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Economic Evaluations of a Pharmacogenomics Test for Statin-induced Myopathy in Secondary Cardiovascular Prevention

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Résumé

Les statines constituent la pierre angulaire du traitement des dyslipidémies. Les myopathies secondaires aux statines seraient l'une des principales causes d'abandon. Le diagnostic de myopathie repose sur la comparaison du taux de créatine kinase (CK) avec des valeurs de référence normales. Or, des études ont révélé que ces valeurs ne sont pas représentatives de l'ensemble de la population. Le test du taux de CK n'a donc qu'une utilité diagnostique restreinte. Un test pharmacogénomique (PGx) pour le diagnostic des myopathies chez les patients qui affichent une hausse légère ou modérée du taux de CK après l'amorce d'un traitement par une statine est en développement.

Nous avons évalué l'impact économique de ce test PGx hypothétique grâce à deux techniques de modélisation : un modèle de Markov et un modèle de simulation par événement discret (SED). Nous avons examiné les modèles avec la perspective d'un payeur canadien, avec un horizon temporel de la vie entière, pour les patients à risque cardiovasculaire (CV) élevé initiant une statine en prévention secondaire.

La détermination des taux de faux positifs (TFP) et de faux négatifs (TFN) du test revêt encore plus d'importance que le choix de la technique de modélisation. Dans cette thèse, nous avons opté pour une interprétation globale des résultats des tests, afin que les décisions des médecins et des patients s'apparentent à des erreurs de test. Cette définition permet de mesurer l'utilité clinique du test à influencer les décisions de prescription des médecins et, surtout, la volonté des patients de poursuivre le traitement. Ce dernier aspect s'applique particulièrement aux médicaments prescrits à titre préventif dont les bienfaits à long terme dépendent de l'adhésion du patient au traitement.

Les articles I et II présentent les résultats des modèles de Markov et SED. Les résultats concordent sur le plan qualitatif. Au Canada, un test PGx pour le dépistage des myopathies secondaires aux statines serait rentable avec une faible disposition à payer. Selon les analyses de sensibilité probabilistes, les modèles de Markov et SED donnaient des résultats favorables dans au moins 90 % des simulations assorties d'une disposition à payer de seulement 6150 $ et 12000 $ par année de vie pondérée par la qualité.

L'article III poursuit la réflexion des modèles présentés dans les articles I et II. Ceux-ci ont permis de constater qu'un test PGx complètement erroné (TFP = TFN = 100 %) se traduirait par un avantage différentiel monétaire net positif pour les payeurs. Ce résultat s'explique par le déséquilibre du risque entre les bienfaits d'une réduction des manifestations CV chez les patients atteints d'une myopathie légère ou modérée et le risque extrêmement faible de rhabdomyolyse. Cependant, ce résultat n'est pas plausible lorsque qu'on prend en considération les décisions à long terme des médecins et des patients, notamment le haut niveau de non-adhésion aux statines.

Dans l'ensemble, cette thèse souligne l'importance d'évaluer l'impact économique des erreurs de test. Cette démarche ne doit pas se limiter à une supposition *a priori* des paramètres de rendement du test. Il convient d'examiner la fourchette complète des TFP et des TFN pour bien cerner l'incidence économique des tests diagnostiques, surtout lorsque le résultat du test influence la prescription d'un médicament préventif administré à long terme.

Mots-clés : pharmacoéconomie, test pharmacogénomique, Markov, simulation par événement discret, prévention cardiovasculaire secondaire, dyslipidémie, statines, myopathie

Abstract

Statins are the mainstay of treatment for dyslipidemia. Statin-induced myopathies are thought to be a major cause of patients discontinuing statin treatment. Myopathy diagnoses are based on creatine kinase (CK) elevation, which is compared to age-gender specific CK upper limit of normal values. Studies have shown, however, reference CK values are not representative of all population subgroups. Thus, CK tests have limited diagnostic capacity due to poor internal validity and limited external validity. A pharmacogenomics (PGx) test for statin-induced myopathies is in development for patients who have initiated statin therapy and who have mild to moderate CK elevation.

We conducted economic evaluations of this hypothetical PGx test using two modelling techniques: a Markov health state model and a discrete event simulation (DES) model. We evaluated the economic models with a lifetime horizon from the Canadian payer perspective for high cardiovascular (CV) risk patients initiating a statin in secondary prevention.

We found that even more important than the choice of modelling technique when evaluating the economic value of diagnostic tools, was the assessment of the diagnostic test false-positive and false-negative results. In this thesis, we have proposed an approach for interpreting diagnostic test results broadly such that physician and patient behaviours are akin to test errors. This definition addresses the clinical utility of the test in influencing physician prescribing recommendations and, importantly, patient decisions to adhere to therapy. This point is especially true for preventive medications, such as statins where the long-term benefits of therapy depend on patient adherence.

Articles I and II present the model results from the Markov health state model and the DES model. We found that, although the Markov and DES model results differed slightly, the qualitative model results were in agreement. A PGx test for statin-induced myopathy was cost-effective at a relatively low willingness-to-pay (WTP). In the probabilistic sensitivity analyses, the Markov and DES strategies were favoured in at least 90% of the model simulations with a payer WTP as low as $6,150 and $12,000 per quality-adjusted life year, respectively.

Article III was a reflection on the implications of model results presented in Articles I and II. Articles I and II highlighted that a totally inaccurate PGx test (i.e., false-positive rate [FPR] = false-negative rate [FNR] = 100%) would yield a positive incremental net monetary benefit for the payers. This result is explained by the risk imbalance between the benefit in reduction of CV events for patients suffering from mild to moderate myopathy compared to the extremely low risk of rhabdomyolysis. Although the totally inaccurate test result helped us understand the consequences of test errors, we recognize that a PGx test that is completely inaccurate, is not a plausible solution. The PGx test must be clinically valid and account for long-term physician and patient behavioural responses to the test results. As we have argued, the economic value of the PGx test for statin-induced myopathy in high CV risk patients depends on its ability to influence lifetime adherence to statin therapy.

Overall, this thesis highlights the importance of assessing the economic consequences of test errors. The assessment of test errors should not be limited to an *a priori* supposition of test performance parameters. The complete range of FPR and FNR test values should be investigated to fully understand the economic consequences of diagnostic tests. This is even more important when the diagnostic test is used to prescribe a long-term preventive medication.

Keywords: pharmacoeconomics, pharmacogenomics test, Markov, discrete event simulation, secondary cardiovascular prevention, dyslipidemia, statins, myopathy

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Abbreviations

4S	Scandinavian Simvastatin Survival Study
ACC	American College of Cardiology
AF	Atrial fibrillation
AHA	American Heart Association
AIC	Akaike information criterion
AICc	Akaike information criterion correction
AMI	Acute myocardial infarction
BIC	Bayesian information criterion
BMI	Body Mass Index
CADTH	Canadian Agency for Drugs and Technologies in Health
CCS	Canadian Cardiovascular Society
CCWG	Canadian Consensus Working Group
CDR	Challenge-dechallenge-rechallenge
CEAC	Cost-effectiveness acceptability curve
CHMS	Canadian Health Measures Survey
CI	Confidence interval
CK	Creatine kinase
CSV	Comma-separated value
CTT	Cholesterol Treatment Trialists
CV	Cardiovascular
CVD	Cardiovascular disease
CVE	Cardiovascular event
DES	Discrete event simulation
DSA	Deterministic sensitivity analysis
FDA	Food and Drug Administration
FPR	False-positive rate
FNR	False-negative rate
FRS	Framingham Risk Score

GIMP	GNU Image Manipulation Program
HDL-C	High-density lipoprotein cholesterol
HR	Hazard ratio
HTA	Health Technology Agency
ICER	Incremental cost-effectiveness ratio
ICUR	Incremental cost-utility ratio
INESSS	Institut national d'excellence en santé et services sociaux
IPD	Individual patient data
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
MRR	Mortality rate ratio
MSP	Musculoskeletal pain
NHANES	National Health and Nutrition Examination Survey
NHLBI	National Heart, Lung and Blood Institute
NLA	National Lipid Association
NNT	Number needed to treat
OR	Odds ratio
PCSK9	Proprotein convertase subtilisin/kexin type 9
PGx	Pharmacogenomics
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
RAMQ	Régie de l'assurance maladie du Québec
RR	Relative risk
ULN	Upper limit of normal
UK	United Kingdom
US	United States
VBA	Visual basic for application
WTP	Willingness-to-pay

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Chapter 1. Introduction

1.1 Burden of Dyslipidemia

Dyslipidemia is defined as an elevation of plasma cholesterol, triglycerides, or low- and high-density lipoprotein cholesterol (LDL-C and HDL-C). It is an important cardiovascular (CV) risk factor contributing to the development of atherosclerosis [1]. Millions of Canadians have dyslipidemia. According to the 2012 to 2013 Canadian Health Measures Survey (CHMS) and the 2012 Canadian population estimate, approximately 13.3 million individuals have elevated cholesterol levels (i.e., dyslipidemia[i]) [2]. The economic burden of dyslipidemia is substantial. In 2013, the direct drug costs associated with cholesterol-lowering drugs in Canada was estimated at $1.6 billion annually, with 85% of direct costs accounted for by provincial drug programs [3].

Millions of Canadians are prescribed statins to manage their dyslipidemia to reduce their risk of cardiovascular disease (CVD) [4]. Using the CHMS survey data, Hennessy et al. (2016) estimated that 2.8 million Canadian adults are currently prescribed a statin to reduce their cholesterol level; of these, 2.1 million are considered at high CV risk [4]. Estimates from the Canadian Cardiovascular Society (CCS) Guidelines (2012) [5], showed that 6.5 million Canadians (4.7 million considered at high CV risk) should be prescribed a statin. Assuming perfect adherence to therapy, Hennessy et al. (2016) further estimated that, among high CV risk patients currently treated and those recommended for treatment, close to 14,600 and 29,000 annual CV events (CVEs)[ii], respectively, could be potentially avoided with statin therapy [4].

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[i] In the CHMS, dyslipidemia was defined as having unhealthy blood concentrations of LDL-C (≥3.5mmol/L), or a total cholesterol to high-density cholesterol ratio ≥5.0, or self-reported use of a lipid-modifying medication.

[ii] The numbers presented above differ from those in Hennessy et al. (2016). The authors made an error in calculating the number needed to treat by multiplying a risk with a relative risk. To perform the risk adjustment, the authors should have used standard formulas to transform the CV risk into a rate that can then be adjusted by multiplying with the relative risk. The adjusted risk is obtained by converting back into a probability [6].

1.2 Statin Therapy

1.2.1 Statins

Statins, inhibitors of 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase, are the mainstay treatment for dyslipidemia [7-9]. Lovastatin was the first commercial statin approved by the United States (US) Food and Drug Administration (FDA) in 1987 [10, 11]. Six other statins followed: simvastatin was initially approved for marketing in Sweden in 1988 and subsequently worldwide, pravastatin followed in 1991, fluvastatin in 1994, atorvastatin in 1997, cerivastatin in 1998, and rosuvastatin in 2003 [12]. However, in 2001, after statins were perceived as a safe drug class, the newly introduced cerivastatin was withdrawn from the market by its manufacturer following a large number of reports of rhabdomyolysis, of which more than 50 cases were fatal [12-15]. In 2002, the Heart Protection Study, the largest placebo-controlled 5-year statin trial, confirmed the safety of simvastatin in 20,536 high CV risk individuals in the United Kingdom (UK).

Several statin molecules are available. These can be classified based on their potency to lower LDL-C. **Table 1** shows an adapted list of statin molecules/dosages reimbursed by the Régie de l'assurance maladie du Québec (RAMQ) [9, 16-18].

Table 1 List of statins available on the RAMQ listing by potency

Potency	Statin molecule	Dosage (mg)
Low intensity (↓ LDL-C <30%)	Fluvastatin	20, 40
	Lovastatin	20
	Pravastatin	10, 20
	Simvastatin	5, 10
Medium intensity (↓ LDL-C 30% to 50%)	Atorvastatin	10, 20
	Fluvastatin	40 (BID), 80 (QD)
	Lovastatin	40, 80
	Pravastatin	40, 80
	Rosuvastatin	5, 10
	Simvastatin	20, 40, 80
High intensity (↓ LDL-C ≥50%)	Atorvastatin	40, 80
	Rosuvastatin	20, 40

BID two times per day, *LDL-C* low-density lipoprotein-cholesterol, *mg* milligram, *QD* once per day, *RAMQ* Régie de l'assurance maladie du Québec.

1.2.2 Mechanism of Action

Statins are selective, competitive inhibitors of a HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methyl-glutaryl coenzyme A into mevalonic acid, a precursor of sterols, including cholesterol [19-21]. As a result, the expression of low-density lipoprotein (LDL)-receptors, followed by the uptake of LDL from blood to liver, is accelerated and the plasma total cholesterol decreases [22]. Statins reduce LDL-C non-linearly, in a dose-dependent manner, after administration of a single daily dose [21, 23].

1.2.3 Benefits of Treatment

As recognized by the CCS, statins reduce the relative risk of CVD in individuals by 25% to 35%, with better prevention of vascular events achieved with higher doses [5]. As statins are preventive medications, the cardio-protective benefits are observed after the first year of follow-up in clinical trials [24, 25]. To help answer statin-related efficacy and safety questions, the Cholesterol Treatment Trialists (CTT) Collaboration has carried out a series of meta-analyses. The CTT Collaboration was established in 1994 after it was recognized that not a single lipid trial would have sufficient numbers of patients to reliably establish mortality or to investigate events in specific populations [26]. To date, they have investigated statin-related questions on cancer, major vascular events, and mortality from nearly 30 major statin trials combining approximately 175,000 trial participants [26]. The meta-analyses conducted by the CTT have been used to inform national clinical guidelines [7, 8].

In 2005, the CTT Collaborators conducted a meta-analysis to establish the efficacy and safety of statins from 14 randomized clinical trials with 90,956 participants [27]. Their results indicated a 12% proportional reduction in all-cause mortality per mmol/L reduction in LDL-C (rate ratio=0.88, 95% confidence interval [CI] 0.84–0.91; $p<0.0001$). This difference was driven by the 19% reduction in coronary mortality (rate ratio=0.81, 95% CI 0.76–0.85; $p<0{\cdot}0001$), with non-significant reductions in non-coronary vascular and non-vascular mortality [27]. The combined major vascular event reduction was 21% (rate ratio=0.79, 95% CI 0.77–0.81; $p<0.001$). These benefits were significant in the first year, but they were greater in subsequent years. In addition, the results indicated that the hazards of lowering LDL-C with statins appeared

extremely small compared to the benefits. The meta-analysis showed an extremely low incidence risk of rhabdomyolysis (5-year excess=0.01%; standard error=0.01) [27].

In 2010, the CTT Collaboration published another meta-analysis assessing the efficacy and safety of more intensive regimens to lower LDL-C [28]. The meta-analysis combined data from 26 randomized trials with 129,526 individuals and a median follow-up of 4.8 years. The results indicated that, compared with less intensive statin regimens, higher dose regimens significantly reduced major CVD events by a further 15% [28]. Across the 26 trials, all-cause mortality was reduced by 10% per 1.0 mmol/L LDL-C reduction (rate ratio=0.90, 95% CI 0.87–0.98; $p<0.0001$), reflecting largely the reduction in death due to coronary heart disease and other cardiac causes [28].

The benefits and safety of statins in patients at high vascular risk is well established and recognized in the CCS Guidelines [7]. The 2012 CTT meta-analysis looked at the impact of statins on lowering LDL-C in patients at low risk of vascular disease in 174,149 patients from 27 randomized clinical trials [29]. They concluded that in individuals with a 5-year risk of major vascular events below 10%, each 1 mmol/L reduction in LDL-C generated an absolute reduction in major vascular events of approximately 11 per 1,000 over 5 years, a reduction which greatly outweighs any known hazards of statin therapy [29]. Similar findings were observed in a Cochrane review of statins for the primary prevention of CVD[iii] based on 18 randomized trials including 56,934 patients [31]. In 2013, the American College of Cardiology/American Heart Association (ACC/AHA) revised the US Cholesterol Treatment Guidelines; their revisions included lowering the risk threshold for treating primary prevention patients [32, 33]. Compared to the CCS Guidelines (2012), the US Cholesterol Treatment Guidelines (2013) recommend initiating a statin in primary prevention when the 10-year risk of atherosclerotic CVD exceeds 7.5%, whereas the CCS threshold was 20% [5, 7, 32, 33].

[iii] Primary prevention refers to health strategies delaying or preventing the onset of CVD. Secondary prevention refers to health strategies applied after the onset of CVD (in early stages of the disease) and include interventions to prevent disease progression and complications [30].

1.2.4 Canadian Cardiovascular Society Statin Therapy Recommendations

The most recent CCS Guidelines (2016) for dyslipidemia provide guidance on the population, risk assessment, management of dyslipidemia, and prevention of CVD [7, 34]. The guidelines recommend screening men ≥40 years, women ≥40 years (or postmenopausal), and all patients presenting with CV risk factors regardless of age[iv][7, 34]. The two key messages from the CCS Guidelines are:

- LDL-C levels are directly linked to the development of atherosclerosis and its reduction is directly linked to the reduction in CVEs
- Health behaviour modification remains a cornerstone of risk reduction

The CCS Guidelines stratify patient management into three risk categories:

- Statin-indicated conditions
- Primary prevention conditions
- No pharmacotherapy

1.2.4.1 **Statin-Indicated Conditions**

The CCS Guidelines recommend initiating a statin in patients with an established CV risk (i.e., secondary prevention) [7]. For example, in patients with:

- Clinical atherosclerosis
- Abdominal aortic aneurysm

[iv] The list of risk factors includes: clinical evidence of atherosclerosis, abdominal aortic aneurysm, diabetes mellitus, arterial hypertension, current cigarette smoking, stigmata of dyslipidemia (arcus cornealis xanthelasma or xanthoma), family history of CVD (men <55 and women <65 years in first degree relative), chronic kidney disease (estimated glomerular filtration rate <60 ml/min/1.73m^2 or albumin:creatinine ratio >3 mg/mmol for at least 3 months duration), obesity, inflammatory disease, HIV infection, erectile dysfunction, chronic obstructive pulmonary disease, and hypertensive disease of pregnancy.

- Diabetes
    - Age ≥40 years
    - Age ≥30 years and disease duration ≥15 years (type 1 diabetes mellitus)
    - Microvascular disease
- Chronic kidney disease
- Genetic dyslipidemia with LDL-C ≥5 mmol/L

The CCS Guidelines recommend initiating statin therapy in target patient groups when the benefits of treating with a statin (as measured by the number needed to treat[v] [NNT] to avoid one CVD event for 5 years of treatment per 1 mmol/L reduction in LDL-C) fall below the threshold considered acceptable by physicians; generally an NNT <50 is considered acceptable [7, 36]. The CCS Guidelines recommend pharmacotherapy in patient groups where the NNT falls below 40. For statin-indicated conditions where statins are indicated as initial therapy, the threshold NNT value is 20.

1.2.4.2 **Primary Prevention Conditions**

In primary prevention, the CCS Guidelines use the 10-year CV risk score from the Framingham Risk Score (FRS) to inform their recommendations [37]. The CCS Guidelines recommend initiating a statin therapy for patients with a FRS score above 20% (high CV risk patients, NNT=35) or a FRS score 10% to 19% (NNT=40) combined with other criteria:

- LDL-C ≥3.5 mmol/L; or
- Non-HDL-C ≥4.3 mmol/L; or

[v] The NNT is a measure of the efficacy of health interventions. The NNT indicates the number of patients needed to treat to avoid one health event. An NNT equal to one indicates that one health intervention would avoid one health event. From a public perspective, lower NNT values are desirable. NNT measures are time-specific [35].

- Apolipoprotein B ≥1.2g/L; or
- Men ≥50 and women ≥60 years of age and one additional CVD risk factor

1.2.4.3 No Pharmacotherapy

The CCS Guidelines do not recommend treating patients in primary prevention when the estimated 10-year FRS is less than 10% [7]. Note that the US Cholesterol Clinical Practice Guidelines have a lower FRS threshold for treating patients with a statin: their definition of the intermediate-risk category includes patients with an FRS above 7.5% to 20% [8, 32].

1.2.5 Statin Non-Adherence

Adherence to statin therapy is essential for patients to achieve the full benefits of treatment. DiMatteo et al. (2002) conducted a meta-analysis using 63 articles from different disease areas to assess the relationship between treatment adherence and clinical outcomes [38]. Their meta-analysis included seven studies in hypercholesterolemia. Three studies defined adherence as a dichotomous variable (e.g., 80% intake or greater vs. less) and four studies used a continuous definition (e.g., mean percentage daily dose taken). They found an odds ratio (OR) of 2.81 [95% CI 1.67–4.71] between non-adherent and adherent patients with hypercholesterolemia; that is, non-adherent patients were 2.81 times more likely to have a CVE than patients who adhered to therapy.

Adherence to therapy is a problem with statins. Many studies have highlighted the poor adherence and poor persistence to statin therapy. In a claims database study, Avorn et al. (1998) analyzed the persistence and adherence to lipid-lowering therapy in Canada and the US [39]. They found that, on average, patients remained without filled prescriptions for over one-third of the year and approximately 50% of the cohort from the US had discontinued treatment. Catalan et al. (2000) showed that, in a cohort of patients initiating a statin, only 33% still adhered to treatment after one year [40]. Guertin et al. (2016) reported that 18.7% and 58.0% of incident statin users had discontinued statin therapy at 30 days and at 1 year, respectively [41]. As shown by Nielsen and Nordestgaard (2016), early statin discontinuation (within 6 months of statin initiation) increased three-fold (6% to 18%) between 1995 and 2010 [42]. Their analyses indicated that early statin discontinuation increased with negative statin-related news stories.

Dorais et al. (2010) reported that, among 19,727 patients initiating a statin, 53.3% had discontinued treatment after 1 year [43]. Maningat et al. (2013) highlighted that statin adherence is lower than other preventive medications (aspirin: 71%; β-blockers: 46%; vs. statins: 44%) [44, 45]. Brown et al. (2017) conducted a chart review using the Manitoba Primary Care Research Network repository [46]. Their study showed that, among the secondary prevention CVD patients, less than 30% had received a repeat statin prescription from their primary care providers.

There are several reasons a patient may not adhere to statin therapy [44]. In clinical trials, the observed benefits of statin therapy only start to materialize after 1.5 years of treatment. For instance, in the large, double-blind, randomized controlled Scandinavian Simvastatin Survival Study (4S), the Kaplan-Meier curves for all-cause mortality for the placebo and simvastatin treatment groups start to diverge after 1.5 years [25]. Furthermore, as statin therapy is a preventive treatment, patients do not observe the benefit of statins in their daily lives. This may raise doubts in patients as to the necessity of treatment. Wouters et al. (2016) showed that among 229 patients, 40% to 70% doubted the need for therapy and lacked knowledge about statin efficacy, while 20% to 35% worried about joint and muscle side effects [47].

These data indicate that many patients do not fully understand the benefits of statin therapy and do not adequately adhere to treatment; thus, patients are potentially placing themselves at risk of having a CVE. A detailed description of which patients should remain on treatment may help improve adherence and treatment outcomes. Statin-induced myopathies are thought to be a major cause of statin discontinuation leading to many patients being untreated [48]. As such, there is a need for an accurate diagnostic test to convince patients to adhere to the treatment when the test indicates that the statin is not the cause of their muscle pain.

1.3 Statin-Induced Myopathy

Statins are generally well tolerated for most patients, and their widespread usage has had a major impact on reducing the global burden of CVD [49]. However, a proportion of patients may experience statin intolerance. Statin intolerance can be partial or complete. Partial statin intolerance may resolve with a switch to a different statin molecule and/or by reducing the statin dosage. Complete statin intolerance occurs when a patient cannot tolerate any statins at any

dosage [50]. The most common forms of statin intolerance are myopathies, which include muscle weakness, pain, inflammation, spasms, or paralysis [51]. Myopathies develop either as the result of inherited or acquired conditions of the muscle [52]. Statin-induced myopathies are in the category of acquired myopathy.

Myopathy is a broad term used to describe muscle toxicity, which can range from muscle ache to the extreme case of rhabdomyolysis. Myopathies are classified based on the level of creatine kinase (CK) in serum plasma, creatinine elevation (with brown urine or urinary myoglobin), and evidence of organ damage [53]. The serum CK test compares the level of CK in blood serum with the gender-/age-specific range of reference values (i.e., normal values) [54, 55]. Creatine kinase levels are a rough proxy for the severity of statin-induced myotoxicity, but the correlation between symptoms and CK levels remains incomplete. The clinical interpretation of CK levels is complex and there is yet no consensus on the definition of statin myopathy. Typically, myopathies are classified into three levels of severity: 1) myalgia, defined as muscle symptoms, such as ache or weakness, with normal CK levels; 2) myositis, defined as muscle symptoms with elevated CK levels; and 3) rhabdomyolysis, defined as muscle symptoms with CK elevation (typically >10x the upper limit of normal [ULN]) and creatinine elevation [52]. The ACC/AHA/National Heart, Lung and Blood Institute (NHLBI) [52], the FDA [56], National Lipid Association (NLA) [57], and the Canadian Consensus Working Group (CCWG) [58], have each proposed different definitions for statin-related muscle effects. These definitions are anchored on the CK ULN values. Hence, the importance of ULN reference values. **Table 2** presents the definition of myopathy from the CCWG Guidelines (2016) for the management of statin adverse effects [58].

Table 2 Integrated CCWG terminology for myopathic syndromes

Term	Characteristics	
	Laboratory	Clinical
Myopathy	NA	General term referring to any disease of muscle
Symptomatic myopathy		
Myalgia	CK ≤ ULN	Muscle ache/weakness
Myositis	CK > ULN	Muscle ache/weakness
Rhabdomyolysis	CK >10x ULN (CK >10,000 U/L)	Muscle ache/weakness; renal dysfunction might result from myoglobinuria; need for hydration therapy

CCWG Canadian Consensus Working Group, *CK* creatine kinase, *NA* not applicable, *ULN* upper limit of normal.
Modified from Mancini et al. (2016) [58] with permission from Elsevier.

Rhabdomyolysis, the most extreme form of myopathy, can lead to complications, such as renal damage and, in rare cases, death [59, 60]. The incidence of suspected statin-induced myopathy is 5% to 10% in randomized clinical studies [60, 61], and as high as 25% in some observational studies [53, 61, 62]. Radillis et al. (2012) argued that statin-related myopathies were systematically underestimated in randomized controlled trials [60]. Exclusion of patients with risk factors for myopathy, failure to systematically document myalgias, application of strict criteria to define myopathy (i.e., CK elevations >10 ULN), and the inclusion of a run-in phase excluding patients with muscle symptoms, are reasons why statin-induced intolerance may be under-reported in clinical trials [48, 60]. Identification and management of these patients is critical for them to fully achieve the benefits of chronic, generally life-long, lipid-lowering therapy [48]. Typically, statin myopathy symptoms are completely reversible and CK activity decreases within a few weeks after statin therapy discontinuation [50, 63, 64]. Serious muscle damage or rhabdomyolysis associated with statin treatment is extremely rare; for instance, occurring in 1 in 23 million individuals with prescriptions for atorvastatin [50]. In 2012-2013, atorvastatin was the leading cholesterol-lowering drug, representing 43% of the prescription volume, followed by rosuvastatin with 33.3% of the prescription volume [3]. Early treatment of rhabdomyolysis is key to a successful outcome and patients can expect full recovery with prompt treatment; however, if it is not treated early, it may cause lasting damage [65].

1.3.1 Canadian Consensus Working Group Guidelines

The CCWG established the Canadian Guidelines for diagnosis, prevention, and management of statin adverse effects and intolerance in 2011 with revision updates published in 2013 and 2016 [48, 58, 66]. The objective of these guidelines is to provide clinicians with an algorithm for managing patients in need of statin therapy who have drug intolerances (true or perceived) undermining compliance.

According to the guidelines, a diagnosis of statin intolerance should only be considered when a patient reports symptoms associated with the use of a statin, symptoms resolve when the statin is stopped, and the symptoms recur with the same or a different statin, regardless of abnormal laboratory findings [48].

There are several predisposing risk factors for adverse effects from statin-induced myopathy. The CCWG Guidelines (2016) present an exhaustive list under two categories: endogenous and exogenous factors [58]. Endogenous risk factors are non-modifiable patient characteristics[vi], whereas exogenous risk factors are behavioural and treatment-related[vii] [58].

The CCWG Guidelines (2016) summarize the principles of the management of goal-inhibiting statin intolerance, which is described below [58]. First, the need for statin therapy as indicated by the CCS Guidelines [7] must be re-evaluated. Once the need has been established, then the practicing physician should assess the risk of statin-intolerance using the list of potential risk factors[vi,vii]. The practicing physician should investigate whether a behavioural plan was set,

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[vi] The list of endogenous factors includes: advanced age, female sex, low BMI, small body, frailty, history of pre-existing/unexplained muscle/joint/tendon pain, history of CK elevation, family history of myopathy, family history of myopathy with statin therapy, neuromuscular diseases, severe renal disease, acute/decompensated hepatic disease, hypertension/heart failure (renal side effects mainly), hypothyroidism (untreated), diabetes mellitus, genetic polymorphisms (e.g., *SLCO1B1* gene variants) [58].

[vii] The list of exogenous factors includes: high statin dose, alcohol abuse, illicit drug use (cocaine, amphetamines), antipsychotics, fibrates (particularly gemfibrozil), nicotinic acid, amiodarone, verapamil, warfarin, cyclosporine, macrolide antibiotics, azole antifungals, protease inhibitors, nefazodone, large quantities of grapefruit (> 1 quart per day), pomegranate juice, unregulated supplements (e.g., red yeast rice, oyster mushrooms, etc.), surgery with severe metabolic demands, and heavy and/or unaccustomed exercise [58].

including dietary, weight, and exercise goals. Before confirming a diagnosis of statin-intolerance, the physician should ensure that a proper challenge-dechallenge-rechallenge[viii] (CDR) protocol occurred and failed [58]. In addition, another important aspect of the management of statin-intolerance is to ensure that the patient is fully aware of the indication for statin treatment, the intended benefits, and the safety of statins [58].

Figure 1 below illustrates the statin intolerance management algorithm from the CCWG Guidelines (2016) [58]. The objective is to maintain patients on statin therapy with a CDR protocol [67]. Even though the CDR approach recommended by the CCWG is to ensure that patients in need of statin treatment be maintained on treatment, the CCWG Guidelines indicate that these obvious and axiomatic criteria are seldom met in clinical practice, leading to many patients who are in need of statin therapy being untreated [48].

[viii] The CDR protocol is a medical protocol for investigating adverse drug reactions, where a drug is administered (challenge), withdrawn (dechallenge), and readministered (rechallenge) [67]. In statin-intolerance management, the rechallenge could be done with the same statin molecule/dosage, a reduction in statin dosage, or a switch to another statin with the same or lower potency [58].

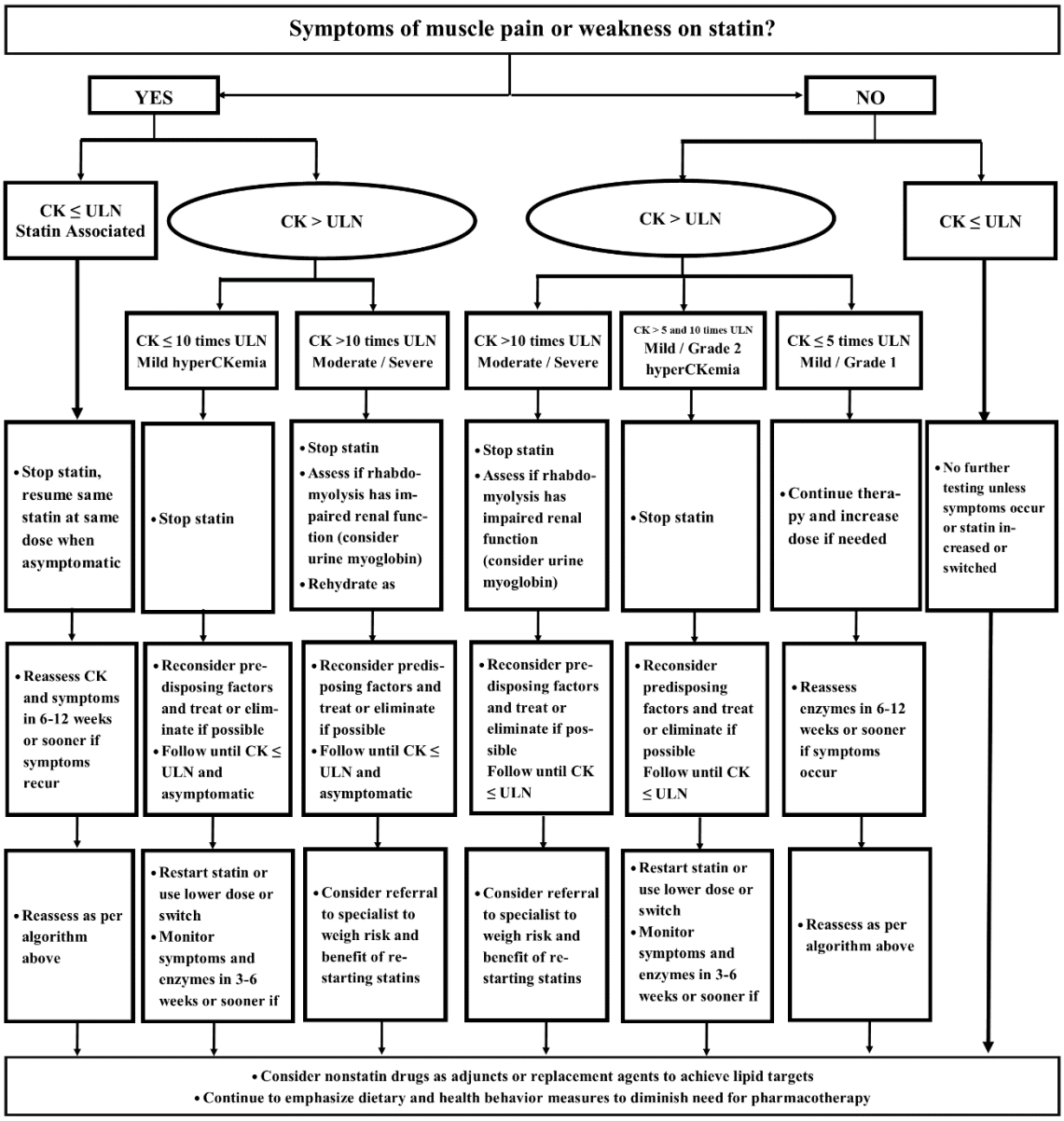

Figure 1 Management approach for muscle symptoms or hyperCKemia.

CK creatine kinase, *ULN* upper limit of normal.
Adapted from Mancini et al. [58] with permission from Elsevier.

1.3.2 Diagnosis of Myopathy

Myopathies are currently diagnosed using a CK test, also known as a total CK or creatine phosphokinase test [68]. Creatine kinase is an enzyme expressed by various tissues and cell types. Conditions associated with muscle damage increase CK levels. These conditions include heart attack, strenuous physical activity, prolonged surgeries, muscular dystrophy, renal failure, and any drug or toxin that interferes with muscle energy production or increase in energy requirements, among others [68]. Preclinical statin studies show that statins decrease mitochondrial function, attenuate energy production, and alter muscle protein degradation, thereby providing a potential link between statins and muscle symptoms [69].

Factors other than age/gender affect the population normal range of CK values [70]. George et al. (2016) examined the distribution of CK values in 10,096 nonpregnant adults using the cross-sectional National Health and Nutrition Examination Survey (NHANES) 2011 to 2014 [71]. The Black race was strongly associated with CK values: the OR for an abnormal CK value was 5.08 (95% CI 3.65, 7.08) in Black women and 8.39 (95% CI 6.11, 11.52) in Black men. The differences in CK values by age, when excluding race ethnicity, were largely explained by body composition. Women with low body mass indices (BMIs) were less likely to have elevated CK values, while overweight or obese men had two-fold greater odds of having elevated CK values. Although the CCWG report uses multipliers to adjust the CK ULN values for ethnicity and gender, the magnitude of adjustment is much smaller than those reported by George et al. (2016) (2.0 for Black women and 2.5 for Black men), and the recommendations exclude adjustment for body composition [58]. These studies highlight that normal CK values are highly dependent on individual characteristics, which are not always included in the reference CK normal values. For instance, the Center for Disease Control and Prevention reference values from the laboratory manual, only account for patient age and gender [54]. The Mayo Clinic reports similar age and gender-specific reference CK normal values [55].

1.3.3 Risk Factors

Risk factors for statin-induced myopathy exist. These include female gender, low BMI, concomitant treatment with some cytochrome P450 inhibitors, declining kidney/liver function, and changes in statin level due to fluctuating albumin and α-1 glycoprotein levels [72]. The risk

of myopathy is greater with increasing statin dose and statin systemic exposure [72]. A link between the risk of simvastatin-induced myopathy and common variants in *SLCO1B1* has been identified [73]. These findings have been replicated in both an independent trial and a practice-based longitudinal cohort [74, 75]. In addition, there is a genetic component associated with individual CK levels. In a genome-wide association study with 3,412 statin users, Dube et al. (2014) found genetic variants in a muscle CK gene (rs11559024) and leukocyte immunoglobulin-like receptor subfamily B member 5 gene (rs2361797) independently associated with CK levels in statin users [76]. These results were successfully replicated in an analysis of 5,330 statin/non-statin users from the Montreal Heart Institute Biobank [76].

1.3.4 Need for a New Diagnostic Test

Creatine kinase activity is neither sensitive to nor specific for statin-induced myopathy, and more appropriate laboratory parameters are not known [63]. Currently, given that statin-induced myopathy is diagnosed using CK tests, which have limited diagnostic capacity due to poor internal validity (elevated CK levels may be caused by a variety of factors others than statin therapy) [48, 77] and limited external validity (reference CK normal values vary between different populations) [70, 71], there is a need for a new diagnostic test to identify patients with statin-induced myopathy.

1.4 Pharmacogenomics Testing for Statin-Induced Myopathy

There is an ongoing effort to develop a pharmacogenomics (PGx) test for statin-induced myopathy at the Beaulieu Saucier Pharmacogenomics Centre, led by Jean-Claude Tardif and Marie-Pierre Dubé, and funded by Genome Canada and Génome Québec (Grant number: 4530) [78, 79]. The research objective is to develop a PGx test to help physicians interpret personalized CK normal values for patients who have mild to moderate CK elevation (<5x ULN). The algorithm was planned to develop the personalized CK values for each patient, which would control for genetic markers (CKM and LILRB5 genetic variants), *SLCO1B1* carrier status, age, sex, race, pre-statin CK measure, statin used, dose, duration of treatment, concomitant

medications, physical activity level (above or below Health Canada/FDA recommendations), smoking, height, weight, and BMI.

The purpose of this PGx test is to provide clinicians with a diagnostic tool for patients with muscle pain. Patients with negative test results would most likely be maintained on statin treatment and alternative causes of myalgia would be investigated. This approach is different from the earlier research program, which aimed at developing a test that would predict statin-induced-myopathy before statin initiation. Previous studies have identified a strong association between a non-synonymous coding single-nucleotide polymorphism, rs4149056, in the *SLCO1B1* gene and the risk of statin-induced myopathy [74, 80, 81]. To manage the risk of statin-induced myopathy, Wilke et al. (2012) proposed pre-emptive genetic testing of *SLCO1B1* gene variants prior to statin initiation to identify patients at risk of statin-induced myopathy [82]. However, subsequent studies have failed to show the clinical utility of initiating statin prescriptions guided by *SLCO1B1* genetic testing [83, 84]. As CVE rates are much higher than serious myositis and rhabdomyolysis, reducing statin usage guided by the *SLCO1B1* genotype may result in net harm [84].

The economic evaluation effort of the PGx test was conducted in parallel and independently from the test development team. We developed the economic evaluation from a theoretical perspective. The perspective of our economic evaluation was to determine the potential value of a PGx test. This approach has the advantage of being generic. It is not specific to a PGx test based on personalized CK values or any other genetic marker. Answering the question on the potential economic value of a hypothetical PGx test will provide answers on the potential market for this type of test.

We assumed this hypothetical PGx test would be used to diagnose statin myopathy in patients with mild to moderate CK values (CK <5 ULN). This PGx test would not be required for rhabdomyolysis, as it is associated with extremely high CK values, myoglobinemia and/or myoglobinuria, and pain symptoms that already have valid diagnostic tools [69].

1.5 Economic Evaluations of Diagnostic Tests

Guidelines on economic evaluations of medical devices are lacking. Drummond et al. (2009) reported that although the general method for economic evaluations is well established, medical

devices may require particular attention [85]. Ideally, when conducting an economic analysis, the objective is to value all long-term costs and benefits of a technology using a full economic evaluation, such as a cost-effectiveness, cost-utility, or cost benefit analysis [86]. Thus, when valuing a medical device, we need to understand its usage. For instance, when a device is used for both diagnostic and therapeutic purposes, complete efficacy and safety profiles for each use are required for the economic evaluation [85].

Other challenges in conducting economic evaluations of diagnostic tests exist. For example, inconsistencies in the quality assurance of laboratory tests may lead to complex interpretations of results and impact decision making [87]. In addition, Canadian health technology assessment (HTA) agencies lack guidance on the need for full evaluations of the costs and benefits of diagnostic tests. In Québec, l'Institut national d'excellence en santé et services sociaux (INESSS) does not require a full economic evaluation of long-term costs and benefits of medical devices [86] and the Canadian Agency for Drugs and Technologies in Health (CADTH) does not consider the economic evaluation of companion diagnostic tests in their evaluation of new pharmaceutical products [88]. This lack of guidance undervalues the importance of economic evaluations of diagnostic tests.

Another issue to consider for economic evaluations of diagnostic tests is the need to conduct modelling earlier in the development of these tests. Bern et al. (2016) conducted a systematic review of economic evaluations of pharmacogenetic and PGx screening tests [89]. They concluded that a majority of evaluations did not provide information regarding the intrinsic value of the PGx test. The importance of including the performance characteristics (i.e., accuracy, predictive value, and clinical utility) of the PGx test, while assessing the cost-effectiveness of a PGx test, was reported by several studies [87, 90-93]. The sensitivity and specificity (i.e., accuracy of a test) and especially the clinical and economic consequences of a false-positive and false-negative result of the investigated test, are key elements in the economic evaluation for Annemans et al. (2013) [92], Elkin et al. (2011) [94], Thariani et al. (2012) [87], and Epstein et al. (2009) [93]. Annemans et al. (2013) [92], Doble et al. (2013) [95], and Koelsch et al. (2013) [96] who suggest conducting economic modelling in the early stages of test development as this would provide a better understanding of the key economic challenges,

which would reduce potential uncertainty surrounding the value of the test, and thereby potentially lead to a better cost-effectiveness profile.

Chapter 2. Thesis Objective

The objective of this thesis was to conduct an early economic evaluation of the PGx test, which is in development by the research team from the Beaulieu Saucier Pharmacogenomics Centre, led by Jean-Claude Tardif and Marie-Pierre Dubé, and funded by Genome Canada and Génome Québec for the project, *"Personalized medicine strategies for molecular diagnostics and targeted therapeutics of cardiovascular diseases"* (Grant number: 4530) [78, 79].

2.1 Article I Objective

The objective of this article was to evaluate the economic value of a hypothetical PGx test for statin-induced myopathy in a cohort of patients at high CV risk using a Markov model. The model compares two strategies: with and without a PGx test in patients experiencing musculoskeletal pain (MSP).

2.2 Article II Objective

The objective of this article was to perform a cross-validation of the Markov model (Article I) developed for the evaluation of a hypothetical PGx test for statin-induced myopathy in a cohort of patients at high CV risk using a discrete event simulation (DES) model.

2.3 Article III Objectives

The objectives of this article were two-fold. First, this article compares the Markov and DES model results in light of the model differences. Second, the article summarizes our reflection on key points: 1) the economic evaluations of diagnostic tests, 2) the place in therapy of the PGx test for statin-induced myopathy, and 3) the impact of changes in treatment options on the economic evaluation.

Chapter 3. Methodological Approach

This chapter presents the general methodological approach relevant to all articles used in this thesis. The methodological considerations specific to Article I and Article II are presented in Section 4.1 and Section 5.1.

3.1 Sensitivity and Specificity

Upon developing the Markov health state model for assessing the value of a hypothetical PGx test, there were no existing models in CVD assessing the economic value of a PGx test. When we started the thesis, the information on the PGx test characteristics (i.e., specificity and sensitivity) were unknown, as the PGx test research team led by Jean-Claude Tardif and Marie-Pierre Dubé were in the early development stages of the test. Hence, the *de novo* economic evaluation of the PGx test was conducted in parallel with the test development.

Although, not having the test parameters may be seen as a limiting aspect of the economic evaluation conducted in this thesis, we argue that it is one of the major strengths of this thesis project. An important aspect of the economic evaluation of diagnostic tests is the assessment of the consequences of false-positive and false-negative test outcomes. One approach for the economic evaluations would have been to assume a plausible range of test parameter values. Instead, we evaluated the value of the PGx test over the complete range of false-positive rates (FPRs) and false-negative rates (FNRs) (i.e., 0% to 100%). This choice allowed us to explore the consequences of false-positive and false-negative test results. Furthermore, we claim that exploring the FPRs and FNRs of the PGx test is a key element in the evaluation of diagnostic tests. Even with a perfect test (i.e., FPR=FNR=0%), if a proportion of physicians decide to ignore the test results or if patients decide to ignore their physician's recommendation, it would be equivalent to an imperfect test (i.e., FPR≥0% and FNR≥0%). This could happen when a perfectly accurate PGx test result is negative; that is, the patient's MSP is unrelated to the statin treatment. In a perfect clinical environment, the physician would maintain the statin therapy and the patient would adhere to their physician's recommendation even if the patient suffers from MSP unrelated to the statin therapy. However, if this patient interrupted statin treatment regardless of the test result, the end outcome would be equivalent to a PGx false positive (FP)

test error, where the physician would prescribe the interruption of statin therapy. With a FP test result, the patient does not have a statin-induced myopathy, but the test falsely indicates that the patient has statin-induced myopathy. The FP erroneous test result, leading to statin discontinuation, is equivalent to a true-negative test result, with a patient interrupting the statin; they both lead to an unwarranted statin discontinuation. Using a broad interpretation of test performance parameters can be viewed as investigating the "real-world" test performance. Hence, as part of the thesis, we developed models with scenarios to assess the economic costs of false-positive and false-negative test outcomes.

Figure 2 shows the concept of test sensitivity and specificity [97, 98]. Sensitivity of a diagnostic test characterizes the capacity of the test to identify true-positive cases. Specificity characterizes the ability of the test to identify true-negative cases. A perfect test would have the sensitivity and specificity parameters equal to 100%. In the articles, we refer to FPR and FNR values.[ix] A perfect test is characterized by FPR=FNR=0%, while a totally inaccurate test has a FPR=FNR=100%.

		True condition	
		Condition positive	Condition negative
Test results	Positive test result	True positive	False positive
	Negative test result	False negative	True negative
		Sensitivity= $\frac{\sum True\ positive}{\sum Condition\ positive}$	Specificity= $\frac{\sum True\ negative}{\sum Condition\ negative}$

Figure 2 Test sensitivity and specificity parameters

[ix] The FPR can be expressed as 1 minus specificity and the FNR can be expressed as 1 minus sensitivity.

Instead of assuming a plausible range of FPR and FNR values of the hypothetical PGx test, we evaluated the economic model over the complete range of FPR and FNR values. This approach has enabled us to fully characterize the consequences of all possible false-positive and false-negative test outcomes.

3.2 The Perfect Clinical Environment

We approached the economic evaluation of the PGx test from a broad perspective that includes both the test performance parameters and the behaviour of physicians and patients. We defined the "Perfect Clinical Environment" as follows:

- The PGx test is perfect (i.e., FPR=FNR=0%); and
- Physicians base their prescribing recommendations solely on test results; and
- Patients are fully compliant with the prescribing recommendations of their physicians.

Deviation from one of the above physician or patient behaviour assumptions could be compared to the outcome of an imperfect test (i.e., FPR>0% and/or FNR>0%). This approach allowed us to have a broad interpretation of test results. For instance, if all patients without statin-induced myopathy interrupted their statin treatment, either because their physician did not prescribe according to the test result or the patient decided to ignore the physician's recommendations, this would be equivalent to a PGx test with a FNR=100%. As we mentioned in Section 1.4, the PGx test for statin-induced myopathy will not be used in patients with rhabdomyolysis.

3.3 The Environment Without the Pharmacogenomics Test

We assumed that without access to a PGx test, physicians would interrupt the statin therapy of patients presenting with MSP. This scenario is equivalent to a diagnostic test with FPR=100% (i.e., all patients without statin-induced myopathy interrupt the statin therapy) and FNR=0% (i.e., none of the patients with statin-induced myopathy are maintained on statin therapy). In light of the CCWG Guidelines [58], which recommend a management algorithm based on a CDR approach, our assumption may be seen as not reflecting clinical practice. However, the CCWG Guidelines recognize that the CDR criteria are seldom met in clinical practice, leading to many patients who are in need of statin therapy being untreated [48]. Furthermore, patient

compliance needs to be considered in the economic evaluation as it is a key element in the PGx test evaluation. If the PGx test results do not convince physicians and patients to continue the statin therapy, this severely lessens the value of the PGx test.

In fact, we could argue that the value of the PGx test resides in the subgroup of physicians who would not follow the CCWG Guidelines, and patients who would ignore their physician's prescribing recommendation to remain on treatment. Hence, the environment without the PGx test could be seen as applicable to this subgroup who would otherwise discontinue the statin therapy.

3.4 Digitization of Published Graphics

Most of the time, as researchers, we do not have access to patient level data from either clinical trials or observational studies. Hence, when conducting economic analyses, we use point estimates, and occasionally, 95% CIs. Although, this may be valid for developing Markov health state models, this is a major inconvenience when constructing a DES model where the simulation uses time-to-event to inform the model. Zhou et al. (2016) analyzed the differences in economic evaluation comparing a cohort Markov model, a Markov microsimulation, and a DES [99]. They developed their DES model by transforming the Markov transition probabilities into a time-to-event function. Although, we could have built the DES model using the transition probabilities from the Markov model, we opted to build the DES model using published survival curves (Kaplan-Meier) for the relevant CVEs in the model. There were two main reasons which motivated this decision: 1) data from published graphics would be more suitable for a DES model where events are modeled using time-to-event functions compared to a Markov model using point estimates for transition probabilities; 2) informing the CVE based on a different source of data would add an additional cross-validation dimension when comparing the Markov and DES models.

Converting graphics to time-to-event functions is a time-consuming process that requires three steps: processing images, converting images to numerical values, and estimating the mathematical functions, which are described below.

3.4.1 Processing Images

The resolution of figures in publications is often too low for an efficient conversion to numerical values. This can be observed when zooming to maximal capacity: as you zoom in on a figure, the definition of the lines becomes blurred. This blur introduces noise in the image which often results in the failure of the conversion to numerical values. To avoid this problem, we pre-processed images using the GNU Image Manipulation Program (GIMP) software [100], which is an open source software that allows images to be manually edited at the pixel level. A pixel is the smallest controllable element of a picture represented on the screen [101]. The GIMP software allows increasing the image resolution by recoloring the lines and deleting the blurred regions. This process requires judgment as to which pixel must be deleted and which one must be part of the line. A basic understanding of Kaplan-Meier, or survival analysis, is essential when increasing the image resolution, or after conversion to numerical values when the data is processed. A Kaplan-Meier curve is a step function that either increases or decreases over time, with steps representing the occurrence of events [102]. These concepts must be considered in the figures and data manipulation process. **Figure 3** shows the pre-processed and the post-processed GIMP images.

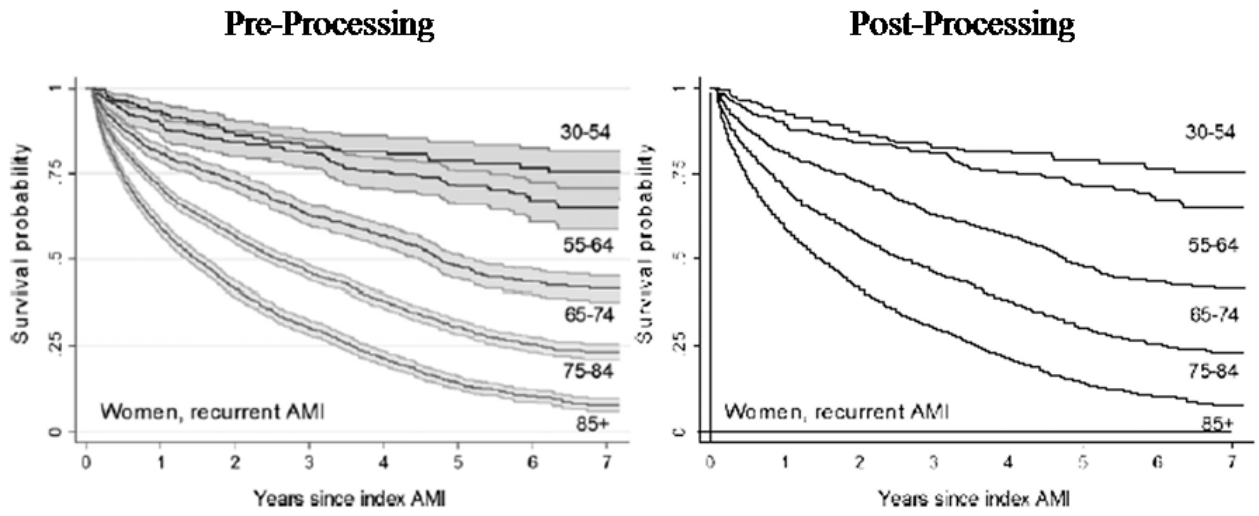

Figure 3 Example of image processing with GIMP

AMI acute myocardial infarction, *GIMP* GNU Image Manipulation Software.

3.4.2 Converting the Images to Numerical Values

The processed figures are converted to numerical values using the software, DigitizeIt [103]. This software automatically converts figures to numerical values in a comma-separated value (CSV) file with minimal manipulation. Once a figure is loaded into DigitizeIt, the x-axis and y-axis minimal and maximal values need to be defined by selecting the start and end of each axis. The definition of the x- and y-axes allows the software algorithm to identify coordinates on the plane. In the ideal situation, the data points on a curve are selected in one single step. **Figure 4** shows an example of the digitization of the survival curve. The green points on the 85+ survival curve indicate data identified by the software. On the right of the figure, two data series are shown, these are the data points to be exported into a CSV file.

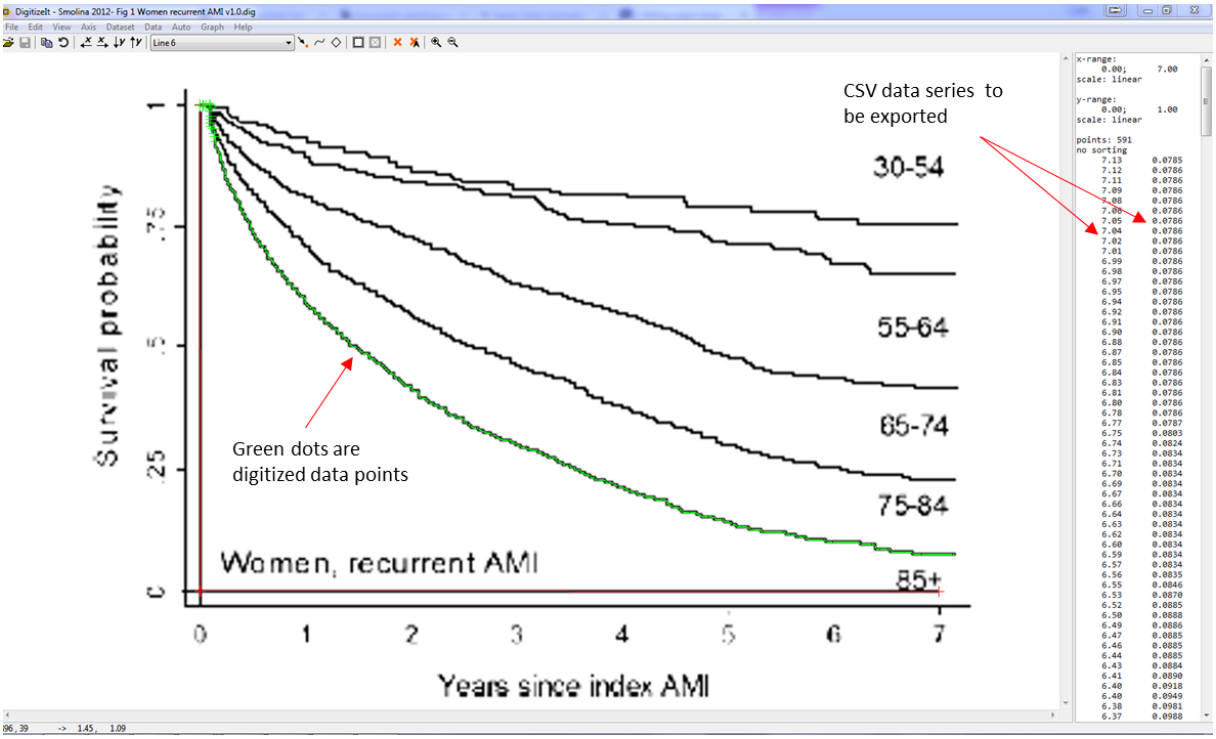

Figure 4 Example of the digitization of the survival curve for AMI recurrence in women 85 years of age and older.

AMI acute myocardial infarction, *CSV* comma-separated value.

During the conversion process, the DigitizeIt software introduces noise at the pixel level. For example, DigitizeIt does not capture the changes in a step function well. At each step change (i.e., 90-degree angles), DigitizeIt will attempt to find data points that minimize the distance. **Figure 5** shows an enlarged section of **Figure 4**. The data points in green obtained with DigitizeIt go through the image line minimizing the distance; that is, the data points avoid 90-degree angles. The image below amplifies the extent of noise for the purpose of illustration.

Once the CVS file is created, the noise in the data is manually cleaned in Excel. As explained in Section 3.4.1, the data cleaning process requires judgment to recover the graphic survival curve.

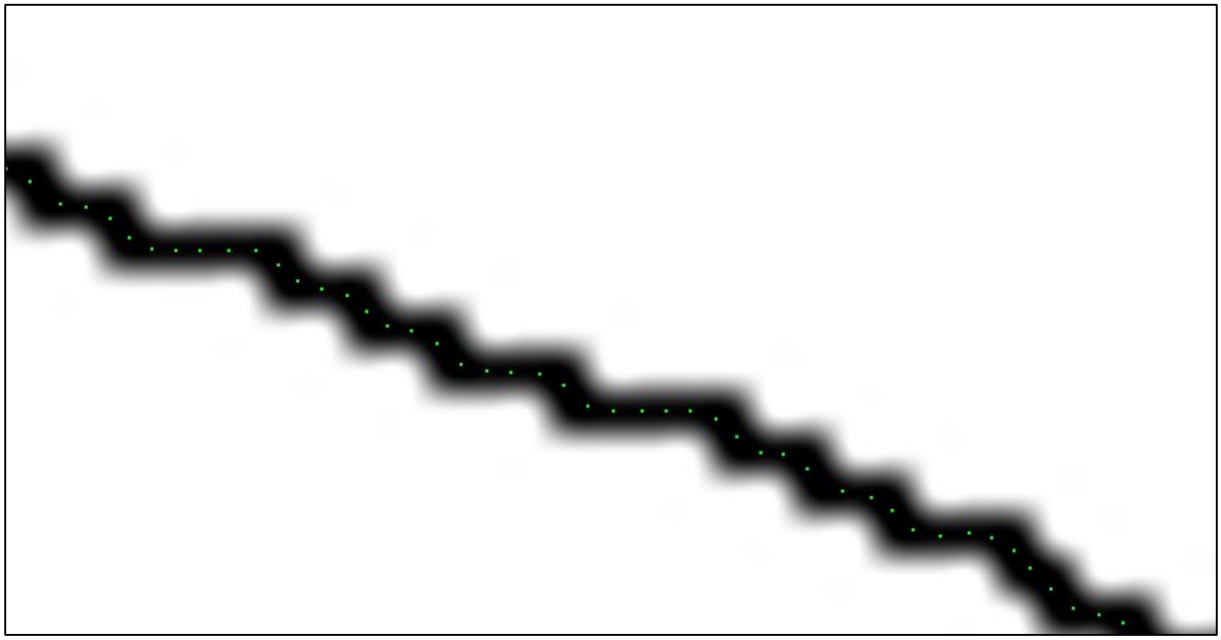

Figure 5 Enlarged screen capture of a digitized curve.

Chapter 4. Article I

4.1 Methodology

For Article I, we developed a *de novo* Markov health state model. The model uses a digitized all-causes mortality survival curve from the 4S [25]. We converted **Figure 1** from the 4S to numerical values using the approach described above in Section 3.4. We applied the method proposed by Guyot et al. (2012) to recover individual patient data (IPD) [104]. The method proposed by the authors uses the digitized figure and the number of patients at risk provided in the publication. We used the R software [105] with the authors' shared R program to reconstruct the IPD. The R program allowed us to estimate the relative risk (RR) with 95% CIs from the IPD data. We obtained a RR of 0.7013 [95% CI 0.5788, 0.8488]. This closely matches the data reported in the study with a RR of 0.70 [95% CI 0.58, 0.85] [25]. The advantage of recovering the IPD and estimating the RR is the ability to validate the numerical conversion of the graphic.

The economic model was designed with a lifetime horizon, while the 4S, used to inform the model, had a shorter follow-up duration than the model's time horizon [25]. Hence, we needed to obtain mathematical functions that would allow us to extrapolate the survival data beyond the study follow-up period. We estimated the parametric survival model to extrapolate the reconstructed IPD from the 4S using standard distribution: exponential, Weibull, log-normal, and log-logistic [102, 106]. We selected the regression model using the Akaike information criterion (AIC) and the Bayesian information criterion (BIC) [102, 107]. These two methods in model selection add a penalty to the log-likelihood function for the number of covariates included in the model. As well, the BIC method penalizes the log-likelihood function for the number of uncensored observations in the data set [107]. The lower AIC values and BIC indicate a better model fit. Using these criteria, we selected an exponential model for the simvastatin all-cause mortality survival curve, and we selected a Weibull model for the untreated patients (i.e., placebo). In addition, to the all-cause, mortality estimated from the 4S IPD, we used data from the Canadian general population life table [108].

As explained in the mortality section of the Supplemental Appendix provided with Article II (see Section 5.1.4), the extrapolation of data beyond a study follow-up period will reflect trends

captured in the within-study period and may fail to capture changes beyond the study period. For instance, the 4S mean age was 58.1 for men and 60.5 for women. The study median follow-up time was 5.4 years [25]. **Figure 6** shows the annual mortality probability for the Canadian population by age based on the 2010-2012 Canadian life tables [109]. The figure shows that at approximately 50 years of age, the probability of death starts to increase at a faster rate (i.e., the probability of dying within the next year). Consequently, an extrapolated all-cause mortality survival curve will underestimate mortality in patients seventy years of age and older if it is based on a study conducted on a cohort with a starting age of 60 years with a 6-year follow-up only. This is explained by the fact that the original data series follow-up period is often too short to capture the increasing mortality rate of an ageing population. This effect is most pronounced for studies with a young cohort age and a short follow-up period. For instance, extrapolating a survival curve for a lifetime model, where the study subject is 50 years of age, and then followed for 6 years. As can be seen in **Figure 6**, the annual mortality in patients 50 years of age is very small. Extrapolated survival curves for patients above 65 years of age would start to underestimate the subjects' increased mortality rate.

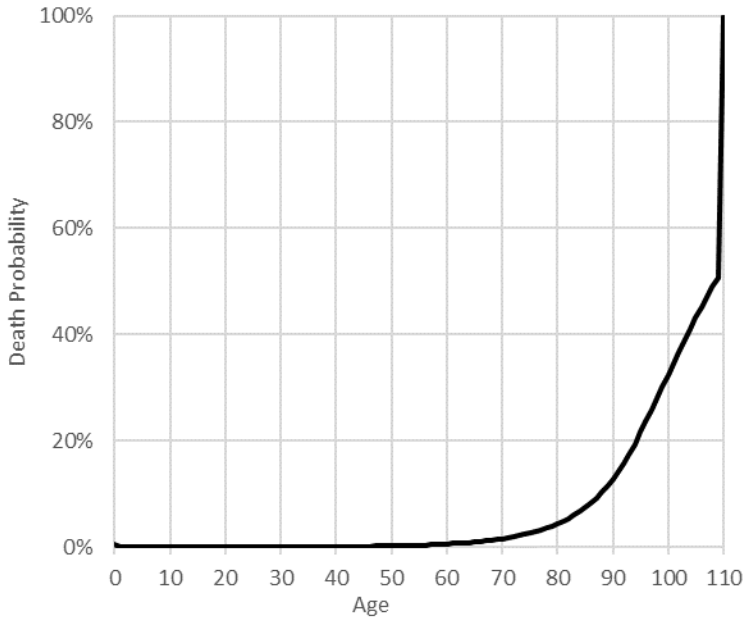

Figure 6 Canadian population annual death probability by age[109]

Article I

Economic evaluation of a pharmacogenomics test for statin-induced myopathy in cardiovascular high-risk patients initiating a statin

This is a post-peer-review, pre-copyedit version of an article published in Molecular Diagnosis & Therapy. The final authenticated version is available online at: http://dx.doi.org/10.1007/s40291-016-0238-8.

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Statement of Authorship

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Economic model conceptualization: DM, JRG, FFA, ACI, and JLL

Statistical analyses: DM

Model programming: DM with advice from JRG

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Economic Evaluation of a Pharmacogenomics Test for Statin-Induced Myopathy in Cardiovascular High-Risk Patients Initiating a Statin

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Abstract

Background: Statins are the mainstay hypercholesterolemia treatment and reduce the risk of cardiovascular events in patients. However, statin therapy is often interrupted in patients experiencing musculoskeletal pain or myopathy, which are common in this patient group. Currently, the standard tests for diagnosing statin myopathies are difficult to interpret. A pharmacogenomics (PGx) test to diagnose statin-induced myopathy would be highly desirable.

Methods: We developed a Markov state model to assess the cost-effectiveness of a hypothetical PGx test, which aims to identify statin-induced myopathy in high-risk, secondary prevention cardiovascular patients. The alternative strategy hypothesized is that physicians or patients interrupt the statin therapy in the presence of musculoskeletal pain. Our model includes health states specific to the PGx test outcome which assesses the impact of test errors.

Results: Assuming a perfect test, the results indicate that the PGx test strategy dominates when the test costs less than $356, when the strategy is cost neutral. These results are robust to deterministic and probabilistic sensitivity analyses.

Conclusion: Our base case results show that a PGx test for statin-induced myopathy in a high-risk, secondary prevention of CVE population would be a dominant solution for a test cost of $356 or less. Furthermore, the modelling of the complete range of diagnostic test outcomes provide a broader understanding of the economic value of the pharmacogenomics test.

Key Points for Decision Makers

- Physicians and pharmacists often discontinue statin therapy in patients with musculoskeletal pain. Even when physicians and pharmacists recommend alternative strategies to maintain the statin therapy, patients may decide to not follow their recommendations. This premature discontinuation results in many patients being deprived of the drug's beneficial cardiovascular prevention.

- An accurate pharmacogenomics (PGx) test to identify musculoskeletal pain resulting from statin therapy is highly desirable. It would fulfill a need for physicians and pharmacists, but it may also be more useful as tool to convince patients to adhere and persist on statin therapy.

- The results of our simulation show that a PGx test to identify statin-induced myopathy is dominant with a test cost of less than $356. Assuming a public payer willingness to pay of $1,000, the PGx test would be cost-effective at a test cost below $906.

1 Introduction

In Canada, 13.7 million individuals suffer from elevated cholesterol levels (i.e., hypercholesterolemia) [1]. Statins are the mainstay hypercholesterolemia treatment; reducing the risk of a cardiovascular event (CVE) by as much as 25% to 35% [2]. It is estimated that 3 to 4 million Canadians are currently prescribed a statin to reduce their cholesterol level [3]. One associated adverse effect of statin therapy is myopathy a form of musculoskeletal pain that may lead to the interruption of treatment.

Musculoskeletal pain consists of common symptoms, with a range of origins, from strenuous physical activity to statin-induced myopathy. Currently statin-induced myopathy is diagnosed using creatine kinase (CK) tests, which have limited diagnostic capacity due to poor internal validity. For instance, musculoskeletal pain detected with CK values could have resulted from heavy exercise rather than statin therapy [4]. In more serious cases, rhabdomyolysis, the extreme condition in which muscle breaks down, potentially leading to severe renal damage or death, could be mistakenly attributed to statin therapy due to CK values, when the source may in fact be variable (e.g., extreme exercise or muscle stress accompanied by dehydration) [5].

In addition to insufficient internal validation of the main test for statin-induced myopathy, the general terminology used to describe muscle toxicities such as myopathy and rhabdomyolysis has been inconsistently represented in the literature. The American College of Cardiology/American Heart Association/National Heart, Lung, and Blood Institute standardized the terminology of muscle toxicity by defining myalgia, myositis, and rhabdomyolysis as statin-induced myopathies. For instance: 1) myalgia is defined as muscle symptoms, such as ache or weakness with normal CK levels; 2) myositis is defined as muscle symptoms with elevated CK levels; and 3) rhabdomyolysis is defined as muscle symptoms with CK elevation (typically > 10x the upper limit normal value) and creatinine elevation [4]. In this paper, the term statin-induced myopathy will encompass all three levels of muscle toxicity defined above.

Clinical studies have reported suspected statin-induced myopathies in 5-10% of patients [6, 7], and as high as 25% in some observational studies [7-9]. Reported rates of myopathy in clinical trials may underestimate the true incidence, because most clinical trials did not use a standard definition for statin myalgia or, in some cases, patients were screened during the run-in period

to eliminate participants with statin intolerance [9]. Researchers are currently developing a pharmacogenomics (PGx) test aimed at diagnosing statin-induced myopathy.

We refer to the PGx test as an In Vitro Diagnostic device to identify a specific patient population (e.g., responders or patients who are susceptible to experience serious adverse events) as part of a personalized medicine strategy aiming to treat patients safely and effectively with a companion targeted therapeutic [10]. In our context, the purpose of the PGx test is to assist physicians in the interpretation of CK values in patients under statin therapy who experience musculoskeletal pain symptoms with low to moderate CK values (5≤ULN). The PGx test would fill the unmet need of determining, among patients having musculoskeletal pain, those who suffer from statin-induced myopathy and are thus at risk of developing rhabdomyolysis. The end purpose of the PGx test is, through a negative test result, to determine which patients can maintain statin therapy and avoid further CVE. Thus, the rational for this study is to evaluate the economic value of a hypothetical PGx test to diagnose statin-induced myopathy in patients who are prescribed statin therapy.

2 Method

2.1 Economic Evaluation

We developed a decision analytic Markov state model in TreeAge Pro software (TreeAge Software, Williamstown, MA, USA) to assess the cost-effectiveness of a hypothetical PGx test to identify statin-induced myopathy in high-risk, secondary prevention cardiovascular (CV) patients experiencing musculoskeletal pain. The model perspective is that of an average statin. The model uses data inputs from previously published studies and public sources (see **Table 1** to **Table 3**). The model was developed as a Markov cohort with one single patient for each strategy using a 1-month cycle with a time horizon of 20 years. All costs were adjusted to 2014 CAD. The perspective of the model is that of a public payer in Canada.

2.1.1 PGx Test

Studies suggest that the risk of statin myopathy could be managed when the *SLCO1B1* genotype is available especially for patients being prescribed a high-dose simvastatin[11, 12].

However, with the analysis of the data from the SEARCH genome-wide association study, Stewart (2013) concluded that there was no direct evidence for the clinical utility of statin prescriptions guided by the *SLCO1B1* genotype[13]. In practice, physicians rely on the CK test when diagnosing statin-induced myopathy[11]. To date, no PGx test for statin-induced myopathy exists. However, researchers are developing a PGx test based on blood-based biomarkers identified in a genome-wide genotyping study, for statin-induced myopathy in patients with moderate or no CK elevation (≤ 5 upper limit normal[ULN]). The PGx test integrates both personalized CK reference values and a lipidomic biomarker. Therefore, there are no PGx test performance parameters currently published, or available. To address this, we used the false-negative rate (FNR)[x] and false-positive rate (FPR)[xi] when reporting the model results. The FNR is the proportion of test results in the presence of statin-induced myopathy that would falsely indicate the absence of statin-induced myopathy (false-negative test result). Similarly, the FPR is the proportion of test results in the absence of statin-induced myopathy that would falsely indicate the presence of statin-induced myopathy (false-positive test result). For the base case scenario, we assume that the PGx test is a perfect test; specifically, that the PGx FNR and FPR are zero. In scenario analyses, we investigate the complete range of possible test performance from 0% to 100% of FNR and FPR. This includes scenarios where the PGx text is subject to misclassification, and assesses the impact of misclassification on the economic evaluation of the PGx strategy.

Furthermore, we assumed that the treating physician will not require a PGx test for patients presenting with rhabdomyolysis. Patients who present with rhabdomyolysis progressed to the True Positive states and discontinue their statin therapy. We assumed that patients experiencing a CVE will return to a statin therapy regardless of the previous PGx test results. The rationale is that high-risk, secondary prevention CV patients will have a greater fear of CVE recurrences than rhabdomyolysis, which has a very low incidence rate (1 per 10,000 person-years) [6, 14] compared to the recurrence of a major CVE (one-year probability of 0.06 major CVE following a myocardial infarction and 0.10 following a stroke) [15].

[x] The false-negative rate can be expressed as 1-sensitivity.

[xi] The false-positive rate can be expressed as 1-specificity.

2.1.2 Model Structure

The model target population are high-risk, secondary prevention, CV patients initiating a statin. The model comprised two alternative strategies, with and without a PGx test to diagnose statin-induced myopathies. The physician diagnosis of statin-induced myopathies, in patients with musculoskeletal pain, will determine whether they continue or discontinue the statin therapy. Without a PGx test, we assumed that when patients experience musculoskeletal pain, their physician permanently interrupts the statin therapy for fear of the patient developing rhabdomyolysis. With a PGx test, only patients experiencing musculoskeletal pain are being tested; thus, public payers only incur the PGx test cost for these patients. We assume that patients and physicians are fully compliant to the PGx test results. That is, physicians will recommend either continuing or permanently discontinuing the statin therapy based on the PGx test results and patients will fully adhere to their physician recommendations. Patients who do not experience any musculoskeletal pain are maintained on statin with perfect adherence.

Figure 1 shows the Markov state model structure. The model has one initial statin state; one transitory state, musculoskeletal pain (MSP); two Discontinue-statin states (True and False Positive); two Remain-on-statin states (True and False Negative); four CV states (Post-AMI, Post-Stroke, "Post-AMI and –Stroke", and Death from CV); and background death. Background death can occur from any states including the CV states whereas CV event death can only occur from any of the CV states.

Patients enter the model upon initiating a statin in secondary prevention. Patients may have a CVE, in which case they may transition to one the three CV states, or remain in the Statin state. Patients who experienced both stroke and AMI, progress to the "Post-AMI and -Stroke" state. Only patients experiencing musculoskeletal pain go through the screening process, which is represented by the transitory state MSP. In MSP, patients are redirected to Discontinue-Statin states for True- and False-Positive or Remain-on-Statin states for True- and False-Negative states. Essentially, these four paths differ in terms of treatment (discontinue or remain on the statin therapy) and whether the musculoskeletal pain is a result of statin-induced myopathy. With the PGx strategy, patients will be redirected to these four paths based on the assumed test parameters. Under a perfect PGx test, patients will either move to the True-Positive, Discontinue-Statin for patients with statin-induced myopathy, and all other patients will

progress to the True-Negative, Remain-on-Statin states. Without a PGx strategy, patients will progress to Discontinue-Statin states; when patients have statin-induced myopathy they progress to the True-Positive, Discontinue-Statin state; all others progress to the False-Positive, Discontinue-Statin state.

2.1.3 Transition Probabilities, Hazard Ratio, Relative Risk and Rates

Table 1 presents the monthly transition probabilities, hazard ratio, relative risk, and rates for the base case scenario; the values used in the deterministic, and probabilistic sensitivity analyses, and the assumed distribution used in the probabilistic sensitivity analysis. The model values were varied with a ±25% for low and high values when the deterministic sensitivity analyses boundaries were not provided in the literature.

We assume that the 5-year major CVE probability is 50% and that major CV recurrent events have a 2-year probability of 30%. Statins protection is captured with the relative risk reduction from major CVE in Pedersen et al. (2004) [16].

The model mortality is derived from the digitized overall survival (OS) reported in the Scandinavian Simvastatin Survival Study (4S), Pedersen et al. (2004) [16]; using the DigitizeIt software (DigitizeIt, Germany), and Statistics Canada published life tables [17]. The 4S OS curve is applied to patients treated with a statin, whereas the placebo OS is applied to patients who discontinued statin therapy. The monthly and annual probabilities of deaths following a stroke or an AMI were assumed to be equal. Indeed, a study from Law et al. (2002) showed that 85% of patients dying within the first year following an AMI, died either before hospital admission or during the hospital admission [18].

A Gamma function was used to simulate the timing of musculoskeletal pain. The function was calibrated to achieve a 3-year musculoskeletal pain probability of 40%. The whole curve was moved by ±25% in the deterministic sensitivity analysis. We assumed that 25% of patients presenting with musculoskeletal pain had statin-induced myopathy.

2.1.4 Costs

The Canadian cost data presented in **Table 2** were obtained from previously published costs studies, cost-effectiveness studies, and governmental public sources. The cost data were inflated to 2014 CAD using the all-components consumer price index table from Statistics Canada [19]. The low and high scenarios are set respectively to 75% and 200% to account for the skewness observed in health care costs data. For physician visits, the low and high values are based on the minimal and maximal values for a physician visit from the RAMQ physician's code book [20]. The statin cost is based on the average cost of a 30-day statin prescription list price in Québec, with ±25% for the high and low values [21].

2.1.5 Health Utilities

Table 3 presents the health state utility values used in the model for the base case, the deterministic sensitivity analysis, and the distribution used in the probabilistic sensitivity analysis. For asymptomatic elderly, post-AMI events, post-stroke events, and expected disutility for myopathy, the health utility values used in the model are converted to monthly utility values. However, for CVE disutility of major events (i.e., AMI, stroke, and rhabdomyolysis) we assumed that the total disutility is incurred within the cycle where the event occurs in the model. We assumed that the disutility value of myopathy is similar to that of going from mild to moderate fibromyalgia [22]. For rhabdomyolysis, we assumed that the disutility is equivalent to that of a stroke. The deterministic sensitivity analysis low and high values for asymptomatic elderly, post-AMI, and post-stroke patients are based on data from van Kempen et al. (2011) [23], whereas the values for disutilities are set to ±25%.

2.2 Base Case Analysis

In the base case analysis with a PGx test, we assume a "perfect world" which is defined as: 1) the PGx test is perfect (FNR=0% and FPR=0%); 2) physicians will require PGx tests for all high-risk secondary prevention CV patients on statin therapy presenting with musculoskeletal pain, and will recommend to either continue or interrupt statins based on the PGx test results; and 3) patients will adhere to their physician recommendations regardless if they still suffer musculoskeletal pain.

For the strategy without a PGx test, we assume that physicians, and patients, are risk-averse in the presence of musculoskeletal pain, and interrupt the statin therapy in fear of rhabdomyolysis. This situation is equivalent to that of a PGx test with FNR=0% and FPR=100%. This would also be the case when patients ignore physicians' recommendations to try alternative statin treatment patterns (e.g., switch molecules, dose reduction, stop and re-challenge, etc.)

2.3 Sensitivity Analysis

We carried out sensitivity analyses to assess the model parameter uncertainty. Deterministic sensitivity analysis and probabilistic sensitivity analysis parameter values are specified in **Table 1** to **Table 3**. The results of the deterministic sensitivity analysis are presented in a tornado diagram while probabilistic sensitivity analysis results are summarized in a cost-effectiveness acceptability curve (CEAC).

2.4 Scenario Analysis

In scenario analyses, we allow the FNR and FPR parameters to vary from 0% to 100%, therefore allowing the analysis of the model sensitivity to the full extent of PGx test parameter values. The purpose of this analysis is to determine the economically acceptable range of PGx test parameter combinations. The scenario analysis is an important aspect of the economic evaluation for three reasons. First, the model evaluates a hypothetical situation, thus we do not know the "real-life" test parameters. Second, evaluating the complete range of test parameters provides comprehensive picture for public payers. Third, if the economic evaluation is done sufficiently early, it allows test developers to understand the optimal combination of test parameters from an economic perspective.

3 Results

3.1 Base Case Analysis

The base case results are presented in **Table 4**. The results indicate that the "with PGx test" strategy dominates "without PGx test" strategy when the PGx test costs less than $250. In fact, the "with PGx" test strategy remains the dominant strategy as long as the PGx test costs less

than $356, where the strategy is cost neutral. At a willingness to pay (WTP) of $1,000, our results show that the "with PGx" strategy would be cost-effective as long as the test costs less than $906.

3.2 Sensitivity Analyses

In order to assess the robustness of the model base incremental cost-effectiveness ratio (ICER) of -$194, we performed deterministic sensitivity analysis (**Figure 2**). The three most important factors are the CVE risk reduction from statins, the cost of AMI, and the cost of statins. The range of ICERs obtained varies from – $2,835 to $4,321 per QALY. The maximal ICER value in the deterministic sensitivity analysis ($4,321 per QALY) is obtained with the high parameter value of the CV relative risk-reduction of 0.825, which was set to ±0.25%. The maximal ICER obtained is well below all accepted WTP thresholds.

Figure 3 shows the CEAC comparing the two strategies. We ran 10,000 simulations for the probabilistic sensitivity analysis. The probabilistic sensitivity analysis model simulations favor the "without PGx test" when the payers WTP is below $750 per QALY. With a WTP of $0 per QALY, the model shows that the "with PGx test" strategy is favored by 43% of the model simulations. When the payers WTP exceeds $750 per QALY, over 50% of the model simulations favor the "with PGx test" strategy and this number reaches 90% when the payers WTP = $6,150 per QALY.

3.3 Scenario Analyses

Because of the uncertain sensitivity of a future PGx test for statin-induced myopathy, we investigated the whole range of possible values of FNR and FPR. **Figure 4** shows the matrix of results for the scenario analyses. The top left corner corresponds to the "perfect test" (FNR=FPR=0%), and the bottom right corner represents the "worst test" (FNR=FPR=100%). The combination of FNR and FPR parameter values where the "with PGx test" dominates is represented the by the light grey region (FNR=80% and FPR=0%) and (FNR=0% and FPR=20%). Thus, we can argue that a PGx would be a dominant strategy for all practical purpose as for a diagnostic test to be considered valid tool would require minimal misclassification (i.e., FNR and FPR below 20%).

The results in **Figure 4** show that even for a PGx test that would totally misclassify patients (i.e., FNR=FPR=100%), the ICER is very low, $5,987 per QALY. To understand this result, we need to consider the PGx test performance compared to the hypothesized alternative. First, in the "without PGx test", every patients presenting with MSP will interrupt the statin the therapy; hence, patients without statin-induced myopathy will be misclassified (i.e., false positive). However, with the worst test possible, both patients with and without statin-induced myopathy are misclassified (i.e., false negative and false positive). Therefore, the difference between the two scenarios are the patients with statin-induced myopathy. In the "without PGx test", these patients are properly classified, the statin therapy is interrupted, but they are at greater risk of a CVE. However, in the "with PGx test", these patients are misclassified as not having statin-induced myopathy; henceforth, the statin therapy is maintained regardless whether patients still experience MSP. Although, patients quality-of-life is penalized with myopathy associated disutility, these patients benefit from the prevention of future CVE, which counterbalance the misclassification. Because of these reasons, the ICER of PGx test that would totally misclassify patients does not increase to an extreme value.

To assess the impact of FPR and FPR on the maximal value of a PGx test, we have analyzed the change in the maximal price value of the PGx test when the payers' WTP is $1,000 per QALY. **Table 5** presents the results of this analysis. The results show that 10% change in FNR reduces the maximal PGx price by less than 1% whereas a change in 10% of FPR reduces the maximal PGx price by 10%.

4 Discussion

SLCO1B1 genotyping has been proposed for managing the risk of statin-induced myopathy, especially in patients using a high dose of simvastatin[11, 12] whereas the purpose of the PGx test in development is to assist physicians and pharmacists to diagnose statin-induced myopathy in patients with moderate or no CK elevation (5≤ULN).

We found that the "with PGx test" strategy to confirm statin-induced myopathies dominates the "without PGx test" strategy in our hypothesized framework where the test costs up to $356. In scenario analyses, we found that for a PGx test cost of $250, the strategy "with PGx test" dominates the "without PGx test" for many FNR and FPR combinations. To our knowledge,

there are no previously published papers on the economic value of a PGx test of statin-induced myopathy.

4.1 PGx False Negative and False Positive

When evaluating the economic value of a PGx test it is important to model the PGx test parameters. In our model, the scenario analyses show that false negative and false positive PGx test results have different impacts on the economic value of the test. To appreciate that point, we need to understand the consequences of a PGx test misclassification. Patients with false-negative test results continue their statin therapy, even though they suffer from statin-induced myopathy. Thus, they suffer from the discomfort, and sometimes danger, of muscle toxicities that we account for with statin-induced myopathy disutility. These patients are at risk of rhabdomyolysis, which can lead to very severe and costly outcomes; however, rhabdomyolysis is a very rare event. Radillis et al (2012)[6] reported the rate of rhabdomyolysis of 3.2 per 100,000 person-years but most studies report a rate of rhabdomyolysis around 10 per 100,000 person years [14, 24]. The rate of rhabdomyolysis development is important, because these patients continue their statin therapy, they benefit from the prevention of CVEs, which are less costly than a hospitalized rhabdomyolysis, but also much more likely to occur. In the case of false positive PGx test results, patients' myopathy is not related to statin therapy, and these patients are mistakenly interrupting their statin therapy. The consequences are that these patients are no longer benefiting from the protection of statin-therapy, which leads to an increase in CVEs with the increased costs, and reduced QALYs, associated with these events. Thus, because of the CVE protection associated with a false negative test results, it turns out that an increase in FNR has a limited impact compared to an increase in FPR.

These patients will no longer benefit from the statin protection of CVE. For payers, patients inadequately interrupting their statin therapy may represent an economic loss. As explained by Cardinal et al. (2006), in preventive health strategies, patients who interrupt their treatment before they incur any benefit represent a resource inefficiency, which they refer as the concept of "percent wasted patients" [25]. Indeed, as can be seen in the study from Pedersen et al. (2004), the statin benefit materializes after 1.5 years of statin treatment when compared to placebo [16].

Furthermore, the development of an accurate PGx test would be a useful tool for physicians and pharmacists to help maintain patients on continuous statin therapy. Many studies highlighted the poor adherence and persistence to statin therapy. In a claims database, Catalan et al. (2000) showed that in a cohort of patients initiating a statin only 33% were still adherent after one year [26]. Dorais et al. (2010), reported that, among 19,727 patients initiating a statin, 53.3% had discontinued treatment after 1 year [27]. Wouters et al. (2014) explored the many reasons for statin non-adherence [28]. Their study results show that among 229 patients, 40-70% doubted the necessity and lacked the knowledge about the statin efficacy, while 20%-35% were worried about joint and muscle side effects [28].

4.2 Strength

The model design was not limited by the lack of "real-world" PGx test parameters. We developed the base case model with a perfect PGx test environment; however, by including the complete range of FNR and FPR in scenario analysis, we gave the model enough flexibility to analyze an imperfect test environment. The concept of an imperfect test encompasses not only test errors, but also non-adherence to test results by physicians and/or patients. Indeed, when physicians or patients do not adhere to the test results, it is comparable to a test misclassification. Our model assesses the impact of FNR and FPR on the economic value of the PGx test. The model shows that FNR and FPR may affect the economic value of the PGx test differently. Evaluating the complete range of test parameters provides essential information to payers on the optimal test parameters.

4.3 Limitations

There is uncertainty surrounding the incidence of statin-induced severe rhabdomyolysis and its associated disutility. An increase in the rate of severe rhabdomyolysis would increase the value of the PGx test. The results we obtained are not generalizable to all patients under statin therapy.

The strategy "without PGx test" may be seen as limiting as we assumed that all physicians and pharmacists will recommend discontinuing statin therapy when patients suffer from musculoskeletal pain. Regardless of their physician or pharmacist recommendation, it is likely

that patients will discontinue the drug as adherence and persistence issues with statins which will lead to an identical outcome [26-28]. Although long term persistence issues are not addressed in the model, we argue that in the context of this model it is not as limiting as it first appears. The reason is that without myopathy, patients will be treated identically in both treatment arms. Therefore, this would have no impact on the incremental costs or incremental QALYs.

5 Conclusion

Our base case results show that a PGx test for statin-induced myopathy in a high-risk secondary prevention of CVE population would be a dominant solution for a test cost of $356 or less. Deterministic and probabilistic sensitivity analyses show that PGx test for statin-induced myopathy is a cost-effective solution for all accepted WTP thresholds. Including the full range of possible PGx test parameters in an economic evaluation is important aspect when assessing the economic value of PGx tests.

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7 Figures

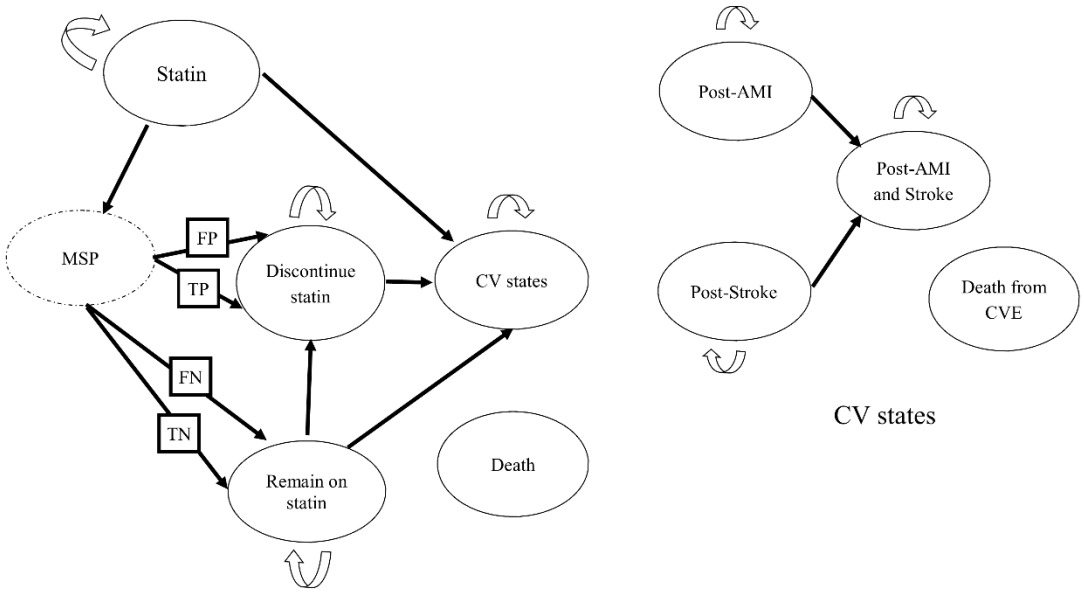

Figure 1 Representation of the Markov state model. Patients enter the model initiating a statin in secondary prevention. AMI: acute myocardial infarction; CV: cardiovascular; CVE: cardiovascular event; FN: false negative; FP: false positive; MSP: musculoskeletal pain; PGx: pharmacogenomics; TN: true negative; TP: true positive.

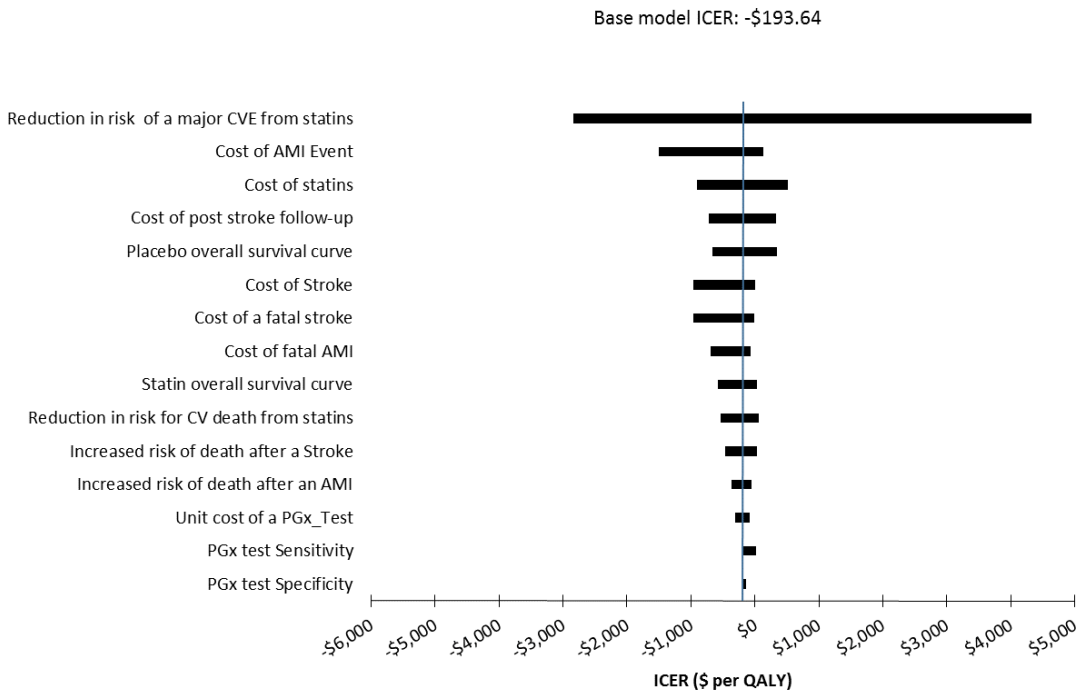

Figure 2 Tornado diagram comparing the strategy "with PGx test" to "without PGx test". The diagram shows 15 scenario variations. The most important factors are the risk reduction of CVE from statin, followed by the cost of AMI events, and the cost of statins. Although the unit cost of the PGx test, the sensitivity, and the specificity appear in the figure, their rank are respectively, 14, 15, and 23 among all parameters varied.

AMI acute myocardial infarction, *CV* cardiovascular, *CVE* cardiovascular event. *PGx* pharmacogenomics.

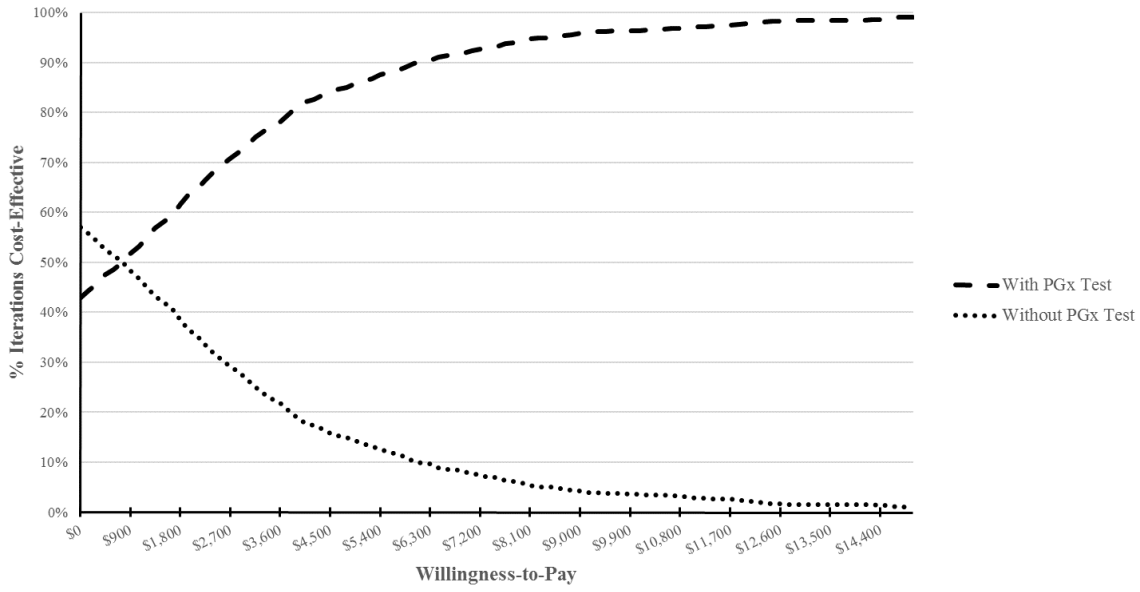

Figure 3 Cost-effectiveness acceptability curve comparing the management of statin-induced myopathy with- and without a PGx test. The curves show the percentage of simulations that favor one strategy over the other. The curves crossover when payers WTP is $750 per QALY. When the payers WTP reaches $6,150 per QALY, 90% of the model simulations favor the strategy "with PGx test".

PGx pharmacogenomics, *QALY* quality-adjusted life year, *WTP* willingness-to-pay.

Improvement over the no PGx situation

Deterioration from the no PGx test situation

Worst Test

False Negative Rate \ False Positive Rate	0% (Perfect Test)	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
0%	-$194	-$143	-$80	$1	$110	$261	$488	$867	$1,625	$3,899	
10%	-$170	-$117	-$52	$32	$143	$298	$528	$906	$1,641	$3,696	$41,721
20%	-$147	-$92	-$25	$62	$176	$333	$566	$942	$1,655	$3,530	$21,819
30%	-$124	-$68	$2	$91	$207	$367	$601	$975	$1,668	$3,393	$15,185
40%	-$101	-$44	$28	$119	$237	$400	$635	$1,006	$1,679	$3,277	$11,867
50%	-$80	-$20	$53	$146	$267	$431	$667	$1,035	$1,690	$3,178	$9,877
60%	-$58	$3	$78	$172	$295	$461	$697	$1,062	$1,700	$3,093	$8,550
70%	-$37	$25	$101	$198	$322	$489	$726	$1,088	$1,708	$3,018	$7,603
80%	-$17	$47	$125	$222	$348	$517	$754	$1,112	$1,717	$2,952	$6,892
90%	$3	$68	$147	$246	$374	$543	$780	$1,135	$1,724	$2,894	$6,339
100%	$23	$89	$169	$270	$398	$569	$806	$1,157	$1,731	$2,842	$5,897

Figure 4 Matrix of ICER results when varying the PGx test FPR and FNR from 0% to 100%. The perfect PGx test is located at the top left corner of the matrix "Perfect Test" (FPR and FNR are 0%) while the "Worst Test" is located at the bottom right corner (FPR and FNR are 100%). The light shaded region shows the combination of test parameters yielding a dominant a PGx strategy. The white cells indicate the region where the PGx test is cost effective (i.e., ICER well below accepted WTP threshold). The black cell indicates the assumed strategy "without PGx test" and thus cannot be evaluated because both strategies yield exactly the same QALYs. In fact, in that situation, the "without PGx test" dominates because with PGx test is systematically more expensive and yields the same level of QALY.

FNR false-negative rate, *FPR* false-positive rate, *ICER* incremental cost-effectiveness ratio, *PGx* pharmacogenomics, *QALY* quality-adjusted life year, *WTP* willingness-to-pay.

8 Tables

Table 1 Model transition probability, hazard ratio (HR), relative risk (RR), and rate inputs and values used in the sensitivity analysis

Variable	Base	Low	High	Distribution	Source
Probability of a MACE[a,b]	0.0115	0.0086	0.0144	Beta	Assumption
Probability of recurrence of a MACE[a,c]	0.0148	0.0111	0.0184	Beta	Assumption
Probability of AMI[a]	0.0010	0.0008	0.0013	Beta	Wagner et al.[15]
Probability of death from AMI	0.0700	0.0600	0.1100	Beta	Erickson et al.[14]
Probability of stroke[a]	0.0005	0.0003	0.0006	Beta	Wagner et al.[15]
Probability of death from stroke	0.1200	0.1000	0.1900	Beta	Erickson et al.[14]
Probability of recurrent AMI[a]	0.0042	0.0031	0.0052	Beta	Wagner et al.[15]
Probability of stroke after AMI[a]	0.0012	0.0009	0.0015	Beta	Wagner et al.[15]
Probability of recurrent stroke[a]	0.0070	0.0053	0.0088	Beta	Wagner et al.[15]
Probability of AMI after stroke[a]	0.0016	0.0012	0.0020	Beta	Wagner et al.[15]
HR of death after AMI	1.4000	1.0500	1.7500	Normal	Erickson et al.[14]
HR of death after stroke[a]	2.3000	1.7250	2.8750	Normal	Erickson et al.[14]
RR: statin reduction of major CVE	0.6600	0.4950	0.8250	Normal	Pedersen et al.[16]
RR: statin reduction of CV deaths	0.5800	0.4600	0.7300	Normal	Pedersen et al.[16]
Probability of myopathy symptoms	0.2500	0.2000	0.3000	Beta	Assumption
Rate of rhabdomyolysis (per 10,000 person-years)[d]	4.64	0.46	46.4	Gamma	Erickson et al.[14]

AMI acute myocardial infarction, *CV* cardiovascular, *CVE* cardiovascular event, *HR* hazard ratio, *MACE* major cardiovascular event. *RR* relative-risk.

[a] The low and high values are set to ± 25% of the base parameter values.

[b] The monthly probability of a MACE is calculated assuming a 5-year 50% probability.

[c] The monthly probability of a recurrent MACE is calculated assuming a 2-year 30% probability.

[d] The rate of rhabdomyolysis is doubled for patients with a false negative PGx test result as the likelihood of rhabdomyolysis will be higher in the subgroup of patients with a false negative PGx test result.

Table 2 Model costs inputs and values used in the sensitivity analysis (2014 CAD)

Variable	Base	Low	High	Distribution	Source
AMI[a]	11,316	8,487	22,632	Gamma	OCCI[29]
Stroke[a]	15,190	11,392	30,380	Gamma	OCCI[29]
Fatal AMI[a]	18,427	13,820	36,853	Gamma	Smolderen et al.[30]
Fatal stroke[a]	30,586	22,940	61,172	Gamma	Smolderen et al.[30]
Follow-up cost					
Monthly cost of managing a stroke survivor[b]	663	497	828	Gamma	Conly et al.[31]
Monthly cost of managing a non-fatal AMI survivor	129	112	147	Gamma	Conly et al.[31]
Rhabdomyolysis cost - Hospitalization[b]	90,475	67,856	113,093	Gamma	Conly et al.[31]
Drug cost (statins)[b]	34	25	42	Triangular	RAMQ[21]
Physician visits[b]	43	21	78	Gamma	RAMQ[20]
Cost of PGx Test	250	0	250	N/A	Assumption

AMI acute myocardial infarction, *OCCI* Ontario case costing initiative, *PGx* pharmacogenomics test, *RAMQ* Régie de l'assurance médicament du Québec, *RR* relative-risk.

[a] The low and high values are set respectively to -25% and +100% of the base parameter values.

[b] The low and high values are set to ± 25% of the base parameter values.

Table 3 Model health utility inputs and values used in the sensitivity analysis

Variable	Base	Low	High	Distribution	Source
Asymptomatic elderly[a]	0.8441	0.8394	0.8494	Beta	van Kempen et al.[23]
Post-AMI event[a]	0.6477	0.6383	0.6677	Beta	van Kempen et al.[23]
Post-stroke event[a]	0.6477	0.6383	0.6677	Beta	van Kempen et al.[23]
Disutility due to AMI[b]	0.1270	0.0953	0.1588	Beta	van Kempen et al.[23]
Disutility due to stroke event[b]	0.1390	0.1043	0.1738	Beta	Wagner et al.[15]
Expected disutility of myopathy[b]	0.0829	0.0622	0.1036	Beta	Hauber et al [22]
Expected disutility of rhabdomyolysis[b]	0.1390	0.1043	0.1738	Beta	Assumption - disutility of stroke

AMI acute myocardial infarction.

[a] The heath-utilities are weighted values of gender specific using the proportion of male aged 55 and older from Pedersen et al.[16]

[b] The low and high values are set to ± 25% of the base parameter values.

Table 4 Results with a perfect test (i.e., FNR=0% and FPR=0%)

PGx test cost	With PGx test		Without PGx test		Δ Costs	Δ QALY	ICER
	Cost	QALY	Cost	QALY			
$0	$41,349	7.18	$41,501	6.95	-$152	0.23	-$648.38
$250	$41,456	7.18	$41,501	6.95	-$45	0.23	-$193.64
$906	$41,735	7.18	$41,501	6.95	$234	0.23	$1,000.00

FNR false-negative rate, *FPR* false-positive rate, *ICER* incremental cost-effectiveness ratio, *PGx* pharmacogenomics, *QALY* quality-adjusted life years.

Table 5 Maximal price of a PGx test when the payers WTP = $1,000

Scenario	Optional PGx price assuming WTP=$1,000	Δ Value of PGx test price
FNR=0% and FPR=0% (Perfect test)	$906	
FNR=10% and FPR=0%	$900	99.37%
FNR=0% and FPR=10%	$816	90.00%
FNR=10% and FPR=10%	$810	89.37%

FNR false-negative rate, *FPR* false-positive rate, *PGx*: pharmacogenomics.

Chapter 5. Article II

5.1 Methodology

A preliminary version of the methodological section of Article II was published as a Supplemental Appendix to the manuscript. The purpose of the Supplemental Appendix was to provide a detailed and transparent description of the methodology that could not be included in the main text due to the word-count restrictions of the target journal.

5.1.1 Introduction

We built the model using the Arena Professional Edition 15 software [110] and Microsoft Excel 2013 [111]. The model approach uses Arena as the core engine; all other aspects of the model are controlled within Excel. We used Excel's Visual Basic for Application (VBA) to communicate with Arena. This approach adds flexibility to perform various scenario analyses. Time-to-event data were obtained from published Kaplan-Meier figures found in published CV studies. The figures were converted to numerical values using DigitizeIt 2.2 [103]. Standard parametric survival models were estimated using SAS 9.4 [112].

5.1.2 Methodology

Contrary to the Markov modeling approach, where point estimate transition probabilities are used to progress between health states, a time-to-event simulation model requires mathematical functions (e.g. parametric survival models) to simulate event times. Parametric survival models require IPD to estimate the distribution parameters. The limitation of this technique that independent researchers often face is inaccessibility to IPD; researchers only have access to information provided in published tables and figures from clinical trials and observational studies [113].

Hoyle and Henley (2011) [114] and Guyot et al. (2012) [104] have proposed methods for recovering IPD from published Kaplan-Meier graphics with corresponding information on the number of patients at risk. However, for the current model, we used another estimation strategy that consisted of digitizing the graphics and using non-linear models to estimate standard parametric survival curves [102, 107]. We estimated the functions using the non-linear least

square SAS procedure, NLIN [115, 116]. The NLIN procedure does not provide standard goodness-of-fit measures, such as the AIC, the Akaike information criterion correction (AICc), or the BIC, we have also estimated the functions using the SAS non-linear mixed model procedure, NLMIXED, which provides these goodness-of-fit measures [117, 118]. For each fitting function, the NLIN and NLMIXED SAS procedures yielded identical mean equation parameter estimates. Thus, to obtain the predicted survival curves, we used the goodness-of-fit measures from the non-linear mixed model to select the parametric function estimated with the NLIN procedure.

5.1.3 Functional Form Selected

Five standard parametric survival model functions (exponential, Weibull, Gompertz, log-logistic, and log-normal) were fitted to the digitized curves using SAS [102, 106, 107]. Based on the statistical selection criteria listed above (see Chapter 1), only two functional forms were selected for all estimated survival curves: Weibull and log-logistic functions, as shown below.

Weibull:

$$y = e^{-\lambda t^{\alpha}} \tag{1}$$

where y is the probability, and t is the time. The equation parameters to be estimated are λ and α.

Log-logistic:

$$y = \left\{1 + \left(\frac{t}{\alpha}\right)^{\beta}\right\}^{-1} \tag{2}$$

where y is the probability, and t is the time. The equation parameters to be estimated are α and β.

To obtain a random time-to-event, the estimated functions were reorganized as follows:

Weibull:

$$t = \left(-\frac{ln(y)}{\lambda}\right)^{1/\alpha} \tag{3}$$

Log-logistic:

$$t = \alpha \left(\frac{1-y}{y}\right)^{1/\beta} \quad (4)$$

The simulated time-to-event estimates are obtained by replacing the variable y using a pseudo-random number drawn from a uniform [0,1] distribution in ARENA [119]. The estimated Weibull and log-logistic functions described below were reorganized as shown in equations 3 and 4.

5.1.4 Mortality

Patients in the model are at risk of death from the estimated CVE-specific all-cause mortality and from the all-cause mortality general population. For instance, if a simulated patient has a model history of a first acute myocardial infarction (AMI) and a first stroke, this patient's death could either be captured in the model by all-cause mortality from: the estimated first AMI survival curve, the estimated first stroke survival curve, or the general population life-table data. In addition, simulated patients can die from 30-day CV death. The CVE-specific all-cause mortality uses estimated functions to extrapolate the survival probability curves beyond the original Kaplan-Meier curves. Compared to the Canadian population life tables for the corresponding cohort (i.e., age group and gender), the CVE extrapolated all-cause survival curves show excess all-cause mortality up to the point where the extrapolated curves cross the general population survival curves, at which point the survival curves from the Canadian life tables have an excess mortality. This is explained by the fact that the original data series follow-up period is often too short to capture the increasing mortality rate. This effect is most pronounced for studies with a young cohort age and a short follow-up period. **Figure 7** shows the mortality probability for the Canadian population by age based on the 2010-2012 Canadian life tables [109]. The figure shows that at approximately 50 years of age, the probability of death starts to increase at a faster rate. Consequently, an all-cause mortality survival curve will underestimate mortality if it is based on a study conducted on a cohort with a starting age of 65 with only a 10-year follow up, as the extrapolation of data extends beyond the study period. The Canadian life tables assume that patients above 110 years of age all die, which explains the vertical line at 110 years of age.

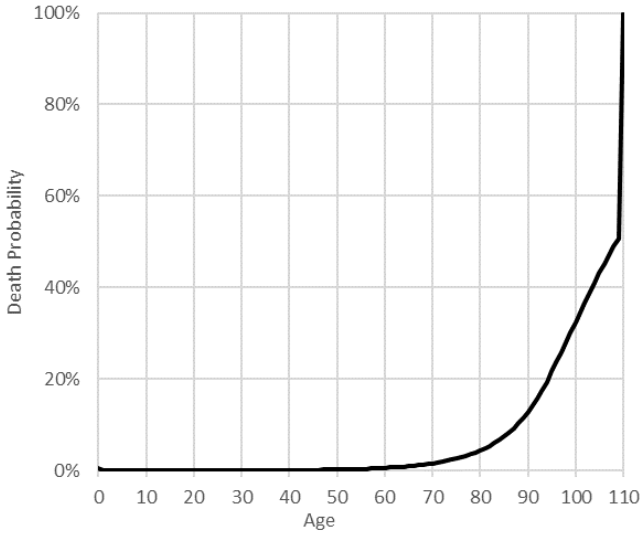

Figure 7 Annual death probabilities in the Canadian population by age

In our model, we interpret the estimated survival curves in the following way: In the first years following a CVE, simulated patients have an excess risk of mortality compared with the general population. As patients advanced through the model, excess mortality related to the CVE decreases such that after a certain amount of time, simulated patients face the same mortality risk as the general population. There is a paucity of data regarding long-term residual excess mortality associated with a prior CVE. The study from Schmidt et al. (2016) compared the mortality rate ratio (MRR) between a cohort of patients with a first acute AMI before 50 years of age with the general population in Denmark over a thirty-year period [120]. The study presents results for the years 1980-2009, broken down into 10-year intervals: 1980-1989, 1990-1999, and 2000-2009. Analysis of the MRR for each of the follow-up times (0-30 days, 31-365 days, 1-10 years, and 11+ years) shows a downward trend in long-term excess mortality over time. Patients who had a first AMI during the 1980-1989 period offer 30-years of follow-up data; however, changes in the management of CV events over the past 30 years render this study period less relevant for inferring the excess mortality in patients with a CV history [121]. Nevertheless, a downward trend in excess mortality was observed over time among patients who had a first AMI between the years 2000-2009.

5.1.4.1 Acute Myocardial Infarction All-Cause Mortality

5.1.4.1.1 All-Cause Mortality After a First AMI

To estimate all-cause mortality following an AMI, we used survival data from Smolina et al. (2012). Smolina et al. studied the long-term survival and recurrence of AMI in 30-day survivors in England from 2004-2010 [122]. Figure 1 of the Smolina et al. publication presents long-term survival Kaplan-Meier figures for men and women following a first and recurrent AMI by age group. We digitized the figures and estimated the corresponding survival curves. The Weibull distribution was selected based on the previously identified selection criteria (see Section 5.1.2). **Table 3** presents Weibull parameters obtained from the estimated functions. Panels A to C of **Figure 8** and **Figure 9** show the digitized Kaplan-Meier and estimated survival curves following a first AMI for each age group, in men and women, respectively. As can be seen in the graphics, the estimated functions fit the digitized Kaplan-Meier data well. Panel D in each figure shows the predicted survival curves with the corresponding age-group survival curves obtained from the gender-specific Canadian life tables [109]. The predicted survival curves for all-cause mortality following a first AMI show excess mortality risk; however, each estimated survival curve crosses the general population survival curve within the model time horizon (45 years). For instance, looking at **Figure 8**, Panel D, the estimated survival curve following a first AMI for men aged 65-74 crosses the all-cause mortality in Canadian men aged 65 years old after 21 years in the model. Up to that point, there is excess mortality in the Canadian population. This is explained by the limited data available to extrapolate beyond the study period. In fact, Smolina et al. estimated the Kaplan-Meier curves using a follow-up period of 7 years [122]. In the 65-74 group, the 7-year follow-up period fails to capture the accelerating mortality occurring in the older age population. Beyond the point where the curves cross, we consider no further excess mortality risk related to the past CV event and the prevailing mortality comes from the all-cause mortality from the Canadian life tables [109].

Table 3 Weibull parameter estimates for all-cause mortality after a first AMI

Age-Group	Parameters			
	Alpha		Lambda	
	Male	Female	Male	Female
65-74	0.7681	0.7696	0.07841	0.0796
75-84	0.7733	0.7766	0.19520	0.1790
85+	0.7794	0.7848	0.41060	0.3655

AMI acute myocardial infarction.

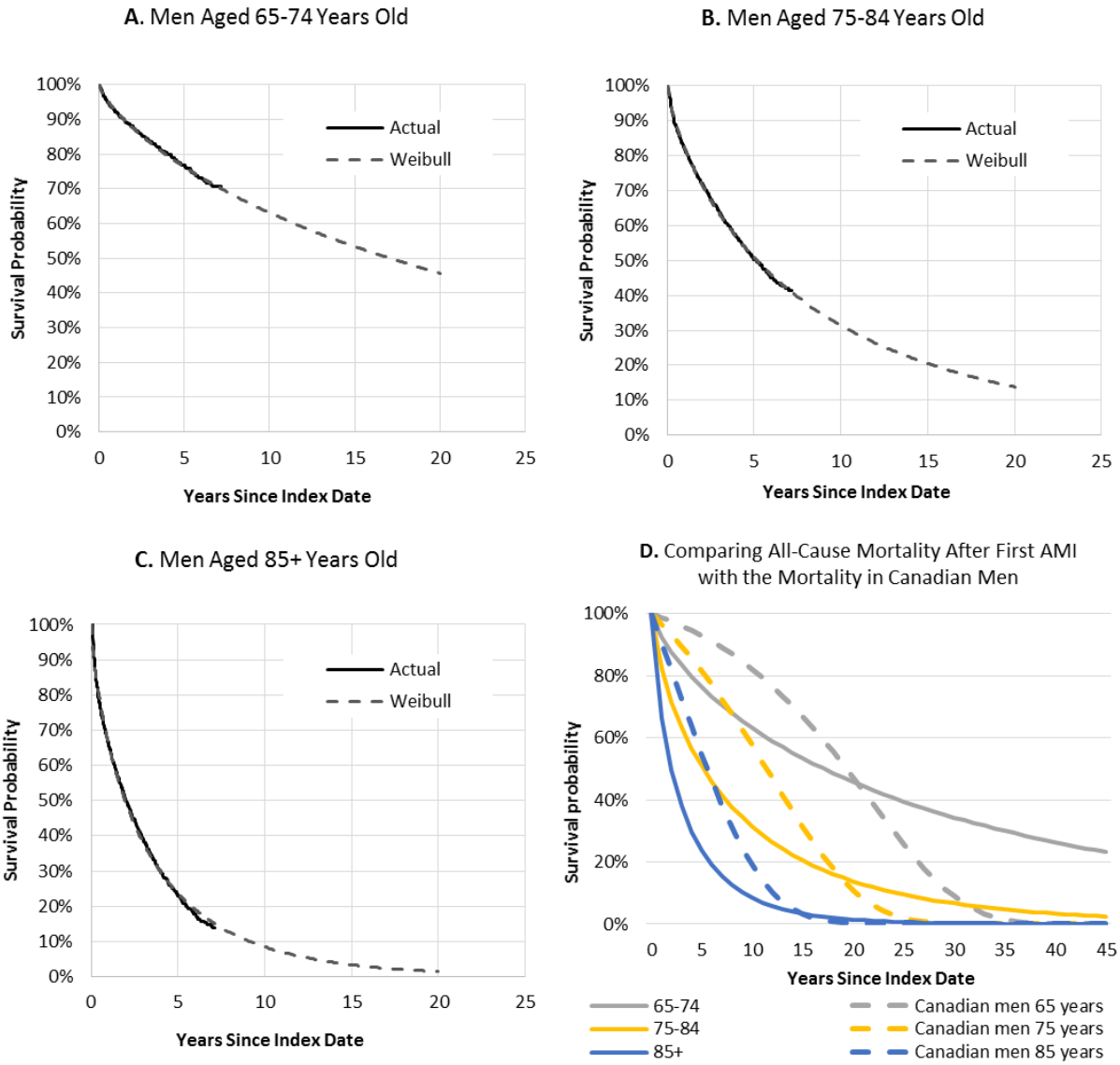

Figure 8 Actual vs. predicted survival after a first AMI in men by age group

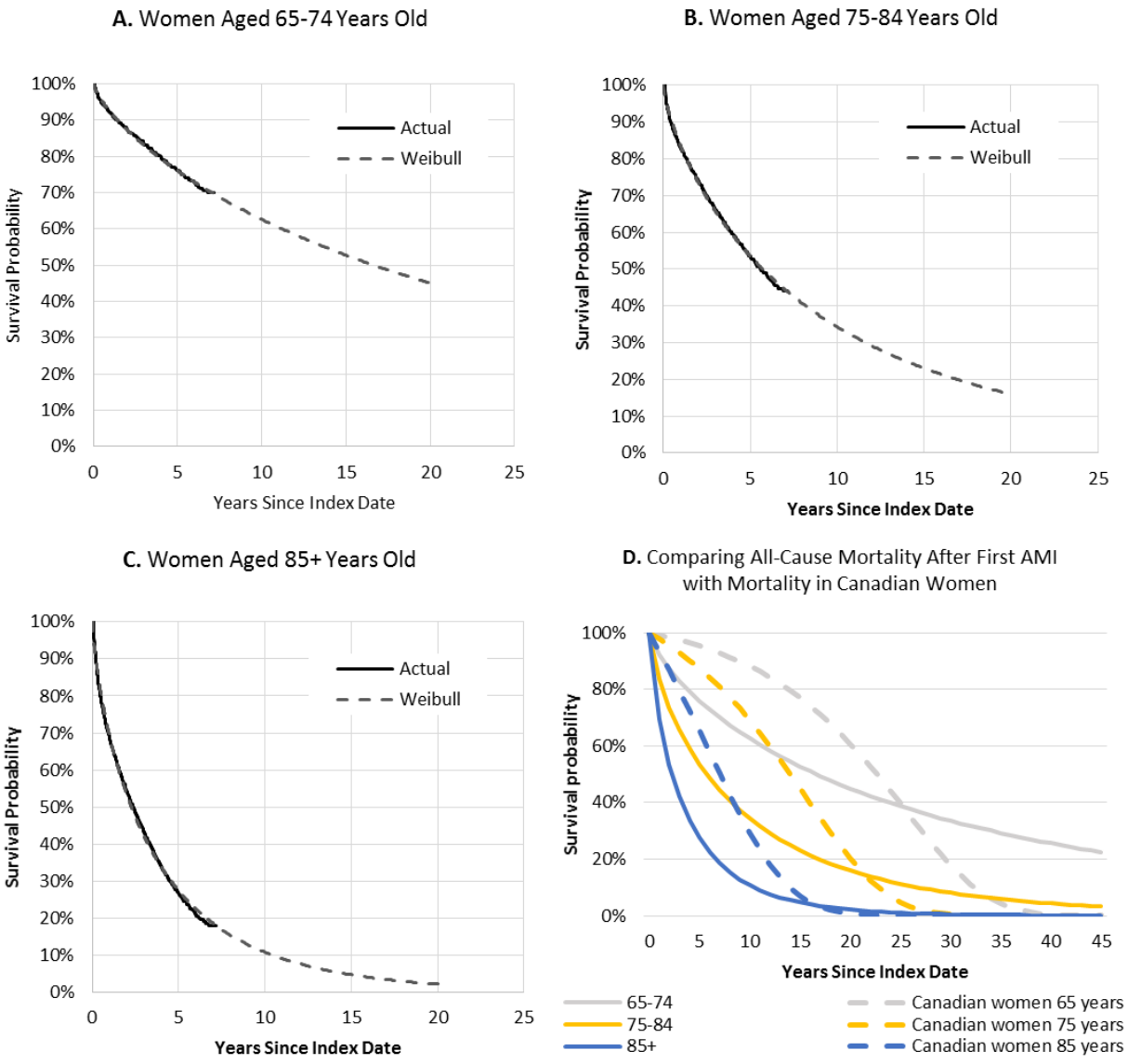

Figure 9 Actual vs. predicted survival after a first AMI in women by age group

5.1.4.1.2 All-Cause Mortality After AMI Recurrence

Smolina et al. (2012) estimated Kaplan-Meier curves for 30-day survivors following a recurrent AMI by age group and gender, as presented in Figure 1 of their publication [122]. We digitized the figures and estimated the corresponding survival curves. The Weibull distribution was selected based on the selection criteria (see Section 5.1.2). **Table 4** below presents the

estimated parameters. Panels A to C of **Figure 10** and **Figure 11** and show the digitized versus estimated survival curve for each age group for men and women, respectively. Panel D of **Figure 10** and **Figure 11** shows the estimated all-cause mortality in patients with a recurrent AMI compared with all-cause mortality from the general population [109].

Table 4 Weibull parameter estimates for all-cause mortality after an AMI recurrence

Age-Group	Parameters			
	Alpha		Lambda	
	Male	Female	Male	Female
65-74	0.7216	0.7961	0.1846	0.1920
75-84	0.7395	0.7817	0.3533	0.3301
85+	0.8160	0.8152	0.5382	0.5016

AMI acute myocardial infarction.

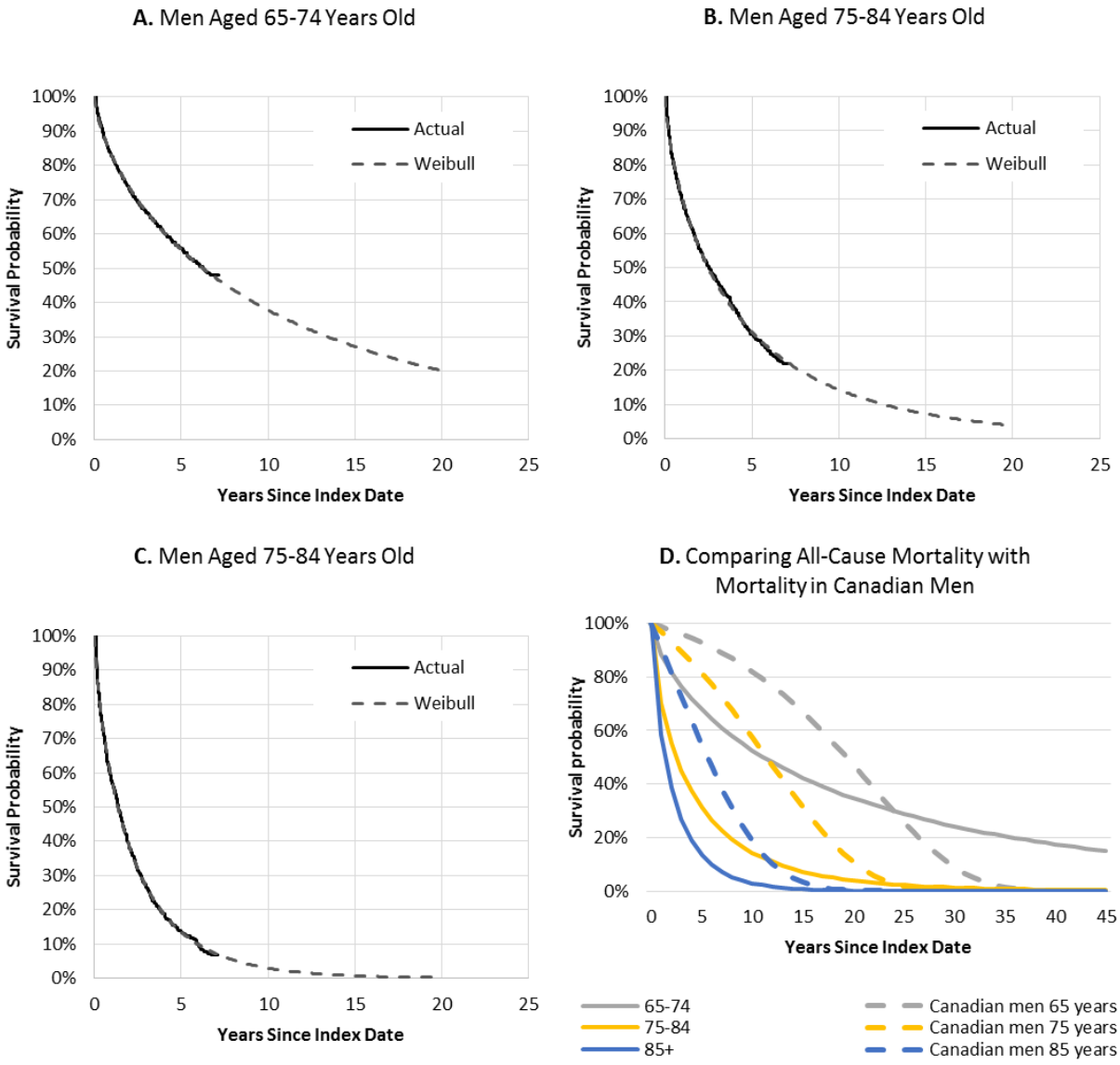

Figure 10 Actual vs. predicted survival after an AMI recurrence in men by age group

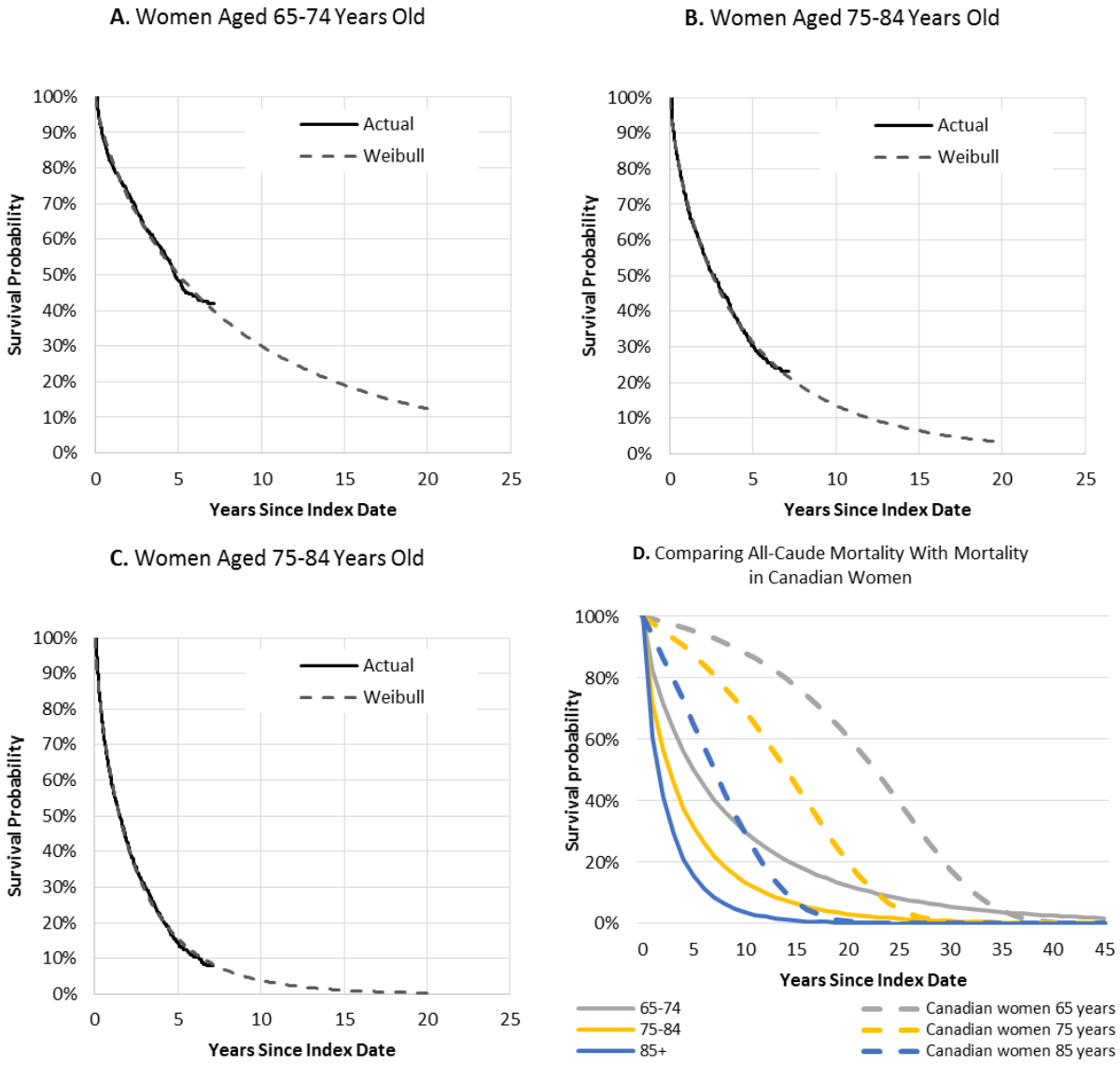

Figure 11 Actual vs. predicted survival after an AMI recurrence in women by age group

5.1.4.2 Stroke All-Cause Mortality

5.1.4.2.1 All-Cause Mortality After a First Stroke

To estimate all-cause mortality after a first stroke, we used survival data from Jones et al. (2013), a study that evaluated long-term post-stroke outcomes by pathogenic stroke subtypes in 30-day survivors of a first-ever stroke [123]. The authors identified 987 participants in the Atherosclerosis Risk in Communities Study cohort [124] with a first-ever stroke. Almost 50%

of participants had a thrombotic stroke, followed by cardioembolic (20%) and lacunar (19%) strokes. In our model, we chose to digitize the Kaplan-Meier data for the thrombotic stroke as it is the most frequent stroke subtype in the study. The median age of participants who had a thrombotic stroke was 67 years [interquartile range: 62-70] of which 53.5% were male. The Weibull distribution was selected based on the selection criteria (see Section 5.1.2). **Table 5** presents the estimated parameters. Panel A in **Figure 12** shows the actual versus predicted survival curves; Panel B shows the predicted survival curve compared with the survival curve for Canadian men and women. At the point where the survival curves cross, there is no residual excess mortality risk from the first stroke.

Table 5 Weibull parameter estimates for all-cause mortality after a first stroke

Parameter	Value
Alpha	0.5551
Lambda	0.1915

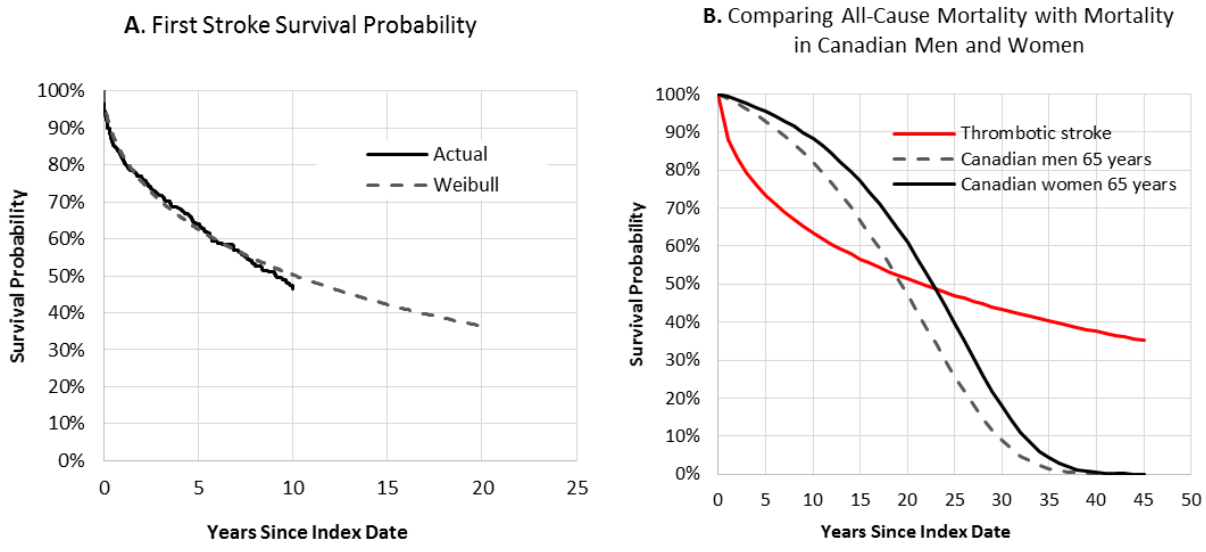

Figure 12 Actual versus predicted survival after a first stroke

5.1.4.2.2 All-Cause Mortality After Stroke Recurrence

To estimate all-cause mortality after stroke recurrence, we digitized survival data from Aarnio et al. (2014), a study that evaluated long-term mortality following first and recurrent strokes in young adults [125]. The authors retained 970 participants from 1,008 consecutive patients aged 15-49 years old with a first-ever ischemic stroke from January 1994 to May 2007, identified from a prospective computerized hospital discharge database and entered into the Helsinki Young Stroke Registry [125, 126]. The mean study follow-up time was 10.2 ± 4.3 years. The participants' median age was 44 years [interquartile range: 37-47] of which 62.7% were male participants.

Even though Aarnio et al. provides all-cause mortality Kaplan-Meier curves for first and recurrent strokes, the study population is too young to provide a valid estimate for our economic model [125]. To address this limitation, we adopted the following strategy: 1) we estimated the parametric survival curves for first and recurrent strokes using Aarnio et al.; 2) we estimated the hazard ratio (HR) between the estimated survival curves for first and recurrent strokes; and 3) we applied the HR to the estimated survival for a first stroke as presented in **Figure 12** [123].

We digitized Figure 3 from Aarnio et al. to estimate the corresponding survival curves. The Weibull distribution was selected based on the selection criteria (see Section 5.1.2). **Table 6** shows the estimated survival curve parameter estimates as well as the HR. Panels A and B of **Figure 13**, respectively, show the estimated survival curves for first and recurrent strokes compared with the digitized Kaplan-Meier curves from Aarnio et al. [125]. Panel C of **Figure 13** shows the estimated all-cause mortality survival curve for recurrent strokes, using the estimated (HR=4.4528) calculated from the survival curve in Panels A and B and applied to the estimated first stroke all-cause mortality from Jones et al. [123].

Table 6 Weibull parameter estimates for all-cause mortality in patients with first and recurrent strokes

Parameter	First Stroke	Recurrent Stroke
Alpha	0.83570	0.68870
Lambda	0.01914	0.10980
Hazard ratio	4.4528	

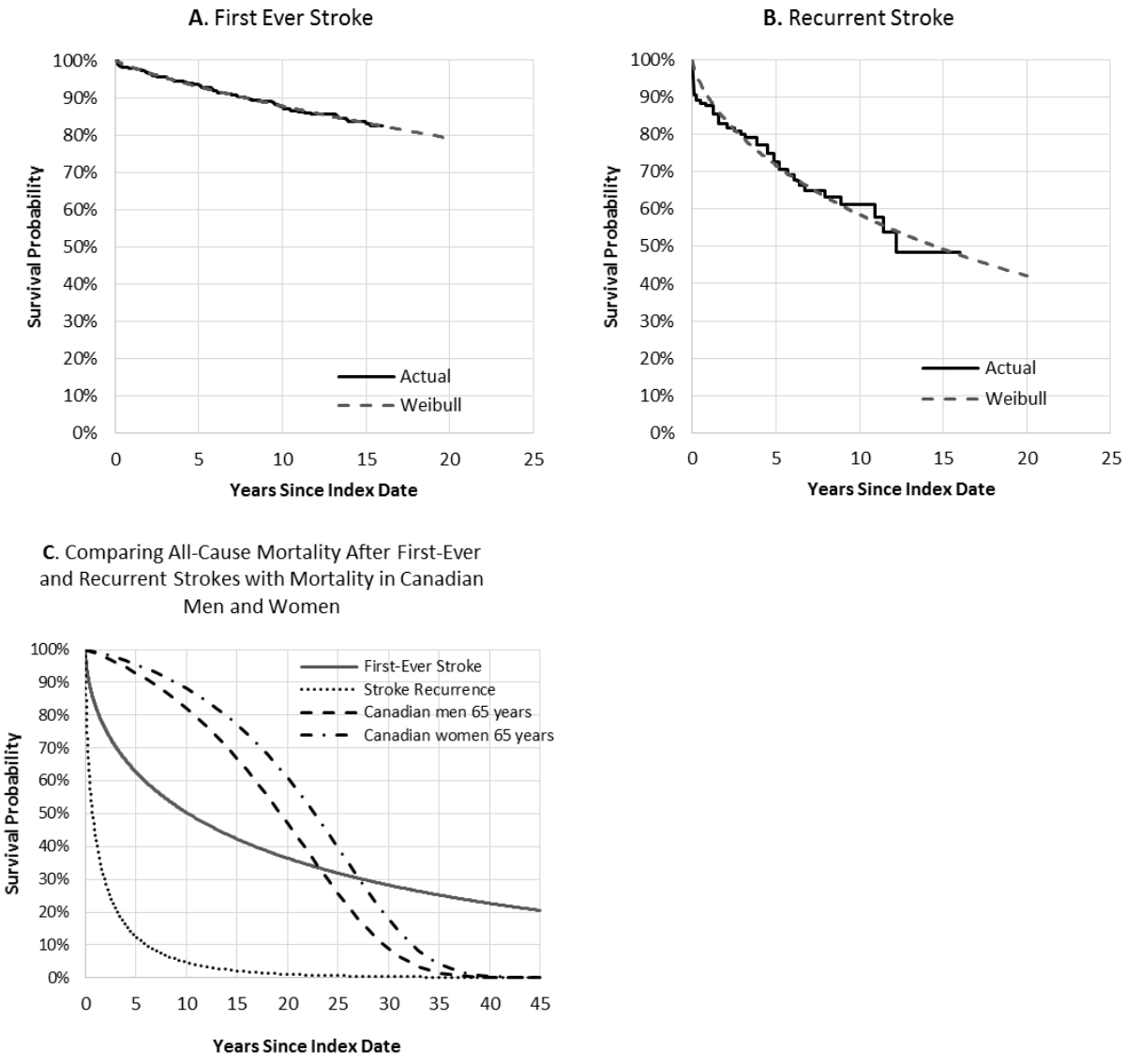

Figure 13 Actual vs. predicted survival after first and recurrent stroke

5.1.5 Cardiovascular Events

5.1.5.1 AMI Recurrence

Smolina et al. (2012) estimated the cumulative incidence of an AMI recurrence after a first AMI among 30-day survivors [122]. The cumulative incidence of AMI recurrence risk functions were estimated by age group and gender. The log-logistic distribution was selected based on the selection criteria (see Section 5.1.2). **Table 7** below presents the parameter estimates for the log-logistic cumulative incidence function. Panels A-C of **Figure 14** and **Figure 15** show the actual versus the predicted cumulative incidence of AMI for each age group and gender specification; Panel D in each figure shows the predicted cumulative incidence over the model time horizon.

Table 7 Log-logistic parameter estimates for the long-term risk of AMI recurrence by gender and age group

Age-Group	Parameter			
	Alpha		Gamma	
	Male	Female	Male	Female
65-74	203.150	250.8300	0.5486	0.5135
75-84	66.61960	100.4600	0.5630	0.5172
85+	35.87540	67.0155	0.5764	0.5275

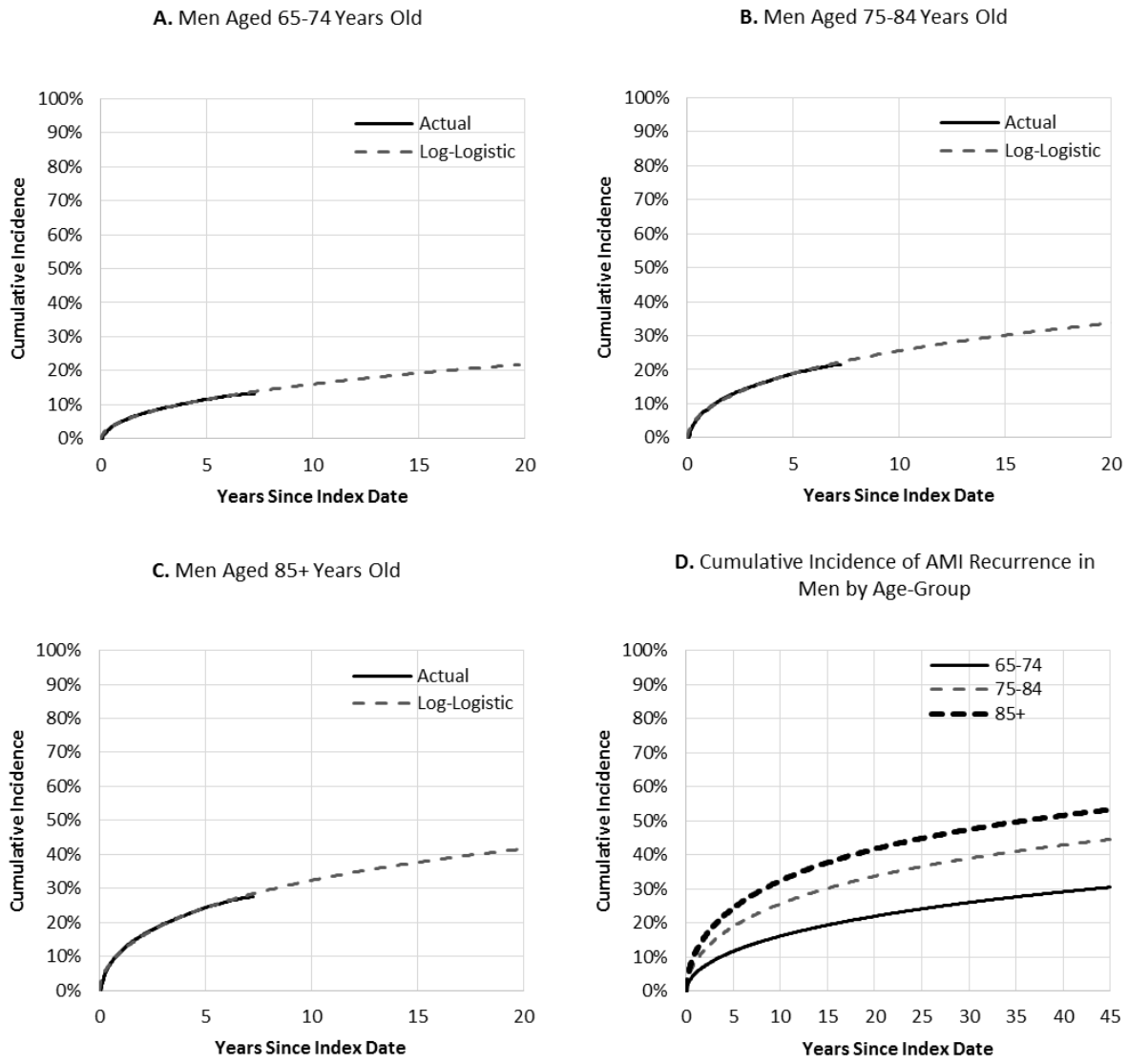

Figure 14 Actual versus predicted cumulative incidence of AMI recurrence in men by age group

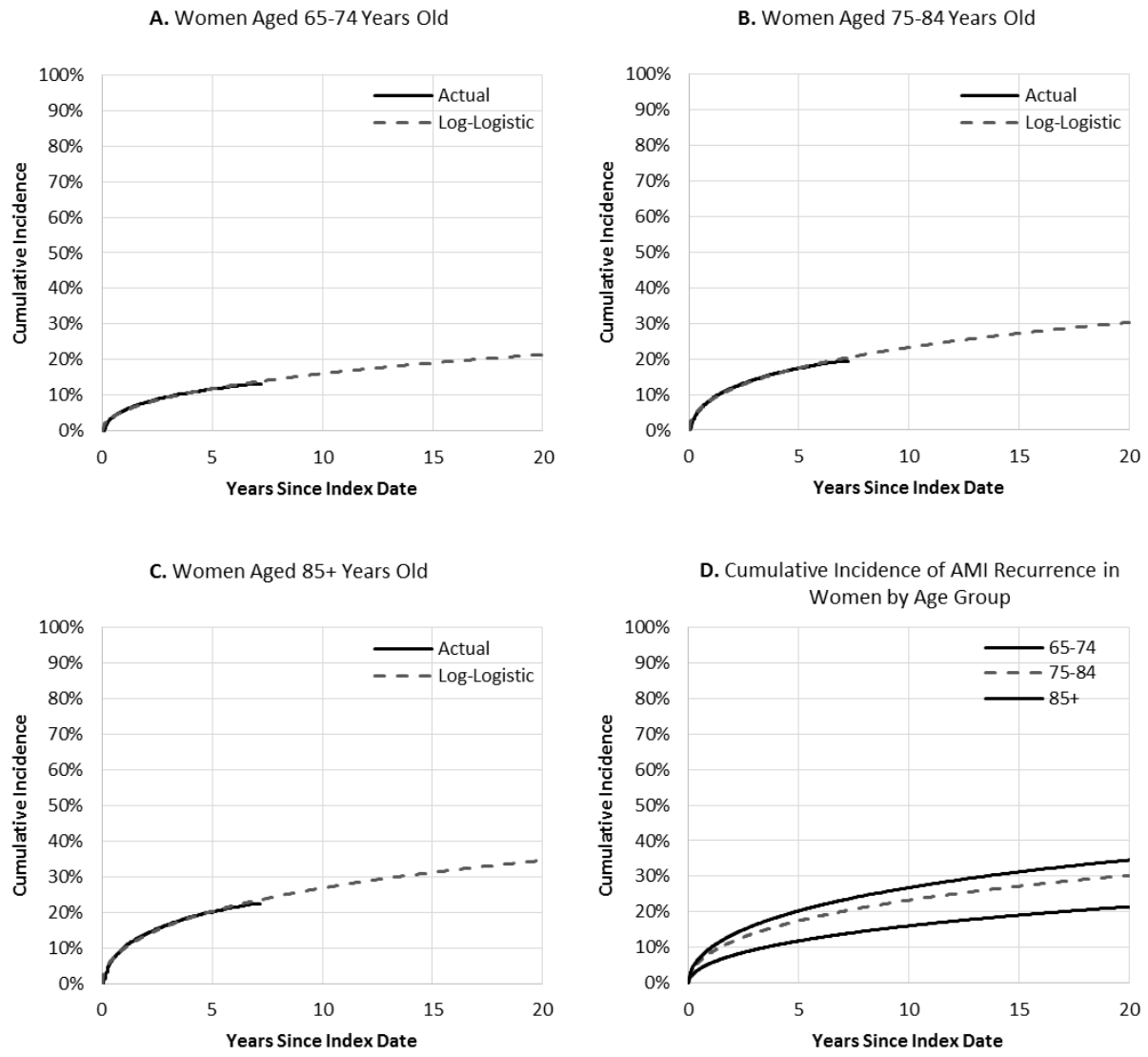

Figure 15 Actual versus predicted cumulative incidence of AMI recurrence in women by age group

5.1.5.2 **Stroke Post-AMI**

Asanin et al. (2009) studied the long-term risk of stroke in patients with new-onset atrial fibrillation (AF) compared with patients without new-onset AF [127]. The mean age was 66.9 ± 9.1 and 58.3 ± 11.6 for patients with and without new-onset AF, respectively. The proportion of males was 68.8% in the new-onset AF group and 72.3% in the without new-onset AF group. We digitized Figure 2 of the publication, which showed the rate of stroke post-AMI in patients

with and without new-onset AF. The Weibull distribution was selected based on the selection criteria described in Section 5.1.2. To extrapolate the stroke risk post-AMI, we estimated the survival curve for both groups. However, based on long-term survival, we predicted the survival curve based on the new-onset AF group and we applied the estimated hazard ratio to obtain the predicted survival curve for the group without new-onset AF. Note that the publication log-rank did not differentiate between the two Kaplan-Meier curves (p-value=0.473). **Table 8** presents the parameter estimates. **Figure 16** shows the actual versus the predicted survival curves for stroke post-AMI for the patient group without new-onset AF.

Table 8 Weibull parameter estimates of long-term risk of stroke post-AMI

Parameters	Value
Alpha	0.7439
Lambda	0.0002
Hazard Ratio	0.6567

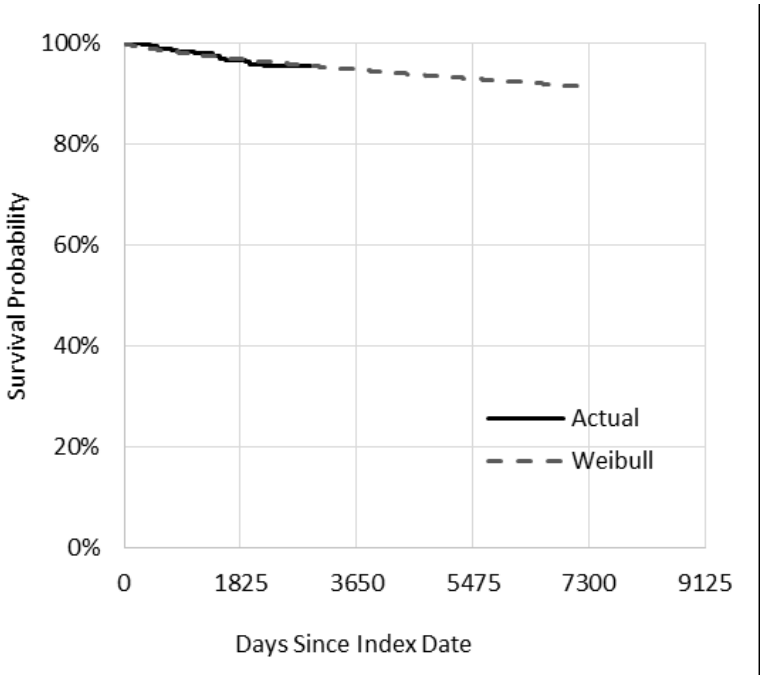

Figure 16 Actual versus predicted cumulative incidence of stroke post-AMI

5.1.5.3 Stroke Recurrence

Dharmoon et al. (2006) studied the stroke recurrence risk and cardiac risk after a first ischemic stroke using the population-based Northern Manhattan Study [128]. The analysis included 655 patients, age ≥ 40, with a first stroke, who resided in Northern Manhattan for at least three months. The mean age of the study population was 69.7 ± 12.7 years and 44.6% of this percentage were male. We digitized the Kaplan-Meier curve for stroke recurrence (Figure 1, Dharmoon et al.). The log-logistic distribution was selected based on the selection criteria described in Section 5.1.2. **Table 9** shows the parameter estimates. **Figure 17** illustrates the actual versus the predicted curves for the cumulative incidence of stroke recurrence.

Table 9 Log-logistic parameter estimates of the long-term risk of stroke recurrence

Parameters	Value
Alpha	40.1630
Beta	0.6777

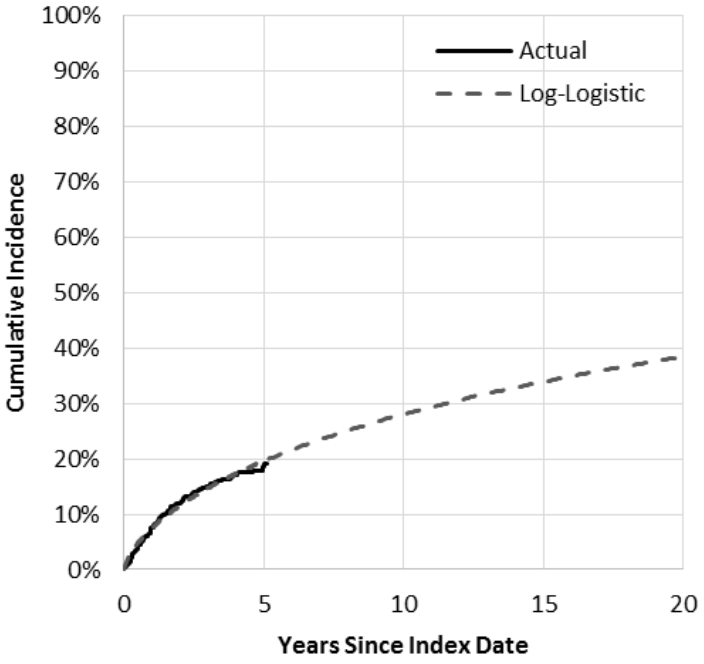

Figure 17 Actual versus predicted cumulative incidence of stroke recurrence

5.1.5.4 AMI Post-Stroke

The model predicts the AMI post-stroke risk based on the digitized Kaplan-Meier curve for myocardial infarctions or fatal cardiac events from Figure 1 in Dharmoon et al. (2006) [128]. The log-logistic distribution was selected based on the selection criteria described in Section 5.1.2. **Table 10** shows the parameter estimates. **Figure 18** illustrates the actual versus the predicted curves for the cumulative incidence of stroke recurrence.

Table 10 Log-logistic parameter estimates of the long-term risk of AMI post-stroke

Parameters	Value
Alpha	244.9800
Beta	0.5714

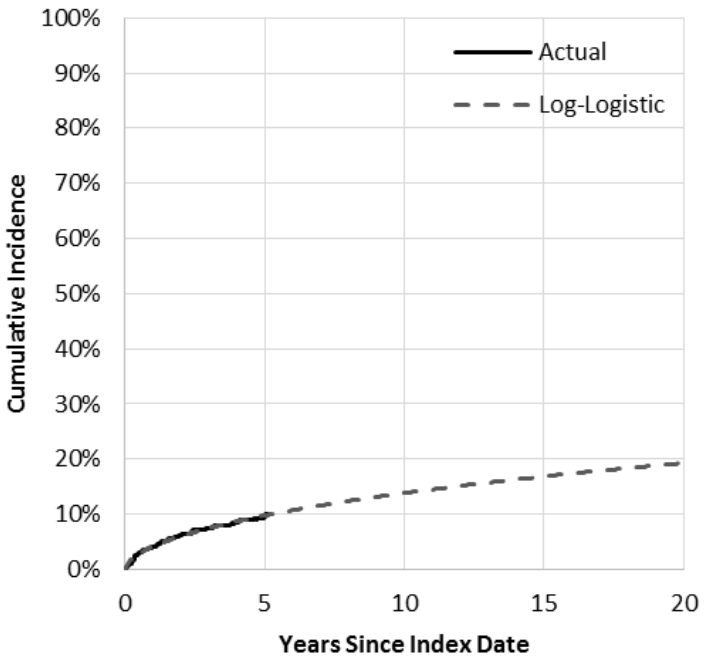

Figure 18 Actual versus predicted cumulative incidence of AMI post-stroke

5.1.6 Time to Musculoskeletal Pain

To our knowledge, no evidence-based survival curve exists for patients on statin therapy who present to their physician with MSP; however, some data on the persistence of statin therapy despite MSP, are available. LeLorier et al. (2000) analyzed statin persistence using the RAMQ claims database [40]. The median persistence on statin therapy was 205 days, with only 13% of patients persisting for 5 years.

In our model, we used a time-to-event curve for MSP which was calibrated based on assumptions about observed statin discontinuation studies. We calibrated a Weibull function such that 40% of patients will have experienced MSP within 3 years of statin initiation. In addition, the functional form was calibrated to have most MSP occurring within the first year of statin initiation. This curve was originally developed for the Markov model [129]. The curve allows for a long-term decreasing residual risk of MSP. **Table 11** presents the Weibull parameter values. **Figure 19** shows the time-to-event curve for MSP.

Table 11 Weibull parameter estimates of the long-term risk of MSP

Parameters	Value
Alpha	0.2617
Lambda	0.2000

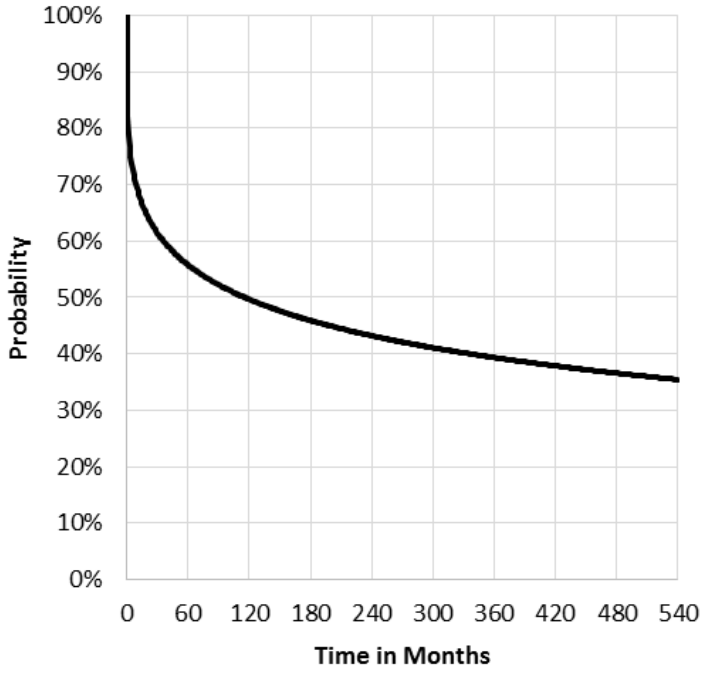

Figure 19 Assumed survival curve for musculoskeletal pain

5.1.7 Time-to-Event and Statin Efficacy

5.1.7.1 Patients Treated with a Statin

Our model assumes that estimated survival curves reflect untreated patients; that is, patients not receiving a statin. Thus, to estimate the survival of patients who have initiated statin therapy, we applied the relative risk reduction in all-cause mortality among patients aged ≥60 years old from Pedersen et al. [25]. The effect of statin therapy is applied to survival curves as follows:

$$S_{t,with\ Satin} = S_{t,without\ statin}^{RR} \quad (5)$$

5.1.8 Patients Interrupting Statin Therapy

Once a simulated patient experiences MSP, they may interrupt the statin therapy based on the PGx test results in the PGx environment, or on their physician's decision in the without PGx test environment. Interrupting statin therapy changes a patient's CV risk profile; thus, all time-to-event estimates need to be updated. A simplistic approach would obtain new time-to-events

from the survival curves without the statin protection. That is, using new random numbers to estimate new time-to-events. However, using this approach could lead to situations where patients would live longer when interrupting statin therapy.

An alternative approach would be that for each instance we need to assess a time-to-event, we assess both the time-to-event with and without the statin therapy using the same random number. This approach would avoid modeling the unrealistic situation in which a patient who interrupts a statin therapy lives longer than those on statin treatment. In our model, whenever a patient experiencing MSP interrupts the statin therapy, the time-to-events without statin therapy are adjusted with the following equation:

$$Updated\ CV\ time = Time\ of\ MSP + \frac{Time\ of\ CV_{no\ statin}}{Time\ of\ CV_{statin}}\left(Time\ of\ CV_{statin} - Time\ of\ MSP\right) \qquad (6)$$

The updated CV time estimate is the actual time of MSP plus the time until the CV event with statin protection, adjusted for the time-to-CVE ratio without and with statin. This equation is based on the following assumptions: Patients live at least until they have experienced MSP, and estimated CV event time without statin exposure cannot occur beyond the estimated CV event time with statin therapy. All relevant CV-related time-to-event estimates are updated based on each patient history.

Figure 20 shows a simplified sequence of events for a patient with myopathy. At $Time_{0,}$ the model's initial event times are randomly allocated. The patient's statin therapy is interrupted at $T_{0\ Myoptahy}$. Thus, the patient's future sequence of events needs to be updated due to the change in the CV risk profile from the statin interruption. A simplistic approach would be to update the event time by drawing a new random time-to-event. However, this would lead to an absurd outcome where this patient's new CV death time could be allocated anywhere between $T_{0\ Myoptahy}$ to past the end of the model time horizon; in which case this patient's death would be derived from the model's general population life table. Thus, to control for any issues, when assessing a CVE or mortality from the estimated survival, we estimated two event times using the same random number value: with and without statin protection. At statin interruption, we used equation (6) above to update the patient's event time.

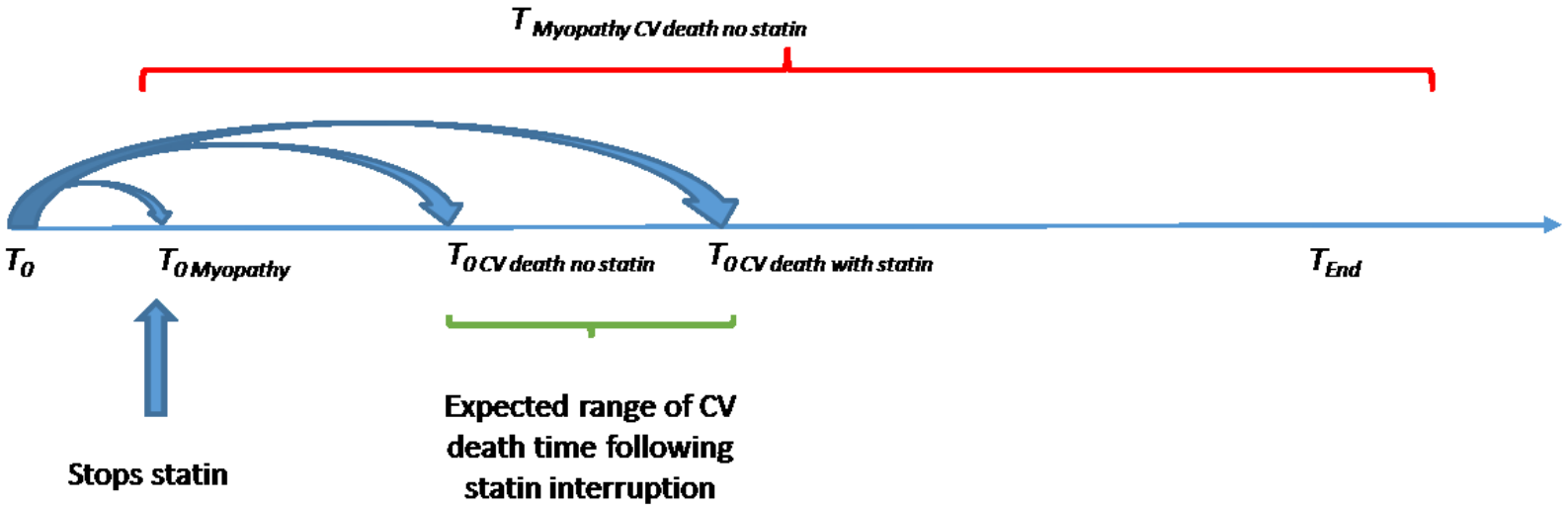

Figure 20 Illustration of the random allocation death time

CV cardiovascular, T_0 model time 0, $T_{0\ CV\ death\ no\ statin}$ *model initial time of death without statin protection,* $T_{0\ CV\ death\ with\ statin}$ *model initial time with statin protection,* $T_{0\ Myopathy}$ model initial time to statin myopathy, $T_{Myopathy\ CV\ death\ no\ statin}$ possible range of time value after statin interruption if selecting in new random time to death at $T_{0\ Myopathy}$, T_{End} *end of model time horizon.*

Article II

A discrete event simulation model to assess the economic value of a hypothetical pharmacogenomics test for statin-induced myopathy in patients initiating a statin in secondary cardiovascular prevention

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Statement of Authorship

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Economic model conceptualization: DM, JRG, FFA, ACI, AM, and JLL

Statistical analyses: DM

Model programming: DM

Economic analyses: DM

Manuscript writing: DM

Manuscript revisions: DM, JRG, FFA, ACI, AD, MPD, JCT, AM, and JLL

A Discrete Event Simulation Model to Assess the Economic Value of a Hypothetical Pharmacogenomics Test for Statin-Induced Myopathy in Patients Initiating a Statin in Secondary Cardiovascular Prevention

Running head: Discrete event simulation model to assess economic value of a hypothetical pharmacogenomics test in secondary cardiovascular prevention

Molecular Diagnosis & Therapy

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Compliance with ethical standards

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Conflicts of interest Dominic Mitchell, Jason R. Guertin, Anick Dubois, Marie-Pierre Dubé, Jean-Claude Tardif, Ange Christelle Iliza, Fiorella Fanton-Aita, Alexis Matteau, and Jacques LeLorier declare that they have no conflicts of interest that are directly relevant to the content of this review.

Author contributions Dominic Mitchell contributed to the conception and design of the study, data acquisition, analysis and interpretation of data, drafting the article and final approval. Jason R. Guertin, Anick Dubois, Marie-Pierre Dubé, Jean-Claude Tardif, Ange Christelle Iliza, Fiorella Fanton-Aita, Alexis Matteau, and Jacques LeLorier, contributed to the conception and design of the study analysis and interpretation of data, drafting the article and final approval.

Abstract

Background: Statin therapy is the mainstay dyslipidemia treatment and reduces the risk of a cardiovascular event (CVE) up to 35%. Adherence to statin therapy is poor. One reason patients discontinue statin therapy is musculoskeletal pain and the associated risk of rhabdomyolysis. Research is ongoing to develop a pharmacogenomics (PGx) test for statin-induced myopathy as an alternative to the current diagnosis method, which relies on creatine kinase levels. The potential economic value of a PGx test for statin-induced myopathy is unknown.

Methods: We developed a lifetime discrete-event simulation (DES) model for patients 65 years of age initiating a statin after a first CVE consisting of either an acute myocardial infarction (AMI) or a stroke. The model evaluates the potential economic value of a hypothetical PGx test for diagnosing statin-induced myopathy. We have assessed the model over the spectrum of test sensitivity and specificity parameters.

Results: Our model showed that a strategy with a perfect PGx test had an incremental cost-utility ratio of $4,273 per quality-adjusted life year (QALY). The probabilistic sensitivity analysis shows that when the payer willingness-to-pay per QALY reaches $12,000, the PGx strategy is favored in 90% of the model simulations.

Conclusion: We found that a strategy favoring patients staying on statin therapy is cost-effective even if patients maintained on statin are at risk of rhabdomyolysis. Our results are explained by the fact that statins are highly effective in reducing the cardiovascular (CV) risk in patients at high CV risk, and this benefit largely outweighs the risk of rhabdomyolysis.

Key Points for Decision Makers

- Preventive cardiovascular (CV) treatments, such as statin therapy, are known to have suboptimal treatment adherence. Even when physicians and pharmacists recommend the continuation of statin therapy, especially in patients at high risk of a cardiovascular event (CVE), patients will often decide not to follow their recommendations. Premature discontinuation deprives many patients of the benefits of CVE prevention.

- An accurate pharmacogenomics (PGx) test to identify musculoskeletal pain resulting from statin therapy is highly desirable. In secondary prevention patients at high-risk of a CVE, the primary strength of the PGx diagnostic test would be its ability to convince patients to adhere and persist on the statin therapy.

- Our findings indicate that in a high-risk CV patient population, a strategy favoring the maintenance of statin therapy, even in patients who are at risk of rhabdomyolysis, is cost-effective. We reason that statins are highly effective in reducing the CV risk and this largely dominates the rhabdomyolysis risk.

1 Introduction

It is estimated that 13.3 million Canadians have elevated cholesterol levels (i.e., dyslipidemia[xii]) [1]. Statins are the mainstay treatment for dyslipidemia and effectively reduce the risk of a cardiovascular event (CVE) by 25% to 35% [2]. In Canada, the estimated direct cost of cholesterol-lowering medications, with statins being the most commonly prescribed drugs in this class, is $1.6 billion annually [3].

Statin-induced myopathy is a potential adverse effect of statin therapy that often manifests as musculoskeletal pain (MSP) and may lead to treatment interruption [4]. Myopathy is a broad term used to describe muscle toxicity which is classified into three levels of severity: 1) myalgia: muscle symptoms, such as ache or weakness with normal creatine kinase (CK) levels; 2) myositis: muscle symptoms with elevated CK levels; and 3) rhabdomyolysis: muscle symptoms with CK elevation (typically > 10x the upper limit normal value) and creatinine elevation [5]. Rhabdomyolysis can lead to complications such as renal damage and, in rare cases, death [6, 7]. The incidence of suspected statin-induced myopathy is 5% to 10% in randomized clinical studies [7, 8], and as high as 25% in some observational studies [8-10].

Currently statin-induced myopathy is diagnosed using CK tests, which have limited diagnostic capacity due to poor internal validity as elevated CK levels may be caused by a variety of factors others than statin therapy [5, 6, 11, 12]. A pharmacogenomics (PGx) test could serve as a diagnostic tool in patients who have initiated statin therapy and suffer from MSP and could provide physicians with an accurate diagnostic tool. More importantly, this tool would help physicians guide patients suffering from MSP unrelated to statin to continue statin therapy to prevent future CVEs.

The guidelines and recommendations regarding statin intolerance involve various strategies specific to patients, including stop and re-challenge, changes in molecule, changes in dosage, and ensuring patients fully understand the long-term benefits of statin therapy [13-15]. Nevertheless, patients may decide not to follow their physician's prescribing recommendations

[xii] In the Canadian Health Measures Survey, dyslipidemia was defined as having unhealthy blood concentrations of LDL-C (≥3.5mmol/L), or a TC:HDL-C ratio ≥5.0, or self-reported use of a lipid-modifying medication.

without their physician's knowledge. As the Canadian Cardiovascular Society Dyslipidemia Guidelines point out: "statin intolerance and adverse effects remain of great interest in the media and in lay materials readily available to patients." [16]

The potential economic value of a PGx test for the diagnosis of statin-induced myopathy is unknown [17]. Although, a PGx test for statin-induced myopathy does not yet exist, it is the target of ongoing research [17, 18]. The current economic evaluation is an early assessment of the coauthors' (JCT, MPD, and AD) PGx test development effort funded by Genome Canada and Genome Quebec (Grant number: 4530) [19, 20]. Our previous economic model assessed the potential economic value of this theoretical PGx test using a Markov health state model [21]. The model results showed that a totally imperfect PGx test (false-positive rate [FPR] and false-negative rate [FNR] of 100%) would still be cost-effective with an incremental cost-utility ratio (ICUR) well below the commonly referred to willingness-to-pay (WTP) threshold. We revisited the economic evaluation of the theoretical PGx test [21] using a discrete event simulation (DES) method.

The main difference between the two models is how the models are informed on the survival of events. The Markov health state model uses point estimate transition probabilities obtained from published cost-effectiveness models. The DES uses estimated survival curve functions obtained from published Kaplan-Meier graphics converted to numerical values. The other differences in the DES model are consequences of the change in risk of events from the representative population captured by the survival curves. The DES population captured by the survival curves are representative of patients 65 years of age. In the Markov model, we used the statin efficacy estimates from the subgroup of patients < 60 years of age, whereas for the DES we used those in the subgroup of patients ≥ 60 years of age from the Scandinavian Simvastatin Survival Study (4S) [22]. As the efficacy of statins for the subgroup of patients who are ≥ 60 years of age is lower, this reduces the benefit of the PGx test which aims to maintain patients on statin therapy.

2 Method

2.1 Economic Evaluation

We developed a DES model to assess the cost-effectiveness of a hypothetical PGx test to identify statin-induced myopathy in high-risk, secondary prevention cardiovascular (CV) patients experiencing MSP. Although Markov modelling is the most common approach in pharmacoeconomics, DES modelling is an alternative approach that has been used in various health care problems over the past 30 years [23]. DES modelling offers several advantages over a Markovian approach: simulation and retention of patient history, CV-risk patient profile update after each event, and time flexibility (compared to a Markov which relies on a fixed-cycle length) [24]. The Supplemental Appendix[xiii] provides detailed information on the estimation of the time-to-event functions as well as the information on the software used for this study.

To assess the economic value of the PGx test across the full range of the test performance outcomes, from perfectly accurate to totally inaccurate, we varied the FNR and FPR. The FNR (FPR) is the proportion of test results in the presence (absence) of statin-induced myopathy that would falsely indicate the absence (presence) of statin-induced myopathy. We developed the model with a lifetime horizon from the perspective of a public payer in Canada. All costs were inflated to 2016 CAD values.

2.1.1 Model Assumptions

The model comprises two strategies to diagnose statin-induced myopathy: with or without the PGx test. We assumed patients who have MSP after initiating a statin for secondary CV prevention, ask their physicians about statin-induced myopathy. The decision whether to maintain patients on statin therapy depends on the: 1) diagnostic tool (CK vs. PGx test), 2)

[xiii] The Online Supplemental Appendix is included in the methodology chapter of the thesis (see Section Chapter 5).

physician prescribing recommendation, and 3) patient's decision to follow their physician's recommendation.

Aligned with the coauthors current research on the PGx test previously described, we assumed physicians will not require the PGx test for patients who present with rhabdomyolysis, which is easily diagnosed with the current diagnosis tools [9, 21, 25]. Patients diagnosed with rhabdomyolysis will have their statin therapy interrupted permanently.

In the environment without the PGx test, we assumed patients with MSP will interrupt their statin therapy based on either the physician recommendation to discontinue or a fear of rhabdomyolysis despite a physician recommendation to continue therapy. This assumption is relaxed in sensitivity analyses.

In the PGx test environment, we assumed physicians would require a test for all patients presenting with MSP. Thus, public payers incur the PGx test cost only for these patients. Physicians would base their prescribing recommendation on the PGx test result.

2.1.2 Model Structure

Figure 1 shows the DES model structure. The model was designed to simulate the lifetime histories of patients 65 years of age initiating a statin for secondary prevention after surviving a first CVE consisting of either a stroke or an acute myocardial infarction (AMI). Each patient is initially assigned a sequence of events based on their characteristics. The model first checks whether each simulated patient has an MSP event occurring before any mortality events. Patients not satisfying this condition are rejected from the model. Patients continuing in the model are duplicated to each strategy (with or without PGx test). The model then processes the sequence of events by jumping forward to the first event time. The CV history profile of the simulated patient is updated as well as the CVE counter, statin status, quality-adjusted life year (QALY), and costs incurred from time 0 until the event time. Each patient time-to-event sequence is updated to account for a change in their CV risk profile. Thus, for patients experiencing a CVE, the model updates the time-to-event sequence by randomly assigning new event times which correspond to patients' current CV history. The model evaluates whether the patient died; otherwise, the model reprocesses the sequence of events until the patient dies.

2.1.3 Model CV Events

Patients enter the model after having survived a first CVE consisting of either a first stroke or a first AMI. A stroke survivor could experience stroke recurrences or have a first AMI and AMI recurrences. Similarly, an AMI survivor could experience AMI recurrences or have a first stroke and stroke recurrences. The CVE risks are modelled using estimated survival curves found in the literature [26-28]. Detailed information on the time-to-event functions are presented in the Supplemental Appendix.[xiii]

2.1.4 Model Mortality

For each CVE in the model simulation, patients are at risk of 30-day mortality [29, 30]. **Table 1** presents the 30-day CVE mortality probabilities used in the base case, deterministic sensitivity analysis (DSA), and probabilistic sensitivity analysis (PSA). We assumed that patients who have a third CVE, excluding their initial event, die on the day of the event. Patients surviving beyond the 30-day mortality are subject to mortality based on their updated CV risk profile using published all-cause mortality survival curves [26, 31, 32]. In addition, patients may die from all-cause mortality from the general population based on gender-specific Canadian life tables [33]. Detailed information on the time-to-event functions are presented in the Supplemental Appendix.[xiii]

2.1.5 Statin Efficacy

Simulated patients entered the model initiating a high-dose statin. To capture the CVE and mortality risk reduction associated with statin therapy, we based the statin efficacy on the relative risk reduction of treatment compared with placebo for the subgroup of patients aged ≥ 60 years of age from Pedersen et al. [22]. We applied the relative risk to the estimated survival curves. **Table 1** presents the model statin risk reduction parameters used in the base case, DSA, and PSA.

2.1.6 Statin Interruption

In the model, we only considered statin interruption related to MSP and that a fraction of patients presenting to their physician will have statin-induced myopathy. Patients interrupting statin therapy for any other reasons would be similar in each group and would not contribute to the incremental analysis. We assumed that statin interruption is permanent.

Statin interruption changes the CV risk profiles of patients as they no longer benefit from the CV risk reduction associated with statin therapy. Thus, the model reassesses the complete sequence of events after statin interruption based on the new CV risk profile. The naïve method to update the sequence of events would be to draw new event times from the survival curves. However, this approach would lead to cases where patients would live longer, even though they no longer benefit from the statin CV risk reduction. Therefore, we updated event times considering that:

1. Patients lived at least until they experienced MSP
2. Estimated CV-related event time without statin protection cannot occur after a longer duration than the previously estimated CV-related event time with statin protection
3. Hence, the updated CV-related event time is contained in the time interval between the time of MSP and the previously estimated CV-related event time with statin protection

The Supplemental Appendix[xiii] provides further details on the method for updating CV-related event times.

2.1.7 Costs

Canadian cost data presented in **Table 1** were obtained from previously published cost studies, cost-effectiveness studies, and public governmental sources. Cost data were inflated to 2016 CAD using the all-components consumer price index table from Statistics Canada [34]. To account for the skewness observed in health care costs data, we set the low and high scenarios to 75% and 200%, respectively [35]. For physician visits, low and high values were based on the minimal and maximal values from the RAMQ Physician Code Book [36]. The daily statin cost was based on the daily cost of generic simvastatin 80 mg from the prescription list price in Québec [37]. We assumed a PGx test cost of $250.

2.1.8 Health Utilities

Table 1 presents the health utility values used in the model for the base case, the DSA, and the PSA. The CV utility and disutility data were obtained from Sullivan et al. [38]. We did not identify data for the disutility related to myopathy and rhabdomyolysis. We therefore assumed that the myopathy-related disutility was similar to the disutility in patients going from mild to moderate fibromyalgia reported by Hauber et al. [39]. For rhabdomyolysis, we assumed the disutility was equivalent to the relative change in utility between patients with an estimated glomerular filtration rate (eGFR)≥60 to patients with eGFR<15 or on dialysis reported by Gorodetskaya et al. [40].

2.2 Base Case Analysis

The DES model simulates a cohort of 60,000 patients. The subset of patients satisfying the MSP condition (see Section 2.1.2) are duplicated between the two model strategies.

For the strategy with the PGx test, we assumed a "perfect world" defined as: 1) the PGx test is perfect (FNR=0% and FPR=0%); 2) physicians will recommend to either continue or interrupt statins based on the PGx test result; and 3) patients will adhere to their physician recommendation regardless if they still suffer from MSP.

For the strategy without the PGx test, we assumed that physicians and/or patients are risk-averse in the presence of MSP and interrupt the statin therapy in fear of developing rhabdomyolysis. This situation is equivalent to that of a PGx test with FNR=0% and FPR=100%. This would also be the case when patients ignore physician recommendations to try alternative statin treatment patterns (e.g., molecule switch, dose reduction, stop and re-challenge).

2.3 Sensitivity Analyses

We carried out sensitivity analyses to assess parameter uncertainty. For each scenario of the DSA, 60,000 patients are simulated similar to the base case. For the PSA, we chose to reduce the number of patients simulated to 5,000 as the computer time for running the base model with 60,000 patients is close to 30 minutes. Instead, we opted for replicating the model with 1,000 simulations. For each sensitivity analysis, the model parameters are varied as specified in **Table**

1. The DSA results are presented in a tornado diagram while the PSA results are summarized in a CEAC.

2.4 Scenario Analyses

In the scenario analyses, we re-evaluated the base case model varying the FNR and FPR parameters from 0% to 100%. As we previously argued, this scenario analysis is an important aspect of the present economic evaluation for three reasons [21]. First, the model evaluates a hypothetical situation, thus we do not know the "real-life" test performance parameters. Second, evaluating the complete range of test efficacy parameters provides public payers with a comprehensive picture of the economic value of the PGx test, especially when we use a broader interpretation of test parameters including cases where physicians and/or patients do not completely adhere to the test results. Third, if the economic evaluation is made sufficiently early in the development process, it allows test developers to understand the optimal combination of test parameters from an economic perspective.

The scenario analyses are presented using an incremental net monetary benefit (INMB) method as opposed to the ICUR used in Mitchell et al. [21]. Although the INMB method requires the payer's WTP threshold to be specified, we believe this method allows us to explore the impact of the payer's WTP on the PGx value.

3 Results

3.1 Base Case Analysis

The main results for the base case are shown in **Table 2**. Overall, about half (48.3%) of the 60,000 patients created were retained in the model and assigned to each strategy. The ICUR was $4,273 per QALY for the strategy with the PGx test versus without the test. For a PGx test cost of $250, assuming an arbitrary WTP of $10,000 per QALY, the incremental net monetary benefit (INMB) was $4,962.

Table 3 presents the proportion of patients with none to three CVEs during the model simulation. Seventy-six percent of patients with the PGx strategy had no additional CVEs, a 2.8% reduction compared with the strategy without the PGx test. Fewer patients with the PGx

strategy experienced one CVE (-2.3%) or two CVEs (-0.6%) compared with the strategy without the PGx test. Although, there was a negligible increase in the proportion of patients who had three CVEs with the PGx strategy versus without the PGx strategy (4.2% vs 4.1%), this may be caused by patients living longer with the PGx strategy (78 vs. 76 years, respectively).

3.2 Sensitivity Analyses

We assessed the robustness of the INMB model base case of 4,962 in a DSA, assuming a payer's WTP of $10,000 per QALY (see **Figure 2**). The four parameters most sensitive to change were the discount rate, efficacy of statin therapy in reducing all-cause mortality, overall statin efficacy, and annual cost of managing a long-term CVE survivor. The INMB values in the DSA ranged from $481 to $16,197. The maximal INMB value ($16,197) was obtained with the low parameter value of the discount rate, 0% (i.e., undiscounted results). As all INMB values are positive, this indicates that, at an arbitrary WTP of $10,000, the PGx test strategy is cost-effective.

Figure 3 shows the CEAC comparing the two strategies. The PSA consisted of repeating 1,000 random evaluations of the model with 5,000 patients for each simulation. The PSA simulations favored the strategy without the PGx test when the payer's WTP was below $3,500 per QALY. When the payer's WTP exceeded $3,500 per QALY, over 52% of simulations favored the strategy with the PGx test. This number reached 90% when the payer's WTP was $12,000 per QALY.

3.3 Scenario Analyses

As the performance parameters of a future PGx test are unknown, we investigated the full range of possible FNR and FPR values. **Figure 4** presents two INMB matrix results using two arbitrary levels of WTP ($10,000 and $50,000 per QALY). The grey zone indicates FNR and FPR combinations favoring the scenario without PGx test (INMB<0). Both matrices show that, as the PGx test becomes increasingly imperfect, the INMB values decreases along the diagonal.

With a WTP of $10,000 per QALY and a poorly performing PGx test (FNR>40% and FPR>60%), the model favors the without PGx test strategy (i.e., INMB <0; **Figure 4**, Panel A).

With a WTP of $50,000 per QALY, the model favors the PGx test strategy in all but one performance combination (FNR=0% and FPR>100% **Figure 4**, Panel B).

4 Discussion

We found that the strategy with a perfect PGx test to diagnose statin-induced myopathy is cost-effective. Our results were consistent even when considering the full range of possible PGx test performance outcomes (FPR and FNR combinations) at payer WTP thresholds of $10,000 and $50,000 per QALY, which are well within the WTP threshold values reported for Canada [41]. Even at the lowest WTP threshold, the model generated positive INMB values for all test performance outcomes that would be considered for a valid diagnostic tool. Our findings are consistent with the previous economic evaluation we conducted using a Markov model approach [21].

4.1 Consequences of False Negative and False Positive PGx Test Results

The consequences of false negative (FN) and false positive (FP) test results do not balance out. The benefit from the statin protection outweigh the extremely small risk of a rhabdomyolysis. For instance, based on the Canadian Cardiology Society Dyslipidemia Management Guidelines, primary prevention patients are considered at high CV risk when they have a 10-year Framingham Risk Score ≥20%, which corresponds to a ≥2.2% annual probability of having a CVE [16]. This CVE risk is much higher than the risk of rhabdomyolysis. Radillis et al. [7] reported that the rate of rhabdomyolysis was 3.2 per 100,000 person-years, but most studies report rates of around 10 per 100,000 person-years [42, 43]. These estimates correspond to an annual risk of rhabdomyolysis of 0.003% to 0.01%. Furthermore, rhabdomyolysis is often diagnosed early before it leads to renal damage and, therefore, does not require hospitalization.

Our scenario analysis captures this asymmetry in consequences. Although increasing the FNR and FPR rates simultaneously creates a decreasing trend in the economic value of the PGx test, we found that independently increasing the proportion of FN results does not have the same economic impact as independently increasing the proportion of FP results. For any level of FNR, the economic value of the PGx test for the payer *decreases* as the FPR increases. This is the case

for any payer WTP threshold. However, the reverse does not hold true when independently increasing the proportion of FN results, holding FPR constant. In this latter situation, the economic value of the PGx test depends on the payer's WTP. At lower payer WTP thresholds (<$20,000 per QALY), the economic value of the PGx test *decreases* as the FNR increases. At higher payer WTP thresholds, the value of the PGx test *increases* as the FNR increases, as patients continue to benefit from statin protection.

Patients inadequately interrupting their statin therapy may represent an economic loss for payers. As explained by Cardinal et al., in preventive health strategies, patients who interrupt their treatment before they incur any benefit represent a resource inefficiency [44]. As can be seen in the study from Pedersen et al., the statin benefit materializes after 1.5 years of statin treatment when compared with placebo [22].

Furthermore, the development of an accurate PGx test would be a useful tool for physicians and pharmacists to help maintain patients on continuous statin therapy. Many studies highlighted the poor adherence and persistence to statin therapy [45-48]. Wouters et al. reported that among 229 patients, 40% to 70% doubted the need for statin therapy and lacked knowledge about its efficacy, while 20% to 35% worried about joint and muscle side effects [49].

4.2 Strength

Our DES model has several strengths, such as the use of estimated all-cause mortality and CVE risk survival curves obtained from the literature. This allowed us to conduct a DES model without access to patient level data. With the DES approach, we were able to simulate patient characteristics and follow their history within the model. In contrast, this was not possible with the previous Markov model approach, which had limited memory [21]. Furthermore, the model design was not limited by the lack of "real-world" PGx test parameters. We assessed the economic benefit across the full range of FNR and FPR test performance outcomes, providing a broad understanding of the expected value of such a test and allowing for the flexibility to analyze an imperfect test environment. Even if we had the true PGx test parameters, we would argue that analysing the complete range of FPRs and FNRs is essential. Even with a perfect test (i.e., FPR and FNR=0%), physician and patient responses to the test results influence treatment outcomes. Despite a perfect PGx test result indicating the absence of statin-induced myopathy,

if physicians recommend interrupting the statin therapy, or if patients decide to ignore their physician's recommendations (i.e., statin non-adherence), this would be equivalent to an environment with an imperfect PGx test (i.e., FPR>0% and FNR=0%). The extreme result would be a situation where all patients without statin-induced myopathy interrupted their statin therapy even though the PGx test result indicated they should continue. This would be equivalent to a PGx test with a FPR of 100%. Thus, this broad interpretation of test parameters encompasses statin non-adherence. As such, conducting the economic evaluation using the complete range of test parameters provides essential information to payers on what the consequences of FN and FP test results.

4.3 Limitations

There are many uncertainties surrounding the incidence of severe statin-induced rhabdomyolysis and its associated disutility. An increase in the rate of severe rhabdomyolysis would increase the value of the PGx test. Our model simulates a secondary prevention population and results are not generalizable to all patients on statin therapy, such as those receiving statins for primary prevention of cardiovascular disease.

The model predicted survival curves were limited to data that could be extracted from the published figures and the population characteristics underlying those figures. For instance, the study from Smolina et al. allowed us to derive age-group/gender specific survival curves [26], which was not available in other studies. To address these limitations, we explored the uncertainties by applying multipliers varying ± 20% to each survival curve in the DSA and PSA.

The strategy "without the PGx test" may be seen as limiting as we assumed that all physicians and pharmacists will recommend discontinuing statin therapy when patients suffer from MSP. Regardless of their physician's or pharmacist's recommendations, as suggested by the literature on statin adherence, a significant proportion of patients will interrupt their statin therapy leading to the same outcome [45, 47-49].

5 Conclusion

We found that a PGx test strategy favoring patients staying on statin therapy is cost-effective even if patients maintained on treatment are at risk of rhabdomyolysis. These results are explained by the fact that, in patients at high CV risk, statins can effectively reduce the CV risk, outweighing the risk of rhabdomyolysis. These results are consistent with our previous Markov model from a payer's perspective, even though the Markov model used different data sources for capturing CV risk and higher statin efficacy parameters due to the younger target population [21].

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7 Figures

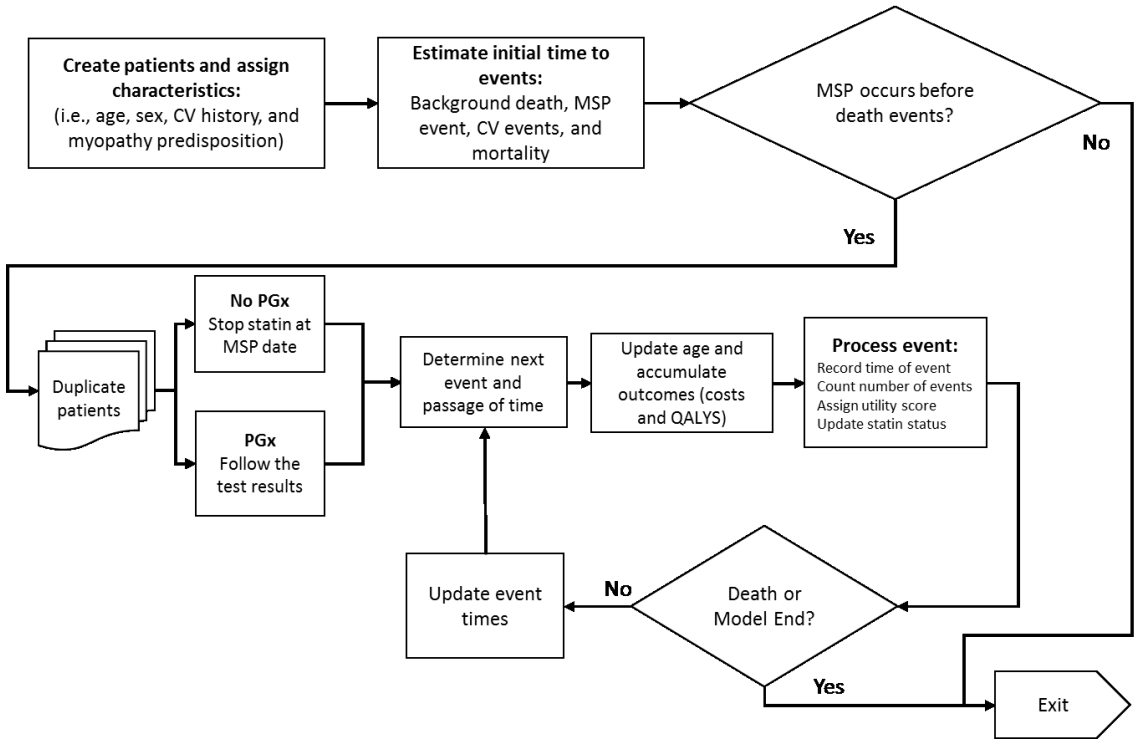

Figure 1 Representation of the DES model. Patients enter the model initiating a statin for secondary CV prevention. The model first assigns patient characteristics, including predisposition for statin-induced myopathy that allows us to identify the PGx test performance (i.e., true [false] positive or negative test results). Based on individual patient characteristics, the model calculates the initial sequence of time-to-events. Before processing the patients, the model validates whether each patient was assigned an MSP date occurring before any of the model death events or before the end of the model time horizon. Patients retained in the model are duplicated to each strategy. Patients then progress in the model through the sequence of event-time. Patients accrue costs and QALYs at each passage through the model loop until they die or the end of the model time horizon. CV risk profiles are updated when patients experience simulated CVEs. Statin therapy status is updated once in the model, when patients experienced MSP. Based on the myopathy predisposition of each patient, the PGx test performance is recorded.

CV cardiovascular, *MSP* musculoskeletal pain, *PGx* pharmacogenomics, *QALY* quality-adjusted life year

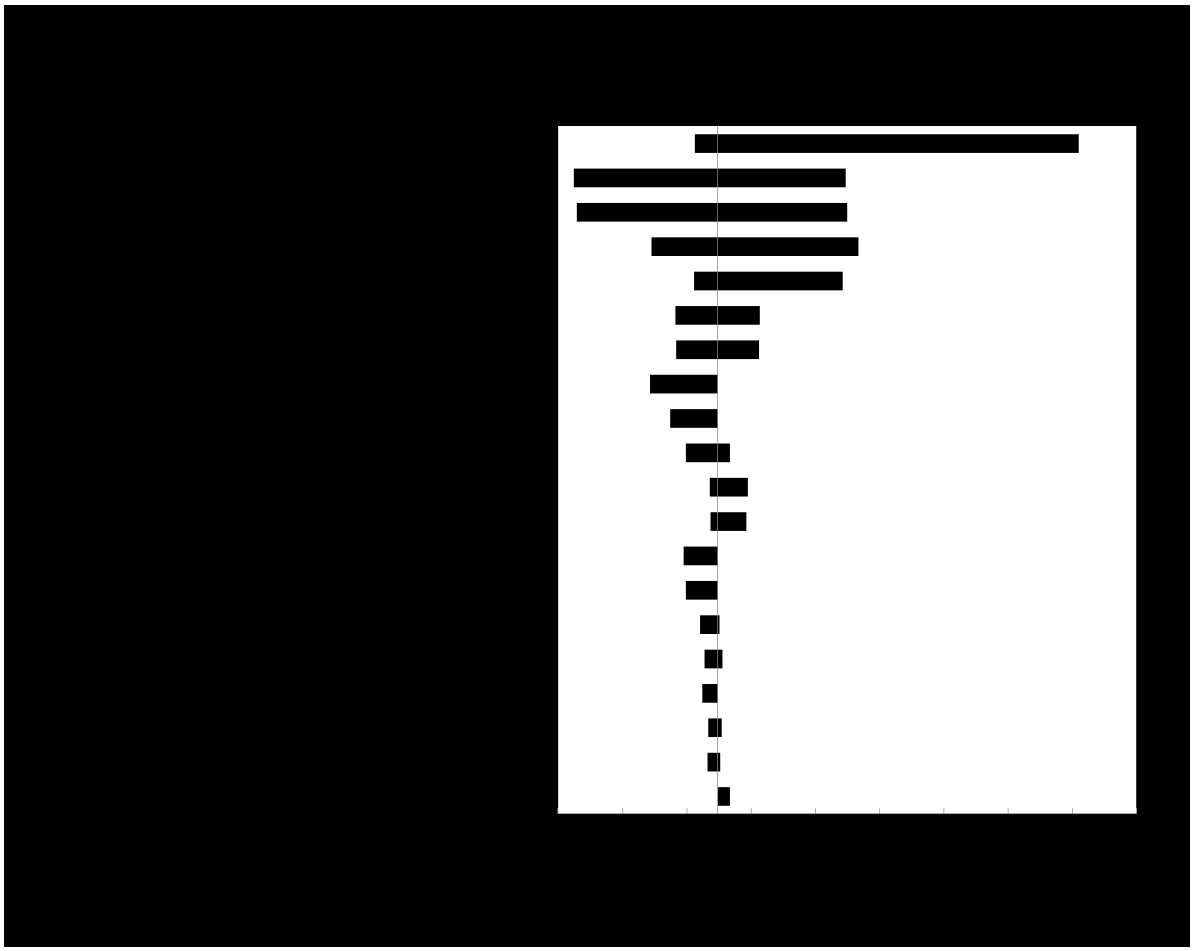

Figure 2 Tornado diagram comparing the strategy "with PGx test" to "without PGx test". The diagram shows 20 scenario variations assuming a WTP of $10,000 per QALY. The INMB was most sensitive to changes in the discount rate, statin reduction in all-cause mortality, statin efficacy, followed by the cost of managing a long-term CVE survivor. The PGx test-related parameters that ranked among all parameter scenarios were: PGx test sensitivity and sensibility (9th for both), PGx test specificity (13th), PGx test sensitivity (21st), and PGx test cost (24th).

AMI acute myocardial infarction, *CVD* cardiovascular disease, *CVE* cardiovascular event, *DSA* deterministic sensitivity analysis, *INMB* incremental net monetary benefit, *PGx* pharmacogenomics, *QALY* quality-adjusted life year, *RR* relative-risk, *WTP* willingness to pay.

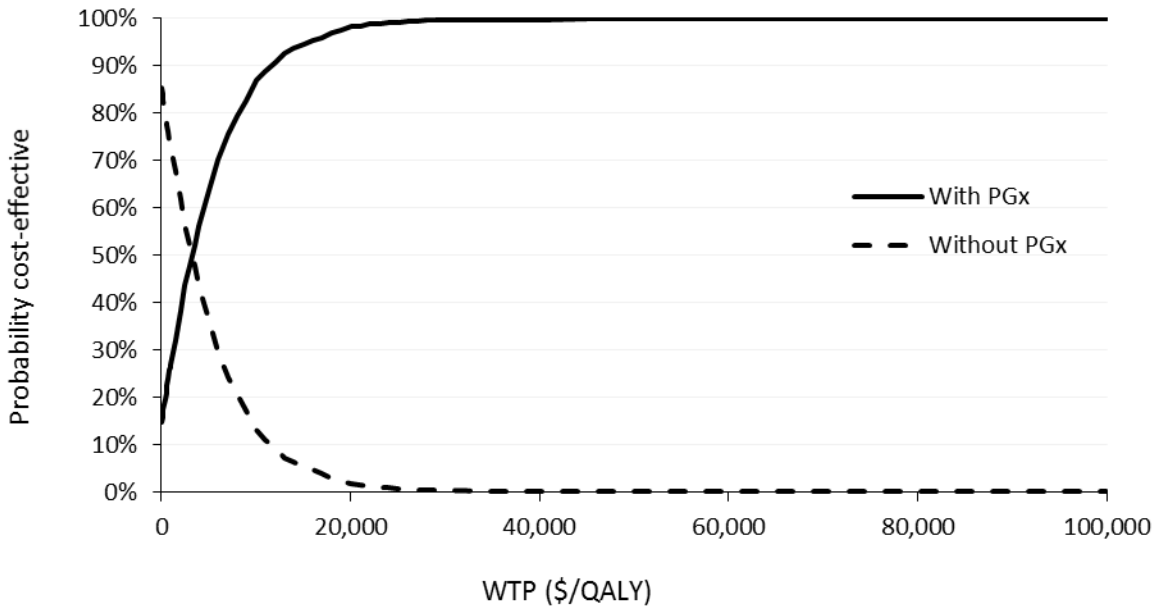

Figure 3 Cost-effectiveness acceptability curve comparing the management of statin-induced myopathy with and without a PGx test. The curves show the percentage of simulations that favor one strategy over the other. The curves cross when the payer WTP is $3,750 per QALY, the threshold above which more than 50% of simulations favor the PGx test strategy. When the payer WTP reaches $12,000 per QALY, 90% of the model simulations favor the strategy with the PGx test.

PGx pharmacogenomics, *QALY* quality-adjusted life year, *WTP* willingness to pay.

Panel A WTP=$10,000 per QALY

False Negative Rate \ False Positive Rate	0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
0%	4,962	4,374	3,899	3,403	2,885	2,378	1,808	1,397	824	278	-243
10%	4,787	4,273	3,856	3,295	2,903	2,233	1,686	1,246	529	284	-299
20%	4,618	3,902	3,486	3,094	2,495	2,119	1,726	1,066	434	216	-449
30%	4,476	4,284	3,681	2,789	2,545	2,031	1,688	1,188	665	105	-611
40%	4,488	3,724	3,348	2,722	2,210	1,881	1,245	924	552	9	-345
50%	4,263	4,196	3,415	2,900	2,179	2,046	1,326	756	188	-68	-572
60%	4,156	3,341	3,314	2,721	2,006	1,895	1,239	769	101	-455	-1,105
70%	4,197	3,799	3,077	2,594	2,170	1,729	928	213	-97	-407	-1,064
80%	4,122	3,514	3,171	2,223	1,779	1,380	1,368	-27	271	-337	-1,029
90%	3,929	3,403	2,685	1,913	1,695	1,626	733	537	-3	-364	-1,145
100%	3,906	3,650	2,877	2,629	2,130	939	521	125	105	-708	-1,569

Worst test

Panel B WTP=$50,000 per QALY

False Negative Rate \ False Positive Rate	0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
0%	39,619	35,160	31,462	27,735	23,698	19,373	15,469	12,516	7,336	3,907	-143
10%	39,800	35,182	32,216	28,116	24,472	19,806	15,610	11,950	7,588	4,494	545
20%	40,000	35,430	31,240	27,968	24,174	20,532	16,204	12,429	7,425	4,223	906
30%	40,125	36,863	32,277	28,900	25,605	20,941	17,003	13,120	9,423	5,408	1,192
40%	40,071	36,188	32,962	27,912	24,808	21,316	16,804	12,894	9,538	5,476	1,508
50%	41,706	38,166	33,679	29,672	24,702	21,861	17,655	13,430	9,393	5,861	1,708
60%	40,877	37,006	33,840	30,208	25,202	22,259	18,197	14,745	9,833	5,976	1,638
70%	42,457	38,392	33,655	30,407	25,837	22,181	17,995	13,743	10,089	6,698	1,898
80%	42,510	38,508	34,669	29,837	26,311	22,982	18,913	14,421	11,157	7,190	2,461
90%	43,316	39,098	35,141	30,469	27,553	23,175	19,019	15,319	12,207	7,589	3,545
100%	43,363	39,247	35,405	32,026	27,547	23,396	19,696	16,154	12,196	7,720	3,221

Worst test

Figure 4 Matrices of INMB results when varying the PGx test performance parameters FPR and FNR from 0% to 100%. The top matrix shows the results assuming a WTP of $10,000 per QALY while the bottom matrix shows the results assuming a WTP of $50,000 per QALY. The arrows indicate the worsening of the PGx test parameters. The "Perfect Test" is located at the top left corner of the matrices (FPR and FNR are 0%); the "Worst Test" is located at the bottom right corner (FPR and FNR are 100%). Grey cells show test parameter combinations favoring the strategy without the PGx test. White cells indicate when the PGx test provides excess value for the payer.

FNR false-negative rate, *FPR* false-positive rate, *INMB* incremental net monetary benefit, *PGx* pharmacogenomics, *QALY* quality-adjusted life year, *WTP* willingness to pay

8 Tables

Table 1 Model inputs used in the base case, DSA, and PSA

Variable	Base	Low	High	SE[i]	Distribution	Source
Demographics						
Age	65					Assumption
Gender (% male)[a]	58.0	46.4	69.6	5.9	Beta	PHAC[50]
CVD history						
Male (% AMI vs. stroke)[a]	67.3	53.9	80.8	6.9	Beta	PHAC[50]
Female (% AMI vs. stroke)[a]	53.2	42.6	63.8	5.4	Beta	PHAC[50]
Treatment Decision Parameters						
Test Parameters						
PGx sensitivity[a]	100%	80%	100%	5.1%	Beta	Assumption
PGx specificity[a]	100%	80%	100%	5.1%	Beta	Assumption
No PGx Test - Decision						
True myopathy - discontinue statin[a]	100%	80%	100%	5.1%	Beta	Assumption
False myopathy - continue statin[a]	0%	0%	20%	5.1%	Beta	Assumption
Myopathy						
Minimum days of exposition to statin required[b]	30	10	45	30	Gamma	Assumption
Probability of myopathy symptoms[a]	0.25	0.20	0.30	0.03	Beta	Assumption
Rhabdomyolysis						
Rate of rhabdomyolysis (per 10,000 person-years)[c]	4.64	0.46	46.4	1.35	Gamma	Erickson et al. [43]
Rhabdomyolysis probability of death[c]	0.08	0.07	0.08	0.003	Beta	Erickson et al. [43]
Relative risk of rhabdomyolysis[b]	3	2	6	1.02	Norm	Assumption
Statin Efficacy						
Reduction in all-cause mortality[b]	0.73	0.73	0.58	0.09	Norm	Pedersen et al.[22]
Reduction in coronary deaths[b]	0.71	0.71	0.6	0.07	Norm	Pedersen et al.[22]
Death Probability - within 30-days post-CVE						
First stroke[c]	0.135	0.131	0.139	0.002	Beta	CIHI [30]
Recurrent stroke[c]	0.135	0.131	0.139	0.002	Beta	CIHI [30]
First AMI - male[c]	0.324	0.320	0.329	0.002	Beta	Smolina et al. [29]
First AMI - female[c]	0.303	0.298	0.309	0.003	Beta	Smolina et al. [29]
Recurrent AMI - male[c]	0.297	0.287	0.307	0.005	Beta	Smolina et al. [29]
Recurrent AMI - female[c]	0.267	0.255	0.279	0.006	Beta	Smolina et al. [29]

CV Risk Multipliers[j]						
Increased risk of 3rd stroke[b]	2.0	1.0	3.0	0.5	Norm	Assumption
Increased risk of 3rd AMI[b]	2.0	1.0	3.0	0.5	Norm	Assumption
Increased risk of AMI post stroke[b]	2.0	1.0	3.0	0.5	Norm	Assumption
Increased risk of stroke post AMI[b]	2.0	1.0	3.0	0.5	Norm	Assumption
Time-to-event Relative Risk Multipliers[k]						
Time to MSP[b]	1.0	0.8	1.2	0.1	Norm	Assumption
Time to first AMI mortality[b]	1.0	0.8	1.2	0.1	Norm	Assumption
Time to second AMI mortality[b]	1.0	0.8	1.2	0.1	Norm	Assumption
Time to first stroke mortality[b]	1.0	0.8	1.2	0.1	Norm	Assumption
Time to recurrent stroke mortality[b]	1.0	0.8	1.2	0.1	Norm	Assumption
Time to AMI recurrence[b]	1.0	0.8	1.2	0.1	Norm	Assumption
Time to stroke post-AMI[b]	1.0	0.8	1.2	0.1	Norm	Assumption
Time to stroke recurrence[b]	1.0	0.8	1.2	0.1	Norm	Assumption
Time to AMI post-stroke[b]	1.0	0.8	1.2	0.1	Norm	Assumption
Cost Parameters (2016 CDN)						
AMI[d]	10,868	8,151	21,736	10,868	Gamma	OCCI [51]
Stroke[d]	14,589	10,941	29,177	14,589	Gamma	OCCI [51]
Fatal AMI[d]	18,898	14,173	37,795	18,898	Gamma	Smolderen et al. [52]
Fatal stroke[d]	31,368	23,526	62,736	31,368	Gamma	Smolderen et al. [52]
Annual cost of managing a long-term CVE survivor[c]	4,058	143	5,899	4,058	Gamma	Conly et al. [53], Ghali et al. [54]
Rhabdomyolysis cost - hospitalization[a]	86,893	65,170	108,616	86,893	Gamma	Skrabal et al. [55]
Annual statin cost[e]	137	137	205		Not varied	RAMQ[37]
GP visits[f]	92	70	105		Not varied	RAMQ [36]
Cost of PGx test[b]	250	250	500		Not varied	Assumption
Health Utilities						
Stable coronary heart disease utility[c]	0.7780	0.6610	0.8950	0.0597	Beta	Sullivan et al. [38]
Disutility due to AMI[c]	0.1270	0.1080	0.1470	0.0099	Beta	Sullivan et al. [38]
Disutility due to stroke event[c]	0.1390	0.1180	0.1600	0.0107	Beta	Sullivan et al. [38]
Disutility due to stroke and AMI[g]	0.1660	0.1409	0.1911	0.0128	Beta	Sullivan et al. [38]
Disutility of myopathy[c]	0.0829	0.0663	0.0995	0.0085	Beta	Hauber et al.[39]
Disutility of rhabdomyolysis[c,h]	0.1444	0.1250	0.1600	0.0089	Beta	Gorodetskaya et al. [40]
General Model Parameters						

Discount rate[c]	1.5%	0.0%	3.0%	Not varied	CADTH [56]
Time horizon[b]	45	10	50	Not varied	CADTH [56]

AMI acute myocardial infarction, *CADTH* Canadian agency for drugs and technologies in health, *CIHI* Canadian institute for health information, *CV* cardiovascular, *CVD* cardiovascular disease, *CVE* cardiovascular event, *GP* general practitioner, *MSP* musculoskeletal pain, *OCCI* Ontario case costing initiative, *PGx* pharmacogenomics, *PHAC* Public Health Agency of Canada, *RAMQ* Régie de l'assurance-maladie du Québec, *RR* relative risk, *SE* standard error

[a] The low and high values are set to ± 20% of the base parameter values.

[b] The low and high values are based on an assumption.

[c] The low and high values are based on the source.

[d] The low value set to -25% and high value set to 200% to allow for skewness in health care cost data.

[e] The low and high values are based on the generic and brand price of simvastatin from the RAMQ drug price list.

[f] The low and high values are based on the on the RAMQ physician code book.

[g] The low and high values are calibrated on the relative disutility of stroke.

[h] Assumed relative change for patients with eGFR<15 + Dialysis compared with patients with eGFR≥60.

[i] Standard errors are based on the publication when available. When unavailable, the standard errors for gamma distributed variables are set to the base value; otherwise, the standard errors are calculated as (high-low)/(2*1.96).

[j] We assumed an increased risk of CVE in cases where evidence-based data is lacking. The model uses survival curves for CVE recurrences and the risk of post-stroke or post-AMI events. However, there is no evidence-based data for the increased CV risk in patients with a CV history of two CVEs. Hence, for these patients we assumed a CVE risk multiplier of RR=2, with low and high values of RR=1 and RR=3.

[k] Time-to-event risk multipliers are used to add variations to the model survival curves. The default values are RR=1, with low and high values of RR=0.8 and RR=1.2.

Table 2 Main model results for the base case

	With PGx Test	Without PGx Test	Δ
N	28,984	28,984	
Total costs	61,139	57,437	3,702
Total LYG	11.00	9.88	1.12
Total QALYs	8.51	7.64	0.87
Average death age	77.65	76.27	1.38
ICER	–	–	3,299
ICUR	–	–	4,273
INMB (WTP=$10,000)	–	–	4,962

ICER incremental cost-effectiveness ratio, *ICUR* incremental cost-utility ratio, *INMB* incremental net monetary benefit, *LYG* life-years gained, *PGx* pharmacogenomics, *QALY* quality-adjusted life year

Among the 60,000 patients simulated, 28,984 were retained and duplicated between the environments with and without the PGx strategy. The three costs-effectiveness summary measures (ICER, ICUR, or INMB) indicate that the PGx test strategy is cost-effective for commonly reported payer's WTP thresholds in Canada.

The incremental cost with the PGx test is $3,702, with 1.12 incremental LYGs and 0.87 incremental QALY compared with without the PGx test, yielding an ICER of $3,299 per QALY and an ICUR of $4,273 per QALY. The model base case INMB is $4,962 indicating that the PGx strategy is cost-effective for an assumed payer's WTP=$10,000 per QALY.

Table 3 CVD outcomes with the base case model

	With PGx Test	Without PGx Test	Δ
Number of CV events			
No additional CVE	76.0%	73.2%	2.8%
1 CVE	17.2%	19.4%	-2.3%
2 CVEs	2.7%	3.3%	-0.6%
3 CVEs	4.2%	4.1%	0.1%
Total	100.0%	100.0%	0.0%

CVD cardiovascular disease, *CVE* cardiovascular event, *LG* life years, *PGx* pharmacogenomics, *WTP* willingness to pay

The PGx strategy increases the percentage of patients who do not experience an additional CVE by 2.8% compared with the without PGx strategy. The PGx test strategy reduces the percentage of patients experiencing one or two CVEs by 2.3% and 0.6% compared with no PGx test. There is a 0.1% increase in patients experiencing three CVEs with the PGx strategy; however, this may be caused by the gain in LYs with the PGx test compared with without test PGx test.

Chapter 6. Article III

Article III is a reflection exercise in relation to Articles I and II. Firstly, it compares the differences in the modelling approaches between the two articles. Secondly, the article broadly discusses what we have learned from the economic evaluation of a hypothetical PGx test for statin-induced myopathy.

Article III

Value of a Hypothetical Pharmacogenomics Test for the Diagnosis of Statin-Induced Myopathy in Patients at High Cardiovascular Risk

This is a post-peer-review, pre-copyedit version of an article published in Molecular Diagnosis & Therapy. The final authenticated version is available online at: http://dx.doi.org/10.1007/s40291-018-0356-6.

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Statement of Authorship

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Manuscript writing: DM

Manuscript revisions: DM, JRG, and JLL

Value of a Hypothetical Pharmacogenomics Test for the Diagnosis of Statin-Induced Myopathy in Patients at High Cardiovascular Risk

Running head: Economic Value of a PGx Test for Statin-Induced Myopathy in High CV Risk Patients

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Compliance with ethical standards

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Conflicts of interest Dominic Mitchell, Jason R. Guertin, and Jacques LeLorier declare that they have no conflicts of interest that are directly relevant to the content of this review.

Author contributions Dominic Mitchell contributed to the conception and design of the study, data acquisition, analysis and interpretation of data, drafting the article and final approval. Jason R. Guertin, and Jacques LeLorier, contributed to the conception and design of the study analysis and interpretation of data, drafting the article and final approval.

Abstract

We recently conducted two economic evaluations of a hypothetical pharmacogenomics (PGx) test for statin-induced myopathy (SIM) in patients at high cardiovascular (CV) risk. Although the models differed in modeling technique and data inputs, both yielded similar results.

We believe that our approach to assess the economic value of a diagnostic test is highly advantageous as it characterizes the complete range of false negative and false positive test outcomes. We used a broad interpretation of test parameters that reflects physician and patient behavioral responses to the test results and accounts for patient adherence to treatment.

Both economic evaluations indicated that a highly accurate PGx test for SIM would provide a positive incremental net monetary benefit (INMB) for a provincial payer in Canada. However, the value of the test would depend on its ability to accurately diagnose patients when they experience musculoskeletal pain symptoms and guide patients with a test result indicating no SIM to adhere to treatment. Interestingly, our results indicated that a highly inaccurate test would still yield a positive INMB. We found this surprising result was driven by the imbalance of the risk of CV events outweighing the risk of rhabdomyolysis in high CV-risk patients.

A highly accurate PGx test for SIM in high CV-risk patients would provide economic value for payers. However, the economic and clinical value of the test would depend on the credibility of the test results to succeed in influencing patients without SIM to adhere to therapy.

Key Points for Decision Makers

- The cross-validation of a Markov model with a discrete event simulation model showed that a highly accurate PGx test for SIM in patients at high CV risk would be cost-effective in the Canadian setting.
- The clinical and economic value of the PGx test for SIM is directly linked to the outcome of influencing patients, who would otherwise discontinue statin therapy, to lifetime adherence when a receiving a negative test result (no SIM).
- Early-stage economic evaluations of diagnostic tests would benefit from an assessment of the complete spectrum of test sensitivity and specificity parameters to characterize the consequences of false negative (positive) test results. In the absence of evidence-based data, this approach allows integration of physician and patient decisions in the economic evaluation.

1 Introduction

Statins are the mainstay treatment for dyslipidemia in secondary cardiovascular (CV) prevention. Secondary CV prevention refers to health strategies applied after CV disease onset and includes interventions to prevent disease progression and complications [1]. In this patient population, statins effectively reduce cardiovascular event (CVE) risk by 25% to 35% [2]. Although statins are effective in reducing long-term CVE risk, statin adherence remains a major concern [3, 4]. Guertin et al. reported 58.0% of incident statin users had discontinued treatment within 1 year [5]. In addition, statins have received considerable negative press over the past 20 years, which exacerbated the burden of early statin discontinuation [6, 7]. Nielsen and Nordestgaard reported that early statin discontinuation (within 6 months of statin initiation) increased three-fold (6% to 18%) between 1995 and 2010 [6]. Their analyses indicated that early statin discontinuation increased with negative statin-related news stories.

Statin myopathies are thought to be one major cause of statin discontinuation. The incidence of suspected statin-induced myopathy (SIM) in randomized clinical studies ranges between 5% to 10% [8, 9], but is as high as 25% in some observational studies [9-11]. The Canadian Consensus Working Group (CCWG) established the Canadian guidelines for managing statin adverse effects and intolerance [12-14]. The 2016 CCWG Guidelines propose a management algorithm relying on a statin challenge-dechallenge-rechallenge (CDR) protocol while monitoring creatine kinase (CK) levels as an indicator of muscle breakdown and other risk factors [14]. However, the CCWG's opinion is that the CDR protocol is seldom met in clinical practice, leaving many patients in need of statin therapy, untreated [12]. Compounding this issue is that currently, SIM is diagnosed using CK tests, which have limited diagnostic capacity due to poor validity: elevated CK levels may be caused by many factors other than statin therapy [15-18]. Thus, in practice, SIM is over diagnosed, leading some patients to be falsely identified as statin-intolerant with inappropriate drug discontinuation [19].

Previous studies have identified a strong association between a non-synonymous coding single-nucleotide polymorphism, rs4149056, in the *SLCO1B1* gene, and the risk of SIM [20-22]. To manage the risk of SIM, Wilke et al. proposed preemptive genetic testing of

SLCO1B1 gene variants prior to statin initiation to identify at-risk patients [23]. However, subsequent studies have shown no direct evidence for the clinical utility of initiating statin prescriptions guided by *SLCO1B1* genetic testing [24, 25]. As CVE rates are much higher than serious myositis and rhabdomyolysis, reducing statin usage, guided by the *SLCO1B1* genotype may result in net harm [25].

An alternative pharmacogenomics (PGx) test development effort for SIM is being pursued by researchers at the Montreal Heart Institute funded by Genome Canada and Genome Quebec (Grant number: 4530) [26, 27]. The goal of this research is to develop a diagnostic tool for SIM based on personalized CK values, which differs from the preemptive *SLCO1B1* genetic testing strategy to predict *a priori* an individual's risk of SIM [23]. The rationale for this hypothetical PGx test strategy is that patients at high CV risk and in need of statin therapy should be treated until they experience musculoskeletal pain (MSP). This PGx test strategy aligns with the current consensus that high CV risk patients should be treated with a statin while proper management of statin intolerance is investigated to minimize the potential harm of discontinuing therapy. For the subgroup of patients experiencing MSP, the hypothetical PGx test would provide a tool to help physicians interpret CK values and, more importantly, help patients adhere to therapy when test results are negative (no SIM).

The objectives of this article are to 1) compare our previously published Markov and discrete event simulation (DES) approaches for evaluating the economic value of the hypothetical PGx test for SIM in patients initiating a statin in secondary CV prevention [28, 29]; and 2) discuss the implications of our findings for future economic evaluations of diagnostic tests and the place in therapy of such tests.

2 Cross-Validation

2.1 Markov and DES Models

We recently developed two models (Markov and DES) to assess the potential economic value of a hypothetical PGx test for diagnosing SIM in patients having initiated a statin in secondary CV prevention. Although full model descriptions are beyond the scope of the

present article, we present a broad overview of the model structures and key differences. The Supplemental Appendix provides additional information on the model inputs [28, 29].

2.1.1 Model Intervention and Comparator

The target population of each model is a cohort at high CV risk initiating a statin after a first-ever CVE consisting of either a stroke or an acute myocardial infarction. Following statin initiation, patients may develop MSP, in which case they will seek advice from their physician. In the intervention environment, physicians based their prescribing recommendations on the PGx test result. In the comparator environment, without a PGx test, all patients with MSP interrupt the statin therapy either in compliance with their physician's recommendation or by not following the recommendation. The models address only MSP-related statin discontinuation as the PGx test does not impact other causes of discontinuation. The perspective was that of provincial payers in Canada.

2.1.2 Test Parameters

As the purpose of the PGx test is to guide the choice to continue statin therapy, its clinical utility, and therefore its economic value, is directly linked to patient adherence to treatment. Economic models should ideally account for choice parameters separately from test accuracy parameters; however, our models were developed during the pre-development stage and no evidence-based data existed to inform the parameters of the targeted PGx test for SIM. We therefore opted to use a broad interpretation of test parameters that include physician prescribing recommendations and patient adherence decisions. We contend that, in the context of an early-stage economic evaluation of a hypothetical PGx test, the broad interpretation of test parameters provides valuable information to stakeholders. In health outcomes terms, a patient choosing to discontinue statin therapy following a true negative test result (no SIM) is equivalent to a false positive test result leading to statin therapy interruption. These two situations will lead to identical costs and quality-adjusted life years (QALYs).

2.2 Key Model Differences

Although both models shared the same objective, they differed in structure and inputs. **Figure 1** and **Figure 2** present the Markov health state and DES model structures, respectively. **Table 1** presents the key differences between the models.

2.2.1 Differences related to DES survival curves

2.2.1.1 Starting Age

We opted to develop the DES model based on a comprehensive literature search to obtain survival curves and cumulative incidence risk functions for all model events. This choice implied the DES model is not a mere replication of the Markov model. We built the DES model using estimated time-to-event functions derived from digitized published graphics [29].[xiv]

The Markov model simulated a cohort of patients 55 years of age based on the Scandinavian Simvastatin Survival Study (4S) study survival curves (i.e., average 58 years of age) [30]. The DES model simulated a cohort of men and women 65 years of age, representative of patients captured in the estimated stroke-related survival curves in Jones et al. (i.e., average 67 years of age in thrombotic group) [31]. Thus, patients in the DES model were older. The age difference was also reflected in the statin efficacy parameters. Statin relative risk reduction parameters were based on patients <60 years of age in the Markov model, and ≥60 years of age in the DES model, which resulted in a lower protection effect of statin therapy [30].

2.2.1.2 Statin Interruption

In the Markov model, we assumed patients interrupting statin therapy due to MSP would resume therapy after experiencing a second CVE to reduce the risk of having a third

[xiv] The Supplemental Appendix from Mitchell et al. (2018) provides detailed methodological information on the estimated time-to-event functions and the formula used to adjust time-to-event for statin interruption [130].

CVE[xv]. Our assumption was based on expert opinion that, after a second CVE, patients would fear having a third CVE more than rhabdomyolysis. Patients with SIM incur disutility from myopathy and are at risk of rhabdomyolysis. In the DES model, we assumed the statin interruption is permanent due to data limitations (see Supplemental Appendix [29]).

2.2.1.3 Third CVE

In the DES model, we assumed that simulated patients die on the occurrence of a third CVE due to the absence of evidence-based data. This assumption has limited impact on the results as less than 5% of simulated patients had three CVEs in the model. In the Markov model, patients are always at risk of having a CVE because patient CVE history is not recorded.

2.3 Models Results Comparison

In probabilistic sensitivity analyses, the Markov and DES results favored the PGx test strategy in ≥90% of simulations with a payer willingness-to-pay (WTP) as low as CAN$6150 and CAN$12000 per QALY, respectively. Thus, even though the models differed in key elements, both models led to the same conclusion from a provincial payer perspective as these values are well below commonly reported WTP thresholds in Canada [32].

DES models are more complex to build and are often used when economic evaluations must account for constrained resources (e.g., waiting lists) or agent interactions (e.g., infectious disease) [33-35]. Not surprisingly, the DES model proved much more laborious than the Markov model for several reasons, including data requirements, programming, auditing, and validation. Moreover, to achieve numerical stability, the DES model simulates 60,000 patients, while the cohort Markov model simulates an average patient. This difference translated into significantly more computer processing time for the DES model. When generating the test result matrix for scenario analyses, the processing time

[xv] The first model CVE corresponds to patients second CVE as patients enter the model initiating a statin after their first-ever CVE.

was 96 hours for the DES model and one hour for the Markov model. Considering the Markov and DES models yielded similar results, we conclude this cross-validation favours the Markov model for the economic evaluation of the PGx test.

3 Economic Value of a PGx Test for Statin-Induced Myopathy

3.1 Importance of Assessing Consequences of Test Errors

Test sensitivity and specificity (i.e., accuracy), and especially the clinical and economic consequences of false positive (FP) and false negative (FN), outcomes are key elements in an economic evaluation [36-39]. Ideally, a diagnostic test would be perfect; however, in practice there is a trade-off between high sensitivity and high specificity [38, 40, 41]. Selecting appropriate cut-offs for test parameters can be achieved using various methods, mostly based on a receiver operating characteristic analysis [42]. The optimal cut-off point will depend on the clinical consequences of test errors. For instance, if missing a diagnosis leads to severe clinical conditions, then a test with high sensitivity would be needed. However, when a FP result leads to serious consequences, a test with high specificity would become important [43]. Despite the importance of assessing consequences of test errors, many economic evaluations fail to provide information regarding PGx screening tests' specific value when evaluating companion diagnostic tests [44].

In the context of a PGx test for SIM, including physician/patient behavioural responses plays an important part in assessing the economic value of the test. Paulden et al. assessed the economic value of the 21-gene breast cancer assay using evidence-based parameters for both the diagnostic test and the behavioural responses [45]. However, in the absence of evidence-based parameters for our hypothetical PGx test, we posit that assessing the economic value of test parameters using a broad interpretation of test performance that includes physician and patient responses to the diagnostic results is crucial. This is especially important in prevention therapies where patient adherence is problematic [3, 46-48].

In our economic evaluation, we analyzed the impact of varying the PGx test parameters over the complete range of test performance parameters (i.e., false-positive rates [FPRs] and false-negative rates [FNRs] ranging from 0% to 100%) to characterize the cost of test errors.[xvi] The consequences of a FP test result would be interrupting the statin therapy in the absence of SIM leaving patients at increased risk of a CVE. On the other hand, the consequences of a FN test result for patients would be to continue statin therapy despite having SIM. While these patients are at risk of rhabdomyolysis, they are also benefitting from the statin protection. In patients at high CV risk, CV risk reduction from statin outweighs the extremely low risk of rhabdomyolysis.

Figure 3 (Panel A) presents the DES model scenario analysis results using incremental net monetary benefit (INMB)[xvii] values, assuming a payer WTP threshold of CAN$50000/QALY. The extreme corners on the diagonal of this matrix (top left and bottom right) show the INMB values of a perfect test and a totally inaccurate test assuming perfect life-time patient adherence to statin therapy based on the test result.

We could have limited the economic assessment to a restrained plausible range of FNR and FPR values; however, this approach would have failed to fully characterize the consequences of FP and FN test outcomes. Namely, we found that a totally inaccurate test with a FNR of 100% would still yield a positive INMB at a low WTP threshold of CAN$10000/QALY. This result was surprising. Obviously, a totally inaccurate PGx test would have no clinical value. Furthermore, this result assumes that physicians base their treatment recommendations exclusively on the test result knowing it is inaccurate and that all patients with a FN test result fully adhere to statin therapy, which is not plausible. Nevertheless, this unexpected result proved important to understanding the economic

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[xvi] With modern technology, it is straightforward to design computer programs to assess the complete matrix of results across all test parameters. In most cases, the results will indicate the minimal combinations of test parameters required to be cost-effective.

[xvii] The INMB measure expresses the excess value for payer when the WTP for a QALY is known. The INMB is expressed as INMB = ΔQALYs times WTP - ΔCosts. A positive INMB value represents a monetary gain for the payer considering how much is willing to pay for an additional QALY. Similarly, a negative INMB value represents a monetary loss.

impact of risk imbalance between CVE risk reduction and the extremely low risk of rhabdomyolysis with statin therapy. Although rhabdomyolysis is a serious condition, in patients at high CV risk, the CV risk largely outweighs the extremely low rhabdomyolysis risk. Accordingly, our results suggest that tests with high specificity would be favoured as test errors leading to statin interruption (FP) would have higher expected CVEs. This can be seen in **Figure 3** (Panel A) where the INMB values decrease with an increase in the FPR while the INMB values increase with an FNR increase. We found that an imbalance in CVE risk versus rhabdomyolysis risk in our CV high-risk patient population explains why a totally inaccurate PGx test would yield a positive INMB. **Table 2** shows the 10-year CVE risk with and without statin therapy. Over a 10-year period, statin therapy reduces the CVE risk by 6.6%, corresponding to an annual risk reduction of 0.68%. Statin-related rhabdomyolysis rates reported in the literature range from 1 to 19 cases per 10,000 patient-years [8, 10]. In our models, we assumed a rate of rhabdomyolysis of 4.64 per 10,000 patient-years, corresponding to an annual risk of 0.05% [49]. Hence, the annual CVE risk on statin therapy is almost 15 times greater than the annual risk of rhabdomyolysis. In addition, mild to moderate myopathies are not costly to manage. Typically, muscle symptoms are completely reversible and CK activity decreases within a few weeks after statin discontinuation [50-52]. Furthermore, we assumed the PGx test would not be used to diagnose rhabdomyolysis. Rhabdomyolysis is a severe form of muscle damage associated with extremely high CK levels with myoglobinemia and/or myoglobinuria [53] which can be diagnosed with currently available diagnostic tools. To illustrate the impact of the risk imbalance, we conducted scenario analyses assuming the 10-year rhabdomyolysis risk was similar to the CVE risk. Using data from **Table 2**, we selected two scenarios: 10-year risk of rhabdomyolysis set to 20% (Panel B) and 30% (Panel C). The shaded area in **Figure 3** indicates negative INMB values. Whereas only one single combination of FPR and FNR yielded a negative INMB value when assuming the default risk of rhabdomyolysis (Panel A), many more combinations yielded negative INMB values when the risk of rhabdomyolysis increased (Panels B and C). In these scenario analyses, the benefits associated with statin protection do not outweigh the reduced quality of life associated with myopathy symptoms and the increased likelihood of rhabdomyolysis. Another noteworthy point is, when the risk of CVE substantially outweighs the risk of

rhabdomyolysis, the INMB values increase when holding the FPR fixed while increasing the FNR. This indicates the payer's net benefit increases as the FNR increases, as more patients continue on statin therapy. This pattern no longer holds true when the 10-year risk of rhabdomyolysis is calibrated within the CVE risk range in patients at high CV risk. In this case, the INMB values decrease when holding the FPR fixed while increasing the FNR, indicating the payer's net benefit decreases as more patients with SIM continue on statin therapy with a penalized quality of life due to myopathy symptoms and the increased risk of rhabdomyolysis.

Selecting a patient population at high CV risk led to a situation where the economic evaluations favored maintaining patients on statins regardless of the test results. This result is in line with the guidelines on the management of statin intolerance management in patients at high CV risk: these patients should be maintained on statin therapy with possibly a statin molecule switch and/or dose reduction [14]. In primary CV prevention patients, the risk imbalance between the CV events and rhabdomyolysis would have been significantly reduced. This would have reduced the value of test leading to combinations of test parameters with negative INMB values.

3.2 Role of PGx-Guided Statin Therapy

There are two possible PGx testing strategies for SIM:

- To identify patients at risk of developing SIM prior to statin initiation; or
- To diagnose SIM in patients who have initiated a statin.

SLCO1B1 genotyping has been proposed for managing the risk of SIM, especially in patients receiving a high dose of simvastatin [23, 54]. The purpose of the *SLCO1B1* genotyping test is to inform physicians and patients, prior to statin initiation, on the potential risk of developing a myopathy. On the other hand, the objective of the PGx test in development is to assist physicians and pharmacists to diagnose SIM in patients presenting with MSP.

Potential harms and benefits of treatment strategies must be weighed when evaluating the risk–to–benefit balance of health technologies. As we discussed in Section 3.1, in patients

at high CV risk, the CV risk largely outweighs the rhabdomyolysis risk. Not surprisingly, no evidence supports an *a priori* testing strategy based on *SLCO1B1* genotyping and, therefore, this test is not recommended to help in the decision to initiate statin therapy; its use is even questioned in the literature and current guidelines [14, 25, 55-57].

We believe an accurate PGx test for the diagnosis of SIM could be part of the practical tool set within the current dyslipidemia [58] and statin-intolerance guidelines [14]. However, to have clinical utility, the PGx test must:

- be highly accurate; and
- successfully guide patients to adhere to their statin therapy in the absence of SIM.

As our model indicated, a highly accurate PGx test would yield a positive INMB for payers. However, even with a highly accurate PGx test, if patients with test results indicating no SIM choose to discontinue statin therapy, this would be equivalent in health outcomes to an increase in the FPR. For instance, if we assume the test has 90% sensitivity and specificity (FNR=FPR=10%) and that we expect 50% of patients would discontinue the statin regardless of the test results, then we can assess the INMB test value using **Figure 3** (Panel A). Without statin discontinuation, the PGx test INMB=CAN$35182; however, with statin discontinuation, the FPR increases to 55% thereby reducing the INMB value somewhere between CAN$19806 and CAN$15610. Therefore, the economic value of the test depends on patient adherence to treatment, a central issue for prevention drugs, such as statins.

The economic value of the test is intrinsically linked to its ability to guide patients in need of statin therapy to comply with treatment recommendations. As the 2016 Canadian Cardiovascular Society Dyslipidemia Guidelines state: “statin intolerance and adverse effects remain of great interest in the media and in lay materials readily available to patients.” [58] In the real-world setting physicians and patients would not adhere to the test results of a highly inaccurate test. The PGx test for SIM would only provide value for payers if it succeeds at convincing patients (with no SIM) who would otherwise discontinue the statin therapy, to continue the statin therapy based on a negative test result.

3.3 Changes in Treatment Options

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are a new class of lipid lowering drugs available for patients with dyslipidemia. These drugs can lower LDL-C levels 50%-60% more than statin therapy [59, 60]. In long-term studies, PCSK9 inhibitors reduced major CVEs by close to 50% [61-63]. The products (alirocumab and evolocumab) within this new class are very expensive compared to statins. The British Columbia PharmaCare Formulary lists the annual cost of these new drugs at CAN$7844 to CAN$10862 per year, almost 80-fold higher than generic statins (annual cost range: CAN$96 to CAN$138) [64].

In Canada, coverage type for these new drugs is still under review [64], and are not currently indicated for statin-intolerant patients [65, 66]. If the indications change to include statin-intolerant patients, the landscape assessment for the PGx test would also change. Compared to a situation where physicians could prescribe a PCSK9 inhibitor based on the current diagnostic methods, an accurate PGx test with a low FPR in patients with mild to moderate statin intolerance would provide added value.

In our models, a FP test result corresponds to the without PGx test strategy as we assumed that without a PGx test all patients with MSP interrupt statin therapy. If a FP result triggers PCSK9 therapy initiation, this would significantly alter the evaluation and the exact impact would depend on the relative efficacy of PCSK9 inhibitors to prevent CVEs compared to statins, patient adherence to PCSK9 inhibitors, and the ability of the PGx test to accurately identify patients with SIM.

4 Strengths and Limitations

Our evaluations were conducted as an early assessment of the economic value of a hypothetical PGx test for SIM as part of a research program investigating the development of personalized CK values. The models were developed independently of the PGx test development program. Although we could have conducted our analyses assuming "reasonable" test performance parameters, we chose instead to characterize the consequences of all possible FPR and FNR test outcomes. By assessing the complete range

of test performance parameters, the economic evaluations are translatable to other PGx tests. We believe these economic analyses provide valuable information for researchers, manufacturer, and investors. As this test does not yet exist, our evaluations assess the potential economic value for developing a PGx test for SIM.

Our results are not generalizable to all contexts. The economic value of the test was assessed for patients at high CV risk. The reason for selecting this patient group is it reflects patients most likely to benefit from statin therapy. Changing the target population to include primary prevention patients would reduce the PGx test value. A primary prevention population would have a lower risk imbalance between CVE and rhabdomyolysis. Reducing this risk imbalance would reduce the value to payers.

The economic models assumed that in the alternative strategy (i.e., without the PGx test) patients would interrupt statin therapy in the event of MSP. Although, one can argue this does not represent clinical practice, we believe it represents the subgroup of patients who would otherwise interrupt statin therapy. However, if the PGx test was used to guide statin-intolerant patients toward treatment with expensive PCSK9 agents, this would require new economic analyses because a FP test result erroneously indicating statin intolerance would mean these patients could be offered a PCSK9 agent. In this case, understanding the consequences of FPR test results would become highly valuable for payers.

5 Conclusion

The Markov and DES models evaluating a hypothetical PGx test for SIM in secondary CV prevention yielded similar results from a provincial payer perspective. When assessing the economic value of a diagnostic test in early development, evaluating the complete spectrum of test parameters is more important than the modeling technique. A broad interpretation of test parameters allows physician and patient responses to the test results to be included in the analysis and accounts for patient adherence to treatment, a central issue for prevention drugs, such as statins. The clinical use of an accurate PGx test for SIM would be to guide patients with MSP unrelated to statin therapy to adhere to treatment. An accurate PGx test for SIM would be a valuable addition to complement monitoring CK levels as part of the CCWG CDR protocol for managing statin adverse effects and

intolerance. However, the value of this test is highly dependent on its ability to convince patients with no SIM to adhere to their life-time statin therapy.

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7 Figures

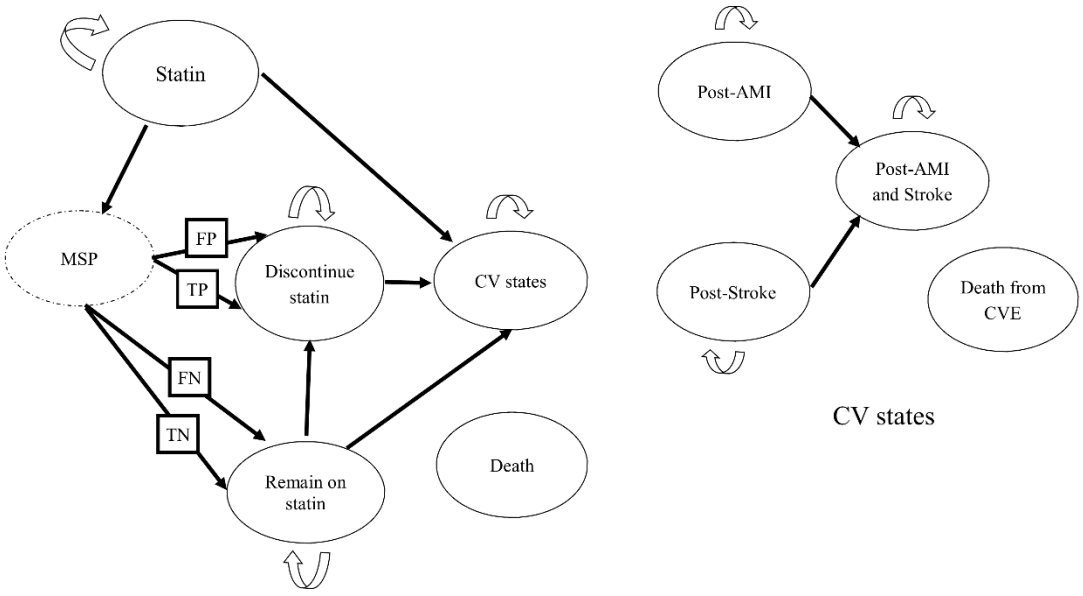

Figure 1 Representation of the Markov health state model. High-risk CV patients enter the model initiating a statin in secondary prevention. The model has one initial statin state; one transitory state, MSP; two discontinue-statin states (true- and false-positive); two remain-on-statin states (true and false-negative); four CV states (post-AMI, post-stroke, post-AMI and stroke, and death from CV); and background death. Background death can occur from any states including the CV states whereas CV event death can only occur from any of the CV states. The model compares two strategies, with and without a PGx test to diagnose statin-induced myopathies. We assumed that without a PGx test, all patients discontinue the statin therapy. With a PGx test we assume that physicians base their prescribing recommendations on the test results and that patients adhere to the recommendation. Only patients experiencing MSP are evaluated for statin-induced myopathies. Patients with MSP are redirected to discontinue-statin states for true- and false-positive or remain-on-statin states for true- and false-negative states.

AMI acute myocardial infarction, *CV* cardiovascular, *CVE* cardiovascular event, *FN* false negative, *FP* false positive, *MSP* musculoskeletal pain, *PGx* pharmacogenomics, *TN* true negative, *TP* true positive.

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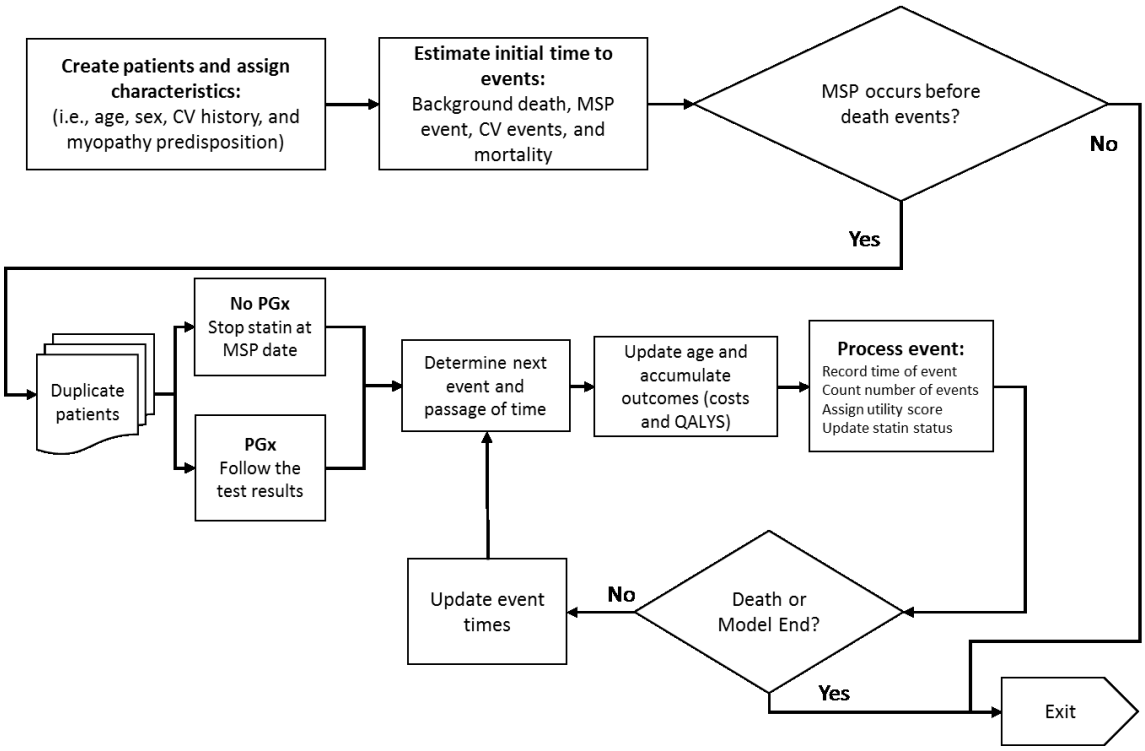

Figure 2 Representation of the DES model. Patients enter the model initiating a statin for secondary CV prevention. The model first assigns patient characteristics, including predisposition for statin-induced myopathy that allows us to identify the PGx test performance (i.e., true [false] positive or negative test results). Based on individual patient characteristics, the model calculates the initial sequence of time-to-events. Before processing the patients, the model validates whether each patient was assigned an MSP date occurring before any of the model death events or before the end of the model time horizon. Patients retained in the model are duplicated to each strategy. Patients then progress in the model through the sequence of event-time. Patients accrue costs and QALYs at each passage through the model loop until they die or the end of the model time horizon. CV risk profiles are updated when patients experience simulated CVEs. Statin therapy status is updated once in the model, when patients experienced MSP. Based on the myopathy predisposition of each patient, the PGx test performance is recorded.

CV cardiovascular, *DES* discrete event simulation, *MSP* musculoskeletal pain, *PGx* pharmacogenomics, *QALY* quality-adjusted life year

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Panel A Default rhabdomyolysis risk 10-year risk 0.46%

Perfect Test

False Negative Rate \ False Positive Rate	0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
0%	39,619	35,160	31,462	27,735	23,698	19,373	15,469	12,516	7,336	3,907	-143
10%	39,800	35,182	32,216	28,116	24,472	19,806	15,610	11,950	7,588	4,494	545
20%	40,000	35,430	31,240	27,968	24,174	20,532	16,204	12,429	7,425	4,223	906
30%	40,125	36,863	32,277	28,900	25,605	20,941	17,003	13,120	9,423	5,408	1,192
40%	40,071	36,188	32,962	27,912	24,808	21,316	16,804	12,894	9,538	5,476	1,508
50%	41,706	38,166	33,679	29,672	24,702	21,861	17,655	13,430	9,393	5,861	1,708
60%	40,877	37,006	33,840	30,208	25,202	22,259	18,197	14,745	9,833	5,976	1,638
70%	42,457	38,392	33,655	30,407	25,837	22,181	17,995	13,743	10,089	6,698	1,898
80%	42,510	38,508	34,669	29,837	26,311	22,982	18,913	14,421	11,157	7,190	2,461
90%	43,316	39,098	35,141	30,469	27,553	23,175	19,019	15,319	12,207	7,589	3,545
100%	43,363	39,247	35,405	32,026	27,547	23,396	19,696	16,154	12,196	7,720	3,221

Worst test

Panel B Rhabdomyolysis 10-year risk calibrated to 20%

Perfect Test

False Negative Rate \ False Positive Rate	0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
0%	38,951	34,397	31,624	27,697	24,000	19,167	15,870	12,055	7,240	3,410	35
10%	34,465	30,038	25,029	20,785	18,663	14,729	9,989	6,217	3,921	-1,308	-5,761
20%	29,213	24,876	21,959	17,840	13,585	7,778	3,259	2,924	-2,170	-5,960	-11,075
30%	23,126	21,238	17,540	11,286	7,204	1,886	-2,857	-3,818	-8,963	-13,016	-15,147
40%	17,284	11,135	8,448	6,231	-424	-2,280	-5,540	-10,419	-14,339	-17,978	-21,633
50%	13,329	7,917	5,226	436	-4,478	-7,256	-10,334	-15,407	-19,415	-20,269	-27,686
60%	8,007	3,424	-1,237	-4,273	-9,128	-14,522	-17,696	-22,824	-23,282	-29,710	-32,552
70%	1,157	-3,604	-5,604	-8,709	-12,751	-16,644	-20,489	-25,480	-32,612	-33,113	-39,135
80%	-456	-7,107	-9,320	-13,456	-19,262	-21,591	-25,201	-26,881	-33,192	-39,785	-42,758
90%	-6,387	-16,432	-13,903	-18,246	-25,657	-27,079	-35,838	-34,967	-40,423	-47,984	-50,169
100%	-15,699	-24,060	-21,925	-30,383	-32,766	-34,100	-37,188	-43,425	-48,156	-45,314	-52,780

Worst test

Panel C Rhabdomyolysis 10-year risk calibrated to 30%

Perfect Test

False Negative Rate \ False Positive Rate	0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
0%	38,485	35,228	31,272	27,265	23,431	19,315	15,957	11,847	7,604	2,834	148
10%	32,484	28,814	23,782	20,628	16,857	12,708	9,241	3,712	152	-3,613	-8,374
20%	24,647	20,635	16,015	11,995	8,267	5,747	1,393	-2,614	-8,348	-11,239	-14,542
30%	15,201	11,224	9,394	5,174	373	-3,598	-7,261	-11,848	-16,286	-20,204	-22,538
40%	7,866	2,508	2,103	-4,571	-8,230	-12,373	-14,864	-19,433	-23,156	-27,950	-32,578
50%	-337	-3,759	-8,726	-10,368	-14,372	-19,561	-22,866	-27,371	-31,235	-37,218	-39,423
60%	-5,765	-10,608	-13,870	-19,979	-24,069	-25,541	-29,778	-33,419	-39,749	-43,081	-45,618
70%	-14,563	-18,220	-19,815	-27,894	-29,997	-33,969	-36,545	-43,706	-46,863	-53,259	-55,432
80%	-25,455	-25,148	-29,991	-34,330	-38,010	-38,635	-47,978	-54,851	-51,702	-58,484	-64,534
90%	-32,360	-36,523	-41,012	-45,296	-44,467	-51,609	-55,732	-60,465	-63,538	-68,425	-71,277
100%	-43,083	-44,107	-48,773	-52,533	-52,668	-64,009	-63,425	-66,274	-72,771	-77,538	-81,201

Worst test

Figure 3 Matrices of INMB results according to PGx test performance parameters (FPR and FNR). Using the DES model, we conducted scenario analyses varying the PGx test FPR and FNR from 0% to 100% assuming an arbitrary WTP of $50,000/QALY. Arrows indicate worsening of PGx test parameters. The "Perfect Test" is located at the top left corner of the matrices (FPR and FNR are 0%); the "Worst Test" is located at the bottom right corner (FPR and FNR are 100%). Dark grey shaded cells show test parameter

combinations favoring the strategy without the PGx test. White cells indicate when the PGx test provides excess value for the payer. **Panel A** shows the INMB results assuming a 10-year rhabdomyolysis rate of 4.64 per 10,000 person-years (i.e., 10-year risk equal to %0.46) [49]. Although rhabdomyolysis is a serious condition, in patients at high CV risk, the CV risk largely outweighs the extremely low rhabdomyolysis risk. Accordingly, our results suggest that tests with high specificity would be favored as test errors leading to statin interruption (FP) would have higher expected CVEs. This can be seen in **Figure 4** (Panel A) where for similar increases FPR and FNR, the INMB decreases more with increases in FPR than FNR. **Panels B and C** show the results assuming higher rhabdomyolysis risk rates calibrated within CVE risk range, with 10-year risks equal to 20% and 30% respectively. Panel A shows that increasing the FNR while holding the FPR fixed generates more INMB value for the payer. Panels B and C show this result no longer holds true when the 10-year rhabdomyolysis risk is increased to a value comparable to the 10-year risk of CVE.

DES discrete event simulation, *FNR* false-negative rate, *FPR* false-positive rate, *INMB* incremental net monetary benefit, *PGx* pharmacogenomics, *QALY* quality-adjusted life year, *WTP* willingness to pay.

8 Tables

Table 1 Comparison between Markov and DES models

Model characteristics	Markov	DES
Time horizon	20 years	Lifetime (45 years)
Cycle length	Monthly	Continuous time
Perspective	Canadian provincial payer	Same as Markov model
Discount rate*	5% [0%,3%] [67]	1.5% [0%, 3%] [68]
Costs	2014 CAD	Inflated to 2016 CAD
Health utilities	Uses a weighted average gender-specific utilities from van Kempen et al. [69] for asymptomatic elderly, post-AMI and post-stroke events Assumed the disutility of having both stroke and AMI equivalent to stroke disutility Assumed rhabdomyolysis disutility equivalent to stroke disutility	Stable coronary heart disease utility and CVE disutilities are based on Sullivan et al. [70] Assumed the rhabdomyolysis disutility is equivalent to the relative utility change for patients with eGFR<15 + Dialysis compared with patients with eGFR≥60 in Gorodetskaya et al. [71]
Patient age	Assumed 55 years	Assumed 65 years based on patient characteristics of estimated survival curves
Statin discontinuation		
Type of discontinuation	Only related to MSP	Same as Markov model
Duration of discontinuation	Statin therapy resumed after the first model CVE	Permanent
Model probabilities		
Probability of statin-induced myopathy		
MSP	Assumed a Weibull function calibrated to obtain 40% of patients presenting with MSP within three years of statin initiation	Same as Markov model
Proportion of patients with myopathy	25%	Same as Markov model
CVE		
Type of data	Transition probabilities	Estimated from survival curves
Gender	Non specific	When available from the survival curve
Statin efficacy	4S study statin risk reduction in patients <60 years [30]	4S study statin risk reduction in patients ≥60 years [30]
Mortality		
CVE		
Death following event	Based on transition probabilities from the literature	Based 30-day CV mortality
Increased risk of death	HR (RR) for increased risk of death based on CV history	All-cause mortality based on estimated survival curves from CV studies
Gender	Non specific	When available from survival curves

Model characteristics	Markov	DES
Three CVEs	N/A	Assumed patient dies on third model CVE
Background death		
Source	Canadian life tables	Canadian life tables
Gender	Non specific	Canadian gender-specific life tables

4S Scandinavian Simvastatin Survival Study, *AMI* acute myocardial infarction, *CAD* Canadian dollar, CV cardiovascular, *CVE* cardiovascular event, *DES* discrete event simulation, *HR* hazard ratio, *MSP* musculoskeletal pain, N/A not applicable, *RR* relative risk.

* The DES model was built based on the updated CADTH economic evaluation guidelines which recommend a 1.5% discount rate compared to the 5% value from the previous version[67, 68]. For comparison, we ran the Markov model with the 1.5% discount rate to compare with the DES model. The results obtained were closer to the DES model, further reducing the small discrepancy observed between the published models.

Table 2 10-year risk of a CVE in the DES model

	Without Statin	With Statin	Δ
Patients with a history of AMI			
Risk of AMI recurrence	16.2%	12.1%	-4.1%
Risk of stroke post-AMI	2.5%	1.8%	-0.7%
Total CVE risk	***18.7%***	***14.0%***	***-4.8%***
Patients with a history of stroke			
Risk of stroke recurrence	28.0%	21.4%	-6.7%
Risk of AMI post-stroke	13.9%	10.3%	-3.5%
Total CVE risk	***41.9%***	***31.7%***	***-10.2%***
Model weighted average	**26.3%**	**19.8%**	**-6.6%**

4S Scandinavian Simvastatin Survival Study, *AMI* acute myocardial infarction, *CVE* cardiovascular event, *DES* discrete event simulation.

The table above shows the 10-year CVE risk for patients entering the DES model with either an AMI or a stroke event as their first-ever CVE. The results are presented for patients with and without statin therapy assuming a statin therapy risk reduction of 0.73 based on the 4S study [30]. Thus, on average, patients without statin (with statin) therapy face a 10-year risk of CVE 18.7% (14.0%) with a prior history of AMI and 41.9% (31.7%) with a prior history of stroke.

Chapter 7. Discussion

The objective of this thesis was to explore the economic value of a hypothetical PGx test for statin-induced myopathy as part of the project, *"Personalized medicine strategies for molecular diagnostics and targeted therapeutics of cardiovascular diseases"* funded by Genome Canada and Génome Québec (grant number: 4530) [78, 79]. In the early stages of the thesis, we chose to explore the methodology for conducting the economic evaluation of diagnostic devices without considering the specific details or performance parameters of the test in development. One major reason for this approach was to explore the economic value of a PGx test for statin-induced myopathy from a payer perspective, but also from the perspective of the test developers. The choice to fully characterize the economic consequences of the FPR and FNR of the diagnostic test is a major contribution of this thesis.

7.1 Article I

We developed the Markov model first. It was clear, from initial discussions at the outset of the model's inception, that an economic evaluation of a diagnostic test required assessing the consequences of test errors (i.e., false positives and false negatives). As mentioned in Section 1.5, economic analyses of PGx tests do not address the intrinsic value of the tests [89] and several authors view including test performance parameters in the economic evaluation as essential [87, 90-93]. As the PGx test for statin-induced myopathy was in development, we had no information on the expected performance parameters of the test. We could have reviewed the literature on recently-marketed PGx tests to inform the model with "reasonable" test performance parameters to be expected for regulatory approval; however, we chose another approach.

The first question we attempted to answer was "what is the economic value of a perfect test?" We defined the "Perfect Clinical Environment" as follows (see Section 3.2):

- The PGx test is perfect (i.e., FPR=FNR=0%); and
- Physicians base their prescribing recommendations solely on test results; and
- Patients are fully compliant with the prescribing recommendations of their physicians.

Using this definition of a "Perfect Clinical Environment" allowed us to broadly interpret the test performance parameters, such that they could reflect physician and patient responses to the test results. With this definition, even a perfect test (i.e., FPR and FNR=0%) could be viewed as an imperfect test with (i.e., FPR>0 and/or FNR>0%) if physicians or patients do not adhere to the test results.

When we conducted the scenario analyses on the test parameters for the first article, we decided to perform a matrix evaluation with the complete range of test parameters to fully assess the economic consequences of test errors. At that time, this was purely an academic exercise. However, the results obtained were at first puzzling. We had expected that there would be a combination of FPR and FNR outcomes that would cause the economic value of the PGx test to collapse. The fact that a perfectly inaccurate test still provided economic value was a startling result (see Article I Figure 4). Of course, the notion of a perfectly inaccurate test yielding this result does not make sense. If a totally inaccurate test were developed, then simply reversing the test decision would lead to a perfectly accurate test. This perplexing result initiated a deeper reflection on the purpose of the test and the place in therapy should such a test be developed and marketed. This reflection was developed in Article III where we stressed the importance of assessing the complete range of test parameters and described what the results mean for a PGx test for statin-induced myopathy.

7.2 Article I and Article II Modelling Comparison

7.2.1 Dominance of Markov Models in the Literature

Markov models are the predominant modelling approach for conducting pharmacoeconomic evaluations of health technologies. As shown in **Figure 21**, in the CV literature, DES models remain marginal compared to Markov models, with a share of only 6% of the literature in 2017. There are many reasons that explain this situation. Compared to Markov models, DES models require extensive data and are often developed in expensive specialized software. HTAs do not always have the expertise to review DES models and, therefore, will often require a Markov model developed in Microsoft Excel.

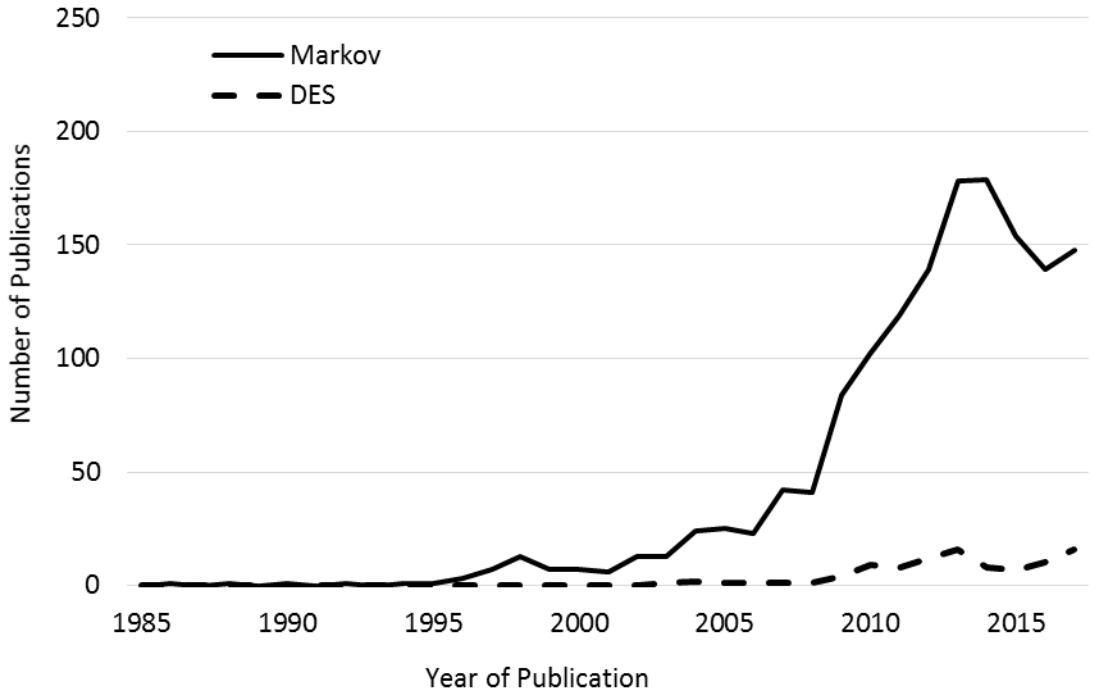

Figure 21 Number of Markov- and DES-related publications since 1985.

7.2.2 Published Comparisons of Markov and Discrete Event Simulation Models

Published comparisons of Markov and DES models tend to suggest that both methods yield similar results [131-135]. Jahn et al. (2016) concluded that the cross-validation between the models was crucial for identifying and correcting programming errors [135]. Simpson et al. (2009) compared a Markov model and a DES model in human immunodeficiency virus (HIV) [136]. They concluded that the DES model had a slight predictive advantage over the Markov model and it also allowed the reporting of more detailed outcomes. Zhou et al. (2016) compared various model approaches in chronic hepatitis C virus, including a Markov cohort model, a Markov microsimulation model, and a DES model [99]. Their DES model was developed by converting transition probabilities into time-to-event. The authors conferred a slight advantage to the Markov model microsimulation approach, although they recognized that the derivation of time-to-event from transition probabilities may not be accurate [99].

Chrosny et al. (2013) compared Markov and DES modelling approaches using computer simulations [137]. They concluded that Markov models introduce biases due to fixed cycle length and half-cycle correction. However, their simulations compared two modelling approaches in the context of perfect information, as their comparison is based on simulation data. In practice, compared to a Markov cohort model, a DES model requires more detailed information to simulate individual patient histories as opposed to the health-state averages required for a Markov model [138, 139]. Another constraint to the adoption of a DES model is that it requires specialized and expensive software with additional computer programming knowledge [138, 140]. Performing scenario and sensitivity analyses in a DES model can also be highly computer intensive, requiring a significant increase in processing time [140].

7.2.3 Key Model Differences Between the Markov and Discrete Event Simulation Models

We developed the DES model as a cross validation of the Markov model [129] while retaining these key elements of the Markov modelling strategy:

- The "Perfect Clinical Environment" (see Section 3.2)
- The PGx test strategy compared to a without PGx test strategy where all patients with MSP have their statin therapy interrupted

Although we could have developed the DES model from the Markov model transition probabilities, as described in Chapter 5, we chose to develop the DES model using published survival curves from the literature. This choice led to some differences between the two models. **Table 12** lists the differences between the two models.

Table 12 Differences between the Markov and DES approaches

	Markov	DES
Patient age	55	65
Gender	Not specific	Gender specific
CVE probability	Transition probabilities	Estimated from survival curves
Statin efficacy	4S statin risk reduction in patients <60 years of age [25]	4S statin risk reduction in patients ≥60 years of age [25]
Statin discontinuation	Statin therapy resumed after a model CVE	Permanent
Discount rate†	5% [0%, 3%] [141]	1.5% [0%, 3%] [88]
Three CVEs	N/A	Patient dies
Costs	2014 CAD	2016 CAD

4S Scandinavian simvastatin survival study, *CAD* Canadian dollar, *CVE* cardiovascular event, *DES* discrete event simulation, *N/A* not applicable.

† We ran the Markov model with the 1.5 discount rate to compare with the DES model. The results obtained were closer to the DES model, reducing the small discrepancy observed between the two published models.

7.2.3.1 Transition Probabilities Versus Time-to-Event

The Markov model [129] was built using transition probabilities obtained from previously published cost-effectiveness models from Erickson et al. (2013) [142] and Wagner et al. (2009) [143]. Although previous DES models have been built by converting transition probabilities into time-to-event functions (Zhou et al. [2016] [99]), we built our DES model using estimated time-to-event functions derived from digitized published graphics. Hence, we conducted an extensive literature search to obtain survival curves and cumulative incidence risk functions for all model events (see Chapter 5).

The Markov model assumed a cohort of patients 55 years of age initiating a statin in secondary prevention. To align the DES simulated patients with the representative patients from the estimated survival curves, we assumed a cohort of patients 65 years of age initiating a statin in secondary prevention. The difference in patient age between the two models was also reflected in the statin efficacy parameters selection. The Markov model statin relative risk reduction parameters were obtained from the 4S estimated in patients <60 years of age, whereas for the DES model we assumed the estimated parameters in patients ≥60 years of age, which results in a lower protection effect of statin therapy [25].

7.2.3.2 Statin Interruption

In the Markov model, patients who interrupt their statin therapy due to MSP resume their statin therapy after experiencing a CVE. As these patients entered the model with a prior CVE, this model event constitutes their second CVE. We assumed that patients have a greater fear of having a third CVE compared to the risk of rhabdomyolysis. For patients with statin-induced myopathy, they incur disutility from myopathy and are at risk of developing a rhabdomyolysis. In the DES model, we assumed that the statin interruption is permanent. This decision was made due to data limitations (see Chapter 5). In our models, we did not adopt the complex statin-intolerance CDR management advised by the CCWG [58]. This would have been highly complex to model and would have required additional assumptions. Furthermore, the CCWG Guidelines indicate that CDR is seldom met in clinical practice leading to many patients who are in need of statin therapy being untreated [48]

7.2.3.3 Mortality

Due to the absence of evidence-based data, we assumed that patients experiencing a third CVE in the DES model would die on the date of the CVE. This assumption has limited impact on the model results for two reasons. First, less than 5% of the patients in the model experienced three CVEs (see Article II Table 3). Second, the impact is similar for the two strategies, 4.2% with the PGx test and 4.1% without the PGx test. The Markov model does not use this assumption because patient CVE history is not recorded. In the Markov model, patients can move between CV health states, but they are always at risk of having a CVE.

7.2.4 Impact of the Change in Discount Rate and Usage of Incremental Net Monetary Benefit

The Markov model was developed using the 2006 CADTH Economic Guidelines that recommended using a 5% discount rate for costs and health benefits [141]. The updated version of the guidelines was released in March 2017 [88]. In the new version, CADTH changed the recommended discount rate to 1.5%. As the DES model was developed after the release of the new guidelines, we used the updated guidelines.

In addition, the test performance scenario analyses for the DES model reported incremental net monetary benefit (INMB) values for two pre-specified payer's willingness-to-pay (WTP) per quality-adjusted life year (QALY) thresholds, instead of presenting incremental cost-utility ratio (ICUR) values. Although the INMB method requires specifying a WTP threshold value, we believe that the INMB method has some advantages over ICURs. The equation below shows the calculation for ICURs:

$$ICUR = \frac{\Delta\ Costs}{\Delta\ QALYs} \quad (7)$$

The equation below shows the INMB equation. As demonstrated, this is a reorganization of the ICUR.

$$INMB = \Delta QALYs \times WTP - \Delta Costs \quad (8)$$

The interpretation of the INMB is straightforward. For a given WTP threshold value, payers will benefit from the new strategy when the INMB value is positive.

Typically, we would assess whether the ICUR value is below a payer's WTP per QALY threshold. This assumes that the ICUR is in the northeast quadrant of the cost-effectiveness plane; that is, the new strategy is costlier and provides additional QALYs compared to the old strategy. This is not always the case. As the ICUR is a ratio, it will be positive when the Δ Costs and Δ QALYs both have the same sign; either positive or negative.

Table 13 presents four scenarios comparing the new and old strategies. In all scenarios, the old strategy costs and QALYs are identical. We varied the costs and QALYs of the new strategy to understand the relationship between the quadrants of the cost-effectiveness plane, the ICUR, and the INMB. **Figure 22** shows the cost-effectiveness plane for four scenarios presented along with the dotted line representing a WTP of $50,000 per QALY.

Table 13 Example of ICUR in the northeast and southwest quadrant assuming a payer's WTP of $50,000 per QALY

	Cost	Δ Cost	QALY	Δ QALY	ICUR	INMB	Decision
Northeast quadrant							
Scenario A							
New strategy	$30,000		7.0				
Old strategy	$20,000	$10,000	6.0	1.0	$10,000	$40,000	ICUR <50,000$ Select the new strategy
Scenario B							
New strategy	$30,000		6.1				
Old strategy	$20,000	$10,000	6.0	0.1	$100,000	-$5,000	ICUR >50,000$ Reject the new strategy
Southwest quadrant							
Scenario C							
New strategy	$2,000		5.7				
Old strategy	$20,000	-$18,000	6.0	-0.3	$60,000	$3,000	ICUR >50,000$ Select the new strategy
Scenario D							
New strategy	$2,000		4.0				
Old strategy	$20,000	-$18,000	6.0	-2.0	$9,000	-$82,000	ICUR <50,000$ Reject the new strategy

ICUR incremental cost-utility ratio, *INMB* incremental net monetary benefit, *QALY* quality-adjusted life year, *WTP* willingness-to-pay.

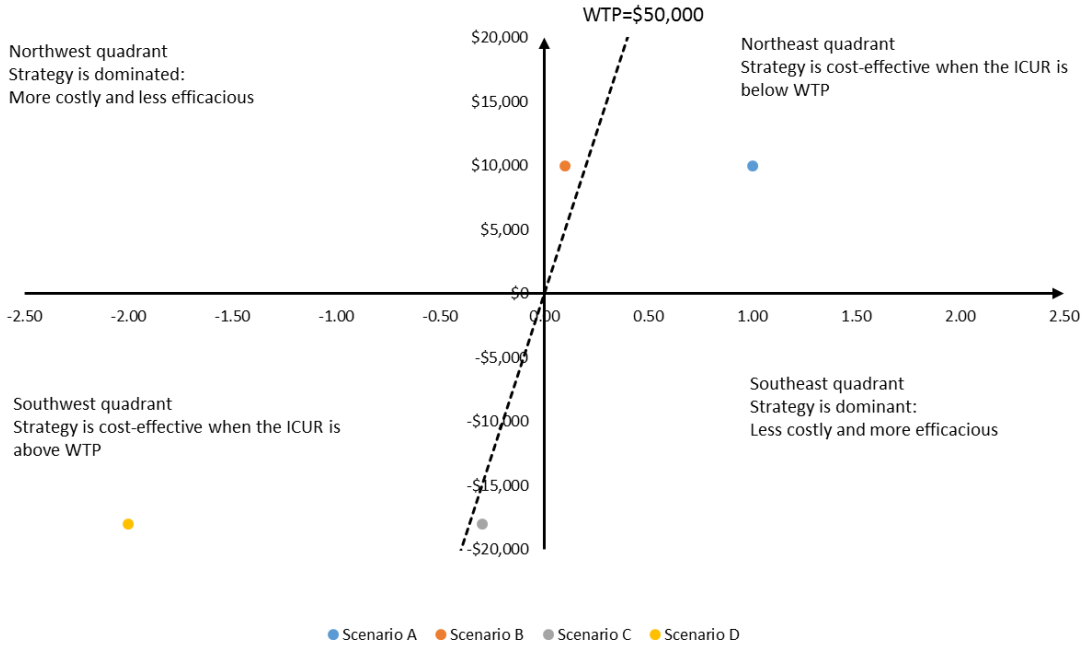

Figure 22 The cost-effectiveness plane

ICUR incremental cost-utility, *WTP* willingness-to-pay.

In the northeast and southwest quadrants, ICUR values are positive; however, the relationship with the payer's WTP is completely reversed. In the northeast quadrant, a strategy is cost effective when the ICUR is *below* the WTP threshold: the new strategy is costlier and provides additional gains in QALYs compared to the old strategy. In **Figure 22**, Scenario A and Scenario B are located within the northeast quadrant. In this quadrant the new strategy is favoured if the ICUR is below the WTP. As can be seen in the figure, Scenario A provides more additional QALY gains than Scenario B. Scenario A has an ICUR of $10,000, which is below the WTP. In other words, in the northeast quadrant, the new strategy is favoured when the slope measured by the ICUR is flatter or equal to the slope represented by the WTP dotted line.

In **Figure 22**, Scenario C and Scenario D are located within the southwest quadrant. In this quadrant, the new strategy is favoured if the ICUR is above the WTP. In this quadrant, the new strategy is less costly than the old strategy, but it is also less efficacious. Obviously, payers will be more inclined to choose the new strategy as the savings it generates increase while the loss in QALYs decreases. As the Δ QALYs corresponds to the ICUR denominator, for a fixed Δ

Costs, the ICUR will increase as the loss in QALYs decreases to zero. Scenario C and Scenario D share a Δ Costs of -$18,000, but the loss of QALYs is -0.3 in Scenario C and -2 in Scenario D. Scenario C has an ICUR of $60,000 compared to Scenario D, which has an ICUR of $9,000. Hence, Scenario C has an ICUR above the $50,000 WTP threshold, but it is the cost-effective option between Scenario C and D.

Table 13 presents the detailed information with the INMB value and the decision rule for a WTP of $50,000. As shown in the table, positive INMB values are indicative of the payer's decision.

The Markov model results for test performance parameters were presented using ICUR instead of the INMB, which was used for the DES model. In addition, the Markov model used a 5% discount rate, while the DES model used a 1.5% discount rate. To compare the Markov model scenario analyses results with those from the DES model, we repeated the test performance scenario using the INMB method and compared the impact of the change in discount rate. **Figure 23** and **Figure 24** show the results of the test performance scenario analyses assuming a payer's WTP threshold of $10,000 and $50,000 per QALY, respectively. The grey shaded zones in the figures highlight cases where the INMB values are negative. As can be observed, the change in discount rate has a marginal impact on the model results (see Article I Figure 4).

Panel A Discount rate = 5%

Perfect Test / False Negative Rate	False Positive Rate: 0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
0%	$2,389	$2,139	$1,890	$1,640	$1,391	$1,141	$892	$642	$393	$143	-$107
10%	$2,410	$2,161	$1,911	$1,662	$1,412	$1,163	$913	$664	$414	$165	-$85
20%	$2,432	$2,183	$1,933	$1,683	$1,434	$1,184	$935	$685	$436	$186	-$63
30%	$2,454	$2,204	$1,955	$1,705	$1,456	$1,206	$957	$707	$457	$208	-$42
40%	$2,475	$2,226	$1,976	$1,727	$1,477	$1,228	$978	$729	$479	$230	-$20
50%	$2,497	$2,247	$1,998	$1,748	$1,499	$1,249	$1,000	$750	$501	$251	$2
60%	$2,519	$2,269	$2,020	$1,770	$1,521	$1,271	$1,021	$772	$522	$273	$23
70%	$2,540	$2,291	$2,041	$1,792	$1,542	$1,293	$1,043	$794	$544	$294	$45
80%	$2,562	$2,312	$2,063	$1,813	$1,564	$1,314	$1,065	$815	$566	$316	$67
90%	$2,584	$2,334	$2,085	$1,835	$1,585	$1,336	$1,086	$837	$587	$338	$88
100%	$2,605	$2,356	$2,106	$1,857	$1,607	$1,358	$1,108	$858	$609	$359	$110

Worst test

Panel B Discount rate = 1.5%

Perfect Test / False Negative Rate	False Positive Rate: 0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
0%	$3,318	$2,975	$2,632	$2,289	$1,946	$1,603	$1,260	$917	$574	$231	-$112
10%	$3,355	$3,012	$2,669	$2,326	$1,983	$1,640	$1,297	$954	$611	$268	-$75
20%	$3,392	$3,049	$2,706	$2,363	$2,020	$1,677	$1,334	$991	$648	$305	-$38
30%	$3,429	$3,086	$2,743	$2,400	$2,057	$1,714	$1,371	$1,028	$685	$342	-$1
40%	$3,465	$3,122	$2,779	$2,436	$2,093	$1,750	$1,407	$1,064	$721	$378	$35
50%	$3,502	$3,159	$2,816	$2,473	$2,130	$1,787	$1,444	$1,101	$758	$415	$72
60%	$3,539	$3,196	$2,853	$2,510	$2,167	$1,824	$1,481	$1,138	$795	$452	$109
70%	$3,576	$3,233	$2,890	$2,547	$2,204	$1,861	$1,518	$1,175	$832	$489	$146
80%	$3,613	$3,270	$2,927	$2,584	$2,241	$1,898	$1,555	$1,212	$869	$526	$183
90%	$3,650	$3,307	$2,964	$2,621	$2,278	$1,935	$1,592	$1,249	$906	$563	$220
100%	$3,687	$3,344	$3,001	$2,658	$2,315	$1,972	$1,629	$1,286	$943	$600	$257

Worst test

Figure 23 Matrices of the INMB results for the Markov model test performance scenario analysis assuming a payer's WTP per QALY of $10,000

INMB incremental net monetary benefit, *QALY* quality-adjusted life year, *WTP* willingness-to-pay.

Panel A Discount rate = 5%

Perfect Test / False Negative Rate	False Positive Rate 0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
0%	$11,763	$10,576	$9,389	$8,202	$7,015	$5,828	$4,641	$3,454	$2,267	$1,080	-$107
10%	$11,891	$10,704	$9,517	$8,331	$7,144	$5,957	$4,770	$3,583	$2,396	$1,209	$22
20%	$12,020	$10,833	$9,646	$8,459	$7,272	$6,085	$4,899	$3,712	$2,525	$1,338	$151
30%	$12,149	$10,962	$9,775	$8,588	$7,401	$6,214	$5,027	$3,840	$2,653	$1,467	$280
40%	$12,277	$11,091	$9,904	$8,717	$7,530	$6,343	$5,156	$3,969	$2,782	$1,595	$408
50%	$12,406	$11,219	$10,032	$8,845	$7,659	$6,472	$5,285	$4,098	$2,911	$1,724	$537
60%	$12,535	$11,348	$10,161	$8,974	$7,787	$6,600	$5,413	$4,227	$3,040	$1,853	$666
70%	$12,664	$11,477	$10,290	$9,103	$7,916	$6,729	$5,542	$4,355	$3,168	$1,981	$795
80%	$12,792	$11,606	$10,419	$9,232	$8,045	$6,858	$5,671	$4,484	$3,297	$2,110	$923
90%	$12,921	$11,734	$10,547	$9,360	$8,173	$6,987	$5,800	$4,613	$3,426	$2,239	$1,052
100%	$13,050	$11,863	$10,676	$9,489	$8,302	$7,115	$5,928	$4,741	$3,555	$2,368	$1,181

Worst test

Panel B Discount rate = 1.5%

Perfect Test / False Negative Rate	False Positive Rate 0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
0%	$16,888	$15,188	$13,488	$11,788	$10,088	$8,388	$6,688	$4,988	$3,288	$1,588	-$112
10%	$17,118	$15,418	$13,718	$12,018	$10,318	$8,618	$6,918	$5,218	$3,518	$1,818	$118
20%	$17,348	$15,648	$13,948	$12,248	$10,548	$8,848	$7,148	$5,448	$3,748	$2,048	$348
30%	$17,578	$15,878	$14,178	$12,478	$10,778	$9,078	$7,378	$5,678	$3,978	$2,278	$578
40%	$17,808	$16,108	$14,408	$12,708	$11,008	$9,308	$7,608	$5,908	$4,208	$2,508	$808
50%	$18,038	$16,338	$14,638	$12,938	$11,238	$9,538	$7,838	$6,138	$4,438	$2,738	$1,038
60%	$18,268	$16,568	$14,868	$13,168	$11,468	$9,768	$8,068	$6,368	$4,668	$2,968	$1,268
70%	$18,498	$16,798	$15,098	$13,398	$11,698	$9,998	$8,298	$6,598	$4,898	$3,198	$1,498
80%	$18,728	$17,028	$15,328	$13,628	$11,928	$10,228	$8,528	$6,828	$5,128	$3,428	$1,728
90%	$18,958	$17,258	$15,558	$13,858	$12,158	$10,458	$8,758	$7,058	$5,358	$3,658	$1,959
100%	$19,188	$17,488	$15,788	$14,088	$12,388	$10,688	$8,988	$7,288	$5,588	$3,889	$2,189

Worst test

Figure 24 Matrices of the INMB results for a Markov model test performance scenario analysis assuming a payer's WTP per QALY of $50,000

INMB incremental net monetary benefit, *QALY* quality-adjusted life year, *WTP* willingness-to-pay.

7.2.5 Comparing the Model Results

The Markov and DES base-case scenarios assumed a perfect PGx test. The Markov model's incremental cost was -$45 and the incremental QALY was 0.23, suggesting a dominant strategy

for the PGx test. The DES model had an incremental cost of $3,702 and an incremental QALY of 0.87, yielding an ICUR of $4,703.[xviii]

In the probabilistic sensitivity analyses in the Markov and DES models, the PGx test strategy is favoured in 90% of the model simulations when the payer's WTP reaches $6,150 and $12,000 per QALY, respectively. Thus, even though the two models are different in the key model elements, for all practical purposes, both models would lead to the same conclusion from a Canadian payer perspective. The Markov and DES models test parameters scenario analyses also yielded similar results.

7.2.5.1 Selection of an Economic Model

In light of the results we obtained with the Markov and the DES models, we conclude that both the Markov and DES models produce similar results. However, in our experience, developing the DES model was significantly costlier in all respects: data requirements, time to develop, software, and computer time. The computer time was not negligible. We realized that to obtain stable results with the DES approach required simulating a high number of patients. We observed this point when running the test performance scenario parameters. As shown in Article II Figure 4, we observed that for a FPR=0% and FNR=40% in both Panel A and B, the INMB value should be decreasing as the FNR increases. However, the INMB value with the FNR=40% was higher than the INMB with the FNR=30%. This numerical problem is minor compared to the previous simulations with only 20,000 or 30,000 simulated patients. In the validation stages of model development, we cross-validated the expected cumulative 20-year incidence of survival curves obtained in the DES software (i.e., ARENA) with the 20-year cumulative value from the survival curves in Excel. These validation exercises have shown that, to converge to the 20-year expected cumulative incidence, it required a very high number of simulated patients.

[xviii] The Markov model costs are in 2014 CAD, whereas the DES model costs are in 2016 CAD. Another difference is the discount rates, which was 5% in the Markov model and 1.5% in the DES model, respectively, based on the CADTH Third Edition and Fourth Edition Guidelines [88, 141].

For these reasons we chose to simulate 60,000 patients. For the test performance scenario analyses, this required running the model 121 times. The completion of these 121 scenarios, with each of the 60,000 simulated patients, required 4 days of computer time. A similar amount of time was required when running the probabilistic sensitivity analyses or deterministic sensitivity analysis. This is why we chose to reduce the number of patients simulated in each loop of the probabilistic sensitivity analyses to achieve 1,000 simulations. Increasing the number of simulated patients to 80,000 might have fixed the issue; however, it would have increased the computer time dramatically without a qualitative impact on the model results.

Whether the additional investment required for the development of a DES model has a significant impact on the economic evaluation depends on many factors (i.e., interaction between individuals, capacity constrained, waiting lists, etc.). The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Best Practice Guidelines recommend a DES approach when the problem evaluated involves constrained or limited resources [144]. Published comparisons of Markov and DES models tend to suggest that both methods will yield similar results [99, 131-137].

7.3 Article III

Article III included a reflection on the complete research project.

7.3.1 Importance of Assessing Test Performance Parameters

We strongly believe economic evaluations of diagnostic tests should include performance test parameters. In our economic evaluations, we tested the complete range of performance test parameters (FPR and FNR) to fully understand the economic consequences of the hypothetical PGx test. Understanding the consequences of false-positive and false-negative test results is key to determining the value of a diagnostic test. Furthermore, using the complete range of test parameters is of paramount importance in PGx-guided therapy. This is especially true when the PGx test objective is to ensure patients adhere to long-term therapy of preventive treatments, such as statins. As we have argued, a broad interpretation of test parameters allows physician and patient behaviours to be included in the evaluation of the test.

In addition, for a PGx test to come to market, it would require evaluation of its performance parameters. Ideally, a diagnostic test would be perfect; however, in practice there is a trade-off between high sensitivity and high specificity [87, 145, 146]. Selecting appropriate cut-offs for test parameters can be achieved using various methods, most of which are based on a receiver operating characteristic analysis [147]. What the optimal cut-off point will be depends on the clinical consequences of diagnostic test errors. Our results suggest a diagnostic PGx test would ideally have a high specificity (i.e., high ability to identify true-negative cases and thus minimize false-positive test results in patients without statin-induced myopathy).

Furthermore, performing an early economic evaluation of a PGx test, as we have done, allows decision makers to understand the economic value of the technology. This information is highly valuable not only to payers, but in the current context, it provides essential information on the economic perspective of the test to researchers and investors.

7.3.2 The Role of PGx-Guided Statin Therapy

In recent years, two PGx testing strategies for statin-induced myopathies have been pursued, each with a different objective:

- To identify the risk of developing statin-induced myopathy prior to patients initiating a statin; or
- To diagnose statin-induced myopathy in patients who have initiated a statin.

SLCO1B1 genotyping has been proposed for managing the risk of statin-induced myopathies, especially in patients receiving a high dose of simvastatin [82, 148]. The purpose of the *SLCO1B1* genotyping test is to inform physicians and patients, prior to statin initiation, on the potential risk of developing a myopathy. On the other hand, the objective of the PGx test in development is to assist physicians and pharmacists to diagnose statin-induced myopathies in patients presenting with MSP.

The potential harms and benefits of treatment strategies must be weighed when evaluating the risk–to–benefit balance of health technologies. As we discussed in Section 3.1, in patients at high CV risk, the CV risk largely outweighs the rhabdomyolysis risk. Not surprisingly, no evidence supports an *a priori* testing strategy based on *SLCO1B1* genotyping and, therefore, this

test is not recommended to help in the decision to initiate statin therapy; its use is even questioned in the literature and current guidelines [58, 84, 149-151]. This highlights the clinical value of a strategy allowing physicians to diagnose statin-induced myopathy in patients who have already initiated a statin. The hypothetical PGx test evaluated in our work fits in with the second strategy and, if developed, would be used to diagnose statin-induced myopathies in patients having initiated statin therapy and who have mild to moderate CK elevation.

7.3.3 The Economic Value of a PGx Test for Statin-Induced Myopathy

7.3.3.1 Economic Evaluation Framework

The objective of the thesis was to develop a theoretical framework for the evaluation of a hypothetical PGx test in early stages of development. In a standard economic analysis framework, where the evaluation is conducted to support reimbursement decisions, the economic analysis would have included a reference case incorporating the best supportive evidence-based data, including test efficacy parameters. In addition, scenario and sensitivity analyses would have been conducted to support the robustness of the reference-case results. In a standard economic analysis developed to support reimbursement decisions, it would be highly unlikely that the matrix of results for the complete range of test parameters would have been provided. In fact, even if we had limited our evaluation to a plausible range of test parameters, it would have been considered a reasonable approach. However, we believe that the scientific value of this thesis is the proposition to evaluate the complete matrix, especially in the context of treatments that require lifetime adherence, such as statins.

The target population selected in our economic evaluation led to surprising results, which we had not foreseen. We often think of an economic evaluation as comparing the benefits and costs of a new drug product compared to another drug product. In doing so, we expect there will be a threshold at which point the new technology is not cost-effective. The reasons for not being cost-effective may depend on various factors, including the cost, efficacy, and safety of the new drug. In this respect, our result showing that a totally inaccurate test was cost-effective was puzzling. However, to fully interpret our result required additional considerations that we have summarized in the following subsections.

7.3.3.2 The Importance of Cardiovascular and Myopathy Risk Imbalances

The selected target population of our economic evaluations was high CV risk patients. According to the CCS Guidelines (2016) CVD risk categories, these high-risk patients belong to the group of patients with statin-indicated conditions. For these patients, the CCS Guidelines (2016) report an NNT of 20 to avoid one CVE for 5 years of treatment per 1 mmol/L reduction in LDL-C [7]. Thus, our target population was patients in which statin therapy is highly effective and relatively safe (see Section 1.2.4.1). We selected this population because it represented the group of patients for which a PGx test for statin-induced myopathy would be most beneficial for improving lifetime adherence to statin therapy in patients who might otherwise discontinue therapy.

Myopathy is more frequently associated with statin therapy than rhabdomyolysis, which is an extremely rare form of myopathy. Statin-related rhabdomyolysis rates reported in the literature range from 1 to 19 cases per 10,000 patient-years [53, 60]. Mitchell et al. (2015) reported that, in a cohort of 1,294 patients at high CV risk, the incidence rate of statin-intolerance was 125 per 10,000 person-years, with 9 cases of rhabdomyolysis, 30 cases of myositis, and 131 cases of myalgia [152]. Among the statin-intolerance events reported in the study, only 1.2% were events of rhabdomyolysis that required hospitalization; of the cases of rhabdomyolysis, 2 out 9 required hospitalization [152]. Thus, in the high CV risk patient population, the health benefits gained with statins largely outweigh the extremely low risk of rhabdomyolysis.

Table 14 shows the 10-year CVE risk with and without statin therapy in the DES model [153]. Statin therapy reduces the 10-year risk of CVE by 6.6%, which corresponds to an annual risk reduction of 0.675%. This reduction in CVE is 15x higher than the 1-year risk of rhabdomyolysis (0.05%) assuming a rhabdomyolysis rate of 4.54 per 10,000 patient-years [142, 153].

Table 14 10-year CVE risk in the DES model[153]

	Without Statin	With Statin	CV Risk Reduction with Statins
Patients with a history of AMI			
Risk of AMI recurrence	16.2%	12.1%	-4.1%
Risk of stroke post-AMI	2.5%	1.8%	-0.7%
Total CVE risk	18.7%	14.0%	-4.8%
Patients with a history of stroke			
Risk of stroke recurrence	28.0%	21.4%	-6.7%
Risk of AMI post-stroke	13.9%	10.3%	-3.5%
Total CVE risk	41.9%	31.7%	-10.2%
Model weighted average	26.3%	19.8%	-6.6%

AMI acute myocardial infarction, *CV* cardiovascular, *CVE* cardiovascular event, *DES* discrete event simulation.

While it is true that patients with myopathy who continue statin therapy incur a myopathy-related disutility and are at risk of rhabdomyolysis, the costs associated with mild and moderate myopathy are low. Furthermore, though severe rhabdomyolysis is associated with high costs, the overall risk of rhabdomyolysis is extremely low in patients with myopathy who continue statin therapy. We found the benefits from CV risk reduction in these patients outweighed the consequences of continuing statin therapy despite having a statin-induced myopathy. Thus, there is a net advantage for staying on statin therapy because the benefit of avoiding CVEs in high CV risk patients far exceeds the extremely low risk of rhabdomyolysis.

7.3.3.3 Interpretation of the Complete Test Matrix Results

7.3.3.3.1 There is no Such Thing as a Totally Inaccurate Diagnostic Test

The evaluation of the complete matrix of test parameters provides insight into the management of statin-induced myopathy in patients at high CV risk. However, our result showing that a totally inaccurate test is cost-effective, should be interpreted with caution. We argue that a totally inaccurate test cannot exist. A totally inaccurate test would simply misclassify the diagnosis of the condition: all patients with a true condition would be classified as not having the condition and all patients without the condition would be classified as having the condition. Thus, if a research group was to develop this totally inaccurate test, they would simply need to reverse the test decision to obtain a perfectly accurate test.

7.3.3.3.2 The Test Decision Implies Lifetime Adherence to Statin

One aspect to bear in mind when interpreting the model results, especially the matrix of test results, is that we have assumed the decision to continue statin therapy is permanent (except for rhabdomyolysis where we assumed treatment discontinuation). Under this assumption, a totally inaccurate test would result in all patients with a statin-induced myopathy fully adhering to their statin therapy, until death or rhabdomyolysis. We believe this situation is not plausible given the reality that patient adherence to statin therapy is poor and patients discontinue treatment for a variety of reasons [39-41, 53]. The section below describes how the matrix of results can account for treatment discontinuation.

7.3.3.3.3 A Test for Statin-Induced Myopathy Can Only Have Value if it Increases Lifetime Statin Adherence

A key point to consider when interpreting the model results is the impact of statin non-adherence on the PGx test classification (i.e., whether a patient is classified as having a false-positive, false-negative, true-positive, or true-negative myopathy). In our model, we have assumed complete adherence for each FNR and FPR combination (e.g., all patients with a false-negative or true-negative result will permanently continue statin therapy). In reality; however, if patients are non-adherent, this would fundamentally change the test classification.

Figure 25 presents the two-by-two matrix for the sensitivity and specificity of a diagnostic test. For a patient with a false-negative test result, but who is non-adherent to therapy, the outcome would be essentially the same as having received a true-positive test result (i.e., to discontinue therapy). Thus, non-adherence among patients with a false-negative test result will increase the number of patients in the true-positive cell, thereby increasing the effective test sensitivity. On the other hand, for patients with a true-negative result, non-adherence is akin to a false-positive result; therefore, decreasing the effective test specificity.

		Myopathy	
		Condition positive	Condition negative
Test results	Positive test result	True positive	False positive
	Negative test result	False negative	True negative
		Sensitivity= $\frac{\sum True\ positive}{\sum Condition\ positive}$	Specificity= $\frac{\sum True\ negative}{\sum Condition\ negative}$

Figure 25 PGx test two-by-two table: sensitivity and specificity

Figure 26 shows the DES model results assuming a payer's WTP of $50,000 per QALY. Each matrix cell indicates the model result for the assumed FNR and FPR test values. Physician and patient decisions that do not comply with the test results would change the effective FNR and FPR. We present three cases in the following pages to show how the matrix of results can incorporate whether physicians and patients comply with the test results and to illustrate how adherence impacts the value of the economic test.

For illustrative purposes, we have assumed the PGx test performance parameters are FNR=FPR=10%, which would provide a reference INMB scenario of $35,182 (see the parameter combination in the matrix below, assuming a WTP per QALY of $50,000).

Perfect Test	False Positive Rate										
False Negative Rate	0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
0%	39,619	35,160	31,462	27,735	23,698	19,373	15,469	12,516	7,336	3,907	-143
10%	39,800	35,182	32,216	28,116	24,472	19,806	15,610	11,950	7,588	4,494	545
20%	40,000	35,430	31,240	27,968	24,174	20,532	16,204	12,429	7,425	4,223	906
30%	40,125	36,863	32,277	28,900	25,605	20,941	17,003	13,120	9,423	5,408	1,192
40%	40,071	36,188	32,962	27,912	24,808	21,316	16,804	12,894	9,538	5,476	1,508
50%	41,706	38,166	33,679	29,672	24,702	21,861	17,655	13,430	9,393	5,861	1,708
60%	40,877	37,006	33,840	30,208	25,202	22,259	18,197	14,745	9,833	5,976	1,638
70%	42,457	38,392	33,655	30,407	25,837	22,181	17,995	13,743	10,089	6,698	1,898
80%	42,510	38,508	34,669	29,837	26,311	22,982	18,913	14,421	11,157	7,190	2,461
90%	43,316	39,098	35,141	30,469	27,553	23,175	19,019	15,319	12,207	7,589	3,545
100%	43,363	39,247	35,405	32,026	27,547	23,396	19,696	16,154	12,196	7,720	3,221

Worst test

Figure 26 Matrices of the INMB results for the DES model test performance scenario analysis assuming a payer's WTP per QALY of $50,000

Case 1: Patients are Lifetime Adherent

When physician and patient decisions are based on the test result and those decisions are permanent, then the effective test parameters are simply the test parameters (i.e., FPR=FNR=10%), with an INMB value of $35,182 for an assumed payer's WTP per QALY of $50,000.

Case 2: All Patients are Non-Adherent

In this case, all patients who have a true-negative or false-negative test result, and are thus recommended a statin, interrupt their therapy; the effective test FNR and FPR values do not correspond to the true test parameters. **Figure 27** illustrates the classification of the test assuming a population of 100,000 patients with a 25% prevalence of myopathy and a test with FNR=FPR=10% values. Yellow cells indicate the misclassified patients due to erroneous test results. If we assume 100% statin adherence, 70,000 patients continue statin therapy, while, 75,000 patients who do not have statin-induced myopathy should be continuing therapy. In comparison, **Figure 28** shows the classification of the test when all false-negative (2,500) and all true-negative (67,500) patients discontinue their statin therapy (100% non-adherence). With complete statin discontinuation, the effective FNR and FPR values are respectively, 0% and 100%. **Figure 26** shows that in this case, the corresponding INMB value is -143. Thus, even

though the PGx test is highly effective, if all patients discontinue the statin therapy despite the test correctly identifying true-negative patients, the PGx test loses its economic value.

		Myopathy		
		Positive	**Negative**	**Total**
Test	**Test +**	22,500	7,500	30,000
	Test -	2,500	67,500	70,000
	Total	25,000	75,000	
		Sensitivity = 90.0%	Specificity = 90.0%	
		FNR = 10.0%	FPR = 10.0%	

Figure 27 Two-by-two table for the test classification assuming 100% statin adherence

		Myopathy		
		Positive	**Negative**	**Total**
Test	**Test +**	25,000	75,000	100,000
	Test -	0	0	0
	Total	25,000	75,000	
		Sensitivity = 100.0%	Specificity = 0.0%	
		FNR = 0.0%	FPR = 100.0%	

Figure 28 Two-by-two table for the test classification assuming 100% statin non-adherence

Case 3: A Proportion of Patients are Non-Adherent

To analyze the case where a proportion of patients are non-adherent, we assumed that patients with a false-negative result (presence of statin-induced myopathy) are more likely to discontinue the statin compared to patients with a true-negative result (absence of statin-induced myopathy). Thus, for illustrative purposes we assumed that 50% of patients with a true-negative result and 90% of patients with a false-negative result are non-adherent. As **Figure 27** shows, there are 2,500 patients with a false-negative result. If 90% of false-negative patients discontinue therapy, this would result in a situation where only 250 patients would continue their statin therapy, while 2,250 patients would discontinue treatment; the 250 patients who stopped therapy would, in terms of the test classification, fall into the true-positive cell in the matrix, which would now have 22,500+2,250=24,750 patients, as shown in **Figure 29**. Among the 67,500

patients with a true-negative result, if we assume that 50% discontinue statin therapy, only 33,750 patients would continue the statin, while the remaining 33,750 would be added to the 7,500 patients with a false-positive result (false-positive cell now totalling 41,250). Thus, considering patient adherence, the resulting FNR and FPR are respectively 1% and 55%, as shown in **Figure 29.** Looking back at **Figure 26,** the INMB value in this case would be between $15,469 and $19,373.

		Myopathy		
		Positive	**Negative**	**Total**
Test	**Test +**	24,750	41,250	66,000
	Test -	250	33,750	34,000
	Total	25,000	75,000	
		Sensitivity = 99.0%	Specificity = 45.0%	
		FNR = 1.0%	FPR = 55.0%	

Figure 29 Two-by-two table for the test classification with partial statin adherence

These three cases show that, regardless of the test performance parameters, the economic value of the test is determined by its usefulness as a tool to help physicians convince their patients to continue statin therapy when the PGx test result is negative, indicating patients suffer from pain unrelated to their statin therapy. Thus, the economic value depends on these three conditions:

- The test is clinically valid with high specificity and sensitivity as to be regarded as highly effective by physicians.
- Physicians must be able to convince their patients of the clinical validity of the test, especially in patients with pain unrelated to statin therapy.
- Patients must be receptive to their physicians' recommendation.

Thus, the PGx test will only have value if it effectively convinces patients, who would otherwise discontinue their statin, to adhere to statin therapy despite having pain unrelated to statins. For physicians to use the test in their clinical practice and base their recommendation on the test, they would have to believe in the clinical validity of the test. Using a test with dubious clinical validity to guide their patient's treatment would violate the medical deontological code. We

believe an accurate PGx test for the diagnosis of statin-induced myopathy could be part of the practical tool set to be used within the current dyslipidemia [7] and statin-intolerance guidelines [58], provided that it satisfies the three conditions above.

Although our result may seem to suggest that a PGx test with a high FNR leads to better outcomes, this result must be interpreted with caution as we illustrated above. The point of interest regarding the PGx test is the resulting health outcomes, which depend on acceptable test performance parameters and adherence to treatment. The benefits associated with a false-negative result (i.e., staying on treatment despite statin-induced myopathy) assume that physicians/patients would not even consider interrupting the statin therapy. In light of the high discontinuation rates associated with statins, this is unlikely [38-41, 44]. Furthermore, to sustain such a result would require the assumption that physicians and patients are unaware of possible test errors and the magnitude of the likelihood of such errors.

In summary, our findings confirm what is already known about statin therapy in high CV risk patients. These patients must be properly managed to confirm statin-intolerance before interrupting their statin therapy. The value of a PGx test for statin-induced myopathy is intrinsically linked to its ability to guide patients in need of statin therapy who would otherwise discontinue to comply with treatment recommendations. To reach this objective, the test results need to be highly credible to both physicians and patients, which requires a highly accurate test. As we have argued above, in real-world practice, a PGx test for statin-induced myopathy would be useless if it is not highly accurate. A poorly performing test would not succeed at influencing statin adherence. Thus, although a highly accurate PGx test could be a valuable addition to the current statin-intolerance management guidelines, its clinical and economic value is highly dependent upon its ability to guide patients with MSP unrelated to statin therapy to adhere to treatment.

7.4 The Cost-Effectiveness Threshold

The cost-utility analysis framework, which is expressed in dollars per QALY, provides stakeholders/payers with a monetary value of a health technology compared to other health technology alternatives. Thus, the objective of a cost-utility analysis is to identify cases in which a technology can be considered cost effective.

There are two clear cases where the cost-utility analysis provides an unambiguous answer:

- A new technology is more expensive and provides fewer health benefits (i.e., QALYs) than its alternatives; the new technology is dominated.
- The new technology is less costly and provides more health benefits than its alternatives; the new technology is a dominant strategy.

There are also two clear cases where the cost-utility analysis provides an ambiguous answer. In these cases, there is a trade-off in costs and health benefits:

- The new technology is costlier, but provides more health benefits.
- The new technology is less costly but provides fewer health benefits.

In a cost-utility analysis, the payer's WTP per QALY is the threshold dollar value used to inform decisions on the cost effectiveness of health technologies. For example, if the cost per QALY of a new technology is below a predefined WTP threshold, the technology is considered cost effective.

7.4.1 Historical Perspective

Over the past decades, the WTP threshold value has been extensively debated. In the 1980s and 1990s, the concept of league tables was popular [86, 154-158]. A league table was originally proposed by Williams (1985) to decide whether the number of coronary artery bypass grafting operations should be increased, maintained, or decreased compared to other health technology claimants on the National Health Service [156]. The general idea behind league tables is that cost-effectiveness and cost-utility studies provide an estimate of the opportunity cost of investing in healthcare in terms of dollars by health outcome (i.e., effectiveness, life-year gains, or QALYs) [159]. A league table presenting cost-effectiveness results for all the health

technologies ranked by their cost-effectiveness ratio would allow decision makers/payers to assess where to invest additional dollars in the health system. However, the creation of such a complete list is not feasible, which is why cost-effectiveness WTP thresholds are used instead [155].

In the UK, the National Institute for Health and Care Excellence (NICE) has put forward the 20,000 £ – 30,000 £ per QALY ($28,446 - $42,669 in 2017 CAD)[xix] threshold range in their Technology Appraisal Guidelines, as early as 2001. This threshold has not been updated in their most recent 2013 Guidelines [162-164]. In Canada, the CADTH Guidelines do not suggest the usage of a particular threshold value [88, 141]. However, the literature often cites the $50,000 per QALY threshold, which has been employed in cost-effectiveness studies since the early 1980s [165]. Recent reports from the CADTH Canadian Drug Expert Committee have explicitly referred to the $50,000 per QALY threshold [166-168]. For instance, in the pharmacoeconomic report for ocrelizumab, it stated:

> "The probability that ocrelizumab was cost-effective at a willingness-to-pay threshold of up to $200,000 per QALY gained was 0%. CADTH reanalysis suggested that an 82% reduction in the submitted price would be required to achieve an incremental cost per QALY of $50,000 [167]."

Interestingly, the $50,000 per QALY threshold has its origin in the estimated cost-effectiveness of renal dialysis in the US; the threshold was applied to Canada without exchange rate or inflation adjustments [165, 169, 170]. Ignoring the US dollar exchange rate, the $50,000 threshold represented $118,761 in 2017 Canadian dollars [171]. As Neumann et al. (2014) suggest, referencing the $50,000 per QALY threshold can be viewed as adding new "favourable" interventions without displacing any "unfavourable" interventions with cost-effectiveness ratios above this threshold [170].

The World Health Organization, assisted by some of the world leading health economists, formed the Commission on Macroeconomics and Health to study the macroeconomics of health

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[xix] The NICE threshold values were inflated to 2017 using the consumer price index (annual rate for all items) published by the Office for National Statistics [160] and converted to Canadian dollars using the 2017 yearly average exchange rate between the British pound and the Canadian dollar [161].

services [172, 173]. The Commission expressed their suggestion for assessing cost effectiveness in terms of disability-adjusted life years (DALYs) saved relative to a country's gross domestic product (GDP) per capita. The rationale supporting this approach was that one year of disability could be conservatively comparable to one year of income loss, which can be estimated to be a country's GDP per capita. Thus, an intervention that saves one DALY for less than the average GDP per capita should be considered highly cost effective [174, 175]. The NICE 20,000 £ – 30,000 £ per QALY threshold range represented 0.79 – 1.19 times the UK GDP per capita in 2000, and in turn, 0.66 – 0.99 GDP per capita in 2017 [176].

7.4.2 Other Factors Influencing the Decision Rule

NICE decisions have been favourable to interventions exceeding the 30,000 £ per QALY threshold [165, 177, 178]. Similarly, CADTH has approved interventions with the incremental cost-effectiveness ratio (ICER) exceeding the $50,000 per QALY threshold [166, 179, 180]. In fact, for HTAs, the cost-effectiveness threshold is only one part of the decision framework. Griffiths et al. (2015) reviewed HTA appraisals from May 2000 to May 2014 from NICE, the Scottish Medicines Consortium, the Pharmaceutical Benefits Advisory Committee, and CADTH [178]. Their review indicated that the clinical evidence was a key driver for receiving a positive recommendation in cases where submissions had an ICER above the WTP threshold. The clinical criteria included:

- Strong clinical evidence supported by head-to-head trial(s) with the relevant comparator(s) or an adjusted indirect comparison with low levels of uncertainty;
- Unmet therapeutic needs;
- Orphan disease;
- End-of-life therapies.

Griffiths et al. (2014) [181], using the same data as above for Griffith et al. (2015) [178], reported that 30% of submissions with an ICER below the threshold were rejected. The main reasons for these rejections were non-robust economic analyses.

In Canada, Rocchi et al. (2012) reviewed the Common Drug Review recommendations from September 2003 to December 2009 [180]. They assessed the impact of multiple factors

influencing the "do not list" recommendation using a multivariable logistic regression. Four factors were identified as significantly contributing to a negative recommendation: clinical uncertainty (OR 13.6), price higher than comparators (OR 9.2), request for reconsideration (OR 10.2), and price as the only economic evidence used (OR 17.9).

7.4.3 Thresholds Used in Articles I-III

We used WTP thresholds of $50,000 per QALY or below in the three articles. In Article I, we used a $1,000 per QALY threshold [129]. The reason for using such a low threshold value was to highlight that a perfectly accurate PGx test would be cost effective even if the payer had a very low WTP threshold per QALY. In probabilistic sensitivity analyses, at a WTP of $750 per QALY, 50% of the model iterations favoured the PGx strategy; at a WTP of $6,150 per QALY, 90% of the model iterations favoured the PGx strategy.

In Articles II and III, we reported the results using two thresholds: $10,000 and $50,000 per QALY [130]. The reason for using these two thresholds is related to our choice to report results using the INMB values instead of the ICUR values. Contrary to reporting ICUR results, the INMB method requires specifying the WTP threshold. Furthermore, as the results of the PGx scenario analyses have shown, increasing the payer's WTP threshold also increases the value of maintaining patients on statins, regardless of whether patients have MSP.

7.5 Thesis Strengths and Limitations

7.5.1 Thesis Strengths

The research conducted for this thesis has many strengths. We conducted two distinct economic evaluations. The two models attempted to assess the economic value of a hypothetical PGx test for statin-induced myopathy in high CV risk patients compared to a strategy where all patients presenting with MSP interrupt their statin therapy. Although, the models shared most of the cost components and health utilities data, they differed in all other aspects. Nevertheless, results were similar between the two models. The probabilistic sensitivity analyses showed that the PGx strategy in Markov and DES models was favoured in 90% of the model simulations when the payer's WTP reaches $6,150 [129] and $12,000 per QALY, respectively [130].

The broad interpretation of test performance parameters allowed us to interpret test results as real-world test performance outcomes. In practice, the benefit of PGx-guided therapy resides in adherence to treatment. Failure to account for non-adherence will overestimate the benefits of the PGx test. Our interpretation of test results includes real-world situations where a proportion of physicians or patients do not follow the test results; with a perfect PGx test, this situation would be equivalent to having a PGx test with errors (i.e., FPR>0% and/or FNR> 0%). The most extreme result (worst-case scenario) would be a situation where all patients without statin-induced myopathy interrupt their statin therapy even though the PGx test results indicated they should continue. This would be equivalent to a PGx test with a FPR of 100%.

In addition, we argued that it is of utmost importance to understand the consequences of false-positive and false-negative test results. The fact that we were evaluating a PGx test in development meant that we had no evidence-based data to inform the PGx test parameters. Therefore, we chose to have a very agnostic approach toward the test performance parameters; we evaluated the value of the PGx over the complete range of FPR and FNR parameters. Performing these analyses highlighted one very important characteristic of the analysis, namely that even a totally inaccurate test would still yield a positive INMB at low WTP per QALY threshold.

Although, we showed that a totally inaccurate PGx for statin-induced myopathy in high CV risk patients would provide a positive INMB for payers even at a low WTP per QALY threshold (e.g., $10,000), this result does not indicate that a totally inaccurate PGx test leads to better outcomes. As we have argued in Section 7.3.3, a totally inaccurate test is not a viable solution as it requires the assumption that all patients who received a false-negative result to continue their statin therapy, even if their MSP persists. Having evaluated the complete matrix of test parameters, however, has allowed us to better understand the consequences of the FNR and FPR.

Evaluating the consequences of the FNR and FPR allowed us to understand the impact of a risk imbalance in this environment. False-negative test results in high CV risk patients with mild to moderate myopathy yielded net benefits. Although these patients suffer from myopathy and are penalized with poorer quality of life, the benefit in risk reduction from the statin therapy outweighs the extremely small risk of rhabdomyolysis. We were first puzzled by the outcome

with totally inaccurate test results; however, we believe these results are in line with the current medical opinion that high CV risk patients must be managed to reduce their lipid levels and, that until the introduction of proprotein convertase subtilisin/kexin type 9 (PCSK9) for statin-intolerance, statins are the most effective drugs to reduce lipid levels and to provide CV protection [7, 33, 58, 182].

As PCSK9 may eventually be considered as an option for patients with statin-induced myopathy, payers may be interested in a PGx test for statin-induced myopathy. Pharmaceutical companies may see a PGx test as an opportunity for their drug product if it allows them to offer their product to the statin-intolerant patient group. There is a need to reassess the economic value of the PGx test as a market access condition for PCSK9.

7.5.2 Thesis Limitations

Although we believe that the thesis results are robust, the models have some limitations. We assessed the value of a hypothetical PGx test for statin-induced myopathy in high CV risk patients. This population was selected as we believe they represent the target population who benefit most from statin therapy. As the models showed, for this target population, the risk reduction in CVE largely outweighed the extremely low risk of rhabdomyolysis by 15-fold based on the DES model 10-year CV risk (see Article III - Section 3.1). Thus, the value of the PGx test in primary prevention would be lower as these patients are at lower CVE risk. According to the CCS Guidelines (2016), the NNT[xx] in primary prevention is 35 for patients with a high FRS (≥20%) and 40 for an intermediate FRS (10% to 19%) [7]. In statin-indicated conditions, which include secondary prevention to stroke and AMI, the guidelines report an NNT of 20, which indicates a higher benefit of statin therapy in this target population.

We assumed that in an environment without the PGx strategy, patients would interrupt their statin therapy in the presence of MSP. In our models, we did not incorporate the recommended CDR algorithm for patients suspected of statin-intolerance. Adopting the CDR algorithm would have required including patients who switch statin therapies and/or have a dose reduction (i.e.,

[xx] The CCS Guidelines define the NNT as: NNT to prevent one CVD event for 5 years of treatment per 1 mmol/L reduction in LDL-C [7].

partial statin intolerance). Statin dose reduction would have reduced the benefit of statin therapy and reduced the PGx test value.

In the models, we only considered statin interruption related to MSP. Accounting for other reasons of statin interruptions (e.g. patient preference, other statin-related risk factors) would have been similar in both model strategies (with and without the PGx). As such, adopting other causes of statin interruption in the models would not have contributed to the evaluation of the PGx test or impacted the results as the effects would have cancelled out.

We assumed that the PGx test in development only applied to the diagnosis of statin-induced myopathy. Often, medical devices may have multiple usages. If the PGx test turns out to be applicable in other health conditions, then the current evaluation would not be applicable to these other conditions as this would be an incomplete evaluation of the PGx test.

Finally, when we initiated the thesis, PCSK9 drugs were not available on the market. They are currently not indicated in Canada for statin-intolerance; however, if the development of a PGx test for statin-induced myopathy succeeded and was used to access reimbursement for PCSK9 drugs for patients with statin-intolerance, then the economic evaluation of the PGx test would need to be reassessed. In this context, the consequences of false-positive test results would need to be investigated.

Chapter 8. Conclusion

We initiated this thesis project in 2013 as part of the *"Personalized Medicine Strategies for Molecular Diagnostics and Targeted Therapeutics of Cardiovascular Diseases"* funded by Genome Canada and Génome Québec (grant number: 4530). The objective of this study was to conduct an economic evaluation of a hypothetical PGx test for statin-induced myopathy in high CV risk patients. Contrary to the *SLCO1B1* genotyping test used to predict the risk of statin-intolerance prior to statin-initiation, possibly causing net harm by leaving patients in need of statin treatment untreated, the PGx test for statin-induced myopathy would provide a tool to diagnose statin-myopathy in patients manifesting MSP after statin initiation. This test was to be developed as a diagnostic tool for patients with mild to moderate myopathy with CK elevation ≤5 ULN. This test would not be used for extreme cases of rhabdomyolysis.

In the early stages of this thesis, we decided to conduct two economic analyses. As a first step, we developed a Markov health state model using published data for the first article. As a second step, we developed a DES model as a cross-validation of the Markov model for the second article. Finally, as a third step, the third article was a comparison between the Markov and DES modelling approaches. In light of the similar results between the two models, we reduced the emphasis on the comparison between the Markov and DES techniques to focus on the implications of the model results.

In our reflection, economic evaluations of diagnostic devices should assess the economic consequences of test errors. The starting point of our economic analyses was an "ideal" situation that we defined as the "Perfect Clinical Environment": 1) the PGx test is perfect (FPR=FNR=0%), 2) physicians' prescribing recommendations are based solely on the test results, and 3) patients fully adhere to their physicians' recommendations. Any departure from the "Perfect Clinical Environment" could be interpreted broadly as akin to "PGx test errors" (i.e., FPR >0% and/or FNR >0%). The general idea is that the clinical utility of a PGx test resides, not only on the test parameters themselves, but on how the PGx test influences patient treatment patterns to reach the desired clinical outcomes. With that framework, analyzing the consequences of false-positive and false-negative results over the complete spectrum of testing

FPR and FNR values, gave a comprehensive overview of the potential economic value of the hypothetical PGx test.

The two economic evaluations conducted with the Markov and DES modelling techniques yielded similar results in agreement with the literature comparing Markov and DES model cross-validation. Probabilistic sensitivity analyses showed that the PGx strategy in the Markov and DES models was favoured in 90% of the model simulations when the payer's WTP reached $6,150 and $12,000 per QALY, respectively, which can be considered a low WTP per QALY in the Canadian setting.

The scenario analyses conducted on the complete range of test parameters in the context of an early economic evaluation of a diagnosis are key analyses that may be considered more informative than the models' base-case INMB estimate or probabilistic sensitivity analyses. These analyses uncovered that a totally inaccurate test would yield a positive INMB value from a payer's perspective at a low WTP per QALY. We were not expecting this result. Our expectations were that there would be a combination of test parameters where the PGx test value would have been considered dominated (i.e., being costlier and providing less health benefits) or at best, not being cost effective (i.e., INMB <0 [ICUR > WTP]). At first glance, these results were highly disappointing. Upon reflection, these results are logical and can be explained. In high CV risk patients with mild to moderate myopathy, the benefit of statin therapy in reducing CVE risk largely outweighs the risk of rhabdomyolysis with false-negative test results. This can be seen in the scenario matrix results: holding the FPR fixed while increasing the FNR value (i.e., moving down a column) increased the economic value of the PGx test. However, the fact that the models yielded a positive INMB for a totally inaccurate PGx test should not be considered as indicating that a poorly performing test in clinical practice would be justifiable. Instead, a strategy that maintains patients on statin therapy, even if patients are at risk of rhabdomyolysis, would lead to better outcomes due to the risk imbalance between CVE and rhabdomyolysis in high CV risk patients on statin therapy.

In the third article, we demonstrated the impact of risk imbalance by performing two additional test performance scenario analyses using the DES model. In the DES model, the 10-year risk of a CVE was 26.3% for untreated patients and 19.8% for treated patients. As a demonstration of the impact of risk imbalance, we performed two scenario analyses assuming a 10-year risk of

rhabdomyolysis of 20% and 30%. These new analyses confirmed what we were expecting, which was that increasing the risk of rhabdomyolysis would cause an increase in the number of combinations of FPR and FNR where the test is no longer cost effective. Furthermore, holding the FPR fixed while increasing the FNR results in lower INMB values, indicating a loss in net benefits when maintaining patients with mild to moderate myopathy on statin therapy while exposing them to the risk of rhabdomyolysis.

Although, the additional analyses on increased risk of rhabdomyolysis are purely theoretical, they served the purpose of illustrating the impact of risk imbalance. We argue that these results are in line with the current guidelines for managing statin-intolerance. Patients manifesting symptoms of statin intolerance should be investigated with a proper CDR approach. In addition, patients need to be adequately informed on the benefits of statin therapy, especially in the high CV risk population. The PGx test in development would be a useful addition to the current diagnosis of statin-intolerance management guidelines. However, to be a clinically useful addition, the PGx test will need to be highly accurate as its value will reside in its ability to influence a patient's decision to adhere to therapy. If the PGx test is not highly accurate, its credibility among healthcare professionals would hinder its clinical and economic value.

Pre-emptive *SLCO1B1* genotyping has been proposed for predicting statin intolerance to guide statin treatment initiation decisions. Clinical evidence does not support this testing approach even though the test is available on the market. Prior testing for statin intolerance using *SLCO1B1* genotyping is not recommended and is viewed as potentially causing net harm. Our test performance scenario analyses showed why the pre-emptive testing approach to statin initiation is at best problematic. On the contrary, testing once the patient manifests symptoms of statin-intolerance, does not suffer from these problems. Hence, compared to a pre-emptive testing, the hypothetical PGx test would fit well within the current guidelines.

In conclusion, as our research has shown, economic evaluations of diagnostic devices need to fully characterize the consequence of test errors. This type of approach allows for a broader interpretation of test parameters, including physician and patient responses to the test results, thereby including the notion of clinical utility of the test where the therapeutic treatment is a preventive drug, such as a statin.

In the context where a drug has demonstrated clinical benefit with extremely rare severe drug-related adverse events, and when there are no established alternatives, the proper management of patients would warrant that all efforts be made to maintain patients on the drug therapy. This situation applies in the management of patients with mild to moderate myopathy where symptoms are completely reversible.

Chapter 9. References

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