INSTITUTE OF HEALTH ECONOMICS
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Summary Report of Session A1: Research Challenge – Health Economics Methodology:

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CONTENTS

INTRODUCTION AND BACKGROUND

The IHE has established a series of methodologic forums with the intent identifying and addressing major methodological challenges in informing policies and decisions around the funding and use of health technologies, in partnership with its private and public stakeholders that are involved in the production of evidence and use of assessment.

Health economic evaluation is used to examine the cost and consequences of health interventions or programs. Economic evaluation is increasingly used to inform decision processes as a policy tool to inform health policy including reimbursement decisions. The concept of "personalised medicine" in health is garnering increased attention. Personalised medicine can be defined as the tailoring of preventive, diagnostic, or therapeutic interventions to the characteristics of an individual or population. This may involve genetic or laboratory biomarker information. The increasing and importance of economic evaluation in informing reimbursement decisions raises questions as to whether existing approaches need to be improved or changed to accommodate the evaluation of personalized interventions.

Standards for the conduct of economic evaluation have already been developed, but increased attention toward personalized medicine interventions may create new challenges for those tasked with evaluating the economic impact of introducing personalized medicine interventions. It is important that standards for evaluation are consistently applied, in order to inform decision making in a consistent manner, and achieve fair and equitable access to health technologies. The purpose of this session was to discuss challenges that may arise when evaluating personalised medicine interventions and propose strategies to overcome some specific examples. An outline of the session is in the Appendix.

SESSION OBJECTIVES

The specific objectives of this concurrent session/workshop are to:

1. **Explore** issues relevant to economic evaluation of personalized medicine
2. **Present research** in the form of case examples and from those who have evaluated personalized medicine interventions.
2. **Discuss** the **strengths and limitations** of proposed methods options and their implementation.

PART 1: CONTEXT

Dr. Anirban Basu, Associate Professor in the Department of Health Services at the School of Public Health at the University of Washington provided an overview of personalised medicine from a health economics perspective.

He began the session reminding us that identifying individuals who may benefit more or less than the average population benefit is strongly grounded in economics. He then discussed how using a local instrumental variables approach (pioneered by Heckman) could serve to help us identify individuals who might benefit more or less due to processes of natural selection among physicians and patients. Rather than wait for a personalised intervention to be developed and then evaluate it (a process he called *active* personalization), econometric methods allow us to study existing factors that lead to better health outcomes and use this to improve the delivery of care (a process he called *passive* personalization).

Dr. Basu concluded by reminding us that personalisation already happens in practice to some extent and quantifying the effect of such passive personalisation is important for the economic evaluation of existing treatments. Such analyses can also help quantify the Expected Value of Individualized Care (EVIC) based on current knowledge in practice. They can also help ascertain the increment value of any new active personalization agenda.[1]

Mr. Don Husereau, Adjunct Professor in the Faculty of Medicine at the University of Ottawa then presented the findings of an informal survey and literature review, which attempted to identify potential issues in the evaluation of personalised medicine. After consulting National and International Experts[2], and using the framework of National standards for the economic evaluation of health technologies[3], several issues were highlighted. Notably, the main challenges identified were: 1) how comparisons of interventions should be framed and what accompanying question should be asked; 2) how effectiveness might be properly estimated if adherence to personalised medicine regimes is suboptimal and when information that allows us to estimate patient and physician behaviour is lacking; 3) how outcomes and costs might be appropriately valued; and 4) how to incorporate potential benefits that exist outside of an economic framework. The second and third parts of the session focused on challenges 1) and 2) above. The findings of the study are presented in Table 1 (below)

PART 2: SPECIFIC CHALLENGE IN ECONOMIC EVALUATION - HOW TO ESTIMATE PHYSICIAN/PATIENT RESPONSES TO PERSONAL INFORMATION?

[1] See for example, Anirban Basu et al., "Use of instrumental variables in the presence of heterogeneity and self-selection: an application to treatments of breast cancer patients," *Health Economics* 16, no. 11 (November 1, 2007): 1133-1157.

[2] Those surveyed included the discussant panel (Jeffrey Hoch, Adrian Levy, Deborah Marshall, Stuart Peacock) and presenters (Malek Bassam, Natasha Leighl, Michael Paulden, Robyn Ward) as well as National (Douglas Coyle, Gregory Zaric) and International (Anirban Basu, Scott Grosse, Uwe Siebert) experts.

[3] Canadian Agency for Drugs and Technologies in Health, *Guidelines for the Economic Evaluation of Health Technologies: Canada* (Canadian Agency for Drugs and Technologies in Health, 2006).

Economic evaluation must anticipate real-world effectiveness given current data. In the realm of personalized medicine, this requires establishing appropriate links between establishing links between the use of a test, patient management, and outcomes. One notable example is the use of pharmacogenomic and thiopurine S-methyltransferase (TMPT) testing for patients taking 6-

Table 1 Specific Issues in the Economic Evaluation of Personalized Medicine based on Canadian Guidelines for Evaluation

Canadian Guideline Item	Description	Specific Issues in Evaluation of Personalized Medicine?
Study Question	State the decision problem oriented to target audience in answerable form with interventions and populations stated.	Personalized medicine may lead to highly variable framing of questions because decision makers may only be responsible for one part of reimbursement (e.g., a drug rather than a test and drug), clinical treatment pathways may differ or be in development, and access to non-personalized options may or may not already exist. Some PMs also have application in multiple therapeutic areas (e.g. interventions that target a generic immune system pathway); reimbursement may be given for one therapeutic use where drug is cost-effective, but not another (see Comparators) Personalized interventions in drug therapy may also be at odds with current trends in Canadian drug reimbursement policy; promoting access to care and moving away from limited use policies. Given future interest in examining the impact of PM, analysts should clearly identify evaluations of PM through the titles and questions of their research reports.
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.	No specific issues, however, conducting cost-utility analysis may lead to specific problems regarding how preferences for health states should and can be valued (see Valuing Outcomes)
Target Population	The target population for the intended use of the intervention should be stated	PM could create uncertainty about target population definition– creating new disease definitions/categories, fracturing the clinical definition. As with any intervention, it is likely that personalized medicine interventions will not be used as they were originally designed. However, the consequences of this phenomenon will be more difficult to evaluate-- Tests will be conducted in inappropriate populations *or* tests in appropriate populations that indicate treatment is unnecessary will still lead to treatment. There may be clinical disagreement on who should be tested or what personal information is needed to take further action. (see Variability and Uncertainty)
Comparators	Interventions and a reference case (the most common or frequently used care) must be chosen	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. Make clear whether 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) There will be difference between the ICER for joint strategy combining diagnostic and therapeutic procedures or for diagnostics or therapeutic separately
Perspective	In the Reference case, use the perspective of the publicly funded health system	No issues.
Effectiveness	Use a systematic review to estimate the magnitude	Appropriate data may be unavailable given current regulatory environment; for example, randomized

	of effectiveness and adjust for "real-world" factors	trials showing efficacy are not required for approval of companion diagnostics. Even with efficacy, demonstrating effectiveness is a challenge because of variable behavioral responses by physicians and patients to personal information and because population heterogeneity may limit the ability to extrapolate to responses across population groups. (i.e., compliance and adherence)
Time Horizon	Use a time horizon based on the natural course of the condition.	No issues.
Modeling	Explain how and why model assumptions occur and whether the model has been validated.	No issues.
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.	There may be underlying an important heterogeneity that sharply contrasts average population-based valuations of preferences with the preferences of those who are actually eligible for personalized treatment. (i.e., population heterogeneity may lead to preference heterogeneity) This difference may be meaningful from a decision standpoint. 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.
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).	Guidelines suggest using economic (opportunity) costs as the basis for valuing resources and in principle, using total average cost (including capital and allocated overhead costs) as the unit cost measure. Costs of tests may depend on number of tests performed and be difficult to value. The guidelines do not currently speak to how to value costs in cost-sharing arrangements between private sector producers and patients. In theory, companion diagnostics may be offered at "no cost" (although the cost is actually born by the third-party payer through the price paid).
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.	No issues.
Variability and Uncertainty	Explore the effects of uncertainty (differences in effects reducible by further information) and variability (differences not reducible by further information)	Personalized medicine is at its core an evaluation of variability.
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 PM interventions will have distributional consequences. People may want (and see no harm in wanting) access to a test intended for others. Knowledge of test results can be an issue, even for descendants of patients or others societally.
Generalizability	Justify the use of non-Canadian data and its economic impact in a Canadian setting	No issues. Although analysts must take into account prevalence of disease/genotype/test results can influence ICER.

mercaptopurine or allopurinol. These tests can help physicians optimize therapeutic response to treatment. Although dose adjustment is a relatively straightforward intervention, we lack information on how physicians alter their practice in response to the revised probabilities of poor outcomes given the results of these tests for individual patients. [4]

In the Canadian setting robust data from Canadian patients are likely not be available, and patient management may also vary across provider settings. Taken together, this highlights the need for innovative approaches to inform economic evaluation in decision making; this includes expert elicitation methods to populate models and address gaps, and an increased emphasis on parameter and structural sensitivity analysis to test key assumptions.

Dr. Natasha Leighl, a Medical Oncologist and Associate Professor in the Department of Medicine at the University of Toronto describes unique challenges in the evaluation of a personalized approach to cetuximab therapy for end-stage colorectal cancer. Patients are tested for a mutation in a specific gene (KRAS) because patients with the mutation will have worse outcomes than patients without the mutation. This, in turn, leads to more dollars spent to improve quality and quantity of life in these patients. In their evaluation of personalised medicine, data from the National Cancer Institute of Canada (a trial) was used to support the valuation of costs and health outcomes.

Dr. Leighl highlighted how little we know when it comes to patient and physician responses. She suggested analysts should consider 100% uptake of testing and treatment in the reference case and then vary these estimates according to expert opinion or indirect evidence. She cited an example of a survey that determined how likely a patient would be willing to take a test and how much they would be willing to pay for it. She highlighted that analysts should not be paralyzed by uncertainty – by working closely with care providers, using the best available information, and potentially limiting the scope of the question, they should be able to achieve a reasonable evaluation.

Malek Bassam Hannouf, PhD candidate from the Schulich School of Medicine and Dentistry at the University of Western Ontario, described the unique approach taken by he and his colleagues to assess the 21-gene recurrence score to guide adjuvant chemotherapy decision making in early stage breast cancer. In their evaluation, specific information required to model the disease and outcomes from using a personalised intervention were not available in the Canadian setting. He said the use of Canadian administrative data from the Province of Manitoba for modeling real-world current clinical practice was the only tool to predict the clinical and economic impact of the assay on current clinical practice. He highlighted that they couldn't be definitive in their results due to the uncertainty on patient and physician responses based on the assay in the Canadian setting. He said efforts to overcome these issues should focus on value of information analysis and coverage with evidence development when facing a promising personalized medicine technology with clinical uncertainty. At the same time, efforts should

[4] Conti R, Veenstra DL, Armstrong K, Lesko LJ, Grosse SD. Personalized Medicine and Genomics: Challenges and Opportunities in Assessing Effectiveness, Cost-Effectiveness, and Future Research Priorities. Medical Decision Making. 2010 Jan 4;30(3):328–40. ; Fargher EA, Tricker K, Newman W, et al. Current use of pharmacogenetic testing: a national survey of thiopurinemethyltrans-ferase testing prior to azathioprine prescription. J Clin Pharm Ther. 2007;32:187–95)

focus on improving information captured in the administrative data across provinces, specifically to monitor emerging personalized medicine technologies through the development of specific billing codes would be helpful in building a strong evidence base for examining these technologies in real-world Canadian setting and allowing for cross-regional comparisons.

In the discussion, panelists reflected on the historical difficulties of developing data standards that capture the use of technology. Although these administrative data would be useful to capture current value, there has been little coordination across provinces and technology-specific data available.

PART 3: HOW TO GET COMPARATORS RIGHT?

Economic evaluation is, by definition, oriented towards decision-making and reimbursement. Because of this, some personalised interventions like companion diagnostics (test and treat strategies) present considerable challenges since the decision maker may not have resources to fund both technologies. This makes comparison difficult since the real economic impact must consider a multitude of appropriate strategies, or strategies that require reimbursement outside of a payer's budget

Additionally, standard testing strategies may not always be available – strategies continue to evolve and multiple test and treat strategies might be available or under investigation. What clinical strategy you choose, how a comparative analysis is framed and what questions are asked may greatly affect estimates of cost-effectiveness.

Dr. Robyn Ward, Professor and Head of School of Prince of Wales Clinical School in Sydney, Australia, shared her experience and experiences from working on reimbursement policy in Australia with this particular issue. Dr. Ward reminded participants that not only are there multiple potential comparators, but the definition of these may change. For a diagnostic technology, there may or may not be a reference standard and this may or may not be well established. Even if a standard is available, the *effective* analytic validity, that is the accuracy and consistency of the test in the real world may be largely unknown.

She suggested focusing on those comparators that are most relevant to decision makers. She also suggested that both the personalized package and its component parts should be evaluated.

Mr. Mike Paulden, a research associate at the Toronto Health Economic Technology Assessment (THETA) Collaborative , then spoke about recent experience with evaluating the 21-gene recurrence assay for the treatment of early stage breast cancer. He highlighted the complication in testing this personalised intervention when other diagnostic strategies were also available. In his example, they identified 1000 unique clinical strategies for treatment but was able to narrow this to 8 strategies if tests and treatment were considered separately.

He suggested analysts should compare all plausible strategies and we should not over-simplify the set of strategies since potential economic gains may be missed. He also emphasized that in a world with multiple strategies, analysts will need to think about how to convey winning strategies in a meaningful way – ICER approaches and examinations of dominance become much less useful in a world with more

than 100 plausible strategies. Popular software may also be inadequate for dealing with this number of comparators.

Although both analysts proposed differing approaches (narrowing list of eligible comparators versus exploring larger number of comparators), there was no panel consensus on which of these approaches might be best.

OVERALL DISCUSSION AND FINDINGS

Discussants and session participants weighed in on issues. The following themes emerged from the discussion:

1. Personalised medicine further highlights the need for analyses outside of economic evaluation to support decision making. Patients may value being offered a test, or being given information for which there is no immediate clinical consequence, and offering tests and treating selected individuals will lead to distributional and equity concerns. None of these factors can be captured by economic evaluation and this highlights the importance for additional analysis and information to support decision making.

2. Better evidence is required to support decision making through economic evaluation. Personalised medicine underscores the need for additional information, such as patient and physician response to diagnosis, which is not readily available from clinical trials or administrative data sets. Increased uncertainty and using next-best information will lower the value of personalised interventions to payers. Evaluating real-world effectiveness of personalised medicine could be better accomplished through coverage with evidence development schemes, or through improving standards for data collection. The latter highlights an additional issue, *how can provincial data standards be better coordinated to meet the needs of those evaluating personalised medicine?*

3. There are opportunities to evaluate personalised medicine beyond new products. Administrative data provides opportunities to observe and analyse patterns of physician and patient response to treatment. Newer statistical methods can help identify factors that lead to patterns of improved response allowing for better individualized treatment with existing therapies. This highlights some additional issues – *are administrative data adequate* currently to conduct these analyses? Also, *who is responsible for making investments in better statistical and evaluative methods?*

4. The evaluation of personalised medicine requires standard approaches to comparison. Current Canadian guidelines for economic evaluation are inadequate for providing analysts with a consistent approach to comparison. This could lead to large variations in findings due to different approaches to framing. There was some consensus that focusing on both the 'packages' of personalised medicine and their individual components. However, how strategies should be best identified and how initial identification and stratification of populations prior to testing should be accounted for was less clear. Analysts must also recognize comparator definitions are in constant evolution and that reference standards for diagnostics may not always exist. How the strategy was developed will also give the analyst some insight into how likely it will change in the future.

5. Evaluation of personalised medicine may be more complex, but does not require a new paradigm for evaluation. Some existing approaches and tools used to support analyses, such as the use of incremental cost-effectiveness ratios, efficiency frontiers, and software intended for small numbers of treatment strategies, may be inadequate for the evaluation of more complex personalised medicine strategies. Compared to more straightforward health interventions, anticipating real-world effectiveness by adjusting for factors such as patient adherence will further increase the complexity of analyses. More time and resources may be required to conduct evaluations of personalised strategies versus evaluations of non-personalised interventions. However, a new approach to evaluation is not required.

APPENDIX – SESSION OUTLINE

Start	End	Activity	Lead
Opening			
13:30	13:35	Welcome and framing of the day, introduction to Guest Speaker and Panel Members (**Panel members:** Deborah Marshall, Jeffrey Hoch, Stuart Peacock, Adrian Levy)	John Sproule, IHE
13:35	13:50	Overview of economic evaluation and personalized medicine: Personalization & Economic evaluations	Guest Speaker: Anirban Basu
13:50	13:55	Canadian and International Experience	Don Husereau
13:55	14:20	Panel Discussion (15 min) and comments from from Group (10 min)	John Sproule

Example 1: How to Estimate Physician/Patient Responses to Personal Information?			
14:20	14:25	Introduction to topic	Moderator: Don Husereau
How should the analyst appropriately account for patient and physician responses to personal information? - What approaches are appropriate if no information is available? - Is assuming that everyone will respond in a manner that maximized patient outcomes realistic? - What data is appropriate for informing parameter estimates? - Is information from other jurisdictions generalizable?			
14:25	14:35	First Presentation	Natasha Leighl
14:35	14:45	Second Presentation	Malek Bassam

14:45	15:05	Panel Discussion (10 min) , Questions and Comments from Group (5 min) and Vote	Don Husereau

15:05	**15:10**	**Break**	

Example 2: How to Get Comparators Right?			
15:10	15:15	Introduction to topic	Moderator: Tammy Clifford
How should the analyst appropriately compare personalized medicine strategies? - What if the decision maker is responsible for only one aspect of reimbursing the PM intervention (e.g., a test, but not a drug or vice-versa?) - What if the test and treat sequence is ill-defined? - Is the right comparison a test versus no test? Access to a test versus no access? Access to both a test and treatment versus treatment alone?			
15:15	15:25	First Presentation	Robyn Ward
15:25	15:35	Second Presentation	Mike Paulden
15:35	15:50	Panel Discussion (10 min) , Questions and Comments from Group (5 min)	Tammy Clifford

Wrap Up			
15:50	15:55	Quick Summary Thoughts, Thanks and Next Steps	John Sproule

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