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ORIGINAL REPORT

Evidence-Based Approach to the Introduction of Positron Emission Tomography in Ontario, Canada

William K. Evans, Andreas Laupacis, Karen Y. Gulenchyn, Les Levin, and Mark Levine

From the Juravinski Cancer Centre at Hamilton Health Sciences and McMaster University, Hamilton; Keenan Research Centre at the Li Ka Shing Knowledge Institute of St. Michael's Hospital and University of Toronto; and Ministry of Health and Long-Term Care, Toronto, Ontario, Canada.

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Corresponding author: William K. Evans, MD, c/o Juravinski Cancer Centre, 699 Concession St, Hamilton, Ontario, Canada L8V 5C2; e-mail: bill.evans@jcc.hhsc.ca.

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

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ABSTRACT

Purpose
The uptake of new health care technologies is usually driven by industry promotion, physician interest, patient demand, and institutional ability to acquire the technology. The introduction of positron emission tomography (PET) scanning in the province of Ontario, Canada, followed a different path.

Methods
The Ontario provincial government, through its Ministry of Health and Long-Term Care, commissioned a systematic review of the literature. When this found only weak evidence that PET has a positive impact on clinical outcomes, the Ministry introduced a provincial PET evaluation program to close the evidence gap.

Results
This article describes the challenges encountered establishing the PET evaluation program. These included the design and conduct of the initial clinical trials, the establishment of a PET cancer registry, standardizing how PET scans were performed and reported, and gaining acceptance by health professionals for the evaluative program.

Conclusion
The proliferation of health technologies is a key driver of increasing health care costs. The Ontario approach to the introduction of PET is a model worth consideration by health systems seeking to ensure that they receive value for money based on a strong evidentiary base when introducing new health technologies.

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INTRODUCTION

Positron emission tomography (PET) scanning is a form of imaging based on biologically active compounds labeled with positron emitters.[1] When combined with computed tomography (CT) scanning, it provides both functional and anatomic images. [^{18}F]fluorodeoxyglucose ([^{18}F]FDG) is preferentially taken up by cancer cells compared with normal tissue, which makes [^{18}F]FDG-PET attractive in oncology.[2-4]

PET has been adopted in many countries, but much less so in Canada.[5] Ontario, a province of approximately 12 million people in central Canada, decided through its Ministry of Health and Long-Term Care (the Ministry) that it would only fund PET based on high-quality evidence of its value in clinical decision making. In this article, the evidence-based approach used to introduce PET in Ontario is described.

METHODS

Evidence

In 2000, the Institute for Clinical Evaluative Sciences (ICES) was asked by the Ministry to review the literature on the diagnostic accuracy of PET and its impact on patient outcomes. The review focused on lung cancer, solitary pulmonary nodules, breast cancer, malignant lymphomas, head and neck cancer, melanoma, and colon cancer.[6] Although a large number of studies was identified, ICES reported that "despite the availability of PET scanning for almost three decades, the number of methodologically high quality studies (and the numbers of patients within these studies) is distressingly small."[6]

Developing a Policy

On the basis of this review, policy makers within the Ministry and an advisory group of medical experts recommended against funding PET in Ontario as an insured service, other than for a few clinical circumstances where the evidence was of high quality. The advisory group, which became the PET Steering Committee, recommended that Ontario generate some of the needed evidence by undertaking a series of trials to address clinically

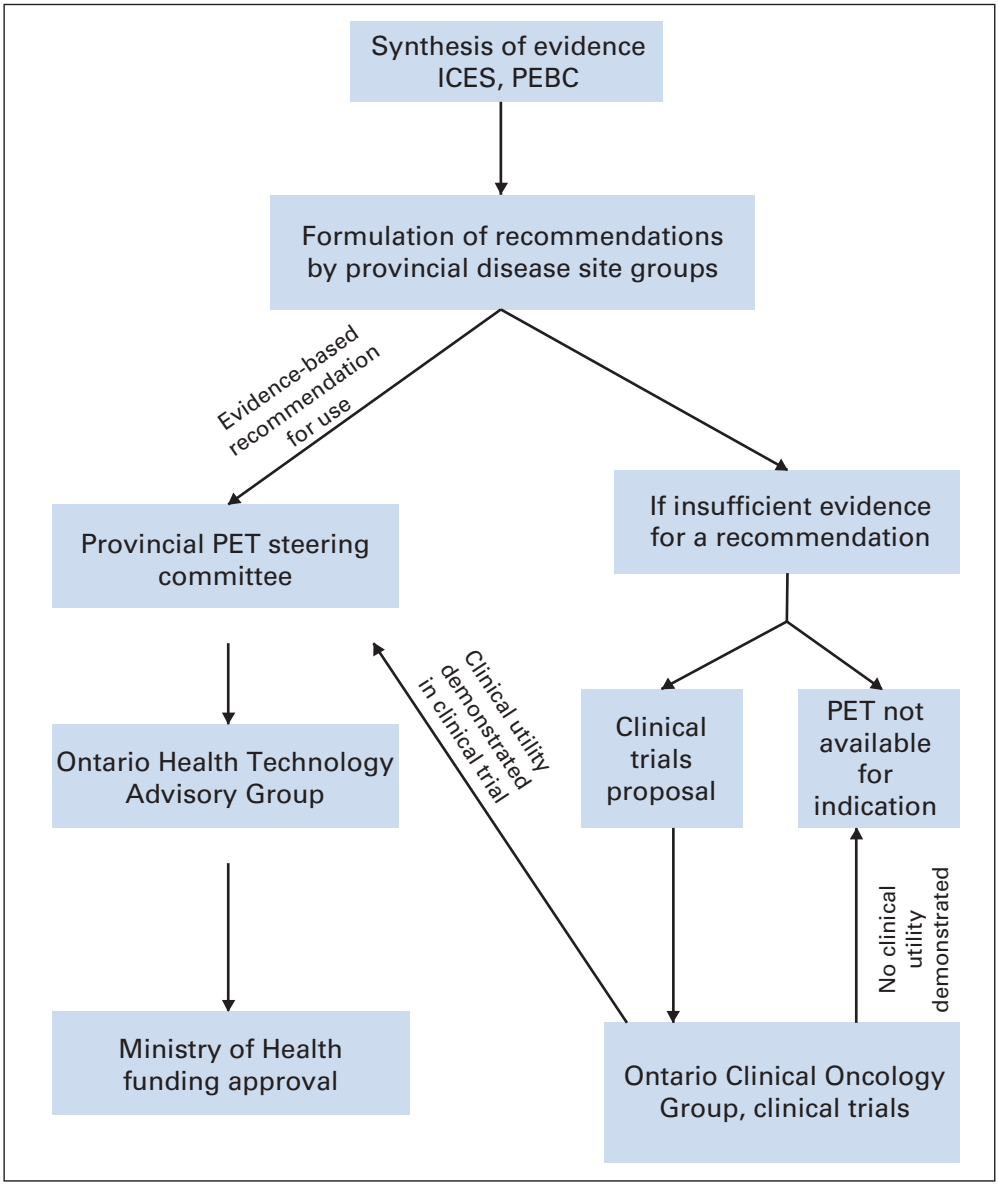

Fig 1. Process of positron emission tomography (PET) approval in Ontario. ICES, Institute for Clinical Evaluative Sciences; PEBC, Program in Evidence-Based Care.

important questions. The key components of this strategy and the PET approval process are shown in Figure 1.

Clinical Studies of PET

The provincial Disease Site Groups (DSGs) were asked to propose studies that addressed key clinical management questions. Seven proposals were received, and five proposals were selected for protocol development and funding. The trials selected included two studies in lung cancer and one each in breast cancer, squamous cell carcinoma of the head and neck, and colorectal cancer metastatic to liver.

Five academic health sciences centers in Ontario were encouraged by the Ministry to purchase PET/CT scanners and to participate in the PET evaluation program. Clinical researchers from each of the designated PET centers were linked with methodologists at the Ontario Clinical Oncology Group (OCOG) in Hamilton, Ontario, Canada, for each study. Complete protocols were developed, approved by local institutional review boards, and activated after an investigator workshop. Quality control issues (dose of [^{18}F]FDG, technical factors related to PET, and scan interpretation) were discussed, and consensus was achieved on provincial standards for the conduct of the PET imaging studies. OCOG also arranged for each PET scan to be read by two nuclear medicine physicians from different centers. For a summary of the organizations involved in the Ontario PET evaluation program, see the Appendix Table A1 (online only).

Health Canada, the federal government department that regulates the marketing of radiopharmaceuticals in Canada, considers [^{18}F]FDG to be an investigational agent,[7] and reviewed each study before it was approved under a Clinical Trials Agreement. The Ministry provided funds to support data collection, the cost of the [^{18}F]FDG, a stipend for nuclear medicine physicians reading the scans, and the costs of trial coordination by OCOG. An annual budget of approximately $4 million CAD was established in support of the trials, the PET cancer registry, and a Special Access Program for clinical situations not covered by the trials or registry.

A brief description of the trials, their target accrual, and status as of March 31, 2009 are listed in Table 1. Four studies have reached their accrual goal or predetermined clinical end point. The results of the early lung cancer trial (ELPET [PET Imaging in Potentially Surgically Resectable Non–Small-Cell

Table 1. Ontario PET Clinical Trials

Trial and Start Date	Purpose	Patients	Intervention	Trial Design	No. of Patients Recruited/Target No. (as of March 31, 2009)	Status
PET PREVENT; May 2006	To determine the ability of [^{18}F]FDG PET to detect metastatic cancer in neck lymph nodes in patients with head and neck cancer who have received radiation treatment	Advanced N2 or N3 squamous cell carcinoma of the head and neck arising in the oral cavity, larynx, or pharynx being considered for neck dissection after primary curative radiation therapy	Patients receive a PET scan before and after treatment	Cohort study	400/400	Trial closed; data analysis underway
PET START; June 2004	To determine whether PET can detect lung cancer spread beyond the chest after the patient has undergone all the usual standard diagnostic tests and whether PET results will change the radiation treatment volume	Stage III NSCLC suitable for combined-modality therapy, radical radiation therapy, or trimodality therapy	Patients are randomly assigned to usual radiation planning with CT or planning with PET/CT	RCT	310/400; closed	Data from trial to be reported at ASCO 2009 meeting; trial data resulted in approval of PET for stage III NSCLC being considered for combined-modality therapy
ELPET; June 2004	To determine whether PET can detect occult metastatic disease and avoid futile thoracotomy	Stage I, II, or IIIA NSCLC cancer in which the primary lesion appears technically appropriate for surgical resection based on standard diagnostic tests	Patients are randomly assigned to bone scan, CT of abdomen (liver and adrenals) plus cranial imaging, or PET plus cranial imaging	RCT	337/322; closed	Trial data led to approval of PET for NSCLC being considered for surgical resection
PETCAM; November 2005	To determine the impact of preoperative PET on patients who have potentially resectable colorectal cancer liver metastases by conventional imaging by determining the proportion of patients who have a change in management resulting from PET imaging	Colorectal adenocarcinoma with potentially resectable metastasis isolated to the liver	Patients who have solitary metastasis to the liver with conventional imaging are randomly assigned 2:1 to PET or not	RCT	323/400	Trial accruing patients
PET PREDICT; January 2005	To determine the ability of PET to detect axillary lymph node metastases in newly diagnosed breast cancer patients with no clinical evidence of disease spread	Patients with early-stage breast cancer undergoing sentinel lymph node biopsy	PET is performed before sentinel lymph node biopsy	Cohort study	336/320; closed	Trial results demonstrated insufficient sensitivity for staging of axilla

Abbreviations: PET, positron emission tomography; PET PREVENT, PET Imaging in Post Radiation Evaluation of Head and Neck Tumours; [^{18}F]FDG, [^{18}F]fluorodeoxyglucose; PET START, PET Imaging in Stage III Non–Small-Cell Lung Cancer; NSCLC, non–small-cell lung cancer; CT, computed tomography; RCT, randomized controlled trial; ASCO, American Society of Clinical Oncology; ELPET, PET Imaging in Potentially Surgically Resectable Non–Small-Cell Lung Cancers; PETCAM, Impact of PET Imaging Prior to Liver Resection for Colorectal Adenocarcinoma Metastases; PET PREDICT, PET imaging to determine the role of PET in the assessment of regional disease in breast cancer.

Lung Cancers]) and the breast cancer trial (PET PREDICT) were presented at the annual meeting of the American Society of Clinical Oncology in 2008.[8,9] The locally advanced lung cancer (PET START [PET Imaging in Stage III Non–Small-Cell Lung Cancer]) trial results will be presented at the American Society of Clinical Oncology 2009 annual meeting. The head and neck trial recently closed having achieved its accrual goal, and results are being analyzed.

PET Registries

For those clinical conditions where the PET Steering Committee felt that there was already sufficient evidence in the literature to establish the clinical utility of PET, the Ministry was advised to approve funding. The first approved indication was for the solitary pulmonary nodule[6,10-12] when a diagnosis could not be established pathologically. The other three indications were treated thyroid,[13,14] germ cell,[15] and colorectal cancers,[16] where an increase in serum biomarkers (thyroglobulin, β-HCG, and α-fetoprotein, and carcinoembryonic antigen, respectively) suggested recurrent cancer but the tumor location could not be determined by conventional imaging. A PET cancer registry was established at ICES to collect the registry data. Patients were asked to consent to the collection of information on their clinical condition and the results of their scan and to a subsequent linkage of the registry data to administrative data housed at ICES. This linkage will enable the assessment of patterns of care and possibly outcomes after PET scanning.

The first patient was registered in December 2005. As of January 1, 2009, 2,818 patients were registered (1,087 had solitary pulmonary nodules, 335 had thyroid cancers, 545 had colorectal cancers, and 81 had germ cell tumors). On the basis of the positive results of the ELPET trial, patients with non–small-cell lung cancer (NSCLC) being considered for surgical resection became a registry indication in December 2007 (542 patients have been registered). Health Canada regulations continue to necessitate a Clinical Trials Agreement and the maintenance of a registry to access FDG. As new evidence has been generated either from the Ontario trials or from Cancer Care Ontario DSG reviews of the literature, the PET Steering Committee has made recommendations to the Ontario Health Technology Advisory Committee. If this body, composed of medical experts, professional association leaders, and health care administrators, approves the recommendation, it advises the Minister of Health that the indication should be funded by government. Implementation is through the registry mechanism.

RESULTS

Successes of Ontario's Approach

Clinical trials themselves. The overall success of this approach will be judged by the usefulness of the evidence generated by the trials to clinicians and policy makers. There have already been several important successes (Table 2). First, oncologists and nuclear medicine physicians, who, in Canada, have rarely collaborated on research,[17] have worked together to design and execute clinical trials. The knowledge from this collaborative effort will hopefully form the basis for future imaging trials in Ontario. Second, standards on how to perform a PET examination and interpret the results were established, something that would not have occurred had the technology been allowed to diffuse randomly. Third, the double reads of PET scans in the trials reduced interobserver variation and built expertise in PET scan interpretation in the province. Importantly, four trials have achieved their accrual goals, and results from three of these trials have led to funding decisions. The breast cancer trial found that PET scanning was not accurate enough in identifying metastases in axillary nodes or distant sites to change current staging practices.[8] Consequently, PET is not funded for breast cancer staging in Ontario. In the early NSCLC trial, PET identified metastatic disease that precluded a curative surgical resection significantly more often than conventional staging.[9] The results of this trial led directly to the government decision to fund PET scans for this indication. The trial in locally advanced NSCLC demonstrated a significant difference in the frequency of extrathoracic disease compared with conventional staging and led to funding for the staging of NSCLC patients who are being considered for combined-modality therapy. The trial in head and neck cancer has recently closed, having reached its accrual goal of 400 randomly assigned patients.

Development of guidelines for PET. For 3 years after the original systematic review, ICES updated its review every 6 months.[6,18-22] This role was then transferred to Cancer Care Ontario's DSGs. A systematic review of the medical literature on the role of PET in the management of lung cancer by the provincial Lung Cancer DSG has been published.[10] The Hematology DSG also conducted a systematic review of PET in Hodgkin's disease and non-Hodgkin's lymphoma. Recommendations on the use of PET in malignant lymphoma have been funded through the PET registry on the basis of these reviews.

Because there were concerns that other DSGs were not developing guidelines for the use of PET (treatment-related guidelines were commonly given a higher priority), Cancer Care Ontario directed the Program in Evidence-Based Care to undertake systematic reviews of the literature for those tumor types where there seemed to be significant new evidence. On the basis of reviews of 10 tumor types, recommendations were formulated by the DSGs regarding whether there is a role for PET in the diagnosis and staging of each specific cancer, the assessment of response to treatment, the diagnosis of recurrence, and the investigation of a solitary metastasis. In the fall of 2008, two workshops were held at which the recommendations from the DSGs were reviewed by a multidisciplinary group of oncologists

Table 2. Successes and Challenges Encountered With the Ontario Approach to PET Evaluation

Successes and Challenges
Successes
Five clinical trials successfully launched
Collaboration between imagers, oncologists, and trialists achieved
Experience gained in the conduct of diagnostic imaging trials; strong base for future diagnostic imaging trials
Process of PET imaging standardized across Ontario
Double reads of PET images during trials reduced variance in reporting; will likely improve PET interpretation in routine clinical practice
Trials generated evidence on value of PET to clinicians and policy makers:
Role of PET in early and locally advanced lung cancer
PET not useful for the staging of breast cancer
PET registry generating additional information on clinical utility in uncommon cancers
Systematic literature reviews for 10 disease sites led to funding approval and identified areas of insufficient evidence that may lead to additional trials
Challenges
Some nuclear medicine physicians challenged the need for further evaluation of PET at professional meetings and through the media
Patient accrual to trials was slower than expected
PET cancer registry has been capturing incomplete data in the absence of enabling technologies (Web-based registration)
Registry data capture not as complete as necessary for high-quality analysis
Communication to the province's physicians was difficult
Updating Clinical Trials Agreements for each new indication is very time consuming
PET centers require IRB approval for each registry indication

Abbreviations: PET, positron emission tomography; IRB, institutional review board.

and diagnostic imagers. Those recommendations that were strongly supported were then presented to Ontario Health Technology Advisory Committee, and all have been approved for funding (Fig 1).

Challenges of Ontario's Approach

Opposition to the Ontario approach. Many nuclear medicine physicians have argued that it is unreasonable to expect a diagnostic test such as PET to show an impact on clinical outcomes, that current evidence is sufficient, and that the rigorous evaluation being required for PET was not required for CT or magnetic resonance imaging.[23] Investigators leading our studies have been criticized at medical meetings and through the media for not accepting PET as an established technology. Media stories have focused on patients being denied access to essential care and needing to pay out of pocket for PET scans at private facilities in Ontario or the United States.

Patient accrual. Patient accrual to these studies was slower than expected. The reasons for the slower enrollment are multifactorial, including the small number of clinical PET scanners (five scanners to serve the Ontario population of 12 million), the desire of many patients with newly diagnosed cancer to get on with treatment and not participate in a trial, and the feeling of some oncologists and surgeons that determining the role of PET was not a high priority.[24] A greater number of PET scanners or collaboration with other clinical trials groups might have shortened the time to complete the studies.

Registry data quality. The Ontario PET cancer registry was originally established as a means to comply with federal regulations. It was also part of the evaluation plan to use the registry to evaluate patterns of care and patient outcomes after PET scan imaging. As we have begun to analyze the registry data, we have learned that some data elements have not been optimally captured (eg, actual values of biomarkers), and this has required additional chart review. Going forward, it is our hope that those indications for which the evidence is robust (eg, lung cancer indications) can be moved out of the registry and funded as an insured service. Where evidence is thought to be compelling but still not robust because of lack of well-designed trials or small number of patients studied, the registry should be a source of additional valuable information. However, there will have to be an investment in people to capture the data and improvement in the information management systems.

DISCUSSION

A judgment on whether evidence is sufficient to justify the routine use of PET scanning is complex and value driven. It includes factors such as the quality of the existing evidence, the likelihood that better quality evidence will be generated in the future (the rarity of thyroid and germ cell tumors convinced us that this was unlikely in the case of these tumors), and the magnitude of the clinical implications of relying on PET to influence clinical decisions (eg, if a positive PET scan proves incorrect).

In a publicly funded health care system, governments attempt to fund interventions with clear benefit to patients. In recent years, health care expenditures in Ontario have increased by an average annual compound rate of 8.4%.[25] Such growth is not sustainable, and thus, each new technology is now looked at more critically for its benefits, harms, and cost. Because the evidence that PET has a positive effect on patient outcomes was judged to be weak, the Ontario government limited the availability of PET scanners to a small number of academic centers and regulated the rate of reimbursement for FDG, the amount of funding per case, and the stipends for reading a scan. These controls made it possible to conduct trials to generate evidence about clinical utility.

In a health care system such as the one in Canada, hospitals incur a financial liability if they acquire technologies for which the government does not provide operating dollars. They would have to purchase the PET scanner, usually through private fundraising, and then reallocate operating dollars from within their global funding envelope. Most Canadian hospitals struggle to balance their operating budgets, so there is little incentive to take on additional operating costs.

The Center for Medicare and Medicaid Services in the United States has begun to fund new technologies using an approach called Coverage With Evidence Development.[26,27] For PET scanning, the National Oncologic PET Registry (NOPR) has been created as an Internet-based registry to collect information about cancer indications for which the evidence of benefit from PET scanning is promising but not conclusive.[28,29] Medicare will reimburse PET scans for patients who have "…an oncologic indication that is either not currently covered or not specifically covered by Medicare"[28] if they participate in the NOPR. It was hoped that the NOPR data could be linked to administrative data to evaluate outcomes and patterns of care, but this has not yet occurred, and it is unclear whether it will be possible to link individuals' NOPR data to their data in Medicare files.

The difference between the Ontario and Medicare approaches is undoubtedly a result of the different values, medical cultures, and politics of the two jurisdictions. Ontario has a long tradition of basing pharmaceutical funding decisions on evidence of clinical benefit and cost effectiveness, and so it was a natural step to approach PET imaging in a similar fashion. However, cost and cost effectiveness have not played a significant role in Medicare's decision making to date, which may account for the fact that Medicare is reimbursing many more indications for PET scanning than Ontario.[28] This may change given the current political climate and the growing interest in comparative effectiveness research. Ontario decided that an investment in additional clinical research would aid the development of public policy. This has proven correct; two randomized controlled trials that demonstrated benefit led directly to a decision to fund specific indications, whereas a cohort study did not support funding for a third indication. Medicare has occasionally funded trials designed to influence policy[30] but decided, perhaps because of the expense and the length of time to complete the trial, not to undertake a similar approach with PET. In the United States, there is a strong focus on access to care for those with health insurance. Not surprisingly, much that has been written about Coverage With Evidence Development describes it as an approach to provide access in the face of suboptimal evidence.[26,27,31] It will be interesting to see how willing Medicare will be to deny funding for PET indications that are found to have little clinical value. In Ontario, the Ministry of Health acts as the gatekeeper for health care funding, and this has fuelled concern by some that the small number of indications for which PET is reimbursed reflects the Ministry's desire to contain costs. In reality, Ontario has moved quickly to fund PET for indications clearly established by high-quality studies.

Some would argue that the process used in Ontario for the evaluation of PET is not generalizable to the United States because health care in Canada is largely (70%) publicly funded. In reality, almost 50% of Americans receive their health care through a government-funded

system, and many others receive health care through some form of managed care, so the Ontario approach could be relevant to at least these components of the US health care sector.

Although the Ontario trials address important clinical management questions in a number of tumor types, there are many other cancers and clinical indications that are not being evaluated. Although additional trials are in development (diagnosis of tumor recurrence and staging locally advanced cervical cancer), Ontario's trials can only address a fraction of the clinical circumstances for which PET has been suggested to be of value. If Ontario is to introduce PET only when high-quality evidence is available, other jurisdictions will also need to contribute to evidence generation, and cooperative clinical trials groups will need to develop a focus in diagnostic imaging. Jurisdictions including the Netherlands[32-34] and Australia[35] have already undertaken randomized trials, and the United Kingdom, through its National Cancer Research Institute 2008 to 2013 Strategic Plan, is proposing a research agenda to evaluate the impact of PET on patient outcomes and cost effectiveness.[36]

The current global financial recession is forcing many governments, including those of the United States, Canada, and Western Europe, to stimulate their economies through deficit spending. Given this economic reality, governments can ill afford to fund technologies of uncertain value. As clinicians, we must recognize that the funds available for health care are not limitless and the key to access new technologies will be high-quality evidence demonstrating that an intervention improves patient outcomes. In today's fiscal environment, the Ontario model may prove to be an approach worthy of consideration by health systems seeking a strong evidentiary base to ensure that they receive value for money.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: William K. Evans, Andreas Laupacis, Karen Y. Gulenchyn, Les Levin, Mark Levine
Collection and assembly of data: William K. Evans, Andreas Laupacis
Data analysis and interpretation: William K. Evans, Andreas Laupacis
Manuscript writing: William K. Evans, Andreas Laupacis, Karen Y. Gulenchyn, Les Levin, Mark Levine
Final approval of manuscript: William K. Evans, Andreas Laupacis, Karen Y. Gulenchyn, Les Levin, Mark Levine

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