Personalized Medicine and Health Care Policy: From Science to Value

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Editor's Preface

Launched in 2009, GPS: *Where Genomics, Public Policy and Society Meet* is a series hosted by Genome Canada to facilitate a dialogue between federal policymakers and researchers exploring issues at the interface of genomics and its ethical, environmental, economic, legal and social aspects (or GE^{3}LS).

Overarching themes for the series and specific topics are selected on the basis of their importance and timeliness, as well as the "ripeness" of the underlying scholarship. Accordingly, the series focused on "Genetic information," whereas in year two, attention shifted to "Translational Genomics". Our third series, "The Innovation Continuum" broadens the discussion by casting the process of innovation in a broader societal context.

At the core of these exchanges is the development of policy briefs that explore options to balance the promotion of science and technology while respecting the many other considerations that affect the cultural, social, or economic well-being of our society.

Co-authors of the briefs are leaders in their field and are commissioned by Genome Canada to synthesize and translate current academic scholarship and policy documentation into a range of policy options. The briefs also benefit from valuable input provided by invited commentators and other experts who participate in GPS events. Briefs are not intended to reflect the authors' personal views, nor those of Genome Canada. Rather than advocating a unique recommendation, briefs attempt to establish a broader evidence base that can inform various policymaking needs at a time when emerging genomic technologies across the life sciences stand to have a profound impact on Canada.

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Executive Summary

This Policy Brief explores needed steps in research, development and regulation to facilitate the translation and adoption of high value personalized medicine in the Canadian health care system. It examines the basis of effective development and commercialization including coordination across science, industry and payer communities. All stakeholders will need to fully understand and identify the societal value associated with research and commercialization to make the most of investment in research and to realize the full potential of these interventions for patients, while ensuring they do not drive out existing high value health care activities. As researchers may not have clearly specified value targets from payers or have the capacity to link to those who understand payer need, there may be inherent inefficiencies in approaches to the financing of and conduct of translational research.

Our specific recommendations offered with implications to both science policy and universities include 1) insisting that health system payers clearly define what constitutes value; 2) exploring options to more clearly align evidentiary requirements and processes between regulators and health technology assessment bodies that support payers; and 3) increasing strategic focus in applied and technology-oriented basic research that includes emphasizing the need and alignment of experts in HTA, decision-making and economic evaluation in all applied health research activities.

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I. Context

Over the last three decades, governments in Canada and elsewhere, have invested many billions of dollars in basic bioscience research with the explicit intention of developing technologies that would transform the face of medical care; investments in the bio-economy are intended to improve health care outcomes and efficiency while at the same time generating substantial economic growth through the sale and licensing of the intellectual property and technologies to health care systems (Industry Canada 2007).

While the last decade has seen some innovative health technologies based upon these strategic investments, there is a strong perception that the volume of technologies delivered is small in relation to the initial investment and the return on investment in terms of improved health outcomes and efficiency have not been delivered (Health Economics Research Group (Brunel University) 2008). The picture of the family doctor appointment of today, full of individualized genome-based tests and treatments, and as suggested by Francis Collins 20 years ago has not been realized (Gottesman and Collins 1994). There has been more recent attention by Federal research funders to examine how to better yield return on investments in research and challenging funded researchers to directly demonstrate improvements in patient and population health and wider socio-economic benefits (Lane and Bertuzzi 2011; Bisias, Lo, and Watkins 2012; Frank and Nason 2009).

Despite the increasingly challenging research funding environment and an even more challenging health care funding environment in many health care systems, there remains substantial enthusiasm for the idea of personalized medicine (Faulkner et al. 2012). Also called "precision" or "personalized healthcare" medicine, this concept has been driven by a confluence of academic, clinical and patient advocacy and commercial interests. Market analysts see the industry of personalized medicine as "poised for rapid growth" (McKinsey 2013). There are over 50 gene test-treat combinations intended to personalize drug therapy that are in clinical trial research and an estimated 30–40% of pipeline drugs have a companion genomic or proteomic marker (McKinsey 2013). Personalized medicine has also been promoted as a means to improve safety by predicting future adverse reactions to drugs (Samer et al. 2013).

However, it is increasingly clear that personalized medicine technologies will need to demonstrate that they deliver value compared to existing uses of limited health care resources, if they are to be adopted into routine clinical practice. Among first market entrants, some have demonstrated clear advantages and value to payers while others less so, leading to a wide range of uptake and payer decisions (Meckley and Neumann 2010).

In this paper we consider the concept of value in health care, as a necessary pre-requisite to exploring the challenges to the implementation of personalized medicine technologies; we then consider the challenges that personalized medicine technologies may present to conventional health care reimbursement appraisal frameworks and offer policy options for translation, regulation and reimbursement authorities to improve the identification, development and adoption of high value personalized medicine technologies.

The term 'personalized medicine' is used to refer to many activities and there are many competing definitions in the literature. In part this may be due to relevant stakeholders in genomics having "disparate professional interests, languages, and norms." (Health Canada and Canadian Institutes of Health Research 2012). Beyond information from genetic and molecular laboratory-based diagnostics, the term "personalized medicine" can also be used to refer to technologies that rely on any type of patient-specific information (e.g., derived from 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) (Health Canada and Canadian Institutes of Health Research 2012).

Despite these varied definitions, this report specifically addresses issues related to investments in genome-based applications in health. Therefore, for the purposes of this paper we are defining "personalized medicine interventions" as those that rely on molecular genetic, proteomic, or metabolic characteristics of an individual or condition to identify the most effective or efficient clinical management strategy, including prevention and diagnosis as well as curative, chronic and palliative care.

II. Issues

For policy makers, those PM technologies with large budgetary impact, questionable value, and poor mechanisms to manage uptake are of particular concern, regardless of their underlying mode of action. Health systems need to both signal what they value that PM technologies might provide and how much they are willing to pay. They must also have mechanisms to manage significant uncertainty surrounding technology value. Decisions regarding whether and how to invest in research require a clear definition of value and the methods to determine value (Ijzerman and Steuten 2011). These value definitions do not explicitly exist in Canada's PM testing reimbursement environment.

Historically, the implicit social contract with health technology developers has been that any technology, which meets regulatory standards, will be paid for if a physician chooses to prescribe it. However, this approach is increasingly recognized as financially unsustainable. Health systems now require evidence of value. However, translational researchers may mistakenly believe that passing regulatory requirements is consistent with demonstrating health system value. Providers of testing may also promote uptake based on technical assessments of accuracy and feasibility, rather than clinical consequences. If translational research investments are not guided by an understanding of value and hence health system uptake, the health and economic return on the investment is likely to be significantly less than presumed, representing a waste of both public and private resources (Kirisits and Redekop 2013).

A final issue is the appropriate balance of translational versus basic research funding in the realm of genome-based science. Funding for technology-oriented basic research and translational research should be based upon the likelihood that technology delivers 'value'. This needs to include appropriate assessments of return on investment that capture both the health system and the broader socio-economic policy payoffs associated with successful translation. It also requires researchers to adopt more strategic approaches to research and having adequate capacity on research teams as well as governance models that have an appropriate mix of expertise, including expertise regarding the values and priorities of health care systems.

III. Background

Driven by limited health care budgets and increasing demand for health care driven by aging populations and technological advances, health care systems have been adopted increasingly sophisticated processes for assessing the value of new technologies prior to deciding whether and how much to pay for them (Henshall and Schuller 2013). The use of value-based pricing for new pharmaceuticals in Germany, Sweden and shortly the United Kingdom (Husereau and Cameron 2011; Husereau and Jacobs 2013), as well as the use of cost-effectiveness analysis as a decision criterion by health care systems in North America, Europe and Australia, all reflect the principle that the price paid for new technologies should reflect their value (Eldessouki and Dix Smith 2012).

A pre-requisite for the effective implementation of these processes is clarity regarding the definition of value that reimbursement authorities would use for the assessment. Value is technically defined as what consumers individually would be willing to give up for an additional good or service and under certain conditions. It is a measure of lost opportunity from use of resources. Strictly applying this definition in healthcare is complicated for various reasons and has resulted in a substantial literature around the definition and measurement of value for health care reimbursement (Henshall and Schuller 2013).

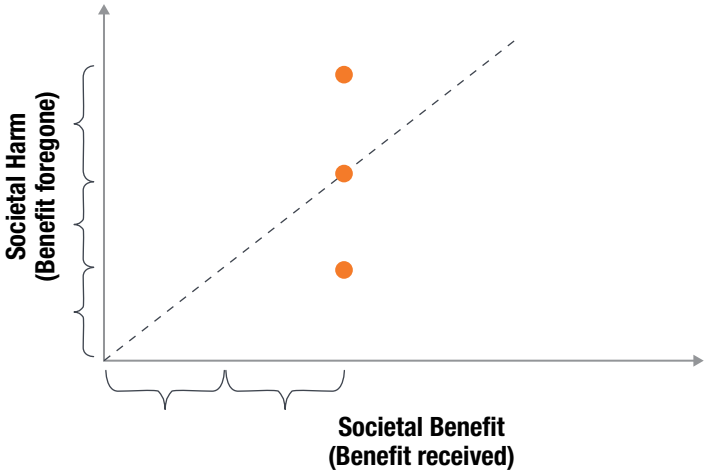
Broadly there are two schools of thought on defining value in health. The first is broadly consistent with the welfarist school of economics and proposes that the value of health care used by decision makers should reflect individuals' willingness to pay for it. An alternative approach – sometimes referred to as the extra-welfarist framework, argues that the value of a health technology should be consistent with the policy objectives of the health care system. It relies on societal, rather than individual preferences for health system-relevant goals, such as states of health (Coast, Smith, and Lorgelly 2008; Brouwer et al. 2008).

The legitimacy of extra-welfarist approaches rests on two observations: (1) health care is normally funded through pooling of financial risk and individuals typically do not bear the direct cost of the reimbursement decisions. Rather, the cost of a particular reimbursement decision is expressed through its impact upon the portfolio of treatments available to the population whose health care is funded through pooled resources; and (2) The size of the financial pool made

available to fund health care provision provides an *observed* value of health care, that has a more obvious legitimacy than the *stated* value of health care that the proponents of the welfarist approach offer decision makers. This is also predicated on the notion that individuals are typically *willing* to pay more from pooled resources than what is actually available (Hardin 1968).[1] There may also be variation in individual preferences that would lead to a potentially unfair use of resources (Brouwer et al. 2008).

The extra-welfarist approach underpins the use of economic evaluation and a cost-effectiveness threshold used by many health systems (Eldessouki and Dix Smith 2012). Conceptually, this is consistent with the notion that the value of any commodity can be identified by observing what will be given up in order to obtain the commodity. The cost-effectiveness threshold is the value (cost per unit of benefit produced) of the least valuable health care activity currently funded from the health care budget (McCabe, Claxton, and Culyer 2008). If a new technology produces more valuable effects than the technology(ies) that have to be displaced to pay for it, then paying for it will increase the total value produced by the health care budget. If the effects of a new technology are less valuable than the technologies that must be displaced to pay for it, then the opposite occurs and implies it should not be paid for. (See Figure 1)

Figure 1: Opportunity costs in population decisions for health



Each circle represents an average of decisions based on a population. In population-based decisions, benefit is a result of health outcomes from dedicating resources to a new intervention and harm is health foregone from using resources from somewhere else within the health system. Decisions on the line produce as much benefit as they displace from use of scarce resources.

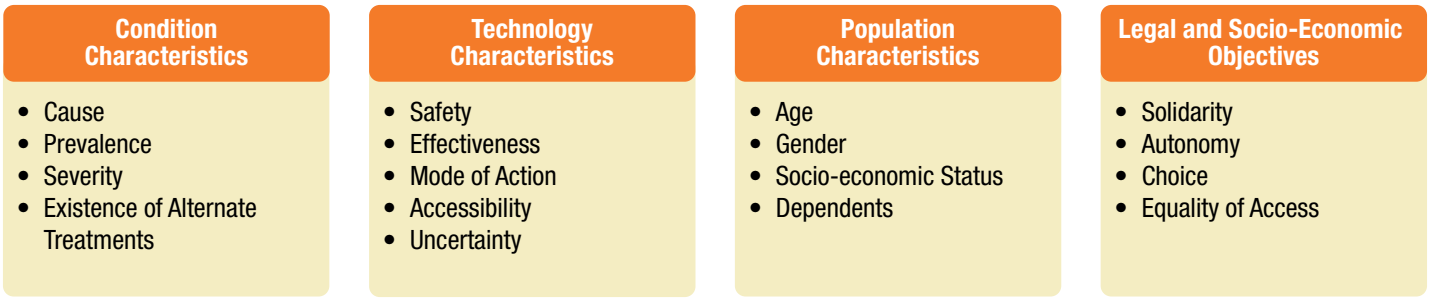
In its simplest form, the effects of health care valued by health care decision makers are assumed to be health-related – these can be captured through single measures such as quality-adjusted life-years, or QALYS, (Sugden and Williams 1978), and less often disability-adjusted life-years ("WHO | Metrics: Disability-Adjusted Life Year (DALY)" 2013), or other measures that capture duration of life and health-related quality of life. However, commentators have increasingly observed that health care systems have many objectives other than the production of health and measures of value should reflect these (Henshall and Schuller 2013; Hausman 2010). Some of these other value propositions are actually embedded in the legal frameworks of health care systems – such as portability and equality of access independent of the ability to pay. Others have been identified through precedent – e.g. the rule of rescue (Jonsen 1986; Cookson, McCabe, and Tsuchiya 2008); through broader public policy development – e.g. the value of innovation (Goldman et al. 2010); and priority funding of specific programs such as children's hospitals, cancer and HIV. There is also substantial evidence that health system decision makers attach higher values to technologies for unmet needs or severe conditions (Dolan et al. 2005).

While the evidence base is most robust for the value that people attach to the health impact of health care, there is an increasing literature on these broader sources of value in health care (Sussex, Towse, and Devlin 2013; Henshall and Schuller 2013, Brazier et al, 2013). A framework for defining factors that may influence value in health care is emerging; consisting of four categories: (1) the characteristic of the health care technology including its safety, effectiveness, mode of administration, the existence of equivalent technologies and the evidence for each of these; (2) the characteristics of the condition treated including natural history, prognosis, severity prevalence; and the portfolio of current therapies (3) the characteristics of the individuals/population affected by the condition including age, gender and socio-economic conditions; and (4) legal duties and social policy objectives including inter alia improved labour force participation, economic growth and reduced socio-economic inequality (Menon, McCabe, and Stafinski 2011). (See Figure 2)

Building on this more comprehensive characterization of the value of health care; researchers, decision makers and other stakeholders in the technology translation and adoption process are increasingly interested in approaches to combining these varied sources of value (Dowie 2013; Goetghebeur et al. 2011). Multi-criteria decision analysis (MCDA) has emerged as one proposed vehicle

[1] As Bob Evans observed: "the economic value of anything is defined in terms of what some individual or group is willing to give up in return for it. In a competitive market, under various stringent conditions on demand and supply, this value will tend to be equated with cost of production, i.e., what must be given up to produce the commodity. But there is no competitive or any other production of lives, independent of the people concerned. My life is unique, no other lives compensate me for the loss of it." (Evans 1984)

Figure 2: Social values in health technology assessment



for describing and quantifying the value of new health technologies (Devlin and Sussex 2011; Thokala and Duenas 2012). Concerns about the misapplication and feasibility of MCDA-based value assessments have been raised (Thokala and Duenas 2012). For example, some proponents have suggested counting health system or supply chain efficiency gains as benefits rather than costs, (Henshall and Schuller 2013) introducing an important risk of double-counting for technology evaluation. There are also other potentially legitimate benefits that are not conventionally considered including the impact of technology and the legal consequences of widespread use and adoption.

Whatever the framework for characterizing the value of a new technology, health care reimbursement authorities increasingly recognize that it must be applied equally to the new technologies and to the technologies that are likely to be displaced (McCabe, Claxton, and Culyer 2008; NICE Decision Support Unit and Devlin 2011; Claxton and Culyer 2006).

The extent to which PM technologies will be differentiated from existing health care technologies or more conventional new technologies will likely be technology specific (Meckley and Neumann 2010). There are a few potential sources of value on which PM technologies are expected to do well – including safety, existence of equivalent treatments, effectiveness and broader socio-economic benefits. However, PM technologies are by their very nature new and underpinned by limited and uncertain evidence compared to established technologies. To understand the reimbursement challenge facing PM technologies; it is necessary to consider the nature of health technology assessment (HTA). HTA is the process of examining the incremental value of a new technology to support health care decision making. It is also necessary to understand the type of evidence on PM technologies that HTA processes will require. There are also challenges for HTA organizations in appraising the evidence for performance, effectiveness and safety of PM technologies that is likely to be available at the time of market access.

Health Technology Assessment and Personalized Medicine

Health technology assessment is focused on informing a decision; whether a new technology should be added to the portfolio of treatments that is available from the health system the decision maker is responsible for. Health technology assessment is not hypothesis testing – rather, it is a multidisciplinary form of policy analysis that provides a framework for assembling knowledge and values from different sources (Banta 2009). Hence, the way HTA deals with uncertainty is a departure from the standard hypothesis testing and p-value oriented approaches which basic, translational and clinical scientists are most familiar with. Ultimately, HTA seeks to best support decision making and is guided by expectation given current data rather than significance testing (Dowie 2004; Claxton 1999).

In order to arrive at an expectation of whether a new technology will produce more health-related value for the health care system than is displaced through its cost, the HTA process gathers evidence on the aetiology, epidemiology and burden of the condition to be treated; the technical characteristics of the new technology and the existing treatment it would replace as well as the evidence for its safety and effectiveness; the impact of these on the short, medium and long term health (including quality of life and life expectancy) of patients; the impact of the technology on the organization of health services and clinical practice and health system resource use for the management of affected patients, utilization of non-health care services, and on reliance on family members and care providers.

These data can be formally synthesized through decision analytic models, which produce a quantified characterization of the expected health care system and broader societal costs and

health outcomes for the affected patients given current treatment strategies and assuming the new technology was adopted (Dowie 1996b). Such models provide an opportunity to examine relationships between various impacts of technology and in differing contexts, in turn allowing policy decisions to be more transparent, thereby improving legitimacy and accountability (Dowie 1996a; Dowie 1996b). These data are then used to assess whether additional costs of the new technology – which is actually other people's health care displaced – are justified by the additional value the new technology produces.

As well as the expected costs and health outcomes, a description of the uncertainty around the expectation will typically be provided – in Bayesian terms a statement of the credible range for the expected costs and outcomes with current technologies and the new technology. The same data can be used to characterize the risk that the decision indicated by the expectation of the incremental value of the new technology will prove to be wrong; i.e. the risk that the decision maker will reject a valuable technology or pay for one that is not valuable (Claxton et al. 2012; Claxton et al. 2005; McCabe et al. 2010).

The final component of the evidence base that HTA provides to decision makers focuses on additional issues of value that are not captured in the quantitative value information incorporated into the decision analytic model. This may include ethical considerations, such as issues of equity or notions of justice; psycho-social issues such as effects on doctor-patient relationships or individual stigma; legal implications of its use and issues of public policy such as fit with current legislation or unmet needs. There may be different kinds of qualitative information on value that require consideration by different stakeholders attached to different aspects of the alternative technologies (Banta 2009).

HTA also uses deliberative approaches to determining value as a final aid to good decision-making (Culyer 2009; Culyer and Lomas 2006). This entails having representative stakeholders reflect on available evidence in a constructive and involved manner and is particularly helpful when there are multiple stakeholders with competing perspectives impacted by the adoption of new technology, coupled with uncertainties about social values, or issues of fairness and equity (See Box 1). In these circumstances it is important to differentiate the role of evidence assessor – the stakeholders who provide greater insight into the expected impact of the technology – and decision maker, who has responsibility for the budget and balancing the interests of identified and unidentified beneficiaries of the decision making process.

Box 1 : Deliberative Processes

Deliberative processes address the question of how to best combine key values, operational feasibility and stakeholder interests in health care decision making.

Definition

"A deliberative process entails the careful, deliberate consideration and discussion of the advantages and disadvantages of various options and an important element in this 'consideration and discussion' is the weighing up of the 'evidence'. Deliberative processes are mechanisms for both eliciting and combining evidence."

Why use them?

Since the evidence generated by technology producers will always be unclear, social engagement through deliberative mechanisms is a means to resolving ambiguity. A short list of situations where these might be most effective includes:

- evidence from more than one expert discipline is involved
- evidence from more than one profession is involved
- some stakeholders' interests are threatened by evidence
- there are technical disputes to resolve
- evidence is controversial, incomplete, lacking or not generalizeable
- there is substantial uncertainty about key values

Adapted from (Culyer 2009)

Health technology assessment in the Canadian context is further complicated by the federated nature of health care funding and provision. Although the Canada Health Act provides a legislative framework for provision of health services to Canadians, responsibility for specific funding decisions remain with provinces and are often made at regional and hospital levels (Busby, Blomqvist, and Husereau 2013). The impact of this phenomenon on the scope for inter-provincial co-ordination is further exacerbated by variation in drivers of health need, and the priorities of the provincial populations. In this context, binding funding recommendations through a Canadian process – such as those provided by NICE in England and HAS in France, are not as practicable. Each health care reimbursement authority will operate a different formal or implicit value threshold. In most cases, formal HTA processes do not exist for new diagnostic and device technology. This potentially increases the chance of politicizing decisions or failing to consider cost offsets beyond individual silo budgets. (Busby, Blomqvist, and Husereau 2013).

The decentralized nature of Canadian reimbursement decisions is not an insurmountable obstacle to using a centralized Canadian HTA processes. Analytical strategies, such as sensitivity analyses to test the impact of using different willingness to pay thresholds can allow decision makers to tailor analyses findings to their specific decision problem; the use of jurisdictional deliberative processes can then ensure that differences in values and priorities are taken into account. The need for a pan-Canadian process for evaluating personalized medicine diagnostics has recently been identified by Canadian laboratory leaders (Butts et al. 2013). A national HTA process has the potential to promote consistency and transparency in health care funding decisions by providing unified methods and analytical inputs.

Even if the use and application of HTA in diagnostics-based PM were to become widespread, there are several unique challenges that will need to be addressed. We consider these challenges below:

Evidentiary challenges

Regulatory requirements for new diagnostic tests typically require information establishing technical characteristics (e.g., analytic specificity, precision, limit of detection) and do not require proof of clinical validity (i.e., that the test provides information that would consistently change clinical decisions) or clinical utility (i.e., that the test provides information that changes clinical outcomes). The relationship between technical information and the value of a test is complex and relies on the combining of the test with information on the clinical decisions that will flow from alternative test results and how they impact on subsequent health care costs and outcomes. It also requires some notion of how patients and physicians will respond to receiving test results in practice – which may be difficult to predict for newly developed tests. If this information is lacking, there will be much greater uncertainty about the test's value.

Indeed the optimum test cut-off to maximize value is likely to be different from the one chosen to optimize clinical utility, as the value pay-off from false positive and false negative results are unlikely to be symmetrical. Decision makers will require access to test's receiver operating characteristics (ROC) data to identify the most valuable cut-off, given the willingness to pay. Rather than deciding whether to reimburse a test technology at a fixed test cut-off; decision makers may wish to identify the cut-off at which the technology represents good value, given their budget and value framework (Longo et al. 2013; Sutton et al. 2008). Developers of tests may not expect or be prepared to provide this type of information to health care systems and providers of testing services (Garfield 2013).

A further complication for PM tests is the nature of the tests. The majority of the tests are unlikely to be measures of a single biological readout; rather they will be test scores produced from a statistical risk model linking multiple biological readouts with the probability of observing the event of interest. To a degree, for these types of test, the process is the product and expertise on the assessment of the laboratory testing processes rests with professionals not typically engaged in the health technology assessment process. Similarly, the statistical expertise for assessing the generalizability of risk scores estimated on one population to other populations is different from the trial design expertise that HTA conventionally draws upon. Hence a further widening of the professional network supporting HTA processes will be required.

In principle, regulators such as Health Canada, the FDA and EMA could direct developers of PM technologies to produce this type of information to facilitate a more effective and efficient reimbursement process at the end of the technology translation process. However, despite some recent collaboration between regulators and HTA bodies, these have largely been focused on drugs (Tsoi et al. 2013). Current indications from regulatory organizations indicate that they plan to focus on the technical aspects of tests, and in the context of companion technologies – undertake separate evaluations of the tests and treatments prior to arriving at a licensing decision for the combination (MaRS Discovery District 2010; US Department of Health and Human Services 2013). If this remains the case, the evidence base mandated by regulatory processes for PM technologies will be of limited utility to reimbursement decision makers (Faulkner et al. 2012).

Analytic Challenges

Even if appropriate evidence (e.g., ROC, clinical validity and utility) were provided, there may still be considerable analytic challenges for HTA bodies. For example, there may be numerous clinical pathways that either exist or could exist from the use of multiple tests making it difficult to characterize the appropriate questions and decision alternatives. A recent evaluation of a gene recurrence score assay enumerated 1,000 potential clinical strategies from 24 clinical testing pathways and12 unique risk categories based on two tests with two chemotherapeutic regimens (Paulden et al. 2011).

There may also be considerable challenges for HTA processes as they move from providing population-based assessments to those based on PM. The public has traditionally been used to value the relative importance of various states of health based on population averages, as they are the source of funding for health systems. However PM interventions stratify and may even individualize care,

and it is possible that population-based valuations from the public will sharply contrast with the preferences of those who are actually eligible for personalized treatment. It is likely that deliberative processes will ensure such differences are brought to bear on reimbursement decisions. However, the role of values in PM is more complex. PM will reduce access for some patients to the latest treatments, rarely on the basis that the patients would gain no benefit from treatment but rather that the magnitude of benefit would be substantially less for any given test result. Countervailing value propositions – such as greater safety and effectiveness versus solidarity, are likely to be important considerations more frequently in the assessment of PM technologies than for conventional treatments. Further, the nature of the PM technology decision will bring the issue of balancing the interests of identified and unidentified beneficiaries of the health care system into even greater focus (Grosse, Wordsworth, and Payne 2008; Conti et al. 2010).

Additionally, it may be difficult for HTA bodies to characterize uncertainty given the complex characteristics of PM interventions. This in turn will create considerable challenges in analyzing the potential for lost opportunity from making incorrect decisions (Claxton et al. 2005).

Establishing and projecting costs from testing with certainty may also be a challenge. Cost calculations in economic evaluation require total average costs (including capital and allocated overhead costs) derived from resources consumed and unit cost measures based on economic (opportunity) costs (Conti et al. 2010). Depending upon the testing model adopted – locally provided quality assured laboratory test services vs. centralized laboratory testing or off-the-shelf testing kits, the costs of PM will vary, reflecting economies of scale. In Canada, these costs may have a wide range due to differences in population density and geography. High throughput systems may exist and lower per-test costs, while labs without these systems will have higher costs. Whilst these are primarily operational challenges, their potential impact on the assessed cost effectiveness will affect the portability of evaluations between health systems – an issue of particular importance in the Canadian context.

Finally, deliberative processes in HTA will require a much wider pool of experts than are traditionally used for drug and device recommendations. These include laboratory clinical scientists and medical directors; genetic testing experts; ethics experts; providers ordering tests; biostatisticians with expertise in case-mix algorithms, patients and others. The broadened perspective will require increased time and resources to have groups effectively work together and understand the values, perspectives and expertise that each brings to the decision making process.

IV. Policy Options

Option 1: Define a Value Target

Explicitly defining what sources of value are important for funding and reimbursement gives translational researchers a specific target regarding what inventions are likely to enjoy uptake. It stimulates real innovation by allowing private and public sector funders of research to have clear information to guide decisions intended to maximize the return on investment of their research portfolios. This may be as simple as declaring a cost-effectiveness threshold or could be more sophisticated and attempt to incorporate multiple dimensions of social value.

This may present a challenge, as policymakers in Canada have traditionally been reluctant to define what is valuable in health technology adoption decisions. This may be due to the decentralized nature of Canada's health system or concerns about committing to a single value over multiple political cycles. There is some evidence based on adoption decisions and recommendations made on behalf of provinces in public funding of outpatient drugs that there is a tipping point – where a drug is considered too costly to reimburse (Clement et al. 2009; Rocchi et al. 2008; Rocchi et al. 2012). Detractors of this approach suggest it may provide incentives for price fixing – where the prices of new technologies are artificially inflated based on the maximum a decision maker is willing to pay rather than prices that more strongly consider competition with other technologies and marginal costs of production. However, these criticisms conflate the production cost and reimbursement decision in a manner that is inconsistent with the objective of the reimbursement decision.

In addition, pricing to the threshold increases the risk that the optimum reimbursement decision will require access-with-evidence schemes. This is because the value of further research increases as the expected incremental cost effectiveness ratio (ICER) approaches the maximum willingness to pay for health. The closer the expected ICER gets to this maximum the more likely it is that additional information could change the decision. Hence, the presumption that manufacturers will price to the threshold is dependent assuming decision makers will not choose to require more research rather than reimburse the technology. Evidence development schemes impose significant commercial costs on the manufacturer through constrained market access over an extended portion of the patent life. Further, Claxton and colleagues have demonstrated how a threshold-based price can be fixed to ensure a pricing mechanism that does not transfer all the value of the new technology to the manufacturer (Claxton 2007).

If a government-sanctioned target cannot be defined, a value target can still theoretically be determined through study of societal value and using social science approaches. Ultimately, policymakers in a liberal democracy are making decisions on behalf of society who elected them to represent their interests. There have been some recent efforts to study societal preferences for health and broader sources of value in Canada (Skedgel, Wailoo, and Akehurst 2013; Health Council of Canada 2013). However, further work in this area will likely be required if it is to be sufficient evidence to support decisions leading to differential access to PM and conventional technologies.

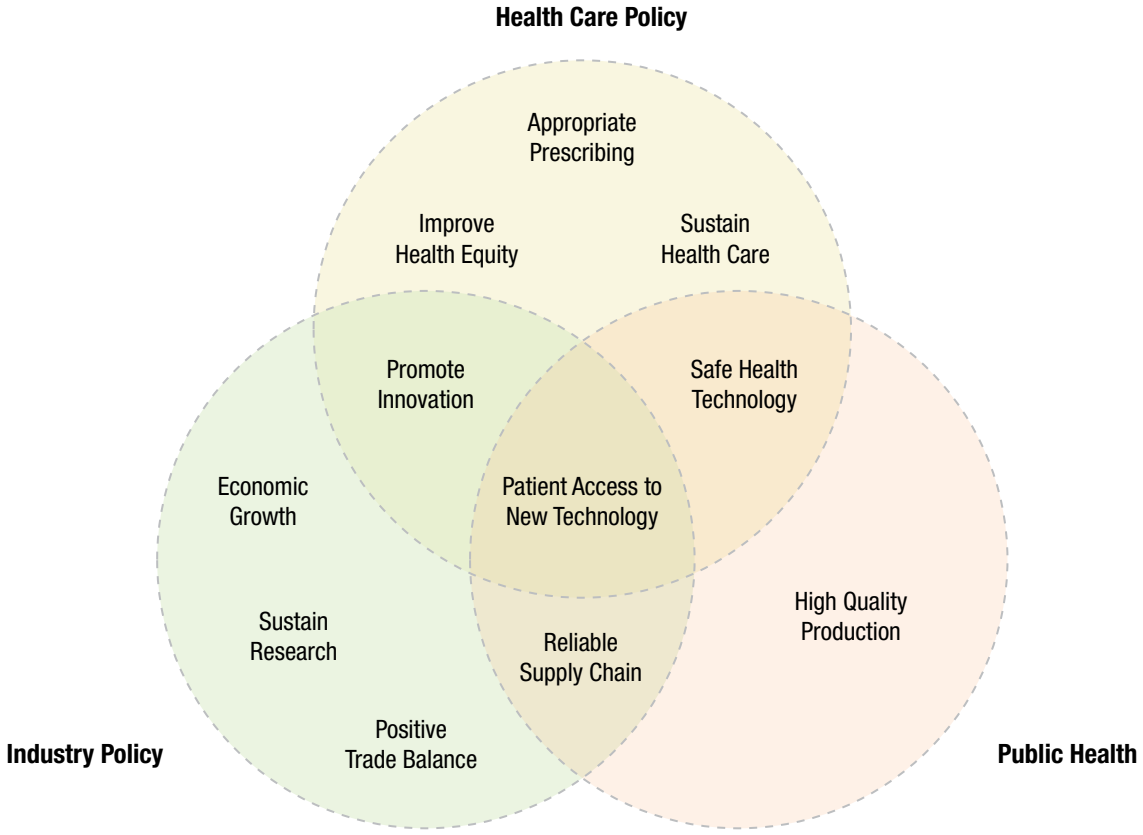
Setting a value target may also provide opportunities to align health system, industry and regulatory policy goals (Busby, Blomqvist, and Husereau 2013) which are often perceived as working independently and at times at odds with each other in regards to health technology (Figure 2). All have a common goal of providing patients access to valuable technologies and using science-based information as a means to making best decisions.

Option 2: Align Regulatory and HTA Requirements

There has been increasing recognition of some of the overlapping roles in regards to regulation and HTA. This has led to numerous documented interactions between HTA bodies and regulators ranging from enhanced communication and information sharing to proposals for aligning evidentiary requirements and processes of assessment (Tsoi et al. 2013).

Proponents of enhancing interactions between regulators and HTA bodies argue that it may accelerate patient access to new technologies, promote economic growth through minimizing the administrative burden of commercializing inventions, provide clear signals and reduce development costs for innovators, and ultimately improve system efficiencies.

Figure 3: Health technology policy goals



Health care policy can be supported by HTA bodies, while public health and industry policy (to a lesser extent) are supported by regulatory processes. Adapted from (Altenstetter and Permanand 2007)

However, there have also been some arguments suggesting these functions should remain separate. Given the conceptual model of value based reimbursement decision making, the differences in the budgets being allocated, the portfolio of therapies provided and the needs of the population served; the adoption of a single reimbursement process and decision for multiple health systems would not be appropriate. An additional challenge will be the feasibility of an integrated approach, which will require additional resources, enhanced coordination and interaction across HTA, payer, provider regulator and industry groups (Henshall et al. 2011).

Although many technology-based markets have some amount of regulation, most separate regulator and payer functions to allow prices and functions of products to be determined through competition. There may be considerable post-market learning to inform a revised, upwards or downwards, assessment of a product's value. A combined HTA-regulatory function could stifle this important mechanism for developing the evidence base for innovative technologies. It may also stifle prospects for off-label prescription leading to the identification of a new high value application of the new technology. This approach may not be compatible with the ongoing prospects for innovation through non-commercial and hospital-based clinical research that are common in PM.

Option 3: Emphasize distinctions between discovery and applied research activities

Life-science research has been a cornerstone of Western science policy since the beginning of the previous century. The end of the Second World War introduced a belief that the public sector would be required to support research that would provide numerous benefits to society and if left to the private sector alone would result in a market failure (Nelson 1959; Arrow 1962). Surrounding these research activities were a realization of the different intentions of research; subsequently 'basic' and 'applied' research were defined and led to numerous schemes for setting priorities of these different types of government-funded research.

During the Cold War era of scientific research funding, there was increasing recognition that the output of research may not always have positive consequences for society. Technology was increasingly recognized as something that may have large positive and negative impacts. Subsequently, the US Technology Assessment Act was passed in 1972 and led to the subsequent establishment of the United States Office of Technology Assessment (OTA) (Coates 1977). The remit of the OTA was to synthesize available evidence on new technology to inform technology polices.

There was also recognition that technology with positive societal benefits could be a vehicle for economic competitiveness and attempts to make science more oriented to technology development and accountable and responsive to the needs of society were re-introduced. For example, Great Britain, in 1971, began implementing recommendations outlined in a report prepared by Lord Victor Rothschild renouncing the selection of scientific priorities independent of government in applied research (Rothschild 1971).

Along with shift in attitude toward the intent of scientific research have been shifts in approaches to funding basic and applied research. In an era where economic competitiveness from technologically-oriented is sought, distinctions between *pure* basic research, not intended to have economic or social benefits, versus technology-oriented basic research have been made (OECD). Basic researchers in health now discover genes for diseases which are heralded in popular media as equivalent to cure (Sugawara, Narimatsu, and Fukao 2012). In some cases, these investigations have realized returns, but more often these discoveries will have no consequence. With a growing number of genome-wide association studies, and with their inherent uncertainty in prediction, one scholar famously concluded that most published research studies in the post-genome era are false (Ioannidis 2005).

The currently stated goals and missions of federal funding agencies confirm the emphasis on technology development and economic gains through research (See Box 2). This limits incentives for pure basic research in the realm of genomic and molecular science. Further, it may encourage basic science researchers to justify investments on the basis of highly uncertain future applications, which will only exacerbate the current perception of an inadequate return on investment. In addition, an excessive focus on applied research may reduce the number of chance discoveries required for disruptive innovation or incent researchers interested in pure basic research to speculate on its application.

These observations are not intended to discount the intent of translational and applied research and its value. Rather, we would suggest a stronger strategic differentiation between applied/translational/technology-oriented basic and pure basic science funding; freeing basic science researchers from the pursuit of barely attainable and largely inappropriate deliverables of showing value. Good funding strategies also require enhanced capacity building and awareness for researchers interested in truly translational and applied research, including how to understand, measure and realize social value. It would also require other mechanisms to accelerate excellence in understanding of what social and economic benefits can be realized from research. This model would emphasize the need and alignment of experts in HTA, decision-making and economic evaluation in all applied health research activities.

Box 2: Current Stated Goals and Objectives of Research Funding Bodies

CANADIAN INSTITUTES OF HEALTH RESEARCH

Goals

1. Invest in World-Class Research
    1. Train, retain and sustain outstanding health researchers
    2. Select and sustain research excellence
    3. Promote interdisciplinary and international innovation
2. Address Health and Health System Research Priorities
    1. Improve focus, coherence and impact from CIHR's strategic investments
    2. Build strategies and initiatives that address health and health system priorities
3. Accelerate the Capture of Health and Economic Benefits of Health Research
    1. Reap the socioeconomic benefits from research through KT and partnerships
    2. Enhance the application of research and its evaluation
4. Achieve Organizational Excellence, Foster Ethics and Demonstrate Impact
    1. Advance organizational excellence and ensure transparency and accountability
    2. Evaluate the overall success of CIHR
    3. Foster a culture of ethical research by promoting and assisting the discussion and application of ethical principles to health research
    4. Assess progress and impact by demonstrating the impacts of CIHR investments

NATIONAL RESEARCH COUNCIL GENOMICS R&D INITIATIVE

Research-related goals

1. Demonstration of Efficiency and Economy
2. Alignment with Government Priorities
3. Alignment with Federal Roles and Responsibilities

NATURAL SCIENCES AND ENGINEERING RESEARCH COUNCIL

1. Advancing Knowledge, Seizing Opportunities

    Fuel the advancement of knowledge in science and engineering and ensure that Canadian scientists and engineers are leaders and key players in a global knowledge community.
2. Building Prosperity Through Research

    Connect and apply the strength of the academic research system to addressing the opportunities and challenges of building prosperity for Canada.
3. Inspiring the Next Generation

    Ensure that Canadian youth are exposed to activities that capture their imagination and generate curiosity and excitement about science, mathematics and technology.
4. Showing the Value of R&D Investments

    Demonstrate NSERC's accountability and how the results of its investments in Canadian research and training benefit Canadians.
5. Increasing Visibility of Research

    Celebrate the accomplishments of Canadian natural sciences and engineering researchers and institutions, and increase their visibility in Canada and worldwide.

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