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HEALTH TECHNOLOGY ASSESSMENT AND PERSONALIZED MEDICINE: ARE ECONOMIC EVALUATION GUIDELINES SUFFICIENT TO SUPPORT DECISION MAKING?

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Background: Many jurisdictions delivering health care, including Canada, have developed guidance for conducting economic evaluation, often in the service of larger health technology assessment (HTA) and reimbursement processes. Like any health intervention, personalized medical (PM) interventions have costs and consequences that must be considered by reimbursement authorities with limited resources. However, current approaches to economic evaluation to support decision making have been largely developed from population-based approaches to therapy—that is, evaluating the costs and consequences of single interventions across single populations. This raises the issue as to whether these methods, as they are or more refined, are adequate to address more targeted approaches to therapy, or whether a new paradigm for assessing value in PM is required.
Objectives: We describe specific issues relevant to the economic evaluation of diagnostics-based PM and assess whether current guidance for economic evaluation is sufficient to support decision making for PM interventions.
Methods: Issues were identified through literature review and informal interviews with national and international experts ($n = 10$) in these analyses. This article elaborates on findings and discussion at a workshop held in Ottawa, Canada, in January 2012.
Results: Specific issues related to better guiding economic evaluation of personalized medicine interventions include: how study questions are developed, populations are characterized, comparators are defined, effectiveness is evaluated, outcomes are valued and how resources are measured. Diagnostics-based PM also highlights the need for analyses outside of economic evaluation to support decision making.
Conclusions: The consensus of this group of experts is that the economic evaluation of diagnostics-based PM may not require a new paradigm. However, greater complexity means that existing approaches and tools may require improvement to undertake these more analyses.

Keywords: Costs and cost analysis, Biomedical research/methods, Biomedical research/standards, Decision support techniques, Delivery of health care, Diagnostic techniques and procedures, Health policy, Humans, Individualized medicine/methods, Technology assessment, Biomedical

Many jurisdictions have developed guidance for conducting and interpreting economic evaluation, often in the service of larger health technology assessment (HTA) and reimbursement processes (1;2). However, methodological challenges can arise with specific interventions or disease states. In Canada for example, recent guidance for economic evaluations for oncology products has been developed to address some ambiguities in the general guidance (3). The specific guidance implicitly recognizes the need for more consistent application of economic evaluation as more generic guidance provides opportunities for analysts to use significantly different approaches that in turn could lead to significantly different findings. Methodologic guidance may also enhance the confidence and strengthen the credibility of the use of these analyses by end users (4).

Personalized approaches to medicine can be broadly defined as those using any type of patient-specific information (e.g., genetic and molecular laboratory-based diagnostic, questionnaires, risk scores, patient-reported outcomes, imaging, biometric/functional measures, laboratory-based anatomic pathology, point of care testing, and from-home testing) or patient-specific therapy (e.g., autologous cell therapy). Collecting and creating new information metrics for personalizing therapy to patients has been greatly facilitated by developments in the

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application of organizational (e.g., databases) and consumer-driven information technology (e.g., cellular phones and home computers). For the purposes of this article and because of its health technology policy relevance, we more narrowly define personalized medicine approaches as "the use of genetic or other biomarker information to improve the safety, effectiveness, and health outcomes of patients by means of more efficiently targeted risk stratification, prevention, and tailored medication and treatment-management approaches" (5).

Diagnostics-based personalized medicine potentially hold the promise to be of benefit to multiple stakeholders, including nations seeking to improve economic opportunities through knowledge- and genome-based applications; drug innovators who aspire to curb expensive development costs (6); healthcare providers who believe safer and more effective care will result from personalized medicine interventions in an aging population with more complex disease; and the health informatics industry which continues to seek health systems applications for "big data." The use of diagnostic-based information has seen recent growth from these factors as well as incentives for higher levels of coordination and human resource cost pressures, leading to innovation in computed interpretation, automation, and digital reporting (7;8).

With accelerated growth in both the volume and price of diagnostic tests in the last decade, the current and potential economic burden for payers has made this a priority for discussion across the HTA community (9). Interest in the evaluation of PM can be seen as an extension of previous attempts to standardize evidence-based approaches to assessing diagnostic tests. These include a 2003 International Task Force, (10) and the 2004 Evaluation of Genomic Applications in Practice and Prevention (EGAPP) initiative (11).

The potential to access this new technology, in turn, is driving the need for assessments to support decision making. Like any health intervention, PM interventions have costs and consequences that require consideration by reimbursement authorities who seek to derive maximum value from limited resources. The increased need for evaluation from decision makers can be observed in a 13 percent annual growth in the number of published economic evaluations of diagnostic interventions (12).

Current approaches to economic evaluation to support decision making are largely focused on reimbursement of drugs. Drug reimbursement evaluations are typically population-based, involving single interventions in single populations. Because personalized medicine, by definition, leads to restricted populations or individual care there are questions as to whether current approaches to economic evaluation are adequate for PM interventions. Of specific concern is whether current guidance for economic evaluation is specific enough to avoid inconsistent evaluation and contradictory findings. This, in turn, may lead to inconsistent decisions and may also lower decision-makers' confidence in the usefulness of economic evaluations to support decision making.

This article addresses the question of whether current guidance for economic evaluation is adequate to support decision making for personalized medicine interventions. It may also be useful to decision makers rely on economic evaluations of PM and those who are updating jurisdiction-specific guidance for economic evaluation or considering the future of health technology assessment and reimbursement policy.

METHODS

The key issues in the economic evaluation of personalized medicine were identified through a workshop and informed discussion by a panel of experts (J.H., A.L., D.M., S.P.). Key issues were believed to be those choices in methods that may cause the most variability in findings unless further specified. Members of the panel were selected based on long-standing expertise in economic evaluation and health technology assessment. The workshop was held in Ottawa, Canada, in January 2012 and sponsored by Health Canada, with 150 participants attending from federal and provincial programs across Canada, as well as academia, and not-for-profit organizations.

The panel was presented with potential issues based on the results of an informal survey and rapid review of the literature. The literature search and selection of review articles was conducted by a single author (D.H.) using PubMed Medline and keywords MeSH terms ("Cost-Benefit Analysis"[MeSH] AND ("review"[Publication Type] OR "review literature as topic"[MeSH Terms] OR "review"[All Fields]) AND "genetic testing/economics"[MeSH]). Given only a purposive sample of issues was required to initiate discussion, and the literature is nascent, a systematic review was not conducted in favor of using a less resource-intensive approach. International subject matter experts (see acknowledgements) were identified from this literature search and contacted to discuss issues identified from the review. A second informal search was conducted using the CADTH Web site to identify recent Canadian economic evaluations of personalized medicine. Authors from these studies (see acknowledgements) were contacted to discuss and review issues identified from the original search and those revealed after discussion with international experts.

Potential issues were categorized according to key methodologic categories in the current Canadian guidelines for the economic evaluation of health technologies (13) and presented to the expert panel. These economic evaluation guidelines are divided into fourteen separate sections prescribing appropriate methods. For example, one section titled "Type of Evaluation" suggests the form of analysis undertaken should be a cost-effectiveness analysis using an outcome that is adjusted for health-related quality of life unless another form can be justified. Each identified issue was mapped onto one or more sections. Panelists were presented with experiences from those conducting economic evaluations in Canada (as per above) and from invited international subject experts of using economic

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evaluation of personalized medicine for decision making (see acknowledgments). There was also more focused discussion regarding two specific issues. Experts were also invited to comment on potential remedies to the issues identified. In addition to the expert panel, workshop attendees were invited to comment on other issues.

A draft report of the workshop along with a final set of issues was prepared and circulated among the expert panel and wider group of workshop participants for comment. This article represents a summary and elaboration of the workshop findings.

RESULTS

Two recent systematic reviews of economic evaluation of pharmacogenomic tests were identified (14;15). A third un-indexed review of reviews known to one of the authors was also used (16). The presentations and discussion summary from the workshop are available online (http://ihe.ca/research/knowledge-transfer-initiatives/–methodology-forum/personalized-medicine-research-challenge—health-economics-methodology-1/) and economic evaluations are in a Supplementary File, which can be viewed online at http://dx.doi.org/10.1017/S0266462314000142. The workshop discussion led to the prioritization of six specific issues and potential modifications necessary to existing guidelines that would promote consistent evaluations for decision making (Table 1). These six areas of concern related to how study questions are developed ("Study Question"), how populations are characterized ("Target Population"), how comparators are defined ("Comparators"), how the effectiveness of a PM intervention is evaluated ("Effectiveness"), how outcomes are valued ("Valuing Outcomes"), and how resources are measured and valued ("Resource Use and Costs"). Examples and an elaboration of each of these issues are presented in the next section with a summary, examples and a rationale for each in Table 2.

Specific Issues and Potential Solutions

Study Question. First, there was recognition that personalized medicine creates problems for analysts when being asked to frame evaluative questions. Analysts are confronted with either developing a question that is most important for a program-specific decision maker, such as a drug formulary director who is responsible for one part of reimbursement (e.g., a drug rather than a drug and test combination) or for a nonexistent (in Canada) third-party payer administrator that can consider all technologies together. For example, Mittmann and colleagues conducted a trial-based economic evaluation of the effectiveness of cetuximab plus best supportive care versus best supportive care only in patients with advanced colorectal cancer refractory to chemotherapy (17). Through this assessment, they were able to examine the subgroup of almost half of patients who had tested positive for a tumor with a wild-type KRAS mutation. Their findings suggest a lower incremental cost-effectiveness ratio (ICER) associated with treatment of these patients (186,000 versus 300,000 CAD /quality-adjusted life-year (QALY). Despite being a high-quality evaluation, this study does not explicitly address the policy question of the value of providing patients access to testing. Rather, it addresses a clinically-relevant but less-policy-relevant question—namely, the value of treating patients with cetuximab who have positive and negative test findings. A model-based analysis by a different group of investigators in 2012 more directly addresses the question of access to testing. Their analysis reveals performing a test improves health outcomes compared with not performing a test and is more costly if cetuximab is part of the treatment pathway (18).

Target Population

In a similar vein, specification of target population groups within the question asked creates particular challenges for analysts. Personalized medicine interventions may accelerate the evolution and development of clinical treatment pathways. Testing reveals heterogeneity and creates multiple subpopulations which unfold according to the sequence information is gathered. Framing questions around PM interventions that have application in multiple therapeutic areas (e.g., interventions that target a generic immune system pathway) then becomes a challenge. Unlike more conventional HTA, Analysts must make clear whether the target population is understood as the total (still unstratified, e.g., biomarkers not yet measured) population or already "personalized" strata (e.g., individuals with specific previously known biomarker values).

An example of this issue can be seen in two independently conducted analyses intended to examine the value of HER2 testing. In one study, analysts used a patient population of pre- and postmenopausal women diagnosed with breast cancer stratified by breast cancer stage and recurrence (19). One testing sequence to confirm HER2 positivity was applied to both recurring and newly diagnosed cases. In an alternate analysis, seven testing strategies were used but newly diagnosed and recurrent populations were analyzed together (20). Both analyses focused solely on testing and assumed therapy would be offered regardless.

Comparators

The rapid evolution of clinical pathways from personalized interventions also makes defining interventions and comparators a challenge. The most common intervention may be no treatment or treatment without the use of specific tests yielding further personal information. Clinical pathways may be ill-defined or in development and decision makers may not be able to make reimbursement decisions that encompass all technologies (e.g., companion diagnostics). Interventions may be access to personalized medicine versus no access, a test versus no test, test and treat versus no test and treat, etc. There may also be debate regarding in what sequence testing should be conducted. Sequencing and uncertainty regarding optimal pathways makes the problem of comparators especially significant in PM interventions.

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Table 1. Specific Issues in the Economic Evaluation of Diagnostics-Based Personalized Medicine Based on Canadian Guidelines for Evaluation

No	Canadian guideline item	Description	Issue	Solution
1	Study question	State the decision problem oriented to target audience in answerable form with interventions and populations stated.	Variable framing if questions due to multiple/evolving clinical pathways and decision maker scope.	More specification regarding identification of base case clinical pathway.
2	Type of evaluation	i.e., Form of analysis - cost-utility analysis where a final outcome is adjusted for health-related quality of life is preferred unless another form is justified.	Similar to other non-PM interventions.	
3	Target population	The target population for the intended use of the intervention should be stated.	PM sometimes fractures traditional clinical definitions. Consequence of testing in non-target populations also important.	Develop population definitions that define what is stratified and unstratified.
4	Comparators	Interventions and a reference case (the most common or frequently used care) must be chosen.	Test sequences combined with treatment lead to multiple strategies.	Require testing of all relevant strategies.
5	Perspective	In the Reference case, use the perspective of the publicly funded health system.	Similar to other non-PM interventions.	
6	Effectiveness	Use a systematic review to estimate the magnitude of effectiveness and adjust for "real-world" factors.	Compliance and adherence to testing important.	Further emphasis on adjustment for real world factors.
7	Time horizon	Use a time horizon based on the natural course of the condition.	Similar to other non-PM interventions.	
8	Modeling	Explain how and why model assumptions occur and whether the model has been validated.	Similar to other non-PM interventions.	
9	Valuing outcomes	Use appropriate preference-based measures to value differences between the intervention and alternatives in terms of HRQL. A representative sample of the public is the preferred source for preferences. Patients who have direct experience of the relevant health states may be an acceptable source.	Preference heterogeneity may exist. Valuing avoidance of unintended, harmful consequences poorly defined.	Further research on accounting for population preference heterogeneity and standards for disutility from harm.
10	Resource use and costs	Systematically identify, measure, and value resources that are relevant to the study perspective(s). Classify resources in categories that are appropriate to the relevant decision maker (e.g., primary care, drug plan, hospitals).	Costs of tests may depend on number of tests performed and be difficult to value. Analysts may also mistakenly omit costs of tests offered "free" (i.e., costs borne by manufacturer).	Improved guidance on accurate valuation of categories of costs from testing, including, opportunity, fixed, variable and other costs.
11	Discounting	In the Reference Case, discount the costs and health outcomes that occur beyond one year to present values at the (real) rate of 5% per year.	Similar to other non-PM interventions.	
12	Variability and uncertainty	Explore the effects of uncertainty (differences in effects reducible by further information) and variability (differences not reducible by further information).	Similar to other non-PM interventions.	
13	Equity	The distributional impact (e.g., benefits, harms, and costs) and cost-effectiveness of the intervention for those subgroups predetermined to be relevant for equity purposes.	No issues, although analysts should be aware of distributional consequences and spillovers from unactionable knowledge.	
14	Generalizability	Justify the use of non-Canadian data and its economic impact in a Canadian setting.	None identified.	

Table 2. Rationale, Examples and Elaboration of Specific Issues Identified in the Economic Evaluation of Diagnostics-Based Personalized Medicine

Name	Elaboration of issue	Solution and rationale	Example
Study question	• Funding silos may lead to different payer perspectives (e.g., those who pay for drugs versus those pay for diagnostics) requiring different questions. • There may be different clinical perspectives (e.g., treating patients already tested versus deciding to test) requiring different questions.	Further specification of what defines a third-party payer and what constitutes usual care will reduce variability of findings from similar evaluations and increase relevance for decision-making.	Evaluations of KRAS testing by Mittmann (17) and Health Quality Ontario (18) in patients with advanced chemorefractory colorectal cancer asked different but relevant questions.
Target population	• Testing creates multiple subpopulations which unfold according to test sequence. • PM interventions may have application in multiple therapeutic areas.	Rules to define target populations according testing rules will reduce variability of findings from similar economic evaluations.	One evaluation of HER2 testing in stratified population suggested cost savings (19) while another suggested additional costs (20).
Comparators	• Rapid evolution of clinical pathways from personalized interventions makes defining interventions a challenge. • The sequence of testing and the inclusion of a "no-test" comparator is often variable and can lead to different recommendations funding.	Requiring analysts to test all realistic strategies may be computationally heavy but will not exclude important but un-evaluated strategies.	One comprehensive study identified 24 clinical pathways and 1,000 unique strategies based on permutations from sequencing tests (21).
Effectiveness	• Estimates of effectiveness may be more reliant on data sources and more sensitive to adherence and compliance[1] effects.	Strict recommendations that compliance and adherence must be accounted for and that synthesis-based estimates must be used in either the base case or sensitivity analysis will reduce variability of findings.	Two evaluations using different data sources in a Canadian setting yielded a more than twenty-fold difference in QALY estimates (1.32 vs. 0.05). (23,24)
Valuing outcomes	• Average population-based valuations of preferences may sharply contrast with the preferences of those who are actually eligible for personalized treatment. • Some personalized medicine interventions are intended to reduce harm while others are intended to augment benefits.	Further investigation is needed to explore the relevance of preference heterogeneity and its relevance to decision-making. Analysts should consider analyzing the potential for this effect in sensitivity analyses.	Individualizing prostate cancer treatment resulted in an additional value of $2,958 per patient (assuming an additional QALY is USD 100K).(25)
Resource use and costs	• Opportunity costs of tests depend on number of tests performed and may be variable due to large geography and population density variability. • Guidelines do not say how to value cost-sharing arrangements between producers and payers.	Sensitivity analysis of cost of testing by volume should be performed in every evaluation to better inform payers. Specific rules for valuing cost-sharing arrangements should be developed to avoid variability in findings.	None identified.

This is illustrated in an evaluation conducted by Paulden and colleagues examining the impact of introducing a twenty-one-gene recurrence score assay in Ontario (21). The analysts enumerated twenty-four clinical pathways from twelve unique risk categories based on two tests with two chemotherapeutic regimens. This resulted in 1,000 unique strategies based on permutations from sequencing test (21).

Effectiveness

Another issue for analysts identified is how to best characterize the effectiveness of the intervention. There is general acknowledgement that appropriate data may be largely unavailable as currently regulators do not require proof of clinical efficacy for a test or even sensitivity/specificity which could be used to estimate model effectiveness. Even in cases where reliable information is available, such as companion diagnostic technologies with clinical efficacy information, variable behavioral responses by physicians and patients to personal information and population heterogeneity may limit the ability of analysts to extrapolate across population groups. As with drug therapies, it will be is important to have good information about how likely patients are to comply and adhere to the interventions. However, unlike drug therapies, the issue of compliance in diagnostics-based PM is exaggerated, because there is multiple stages of compliance, including caregiver compliance to ordering a test, patient compliance to receive a test, caregiver compliance to interpret and act on test results, and compliance to subsequent interventions.

Two separately conducted evaluations of use of the twenty-one-gene score assay in a Canadian setting relying on different sources for effectiveness demonstrate this point. They yielded a more than twenty-fold difference in QALYs (1.32 versus 0.05) (21;22). This issue suggests current recommendations could be strengthened so that compliance and adherence are always accounted for and that synthesis-based estimates must be used in either the base case or sensitivity analysis. This in turn will reduce variability of findings from seemingly arbitrary choices in analytic judgments.

Valuing Outcomes

Another challenge not fully addressed in the guidelines is valuing patient outcomes from an individual versus population-based standpoint. Even if outcomes and their associated heterogeneity are well estimated and defined, it is possible that average population-based valuations of preferences will sharply contrast with the preferences of those who are actually eligible for personalized treatment (i.e., population heterogeneity leads to preference heterogeneity). This difference may lead to a different direction or magnitude in measures of preference-based outcomes and be meaningful from a decision-makers standpoint. Additionally, some personalized medicine interventions are intended to reduce harm while others are intended to augment benefits. There may also be important underlying heterogeneity in preferences (for reduced harm versus improved benefit) from a population and patient standpoint that need to be considered in the analysis.

The importance of this issue and its effect on the findings of economic evaluation should be investigated further. In a modeling study, Basu and Melzer showed that treating individuals for prostate cancer according to individual preferences versus using population-based averages resulted in an additional value of 2,958 USD per patient (assuming an additional QALY is 100,000 USD) (23). However, how this issue should ultimately affect current recommendations is not straightforward. There are additional philosophical questions as to whether this type of approach is even appropriate to support decision making. Until more is known, analysts should consider analyzing the effect of preference heterogeneity based on current information in sensitivity analyses.

Resource Use and Costs

Another issue identified was that of resource valuation (costing). Canadian economic evaluation guidelines suggest using economic (opportunity) costs as the basis for valuing resources and in principle, using total mean cost (including capital and allocated overhead costs) as the unit cost measure (13). Others have noted that the costs of tests may depend on number of tests performed and be difficult to value (24). In Canada, the cost of testing may be particularly variable due to a large geography and high variability in population density. While some labs may be able to offer high throughput systems and low marginal costs, others may be faced with much higher per-test costs. This issue suggests sensitivity analysis of cost of testing by volume should be performed in every evaluation to better inform payers.

The guidelines also do not currently speak to how to value costs in cost-sharing arrangements between private sector producers and patients. Some companion diagnostics may be offered by a pharmaceutical innovator at "no cost" but analysts must be sure to capture costs because it is actually borne by the third-party payer through the price paid. One remedy would be to develop specific rules for valuing cost-sharing arrangements to avoid variability in findings. This may be particularly important when evaluations are conducted using different funding sources that must cover these costs.

DISCUSSION

The findings presented here suggest that the economic evaluation of personalized medicine may require further specification of approaches than exists in Canadian guidelines. Without specific remedies to the issues identified, there is the real potential for large variations in findings and interpretations, and ultimately, inconsistent decision making. Nevertheless, there was consensus that a new paradigm for evaluation is not required.

The issues identified should not be considered a comprehensive list in the realm of evaluating diagnostics-based personalized medicine nor are our proposed solutions definitive.

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The approach taken has limitations worth mentioning. First, the majority of the expert panel, workshop attendees were Canadian and the examples used to prioritize the issues were mostly restricted to conducting economic evaluation within the Canadian context. The selection process to identify relevant literature was not systematic, and used a single database and reviewer. This was appropriate as the intent was only to develop a purposive sample of issues and evaluations to inform discussion and not a definitive list. We also did not use a structured method for consensus development. Given these limitations, the issues identified here should be seen as a starting point for further conversation and guideline development.

Despite these limitations, we believe the experience of the panel and the use of reviews to identify potential issues adds strength to our findings. Despite an examination of Canadian experiences, we would also surmise these findings are generalizable to other jurisdictions as they are consistent with other reports outside of Canada using similar methods to identify issues. This includes a recent report from the Institute of Medicine identified several challenges with economic evaluation that we identified (25). Another recent recommendation for evaluating targeted cancer interventions emphasized the need to capture costs and health outcomes in either testing or risk algorithms (26;27). Most recently, Annemans and colleagues have similarly suggested standard approaches are sufficient but certain areas require further emphasis (28). They identified, as we have, two key challenges are creating research questions and defining comparators when tests are sequenced (29). They also highlighted the various technical challenges with translating analytic validity into clinical consequences and some of the implications of decision making from the use of economic evaluation.

Unlike our findings, others have questioned the overall value of current frameworks and suggesting they may represent barriers to uptake. Notably, the Personalized Medicine Coalition has asked for more "transparency and predictability" in evaluation and that "different approaches taken by the FDA and (Centers for Medicare and Medicaid Services) in their evaluation of the evidence to cover the cost of the test for patients pose significant challenges to bringing products to market" (30). Similar comments and proposals have arisen from the European Device Manufacturers Association; European Personalized Medicine Diagnostics Association and, in Canada, the Center of Excellence in Personalized Medicine. Issues such as the non-health related value of "knowing" have been used to highlight the limitations of economic evaluation (31;32). Additional information from personalized medicine interventions, it has been argued, may lead to improved social welfare from nonhealth decisions related to the interventions (33).

We believe our findings are generalizable to other jurisdictions that use HTA to inform decision making, particularly to publicly funded systems that use economic evaluation to aid resource allocation. This is because many jurisdictions have developed similar guidance for economic evaluation and HTA (1). However, even if current approaches to evaluation *are* adequate, policy makers in other jurisdictions still face challenges when applying the findings from economic evaluations—specifically when faced with decisions on how to fund new drugs that require companion nondrug technology (i.e., diagnostics). In Canada, this was observed when authorities responsible for approving reimbursement of a new and expensive drug (ivacaftor) in an out-patient setting were not responsible for reimbursement of the genetic test required for its indicated use. The lack of integrated HTA and reimbursement structures has been seen in other jurisdictions, notably Australia, which has attempted to merge separate processes for drug and non-drug technology decision making. Planning for the emergence of companion diagnostics required an inevitable coordination between Australia's Medicare Benefits Schedule and Pharmaceutical Benefits Scheme (34). Co-dependent and hybrid technologies have been granted a single access point to ensure vendors will be steered through to a decision in a timely manner (35). This, in turn, has required underlying coordination of its three HTA advisory committees and methods used for assessment, building on already-extensive guidance on restrictions and the use of diagnostics.

In a similar manner, the parallel evolution of drug and nondrug will require the parallel development of administrative datasets. One evaluation identified revealed significant limitations with the use of administrative data (36) and the need for laboratory records that are linked (or can be linked) to other sources of drug performance information. Personalized medicine also underscores the need for additional information, such as patient and physician responses to diagnosis, which are not readily available from clinical trials or administrative data sets. Trialists or those creating observational data sets should consider the value to payers of these factors when planning protocols.

A small but critically important field of research continues to highlight opportunities to identify and evaluate personalized medicine beyond a traditional companion diagnostic paradigm (37). Administrative data have the great potential to allow analyses of patterns of physician and patient response to treatment. However, administrative data may also be inadequate, missing important pieces of information critical for evaluation (38). Statistical methods can help identify factors that lead to patterns of improved response allowing for better individualized treatment with existing therapies (39). This new arm of inquiry suggests we can discover how to achieve improvements on an individual level without the need for developing a companion diagnostic test.

Our findings also highlight areas for future research. This includes empirical exploration of the issues identified by us and others to gauge the sensitivity of results to analytic judgments. It may also include the use of stronger consensus methods to identify issues or create methods manuals such as the UK Diagnostics Assessment Program manual (40). Further development of methods and the need for additional analysis may also have

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implications for reporting. Another possible avenue of research is to examine the adequacy of the recently published Consolidated Health Economic Evaluation Reporting Standards (CHEERS) for reporting evaluations of personalized medicine (41).

CONCLUDING REMARKS

We have described current issues facing analysts conducting economic evaluation to support decision making. The findings suggest there may be opportunities to improve current guidelines for economic evaluation of personalized medicine interventions in Canada. We believe the lessons learned here may also be helpful to addressing shortcoming in other jurisdictional guidelines.

Our findings suggest the economic evaluation of personalized medicine may be more complex, but may not require a new paradigm. Rather, existing approaches and tools used to support analyses can be improved to undertake more complex analyses required for diagnostics-based PM.

SUPPLEMENTARY MATERIAL

Supplementary File: http://dx.doi.org/10.1017/S0266462314000142

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CONFLICTS OF INTEREST

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