Economic Evaluation of a Point of Care Pharmacogenetic Test (CYP2C19) from an Ontario Perspective

by

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A thesis submitted in conformity with the requirements for the degree of Doctor of Philosophy
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Abstract
Background: Appropriate pharmacotherapy for patients with acute coronary syndrome depends on the functional capacity of their CYP2C19*2 allele. Patients with a fully functional allele could be treated with clopidogrel while prasugrel or ticagrelor could be prescribed to patients with a loss of function allele. Pharmacogenetic (PGx) testing could optimize pharmacotherapy (i.e. fewer adverse event rates with PGx option, where results are available in 1 hour) Purpose: To quantify net social benefit of implementing a PGx test in Ontario hospitals. Methods: A systematic review identified the evidence from full economic evaluations related to the CYP2C19*2 PGx test. An exploratory review highlighted the structure of published discrete choice experiments (DCEs) related to pharmaceutical therapeutics. Components used to quantify net social benefit were: patient preference expressed as willingness to pay, budget impact (BIA) analysis (aggregate Ontario hospitals, and Ontario Drug Formulary) and impact on productivity. Principles and good practice guidance as presented by the International Society for Pharmacoconomic and Outcome Research Task force were adhered to for the BIA. A web survey tool that included a DCE was developed to assess preferences for attributes (levels) of a PGx test (i.e. mode of sample collection (cheek swab, blood, or finger prick), and turnaround time for results (1 hour, 3 days and 1 week). Cost was added to quantify the WTP of each attribute. To ascertain starting point bias with respect to the cost attribute, respondents were presented with one of two sets of costs (Version 1: $0, $1, and $5 or Version 2: $0, $2 and $10). Conditional logit regression was used to analyze data. Results: Regression coefficients were statistically significant for turnaround times as well as for cost regardless of the sample on which they were calculated. WTP for 1 hour versus a 3 day turnaround time was $2.91 (Confidence intervals (CI $1.90, $4.07) in additional annual premiums. WTP values were higher for 1 hour versus 1 week turnaround times. The results suggest that a net social benefit of over $9 million. Conclusions: Respondents showed a preference for 1 hour turnaround time for test results but no statistically significant preference in how samples were extracted. Given the financial constraints, hospital administrator decision to fund the PGx test would need to balance the additional $3.5 million expenditure to cover the PGx option with the potential benefit of 981 fewer adverse events.
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<td>ACS</td>
<td>Acute coronary syndrome</td>
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<tr>
<td>AE</td>
<td>Adverse event</td>
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<tr>
<td>AIC</td>
<td>Akaike information criterion</td>
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<tr>
<td>AMI</td>
<td>Acute myocardial infarction</td>
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<tr>
<td>ASA</td>
<td>Acetylsalicylic acid</td>
</tr>
<tr>
<td>BIA</td>
<td>Budget impact analysis</td>
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<tr>
<td>BIC</td>
<td>Bayesian information criteria</td>
</tr>
<tr>
<td>CABG</td>
<td>Coronary artery bypass grafting</td>
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<td>CAN</td>
<td>Canada</td>
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<tr>
<td>CBA</td>
<td>Cost benefit analysis</td>
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<tr>
<td>CDRH</td>
<td>Center for devices and radiological health</td>
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<tr>
<td>CEA</td>
<td>Cost effectiveness analysis</td>
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<tr>
<td>CIHI</td>
<td>Canadian Institute for Health Information</td>
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<tr>
<td>CV</td>
<td>Cardiovascular</td>
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<tr>
<td>CYP</td>
<td>Cytochrome P450</td>
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<tr>
<td>DCE</td>
<td>Discrete choice experiment</td>
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<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
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<tr>
<td>EM</td>
<td>Extensive metabolizer;</td>
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<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
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<tr>
<td>HPR</td>
<td>High on-treatment platelet reactivity</td>
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<tr>
<td>IM</td>
<td>Intermediate metabolizer</td>
</tr>
<tr>
<td>LOF</td>
<td>Loss of function</td>
</tr>
<tr>
<td>MACE</td>
<td>Major adverse cardiovascular events</td>
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<tr>
<td>MDIC</td>
<td>Medical Device Innovation Consortium</td>
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<tr>
<td>MI</td>
<td>Myocardial infarction</td>
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<tr>
<td>MOHLTC</td>
<td>Ministry of Health and Long-Term Care</td>
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<tr>
<td>NA</td>
<td>Not applicable</td>
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<tr>
<td>NSTEMI</td>
<td>Non-ST elevation myocardial infarction</td>
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<td>NZ</td>
<td>New Zealand</td>
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<tr>
<td>ODB</td>
<td>Ontario drug benefit</td>
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<tr>
<td>PCBR</td>
<td>Patient centered benefit risk</td>
</tr>
<tr>
<td>PCI</td>
<td>Percutaneous coronary intervention</td>
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<tr>
<td>PGx</td>
<td>Pharmacogenetic</td>
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<tr>
<td>PM</td>
<td>Poor metabolizer</td>
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<tr>
<td>POC</td>
<td>Point of care</td>
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<tr>
<td>QALY</td>
<td>Quality adjusted life year</td>
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<td>RUT</td>
<td>Random utility theory</td>
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<td>SAS</td>
<td>Statistical analysis system</td>
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<tr>
<td>STEMI</td>
<td>ST Segment elevation myocardial infarction</td>
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<tr>
<td>UM</td>
<td>Ultra-rapid metabolizer</td>
</tr>
<tr>
<td>US</td>
<td>United States</td>
</tr>
<tr>
<td>USD</td>
<td>United States Dollars</td>
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<tr>
<td>WTP</td>
<td>Willingness to pay</td>
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Chapter 1: Introduction, reviews of literature and study research questions

Introduction
The management of patients with cardiovascular disease in Canada continues to evolve with the introduction of pharmacological and alternative interventions. Patients with acute coronary syndrome (ACS) now have a variety of effective pharmacotherapeutic options with varying benefit and risk profiles. One of the challenges in deciding which of the available agents is appropriate for a specific patient depends on the functional capacity of their CYP2C19*2 allele. Patients with a loss of function (LOF) CYP2C19*2 allele could be at a higher risk for adverse events due to treatment with clopidogrel than patients with a fully functioning allele. As such, ACS patients with a fully functional allele could be treated with clopidogrel while prasugrel or ticagrelor could be prescribed to patients with a LOF allele. A patients’ gene status can be assessed using a pharmacogenetic (PGx) test specific to the CYP2C19*2 allele. Therefore, the inclusion of PGx testing creates a novel paradigm to identify appropriate pharmacotherapy.

In Canada, clopidogrel (Plavix®) is approved for use in patients with:

1) Atherosclerosis documented by stroke, myocardial infarction, or established peripheral arterial disease
2) Acute coronary syndromes (ACS)
   a. Without ST segment elevation (i.e. unstable angina or non-Q-wave myocardial infarction).
   b. With ST-segment elevation acute myocardial infarction
3) Atrial fibrillation
   a. With at least one risk factor for vascular events, who are not suitable for treatment with an anticoagulant and who have a low risk of bleeding
   b. With an increased risk of vascular events and who can take vitamin K antagonist

In March 2010, the United States (US) Food and Drug Administration (FDA) issued a warning related to the effectiveness of clopidogrel in patients with a reduced or LOF CYP2C19*2 allele. The warning, also found in the Canadian product monograph, states that “poor metabolizers (i.e.
LOF patients) treated with (clopidogrel) at recommended doses exhibit higher cardiovascular event rates following ACS or percutaneous coronary intervention (PCI) than patients with a normal CYP2C19*2 function”.¹

Knowledge of the level of functioning of patient genes would therefore be helpful when prescribing appropriate drug therapy. Such information can be extracted through the use of PGx testing. Pharmacogenetic testing is a type of genetic test that assesses a patient’s risk for an adverse event or the likelihood of the level of response to medication, thereby informing drug selection and dosing.³ There are different types of CYP2C19*2 pharmacogentic tests; each with different attributes. Recently, a genetic test has been developed by Spartan Bioscience that differs from currently available CYP2C19*2 tests. First, the Spartan RX™, analyzes patient samples at point of care (POC), eliminating the need to batch and send the sample to a laboratory for analysis. Moreover, results from the novel test (hereinafter referred to as POC PGx) are available to the clinician within one hour, compared to the 3-7 days required using the standard CYP2C19*2 (hereinafter referred to as ‘standard PGx’) tests. As such, the POC PGx test reduces the turnaround time needed to identify the level of functioning compared to the standard PGx. As a result the shortened turnaround time may reduce the risk of adverse events. Also, the POC PGx test enables health care personnel with no previous training in genetic laboratory techniques to undertake genotyping. The novel POC PGx test identifies CYP2C19*2 *3 and *17 genotypes.⁴ This test has received regulatory approval in Europe, and Canada, and has been submitted for FDA approval in the United States.⁴

Neither the “standard” nor the “POC PGx” tests specifically related to the CYP2C19*2 gene are funded for use in Ontario hospitals. Given that ACS patients are faced with an acute situation, (i.e. whether or not to immediately prescribe or initiate therapy with either clopidogrel, prasugrel or ticagrelor) one could infer that the turnaround time for the standard PGx test, limits the clinical usefulness of this test. For example, prescribing clopidogrel while waiting for the standard PGx test results, may increase the risk of an adverse event (AE) when compared to administering a POC PGx test and receiving the results within 60 minutes. The introduction of a novel POC PGx test may be of more use to the clinician and patient given the quicker turnaround time (1 hour compared to 3-5 days).
Implementing the POC PGx test in Ontario hospitals would likely have an impact on healthcare budgets. For example, based on the Canadian Institute for Health Information (CIHI) data from 2008-2009, the estimated number of hospitalizations due to ACS events in Ontario was 38,465 and 109,109 in Canada. When multiplying the incidence of Ontario hospitalizations (a measure of potential use of the test) by the cost of the POC PGx test, yields a cash outlay by Ontario hospitals of approximately $7.69 million (assuming a cost of $200 per test).

Furthermore, given that the implementation of a POC PGx test would incur an initial cash outlay for this test, this outlay, in turn, may be offset by the number of major adverse cardiovascular events (MACE) or the number of bleed events averted. The term MACE refers to one of several conditions: fatal or non-fatal myocardial infarction or non-fatal stroke. Administering the POC PGx, reduces the number of MACE or bleed events compared to the universal clopidogrel treatment pathway. The turnaround time for the POC PGx test is 1 hour. The turnaround time for the standard PGx test ranges from 3 to 7 days. As such one could infer that the number of MACE events would decrease as the turnaround time also decreases. Therefore, the number of MACE events for the standard PGx test could fall in the range between the number under the events under the universal clopidogrel option and the number of events under the POC PGx option. Given the novel characteristics of the POC PGx test (e.g. quicker turnaround time), a budget impact to Ontario hospitals (i.e. consideration of money saved by averting a MACE or bleed compared to a cash outlay for the POC PGx test) is both relevant and unknown.

This thesis contains research related to the economic feasibility of introducing a POC PGx test to the Ontario hospital system. Components of the CBA are: the aggregate WTP (stated preference) for at least one attribute, the BIA of Ontario hospitals, the BIA of the Ontario Drug Benefit formulary, and indirect costs expressed as productivity gains/losses.

The cost of the pharmacogenetic test was based on personal communication with Dr. Derek So, a member of the committee. Furthermore, Table 1 shows the cost used in full economic evaluations of a pharmacogenetic test. The cost ranged from $38 USD to $550 USD. As such the use of $200 would seem reasonable. A one-way sensitivity analysis using the range of costs listed in Table 1 will be incorporated in the budget impact and CBA.
Indicated pharmacotherapy for acute coronary syndrome patients in Ontario

Combination therapy with P2Y$_{12}$ receptor blockers and acetylsalicylic acid (ASA) is recommended to prevent blood clots in patients with ACS and those undergoing PCI. While the standard of care in patients with ACS is clopidogrel; prasugrel or ticagrelor (novel P2Y$_{12}$ inhibitors) have also been recommended. While clopidogrel is activated by the cytochrome P450 enzyme CYP2C19*2, neither prasugrel nor ticagrelor is expressed by the CYP2C19*2 genotype. As such, prasugrel or ticagrelor may be considered as an alternative to clopidogrel in individuals with a CYP2C19*2 LOF allele.

However, while prasugrel and ticagrelor have a more rapid onset of action and exhibit lower rates of MACE than clopidogrel, these benefits are somewhat offset by increased rates of bleeding when compared to clopidogrel. Meanwhile prasugrel is contraindicated in patients with a history of transient ischemic attack or stroke. Furthermore, prasugrel is generally not recommended in patients 75 years of age and over or in patients weighing <60 kilograms. On the other hand, ticagrelor requires twice-daily dosing compared to the once daily dose recommend for either clopidogrel or prasugrel.

Acute coronary syndrome: A description of the underlying condition

Acute coronary syndrome describes a spectrum of clinical manifestations that can be categorised into one of three conditions: unstable angina, non-ST-elevation myocardial infarction (NSTEMI) or ST-elevation myocardial infarction (STEMI). These clinical manifestations can be attributed to a common link; the obstruction of coronary arteries resulting in the undersupply of oxygen to the heart. If the blood supply is not restored, the condition can lead to death. In cases where an electrocardiogram (ECG) shows an ST-segment elevation, patients are diagnosed with STEMI and need to be evaluated for an urgent percutaneous coronary intervention (PCI). PCI is a minimally invasive procedure that restores blood flow to narrowed arteries. For patients with NSTEMI or unstable angina, treatment usually entails anti-thrombotic therapy (clot busting...
drugs). Acute coronary syndrome patients may then need to be chronically medicated with P2Y$_{12}$ receptor blockers to decrease the risk of further life threatening ACS events.

Pharmacogenetic test: Proof of concept

The use of a PGx test has been suggested to guide selection of P2Y$_{12}$ receptor blocker therapy. The test would allow for personalised therapy in patients with ACS. Patients with fully functional CYP2C19*2 alleles could be treated with clopidogrel, while prasugrel or ticagrelor could be prescribed to patients with LOF CYP2C19*2 alleles. The PGx test would only be necessary once in a lifetime. Patients with a LOF CYP2C19*2 allele, and who are treated with clopidogrel, are at a higher risk for MACE (i.e. fatal or non-fatal myocardial infarction or non-fatal stroke).

Genetic sub-studies examined the effect of the CYP2C19*2 polymorphism on clinical outcomes in patients treated with clopidogrel or a comparison. In those studies, the primary efficacy endpoint was a composite of fatal or non-fatal myocardial infarction or non-fatal stroke. In this thesis these events (fatal or non-fatal myocardial infarction or non-fatal stroke) will be referred to as MACE.

In a proof of concept study, 200 patients were assigned to a treatment algorithm that included a rapid POC (bedside) genotyping or to standard therapy (i.e. clopidogrel for all patients). Carriers of a LOF allele were prescribed prasugrel, while fully functioning patients were prescribed clopidogrel. The authors concluded that POC genetic testing after PCI can be done effectively at the patient’s bedside and that personalised treatment reduces the number of CYP2C19*2 carriers that have high on-treatment platelet reactivity (HPR). HPR is a marker associated with increased adverse cardiovascular events. The study reported that the novel POC CYP2C19*2 test had a sensitivity of 100% (95% CI 92.3-100) and a specificity of 99.3% (96.2-100%).

Estimated number of acute coronary syndrome patients with a loss of function allele in Ontario

Proportion of the population with a LOF CYP2C19*2 allele varies by race. An estimated 25-30% of Caucasians, 35% of African Americans, and 30-60% of Asians carry a loss of function
CYP2C19*2 allele. In 2006, 17% of the Ontario population described themselves as Asian, and 4% as black. As at April 1st, 2015, the Ontario population was estimated to be 13.7 million. Assuming mid-point values of the prevalence rates of LOF by race, the weighted prevalence of LOF carriers in Ontario would be 30.8%. The estimated incidence of ACS in the Ontario population is 193 per 100,000 adults. As such the estimated number of ACS patients in Ontario is 26,537 per annum, while the number of ACS patients with LOF is 8,174.

Price, patents and coverage of therapeutic alternatives for acute coronary syndrome patients in Ontario

Clopidogrel, prasugrel and ticagrelor have all been approved by Health Canada. In Ontario, clopidogrel is listed with the Ontario Drug Benefit (ODB) formulary and priced at CAN$0.4735 for a maintenance daily dose. Prasugrel is currently funded by the ODB on a limited basis, and is available through private insurance, for a daily cost of CAN$3.13. Ticagrelor was listed with the ODB formulary on April 30th, 2013. As of June 1st, 2016, the daily maintenance dose price for ticagrelor is CAN$2.9984. While the patents for prasugrel and ticagrelor are expected to expire in 2019 and 2018 respectively, clopidogrel came off-patent in September 2012.

Shifting pharmacotherapeutic paradigm for acute coronary syndrome patients

Advances in PGx testing technology (i.e. 1 hour turnaround time for results) may influence the pharmacotherapeutic paradigm. Standard PGx testing may not be a viable alternative given the longer turnaround time for this version of the test. Therefore, the current treatment option of universal clopidogrel could shift to a choice between personalised treatment (using a PCC PGx test) of a P2Y₁₂ receptor blocker, or an offering of the status quo (i.e.universal clopidogrel). The suggested alternatives to the current paradigm are illustrated in Figure 1.

Measuring economic efficiency: Components of a cost benefit analysis

This thesis evaluates the economic feasibility of introducing a POC PGx test to hospitals in Ontario. This assumes that patients first present themselves to hospitals for ACS are are administered a POC PGX. Economic feasibility was measured using a cost benefit analysis (CBA). A CBA is a full economic evaluation that measures both costs and consequences of
competing health care technologies. The CBA will be informed by two budget impact analysis (BIA), a stated patient preference value (WTP) and a productivity value.

Universal Clopidogrel  (Current standard)

<table>
<thead>
<tr>
<th>ACS Treatment options</th>
<th>PGx test</th>
<th>Universal prasugrel</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fully functional</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Loss of function</td>
<td></td>
</tr>
<tr>
<td></td>
<td>prasugrel/ticagrelor</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1. Alternatives to current standard pharmacotherapy (universal clopidogrel) for ACS patients in Ontario

A BIA addresses the expected changes in expenditure of a health care system after a hypothetical adoption of a new intervention in a specific jurisdiction. In Canada, BIAs are widely used; where 50% of the Canadian health technology assessment reports with an economic evaluation. Results from the two BIAs were used to inform funding or resource planning decisions.

A discrete choice experiment (DCE) will inform the patient preference value by quantifying the willingness to pay (WTP) for attributes of a POC PGx test. Willingness to pay is a measurement technique that quantifies individual preferences for a health care programme and enables translation of health and non-health benefits into monetary values. One method of quantifying WTP is through a DCE approach.

A DCE is a survey that elicits an individual’s stated preference for product attributes. Stated preference studies ask respondents to express their preference for goods under a hypothetical market situation. Use of a stated preference are informative in situations where: a consumer is not exposed to market prices, an agency relationship exists and as such the consumer is not the sole decision maker, or when markets are not available. Stated preference studies eliciting a
WTP can be carried out through either a contingent valuation or a variation thereof, and is also referred to as choice modelling methods. Respondents to a contingent valuation study are asked to think about the possibility of a market existing for the underlying programme or technology or possibility of a health benefit arising from the intervention. Implicit in contingent valuation studies is that respondents are asked to state their maximum WTP. The reasoning behind asking for a maximum WTP is that contingent valuation studies measure the value of the underlying intervention in relation to the cost, for purposes of collective funding (i.e. public or private insurance as opposed to out of pocket). This concept is referred to as the ‘consumer surplus’. In other words, contingent valuation measures preferences in monetary terms. This concept should not be confused or translated into what respondents would pay in the market place. To determine what consumers would actually pay, a researcher could carry out revealed preference (as opposed to stated preference) studies. Revealed preferences elicit what respondents would pay by examining their actions in actual markets (monetary transactions such as purchases at retail stores) or through court documents (e.g. labour contract settlements).

As a stated preference technique, the DCE differs from contingent valuation in that the underlying technology or service is disaggregated into attributes (broken down into characteristics of the product or programme). In a DCE, respondents are asked to choose between two or more scenarios wherein each scenario consists of several attributes, each with several levels (i.e. characteristics). In the DCE survey, the attribute levels that describe the product or service are varied. Individual preferences are then elicited by monitoring individuals’ choices over a series of choice tasks. While a contingent valuation method may ask for a maximum a respondent would pay for a program or technology, a choice model would compare two or more sets of product characteristics which would include a cost component. The DCE (choice modelling) method does not expressly ask for the maximum WTP, however this method does quantify respondent preferences through monetary values.

Literature reviews

This section contains a systematic literature review as well as an exploratory review. The systematic review identifies current evidence of economic efficiency related to implementing any type (i.e. standard or POC) of PGx test in cardiovascular patients. The purpose of the
systematic review was to inform the research question for this thesis. The second (exploratory) review identifies DCEs that were carried out with pharmaceutical agents as the intervention of interest. The purpose of the second review was to inform the structure of the DCE.

Systematic review title: A systematic review of economic evaluations related to PGx tests administered to patients with an underlying cardiovascular condition

Systematic review of economic efficiencies related to a CYP2C19*2 PGx test: Structured summary

The systematic review identified economic evidence related to pharmacogenetic tests administered to patients with a cardiovascular condition. Data sources accessed were Embase and Medline as well as Pubmed. The latter was accessed to identify studies published in the last 12 months. Study eligibility criteria included publications from peer reviewed journals. There were no restrictions as to the age of the study sample. No restrictions were placed on ethnicity or country. Results were tabulated and presented descriptively. The search yielded 585 studies from all databases. A total of 15 studies were included in the final analysis. Publication dates ranged from 2009 to 2017. Countries in which the analysis was undertaken were: Australia, China, New Zealand, Thailand, United Kingdom, and United States. The underlying conditions in the studies were: atrial fibrillation, acute coronary syndrome, cardiovascular disease and any indication listed for warfarin. In the studies included, PGx testing was administered for two purposes: to determine the optimal therapeutic agent or to determine the optimal doing of warfarin. Studies reporting the economic efficiency of testing for LOF of CYP2C19 were for the most part cost effective. Studies related to warfarin dosing concluded that testing were also cost effective. However, none of the studies focused on the importance of the turnaround time in assessing the cost effectiveness of their related PGx test. Cost per administered PGx test ranged from 38 USD to 550 USD. None of the studies referenced whether the standard or POC PGx test was used for the analysis.
Systematic review of economic efficiencies related to a CYP2C19*2 PGx test: Introduction

Several reviews identified economic evaluations of PGx testing. In 2005, Carlson et al (2005)\textsuperscript{42} reviewed economic studies related to pharmacogenetic testing published between 1995 and 2004. Djalalov et al (2010)\textsuperscript{43} followed up by publishing an updated review that included studies published between 2004 and 2009. Since then, some reviews tended to be focused on PGx testing under specific underlying conditions.\textsuperscript{44,45} Currently there is no review of economic evaluations related specifically to PGx testing for patients with cardiovascular conditions. The objective of this review was to summarize the data and assess the quality of economic evaluations related to implementing a pharmacogenetic test in patients with cardiovascular conditions. Results from this review informed the research question for this thesis.

Systematic review of economic efficiencies related to a CYP2C19*2 PGx test: Methods

Protocol and registration

No registration was sought for this review (the methods are part of a thesis submission).

Eligibility criteria

Studies in peer reviewed journals were included (full text or abstracts). Full economic evaluations (i.e. self described as cost-effectiveness, cost-utility, cost benefit or cost minimization studies) were accepted for review. Any type of PGx test administered to patients with cardiovascular events were considered. There was no restriction as to language, country or date published.

Databases

Three databases were used: Embase, Medline, both from inception to May 2017 as well as PubMed (to identify any studies published in the last 12 months i.e. June 2016 to May 2017). Manual (i.e. hand) searches of relevant articles were undertaken.

Search

Search terms used were as follows: “Cardiovascular Diseases”, “Coronary Artery Disease”, “Cerebrovascular Disorders”, “Rheumatic Heart Disease” and “Venous Thrombosis/ or
Pulmonary Embolism”. The resulting yield from this search would be combined with “genetic” as well as "Costs and Cost Analysis", “Cost-Benefit Analysis”, “cost utility” and “cost effectiveness” The strategy for Embase and Medline searches are presented in Appendix 1.

Data collection process
A spreadsheet in Excel was created to capture data points. The search process was carried out by BGB. Data was extracted by BGB and validated by MEH. Quality assessment of included studies was carried out independently by the two reviewers (BGB and MEH).

Data items
The following data points were extracted from studies:

- First author
- Country
- Underlying condition
- Gene
- Cost of PGx test
- Base Case results

Risk of bias in individual studies
A quality assessment was done using the QHES46. Results were compared to the Carlson and Djalalov papers.

Summary measures
A quantitative summary measure cannot be operationalized for economic evaluations. A descriptive summary was presented of the data points listed.

Synthesis of results
Quantitative synthesizing data points is beyond the scope of this review. Descriptive synthesis is presented along with a quality of study assessment.

Risk of bias across studies
No risk of bias across studies was reported.
Additional analysis
A brief summary of the included articles is presented.

Systematic review of economic efficiencies related to a CYP2C19*2 PGx test: Results

Study selection
The literature search yielded a total of 585 hits from the Medline and EMBASE data base searches and three more from manually reviewing the reference list from manually searched articles. Once duplicates and items related to exclusion criteria were taken into consideration, there were 15 articles \(^{27,28,30-39,41,47,48}\) that were considered for data extraction. Figure 2 illustrates the search process for this systematic review.

![Figure 2. Literature search tree: Economic evaluations of PGx (CYP2C19*2) tests in patients with an underlying cardiovascular condition](image-url)
Study characteristics for the economic evaluation review are presented in Table 2.

Dates of publication ranged from 2009 to 2016. The jurisdiction upon which the analysis took place included Australia, China, New Zealand, Thailand, United Kingdom, United States, and. Economic efficiency was assessed using a cost utility framework in all included studies. The studies included in this review assessed the implementation of a PGx test for four underlying condition: acute coronary syndrome, cardiovascular disease, atrial fibrillation, hypertension. These studies correspond to LOF testing of the following genes: CYP2C19, LPA, CYP2C9 and VKORC1 as well as KIF6. Eight studies assessed the CYP2C19 test (ACS), 5 study assessed tests for the CYP2C9, VKORC1 alleles (warfarin dosing) and one study for each of the following: Gly460Trp (hypertension), LPA variants (cardiovascular disease) and KIF6 for high-dose atorvastatin to treat for ACS.

Overview of economic studies

Five economic evaluations tested patients for LOF of CYP2C9 and VKORC1 to inform warfarin dosing. The underlying condition in three of the five studies were atrial fibrillation, one with venous thromboembolism and another that assessed all conditions that are indicated for warfarin. In Chong et al. PGx test of CYP2C9 and VKORC1 increased QALY by 0.002 and cost by 99 USD from a healthcare system perspective, compared with standard of care resulting in an ICER of 49,234 USD per QALY gained. From societal perspective, PGx testing resulted in a 0.002 QALY gained, and increased cost by 98 USD compared with standard of care resulting in an ICER of 49,128 USD per QALY gained. Based on these threshold levels, Chong et al concluded that PGx-guided warfarin dosing was unlikely to be a cost-effective intervention in Thailand. That message was echoed by Eckman et al. In that study Eckman et al reported that in the base case the PGx testing resulting in an overall, ICER that exceeded 170 000 USD per QALY. Meanwhile, the study by Leey was a bit cryptic, stating that genotype-guided warfarin therapy for anticoagulation in elderly patients with atrial fibrillation was potentially cost-effective, and its benefits were closely related to efficacy in preventing bleeding events. However incremental costs or benefits were not clearly presented. Patrick et al concluded that genotyping before warfarin initiation would be cost-effective for patients with atrial fibrillation.
Table 1. Study characteristics of economic evaluations of pharmacogenetic interventions in patients with cardiovascular conditions.

<table>
<thead>
<tr>
<th>AU</th>
<th>Country</th>
<th>Underlying condition</th>
<th>Gene</th>
<th>Cost per PGx test †</th>
<th>Base case</th>
</tr>
</thead>
<tbody>
<tr>
<td>Charland (2011)</td>
<td>U.K.</td>
<td>ACS</td>
<td>P450 2C19</td>
<td>$60 to $250</td>
<td>No genotype = dominated</td>
</tr>
<tr>
<td>Chong (2014)</td>
<td>Thailand</td>
<td>Warfarin*</td>
<td>CYP2C9; VKORC1</td>
<td>$38</td>
<td>PGx test = $49,234 per QALY</td>
</tr>
<tr>
<td>Crespin (2011)</td>
<td>U.S.A.</td>
<td>ACS</td>
<td>P450 2C19</td>
<td>$200</td>
<td>Universal ticagrelor = $10,059 per QALY</td>
</tr>
<tr>
<td>Eckman (2009)</td>
<td>U.S.A.</td>
<td>AF</td>
<td>CYP2C9; VKORC1</td>
<td>$400</td>
<td>PGx testing &gt; $170,000 per QALY</td>
</tr>
<tr>
<td>Kazi (2014)</td>
<td>U.S.A.</td>
<td>ACS</td>
<td>P450 2C19</td>
<td>Not stated</td>
<td>PGx testing = $35,800 per QALY</td>
</tr>
<tr>
<td>Lala (2013)</td>
<td>U.S.A.</td>
<td>ACS</td>
<td>P450 2C19</td>
<td>$500</td>
<td>No genotype = dominated</td>
</tr>
<tr>
<td>Leey (2008)</td>
<td>U.S.A.</td>
<td>AF</td>
<td>CYP2C9; VKORC1</td>
<td>$250</td>
<td>Genotyping = cost effective</td>
</tr>
<tr>
<td>Meckley (2006)</td>
<td>U.S.A.</td>
<td>Hypertension</td>
<td>CYP2C9; VKORC1</td>
<td>$250</td>
<td>No genotype = dominated</td>
</tr>
<tr>
<td>Parthan (2013)</td>
<td>U.S.A.</td>
<td>ACS</td>
<td>KIF6</td>
<td>$100</td>
<td>Genotyping = cost effective</td>
</tr>
<tr>
<td>Patrick (2009)</td>
<td>U.S.A.</td>
<td>AF</td>
<td>CYP2C9; VKORC1</td>
<td>$400-550</td>
<td>KIF6 Testing strategy = US$45,000/QALY</td>
</tr>
<tr>
<td>Sorich (2013)</td>
<td>Australia</td>
<td>ACS</td>
<td>P450 2C19</td>
<td>Not stated</td>
<td>Genotyping = cost effective</td>
</tr>
<tr>
<td>Teschemaker (2009)</td>
<td>U.S.A.</td>
<td>VT</td>
<td>CYP2C9; VKORC1</td>
<td>Not stated</td>
<td>CYP2C9 and VKORC1 genotype-guided dosing exceeded $100,000/QALY compared with VKORC1 testing alone.</td>
</tr>
</tbody>
</table>

ACS = Acute coronary syndrome, AF = atrial fibrillation, CVD = Cardiovascular disease; NS = not specified; N.Z. = New Zealand; PGx = pharmacogenetic; QALY = quality adjusted life year; U.K. = United Kingdom; U.S.A. = United States; VT = Venous thromboembolism; *any indication for warfarin
† reported in United States dollars
on the condition that warfarin reduces out-of-range international normalized ratio values by more than 5 to 9 percentage points compared with usual care. In that study the authors concluded that given the uncertainty surrounding efficacy, caution should be taken in advocating the widespread adoption of this strategy.

Quality of Health Economic Studies (QHES)
The quality scores for each study included this review is presented in Appendix 2. The mean value is 71% (41%-94%)

Cost of PGx test
The cost for a pharmacogenetic test was presented in several papers. In Thailand, the cost of a CYP2C9, VKORC1 (warfarin dosing) pharmacogenetic test was 38 USD. Costs were much higher in the analysis carried out in the United States which ranged from 200 to 550USD. Similarly, for ACS, the CYP2C19 pharmacogenetic test ranged from 68 to 500USD.

Turnaround time for PGx test
Only two studies mentioned the 3 to 5 day turnaround time for results. Of those two studies, only one study took this into consideration the delay in turnaround time, when creating their economic model. This is surprising given the acute nature of the underlying conditions.

Risk of bias within studies
Of the 15 studies included in this review, 6 studies explicitly discussed the direction potential biases. Reporting the magnitude of the direction was not consistently reported. For example, Crespin et al assumed that the genotyping assay utilized a buccal swab rather than blood for DNA collection. The buccal swab may be self administered, and as a result, Crespin et al excluded costs for obtaining a sample. The authors point out that this assumption would underestimate the cost of the genotype-driven treatment. Crespin et al also assumed that only one test per patient be administered and that the PGx test would be taken simultaneously with their index ACS diagnosis. The authors also assumed that the test had both 100% sensitivity and specificity. The authors state that these assumptions would likely bias their results in favor of the genotype-driven therapy.
Synthesis of results
There was no synthesis of data. A descriptive and qualitative assessment was carried out.

Risk of bias across studies
An assessment of bias across studies was not undertaken (i.e. publication bias)

Discussion
Two studies reviewed economic evaluations related to pharmacogenetic testing. The Carlson et al study revealed that most (59%) of the economic evaluations were cost effectiveness studies followed by cost utility studies (25%). That review included 63 papers, that yielded a quality ranking of 87 out of 100 (48-100). Djalalov et al. included 25 article which yielded a quality score of 89 (41-100). Of the included articles 65% were cost effectiveness studies, and 12% were cost utility studies. Meanwhile this review showed that the results for a PGx CYP2C9 were mixed while the results for CYP2C19 were mostly cost effective. The quality assessment scores were lower in this review when compared to either the Carson or Djalalov scores.

Limitations
The terms genetics and genomics are very broad and include a wide field of biomedical research that may not have been captured by this review. Furthermore, economic evaluations of genetic interventions may be improperly indexed and thus hidden in databases under a variety of underlying conditions. Finally, QHES criteria tends to be vague and difficult to interpret.

Conclusion
PGx testing for patients with underlying cardiovascular conditions were, for the most part, cost effective. Utility of adverse event health states were considered, however, none of the studies considered the consequences of rapid turnaround time available through newer technology in novel PGx tests. This aspect is particularly relevant in acute settings. Quality assessment of studies was lower in this sample, than in previous reviews. Future studies should take into consideration the rapid turnaround time provided by newer technology in PGx tests.
Exploratory review of discrete choice experiments on pharmacotherapeutic interventions:
Structured Summary

The exploratory review assessed preference techniques and parameters from sample populations related to pharmaceutical interventions. Data sources accessed were Embase and Medline as well as Pubmed. The latter was accessed to identify studies published in the last 12 months. Study eligibility criteria included publications from peer reviewed journals. There were no restrictions as to the age of the study sample. No restrictions were placed on ethnicity or country. Results were tabulated and presented descriptively. The search yielded 103 studies from all databases. A total of 33 studies were included in the final analysis. Publication dates ranged from 2009 to 2015. Countries in which the analysis was undertaken were: Australia,27 China,28 New Zealand,29 Thailand,30 United Kingdom,31 and United States32-41.

Exploratory review of discrete choice experiments on pharmacotherapeutic interventions:
Introduction

The second literature review (explanatory) identified DCE studies related to pharmaceutical agents. While the DCE practitioner has several publications to help guide the development of their survey,22,23 the purpose of the second review was to describe how DCEs were developed and how the data has been analyzed. Of interest was whether studies included a cost component and the description of sample size calculations. The systematic review of the literature would help describe how practitioners create and disseminate their surveys, how they are analyzing the data and the conclusions that they glean from their studies. Naik-Panvelkar et al published a review of DCE related to pharmacy delivered specialised services.51 In contrast, this review focuses on DCEs related to pharmaceutical agents. Outcomes of interest were: how sample size was determined, the estimation methods used, the response rates of dissemination methods and the prevalence of DCEs that included a cost component that could in turn be used to quantify WTP.
Exploratory review of discrete choice experiments on pharmacotherapeutic interventions: Methods

Criteria for acceptable studies included:

Patients and disease: There was no restriction as to the age of the respondents or whether a caregiver was included in the respondent population. No restrictions were placed on ethnicity or country. Studies that included observations from multiple countries were considered regardless of whether the results were disaggregated by country.

Drugs: There was no restriction on the underlying drugs. Studies that observed attributes of pharmacogenetic tests (i.e. genetic tests that were related to the metabolism of drugs were also included).

Study type/design: Only full text articles that were peer reviewed were considered. Only self-described DCE studies were considered. Only primary data were allowed.

Patient outcomes: All outcomes related to the creation and analysis of the DCE were considered. Exclusion criteria were: health care services, formulary decision making attributes, abstracts, conference papers.

Articles obtained from the Medline (from 1996) and Embase (from 1980) search until the end of December 2015 were included. Key words included “discrete choice experiment” “drugs” “Pharmaceutical Preparations”. A hand search was performed of the references from accepted papers and recent reviews of the topic. Papers citing accepted articles were also accessed.

Data extraction and analysis

- name of first author
- year of publication
- name of publication
- software used
- estimation method used
- diagnostic criteria reported (i.e. goodness of fit)
- underlying condition
- underlying pharmaceutical agent
- source of preference
- attributes (number of attributes and number of levels)
- number of choice sets
- sample size
- description of how sample size was determined
- sampling technique
- whether tariff included as attribute
- tariff perspective
- zero cost or opt out option availability

Exploratory review of discrete choice experiments on pharmacotherapeutic interventions:

Results

In total, 32 publications were available for review. Figure 3 illustrates the literature search tree. Study characteristics such as first author, year, country, sample size and number of possible combinations available to choose from and inclusion of a cost component are listed in Table 2. Studies were carried out in 20 countries and elicited responses from 6636 respondents. The highest concentration of DCEs was carried out in the United Kingdom (n=7) followed by Australia and the United States (n=4 each) and Canada (n=3). The remaining countries produce either 2 or 1 DCE each.

While the search included databases from the years 1980 or 1996 (1996 Medline; 1980 Embase), the first DCE study in this review was published in 2004. Since then there has been at least one study published per year. Furthermore, there has been an increasing trend in the number of studies over time with 8 DCE studies published in 2012. (Figure 5) DCE studies were based on a wide range (n=14) of treatment options. The highest number of studies dealt with insulin (n=3) and biosimilar (n=3) agents. Vaccines, non-steroidal anti-inflammatory agents and cox 2 inhibitors were each considered in 2 studies. (Figure 6) Perspectives of the studies included: the general population, patient population, physicians, children or caregivers. (Figure 7) Most studies (14) were undertaken from the patient perspective. Physician preferences were considered in 7 and caregiver preferences were considered in 4. Smokers’ perspective was considered in one study.
Figure 3. Literature search review of discrete choice experiment for underlying pharmacotherapeutic agents.
Table 2. Study characteristics (N=32) of the discrete choice experiments related to pharmacotherapy

<table>
<thead>
<tr>
<th>First Author (year)</th>
<th>Country</th>
<th>Sample Size (Analysis)</th>
<th>Possible combinations</th>
<th>Cost component included</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arden (2012)</td>
<td>United Kingdom</td>
<td>477</td>
<td>4096</td>
<td>No</td>
</tr>
<tr>
<td>Arellano (2015)</td>
<td>Canada</td>
<td>200</td>
<td>324</td>
<td>No</td>
</tr>
<tr>
<td>Aristides (2004)</td>
<td>France, Germany, Italy, Spain, United Kingdom</td>
<td>235</td>
<td>324</td>
<td>Yes</td>
</tr>
<tr>
<td>Augustovski (2013)</td>
<td>Argentina</td>
<td>240</td>
<td>1944</td>
<td>Yes</td>
</tr>
<tr>
<td>Baji (2015)</td>
<td>Hungary</td>
<td>51</td>
<td>16</td>
<td>No</td>
</tr>
<tr>
<td>Benjamin (2012)</td>
<td>France</td>
<td>203</td>
<td>16</td>
<td>Yes</td>
</tr>
<tr>
<td>Burnett (2014)</td>
<td>Canada</td>
<td>105</td>
<td>3072</td>
<td>Yes</td>
</tr>
<tr>
<td>De Bekker-Grob (2008)</td>
<td>Netherlands</td>
<td>120</td>
<td>512</td>
<td>Yes</td>
</tr>
<tr>
<td>Diaby (2011)</td>
<td>Cote D'Ivoire</td>
<td>70</td>
<td>64</td>
<td>Yes</td>
</tr>
<tr>
<td>Eberth (2009)</td>
<td>Ireland</td>
<td>100</td>
<td>2592</td>
<td>Yes</td>
</tr>
<tr>
<td>Gidengil (2012)</td>
<td>United States</td>
<td>558</td>
<td>128</td>
<td>Yes</td>
</tr>
<tr>
<td>Glenngard (2013)</td>
<td>Sweden, Denmark</td>
<td>285</td>
<td>96</td>
<td>No</td>
</tr>
<tr>
<td>Guimaraes (2009)</td>
<td>Brazil</td>
<td>291</td>
<td>128</td>
<td>No</td>
</tr>
<tr>
<td>Hauber (2013)</td>
<td>United Kingdom</td>
<td>289</td>
<td>4096</td>
<td>No</td>
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<tr>
<td>Hauber (2009)</td>
<td>United States</td>
<td>509</td>
<td>64</td>
<td>No</td>
</tr>
<tr>
<td>Author (Year)</td>
<td>Country</td>
<td>n</td>
<td>n</td>
<td>Response</td>
</tr>
<tr>
<td>----------------------------</td>
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<td>3456</td>
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NS = Not stated
Figure 4. Number of included DCE studies by jurisdiction (Some studies reported from several jurisdiction)

Figure 5. The number of discrete choice experiment studies of pharmaceutical agents by year of publication
Figure 6. Discrete choice experiment studies by underlying pharmaceutical agent of interest

Figure 7. Number of DCE articles included by stated perspectives. (Some studies included more than 1 perspective)
Discrete choice experiment characteristics

Attributes

The number of attributes examined a range from 3 to 10. Most studies used 5 or 6 attributes. (Figure 8) The number of levels ranged from 2 to 7. Levels were even (i.e. same number of levels for each attribute in the study) in 18 of the 32 studies. The number of possible choices ranged from 16 to 131,072. As such, most (24/32) of the choice sets were derived using a fractional factorial design. The number of choice sets presented to respondents ranged from 3-19 with most using 10, 16 or 17 choice sets. (Figure 9) Sample sizes ranged from 41 to 1,020 respondents. None of the articles offered a rationale for determining the sample size.

![Frequency of attributes](image)

Figure 8. The number of included studies with corresponding attribute levels. (Not all studies specifically reported attribute levels)
Figure 9. Number of studies corresponding to the number of choice sets offered to respondent.

Distribution & Response rates
Of the 32 studies that were reviewed 30% of the questionnaires were disseminated by mail or manually handed out in a clinic, 43% were disseminated through an online invitation. Another 20% did not report method of invitation. A response rate was defined as the number of responses to invitations divided by the number of invitations sent. Of those studies that reported, the ‘pen and paper’ technique, where respondents were contacted by mail or individually through clinics, yielded a 15.7% response rate where 1048 respondents answered the call to complete a survey after 6,674 invitations were sent out. This number is skewed in that in one study, 6,000 invitations were sent with only 555 respondents responding. If this large data point was taken out, 674 invitations were sent out with 493 responding, yielding a much higher response rate of 73% (62%-78%). Response rates from studies where invitations and the survey were provided on an on-line platform were 17% (13%-64%).

Analysis
The software used to analyze the data was not reported in 8 articles. A further 8 used various versions of STATA and 8 used NLOGIT. SAS was used in 5, while LIMDEP was used in 2 and SPSS and GAUSS were used once. The most often used model estimation technique was the conditional logit method (n=14). More specifically, authors referred to: the conditional logit
technique in nine studies, the multinomial in 2 and the mixed logit in three. Random parameters logit technique was used in 7 studies and random effects in five. The frequency of software tools and techniques used to analyse the panel data is described in Figure 11.

Scalar measures of fit
Measures of fit were reported in 17 of 32 studies. A list of the diagnostic test as well as the high and low values extracted from the articles is presented in Table 3. Log likelihood, AIC and pseudo r2 were the most reported tests.
Table 3. Frequency and values of reported goodness of fit and deviance values from included DCEs.

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Number of appearances in articles</th>
<th>High value</th>
<th>Low value</th>
</tr>
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<tbody>
<tr>
<td>AIC</td>
<td>9</td>
<td>1904.4</td>
<td>0.83586</td>
</tr>
<tr>
<td>BIC</td>
<td>5</td>
<td>1934.8</td>
<td>1.048</td>
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<tr>
<td>Log Likelihood</td>
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<td>Restricted likelihood function</td>
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<tr>
<td>Wald chi</td>
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<td>27.23</td>
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<tr>
<td>chi square</td>
<td>5</td>
<td>1249.61</td>
<td>572.88</td>
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<td>0.494</td>
<td>0.494</td>
</tr>
<tr>
<td>adjusted $r^2$</td>
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<td>0.489</td>
<td>0.489</td>
</tr>
<tr>
<td>McFadden’s $r^2$</td>
<td>3</td>
<td>0.4001</td>
<td>0.3</td>
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<tr>
<td>Ephron’s $r^2$</td>
<td>1</td>
<td>0.3903</td>
<td>0.3903</td>
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<tr>
<td>pseudo $r^2$</td>
<td>9</td>
<td>835.36</td>
<td>524.22</td>
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</table>

Figure 10. Frequency of computer software packages used in included DCE reviews (not all studies reported type of software used)
Figure 11. Frequency of model estimation techniques used in included DCE studies. (Not all studies reported estimation techniques used)
Willingness to pay

A cost component was included in 17/32 studies. Eleven of the studies included either a ‘zero cost’ or ‘opt out’ option. Most of the studies (n=13) framed the cost question as “out of pocket” to either the general population or to the patient. One study framed the question as “cost to physician”. Willingness to pay (WTP) values were reported in the following currencies: Argentinian peso, Australian dollar, British pound, Canadian dollar, Eurodollar, Swiss franc, United States dollar, and Japanese yen. Frequency of reports by currency are presented in WTP values by attribute and by currency are provided in the figures below. Negative WTP values were reported in five studies.52-56

Burnett et al quantified the value for money in treating juvenile idiopathic arthritis with either biologic or non-biologic therapeutics.53 A negative value of -$148 (95%CI -$504 to $236), or -$585(-$1060 to -$132) (Canadian dollars) was attributed to the preference of biologic treatment (injection; IV respectively) where the non-biologic was assumed to have equal effect when compared to biologic therapy. The authors interpreted the negative value as parents no longer willing to pay more for the biology injection. In another Canadian study, Guimaraes et al. measured the WTP of attributes related to an insulin delivery system.52 WTP was negative for the number of glycaemic events [8 versus 0; Type 1 diabetes, −102.33 (−83.20, −121.46); Type 2 diabetes −62.83(−48.21, −77.45)], weight gain [High (10 kg) versus low 2kg; Type 1 diabetes −151.27(−101.27, 201.27), Type 2 diabetes −88.76(−74.75, −102.77) and route of administration

Figure 12. Frequency of DCE studies reporting willingness to pay values by type of currency.
for the short-acting insulin inhaled vs subcutaneous [Type 1 diabetes; \(-27.44(15.33, -70.21)\)
Type 2 diabetes 7.97(\(-5.38, 21.32\))]. The authors interpreted these negative values as
respondents willing to pay money to avoid the related attribute.\(^{52}\) Meanwhile Glenngard et al
assessed WTP for different attributes in treating attention deficit hyperactivity disorder (ADHD)
with pharmaceutical therapies.\(^{54}\) Negative WTP values were assessed for side effects compared
to no side effects (-218 USD for adolescents; -96 USD for adults) and no dosage – 96 USD
(adolescents), -43USD (adults). The authors did not provide interpretation of the negative WTP
values. In the United Kingdom, Powell et al the assessed the preferences of patients with
epilepsy and neurologists when considering testing for HLA-A*31:01 prior to prescribing
carbamazepine.\(^{55}\) In Table 4 of that article, there was an example of a positive WTP value of
£39.35 (10.97, 71.05) for inclusion of the test on the British National Formulary. There was also
a negative WTP value of £31.29 (\(-60.06, -7.20\)) which is listed for “coverage”. Yet the authors
interpreted both values as respondents willing to pay for the related attribute. Finally, Marti et al.
quantified preference weights for pharmaceutical smoking cessation treatments. Negative WTP
values were assessed for side effects of the treatments. Marti writes that “A 1%-point reduction
in the probability of experiencing minor side effects is valued at around 8 Swiss francs.”\(^{56}\)
Exploratory review: Discussion

Literature review of economic evaluations related to the CYP 2C19*2 PGx test

None of the economic evaluations in the literature reviewed, assessed cost effectiveness of implementing a PGx test for ACS from the Canadian perspective. Nor did any economic evaluations present an impact to the hospitals in their related jurisdictions. Furthermore, while quality of life years related to adverse events were quantified under a PGx and current treatment algorithms, none of the studies assessed patient preference for the underlying pharmacogenetic test itself. There was also no mention of productivity losses associated with patients experiencing MACE or bleed events. As expected, none of the studies reported results from a cost benefit analysis. Furthermore, this review did not yield studies that reported economic feasibility specific to the hospital system in Ontario. Given that none of the full economic evaluations reported outcomes from the societal perspective, a cost benefit analysis would provide evidence of whether implementing a PGx test would provide net social benefit. A CBA and BIA specific to the Ontario hospital system is warranted.

Literature review of DCEs related to pharmacotherapy

Thirty-two studies were included in this review. Approximately half of these studies included a cost component which led to quantifying a WTP. The DCEs included in this review analyzed populations from 20 countries and from the perspective of the: general population, physician, caregiver, and patient.

Of studies that reported sample sizes, the number respondents surveyed was between 41 and 1020. However, no studies provided a rationale for the determination of the sample size used in their respective studies. In 2015, deBekker-Grob et al\textsuperscript{57} present a practical guide to sample size requirements for DCEs. The authors list five elements that are needed before the minimum parameters in a DCE can be calculated. They are as follows:
Significance level

1) Statistical power level
2) Statistical model used
3) Initial belief about the parameter values
4) The DCE design

The significance level $\alpha$ sets the probability for an incorrect rejection of a true null hypothesis. If we want to be 95% confident that the null hypothesis will not be rejected when it is true, then $\alpha$ is set at 0.05. At this level, this also means that there is a 5% chance of finding a significant deviation when there is no effect. The smaller the significance level, the larger the sample size required.

The probability of failing to reject a null hypothesis when it is actually false is commonly denoted by $\beta$. The chosen power of a test (i.e. $1 - \beta$) is related to a statistical power of a test. Since we need to assess whether a coefficient is statistically different from zero, we define the sample size that enables us to find a significant deviation from zero in at least $(1 - \beta)$ times 100% of the cases. For example, an 80% power means that a study is likely to produce a statistically significant result 8 times out of ten. The larger the statistical power, the larger the sample required.

Furthermore, Ryan et al outline several factors to consider when determining the sample size for a DCE. First, the level of accuracy (precision) needs to be addressed. The higher the level of accuracy required the larger the sample size needed. Another issue is whether estimates from subgroup analyses are required. The overall sample needs to be large enough to ensure an adequate level of accuracy for subgroup analysis. Furthermore, the less variable the responses, the fewer respondents are required. However, Ryan et al do not define what is meant by ‘variability’.

While there are several techniques to determine sample size for a DCE, most of these techniques rely on a rule of thumb threshold. In 2015 de Bekker-Grob et al reported a literature review of DCE’s. In that review, 32% (n=22) had sample sizes smaller than 100 respondents, whereas 23% (n=16) had sample sizes larger than 600 respondents. More than 70% (n=49) of the DCE studies did not (clearly) report whether and what kind
of sample size method was used. de Bekker-Grob et al also include a sample size calculation by Johnson and Orne which suggests that the sample size required for the main effects depends on the number of choice tasks (t), the number of alternatives (a), and the number of analysis cells (c) according to the following equation:

\[ N > \frac{500c}{(t \times a)} \]

However, when including interactions between main effects, ‘c’ is equal to the largest number of levels for any of the attributes. Another rule of thumb was proposed by Pearmain et al\(^2^5\) and suggests that, for DCE designs, sample sizes over 100 are able to provide a basis for modeling preference data. Meanwhile Lancsar and Louviere report that “our empirical experience is that one rarely requires more than 20 respondents per questionnaire version to estimate reliable models, but undertaking significant post hoc analysis to identify and estimate co-variate effects invariably requires larger sample size”.\(^5^8\) Despite the number of methods available to determine sample size for a DCE, justification for the sample sized used eluded description in the studies in included in our review of DCEs related to pharmacotherapy.

Scalar measures of fit were reported in one form or another in 17 of the 33 studies. Log likelihood was the most frequently reported measure of fit. Five different types of coefficients of determination were reported; with pseudo \( r^2 \) being the most commonly reported.

Of the 17 studies that included a cost component and thus derived a WTP, all reported a base case positive value for WTP. Five studies reported a negative WTP in their sensitivity analysis. This review does not ascertain whether reporting a positive WTP was due to a publication bias or an inherent issue in the DCE process. Furthermore, this review did not determine whether the WTP values were subsequently used in a CBA.

Limitations

The reviews were limited to Embase and Medline databases. Including other databases may have added more studies for assessment. As such there may have been economic evaluations of the CYP 2C19 PGx test that carried out their research from a societal
perspective. Furthermore, searches were limited to peer-reviewed full text publications in English. Conference proceedings or publications in other languages may also have reported economic evaluations from a societal perspective.

Exploratory review: Conclusion

There is currently a lack of evidence for an economic argument of introducing a PGx test for the CYP 2C19*2 allele in Ontario hospitals. In addition to the clinical value of the PGx test, decision makers responsible for the Ontario hospital budget would need to understand the monetary impact of implementing a CYP2C19*2 PGx test. Decision makers would need to take into consideration not only the cash outlay required for the PGx test, but also the money saved from side effects and clinical events avoided as a result of prescribing the PGx. Furthermore, from the Ministry of Health perspective, downstream costs would need to be considered. Given the costs of the various drugs prescribed, ODB formulary decision makers will also need to be informed of the impact the PGx test would have on their budgets. There is no information on the budget impact of implementing a CYP2C19*2 PGx test in Ontario hospitals. Information on the impact a PGx test would have on the ODB budget is lacking. Furthermore, there is no information on patient preference related to PGx testing. Given this lack on information, a budget impact and a discrete choice experiment is suggested to inform Ontario decision makers on the financial feasibility of covering such a test. Furthermore, the budget impact and discrete choice experiment would inform a cost benefit analysis thus incorporating a societal perspective to the question of whether a PGx test should be covered by the provincial government in Ontario.

Summary of key points

- Economic evaluations related to the CYP 2C19 *2 allele focus on the utility associated with the underlying conditions and not the patient preference of the PGx test itself
- Rationale for sample sizes in discrete choice experiments generally not reported in literature
- Power of studies was not explicitly stated
• Approximately one half of the DCEs focusing on pharmacotherapy included a cost component that allowed for quantifying a willingness to pay

• Number of attributes and levels varied between studies, as such, the number of possible choices available to respondents also varied

• Most DCEs were performed from the patient’s perspective

• Conditional logit was the regression method of choice

• Goodness of fit measures varied widely between reviewed studies.
Statement of problem

The clinical feasibility and efficacy of a personalised combination treatment of a P2Y$_{12}$ receptor blocker and ASA in patients suffering from ACS has been established.$^{14,15,17,59}$ However, the paucity of economic evidence and patient preference related to the PGx test from a Canadian perspective may hinder coverage of the test by either the public or private payer in Ontario. Specifically, economic evaluations to determine whether healthcare budgets should be expanded to include a PGx test have not been performed.

Alternatively, no research has been undertaken to address whether funds should be allocated to a CYP2C19*2 PGx programme in a fixed budget environment.

A cost benefit analysis (CBA), was undertaken to quantify the population’s WTP for a POC PGx. The comparator for this analysis is the status quo (i.e. universal clopidogrel scenario). Since the standard PGx test may not be clinically feasible due to the longer turnaround time for results, the comparison of universal clopidogrel directly to the POC PGx is more clinically realistic and thus more informative. The underlying assumption is that since the turnaround time for the standard PGx is 3-7 days, the standard PGx test may not prevent adverse side effects for patients treated with clopidogrel and who have a loss of function allele.

The CBA includes a budget impact analysis, a WTP value and net productivity gains. The BIA would assess the net budget impact to the Ontario hospital system of implementing the PGx test to ACS patients. This analysis would provide information on whether targeting drug therapies to ACS patients would generate cost savings to hospitals. A separate BIA would assess the downstream impact on the Ontario Drug Benefit budget. A CBA will include a willingness to pay input elicited through a DCE. A DCE would also assess the preference of the characteristics of the PGx test from the general population in Ontario. Net productivity gains was based on data reported by the Conference Board of Canada.
Hypothesis

i. The general population may pay additional insurance premiums to have specific (quicker turnaround time/cheek swab) attributes of a PGx test privately covered.

ii. There is no a priori expectations as to the budget impact on Ontario hospitals

iii. There is no a priori expectations as to the budget impact on the ODB

iv. There may be a net social benefit to implementing the PGx test in Ontario hospitals

Goal: To quantify the net social benefit of implementing a PGx test in Ontario hospitals

Objectives:

i. To create a survey that would quantify preference and willingness to pay for a PGx test in Ontario

ii. To create a budget impact analysis that would measure the financial impact of introducing a PGx test to the Ontario hospital system

iii. To create a budget impact analysis that would measure the clinical impact of introducing a PGx test to the Ontario drug formulary

iv. To quantify the productivity losses as a result of implementing a POC PGx test in Ontario.

v. To operationalize the cost of illness formulae thus measuring the net social benefit of introducing a PGx test in Ontario

Research questions

Primary research question is:

What is the net social benefit of introducing a point of care pharmacogenetic test to patients with acute coronary syndrome in Ontario hospitals?

Secondary research questions:

i. What is the willingness to pay by Ontario residents in additional annual insurance premiums when introducing a point of care pharmacogenetic test (CYP2C19*2) to Ontario hospitals? (presented in chapter 2 and 3).
ii. What is the budget impact of administering a POC PGx (CYP2C19*2) test compared to the status quo of administering clopidogrel to patients diagnosed with ACS in Ontario hospitals? (presented in Chapter 3)

iii. What is the budget impact to the Ontario Drug Formulary, after administering a POC PGx test (CYP2C19*2) in patients diagnosed with ACS? (presented in Chapter 3)

iv. What is the productivity lost/gained of implementing a CYP2C19*2 PGx test to acute coronary system patients in Ontario hospitals? (presented in Chapter 3)
Chapter 2: Preference for attributes of a point of care pharmacogenetic test (CYP2C19*2): A Discrete choice experiment

Overview of techniques available to evaluate preferences and how to operationalize a cost benefit analysis

A feature of economic evaluations is that there are no absolute measures of value but only equivalences of value between (at least two) compared products or services. This feature gives rise to the notion of preferences. Quantifying preferences can help describe the benefits and costs enjoyed or incurred by an individual. For example, to measure the extent of the benefit enjoyed by an individual, we could measure how much that individual is willing to give up in return for receiving that benefit. Alternatively, a cost is incurred whenever an individual gives up something of value presumably in return for some form of compensation. By not claiming that any specific dimension of life (health, happiness, wealth) has absolute value, economic evaluations avoid taking a definitive stance on what is ‘good’ for people. Economic evaluations simply use relative valuations that are revealed through individual preferences.25

A cost benefit analysis (CBA) is a type of a full economic evaluation that takes into consideration patient preference. CBA is based on the principles of welfare economics.24 The key assumptions of welfare economics are that: 1) social welfare is made up of the welfare of each member of society and that 2) individuals are the best judges of their own welfare. The CBA is operationalized as follows:

\[(\text{WTP + Savings}) - \text{Cost} = \text{Net Social Value}\]

The value associated with individual preferences (health and non-health benefits) is represented in monetary terms and expressed as ‘willingness to pay’ (WTP). WTP is the amount of a person’s own money or resources that they are willing to give up in exchange for acquiring a benefit. [“Savings” is the amount saved by not implementing an existing service or product and “Cost” is the amount required to fund a new service or
Valuing benefits (health and non-health related) in monetary terms allows for the CBA to be expressed in a single dimension (i.e. dollars). Other full economic evaluations (i.e. cost utility or cost effectiveness studies) are expressed using two dimensions such as cost per quality adjusted life year or cost per adverse event avoided.

WTP can be measured through either revealed or stated preference techniques. Revealed preferences rely on consumers’ actual spending patterns. As such, revealed preferences can be measured through market transactions or through other transactions such as court based decisions (awards). Alternatively, stated preferences rely on what consumers say they will do; that is, the amount that they would pay for a benefit if they were given the opportunity to purchase a good or service. Stated preferences are used in health care studies over revealed preferences for several reasons. First, most health care consumers are insured and thus do not pay out of pocket at the point of consumption, second, the agency relationship between clinician and patient confounds patient preference for healthcare technology, and third, market data for the healthcare intervention in question may not yet exist.

Other techniques are available to elicit stated preferences from the general population: contingent valuation or choice modelling. Contingent valuation methods ask respondents their maximum willingness to pay for a product or service, whereas choice modelling presents respondents with different attributes of a product or service. Individuals are then asked to indicate which of the hypothetical options in a choice set of attributes they would prefer. Data on individuals’ preferred options can be used to estimate individuals’ preferences over the different options.

A DCE is a type of choice modelling technique and is used when one assesses preferences (expressed as a WTP) for attributes or characteristics of a product or service. In a DCE, the different hypothetical products in the choice set consist of the different attributes or characteristics that make up a particular product or service. The resulting selections can be used to estimate individuals’ preferences or WTP for different levels of the different attributes.
DCE’s contribute to CBA in several ways: first by eliciting preferences, quantifying tradeoffs and predicting market uptake and second, measuring outcomes as inputs in an economic evaluation. Since the DCE has the ability to quantify the marginal values in monetary terms, it could be used to quantify a WTP. Coefficient estimates derived through a DCE can be transformed into WTP values which will help operationalize the CBA equation.

The attributes for this study include turnaround time for results, and how the sample is taken from a patient. Of particular interest to decision makers could be the respondents’ preferences for a quicker turnaround time. In an ACS setting, the quicker the clinician has access to the results, the quicker the clinician would be able to prescribe appropriate pharmacotherapy. Turnaround time for results from standard PGx test could take between 3 to 7 days while results from a bedside PGx test could take approximately 1 hour. For patients with ACS, waiting for 3 to 7 days to learn the outcome of the PGx test may be moot since prescribing clopidogrel may already have incurred adverse events during the wait, thus rendering the standard PGx tool as immaterial. Alternatively, turnaround time from the POC PGx test is provided in an hour, thus reducing the risk of adverse events for the patient.

In this study, DCE was used for the following reasons: first, unlike contingent valuation, choice modelling does not explicitly ask about their maximum willingness to pay and therefore may be easier for people to understand and respond to; second, the research question requires a WTP for different levels of each individual attribute of a pharmacogenetic test; also, more data can be collected from each individual when using choice modelling which may offer a more ‘efficient’ means of sampling than contingent valuation. Furthermore, the internal and external validity of DCE has been established in literature. DCEs have the capacity of providing welfare consistent estimates and as such can be used as part of a CBA. Finally DCE avoids some of the bias that may be associated with contingent valuation method, including lack of scope sensitivity, strategic biases, warm glow effect, and ‘yea-saying’.
Patient preference is gaining some recognition from regulatory agencies. A report by the Food and Drug Administration (FDA) Centers for Devices and Radiological Health (CDRH) discusses the importance of bringing the patient’s perspective into CDRH benefit risk assessments, and recommends that sponsors interact with FDA staff regarding the development of patient centered benefit risk information.\textsuperscript{61} As a result of this initiative, the Medical Device Innovation Consortium (MDIC) Patient Centered Benefit Risk (PCBR) Project was formed. While there are no widely accepted approaches for assessing patient preferences for use in a regulatory process, the MDIC has set out to help the FDA incorporate patient preference data into their decision making process.\textsuperscript{61} A list of considered techniques to quantify individual preferences is listed in that report and includes the discrete choice experiment (DCE) methodology.

In contrast, the alternative to choice modelling is contingent valuation. In one type of contingent valuation, a “bidding game” is employed to estimate WTP. A WTP value is obtained through an iterative mechanism. The iterative process begins when the researcher chooses a starting point WTP value that is presented to the respondent. The respondent either accepts or refuses that value. If the respondent accepts, the bid value is raised. This process is repeated until the respondent no longer accepts the WTP value. On the other hand, if the respondent refuses the starting point value, the bid value is lowered. This process is repeated until they arrive at a cost value that the respondent is WTP. One of the major disadvantages of the bidding game method, for eliciting willingness to pay values, is the possibility of anchoring or a “starting point bias”. This bias would be present if respondents were found to be influenced by starting values and the succeeding bids resulting from the starting point of the bidding game. DCE results could also be potentially affected by starting point bias. As far as I am aware, no published DCEs have examined this issue. Another disadvantage to the bidding game method is the risk of “yea-saying”. “Yea saying is described as a situation where respondents accept to pay specified amounts in order to avoid the socially embarrassing position of saying no.”\textsuperscript{62}

Funding for novel POC PGx tests in the Canadian setting will depend on the economic efficiency of the technology. Assessment of the WTP would facilitate cost benefit analysis by capturing preferences for attributes associated with a PGx test. Thus, a
discrete choice experiment was developed to quantify preference weights as well as a 
willingness to pay for attributes of a PGx test for the CYP 2C19*2 allele.

Research question
The research question specific to this chapter is as follows:
What is the willingness to pay by Ontario residents in additional annual insurance 
premiums upon introducing a point of care pharmacogenetic test to Ontario hospitals?

Methods
This portion of the thesis describes the design of the DCE, how the DCE was delivered 
how the respondents were sampled. Furthermore, a description of the data, and the 
regression analysis used to generate the coefficients and the method by which willingness 
to pay was calculated is also presented.

Generation of data
Survey platform

A web (internet) based survey tool was developed to deliver the survey to respondents. 
The web design used PHP (Post Hypertext Preprocessor) scripting language. The web 
pages were linked to a MySQL database used to store the pre-defined choice sets and to 
capture the responses from survey participants. JavaScript was used on some of the 
pages to control navigation options.

Subject recruitment

The target population from which preferences were elicited included both potential 
‘users’ and ‘non-users’ of the PGx test. For this study, the ‘user’ population includes 
people who are currently at risk of suffering from ACS. Non-users are people who may 
want the product available even though they have no intention of purchasing it at the 
present time or currently exhibit any of the risk factors listed.

Sample size
Lancsar et al state that the sample size calculation is dictated by numbers of choice sets and number of versions. Furthermore, empirical evidence suggests that 20 respondents per group of choice sets are sufficient to estimate reliable models. Given this assumption, and based on 8 choice sets, the sample size is estimated to be $8 \times 20 = 160$ respondent. Furthermore, two versions of the questionnaire were created. Respondents would be randomly allocated to a version of the DCE where the cost components are either $0, $1, $5 or $0, $2, $10. As such the target sample size will be doubled to 320 respondents.

Overview of data collection

Each respondent to the DCE portion of the survey was provided with two hypothetical pharmacogenetic tests. These tests varied in the values of two test attributes (sample extraction and turnaround time) and an additional annual insurance premium that the respondent would be required to pay to have the test covered by the health plan. Therefore, each respondent was provided with 8 choice sets, each consisting of two alternative options. As such the maximum number of observations given an expected sample of 320 respondents (assuming all agree to take the DCE) could be 5,120. A screenshot of a choice set example is presented hereunder.

Methods used to estimate WTP using these data are described below. The survey was disseminated electronically. A market research firm was contracted to disseminate the full survey. The participants were recruited through EKOS Research database. EKOS uses random digit dialing to recruit panelists. EKOS does not compensate their panelists. Invitations to their database of panelists were sent out for this DCE. EKOS continued recruiting respondents until approximately 320 respondents had accessed the consent form.

The inclusion criteria were:

- Residents of Ontario
- General population 18 years of age or older
- Ability to understand and read basic English
Figure 13. Example of a discrete choice set presented to respondents who chose a POC PGx option.
Survey components

Consent form

The first page of the survey consisted of an informed consent form. At the bottom of the page, respondents were directed to three questions. The purpose of the questions was to assess potential respondents’ understanding of the content of the informed consent. Correct answers to all three questions implied consent and allowed respondents to continue. Incorrect answer to any of the three questions blocked respondent access to the survey. After this point, respondents could skip any question or exit the survey altogether. Respondents who provided their consent proceeded with the survey which was comprised of three components: an initial questionnaire, a decision tool and a discrete choice experiment (DCE). Screen shots of the survey are presented in Appendix 3.

Initial questionnaire

The initial questionnaire was designed to gather respondent characteristics. Questions included:

- What is your sex?
- What year were you born?
- What is the highest level of education attained?
- What is your labour force status?
- What is your marital status?
- Do you have private health insurance?
- Residence (urban/rural)
- Have you ever had a genetic test?
- Do you currently have or ever had heart disease?
- Is there heart disease in your family?
- Do you know of anyone who has or has had heart disease?
- Have you ever reacted badly to medication?
- Do you know of anyone who has reacted badly to medication?
- Have you ever been treated in hospital because you reacted badly to medication?
- Have you ever been prescribed?
  - Clopidogrel
  - Ticagrelor
  - Prasugrel
- Do you have any concerns about any type of genetic test?
- What is your family annual income?

The next section of the survey presented to the respondents was the decision board. A decision board is a decision support tool, which displays alternative clinical issues and consequences for each treatment option. To provide context, the decision board contained descriptions of: ACS, MACE, PGx test, risk of MACE by treatment option and the decision question. The clinical descriptions (ACS, MACE and Genetic test) were based on patient advocacy web sites and patient information sheets provided by the Ottawa Heart Institute. The clinical descriptions have been initially validated by a cardiologist, pharmacist and statistician. In this study, the purpose of the decision board was to have respondents choose between three generically labelled treatment options to treat their hypothetical ACS; status quo (without a PGx test), novel P2Y12 receptor blocker (without a PGx test) or a PGx test (which incorporates effects of both the status quo and a novel P2Y12 receptor blocker). The goal of the decision board was to help respondents answer the survey question: Which treatment option would you choose? A, B or C. Respondents choosing “C” (i.e. The PGx treatment option) proceeded to the DCE. The purpose of the DCE was to quantify the preference for each attribute that makes up the PGx, including a cost attribute, which will in turn be used to estimate a WTP value for each attribute of the PGx test.
Risk of clinical effect

The clinical effects that were communicated to the respondent were major adverse coronary event (MACE) and bleeding. Explanation of MACE was provided to the respondents. The probability of experiencing a MACE was expressed visually using a group of 100 dots filled with green, or red dots. (see screen shot of the decision board hereunder) Green dots (smiling faces) represent patients not experiencing a MACE or bleed under the treatment option, while red dots (sad faces) represent patients experiencing MACE or a bleed.

Rate of MACE and bleeding for each treatment option in the Decision Board was based on two head to head randomized controlled studies (TRITON-TIMI-38\textsuperscript{63} study and PLATO\textsuperscript{64}) as well as the genetic sub-studies\textsuperscript{14-16} from the respective trials. The TRITON-TIMI-38 compared efficacy and safety endpoints between clopidogrel and prasugrel; while the PLATO trial compared clopidogrel with ticagrelor. The rates of MACE are similar for clopidogrel compared to either prasugrel (12.10\% vs. 9.90\%; p<0.001) or ticagrelor (11.70\% vs. 9.80\%; p<0.001) trials. The numbers were rounded; as such the rate of MACE for Treatment A (clopidogrel) was 12\% and for Treatment B (ticagrelor) was 10\%. MACE rates are presented by pharmacotherapy and by polymorphism in Table 4. Risk of bleed rates are presented in Table 5.
Imagine a group of 190 patients who are treated for acute coronary syndrome with one of three treatment options listed on the left hand side of the page. On the right hand side of the page, there are pairs of boxes with faces that represent patients who will or will not have had a bad outcome.

- Patients with the green smiley face will not have had any bad outcomes from the drug.
- Patients with red frowning faces will have had bad outcomes from the drug.

<table>
<thead>
<tr>
<th>Description</th>
<th>MACE</th>
<th>Major and Minor Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment A</strong>: All patients are given a blood thinner.</td>
<td>![MACE Icon]</td>
<td>![Major and Minor Bleeding Icon]</td>
</tr>
<tr>
<td>Out of every 100 patients treated:</td>
<td>![88 patients have had a bad effect (MACE)]</td>
<td>![90 patients have had a major or minor bleed]</td>
</tr>
<tr>
<td>88 patients will NOT have had a bad effect (MACE).</td>
<td>![12 patients have had a bad effect (MACE)]</td>
<td>![5 patients have had a major or minor bleed]</td>
</tr>
<tr>
<td>4 patients will have had a major or minor bleed.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Treatment B</strong>: All patients are given a blood thinner.</td>
<td>![MACE Icon]</td>
<td>![Major and Minor Bleeding Icon]</td>
</tr>
<tr>
<td>Out of every 100 patients treated:</td>
<td>![90 patients have had a bad effect (MACE)]</td>
<td>![5 patients have had a major or minor bleed]</td>
</tr>
<tr>
<td>90 patients will NOT have had a bad effect (MACE).</td>
<td>![10 patients have had a bad effect (MACE)]</td>
<td>![5 patients have had a major or minor bleed]</td>
</tr>
<tr>
<td>5 patients will have had a major or minor bleed.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Treatment C</strong>: All patients are given a pharmacogenetic test. Some patients will get blood thinner “A”, others will get blood thinner “B”. Out of every 100 patients treated:</td>
<td>![MACE Icon]</td>
<td>![Major and Minor Bleeding Icon]</td>
</tr>
<tr>
<td>91 patients will NOT have had a bad effect (MACE).</td>
<td>![9 patients have had a bad effect (MACE)]</td>
<td>![4 patients have had a major or minor bleed]</td>
</tr>
<tr>
<td>9 patients will have had a bad effect (MACE).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 patients will have had a major or minor bleed.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 14. The decision board used to quantify the proportion of respondents who preferred the POC PGx option (i.e. Treatment C)
<table>
<thead>
<tr>
<th>Clinical trial</th>
<th>Type of allele</th>
<th>Clopidogrel</th>
<th>Prasugrel</th>
<th>Ticagrelor</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRITON TIMI</td>
<td>All patients</td>
<td>12.10%⁶³</td>
<td>9.90%⁶³</td>
<td>NA</td>
</tr>
<tr>
<td>TRITON TIMI/Genetic Sub studies</td>
<td>IM or EM (Fully functional)</td>
<td>8.00%¹⁴</td>
<td>9.80%¹⁶</td>
<td>NA</td>
</tr>
<tr>
<td>TRITON TIMI/Genetic Sub studies</td>
<td>PM or UM (LOF)</td>
<td>12.10%¹⁴</td>
<td>8.50%¹⁶</td>
<td>NA</td>
</tr>
<tr>
<td>PLATO</td>
<td>All patients</td>
<td>11.70%⁶⁴</td>
<td>NA</td>
<td>9.80%⁶⁴</td>
</tr>
<tr>
<td>PLATO/Genetic Sub studies</td>
<td>IM or EM</td>
<td>9.40%¹⁵</td>
<td>NA</td>
<td>8.30%¹⁵</td>
</tr>
<tr>
<td>PLATO/Genetic Sub studies</td>
<td>PM or UM</td>
<td>10.70%¹⁵</td>
<td>NA</td>
<td>8.30%¹⁵</td>
</tr>
</tbody>
</table>

LOF = Loss of function; IM or PM= Intermediate or poor metabolizer; MACE = Major adverse coronary event, UM or EM = ultra-rapid or extensive metabolizer; NA = not applicable
Table 5. Rate of bleed by pharmacotherapy (clopidogrel, prasugrel, ticagrelor).

<table>
<thead>
<tr>
<th>Clinical trial</th>
<th>Type of allele</th>
<th>Clopidogrel</th>
<th>Prasugrel</th>
<th>Ticagrelor</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRITON TIMI</td>
<td>All patients</td>
<td>1.8%†</td>
<td>2.4%†</td>
<td>NA</td>
</tr>
<tr>
<td>TRITON TIMI/Genetic Sub studies</td>
<td>IM or EM (Fully functional)</td>
<td>3.0%†</td>
<td>3.8%†</td>
<td>NA</td>
</tr>
<tr>
<td>TRITON TIMI/Genetic Sub studies</td>
<td>PM or UM (LOF)</td>
<td>2.9%†</td>
<td>4.5%†</td>
<td>NA</td>
</tr>
<tr>
<td>PLATO</td>
<td>All patients</td>
<td>3.8%†</td>
<td>NA</td>
<td>4.5%†</td>
</tr>
<tr>
<td>PLATO/Genetic Sub studies</td>
<td>IM or EM (Fully functional)</td>
<td>3.6%†</td>
<td>NA</td>
<td>3.9%†</td>
</tr>
<tr>
<td>PLATO/Genetic Sub studies</td>
<td>PM or UM (LOF)</td>
<td>3.2%†</td>
<td>NA</td>
<td>4.6%†</td>
</tr>
</tbody>
</table>

LOF = Loss of function; IM or PM = Intermediate or poor metabolizer; UM or EM = ultra-rapid or extensive metabolizer †Major bleeding related to non-CABG

Genetic sub-studies reported the rates of MACE by CYP polymorphism. Under the PGx option in the Decision Board (Treatment C), clopidogrel was prescribed to subjects with fully functional CYP2C19*2 allele, and either prasugrel or ticagrelor was prescribed to patients who carry a LOF CYP2C19*2 allele. The rate of MACE for Treatment C was based on the MACE rates by polymorphism for each drug and weighed by the proportion of either fully functional or LOF carriers to the total study population. The proportion of LOF carriers was similar in both the TRITON and PLATO genetic sub studies (28%). As such the rate of subjects with fully functional alleles was 72%. Therefore, MACE rates for the PGx option is 8.14% (28%*8.50% + 72%*8.00%) using the TRITON genetic sub-study and slightly higher at 8.60% (28%*9.40% + 72%*8.30%) based on the PLATO sub study. Conservatively, the rate of MACE under the PGx option was rounded up to 9.
Respondents choosing either Treatment A or Treatment B did not proceed to the DCE. A status quo option was represented by Treatment option A. As such, a forced choice alternative was avoided by using a status quo option (i.e. forcing respondents to choose between potentially unappealing alternatives). Those choosing Treatment C proceeded with the DCE.

Attributes, levels and choice sets

Respondents who chose the PGx option were presented with a series of choice sets. Each choice set described two hypothetical PGx tests, labelled generically “Choice A” or “Choice B” with different attribute levels. For each choice set, respondents were asked to choose their most preferred option.

Defining attributes and attribute levels

Selection of PGx test attributes and their related levels was based on a qualitative study and input from the committee members. First, a literature search yielded the qualitative study by Fargher et al, which identified patients’ and healthcare professionals’ perception about PGx testing. Second, an expert panel including a cardiologist (DS), epidemiologists (DC, GW) and health economists (PG, AL) was convened to validate the attribute and attribute levels. Third, characteristics of a novel PGx test and how they differed from currently available tests was also considered when determining attributes. The combination of these approaches led to the identification of the attributes and determining attribute levels. It is likely that the DCE did not include every attribute important to every respondent. However, the literature review and the face validation process likely captured attributes that were relevant to most of the respondents. For each respondent, each choice set was randomly paired and chosen from Table 6.
Table 6. List of possible choices for survey respondents (Choices derived from three attributes and three levels).

<table>
<thead>
<tr>
<th>Choice</th>
<th>Sample</th>
<th>Turnaround time</th>
<th>Cost, Version 1</th>
<th>Cost, Version 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Blood test</td>
<td>1 hour</td>
<td>$0</td>
<td>$0</td>
</tr>
<tr>
<td>2</td>
<td>Blood test</td>
<td>3 days</td>
<td>$0</td>
<td>$0</td>
</tr>
<tr>
<td>3</td>
<td>Blood test</td>
<td>1 week</td>
<td>$0</td>
<td>$0</td>
</tr>
<tr>
<td>4</td>
<td>Blood test</td>
<td>1 hour</td>
<td>$1</td>
<td>$2</td>
</tr>
<tr>
<td>5</td>
<td>Blood test</td>
<td>3 days</td>
<td>$1</td>
<td>$2</td>
</tr>
<tr>
<td>6</td>
<td>Blood test</td>
<td>1 week</td>
<td>$1</td>
<td>$2</td>
</tr>
<tr>
<td>7</td>
<td>Blood test</td>
<td>1 hour</td>
<td>$5</td>
<td>$10</td>
</tr>
<tr>
<td>8</td>
<td>Blood test</td>
<td>3 days</td>
<td>$5</td>
<td>$10</td>
</tr>
<tr>
<td>9</td>
<td>Blood test</td>
<td>1 week</td>
<td>$5</td>
<td>$10</td>
</tr>
<tr>
<td>10</td>
<td>Finger prick</td>
<td>1 hour</td>
<td>$0</td>
<td>$0</td>
</tr>
<tr>
<td>11</td>
<td>Finger prick</td>
<td>3 days</td>
<td>$0</td>
<td>$0</td>
</tr>
<tr>
<td>12</td>
<td>Finger prick</td>
<td>1 week</td>
<td>$0</td>
<td>$0</td>
</tr>
<tr>
<td>13</td>
<td>Finger prick</td>
<td>1 hour</td>
<td>$1</td>
<td>$2</td>
</tr>
<tr>
<td>14</td>
<td>Finger prick</td>
<td>3 days</td>
<td>$1</td>
<td>$2</td>
</tr>
<tr>
<td>15</td>
<td>Finger prick</td>
<td>1 week</td>
<td>$1</td>
<td>$2</td>
</tr>
<tr>
<td>16</td>
<td>Finger prick</td>
<td>1 hour</td>
<td>$5</td>
<td>$10</td>
</tr>
<tr>
<td>17</td>
<td>Finger prick</td>
<td>3 days</td>
<td>$5</td>
<td>$10</td>
</tr>
<tr>
<td>18</td>
<td>Finger prick</td>
<td>1 week</td>
<td>$5</td>
<td>$10</td>
</tr>
<tr>
<td>19</td>
<td>Cheek swab</td>
<td>1 hour</td>
<td>$0</td>
<td>$0</td>
</tr>
<tr>
<td>20</td>
<td>Cheek swab</td>
<td>3 days</td>
<td>$0</td>
<td>$0</td>
</tr>
<tr>
<td>21</td>
<td>Cheek swab</td>
<td>1 week</td>
<td>$0</td>
<td>$0</td>
</tr>
<tr>
<td>22</td>
<td>Cheek swab</td>
<td>1 hour</td>
<td>$1</td>
<td>$2</td>
</tr>
<tr>
<td>23</td>
<td>Cheek swab</td>
<td>3 days</td>
<td>$1</td>
<td>$2</td>
</tr>
<tr>
<td>24</td>
<td>Cheek swab</td>
<td>1 week</td>
<td>$1</td>
<td>$2</td>
</tr>
<tr>
<td>25</td>
<td>Cheek swab</td>
<td>1 hour</td>
<td>$5</td>
<td>$10</td>
</tr>
<tr>
<td>26</td>
<td>Cheek swab</td>
<td>3 days</td>
<td>$5</td>
<td>$10</td>
</tr>
<tr>
<td>27</td>
<td>Cheek swab</td>
<td>1 week</td>
<td>$5</td>
<td>$10</td>
</tr>
</tbody>
</table>

The tariff questions were asked in the context of hypothetical insurance purchase. The WTP related to this DCE was expressed as an additional annual expenditure in health insurance premiums.
Developing the experimental design

Factorial design

An experimental design is one where a sample is taken from a list of possible combinations given a set of attributes and attribute levels. (Complete list in Table 6) There are two types of experimental designs: full factorial or fractional factorial. A full factorial design elicits preferences from respondents based on all possible combinations of attributes and attribute levels. Given 3 attributes, each with 3 levels; the total number of possible scenarios, or a full factorial design is 27 ($3^3$). This type of design allows estimation of all main effects (effect of each attribute) and interaction effects (effect of interaction between two or more attributes) independently of one another. This study employed a full factorial design. However, when a full factorial is too large to be used in practice, a fractional factorial approach can be taken. Alternatively, a fractional factorial is a sample from the full factorial approach selected in such a way that all the effects of interest can be estimated. This can be achieved through the use of software packages such as SAS.

Ethics approval

The complete design of the DCE survey (including screenshots) was submitted for ethics approval. This study was approved by the Office of Research Ethics at the University of Toronto. (Protocol reference # 31225) A study completion form was submitted in February 2016 with the Office of Research Ethics and the file is now deemed complete as per the Tri-Council Policy Statement guidelines.

Piloting

Piloting was carried out using an initial version of the web based survey. This pilot study consisted of administering a draft version of the questionnaire to a convenience sample of 25 respondents. Respondents were recruited through friends and acquaintances.
Consideration was also given to identifying possible respondents who were 65 years of age or older in anticipation that this age group would be answering the online final version of the survey. Piloting the DCE helped assess task complexity through an informal feedback from participants. Adjustments to the survey were made based on participant feedback. Results of the pilot have been presented in poster format.68

Generation of coefficients
A description of data analysis is described next. This section describes how the data is transformed from the DCE responses to the coefficients used to quantify preferences and WTP. As such, a brief review of the DCE may be useful.

Once in the DCE section of the survey, each respondent is presented with a choice set that lists two attributes and a cost component (an example of a choice set is presented hereunder). Each respondent is presented with eight of these choice sets.

![Figure 15. Example of choice set presented to respondents](image)

Each choice set is generated randomly from a list of alternatives presented in Table 6. A value of 1 is attributed to the alternative chosen by the respondent. By default, a value of 0 is attributed to the alternative not chosen. Therefore, each respondent generates 8 sets of responses or vectors with a value of 1. (i.e. each vector describes the preferred type of PGx test chosen by the respondent, each with its own set of attributes and cost level). Coefficients used to quantify preferences and WTP are estimated using the maximum
likelihood estimation. The maximum likelihood estimate of a vector of parameter values $\beta$ is simply the specific vector $\beta^{MLE}$ that gives the greatest probability of obtaining the observed data.

DCEs are based on integrated behavioural theory of decision making and choice behaviour; the random utility theory (RUT). More descriptively, DCE is based on Lancaster’s economic theory of value, wherein the underlying assumption is that individuals derive utility from components, characteristics or attributes of the product or service under valuation. The underpinning of DCE also includes elements of the economic theory of consumer behaviour that assumes consumers are rational decision makers and that they seek to maximize their benefits from their choices. Under the traditional properties of the neoclassic consumer, Ryan et al describe DCEs as the “optimisation problem in which the consumer selects the consumption bundle such that their benefit (utility) is maximised subject to their budget constraint.” However, Ryan et al go on to describe three extensions of classic consumer theory: the assumption of homogenous goods, the continuous space of products (i.e infinitely available products) and the assumption of a deterministic behaviour of consumers. In furtherance to the classic consumer theory, Lancaster’s theory relaxes the assumption of the homogenous good and allows for the attributes of the good or service to determine the utility provided to the consumer. Changes in the availability of the attribute, can result in a discrete switch from one product with one set of attributes to another product with a different set of attributes. Seemingly, this would allow for a better understanding of consumer preferences. Secondly, discrete choice theory allows for a finite set of products that are mutually exclusive. This means that the consumer may only choose one set of attributes at a time. Finally, compared to the classic consumer theory which assumes consumer behaviour as deterministic, discrete choice theory allows for the ‘randomness’ of consumer behaviour. Random utility in economic theory suggests that individuals have some idea of what utility they may glean from a set of alternatives and that they have complete discretion over that value. However, there are practical implications to deciphering how and why consumers respond to a given set of attributes. Short of entering the realm of the consumers’ mind and observing all factors that affect
preferences there is really no way of taking into consideration all possible reasons upon which consumers base their decisions.

However, there are options. An econometric description of a latent utility given alternative $i$ in a choice set $C_n$ (as presented to individual $n$) can be disaggregated into two parts: a systematic or explainable component and a random or unexplainable component ($\epsilon$). The explainable component can be expressed as a function of attributes of the alternatives presented to individual $n$, $V(X_{in}, \beta)$ while the idiosyncratic preferences unique to individual $n$ and alternative $i$. According to Lancsar, economists view random components as being due to several factors including: unobserved attributes affecting choice, inter-individual differences affecting choice, heterogeneity of tastes, measurement errors and functional specification while psychologists view this component as being due to inherent variability between and within individuals. The latent utility can be expressed as follows:

$$U_{in} = V(X_{in}, \beta) + \epsilon_{in}$$

The underlying assumption is that individual $n$ will choose alternative $i$ if and only if that alternative maximizes their utility amongst $N$ alternatives included in the choice set $C_n$. In other words, the underlying assumption is that the subject will choose the option that maximizes their utility value given the two alternative presented to them. Meanwhile, the systematic component is a function of the observed attributes of the alternatives to the utility $U_{in}$ derived from $i$ is commonly expressed as:

$$V(X_{in}, \beta) = a + \beta_1 x_{1n} + \beta_2 x_{2n} + \ldots + \beta_k x_{kn}$$

Where $X$ is the vector of attributes, (e.g, cost, turnaround time, sample extraction) and a constant capturing the mean effect of the unobserved factors of the error terms for each of the alternatives, $k = 1,2,3\ldots$ of $K$ attributes (including cost) and $\beta$ representing the unknown parameters associated with each attribute.

Model estimation

Lancsar and Louviere state that the form of the model depends on two factors: first, on the experimental design, specifically whether interaction effects are identified and/or alternatives are labelled and second, the type of choice modelled (i.e. binary choices which would imply binary models or multiple choices implying multinomial models).
In this study, respondents were provided two choices per choice set. Different choice models offer different assumptions about distributions and properties around error components.\textsuperscript{58}

Both Ryan et al\textsuperscript{26} and Kennedy\textsuperscript{72} describe various alternatives to model estimation. Binary or dichotomous choice models are appropriate when the respondents in the DCE are presented with two alternatives (as is the case in this study). In this study, respondents were presented with two generically labelled options (option A or option B). Probit specification is assumed to be appropriate where the error terms is distributed as a normal distribution, with a zero mean and a constant variance. Alternatively, given an assumption of a logistic distribution, a binary logit model can be used. Both binary and logit model could lead to similar parameter estimates up to scale. With panel (survey data), random effects can be used to take into account the multiple (i.e. 8 choice sets) observations obtained from each respondent. Most DCE analysis for binary data has been carried out using a conditional (binary) logit method.\textsuperscript{72}

In this study, respondents choose one of two options presented to them. In each choice set, respondents were presented with a set of attributes for two hypothetical PGx tests. As such the dependent variable is discrete (not continuous). The analysis is concerned with whether an event has occurred or not. Binary logistic regression is a type of regression analysis where the dependent variable is a dummy variable (coded 0, 1). Predicted probabilities from a linear regression model would be problematic in this situation for several reasons: First, the error terms would likely be heteroskedastic. (does not validate the assumption that the error of the dependent variable are uncorrelated and uniform—hence that their variances do not vary with the effects being modeled). Second, the error term is not normally distributed because the probability takes on two values (0,1) thus violating another linear model assumption. Finally, in a linear model, the predicted probabilities can be greater than 1 or less than 0. The logistic regression model is simply a non-linear transformation of the linear regression. The "logistic" distribution is an S-shaped distribution function which is similar to the standard-normal distribution. The logit distribution constrains the estimated probabilities to lie between 0 and 1. For each estimator, either a standard frequentist approach or a Bayesian approach can be used.
Kennedy refers to the “violent” controversy among statisticians concerning the relative merits of Bayesian and non-Bayesian methods. The main difference between a Bayesian and non-Bayesian conditional logit analysis is their approach to probability. The Bayesian analyst views probability as a degree of ‘reasonable belief”; wherein probabilities are associated with degrees of confidence. However, for the frequentist, probability is viewed as a frequency with which an event would occur in repeated trials. This may seem counterintuitive given the interpretations we usually see regarding confidence intervals. Bayes analysis is a way of incorporating prior evidence on the values of the parameters that one is attempting to estimate. This prior evidence is expressed as a probability distribution over the possible values of the parameters. The estimates one gets from the dataset are combined with the prior evidence to generate updated set of beliefs re the probability distribution over parameters – this is known as a posterior distribution. In some circumstances, one might not have strong prior evidence regarding the parameter values, yet one would nonetheless use the Bayesian approach because making decisions on the basis of the parameter estimates (for instance to adopt or not adopt the genetic tests) is more natural when one expresses uncertainty in terms of a formal probability distribution over the parameters.

The Bayesian approach consists of several steps: 1) a distribution is identified a priori, most likely reflecting the researcher’s belief about the parameters in questions before looking at the data 2) The prior distribution is combined with the data to produce a posterior distribution which is the main output of the Bayesian analysis and 3) the posterior distribution is combined with a loss or utility function to allow a decision to be made on the basis of minimizing expected loss or maximizing expected utility.

However, in this case, there was no strong ‘belief” about the distribution of the parameters in question. As such a ‘non-informative’ or uninformative prior distribution was used to describe the values of the parameter. This infers that an equal probability is assigned to each parameter value which may in turn describe the distribution as rectangular or uniform.
The main advantages of using a Bayesian approach over the frequentist (i.e. conditional logit) approach is summarized by Kennedy. First, the Bayesian approach considers how the information in data modifies a researcher’s belief about parameter values. (In this case – a rectangular distribution). Secondly, extraneous information is consistently applied as opposed to ignored in the frequentist approach. Furthermore, the Bayesian approach is justified solely on the basis of prior and sample data and there is no need to justify the performance of the estimator in hypothetical repeated samples.

Once collected, the data was analyzed from the frequentist fixed effects and the Bayesian perspective. Both the fixed effects and random effects methods were used under the Bayesian paradigm. As such, there were three sets of output; frequentist, Bayesian random effects, and Bayesian fixed effects. Furthermore, analysis was based on three sets of data; the full sample size, the subset of the sample of respondents that was provided with the 0, 1 and 5 dollar cost attribute levels and the sample of respondents that was provided 0, 2 and 5 dollar attribute levels.

For completeness, the Hausman test was used to assess the equivalence of the Bayesian fixed and random effects estimates. If there is indeed no correlation between covariates and error term, then the two sets of estimates should produce similar results.

Regression analysis was generated using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA). Specifically, a BCHOICE procedure was used within SAS software to run a regression analysis for the discrete choice model. The SAS script for all three methods is in Appendix 4.

Welfare analysis

Welfare analysis refers to the estimation of the WTP. WTP for the various attribute levels is calculated in a relatively straightforward manner from the estimated coefficients. Assuming that respondents are utility maximizers, improvements to one attribute can be expressed as an equivalent to the deterioration of another attribute (compensation for improvement of an attribute). Functionally, WTP is derived by dividing the negative of: the estimated coefficient for a specific attribute level by the coefficient of cost.
More generally, in discrete choice models, the negative of the ratio of any two coefficients represents the respondent’s willingness to give up some amount of one attribute in order to achieve more of another. This concept stems from a standard economic model, wherein a consumer is faced with choosing between two goods A, or B. Assume the amount of A chosen is denoted as qA and the amount of good B chosen is qB where Q is the quantity desired. Utility from this basket of goods is expressed as U(qA, qB). Suppose that the amount of A consumed increases. This would increase U. What reduction in B would result in individual having same utility as before? This amount can be thought as the maximum willingness to pay (in terms of units of B) for the gain in A. When the increase in A is very small, then this maximum WTP is the ratio of the marginal utility of B to the marginal utility of A.

Consider now the utility function embedded in the econometric model

\[ V = \beta_1 \text{Turnaround time} + \beta_2 \text{Sample} + \beta_3 \text{cost} + \epsilon \]

The two attribute levels “Turnaround time” and “Sample” take on values of 0 or 1, whereas cost refers to the cost of the individual. The coefficient \( \beta_1 \) represents the change in utility (i.e. marginal utility) when the value for turnaround changes from 0 to 1. Similarly, the coefficient \( \beta_2 \) represents the change in utility when the value for sample changes from 0 to 1. \( \beta_3 \) represents the change in utility from a one dollar increase in cost. The “0” and “1” values for the two attributes correspond to the two options offered to the respondent. For example, the two values attributed to turnaround time in a given choice set offered to respondents are 1 week (turnaround = 0) and 1 hour (turnaround = 1). \( \beta_1 \) is the marginal utility from changing turnaround time from 1 week to 1 hour. Similarly, \( \beta_2 \) is the marginal utility from changing sample from one attribute level to another.

One can assess the maximum willingness to pay for a change in Turnaround time from 0 to 1 in terms of money (cost) by forming the ratio of the marginal utilities where the marginal utility of Turnaround time is \( \beta_1 \) and the marginal utility of cost = \( -\beta_3 \) thus the maximum willingness to pay for a turnaround time of one hour instead of one week is \( -\beta_1/\beta_3 \). Similarly, the marginal utility of the sample is \( \beta_2 \) and the marginal utility of cost =
- $\beta_3$ thus the maximum willingness to pay for a specific sample method is $- \beta_2/\beta_3$. In this DCE, survey participants were asked to consider trading off attribute levels for money.

The “delta” approach was used to quantify the confidence interval of the WTP values. This approach is described by Arne Risa Hole and is expressed as:

$$\text{VAR (WTP)} = \left((-1/\beta_{\text{cost}})^2 \text{VAR } \beta_{\text{cost}} + (\beta_{\text{attribute}}/\beta_{\text{cost}})^2 \text{VAR } \beta_{\text{cost}} + 2 (-1/\beta_{\text{cost}})(\beta_{\text{attribute}}/\beta_{\text{cost}}^2) \text{COVAR } \beta_{\text{attribute}}, \beta_{\text{cost}}\right)^2$$

$$\text{WTP} \pm Z_{\alpha/2} \sqrt{\text{VAR WTP}}$$

where $Z_{\alpha/2}$ is the inverse of the cumulative standard normal distribution.

Furthermore, the exponent of the coefficient was calculated to determine the odds ratio of an attribute being chosen over the reference attribute.

The regression model was specified using the “Average Economic Regression” (AER) approach described by Kennedy. Under the AER approach, the researcher begins with a specification that is assumed to be correct. In this study, the $R^2$, adjusted $R^2$ (maximum scaled $R^2$), determine whether variables should be added to the specification for a more correctly specified model (i.e. “testing up”).

Inter-respondent variation was dealt with in the design of the DCE, as each respondent was presented with eight randomly generated choice sets. Willingness to pay (WTP) for each level of a given attribute was calculated by dividing the negative of the estimated $\beta$ coefficient for each attribute by the coefficient of price.

SAS coding

SAS coding for conditional logit, Bayesian fixed effects and Bayesian random effects is provided in Appendix 2.

Starting bias

An interaction term was added to the regression model with the purpose of determining starting point bias in the DCE. For the cost attribute, approximately half of the
respondents to the survey were presented to each version. The interaction term considered data from the entire set and Version 1. Signs of the interaction term was assessed to determine whether there was any indication of starting point bias. If the starting point bias was significant then a regression for each version was carried out independently.
Results

Pilot study

Results from the pilot study were presented as a poster at the 37th Annual North American Meeting of the Society of Medical Decision Making in St. Louis. Responses were provided by 23 individuals for analysis. One individual completed the survey but chose a treatment option that did not include a PGx test. Therefore, 184 choice sets were completed providing 368 observations. Direction of the coefficients were as expected. Respondents were willing to pay slightly higher insurance premiums for quicker turnaround times for results and for a cheek swab compared to finger prick. While coefficients for the turnaround time were significant, the coefficients for sample method were not.

The feedback from pilot study participants were consistent. Navigation of the web site was improved so that respondents could go back and forth between pages. This was most helpful when participants wanted to refresh their memory about the definition of the underlying conditions, or see the rates of MACE or bleed. An information icon was added per respondent suggestions to provide clarity to either context or directions.

Full survey

Preliminary results were presented in poster format at the International Society of Pharmacoeconomic and Outcomes Research in Milan. The survey was conducted between June 1st and 10th, 2015. Invitations to participate in the survey were sent to 4,234 panel members. Of these, 387 initiated and 329 completed the survey, while 220 (66%) respondents chose the PGx treatment option.

Approximately 98% of respondent replied to each of the demographic questions with the exception of family income which garnered a 91% response rate. Table 7 presents sex, age, education and family income attributes of the respondents to the survey and
compared them the rates of the 2011 Census. The DCE survey under-represented the under 25 years of age category and those with a bachelor’s degree; while those with a graduate degree and households with an income of over $100,000 (CDN) were over-represented. Table 8 presents the remaining respondent characteristics. Over 60% were employed, 57% were married, and 76% were covered by private insurance. Most respondents were never exposed to a genetic test. With regards to concerns about genetic testing, 38% were concerned about confidentiality and 44% were concerned about privacy. Verbatim responses to an open-ended question about genetic tests are presented in Table 9. No changes were made to spelling or grammatical errors that may occur in the responses.

Among 328 respondents who completed an informed consent for the survey, 219 chose the PGx test option providing 3472 observations. Verbatim responses to open ended questions as to why the PGx test was not chosen are presented in Table 10.

The proportion of respondents who answered each question is illustrated in Figure 16. The figure shows that most of the respondents answered all the demographic questions presented to them. In this sample, respondents were most averse to answering questions related to annual family income and occupational status.

Figure 16. Proportion of respondents responding to demographics questions prior to filling out the DCE.
Starting point bias

Coefficient for the starting point bias was statistically significant regardless of the methods used to estimate the regression. The interaction term between “cost” and a version of the cost levels was significant regardless of the approach used. This coefficient (standard deviation) [Highest posterior density] for the frequentist and Bayesian random effects was 0.2268 (0.0354) [0.1557-0.2936] and 0.5481 (0.1483) [0.2583 - .8386]. The fixed effects results (standard error) were 0.2254 (0.0357) and was significant (<0.0001). These values suggest that starting point bias exists for this DCE. As such, analysis on all three data sets was carried out independently.
# Table 7. Survey demographics and comparison to Ontario population

<table>
<thead>
<tr>
<th></th>
<th>DCE Survey %</th>
<th>Ontario 2011 %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>46.7</td>
<td>48.1</td>
</tr>
<tr>
<td>Female</td>
<td>53.3</td>
<td>51.9</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>3.1</td>
<td>11.8</td>
</tr>
<tr>
<td>25-34</td>
<td>18.0</td>
<td>15.9</td>
</tr>
<tr>
<td>35-44</td>
<td>15.9</td>
<td>17.4</td>
</tr>
<tr>
<td>45-54</td>
<td>22.4</td>
<td>20.5</td>
</tr>
<tr>
<td>55-64</td>
<td>19.0</td>
<td>16.0</td>
</tr>
<tr>
<td>65+</td>
<td>21.9</td>
<td>18.5</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High school</td>
<td>22.1</td>
<td>40.9</td>
</tr>
<tr>
<td>College</td>
<td>26.1</td>
<td>33.6</td>
</tr>
<tr>
<td>Bachelor</td>
<td>4.5</td>
<td>15.7</td>
</tr>
<tr>
<td>Graduate</td>
<td>28.5</td>
<td>9.7</td>
</tr>
<tr>
<td><strong>Family Income</strong>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than 10,000</td>
<td>not captured</td>
<td>4.1</td>
</tr>
<tr>
<td>10,000-19,000</td>
<td>4.2</td>
<td>7.3</td>
</tr>
<tr>
<td>20,000-29,000</td>
<td>5.6</td>
<td>8.3</td>
</tr>
<tr>
<td>30,000-39,000</td>
<td>6.5</td>
<td>8.7</td>
</tr>
<tr>
<td>40,000-49,000</td>
<td>7.6</td>
<td>8.7</td>
</tr>
<tr>
<td>50,000-59,000</td>
<td>5.6</td>
<td>8.2</td>
</tr>
<tr>
<td>60,000-79,000</td>
<td>15.0</td>
<td>13.9</td>
</tr>
<tr>
<td>80,000-99,000</td>
<td>12.7</td>
<td>11.3</td>
</tr>
<tr>
<td>100,000 +</td>
<td>42.6</td>
<td>29.5</td>
</tr>
</tbody>
</table>
Table 8. Description of the demographics of the sample population that participated in the survey.

<table>
<thead>
<tr>
<th>Labour Force Status</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Employed at work</td>
<td>60.5%</td>
</tr>
<tr>
<td>Employed absent from work</td>
<td>2.4%</td>
</tr>
<tr>
<td>Not in labour force - able to work</td>
<td>27.3%</td>
</tr>
<tr>
<td>Not in labour force - permanently unable to work</td>
<td>9.2%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Marital Status</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Married</td>
<td>57.7%</td>
</tr>
<tr>
<td>Living common law</td>
<td>9.7%</td>
</tr>
<tr>
<td>Widow</td>
<td>4.4%</td>
</tr>
<tr>
<td>Separated</td>
<td>4.7%</td>
</tr>
<tr>
<td>Divorced</td>
<td>5.7%</td>
</tr>
<tr>
<td>Single, never married</td>
<td>17.8%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Private Health Insurance (Covered)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>76.6%</td>
</tr>
<tr>
<td>No</td>
<td>23.5%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Place of residence</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1000 people</td>
<td>6.3%</td>
</tr>
<tr>
<td>1000-29,999 people</td>
<td>13.4%</td>
</tr>
<tr>
<td>30,000-99,000 people</td>
<td>11.6%</td>
</tr>
<tr>
<td>over 100,000 people</td>
<td>68.7%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Have you ever had a genetic test?</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>9.7%</td>
</tr>
<tr>
<td>No</td>
<td>85.2%</td>
</tr>
<tr>
<td>I don’t know</td>
<td>5%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Have you ever had heart disease?</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>7.9%</td>
</tr>
<tr>
<td>No</td>
<td>92.1%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Family member with heart disease?</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>59.5%</td>
</tr>
<tr>
<td>No</td>
<td>40.5%</td>
</tr>
<tr>
<td>Question</td>
<td>Yes (%)</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Know of anyone with heart disease</td>
<td>84.7%</td>
</tr>
<tr>
<td>Have you reacted badly to medication?</td>
<td>41.3%</td>
</tr>
<tr>
<td>Family or friend reacted badly to medication?</td>
<td>61.3%</td>
</tr>
<tr>
<td>Have you been hospitalized because you reacted badly to medication?</td>
<td>10.8%</td>
</tr>
<tr>
<td>(To your knowledge) Have you ever been prescribed clopidogrel?</td>
<td>2.1%</td>
</tr>
<tr>
<td>Clopidogrel (% Yes)</td>
<td></td>
</tr>
<tr>
<td>Prasugrel (% Yes)</td>
<td>0.3%</td>
</tr>
<tr>
<td>Ticagrelor (%Yes)</td>
<td>0%</td>
</tr>
<tr>
<td>Concerns with genetic test?</td>
<td></td>
</tr>
<tr>
<td>Confidentiality (% Yes)</td>
<td>38.2%</td>
</tr>
<tr>
<td>Privacy (% Yes)</td>
<td>44.2%</td>
</tr>
<tr>
<td>Payment (%Yes)</td>
<td>51.1%</td>
</tr>
</tbody>
</table>
Table 9. Verbatim responses to survey from participants related to their concerns about genetic testing.

<table>
<thead>
<tr>
<th>Concern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethics, morals etc depending on specific test</td>
</tr>
<tr>
<td>Where the information ends up?</td>
</tr>
<tr>
<td>Unwillingness to know</td>
</tr>
<tr>
<td>Possible impacts on insurance / health care provision / acceptance by GP into a practice.</td>
</tr>
<tr>
<td>It may increase anxiety about condition</td>
</tr>
<tr>
<td>Unsure how the information would be used - for example, given to insurance companies/agencies</td>
</tr>
<tr>
<td>When private for profit establishments carry out such tests - does the doctor have financial interest</td>
</tr>
<tr>
<td>What to do when you knew definitively one way or the other.</td>
</tr>
<tr>
<td>I wonder if a genetic predisposition might be seen as a guarantee of an illness</td>
</tr>
<tr>
<td>But I did pay to have one done</td>
</tr>
<tr>
<td>How useful are they?</td>
</tr>
<tr>
<td>Long term ethical questions if a condition was identified .. Concern re false positives or negatives.</td>
</tr>
<tr>
<td>Does it have any useful options for treatment</td>
</tr>
<tr>
<td>Efficacy, what medical professional performing the tests</td>
</tr>
<tr>
<td>Legal concerns related to discrimination based on genetic testing results, as there is no law.</td>
</tr>
<tr>
<td>Proper counciling</td>
</tr>
<tr>
<td>Evidence regarding genetic testing</td>
</tr>
</tbody>
</table>
Table 10. Verbatim responses from sample population as to why PGx test was not chosen

1) The differential was not worth it

2) No significant difference between B and C while C requires additional work on my part

Option c provides very little benefit over option b. Difference was not significant related to cost.
At my age there is little use of much testing
The results do not significantly differ. The improvement of C over B is minimal.
There is not enough of a difference in outcomes between option B and C to warrant additional tests
most reasonable option
Risk : reward. Adding the pharmacogenetic test did not seem to affect the outcomes significantly.
What was the difference between a and b? unclear.
If the test is not covered by health care, and i not able to afford it, i would take the least risk.
The odds difference was negligible so why waste the time and money?
The risk didn't really seem to be much less than treatment C and there'd be no waiting for the test.
Didn't want to wait for the test results. Want to begin treatment immediately.
I did not perceive that the pharmacogenetic test would reduce the risk by enough to make taking it
Differences in results so minimal there is no major advantage to C
There doesn't seem to be much difference either way.
There didn't seem to be much difference in the outcome if I had gone for the test. So why bother?
The statistical difference between B and C is minor. Testing gives no real benefit.
Similar result but with a lower cost.
I have no problem having a pgx test, even if costly, but it would not make a big diff in this case.
Simple, not much difference
The results between B-C are so similar that it is a waste of money to test all people.
it might be faster and save your life without waiting for the test
There was not enough of a difference to warrant the cost associated with the test.
The risk of me experiencing less mace ,minor/major bleeding are almost identical to treatment c
I was conflicted about this. Had a hard time choosing between b and c.
There was very little difference in the outcome between B and C. Not worth getting test.
minimize time to treatment (delay)
The difference between option B and option C was negligible considering the cost and time needed. The results are close between B and C. Not enough benefit over-rule my concerns on Genetic testing. It looks like the decreased number of reactions is not worth the cost or time of 100 tests. 90% unaffected is a good number. The data indicates a relatively insignificant difference between having or not having the test. Percentage wise B was similar risk to C (which required MACE). Choice was random because no info on: urgency and severity, time of obtaining the results, cost. Outcome was negligible, that the added cost seems wasteful. Not a significant reduction in risk.

Regression analysis

Results from regression analysis are presented in Table 11. Estimates are statistically significant for three day and one week turnaround and well as for cost regardless of the sample on which they were calculated. The odds that a respondent chose the 1 hour turnaround time was 14 times that of the 1 week turnaround time (23 times for Version 1 and 12 times for Version 2). For the full data set as well as the C$0, $2, $10 costs attribute version, estimates are not significant for coefficients related to the method of sample extraction. Demographic characteristics (family income level, sex, age, access to private insurance, current heart disease, hospitalization due to adverse events) were not associated with the cost attribute.

Willingness to pay values for all attributes are presented in Table 12. From a frequentist approach, WTP for a 1 hour compared to a 1 week turnaround time for results was $10.77(9.58,12.25), $6.77(5.82,7.91), 12.72(10.82,15.01) for the entire data set, Version 1 and Version 2 respectively. Values were lower when comparing 1 hour turnaround times to 3 day turnaround times. Furthermore, WTP values were lower when using coefficients from the random effects approach for the entire data set, as well as for the $0,2,10 set. For the $0,1,5 set, WTP values were similar to slightly higher for turnaround time.
Diagnostic results are presented in Table 13. Adjusted rsquare values are comparable to those found in literature (see Table 3). This regression model yielded an adjusted rsquare of 0.4155 compared to those found in literature of 0.4850. AIC values were also comparable to those found in literature (1904 in the literature review vs 1606 in this study. The Durbin Watson values suggest that there is no serial correlation in the model. Furthermore, based on AIC values, Version 1 and Version 2 define what these mean models fit better than if data were analyzed as a full data set.
Table 11. Summary of coefficient estimates: Bayesian Fixed effects, Bayesian Random effects and frequentist approach.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Bayesian Fixed Effects</th>
<th>Bayesian Random Effects</th>
<th>Frequentist</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Standard Deviation</td>
<td>95% HPD Interval</td>
</tr>
<tr>
<td><strong>Entire Data Set</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost</td>
<td>-0.2451</td>
<td>0.0153</td>
<td>0.2379 - 0.2146</td>
</tr>
<tr>
<td>TurnaroundTime 1_hour</td>
<td>2.6370</td>
<td>0.1420</td>
<td>2.3703 - 2.9186</td>
</tr>
<tr>
<td>TurnaroundTime 3_days</td>
<td>1.0751</td>
<td>0.1121</td>
<td>0.8470 - 1.2839</td>
</tr>
<tr>
<td>Sample Blood_cheek swab</td>
<td>0.0826</td>
<td>0.1043</td>
<td>-0.1210 - 0.2811</td>
</tr>
<tr>
<td>Sample Finger_prick</td>
<td>-0.0119</td>
<td>0.1070</td>
<td>-0.2188 - 0.1968</td>
</tr>
<tr>
<td><strong>Choice version ($0, $1, $5)$</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost</td>
<td>-0.4682</td>
<td>0.0401</td>
<td>-0.5451 - 0.3859</td>
</tr>
<tr>
<td>TurnaroundTime 1_hour</td>
<td>3.1676</td>
<td>0.2515</td>
<td>2.6787 - 3.6624</td>
</tr>
<tr>
<td>TurnaroundTime 3_days</td>
<td>1.3833</td>
<td>0.1842</td>
<td>0.9945 - 1.7158</td>
</tr>
<tr>
<td>Sample Blood_cheek swab</td>
<td>0.3333</td>
<td>0.1678</td>
<td>0.0100 - 0.6599</td>
</tr>
<tr>
<td>Sample Finger_prick</td>
<td>0.00596</td>
<td>0.1676</td>
<td>-0.3187 - 0.3335</td>
</tr>
<tr>
<td><strong>Choice version ($0, $2, $10$)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost</td>
<td>-0.1978</td>
<td>0.0161</td>
<td>-0.2278 - 0.1648</td>
</tr>
<tr>
<td>TurnaroundTime 1_hour</td>
<td>2.5107</td>
<td>0.1849</td>
<td>2.1582 - 2.8676</td>
</tr>
<tr>
<td>TurnaroundTime 3_days</td>
<td>0.9510</td>
<td>0.1491</td>
<td>0.6541 - 1.2348</td>
</tr>
<tr>
<td>Sample Blood_cheek swab</td>
<td>-0.0741</td>
<td>0.1375</td>
<td>-0.3447 - 0.1860</td>
</tr>
<tr>
<td>Sample Finger_prick</td>
<td>0.0103</td>
<td>0.1445</td>
<td>-0.2602 - 0.2976</td>
</tr>
</tbody>
</table>

HPD = Highest posterior density
Table 12. Summary of willingness to pay estimates: Bayesian Fixed effects, Bayesian Random effects and frequentist approach.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Bayesian Fixed Effects</th>
<th>Bayesian Random Effects</th>
<th>Frequentist</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>WTP C$</td>
<td>WTP C$</td>
<td>WTP C$</td>
</tr>
<tr>
<td>Entire Data Set</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TurnaroundTime 1_hour vs 1 week</td>
<td>10.75 (9.48, 12.22)</td>
<td>9.62 (7.91, 11.75)</td>
<td>10.77 (9.58, 12.25)</td>
</tr>
<tr>
<td>TurnaroundTime 3_days vs 1 week</td>
<td>4.38 (3.44, 5.36)</td>
<td>4.01 (2.98, 5.16)</td>
<td>4.40 (3.50, 5.42)</td>
</tr>
<tr>
<td>Sample Blood_cheek swab vs blood</td>
<td>0.34 (-0.50, 1.17)</td>
<td>0.58 (-0.20, 1.38)</td>
<td>0.34 (-0.47, 1.18)</td>
</tr>
<tr>
<td>Sample Finger_prick vs blood</td>
<td>-0.05 (-0.92, 0.80)</td>
<td>0.18 (-0.45, 0.83)</td>
<td>-0.06 (-0.95, 0.80)</td>
</tr>
<tr>
<td>Choice version ($0, $1, $5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TurnaroundTime 1_hour vs 1 week</td>
<td>6.77 (5.81, 7.99)</td>
<td>6.81 (5.23, 8.81)</td>
<td>6.77 (5.82, 7.91)</td>
</tr>
<tr>
<td>TurnaroundTime 3_days vs 1 week</td>
<td>2.95 (2.19, 3.78)</td>
<td>2.91 (1.90, 4.07)</td>
<td>2.96 (2.21, 3.78)</td>
</tr>
<tr>
<td>Sample Blood_cheek swab vs blood</td>
<td>0.71 (0.00, 1.44)</td>
<td>0.83 (0.04, 1.50)</td>
<td>0.72 (0.01, 1.44)</td>
</tr>
<tr>
<td>Sample Finger_prick vs blood</td>
<td>0.01 (-0.71, 0.74)</td>
<td>0.11 (-0.45, 0.72)</td>
<td>0.00 (-0.72, 0.72)</td>
</tr>
<tr>
<td>Choice version ($0, $2, $10)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TurnaroundTime 1_hour vs 1 week</td>
<td>12.69 (10.81, 14.95)</td>
<td>10.99 (8.31, 14.75)</td>
<td>12.72 (10.82, 15.01)</td>
</tr>
<tr>
<td>TurnaroundTime 3_days vs 1 week</td>
<td>4.37 (3.26, 6.42)</td>
<td>4.37 (2.71, 6.34)</td>
<td>4.83 (3.44, 6.44)</td>
</tr>
<tr>
<td>Sample Blood_cheek swab vs blood</td>
<td>-0.37 (-0.82, 1.02)</td>
<td>-0.07 (-1.42, 1.19)</td>
<td>-0.36 (-1.73, 1.01)</td>
</tr>
<tr>
<td>Sample Finger_prick vs blood</td>
<td>0.05 (-1.45, 1.49)</td>
<td>0.00 (-1.23, 1.18)</td>
<td>0.04 (-1.44, 1.42)</td>
</tr>
</tbody>
</table>

WTP C$ = Willingness to pay in Canadian dollars
Table 13. Diagnostic: Predictive, Deviance and Goodness of fit of the regression model.

<table>
<thead>
<tr>
<th></th>
<th>R²</th>
<th>Adjusted R²</th>
<th>AIC w/o covariates</th>
<th>AIC w covariates</th>
<th>Likelihood ratio</th>
<th>p value</th>
<th>Wald</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>entire data set</td>
<td>0.2078</td>
<td>0.4155</td>
<td>2403.834</td>
<td>1606.181</td>
<td>807.65</td>
<td>&lt;0.0001</td>
<td>428.17</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>version 1</td>
<td>0.2108</td>
<td>0.4217</td>
<td>1296.185</td>
<td>863.415</td>
<td>442.77</td>
<td>&lt;0.0001</td>
<td>241.49</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>version 2</td>
<td>0.2298</td>
<td>0.4596</td>
<td>1107.649</td>
<td>700.376</td>
<td>417.27</td>
<td>&lt;0.0001</td>
<td>195.5</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Deviance</th>
<th>Pr &gt; ChiSq</th>
<th>Pearson</th>
<th>Pr &gt; ChiSq</th>
<th>Hosmer Lemeshow (Chi sq)</th>
<th>Pr &gt; ChiSq</th>
<th>Durbin Watson (cost)</th>
<th>1st order autocorrelation (cost)</th>
</tr>
</thead>
<tbody>
<tr>
<td>entire data set</td>
<td>92.6709</td>
<td>&lt;0.0001</td>
<td>91.7189</td>
<td>&lt;0.0001</td>
<td>41.1573</td>
<td>&lt;.0001</td>
<td>1.698</td>
<td>0.151</td>
</tr>
<tr>
<td>version 1</td>
<td>92.6709</td>
<td>&lt;0.0001</td>
<td>91.7189</td>
<td>&lt;0.0001</td>
<td>41.1573</td>
<td>&lt;.0001</td>
<td>2.01</td>
<td>-0.005</td>
</tr>
<tr>
<td>version 2</td>
<td>92.6709</td>
<td>&lt;0.0001</td>
<td>91.7189</td>
<td>&lt;0.0001</td>
<td>41.1573</td>
<td>&lt;.0001</td>
<td>2.01</td>
<td>-0.005</td>
</tr>
</tbody>
</table>
Discussion

Both the frequentist and Bayesian fixed effects approaches yielded consistently similar WTP results regardless of data set used. Bayesian random effects yielded slightly lower WTP values when using the entire data set and when using the ($0, $2, $10) data subset. Results from the entire sample set were significant for the turnaround time of the PGx test results. Results for how the patient’s sample was extracted were not significant. The significance of results were similar for the subset of data ($0,$1,$5) and ($0,$2, $10).

The results were significant for the coefficients related to the turnaround time and not for the method by which the patients’ sample was extracted. For the ($0,$1,$5) data subset, the WTP values were similar regardless of the approach used; $6.77 ($5.81, $7.99) for Bayesian fixed effects, $6.77 ($5.82, $7.91) for frequentist and $6.81 ($5.23, $8.81) for the Bayesian random effects. However, WTP value differed for the ($0,$2,$10) data subset; with Bayesian fixed effects and frequentist approaches yielding similar results, $12.69 ($10.81, $14.95) and $12.72 ($10.82, $15.01) respectively and lower for the Bayesian random effects, $10.99 ($8.31, $14.75). The odds ratio of choosing the 1 hour turnaround time over the 1 week turnaround time were higher (OR = 23) using the $0,$1,$5 data set than the $0,$2,$10 data set (OR=13).

The primary objective of this DCE was to determine WTP for attributes of a PGx test in order to inform a CBA. Table 12 presents thirty-six possible WTP values, generated from 3 data sets and 3 approaches to regress the data. The question now becomes which value(s) to use for the CBA and its ensuing sensitivity analysis? While no rule was found that states whether separate sets of cost values can be used to generate an aggregate cost coefficient (and by extension a WTP value), the exercise would be similar to presenting one result for two research questions. This leaves twenty-four values to consider from either the $0,$1,$5 data set or the $0,$2,$10 data set. One can argue that coefficient values that are statistically non-significant could be removed from consideration. In this case, the coefficient values for how the patients’ sample would be obtained, could be ignored. This leaves us with WTP values for the 2 attributes of turnaround time. Since the novel product offers a 1 hour turnaround time, the WTP for 1 hour versus 1 week would be more informative to the decision makers.
Next, we decide which turnaround time results to use in the CBA, ones generated from the Bayesian random effect, Bayesian fixed effects or frequentist approach. Given than results are similar between all three approaches of values generated from the $0,$1,$5 dataset, the questions is moot. The results are wider in the $0,$2,$10 dataset. To take a conservative approach, the random effects value for the 1 hour versus 3 day turnaround time will be used for the CBA. Therefore, the mean WTP value of $2.91 will be used to inform the subsequent base case CBA. For the sensitivity analysis, the confidence interval will be used (1.90,4.07)

Goodness of fit and deviance
The goodness of fit and deviance statistics is within the ranges reported in published articles. Table 3 Specifically, the AIC in this DCE was 1606 compared to a range of 1904.4 and 0.8386 from published studies. The AIC was lower (i.e. better) for the data subsets, suggesting the Version 1 and Version 2 models fit better than the model for the aggregate dataset. Similarly, the log likelihood (807 in this study compared to a range of 1426 and -940614) and Wald statistics (428 compared to a range of 729 and 27) were comparable. As with the AIC values, the log likelihood was lower for the data subsets. The adjusted r square value of .4155 (i.e. the model explained 41% of the data variation) was close to the .4890 value reported in the only other article reported r square values in our sample set. A Durbin Watson test of approximately 2 suggests no autocorrelation in the residuals.

Bias
The random effects estimator is considered unbiased whenever its composite error is uncorrelated to the explanatory variables. In this study, the random assignment of choice sets to individuals rendered the independent variables uncorrelated with the error term. In this situation, the random effects estimator is preferred to the fixed effects estimator since the former is more efficient (has lower variance) than the latter. The WTP value generated from the random effects model will be used as an upper limit for the CBA sensitivity analysis.

The respondents generated for this survey were randomly sampled from the general population. Specifically, no respondents were targeted for this survey. Nevertheless, the fixed effects
estimator is more robust than the random effects estimator to selection bias issues. Results from
the fixed effects model will be used as a base case for the CBA.

Strategic bias

Behavioural economists have looked at the extent to which people can be expected to answer
truthfully and to what extent they are liable to tailor their answers in order to try to manipulate the
outcome of a survey. For example, Dan Ariely in his book “The honest truth about dishonesty”
argues that almost all people lie and cheat by a small amount (10-15% of respondents) at every
opportunity they get. In other words it is possible that 10-15% of participants provided a
response that differs from their true response in an attempt to influence the provision of the good.

For example, a respondent could have chosen consistently high cost attribute levels if they
believed this would enable the pharmacogenetic test to get covered by either a public or private
plan. While it is possible that respondents to this DCE could have chosen consistently high or
consistently low cost attribute levels, the choice sets were randomly generated; meaning that cost
attributes of some pairs of choice sets could have been either a low of $0 for both choice sets or,
alternatively, $5 (depending on the version) for both choice sets; forcing the respondent to
choose between levels of the other two attributes.

Furthermore, for strategic bias to occur, the respondent would need to comprehend the
relationship between 1) what they say they are willing to pay for the attribute levels presented, 2)
the consequent likelihood of provision of the PGx test and 3) the amount they would then actually
have to pay. Given that the respondents were presented with 16 different hypothetical products,
it is unlikely that they could identify this relationship. It is therefore unlikely that strategic bias
would be possible in a DCE.

Compliance bias - Interviewer

The quality of data collection can be affected both positively and adversely by the
presence of an interviewer. Interviewer bias occurs when a respondent provides an
answer that differs from their true answer in an attempt to please an interviewer. Given
that this DCE was presented on a web based platform, the absence of an interviewer
provides greater anonymity for eliciting information about income, or attitudes about
genetic testing. There was no need to address interviewer bias by training interviewers
and ensuring quality control by monitoring interviewer presentation during the course of
the survey.

Positive elements of the using interviewers to present surveys included the function of
acting as an agent for the researcher. The interviewer could intervene when the
respondent is unclear about the question, or if the respondent overlooks a question or
fails to follow the instructions of the questionnaire. In this web-based survey, all
respondents who were directed to proceed to the DCE part of the questionnaire
completed the DCE. No choice sets were overlooked or skipped.

Compliance bias - Sponsor bias

This type of bias occurs when respondents provide an answer to please the sponsor of
the survey. My name along with that of Dr Papadimitropoulos was clearly stated at the
outset of the survey along with the statement that the questionnaire was part of my
doctoral thesis. Sponsor bias was hopefully mitigated by stating at the outset of the
survey that the answers provided would not affect the academic standing of the
researcher.

Starting point

Starting point bias occurs when respondents are found to be influenced by the starting
values (in the case of other methods – succeeding bids) used in the survey. Starting point
bias may lead to a large number of outliers (i.e. unrealistically large bids) and to ‘yea-
saying’ (i.e. accepting to pay the specified amounts to avoid the socially embarrassing
position of having to say no.

There was evidence of starting point bias in this DCE. However, given that there was no
bidding game, there was no opportunity for ‘yea-saying’ and therefore no unrealistically
large values related to costs. Nevertheless, this study shows the importance of choosing
‘reasonable’ levels for cost attributes included in DCEs.
Item non-response

This occurs when a respondent fails to answer a key question. Over 90% of respondents need spell check the doc answer all demographic questions. All respondents who were directed to the DCE completed all 8 choice sets.

Sample frame bias

Bias could occur if the sample list of potential interviewees is incomplete in some manner. Because of the platform used, those individuals who do not have access to internet were not asked to participate. Nevertheless, from a gender perspective, the respondent population is similar to that of the population that answered the Canadian Census for 2011 in Ontario. However, there are some differences in the ages of the respondents compared to the census. One would expect that the younger population would be more responsive to replying to an online survey. What in fact happened was that there was proportionally fewer respondents in the under 25 year age category compared to the Ontario census. This may be due to the fact that potential respondents were told that the survey was health related – a topic that may not be of interest to the average 18 year old.

Self-selection

The National Oceanic and Atmospheric Administration (NOAA) panel by Arrow et al (1993), recommended that face to face surveys be used for all “major” studies involved with litigations for natural resource damages. The options available to the panel were either face to face or postal–telephone surveys. The argument for postal–telephone surveys was that this method was a more affordable alternative. The argument against the postal–telephone survey was that these methods would lead to self-selection bias since a large proportion of those who return the survey would likely be those who are interested in the topic of the survey. This may lead to unrepresentative samples. One can argue that the same can be said about internet based surveys. In this DCE, over 4000 invitations were sent out before the target sample size was gathered.

A simple random sample is one where each member of the population has an equal probability of being included in the sample. A skewed sample would be one where certain members of the population are more likely to be in the sample than others. To correct for skewness (if
necessary), an analyst would attribute an above average weight to observations that have a low probability of being in the sample and a below average weight to observations that have a high probability of being in the sample.

Generalizability of results
In this survey, the percentage of male and female respondents were similar to that of the 2011 Canadian Census for Ontario. (Male: Survey vs 2011 census = 46.7% vs 48.3 %.) As such no weighting was warranted. However, for other demographic characteristics, the values between the sample population and the 2011 Census population are larger than those observed for gender. For example, the survey is especially underweighted in the 25-year-old and younger age bracket. (Survey vs 2011 Census: 3.1% vs 11.8%), and somewhat in the 35-44 year-old bracket (15.9% to 17.4%). The survey was slightly overweighed the 25-34 year-old bracket (18.0% vs 15.9%) 45-54-year-old bracket (22.4% vs 20.5%) and the 65-year-old and over bracket (21.0% vs 18.5%). Overall, younger respondents (i.e. <65) were 15% more likely to choose a higher cost value than older respondents (i.e. 65 +). This suggests that the values generated by the model are conservative. However, given that the sample population is underweight respondents who are 65 years of age or younger, and that this group tended to choose higher cost values, one can extrapolate that the weighting this demographic variable to match the 2011 Census would likely generate higher WTP values. On the other hand, wealthier (100-150K+) families were more likely to choose an option with higher cost than families with other income brackets (60-89K). The sample population for this study was over represented by families earning $100,000 and higher compared to families earning less than $100,000 (42.6% vs 29.5%). As such, this differential may have biased results to the upside. Lastly, the survey was over represented by respondents with a graduate degree.

External validity

The male:female proportion of the respondents in this survey are similar to those of the 2011 Census figures for Ontario. With the exception of the under 25-year-old age bracket, proportion of other age brackets are also similar to the 2011 Census.
Internal validity

The signs of the parameters were consistent with a priori expectations. It was expected that a quicker turnaround time would be preferable to a longer turnaround time. Also expected was that the cheek swab method of sample extraction would be preferable to the finger prick or blood drawn methods. While the cheek swab method was preferred, the coefficients were not statistically significant.

This DCE did not test for ‘rationality’ of choices. The conventional approach to test for ‘irrationality’ within a DCE is to include non-satiation or dominance tests. A non-satiation test is one where one of the options has no worse levels for any of the attributes and better levels for at least one of them. However, some authors have suggested that such tests are easy to satisfy.

Limitations

Common endpoints from the TRITON and PLATO and their related genetic sub studies are MACE and bleeding. In each study, MACE was described as a composite endpoint that included cardiovascular death, myocardial infarction and stroke. As such, a comparable rate for MACE for each treatment alternative was taken from all studies and conveyed to survey respondents. However, a comparable rate for bleeding, one that is reported in all studies was not identified. While the rate for major or minor bleeds was reported in the TRITON, PLATO and the genetic sub study for TRITON; only the rate for major bleeding was reported in the PLATO genetic sub-study. Since a common rate was not reported in all trials, a common bleeding rate cannot be conveyed in the survey.

While another limitation of DCE, and contingent valuation more generally, is that individuals are not spending actual dollars. As such, their responses are not constrained by their own budgets or incomes. One limitation of this study is that the data did not capture respondents’ ability to pay for their choices. In retrospect, the survey could have asked an exit question to determine whether respondents were able to, or could afford to, pay for the PGx test they chose.

Another limitation is related to the attributes included in the DCE. For example, some respondents were concerned about confidentiality and privacy issues related to the DCE. Had there been an attribute that described levels of privacy, the resulting WTP may have varied from...
the reported results. Patients were also not told about the twice daily administration of ticagrelor compared to the once daily prasugrel or clopidogrel. This may also have swayed the eventual WTP results. On the other hand, this DCE also excluded the hospitals’ perspective or preference related to the PGx test. The novel POC PGx test would not have needed addition training to operate and as such may have provided some value to the hospital administrators.

A further limitation is related to the attribute levels for the WTP. The question that is asked of the respondent is how much more they are willing to spend in annual health insurance premiums in exchange for coverage of the PGx test. This question pre-supposes that the respondent is aware of their current level of health insurance premium expenditure. Although no studies have been located that shed light on this particular aspect of consumer awareness, it is unlikely that the average respondent would be aware of this amount. Therefore, providing a national average prior to the survey may be helpful for the respondent. Furthermore, knowing this amount would provide the basis of creating the attribute levels for the WTP.

Conclusion
Nine percent of those contacted online chose to respond to the survey, and 85% of those who initiated the survey completed all answers. Two thirds of those who responded chose the PGx option. The direction of the coefficients were as expected with respondents preferring shorter turnaround times to longer turnaround times and a cheek swab to blood draw (although the coefficients for the latter were not statistically different). Coefficient values were similar between conditional logit and the Bayesian fixed effects approaches to the data. Analysis suggests that starting bias is present. This means that determining values for cost components influence the results. Some respondents were concerned about privacy and confidentiality issues around PGx testing.

Key points
- An on-line survey was created
- Clinical data from 5 studies were used to inform clinical parameters
- A market research firm (EKOS) was contracted to disseminate the full survey. EKOS uses random digit dialing to recruit panelists.
- Attributes and levels were based on a previously published qualitative study
• Three attributes with three levels each were used allowing for a full factorial design
• Only main effects were measured
• Choice sets were randomly produced and presented to each respondent
• The clinical benefit presented to respondents was approximately 3% for MACE and between 0% and 1% for major bleeds
• A conditional logit, Bayesian random effects and Bayesian fixed effects approached were used to regress panel data
• Coefficient values for attributes were similar regardless of the approaches
• Over 4,000 members from the EKOS database were contacted
• 387 respondents initiated the survey and 329 completed the survey
• 66% of respondents chose the PGx option
• The 25 and younger age group was under-represented in the sample while the 65 and older group was overrepresented in the sample
• The sample had a higher proportion of respondents with a graduate degree than that of the general population
• Respondents were concerned about privacy and confidentiality around the PGx test
• Respondents seem to understand the benefit of the PGx test
• It is possible that not all relevant attributes were presented to the respondents
Chapter 3: Economic evaluations of a Point of Care Pharmacogenetic Test (CYP2C19*2) in Ontario: A Cost Benefit Analysis

Introduction

This chapter brings CBA components together in order to quantify the net social benefit of introducing a POC PGx test to all Ontario hospitals. The components of a CBA include: a population level WTP, a hospital BIA and a BIA for the ODB as well as indirect costs. WTP will be derived using values presented in Chapter 2. Indirect costs will be derived in this chapter and presented as changes in productivity.

Willingness to pay

An overview of the type of preference used to quantify the aggregate WTP is presented in the Introduction section of Chapter 2. In short, the aggregate WTP value in this study is a measure of a populations’ aggregate stated preference. Stated preference quantifies the hypothetical amount paid for a good or service. In contrast, revealed preference can be interpreted as the amount an individual would pay in the market. Given that the POC PGx is not currently funded by the provincial government, a stated preference was quantified.

The aggregate WTP will be derived using two components of the survey presented in Chapter 2. The first component will be derived from a survey question that immediately preceded the DCE. After the presentation of the decision board, respondents to the survey were asked which treatment option they would prefer. This decision would have been made based on the decision board. The decision board compared rates of adverse events and bleeds between universal treatment options and a POC PGx option. This portion essentially measures the proportion of the population that would be willing to pay zero (WTP = 0) for the POC PGx test. Now the task is to find the incremental value of the POC PGx test. The key feature that distinguishes universal treatment options and the POC PGx test option is the rates of adverse events and bleeds. The lower rates of AE and bleed under the POC PGx option is due to the knowledge that some patients have a LOF of the CYP2C19*2 allele. Arguably, the quicker we know this information, the quicker the clinicians can optimize treatment for ACS patients. While results from standard
PGx test take 3-5 days, results from the POX PGx test take 1 hour. Assuming that the rates of
AE and bleeds are positively correlated to the turnaround time, one could assume the WTP for
the standard PGx test would fall somewhere between the WTP for universal clopidogrel and the
WTP for the POC PGx test. In other words, the incremental WTP between the universal
treatment options and standard PGx test would be lower than the incremental WTP between the
universal treatment options and the POC PGx. Nonetheless, this study will assume an equivalent
WTP for the universal treatment options and the standard PGx test (i.e. WTP=0). This will
provide a conservative incremental WTP for the POC PGx test.

The survey results (presented in Chapter 2) indicate that 34% of the respondents preferred the
universal clopidogrel or ticagrelor option to the POC PGx option. Therefore, the WTP for the
POC PGx is thus zero for all those who chose the universal clopidogrel option (i.e. 34% of the
respondents). Alternatively, 66% of respondents preferred a POC PGx option. The individual
WTP for turnaround time was applied to the 66% of the working population in Ontario that
preferred the use of a PGx test. This value was used to reflect the incremental population level
stated preference for the POC PGx over universal clopidogrel. As such this aggregated value will
be included as the WTP value in the CBA formula.

Budget impact analysis

The next component of the CBA includes two BIA’s; one from the hospital perspective and one
from the ODB perspective. However, a BIA is not considered a full economic evaluation. As a
review, Drummond et al define a full economic evaluation as “…the comparative analysis of
alternative courses of action in terms of both their costs and consequences.”

Full economic evaluations include: cost utility analysis (CUA), cost effectiveness analysis (CEA) and
cost benefit analysis (CBA). While the types of costs that are considered in each of these analyses are
the same within a stated perspective, consequences are dealt with differently. For example,
consequences in a cost effectiveness analysis are measured in natural units (i.e. number of
fractures avoided, disability live years gained). Consequences in a CUA are measured in quality
adjusted life years. In a CBA, consequences are measured in monetary terms and are expressed
in terms of “willingness to pay”.

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The outcome from a cost utility or cost effectiveness analysis informs decision makers as to the price of implementing the technology in question. To decide whether to cover this technology, a decision maker would need some threshold to compare this price against. Alternatively, the output from a CBA does not require a threshold, and explicitly informs the decision maker on whether to implement a technology. A CBA measures the net social benefit of implementing a new technology. Since consequences are measured in monetary terms, adding them to costs saved from abandoning one technology then subtracting the costs incurred from implementing a new technology yields a simple numeric output. A positive net social value suggests that implementing the new technology is worthwhile to society (i.e. a positive social benefit) while a negative number would suggest otherwise.

A BIA can be used to inform a full economic evaluation (specifically a CBA). A BIA assesses the differential in the estimated (monetary) expenditure of implementing one intervention within a health care system compared to implementing a comparison intervention. A BIA facilitates the task of ranking reimbursement activities for decision makers. BIA assessments could be ranked or compared by the extent to which a new technology would impact the budget of a pre-specified health care system budget. For example, the Ontario Ministry of Health may use the BIA to prioritize which interventions to cover in the hospital system.

The BIA assesses the costs saved by not implementing the status quo (universal clopidogrel) and assesses as the costs incurred by introducing the novel POC PGx intervention. The BIA in this thesis considers these costs from the Ontario hospital perspective and from the ODB perspective. In this analysis, costs include, not only the costs of the intervention, but the costs incurred from the adverse events under each scenario. Since the standard PGx intervention may not avert a higher number of adverse events or bleeds than the universal clopidogrel scenario, the assumption for this thesis is that the costs incurred from adverse events and bleeds incurred under the standard PGx test and universal clopidogrel and equivalent. The BIA will inform the net financial impact to the hospital system in Ontario and the net financial impact to the ODB. A CBA will incorporate BIA values and along with the WTP value and the productivity values, help answer the question of whether or not the programme is worthwhile. A resulting positive net social value will suggest that the hospitals expand their budget, while a negative social value would suggest otherwise.
The Ontario provincial government will spend $17.4 billion funding hospitals for the 2016-2017 fiscal year.\textsuperscript{77} This represents an increase of approximately $345 million from the 2015-2016 budget and an end to a four year freeze on hospital budgets.\textsuperscript{78} The province of Ontario spends over one third of its total health care budget on hospitals.\textsuperscript{79} Despite the 1.9\% increase in funding, there are continued financial constraints on Ontario hospitals. For instance, hospitals in the Toronto, Hamilton, Windsor and Kitchener area, announced layoffs of more than 500 registered nurses in the first weeks of 2016.\textsuperscript{80} Therefore, given hospital budget constraints, hospital administrators are unlikely to adopt novel health technologies that will lead to an overall increase in the hospital budgets.

Implementing a POC PGx test to identify LOF carriers of the CYP2C19*2 allele would require an initial cash outlay by hospitals. However, the test may save money by avoiding expenditures on averted MACE or bleed events. On the other hand, the test may incur additional outlay downstream by the Ontario Drug Formulary, given that more patients would be prescribed the more expensive treatment, ticagrelor, under the PGx scenario.

A hospital specific BIA determines the net amount incurred by Ontario hospitals should a POC PGx test be covered by the Ontario government. A separate BIA for the net amount incurred by the Ontario Drug Benefit Formulary assesses the downstream impact should the PGx test be covered. Two BIAs will inform a CBA related to implementing a POC PGx test treatment strategy in Ontario: one for the Ontario hospital system and the other for the Ontario Drug Benefit formulary.

Indirect costs

The last component of the CBA formula considers the indirect costs attributable to the POC PGx. In this thesis, indirect costs will be determined by quantifying the productivity changes to society given the introduction of the POC PGx. Productivity changes can be measured through either the human capital approach or the friction method approach. The human capital approach suggests that the productivity lost depends on the time and cost of organizing a replacement, and the resulting adjustment in the economy. Under the friction method on the other hand, the productivity lost depends on the time span organizations need to restore the initial production
level. Several publications show that the human capital approach yield much higher values than the friction cost method. Both methods will be used to inform the CBA in this thesis.

Research Questions

This chapter addresses the following research question: What is the net social benefit of introducing a point of care pharmacogenetic (CYP2C19*2) test to patients with acute coronary syndrome in Ontario hospitals?

This research questions requires that the CBA be operationalized. As such, answers to the following research questions informed the CBA:

i. What is the willingness to pay (aggregated) by the Ontario population in additional annual insurance premiums when introducing a point of care pharmacogenetic test to Ontario hospitals?

ii. What is the budget impact to Ontario hospitals of administering a POC PGx test compared to the universal administering of clopidogrel to patients diagnosed with ACS?

iii. What is the budget impact to the ODB of administering a POC PGx test compared to the administering universal clopidogrel to patients diagnosed with ACS in Ontario hospitals?

iv. What is the productivity lost/gained of implementing a CYP2C19 PGx test to acute coronary system patients in Ontario hospitals?

To inform the CBA, an aggregate WTP value will be determined. This will be followed by quantifying the hospital and ODB BIA. Finally, productivity costs will be quantified under each scenario. A net social value will then be presented.

Methods

Quantifying an aggregate willingness to pay

The 2016 Ontario labour force figure of 7,525,600 workers was taken from the Statistics Canada website. An assumption is made that the working population will be covered by private insurance. Furthermore it is assumed that this population will be the hypothetical users of the PGx test. Individual WTP values were taken from the Chapter 2 results section of this thesis. The value of the turnaround time attribute (1hr vs 3 day week) was used. This is the only
attribute that generated statistically significant values. [$2.91 ($1.90, $4.01)] Furthermore, it is a more conservative value than the individual WTP for the turnaround time of 1 hour vs 1 week. This value ($2.91) will be multiplied by the population willing to take the POC PGx test and thus determine the aggregate WTP (societal incremental stated preference). This aggregate value will in turn inform the CBA. The proportion of those willing to pay for the test was taken from the survey. Of those respondents that initiated a survey, 66% chose the PGx treatment option. It is assumed that the rest of the population will have a stated preference value for the POC PGx test of zero. The WTP for method of sample extraction was not added, thus biasing the results to the downside.

Ontario Hospital and Ontario Drug Benefit Budget Impact Analysis

A BIA for Ontario hospitals in aggregate as well as for the Ontario Drug Formulary (ODB) is presented here. This BIA adheres to the principles and good practice guidance presented by the ISPOR Task force, authored by Sullivan et al.\textsuperscript{20} in “Budget Impact Analysis Principles of Good Practice: Report of the ISPOR 2012 Budget Impact Analysis Good Practice II Task Force”. The suggested key elements of the BIA are:

Perspective: The recommended perspective is that of the budget holder which in this case is the Ministry of Health and Long Term Care (MOHLTC). The research questions will be analyzed from the Ontario hospital budget perspective and a separate BIA will be carried out for the Ontario Drug Benefit formulary perspective.

Eligible population: The population considered in this BIA are patients who have been admitted to Ontario hospitals diagnosed with ACS. The proxy for a patient with ACS was a patient suffering from acute myocardial infarction (AMI). The incidence rate of 193 per 100,000 population for AMI was taken from the Canadian Institute for Health Information (CIHI) – Discharge abstract database. Assuming a population of 13,750,073 in 2015 for Ontario, the number of patients estimated to be diagnosed with AMI was 26,538 per annum or 2211 per month. Patients who are readmitted due to complications that arise from treatment of ACS were also considered. Readmissions are taken into consideration beginning from month 2 and considered in each month thereafter of a 12-month analysis. This BIA will assume that the status
quo option is: clopidogrel prescribed to all ACS patients. The base case comparison will be status quo compared to patients being administered a POC PGx test; with LOF carriers being prescribed ticagrelor and non-carriers being prescribed clopidogrel. This BIA will not consider ‘beyond restriction use’. That is to say, hospital patients who have not been diagnosed with ACS and may be candidates of being treated with clopidogrel for other conditions (established peripheral arterial disease; atrial fibrillation) are not considered in this BIA. Eligible patients for the ODB BIA are those individuals who are 65 years of age or older.

Current interventions: Currently, ACS patients are prescribed clopidogrel. Ticagrelor is also indicated for ACS. Prasugrel may also be considered with restriction, specifically prasugrel is not indicated for patients 75 years of age or older because of increased risk of fatal and intracranial bleeding. However, prasugrel is contraindicated in patients with transient ischemic attack (TIA) or stroke.

Uptake of new intervention and market effects: The introduction of the POC PGx test will have an impact on the number of follow up scripts written for clopidogrel, ticagrelor or prasugrel. As such, a separate BIA for the Ontario Drug Formulary was undertaken.

Off label use of intervention: No off-label use will be considered.

Cost of the current and new intervention mix: Only the cost of the POC PGx test will be considered. The standard PGx test or the non – POC version will not be considered as the clinical usefulness of this intervention is questionable. The standard PGx test may not avert more adverse events than the universal clopidogrel approach and may be costlier. Given these parameters, an economic evaluation may not be informative given the presumed dominance of universal clopidogrel over the standard PGx test.

A decision tree will inform the BIA. The decision tree takes into consideration the quicker turnaround time attribute of the POC PGx. Clopidogrel is generically priced in this model. Ticagrelor and prasugrel are currently in patent protection and will be off patient in 2018 and 2021 respectively.\textsuperscript{10,82}

Condition related costs: Hospital costs for fatal and non-fatal myocardial infarction, non-fatal stroke, major bleeds and death will be taken into consideration.
Indirect costs: In the BIA, no indirect costs will be considered. Impact on patient productivity or social services will not be considered as they have no impact on the hospital budget of the MOHLTC. Productivity costs will however be considered in a CBA context.

Time horizon: The decision tree was created to depict the patient pathway for 1 month. ACS patients were assumed to be treated within one month. Results from the one month decision tree were then extended to a one year time horizon. MACE events and bleeds related to the medication were assumed to be treated within one year of the intervention. As such no discounting, was used. For the secondary research question, (the Ontario Drug Benefit Formulary impact) a 5-year time horizon was taken into consideration since both prasugrel and ticagrelor will be going off patent within 5 years.

Choice of computing framework: The BIA will be computed using an Excel spreadsheet.

Uncertainty and scenario analysis: One way sensitivity analysis by changing the value of the following parameters will be undertaken:

- Number of estimated ACS patients
- Cost of PGx test
- Reducing the price of ticagrelor and prasugrel by 50% in anticipation of off patent pricing
- Mutually exclusive bleed rates with MACE (reducing the MACE rates by 50% or reducing the bleed rates by 50%)

Validation:
Internal validation: Validation included the verification of the model structure, including all formulae. Probabilities for each arm were summed to ensure they add to 1. Furthermore, the rate of MACE and bleed events was measured as patients move through the decision model and compared to clinical trials. Finally, results of the sensitivity analysis were compared to a priori expectations as another form of internal validation.

External validation: The ISPOR task force suggests that face validity be determined through agreement with relevant decision makers on the computing framework, aspects included, and
how they are addressed. This will not be taken into consideration for this thesis. However, external validation will be carried out should this academic research be presented at the Ministry level.

Decision tree: A decision tree was created to model the clinical pathway of ACS patients in Ontario hospitals. The decision tree was comprised of 6 arms or comparison treatment strategies:

Tree # 1) (Figure 17) PGx test Clopidogrel/Ticagrelor: In this arm, all ACS patients are given a POC PGx test prior to being prescribed anti-platelet treatment. Sensitivity and specificity of the test were taken into consideration. Patients with a fully functioning allele were prescribed clopidogrel. Patients with a LOF allele were prescribed ticagrelor. Patients then proceed to one of 5 possible branches: event free survival, non-fatal myocardial infarction, fatal myocardial infarction, non-fatal stroke and major bleed.

Tree # 2) (Figure 18) PGx test Clopidogrel/Prasugrel: In this arm all ACS patients are given a POC PGx test prior to being prescribed anti-platelet treatment. Sensitivity and specificity of the test will be taken into consideration. Patients with a fully functioning allele will be prescribed clopidogrel. Patients with a LOF allele will be prescribed prasugrel. Patients will then proceed to one of 5 possible branches: event free survival, non-fatal myocardial infarction, fatal myocardial infarction, non-fatal stroke and major bleed.

Tree # 3) (Figure 19) Clopidogrel (using ticagrelor head to head trial values): All ACS patients are prescribed clopidogrel. Patients will then proceed to one of 5 possible branches: event free survival, non-fatal myocardial infarction, fatal myocardial infarction, non-fatal stroke and major bleed.

Tree # 4) (Figure 21) Clopidogrel (using prasugrel head to head trial values): All ACS patients are prescribed clopidogrel. Patients will then proceed to one of 5 possible branches: event free survival, non-fatal myocardial infarction, fatal myocardial infarction, non-fatal stroke and major bleed.

Tree # 5) (Figure 20) Ticagrelor: All ACS patients are prescribed ticagrelor. Patients will then proceed to one of 5 possible branches: event free survival, non-fatal myocardial infarction, fatal myocardial infarction, non-fatal stroke and major bleed.
Tree # 6) (Figure 21) Prasugrel: All ACS patients are prescribed prasugrel. Patients will then proceed to one of 5 possible branches: event free survival, non-fatal myocardial infarction, fatal myocardial infarction, non-fatal stroke and major bleed.

Rates:

Estimated CYP2C19*2 LOF prevalence: The estimated prevalence of the Ontario population with a LOF was determined by combining several sources: data from published literature and data from the Ministry of Finance. First, Griese⁸³ reported an estimated prevalence of LOF for CYP2C19*2 by race in the general population from Western Australia. Santos⁸⁴ also reported CYP2C19*2 LOF by race based on samples taken from the general Brazilian population. The rates are reported in . This rate will be used to estimate the adverse events incurred in the universal clopidogrel arms.

Table 14. This rate will be used to estimate the adverse events incurred in the universal clopidogrel arms. Second, the proportion of the Ontario population disaggregated by race was taken from figures reported by the Ontario Minister of Finance.⁸⁵ A weighted mean was used to quantify the mean prevalence of the CYP2C19 LOF in the Ontario population. The BIA model used an prevalence estimate of 18.1%. This rate will be used to estimate the adverse events incurred in the universal clopidogrel arms.

Table 14. Estimated loss of function prevalence in the Ontario population based on published rates

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Range (%)</th>
<th>Mid-point taken (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ontario population by race</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>nr</td>
<td>79.00</td>
<td>Minister of Finance</td>
</tr>
<tr>
<td>Asian</td>
<td>nr</td>
<td>17.00</td>
<td>Minister of Finance</td>
</tr>
<tr>
<td>African American</td>
<td>nr</td>
<td>4.00</td>
<td>Minister of Finance</td>
</tr>
<tr>
<td><strong>Prevalence of LOF CYP2C19*2 allele by race</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>13-16.9</td>
<td>14.95</td>
<td>Griese; Santos</td>
</tr>
<tr>
<td>Asian</td>
<td>Nr</td>
<td>32.00</td>
<td>Griese</td>
</tr>
<tr>
<td>African American</td>
<td>Nr</td>
<td>20.20</td>
<td>Santos</td>
</tr>
<tr>
<td>Weighted average</td>
<td></td>
<td>18.10</td>
<td></td>
</tr>
</tbody>
</table>

nr=not reported

Sensitivity and specificity rates: Once the sub trees with the estimated prevalence of a LOF probability were inserted, sensitivity and specificity rates were taken into consideration.
Specificity rates (false positives) were applied to the LOF group. Sensitivity rates were applied to the fully functioning group. Sensitivity and specificity rates for the underlying POC PGx test was taken from the proof of concept study by Roberts et al.\textsuperscript{17} In that study 91 patients were included in the rapid genotyping group and 96 in the standard treatment arm. The point-of-care genetic test had a sensitivity of 100\% (95\% CI 92.3–100.0) and a specificity of 99.3\% (96.3–100.0).

Clinical rates: Clinical input rates are presented in Table 15. The rates for non PGx arms were taken from head to head randomized clinical trials. Rates for the clopidogrel and ticagrelor non PGx test arms were taken from the PLATO trial.\textsuperscript{64} In the PLATO trial; patients were included if they were hospitalized for an ACS, with or without ST-segment elevation, with an onset of symptoms during the previous 24 hours. Patients in the ticagrelor arm of PLATO were prescribed a loading dose of 180 mg followed by a dose of 90 mg twice daily. Patients in the clopidogrel arm were given a 300 mg loading dose followed by a dose of 75mg daily. For the PGx test arms (clopidogrel/ticagrelor), rates were taken from the PLATO genetic sub study reported by Wallentin et al.\textsuperscript{15} In the 2010 genetic sub-study Wallentin et al reported proportions for aggregate MACE. Rates for specific MACE events were not reported. As such, the proportion of the aggregate MACE rate to specific MACE events from the head to head trials was applied to the aggregate values for the loss of function rates and fully functioning rates. As such, rates for fatal MI, non-fatal MI and non-fatal stroke for the PGx arm (clopidogrel/ticagrelor) were derived from the published aggregate rates. Rates for the non PGx test arms related to clopidogrel and prasugrel were taken from the TRITON-TIMI 38 study. In that study, patients with moderate-to-high-risk unstable angina, with or without ST-elevation myocardial infarction were randomly assigned to either clopidogrel or prasugrel.\textsuperscript{63} Furthermore, patients were administered a loading dose of prasugrel 60 mg followed by maintenance doses of 10 mg; or a loading dose of clopidogrel 300 mg, followed by a maintenance dose of 75 mg daily. Rates used for PGx arms were taken from the TRITON-TIMI genetic sub studies published separately for clopidogrel and prasugrel.\textsuperscript{14,16}

Cost values: Cost values input into the model are presented in Table 16. The Canadian hospital cost data was based on the Canadian case mixing group “plus” (CMG) unit costs. While CMG is
based on the International classification of diseases (ICD) – 9th revision codes; CMG + is based on the ICD 10 classification codes.

Discount values: A discount rate of 1.5% will be applied to cost values.

Readmission rates: Readmission rates for stroke and non-fatal myocardial infarction were taken into consideration. The model assumed that readmission for either condition would occur in the month following the index hospitalization. Canadian readmission rates for stroke was 10.3% of patient initially treated for stroke and was taken from Johanssen et al. The corresponding rate for myocardial infarction was 5.6% taken from Kocial et al. 86

Mutually exclusive MACE and bleed rates: In the TRITON-TIMI trial, death from cardiovascular causes and fatal bleeding are not mutually exclusive, since intracranial hemorrhage and death after cardiovascular procedures that were complicated by fatal bleeding were included in both end points. However, these rates were assumed to be mutually exclusive in the decision model. This was done to account for the cost of each condition separately. This assumption will be dealt with in the sensitivity analysis by varying the bleed rates.

Decision trees: Decision tree diagrams for both the PGx test and non PGx test arms are shown below.
Table 15. Clinical data inputs used in the decision trees to calculate MACE and bleed rates

<table>
<thead>
<tr>
<th>Clinical parameter</th>
<th>Clopidogrel</th>
<th>Ticagrelor</th>
<th>Prasugrel</th>
<th>Author/Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head to Head trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MACE (Clopidogrel/Ticagrelor)</td>
<td>0.123</td>
<td>0.102</td>
<td>na</td>
<td>Wallentin 2009</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>0.069</td>
<td>0.058</td>
<td>na</td>
<td>Wallentin 2009</td>
</tr>
<tr>
<td>CV death (Fatal MI)</td>
<td>0.051</td>
<td>0.040</td>
<td>na</td>
<td>Wallentin 2009</td>
</tr>
<tr>
<td>Non – fatal Stroke</td>
<td>0.013</td>
<td>0.015</td>
<td>na</td>
<td>Wallentin 2009</td>
</tr>
<tr>
<td>Major bleed- non-CABG related</td>
<td>0.038</td>
<td>0.045</td>
<td>na</td>
<td>Wallentin 2009</td>
</tr>
<tr>
<td>MACE (Clopidogrel/Prasugrel)</td>
<td>0.121</td>
<td>na</td>
<td>0.099</td>
<td>Wiviott 2007</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>0.069</td>
<td>na</td>
<td>0.073</td>
<td>Wiviott 2007</td>
</tr>
<tr>
<td>CV death (Fatal MI)</td>
<td>0.051</td>
<td>na</td>
<td>0.021</td>
<td>Wiviott 2007</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.013</td>
<td>na</td>
<td>0.010</td>
<td>Wiviott 2007</td>
</tr>
<tr>
<td>Major bleed- non-CABG related</td>
<td>0.018</td>
<td>na</td>
<td>0.024</td>
<td>Wiviott 2007</td>
</tr>
</tbody>
</table>

Genetic sub-study Clopidogrel/Ticagrelor

<p>| MACE LOF                           | 0.112       | 0.086      | na        | Wallentin 2010|
| MACE Fully functioning             | 0.100       | 0.086      | na        | Wallentin 2010|
| Non-fatal MI LOF                   | 0.063       | 0.049      | na        | Derived proportion /MACE Wallentin 2009|
| Non fatal MI fully Functioning     | 0.056       | 0.049      | na        | Derived proportion /MACE Wallentin 2009|
| CV death (Fatal MI) LOF            | 0.043       | 0.030      | na        | Derived proportion /MACE Wallentin 2009|
| CV death (Fatal MI) Fully Functioning | 0.038     | 0.031      | na        | Derived proportion /MACE Wallentin 2009|
| Stroke LOF                         | 0.006       | 0.007      | na        | Subtract MACE from CV death and MI|
| Stroke Fully functioning           | 0.006       | 0.006      | na        | Subtract MACE from CV death and MI|
| Major bleed (non-CABG related) LOF | 0.032       | 0.046      | na        | Wallentin 2010|
| Major bleed (non-CABG related) non LOF | 0.036    | 0.039      | na        | Wallentin 2010|</p>
<table>
<thead>
<tr>
<th>Clinical parameter</th>
<th>Clopidogrel</th>
<th>Ticagrelor</th>
<th>Prasugrel</th>
<th>Author/Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic sub-studies Clopidogrel/Prasugrel</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-fatal MI LOF</td>
<td>0.101</td>
<td>na</td>
<td>0.066</td>
<td>Mega 2009, 2010</td>
</tr>
<tr>
<td>Non-fatal MI fully Functioning</td>
<td>0.075</td>
<td>na</td>
<td>0.081</td>
<td>Mega 2009, 2010</td>
</tr>
<tr>
<td>CV death (Fatal MI) LOF</td>
<td>0.020</td>
<td>na</td>
<td>0.010</td>
<td>Mega 2009, 2010</td>
</tr>
<tr>
<td>CV death (Fatal MI) Fully Functioning</td>
<td>0.004</td>
<td>na</td>
<td>0.016</td>
<td>Mega 2009, 2010</td>
</tr>
<tr>
<td>Stroke LOF</td>
<td>0.009</td>
<td>na</td>
<td>0.010</td>
<td>Mega 2009, 2010</td>
</tr>
<tr>
<td>Stroke Fully functioning</td>
<td>0.002</td>
<td>na</td>
<td>0.008</td>
<td>Mega 2009, 2010</td>
</tr>
<tr>
<td>Major bleed (non-CABG related) LOF</td>
<td>0.029</td>
<td>na</td>
<td>0.045</td>
<td>Mega 2009, 2010</td>
</tr>
<tr>
<td>Major bleed (non-CABG related) non LOF</td>
<td>0.030</td>
<td>na</td>
<td>0.038</td>
<td>Mega 2009, 2010</td>
</tr>
</tbody>
</table>

na = not available
Table 16. Cost values used in the budget impact model.

<table>
<thead>
<tr>
<th>DRG or CMG codes</th>
<th>DRG name/Dose</th>
<th>Related decision tree name</th>
<th>Canadian Dollars (2008)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRG 122 or CMG 194</td>
<td>Circulatory disorders with AMI w/o major complication - discharged alive</td>
<td>event free survival</td>
<td>7142.39</td>
</tr>
<tr>
<td>DRG 121 or CMG 193 &amp; CL 1</td>
<td>Circulatory disorders with AMI with major complication - discharged alive</td>
<td>non-fatal MI</td>
<td>11458.77</td>
</tr>
<tr>
<td>DRG 123 or CMG 194</td>
<td>Circulatory disorders with AMI - expired</td>
<td>fatal MI</td>
<td>7791.45</td>
</tr>
<tr>
<td>DRG 014 or CMG 028</td>
<td>Intracranial hemorrhage or cerebral infarction</td>
<td>stroke</td>
<td>5562.45</td>
</tr>
<tr>
<td>DRG 014 or CMG 028</td>
<td>Intracranial hemorrhage or cerebral infarction</td>
<td>major bleed</td>
<td>5562.45</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>75 mg</td>
<td></td>
<td>0.4735</td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>90 mg</td>
<td></td>
<td>2.9984</td>
</tr>
<tr>
<td>Prasugrel</td>
<td>10mg</td>
<td></td>
<td>2.7377</td>
</tr>
<tr>
<td>PGX test</td>
<td></td>
<td></td>
<td>200</td>
</tr>
</tbody>
</table>
Figure 17. Decision tree diagram – PGx test (Clopidogrel/Ticagrelor).

CYP2C19 Test - ticagrelor/clopidogrel

- Loss of function
  - Event free survival: 0.181
  - Non-fatal myocardial infarction: 0.044
  - Non-fatal stroke: 0.039
  - Major bleed - non CABG related: 0.046

- CYP2C19 Test - ticagrelor/clopidogrel
  - Event free survival: 0.934
  - Non-fatal myocardial infarction: 0.038
  - Non-fatal stroke: 0.034
  - Major bleed - non CABG related: 0.038

- Fully functional
  - Event free survival: 0.870
  - Non-fatal myocardial infarction: 0.038
  - Non-fatal stroke: 0.034
  - Major bleed - non CABG related: 0.038

- Does not avoid false positive - specificity (treat with ticagrelor)
  - Non-fatal myocardial infarction: 0.044
  - Non-fatal stroke: 0.039
  - Major bleed - non CABG related: 0.046

- Avoids false negative - sensitivity (treat with clopidogrel)
  - Event free survival: 0.993
  - Non-fatal myocardial infarction: 0.054
  - Non-fatal stroke: 0.006
  - Major bleed - non CABG related: 0.039

- Does not avoid false negative (treat with ticagrelor)
  - Event free survival: 0.878
  - Non-fatal myocardial infarction: 0.045
  - Non-fatal stroke: 0.036
  - Major bleed - non CABG related: 0.039
Figure 18. Decision tree diagram – PGx test (Clopidogrel/Prasugrel)

CYP2C19 Test - prasugrel/clopidogrel

- Carrier 0.181
- Non-Carrier 0.819

Event free survival
- 0.869
- 0.838
- 0.889
- 0.857

Non fatal myocardial infarction
- 0.006
- 0.101
- 0.975
- 0.081

Fatal myocardial infarction
- 0.009
- 0.020
- 0.004
- 0.016

Non fatal stroke
- 0.045
- 0.020
- 0.002
- 0.016

Major bleed - non CABG related
- 0.010
- 0.099
- 0.040
- 0.008

Avoid false positive - specificity (prasugrel)
- 1.000
- 0.100
- 0.993
- 0.007

Does not avoid false positive (clopidogrel)
- 0.006
- 0.020
- 0.004
- 0.016

Avoids false negative - sensitivity (clopidogrel)
- 0.993
- 0.004
- 0.081
- 0.016

Does not avoid false negative (prasugrel)
- 0.007
- 0.016
- 0.008
- 0.038
Figure 19. Clopidogrel only arm.

<table>
<thead>
<tr>
<th>Event</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event free survival</td>
<td>0.829</td>
</tr>
<tr>
<td>Non fatal myocardial infarction</td>
<td>0.069</td>
</tr>
<tr>
<td>Fatal myocardial infarction</td>
<td>0.051</td>
</tr>
<tr>
<td>Non fatal stroke</td>
<td>0.013</td>
</tr>
<tr>
<td>Major bleed - non CABG related</td>
<td>0.038</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Event</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>clopidogrel</td>
<td>1.000</td>
</tr>
</tbody>
</table>
**Figure 20. Ticagrelor only arm.**

<table>
<thead>
<tr>
<th>Event</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event free survival</td>
<td>0.842</td>
</tr>
<tr>
<td>Non fatal myocardial infarction</td>
<td>0.058</td>
</tr>
<tr>
<td>Fatal myocardial infarction</td>
<td>0.040</td>
</tr>
<tr>
<td>Non fatal stroke</td>
<td>0.015</td>
</tr>
<tr>
<td>Major bleed - non CABG related</td>
<td>0.045</td>
</tr>
</tbody>
</table>
Figure 21. Prasugrel only arm.

<table>
<thead>
<tr>
<th>Event</th>
<th>Prasugrel</th>
<th>1.000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event free survival</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non fatal myocardial infarction</td>
<td>0.872</td>
<td></td>
</tr>
<tr>
<td>Fatal myocardial infarction</td>
<td>0.073</td>
<td></td>
</tr>
<tr>
<td>Non fatal stroke</td>
<td>0.021</td>
<td></td>
</tr>
<tr>
<td>Major bleed - non CABG related</td>
<td>0.010</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.024</td>
<td></td>
</tr>
</tbody>
</table>
Decision tree outcome measures:
The decision tree produced the following outcomes:
1) Number/prevalence of MACE or bleed events
2) Proportion treated by each drug considered
3) Probability for each sub tree
4) Addition of the probability of each sub tree
These parameters will be used to internally validate the model. For example, the addition of the probability of all sub trees need to add up to 1. In the POC PGx trees, the proportion of patients treated with clopidogrel should correspond to the proportion of patients who have fully functioning alleles.
Outcomes from the decision tree were linked to an excel worksheet. The BIA was disaggregated into calendar months. Each month contained the estimated number of ACS events in Ontario. This number was multiplied by the cost of a PGx test. Hospitalization costs were determined by the mean costs generated by each arm of the decision tree multiplied by ACS events. Next, readmission costs to treat a stroke or non-fatal myocardial infarction were taken into consideration. Costs were then calculated for the drug used in each arm. The number of MACE events and bleed events were also calculated on a monthly and annual basis.

Ontario Drug Formulary Budget Impact Analysis (ODB BIA)
The following assumptions were applied to the ODB BIA:
• Population growth rate of 1% per year
• Ticagrelor would be available in generic form by 2018
• Prasugrel would be available in generic form by 2019
• Generic pricing will be reduced by 50% of brand
• A constant 15.6% of the Ontario population will be 65 years of age or older over the next 5 years
• The proportion of patients treated with clopidogrel, ticagrelor or prasugrel were informed by the decision tree previously described from the Ontario hospital BIA.

The ODB BIA covered the years 2016 to 2020. The following parameters informed the budget impact for each year: The annual estimated population diagnosed with ACS, the proportion of the
population over 65 years of age, the estimated population treated with clopidogrel, ticagrelor and prasugrel.

An example of the ODB BIA summary worksheet for the PGx option is presented hereunder:

POC PGx with clopidogrel/ticagrelor and ticagrelor

<table>
<thead>
<tr>
<th>Year</th>
<th>2016</th>
<th>2017</th>
<th>2018</th>
<th>2019</th>
<th>2020</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACS population</td>
<td>26538</td>
<td>26803</td>
<td>27071</td>
<td>27342</td>
<td>27615</td>
<td>135369</td>
</tr>
<tr>
<td>ODB population</td>
<td>4140</td>
<td>4181</td>
<td>4223</td>
<td>4265</td>
<td>4308</td>
<td>21118</td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>$212,202.84</td>
<td>$214,324.87</td>
<td>$162,351.09</td>
<td>$163,974.60</td>
<td>$165,614.34</td>
<td>$918,468</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>$154,973.04</td>
<td>$156,522.77</td>
<td>$158,088.00</td>
<td>$159,668.88</td>
<td>$161,265.57</td>
<td>$790,518</td>
</tr>
<tr>
<td>ODB cost</td>
<td>$367,176</td>
<td>$370,848</td>
<td>$320,439</td>
<td>$323,643</td>
<td>$326,880</td>
<td>$1,708,986</td>
</tr>
</tbody>
</table>
Productivity losses

Productivity losses were based on data reported by the Conference Board of Canada.\textsuperscript{87} Productivity losses (referred to as income lost from short and long term disability in the Conference Board Report) were measured as the expected stream of income lost during disability. The Conference Board report shows that 4\% of the healthcare costs are attributable to short and long term disability (i.e. productivity losses). The Conference Board report estimates that healthcare costs attributed to cardiovascular disease were $20.9 billion in Canada in 2005 and estimated to be $28.3 million in 2020. Four percent of the 2005 figure translates into $836 million of lost income due to cardiovascular disease. Assuming that the per capita figure is equal in all provinces and assuming that 38\% of the Canadian population lives in Ontario, one can extrapolate that $317 million of the lost income was incurred in Ontario. Dividing this by the estimated number of patients with AMI in Ontario (26,538), we can estimate that the patients incurred $11,907 per year in lost revenue. This figure jumps to $16,209 using the 2020 figure of $28.3 million.

While the Conference Board took a human capital approach to measuring productivity losses, an alternative method of measuring productivity losses is the friction cost approach. Goeree et al (1999) compared the human capital approach with the friction cost approach in estimating productivity losses due to premature mortality in Canada. The estimated human capital approach was 69 times higher than the results from the friction cost method. While the previous approach was estimated to be $11,907 per year under the human cost method, applying Goeree’s results yields a much lower $173 per year. The arithmetic mean difference between these two figures will serve as the base case estimate in deriving productivity losses for the CBA. Thus the mean value is $6,040 ($173 - $11907). Annual productivity losses will then be applied to the number of MACE per treatment arm to derive population figures.

Cost benefit analysis

This CBA was created based on the relevant chapters from the Drummond et al text. The following treatment lines were considered:
1) Status Quo
   a. All ACS patients prescribed clopidogrel

2) Comparison programs:
   a. PGx given to all ACS patients followed treatment with either clopidogrel or ticagrelor

Drummond et al recommend that in a country with a publicly funded healthcare system, individuals asked about their willingness to pay may not take into account health care resources saved, resources saves in other sectors, or productivity gains. Respondents in the DCE presented earlier were not explicitly asked to take into account health care resources saved, or productivity gains/losses incurred as a result of the underlying condition(s). As such the CBA formulation is as follows:

\[
\text{Net social benefit} = (\text{WTP} + S1 + S2 + S3) - (C1 + C2 + C3)
\]

Where:

\[
\text{WTP} = \text{willingness to pay for attributes of a PGx test}
\]

\[
S = \text{Savings from not implementing a status quo (i.e. the clopidogrel only arm)}
\]

Components:

S1: Hospital budget = Monetary value of treating MACE and major bleed (from the hospital BIA)

S2: Ontario Drug Benefit = Monetary value of clopidogrel prescribed after discharge (From the ODB BIA)

S3: Short and long term disability losses (Productivity losses inferred from the Conference Board of Canada)

\[
C = \text{Cost of implementing the program of interest (PGx test ticagrelor/clopidogrel)}
\]

Components:

C1 = Hospital budget = Monetary value of treating MACE and major bleed (from the hospital BIA)

C2 = Ontario Drug Benefit = Monetary value of prescribing ticagrelor/clopidogrel after discharge (From the ODB BIA)

C2 = Short and long term disability losses (Productivity losses inferred from the Conference Board of Canada)

Costs incurred over a one year time horizon will be considered.
## Data inputs sources

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individual willingness to pay value</td>
<td>DCE (Thesis Chapter 2)</td>
</tr>
<tr>
<td>Proportion who are WTP</td>
<td>DCE (Thesis Chapter 2)</td>
</tr>
<tr>
<td>Ontario population 2005</td>
<td>Minister of Finance (Ontario)</td>
</tr>
<tr>
<td>Ontario working population</td>
<td>Minister of Finance (Ontario)</td>
</tr>
<tr>
<td>Aggregated willingness to pay value</td>
<td>Derived (Thesis Chapter 3)</td>
</tr>
<tr>
<td>Hospital costs</td>
<td>BIA (Thesis Chapter 3)</td>
</tr>
<tr>
<td>ODB costs</td>
<td>BIA (Thesis Chapter 3)</td>
</tr>
<tr>
<td>Productivity losses</td>
<td>Derived/Conference Board of Canada</td>
</tr>
</tbody>
</table>
Results
Results for each component of the CBA as well as the net social benefit is presented hereunder in Table 17.

Table 17. Results for each component of the CBA and net social value

<table>
<thead>
<tr>
<th></th>
<th>Base case</th>
<th>Lower Limit</th>
<th>Upper Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Willingness to Pay</td>
<td>$13,627,530</td>
<td>$8,889,700</td>
<td>$19,059,810</td>
</tr>
<tr>
<td>+ Hospital costs saved – clopidogrel arm</td>
<td>$197,627,530</td>
<td>$130,383,186</td>
<td>$262,821,761</td>
</tr>
<tr>
<td>+ Drug expenditure saved – clopidogrel arm</td>
<td>$982,198</td>
<td>$648,502</td>
<td>$1,068,707</td>
</tr>
<tr>
<td>+ Productivity losses avoided - clopidogrel arm</td>
<td>$22,198,632</td>
<td>$634,246</td>
<td>$43,763,018</td>
</tr>
<tr>
<td>Subtotal WTP + Costs saved</td>
<td>$234,435,890</td>
<td>$140,563,634</td>
<td>$326,713,296</td>
</tr>
<tr>
<td>- Hospital costs incurred – PGx arm</td>
<td>$201,187,311</td>
<td>$132,731,747</td>
<td>$267,555,908</td>
</tr>
<tr>
<td>- Drug expenditure incurred – PGx arm</td>
<td>$1,501,705</td>
<td>$991,510</td>
<td>$1,997,460</td>
</tr>
<tr>
<td>- Productivity losses incurred – PGx arm</td>
<td>$18,776,766</td>
<td>$536,484</td>
<td>$37,017,048</td>
</tr>
<tr>
<td>Subtotal Costs incurred</td>
<td>$221,465,782</td>
<td>$134,259,741</td>
<td>$306,570,416</td>
</tr>
<tr>
<td>Net social benefit (loss)</td>
<td>$12,970,108</td>
<td>$6,303,893</td>
<td>$20,142,880</td>
</tr>
</tbody>
</table>

Aggregate WTP value
An assumption was made that 4,966,896 (i.e. 7,525,600 * 66%) workers would be willing to pay for the PGx test as part of their insurance coverage. The 66% proportion was taken from the results of the survey in Chapter 2, where 66% of the respondents preferred the POC PGx option to the universal clopidogrel or universal ticagrelor option. The WTP value of $2.91 ($1.90, $4.01) represents the mean value that an individual would pay for one of the POC PGx attributes.
This translates into an aggregate level WTP of $13,627,530 ($2.91 times 4,966,896). It is assumed that the WTP of the remaining 33% of the respondents was zero.

Budget Impact Analysis
The BIA from the aggregate Ontario hospital perspective shows that administering the POC PGx test incurs a $3.5 million ($201,187,311 - $197,627,530) cost to Ontario hospitals. This value includes the amount of cash outlay for the test as well as the savings from adverse events averted. This value also assumes the use of ticagrelor as 2\textsuperscript{nd} line to clopidogrel for LOF patients. While incurring an additional financial cost, the model predicts that there would be 981 fewer MACE events and 11 fewer bleed events. A summary of the monetary impact on Ontario hospitals is presented in Table 18. The results differ slightly between the data gathered from the ticagrelor/clopidogrel head to head studies and the prasugrel/clopidogrel head to head studies.

Internal validation
Probabilities for all decision trees added up to 1.0. Probability of being treated with ticagrelor was 17.7% compared to the 18.1% estimated probability of having a loss of function CYP2C19 allele. The prevalence of a bleed rate in the PGx test/ticagrelor tree was 3.78%. This is reasonable given the bleed rates provided by the genetic sub studies for clopidogrel and ticagrelor.

Ticagrelor/clopidogrel data
The model projects that the status quo option of no PGx testing (i.e. clopidogrel only) costs the Ontario hospitals over $197 million dollars (using ticagrelor/clopidogrel data). The clopidogrel only strategy leads to approximately 3,655 MACE events and 1,008 major bleeds. Adding a PGx test (ticagrelor/clopidogrel) would add $3.5 million to the hospital budget. However, by introducing a PGx test, the system would avoid 981 MACE and 11 major bleed events. Next to a clopidogrel only option, the ticagrelor only option is the next least expensive strategy, adding over $700 thousand to the hospital budget. For this additional outlay, there would be 541 fewer MACE events however 186 more patients would experience major bleeds. Since prasugrel is not currently covered by the ODB, the ticagrelor/clopidogrel results will be used in the base case CBA.
Table 18. Base case budget impact analysis results.

<table>
<thead>
<tr>
<th>All arms</th>
<th>Budget Impact</th>
<th>Incremental MACE</th>
<th>Total MACE</th>
<th>Incremental MACE</th>
<th>Total Bleed</th>
<th>Incremental Bleed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel (Ticagrelor head to head)</td>
<td>$197,627,494</td>
<td>3655</td>
<td>1008</td>
<td></td>
<td>186</td>
<td></td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>$198,335,685</td>
<td>$708,191</td>
<td>3114</td>
<td>-541</td>
<td>1194</td>
<td>186</td>
</tr>
<tr>
<td>PGx Ticagrelor/Clopidogrel</td>
<td>$201,187,311</td>
<td>$3,559,817</td>
<td>2674</td>
<td>-981</td>
<td>998</td>
<td>-11</td>
</tr>
<tr>
<td>Clopidogrel (Prasugrel head to head)</td>
<td>$200,631,689</td>
<td>3549</td>
<td>1008</td>
<td></td>
<td>318</td>
<td></td>
</tr>
<tr>
<td>Prasugrel</td>
<td>$196,864,228</td>
<td>-$3,767,460</td>
<td>2884</td>
<td>-665</td>
<td>1327</td>
<td></td>
</tr>
<tr>
<td>PGx Prasugrel/Clopidogrel</td>
<td>$203,360,289</td>
<td>$2,728,600</td>
<td>2295</td>
<td>-1254</td>
<td>863</td>
<td>-145</td>
</tr>
</tbody>
</table>
Prasugrel/clopidogrel data

Base case results using the probabilities from the prasugrel/clopidogrel trials yielded a base case amount of over $200 million for the clopidogrel only option. A PGx option would add $2.7 million to the annual budget. However, 1354 MACE events and 145 bleed events would be avoided. While the prasugrel only option would save hospitals money, this would come at the expense of 318 more bleed events.

Sensitivity analysis

The incidence of myocardial infarction was increased by 33% from 193 per 100,000 population to 257 per 100,000. (Table 19) As expected, the cost of all treatment arms increased by 33%. Furthermore, the number of MACE events and bleed events also rose by 33%.

Table 19. Sensitivity analysis increasing incidence by 33%.

<table>
<thead>
<tr>
<th>All arms</th>
<th>Budget Impact</th>
<th>Incremental</th>
<th>Total MACE</th>
<th>Incremental MACE</th>
<th>Total Bleed</th>
<th>Incremental Bleed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel (Ticagrelor head to head)</td>
<td>$262,788,696</td>
<td></td>
<td>4860</td>
<td></td>
<td>1341</td>
<td></td>
</tr>
<tr>
<td>Ticagrelor PGx</td>
<td>$263,730,390</td>
<td>$941,694</td>
<td>4141</td>
<td>-719</td>
<td>1588</td>
<td>247</td>
</tr>
<tr>
<td>Ticagrelor/Clopidogrel</td>
<td>$267,522,247</td>
<td>$4,733,551</td>
<td>3555</td>
<td>-1305</td>
<td>1327</td>
<td>-14</td>
</tr>
</tbody>
</table>

The next parameter that was varied was the cost of the PGx test. The cost of the test was decreased from $200 to $0. In the event that the PGx test would be prescribed free of charge (zero cash outlay) to the hospital, with approximately 1/3 of patients being prescribed ticagrelor and the rest being prescribed clopidogrel, the PGx test arm would reduce impact by $1.7 million to the Ontario hospital budget. With a zero cost to the PGx test, the clopidogrel only arm and the ticagrelor only arm would incur no changes to the budget (as expected) while the budget of the PGx arms decreased by approximately 1% from the status quo option. As expected, MACE or bleed rates did not vary with the variation of the cost of the PGx test.

Table 20. Sensitivity analysis – Implications to budget impact when reducing the POC PGx cost to $0.
Decreasing the cost of ticagrelor and prasugrel by 50% of their baseline cost did not affect the budget materially; decreasing the incremental difference between the status quo and the PGx option from $3,559,817 to $3,453,982. As expected the number of MACE and bleed events did not change. Decreasing the MACE and bleed rates generated a corresponding reduction in the magnitude and direction of the MACE and bleed rates in the summary table. 

Table 21)

Table 21. Sensitivity analysis – Impact on reduction of MACE or bleed events by 50%.

<table>
<thead>
<tr>
<th>MACE events</th>
<th>Base Case</th>
<th>Reduce Bleed rated by 50% (MACE remains unchanged)</th>
<th>% Change from Base</th>
<th>MACE events</th>
<th>% Change from Base</th>
</tr>
</thead>
<tbody>
<tr>
<td>All arms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>3,530</td>
<td>3,530</td>
<td>0.00%</td>
<td>1765</td>
<td>-50.00%</td>
</tr>
<tr>
<td>PGx</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ticagrelor/Clopidogrel</td>
<td>2,585</td>
<td>2,585</td>
<td>0.00%</td>
<td>1292</td>
<td>-50.00%</td>
</tr>
<tr>
<td>PGx Prasugrel/Clopidogrel</td>
<td>2,185</td>
<td>2,185</td>
<td>0.00%</td>
<td>1093</td>
<td>-50.00%</td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>2,999</td>
<td>2,999</td>
<td>0.00%</td>
<td>1499</td>
<td>-50.00%</td>
</tr>
<tr>
<td>Prasugrel</td>
<td>2,760</td>
<td>2,760</td>
<td>0.00%</td>
<td>1380</td>
<td>-50.00%</td>
</tr>
<tr>
<td><strong>Bleed events</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All arms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>1008</td>
<td>504</td>
<td>-50.00%</td>
<td>1008</td>
<td>0</td>
</tr>
<tr>
<td>PGx</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ticagrelor/Clopidogrel</td>
<td>998</td>
<td>499</td>
<td>-50.00%</td>
<td>998</td>
<td>0</td>
</tr>
<tr>
<td>PGx Prasugrel/Clopidogrel</td>
<td>863</td>
<td>432</td>
<td>-50.00%</td>
<td>863</td>
<td>0</td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>1194</td>
<td>597</td>
<td>-50.00%</td>
<td>1194</td>
<td>0</td>
</tr>
<tr>
<td>Prasugrel</td>
<td>1327</td>
<td>663</td>
<td>-50.00%</td>
<td>1327</td>
<td>0</td>
</tr>
</tbody>
</table>
ODB BIA results
While the PGx test would incur an estimated $3 million to the Ontario hospital budget; implementing the PGx test would also indirectly incur an approximate incremental $519,510 ($1,501,708 – 982,198) annually to the base case ODB budget impact analysis. The base case assumes that 15.6% of the population diagnosed with ACS will be 65 years of age and over and thus eligible for ODB coverage. The assumption is taken from the proportion of the population currently aged 65 years and older in Ontario. However, given the underlying condition, it is likely that a much higher proportion of the ACS population will be 65 years of age and older. As such a sensitivity analysis assuming 100% of the ACS population to be 65 years of age or older is also reported. The worksheets related to the base case and sensitivity analysis for the ODB BIA is presented in Table 22 and Table 23. The summary tables are presented in Table 24 and Table 25.

Productivity losses
Productivity losses were calculated using the mean difference between the human cost approach and the friction cost method. [$6,040 ($173-$11,907)] multiplied by the number of MACE events incurred per arm. Thus productivity losses for the clopidogrel arm were estimated to be $22,076,200 [$632,315 to 43,520,085] (i.e. 3655 MACE) and $16,150,960 [$462,602 to $31,851,225] for the PGx arm (i.e.2674 MACE)
Table 22. ODB results - Base case (15.6% of population 65 and over).

<table>
<thead>
<tr>
<th>PGx Ticagrelor/Clopidogrel</th>
<th>Year</th>
<th>2016</th>
<th>2017</th>
<th>2018</th>
<th>2019</th>
<th>2020</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population with MI</td>
<td>26538</td>
<td>26803</td>
<td>27071</td>
<td>27342</td>
<td>27616</td>
<td>135370</td>
<td></td>
</tr>
<tr>
<td>ODB population</td>
<td>4140</td>
<td>4181</td>
<td>4223</td>
<td>4265</td>
<td>4308</td>
<td>21118</td>
<td></td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>33096.606</td>
<td>33427.572</td>
<td>16880.924</td>
<td>17049.733</td>
<td>17220.231</td>
<td>$117,675</td>
<td></td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>24170.655</td>
<td>24412.362</td>
<td>24656.486</td>
<td>24903.051</td>
<td>25152.081</td>
<td>$123,295</td>
<td></td>
</tr>
<tr>
<td>ODB cost</td>
<td>$57,267</td>
<td>$57,840</td>
<td>$41,537</td>
<td>$41,953</td>
<td>$42,372</td>
<td>$240,970</td>
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</table>

<table>
<thead>
<tr>
<th>PGx Prasugrel/Clopidogrel</th>
<th>Year</th>
<th>2016</th>
<th>2017</th>
<th>2018</th>
<th>2019</th>
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<td>4223</td>
<td>4265</td>
<td>4308</td>
<td>21118</td>
<td></td>
</tr>
<tr>
<td>Prasugrel</td>
<td>30250.645</td>
<td>30553.152</td>
<td>15429.342</td>
<td>15583.635</td>
<td>15739.471</td>
<td>107556.246</td>
<td></td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>24165.178</td>
<td>24406.830</td>
<td>24650.898</td>
<td>24897.407</td>
<td>25146.381</td>
<td>123266.695</td>
<td></td>
</tr>
<tr>
<td>ODB cost</td>
<td>55061.652</td>
<td>55612.269</td>
<td>40739.050</td>
<td>41146.440</td>
<td>41557.905</td>
<td>234117.317</td>
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</table>

<table>
<thead>
<tr>
<th>Clopidogrel only</th>
<th>Year</th>
<th>2016</th>
<th>2017</th>
<th>2018</th>
<th>2019</th>
<th>2020</th>
<th>Total</th>
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<td>4223</td>
<td>4265</td>
<td>4308</td>
<td>21118</td>
<td></td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>29397.191</td>
<td>29691.163</td>
<td>29988.074</td>
<td>30287.955</td>
<td>30590.835</td>
<td>$149,955</td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ticagrelor only</th>
<th>Year</th>
<th>2016</th>
<th>2017</th>
<th>2018</th>
<th>2019</th>
<th>2020</th>
<th>Total</th>
</tr>
</thead>
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<td>4181</td>
<td>4223</td>
<td>4265</td>
<td>4308</td>
<td>21118</td>
<td></td>
</tr>
<tr>
<td>Ticagrelor only</td>
<td>186155.304</td>
<td>188016.857</td>
<td>94948.513</td>
<td>95897.998</td>
<td>96856.978</td>
<td>$661,876</td>
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</table>

<table>
<thead>
<tr>
<th>Prasugrel only</th>
<th>Year</th>
<th>2016</th>
<th>2017</th>
<th>2018</th>
<th>2019</th>
<th>2020</th>
<th>Total</th>
</tr>
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<td>4181</td>
<td>4223</td>
<td>4265</td>
<td>4308</td>
<td>21118</td>
<td></td>
</tr>
<tr>
<td>Prasugrel only</td>
<td>169969.776</td>
<td>171669.474</td>
<td>86693.084</td>
<td>87560.015</td>
<td>88435.615</td>
<td>$604,328</td>
<td></td>
</tr>
</tbody>
</table>
Table 23. ODB BIA Worksheet – Sensitivity analysis 100% over the age of 65.

<table>
<thead>
<tr>
<th>PGx Ticagrelor/Clopidogrel</th>
<th>Year</th>
<th>2016</th>
<th>2017</th>
<th>2018</th>
<th>2019</th>
<th>2020</th>
<th>Total</th>
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<td>27071</td>
<td>27342</td>
<td>27616</td>
<td>135370</td>
<td></td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>$212,157.73</td>
<td>$214,279.31</td>
<td>$108,211.05</td>
<td>$109,293.16</td>
<td>$110,386.09</td>
<td>$754,327</td>
<td></td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>$154,940.10</td>
<td>$156,489.50</td>
<td>$158,054.40</td>
<td>$159,634.94</td>
<td>$161,231.29</td>
<td>$790,350</td>
<td></td>
</tr>
<tr>
<td>ODB cost</td>
<td>$367,098</td>
<td>$370,769</td>
<td>$266,265</td>
<td>$268,928</td>
<td>$271,617</td>
<td>$1,544,678</td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PGx Prasugrel/ Clopoidogrel</th>
<th>Year</th>
<th>2016</th>
<th>2017</th>
<th>2018</th>
<th>2019</th>
<th>2020</th>
<th>Total</th>
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<td>27071</td>
<td>27342</td>
<td>27616</td>
<td>135370</td>
<td></td>
</tr>
<tr>
<td>Prasugrel</td>
<td>$193,914.39</td>
<td>$195,853.54</td>
<td>$98,906.04</td>
<td>$99,895.10</td>
<td>$100,894.05</td>
<td>$689,463</td>
<td></td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>$154,904.99</td>
<td>$156,454.04</td>
<td>$158,018.58</td>
<td>$159,598.76</td>
<td>$161,194.75</td>
<td>$790,171</td>
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</tr>
<tr>
<td>ODB cost</td>
<td>$352,959</td>
<td>$356,489</td>
<td>$261,148</td>
<td>$263,759</td>
<td>$266,397</td>
<td>$1,500,752</td>
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</table>

<table>
<thead>
<tr>
<th>Clopidogrel only</th>
<th>Year</th>
<th>2016</th>
<th>2017</th>
<th>2018</th>
<th>2019</th>
<th>2020</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
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<td>26803</td>
<td>27071</td>
<td>27342</td>
<td>27616</td>
<td>135370</td>
<td></td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>$188,443.53</td>
<td>$190,327.97</td>
<td>$192,231.24</td>
<td>$194,153.56</td>
<td>$196,095.09</td>
<td>$961,251</td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ticagrelor only</th>
<th>Year</th>
<th>2016</th>
<th>2017</th>
<th>2018</th>
<th>2019</th>
<th>2020</th>
<th>Total</th>
</tr>
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<tbody>
<tr>
<td>Population with MI</td>
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<td>27071</td>
<td>27342</td>
<td>27616</td>
<td>135370</td>
<td></td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>$1,193,303.23</td>
<td>$1,205,236.26</td>
<td>$608,644.31</td>
<td>$614,730.76</td>
<td>$620,878.06</td>
<td>$4,242,793</td>
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</table>

<table>
<thead>
<tr>
<th>Prasugrel only</th>
<th>Year</th>
<th>2016</th>
<th>2017</th>
<th>2018</th>
<th>2019</th>
<th>2020</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population with MI</td>
<td>26538</td>
<td>26803</td>
<td>27071</td>
<td>27342</td>
<td>27616</td>
<td>135370</td>
<td></td>
</tr>
<tr>
<td>Prasugrel</td>
<td>$1,089,549.85</td>
<td>$1,100,445.34</td>
<td>$555,724.90</td>
<td>$561,282.15</td>
<td>$566,894.97</td>
<td>$3,873,897</td>
<td></td>
</tr>
</tbody>
</table>
Table 24. ODB Budget Analysis - Base Case 2016 summary

<table>
<thead>
<tr>
<th>Drug Type</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel only</td>
<td>$29,397</td>
</tr>
<tr>
<td>PGx Clopidogrel/Ticagrelor</td>
<td>$57,267</td>
</tr>
<tr>
<td>PGx Clopidogrel/Prasugrel</td>
<td>$55,061</td>
</tr>
<tr>
<td>Ticagrelor only</td>
<td>$186,115</td>
</tr>
<tr>
<td>Prasugrel only</td>
<td>$169,969</td>
</tr>
</tbody>
</table>

Table 25. ODB Budget Impact Analysis – 100% over the age of 65 - 2016 summary

<table>
<thead>
<tr>
<th>Drug Type</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel only</td>
<td>$188,443</td>
</tr>
<tr>
<td>PGx Clopidogrel/Ticagrelor</td>
<td>$367,098</td>
</tr>
<tr>
<td>PGx Clopidogrel/Prasugrel</td>
<td>$352,959</td>
</tr>
<tr>
<td>Ticagrelor only</td>
<td>$1,193,303</td>
</tr>
<tr>
<td>Prasugrel only</td>
<td>$1,089,549</td>
</tr>
</tbody>
</table>
Hospital costs for the clopidogrel and the PGx arm were estimated earlier in this chapter. The clopidogrel only arm incurred over $196 million in hospital costs while the PGx arm incurred over $201 million. Clopidogrel costs incurred by the ODB were approximately ½ of the costs incurred under the PGx arm. Due to the brand pricing in 2016 of ticagrelor. Productivity losses (i.e. losses avoided) were higher in the clopidogrel arm due to the higher number of MACE. Lower productivity losses were incurred under a PGx option. These values generated a net benefit of using the PGx test of a over $11 million. Incorporating the high and low values of the WTP would still yield a net surplus of between $377 thousand and $19.9 million. For a base case and for the upper limits, a CBA result would still yield a net social benefit even if WTP values were set to 0. Net social value would be negative under the lower limit (Table 26.)

<table>
<thead>
<tr>
<th></th>
<th>Base</th>
<th>Lower Limit</th>
<th>Upper Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Willingness to Pay</td>
<td>$0</td>
<td>$0</td>
<td>$0</td>
</tr>
<tr>
<td>+ Hospital costs saved – clopidogrel arm</td>
<td>$197,627,494</td>
<td>$148,166,773</td>
<td>$247,004,199</td>
</tr>
<tr>
<td>+ Drug expenditure saved – clopidogrel arm</td>
<td>$29,397</td>
<td>$29,397</td>
<td>$188,443</td>
</tr>
<tr>
<td>+ Productivity losses avoided - clopidogrel arm</td>
<td>$22,076,200</td>
<td>$633,315</td>
<td>$43,520,085</td>
</tr>
<tr>
<td>Subtotal  WTP + Costs saved</td>
<td>$219,733,091</td>
<td>$148,829,485</td>
<td>$290,712,727</td>
</tr>
<tr>
<td>+ Hospital costs incurred – PGx arm</td>
<td>$201,187,311</td>
<td>$150,835,666</td>
<td>$251,453,427</td>
</tr>
<tr>
<td>+ Drug expenditure incurred – PGx arm</td>
<td>$57,267</td>
<td>$57,267</td>
<td>$367,098</td>
</tr>
<tr>
<td>+ Productivity losses incurred – PGx arm</td>
<td>$16,150,960</td>
<td>$462,602</td>
<td>$37,851,225</td>
</tr>
<tr>
<td>Subtotal Costs incurred</td>
<td>$217,395,538</td>
<td>$151,355,535</td>
<td>$289,671,750</td>
</tr>
<tr>
<td>Net social benefit (loss)</td>
<td>$2,337,553</td>
<td>-$2,526,050</td>
<td>$1,040,977</td>
</tr>
</tbody>
</table>
Discussion
Operationalizing the CBA requires input from various sub studies. In each sub study, the focus was on quantifying the incremental changes between the status quo in treating ACS patients (i.e. universal clopidogrel) compared to a POC PGx test. A DCE based survey was used to quantify the WTP. This value was based on: the proportion of respondents who preferred universal clopidogrel compared to the novel PGx test, and the incremental value of the standard PGx test over the novel POC PGx test. The underlying assumption was that the standard PGx test would generate a preference value of zero. However, the true value is unknown since the differential number of adverse events and bleeds between a standard PGx test and universal clopidogrel is unknown. A further assumption is that the value of PGx test is not less that that of universal clopidogrel. Setting the stated preference for a standard PGx test to zero would likely bias the results to the downside.

Hospital BIA
The results from the hospital BIA sensitivity analysis provided internal validation of the model. Direction of the results, given the one-way sensitivity analysis, demonstrated that there were no unexpected variations to base case results given a change in one parameter. Therefore, the inference is that there were no issues with the formulas or the structure of the model.

The estimated impact on Ontario hospitals of introducing a POC PGx test in the ACS population would require an additional $3.5 million dollars. This additional outlay would be accompanied by substantially fewer MACE events and slightly lower bleed events, based on the probabilities provided by the clopidogrel/ticagrelor head to head trial. Results differ when MACE and bleed event rates were taken from the prasugrel/clopidogrel head to head trial. For example, the model projects a higher cash outlay for the clopidogrel arm when incorporating the prasugrel head to head trial. This is most likely due to the different input values for bleed events for clopidogrel from the ticagrelor or prasugrel head to head trials (3.8% v 1.8%). All other MACE events for clopidogrel were similar in the two head to head trials. Nevertheless, as prasugrel is not covered...
by the ODB, the focus of the BIA and the ensuing CBA will be on the results generated using the ticagrelor head to head data.

A comparison to other BIAs carried out in Ontario may place results from this study into context. To date, (July 2016) Health Quality Ontario has published at least 7 budget impact analyses. A league table of BIA results is presented hereunder.

Table 27. List of BIA by Health Quality Ontario in 2016

<table>
<thead>
<tr>
<th>Underlying condition</th>
<th>Budget year</th>
<th>Annual budget impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrathecal drug delivery systems for non-cancer pain</td>
<td>2015</td>
<td>$1.5 - $5.0 million</td>
</tr>
<tr>
<td>Intrathecal drug delivery systems for cancer pain</td>
<td>2015</td>
<td>$200,000</td>
</tr>
<tr>
<td>Left ventricular assist devices for destination therapy</td>
<td>2015</td>
<td>$13.6 million</td>
</tr>
<tr>
<td>Minimal residual disease evaluation in childhood acute lymphoblastic leukemia</td>
<td>2015</td>
<td>$400,000</td>
</tr>
<tr>
<td>Skin testing for allergic rhinitis</td>
<td>2015</td>
<td>$2.5 –$3.0 million</td>
</tr>
<tr>
<td>Vertebral augmentation involving vertebroplasty for kyphoplasty for cancer related vertebral compression fractures</td>
<td>2015</td>
<td>$2.5 million</td>
</tr>
</tbody>
</table>

If the Ontario government were to consider an additional $3 million-dollar influx into the hospital system, the administrators would be faced with a choice of covering PGx tests for all hospital-admitted ACS patients or intrathecal drug delivery systems for both cancer and non-cancer pain, skin testing for allergic rhinitis and treatment for vertebral compression fractures. Alternatively, the $3.5 million could go towards most of the left ventricular assist devices for destination therapy.

Limitations

The BIA relied on several sets of data. MACE and bleed events for clopidogrel and ticagrelor were provided by the head to head trial reported by Wallentin et al. 64 Similar rates were provided for clopidogrel and prasugrel by Wiviott et al. 63 Rates for the PGx arms were taken from the genetic sub studies. While the MACE and bleed event parameters were reported in the genetic sub studies for the prasugrel head to head trial by Mega et al., 14,16 MACE event rates were reported in aggregate in the genetic sub study for ticagrelor. 15 As such, the specific MACE rates...
used in the BIA were inferred, based on the head to head and genetic sub study. This may be significant as the cost for non-fatal and fatal MI differ substantially in Ontario (approximately $11,500 vs $7,800). Furthermore, type of bleed rates differed between studies. As such the bleed event rates between the ticagrelor and prasugrel arms may not be directly comparable.

ODB BIA
Limitations
The ODB BIA used data generated from the hospital BIA results. A more accurate starting point for the ODB BIA would have been to use anonymized pharmaceutical hospital sales data (i.e. IMS data) for the respective drugs (specific to ACS) at the end of 2015 and project this data forward. Unfortunately, we did not have access to this data. Resource utilization was based on the assumptions from the BIA which may differ from the hospital sales data. Follow-up analysis to this thesis could use the related sales data as a validation tool of the ODB BIA results.

CBA
When considering costs from a ‘societal perspective’ that is to say, when we consider: costs from the hospital and drug formulary costs incurred by the Ministry of Health (Ontario), productivity losses incurred by patients, and the WTP stated by the general population for the attribute of quick turnaround response for the POC PGX, there is a net social benefit to implementing this new technology in Ontario hospitals.

The CBA values are bias to the downside for several reasons. First, the base case net social value was quantified using the WTP values calculated using the lower cost attribute levels from the DCE. Furthermore, the smaller value between the 3 day and 1 hour differential in attributes was taken. Second, long term care costs (beyond one year) of caring for stroke patients were not taken into consideration. Given that a higher number of strokes were incurred under the status quo, one would assume a higher net social benefit given the higher cost associated with long term stroke care under the status quo option. Furthermore, it should be noted that the WTP asked of the respondents to the survey were from a ‘restrictive’ perspective. Respondents were implicitly asked to value components of the benefit or which no monetary value exists. As such, the WTP estimates are restricted to quantifying the value of changes in health per se.
Respondents may have placed a higher (subjective) value on their productivity losses and offsetting future health care costs than those quantified in this study.
Given the financial constraints faced by Ontario hospitals, hospital administrators may not cover the additional $3.5 million needed to cover the PGx option; unless they consider the avoided MACE and bleed events. Higher ODB costs were also incurred under the POC PGx scenario. However, given the stated preference from the general population for the quicker turnaround time for the PGx test, a net social benefit exists for covering the POC PGx by the Ontario government.

Conclusion
Implementing a POC PGx test to all patients presenting with ACS in Ontario hospitals will increase the aggregate hospital budget by $3.5 million. This figure includes the amount saved from the number of MACE and bleed events avoided because of the PGx test. In exchange for the $3.5 million addition cash outlay, there will be 26% fewer MACE events and slightly fewer bleed events. Implementing a PGx test in Ontario hospitals would have an incremental addition of over $91,000 to the ODB budget. A net social benefit was observed.

Key points
- Five studies (2 head to head and 3 genetic sub studies) informed the budget impact analysis
- The base case result showed an impact of $3.5 million additional needed in the aggregate Ontario hospital budgets to implement the PGx test.
- The additional funding would result in substantially fewer MACE events and slightly fewer bleed events.
- In the event the PGx test would be implemented, the Ontario Drug Formulary would need an injection of an additional $178,000. This would cover the cost of the more expensive alternative (ticagrelor) to clopidogrel.
- There is a net social benefit to covering the PGx test in Ontario

References


40. !!! INVALID CITATION !!! {}.
60. Lancsar E. Deriving welfare measures from stated preference discrete choice modelling experiments, CHERE Discussion Paper No 48. Sydney: Centre for Health Economics Research and


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Appendices

Appendix 1. Search strategy for the systematic review of economic evidence related to pharmacogenetic testing for the CYP2C19*2 allele.

Search terms are presented below:

Database: Embase Classic+Embase <1947 to 2017 April 26>
Search Strategy:

1 exp Cardiovascular Diseases/ (3705756)
2 exp Coronary Artery Disease/ (277479)
3 cerebrovascular.mp. or exp Cerebrovascular Disorders/ (532108)
4 exp Rheumatic Heart Disease/ (14531)
5 exp Venous Thrombosis/ or exp Pulmonary Embolism/ (166666)
6 1 or 2 or 3 or 4 or 5 (3718247)
7 genetic.mp. (1634700)
8 exp "Costs and Cost Analysis"/ (300709)
9 exp Cost-Benefit Analysis/ (73518)
10 cost utility.mp. (9013)
11 cost effectiveness.mp. (141112)
12 8 or 9 or 10 or 11 (448564)
13 6 and 7 and 12 (1859)
14 limit 13 to (full text and english language) (370)
Database: Ovid MEDLINE(R) <1946 to April Week 3 2017>

Search Strategy:

1  exp Cardiovascular Diseases/ (2165220)
2  exp Coronary Artery Disease/ (51460)
3  cerebrovascular.mp. or exp Cerebrovascular Disorders/ (370994)
4  exp Rheumatic Heart Disease/ (12619)
5  exp Venous Thrombosis/ or exp Pulmonary Embolism/ (78480)
6  1 or 2 or 3 or 4 or 5 (2202738)
7  genetic.mp. (1350331)
8  exp "Costs and Cost Analysis"/ (210416)
9  exp Cost-Benefit Analysis/ (71011)
10  cost utility.mp. (3071)
11  cost effectiveness.mp. (41142)
12  8 or 9 or 10 or 11 (224044)
13  6 and 7 and 12 (214)
Appendix 2: Quality of Health Economic Studies (QHES)

<table>
<thead>
<tr>
<th>Quality of Health Economic Studies (QHES)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Was the study objective presented in a clear, specific, and measurable manner?</td>
<td>83%</td>
</tr>
<tr>
<td>2. Were the perspective of the analysis (societal, third-party payer, etc.) and reasons for its selection stated?</td>
<td>88%</td>
</tr>
<tr>
<td>3. Were variable estimates used in the analysis from the best available source (i.e., randomized control trial - best, expert opinion - worst)?</td>
<td>95%</td>
</tr>
<tr>
<td>4. If estimates came from a subgroup analysis, were the groups prespecified at the beginning of the study?</td>
<td>50%</td>
</tr>
<tr>
<td>5. Was uncertainty handled by (1) statistical analysis to address random events,(2) sensitivity analysis to cover a range of assumptions?</td>
<td>73%</td>
</tr>
<tr>
<td>6. Was incremental analysis performed between alternatives for resources and costs?</td>
<td>100%</td>
</tr>
<tr>
<td>7. Was the methodology for data abstraction (including the value of health states and other benefits) stated?</td>
<td>33%</td>
</tr>
<tr>
<td>8. Did the analytic horizon allow time for all relevant and important outcomes? Were benefits and costs that went beyond 1 year discounted (3% to 5%) and justification given for the discount rate?</td>
<td>93%</td>
</tr>
<tr>
<td>9. Was the measurement of costs appropriate and the methodology for the estimation of quantities and unit costs clearly described?</td>
<td>77%</td>
</tr>
<tr>
<td>10. Were the primary outcome measure(s) for the economic evaluation clearly stated and did they include the major short-term, long-term, and negative outcomes?</td>
<td>70%</td>
</tr>
<tr>
<td>11. Were the health outcomes measures/scales valid and reliable? If previously tested valid and reliable measures were not available, was justification given for the measures/scales used?</td>
<td>77%</td>
</tr>
<tr>
<td>12. Were the economic model (including structure), study methods and analysis, and the components of the numerator and denominator displayed in a clear, transparent manner?</td>
<td>63%</td>
</tr>
<tr>
<td>13. Were the choice of economic model, main assumptions, and limitations of the study stated and justified?</td>
<td>58%</td>
</tr>
<tr>
<td>14. Did the author(s) explicitly discuss direction and magnitude of potential biases?</td>
<td>40%</td>
</tr>
<tr>
<td>15. Were the conclusions/recommendations of the study justified and based on the study results?</td>
<td>93%</td>
</tr>
<tr>
<td>16. Was there a statement disclosing the source of funding for the study?</td>
<td>47%</td>
</tr>
</tbody>
</table>

Quality score (Range) 71% (41%-94%)
Appendix 3. DCE survey screenshots
Before you begin... please note that:

When you wish to revisit a particular page — please click on the ‘go back’ button — it looks like this...

When you are finished with a particular page and wish to continue — please click on the ‘continue’ button — it looks like this...
You have agreed to participate in a willingness to pay study.

The purpose of this study is to:

- Determine which treatment option you would prefer if you were diagnosed with acute coronary syndrome.
- Determine how much you would be willing to pay for one of the treatment options in additional annual insurance premiums.

Before you decide, you will be provided with some information about:

- Acute coronary syndrome
- Major adverse cardiovascular events
- Genetic tests
Before we begin with the willingness to pay study - we would like to ask you a few questions. Please click the box that applies to you.

**Initial respondent questionnaire. 1 of 15**

**Sex**

What is your sex?

- ○ Female
- ○ Male

[Go Back]  [Continue]
Initial respondent questionnaire. 2 of 15

Age
What year were you born? 1997

Go Back  Continue
Initial respondent questionnaire. 3 of 15

**Education**
(What is the highest level of education attained?)

- No certificate, diploma or degree
- High school diploma or equivalent
- Apprenticeship or trades certificate or diploma
- College, CEGEP or other non-university certificate or diploma
- University certificate or diploma below bachelor level
- University certificate, diploma or degree at bachelor level
- Post graduate certificate, diploma or degree at a Master's level
- Doctorate
Initial respondent questionnaire. 4 of 15

What is your labour force status?

- Employed, at work
- Employed, absent from work
- Not in labour force, able to work
- Not in labour force, permanently unable to work

Go Back  Continue
Initial respondent questionnaire. 5 of 15

What is your marital status?

- Married
- Living common-law
- Widowed
- Separated
- Divorced
- Single, never married

Go Back  Continue
All Ontarians are eligible for government health insurance that covers physician visits and hospital services. Some Ontarians also have private health insurance, such as that provided by an employer, or purchased directly that covers dental care, eye care or prescription drugs. Do you have any private health insurance?

- Yes
- No
Initial respondent questionnaire. 7 of 15

Residence: I live in a:
- Rural population centre (less than 1,000 people)
- Small population centre (1,000-29,999 people)
- Medium population centre (30,000 - 99,999 people)
- Large urban population centre (100,000 people or greater)
Have you ever had a genetic test?  

- Yes
- No
- Don't know
Initial respondent questionnaire. 9 of 15

Do you currently have or have you ever had heart disease?  
○ Yes  ○ No

Is there heart disease in your family (that you know of)?  
○ Yes  ○ No

Do you know of anyone who has or has had heart disease?  
○ Yes  ○ No
Initial respondent questionnaire. 10 of 15

Have you ever reacted badly to a medication?

- Yes
- No

Go Back  Continue
Initial respondent questionnaire. 11 of 15

Do you know of a friend or family member that has reacted badly to medication?

- Yes
- No

Go Back  Continue
Have you ever been treated in hospital because you reacted badly to medication (side effects due to medication?)

- [ ] Yes
- [ ] No
Initial respondent questionnaire. 13 of 15

Have you ever been prescribed the following medication?

a. Clopidogrel (also known as Plavix)  ○ Yes  ○ No
b. Ticagrelor (also known as Brilinta)  ○ Yes  ○ No
c. Prasugrel (also known as Effient)  ○ Yes  ○ No

Go Back  Continue
Do you have concerns related to any type of genetic test? If so what are you concerns?

<table>
<thead>
<tr>
<th>Option</th>
<th>Choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Confidentiality</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>No</td>
</tr>
<tr>
<td>b. Privacy (Disclosure)</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>No</td>
</tr>
<tr>
<td>c. Payment</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>No</td>
</tr>
<tr>
<td>d. Other</td>
<td></td>
</tr>
</tbody>
</table>
Initial respondent questionnaire, 15 of 15

Annual family income (Canadian dollars)

What was your total family income in the previous year?

☐ 10,000 - 19,999
☐ 20,000 - 29,999
☐ 30,000 - 39,999
☐ 40,000 - 49,999
☐ 50,000 - 59,999
☐ 60,000 - 69,999
☐ 70,000 - 79,999
☐ 80,000 - 89,999
☐ 90,000 - 99,999
☐ 100,000-149,000
☐ 150,000 and over
We will now describe a medical condition....

Acute coronary syndrome (ACS)

- The following is a description of a health state.
- ACS occurs when there is a lack of oxygen supply to the heart muscle.
- There are 2 main types of ACS (unstable angina and myocardial infarction (heart attack)).
- Angina (chest pain) occurs from a lack of oxygen to the heart.
- This can result in unstable angina or (if prolonged and heart muscle starts dying) a heart attack.
- The most common reason for an ACS is a blocked coronary artery.
- Patients with ACS require immediate treatment including a balloon procedure to open the artery and strong blood thinners.
- Doctors for patients with ACS will recommended that these patients undergo a surgical procedure to open this blockage. The aim of the operation is to open the blockage and restore normal blood flow to the heart.
- Along with this procedure, doctors for patients with ACS, will prescribe aspirin and one other blood thinner.
Major adverse cardiovascular event (MACE)

- The following is a description of a health state.
- Imagine that your doctor will need to treat you within hours of seeing you, with a combination of aspirin and another blood thinner.
- Some people may not get the full benefit of the blood thinner.
- People who do not get the full benefit of the blood thinner are at risk having a MACE.
- A MACE event happens when at least one of the following occur:
  - You die because of heart related complications
  - You have a heart attack but do not die
  - You have a stroke
- You have already been provided with a description of a 'heart attack'.
- A stroke occurs when blood flow is interrupted to part of the brain. A stroke occurs when a blood vessel in the brain is blocked or bursts.
- Without blood and the oxygen it carries, part of the brain starts to die. The part of the body controlled by the damaged area of the brain cannot work properly.
Pharmacogenetic test

- You will NOT need to submit to a genetic test to complete this questionnaire.
- There are several kinds of genetic tests.
- The kind of genetic test that we are talking about today is called a PHARMACO-GENETIC test.
- This kind of test figures out the type or dose of a medicine that is best for a certain person.
- This kind of genetic test DOES NOT identify whether or not you have or are susceptible of getting a disease; either today or in the future.
- This test will allow your doctor to prescribe the right medication and avoid potentially bad effects from medicine.
- You will only need to take this genetic test once in your life.
- More than 1,000 genetic tests are currently in use and more are being developed.
Pharmacogenetic test

- You will NOT need to submit to a genetic test to complete this questionnaire.
- In this survey you will be presented with different options.
- First you will choose whether or not you would want a pharmacogenetics test under certain conditions.
- IF you choose a pharmacogenetics test option - you will be presented with choices for different kinds of pharmacogenetics tests.
- In this study, the pharmacogenetic tests differ in:
  - how sample is collected.
  - the time it takes for results to be given to your doctor.
  - and the amount of additional insurance premium it may cost.
- Samples that can be taken from you to carry out the pharmacogenetic tests include:
  - Saliva taken from a cheek swab.
  - Blood taken from the arm.
  - Blood taken from a finger prick.
- Results that are provided to your doctor can be returned:
  - In 7 days after the sample is taken.
  - In 3 days after the sample is taken.
  - 1 hour after the sample is taken.
Imagine a group of 100 patients who are treated for acute coronary syndrome with one of three treatment options listed on the left hand side of the page. On the right hand side of the page, there are pairs of boxes with faces that represent patients who will or will not have had a bad outcome.

- Patients with the green smiley face will not have had any bad outcomes from the drug.
- Patients with red frowning faces will have had bad outcomes from the drug.

<table>
<thead>
<tr>
<th>Description</th>
<th>MACE</th>
<th>Major and Minor Bleeding</th>
</tr>
</thead>
</table>
| **Treatment A: All patients are given a blood thinner:**
Out of every 100 patients treated:
  - 88 patients will NOT have had a bad effect (MACE). ✔
  - 12 patients will have had a bad effect (MACE). ✗
  - 4 patients will have had a major or minor bleed. ✗
| **Treatment B: All patients are given a blood thinner.**
Out of every 100 patients treated:
  - 90 patients will NOT have had a bad effect (MACE). ✔
  - 10 patients will have had a bad effect (MACE). ✗
  - 5 patients will have had a major or minor bleed. ✗
| **Treatment C: All patients are given a pharmacogenetic test.**
Some patients will get blood thinner “A”, others will get blood thinner “B”. Out of every 100 patients treated:
  - 61 patients will NOT have had a bad effect (MACE). ✔
  - 9 patients will have had a bad effect (MACE). ✗
  - 4 patients will have had a major or minor bleed. ✗
• You have just seen a decision board that describes the rates of MACE as well as major and minor bleeding.
• Please note that:
  ◦ Treatment A and Treatment B do NOT require a pharmacogenetic test prior to prescribing the medication
  ◦ Treatment C requires a pharmacogenetic test prior to prescribing the medication
Which treatment option would you prefer?

- Treatment A
- Treatment B
- Treatment C
You chose A or B - please tell us why:

Was it because:

☐ 1) You did not want to undergo a pharmacogenetic test
☐ 2) You thought you would experience less MACE
☐ 3) You thought you would experience less major or minor bleeding
☐ 4) Other

[Text input field]

[Continue button]
Discrete choice experiment

You have chosen treatment option C

- Imagine that you will want your insurance company to cover the costs of the pharmacogenetic test described earlier.
- 7 in 10 (70%) employers provide supplementary health benefits for their employees.
- The majority (78%) of supplementary health benefit programs offered by employers require an employee contribution such as a payroll deduction.
- In 2009, in Canada, households spent an average of $650 on private insurance. Insurance expenditures included premiums for provincial or territorial hospital, medical or drug plans, private health insurance plans, dental plans sold as separate policies, and accident or disability insurance.
- In order for the pharmacogenetic test to be covered by your health insurance provider, your provider may increase your premiums. This means that you may either pay higher insurance premiums or have a higher amount deducted from your payroll if your employer offers supplementary health coverage.
- The willingness to pay (WTP) amount presented to you represents that amount of additional insurance premiums you would be willing to pay on an annual basis to ensure that this pharmacogenetic test be covered by your plan.
- It is possible that during the course of the year, other new health technologies may become available that you would also want to be covered by your health insurance provider.
- Please consider this when answering the following questions.
### Example of a choice set

<table>
<thead>
<tr>
<th></th>
<th>Choice A</th>
<th>Choice B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample</td>
<td>Blood</td>
<td>Checkswab</td>
</tr>
<tr>
<td>Turnaround time</td>
<td>1 hour</td>
<td>3 days</td>
</tr>
<tr>
<td>Willingness to pay</td>
<td>$5</td>
<td>$1</td>
</tr>
</tbody>
</table>

- I would prefer Choice A
- I would prefer Choice B

This is only an example of a choice set. You will be presented with 8 of these choice sets, then you're done!
You are almost done – a few more questions...

Go Back    Continue
Example of a choice set

<table>
<thead>
<tr>
<th></th>
<th>Choice A</th>
<th>Choice B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample</td>
<td>Blood</td>
<td>Checkswab</td>
</tr>
<tr>
<td>Turnaround time</td>
<td>1 hour</td>
<td>3 days</td>
</tr>
<tr>
<td>Willingness to pay</td>
<td>$5</td>
<td>$1</td>
</tr>
</tbody>
</table>

☐ I would prefer Choice A

☐ I would prefer Choice B

This is only an example of a choice set. You will be presented with 8 of these choice sets. Then you're done!
### Choice set 1 of 8

<table>
<thead>
<tr>
<th></th>
<th>Choice A</th>
<th>Choice B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample</td>
<td>Finger prick</td>
<td>Blood test</td>
</tr>
<tr>
<td>Turnaround time</td>
<td>1 hour</td>
<td>1 hour</td>
</tr>
<tr>
<td>Cost to you</td>
<td>$10</td>
<td>$2</td>
</tr>
</tbody>
</table>

- I would prefer Choice A
- I would prefer Choice B

[Go Back] [Continue]
<table>
<thead>
<tr>
<th></th>
<th>Choice A</th>
<th>Choice B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample</td>
<td>Blood test</td>
<td>Blood test</td>
</tr>
<tr>
<td>Turnaround time</td>
<td>1 week</td>
<td>1 week</td>
</tr>
<tr>
<td>Cost to you</td>
<td>$2</td>
<td>$10</td>
</tr>
</tbody>
</table>

- I would prefer Choice A
- I would prefer Choice B
### Choice set 3 of 8

<table>
<thead>
<tr>
<th>Sample</th>
<th>Choice A</th>
<th>Choice B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turnaround time</td>
<td>1 hour</td>
<td>1 week</td>
</tr>
<tr>
<td>Cost to you</td>
<td>$2</td>
<td>$10</td>
</tr>
</tbody>
</table>

- [ ] I would prefer Choice A
- [ ] I would prefer Choice B
<table>
<thead>
<tr>
<th>Sample</th>
<th>Choice A</th>
<th>Choice B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Check swab</td>
<td>Blood test</td>
</tr>
<tr>
<td>Turnaround time</td>
<td>1 hour</td>
<td>1 week</td>
</tr>
<tr>
<td>Cost to you</td>
<td>$2</td>
<td>$0</td>
</tr>
</tbody>
</table>

- I would prefer Choice A
- I would prefer Choice B
### Choice set 5 of 8

<table>
<thead>
<tr>
<th></th>
<th>Choice A</th>
<th>Choice B</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sample</strong></td>
<td>Check swab</td>
<td>Blood test</td>
</tr>
<tr>
<td><strong>Turnaround time</strong></td>
<td>3 days</td>
<td>3 days</td>
</tr>
<tr>
<td><strong>Cost to you</strong></td>
<td>$2</td>
<td>$2</td>
</tr>
</tbody>
</table>

- [ ] I would prefer Choice A
- [ ] I would prefer Choice B

[Go Back] [Continue]
<table>
<thead>
<tr>
<th></th>
<th>Choice A</th>
<th>Choice B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample</td>
<td>Finger prick</td>
<td>Blood test</td>
</tr>
<tr>
<td>Turnaround time</td>
<td>1 hour</td>
<td>1 hour</td>
</tr>
<tr>
<td>Cost to you</td>
<td>$2</td>
<td>$0</td>
</tr>
</tbody>
</table>

- [ ] I would prefer Choice A
- [ ] I would prefer Choice B

Go Back  Continue
### Choice set 7 of 8

<table>
<thead>
<tr>
<th></th>
<th>Choice A</th>
<th>Choice B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample</td>
<td>Finger prick</td>
<td>Blood test</td>
</tr>
<tr>
<td>Turnaround time</td>
<td>1 hour</td>
<td>3 days</td>
</tr>
<tr>
<td>Cost to you</td>
<td>$0</td>
<td>$0</td>
</tr>
</tbody>
</table>

- [ ] I would prefer Choice A
- [ ] I would prefer Choice B
## Choice set 8 of 8

<table>
<thead>
<tr>
<th></th>
<th>Choice A</th>
<th>Choice B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample</td>
<td>Finger prick</td>
<td>Check swab</td>
</tr>
<tr>
<td>Turnaround time</td>
<td>1 week</td>
<td>1 hour</td>
</tr>
<tr>
<td>Cost to you</td>
<td>$2</td>
<td>$2</td>
</tr>
</tbody>
</table>

- [ ] I would prefer Choice A
- [ ] I would prefer Choice B
Appendix 4 SAS Coding Conditional Logit.

ods listing gpath="%sysfunc(pathname(work))"

PROC IMPORT OUT= WORK.manny
   DATAFILE= "/home/xv04186/r/manny/data.csv"
   DBMS=CSV REPLACE;
   GETNAMES=YES;
   DATAROW=2;
RUN;

proc sql;
   select mean(BirthYear) into :mBirthYear from manny;
   select mean(BirthYear) into :m1BirthYear from manny where ChoiceSetVersion=1;
   select mean(BirthYear) into :m2BirthYear from manny where ChoiceSetVersion=2;
quit;

data manny;
   set manny;
   format _all_;  
   informat _all_; 
   cBirthYear=BirthYear-&mBirthYear; 
   c1BirthYear=BirthYear-&m1BirthYear; 
   c2BirthYear=BirthYear-&m2BirthYear;
RUN;
c2BirthYear=BirthYear-2BirthYear;
if AnnualFamilyIncome in (1 2 3 4) then Income3cats='01-04';
if AnnualFamilyIncome in (5 6 7 8 9) then Income3cats='05-09';
if AnnualFamilyIncome in (10 11) then Income3cats='10-11';
run;

proc sort;
  by Response_ID ChoiceNumber ChoiceSetVersion;
run;

ods graphics on;

ods rtf file='clog_models4_demog3.rtf' CONTENTS=YES TOC_DATA;

%let cat=Sex Insurance ReactedBadly;

title1 'clog, entire data set';
%let cnt=;
%let CostDem=%sysfunc(tranwrd(%str( )%cmpres(&cnt &cat),%str( ),%str( )Cost*));
proc print data=manny(obs=48 keep=ChoiceSetVersion Response_ID ChoiceNumber Utility TurnaroundTime Cost Sample);
  by Response_ID ChoiceNumber ChoiceSetVersion;
  id Response_ID ChoiceNumber ChoiceSetVersion;
run;

proc logistic data=manny simple;
  class Response_ID ChoiceNumber TurnaroundTime(ref='1_week') Sample(ref='Blood_test') &cat/param=ref;
  model Utility(event='1') = Cost TurnaroundTime Sample &CostDem/corrb covb;
  strata Response_ID ChoiceNumber;
run;

title1 'clog, ChoiceSetVersion=1';
%let cnt=;
%let CostDem=%sysfunc(tranwrd(%str( )%cmpres(&cnt &cat),%str( ),%str( )Cost*));
proc print data=manny(obs=48 keep=ChoiceSetVersion Response_ID ChoiceNumber Utility TurnaroundTime Cost Sample);
  by Response_ID ChoiceNumber ChoiceSetVersion;
  id Response_ID ChoiceNumber ChoiceSetVersion;
  where ChoiceSetVersion=1;
run;
proc logistic data=manny simple;
   class Response_ID ChoiceNumber TurnaroundTime(ref='1_week') Sample(ref='Blood_test') &cat/param=ref;
   model Utility(event='1') = Cost TurnaroundTime Sample &CostDem/corr b covb;
   strata Response_ID ChoiceNumber;
   where ChoiceSetVersion=1;
run;

title1 'clog, ChoiceSetVersion=2';
%let cnt=;
%let CostDem=%sysfunc(tranwrd(%str( )%cmpres(&cnt &cat),%str( ),%str( )Cost*));
proc print data=manny(obs=48 keep=ChoiceSetVersion Response_ID ChoiceNumber Utility TurnaroundTime Cost Sample);
   by Response_ID ChoiceNumber ChoiceSetVersion;
   id Response_ID ChoiceNumber ChoiceSetVersion;
   where ChoiceSetVersion=2;
run;
proc logistic data=manny simple;
   class Response_ID ChoiceNumber TurnaroundTime(ref='1_week') Sample(ref='Blood_test') &cat/param=ref;
   model Utility(event='1') = Cost TurnaroundTime Sample &CostDem/corr b covb;
   strata Response_ID ChoiceNumber;
   where ChoiceSetVersion=1;
run;

proc logistic data=manny simple;
   class Response_ID ChoiceNumber TurnaroundTime(ref='1_week') Sample(ref='Blood_test') &cat/param=ref;
   model Utility(event='1') = Cost TurnaroundTime Sample &CostDem/corr b covb;
   strata Response_ID ChoiceNumber;
run;

title1 'clog, entire data set, model with Cost*ChoiceSetVersion';
%let cnt=;
%let CostDem=%sysfunc(tranwrd(%str( )%cmpres(&cnt &cat),%str( ),%str( )Cost*));
proc print data=manny(obs=48 keep=ChoiceSetVersion Response_ID ChoiceNumber Utility TurnaroundTime Cost Sample);
   by Response_ID ChoiceNumber ChoiceSetVersion;
   id Response_ID ChoiceNumber ChoiceSetVersion;
run;
proc logistic data=manny simple;
   class ChoiceSetVersion Response_ID ChoiceNumber TurnaroundTime(ref='1_week') Sample(ref='Blood_test')
     &cat/param=ref;
   model Utility(event='1') = Cost*ChoiceSetVersion TurnaroundTime Sample &CostDem/corr b covb;
   strata Response_ID ChoiceNumber;
run;

title1;
ods graphics off;

data manny; delete; run;

ods rtf close;

SAS coding Bayesian fixed effects

ods listing gpath="%sysfunc(pathname(work))";

%let bopts=dic diag=all plots=all nthreads=20 stats=all;

%let nbi=1000;
%let nmc=55000;
%let thin=11;

%let nbi=10000;
%let nmc=555000;
%let thin=111;

PROC IMPORT OUT= WORK.manny
   DATAFILE= "/home/xv04186/r/manny/data.csv"
   DBMS=CSV REPLACE;
   GETNAMES=YES;
   DATAROW=2;
RUN;

proc sql;
   select mean(BirthYear) into :mBirthYear from manny;
   select mean(BirthYear) into :m1BirthYear from manny where ChoiceSetVersion=1;
   select mean(BirthYear) into :m2BirthYear from manny where ChoiceSetVersion=2;
quit;
**data** manny;
  set manny;
  format _all_;
  informat _all_;
  cBirthYear=BirthYear-&mBirthYear;
  c1BirthYear=BirthYear-&m1BirthYear;
  c2BirthYear=BirthYear-&m2BirthYear;
  if AnnualFamilyIncome in (1 2 3 4) then Income3cats='01-04';
  if AnnualFamilyIncome in (5 6 7 8 9) then Income3cats='05-09';
  if AnnualFamilyIncome in (10 11) then Income3cats='10-11';
run;

**proc sort;**
  by Response_ID ChoiceNumber ChoiceSetVersion;
run;

ods graphics on;
ods rtf file='FE_models4_demog3.rtf' CONTENTS=NO TOC_DATA;

%let cat=Sex Insurance ReactedBadly;

**title1 'FE, entire data set';**
%let cnt=;
%let CostDem=%sysfunc(tranwrd(%str( )%cmpres(&cnt &cat),%str( ),%str( )Cost*));
**proc print data=manny(obs=48 keep=ChoiceSetVersion Response_ID ChoiceNumber Utility TurnaroundTime Cost Sample);**
  by Response_ID ChoiceNumber ChoiceSetVersion;
  id Response_ID ChoiceNumber ChoiceSetVersion;
run;

**proc bchoice data=manny seed=123 nbi=&nbi nmc=&nmc thin=&thin &bopts;**
  class Response_ID ChoiceNumber TurnaroundTime(ref='1_week') Sample(ref='Blood_test') &cat;
  model Utility = Cost TurnaroundTime Sample &CostDem / choiceset=(Response_ID ChoiceNumber);
run;

**title1 'FE, ChoiceSetVersion=1';**
%let cnt=;
%let CostDem=%sysfunc(tranwrd(%str( )%cmpres(&cnt &cat),%str( ),%str( )Cost*));
**proc print** data=manny(obs=48 keep=ChoiceSetVersion Response_ID ChoiceNumber Utility TurnaroundTime Cost Sample);
  by Response_ID ChoiceNumber ChoiceSetVersion;
  id Response_ID ChoiceNumber ChoiceSetVersion;
  where ChoiceSetVersion=1;
run;

**proc bchoice** data=manny seed=123 nbi=&nbi nmc=&nmc thin=&thin &bopts;
  class Response_ID ChoiceNumber TurnaroundTime(ref='1_week') Sample(ref='Blood_test') &cat;
  model Utility = Cost TurnaroundTime Sample &CostDem / choiceset=(Response_ID ChoiceNumber);
  where ChoiceSetVersion=1;
run;

**title1 'FE, ChoiceSetVersion=2';**
%let cnt=;
%let CostDem=%sysfunc(tranwrd(%str( )%cmpres(&cnt &cat),%str( ),%str( )Cost*));
**proc print** data=manny(obs=48 keep=ChoiceSetVersion Response_ID ChoiceNumber Utility TurnaroundTime Cost Sample);
  by Response_ID ChoiceNumber ChoiceSetVersion;
  id Response_ID ChoiceNumber ChoiceSetVersion;
  where ChoiceSetVersion=2;
run;

**proc bchoice** data=manny seed=123 nbi=&nbi nmc=&nmc thin=&thin &bopts;
  class Response_ID ChoiceNumber TurnaroundTime(ref='1_week') Sample(ref='Blood_test') &cat;
  model Utility = Cost TurnaroundTime Sample &CostDem / choiceset=(Response_ID ChoiceNumber);
  where ChoiceSetVersion=2;
run;

**title1 'FE, entire data set, model with Cost*ChoiceSetVersion';**
%let cnt=;
%let CostDem=%sysfunc(tranwrd(%str( )%cmpres(&cnt &cat),%str( ),%str( )Cost*));
**proc print** data=manny(obs=48 keep=ChoiceSetVersion Response_ID ChoiceNumber Utility TurnaroundTime Cost Sample);
  by Response_ID ChoiceNumber ChoiceSetVersion;
  id Response_ID ChoiceNumber ChoiceSetVersion;
run;

**proc bchoice** data=manny seed=123 nbi=&nbi nmc=&nmc thin=&thin &bopts;
  class Response_ID ChoiceNumber ChoiceSetVersion TurnaroundTime(ref='1_week') Sample(ref='Blood_test') &cat;
model Utility = Cost*ChoiceSetVersion TurnaroundTime Sample &CostDem / choiceset=(Response_ID ChoiceNumber);
run;

title1;
ods graphics off;

data manny; delete; run;

ods rtf close;

SAS coding Bayesian random ods listing gpath="%sysfunc(pathname(work))";

%let bopts=dic diag=all plots=all nthreads=20 stats=all;

%let nbi=1000;
%let nmc=55000;
%let thin=11;

%let nbi=10000;
%let nmc=555000;
%let thin=111;

PROC IMPORT OUT= WORK.manny
   DATAFILE= "/home/xv04186/r/manny/data.csv"
   DBMS=CSV REPLACE;
   GETNAMES=YES;
   DATAROW=2;
RUN;
PROC SQL;
    SELECT MEAN(BirthYear) INTO :mBirthYear FROM manny;
    SELECT MEAN(BirthYear) INTO :m1BirthYear FROM manny WHERE ChoiceSetVersion=1;
    SELECT MEAN(BirthYear) INTO :m2BirthYear FROM manny WHERE ChoiceSetVersion=2;
QUIT;

DATA manny;
    SET manny;
    FORMAT _all_;
    INFORMAT _all_;
    cBirthYear=BirthYear-&mBirthYear;
    c1BirthYear=BirthYear-&m1BirthYear;
    c2BirthYear=BirthYear-&m2BirthYear;
RUN;

PROC SORT;
    BY Response_ID ChoiceNumber ChoiceSetVersion;
RUN;

ODS GRAPHICS ON;
ODS RTF FILE='FE_models4_noDemographics.rtf' CONTENTS=YES TOC_DATA;

%LET cat=;

TITLE 'RE, entire data set';
%LET cnt=;
%LET CostDem=;
PROC PRINT DATA=manny(obs=48 keep=ChoiceSetVersion Response_ID ChoiceNumber Utility TurnaroundTime Cost Sample);
    BY Response_ID ChoiceNumber ChoiceSetVersion;
    ID Response_ID ChoiceNumber ChoiceSetVersion;
RUN;
PROC BCHOICE DATA=manny seed=123 nbi=&nbi nmc=&nmc thin=&thin &bopts;
    CLASS Response_ID ChoiceNumber TurnaroundTime(ref='1_week') Sample(ref='Blood_test') &cat;
    MODEL Utility = Cost TurnaroundTime Sample &CostDem / choiceset=(Response_ID ChoiceNumber);
    RANDOM Cost TurnaroundTime Sample / sub=Response_ID type=un monitor=(1 to 5);
title1 'RE, ChoiceSetVersion=1';
%let cnt=
%let CostDem=;
proc print data=manny(obs=48 keep=ChoiceSetVersion Response_ID ChoiceNumber Utility TurnaroundTime Cost Sample);
  by Response_ID ChoiceNumber ChoiceSetVersion;
  id Response_ID ChoiceNumber ChoiceSetVersion;
  where ChoiceSetVersion=1;
run;
proc bchoice data=manny seed=123 nbi=&nbi nmc=&nmc thin=&thin &bopts;
  class Response_ID ChoiceNumber TurnaroundTime(ref='1_week') Sample(ref='Blood_test') &cat;
  model Utility = Cost TurnaroundTime Sample &CostDem / choiceset=(Response_ID ChoiceNumber);
  random Cost TurnaroundTime Sample / sub=Response_ID type=un monitor=(1 to 5) ;
  where ChoiceSetVersion=1;
run;


title1 'RE, ChoiceSetVersion=2';
%let cnt=
%let CostDem=;
proc print data=manny(obs=48 keep=ChoiceSetVersion Response_ID ChoiceNumber Utility TurnaroundTime Cost Sample);
  by Response_ID ChoiceNumber ChoiceSetVersion;
  id Response_ID ChoiceNumber ChoiceSetVersion;
  where ChoiceSetVersion=2;
run;
proc bchoice data=manny seed=123 nbi=&nbi nmc=&nmc thin=&thin &bopts;
  class Response_ID ChoiceNumber TurnaroundTime(ref='1_week') Sample(ref='Blood_test') &cat;
  model Utility = Cost TurnaroundTime Sample &CostDem / choiceset=(Response_ID ChoiceNumber);
  random Cost TurnaroundTime Sample / sub=Response_ID type=un monitor=(1 to 5) ;
  where ChoiceSetVersion=2;
run;
title1 'RE, entire data set, model with Cost*ChoiceSetVersion';
%let cnt=
%let CostDem=;
proc print data=manny(obs=48 keep=ChoiceSetVersion Response_ID ChoiceNumber Utility TurnaroundTime Cost Sample);
  by Response_ID ChoiceNumber ChoiceSetVersion;
  id Response_ID ChoiceNumber ChoiceSetVersion;
proc bchoice data=manny seed=123 nbi=&nbi nmc=&nmc thin=&thin &bopts;
  class Response_ID ChoiceNumber ChoiceSetVersion TurnaroundTime(ref='1_week') Sample(ref='Blood_test') &cat;
  model Utility = Cost Cost*ChoiceSetVersion TurnaroundTime Sample &CostDem / choiceset=(Response_ID ChoiceNumber);
  random Cost TurnaroundTime Sample / sub=Response_ID type=un monitor=(1 to 5) ;
run;

title1;
ods graphics off;

data manny; delete; run;

do s rtf close;