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Does comparative effectiveness research promote rationing of cancer care?

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Comparative effectiveness research aims to inform health-care decisions by patients, clinicians, and policy makers. However, questions related to what information is relevant, and how to view the relative attributes of alternative interventions have political, social, and medical considerations. In particular, questions about whether cost is a relevant factor, and whether cost-effectiveness is a desirable or necessary component of such research, have become increasingly controversial as the area has gained prominence. Debate has emerged about whether comparative effectiveness research promotes rationing of cancer care. At the heart of this debate are questions related to the role and limits of patient autonomy, physician discretion in health-care decision making, and the nature of scientific knowledge as an objective good. In this article, we examine the role of comparative effectiveness research in the USA, UK, Canada, and other health-care systems, and the relation between research and policy. As we show, all health systems struggle to balance access to cancer care and control of costs; comparative effectiveness data can clarify choices, but does not itself determine policy or promote rationing of care.

Introduction

Two facts are indisputably true in modern oncology. First, an increasing amount can be done to diagnose, molecularly define, and manage most types of cancer. Second, the costs of cancer care, as with health care generally, are high, rising, and projected to increase at an unsustainable rate; indeed, the costs of health care are threatening access to care and other social priorities in nearly all health-care systems worldwide. Thus, there is great interest in determining not only how to improve cancer care, but also how to obtain the best outcomes within a financially sustainable framework. Comparative effectiveness research is designed for this task. The US Institute of Medicine defines comparative effectiveness research as the “generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care”. The goal of comparative effectiveness research is to compare two or more health-care options (which can be diagnostic strategies, treatment interventions, or even health-care delivery models), and determine which is best, generating data that can inform treatment decisions and coverage policies.

Comparative effectiveness research builds on clinical trials and evidence-based medicine, but includes a distinct focus on identification of results that will be achieved in real-world clinical practice—as opposed to those from the regulated context of a clinical trial of selected patients. It can include cost-effectiveness analysis, but is frequently designed only to evaluate the safety or effectiveness of interventions in patients who were not well represented in clinical trials (based on age, comorbidity, or socioeconomic status). Comparative effectiveness research includes several methods, such as randomised trials, prospective observational studies, systemic review, meta-analysis, and retrospective review of clinical or administrative datasets. Such research aims to augment data from randomised controlled trials to inform health-care decisions by patients, clinicians, and policy makers. However, questions related to what information is relevant and how to view the relative merits of different interventions, have political, social, and medical considerations. In particular, questions about whether cost is a relevant factor and whether cost-effectiveness is a desirable—or necessary—component of comparative effectiveness research are increasingly controversial as the specialty gains prominence.

Despite previous general agreement on the value of comparative effectiveness research to inform decision making, debate has emerged about whether comparative effectiveness research actually serves as a scientific cover for rationing, supporting policy that will control costs at the expense of patients who might be deprived of access to potentially beneficial cancer treatment. The politically conservative US-based Heritage Foundation produced a white paper calling comparative effectiveness research a “slippery slope to health-care rationing”. This concern is not unique to oncology, but the tensions and implications for policy and research are intensified because of cancer’s associations with mortality, and the fact that oncology has become a dominant focus for drug development. Highly publicised examples of novel cancer drugs that do not cure disease, but cost more than US$100,000 for a treatment course, heighten tensions related to drug access, drug-development sustainability, and health-care rationing. Policy makers and political advocates in the USA are actively engaged in a debate about the future funding and effect of comparative effectiveness research. Concern about the potential for such research to constrain access to effective treatment is not unique to the USA, and also occurs in countries...
where comparative effectiveness research is explicitly considered to guide coverage decisions (eg, the UK). At the heart of this debate are questions about the role and limits of patient autonomy and physician discretion in health-care decision making, and the nature of scientific knowledge as an objective good versus a subjective function of its historical and political context. In this article, we add to this debate by examining the role of comparative effectiveness research in several national health-care systems and the relation between comparative effectiveness research and policy.

The relationship between rationing and research: in theory

Health-care rationing can be defined as a policy to place limits on an individual’s access to potentially beneficial medical care as a means to conserve or fairly allocate a scarce resource. Rationing can take place at multiple levels (eg, individual clinical encounters, medical institutions, or national policy), and has three elements: medical need, scarcity of resources, and allocation on the basis of established criteria (clinical characteristics or sociodemographic factors), or planned distribution (first-come, first-served; lottery, etc). Health-care rationing has a long history dating back to at least the time of battlefield triage under Napoleon (in the 17th century), and has been a necessary consideration for specialties characterised by chronic scarcity such as solid-organ transplantation. In oncology, consideration of rationing has emerged when demand for a novel drug exceeds initial supply (eg, with palonosetron in the 1990s) or when manufacturing problems have led to sudden shortages for common, older drugs. In cases of inadequate supply, there can be concern about the fairness of the allocation scheme, but no meaningful debate about the need for rationing. Debate emerges when rationing is based not on scarcity of an intervention, but on the relative cost needed to provide it in relation to the degree of benefit.

Although most people accept that health-care resources are finite, and that control of medical costs is an important social goal, there is little consensus about how cost control should be achieved. Comparative effectiveness research can inform policy in several ways. First, it can identify which of several intervention options is best, and this use generates little controversy. Second, it can show that there is a less expensive option among equally effective options. On a population basis, this method provides a policy rationale to encourage (or require) use of the less expensive option and to discourage (or restrict) use of the more expensive option. However, this practice raises questions about balance between guidance of care with allowance for patient and physician discretion, and enforcement of more cost-effective care through formulae or other restrictions. There might be patients, and there definitely will be providers of more expensive options, whose interests will be compromised by restrictive policies. Still more challenging, comparative effectiveness research might show that an intervention is more effective than alternatives, but with marginal benefits at substantially higher cost. This scenario goes to the heart of the debate about the role of comparative effectiveness research, cost-effectiveness analysis, and the balance between cost control and access to treatment. Concerns about the role of comparative effectiveness research are attributable both to relatively transparent political calculations in the context of debates about health-care reform in the USA, but also to deeper philosophical questions about the correct balance between individual and societal interests in health care.

A major component of the debate about comparative effectiveness research focuses on the fear that results will be used by the state or by insurers to constrain—rather than inform—medical decision-making, and to limit physician discretion. These concerns are heightened by studies that directly consider cost or cost-effectiveness, but they can extend to any comparative effectiveness research in which population-level data might determine access to interventions at the expense of the clinician’s ability to make case-by-case decisions. Opponents of comparative effectiveness research voice specific concerns about the nature of population-based science to discriminate against individuals on the basis of age, sex, comorbidities, rare presentations, and other characteristics. Some argue that use of cost-effectiveness data in oncology might lead to people directing resources towards treatment of younger patients with cancer who potentially have more years of life to gain than older patients with cancer. Others suggest that patients who have a worse prognosis, but who might still benefit from a cancer treatment, will not get access because the average cost–benefit ratio for someone in their condition will not be supported at a policy level.

Debates about comparative effectiveness research focus on explicit rationing in which some aspect of the health-care system (state, payer, facility, clinician, etc) will restrict an individual’s access to a potentially effective intervention on the basis of cost to the health-care system. However, a health-care system that, in theory, makes all appropriate medical care available to all patients, but in practice restricts access to the clinician or the technology on the basis of ability to pay, involves at least implicit rationing. For example, in 2012, more than 48 million people in the USA (about 15% of the population) did not have health insurance, and thus no guaranteed access to cancer care. Although many uninsured patients with cancer in the USA receive treatment through a combination of philanthropy, industry-sponsored programmes, and free care, access is often late and outcomes are inferior to those of patients with private health insurance.

The degree and nature of rationing varies across health systems. Similarly, how comparative effectiveness
research is used, and the role of cost-effectiveness analysis in policy decisions, varies substantially. A key question as we review these systems is whether comparative effectiveness research is only an instrument used to support a predetermined policy to ration health care at some level, or whether data from comparative effectiveness research contribute to the establishment of such policies (figure). The related question is whether our debate should really be about generation of data (i.e., comparative effectiveness research or even cost-effectiveness analysis), or about how we use such data to formulate health-care policy.

The relationship between rationing and research: in practice

In the USA, access to cancer treatments and most diagnostics is determined by the Food and Drug Administration (FDA). The FDA reviews scientific data, including those for toxicity and efficacy, and considers the medical justification for an intervention compared with standard care for a specific indication in issuing its approval. For drugs, FDA approval makes an intervention commercially available for a given indication, and for off-label use at the discretion of licensed clinicians. Off-label use provides potential access to cancer drugs for an expanded amount of indications in the USA that are not limited by comparative effectiveness research, or even randomised controlled trial data. However, off-label use is governed by norms of practice (ultimately reinforced by malpractice laws) and professional guidelines, and is constrained by insurance coverage or the patient’s ability to pay out-of-pocket expenses. For expensive interventions, including most cancer drugs, access is thus controlled by a mixed public–private system. The publicly-funded Medicare and Medicaid systems cover patients who are older than 65 years and very poor, respectively. 64% of people in the USA are covered by private insurance which is often provided by their employer. The Centers for Medicare and Medicaid Services determine payment for cancer interventions for patients with publicly-funded insurance, and private insurers in the USA tend to follow the guidance provided by the Centers’ coverage policies. The Centers are explicitly prohibited by law from considering cost-effectiveness in their coverage decisions, and instead base payment decisions on statutory criteria of what is “reasonable and necessary”. Thus, in the USA, comparative effectiveness research cannot affect state coverage decisions, or lead to government rationing. However, as we noted above, cancer care is implicitly rationed in the USA on the basis of ability to pay.

The 2009 Patient Protection and Affordable Care Act was designed mainly to expand access to health care, and, in aspiration at least, to help control costs of health care. It is hoped that expanded access will be achieved through the expansion of Medicaid, and the

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**Figure:** Models of relation between comparative effectiveness research and rationing of cancer care
suspicions of industry-funded comparative effectiveness research that might be biased. Payers also noted that they use comparative effectiveness research techniques to understand and inform resource allocation in their organisations, but they tended to rely on internal data rather than externally published scientific work.\textsuperscript{12} The investigators concluded that US payers were interested in comparative effectiveness research, but preferred state or professional organisations to lead in development of guidelines.\textsuperscript{22} With the support of comparative effectiveness research, such efforts in the professional sphere (by the American Society of Clinical Oncology and the American Board of Internal Medicine, for example) are continuing.\textsuperscript{22,27}

By stark contrast with the USA, the UK’s National Health Service (NHS) is characterised mostly by public funding and public delivery of healthcare. The National Institute for Health and Care Excellence (NICE) reviews the evidence for safety and clinical effectiveness of novel interventions and explicitly considers cost-effectiveness. NICE then issues guidance for or against provision, which then determines access in the NHS. This system, established in 1999, has led to rationing in which some effective drugs are not available to most British citizens because of cost.\textsuperscript{28} For example, although sorafenib showed improved survival by several months compared with placebo in patients with hepatocellular carcinoma, NICE determined that the incremental cost-effectiveness ratio was too high (at more than £50,000 per quality-adjusted life-year), and the NHS did not provide the drug.

Debate continues in the UK about what the threshold for incremental cost-effectiveness should be, how best to balance cost control and access generally, and how to regulate access to cancer drugs in particular.\textsuperscript{29} Although exceptions have been made in the context of public pressure for markedly effective treatments such as trastuzumab and imatinib, a traditional threshold of £30,000 per quality-adjusted life-year has been a barrier for many cancer drugs.\textsuperscript{30} The UK Cancer Drugs Fund was established in 2010 to allow access to high-cost cancer drugs outside of the usual constraints of NICE.\textsuperscript{31} Additionally, an effort to move away from strict thresholds and towards what is termed value-based pricing is due to start in 2014, but this framework is controversial. Findings from a survey of 4000 randomly selected adults in the UK showed strong support for value-based pricing, but, by contrast with the direction of recent policy in the UK, no special preference for access to drugs for cancer or terminal disorders.\textsuperscript{32}

Canada has another model, in which most health care is publicly funded, but provided in the private sector (the state pays for health-care, but most doctors and hospitals do not work directly for the government), and all citizens are guaranteed health care. Cost is taken into consideration to determine what can and will be provided. The Canadian system is complex, and coverage varies between provinces. For cancer drugs and devices, Health Canada reviews clinical evidence provided by the manufacturer and determines nationwide approval—but not access—in the provincial health-care systems. Hoch and colleagues\textsuperscript{33} have described the journey from evidence to clinic in Ontario. After national approval, the Ontario Program in Evidence-Based Care reviews the clinical data without considering cost, and makes a recommendation for or against further consideration of a drug to Cancer Care Ontario. The Cancer Care Ontario Committee to Evaluate Drugs then considers both benefit and cost (although the assessment of cost is not based on any explicit threshold). These data then contribute to Cancer Care Ontario’s recommendation to the provincial Ministry of Health and Long-Term Care, which makes a funding decision to determine access to the treatment in the province. Cancer treatment can be paid for out-of-pocket by the patients, or covered by private insurance: roughly 68% of Canadians have some form of private supplemental coverage for prescription drugs. However, Canadians rely on the state health-care system for most aspects of cancer care.\textsuperscript{34,35}

In the Canadian system, comparative effectiveness research is used to inform coverage decisions, but the system evolved through a desire to provide quality health care on a sustainable basis.\textsuperscript{36} There is debate and concern about access to cancer care in Canada, independent of comparative effectiveness research. For example, Hoch and colleagues\textsuperscript{37} described a woman with HER2-positive breast cancer who was initially denied adjuvant trastuzumab based on the fact that her tumour size was 1 mm less than the eligibility required in a landmark randomised controlled trial that had informed state coverage policy. Concerns about state-imposed rationing and restriction on physician and patient discretion were raised, but had nothing to do with comparative effectiveness research. In fact, comparative effectiveness research studies after the trial have provided evidence that trastuzumab is potentially beneficial even for very small tumours.\textsuperscript{38} In response to this case and others, in 2011, the Evidence Building Program and the Case by Case Review Program were established to try to prioritise access and flexibility in the face of rapidly changing areas such as oncology in which individual patients might not always be well served by population-based policy.\textsuperscript{39} Chalkidou and colleagues\textsuperscript{40} noted in a review of the national health systems of Australia, Britain, France, and Germany that comparative effectiveness research is specifically commissioned in each country by a national health policy body. They emphasised that in each system, comparative effectiveness research is a “demand-driven” activity, meaning that research is specifically commissioned to address the needs of the policy makers. In each of these countries, comparative effectiveness research includes cost-effectiveness information, but how this information affects access to cancer treatment varies, and comparable data can lead to different policy decisions.\textsuperscript{41}
Further consideration of the role of comparative effectiveness research in oncology

Beyond consideration of how comparative effectiveness research is currently used in different health systems, it is difficult to systematically assess the role of this research in oncology policy. It is even more difficult to determine the potential effect of such research on future policy in oncology—i.e., to assess the argument that comparative effectiveness research will lead to rationing.

In 2007, Drummond and Mason noted that use of cost-effectiveness to guide access to cancer drugs was increasing in Europe, but that the effect of such policies on outcomes, cost, or access, was not known. They showed substantial variation between European countries in how economic data were used to guide national policy, inform clinical practice guidelines, and affect physician prescribing. Clement and colleagues assessed the effect of comparative effectiveness research on drug coverage decisions in Australia, Canada, and the UK, and reported that comparable data led to diverse coverage decisions on the basis of different countries’ national priorities and preferences. In each country, investigators reported evidence of a threshold for cost-effectiveness, explicit or implicit, but that exceptions were made for some high-cost drugs in all settings.

In 2012, Meyer and colleagues proposed a framework for comprehensive assessment of comparative effectiveness research in oncology, but concluded that the specialty was rapidly evolving, as yet poorly organised, and that effects on care could not be assessed at present. They highlighted the need to develop large cancer-specific datasets, designed for research, to improve the quality of comparative effectiveness research and its potential to guide oncology practice and policy in the future. Similarly, in an attempt to assess the effect of comparative effectiveness research on cancer genomics by reviewing published work and interviewing with stakeholders, Goddard and colleagues were limited to reporting the current technical limitations, and the difficulty in application of cost-effectiveness research to the quickly emerging technologies. They articulated a need for comparative effectiveness research in cancer genomics, but provided no evidence that it is guiding practice or policy at present.

In the absence of reviews showing a role for comparative effectiveness research in shaping oncology policy, consideration can be given to differences in access to cancer treatment between countries with different approaches to comparative effectiveness research. Mason and colleagues identified all drugs approved by the US FDA between 2004 and 2008, and compared approval and access to the same drugs in the USA, Europe, and the UK. Of 59 cancer drugs approved during this period, 46 were also approved in Europe (not including the UK). Of these drugs, only 23 were evaluated by NICE, and only 18 were approved in the UK, including ten with restricted access based on indication. Additionally, evaluation and approval by NICE took more than 2 years longer than did approval by the European Medicines Agency in Europe. The investigators note that in the USA, private insurance providers still restrict coverage to some of the 59 approved drugs, and that in some cases coverage decisions took up to 2 years. In the US Medicare system, all 59 drugs were covered (fully paid for by the insurance provider) near the time of approval. On balance, access to cancer treatment appeared to be far more liberal in the USA than in Europe or the UK.

Roberts and colleagues compared approval of oncology drugs in the USA, Canada, and Europe between 2003 and 2010. Approval was substantially faster in the USA, taking an average of 6 months, than in Canada (12 months) and Europe (14 months). However, beyond differences in time to approval, it is helpful to assess drugs that were approved in the USA, but not in Europe or Canada. Such drug is sipuleucel-T, a novel immunotherapy for advanced castration-resistant prostate cancer, which improved survival by 4 months compared with placebo in a large randomised controlled trial. However, the drug costs $93 000 per course of treatment, and there is no biomarker or clinical factor to predict which patients will benefit. Approved or not, use of this intervention raises challenges in all settings. In Europe, there is a desire to make such interventions available, and the European Medicines Agency has recently issued approval for sipuleucel-T, shifting the question of access to individual member nations that must struggle with the cost. In the USA, the drug’s cost is viewed as unsustainable and is used as a key example of the need for payment reform and cost controls in cancer care. The recently reported decline in sipuleucel-T use in the USA might be attributable to both the increases in possible alternative interventions and the reconsideration of the value of this intervention by clinicians, irrespective of access.

Where should the real debate about comparative effectiveness research and access to cancer care be? Despite concerns about public funding of comparative effectiveness research in the USA and the explicit use of cost-effectiveness thresholds in the UK, the role and value of comparative effectiveness research is an evolving issue in all health systems. There is no evidence to support the belief that increased attention to comparative effectiveness research will lead to rationing. However, when cost-effectiveness of cancer treatment in any system is assessed, difficult questions emerge related to financial sustainability, access to care, and choice of therapy. A wider view of the research is needed to guide both practice and health-system policy in oncology. Even policy weighted strongly towards support of patient autonomy and physician discretion could diminish the controversy about comparative effectiveness research, and help the public and policy makers to
Search strategy and selection criteria

We searched PubMed for articles published from July 1, 2008, and Dec 1, 2013, with the terms "comparative effectiveness research", "rationing", "access", "oncology" and "cancer" in various combinations. We also identified articles through searches of our own files and from reference lists of papers identified from this search. We reviewed only articles written in English. The final reference list was generated on the basis of originality and relevance to the relation between comparative effectiveness research and rationing or access to care in oncology.

discriminate between questions of what studies to do, and how results should be used to guide practice.

Comparative effectiveness research can potentially accomplish two major goals, and both might be valuable for patients, clinicians, and policy makers. First, comparative effectiveness research can identify better options that should determine care in any rational system. A test or intervention might be better on the basis of clinical effectiveness alone or because it is less expensive than an equivalent alternative; in either case, there is no clinical basis to prefer the alternative. Comparative effectiveness research guiding either clinical practice or policy and access in this way should not be considered rationing in a meaningful sense. Second, comparative effectiveness research can identify cost–quality trade-offs. One option might be the most effective, but also the most expensive, leaving decision makers without a win–win opportunity. Especially if the less effective option is chosen to save money, care will have been rationed by some definitions. In both scenarios, relative value of specific interventions is considered, and consideration of value is likely to assume greater prominence in all health systems worldwide.

Comparative effectiveness research can provide data to guide these decisions, but how data affects clinical and policy decisions is dependent on policy makers’ goals. The relative weight is attached not only to cost, but also to disease outcomes, toxic effects, and patient-reported outcomes. Thus value is not determined by an objective formula, but by what is valued in a given context. How a clinician or policy maker reacts to differences in these variables when providing or restricting access to an intervention for an individual or population depends on how issues such as choice, individualisation of care, potential benefit, likelihood of harm, and use of resources are prioritised. Public debate is needed on the issue of how care is valued and what is prioritised.

The amount of scientific resources that should be devoted to comparative effectiveness research needs to be determined. In oncology, drug development is increasingly funded by the pharmaceutical industry, which has efficiently brought new drugs to the market. However, some important clinical questions are less likely to be addressed by industry-sponsored research. Once a drug is available on the market, studies to define optimum treatment duration, subpopulations of greatest benefit, comparison between two marketed drugs, or any study with potential to diminish use of an available product are unlikely to be supported by industry, but might be highly valuable to doctors and patients making bedside decisions, and to payers trying to maximise cost-effectiveness. If cost-effectiveness data are not going to be used to decide policy then, arguably, legitimate debate could occur about whether state-sponsored research should be done to collect these data. However, even if costs at a national-level are ignored, they still have real-world effects on patients. Thus it is difficult to argue that cost data are irrelevant to clinical care, should not be collected, and do not provide a legitimate public health interest for research. That said, for such research to have maximum effect, development of both rigorous standards for comparative effectiveness research and infrastructure that will maximise potential for this type of evidence collection is needed. For example, databases developed specifically for evidence development might prove more useful and reliable than secondary analysis of insurance claims data, pharmacy records, or other non-research grade sources.

Although questions could be asked about whether comparative effectiveness research tends to support rationing of cancer care or more rational or evidence-based cancer care, clearly it is not the research results, but the policy environment that determines the effect of data for health-care delivery. Although opponents of increased use of comparative effectiveness research to inform policy are concerned with limitations on physician discretion, no system is without some of these constraints. In the UK, physician constraints might be based explicitly (eg, due to NICE guidance), whereas in the USA, they might be implicit (eg, due to absence of health insurance or because a patient cannot pay for prescription drugs). It seems more productive to debate the appropriate balance between physician discretion, patient autonomy, and system-level restrictions, than to debate the need for research that can inform us of the effectiveness of interventions in a real-world setting or of trade-offs between financial costs and marginal benefit that might be encountered. No system has solved the riddle of how to provide access to cancer treatment to all who need it at sustainable costs, and to the satisfaction of all citizens or policy makers. As we seek clinical data to inform bedside practice, and cost-effectiveness data to promote high-value care, a responsive and flexible system must be developed that makes allowances for the complexity of cancer care, and the rapid scientific development in oncology so that patients with cancer can gain reliable access to high-quality care.
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