Can J Diabetes xxx (2020) 1–8

Contents lists available at ScienceDirect

Canadian Journal of Diabetes

journal homepage: www.canadianjournalofdiabetes.com

Original Research

Economic Evaluation of a New Polygenic Risk Score to Predict Nephropathy in Adult Patients With Type 2 Diabetes

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Key Messages

- The current screening methods for nephropathy in patients with type 2 diabetes is based on detection of albuminuria and decline of glomerular filtration rate.
- A polygenic risk score (PRS) for early prediction of the risk for diabetic nephropathy in patients with type 2 diabetes was recently developed.
- This study provides an overview of the clinical and cost benefits related to the use of the PRS compared with usual screening methods for diabetic nephropathy.

ARTICLE INFO

Article history:
Received 22 December 2019
Received in revised form
31 May 2020
Accepted 9 June 2020

Keywords:
cost-utility analysis
diabetic nephropathy
end-stage renal disease
Markov model
polygenic risk score
type 2 diabetes mellitus

ABSTRACT

Objectives: The current screening method for diabetic nephropathy (DN) is based on detection of albumin in the urine and decline of glomerular filtration rate. The latter usually occurs relatively late in the course of the disease. A polygenic risk score (PRS) was recently developed for early prediction of the risk for patients with type 2 diabetes (T2D) to develop DN. The aim of this study was to assess the economic impact of the implementation of the PRS for early prediction of DN in patients with T2D compared with usual screening methods in Canada.

Methods: A cost-utility analysis was developed using a Markov model. Health states include pre-end-stage renal disease (ESRD), ESRD and death. Model efficacy parameters were based on prediction of outcome data by polygenic risk testing of the genotyped participants in the Action in Diabetes and Vascular Disease PreterAx and DiamicronN Controlled Evaluation trial. Analyses were conducted from Canadian health-care and societal perspectives. Deterministic and probabilistic sensitivity analyses were conducted to assess results robustness.

Results: Over a lifetime horizon, the PRS was a dominant strategy, from both a health-care system and societal perspective. The PRS was less expensive and more efficacious in terms of quality-adjusted life-years compared with usual screening technics. Deterministic and probabilistic sensitivity analyses showed that results remained dominant in most simulations.

Conclusions: This economic evaluation demonstrates that the PRS is a dominant option compared with usual screening methods for the prevention of DN in patients with T2D. Adoption of the PRS would reduce costs saving but would also help prevent ESRD and improve patients' quality of life.

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1499-2671/
https://doi.org/10.1016/j.jcjd.2020.06.010

Mots clés:
analyse coût-utilité
néphropathie diabétique
insuffisance rénale en phase terminale
modèle de Markov
score de risque polygénique
diabète sucré de type 2

RÉSUMÉ

Objectifs : La méthode de dépistage actuelle de la néphropathie diabétique (ND) repose sur la détection de l'albumine dans l'urine et le déclin du débit de filtration glomérulaire. Ce dernier survient en général assez tardivement dans l'évolution de la maladie. Un score de risque polygénique (SRP) a récemment été élaboré pour prédire de façon précoce le risque de ND chez les patients atteints de diabète de type 2 (DT2). L'objectif de la présente étude était d'évaluer les répercussions économiques de la mise en place du SRP pour la prédiction précoce de la ND chez les patients atteints de DT2 et de le comparer aux méthodes de dépistage habituelles au Canada.

Méthodes : Une analyse coût-utilité a été élaborée à l'aide d'un modèle de Markov. Les états de santé étaient l'insuffisance rénale en phase pré-terminale (IRPPT), l'insuffisance rénale en phase terminale (IRPT) et le décès. Les paramètres d'efficacité du modèle étaient fondés sur la prédiction de données sur les issues par le test polygénique des participants génotypés de l'étude ADVANCE (Action in Diabetes and Vascular Disease PreterAx and DiamicronN Controlled Evaluation). Les analyses ont été réalisées selon les perspectives des soins de santé du Canada et de la société. Les analyses déterministes et probabilistes de la sensibilité étaient réalisées pour évaluer la robustesse des résultats.

Résultats : Selon un horizon temporel à vie, le SRP était une stratégie dominante de la perspective du système de soins de santé et de la perspective de la société. Le SRP était moins coûteux et plus efficace au point de vue des années de vie pondérées par la qualité que les techniques de dépistage habituelles. Les analyses déterministes et probabilistes de la sensibilité montraient que les résultats demeuraient dominants dans la plupart des simulations.

Conclusions : Cette évaluation économique démontre que le SRP est une option dominante par rapport aux méthodes de dépistage habituelles pour la prévention de la ND chez les patients atteints de DT2. L'adoption du SRP permettrait de réduire les coûts, mais elle permettrait aussi de prévenir l'IRPT et d'améliorer la qualité de vie des patients.

Introduction

Diabetic nephropathy (DN) is the most frequently reported primary cause of end-stage renal disease (ESRD), accounting for 36% of cases (1). In Canada, approximately 50% of patients with diabetes will develop signs of renal damage throughout their lifetime. DN is characterized by a slow and progressive increase in albuminuria, followed by a reduction in glomerular filtration rate (2). Therefore, the current screening methods for DN are based on tests evaluating the albumin-to-creatinine ratio (ACR) along with serum creatinine for glomerular filtration rate. Although these tests have a good positive predictive value, they only capture patients after clinical symptoms of DN (3).

The Steno-2 randomized controlled trial evaluated the death from any cause of participants with type 2 diabetes (T2D) treated with either intensive or conventional therapy (4,5). This study demonstrated that although intensive treatment significantly decreases the number of cases of ESRD, the rate of progression from micro- to macroalbuminuria remains elevated. Therefore, this information portrays the importance of early screening of patients with T2D with genomic tools, prior to the development of clinical symptoms, to prevent DN.

Recently, Tremblay et al genotyped 4,098 patients from the Action in Diabetes and Vascular Disease PreterAx and DiamicronN Controlled Evaluation (ADVANCE) trial, a randomized controlled trial of blood pressure lowering and intensive glucose control in patients with T2D, to build a polygenic risk score (PRS) for both renal and cardiovascular outcomes (6–10). The PRS was composed of 598 single nucleotide polymorphisms predicting renal and cardiovascular complications in individuals with T2D of European descent, adjusted for principal components of genetically defined ethnicity, sex, age at onset and diabetes duration. Its clinical utility in predicting complications of diabetes was tested in 4,098 participants with diabetes of the ADVANCE trial during a period of 5 years and an additional 5 years in ADVANCE-ON and was replicated in 3 independent nontrial cohorts. The study demonstrated an increased risk for renal events in patients with a high PRS and early-onset diabetes. For instance, 60% of ESRD cases occurred in the highest PRS third of ADVANCE participants. Intensive glycemic control demonstrated a 65% ESRD reduction in this high-risk group (hazard ratio [HR], 0.345; p=0.043 in ADVANCE), remaining significant at the end of ADVANCE-ON (HR, 0.455; p=0.026). However, intensive blood pressure control did not lead to significant reductions in ESRD in both ADVANCE (HR, 0.1276; p=0.608) and ADVANCE-ON (HR, 0.834; p=0.586). It was, therefore, suggested that the implantation of the PRS as the main screening method for DN, along with intensive glucose control treatment, would result in an important clinical benefit and would potentially provide substantial cost savings for the health-care system.

Health economic evaluations are an essential tool to assist the decision of policymakers, whether the added health benefits justify their costs. To date, no study has assessed the cost-effectiveness of a PRS as a screening method for DN. Therefore, the objective of this study was to assess the economic impact of the implementation of the PRS for the prevention of DN in patients with T2D compared with usual screening methods in Canada.

Methods

A cost-utility analysis was performed to assess the economic impact of a PRS for the prevention of DN in patients with T2D. This economic evaluation is based on the prediction of ESRD by polygenic risk testing within the ADVANCE trial (6,7).

Comparative treatment

The intervention evaluated in this economic evaluation was the PRS, administered only once, to patients with T2D. No follow-up screening tests were assumed to be required post-PRS assessment.

According to the most recent Canadian Agency for Drugs and Technologies in Health (CADTH) guidelines, comparative treatment

should reflect current practice and constitute the current treatment that should be replaced by the study intervention (11). In a population of patients with T2D, usual screening for DN is the best comparator because this is the standard diagnostic method and is most likely to be replaced by the PRS. Usual screening for DN is primarily composed of yearly testing for urinary ACR and serum creatinine, starting at diagnosis of T2D (2). If both tests results are positive, further tests including urine routine and microscopic, urine dipstick and serum electrolytes are performed.

Furthermore, patients receiving the PRS and obtaining a high-risk result were assumed to receive the intensive glucose control treatment of the ADVANCE trial, whereas medium- and low-risk groups received standard glucose control treatment. The intensive glucose control treatment was based on the administration of gliclazide (modified release), which was compared with a non-gliclazide standard glucose control regimen. The details of the drugs administered in both intensive and standard treatment groups of the ADVANCE trial were published in Patel et al (8). The treatments were stratified as such because the intensive treatment had the most beneficial impact for high-risk group patients ($p=0.043$) compared with other PRS groups.

Target population

The study population consisted of patients with T2D of Caucasian origin. More specifically, the population was retrieved from the ADVANCE and ADVANCE-ON trials, of which a subgroup of 4,098 patients were genotyped to establish a PRS (6,7). At baseline, the mean age of the population was 67±7 years, the mean age at diagnosis of T2D was 60±9 years and the median duration of diabetes was 8±7.4 to 8.9 years. A detailed overview of the characteristics of the ADVANCE genotyped participants by risk group is presented in Supplementary Appendix A.

Time horizon

As per CADTH guidelines, the time horizon should be long enough to capture all potential differences in costs and outcomes associated with the interventions being compared (11). The different outcomes from the pivotal trials were collected over 4.5 years in the ADVANCE trial, and extended another 5 years (for a total of 9.5 years) in the ADVANCE-ON post-trial follow up, in which patients were not randomized to their respective treatments (8–10).

This economic evaluation was conducted over a time horizon of 5 years because trial data under randomized treatment was only available for this time period. However, scenario analyses of varying time horizons were conducted. Time horizons of 10 and 30 years (lifetime) were tested in scenario analyses to capture all the ESRD and death-related events.

Model structure

Based on the course of the disease, a Markov model was developed to assess the cost-effectiveness of the PRS compared with usual screening for the detection/prevention of DN in patients with T2D. The following 3 health states were included in the model: pre-ESRD, ESRD and death.

Within the PRS scenario, it was assumed that the entire cohort would be subdivided according to their respective PRS (high, medium and low risk), as captured in the genotyped ADVANCE population (Table 1). The pre-ESRD health state was composed of all stages of DN preceding ESRD, including normo-, micro- and macroalbuminuria. The ESRD health state included patients with renal failure, all treated with either dialysis or renal transplantation (RT) (12). For patients receiving dialysis, in-centre hemodialysis (ICHD) and peritoneal dialysis (PD) were considered (12).

The Markov model was developed using Microsoft Excel 2019 (Microsoft Inc).

Transition probabilities

Transition between health states was calculated using patient-level data of the ADVANCE trial, stratified by time of event, type of event, type of treatment (intensive vs standard glucose control treatments) and risk group (high, medium or low PRS). To calculate the probability of ESRD and all-cause death, Kaplan-Meier (KM) curves were generated using SPSS (IBM) based on the prediction of ESRD by PRS testing. The transition rate probabilities were calculated on a yearly basis, using the last cumulative observation before the end of each year. Beyond 4 years, data were extrapolated based on the best fit curve using R Software for Statistical Computing (IBM) (25,26).

The parametric distributions fitted to the KM data were Weibull, exponential, log-normal and log-logistic (25). The best fitting parametric distribution was chosen by statistical consideration (Akaike information criterion and the Bayesian information criterion), visual inspection (comparing fitted distribution with the study KM plots) and clinical plausibility.

More specifically, the probability of ESRD was measured differently for all 3 PRS levels. For low PRS, no ESRD events were captured within the 4.5 years of the trial, for both standard and intensive treatments. Therefore, a probability of event of 0% was assumed for all time points within the model. For medium PRS, no statistically significant difference was observed between intensive and standard treatments. Therefore, the probability of ESRD for standard treatment was calculated and assumed to be equivalent for intensive treatment. However, for the high PRS subgroup, a statistically significant difference was observed between intensive and standard treatments. Therefore, the probability of ESRD from standard treatment was obtained from the projected KM curves, whereas the probability of intensive treatment was derived by applying the HR reported in the ADVANCE trial (Table 1) (6,7).

The probability of death from pre-ESRD health state was assumed to be equivalent to the rate of all-cause death of patients with low PRS, which is representative of the death rate for typical patients with T2D, without related complications. Furthermore, the death rate from ESRD health state was calculated by considering the all-cause death rate from pre-ESRD, for medium and high PRS subgroups, to prevent double counting.

Finally, although the rate of progression through different albuminuria stages within the pre-ESRD health state is not essential to the transition between health states, this information was valuable to calculate the annual costs of usual screening for DN. The categorization of urinary ACR at baseline was derived from the genotyped ADVANCE trial patient population (7). To determine the proportion of patients within each pre-ESRD health state at each model cycle, transition probabilities were obtained from the United Kingdom Prospective Diabetes Study 64, a randomized, nonblinded clinical trial that investigated the effects of intensive policies for blood glucose and blood pressure on the complications of T2D (27).

Detailed probability data are presented in Supplementary Appendix B.

Costs data

All analyses were performed from a Canadian Ministry of Health (MoH) and a societal perspective. All costs were expressed in 2019 Canadian dollars and were discounted at a rate of 1.5% as required by CADTH guidelines (11). Costs estimated prior to 2019 were adjusted to June 2019 levels based on the health component of the Canadian Consumer Price Index.

Table 1
Key model inputs

Parameters	Base-case value	Lower bound	Upper bound	Distribution	Reference
Hazard ratio of ESRD for high PRS patients	1.345	1.123	1.969	Log-normal	Hamet et al (6) and Tremblay et al (7)
Probabilities (%)					
Probability of albuminuria stage at diagnosis					
Normoalbuminuria	70.0	60.0	80.0	β	Hamet et al (6) and Tremblay et al (7)
Microalbuminuria	26.0	32.5	19.5	β	
Macroalbuminuria	4.0	7.5	0.5	β	
Probability of PRS group					
Low PRS	37.1	22.1	36.8	β	Hamet et al (6) and Tremblay et al (7)
Medium PRS	33.5	41.9	251.	β	
High PRS	29.4	36.1	38.1	β	
Type of ESRD treatment					
Dialysis	57.9	43.4	72.4	β	Canadian Institute for Health Information (12)
Transplantation	42.1	56.6	27.6	β	
Type of dialysis treatment					
In-centre hemodialysis	75.0	50.0	94.1	β	Canadian Institute for Health Information (12)
Peritoneal dialysis	25.0	50.0	5.9	β	
Home hemodialysis	0.0	0.0	0.0	β	
Costs $					
Screening test (unit cost)					
PRS	400.00	300.00	500.00	γ	OPTITHERA Inc
Urinary ACR	11.41	8.56	14.26	γ	British Columbia - Ministry of Health (13)
Serum creatinine	5.10	3.83	6.38	γ	
Urine routine and microscopic	7.17	5.38	8.96	γ	
Urine dipstick	6.68	5.01	8.35	γ	
Serum electrolytes	10.17	7.63	12.71	γ	
Drug acquisition cost ($/patient/y)					
Standard glucose control therapy, year 1	205.83	Drug costs not varied			Government of Ontario (14) and Chalmers (15)
Standard glucose control therapy year 2 and onwards	206.83				
Intensive glucose control therapy, year 1	201.02				
Intensive glucose control therapy, year 2 and onwards	203.87				
Monitoring/follow-up costs (unit cost)					
Family physician visits	84.45	63.34	105.56	γ	Ontario Ministry of Health and Long-Term care (16)
A1C	5.30	3.98	6.63	γ	British Columbia - Ministry of Health (13)
Cost of ESRD (annual cost)					
In-centre HD	100,000.00	95,000.00	107,000.00	γ	Alberta Health Services (17) and The Kidney Foundation of Canada (18)
PD	56,000.00	42,000.00	70,000.00	γ	
Transplantation (year 1)	23,000.00	17,250.00	28,750.00	γ	
Transplantation (year 2)	6,000.00	4,500.00	7,500.00	γ	
Productivity loss related to ESRD					Klarenbach et al (2), Von Zur-Mühlen (19) and Statistics Canada (20)
Year 1	20,803.93	20,341.50	21,266.35	γ	
Year 2 onwards	3,782.24	3,319.82	4,244.66	γ	
Cost of terminal care	10,314.00	7,735.50	12,892.50	γ	Ontario Case Costing (21)
Disutility inputs					
HD	0.164	0.27	0.05	Log-normal	Wasserfallen et al (22)
PD	0.204	0.34	0.07	Log-normal	Wasserfallen et al (22)
Utility inputs					
Pre-ESRD	0.785	0.681	0.889	β	Clarke et al (23)
ESRD	0.675	0.563	0.786	Vary according to disutility	
HD	0.620	0.511	0.731		Calculation
PD	0.580	0.443	0.719		Calculation
Renal transplantation	0.762	0.658	0.866	β	Kiberd et al (24)
Death	0.0				

A1C, glycated hemoglobin; *ACR:* albumin-to-creatinine ratio; *ESRD*, end-stage renal disease; *HD*, hemodialysis; *PD*, peritoneal dialysis; *PRS*, polygenic risk score.

From a MoH perspective, only direct medical costs were considered. Cost data included the following: cost of screening for DN, drug acquisition costs, monitoring and follow-up costs, the costs related to ESRD management and the cost of terminal care (Table 1). The unit cost of the PRS was estimated at $400 by OPTITHERA, whereas the cost of usual screening tests (ACR, serum creatinine, urine routine and microscopic, urine dipstick and serum electrolytes) were obtained from the British Columbia Schedule fees for Laboratory services (13). The annual screening costs by stage of renal dysfunction were based on the unitary cost per test and the Canadian guidelines for screening of DN in patients with T2D (28). Drug acquisition costs of the standard and intensive glucose-lowering treatments were obtained from the Ontario Drug Benefit formulary and their respective treatment regimens (14). Treatments were selected based on the standard and intensive glucose-lowering drugs administered in the ADVANCE trial (15). If 2 treatments were available within the same drug category, assumptions were made by clinical experts on the proportion of patients receiving each type of treatment. Total treatment acquisition costs were calculated using treatment regimens, percent

utilization in the ADVANCE trial and the cost per unit. Detailed costs calculations are presented in Supplementary Appendix C.

Costs of monitoring and follow up were based on the study by Patel et al (8), which established 2 and 4 visits annually, for standard and intensive treatment groups, respectively. These visits included the cost of a family physician visit and the monitoring of glycated hemoglobin. Costs were retrieved from the Ontario Schedule of Benefits and the British Columbia Schedule fees for Laboratory services (13,16).

Costs associated with ESRD include the costs of dialysis and RT. ESRD-related unit costs were obtained from the Kidney Foundation of Canada for RT and from the Alberta Annual Kidney Care Report for the dialysis methods (17,18). The average annual cost for dialysis was calculated by performing a weighted average using the annual costs for both ICHD and PD and their respective percent utilization. RT costs were calculated as a cost for the first year of transplantation and an annual cost for the following post-transplantation years. An average annual cost for the first year with ESRD and a cost for the following years was calculated using a weighted average of the costs of each renal failure treatments and their respective utilization. The cost of terminal care was obtained from the Ontario Care Costing Initiative (21).

The costs of productivity loss associated with ESRD were added from a societal perspective. ESRD requires treatment in 100% of cases; therefore, it was assumed that patients must be absent from work and encounter various productivity losses associated with their treatments. The cost of productivity loss associated with dialysis was obtained from a study by Klarenbach et al (29), a Canadian economic evaluation of frequent home nocturnal hemodialysis (HD) based on a randomized controlled trial. This study evaluated the productivity costs of both ICHD and home HD. Because no data are available to inform on the Canadian patient-borne and out-of-pocket costs related to PD, a cost adaptation was performed using the costs related to home HD. According to a report by CADTH, it was assumed that cost of productivity loss associated with PD was equivalent to 25% of the costs related to home HD (30).

The cost of productivity loss associated with RT was obtained from a study by Von Zur-Mühlen et al (19), who estimated the proportion of patients and the number of sick leave days encountered for 3 years preceding transplantation, transplantation year and the years after transplantation. Using the average Canadian hourly rate and hours worked per day, for people $\geq$25 years of age, total costs per transplanted patients were calculated (20).

Utility

An exhaustive literature review was conducted to obtain utility values for each health state. For the pre-ESRD health state, the following 2 assumptions were made: 1) all patients (including normo-, micro- or macroalbuminuria stages) would have the same utility value, and 2) the utility value was assumed to be equivalent to that of patients with T2D without complications (23). Within the ESRD health state, multiple utility values were considered depending on the type of treatment received. To estimate the utility values related to dialysis, disutility associated with different types of dialysis treatments (HD and PD) were retrieved from the literature (22). The utility value for each dialysis method was calculated by subtracting the disutility from the utility of patients with T2D without complications. Conversely, for RT, a utility value was directly obtained from the study by Kiberd et al (24). A weighted average utility value for the ESRD health state was calculated based on the utilities for each ESRD treatment and their respective utilization.

Adverse events

No adverse events costs were considered in this analysis because the prevalence of adverse events was considered similar between both standard and intensive glucose control treatments.

Incremental cost-utility analyses

The effectiveness outcome was the average quality-adjusted life-years (QALYs). The incremental QALYs were calculated as the difference in the average QALYs over the time horizon between the 2 comparators. The incremental cost-effectiveness ratios were calculated by dividing the difference in total costs of the PRS arm and the usual screening arm by the difference in QALYs between both treatment arms. The cost-effectiveness of PRS vs usual screening was compared with the established willingness-to-pay threshold of $50,000/QALY, which has been viewed as a generally acceptable willingness-to-pay threshold in Canada for drug decision-making.

Sensitivity analyses

The robustness of the base-case results was assessed through deterministic sensitivity analyses. This was performed by varying each single variable individually within lower and upper bounds of all key parameters including proportion of patients within each PRS risk group, albuminuria stage at baseline, utility values, costs associated with ESRD treatments, productivity loss, etc. For this analysis, model parameters were varied using a range of $\pm$25% and 95% confidence interval, specifically for utility values and HRs. The model efficacy parameters were varied directly through the rate of HR.

In addition, a probabilistic sensitivity analysis (PSA) was performed to assess the overall impact of uncertainty associated with study parameters. Simultaneous variations in all key parameters were performed using Monte Carlo simulations. A total of 5,000 Monte Carlo simulations were performed using appropriate distributions (beta distribution for transition probabilities and utility values, log-normal distributions for disutilities and HRs and gamma distribution for cost parameters). Results of the PSA were presented in a scatterplot diagram.

Results

Base-case analysis

Over a 5-year time horizon, the PRS was associated with an average of 4.26 QALYs, compared with an average of 4.25 QALYs with usual screening methods for DN, for a QALY gain of 0.010 (Table 2). From a MoH perspective, PRS and usual screening tests were associated with total costs of $5,551 and $6,776, respectively (difference of $1,225). Therefore, the PRS is a dominant alternative, being less costly and more effective than usual screening technics. From a societal perspective, PRS and usual screening tests were associated with total costs of $5,797 and $7,343, respectively (difference $1,546), which once again resulted in the PRS being a dominant alternative.

Sensitivity analysis

According to 1-way sensitivity analysis results, the PRS compared with usual screening methods was a dominant alternative in most analyses. The parameters with the greatest impact on the base-case incremental cost-effectiveness ratios from both perspectives were 1) the proportion of patients on dialysis, 2) the proportion of patients with ICHD and 3) the utility of pre-ESRD

Table 2
Cost-effectiveness results: Base-case analysis

	Usual screening	PRS
Basecase (5-year time horizon)		
Total QALYs	4.25	4.26
Incremental QALYs		0.010
Total costs, MoH perspective	$6,776	$5,551
Incremental total costs, MoH perspective		−$1,225
Total costs, societal perspective	$7,343	$5,797
Incremental total costs, societal perspective		−$1,546
Incremental cost/QALY, MoH perspective		Dominant
Incremental cost/QALY, societal perspective		Dominant
Scenario analysis (10-year time horizon)		
Total QALYs	6.53	6.58
Incremental QALYs*		0.054
Total costs, MoH perspective	$13,928	$11,582
Incremental total costs, MoH perspective		−$2,346
Total costs, societal perspective	$15,070	$12,211
Incremental total costs, societal perspective		−$2,858
Incremental cost/QALY, MoH perspective		Dominant
Incremental cost/QALY, societal perspective		Dominant
Scenario analysis (lifetime horizon)		
Total QALYs	8.75	8.88
Incremental QALYs*		0.126
Total costs, MoH perspective	$21,851	$19,356
Incremental total costs, MoH perspective		−$2,495
Total costs, societal perspective	$23,459	$20,391
Incremental total costs, societal perspective		−$3,069
Incremental cost/QALY, MoH perspective		Dominant
Incremental cost/QALY, societal perspective		Dominant

MoH, Ministry of Health; *PRS,* polygenic risk score; *QALY,* quality-adjusted life-year.
* May not sum to total because of rounding.

health state (Figure 1). The PRS was a dominant alternative over the usual screening methods in 91.82% of the Monte Carlo simulations, from both perspectives (Figure 2).

Scenario analyses

Supplementary scenario analyses, including projections over 10 years and lifetime horizons, also resulted in the PRS being dominant. Detailed results of these analyses are presented in Table 2.

Discussion

This economic evaluation indicated that, compared with usual screening methods for detecting DN, the PRS is a dominant alternative among patients with T2D. Results of comprehensive sensitivity analyses confirmed the robustness of the base-case results.

To our knowledge, this is the first economic evaluation of a PRS for the detection of DN in patients with T2D. The study has several strengths. First, scenario analyses extrapolating ADVANCE trial data over 10 years and lifetime horizons allow to capture all the events related to death and ESRD, compared with those captured within the 5-year time horizon of the trial. T2D is a chronic disease with late penetrance; therefore, related complications often occur later in life, which explains the importance of covering the entire patient's lifetime. Moreover, the analysis accounted for productivity losses associated with ESRD, therefore allowing a broader perspective and perhaps a more representative assessment of all the impacts of the disease and related interventions. Finally, although the PRS is administered after an average of 8±7.4 to 8.9 years after T2D diagnosis in the ADVANCE trial, the PRS remained a dominant alternative. In a real clinical setting, the PRS would be administered at diagnosis of T2D and would replace all the usual annual screening tests associated with DN. Although the true target population cannot be captured in this economic evaluation because of the lack of data, it can only be hypothesized that results would be even more dominant in a real-world setting. As demonstrated in the results of the study by Hamet et al (6) and Tremblay et al (7), earlier target and treatment of high-risk patients reduces the chance of developing ESRD. More specifically, patients with a high PRS had the greatest relative risk reduction with the combined intensive therapy of the ADVANCE trial. This study also concluded that the risk of microvascular renal events was highest in patients with high PRS and early onset of diabetes (31). Because the mean age of the ADVANCE population is 67 years, targeting a younger population of patients with diabetes in the real world would result in even greater reductions of ESRD events, directly associated with better cost-effectiveness results.

However, this economic evaluation also has some limitations. The difference in numbers of QALYs between the 2 comparators is

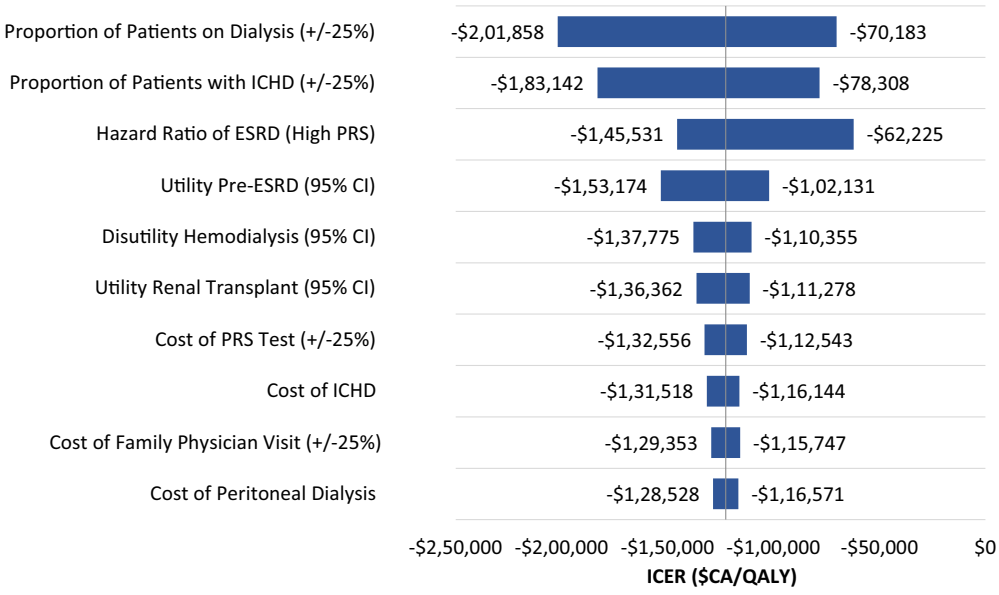

Figure 1. Results of 1-way sensitivity analysis. Results of 1-way sensitivity analysis are presented in a tornado diagram from the Ministry of Health perspective. Lower and upper bounds considered for the sensitivity analysis are indicated in the *y* axis for each parameter. The cost of ICHD was varied according to the cost range available in the Alberta Health Services (21). The base-case incremental cost-effectiveness ratio is −$122,550/QALY (dominant). *$CA,* Canadian dollar; *CI,* confidence interval; *ESRD,* end-stage renal disease; *ICER,* incremental cost-effectiveness ratio; *ICHD, in*-centre hemodialysis; *QALY,* quality-adjusted life-year; *PRS,* polygenic risk score.

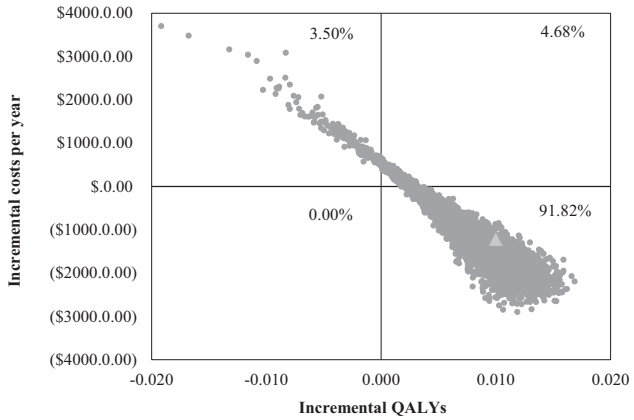

Figure 2. Results of probabilistic sensitivity analysis. Results of probabilistic sensitivity analysis are presented in a scatterplot diagram. These are representative of both the Ministry of Health and societal perspectives. The commonly cited threshold in Canada is $50,000/QALY. *QALY,* quality-adjusted life-year.

small, but the difference in cost is substantial, producing dominant results. As for any model-based analysis, the absence of data leads to making assumptions that may increase the uncertainty of the results. First, sensitivity and specificity of the PRS was not defined in the model analysis. However, it was assumed that all false-positive and false-negative results relative to the PRS were already captured within the clinical trial data. Furthermore, it was assumed that for all patients receiving the PRS, no follow-up screening tests would be administered afterwards. In a real clinical setting, it is unclear whether additional screening tests would be performed post-PRS to capture possible developments in DN. Although this is a limit to the study, usual screening tests cost an average $17 to $68 annually. This represents very low costs and would most probably not alter the dominant results obtained in this analysis. Another limitation of this study involves not using the utility values specific to the ADVANCE trial, published by Hayes et al (32). For this economic analysis, utility values specific to each health state, including those associated with each type of ESRD treatment, were preferred over the general values of the ADVANCE trial. However, to ensure results robustness, the values of the ADVANCE trial were used in a complementary analysis and the results remained dominant with very similar incremental QALYs compared with the base-case analysis. Furthermore, although patients undergoing RT typically receive prior dialysis for an average of 3.8 years, this clinical element was not taken into consideration in the model (12). It was assumed that patients would receive transplantation within the first year of being diagnosed with ESRD. Although this assumption is not representative of reality, it is a conservative approach. ICHD costs on average $100,000 annually; therefore, considering an additional 3.8 years of dialysis for all patients with ESRD would increase the incremental costs between both scenarios, further favouring the dominant result of the PRS (12,17). Despite these limitations, findings of the cost-utility analysis are robust according to the base-case results and the deterministic sensitivity analyses. Finally, the PSA demonstrated that the PRS may also be considered a cost-effective or dominated alternative, from both perspectives. These PSA results are explained by 2 different factors. Firstly, the only parameter that influences this result is based on the HR of ESRD related to high PRS. Because the HR is close to 1, certain PSAs capture values <1 because of the selected distribution. However, because this HR was captured after only 4.5 years in the ADVANCE trial, having more extensive clinical trial data would most probably increase the efficacy of the PRS because the event of ESRD is often captured later in the course of the disease. The ADVANCE trial had a 6-year post-trial follow-up period, called the ADVANCE-ON trial (10). The results of this post-trial follow-up period were tested in additional analyses and proved that the PRS remained a dominant alternative after 9.5 years. However, because of the nonrandomized nature of this post-trial follow-up period, these data were not included in the present study. Secondly, although PSA results should typically be found within the 4 quadrants of the scatterplot, results of this economic evaluation remained mostly in the dominant and dominated quadrants. This was explained by the high costs associated with ESRD. As soon as an alternative became more efficacious, according to the selected HR from the PSA, it was automatically a cost-saving option, because of the drastic differences in costs associated with the number of ESRD events.

Conclusions

This economic evaluation suggests that from a Canadian MoH and societal perspective, the PRS is a dominant option compared with usual screening methods for the prevention of DN in patients with T2D. The adoption of the PRS would not only be cost saving but would also help prevent ESRD and improve patients' lives.

Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Diabetes* at www.canadianjournalofdiabetes.com.

Acknowledgments

This work was supported by a grant from The Quebec Consortium for Drug Discovery (CQDM), OPTITHERA and Servier to P.H., J.T. and J.L. K.G. received funding from the Faculty of Pharmacy from the University of Montreal and the Canadian Association for Healthcare Reimbursement (CAHR). This study was conducted independently of the sponsors as part of a master's research project. The funding sources had no role in the study design, in the collection, analysis and interpretation of the data, or in the writing or submission of the manuscript.

Author Disclosures

J.T. and P.H. are officers of OPTITHERA. No other authors have any conflicts of interest to declare.

Author Contributions

K.G., C.B. and J.L. were involved in designing the study. Markov model development and results assessment were performed by K.G. P.H. participated in the management of the ADVANCE trial with J.T., they were responsible for the development of the clinical polygenic test and both contributed as key opinion leaders in the model development. M.R.T. was responsible for statistical analyses associated with the baseline characteristics of the ADVANCE genotyped population. J.C. and M.W. managed the ADVANCE and ADVANCE-ON studies. The manuscript was prepared by K.G. All authors reviewed the final manuscript.

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