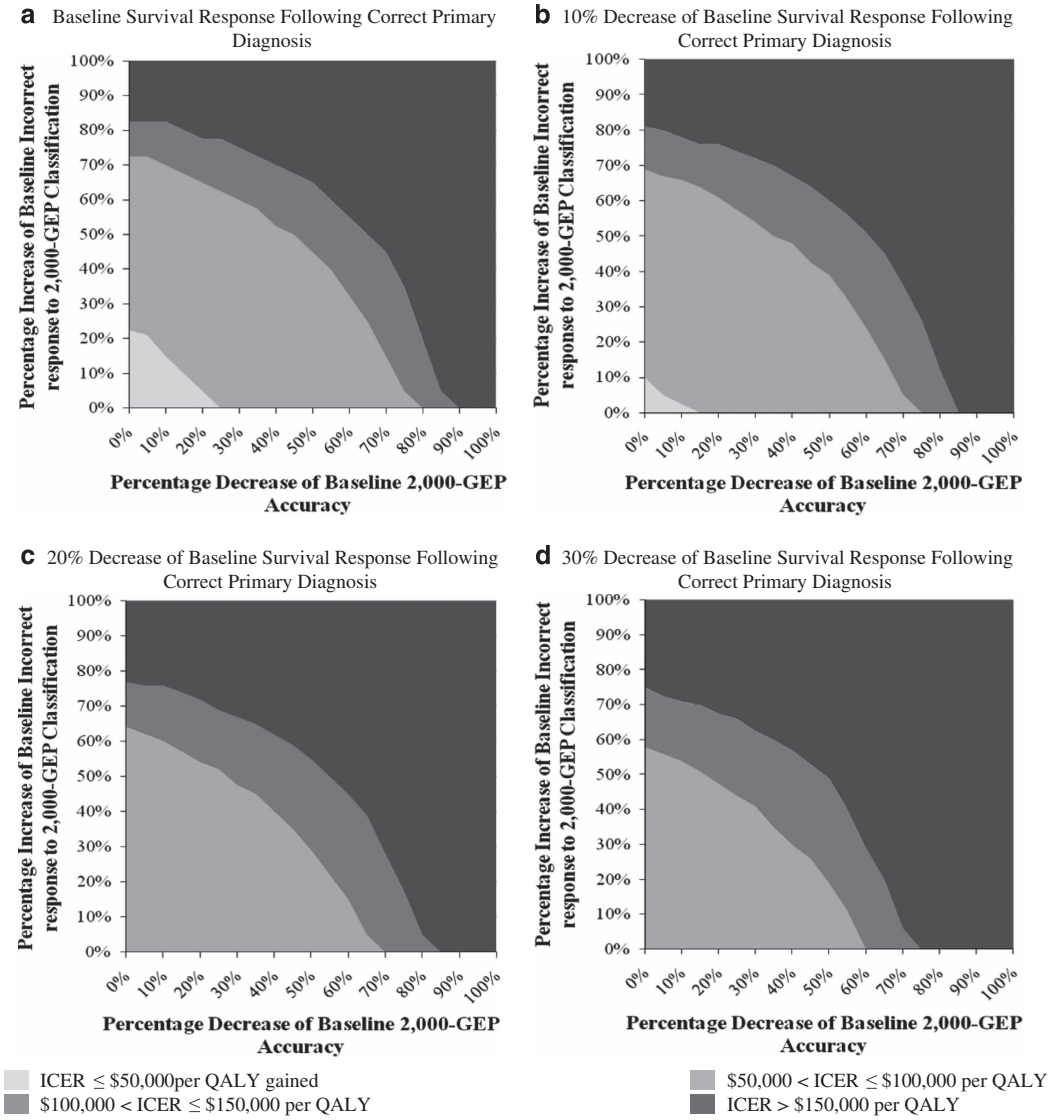
DISCUSSION

We developed a decision-analytic model to evaluate the cost effectiveness of using the 2000-GEP test to help identify primary tumours when current clinical and pathological diagnostic evaluation fails to provide a diagnosis of primary tumour site in CUP patients. In the base case, we estimated that the 2000-GEP-based strategy has an ICER of $37,774 per LY gained and $44,151 per QALY gained. These ICERs are below ICER estimates for a 21-GEP assay[59,60] and cancer drugs that were recently recommended for adoption.[61,62] The clinical benefit of 0.28 LY is comparable to several recently approved drugs for metastatic disease.[63–66] The budget impact analysis shows that adoption of the 2000-GEP testing would lead to total incremental cost of $36.2 million per year.

Hospital laboratories in Canada receive fixed provincial funding to support all their operations and it is unlikely at this time that laboratories would reduce funding of other services to fund GEP tests conducted exclusively out of country.[67] Decisions to adopt these tests for funding are likely made at the provincial level but the processes and criteria used by the provincial ministries of health to evaluate and approve GEP tests are still evolving and yet to be defined.[67] However, the 2000-GEP test characteristics are comparable to those of the 21-GEP test for guiding adjuvant chemotherapy in early stage breast cancer which represents the first and only GEP test translated into clinical practice in Canada. Similar to the 2000-GEP test, the 21-GEP test was found promising as it may improve patient safety and likely pose low risk of harm, but had significant uncertainty associated with its clinical value.[59,60] Budget impact analyses also demonstrated that adoption of the 21-GEP testing would lead to a total incremental cost of up to $23.5 million per year.[59,60] The test was recently funded in several provinces within the context of field evaluations. Given the 2000-GEP test appears to be clinically promising and provides good value for money[34,68] it could also be considered for special coverage such as coverage with evidence development.[57]

A recent cost-effectiveness analysis of the 2000-GEP test was reported among patients with metastatic and poorly differentiated cancer of uncertain primaries (i.e., difficult-to-diagnose primary) for whom the majority had primary tumour site diagnoses reported by their physicians prior to 2000-GEP testing.[69] The test was found to have an ICER of $46,858 per QALY gained from a US third-party payer perspective.[69] These results in uncertain cancers cannot be extrapolated to the CUP setting because CUP patients are left without a primary tumour site diagnosis despite extensive clinical and pathological diagnostic evaluation. As a result management and clinical outcomes of CUP are different from those of cancer of uncertain primary.

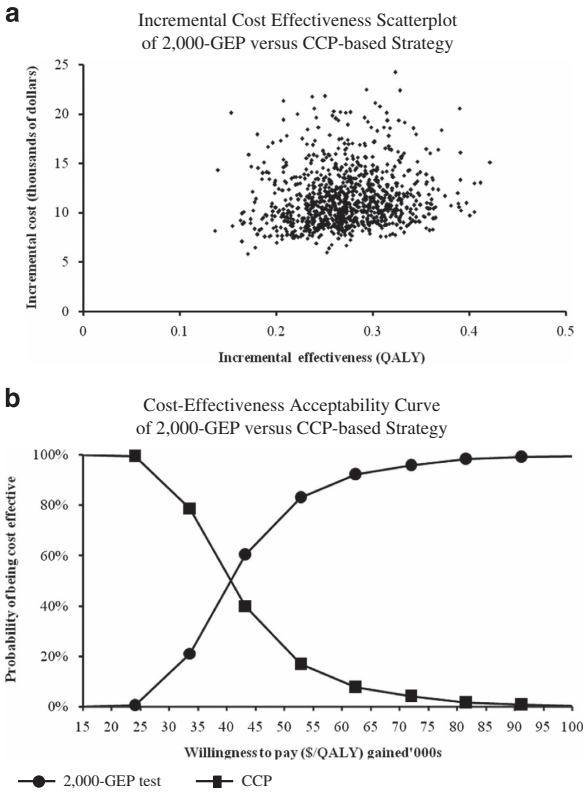
Our sensitivity analyses demonstrated that the 2000-GEP test accuracy, diagnostic results following 2000-GEP test classification and survival response following correct primary diagnosis are important variables that influenced the ICER (Figure 2). For instance, when these three groups of parameters were negatively modified by approximately 35% (Figure 2d) the ICER became well above ranges of a number of cancer treatments recently approved for funding in Canada[61,62] and the 2000-GEP-based strategy may no longer deemed a cost effective use of resources. Our value-of-information analysis demonstrated that there is a significant societal benefit from future research that can better characterize these three groups of parameters. Taken together with the lack of future randomized trials of 2000-GEP testing in CUP population worldwide,[70] this suggests that clinical verifications and field evaluations of the test to establish its impact on Canadian management of CUP and resulting survival outcomes should be a priority.



* 2,000-GEP test agreement with reference cancer diagnosis.
† Incorrect diagnostic result was defined as occurring when either the primary stays undiagnosed following correct 2,000-GEP test classification of the tumour specimen or when the primary tumour is incorrectly diagnosed following incorrect 2,000-GEP test classification of the tumour specimen.
‡ Survival response following correct primary diagnosis was defined as the transition probabilities from IDM to PC, SP, or dead states in the 2,000-GEP Markov models following the chance nodes when the primary is correctly diagnosed. Survival response following correct diagnosis of hepatocellular, pancreas or non-small lung primary site was not included in sensitivity analyses as these potential primary sites were found to have worse QALYs compared to overall CUP group (Table 4).
Abbreviations: 2,000-GEP test = Tissue of Origin test; ICER = incremental cost effectiveness ratio; QALY = quality adjusted life year; CUP = cancer of unknown primary.

Figure 2. Multivariate sensitivity analysis of the ICER with respect to 2000-GEP accuracy*, incorrect diagnostic results† following 2000-GEP test classification and survival response‡ following correct primary diagnosis.

Validation of any diagnostic test accuracy and clinical verification of resulting diagnostic decisions in a real-life CUP population remains a challenge since, by definition, the primary tumour site is not found except rarely in the clinical course of disease or more commonly at autopsy.[33,71] For instance, validation analysis of the 2000-GEP test[24] used in our study was conducted in the United States in patients with known primary cancers. Genetic profiles of occult cancers giving rise to CUP may differ from known primary cancers.[71] A more direct study to evaluate the reliability of any GEP test and its impact on diagnostic decision making in CUP patients would be the correlation with an eventual primary tumour detected later during the course of the disease (latent primary) or at autopsy. This is possible because our analysis demonstrated that those cases are identifiable using cancer registries and future studies can further link such cases with their specimens from banks of tumour tissue samples to study any GEP test. This research approach is warranted to address concerns over potential incorrect 2000-GEP test classification and resulting diagnostic decisions; it would also be valuable for updating our model and verifying our results. Future clinical verification and field evaluations studies of GEP testing in CUP population should also explore any potential impact of



The parameters of distributions were based on the same data sources of baseline estimates listed in Table 1, 2 and 3 to replicate the mean and standard error around the estimates. Sampling distributions and summary estimates of incremental cost and incremental effectiveness were based on 1000 replicates. For each of the 1000 repeated model simulations a random draw from statistical distributions of all model inputs was performed to produce a distribution of model outputs.
Abbreviations: GEP = Gene expression profiling; CCP = current clinical practice.

Figure 3. Incremental cost-effectiveness scatterplot and acceptability curve of 2000-GEP versus CCP-based strategy.

intratumour heterogeneity on its results using multiple tumour-biopsy samples.[72]

Our analysis has limitations. The estimated distribution of underlying primary tumours among CUP patients in our study does not necessarily reflect the distribution of underlying primary tumours among current CUP patients. Potential recent changes in the incidence of underlying different primary tumours in CUP population may affect the cost-effectiveness of the 2000-GEP testing. Outcomes and costs of therapies given in the 2002-2011 population do not also necessarily reflect the possible benefits and costs of newer site-directed therapies or dosing schedules used in very recent clinical practice so analysis with such data would be more applicable to the current practice landscape. It is unclear how the inclusion of these recent therapies may impact our results because patients with CUP represent a heterogeneous group and some new therapies might be marginally effective across certain tumour types.[70] Generalization of our study results to other health care systems may be limited by differences of clinical practice and different approaches to pricing and reimbursement.

CONCLUSION

We found that the 2000-GEP test provides good value for money in CUP patients for whom current clinical and pathological diagnostic evaluation does not provide a diagnosis of primary tumour site. However, clinical verifications and field evaluations of the test using multiple tumour-biopsy samples to establish its accuracy and impact on diagnostic decisions and survival in the CUP setting should be initiated in Canada to ensure its clinical utility.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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