Coverage With Evidence Development and Managed Entry in the Funding of Personalized Medicine: Practical and Ethical Challenges for Oncology

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ABSTRACT

Personalized medicines hold promise for many diseases. However, demonstrating the clinical efficacy and cost effectiveness of these medicines can be difficult. It is essential that decision-making processes for funding new medicines, including personalized medicines, are both robust and fit for purpose. We will argue that randomized trials of personalized medicines should be routinely supplemented with other research methods, such as observational research and single-arm studies, and that managed-entry funding programs, such as coverage with evidence development, may offer a means of providing early access to technologies where there is uncertainty about efficacy, safety, and cost effectiveness. These programs, however, raise a number of practical and ethical challenges that need to be worked through and resolved.

INTRODUCTION

Advances in molecular biology have led to a number of targeted, precision, or personalized medicines (PMs). The full impact of PMs on health care delivery is, however, still to be realized. This is in part a result of the difficulty that regulators and funders have in evaluating the benefits of these medicines and funding them so that they are available to relevant patient populations.

Both regulators and funders of health care are charged with evaluating the clinical effectiveness and safety of health technologies. In addition, funders have an additional mandate: to determine whether new health care technologies represent value for money and warrant public or private funding. However, assessments of value are often difficult to conduct and interpret when it comes to PMs and associated molecular diagnostic tests. This is because they are often expensive and supported by limited evidence at the time they are approved by regulators. In some cases, it may be that new PMs are no more efficacious or cost effective than less expensive alternatives. Alternatively, it might be that they are more effective and/or better value for money, but evidence of these benefits is obscured by methods used in its generation.

It is important that the most suitable methods are applied when assessing clinical efficacy and cost effectiveness. Failing to assess medicines fairly or failing to recognize their potential clinical benefits (where these exist) may create frustration and anxiety for patients and their carers, especially when their life expectancy is short and awareness of seemingly promising results from early studies are presented at congresses, published in the medical press, and available via the Internet. Physicians may also be frustrated by the failure of funders to enable access to new medicines and diagnostics. Although compassionate access programs and clinical trials may provide some with early access, not all patients can be served by these programs, and they raise other problems, such as the potential to undermine traditional clinical research and regulatory and resource allocation processes and to create inequities of their own.

HEALTH TECHNOLOGY ASSESSMENT OF PMS

Health technology assessments (HTAs) are frameworks within which the safety, efficacy, and cost effectiveness of new treatments—including new PMs—are assessed. Health economic and health care experts conduct HTAs on behalf of a public or private decision maker, such as the National Institute for Health and Care Excellence (NICE) in the United Kingdom, the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia, the Canadian Agency for Drugs and Technology in Health (CADTH), or the US Centers for Medicare and Medicaid Services (CMS).

In the United Kingdom, NICE conducts technology appraisals that assess the clinical and cost...
effectiveness of health technologies, including pharmaceuticals. Its recommendations about the use of new medicines and medical technologies serve to “give all NHS [National Health Service] patients access to the most clinically- and cost-effective treatments available.”

The NHS is legally obliged to fund and resource medicines and treatments recommended by NICE appraisals. England also has a Cancer Drugs Fund, which is “money the Government has set aside to pay for cancer drugs that haven’t been approved by the NICE and aren’t available within the NHS in England.”

In Australia, the PBAC is an independent statutory body that makes recommendations to the Minister for Health about which medicines should and should not be subsidized on the Pharmaceutical Benefits Scheme (PBS). If the PBAC makes a positive recommendation, the government decides whether to fund the medicine, with prices then negotiated by the Pharmaceutical Benefits Pricing Authority. In addition to PBS-funded medicines, the federal government has a special program for funding trastuzumab (Herceptin; Genentech, South San Francisco, CA) for metastatic breast cancer. In Australia, there is currently a debate as to whether a separate HTA and funding mechanism should be established for cancer medicines.

In Canada, some medicines receive centralized funding, but most decisions are made at the provincial level. The CADTH is an independent, not-for-profit organization responsible for providing health care decision-makers with objective evidence to help make informed decisions about the optimal use of health technologies. In Canada, there is also the pan-Canadian Oncology Drug Review Process, a “cross-jurisdictional review process for all oncology drugs, based on Ontario’s existing cancer drug review.” Participating provinces “each make their own final funding decision based on input from the Committee to Evaluate Drugs (CED) and the CED-Cancer Care Ontario (CCO) Subcommittee.”

The United States has a highly diverse, multifaceted health payer system. CMS and the Agency for Healthcare Research and Quality conduct HTAs of cancer medicines to determine which medicines should be funded by CMS and to make recommendations about which medicines should be subsidized by private insurers. The responsibilities for regulating and reimbursing commercially available companion diagnostics falls with the US Food and Drug Administration (FDA), Medicare, and private health insurance companies. Although some laboratory-developed tests have not undergone assessment, the FDA-issued “Guidance for Industry: In Vitro Companion Diagnostic Devices” assists companies in identifying the need for companion diagnostics at an earlier stage in the drug development process and in planning for codevelopment of the drug and companion diagnostic test. The ultimate goal of the guidance is to stimulate early collaborations that will result in faster access to promising new treatments for patients living with serious and life-threatening diseases.

In the United States, rising health care costs and concerns about safety and quality have led to increasing demands from regulators and payers for additional evidence that goes beyond that required by the FDA, such as comparative effectiveness of a new drug and/or diagnostic as compared with the market leader or evidence of clinical effectiveness among populations not assessed in regulatory studies. The evolution of Medicare from payer to prudent purchaser represents a transition from an enabler of access to new technology toward an evaluator of whether services are reasonable and necessary. CMS has taken steps to evaluate a number of treatments, such as those for colorectal cancer (irinotecan, oxaliplatin, cetuximab, and bevacizumab), in collaboration with the National Cancer Institute (NCI), and this has led to the identification of a number of high-priority clinical questions. These uncertainties are being addressed through nine NCI-led clinical trials, with interim funding provided by Medicare.

### CHALLENGES OF ASSESSING CLINICAL EFFICACY OF PMS

Although systems and strategies to evaluate the efficacy of PMs vary across different countries and health systems, most of those conducting HTAs, including HTAs of cancer medicines, prefer systematic reviews and meta-analyses of randomized controlled trials (RCTs) over other forms of evidence—generally demanding evidence from at least one adequately powered phase III RCT.

The problem, however, is that although RCTs are appropriate for evaluating drugs used to treat large populations with homogeneous disease and in simple treatment settings, they work less well for small populations and for complex diseases that require multiple forms and lines of therapy, often in conjunction with companion diagnostics, as occurs in PMs. The applicability of evidence generated from RCTs to real-life populations will depend on the degree of alignment between the research and target population in terms of known and possible unknown clinical and molecular characteristics. On the basis of probability alone, this potential for misalignment will increase as RCT participant numbers decrease or where there is uncertainty surrounding the specific molecular mechanisms of response.

Although it is worth noting that there are many examples of high-quality RCTs that have evaluated targeted cancer therapies, the efficacy of targeted therapies may be easier to assess using RCTs for common cancers, such as breast cancer and non–small-cell lung cancer (NSCLC); for example, 20% of women with breast cancer are human epidermal growth factor receptor 2 (HER2) positive and are therefore eligible for HER2-directed therapies, and even uncommon mutations, such as EGFR mutations in NSCLC, occur in sizeable populations because NSCLC is a common disease. RCTs may not, however, be appropriate for all PMs, especially where the target cancer is of low prevalence and/or genomic subtypes are uncommon. Trials of PMs are further complicated by the need to assess codependent diagnostic technologies and by the ethical imperative to allow patients to switch from one arm of a study to another. This, particularly when combined with small numbers of participants, makes it extremely difficult to demonstrate important study end points, such as overall survival. The demand for RCT evidence for PMs may, therefore, result in both type I errors, where ineffective or harmful technologies are made available, and type II errors, where access to beneficial and cost-effective therapies is denied.

### CHALLENGES OF ASSESSING VALUE AND COST EFFECTIVENESS OF PMS

Those conducting HTAs—whether for public or private coverage—need to consider not only the likely effectiveness of a new medicine but also what the medicine costs and its likely impact on overall costs.
health care spending relative to its clinical benefits. Personalized oncology medicines can be extremely expensive both for patients and for health systems, with the price for an average year of cancer treatment now estimated to be more than $100,000.\textsuperscript{16,17} so payers demand not only evidence of efficacy, but also modeling to determine overall cost effectiveness.

Considerations of cost effectiveness can, however, be extremely complex for two reasons. First, the cost of a medicine is a social construct that is derived not from its real or true worth but rather from a combination of how much it costs to develop and the need for a company to make a profit by selling its product at a price the market will bear. This latter aspect is influenced by how unique the drug is, any existing competition from already available medicines, the cost of currently treating the disease for which this drug is used, and whether the new drug changes medical practice—for example, such that patients no longer require hospitalization.

Critically, the perceived cost effectiveness of a new drug will depend on the degree to which particular outcomes are valued by payers, patients, governments, and the community at large. This may preclude an otherwise positive cost-effectiveness assessment if there is disagreement about the economic factors that need to be taken into consideration when determining the cost of the drug.\textsuperscript{18} Given this complexity, assessments of cost and cost effectiveness cannot always be fully determined before market entry. This creates an argument for providing rapid access to potentially beneficial medicines, with post–market entry assessment of their value and cost effectiveness, as well as of their effectiveness.

**ACCELERATED APPROVAL AND COVERAGE WITH EVIDENCE DEVELOPMENT**

In the United States, some new oncology treatments are being approved by the FDA via accelerated approval pathways designed to “hasten the delivery of products appearing to provide a benefit for serious or life-threatening illnesses lacking satisfactory treatments.”\textsuperscript{19} Here, approvals are granted after review of surrogate end points that are considered likely to translate into meaningful clinical benefits. In return, the applicant (usually a pharmaceutical company) is required to provide evidence that verifies these benefits and/or safety via phase IIIb and IV studies. Oncology accelerated approval examples include liposomal doxorubicin, lipo-cytarabine, and ibritumomab, where confirmatory clinical evidence was successfully reported to the FDA subsequent to initial regulatory approval. If clinical benefit is not demonstrated, the FDA can withdraw approval, as it did with bevacizumab for the treatment of HER2-negative metastatic breast cancer.\textsuperscript{20}

Those funding new medicines have also begun exploring mechanisms for providing early access to medicines that are promising and potentially life saving but have not been demonstrated to be cost effective. Efforts have included entering into various types of managed entry arrangements with pharmaceutical companies and prescribers, aimed at managing the budgetary impact and/or use of funded medicines.\textsuperscript{21} The phrase managed entry describes a range of strategies including risk sharing, payment for outcomes, performance-based reimbursement schemes, and various kinds of coverage with evidence development (CED).\textsuperscript{21} CED programs, sometimes referred to as access with evidence development or coverage within research, are processes by which medicines are reimbursed and prices are negotiated based on current evidence of efficacy and/or cost effectiveness, with a view toward generating further evidence and subsequently continuing funding as is, delisting medicines, or adjusting prices on the basis of emergent evidence.

In the United States, the concept of CED emerged a decade ago when CMS drafted a new guidance document describing CED. To date, there has been limited uptake of CED for oncology PMs, with CMS having selected four colorectal treatments (irinotecan, oxaliplatin, cetuximab, and bevacizumab) in collaboration with the NCI to answer a number of high-priority clinical questions. These uncertainties are currently being addressed through nine NCI-led clinical trials, with funding of treatment provided by Medicare.\textsuperscript{10}

The use of CED-generated data to list and delist medicines and to adjust prices on the basis of emergent evidence is more developed in the British Commonwealth and European Union nations than in the United States. In part, this is because systems in the Commonwealth and in Europe are fundamentally concerned with the regulation of drug pricing and universal access to medicines, whereas the United States is more concerned with the regulation of free enterprise. CED programs have been endorsed by many international HTA organizations,\textsuperscript{21} as a means of moving beyond forced yes or no decisions in the face of uncertain evidence. A review conducted in 2010 identified nearly 30 forms of CED in Europe, North America, and Australasia.\textsuperscript{22} In addition to the previous four colorectal cancer examples of irinotecan, oxaliplatin, cetuximab, and bevacizumab, additional oncology treatments include erlotinib, lapatinib, and bevacizumab in Italy and bortezomib and sunitinib in the United Kingdom; additional nononcology examples include ranibuzumab for wet age-related macular degeneration and bosentan for pulmonary artery hypertension.\textsuperscript{10,21}

In Australia, the federal government and pharmaceutical industry reached an agreement in 2010 on the principles underpinning potential CED (referred to there as managed entry) in the PBS. To justify interim funding through the PBS, pharmaceutical sponsors need to demonstrate that there is high clinical need, that no alternative treatments are available, and that new definitive data about cost effectiveness will be generated in a timely manner. They also need to commit to adjusting their prices (in either direction) on the basis of emergent evidence about cost effectiveness. According to an internal Department of Health and Ageing memo, dated August 2014, 10 medicines have been reviewed under provisions of managed entry into the PBS. A similar CED approach has been used since 1998 by the Australian Medical Services Advisory Committee, which funds medical devices and diagnostics.\textsuperscript{15}

The ethical and sociopolitical justifications for CED programs are that they balance the interests of clinicians and patients, who want early access to new diagnostic tests and medicines; payers, which want to address genuine health needs but do not want to pay more for medicines than they are worth; and pharmaceutical companies, which want to be paid fairly for their products. As Pearson et al\textsuperscript{23} argue, such programs “can play an important, ethically legitimate role in balancing needs for better evidence . . . with the needs and desires of patients for rapid access to new technologies.”\textsuperscript{23a}

CED programs are particularly useful when it comes to the funding of PMs and treatments for orphan diseases because of the lack of robust data, as a result of trials not having been conducted or having been conducted in only a small number of patients. In these situations,
The evidence generated to support CED programs differs from data collected via traditional postmarketing surveillance in that it is more systematic, targeted, and defined in advance by both pharmaceutical sponsors and funding bodies. Evidence generation in CED also differs from traditional premarketing clinical research in that RCTs are not necessarily preferred over other research methods. There are two main alternatives to RCTs that can provide useful information to inform CED and that may be particularly important in CED for PMs: observational cohort studies and prospectively designed single-arm studies.

Observational cohort studies track groups of patients defined by clinical or molecular characteristics, disease status, or treatments received. Studies may be prospective or retrospective and can make use of data collected directly from patients (primary data sets) or large administrative and electronic medical record data sets (secondary data sets). Outcomes need to be chosen that can demonstrate clinical effects in the absence of directly comparative data provided by control arms within RCTs. For the purpose of descriptive comparisons, appropriately matched contemporary or historical populations and those treated with previous standards of care may be used.

Alternative approaches to the collection of additional evidence include single-arm studies. Like observational studies, single-arm studies require well-matched historical or contemporary control cohorts and the collection of appropriate outcomes. The application of methods that use propensity score matching may promote the robustness of data by ensuring like-for-like comparisons between external control patient groups with those participating in open-label studies. Although results of single-arm studies may be contrasted with internal control cohorts presented from previous RCTs, caution needs to be taken in the interpretation or contrasting of results. This is because patients participating in RCTs are likely to be generally fitter, with better performance status, and will be managed in ways that differ significantly from those in single-arm studies and in real-world clinical settings.

Although both cohort studies and single-arm studies offer significant benefits in terms of their capacity to reflect real-world clinical practice and patient behavior and the speed with which they can be conducted, there are also a number of disadvantages to these methods. Observational studies often rely on the existence of high-quality administrative and clinical databases, which are not always available, and are easily confounded by unrecognized differences between groups of patients, and single-arm studies may be expensive, require historic or parallel standard-of-care cohorts for comparison, and, like RCTs, not fully reflect natural behavior.

These methods need to focus not only on effectiveness but also on costs and savings, so the value and cost effectiveness of medicines can be determined and prices negotiated accordingly. For this to be effective, clinical, administrative, and insurance databases need to be linked. Methods for doing so are increasingly the focus of learning health care systems that are being encouraged in many countries and of accountable care organizations in the United States.

Although CED programs hold promise as a means of promoting timely and affordable access to medicines, including many PMs, they raise a number of practical and ethical challenges. In addition to the obvious resources needed to establish, run, and govern CED programs, challenges arise in relation to: the effects of CED programs on evidence-based medicine and health resource allocation, the competing interests of different stakeholders, and possible compromising of research participants’ interests.

**Distortion of Evidence and Health Resource Allocation**

The first set of issues raised by CED programs relates to the use of observational and single-arm studies rather than RCTs. To make such studies worthwhile and valid, their design, conduct, and analysis needs to be rigorous and transparent, particularly with regard to minimizing confounding effects and bias needs.

Because these studies also rely on real-world data sources, such as patient registries or administrative databases, and well-matched historical or contemporary comparative cohorts, they also must be supported by funding agencies, sponsoring companies, clinicians, administrators, and insurers. These studies should also complement, rather than replace, RCTs.

Failure to follow through on CED programs might also undermine the capacity for budgetary control if disinvestment or price reductions do not follow when medicines are found to be poor value for money. The reality is that once patients and clinicians have access to, and are familiar with, a new technology, disinvestment is highly unlikely to occur or is likely to be rigorously resisted by pharmaceutical companies. If disinvestment does not occur, CED programs will be responsible for exacerbating the very thing they are designed to prevent—medical practice that is neither evidence based nor cost effective.

**Competing Stakeholder Interests**

Although CED theoretically represents a compromise among various stakeholder groups, there are likely to be tensions between different and potentially competing interests. Companies may wish to obtain the highest prices possible, and payers may wish to pay as little as possible; manufacturers of generic medicines worry that these programs exist to promote early access to expensive patented medicines, and even manufacturers of patented medicines may worry that competitors will make use of the evidence they generate as part of a CED program.

The criteria for instituting CED, such as high clinical need, and other criteria, such as timely return of research results, may also not be easily defined and may be contested. Stakeholders may also disagree about the funding of new diagnostic tests in CED programs, and pharmaceutical companies may disagree with payers about how to interpret emergent evidence—particularly whether it justifies maintenance, escalation, or reduction in drug prices.

The negative effects of these disagreements are likely to be exacerbated by the fact that negotiations about CED programs—particularly discussions of drug prices—may be commercially confidential. Given the centrality of price negotiations to CED programs, commercial confidentiality makes it impossible for funding organizations to be transparent in their decision-making processes. This, in
turn, may undermine their inclusiveness, their perceived trustworthiness, and their legitimacy in the eyes of external stakeholders to thwart efforts on the part of funding agencies to satisfy the principles of accountability for reasonableness.  

**Potential Compromising of Research Participants’ Interests**

The third group of issues raised by CED programs relates to ethical oversight of these programs. The question has been raised, for example, about what kinds of CED programs count as research (eg, whether participation in registries amounts to research or simply as quality improvement) and what, if any, consent and ethical oversight are needed. A related question is whether it is ethical to insist that patients participate in research as a condition of coverage. Although clinical trials often provide the only means of accessing new therapies, CED programs are generally predicated on the basis that the new therapy is likely to be beneficial—meaning that there is unlikely to be genuine equipoise.

It could also be argued that concerns about exploiting research participants in this way are not unique to CED programs—which are simply one component of increasingly popular learning health care systems, in which research and clinical practice are integrally intertwined. One difference, however, is that in the context of a CED program, there is likely to be at least some evidence of benefit associated with the new therapy (ie, there is unlikely to be genuine equipoise), so some research participants will be predictably disadvantaged relative to other research participants.

Medical regulators and funders worldwide face seemingly impossible challenges stemming from advances in medical science, such as PMs, but limited capacity to approve and fund all such advances. It is essential that decisions regarding the regulation and funding of any new medical therapies be made on the basis of clear criteria and according to processes that are transparent and ethically justifiable. Until recently, HTA has relied on RCTs, systematic reviews, meta-analyses, and cost-effectiveness analyses, all conducted before market entry. Such methods are, however, particularly difficult to apply to medicines for patients with orphan diseases and to some PMs—particularly given the lack of clarity as to how the worth of PMs should be determined and the lack of transparency surrounding both the setting of drug prices and negotiations between industry and third-party payers. To strike a balance between the needs of patients, physicians, funders, and industry, different mechanisms for evaluation and translation need to be used. These include alternative forms of clinical trial design, such as observational research and single-arm studies, and flexible strategies for managing access to market, such as CED. These alternatives, however, raise issues of their own and, if not implemented with great care, may ultimately undermine evidence-based medicine and systems for controlling health budgets.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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No relationship to disclose

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