Université de Montréal

Economic Evaluation of a New Genetic Risk Score to Prevent Nephropathies in Type-2 Diabetic patients

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Ce mémoire intitulé

Economic Evaluation of a New Genetic Risk Score to Prevent Nephropathies in Type-2 Diabetic patients

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Résumé

Un score de risque polygénique (SRP) a été mis au point pour permettre une prédiction précoce du risque de néphropathie chez les patients atteints de diabète de type-2 (DT2). Le but de cette étude était d'évaluer l'impact économique de l'implantation du SRP pour la prévention de la néphropathie chez les patients atteints du DT2, par rapport aux méthodes de dépistage habituelles au Canada.

Tout d'abord, une revue systématique de la littérature a été effectuée pour examiner les évaluations économiques publiées sur le DT2 et la néphropathie. Les principales techniques de modélisation observées dans cette revue ont été utilisées pour réaliser une analyse coût-utilité à l'aide d'un modèle de Markov. Les états de santé du modèle étaient la pré-insuffisance rénale (pré-IR), l'IR et le décès. Les paramètres d'efficacité du modèle ont été basés sur les résultats de l'étude ADVANCE. Les analyses ont été menées selon une perspective du système de soins et une perspective sociétale.

Sur un horizon temporel de la vie entière du patient, le SRP était une stratégie dominante par rapport aux méthodes de dépistage habituelles, selon les deux perspectives choisies. En effet, le SRP était moins coûteux et plus efficace en termes d'années de vie ajustée en fonction de la qualité, par rapport aux techniques de dépistage usuelles. Les analyses de sensibilité déterministe et probabiliste ont démontré que les résultats demeurent dominants dans la majorité des simulations.

Cette évaluation économique démontre que l'adoption du SRP permettrait de réduire les coûts et d'améliorer la qualité de vie des patients.

Mots-clés : Néphropathie diabétique, insuffisance rénale, diabète de type 2, score de risque polygénique, analyse coût-utilité, modèle de Markov

Abstract

The current screening method for diabetic nephropathy (DN) is based upon the detection of urinary albumin and the decline of estimated glomerular filtration rate, which occurs relatively late in the course of the disease. A polygenic risk score (PRS) was developed for early prediction of the risk for type 2 diabetes (T2D) patients who experience DN. The aim of this study was to assess the economic impact of the implementation of the PRS for the prevention of DN in T2D patients, compared to usual screening methods in Canada.

First, a systematic literature review was conducted to examine all published economic evaluations in T2D and DN. The main trends in modelling technics obtained from this review were used to conduct a cost-utility analysis using a Markov model. Health states include pre-end-stage renal disease (Pre-ESRD), ESRD and death. Model efficacy parameters were based on prediction of outcome data by polygenic-risk testing of the ADVANCE trial. Analyses were conducted from Canadian healthcare and societal perspectives.

Over a lifetime horizon, the PRS was a dominant strategy compared to usual screening methods, from both a healthcare system and societal perspective. In other words, the PRS was less expensive and more effective in terms of quality-adjusted life years compared to usual screening technics. Deterministic and probabilistic sensitivity analyses showed that results remained dominant in the majority of simulations.

This economic evaluation demonstrates that the adoption of the PRS would not only be cost saving but would also help prevent ESRD and improve patients' quality of life.

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

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A1C	Glycated hemoglobin
ACEI	Angiotensin-converting enzyme inhibitor
ACR	Albumin to creatinine ratio
ADVANCE	Action in diabetes and vascular disease: preterax and diamicron modified release controlled evaluation
ADVANCE-ON	Action in diabetes and vascular disease preterax and diamicron MR controlled evaluation post trial observational study
ARB	Angiotensin II receptor blocker
CADTH	Canadian Agency for Drug and Technology in Health
CAPD	Continuous ambulatory peritoneal dialysis
CBA	Cost-benefit analysis
CCA	Cost-consequence analysis
CCPD	Continuous cycle-assisted peritoneal dialysis
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CHUM	Centre Hospitalier de l'Université de Montréal
CKD	Chronic kidney disease
CKD-EPI	Chronic kidney Disease Epidemiology Collaboration
CMA	Cost-minimization analysis
COI	Cost-of-illness
CPI	Consumer price index
CT	Conventional antihypertensive therapy
CUA	Cost-utility analysis
DCCT	Diabetes control and complications trial
DCT	Distal convoluted tubule
DIMICO	Diabetic microvascular complications
DN	Diabetic nephropathy
DPP-4	Dipeptidyl peptidase-4
DSA	Deterministic sensitivity analysis
EE	Economic evaluation
eGFR	Estimated glomerular filtration rate

ESRD	End-stage-renal-disease
GBP	Great Britain Pound
GFR	Glomerular filtration rate
GWAS	Genome wide association studies
HD	Hemodialysis
HHD	Home hemodialysis
HUI	Health utilities index
ICER	Incremental cost-effectiveness ratio
ICHD	In-center hemodialysis
INESSS	Institut National en Santé et Services Sociaux
IR	Irbesartan
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
KM	Kaplan Meier
MDRD	Modification of diet in renal disease
NICE	National Institute for Health and Care Excellence
ODB	Ontario drug benefit
PCR	Protein to creatinine ratio
PCT	Proximal convoluted tubule
PD	Peritoneal dialysis
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PRS	Polygenic risk score
PSA	Probabilistic sensitivity analysis
QALY	Quality adjusted life years
R&M	Routine and microscopic
RAAS	Renin angiotensin aldosterone system
RENAAL	Reduction of endpoints in non-insulin dependent diabetes with the angiotensin II antagonist losartan
RT	Renal transplantation
SD	Standard deviation
SF-6D	Short form 6-dimensions
SGLT-2	Sodium-glucose cotransporter-2
SNP	Single nucleotide polymorphism
TTO	Time trade off
TZD	Thiazolidinediones

T1D	Type-1 diabetes
T2D	Type-2 diabetes
UACR	Urine albumin creatinine ratio
UK	Unites Kingdom
UKPDS	United Kingdom prospective diabetes study
US	United States
VADT	Veterans affairs diabetes trial

I would like to dedicate this work to my family, friends and colleagues who, throughout this project, have provided their love and support.

1 Introduction to Diabetic Nephropathy

1.1 Type 2 Diabetes and its Associated Renal Complications

Diabetes is a metabolic disorder characterized by persistent elevations in glycemia. There exists two types of diabetes mellitus, either type 1 (T1D) or type 2 (T2D). T1D, also known as insulin-dependent diabetes, is characterized by an inadequate secretion of insulin from the beta cells of the pancreas.[1] This type of diabetes generally develops during childhood or adolescence. Contrary to T1D, T2D, also known as non-insulin-dependent diabetes mellitus, develops when the cells of the body do not respond adequately to insulin.[1] This type of diabetes is the most prevalent, encompassing 90% of cases.[2] The onset of T2D usually occurs later in life and is often associated with a family history of diabetes, an unhealthy diet, physical inactivity or weight gain.[1]

Poor blood glucose control can cause damage to multiple organs, such as the heart, brain, kidneys, lower limbs as well as the retina.[3] The blood vessels may also be affected, both at the microvascular and macrovascular levels. For this reason, diseases such as retinopathy, nephropathy, neuropathy as well as arterial and cardiovascular diseases are very common complications among diabetic patients.[3] More specifically, up to one half of diabetic patients will demonstrate signs of renal damage throughout their lifetime.[4] A variety of forms of chronic kidney diseases (CKD) can be seen in diabetes, including diabetic nephropathy (DN), ischemic nephropathy related to vascular disease, hypertensive nephropathy, as well as other renal diseases that are unrelated to diabetes.[4]

The focus of this master's thesis is on DN in T2D patients. Diabetic nephropathy is classically defined as a progressive increase in albuminuria, which is the presence of albumin in the urine, a typical sign of kidney disease.[4] As the disease progresses, there is a progressive decrease in estimated glomerular filtration rate (eGFR), eventually leading to end-stage renal disease (ESRD), where patients must resort to dialysis and renal transplantation.[4]

1.2 The Pathogenesis of Diabetic Nephropathy

1.2.1 Anatomy and Physiology of the Kidney

The kidneys are complex organs that are essential in order to maintain multiple body functions such as: excreting waste, reabsorbing vital nutrients, controlling osmolality and blood pressure regulation,

maintaining acid-base homeostasis as well as hormonal secretion.[5] The nephron, is the functional unit of the kidney and each kidney contains on average, one million nephrons.[6] The nephron is composed of two main structures, the renal tubule and the renal corpuscle.[7] The renal corpuscle contains a capillary network called the glomerulus, to which blood arrives from the afferent arteriole and leaves from the efferent arteriole.[6] The renal corpuscles main function is blood filtration. Filtration of the blood across the glomerulus wall produces a glomerulus filtrate, which is a macromolecule and protein free solution.[6] The glomerulus filtrate then enters the second main structure of the nephron, the renal tubule. The renal tubule is a long tubular pathway subdivided into three main regions: (1) the proximal convoluted tubule (PCT), (2) the nephron loop (also known as the loop of Henle) and (3) the distal convoluted tubule (DCT).[6] The main function of the entire tubular pathway is the reabsorption of water, albumin, salt and other organic solutes.[6] The filtrate then exits the nephron from the DCT into the collecting duct, which is a structure that plays a role in the balance of fluid and electrolytes through hormonal regulation.[6]

The structure responsible for controlling the filtration rates of the nephron is the juxtaglomerular complex, positioned near the DCT adjacent to the afferent arteriole of the glomerulus.[6] This complex is composed of macula densa cells in the DCT, juxtaglomerular cells in the afferent arteriole as well as extraglomerular mesangial cells, which occupies the space between the glomerulus, DCT and arterioles.[6] Also known as the juxtaglomerular apparatus, these cells create an endocrine structure which is responsible for secreting the hormones renin and erythropoietin, which are directly linked to the renin-angiotensin-aldosterone system (RAAS).[6] These hormones are secreted when renal blood pressure, blood flow or local oxygen levels are low, in order to restore normal filtration rates. More specifically, the RAAS is responsible for the regulation of blood pressure. The secretion of renin from the kidneys converts angiotensin to angiotensin I.[7] Angiotensin I is then converted into angiotensin II, which increases arterial pressure by the vasoconstriction of the arterioles and through the secretion of aldosterone.[7] Aldosterone is responsible for stimulating sodium reabsorption in the DCT and collecting ducts, which consequently increases water reabsorption and volume of plasma; this increased renal blood flow contributes to the elevation of blood pressure.[7] In summary, the secretion of renin enables a cascade of enzymes which acts on the sympathetic nervous system, renal tubules, the adrenal cortex and the pituitary gland in order to increase ion concentration, and consequently blood pressure.

1.2.2 Grading/Classification of Kidney Function

Screening and diagnosis of chronic kidney disease (CKD) involves the assessment of two specific clinical measures: (1) the estimated glomerulus filtration rate (eGFR) and (2) proteinuria. Both measures allow to assess the health of essential kidney functions.

1.2.2.1 Estimated Glomerulus Filtration Rate

The measure of the eGFR involves testing the rate of blood filtration from the glomerulus. According to the 2018 Clinical Practice guidelines for chronic kidney disease (CKD) in diabetes, the estimated glomerulus filtration rate (eGFR) is the most common measurement of kidney function.[4] Since methods associated with 24-hour urine collection are very demanding and often not performed accurately, equations have been developed to measure the eGFR by combining serum creatinine levels along with other factors such as age, weight, gender and race.[4] Two formulas are currently used to measure the eGFR: the four-variable Modification of Diet in Renal Disease (MDRD) and the more recent Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI).[8,9] The CKD-EPI is preferred across laboratories in Canada since it is more accurate than the MDRD at high levels of renal function.[9] Furthermore, the study by Matsushita et al. (2012), evaluated the risk prediction using the CKD-EPI equation compared to the MDRD equation for eGFR.[10] This analysis was performed using meta-analysis data of 1,130,472 adult patients retrieved from the chronic kidney disease prognosis consortium, assessing the overall improvement in reclassification based on clinical eGFR categories.[10] According to the results of this study, the CKD-EPI equation proved to more accurately categorize the risk of mortality and ESRD compared to the MDRD equation.[10]

In order to stratify patients with CKD, different degrees of impairment of the eGFR were aligned with stages of CKD. All eGFR estimated with MDRD or CKD-EPI equations are expressed as ml/min per 1.73m^2. This grading system is presented in **Table 1.**

Table 1. Stages of CKD According to eGFR

Stage	Qualitative description	GFR (ml/min/1.73m^2)
1	Normal GFR	>90
2	Mild GFR	60-89
3a	Moderate GFR	45-59
3b	Moderate GFR	30-44
4	Severe GFR	15-29
5	End-stage renal disease	<15

GFR: Glomerular filtration rate

Adapted from: Philip McFarlane, D. C., Richard E.Gilbert and Peter Senior (2018). "2018 Clinical Practice Guidelines- Chronic Kidney Disease in Diabetes." Canadian Journal of Diabetes 42: S201-S209.

1.2.2.2 Proteinuria

The second measure, known as proteinuria, involves testing the capacity of the tubules for absorption and excretion of materials to and from the filtrate. More specifically, according to the 2018 Canadian diabetes guidelines, proteinuria is measured with the urine-albumin-to-creatinine ratio (UACR).[4] Although the protein-to-creatinine ratio (PCR) is also a valuable test for proteinuria, UACR was proven to have greater accuracy in terms of both specificity and sensitivity.[11,12] Furthermore, in diabetic patients, albuminuria is a surrogate endpoint for early DN, therefore UACR is prioritized.[11] Other types of tests for albuminuria are also available. The 24-hour urine collection for protein/albumin is the gold standard for measuring proteinuria, however, it is an inconvenient test that is more complicated to implement.[4] The random urine albumin is also available, but never used since it is an insufficient measure since urinary albumin may vary according to urine concentration.[4] Therefore, the UACR is the key clinical measure for screening for albuminuria, predicting the 24-hour urinary albumin excretion. Similar to the eGFR measure, different albumin levels represent distinct stages of nephropathy, known as normoalbuminuria, microalbuminuria and macroalbuminuria. The different UACR measures and their associated albuminuria stages are presented in **Table 2**.

Table 2. Stages of Nephropathy by Level of Urinary Albumin

Stage of nephropathy	Urine dipstick for protein	UACR (mg/mmol)	24-hour urine collection for albumin (mg/day)
Normoalbuminuria	Negative	<2	<30
Microalbuminuria	Negative	2-20	30-300
Macroalbuminuria	Positive	>20	>300
End-stage renal disease	Positive	>67	>1000

UACR: Urinary-albumin-creatinine ratio

Adapted from: Philip McFarlane, D. C., Richard E.Gilbert and Peter Senior (2018). "2018 Clinical Practice Guidelines- Chronic Kidney Disease in Diabetes." Canadian Journal of Diabetes 42: S201-S209.

1.2.3 The Pathology of Diabetic Nephropathy

Diabetes is a chronic disease associated with damage to multiple organs, such as the kidneys, and may lead to DN, CKD and eventually ESRD. The deleterious effects of diabetes related to these complications are directly associated with damage to the nephrons, more specifically the renal tubules and the glomerulus. Two pathways are involved in the damage of the kidneys in DN: the hemodynamic and metabolic pathways.[13] The hemodynamic pathway results from the activation of the RAAS, which leads to the vasoconstriction of the efferent arteriole. More specifically, elevated levels of angiotensin II are related to increased albumin levels and nephropathy.[14] The metabolic pathway of DN is directly linked with hyperglycemia. As explained by Brownlee et al., hyperglycemia leads to the upregulation of four distinct pathways, where each one is associated with its distinctive effects on the kidneys: (1) the polyol pathway, (2) the hexosamine pathway, (3) the production of advanced glycation end products and (4) the activation of protein kinase C.[14]

Although the hemodynamic and the hyperglycemic pathways are the two main actors responsible in the development of DN, other factors are also considered to have an influence. Inflammatory pathways associated with the chronically activated innate immune system and low-grade inflammatory state in diabetic patients is also thought to play a role in the process of DN development.[14] Alternative pathways, including decreased autophagic activity, demonstrated in both obese and diabetic patients, may also impact the development of DN.[14]

1.3 Screening and Diagnosis of Diabetic Nephropathy

The current screening technique for DN is based upon the detection of albumin in the urine as well as a decline of the glomerular filtration rate (GFR), as mentioned previously. According to the Canadian diabetes guidelines, T2D patients require screening at diagnosis and annually thereafter.[4] When no transient causes of albuminuria or low eGFR are present, a random UACR and a serum creatinine test are ordered annually. If the eGFR≤60 mL/min or ACR ≥20.0 mg/mmol, another serum creatinine test for eGFR in 3 months and 2 repeat random urine ACR over the next three months are required.[4] If at three months the eGFR≤60 mL/min or two or three of the ACR ≥20.0 mg/mmol, chronic kidney disease (CKD) is diagnosed.[4] Additional tests, such as urine routine and microscopic (R&M), urine dipstick and serum electrolyte tests are required, in order to ensure the diagnosis of CKD is specifically due to diabetes and no other potential diseases.[4]

1.4 Management of Diabetic Nephropathy: Current Treatment Options

The management of DN is primarily based upon prevention and regression of the disease. Although the regression of DN has been evaluated, current treatment options do not allow for the complete reversal of kidney damage. Furthermore, the prevention of DN is based upon early treatment; it has been observed that drugs present higher success rates for the prevention of DN when given at a very early stage in the disease.[15] Therefore, based on these statements, the main objectives in the management of DN rely on (1) preventing renal disease at the time of diagnosis of T2D and (2) mitigating the progression of renal disease for patients who already have renal complications at the diagnosis of T2D.[4]

Lifestyle modifications, including nutritional therapy, weight management and physical activity, should be the initial non-pharmacological prevention interventions for patients with T2D.[4] However, due to the deleterious effects of hemodynamic and hyperglycemic pathways in DN, these two components must be properly controlled. Other components, including inflammatory pathways, may also be managed in the treatment of DN. However, since hemodynamic and hyperglycemic pathways are the two main causes associated with DN, only the current treatment options associated with the control of hypertension and glycemia, will be presented in this memoir.

1.4.1 Glycemic Control

Controlling glycemia as soon as possible after the diagnosis of T2D helps to reduce the risk for developing DN. Furthermore, intensive glucose control may also slow and/or prevent the progression of renal damage. Although the optimal target glycated hemoglobin (A1C) remains controversial, key pivotal studies support that an A1C of approximately 7% would achieve renal protection. The following studies supported this claim: Diabetes Control and Complications Trial (DCCT), Kumamoto study, United Kingdom Prospective Diabetes Study (UKPDS), and Veterans Affairs Diabetes Trial (VADT).[16-19] The Action in Diabetes and Vascular disease: PreterAx and Diamicron MR Controlled Evaluation (ADVANCE) study also demonstrated that an A1C target of less than 6.5% could reduce the progression of nephropathy.[20] It is to note that all of these studies evaluated patients with early renal disease; therefore, there is no clear evidence of the glycemic control management of diabetic patients with more advanced renal problems.

Different antihyperglycemic therapies are available for use in Canada: biguanides, incretins, sodium-glucose cotransporters-2 (SGLT2) inhibitors, alpha-glucosidase inhibitors, insulins, insulin secretagogues and thiazolidinediones (TZD) (**Table 3**). Two specific drug families, PRAP-γ inhibitors and dipeptidyl peptidase-4 (DPP-4) inhibitors, provide a renal protective effect in addition to their hypoglycemic action.[21] However, some drugs require special precautions and/or dose adjustments for patients with advance kidney disease. [22]

1.4.2 Blood Pressure Control

As mentioned previously, the hemodynamic pathology of DN may also benefit from proper blood pressure control. According to the 2018 Canadian diabetes guidelines, a target blood pressure <130/80 mmHg is sufficient to provide renal protection.[4] However, although the control of blood pressure may be important in the prevention and progression of CKD, none of the studies evaluating this impact have demonstrated a statistically significant benefit on reduction of ESRD and/or improvement in kidney function.[23]

Blockade of the RAAS is a common first-line treatment for patients with T2D and hypertension. The blockade of this system is performed with either angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB).[4] Within this target population, these treatments are known to reduce the risk for developing CKD, independent of their effect on blood pressure.[4] More specifically, ACEI are known to decrease albuminuria and prevent the degradation of CKD, while ARB delays the time to ESRD.[4]

Finally, the combination of RAAS blockers with another or second-line treatments are also considered in the clinical guidelines.

Table 3. Antihyperglycemic Agents for use in T2D in Canada

Treatment Class	Mechanism of Action	Drug
Biguanide	• Enhances insulin sensitivity in liver and peripheral tissues by the activation of AMP-activated protein kinase	• Metformin • Metformin Extended release
Incretin	• Increases glucose insulin release • Slows gastric emptying • Inhibits glucagon release	• DPP-4 inhibitors (ex. Linagliptin, saxagliptin, etc.) • GLP-1 receptor agonists (ex. Exenatide, dulaglutide, etc.)
Sodium-Glucose Cotransporter-2 (SGLT2) Inhibitors	• Inhibits SGLT-2 transport protein to prevent glucose reabsorption by the kidney	• Canaglifozin; • Dapaglifozin; • Empaglifozin
Alpha-glucosidase inhibitor	• Inhibits pancreatic α-amylase and intestinal α-glucosidase	• Acarbose
Insulin	• Activates insulin receptors to regulate metabolism of carbohydrate, fat, and protein	• Bolus insulin • Basal insulin • Premixed insulin
Insulin Secretagogues	• Activates sulfonylurea receptor on β-cell to stimulate endogenous insulin secretion	• Meglitinides (ex. Repaglinide) • Sulfonylureas (Gliclazide, glimepiride, glyburide, etc.)
Thiazolidinediones (TZD)	• Enhances insulin sensitivity in peripheral tissues and liver by activation of peroxisome proliferator activated receptor-activated receptor- gamma receptors (PRAP-γ)	• Rosiglitazone; • Pioglitazone.

DDP-4: dipeptidyl peptidase-4, *GLP-1:* Glucagon-like peptide-1, *SGLT-2:* Sodium-Glucose Cotransporter-2, *TZD:* Thiazolidinediones

Adapted from: Lipscombe L, B. G., Butalia S, Dasgupta K, Eurich DT, Goldenberg R, Khan N, MacCallum L, Shah BR, Simpson S, (2018). "2018 Clinical Practice Guidelines: Pharmacologic Glycemic Management of Type 2 Diabetes in Adults." Canadian Journal of Diabetes, **42**: S88–S103.[21]

1.5 Management of End-Stage Renal Disease: Renal Replacement Therapy

DN may eventually lead to irreversible damage to the kidneys, also known as ESRD. At this stage, patients require renal replacement therapy, which may include either dialysis or renal transplantation therapy (RT).[24] The first-choice treatment for eligible patients is a kidney transplant from a live donor.[24] However, if no live donor is available, kidneys from deceased donors are still significantly much better and preferred compared to dialysis.[24]

1.5.1 Dialysis

Dialysis replaces the essential function of the kidney, which is to filter blood. It removes waste, salt and excess water, provides an adequate balance of electrolytes and helps control blood pressure.[5] There exist two types of dialysis: hemodialysis (HD) and peritoneal dialysis (PD).

1.5.1.1 Hemodialysis

In HD, blood is processed out of the body through a filter, called a dialyzer, and then reintroduced into the body. Hemodialysis can be administered either in-centre (ICHD) or at home (HHD).[25]

In-centre HD is the most frequent type of dialysis, since healthcare professionals take care of the set-up and are also present for the proper patient monitoring.[25] The schedule for ICHD is usually three times per week, where each dialysis session lasts approximately four hours.[25] This type of HD is, however, cumbersome and can interfere with work and daily activities.

Home HD allows for longer and more frequent dialysis, which is more representative of actual kidney function. Home HD is usually performed three to seven times per week, with treatment sessions that last approximately 2 to 10 hours.[25] Different modalities exist: standard HHD, short daily HHD or nightly HHD.[25] The physician is responsible for choosing which modality and which frequency is best for the patient. In a systematic literature review and meta-analysis reviewing the health-related quality of life in HHD patients compared to ICHD, it was concluded that HHD improved the health-related quality of life on the physical domain, with a standard mean deviation of 0.14 (95% CI, 0.04 to 0.24).[26] Although HHD has proven to increase patient's quality of life compared to ICHD, training time for HHD is extensive and often discourages many of prioritizing this treatment option.[27]

1.5.1.2 Peritoneal Dialysis

Peritoneal dialysis uses the lining of the abdomen, also known as peritoneum, to filter blood inside the body.[28] Before starting PD, surgery is performed in order to place a catheter in the abdomen. The dialysis procedure involves inserting dialysis solution into the abdomen through the catheter; once the bag is empty, the catheter can be capped, and the patient may proceed to normal activities.[28] The solution that is inside the abdomen absorbs water and extra fluid, which after a few hours are drained out of the abdomen. This process must be down four to six times a day.[28] There exists two types of PD: continuous ambulatory PD (CAPD) and continuous cycle-assisted PD (CCPD).[28] Continuous ambulatory PD does not use a machine and exchanges of solution bags must be done manually. Contrastingly, CCPD involves the use of a machine called a cycler, which fills and empties the abdomen three to five times during the night.

1.5.2 Renal Transplantation

Renal transplantation is the first choice of treatment for patients in need of renal replacement therapy.[24] As mentioned previously, the donor kidney may come from a deceased or living donor.[24] For patients receiving a kidney transplant from a deceased donor, patients are placed on a waiting list and are treated with dialysis until a compatible donor is found. In Canada, the average time on the waiting list is 3.8 years.[29,30] More specifically, 42% of kidney transplants are made possible by living donors, of which 54% are unrelated to the recipient.[30] Lastly, in order to prevent transplant rejection, a variety of immunosuppressant drugs must be taken daily, lowering the immune system. This may result in infections and other multiple complications and diseases.[25]

2 Comprehensive Overview of Diabetic Nephropathy

2.1 Epidemiology

According to the International Diabetes Federation, it is estimated that 425 million adults aged over 18 years old were living with diabetes in 2017; this number is projected to increase to 629 million by the year 2045.[31] This represents an increase over 30 years of approximately 48%. The increasing prevalence is impacted in majority by low and middle-income countries, more specifically south-east Asia, Africa and the Middle East.[31]

In 2015, the Canadian population with diabetes was estimated to be 3.4 million people, representing 9.3% of the population. The prevalence is projected to rise to 5 million (12.1% of the Canadian population) by 2025, representing an increase of approximately 44% over 10 years.[32] According to the Public Health Agency of Canada, it was estimated that 90% of diabetes cases among Canadian adults are type-2, 9% are type-1 and less than 1% have a different type of diabetes.[2] Moreover, one in four Canadians live with either diagnosed diabetes, undiagnosed diabetes, or prediabetes.[32] About 20 to 40% of total diabetes cases are undiagnosed and the prevalence of prediabetes in adults was estimated at 5.7 million people (22.1%) in 2015.[32] In addition, approximately 10% of deaths in Canada were attributable to diabetes in 2008-2009.[32]

One of the most prominent complications related to diabetes are renal problems. It has been estimated that more than 50% of diabetic patients will develop signs of renal damage throughout their lifetime.[4] According to the *Canadian Organ Replacement Register* annual report for the treatment of end-stage organ failure in Canada, diabetes continues to be the most frequently reported primary cause of ESRD, accounting for 36% of cases.[33] The incidence of DN in T2D patients is unclear for the following reasons: variable ages of onset, difficulty in clearly identifying the exact time of diabetes onset as well as the lack of long-term follow-up studies of patients with T2D.[34] Furthermore, the prevalence of renal disease in diabetic patients is variable between ethnicity, being more frequent in African-Americans, Asian-Americans and Native-Americans.[34] However, since T2D is the most common form of diabetes, the prevalence of DN is most closely influenced by this type of diabetes.

2.2 Causes and Risk Factors Along with Associated Genetic Mutations

The key risk factors associated with DN include long duration of diabetes, non-optimal glycemic control, hypertension, high plasma lipid levels, obesity and cigarette smoking.[4] Another important risk factor includes ethnicity. Specifically, African Americans, Mexican Americans and Pima Indians with T2D have increased chances of developing DN, with increased severity.[35] Socioeconomic factors are also associated with the development of DN, such as: diet, poor hyperglycemia control, poor control of blood pressure and obesity.[35] However, genetic susceptibility is also an important risk determinant of DN, for both incidence and severity.

Multiple epidemiological and clinical studies have demonstrated the heritable genetic susceptibility of DN. Within the last few years, many genetic studies in diabetic kidney disease have been performed, assessing over more than 150 genes in association with DN.[36] It was determined that genetic variants, structural variants as well as epigenetic changes may all play a role in the development of DN.[36] Genetic association

studies have identified multiple candidate genes, and more recently, genome-wide association studies (GWAS) have identified the following genes to be associated with DN: ABCG2,AFF3,AGER, APOL1, AUH, CARS, CERS2, CDCA7/SP3, CHN2, CNDP1, ELMO1, ERBB4, FRMD3, GCKR, GLRA3, KNG1, LIMK2, MMP9, NMUR2, MSRB3/HMGA2, MYH9, PVT1, RAET1L, RGMA/MCTP2, RPS12, SASH1, SCAF8/CNKSR3, SHROOM3, SLC12A3, SORBS1, TMPO, UMOD, and ZMIZ1.[36] A recent meta-analysis of GWAS association studies for eGFR, combining the data of 133,413 individuals, identified 24 new and confirmed 29 previously identified loci.[37] Of these 53 loci, 19 were associated with eGFR and the use of bioinformatics identified that these genes are enriched in kidney tissues, pathways relevant to kidney development, kidney structure and the regulation of glucose metabolism.[37] Similarly, epigenome-wide association studies (EWAS) and the analysis of candidate gene DNA methylation have been assessed for DN. A recent EWAS determined that the following genes may have epigenetic effect associated with DN: SLC22A12, TRPM6, AQP9, HP, AGTX, and HYAL2.[38]

The association of DN with genetic susceptibility explains the fact that not all T2D patients will be equally likely to develop DN and not all DN patients will be affected with the same severity of complications. The identification of genes contributing to the risk of DN could eventually help in the development of new drugs targets as well as the development of genetic tests that could screen patients who are more at risk of developing renal complications.

2.3 Economic Burden

The economic burden of diabetes is on the rise, which is directly related to the increasing incidence worldwide. A study by Bommer et al., forecasted the full global costs of diabetes in adults through the year 2030. The absolute global economic burden was estimated to increase from US$1.3 trillion in 2015 to US$2.2 trillion in 2030.[39] In Canada, a recent study estimated the future direct health care costs due to diabetes for a 10-year period (until year 2022). Over this time period, total costs attributable to diabetes were CA$7.5 billion for females and CA$7.81 billion for males, for a total of CA$15.36 billion.[40] The extent of this economic burden is greatly affected by diabetes associated complications. As previously mentioned, a majority of diabetic patients will eventually develop some type of renal damage, which is directly associated with increased costs for treatment and management.

A Canadian study conducted in 2003 by O'Brien et al., evaluated the cost associated to renal complications in T2D from a healthcare system perspective, including the direct medical costs for laboratory tests and physician visits.[41] The cost for the health state of ESRD was valued at CA$63,045 (2019$CA80,937).[41]

Furthermore, based on the Alberta Annual Kidney Care Report published in 2015, the annual cost of ICHD, HHD and PD were valued at, $95,000 to $107,000, $71,000 to $90,000 and $56,000, respectively.[42] Both of these results portray the extensive economic burden associated with DN, when patients reach ESRD. The costs of ESRD are driven by the cost of renal replacement therapy, which can cost on average CA$100,000 annually.[42]

3 Precision Medicine to Improve the Management of Diabetic Nephropathy

3.1 Definition of Precision Medicine and its use in Diabetic Nephropathy

According to the National Institute of Health, precision medicine is defined as an "emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment and lifestyle for each person."[43] The current treatment methods in medicine are primarily based on the idea of "one-size-fits-all", which often prioritizes the average person, and leaves out effective treatments for individuals with more unique needs. The approach of precision medicine should be viewed as a personalized medicine, in which medicine would be based on a practice which would provide unique treatment and management in different groups of individuals.[43] It is thought that precision medicine would improve the practice of medicine in its entirety and consequently, improve patients' quality and duration of life.

3.2 Polygenic Risk Score for the Prevention of Diabetic Nephropathy

3.2.1 ADVANCE Trial

The ADVANCE (Action in Diabetes and Vascular Disease PreterAx and DiamicronN Controlled Evaluation) trial was a factorial randomized controlled trial performed across 20 countries, including Asia, Australia, Europe and North America.[44] A total of 11,140 patients with T2D, 55 years or older with a history of macrovascular or microvascular disease were randomized to a blood pressure and a blood glucose treatment arm.

The aim of the blood glucose arm was to assess the effects on major vascular outcomes of lowering A1C value to a target of 6.5% or less (intensive glucose control treatment) in patients with T2D.[20] More

specifically, the effect of Diamicron (gliclazide) was assessed against standard glucose control therapy. The aim of the blood pressure control arm was to assess the effects on vascular disease of Preterax® (a fixed combination of ACEI, perindopril, and the diuretic, indapamide) compared to placebo, in patients with T2D and a broad range of blood pressure values.[23] The 2x2 factorial design of the study led to the randomization of four distinct sub-groups: perindopril-indapamide and intensive glucose (n=2,783), perindopril-indapamide and standard glucose (2,786), blood pressure placebo and intensive glucose (2,788) and placebo blood pressure and standard glucose (2,783).[44] The primary study outcomes were composed of both macrovascular and microvascular outcomes, assessed during an average follow-up of 4.3 years.[44] The microvascular events specific for renal outcomes were defined as new or worsening nephropathy, such as the development of macroalbuminuria, doubling of serum creatinine to at least 200 μmol/L, the need for renal-replacement therapy or death due to renal disease. Secondary outcomes specific to renal events included the development of microalbuminuria.

The main results of the ADVANCE trial demonstrated that the effects of blood pressure lowering and intensive glucose control therapy are independent of each other. When both treatment arms are combined, additional reductions in macrovascular and microvascular events are observed.[44] The results specific for renal events demonstrated that in the blood glucose arm, the relative risk reduction in new or worsening nephropathy was equivalent to 21% (95% CI: 7%-34%) and the relative risk reduction in new-onset microalbuminuria was 9% (95% CI: 2%-5%).[20] The blood pressure arm revealed that the relative risk reduction for total renal events was equal to 21% (95% CI: 15%-27%).[23]

Some factors may have influenced the trial results between both intensive and standard treatment groups. First, different follow-up schedules were performed; the intensive control group were seen at months 1, 2, 3, 4, and 6 for this first 6-months, and every 3 months thereafter. For the standard control group, patients were seen at months 3, 4 and 6 after randomization and every 6 months thereafter. For patients with intensive treatment, physicians were encouraged to promote lifestyle management such as weight loss and exercise. In addition, other oral agents and glycemic control therapies could be used to help control A1C, within both treatment groups. At the end of trial follow-up, the intensive group generally used more concomitant drugs; for example, insulin was used by 41.0% of the intensive group patients, while in the standard control group, insulin was only received by 24.0% of patients. Therefore, all above-mentioned points may potentially play a role in influencing results, by increasing the patient's overall health due too more frequent and more complete physician control of the patient's diabetes.

Furthermore, very limited side effects associated with intensive glucose control treatment was captured within the trial. This could be explained by first, the incremental approach with gradually increasing number of concomitant glucose control treatments. This method lowered the A1C gradually, achieving the target A1C of 6.5% over 2 years. The slow fall in A1C could explain the limited adverse events, especially those associated with hypoglycemia. Another frequent side effect associated glucose control is weight gain. However, in the ADVANCE trial, no weight gain was recorded. This unexpected result might be explained by the high proportion (37.0%) of Asian patients within the trial, who usually tend to have a lower body mass index. This could also be explained by the inclusion of patients with relatively low A1C levels into the trial. Recruiters were advised to exclude patients whose glycemic control was likely to deteriorate, therefore, mostly excluding newly diagnosed patients with none stabilized A1C levels upon treatment initiation.

3.2.2 ADVANCE-ON Trial

The ADVANCE trial had a follow-up trial, named the ADVANCE-ON trial.[45] This was a 6-year post-trial follow-up of 8,494 patients who had initially participated in the ADVANCE trial. The glucose control cohort demonstrated that after follow-up, the reduction in the rate of incidence of ESRD remained significant (HR 0.54, p=0.007).[45] However, as demonstrated in the trial period, the post-trial follow-up did not reveal a statistically significant difference with respect to death from renal causes (HR 0.89, p=0.56).[45]

3.2.3 The Polygenic Risk Score

Recently, a group from the Centre Hospitalier de l'Université de Montreal (CHUM) genotyped 4,098 patients from the ADVANCE trial, in order to build a polygenic risk score (PRS) for each of the renal and cardiovascular outcomes. In order to build this PRS, 26 risk factors of vascular complications in T2D were selected and divided into 9-risk groups including single nucleotide polymorphisms (SNPs) associated with diabetes, obesity, blood pressure, albuminuria, GFR, biomarker level, lipids, cardiovascular disease and low birth weight. Genome-wide association studies reported in the National Human Genome Research Institute GWAS catalogue were used to extract 612 SNPs of individuals of Caucasian origin, and their effect size for all 26 risk factors. Polygenic risk scores were generated for each of the renal and cardiovascular outcomes by weighting risk alleles by the effect size of their association and adjusted for geo-ethnicity, sex, age at diagnosis and diabetes duration. The predictive performance of each of the PRS was determined as the area under the curve of the receiver operating characteristics (ROC), and was used

to stratify the 4,098 T2D patients of Caucasian origin in the ADVANCE trial followed for a period of 10 years, according to their risk of experiencing complications related to T2D. Results were replicated in three independent population cohorts. The prediction of albuminuria using the PRS was replicated in the Clinpradia and the Czech post-MONICA studies. The prediction of myocardial infarction and stroke using the PRS was replicated in the Canadian Partnership for Tomorrow's Project pan-Canadian population cohort.

Findings of this study revealed that 30% of the ADVANCE trial participants were at increased risk of cardiovascular death compared to other patients. The highest risk of macrovascular events and death was seen in older patients with highest PRS. However, for the risk of microvascular events, including renal events, the risk was highest in patients with high PRS and early-onset diabetes (before age 56). The cumulative incidence rate of death and ESRD was also significantly different between individuals with low, medium and high PRS. It was observed that intensive blood pressure control led to a significant reduction of total death (HR 0.797, p=0.046) and cardiovascular death (HR 0.677, p=0.009) in individuals with the highest PRS, and this reduction remained significant in the ADVANCE-ON. These reductions were not seen with intensive glycemic control; however, it was observed that intensive glycemic control led to a significant reduction in ESRD in individuals with high PRS (HR 0.345, p=0.043) and remained significant at the end of the ADVANCE-ON trial (HR 0.455, p=0.026). Therefore, when considering results specific to renal events, the PRS and its associated intensive glucose control treatment would have a beneficial impact, compared to blood pressure lowering treatments. Overall, the results of this study suggest the usefulness of a PRS in the primary prevention before target organ damage occurs.

4 Economic evaluation – Theoretical Notions

4.1 Rationale for Economic Evaluations

Health economic evaluations are essential in order to guide decision makers for the reimbursement of drugs and technologies coming onto the market. According to Drummond et al., economic evaluations are defined as: "the comparative analysis of alternative courses of action in terms of both their costs and consequences."[46] Resources of the healthcare system are not infinite and under scarcity, it is essential to efficiently allocate resources and maximize benefits. Therefore, economic evaluations serve as a decision-making tool, seeking to compare all treatment alternatives in a fair and effective manner in order to provide the best possible care for patients.

In Canada, there exists two agencies responsible for providing research and analysis to healthcare decision makers regarding the reimbursement of drugs and technologies: the Canadian Agency for Technologies in Health (CADTH) and the Institut national d'excellence en santé et en services sociaux (INESSS). CADTH is responsible for providing evidence, analysis, advice and recommendations to all Canadian provinces. Quebec is the only province with its own agency, INESSS, which does not generate new evidence but rather evaluates new drug submissions.

4.2 The Economic Evaluation

As mentioned in the recent guidelines for the economic evaluation of health technologies, published by CADTH in 2017, different key elements must be considered in the development of an economic evaluation.[47]

4.2.1 Type of Economic Evaluations

There exist 5 types of economic evaluations: cost-benefit analysis (CBA), cost-consequence analysis (CCA), cost-minimization analysis (CMA), cost-effectiveness analysis (CEA) as well as cost-utility analysis (CUA).[46]

The CBA evaluates the cost and consequences of an intervention, both in monetary terms. This technic is used when the consequences of the intervention cannot be measured in terms of natural units or quality-adjusted life years (QALYs). The CCA is presented as an enumeration of all costs and outcomes related to the study intervention. This type of analysis is often used when the intervention has more than one consequence on health outcomes. The CMA is prioritized when all clinical outcomes between the alternative strategies being assessed are assumed equivalent. The goal of this analysis is to assess the least expensive option. The CEA is used when the outcomes of alternative strategies are not equivalent and can only be measured in terms of natural units, such as life years gained, number of cases avoided, etc. This analysis assesses the cost of the interventions to compare in relation to a common efficacy denominator measured in natural units. The CUA is the most widely used economic evaluation in pharmacoeconomics. According to the CADTH guidelines, a cost-utility analysis is the recommended type of economic evaluation and should be used as the reference case analysis.[47] The CUA is similar to a CEA, where the efficacy denominator is measured in terms of QALYs (the QALY if further described in **section 4.2.7**). This use of this generic outcomes measure allows for the comparison between different health outcomes

(including short- and long-term effects), even across different diseases. Typical results of CUAs will be expressed as cost per QALY gained. Other generic outcome measures, such as the disability-adjusted life year (DALY) and the health-years equivalent (HYE), can also be used as alternative to the QALY. One DALY is known as one lost year of healthy life.[48] A DALY quantifies the burden of disease by summing up the years of life lost due to premature mortality as well as the years lost due to disability or disease.[48] In other words, the primary focus of the DALY is the measure of the global burden of disease.[46] Although the majority of CUAs use QALYs as the effectiveness measure, the DALY is the second most common measure used in CUAs.

4.2.2 Target Population

In an economic evaluation, the population should be the target population for the intervention and its expected use, as requested for reimbursement. The population should also be in alignment with the decision problem at hand.

4.2.3 Comparators

According to the most recent CADTH guidelines, comparative treatment should reflect current practice and constitute the current standard of care that is most likely to be replaced by the study treatment.[47] In addition, this treatment should be reimbursed by most Canadian provinces. Sometimes the comparator may be presented as the absence of treatment, especially in certain pathologies where the intervention being evaluated is the first targeted therapy or in situations where the main interventions are associated with watchful waiting.

4.2.4 Perspective

In every economic evaluation, a perspective must be selected. The chosen perspective will guide the point of view of the analysis and determine which costs and results will be included in the analysis. According to the economic evaluation guidelines published by CADTH, a publicly funded health care payer perspective should be used.[47] For this perspective, only direct medical costs are considered, including drug acquisition costs, physician fees, follow-up and monitoring test, nursing fees, cost related to adverse events, etc. More specifically, the health care payer perspective only considers the costs directly paid by the health care payer's budget. According to the INESSS, the societal perspective is required.[49] This perspective also

takes into consideration direct medical costs along with indirect cost, associated with productivity loss of patients and their caregivers. In other words, the societal perspective encompasses the costs paid by the healthcare payer as well as those paid by the society, including the patients budget. When adding indirect costs to an analysis, results favor the alternative that increases the patient's productivity. Therefore, an alternative that may seem less favorable from the healthcare payer perspective may become favorable in terms of cost-effectiveness, when including indirect costs.

4.2.5 Time Horizon

The time horizon corresponds to the time period for which the costs and outcomes are calculated. According to CADTH guidelines, the time horizon should be long enough in order to capture all the relevant differences in cost and outcomes associated with the interventions and comparators.[47] For chronic diseases, a lifetime horizon covering the entire patient's life is to be prioritized.

4.2.6 Discounting

When performing an economic evaluation over a time horizon of more than one year, discounting is applied to take into account time preference, more specifically the time preference of individuals for the present or the future. A good example to display this concept would be: what would be the preference for having $500 today compared to $500 in 5 years? The following formula is used to calculate discounting:

$$P = \sum_{n=0} F_n(1+r)^{-(n-1)}$$

where P = present value, F_n = future cost as year n and r = discounting rate.

Therefore, according to a discount rate of 1.5%, the preference of having $500 today would be valued at the complete $500, while the preference of having $500 in 5 years would be valued at $471. In other words, receiving money today is preferred and more valuable than receiving that same amount of money later in time. According to CADTH guidelines, discounting of costs and results following the first year of the model must be estimated.[47] This must be performed at a discounting rate of 1.5% per year.[47] The impact of the uncertainty around this value should be assessed by using alterative discount rates of 0% and 3% and comparing the consequent results to the base-case analysis (1.5%).

4.2.7 Utility and Quality Adjusted Life Years

Utility is a preference-based measure associated with a specific health state. This measure can vary between 0 and 1, where 0 represents death and 1 represents perfect health. When a health state is worse than death, utility scores are measured in negative values. Utility measures are crucial in CUA, as they are used to weight the years of life gained by the quality of life of these years, in order to establish the number of QALYs. Utility can be measured via two distinct types of methods: direct and indirect.

The direct methods are based on mapping preferences directly onto a utility scale. This can be measured through the methods of time-trade-off (TTO), standard gamble or the visual analogue scale.[46] The TTO reflects the length of remaining life expectancy that a patient is ready to trade-off in order to avoid remaining in a sub-optimal health state. Standard gamble presents a model for decision making under uncertainty; this method involves asking a patient if they rather remain in a specific health state for a certain number of years, or opting for a risky option that may either allow them to live in full health or die immediately. Researchers alter the probability of immediate death until the patient is indifferent and values both options equally. Lastly, the visual analogue scale, which is less favored, involves ordering health states from the most to the least desirables, on a scale from 0 to 100. Indirect methods are time consuming and must be administered without leading or destressing the patient.

The indirect methods combine the principal characteristics of measuring the quality of life and the measure of utility. These methods are based on mapping preferences onto a utility scale, indirectly, through the administration of validated questionnaire, such as the EQ-5D, Health Utilities Index (HUI) and the Short Form 6-Dimensions (SF-6D).[46] The questionnaire responses have been previously tested and calibrated in a population of unaffected individuals, using a direct method, providing conversion tables to transform the quality of life scores into utilities. The EQ-5D evaluates the health status of 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The HUI is very similar to the EQ-5D but is based on a scoring formula of standard gamble utilities measures in the general population. The HUI refers to both the HUI2 and the HUI3 instruments. The HUI2 evaluates the health states of 7 dimensions: sensation, mobility, emotion, cognition, self-care, pain and fertility. The HUI3 evaluates the health states of 8 dimensions: vision, hearing, ambulation, dexterity, emotion, cognition and pain. The SF-6D evaluates the health status of 6 dimensions: physical functioning, role limitations, social functioning, pain, mental health and vitality. Contrary to the EQ-5D, the questionnaire was calibrated using the standard gamble measurement of a random sample of the general population in the United Kingdom.

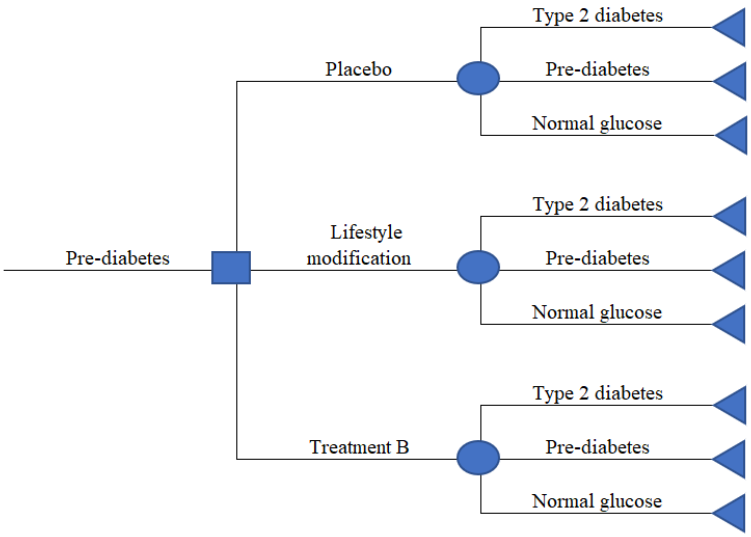
All indirect methods are very different from one another.[46] First, they vary in the dimensions that are evaluated as well as how the questionnaire is leveled and graded. They also differ in the population surveyed, where the conversion algorithms are country specific. The type of instrument used to measure the utility score (TTO or standard gamble) also differs. Finally, the theoretical approach used to model the preference data into a scoring system also varies between methods. The HUI uses the multi-attribute utility theory while he EQ-5D and SF-6D uses econometric modelling. All these differences' present multiple challenges in order to incorporate data into economic evaluations. Since utility data is not always widely available for all diseases and sometimes not specifically tested within each country, some assumptions must be taken in order to integrate utility data to cost-utility analyses. Some evaluations may require the use of utility data obtained from various methods as well as from various populations. However, utility values remain for now, the most appropriate way to value a health state and to compare this health state among other diseases.

4.2.8 Model Structure

The natural course of a disease is composed of a lot of uncertainties. Modelling makes it possible to reproduce and schematize, as realistically as possible, the range of scenarios associated with a disease. Some of the most commonly used modelling technics in pharmacoeconomics include decision trees, Markov models, discrete event simulations as well as two steps models (decision tree followed by a Markov model).

The decision tree is often used to represent an individual's likely course through a disease, following an intervention, by a series of different pathways.[46] In other words, the decision tree allows to visually represent complex processes that include different options as well as different consequences that can arise from these options. The mapping of the decision is done through decision nodes and chance nodes. The decision node is a square box placed at the beginning of a decision tree and represents the decision being addressed in the model, where only one intervention or option may be selected. The chance nodes are placed following the decision node and represents a range of possible events that may occur after the initial decision-making. The events that come after the chance nodes are mutually exclusive events. These pathways are built in the form of a tree, through a series of branches, each representing the likelihood of occurrence of various events. An example of a decision tree is illustrated in **Figure 1**.

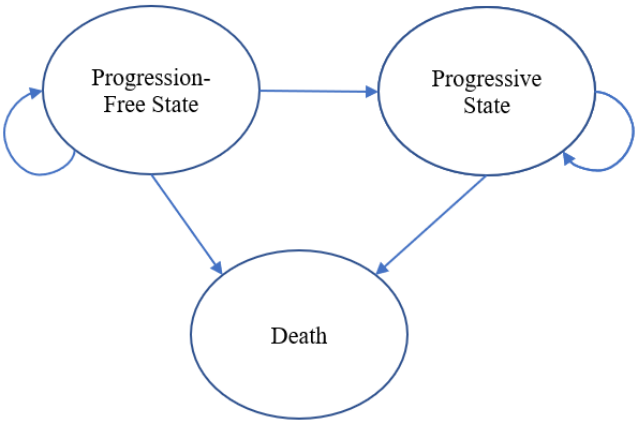
Figure 1. Example of a Decision Tree



However, although the decision tree is widely used in pharmacoeconomics, it is associated with several limitations. Firstly, the decision tree only considers events that are occurring over an instantaneous discrete time period.[46] For this reason, economic evaluations that require time dependence modelling can hardly be performed through this type of model structure. Another limitation is associated with the fact that chronic diseases associated with complicated long-term prognosis are very complex to model with decision trees.[46] In other words, when a patient is at risk for many years, with the possibility of experiencing multiple events over time, the decision tree becomes complicated to model and analyze. For example, modelling a patient with early stage ovarian cancer would have to include all the risks associated with adverse events, cancer recurrence, remissions and death. Since a cancer patient is at risk of many events over a long time period, the decision tree would become extremely big. Such a model would be time consuming as well as hard to program and retrieve analyzed data.

The Markov model, however, is a powerful tool in pharmacoeconomics and is one of the most frequently used in order to represent the natural course of a disease implicating transitions between different health states or clinical events over time.[46] This model is presented in the form of round circles representing different health states of a disease. From a health state, arrows point other possible health states that a patient may transfer too, after the end of each model cycle. The circling arrows within the same health state indicate that patients may remain within a health state for more than one model cycle. An example of a Markov model for cancer, such as that for ovarian cancer explained above, is illustrated in **Figure 2**.

Figure 2. Example of a Markov Model



The transition probabilities from one health state to another are measured at each predefined time period, called the Markov cycle. The length of each cycle is constant throughout the entire time horizon of the model and can be defined by any time period (days, weeks, months, years, etc.) More specifically, patients can transition from one health state to another until they reach the absorbing health state, often defined as death. Patients may also remain in the same health state for the subsequent Markov cycles, if the health condition remains stable. Since health states are considered exclusive, meaning that patients cannot be in more than one health state at a time, the sum of all transition probabilities equal to 1. Furthermore, transition probabilities are independent of the previous health states. This absence of memory of an individual's pathway included in the model for the subsequent cycles, constitutes one of the major limitations of the Markov model.[46] However, this problem may be countered through the addition of more detailed/specific health states, allowing for the creation of an "artificial memory" within the model Finally, transition probabilities may remain constant or vary in function of time. This aspect allows to define two different types of Markov models: Markov chains (constant transition probabilities over time) and time-dependent models (variable transition probabilities over time).

4.2.9 Willingness-to-Pay Threshold

Willingness-to-pay threshold is defined as the maximum amount that an individual is willing to pay for a certain good or service. In health economics, the willingness-to-pay is the valuation of health in monetary terms. In Canada, $50,000/QALY had been viewed as a generally acceptable willingness-to-pay threshold for drug decision-making. More specifically, this threshold represents that the health care system (when

using a health care payer perspective) is willing to pay $50,000 for one additional QALY. Although this threshold is generally accepted, it is not fixed in stone and may vary according to the disease being analyzed.

4.2.10 Sensitivity Analysis

Sensitivity analyses are required in all economic evaluations in order to test the robustness of the base-case results. In other words, sensitivity analyses allow to evaluate and measure the impact of the uncertainty associated with certain key model parameters. Two distinct types of sensitivity analyses may be performed: deterministic sensitivity analyses (DSA) and probabilistic sensitivity analyses (PSA).

Deterministic sensitivity analyses consists of varying one individual parameter at a time, between lower and upper bound values. This type of analysis allows to determine which key parameters have the greatest impact on the base-case results. The upper and lower bounds are often calculated using the confidence intervals (95% CI). When this information is not available, variation of +/-25% of the base-case parameters are frequently used. Finally, the results of DSA are often presented through Tornado diagrams, which visually presents the most to the least influential parameters on the base-case results.

Probabilistic sensitivity analyses, on the other hand, constitute in varying parameters according to predefined probability distributions. PSA are often modelled through Monte Carlo simulations. This type of simulation allows to assess simultaneously the impact of the uncertainty of all parameters, through the selection of random values from the pre-defined distributions of every parameter. The most commonly used probability distributions are the gamma, beta and log-normal distributions. Beta distributions are used for probabilities, while gamma and log-normal distributions are used for cost and utility parameters.[47] The results of the PSA are often presented graphically, in two distinct ways: a cost-effectiveness acceptability curve (CEAC) and a scatter plot diagram. The CEAC illustrates the probability that an intervention will be considered cost-effective in terms of different thresholds of cost-effectiveness. As mentioned previously, in Canada, $50,000/QALY had been viewed as a generally acceptable willingness-to-pay threshold for drug decision-making. An example of a CEAC is presented in **Figure 3**. The scatter plot diagram illustrates all simulations in terms of incremental cost and incremental QALYs, in order to show how one variable is affected by the other as well as which simulations are found within the four quadrants of the cost-effectiveness plane. An example of a scatter plot diagram is presented in **Figure 4**.

Figure 3. Example of a CEAC

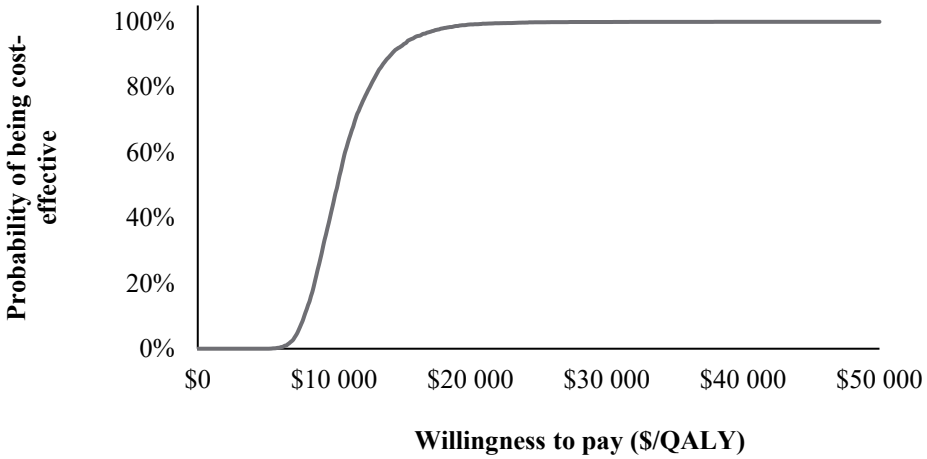
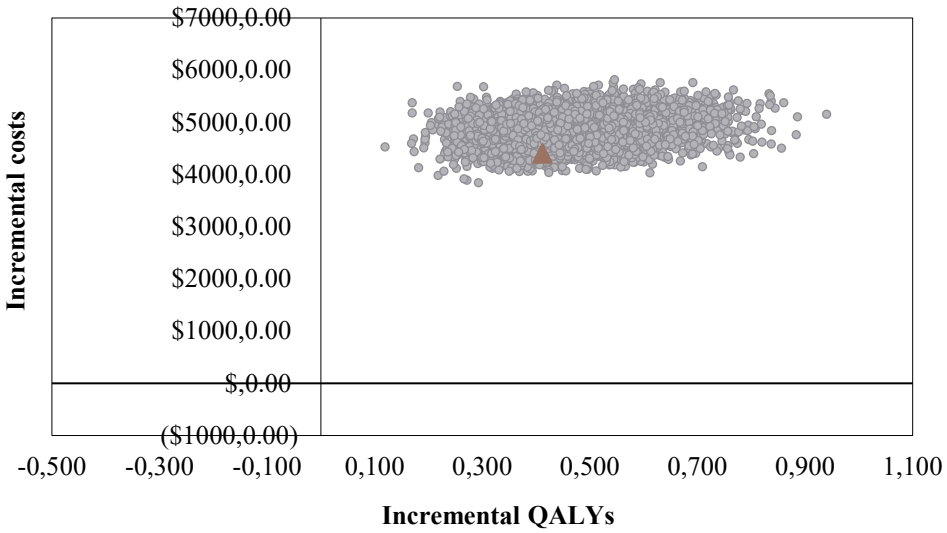


Figure 4. Example of a Scatter Plot Diagram



5 Conclusion on the State of Knowledge

In conclusion, improvement of the risk prediction is crucial to enable targeting individuals at high risk of developing diabetes-related complications that are both serious and costly. The recent development of a PRS for the screening of DN in patients with T2D is a major clinical advancement, which would result in important clinical benefits and potentially economic benefits for the health care system. Health economic evaluations are an essential tool in order to assist the decision of policy makers whether the added benefits justify their costs. To date, no study has assessed the of a cost-effectiveness PRS, as a screening method for DN. An economic evaluation of the PRS would be necessary in order to guide decision makers, such as hospitals and governments, towards a more informed choice related to its implementation in the clinical practice setting.

6 Objectives

The main objective of this research project was to estimate the economic impact of PRS for the prevention of DN in T2D patients. The economic analysis seeks to assess whether the PRS is cost-effective compared to what is done in current practice. More specifically, the project consists of two specific objectives.

Objective #1: The first objective of this study was to perform a systematic literature review examining all the published economic evaluations in patients with T2D and nephropathy. The aim of this review was to evaluate the different characteristics of all economic evaluations (including CBA, CCA,CMA, CEA, CUA as well as COI studies) in the field of DN and T2D as well as to identify the methods that were used in order to assess this economic impact. This literature review will serve as a useful tool in guiding the development of the economic model (objective #2).

Objective #2: The second objective of this study consisted of developing an economic evaluation comparing the usual screening methods for DN to the use of a PRS, for patients with T2D. In other words, the objective was to assess whether the PRS is a cost-effective alternative compared to usual screening methods, from a Canadian health care system and societal perspective.

7 Methods

7.1 Study #1: Systematic literature review of the economic evaluations in type 2 diabetic nephropathy

7.1.1 Information Sources

A systematic literature review was performed according to the most recent guidelines in health economics evaluations according to Cochrane Handbook for Systematic Review of Interventions as well as the INESSS guidelines.[50,51]

The search was designed to identify all economic evaluation publications that included patients with T2D and DN. More specifically, the search could include all different types of economic evaluations assessing any type of intervention for the treatment of DN in patients with T2D. Since any type of intervention(s) and/or comparator(s) could be included within the search, the Cochrane PICO framework was not considered for this review.

7.1.1.1 Literature search strategy

The literature search was performed in MEDLINE and EMBASE for the period of 1995 to 2018 (March 4th, 2018) and in PubMed for the current year (2018), in order to retrieve publications not yet indexed in MEDLINE and EMBASE. The keywords included in the search are presented in presented in **Appendix A (Table A.1-A.3)** and were:

- Diabetic nephropathy
- Economic evaluations, more specifically the search filters provided by CADTH for economic evaluations in health.[52]

7.1.1.2 Snowballing

In addition, snowballing of the selected studies in the literature search was performed. More specifically, the reference list of identified articles as well as those of review articles were manually screened for relevant economic evaluations not identified in the above-mentioned searches.

7.1.1.3 Pragmatic Searches

A non-systematic search of the grey literature was also performed in order to capture all possible economic publications not captured in the literature and snowballing searches. The reviewed grey literature included the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), the CADTH, the INESSS as well as the National Institute for Health and Care Excellence (NICE).

7.1.2 Study Selection

Inclusion criteria for the literature review included the following:

- Nephropathy for patients with T2D
- Economic evaluations, including CUA, CEA, CCA, CMA, cost-study as well as cost of illness (COI) studies.
- Published between 1995 and March 4th, 2018
- Available in full text
- Published in French or English

The study selection was performed in two distinct steps. First, the titles and abstracts of articles retrieved from the search were screened for eligibility. Secondly, the full text of included articles was read in depth and assessed for eligibility using an inclusion criterion grid. For all excluded articles, the reason for exclusion was documented. Two reviewers (Kimberly Guinan and Marie-Ève Richard) independently assessed the eligibility of the articles and differences in study selection were resolved by consensus, for validation purposes.

7.1.3 Data Extraction

The data extraction included: 1) Name of the first author and year, 2) year of publication, 3) type of economic evaluation, 4) model structure, 5) time horizon, 6) intervention and comparators, 7) types of costs included, 8) perspective of the study, 9) sources of cost parameters, clinical data and utility values used in the analysis and 10) results of the economic analysis.

Two reviewers (KG and MR) independently conducted data extraction included in the review. For validation purposes, differences in interpretation by the two reviewers were resolved by consensus.

7.1.4 Synthesis of Findings

A quantitative assessment of the extracted data was performed, for all publications dates as well as two distinct subgroups from 1995-2007 and 2008-2018. These two timeframes were selected in order to distinguish between older and more recent publications, published within the last 10 years from the date of the literature search. For economic evaluations (CUA, CEA, CCA, CMA and cost-study) the following information was analyzed: 1) year and country of publication, 2) the type of economic evaluation, 3) analytical perspective, 4) model structure, 5) time horizon, 6) source of clinical data and 7) intervention and comparators. For COI studies, the following information was analyzed: 1) year and country of publication, 2) analytical perspective and 3) time horizon.

The assessment of heterogeneity between studies was not performed, since the main objective of this review was to evaluate the different study characteristics of the economic evaluations published in T2D and DN. The results retrieved from the publications were not assessed for data pooling or other types of statistical analyses. However, the main trends observed in cost-effectiveness of different treatment options were evaluated. In order to make results comparable between studies, all costs or incremental cost-effectiveness ratios (ICERs) were adjusted to 2019 Canadian dollars. This was done by first, converting costs to the Canadian currency of the retrieved year using a currency converter and secondly, actualizing the costs to 2019 using the Canadian Consumer Price Index (CPI) for Health and Personal Care for the month of June when available (half-year).[53] When the currency and year of currency were mentioned in the studies, the adjustments were made from these data. However, when the information was not available, the country of origin and the year of publication were used as a reference for the adjustment of costs, if possible.

7.1.5 Author Contribution

Kimberly Guinan was responsible for conducting the entirety of the literature search. The search strategy was developed by KG and validated by Michelle Savoie, Catherine Beauchemin and Jean Lachaine. The literature search was done by KG. The study selection as well as the data extraction was performed by both KG and Marie-Ève Richard, as a second reviewer for the systematic analysis. Data synthesis was performed by KG. The manuscript was prepared by KG. All authors reviewed the final manuscript.

7.2 Study #2: Economic evaluation of a new PRS to prevent nephropathies in type-2 diabetic patients

7.2.1 Type of economic evaluation

A CUA was conducted according to the most recent guidelines for the economic evaluation of health technologies published by the CADTH in 2017.[47] As mentioned previously, according to these guidelines, a CUA is the recommended type of economic evaluation and should be used as the reference case analysis.[47] Cost-utility analyses allow for the comparison between different health outcomes (including short- and long-term effects) by "*measuring them all in terms of a single unit, the QALY*"[47] and thus, results of the analysis will be expressed as a cost per QALY gained. For these reasons, this economic evaluation will be a CUA.

7.2.2 Target Population

The study population consisted of T2D patients 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 in order to establish a PRS.[54,55] The mean age of the population was 67 years old (SD: 7), the mean age at diagnosis of T2D was 60 years old (SD: 9) and the median duration of diabetes was of 5 years (SD: 2-10).

Ideally, the polygenic test would be given to patients with newly diagnosed T2D. Since the genotyped data as well as the response to therapy of these patients is not available, this cannot be the target population for this economic evaluation. However, we can only estimate that if the proper intervention was given at diagnosis, better results would be observed to the one's estimated in the ADVANCE trial. In other words, the target population used in this economic evaluation leads to conservative results regarding cost-utility, compared to the actual population that is targeted by the PRS in a real-world clinical scenario.

7.2.3 Comparative Treatments

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

As mentioned previously, comparative treatment should reflect current practice and constitute the current treatment or care that should be replaced by the study treatment.[47] In addition, this treatment should be reimbursed by most Canadian provinces. In a population of patients with T2D, usual screening for DN is the best comparator, since this is the standard diagnostic method and is most likely to be replaced by the PRS. As presented in the introduction, **section 1.3**, usual screening for DN is primarily composed of yearly testing for UACR and serum creatinine, starting at diagnosis of T2D.[4] If both tests results are positive, further tests including R&M, urine dipstick as well as 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, while 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 to 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 Chalmers., 2010.[56] The treatments were stratified as such since the intensive treatment had the most beneficial impact for high-risk group patients ($p = 0.043$) compared to other PRS groups.

7.2.4 Perspective

In order to meet CADTH requirements, analyses of this economic evaluation were conducted from a Canadian Ministry of Health (MoH).[47] The model also allows the possibility to conduct analyses from a societal perspective, meeting the requirements for the INESSS.[49] From a MoH, only direct medical costs were considered. From a societal perspective, costs associated with lost productivity of patients and caregivers were added to the total direct medical costs.

7.2.5 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.[47] 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.

This economic evaluation was conducted over a time horizon of 5 years, since trial data under randomized treatment were only available for this period. However, scenario analyses of varying time horizons were conducted. Data of 4.5-year was extrapolated to time horizons of 10 and 30 years (lifetime) in scenario analyses, in order to capture all events of ESRD and all-cause deaths. A time horizon of 10 years was also tested using 9.5-year non-randomized data, in order to capture the impact of treatment cessation after 4.5 years of trial.

7.2.6 Discount Rate

As per CADTH guidelines, the costs and QALYs beyond the first year have been discounted at an annual rate of 1.5%.[47] Discount rates of 0% and 3% were also used in the sensitivity analyses.

7.2.7 Model Structure

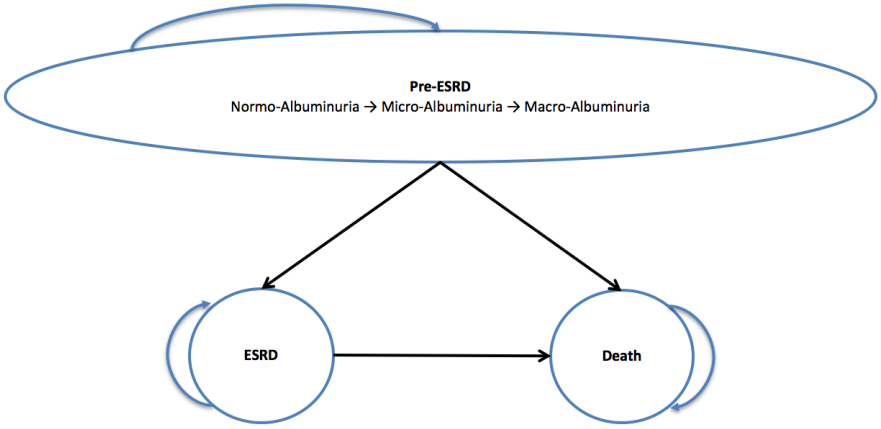
Based on the course of the disease, a Markov model was developed to assess the cost-effectiveness of the PRS compared to usual screening for the detection/prevention of DN in T2D patients. The Markov model captures all the costs and effects of the interventions evaluated for a given period. The model simulates the course of the disease and includes three health states: pre-end-stage renal disease (ESRD), ESRD and death. The model diagram is shown in **Figure 5**.

Within the PRS scenario, it was assumed that the entire cohort would be subdivided according to their respective PRS. As captured in the genotyped ADVANCE population, it was assumed that the PRS would be 37.10%, 33.50% and 29.40% for low, medium and high-risk groups, respectively.[57]

The pre-ESRD health state was composed of all stages of DN preceding ESRD, including normo-albuminuria, micro-albuminuria and macro-albuminuria. At baseline, it was established that 70% of patients would be in normoalbuminuria, 26% in microalbuminuria and 4% in macroalbuminuria.[57]

The ESRD health state included patients with renal failure, all treated with either dialysis or RT. According to the Canadian Institute for Health Information, it was assumed that 57.9% of patients are treated with dialysis and 42.1% are treated with RT.[29] For patients receiving dialysis, ICHD and PD were considered.[29] It was assumed that 75% would receive ICHD, 25% would receive PD, while no patients (0%) would receive HHD.[29]

Figure 5. Markov Model



7.2.8 Effectiveness

Transition between health states were calculated using patient-level data of the ADVANCE trial, stratified by time of event, type of event, type of treatment (intensive versus standard glucose control treatments) and risk group (high, medium or low PRS). In order to calculate the probability of ESRD and all-cause death, Kaplan Meier (KM) curves were generated using the Statistical Package for Social Sciences (SPSS; version 25) 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 the R software for statistical computing.[58,59]

The parametric distributions fitted to the KM data were Weibull, exponential, log-normal and log-logistic.[58] The best fitting parametric distribution was chosen by statistical consideration (Akaike information criterion [AIC]) and the Bayesian information criterion [BIC]), visual inspection (comparing fitted distribution to the study KM plots) as well as clinical plausibility.

More specifically, the probabilities were measured differently for all three PRS levels. These probabilistic distinctions considered in the model will be explained in the following sections.

7.2.8.1 Probability of End-Stage Renal Disease

7.2.8.1.1 Probability of End-Stage Renal Disease for Low Polygenic Risk Score

For the low PRS sub-group, 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.

7.2.8.1.2 Probability of End-Stage Renal Disease for Medium Polygenic Risk Score

For medium PRS sub-group, 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. According to the AIC and BIC scores, combined with visual inspection, the exponential distribution was selected for the base-case analysis. The 4-year parametric distributions are presented in **Figure 6**, while the extrapolated distributions are presented in **Figure 7**.

Figure 6. Kaplan Meier Data with Standard Parametric Curve Fitting for ESRD, Medium PRS Group – 4-Year Data

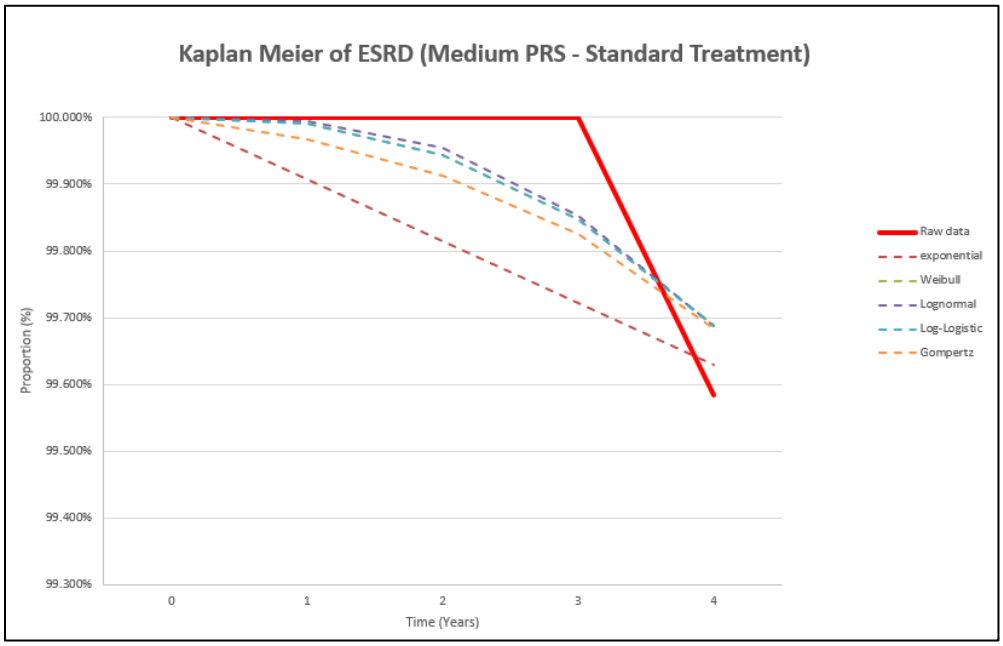
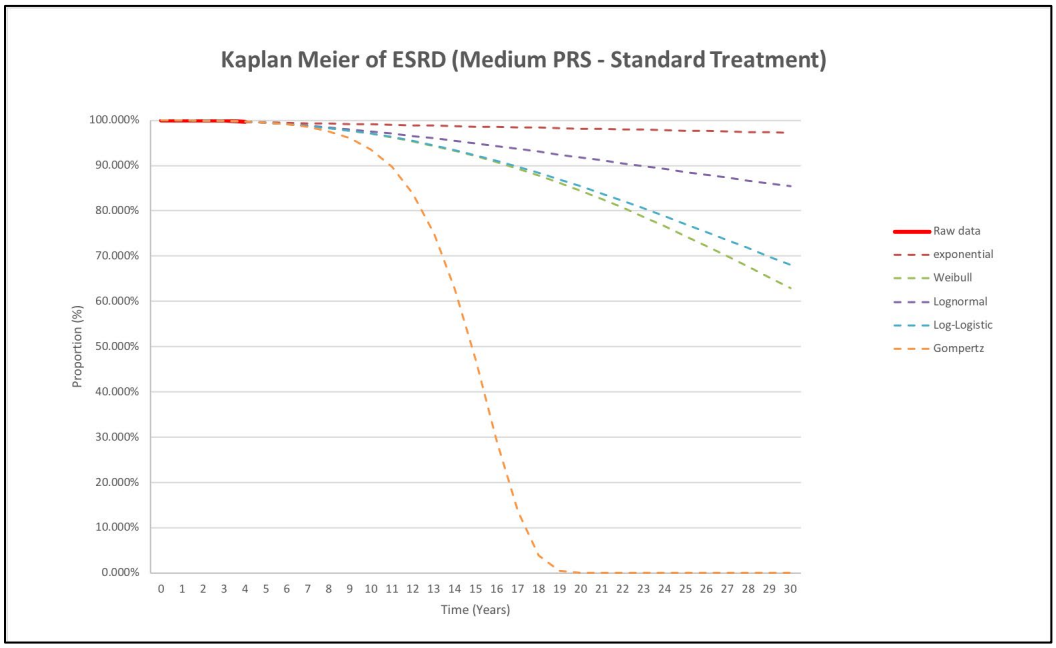


Figure 7. Kaplan Meier Data with Standard Parametric Curve Fitting for ESRD, Medium PRS Group – Extrapolated Data



7.2.8.1.3 Probability of End-Stage Renal Disease for High Polygenic Risk Score

For High PRS sub-group, a statistically significant difference was observed between intensive and standard treatments. Therefore, the probability of ESRD was calculated for both standard and intensive treatments. The probability of ESRD from standard treatment was obtained from the projected KM curves. According to the AIC and BIC scores, combined with visual inspection, the log-normal distribution was selected for the base-case analysis. The 4-year parametric distributions are presented in **Figure 8**, while the extrapolated distributions are presented in **Figure 9**. The probability of intensive treatment was derived by applying the hazard ratio (HR) (0.345 (95% CI: 0.123; 0.969)) reported in the ADVANCE trial.[54,55] **Figure 10** represents the selected projection of the standard treatment relative to the estimated intensive treatment using the HR.

Figure 8. Kaplan Meier Data with Standard Parametric Curve Fitting for ESRD, High PRS Group, Standard Treatment – 4-Year Data

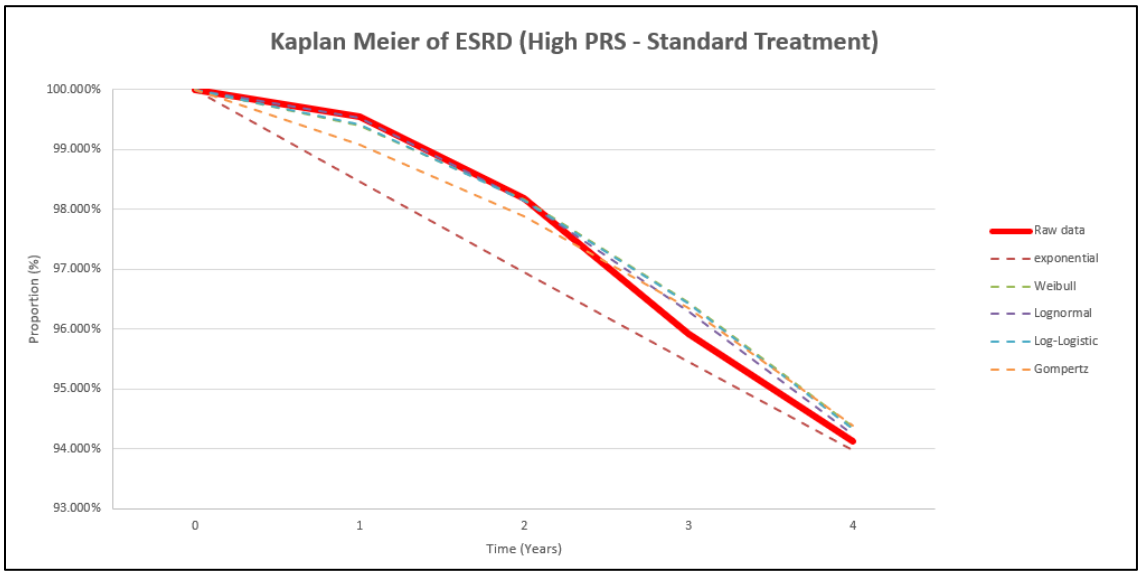


Figure 9. Kaplan Meier Data with Standard Parametric Curve Fitting for ESRD, High PRS Group, Standard Treatment – Extrapolated Data

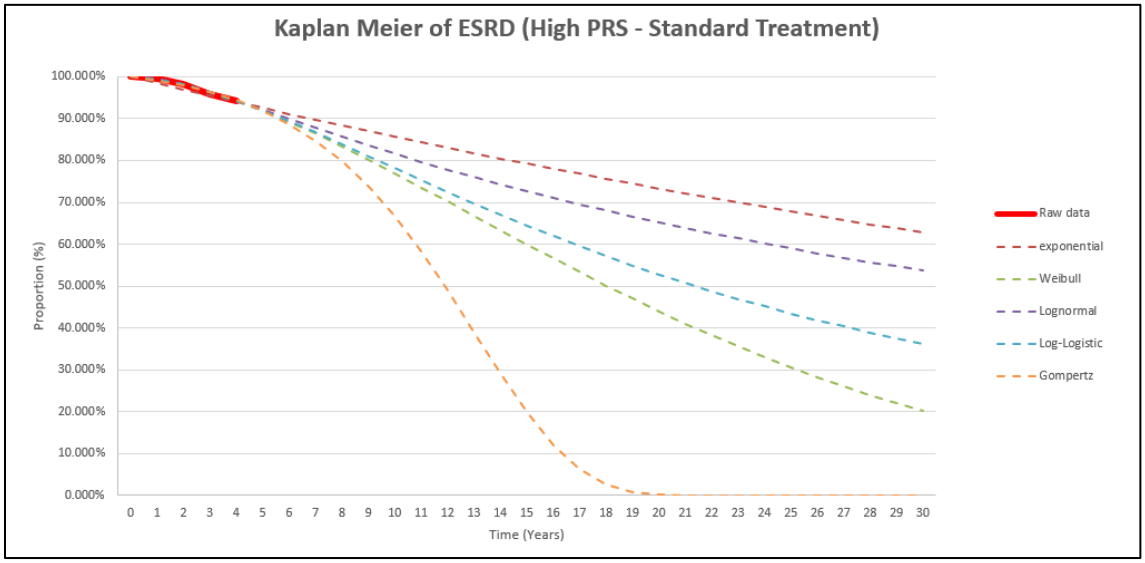
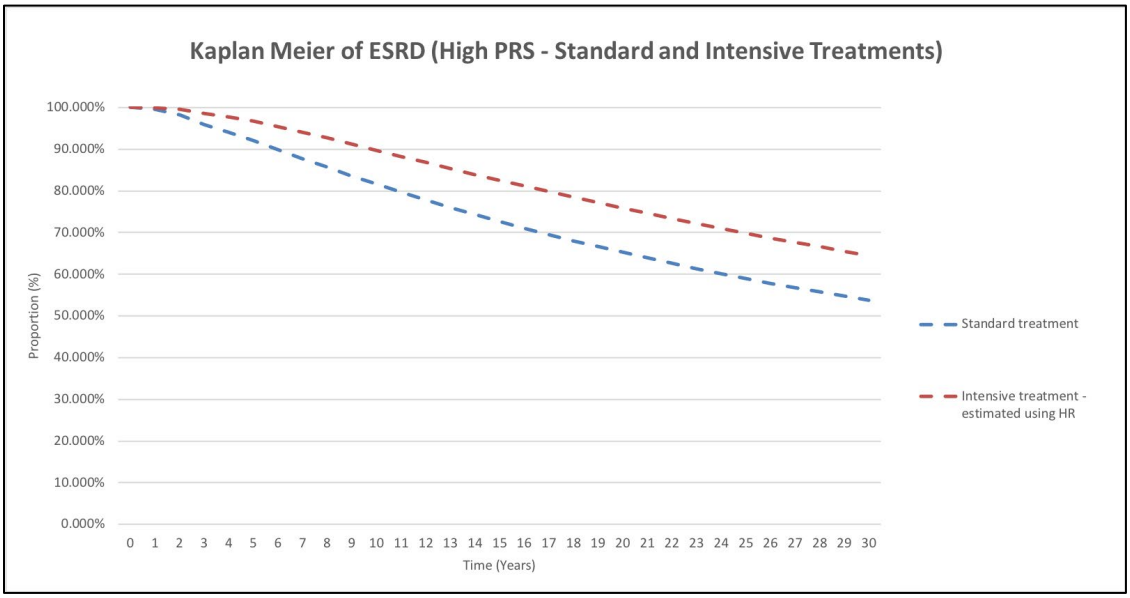


Figure 10. Kaplan Meier Data Projected using HR for ESRD, Intensive Treatment



7.2.8.2 Probability of All-Cause Death

For all PRS sub-groups, no statistically significant difference was observed between intensive and standard treatments for the rate of all-cause death. Therefore, the probability of all-cause death for standard treatment was calculated and assumed to be equivalent for intensive treatment.

7.2.8.2.1 Probability of All-Cause Death for Low Polygenic Risk Score

According to the AIC and BIC scores, the Gompertz distribution had the lowest values for both scores. However, according to the Gompertz distribution results, all patients with a low PRS would be dead after 13 years. This distribution is not clinically possible since low PRS patients have the lowest risk of associated diabetes complications and, therefore, should have a longer life expectancy that that of medium and high PRS subgroups. As confirmed by key opinion leaders in the field, the Gompertz distribution was not selected. The second lowest AIC and BIC scores combined, along with visual inspection, determined the Weibull distribution to be selected for the base-case analysis. The 4-year parametric distributions are presented in **Figure 11**, while the extrapolated distributions are presented in **Figure 12.**

Figure 11. Kaplan Meier Data with Standard Parametric Curve Fitting for All-Cause Death, Low PRS – 4-Year Data

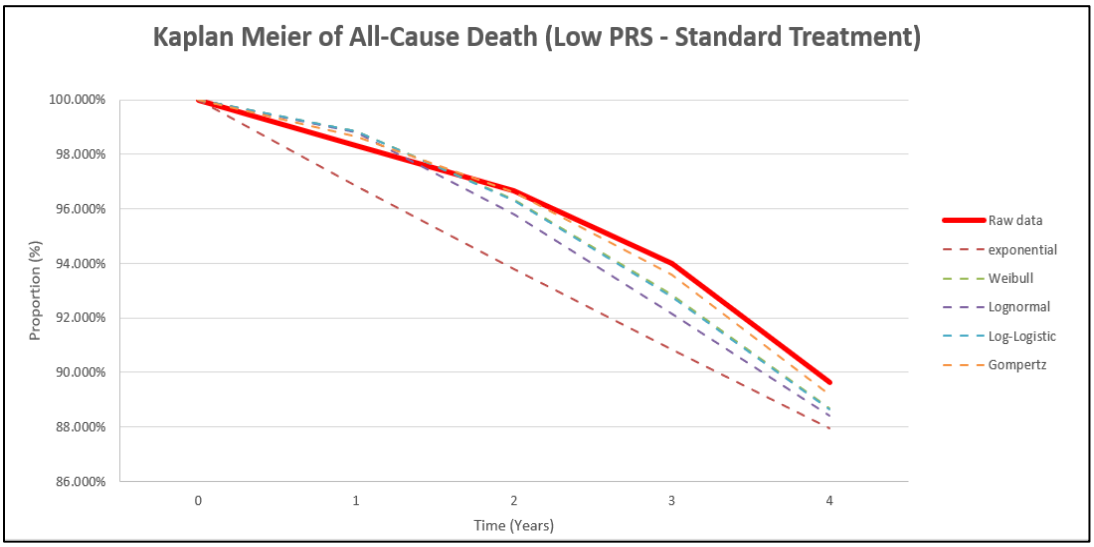
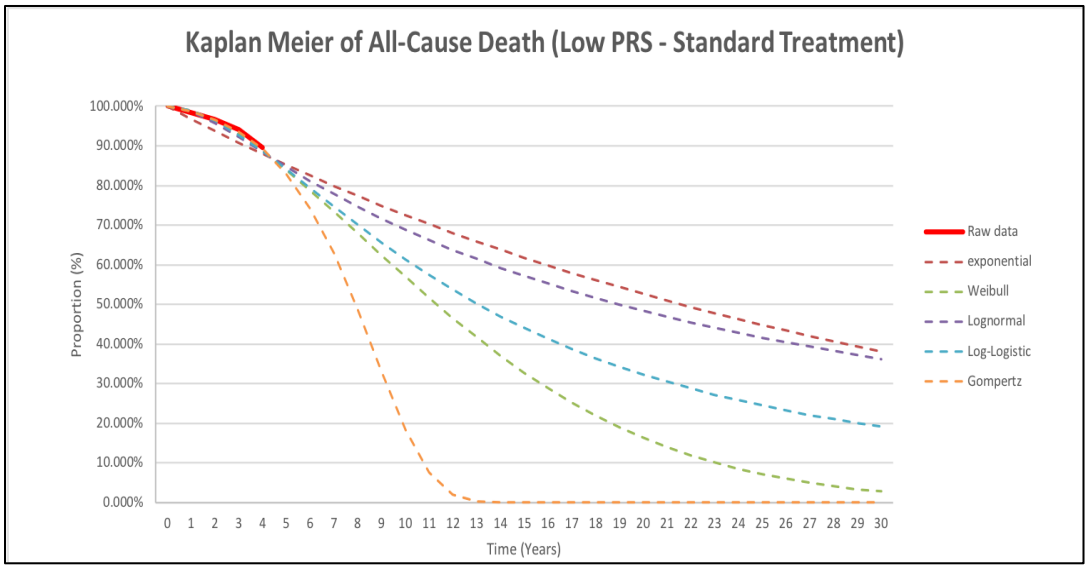


Figure 12. Kaplan Meier Data with Standard Parametric Curve Fitting for All-Cause Death, Low PRS – Extrapolated Data



7.2.8.2.2 Probability of All-Cause Death for Medium Polygenic Risk Score

According to the AIC and BIC scores, combined with visual inspection, the Weibull distribution was selected for the base-case analysis. The 4-year parametric distributions are presented in **Figure 13**, while the extrapolated distributions are presented in **Figure 14.**

Figure 13. Kaplan Meier Data with Standard Parametric Curve Fitting for All-Cause Death, Medium PRS – 4-Year Data

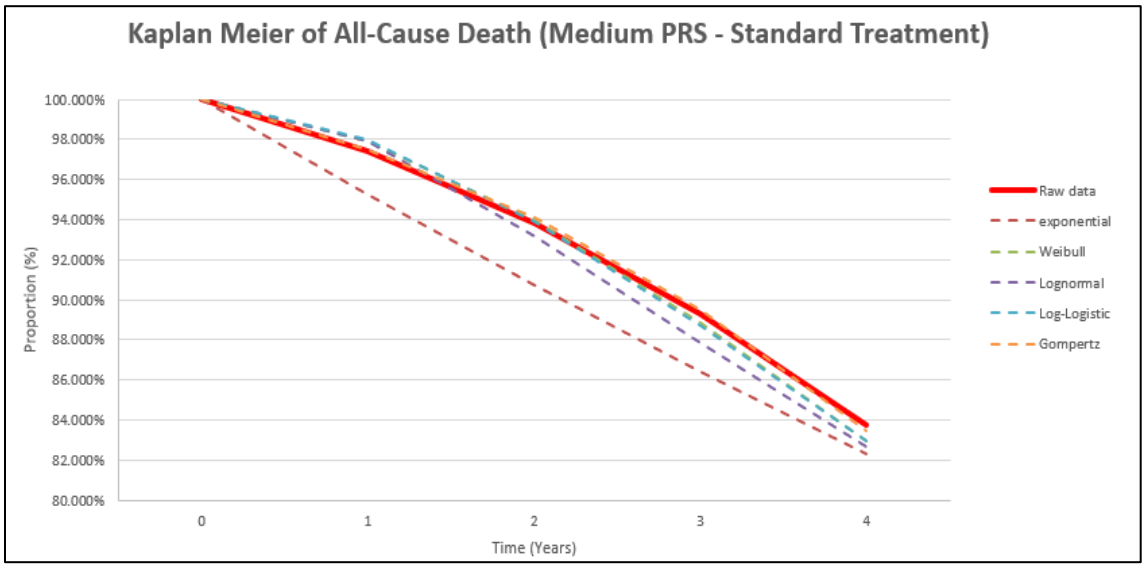
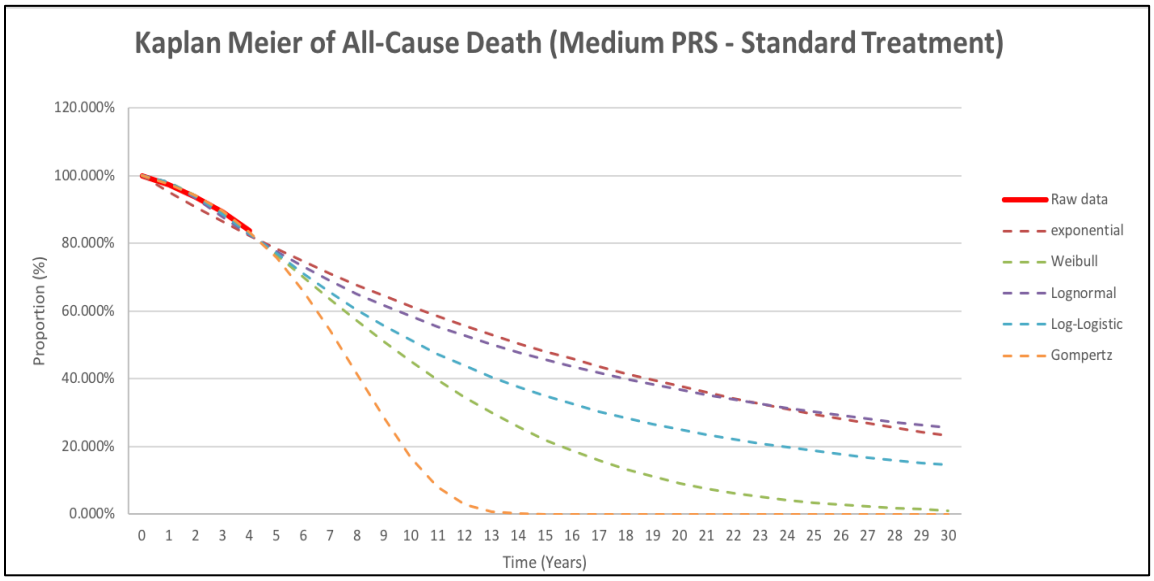


Figure 14. Kaplan Meier Data with Standard Parametric Curve Fitting for All-Cause Death, Medium PRS

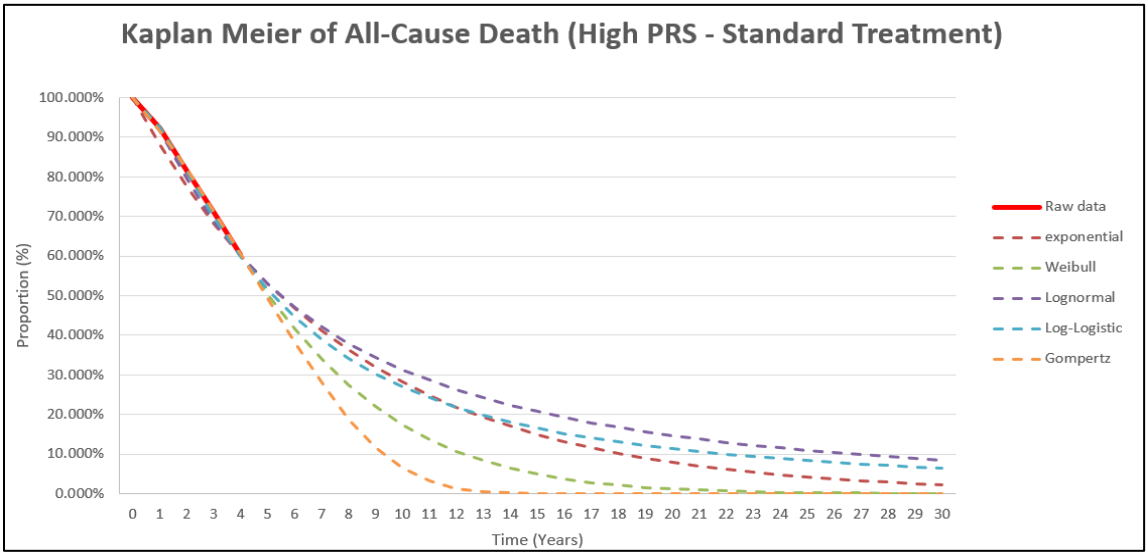


7.2.8.2.3 Probability of All-Cause Death for High Polygenic Risk Score

According to the AIC and BIC scores, combined with visual inspection, the Weibull distribution was selected for the base-case analysis. The 4-year parametric distributions are presented in **Figure 15**, while the extrapolated distributions are presented in **Figure 16.**

Figure 15. Kaplan Meier Data with Standard Parametric Curve Fitting for All-Cause Death, High PRS

Figure 16. Kaplan Meier Data with Standard Parametric Curve Fitting for All-Cause Death, High PRS



7.2.8.3 Pre-End-Stage Renal Disease Death Rate

The probability of death from pre-ESRD health state was assumed to be equivalent to the rate of all-cause death of low PRS patients, which is representative of the death rate for typical T2Dpatients, without related complications. The death rate in the Pre-ESRD health state per follow-up year is presented in **Table 4**.

7.2.8.4 End-Stage Renal Disease Death Rate

The death rate from ESRD health state was calculated by taking into account the all-cause death rate from pre-ESRD, for medium and high PRS sub-groups, in order to prevent double counting. More specifically, the death rate from ESRD health state was calculated by subtracting the difference between all-cause death rate for each PRS subgroup and all-cause death rate from the pre-ESRD health state, from the probability of all-cause death. Since the death rate from pre-ESRD is equivalent to that of low PRS, the death rate from ESRD for low PRS patients was assumed equivalent to the death rate for low PRS patients within the pre-ESRD health state. The rates of all-cause death per year and well as the calculated death rates per health states are presented in **Table 4**.

Table 4. Probability of Death by Health State

Follow-up (Years)	Probability of All-Cause Death			Probability of Death from Pre-ESRD, Any PRS	Probability of Death from ESRD		
	High	Medium	Low		High	Medium	Low
0	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%
1	92.41%	97.39%	98.33%	98.33%	86.48%	96.46%	98.33%
2	81.33%	93.81%	96.66%	96.66%	66.00%	90.97%	96.66%
3	71.20%	89.25%	93.98%	93.98%	48.43%	84.52%	93.98%
4	60.44%	83.71%	89.63%	89.63%	31.25%	77.79%	89.63%
5	50.29%	76.67%	83.94%	83.94%	16.65%	69.40%	83.94%
6	41.54%	70.14%	78.82%	78.82%	4.26%	61.46%	78.82%
7	33.91%	63.58%	73.45%	73.45%	0.00%	53.72%	73.45%
8	27.40%	57.14%	67.95%	67.95%	0.00%	46.34%	67.95%
9	21.94%	50.94%	62.42%	62.42%	0.00%	39.46%	62.42%
10	17.41%	45.07%	56.97%	56.97%	0.00%	33.17%	56.97%
11	13.70%	39.57%	51.65%	51.65%	0.00%	27.50%	51.65%
12	10.70%	34.51%	46.54%	46.54%	0.00%	22.47%	46.54%
13	8.30%	29.88%	41.67%	41.67%	0.00%	18.09%	41.67%
14	6.39%	25.70%	37.10%	37.10%	0.00%	14.31%	37.10%
15	4.89%	21.97%	32.83%	32.83%	0.00%	11.11%	32.83%
16	3.71%	18.66%	28.89%	28.89%	0.00%	8.43%	28.89%
17	2.81%	15.75%	25.28%	25.28%	0.00%	6.23%	25.28%
18	2.11%	13.22%	22.00%	22.00%	0.00%	4.44%	22.00%
19	1.58%	11.03%	19.04%	19.04%	0.00%	3.02%	19.04%
20	1.17%	9.15%	16.40%	16.40%	0.00%	1.91%	16.40%
21	0.87%	7.55%	14.05%	14.05%	0.00%	1.06%	14.05%
22	0.64%	6.20%	11.97%	11.97%	0.00%	0.43%	11.97%

Follow-up (Years)	Probability of All-Cause Death			Probability of Death from Pre-ESRD, Any PRS	Probability of Death from ESRD		
	High	Medium	Low		High	Medium	Low
23	0.47%	5.06%	10.15%	10.15%	0.00%	0.00%	10.15%
24	0.34%	4.11%	8.56%	8.56%	0.00%	0.00%	8.56%
25	0.25%	3.32%	7.19%	7.19%	0.00%	0.00%	7.19%
26	0.18%	2.67%	6.01%	6.01%	0.00%	0.00%	6.01%
27	0.13%	2.13%	4.99%	4.99%	0.00%	0.00%	4.99%
28	0.09%	1.70%	4.13%	4.13%	0.00%	0.00%	4.13%
29	0.07%	1.34%	3.40%	3.40%	0.00%	0.00%	3.40%
30	0.05%	1.06%	2.79%	2.79%	0.00%	0.00%	2.79%

7.2.8.5 Rate of Progression Through Albuminuria Stages

Lastly, although the rate of progression through different albuminuria stages within the pre-ESRD health state are not essential to the transition between health states, this information was valuable in order to calculate the annual costs of usual screening for DN. The categorization of UACR at baseline was derived from the genotyped ADVANCE trial patient population, as previously mentioned.[96]

In order to determine the proportion of patients within each pre-ESRD albuminuria stages at each model cycle, transition probabilities were obtained from the UKPDS 64, a randomized, non-blinded clinical trial that investigated the effects of intensive policies for blood glucose and blood pressure on the complications of T2D.[60] This study evaluated over 5000 patients with newly diagnosed T2D and concluded that the yearly rate of progression from diagnosis to microalbuminuria and microalbuminuria to macroalbuminuria was of 2.0% and 2.8%, respectively.[60] According to these numbers, the yearly proportions between each health states were calculated, as shown in **Table 5**.

Table 5. Proportion of Patients in Each Albuminuria States over the Model Time Horizon

Follow-up (Years)	Normoalbuminuria	Microalbuminuria	Macroalbuminuria
0 (Baseline)	70%	26%	4%
1	68.6%	26.7%	4.7%
2	67.2%	27.3%	5.5%
3	65.9%	27.9%	6.2%
4	64.6%	28.4%	7.0%
5	63.3%	28.9%	7.8%
6	62.0%	29.4%	8.6%
7	60.8%	29.8%	9.4%
8	59.6%	30.2%	10.3%
9	58.4%	30.5%	11.1%
10	57.2%	30.8%	12.0%

7.2.9 Utility

An exhaustive literature review was conducted in order to obtain utility values for each health state. For the pre-ESRD health state, two 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 T2D patients without complications.[61] The study by Clarke et al. estimated the utility value associated with T2D patients who had not experienced any diabetes-related complications at 0.785.[61] This data was obtained on 5,102 patients with newly diagnosed T2D from the UKPDS study, using the EQ-5D utilities derived from population-based time trade-off values.[61] This instrument consists of two distinct measurement techniques: the visual analogue scale and a descriptive system covering five dimensions (mobility, self-care, usual activity, pain/discomfort, anxiety, and depression), each of which has 3 levels (no problem, some problem, extreme problems). This estimation is in line with other utility values associated with T2D, as presented in a systematic literature review by Beaudet et al.[62]

Within the ESRD health state, multiple utility values were considered depending on the type of treatment received. In order to estimate the utility values related to dialysis, disutility associated with different types of dialysis treatments (HD and PD) were retrieved from the literature. A study by Wasserfallen et al., estimated the disutility values at -0.164 and -0.204 for HD and PD, respectively.[63] (**Table 6**) This study was performed on chronic HD and PD patients in 19 centers in Switzerland, requesting patients to fill out the EQ-5D questionnaire, derived from the same population-based time trade-off values described above.[63] The utility value for each dialysis method was calculated by subtracting the disutility from the utility of T2D patients without complications. Conversely, for RT, a utility value was directly obtained from the study by Kiberd et al.[64] This economic evaluation assessed utility values from 17 health care workers (four nephrologists, six houses, six nurses and one social worker) not associated with the study. Health states were ranked and valued using a time trade off method (TTO).[64] The utility value was estimated at 0.762. In order to estimate the utility value for the ESRD health state, a weighted average utility value was calculated based on the utilities for each ESRD treatments and their respective utilization. The calculated utility values per health state are presented in **Table 10**.

Table 6. Disutility Values

Disutility	Base-case	Source
HD	-0.164	Wasserfallen et al. 2004.[63]
PD	-0.204	Wasserfallen et al. 2004.[63]

HD: Hemodialysis, *PD:* Peritoneal Dialysis

Table 7. Utility Values by Health State

Health State	Sub-Type	Utility	Proportion	Model Utility	Source
Pre-ESRD	-	0.785	100%	0.785	Clarke et al., 2002.[61]
ESRD	HD	0.62	43%	0.675	Calculation
	PD	0.58	14%		Calculation
	RT	0.762	43%		Kiberd et al., 1995.[64]
Death	-	0	100%	0.000	-

ESRD: End-Stage Renal Disease, *HD:* Hemodialysis, *PD:* Peritoneal, *RT:* Renal Transplantation

7.2.10 Adverse Events

Adverse events (AEs) were not considered in this analysis, since the incidence of AEs were considered similar between both standard and intensive glucose control treatments. Although a slight increase in hypoglycemia events was recorded for patients treated with intensive glucose control treatment, key opinion leaders in the field suggested that this would not be a major issue and that it was correct to assume no differences in adverse events.[65]

7.2.11 Costs

All analyses were performed from a Canadian MoH and a societal perspective. From a MoH perspective, only direct medical costs were considered. Cost data included: cost of screening for DN, drug acquisition costs, the costs related to ESRD management and the cost of terminal care. From a societal perspective, the costs of productivity losses associated with ESRD for both patients and caregivers were added to the total costs. All costs were expressed in 2019 Canadian dollars and were discounted at a rate of 1.5% as required by CADTH guidelines.[47] Costs estimated prior to 2019 were adjusted to June 2019 levels based on the health component of the Canadian Consumer Price Index.

7.2.11.1 Screening Costs

In the context where the PRS would be the primary screening technique for DN, all patients with newly diagnosed T2D would receive the test once at diagnosis. The unit cost of the PRS was provided by OptiThera and valued at 400$ per test.

The cost of usual screening tests (UACR, serum creatinine, R&M, urine dipstick and serum electrolytes) were obtained from the British Columbia Schedule fees for Laboratory services (**Table 8**).[66] The annual screening costs by stage of renal dysfunction was based upon the unitary cost per test as well as the Canadian guidelines for screening of DN in T2D patients.[4] The annual costs per test by stage of renal dysfunction are presented in **Table 9**.

Table 8. Unit Cost per Usual Screening Tests

Type of Test	Unit Cost	Source
UACR	$11.41	BC Schedule of fees for laboratory services. Code 91985.[66]
Serum creatinine	$5.10	BC Schedule of fees for laboratory services. Code 91420.[66]
R&M	$7.17	BC Schedule of fees for laboratory services. Code 92395.[66]
Urine dipstick	$6.68	BC Schedule of fees for laboratory services. Code 92396.[66]
Serum electrolytes	$10.17	BC Schedule of fees for laboratory services. Code 92232 and 92101.[66]

BC: British Columbia, *R&M:* Routine and Microscopic, *UARC:* Urine albumin creatinine ratio

Table 9. Annual Cost of Usual Screening According Stage of Renal Dysfunction

Screening Type	Type of Test	Testing Frequency	Annual Cost	Total Annual Cost
Normal test results (eGFR ≥60 mL/min OR UACR≤2.0 mg/mmol)	UACR	1 test at diagnosis of T2D. If normal, rescreen in 1 year.	$11.41	$16.51
	Serum Creatinine	1 test at diagnosis of T2D. If abnormal, 2 more tests within 3 months	$5.10	
Abnormal Test Results but no CKD (eGFR ≤60 mL/min OR UACR≥2.0 mg/mmol)	UACR	1 test at diagnosis of T2D. If abnormal, 2 more tests within 3 months	$34.23	$44.43
	Serum creatinine	1 test at diagnosis of T2D. If abnormal, repeat test in 3 months	$10.20	
Diagnosis of CKD (eGFR ≤60 mL/min OR UACR≥2.0 mg/mmol)	UACR	1 test at diagnosis of T2D. If abnormal, 2 more tests within 3 months	$34.23	$68.45
	Serum creatinine	1 test at diagnosis of T2D. If abnormal, repeat test in 3 months	$10.20	
	R&M	One time at diagnosis of CKD	$7.17	
	Urine dipstick	One time at diagnosis of CKD	$6.68	
	Serum Electrolytes	One time at diagnosis of CKD	$10.17	

CKD: Chronic Kidney Disease, *eGFR:* Estimated Glomerular Filtration Rate, *R&M:* Routine and Microscopic, *T2D:* Type-2 Diabetes, *UARC:* Urine albumin creatinine ratio

7.2.11.2 Drug acquisition Costs

Drug acquisition costs of the standard and intensive glucose lowering treatments were obtained from the Ontario Drug Benefit (ODB) formulary and their respective treatment regimens.[67] The costs from Ontario were used, since they are representative of the general Canadian cost. Treatments were selected based on the standard and intensive glucose-lowering drugs administered in the ADVANCE trial (**Table 10**).[56] If two treatments were available within the same drug category, assumptions were made by clinical experts on the proportion of patients receiving each type of treatment. The glucose-lowering drug sub-groups, their treatment regimens, and the proportion of patients receiving each type of treatment are presented in **Table 11**. The total treatment acquisition costs were calculated using the treatment regimens, percent utilization in the ADVANCE trial, as well as the cost per unit. The total treatment cost per year for the entire ADVANCE population by type of glucose therapy is presented in **Table 12**, while the total treatment costs per year per patient for standard and intensive therapies are presented in **Table 13**.

Table 10. Glucose-lowering Drugs Administered in the ADVANCE Trial

Glucose-lowering drugs	Registration Visit (n, %)		End of Follow-Up (n, %)	
	Intensive	Standard	Intensive	Standard
Gliclazide (modified release)	422 (8)	443 (8)	4209 (91)	80 (2)
Other sulfonylurea	3578 (64)	3513 (63)	89 (2)	2606 (57)
Metformin	3397 (61)	3355 (60)	3455 (74)	3057 (67)
Thiazolidinedione	201 (4)	206 (4)	788 (17)	495 (11)
Acarbose	512 (9)	448 (8)	891 (19)	576 (13)
Glinide	103 (2)	84 (2)	58 (1)	127 (3)
Any oral hypoglycemia	5084 (91)	5045 (91)	4525 (94)	4001 (84)
Insulin	82 (2)	77 (1)	1953 (41)	1142 (24)
None	487 (9)	524 (9)	42 (2)	220 (6)

Adapted from: Chalmers J. Protection against cardiovascular and renal disease in type 2 diabetes: ADVANCEs in the control of blood pressure and blood glucose using Preterax and Diamicron MR. Vol Issue IV: Servier/Wolters Kluwer Health; 2010.[56] (Table XXIV)

Table 11. Drug Acquisition Costs

Glucose-Lowering Drugs	Generic name	Daily Dose (mg)	Unit (mg)	Cost per unit	Cost per mg	Cost per Year	Source	Proportion of Utilization
Gliclazide (Modified Release, MR)	Gliclazide MR sustained release (Diamicron)	Week 1-2, 30 mg	30	$0.09	$0.003	Year 1: $128.11 Year 2+: $135.93	ODB, DIN 02429764.[67] Gliclazide MR PM.[68]	50%
		Week 3-4, 60 mg						
		Week 5-6, 90 mg						
		Week 7 +, 120 mg						
	Gliclazide MR ER extended release (Diamicron)	Week 1-2, 30 mg	60	$0.06	$0.00	Year 1: $43.48 Year 2+: $46.14	ODB, DIN 02407124.[67] Gliclazide MR PM.[68]	50%
		Week 3-4, 60 mg						
		Week 5-6, 90 mg						
		Week 7 +, 120 mg						
Other Sulfonylurea	Glyburide (Diabeta)	5-10 mg OPD	2.5	$0.03	$0.01	Year 1+: $44.38	ODB, DIN 01913654.[67] Glyburide PM.[69]	50%
			5	$0.06	$0.01		ODB, DIN 01913662.[67] Glyburide PM.[69]	
	Glimepiride (Amaryl)	Week 1-2, 1 mg	1	$0.49	$0.49	Year 1+: $178.85	ODB, DIN 02295377.[67] Glimepiride PM.[70]	50%
		Week 3-4, 2 mg	2	$0.49	$0.25		ODB, DIN 02295385.[67] Glimepiride PM.[70]	
		Week 5-6, 3 mg	3	$0.49	$0.16		Glimepiride PM.[70]	
		Week 7+, 4 mg	4	$0.49	$0.12		ODB, DIN 02295393.[67] Glimepiride PM.[70]	

Glucose-Lowering Drugs	Generic name	Daily Dose (mg)	Unit (mg)	Cost per unit	Cost per mg	Cost per Year	Source	Proportion of Utilization
Metformin	Metformin (Glucophage)	500 mg 3-4 times per day	500	$0.02	$0.00	Year 1+: $36.06	ODB, DIN 02167786.[67] Metformin PM.[71]	25%
		850 mg 2-3 times per day	850	$0.21	$0.00	Year 1+: $228.86	ODB, DIN 02229785.[67] Metformin PM.[71]	75%
Thiazolidinedione	Pioglitazone (Actos)	15 - 30 mg OPD	15	$1.57	$0.10	Year 1+: $803.62	ODB, DIN 02302942.[67] Actos PM.[72]	80%
			30	$2.20	$0.07		ODB, DIN 02302950.[67] Actos PM.[72]	
			45	3.31 $	$0.07		ODB, DIN 02302977.[67] Actos PM.[72]	
	Rosiglitazone (Avandia)	4 mg OPD	2	1.17 $	$0.58	Year 1+: $669.63	ODB, DIN 02403366.[67] Avandia PM.[73]	20%
			4	1.83 $	$0.46		ODB, DIN 02403374.[67] Avandia PM.[73]	
			8	2.62 $	$0.33		ODB, DIN 02403382.[67] Avandia PM.[73]	
Acarbose	Glucobay	Week 1-2, 50 mg OPD	50	0.27 $	0.01 $	Year 1: $283.78 Year 2+: $295.10	ODB, DIN 02190885.[67] Glucobay PM.[74]	100%
		Week 3-4, 50 mg BID	100	0.37 $	0.004 $		ODB, DIN 02190893.[67] Glucobay PM.[74]	
		Week 5-6, 50 mg TID						
Glinide	Repaglinide (GlucoNorm)	Week 1, 1 mg each meal	0.5	$0.21	$0.42	Year 1: $523.75 Year 2+: $534.58	ODB, DIN 02355663.[67] GlucoNorm PM.[75]	100%
		Week 2, 2 mg before each meal	1	$0.22	$0.22		ODB, DIN 02355671.[67] GlucoNorm PM.[75]	
		Week 3, 4 mg before each meal	2	$0.24	$0.12		ODB, DIN 02355698.[67] GlucoNorm PM.[75]	
Insulin	Insulin glargine	10U once daily	1500	$69.64	$0.05	Year 1+: $169.45	ODB, DIN 02444844.[67] Lantus PM.[76]	50% (90%)

Glucose-Lowering Drugs	Generic name	Daily Dose (mg)	Unit (mg)	Cost per unit	Cost per mg	Cost per Year	Source	Proportion of Utilization
(Long duration of action)	Insulin detemir		1500	$110.41	$0.07	Year 1+: $268.66	ODB, DIN 02271842.[67] Levemir PM.[77]	50% (90%)
Insulin (Short duration of action)	Insulin lispro	4U before each meal, total of 12U per day	1500	$60.06	$0.04	Year 1+: $175.38	ODB, DIN 09853715.[67] Humalog PM.[78]	33.33% (10%)
	Insulin glulisine		1500	$52.65	$0.04	Year 1+: $153.74	ODB, DIN 02279479.[67] Apidra PM.[79]	33.33% (10%)
	Insulin aspart		1500	$61.23	$0.04	Year 1+: $178.79	ODB, DIN 02244353.[67] Novorapide PM.[80]	33.33% (10%)

BID: Twice per day, *ODB:* Ontario Drug Benefit, *MR:* Modified Release, *OPD:* Once Per Day, *PM:* Product Monograph, *TID:* Three Times per day

Table 12. Total Treatment Cost per Year of the ADVANCE Population by Glucose Control Therapy

Treatment type	Cost per year per patients	Intensive (n)	Total Cost Intensive	Standard (n)	Total Cost Standard
Gliclazide MR	Year 1: $85.79	4209	$361,105	80	$6,863
	Year 2+: $91.03		$383,149		$7,282
Other Sulfonylurea	Year 1+: $111.62	89	$9,934	2606	$290,874
Metformin	Year 1+: $180.66	3455	$624,169	3057	$552,268
Thiazolidinedione	Year 1+: $776.82	788	$612,136	495	$384,527
Acarbose	Year 1: $283.78	891	$252,851	576	$163,459
	Year 2+: $295.10		$262,936		$169,979
Glinide	Year 1: $523.75	58	$30,377	127	$66,516
	Year 2+: $534.58		$31,006		$67,892
Insulin	Year 1+: $214.08	1953	$418,099	1142	$244,480
None	0.00 $	42	$0.00	220	$0.00

MR: Modified Release

Table 13. Treatment Cost per Year per Patient for and Intensive Therapies

Treatment type	Year	Total Cost for ADVANCE population	Total Patients (n)	Average Cost per Patient per Year
Standard Glucose Control Therapy	Year 1	$1,708,987	8303	$205.83
	Year 2+	$1,717,302		$206.83
Intensive Glucose Control Therapy	Year 1	$2,308,672	11485	$201.02
	Year 2+	$2,341,429		$203.87

7.2.11.3 Cost of End-Stage Renal Disease

Costs associated with ESRD include the costs of dialysis and RT. End-stage renal disease related unit costs were obtained from the Kidney Foundation of Canada for RT and from the Alberta Annual Kidney Care Report (2015) for the dialysis methods (**Table 14**).[42,81] The average annual cost for dialysis was calculated by performing a weighted average using the annual costs for both ICHD and PD as well as their respective percent utilization. Renal transplantation 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 (**Table 15**).

Table 14. Cost Associated with ESRD Treatments

Treatment type	Cost	Source
ICHD	$100,000	The Alberta Annual Kidney Care Report (2015).[42]
PD	$56,000	The Alberta Annual Kidney Care Report (2015).[42]
RT (Year 1)	$23,000	The Kidney Foundation of Canada. Facing the Facts 2012.[81]
RT (Year 2 +)	$6,000	The Kidney Foundation of Canada. Facing the Facts 2012.[81]

ICHD: In-Center Hemodialysis, *PD:* Peritoneal Dialysis, *RT:* Renal Transplantation

Table 15. Annual Costs of ESRD used in the Model

Treatment type	Proportion within Treatment Type	Proportion by Treatment Type	Weighted Average Costs per Year	Total Cost per Year
ICHD	75%	57.9%	$51,531	Year 1: $63,740 Year 2+: $54,057
PD	25%			
RT	-	42.1%	$12,209	
			$2,526	

ICHD: In-Center Hemodialysis, *PD:* Peritoneal Dialysis, *RT:* Renal Transplantation

1.1.1.1 Cost of Productivity Loss

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 to their treatments. The cost of productivity loss associated with dialysis was obtained from a study by Klarenbach et al., a Canadian economic evaluation of frequent home nocturnal hemodialysis (HD) based on a randomized clinical trial.[82] This study evaluated the productivity costs of both ICHD and home HD. Since no data is 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 were equivalent to 25% of the costs related to home HD.[83] The annual productivity loss associated with different dialysis methods are presented in **Table 16**.

The cost of productivity loss associated to RT was obtained from a study by Von Zur Muhlen et al., who estimated the proportion of patients as well as the number of sick leave days encountered for 3 years preceding transplantation, transplantation year as well as the years following transplantation.[84] Using the average Canadian hourly rate and hours worked per day (**Table 17**), for people aged 25 years and older, total costs per transplanted patients were calculated (**Table 18**).[85]

Table 16. Productivity Loss Associated with Dialysis

Type of Cost	ICHD	PD	Source
Out of pocket cost	$3,104	$437.75	Klarenbach et al. (2014)[82] CADTH Dialysis Report.[83]
Productivity loss (no training time cost)	$795.00	$0.00	
Productivity loss (training time cost)	$0.00	$644.25	
Total Annual Costs	**$3,899**	**$1,082***	

ICHD: In-Center Hemodialysis, *PD:* Peritoneal Dialysis

Table 17. Average Canadian Hourly Wage and Hours Worked

Parameter	Costs / Hours	Source
Average Hourly Wage	$29.40 / hour	Statistics Canada. Table 14-10-0320-02. 25 years and over. March 2019.[85]
Average Number of Hours per Day	7.32 hours	

Table 18. Productivity Loss Associated with RT

Time of Sick Leave	Proportion of Patients on Sick Leave	Duration of Sick leave (Days/Year)	Annual Cost of Sick Leave	Weighted Average Cost per Year	Source
3 years before RT	62.8%	69	$14,849	$9,325	Von Zur Muhlen (2018).[84]
RT year	61.4%	129	$27,762	$17,046	
Years after RT	47.4%	45	$9,684	$4,590	
Total Annual Costs	**Year 1**	**$45,022**			
	Year 2+	**$4,590**			

RT: Renal Transplantation

The total productivity loss was estimated by multiplying the individual costs of productivity loss associated with each ESRD treatment modality, by their respective percentage of utilization, as presented in **Table 19**.

Table 19. Mean Productivity Loss Related to ESRD

Treatment type	Proportion within Treatment Type	Proportion by Treatment Type	Weighted average of costs Per Year
ICHD	75%	57.9%	Year 1+: $1,850
PD	25%		
RT	NA	42.1%	Year 1: $18,954 Year 2+: $1,933
Total Annual Costs	**Year 1**	**$20,804**	
	Year 2+	**$3,782**	

ICHD: In-Center Hemodialysis, *PD:* Peritoneal Dialysis, *RT:* Renal Transplantation

7.2.11.4 Cost of Terminal Care

The cost of terminal care was obtained from the Ontario Care Costing Initiative (OCCI) and was valued at $10,314 (Code Z515).[86]

7.2.12 Sensitivity Analyses

The robustness of the base-case results was assessed through DSA. 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 groups, 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 +/- 25% and 95% CI, specifically for utility values and HR. The model efficacy parameters were varied directly through the rate of HR. The lower and upper bounds used in the deterministic sensitivity analysis are shown in **Table 20**.

In addition, a 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 bounded by 0 and 1 for transition probabilities and utility values, lognormal distributions for disutilities and hazard ratios, and gamma distribution for cost parameters). Results of the PSA were presented as a CEAC and the probability of being cost-effective at a threshold of $50,000/QALY was estimated.[47]

Table 20. Parameters Used for the Deterministic Analysis

Description	Base-case	Lower bound	Upper bound	PSA Distribution
Proportion of Patients with High PRS	29%	22.1%	36.8%	Beta
Proportion of Patients with Medium PRS	34%	25.1%	41.9%	Beta
Proportion of Patients with Low PRS	37%	52.8%	178.6%	Beta
Baseline Proportion of Normolalbuminuria	70%	60.0%	80.0%	Beta
Baseline Proportion of Microalalbuminuria	26%	32.5%	19.5%	Beta
Baseline Proportion of Macroalbuminuria	4%	7.5%	0.5%	Beta
Transition Probability from Normo- to Microalbuminuria	2.0%	1.5%	2.5%	Beta
Transition Probability from Micro- to Macroalbuminuria	2.80%	2.1%	3.5%	Beta
Proportion of Patients on Dialysis	57.9%	43.4%	72.4%	Beta
Proportion of Patients with In-Center Hemodialysis	75.00%	0.56	0.94	Beta
Utility Pre-ESRD	0.79	0.68	0.89	Beta
Disutility Hemodialysis (95% CI)	-0.16	-0.27	-0.05	Lognormal (Utility)
Disutility Peritoneal Dialysis (95% CI)	-0.20	-0.34	-0.07	Lognormal (Utility)
Utility Renal Transplant	0.76	0.66	0.87	Beta
Cost of In-Center Hemodialysis	$100,000	$95,000	$107,000	Gamma
Cost of Peritoneal Dialysis	$56,000	$42,000	$70,000	Gamma
Cost of Transplantation (Year 1)	$23,000	$17,250	$28,750	Gamma
Cost of Transplantation (Year 2)	$6,000	$4,500	$7,500	Gamma
Productivity Loss ICHD	$38,094	$28,571	$47,618	Gamma
Productivity Loss PD	$6,314	$4,736	$7,893	Gamma
Proportion of Patients on Sick Leave (3 Years before transplant)	62.80%	47.10%	78.50%	Beta
Proportion of Patients on Sick Leave (Transplant Year)	61.40%	46.05%	76.75%	Beta
Proportion of Patients on Sick Leave (Years after transplant)	47.40%	35.55%	59.25%	Beta
Sick Leave Days (3 Years before transplant)	69	51.75	86.25	Gamma
Sick Leave Days (Transplant Year)	129	96.75	161.25	Gamma
Sick Leave Days (Years after transplant)	45	33.75	56.25	Gamma
Cost Terminal Care	$10,314	$7,736	$12,893	Gamma
Cost of Urinary ACR	$11.41	$8.56	$14.26	Gamma
Cost of Serum Creatinine	$5.10	$3.83	$6.38	Gamma
Cost of Urine Routine and Microscopic	$7.17	$5.38	$8.96	Gamma
Cost of Urine Dipstick	$6.68	$5.01	$8.35	Gamma
Cost of Serum Electrolytes	$10.17	$7.63	$12.71	Gamma
Cost of PRS Test	$400.00	$300.00	$500.00	Gamma
Hazard Ratio of ESRD (High PRS)	1.345	1.123	1.969	Lognormal

7.2.13 Validation of the model

This model has been developed and validated by several people to ensure its validity. Specifically, Kimberly Guinan was responsible for developing the model using Microsoft Excel and validating the assumptions with Catherine Beauchemin and Jean Lachaine. Key opinion leaders in the field, including Johanne Tremblay and Pavel Hamet, were also responsible for the validation of key clinical assumptions. Subsequently, CB and JL confirmed an internal validation of the model by determining that this model met extreme parameter values.

7.2.14 Model Outputs

The effectiveness outcome was the total QALYs. The incremental QALYs were calculated as the difference in the total QALYs over the time horizon between the two comparators. The ICERs 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 versus usual screening was compared to 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.

7.2.15 Author Contribution

Kimberly Guinan was responsible for conducting the entirety of the economic evaluation. KG along with Catherine Beauchemin and Jean Lachaine were involved in designing the study. The development of the Markov model development, the analysis of the effectiveness data along with the assessment of results were performed by KG. Pavel Hamet participated in the management of ADVANCE trial with Johanne Tremblay and they were responsible for the development of the clinical polygenic test and both contributed as key opinion leaders in the model development. John Chalmers and Mark Woodward managed the ADVANCE and ADVANCE-ON studies. The manuscript was prepared by KG. All authors reviewed the final manuscript.

8 Results

8.1 Article #1

A Systematic Literature Review of the Economic Evaluations in Type 2 Diabetic Nephropathy

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Key Messages

- A literature review was recently published on the economic impact of chronic kidney diseases in types 1 and 2 diabetes. This review included studies up to March 2018.
- There is a need for a more recent literature review, specific to evaluating the economic impact of diabetic nephropathy in type 2 diabetes.
- This review would help guide the development of new economic evaluations in the field.

Key Words

Diabetic nephropathy, type 2 diabetes mellitus, economic evaluation, systematic literature review

Abstract

Introduction: Nephropathy constitutes a major comorbidity in type-2 diabetes (T2D), contributing substantially to the costs associated with this disease. This systematic review aims to examine all published economic evaluations (EEs) in T2D and diabetic nephropathy (DN), to inform new EEs within the field and determine the main trends in treatment efficiency.

Methods: A systematic literature review was performed in MEDLINE and EMBASE for the period from January 1995 to June 2018 and in PubMed for the year 2018. A review of the grey literature was also conducted. Studies reporting any type of EEs were included. Two reviewers independently assessed the eligibility of included articles and extracted data.

Results: Up to June 2018, 1,175 articles were identified. After assessing titles, abstracts and full-text articles for eligibility, 47 articles were included in the review. Of these studies, 35 were EE and 12 were cost-of-illness studies. From the EEs, 74% were published between the years 1995 and 2007, while 26% were published within the past 10-years. 31% of studies were cost-utility analyses, 60% were cost-effectiveness analyses and 9% were cost studies. The most common economic model was the Markov, with a lifetime-horizon.

Conclusions: This systematic review provides an overview of how DN in T2D is typically modelled, and captures the substantial economic impact related to this patient population. Although the cost-effectiveness of multiple therapeutic options have been evaluated, further EEs of screening technics are warranted, in order to provide a better understanding of their potential economic benefit.

Introduction

The prevalence of diabetes is constantly increasing and currently affects 9.3% of the Canadian population. In 2025, it is projected that 12.1% of Canadians will be affected with diabetes, an estimated increase of 44% over 10 years.[87] This increasing trend also follows with a substantial economic burden related to the treatment of diabetes and diabetes-related complications. According to *Diabetes Canada*, the direct costs to the healthcare system was estimated at $3.6 billion in 2018 and was projected to increase to $4.7 billion in 2028.[88] These costs are highly driven by diabetes associated microvascular or macrovascular complications.

One of the most prominent complications related to diabetes is renal impairment. It has been estimated that more than 50% of diabetic patients will develop signs of renal damage throughout their lifetime.[4] According to the *Canadian Organ Replacement Register* annual report for the treatment of end-stage organ failure in Canada, diabetes continued to be the most frequently reported primary cause of end-stage renal disease (ESRD), accounting for 36% of cases.[33]

The most commonly reported renal complication in diabetes is nephropathy. Diabetic nephropathy (DN) is characterized by a slow and progressive increase in albuminuria, followed by an eventual reduction in glomerular filtration rate (eGFR), which may eventually lead to ESRD.[4] The different stages of nephropathy are as follows: normoalbuminuria (<30 mg/day), microalbuminuria (30-300 mg/jour), macroalbuminuria (>300 mg/day) and ESRD (>1000 mg/day).[4] The current treatment for DN includes glycemic control, blood pressure control and blockade of the renin angiotensin aldosterone system (RAAS).

There exist two distinct types of diabetes: type 1 and type 2 (T1D and T2D). According to Canadian chronic disease surveillance data, it was estimated that 90% of diabetes diagnoses were specific to T2D.[89] Although diabetic nephropathy may develop in both types of diabetes, the number of T2D patients with ESRD is rapidly increasing, due to the increasing prevalence of T2D. Due to this increasing prevalence along with the substantial economic costs driven by renal complications, many economic evaluations (EEs) have been published in order to evaluate which treatments are the most cost-effective options. Given the limited resources of the healthcare system, EE are essential in order to determine which treatment strategy for nephropathy in T2D patients should be prioritized according to their cost as well as their effectiveness.

This systematic review aims to retrieve all published EEs in T2D patients with DN, in order to (1) evaluate the different characteristics of the studies to inform new EEs within the field and, (2) evaluate the cost-effectiveness of different treatment options.

Methods

Information Sources

A systematic literature review was performed according to the most recent guidelines in health economics evaluations according to Cochrane Handbook for Systematic Review of Interventions as well as the INESSS guidelines.[50,51]

The search was designed to identify all economic evaluation publications that included patients with T2D and DN. More specifically, the search could include all different types of economic evaluations assessing any type of intervention for the treatment of DN in patients with T2D. Since any type of intervention(s) and/or comparator(s) could be included within the search, the Cochrane PICO framework was not considered for this review.

Literature search strategy

The literature search was performed in MEDLINE and EMBASE for the period of 1995 to 2018 (March 4th, 2018) and in PubMed for the current year (2018), in order to retrieve publications not yet indexed in MEDLINE and EMBASE. The keywords included in the search are presented in presented in **Appendix A (Table A.1-A.3)** and were:

- Diabetic nephropathy
- Economic evaluations, more specifically the search filters provided by CADTH for economic evaluations in health.[52]

Snowballing

In addition, snowballing of the selected studies in the literature search was performed. More specifically, the reference list of identified articles as well as those of review articles were manually screened for relevant economic evaluations not identified in the above-mentioned searches.

Pragmatic Searches

A non-systematic search of the grey literature was also performed in order to capture all possible economic publications not captured in the literature and snowballing searches. The reviewed grey literature included the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), the CADTH, the INESSS as well as the National Institute for Health and Care Excellence (NICE).

Study Selection

Inclusion criteria for the literature review included the following:

- Nephropathy for patients with T2D
- Economic evaluations, including CUA, CEA, CCA, CMA, cost-study as well as cost of illness (COI) studies.
- Published between 1995 and March 4th, 2018
- Available in full text
- Published in French or English

The study selection was performed in two distinct steps. First, the titles and abstracts of articles retrieved from the search were screened for eligibility. Secondly, the full text of included articles was read in depth and assessed for eligibility using an inclusion criterion grid. For all excluded articles, the reason for exclusion was documented. Two reviewers (Kimberly Guinan and Marie-Ève Richard) independently assessed the eligibility of the articles and differences in study selection were resolved by consensus, for validation purposes.

Data Extraction

The data extraction included: 1) Name of the first author and year, 2) year of publication, 3) type of economic evaluation, 4) model structure, 5) time horizon, 6) intervention and comparators, 7) types of costs included, 8) perspective of the study, 9) sources of cost parameters, clinical data and utility values used in the analysis and 10) results of the economic analysis.

Two reviewers (KG and MR) independently conducted data extraction included in the review. For validation purposes, differences in interpretation by the two reviewers were resolved by consensus.

Synthesis of Findings

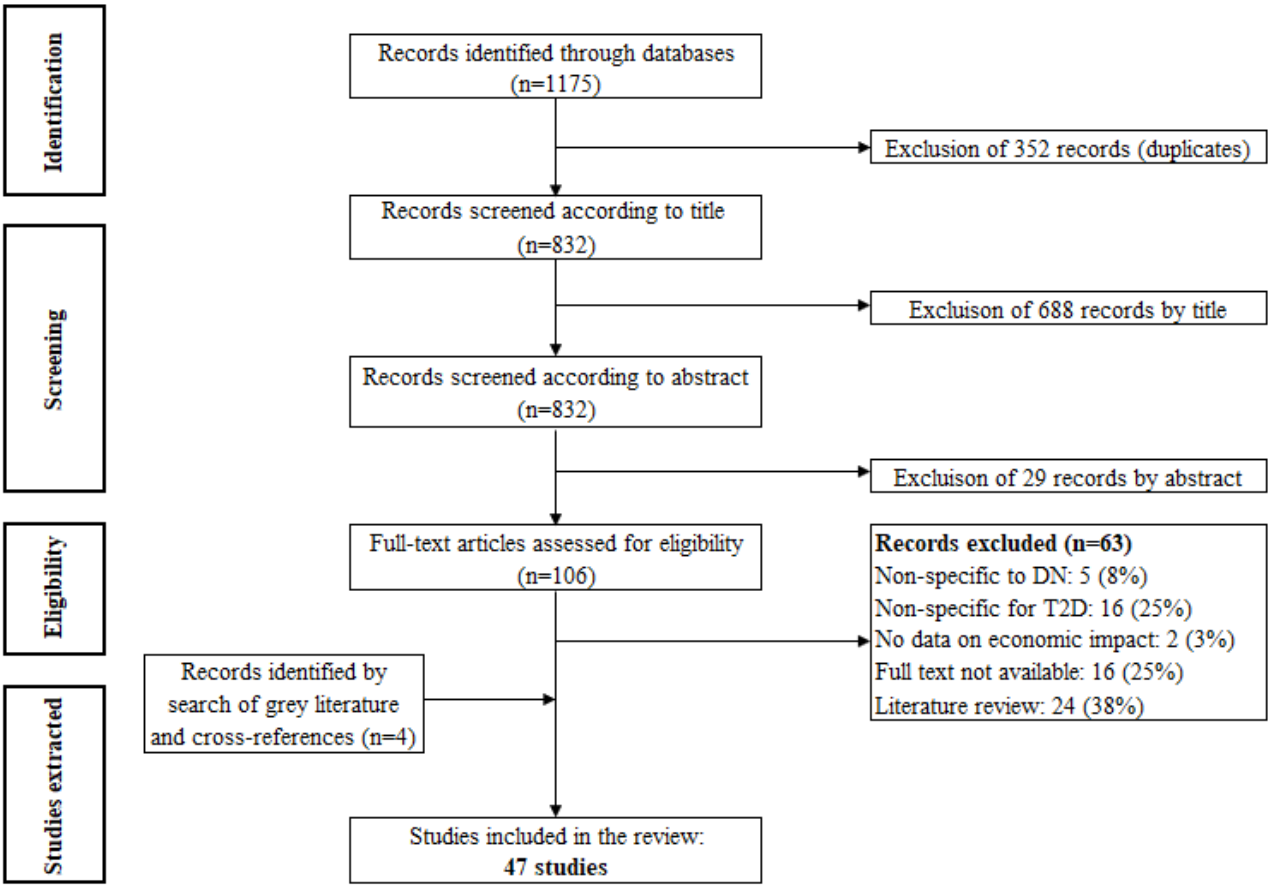
A quantitative assessment of the extracted data was performed, for all publications dates as well as two distinct subgroups from 1995-2007 and 2008-2018. These two timeframes were selected in order to distinguish between older and more recent publications, published within the last 10 years from the date of the literature search. For economic evaluations (CUA, CEA, CCA, CMA and cost-study) the following information was analyzed: 1) year and country of publication, 2) the type of economic evaluation, 3) analytical perspective, 4) model structure, 5) time horizon, 6) source of clinical data and 7) intervention and comparators. For COI studies, the following information was analyzed: 1) year and country of publication, 2) analytical perspective and 3) time horizon.

The assessment of heterogeneity between studies was not performed, since the main objective of this review was to evaluate the different study characteristics of the economic evaluations published in T2D and DN. The results retrieved from the publications were not assessed for data pooling or other types of statistical analyses. However, the main trends observed in cost-effectiveness of different treatment options were evaluated. In order to make results comparable between studies, all costs or incremental cost-effectiveness ratios (ICERs) were adjusted to 2019 Canadian dollars. This was done by first, converting costs to the Canadian currency of the retrieved year using a currency converter and secondly, actualizing the costs to 2019 using the Canadian Consumer Price Index (CPI) for Health and Personal Care for the month of June when available (half-year).[53] When the currency and year of currency were mentioned in the studies, the adjustments were made from these data. However, when the information was not available, the country of origin and the year of publication were used as a reference for the adjustment of costs, if possible.

Results

A total of 1,175 articles were retrieved from the databases. After removing duplicates and screening for title and abstract, a total of 106 articles were assessed for eligibility. After review of article eligibility using fell-text articles, a total of 43 articles met the inclusion criteria's. A total of 63 articles did not respect the following eligibility criteria's: literature reviews (38%), not specific to T2D (25%), no full text available (25%), not specific to DN (8%) or no economic impact data (3%). After cross-referencing and grey literature assessment, 4 additional articles were added to the review. Therefore, a total of 47 articles were included in this systematic literature review, as shown in **Figure 1**. Of these articles, 35 (74%) were economic evaluations (EE) and 12 (26%) were COI studies.

Figure 1. Flow Chart of the Literature Review



Economic Evaluations (EEs)

The 35 EEs included in this study mainly originated from Europe (15 EEs, 42.9%) and North America (14 EEs, 40.0%), with only a few published in Asia (6 EEs, 17.1%). Of all the EEs, 26 (74.3%) were published between 1995 and 2007, while 9 (25.7%) were published within the last 10 years (2008-2018). The key features of the EEs, for all publications dates as well as 1995-2007 and 2008-2018, are detailed in **Table 1** (see **Appendix B, Table B.1** for detailed extraction data of EEs).

Table 1. Key Features of Economic Evaluations

	All years, n (%)	1995-2007, n (%)	2008-2018, n (%)
Publication Year	**35 (100)**	**26 (74.3)**	**9 (25.7)**
Type of Economic Evaluation			
Cost-utility	11 (31.4)	5 (19.2)	6 (66.7)
Cost-effectiveness	21 (60.0)	19 (73.1)	2 (22.2)
Cost-Study	3 (8.6)	2 (7.7)	1 (11.1)
Analytical Perspective			
Healthcare system	18 (51.4)	13 (50.0)	5 (55.6)
Societal	3 (8.6)	2 (7.7)	1 (11.1)
Third-party payer	12 (34.3)	10 (38.5)	2 (22.2)
No perspective	2 (5.7)	1 (3.9)	1 (11.1)
Model Type			
Markov	20 (57.1)	15 (57.7)	5 (55.6)
Decision Tree	1 (2.9)	1 (3.9)	0 (0.0)
Decision Tree + Markov	1 (2.9)	0 (0.0)	1 (11.1)
Cumulative Incidence Risk	1 (2.9)	1 (3.9)	0 (0.0)
Individual Level Simulation	1 (2.9)	0 (0.0)	1 (11.1)
Cross-Sectional	1 (2.9)	0 (0.0)	1 (11.1)
N/A	10 (8.6)	9 (34.6)	1 (11.1)
Time Horizon			
1 year	2 (5.7)	0 (0.0)	2 (22.2)
2 years	0 (0.0)	0 (0.0)	0 (0.0)
3 to 4 years	9 (25.7)	8 (30.8)	1 (11.1)
10 years	1 (2.8)	1 (3.9)	0 (0.0)
Lifetime (>20 years)	20 (57.1)	14 (53.9)	6 (66.7)
Multiple time horizons	3 (8.6)	3 (11.5)	0 (0.0)
Source of Clinical Data			
Clinical trial	15 (42.9)	12 (46.2)	3 (33.3)
Registry	0 (0.0)	0 (0.0)	0 (0.0)
Literature review	6 (17.1)	3 (11.5)	3 (33.3)
Combination of sources	13 (37.4)	11 (42.3)	2 (22.2)
N/A	1 (2.9)	0 (0.0)	1 (11.1)
Intervention and Comparator	**35 (100)**	**26 (100)**	**9 (100)**
Treat at T2D diagnosis vs. at micro/macro-albuminuria diagnosis	5 (14.3)	1 (3.9)	4 (44.4)
Losartan vs. placebo	12 (34.3)	11 (42.3)	1 (11.1)
Early IR vs. Late IR	6 (17.1)	5 (19.2)	1 (11.1)
Other	12 (34.3)	9 (34.6)	3 (33.3)

IR: Irbesartan, *N/A:* Not available; *T2D:* Type 2 Diabetes.

Globally, cost-effectiveness analyses (CEA) were the most frequently used analysis (21 EEs, 60.0%). However, a big contrast was observed between 1995-2007 and 2008-2018, where 73% (19 EEs) of the studies were CEAs and 67% (6 EEs) were cost-utility analyses (CUA), respectively. The most commonly used model structure was the Markov model (20 EEs, 57.1%), with a similar proportion between both timeframes. Eighteen EEs (51.4%) adopted a healthcare system perspective, twelve (25.0%) a third party payer perspective, three (8.6%) a societal perspective, while two (5.7%) had no identified perspectives. The proportions related to the analytical perspectives was similar between both time frames. The lifetime

horizon was used in more than half of all the EEs (20 EEs, 57.1%), for both 1995-2007 (14 EEs, 53.9%) and 2008-2018 (6 EEs, 66.7%) timeframes. Other currently used time horizons were between three and four years (9 EEs, 25.7%) and one year (2 EEs, 5.7%). The source of clinical data was mostly retrieved from clinical trials (15 EEs, 42.9%), while others were retrieved from literature reviews (6 EEs, 17.1%) or a combination of multiple sources (13 EEs, 37.4%).

Many different interventions and comparators were evaluated in the 35 EEs retained for the literature review. The detailed intervention and comparators for each selected study are presented in the data extraction table, found in the **Appendix B (Table B.1)**. The most commonly evaluated interventions were 1) the treatment with angiotensin-converting-enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) at T2D diagnosis OR at micro- or macro-albuminuria diagnosis, 2) blood pressure-lowering treatment with losartan versus placebo or 3) early (microalbuminuria) versus late (microalbuminuria) treatment with Irbesartan (IR), another type of blood pressure-lowering therapy. Older EEs (1995-2007) mainly focused the evaluation of blood pressure lowering treatments (11 EEs, 42.3%) while publications within the last ten years primarily focused on the efficacy of treating patients with ACEI/ARB directly at T2D diagnosis versus at the first appearance of renal damage (4 EEs, 44.4%).

Cost-of-Illness (COI) Studies

Twelve COI studies were included in this literature review. The studies mainly originated from North America (8 COIs, 66.7%) and Asia (2 COIs, 16.7%), with only one published in Europe (8.33%). Of all the COI studies, 7 (58.3%) were published between 1995 and 2007, while 5 (41.67%) were published within the last 10 years (2008-2018). The key features of the studies, for all publications dates as well as 1995-2007 and 2008-2018, are detailed in **Table 2**. (see **Appendix B, Table B.2** for detailed extraction data of COIs).

The analytical perspective used in the COI studies varied between both time frames. From 1995 to 2007, all studies used a healthcare system perspective (7 COIs, 100%). Within the last 10 years, one COIs (20%) adopted a societal perspective, one COIs (20%) a healthcare system perspective, two COIs (40%) a third-party payer perspective and one COI (20%) used both societal and third-party payer perspectives. As usually performed in COI studies, the most commonly utilized time horizon was of one year (9 COIs, 75%), while other time horizons varied between 2-years and lifetime.[90]

Table 2. Key Features of Cost-of-Illness Studies

	All years, n (%)	1995-2007, n (%)	2008-2018, n (%)
Publication Year	**12 (100)**	**7 (58.3)**	**5 (41.7)**
Analytical Perspective			
Healthcare system	8 (66.7)	7 (100.0)	1 (20.0)
Societal	1 (8.3)	0 (0.0)	1 (20.0)
Third-party payer	2 (16.7)	0 (0.0)	2 (40.0)
Societal + third party payer	1 (8.3)	0 (0.0)	1 (20.0)
Time Horizon			
1 year	9 (75.0)	5 (71.4)	4 (80.0)
2 years	1 (8.3)	0 (0.0)	1 (20.0)
9 years	1 (8.3)	1 (14.3)	0 (0.0)
Lifetime (>20 years)	1 (8.3)	1 (14.3)	0 (0.0)

Discussion

The results of the literature review on economic evaluations in DN for T2D patients, puts to evidence the heterogeneity between characteristics of retrieved studies. This study also analyses trends in the cost-effectiveness of multiple treatment options in DN and demonstrates the significant economic burden of DN in T2D. This was shown in the literature review through multiple EEs and COI studies.

The majority of the retrieved studies were published between 1995 and 2007. This could be explained by the fact that most of the pharmaceutical products for DN were developed a while ago, and that within the past 10 years, few innovative research has been done in the field. Furthermore, the type of analysis used for the economic evaluations reflect the increased use of CUA over time, towards becoming the approved type of analysis, as stated in the most recent guidelines for the economic evaluations of health technologies published by the CADTH in 2017, as well as other international guidelines.[47,91] According to these guidelines, a CUA is the recommended type of EE and should be used as the reference case analysis.[46] As shown in this literature review, the most common type of analysis within the past 10 years has been CUAs, while CEA were the most common between 1995-2007. Another interesting trend was found in the treatments and comparators evaluated in the studies. Prior to 2008, the most commonly evaluated treatment was losartan versus. During this time period, blood pressure lowering treatments were the most commonly used technics in order to reduce or help prevent renal damage in patients with T2D. However, from 2008 to 2018, most studies evaluated the economic impact of treating patients with ACEI or ARB at diagnosis of T2D, versus only treating patients at the diagnosis of micro- or macroalbuminuria. These findings demonstrate the consideration of a new treatment pattern, before the appearance of nephropathy symptoms, which focuses on the prevention rather than the treatment of the disease.

From the results obtained within each study, many trends were noticed. According to the COI studies, it was logically observed that the cost of the disease increases according to the disease severity. This result is consistent with the fact that ESRD is extremely expensive, with dialysis treatments costing on average $100,000 per year per patient.[42] Furthermore, treating all patients in an early setting (at T2D diagnosis) versus a late setting (at micro- or macroalbuminuria diagnosis) resulted as a dominant option in all studies. In other words, an early treatment was shown less costly and more effective than a late treatment, either with an antihypertensive or an ACEI/ARB therapy. Lastly, administering an antihypertensive therapy, at any stage of the disease, represented a cost-effective option.

This systematic literature review presents many strengths, offering a complete and current representation of all the EEs performed on DN for T2D patients. Firstly, the review covered a long time period (1995 to 2018), which allowed the observation of trends between old and new EEs. Many databases were used, including EMBASE, MEDLINE and PubMed, allowing to capture the most relevant articles pertinent to this review. The inclusion of grey literature also permitted to limit the risk of publication bias. Finally, the selection as well as data extraction was performed by two independent reviewers, ensuring that the content of the literature review is rigorous and exhaustive, further preventing the possibility of selection bias.

Although the systematic literature review method was thoroughly performed, this study has some limitations. Indeed, all literature reviews are limited by the key words and indexation used within databases. For example, the disease key words were limited to DN. However, although the study focused on T2D, the search was not limited to the key word of T2D. This was done in order to prevent the potential loss of relevant studies discussing both T1D and T2D. Another possible limitation associated to this systematic literature review could include publication bias as well as publication language bias. Indeed, the non-inclusion of unpublished research as well as the restriction of the review to English and French studies might have biased the results. However, the inclusion of grey literature reduced the possibility of this publication bias. Lastly, this systematic literature review did not follow the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) methodology.[92] For example, no evaluation of the quality of the studies was performed for this systematic literature review. It is known that the inclusion of biased studies is more likely to produce misleading results than those that are rigorously performed.[93] The use of Drummond's checklist for assessing EEs would have been a good method to assess study quality and increase the validity of this systematic literature review.[46] Although this is an important limitation, the main objective of this study was to provide an overview of the methodology used in published EEs for nephropathy in T2D patients. Nevertheless, considering the strengths and limits of this literature review,

this study provides a current overview of the EEs in nephropathy for T2D patients and could be useful for future pharmacoeconomic research.

A systematic literature review of economic modelling of chronic kidney disease was recently published in September 2019.[94] Of all the identified articles related to chronic kidney disease, 48 were retrieved as diabetes models related to nephropathy, where 12 studies (25%) were models for T1D and 22 (46%) were for T2D. Therefore, discrepancies between both reviews could be explained by the following: 1) no distinction between T1D and T2D and, 2) the review included data up to November 2017. This present systematic literature review offers a more specific (related to T2D only) and more recent (including articles from 2018) review of the EEs in nephropathy for T2D.

Conclusion

This systematic literature review provides an overview of how DN in T2D is typically modelled. This review also captures the substantial economic impact of DN in T2D patients. Although the cost-effectiveness of multiple therapeutic options have been evaluated, the economic evidence related to DN screening technics are negligible. Further EEs of diagnostic methods are warranted, in order to provide a better understanding of their potential economic benefit.

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Author Disclosures

Authors have no conflict of interest to declare.

Author Contribution

KG, MS, CB and JL were involved in designing the study. Data collection was done by KG as well as MR, as a second reviewer. The search strategy was developed by KG, CB and JL. The manuscript was prepared by KG. All authors reviewed the final manuscript.

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8.2 Article #2

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

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Key Messages

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

Key Words
Diabetic nephropathy, end-stage renal disease, type 2 diabetes mellitus, polygenic risk score, cost-utility analysis, Markov model

Abstract

Introduction: The current screening method for diabetic nephropathy (DN) is based upon 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 type 2 diabetes (T2D) patients 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 T2D patients, compared to usual screening methods, in Canada.

Methods: A cost-utility analysis was developed using a Markov model. Health states include pre-end-stage renal disease (Pre-ESRD), ESRD and death. Model efficacy parameters were based on prediction of outcome data by polygenic-risk testing of the genotyped participants in the ADVANCE trial. Analyses were conducted from Canadian healthcare and societal perspectives. Deterministic and probabilistic sensitivity analyses (DSA; PSA) were conducted to assess results robustness.

Results: Over a lifetime horizon, the PRS was a dominant strategy, from both a healthcare system and societal perspective. The PRS was less expensive and more efficacious in terms of quality-adjusted life years compared to usual screening technics. DSA and PSA showed that results remained dominant in most simulations.

Conclusions: This economic evaluation demonstrates that the PRS is a dominant option compared to 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.

Introduction

Diabetic nephropathy (DN) is the most frequently reported primary cause of end-stage renal disease (ESRD), accounting for 36% of cases.[33] 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 (eGFR).[4] Therefore, the current screening methods for DN are based upon tests evaluating the albumin-to-creatinine ratio (ACR) along with serum creatinine for eGFR. Although these tests have a good positive predictive value, they only capture patients after clinical symptoms of DN.[95]

The Steno-2 randomized controlled trial evaluated the death from any cause of Type-2 diabetes (T2D) participants treated with either intensive or conventional therapy.[96,97] This study demonstrated that although intensive treatment significantly decreases the number of ESRD, the rate of progression from micro- to macroalbuminuria remains elevated. Therefore, this information portrays the importance of early screening of T2D patients with genomic tools, prior to the development of clinical symptoms, in order to prevent DN.

Recently, Tremblay et al. genotyped 4,098 patients from the ADVANCE (Action in Diabetes and Vascular Disease PreterAx and DiamicronN Controlled Evaluation) trial, a randomized controlled trial of blood pressure lowering and intensive glucose control in patients with T2D, in order to build a polygenic risk score (PRS) for both renal and cardiovascular outcomes.[54,55] The PRS was composed of 598 SNPs predicting renal and cardiovascular complications in individuals with T2D of European descent, adjusted for principal components (PC) of genetically defined ethnicity, sex, age at onset and diabetes duration. Its clinical utility in predicting complications of diabetes was tested in 4098 participants with diabetes of the ADVANCE trial during a period of 5 years and an additional 5 years in ADVANCE-ON and replicated in three independent non-trial cohorts. The study demonstrated an increased risk for renal events in patients with a high PRS and early-onset diabetes. For instance, sixty percent of ESRD cases occurred in the highest PRS third of ADVANCE participants and intensive glycemic control, demonstrated a 65% ESRD reduction in this high-risk group (HR=0.345, p=0.043 in ADVANCE) remaining significant at the end of ADVANCE-ON (HR=0.455, p=0.026). It was therefore suggested that the implantation of the PRS as the main screening method for DN 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 in order to assist the decision of policy makers, whether the added 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 T2D patients, compared to 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 T2D patients. This economic evaluation is based on the prediction of ESRD by polygenic risk testing within the ADVANCE trial.[54,55]

Comparative Treatment

The intervention evaluated in this economic evaluation was the PRS, administered only once, to T2D patients. 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.[47] In a population of patients with T2D, usual screening for DN is the best comparator, since 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.[4] If both tests results are positive, further tests including urine routine and microscopic (R&M), urine dipstick as well as 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, while 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 to 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., 2008.[65] The treatments were stratified as such since the intensive treatment had the most beneficial impact for high-risk group patients ($p = 0.043$) compared to other PRS groups.

Target Population

The study population consisted of T2D patients 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 in order to establish a PRS.[54,55] At baseline, the mean age of the population was 67 years old (SD: 7), the mean age at diagnosis of T2D was 60 years old (SD: 9) and the median duration of diabetes was of 8 years (SD: 7.4-8.9). A detailed overview of the characteristics of the ADVANCE genotyped participants is presented in **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.[47] 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.[45,65,98]

This economic evaluation was conducted over a time horizon of 5 years, since 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 in order 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 to usual screening for the detection/prevention of DN in T2D patients. Three 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-albuminuria, micro-albuminuria and macro-albuminuria. The ESRD health state included patients with renal failure, all treated with either dialysis or renal transplantation (RT).[29] For patients receiving dialysis, in-center hemodialysis (ICHD) and peritoneal dialysis (PD) were considered.[29]

Transition probabilities

Transition between health states were calculated using patient-level data of the ADVANCE trial, stratified by time of event, type of event, type of treatment (intensive versus standard glucose control treatments) and risk group (high, medium or low PRS). In order to calculate the probability of ESRD and all-cause death, Kaplan Meier (KM) curves were generated using the Statistical Package for Social Sciences (SPSS) 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 the R software for statistical computing.[58,59]

The parametric distributions fitted to the KM data were Weibull, exponential, log-normal and log-logistic.[58] The best fitting parametric distribution was chosen by statistical consideration (Akaike information criterion [AIC]) and the Bayesian information criterion [BIC]), visual inspection (comparing fitted distribution to the study KM plots) as well as clinical plausibility.

More specifically, the probability of ESRD was measured differently for all three 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 sub-group, 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 while the probability of intensive treatment was derived by applying the hazard ratio (HR) (0.345 (95% CI: 0.123; 0.969)) reported in the ADVANCE trial.[54,55]

The probability of death from pre-ESRD health state was assumed to be equivalent to the rate of all-cause death of low PRS patients, which is representative of the death rate for typical T2D patients, 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 sub-groups, in order to prevent double counting.

Lastly, although the rate of progression through different albuminuria stages within the pre-ESRD health state are not essential to the transition between health states, this information was valuable in order 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.[54] In order 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 (UKPDS) 64, a randomized, non-blinded clinical trial that investigated the effects of intensive policies for blood glucose and blood pressure on the complications of T2D.[60]

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.[47] Costs estimated prior to 2019 were adjusted to June 2019 levels based on the health component of the Canadian Consumer Price Index.

From a MoH perspective, only direct medical costs were considered. Cost data included: cost of screening for DN, drug acquisition costs, the costs related to ESRD management and the cost of terminal care (**Table 1**). The unit cost of the PRS was estimated at $C400 by OPTITHERA, while the cost of usual screening tests (ACR, serum creatinine, R&M, urine dipstick and serum electrolytes) were obtained from the British Columbia Schedule fees for Laboratory services.[66] The annual screening costs by stage of renal dysfunction was based upon the unitary cost per test as well as the Canadian guidelines for screening of DN in T2D patients.[4] Drug acquisition costs of the standard and intensive glucose lowering treatments were obtained from the Ontario Drug Benefit (ODB) formulary and their respective treatment regimens.[67] Treatments were selected based on the standard and intensive glucose-lowering drugs administered in the ADVANCE trial.[56] If two treatments were available within the same drug category, assumptions were made by clinical experts on the proportion of patients receiving each type of treatment. The total treatment acquisition costs of the drugs were calculated using the treatment regimens, percent utilization in the ADVANCE trial, as well as the cost per unit.

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 (2015) for the dialysis methods.[42,81] The average annual cost for dialysis was calculated by performing a weighted average using the annual costs for both ICHD and PD as well as their respective percent utilization. Renal transplantation 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 (OCCI).[86]

The costs of productivity loss associated with ESRD for patients and caregivers were added from a societal perspective. End-stage renal disease requires treatment in 100% of cases, therefore it was assumed that patients must be absent from work and encounter various productivity losses associated to their treatments. The cost of productivity loss associated with dialysis was obtained from a study by Klarenbach et al., a Canadian economic evaluation of frequent home nocturnal hemodialysis (HD) based on a randomized clinical trial.[82] This study evaluated the productivity costs of both ICHD and home HD. Since no data is 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 were equivalent to 25% of the costs related to home HD.[83]

The cost of productivity loss associated to RT was obtained from a study by Von Zur Muhlen et al., who estimated the proportion of patients as well as the number of sick leave days encountered for 3 years preceding transplantation, transplantation year as well as the years following transplantation.[84] Using the average Canadian hourly rate and hours worked per day, for people aged 25 years and older, total costs per transplanted patients were calculated.[85]

Utility

An exhaustive literature review was conducted in order to obtain utility values for each health state. For the pre-ESRD health state, two 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 T2D patients without complications.[61] Within the ESRD health state, multiple utility values were considered depending on the type of treatment received. In order to estimate the utility values related to dialysis, disutility associated with different types of dialysis treatments (HD and PD) were retrieved from the literature.[63] The utility value for each dialysis method was calculated by subtracting the disutility from the utility of T2D patients without complications. Conversely, for RT, a utility value was directly obtained from the study by Kiberd et al.[64] A weighted average utility value for the ESRD health state was calculated based on the utilities for each ESRD treatments and their respective utilization.

Table 1. Key Model Inputs

Parameters	Model	Reference
Probabilities (%)		
Probability of albuminuria stage at diagnosis		
Normoalbuminuria	70.0	
Microalbuminuria	26.0	Hamet et al. (2019) [54,55]
Macroalbuminuria	4.0	
Probability of PRS group		
Low PRS	37.1	
Medium PRS	33.5	Hamet et al. (2019) [54,55]
High PRS	29.4	
Type of ESRD treatment		
Dialysis	57.9	CIHI [29]
Transplantation	42.1	
Type of Dialysis treatment		
In-center hemodialysis	75.0	CIHI [29]
Peritoneal dialysis	25.0	
Home hemodialysis	0.0	
Costs, $		
Screening test (unit cost)		
PRS	400.00	Optithera inc.
Urinary ACR	11.41	
Serum Creatinine	5.10	BC Schedule of fees for laboratory services. [66]
Urine routine and microscopic	7.17	
Urine dipstick	6.68	
Serum electrolytes	10.17	
Drug acquisition cost ($/patient/year)		
Standard glucose control therapy, year 1	205.83	ODBF, drug product monographs and ADVANCE trial [56,67]
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	
Cost of ESRD (annual cost)		
In-center hemodialysis (ICHD)	100,000.00	Alberta Health Services & the Kidney Foundation of Canada. Facing the Facts 2012.[42,81]
Peritoneal dialysis (PD)	56,000.00	
Transplantation (year 1)	23,000.00	
Transplantation (year 2)	6,000.00	
Productivity loss related to ESRD		Klarenbach et al. [82], Von Zur Muhlen et al. [84] & Statistics Canada[85]
Year 1	22,803.93	
Year 2 onwards	3,782.24	
Cost of terminal care	10,314.00	OCC Analysis Tool [86]
Disutility inputs		
Hemodialysis (HD)	0.164	Wasserfallen et al.[63]
Peritoneal dialysis (PD)	0.204	Wasserfallen et al.[63]
Utility inputs		
Pre-ESRD	0.785	Clarke et al.[61]
ESRD	0.675	
HD	0.620	Calculation
PD	0.580	Calculation
Renal Transplantation	0.762	Kiberd et al.[64]
Death	0.0	

ACR: Albumin creatinine ratio, *ESRD:* End-Stage Renal Disease, *HD:* Hemodialysis, *ICHD:* In-center hemodialysis, *PD:* Peritoneal dialysis, *PRS:* Polygenic risk score

Adverse Events

No adverse events (AEs) costs were considered in this analysis, since the prevalence of AEs were 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 two comparators. The incremental cost-effectiveness ratios (ICERs) 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 versus usual screening was compared to 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 were assessed through deterministic sensitivity analyses (DSA). 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 groups, 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 +/- 25% or the 95% CI bounds, specifically for utility values and hazard ratios (HR). 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 bounded by 0 and 1 for transition probabilities and utility values, lognormal distributions for disutilities and hazard ratios, and gamma distribution for cost parameters). Results of the PSA were presented as cost-effectiveness acceptability curves and the probability of being cost-effective at a threshold of $50,000/QALY was estimated.[47]

Results

Base-case analysis

Over a 5-year time horizon, the PRS was associated with an average of 4.26 QALYs, compared to 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 $CA4,334 and $CA5,815, respectively (difference of $CA1,481). 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 $CA4,580 and $CA6,382, respectively (difference $CA1,803), which once again resulted in the PRS being a dominant alternative.

Table 2. Cost-effectiveness results – base-case analysis

	Usual screening	**PRS**
Total QALYs	4.25	4.26
Incremental QALYs		0.01
Total costs, $CA MoH perspective	$5,815	$4,334
Incremental total costs, $CA MoH perspective		-$1,481
Total costs, $CA Societal perspective	$6,382	$4,580
Incremental total costs, $CA Societal perspective		-$1,803
Incremental cost/QALY, $CA MoH perspective		Dominant
Incremental cost/QALY, $CA Societal perspective		Dominant

CA: Canadian Dollars, *MoH:* Ministry of Health, *PRS*: Polygenic Risk Score, *QALY:* Quality-adjusted life years

Sensitivity analysis

According to one-way sensitivity analysis results, the PRS compared to usual screening methods was a dominant alternative in the majority of analyses. The parameters with the greatest impact on the base-case ICERs from both the MoH and societal perspectives were (i) the proportion of patients on dialysis, (ii) the proportion of patients with ICHD and (iii) the utility of pre-ESRD health state (**Figure 1**). The PRS was a dominant alternative over the usual screening methods in 94.08% of the Monte Carlo simulations, from both the MoH and societal perspectives (**Figure 2a and 2b**).

Scenario Analyses

Supplementary scenario analyses, including projections over 10-years (**Appendix B.1**) and lifetime (**Appendix B.2**) horizons also resulted in the PRS being dominant. Detailed results of these scenario analyses are presented in **Appendix B**.

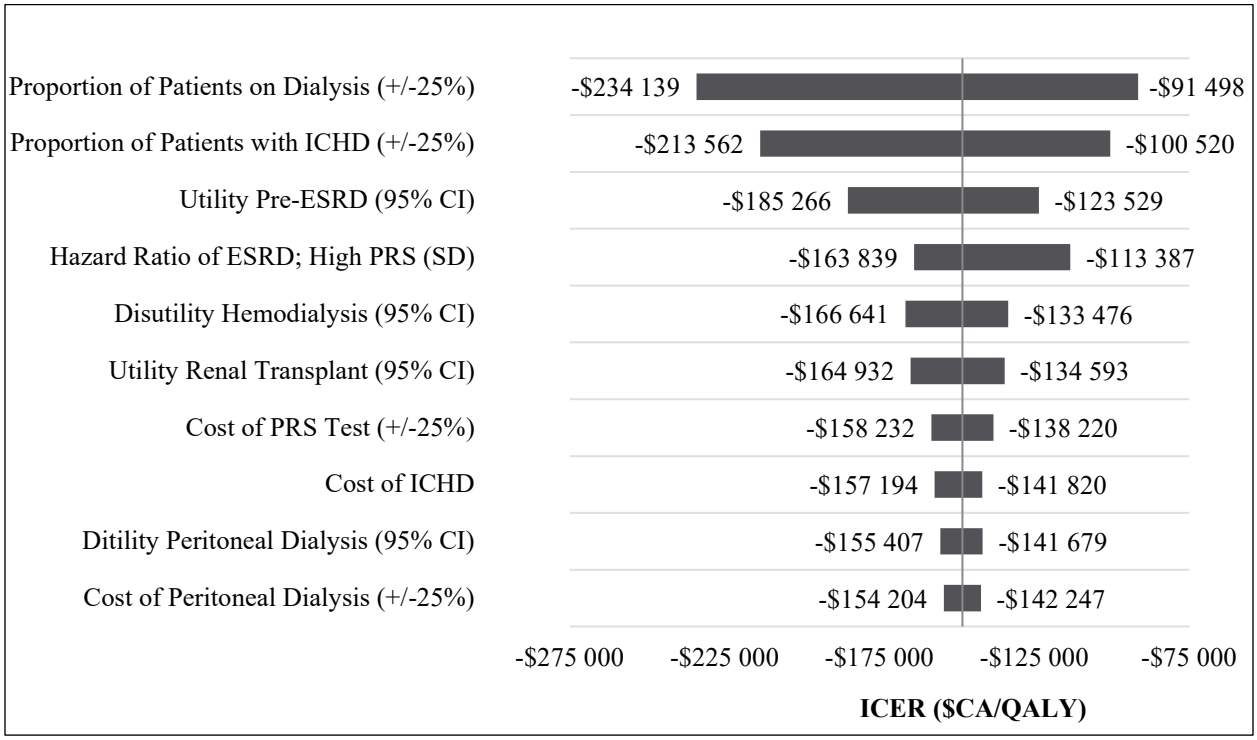
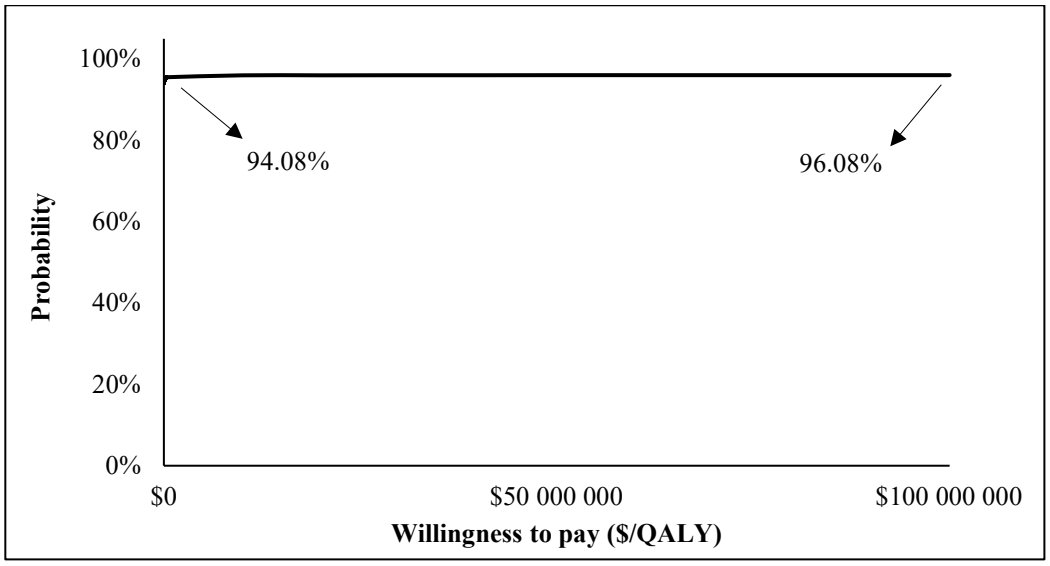


Figure 1. Results of one-way sensitivity analysis. Results of one-way sensitivity analysis are presented in a tornado diagram from the Ministry of Health perspective. Lower and upper bounds considered for the sensitivity analyses are indicated in the y-axis for each parameter. The cost of ICHD was varied according to the cost range available in Alberta Health Services.[42] The base-case incremental cost-effectiveness ratio is -$CA148,226/QALY (dominant). CA: Canadian Dollar, ICER: Incremental cost-effectiveness ratio, QALY: Quality adjusted life years

(a)



(b)

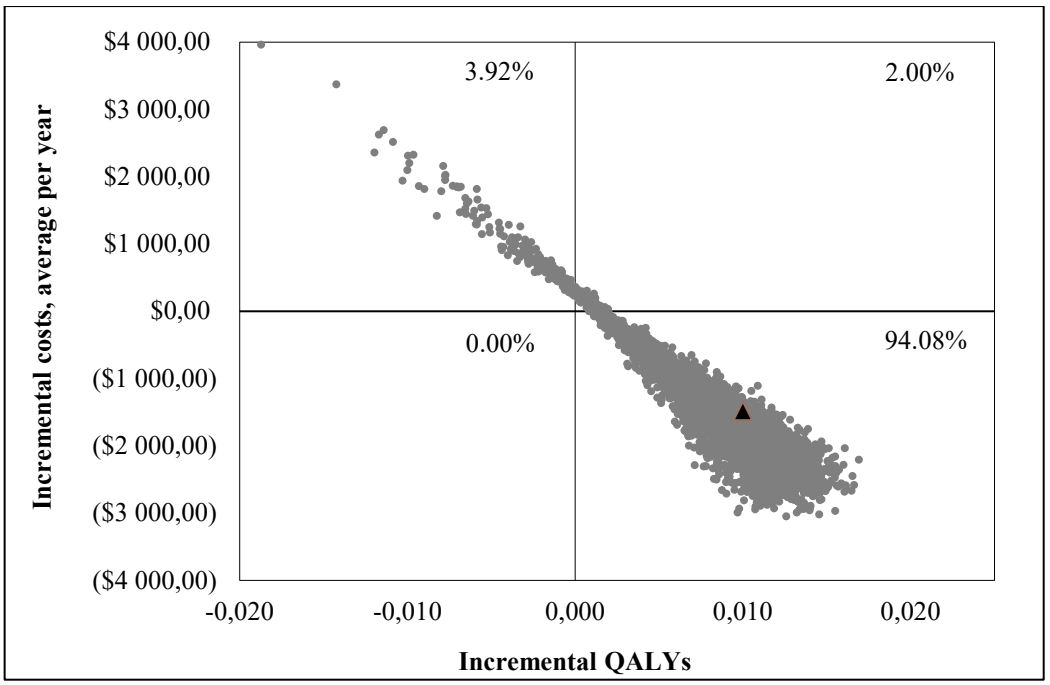


Figure 2. Results of probabilistic sensitivity analysis. Results of probabilistic sensitivity analysis are presented in cost-acceptability curves (a) and scatter plots (b). These are representative of both the MoH and societal perspectives. The commonly cited threshold in Canada is $CA50,000/QALY. CA: Canadian Dollar, QALY: Quality adjusted life years

Discussion

This economic evaluation indicated that, compared to 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.

This is the first economic evaluation of a PRS for the detection of DN in T2D patients. 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 to those captured within the 5-year time horizon of the trial. Type-2 diabetes is a chronic disease with late penetrance and 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, thus allowing a broader perspective and perhaps a more representative assessment of all the impacts of the disease and related interventions. Lastly, although the PRS is administered after an average of 8 years (SD: 7.4-8.9) following 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 due to 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 and Tremblay et al., earlier target and treatment of high-risk patients reduces the chance of developing ESRD.[54,55] More specifically, high PRS patients 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.[45] Since the mean age of the ADVANCE population is 67 years old, targeting a younger population of diabetic patients 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 two comparators is 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 in order 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 the current study involves not using the utility values specific to the ADVANCE trial, published by Hayes et al. [99] 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, in order 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 to the base-case analysis. Furthermore, although RT patients typically receive prior dialysis for an average of 3.8-years, this clinical element was not taken into consideration in the model.[29] 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. In-center HD costs on average $100,000 annually, therefore considering an additional 3.8 years of dialysis for all ESRD patients would increase the incremental costs between both scenarios, further favoring the dominant result of the PRS.[29,42] Despite these limitations, findings of the cost-utility analysis are robust according to the base-case results as well as the DSA. Lastly, the PSA demonstrated that the PRS may also be considered a cost-effective or dominated alternative, from both a MoH and societal perspective. These PSA results are explained by two different factors. Firstly, the only parameter that influences this result is based on the HR of ESRD related to high PRS. Since the HR is close to 1, certain PSA capture values below 1 due to the selected distribution. However, since 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, since 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, called the ADVANCE-ON trial.[45] The results of this post-trial follow-up were tested in additional analyses and proved that the PRS remained a dominant alternative after 9.5 years. However, due to the non-randomized nature of this post-trial follow-up, this data was not included in the present study. Secondly, although PSA results should typically be found within the four quadrants of the scatter plot, 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, due to the drastic differences in costs associated the number of ESRD events.

Conclusion

This economic evaluation suggests that, from a Canadian MoH and societal perspective, the PRS is a dominant option compared to 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.

Author Disclosures

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Author Contribution

KG, CB and JL were involved in designing the study. Markov model development and results assessment were performed by KG. PH participated in the management of ADVANCE trial with JT and they were responsible for the development of the clinical polygenic test and both contributed as key opinion leaders in the model development. JC and MW managed the ADVANCE and ADVANCE-ON studies. The manuscript was prepared by KG. All authors reviewed the final manuscript.

8.3 Additional Results Associated with Article #2

8.3.1 Scenario Analysis - Results Associated with 9.5-Year Raw Data

Over a 10-year time horizon using 9.5-year raw data of the ADVANCE-ON trial, the PRS was associated with an average of 6.97 QALYs, compared to an average of 6.92 QALYs with usual screening methods for DN, for QALY gain of 0.045. From a MoH perspective, PRS and usual screening tests were associated with total costs of $CA9,443 and $CA12,457, respectively (difference of -$CA3,013), which results in a dominant ICER. From a societal perspective, PRS and usual screening tests were associated with total costs of $CA10,211 and $CA13,704, respectively (difference -$CA3,493), which once again results in a dominant ICER. These results are presented in **Table 21**.

Table 21. Cost-Effectiveness Results – Scenario Analysis (10-Year Time Horizon using 9.5-Year Data)

	Usual screening	PRS
Average QALYs	6.92	6.97
Incremental QALYs [a]		0.045
Total costs, $CA MoH perspective	12,457	9,443
Incremental total costs, $CA MoH perspective		3,013
Total costs, $CA Societal perspective	13,704	10,211
Incremental total costs, $CA Societal perspective		3,493
Incremental cost/QALY, $CA MoH perspective		Dominant
Incremental cost/QALY, $CA Societal perspective		Dominant

[a]May not sum to total because of rounding

CA: Canadian Dollars, *MoH:* Ministry of Health, *PRS*: Polygenic Risk Score, *QALY:* Quality-adjusted life years

8.3.2 One-Way Sensitivity Analysis of Cost and Effectiveness Parameters

Figure 17 and Figure 18 present complete results of OWSA, associated with the parameters of effectiveness and costs, respectively.

Figure 17. Results of One-Way Sensitivity Analysis – Tornado for Effectiveness Parameters

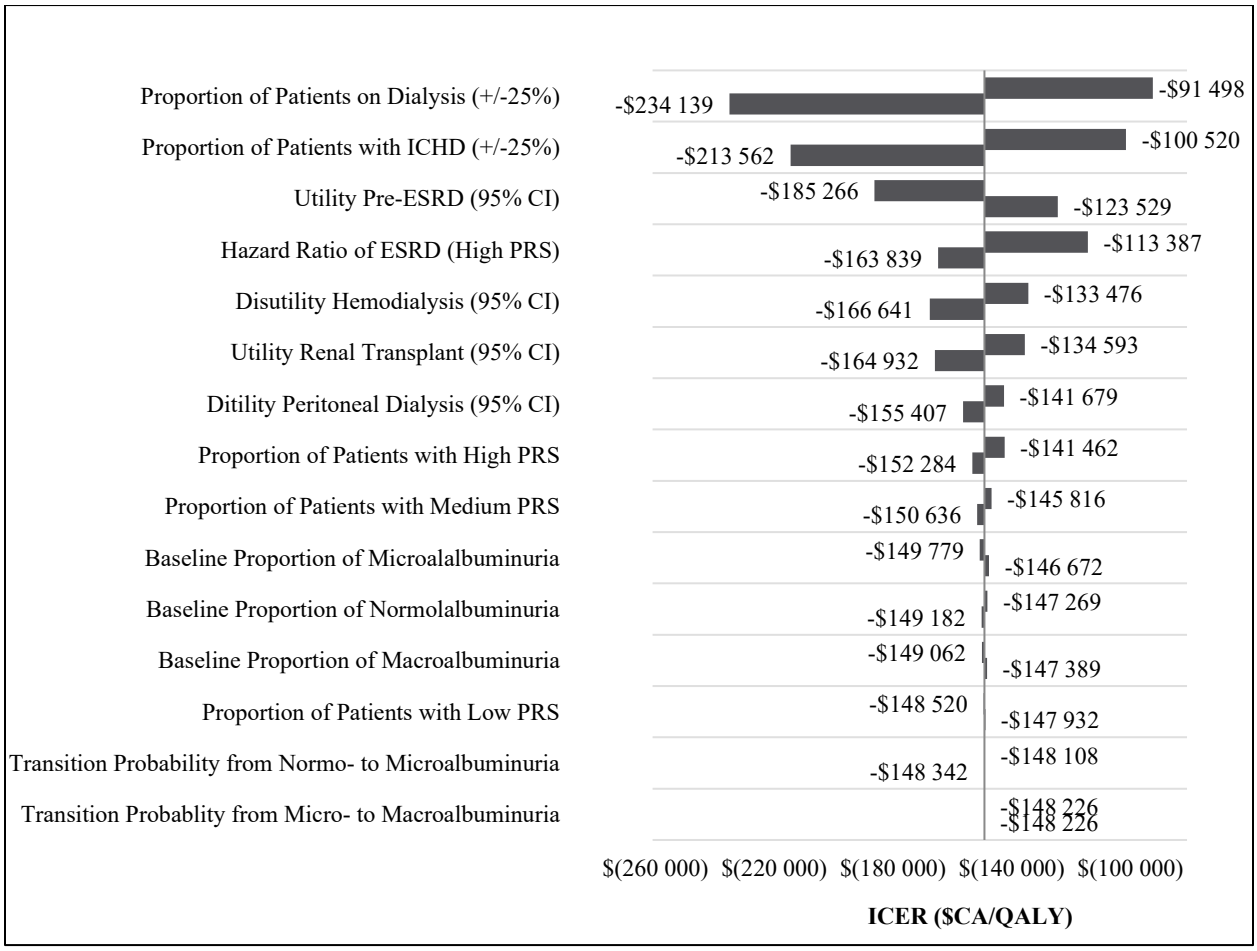
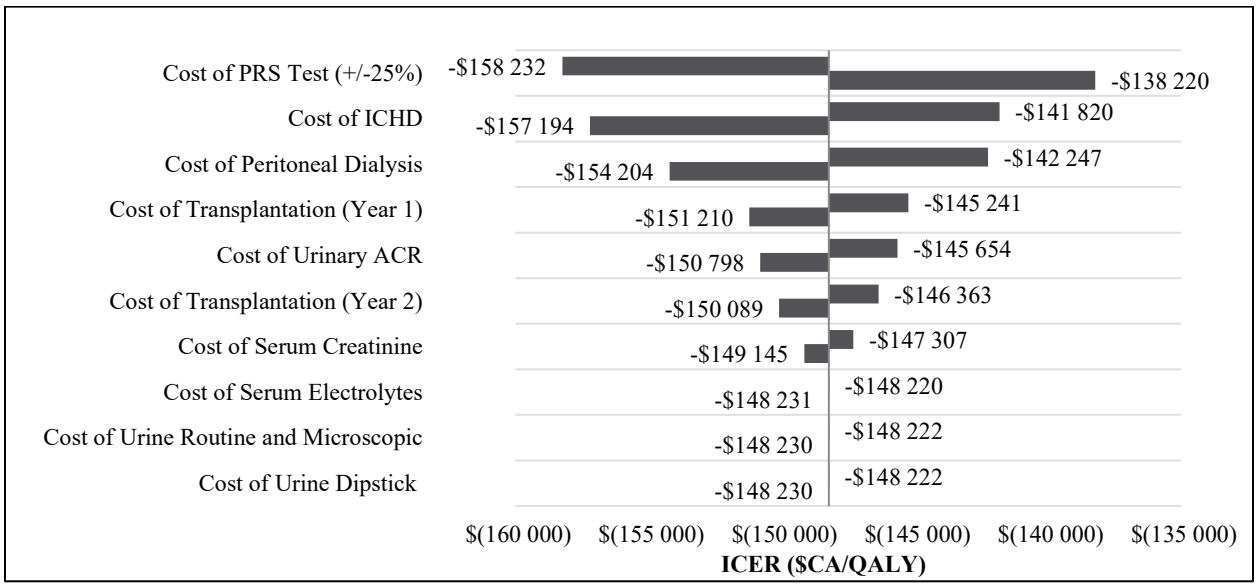


Figure 18. Results of One-Way Sensitivity Analysis – Tornado for Cost Parameters



8.3.3 Probabilistic Results

8.3.3.1 Base-Case Analysis

Over a 5-year time horizon, the PRS was associated with an average of 4.58 QALYs, compared to an average of 4.57 QALYs with usual screening methods for DN, for QALY gain of 0.010. From a MoH perspective, PRS and usual screening tests were associated with total costs of $CA4,541 and $CA6,186, respectively (difference of -$CA1,645), which results in a dominant ICER. From a societal perspective, PRS and usual screening tests were associated with total costs of $CA4,810 and $CA6,794, respectively (difference -$CA1,985), resulting in a dominant ICER. These results are presented in **Table 22**.

Table 22. Cost-Effectiveness Probabilistic Results – Base-Case Analysis

	Usual screening	PRS
Average QALYs	4.57	4.58
Incremental QALYs [a]		0.010
Total costs, $CA MoH perspective	6,186	4,541
Incremental total costs, $CA MoH perspective		1,645
Total costs, $CA Societal perspective	6,794	4,810
Incremental total costs, $CA Societal perspective		1,985
Incremental cost/QALY, $CA MoH perspective		Dominant
Incremental cost/QALY, $CA Societal perspective		Dominant

[a]May not sum to total because of rounding

CA: Canadian Dollars, *MoH:* Ministry of Health, *PRS*: Polygenic Risk Score, *QALY:* Quality-adjusted life years

8.3.3.2 Scenario Analysis – 10-Year Time Horizon

Over a 10-year time horizon, the PRS was associated with an average of 7.08 QALYs, compared to an average of 7.03 QALYs with usual screening methods for DN, for QALY gain of 0.050. From a MoH perspective, PRS and usual screening tests were associated with total costs of $CA10,288 and $CA13,268, respectively (difference of -$CA2,980), which results in a dominant ICER. From a societal perspective, PRS and usual screening tests were associated with total costs of $CA10,967 and $CA14,487, respectively (difference -$CA3,520), resulting in a dominant ICER. These results are presented in **Table 23**.

Table 23. Cost-Effectiveness Probabilistic Results – Scenario Analysis (10-Year Time Horizon)

	Usual screening	PRS
Average QALYs	7.03	7.08
Incremental QALYs [a]		0.050
Total costs, $CA MoH perspective	13,268	10,288
Incremental total costs, $CA MoH perspective		2,980
Total costs, $CA Societal perspective	14,487	10,967
Incremental total costs, $CA Societal perspective		3,520
Incremental cost/QALY, $CA MoH perspective		Dominant
Incremental cost/QALY, $CA Societal perspective		Dominant

[a]May not sum to total because of rounding

CA: Canadian Dollars, *MoH:* Ministry of Health, *PRS*: Polygenic Risk Score, *QALY:* Quality-adjusted life years

8.3.3.3 Scenario Analysis – Lifetime Horizon

Over a lifetime horizon, the PRS was associated with an average of 9.55 QALYs, compared to an average of 9.43 QALYs with usual screening methods for DN, for QALY gain of 0.12. From a MoH perspective, PRS and usual screening tests were associated with total costs of $CA17,881 and $CA21,017, respectively (difference of -$CA3,136), which results in a dominant ICER. From a societal perspective, PRS and usual screening tests were associated with total costs of $CA19,015 and $CA22,735, respectively (difference -$CA3,720), resulting in a dominant ICER. These results are presented in **Table 24**.

Table 24. Cost-Effectiveness Probabilistic Results – Scenario Analysis (Lifetime Horizon)

	Usual screening	PRS
Average QALYs	9.43	9.55
Incremental QALYs [a]		0.120
Total costs, $CA MoH perspective	21,017	17,881
Incremental total costs, $CA MoH perspective		3,136
Total costs, $CA Societal perspective	22,735	19,015
Incremental total costs, $CA Societal perspective		3,720
Incremental cost/QALY, $CA MoH perspective		Dominant
Incremental cost/QALY, $CA Societal perspective		Dominant

[a]May not sum to total because of rounding

CA: Canadian Dollars, *MoH:* Ministry of Health, *PRS*: Polygenic Risk Score, *QALY:* Quality-adjusted life years

8.3.3.4 Scenario Analysis - Results Associated with 9.5-Year Raw Data

Over a lifetime horizon, the PRS was associated with an average of 7.50 QALYs, compared to an average of 7.46 QALYs with usual screening methods for DN, for QALY gain of 0.040. From a MoH perspective, PRS and usual screening tests were associated with total costs of $CA10,182 and $CA13,476, respectively (difference of -$CA3,294), which results in a dominant ICER. From a societal perspective, PRS and usual screening tests were associated with total costs of $CA11,010 and $CA14,802, respectively (difference -$CA3,791), resulting in a dominant ICER. These results are presented in **Table 25**.

Table 25. Cost-Effectiveness Probabilistic Results – Scenario Analysis (10-Year Time Horizon using 9.5-Year Data)

	Usual screening	PRS
Average QALYs	7.46	7.50
Incremental QALYs [a]		0.040
Total costs, $CA MoH perspective	13,476	10,182
Incremental total costs, $CA MoH perspective		3,294
Total costs, $CA Societal perspective	14,802	11,010
Incremental total costs, $CA Societal perspective		3,791
Incremental cost/QALY, $CA MoH perspective		Dominant
Incremental cost/QALY, $CA Societal perspective		Dominant

[a]May not sum to total because of rounding

CA: Canadian Dollars, *MoH:* Ministry of Health, *PRS*: Polygenic Risk Score, *QALY:* Quality-adjusted life years

9 Discussion

This research project allowed, as a first step, to systematically review all the economic evaluations published in DN for T2D patients. As a second step, this project confirmed the positive clinical benefit of the new PRS for early prediction of DN in T2D patients and evaluated for the first time, its economic impact, compared to current screening methods.

9.1 Systematic Literature Review

9.1.1 Summary and Result interpretation

The results of the literature review on economic evaluations in DN for T2D patients, presented in **section 8.1** puts to evidence the heterogeneity between characteristics of retrieved studies. This study also analyses trends in the cost-effectiveness of multiple treatment options in DN and demonstrates the significant economic burden of DN in T2D. This was shown in the literature review through multiple EEs and COI studies.

The majority of the retrieved studies were published between 1995 and 2007. This could be explained by that fact that most of the new pharmaceutical products for DN were developed a while ago, and that within the past 10 years, few innovative research has been done in the field. Furthermore, the type of analysis used for the economic evaluations reflect the increased use of CUA over time, towards becoming the approved type of analysis, as stated in the most recent guidelines for the economic evaluations of health technologies published by the CADTH in 2017, as well as other international guidelines.[47,91] According to these guidelines, a CUA is the recommended type of economic evaluations and should be used as the reference case analysis.[47] As shown in this literature review, the most common type of analysis within the past 10 years has been CUAs, while CEA were the most common between 1995-2007. Another interesting trend was found in the treatments and comparators evaluated in the studies. Prior to 2008, the most commonly evaluated treatment was losartan. During this time period, blood pressure lowering treatments were the most commonly used technics in order to reduce or help prevent renal damage in patients with T2D. However, from 2008 to 2018, most studies evaluated the economic impact of treating patients with ACEI or ARB at diagnosis of T2D, versus only treating patients at the diagnosis of micro- or macroalbuminuria. These findings demonstrate the consideration of a new treatment pattern, before the appearance of nephropathy symptoms, which focuses of prevention rather than treatment of the disease.

From the results obtained within each study, many trends were noticed. According to the COI studies, it was logically observed that the cost of the disease increases according to the disease severity. This result is consistent with the fact that ESRD is extremely expensive, with dialysis treatments costing on average $100,000 per year per patient.[42] Furthermore, treating all patients in an early setting (at T2D diagnosis) versus a late setting (at micro- or macroalbuminuria diagnosis) resulted as a dominant option in all studies. In other words, an early treatment was shown less costly and more effective than a late treatment, either with an antihypertensive or an ACEI/ARB therapy. Lastly, administering an antihypertensive therapy, at any stage of the disease, represented a cost-effective option.

9.1.2 Strengths

This systematic literature review presents many strengths, offering a complete and current representation of all the economic evaluations performed on DN for T2D patients. Firstly, the review covered a long time period (1995 to 2018), which allowed the observation of trends between old and new economic evaluations. Many databases were used, including EMBASE, MEDLINE and PubMed, allowing to capture the most relevant articles pertinent to this review. The inclusion of grey literature also permitted to limit the risk of publication bias. Finally, the selection as well as data extraction was performed by two independent reviewers, ensuring that the content of the literature review is rigorous and exhaustive, further preventing the possibility of selection bias.

9.1.3 Limitations

Although the systematic literature review method was thoroughly performed, this study has some limitations. Indeed, all literature reviews are limited by the key words and indexation used within databases. For example, the disease key words were limited to DN. However, although the study focused on T2D, the search was not limited to the key word of T2D. This was done in order to prevent the potential loss of relevant studies discussing both T1D and T2D. Another possible limitation associated to this systematic literature review could include publication bias as well as publication language bias. Indeed, the non-inclusion of unpublished research as well as the restriction of the review to English and French studies might have biased the results. However, the inclusion of grey literature reduced the possibility of this publication bias. Lastly, this systematic literature review did not follow the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) methodology.[92] For example, no evaluation of the quality of the studies was performed for this systematic literature review. It is known that the inclusion of

biased studies is more likely to produce misleading results than those that are rigorously performed.[93] The use of Drummond's checklist for assessing economic evaluations would have been a good method to assess study quality and increase the validity of this systematic literature review.[46] Although this is an important limitation, the main objective of this study was to provide an overview of the methodology used in published economic evaluations for nephropathy in T2D patients. Nevertheless, considering the strengths and limits of this literature review, this study provides a current overview of the economic evaluations in nephropathy for T2D patients and could be useful for future pharmacoeconomic research.

A systematic literature review of economic modelling of chronic kidney disease was recently published in September 2019.[94] Of all the identified articles related to chronic kidney disease, 48 were retrieved as diabetes models related to nephropathy, where 12 studies (25%) were models for T1D and 22 (46%) were for T2D. Therefore, discrepancies between both reviews could be explained by the following: 1) no distinction between T1D and T2D and, 2) the review included data up to November 2017. This present systematic literature review offers a more specific (related to T2D only) and more recent (including articles from 2018) review of the EEs in nephropathy for T2D.

9.2 Economic Evaluation

9.2.1 Summary and Result interpretation

The cost-utility analysis presented in **section 8.2** demonstrated that, compared to usual screening methods for DN, the PRS is a dominant alternative among patients with T2D. According to the study results, the PRS was proven to be less expensive (difference of $CA1,481) and more effective compared to usual screening methods, generating more QALYs (QALY gain of 0.010). Therefore, the PRS is a dominant alternative compared to usual screening methods, in Canada. This study also demonstrated that the PRS remained a dominant option, from a 10-year and lifetime horizon. The results of comprehensive sensitivity analyses confirmed the robustness of the base-case results.

While the result of this study are positive, it is assumed that in a real world setting, the PRS would be even more cost-effective compared to usual screening methods. Firstly, although the PRS was administered after an average of 5 years (SD: 2-10 years) following 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 due to 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., earlier target and treatment of high-risk patients reduces the chance of developing ESRD.[54,55] More specifically, high PRS patients 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. Since the mean age of the ADVANCE population is 67 years old, targeting a younger population of diabetic patients in the real world would result in even greater reductions of ESRD events, directly associated with better cost-effectiveness results.

9.2.2 Strengths

The study presented in **section 8.2** represent the first economic evaluation of a PRS for the detection of DN in T2D patients. The study has several strengths. First, scenario analyses extrapolating ADVANCE trial data over 10-years and lifetime horizons allowed to capture all the events related to death and ESRD, compared to those captured within the 5-year time horizon of the trial. Type-2 diabetes is a chronic disease and 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, thus allowing a broader perspective and perhaps a more representative assessment of all the impacts of the disease and related interventions.

9.2.3 Limitations

However, this economic evaluation also has some limitations. The difference in numbers of QALYs between the two comparators is 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 in order 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 the current study involves not using the utility values specific to the ADVANCE trial, published by Hayes et al. [99] 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, in order 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 to the base-case analysis. Furthermore, although RT patients typically receive prior dialysis for an average of 3.8-years, this clinical element was not taken into consideration in the model.[29] 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 ESRD patients would increase the incremental costs between both scenarios, further favouring the dominant result of the PRS.[29,42] Despite these limitations, findings of the cost-utility analysis are robust according to the base-case results as well as the DSA. Lastly, the PSA demonstrated that, in some simulations, the PRS was either a cost-effective or dominated alternative, from both a MoH and societal perspective. These PSA results are explained by two different factors. Firstly, the only parameter that influences this result is based on the HR of ESRD related to high PRS. Since the HR is close to 1, certain PSA capture values below 1 due to the selected distribution. However, since this HR was captured after only 4.5 years in the ADVANCE trial, having more extensive clinical trial data would mostly probably increase the efficacy of the PRS, since the event of ESRD is often captured later in the course of the disease. Secondly, although PSA results should typically be found within the four quadrants of the scatter plot, results of this economic evaluation remained mostly in the dominant quadrant. 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, due to the drastic differences in costs associated the number of ESRD events.

10 Conclusion

In conclusion, both the systematic literature review as well as the economic evaluation were key in order to determine the cost-effectiveness of the new PRS for early prediction of DN in T2D patients. The systematic literature review captured the substantial economic impact of DN in T2D patients and provided an overview of how DN in T2D is typically modelled. The information retrieved from this review was used in order to build the economic evaluation of the PRS. This economic evaluation suggests that, from a Canadian MoH and societal perspective, the PRS is a dominant option compared to 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. These results suggest that the PRS

will eventually replace current screening methods and will become the primary technic for early prediction of DN in T2D.

Finally, in light of the dominant results associated with the PRS for the prediction and prevention of nephropathy in T2D patients, it would be interesting to develop additional PRS's for all diabetes-related complications. This would allow to target patients in need of preventive treatment and also reduce the clinical and economic burden associated with diabetes. The economic model developed within the framework of this master's project could be used in order to evaluate additional PRS's to be marketed in Canada.

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Appendix 1: Appendix of Article #1

Appendix A

Table A.1 MEDLINE Search Strategy and Keywords

Search line	Mesh Words
1	*Economics/
2	exp "Costs and Cost Analysis"/
3	Economics, Nursing/
4	Economics, Medical/
5	Economics, Pharmaceutical/
6	exp Economics, Hospital/
7	Economics, Dental/
8	exp "Fees and Charges"/
9	exp Budgets/
10	budget*.ti,ab,kf.
11	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kf.
12	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2
13	(cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kf.
14	(value adj2 (money or monetary)).ti,ab,kf.
15	exp models, economic/
16	economic model*.ab,kf.
17	markov chains/
18	markov.ti,ab,kf.
19	monte carlo method/
20	monte carlo.ti,ab,kf.
21	exp Decision Theory/
22	(decision* adj2 (tree* or analy* or model*)).ti,ab,kf.
23	or/1-22
24	*Diabetic Nephropathies/
25	23 and 24
26	limit 25 to (english or french)

Table A.2 EMBASE Search Strategy and Keywords

Search line	Mesh Words
1	Economics/
2	Cost/
3	exp Health Economics/
4	Budget/
5	budget*.ti,ab,kw.
6	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kw.
7	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2
8	(cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kw.
9	(value adj2 (money or monetary)).ti,ab,kw.
10	Statistical Model/
11	economic model*.ab,kw.
12	Probability/
13	markov.ti,ab,kw.
14	monte carlo method/
15	monte carlo.ti,ab,kw.
16	Decision Theory/
17	Decision Tree/
18	(decision* adj2 (tree* or analy* or model*)).ti,ab,kw.
19	or/1-18
20	*diabetic nephropathy/
21	19 and 20
22	limit 21 to (english or french)

Table A.3 PubMed Search Strategy and Keywords

Search line	Mesh Words
1	Economics[Mesh:NoExp] OR "Costs and Cost Analysis"[mh] OR Economics, Nursing[mh] OR Economics, Medical[mh] OR Economics, Pharmaceutical[mh] OR Economics, Hospital[mh] OR Economics, Dental[mh] OR "Fees and Charges"[mh] OR Budgets[mh] OR budget*[tiab] OR economic*[tiab] OR cost[tiab] OR costs[tiab] OR costly[tiab] OR costing[tiab] OR price[tiab] OR prices[tiab] OR pricing[tiab] OR pharmacoeconomic*[tiab] OR pharmaco-economic*[tiab] OR expenditure[tiab] OR expenditures[tiab] OR expense[tiab] OR expenses[tiab] OR financial[tiab] OR finance[tiab] OR finances[tiab] OR financed[tiab] OR value for money[tiab] OR monetary value*[tiab] OR models, economic[mh] OR economic model*[tiab] OR markov chains[mh] OR markov[tiab] OR monte carlo method[mh] OR monte carlo[tiab] OR Decision Theory[mh] OR decision tree*[tiab] OR decision analy*[tiab] OR decision model*[tiab]
2	Diabetic nephropathies OR diabetic nephropathy

Appendix B

Table B.1 Extraction Data for EEs

First Author (year)	Country	Study population	Type(s) of EE	Model of analysis	Time horizon	Intervention	Comparator	Costs included	Data source	Results (currency year)	2019$C Adjusted Results
Adarkwah, C. C., et al. (2011). [100]	Netherlands	Newly diagnosed T2D Mean age: 50y Normo: 79% Micro: 18% Macro: 3%	Cost-utility	Markov model	50 years	Treat all patients with ACEI at T2D diagnosis (n = 500)	Treat with ACEI at time of micro or macro diagnosis (n = 500)	Healthcare system perspective Direct costs only (Cost of ACEI and ARB, annual screening, ESRD treatment and health care expenditure related or unrelated to diabetes)	-Cost inputs: Literature (de Wit GA, 1998; Schroeder, 2005) and Farmacotherapeutisch Kompas (2010) and Nederlandse Zorgautoriteit (2010) -Clinical inputs: Literature (Niskanen, 1996; Lewis EJ, 1993) -Utility inputs: Literature (Briggs, 2003; Brown GC, 2000; Arnesen, 2004)	Treat-all strategy is dominant compared to treatment at screening of microalbuminuria or macroalbuminuria **Costs** Treat-all: €98,421 Micro: €101,140 Marco: €110,777 **QALYs** Treat-all: 19.63 Micro: 19.54 Macro: 19.15 (Euro 2010)	**Costs** Treat-all: $137,298 Micro: $141,091 Marco: $154,534

First Author (year)	Country	Study population	Type (s) of EE	Model of analysis	Time horizon	Intervention	Comparator	Costs included	Data source	Results (currency year)	2019$C Adjusted Results
Adarkwah et al.; (2010) [101]	Germany	Newly diagnosed T2D Mean age: 50y Normo: 79% Micro: 18% Macro: 3%	Cost-utility	Markov model	50 years	Treat all patients with ACEI at T2D diagnosis (n = 500)	Treat with ACEI at time of micro or macro diagnosis (n = 500)	Healthcare system perspective Direct costs only (cost of ACE inhibitor, ARBs, annual screening procedures, treatment for ESRD and healthcare expenditures related and unrelated to diabetes	-Cost inputs: Literature (Braun S, 2009; Schroeder A, 2005; Koester I, 2006) Rote Liste Service GmbH (2005), K/DOQI clinical practice guidelines (2004) and Kassen¨arztliche Bundesvereinigung Berlin (2006) -Clinical inputs: literature (Niskanen, 1996; Lewis EJ, 1993; Guideline of ADA) -Utility inputs: literature (Churchill DN, 1987; Brown GC, 2000; Arnesen, 2004)	**Treating all with ACE at T2D diagnosis** Cost: €135,555 QALY: 15.21 *Dominant option **No screening and no treatment** Cost: €151,579 QALY: 14.46 **Screening for microalbuminuria** Cost: €144,059 QALY: 14.83 **Screening for macroalbuminuria** Cost: €137,406 QALY: 15.14 (Euro 2006)	**Treating all with ACE at T2D diagnosis** Cost: $224,331 QALY: 15.21 *Dominant option **No screening and no treatment** Cost: $250,849 QALY: 14.46 **Screening for microalbuminuria** Cost: $238,404 QALY: 14.83 **Screening for macroalbuminuria** Cost: $227,394 QALY: 15.14

First Author (year)	Country	Study population	Type (s) of EE	Model of analysis	Time horizon	Intervention	Comparator	Costs included	Data source	Results (currency year)	2019$C Adjusted Results
Alexander, C. M., et al. (2004). [102]	US	T2D and nephropathy Mean age: 60y	Cost-study	N/A	3.5 years	Losartan (n = 751)	Placebo-based conventional antihypertensive therapy (n = 762)	Healthcare system perspective Cost associated to ESRD and the cost of losartan	-Cost inputs: US Renal Data System (USRDS) (2001) -Clinical inputs: RENAAL study	**% of patients who develop ESRD after 3.5 years** Losartan: 20.8% Placebo: 27.1% (p = 0.002) **Mean ESRD days after 3.5 years** Losartan: 76.1 days Placebo: 109.7 days (p = 0.004) **ESRD related costs after 3.5 years** Losartan: $143 Placebo: $6,900 (p = 0.041) (USD 2001)	**ESRD related costs after 3.5 years** Losartan: $274 Placebo: $13,211

First Author (year)	Country	Study population	Type (s) of EE	Model of analysis	Time horizon	Intervention	Comparator	Costs included	Data source	Results (currency year)	2019$C Adjusted Results
Annemans, L., et al. (2008). [103]	China, Malaysia, Thailand, South Korea and Taiwan	T2D, hypertension and micro Mean age: 59y Micro: 100% Males: SBPC 68.7% IR 70.6%	Cost-effectiveness	Markov model	25 years (Lifetime)	Early IR Or Late amlodipine Or Late IR	Standard blood pressure control treatment	Third party payer perspective Cost of medication, dialysis, renal transplantation and cost of transplanted diabetic patients	<u>-Cost inputs:</u> Local sources for each country <u>-Clinical inputs:</u> IRMA-2 and IDNT study	**Number of years after which early Irbesartan is cost-saving** Malaysia: 11-y Taiwan: 11-y South Korea: 13-y China: 16-y Thailand: 20-y At the end of the time horizon of the model, early Irbesartan was consistently found to be the least expensive treatment strategy (USD 2004)	-

First Author (year)	Country	Study population	Type(s) of EE	Model of analysis	Time horizon	Intervention	Comparator	Costs included	Data source	Results (currency year)	2019$C Adjusted Results
Arredondo, A., et al. (2005). [104]	Mexico	T2D and nephropathy (urinary albumin) Mean age: 60y Male: 63%	Cost-effectiveness	N/A	Lifetime	Losartan (n = 751)	Placebo (n = 762)	Third party payer perspective Cost of ESRD, lifetime cost of losartan therapy and other costs (non-ESRD/non-losartan) expected for patients with T2D	<u>-Costs inputs:</u> Literature (Arrendondo, 2004) and price from public institutions <u>-Clinical inputs:</u> RENAAL Study	**Lifetime incidence of ESRD** Losartan: 66% Placebo: 83% **Life years gained by losartan due to ESRD prevention** 0.697 years **Net savings per patient** $24,073 (Mexican pesos 2004)	**Net savings per patient** $4,910

First Author (year)	Country	Study population	Type (s) of EE	Model of analysis	Time horizon	Intervention	Comparator	Costs included	Data source	Results (currency year)	2019$C Adjusted Results
Burgess et al.; (2004) [105]	Canada	T2D and DN Age range: 31-70y	Cost-effectiveness	N/A	3.5-y and 4-y	Losartan + CT (n = 751)	CT (n = 762)	Healthcare system perspective Direct costs (Cost of ESRD treatment, hospitalization costs as well as losartan cost of therapy)	-Costs inputs: Published and public sources (no specifics) -Clinical inputs: RENAAL study	**Losartan reduced the estimated number of ESRD days by** 33.6% over 3.5-y 46.9% over 4-y **Net cost-savings with losartan after X-y of follow-up** 2-y: $130 2.5-y: $908 3-y: $2,033 3.5-y: $3,675 4-y: $5,445 *Losartan is a dominant strategy (CND 2001)	**Net cost-savings with losartan after X-y of follow-up** 2-y: $163 2.5-y: $1,135 3-y: $2,542 3.5-y: $4,595 4-y: $6,808

First Author (year)	Country	Study population	Type(s) of EE	Model of analysis	Time horizon	Intervention	Comparator	Costs included	Data source	Results (currency year)	2019$C Adjusted Results
Caride s et al.; (2006) [106]	US	T2D and nephropathy Mean age: 60y Men: Losartan 61.5% Placebo 64.8%	Cost-effectiveness	Cumulative incidence competing risk (CICR) method	Lifetime	Losartan + CT (n = 751)	Placebo + CT (n = 762)	Healthcare system perspective Cost associated with ESRD, cost of losartan therapy and other costs (non-ESRD/non-losartan) expected for patients with T2D	-Costs inputs: Literature (Manninen, 2004;) -Clinical inputs: RENAAL study	**Lifetime ESRD-related incremental cost-saving per patient** $31,803 **Undiscounted LYG per patient** 0.99 **Lifetime net saving per patient (all costs included)** $24,632 (USD 2002)	**Lifetime ESRD-related incremental cost-saving per patient** $60,188 **Lifetime net saving per patient (all costs included)** $46,616

First Author (year)	Country	Study population	Type (s) of EE	Model of analysis	Time horizon	Intervention	Comparator	Costs included	Data source	Results (currency year)	2019$C Adjusted Results
Coyle et al.; (2004) [107]	Canada	T2D, hypertension and proteinuria	Cost-effectiveness	Markov model	Lifetime (25-y)	IR Or Amlodipine	CT	Third party payer perspective Direct costs (Drug therapy, concomitant medications, monitoring costs as well as inpatient and outpatient care for cardiovascular events, dialysis and renal transplant)	-Costs inputs: ODBF -Clinical inputs: IDNT Trial, USRDR	**LYG** IR: 6.82 Amlodipine: 6.48 CT: 6.40 **Total costs** IR: $89,304 Amlodipine: $109,280 CT: $101,688 *Amlodipine and CT are dominated by IR (CND 2001)	**Total costs** IR: $111,652 Amlodipine: $136,627 CT: $127,136

First Author (year)	Country	Study population	Type(s) of EE	Model of analysis	Time horizon	Intervention	Comparator	Costs included	Data source	Results (currency year)	2019$C Adjusted Results
Coyle et al.; (2007) [15]	Canada	Hypertension, T2D and renal disease	Cost-effectiveness	Markov Model	25-y	Early addition of IR to CT OR Late addition of IR to CT	CT excluding ARB	Healthcare system perspective All direct costs (Health and social services and long-term care)	-Costs inputs: Literature (Coyle D, 2004), IRMA-2 and Ontario Drug Formulary -Clinical inputs: IRMA-2 and IDNT	**Early Irbesartan vs. conventional antihypertensive** ΔLYG: 0.62 ΔCost: -$68,400 **Early Irbesartan vs. late Irbesartan** ΔLYG: 0.45 ΔCost: -$54,100 **Late Irbesartan vs. Conventional antihypertensive** ΔLYG: 0.16 ΔCost: -$14,300 (CDN 2006)	**Early Irbesartan vs. conventional antihypertensive** ΔCost: -$80,198 **Early Irbesartan vs. late Irbesartan** ΔCost: -$63,431 **Late Irbesartan vs. Conventional antihypertensive** ΔCost: -$16,766

First Author (year)	Country	Study population	Type(s) of EE	Model of analysis	Time horizon	Intervention	Comparator	Costs included	Data source	Results (currency year)	2019$C Adjusted Results
de Portu, S., et al. (2011). [108]	Europe and US	T2D and nephropathy Mean age: 60y	Cost-effectiveness	N/A	3.4-y	Losartan + standard care (n = 751)	Standard care alone (n = 762)	Third party payer perspective Direct medical costs (Cost of losartan and ESRD-related hospitalization)	-Costs inputs: Literature (Herman WH, 2003) and Diagnosis related group (DRG) tariffs -Clinical inputs: RENAAL trial	**Mean number of ESRD days** Losartan: 76.1 days Placebo: 109.7 days **Incremental cost per patient (Discounted 3%)** Italy: €3,603 France: €4,531 Germania: €3,020 Switzerland: €3,949 USA: €3,856 (Euro 2009)	**Incremental cost per patient (Discounted 3%)** Italy: $6,126 France: $7,704 Germania: $5,135 Switzerland: $6,714 USA: $6,556

First Author (year)	Country	Study population	Type (s) of EE	Model of analysis	Time horizon	Intervention	Comparator	Costs included	Data source	Results (currency year)	2019$C Adjusted Results
Delea, T. E., et al. (2009). [109]	US	T2D with hypertension and albuminuria Mean age: 61y Male: 71% Micro: 27.8% Early overt nephropathy 62.7% Advanced overt nephropathy: 9.5%	Cost-utility	Markov Model	20-y (Lifetime)	Aliskiren (300 mg) + Losartan (100 mg)	Losartan	Healthcare system perspective Direct health care costs only (Cost of medication, routine care and office visits for patients with T2D and ESRD)	-Costs inputs: USRDS, CDC, wholesale acquisition costs and IMS National Health prescribing therapy -Clinical inputs: Literature (Palmer, 2004), AVOID study, IDNT, USRDS, US vital statistics and published studies -Utility inputs: Literature (Fryback, DG, 1993; Coffey JT, 2002; Kiberd, 1995)	**ICER** $30,500/QALY *Cost-effective in 60% of iterations when willingness to pay is set at $50,000/QALY. ICERs are also available for 5, 10 and 20 years' time horizons (USD 2008)	**ICER** $34,685/QALY

First Author (year)	Country	Study population	Type (s) of EE	Model of analysis	Time horizon	Intervention	Comparator	Costs included	Data source	Results (currency year)	2019$C Adjusted Results
Eastman, R. C., et al. (1997). [110]	US	T2D with diabetes related complications Mean age: 51y Males: 50%	Cost-utility	Incidence based simulation model	Lifetime	Standard care (maintain HbA1C at 10%)	Comprehensive care (maintain HbA1C at 7.2%)	Healthcare system perspective Cost of treatment and all other direct medical costs	-Costs inputs: Literature (Chiang,1992; Eckman, 1995; Fetig 1995; Harris, 1994; Javitt,1995), National survey data and DCCT study group -Clinical inputs: DCCT trial -Utility inputs: DCCT study group	**Cost of renal disease** Standard care: $9,437 Comprehensive care: $960 Incremental: $8,477 **QALY** Standard care: 11.43 Comprehensive care: 12.30 Incremental: 0.87 (USD 1994)	**Cost of renal disease** Standard care: $17,844 Comprehensive care: $1,815 Incremental: $16,028

First Author (year)	Country	Study population	Type (s) of EE	Model of analysis	Time horizon	Intervention	Comparator	Costs included	Data source	Results (currency year)	2019$C Adjusted Results
Farmer, A. J., et al. (2014). [111]	UK	T2D Mean age: 62y Male: 58.5%	Cost-utility	Simulation outcome model	30-y	1 yearly screening	2 yearly screening	Healthcare system perspective Direct costs only (cost monitoring, further investigations, treating diagnosed kidney disease in T2D patients, and cost of subsequent complications)	-Costs inputs: Literature (Clarke, 2002; Klebe, 2007) and Prescription cost analysis England, Unit cost of Health and social care (2010), Chronic kidney disease costing report (2008) -Clinical inputs: UKPDS outcomes model -Utility inputs: Literature (Lung TW, 2011) and UKPDS 68	**ICER (SD)** £606/QALY (SD £1,782) (GBP 2011)	**ICER (SD)** $1,152/QALY (SD £1,782)

First Author (year)	Country	Study population	Type(s) of EE	Model of analysis	Time horizon	Intervention	Comparator	Costs included	Data source	Results (currency year)	2019$C Adjusted Results
Gerth et al,; (2002) [112]	Europe	T2D and nephropathy	Cost-effectiveness	Transposing the RENAAL study results to the general European population to estimate cost-savings from Losartan	3.5-y	Losartan	Placebo	Perspective: NA Specialist dialysis services, medical services, inpatient or outpatient treatment of dialysis complications, transport and erythropoietin medication	-Costs inputs: N/A -Clinical inputs: RENAAL Study -Utility inputs: N/A	64,400 fewer person-years with ESRD and reduced ESRD-related costs by €2.6 billion over 3.5 years €3.6 billion reduction in cost over 4 years (Euro 1999)	64,400 fewer person-years with ESRD and reduced ESRD-related costs by $5.4 billion over 3.5 years $7.4billion reduction in cost over 4 years

First Author (year)	Country	Study population	Type (s) of EE	Model of analysis	Time horizon	Intervention	Comparator	Costs included	Data source	Results (currency year)	2019$C Adjusted Results
Golan et al.; (1999) [113]	US	Newly diagnosed T2D Mean age: 50y Normo: 79% Micro: 18% Proteinuria: 3%	Cost-utility	Markov Model	Lifetime	Treating all patients with ACEI	Screening for micro OR Screening for gross proteinuria	Societal perspective Healthcare costs associated with ACEI, screening or treatment of ESRD	-Costs inputs: Drug Topics Red Book, Medicare clinical diagnostic fee schedule, USRDS -Clinical inputs: Literature (Ravid M, 1993; Ravid M, 1998; Lewis EJ, 1993; Walters DP, 1994) -Utility inputs: Literature (Fryback DG, 1993; Lovell HG, 1998)	**Treating all patients with ACEI** QALY: 11.82 Cost: $15,240 **Screening all patients for microalbuminuria** QALY: 11.78 Cost: $14,940 *Screening for gross proteinuria is dominated **ICER (ACEI vs. microalbuminuria screening)** $7,500/QALY *(USD 1999)	**Treating all patients with ACEI** Cost: $29,434 **Screening all patients for microalbuminuria** Cost: $28,855 *Screening for gross proteinuria is dominated **ICER (ACEI vs. microalbuminuria screening)** $14,485/QALY

First Author (year)	Country	Study population	Type (s) of EE	Model of analysis	Time horizon	Intervention	Comparator	Costs included	Data source	Results (currency year)	2019$C Adjusted Results
Habib, S. H., et al. (2010). [114]	Bangladesh	T2D with DN and at least 1-y of follow-up Age distribution: 40-50y: 57.2% 51-60y: 40.1% >61y: 2.7%	Cost-study	Cross-sectional retrospective study	1-y	Early detection and management of DN (n = 100)	Late detection and management of DN (n = 100)	Perspective: N/A Drugs, hospitalizations, diagnostics and visits	-Costs inputs: NA -Clinical inputs: NA -Utility inputs: NA	**Average annual cost per patient** Late: $198 Early: $81 *Cost distribution also presented *(USD 2010)	**Average annual cost per patient** Late: $225 Early: $92
Hayashino et al.; (2010) [115]	Japan	T2D and advanced-stage CKD (stage 3 or 4) Mean age: 60y	Cost-utility	Markov Model	1-y	AST-120 with Low protein diet and CT	Control (Low protein diet and CT)	Societal perspective Healthcare costs (AST-120 therapy or treatment of ESRD)	-Costs inputs: Literature (Takahashi, 2008) -Clinical inputs: Literature (Akizawa, 2009; Arias E., 2007) and the Japanese Society for Dialysis Therapy -Utility inputs: Literature (Lawrence, 1995; Brown GC, 2000) and CDC 1996	**ICER** Δ QALY: 0.22 Δ Cost: $15,019 *AST-120 is a dominant strategy (USD 2008)	**ICER** Δ Cost: $17,080

First Author (year)	Country	Study population	Type(s) of EE	Model of analysis	Time horizon	Intervention	Comparator	Costs included	Data source	Results (currency year)	2019$C Adjusted Results
Herman, W. H., et al. (2003). [116]	US	T2D and DN Mean age: 60y Male: Losartan 61.5% Placebo 64.8%	Cost-effectiveness	N/A	3.5-y	Losartan and CT (n = 751)	Placebo and CT (n = 762)	Health care system perspective Cost associated with ESRD and cost of losartan therapy	-Costs inputs: USRDS 1997 and 1998 -Clinical inputs: RENAAL Study	**Reduced Number of days with ESRD over 3.5-y per patient** 33.6 days (p = 0.004) **Net savings per patient over 3.5-y** $3,522 (p = 0.041) **Net savings per patient over 4-y** $5,298 (p = 0.017) (USD 2001)	**Net savings per patient over 3.5-y** $6,743 **Net savings per patient over 4-y** $10,144

First Author (year)	Country	Study population	Type (s) of EE	Model of analysis	Time horizon	Intervention	Comparator	Costs included	Data source	Results (currency year)	2019$C Adjusted Results
Linus Jönsson,G.W. C, et al. (2005) [117]	Denmark, Finland, Norway and Sweden	T2D patients with incipient DN	Cost-Study	N/A	3.5 years	Losartan + CT (n = 751)	Placebo + CT (n = 762)	Healthcare system perspective Direct medical costs (renal placement therapy and losartan therapy)	-Costs inputs: Literature (Sennfalt, 2002; Jakobsen, 1990; Salonen, 2003) and the RENAAL study -Clinical inputs: RENAAL study	**Average number of days with ESRD** Losartan: 76.1 days Placebo: 109.7 days (p = 0.004) **Discounted net cost-savings after 3.5y** Sweden: €3,761 Norway: €3,778 Denmark: €2,607 Finland: €3,518 (Euro 2003)	**Discounted net cost-savings after 3.5y** Sweden: $7,500 Norway: $7,533 Denmark: $5,198 Finland: $7,015
Palmer et al.; (2004) [118]	US	T2D, Hypertension and renal disease	Cost-effectiveness	Markov model	25-y	Early IR (initiated at Micro) OR Late IR (initiated at overt nephropathy)	Antihypertensive therapy with standard medications	Third party payer perspective Cost of IR and ESRD treatment (dialysis and transplantation)	-Costs inputs: USRDS, Drugs Topics Red Book -Clinical inputs: Literature (Stehouwer CD, 2002; Rodby RA, 2003, Lewis EJ,2001), IRMA-2, IDNT and Steno-2 study, US Renal Data System, WHO	**Cost saving per patient vs. control** Early IR: $11,922 Late IR: $3,252 **LYG vs control** Early IR: 1.55 Late IR: 0.07 (USD 2000)	**Cost saving per patient vs. control** Early IR: $22,817 Late IR: $6,224

First Author (year)	Country	Study population	Type(s) of EE	Model of analysis	Time horizon	Intervention	Comparator	Costs included	Data source	Results (currency year)	2019$C Adjusted Results
Palmer et al.; (2004) [119]	UK	T2D, hypertension and overt nephropathy	Cost-Effectiveness	Markov model	10-y	IR Or Amlodipine	CT	Healthcare system perspective Direct medical costs (Cost of drugs, dialysis and transplantation)	-Costs inputs: Literature (Clarke, 2003; Lamping DL, 2000), British National Formulary, NHS UK transplant, NHS R&D Health Technology Assessment -Clinical inputs: Literature (Adler, 2003), IDNT trial, UK Renal Registry Report,	**Cost savings after 10-y** IR vs. amlodipine £5,125 IR vs. CT £2,919 **LYG** IR vs. amlodipine 0.08 (0.07) IR vs. CT 0.23 (0.21) (GBP 2003)	**Cost savings after 10-y** IR vs. amlodipine $14,376 IR vs. CT $8,188

First Author (year)	Country	Study population	Type (s) of EE	Model of analysis	Time horizon	Intervention	Comparator	Costs included	Data source	Results (currency year)	2019$C Adjusted Results
Palmer et al.; (2003) [120]	Belgium and France	Patients with T2D, hypertension and DN	Cost-effectiveness	Markov model	10-y and 25-y (Lifetime)	IR	Amlodipine OR Control (CT)	Third party payer perspective Cost of medications and ESRD	-Costs inputs: Literature (Lins R, 2000; Jungers P, 2000; Lins R, 2001, Cogny F, 1995; Engel, 2000; Maynard C, 2001), INAMI tarrifs (Blegium), VIDAL database and Comptabilité analytique hospitaire des Hôpitaux AP-HP (France) -Clinical inputs: Literature (Rodby RA, 2000; Lewis EJ,2001; Leibson CL, 1997; Lins R, 2000; Combe C, 2001), IDNT trial and USRDS	**LYG per patient** IR vs Amlodipine Belgium: 0.71 France: 0.69 IR vs Control Belgium: 0.91 France: 0.90 **Total lifetime cost saving per patient** IR vs Amlodipine Belgium: €21,163 France: €27,044 IR vs control Belgium: €11,885 France: €16,345 (Euro 2002)	**Total lifetime cost saving per patient** IR vs Amlodipine Belgium: $37,380 France: $47,767 IR vs control Belgium: $20,992 France: $28,870

First Author (year)	Country	Study population	Type (s) of EE	Model of analysis	Time horizon	Intervention	Comparator	Costs included	Data source	Results (currency year)	2019$C Adjusted Results
Palmer et al.; (2006) [121]	France	T2D and hypertension Age distribution: <35y: 3 35-44y: 1 45-54y: 11 55-64y: 21 65-74y: 38 75-84y: 17 85y+: 9 Micro: 20-49y : 35.5% ≥50y : 29.9% Overt nephropathy : 20-49y : 6.5% ≥50y : 12.2%	Cost-utility	Markov / Monte Carlo model simulation	25-y (Lifetime)	Screening for albuminuria and adding IR for patients identified with DN	No screening (CT)	Third party payer perspective Cost for screening, medication, treatment of ESRD and transplantation	<u>-Costs inputs:</u> Literature (Cogny F, 1995) and AFS-SAPS <u>-Clinical inputs:</u> Literature (Palmer AJ, 2004; Ruggenenti P, 2004; Palmer AJ, 2003; Stehouwer CD, 2002; Combe C, 2001; Gaede P, 2003), BENEDICT, IRMA-2, Steno-2 and IDNT studies, WHO and NIH <u>-Utility inputs:</u> Literature (Brown GC, 2000; Tengs TO, 2000)	**Over 25 years** <u>ΔLYG</u> 0.38 <u>ΔQALY</u> 0.29 <u>Decrease in cost per patient</u> €4,812 *Cost saving first occurred at 8 years and increased from 8 to 25 years (Euro 2002)	<u>Decrease in cost per patient</u> $8,499

First Author (year)	Country	Study population	Type(s) of EE	Model of analysis	Time horizon	Intervention	Comparator	Costs included	Data source	Results (currency year)	2019$C Adjusted Results
Palmer, A. J., et al. (2006). [122]	Switzerland	T2D, hypertension and micro Age at baseline: 58y	Cost-effectiveness	Markov model	25-y (Lifetime)	IR + CT	CT alone	Third party payer perspective Cost of medication, cost of ESRD, dialysis and transplant	-Costs inputs: SUVA 2002, SVK 1998 and VPN 2004 -Clinical inputs: Literature (Palmer AJ, 2004, Qua-S-Niere GmbH,2000; Gaede P, 2003; Stehouwer CD, 2002; Arzneimittelkompendium DS, 2003), IRMA-2 and IDNT studies and WHO	**Over 25 years** ΔLYG 0.57 Lifetime cost saving per patient $21,487 (CHF 2003)	Lifetime cost saving per patient $27,447

First Author (year)	Country	Study population	Type(s) of EE	Model of analysis	Time horizon	Intervention	Comparator	Costs included	Data source	Results (currency year)	2019$C Adjusted Results
Palmer et al.; (2007) [123]	UK	T2D, hypertension and renal disease	Cost-effectiveness	Markov Model	25-y (Lifetime)	Early IR (Micro) Or Late IR (Overt Nephro)	CT alone	Healthcare system perspective (UK NHS) Cost of medication and ESRD therapy (dialysis and transplantation)	-Costs inputs: Literature (Lamping, 2000; Clarke P, 2003; MacLeod A, 1998; Mowatt G, 2003) and NHS UK Transplant statistics 2002 -Clinical inputs: Literature (Palmer AJ, 2004; Adler AI, 2003), UK Renal Registry Report 2002, IRMA-2 and IDNT study	**Improvement in life expectancy of Early IR vs** Late IR: 1.38 Control: 1.41 **Projected lifetime savings of Early IR vs** Late IR: £2,310 Control: £3,801 (GBP 2002)	**Projected lifetime savings of Early IR vs** Late IR: $6,741 Control: $11,092

First Author (year)	Country	Study population	Type (s) of EE	Model of analysis	Time horizon	Intervention	Comparator	Costs included	Data source	Results (currency year)	2019$C Adjusted Results
Palmer et al.; (2006) [124]	France	T2D and hypertension	Cost-utility	Markov Model	25-y	Early IR (Micro) Or Late IR (Overt Nephro)	CT alone	Third party payer perspective Cost of medication and ESRD treatment	-Costs inputs: Literature (Engel, 2000; Maynard C, 2001; Cogny F, 1995) and Comptabilité analytique hospitalière -Clinical inputs: IRMA-2 and IDNT studies	**Undiscounted LYG per patient compared to control** Early IR: 1.51 Late IR: 0.07 **Discounted QALY per patient compared to control** Early IR: 1.03 Late IR: 0.06 **Cost saving per patient** Early IR vs. CT: €22,314 Late IR vs. CT: €6,619 Early IR vs. Late IR: €15,694 (Euro 2002)	**Cost saving per patient** Early IR vs. CT: $39,413 Late IR vs. CT: $11,691 Early IR vs. Late IR: $27,720

First Author (year)	Country	Study population	Type (s) of EE	Model of analysis	Time horizon	Intervention	Comparator	Costs included	Data source	Results (currency year)	2019$C Adjusted Results
Rodby et al.; (2003) [125]	US	T2D, hypertension and DN Mean age: 59y	Cost-effectiveness	Markov Model	3, 10 and 25-y	IR	Placebo OR Amlodipine	Healthcare System Perspective Direct medical costs (Cost of medication, hospitalization, ESRD, dialysis and transplantation)	-Costs inputs: Average whole sale price, DRG guide 2001 and USRDS -Clinical inputs: Literature (Rodby RA, 1996), IDNT study and USRDS	**At 25 years** ΔLYG with IR vs Placebo: 0.740 Amlodipine: 0.624 Mean cost saving per patient with IR vs: Placebo: $15,607 Amlodipine: $26,290 *IR is a dominant option **At 3 years** ΔLYG with IR vs Placebo: 0.017 Amlodipine: -0.004 Mean cost saving per patient with IR vs: Placebo: $22,312 Amlodipine: $23,751 *IR is dominant vs placebo but not amlodipine (USD 2000)	**At 25 years** Mean cost saving per patient with IR vs: Placebo: $29,869 Amlodipine: $50,315 **At 3 years** Mean cost saving per patient with IR vs: Placebo: $42,702 Amlodipine: $45,456

First Author (year)	Country	Study population	Type (s) of EE	Model of analysis	Time horizon	Intervention	Comparator	Costs included	Data source	Results (currency year)	2019$C Adjusted Results
Rodby, R. A., et al. (1996). [126]	US	T2D and DN *T1D and DN also presented Mean age: 55-74y	Cost-effectiveness	Markov model	4-y, 12-y and 31-y	Captopril (n=207)	Placebo (n=202)	Societal perspective Direct costs (physician fees, medication, diagnostic procedures, dialysis and transplant treatment) and indirect costs (lost patient productivity due to ESRD)	-Costs inputs: Literature (Douglas JB, 1990; Rice DP, 1985) Medicare reimbursement, whole sale drug prices, Drug Topic Red Book, (1993) -Clinical inputs: Literature (Tuttle KR, 1990; Mahnensmith RL, 1993; Bailie GR, 1992; Markell MS, 1992; Mayers JD 1992; Powe NR, 1992; Selby JV,1990) and USRDS	**Cost savings per patient over 12-y** Direct costs: $9,900 Indirect costs: $45,730 **Annual aggregate health care cost savings (direct cost only)** 1999: $189 million 2004: $475 million **LYG** 1.04 years **Dialysis years saved** 0.29 (USD 1994)	**Cost savings per patient over 12-y** Direct costs: $18,719 Indirect costs: $86,467 **Annual aggregate health care cost savings (direct cost only)** 1999: $357 million 2004: $898 million

First Author (year)	Country	Study population	Type(s) of EE	Model of analysis	Time horizon	Intervention	Comparator	Costs included	Data source	Results (currency year)	2019$C Adjusted Results
Saksthong, P., et al. (2001). [127]	Thailand	T2D with micro Mean age: 44y Micro: 100%	Cost-effectiveness	Markov model	25-y (Lifetime)	Enalapril (ACE inhibitor) (n=100)	Placebo	Third party payer perspective Direct costs associated to renal complications (Medication and ESRD treatment)	-Costs inputs: Literature (Homwijitkul, 1998) -Clinical inputs: Literature (Ravid M, 1996; Briggs A, 1998; Nelson RG, 1993, Wuttihichumnog T, 1998) and Public Health Statistics book 1996	**ICER** $788.37 per life-year saved (USD 1999)	**ICER** $1,523 per life-year saved
Seng, W. K., et al. (2005). [128]	Asia (Hong Kong, Japan, Korea, Malaysia, Singapore, taiwan)	T2D and DN Age: 31-70y	Cost-effectiveness	N/A	3.5-y	Losartan + CT (n = 117)	CT alone (n = 135)	Third party payer perspective Direct medical costs only (medication, dialysis and ESRD treatment)	-Costs inputs: Literature (Lim TO, 2004; Hwang SJ, 2003; Lim TO, 2004; Lee G, 2003; Kim SY, 2003; Hwang SJ, 2004; Lui SF, 1999; Li KT, 2001), Society for Dialysis Therapy 2002 and Hong Kong Health Authority -Clinical inputs: RENAAL study	**ΔNumber days with ESRD over 3.5-y** 37.9 days per patient **Net savings over 3.5-y per patient** Hong Kong: $515 Japan: $505 Korea: $55 Malaysia: $255 Singapore: $202 Taiwan: $56 (USD 2004)	**Net savings over 3.5-y per patient** Hong Kong: $850 Japan: $834 Korea: $91 Malaysia: $421 Singapore: $334 Taiwan: $92

First Author (year)	Country	Study population	Type (s) of EE	Model of analysis	Time horizon	Intervention	Comparator	Costs included	Data source	Results (currency year)	2019$C Adjusted Results
Souchet et al.; (2003) [129]	France	T2D with DN Mean age: 60y Male: Losartan 61.5% Placebo 64.8%	Cost-effectiveness	N/A	4-y	Losartan + CT (n = 751)	Placebo + CT (n = 762)	Healthcare system perspective Cost of ESRD, losartan therapy and hospitalization	-Costs inputs: Government agency, VAT included retail price and NHS -Clinical inputs: RENAAL Study	**Mean cumulative total cost per patient after 4 years** Losartan: €17,780 Placebo: €23,615 **Reduced number of ESRD days compared to placebo over 4-y** 46.9 days per patient **Net saving per patient after 4 years** €5,835 (Euro 2002)	**Mean cumulative total cost per patient after 4 years** Losartan: $31,405 Placebo: $41,711 **Net saving per patient after 4 years** $10,306

First Author (year)	Country	Study population	Type(s) of EE	Model of analysis	Time horizon	Intervention	Comparator	Costs included	Data source	Results (currency year)	2019$C Adjusted Results
Szucs et al.; (2004) [130]	Switzerland	T2D with DN Mean age: 60y	Cost-effectiveness	Decision analytical model	3.5-y	Losartan + CT (n = 751)	Placebo + CT (n = 762)	Third party payer perspective Direct costs (Cost of ESRD and medication)	-Costs inputs: Literature (Schweizerischer Dialysevertrag (Position 11,22 and Abschnitt 1), 1998; Schweizerischer Verband Für(Nieren-Pankreastransplantationen), 1999) and SVK -Clinical inputs: Literature (Sandoz MS, 2004) and RENAAL Study	**ESRD-associated net cost savings per patient over a period of 3.5-y** CHF 4,084 **Reduced number of ESRD days compared to placebo** 33.6 days per patient *(CHF 2004)	**ESRD-associated net cost savings per patient over a period of 3.5-y** $5,160

First Author (year)	Country	Study population	Type(s) of EE	Model of analysis	Time horizon	Intervention	Comparator	Costs included	Data source	Results (currency year)	2019$C Adjusted Results
Van Os et al.; (2000) [131]	Netherlands	T1 and T2D without renal disease	Cost-utility	Semi-Markov compartment Model	Lifetime (30-y)	Intensive Blood Glucose Control (IBCG) Or ACEI	Both IBCG and ACEI	Healthcare system perspective Direct medical costs (medication and treatment of ESRD)	-Costs inputs: Literature (Sonnaville JJJd, 1997; Bilo HJG, 1996, Renin E, 1998; Lewis EJ, 1993; Wit AGd, 1997) -Clinical inputs: Literature (Lewis EJ, 1993; Renin E, 1998; DCCT, 1996; Bilo HJG, 1996; Eastman RC, 1997; Rossing P, 1996; Schmitz A, 1988) -Utility inputs: Literature (DCCT, 1996)	**Gain in complication free life years** Total: 0.2 IBGC: 0.2 ACEI: 0.0 **QALY** Total: 0.08 IBGC: 0.08 ACEI: 0.0 **Cost per complication free LY** Total: NLG 11,500 IBGC: NLG 12,500 ACEI: Cost saving **ICER ($/QALY)** Total: NLG 31,000/QALY IBGC: NLG 33,000/QALY *T1D results also presented in the article *(NLG 2000)	**Cost per complication free LY** Total: $9,356 IBCG: $10,169 **ICER ($/QALY)** Total: $25,220/QALY IBGC: $26,847/QALY

First Author (year)	Country	Study population	Type(s) of EE	Model of analysis	Time horizon	Intervention	Comparator	Costs included	Data source	Results (currency year)	2019$C Adjusted Results
Vora, J., et al. (2005) [132]	UK	T2D and DN (N=1,513)	Cost-effectiveness	N/A	3.5-y Lifetime	Losartan + CT	CT (not ACEI)	Healthcare system perspective (UK NHS) Direct medical costs (Costs of losartan and ESRD)	-Costs inputs: Literature (UK NHS, UK transplant 2003), EURODICE study -Clinical inputs: Literature (Brenner, 2001), RENAAL study	**Net cost saving** £6,622 (£2,653 to £10,591) **LYS by delaying ESRD** 0.44 (0.16 to 0.71) **(GBP 2004)**	**Net cost saving** £19,039 (£7,628 to £30,451)

First Author (year)	Country	Study population	Type(s) of EE	Model of analysis	Time horizon	Intervention	Comparator	Costs included	Data source	Results (currency year)	2019$C Adjusted Results
Wu, B., et al. (2018). [133]	China	Newly diagnosed T2D	Cost-utility	Decision tree and Markov model	Lifetime	Universal strategy (ACEI or ARB) OR Screening for micro followed by ACEI or ARB	Control (no treatment)	Healthcare system perspective Direct medical costs only (cost of ACEI, ARB, annual screening procedures, treatment of ESRD as well as health care expenditures related and unrelated to diabetes)	-Costs inputs: Literature (Wang HP, 2013; Kun ZHAO, 2015) -Clinical inputs: Literature (Loh PT, 2015; Haller H, 2011; Chiang SC, 2011; Adarkwah CC, 2011; Imai E, 2011; Chan JC, 2004; Vejakama, 2012; Sai XY, 2007; Tong PC, 2007; Lin CC, 2012; Fox CS, 2012; Jia W, 2009), ROADMAP, ORIENT and RENAAL study -Utility inputs: Literature (Pan CW, 2015; Yang F, 2015)	**ICER (vs control)** Universal strategy: -$7,697/QALY Screening strategy: -$14,380/QALY **ICER (Universal vs. screening strategy)** $30,087/QALY (USD 2014)	**ICER (vs control)** Universal strategy: -$8,726/QALY Screening strategy: -$16,302/QALY **ICER (Universal vs. screening strategy)** $34,108/QALY

Abbreviations: **ACEI:** Angiotensin-converting enzyme inhibitor**, AFS-SAPS:** Agence Francaise de Sécuirité Saniatire des Produits de Santé, **ARB:** Angiotensin II Receptor Blocker, **AVOID:** Aliskiren in the Evaluation of Proteinuria in Diabetes trial, **BENEDICT:** Bergamo Nephrologic Diabetes Complications Trial, **CDC:** Center for Disease Control and Prevention, **CHF:** Swiss Francs, **CICR:** Cumulative incidence competing risk, **CKD:**

Chronic Kidney Disease, **CND:** Canadian Dollar, **COI:** Cost-of-illness, **CT:** Conventional Antihypertensive therapy, **DIMICO:** Diabetic Microvascular Complications, **DN:** Diabetic Nephropathy, **DRG:** Diagnosis related group, **EE:** Economic Evaluation, **ESRD:** End-Stage-Renal-Disease, **Euro:** European Monetary Unit, **HbA1c:** Hemoglobin A1c, **HMO:** Health Maintenance Organization, **GBP:** Great Britain Pound, **IBGC:** Intensive Blood Glucose Control, **ICER:** Incremental Cost Effectiveness Ratio, **IDNT:** Irbesartan Diabetic Nephropathy trial, **INR:** Indian Rupee, **IR:** Irbesartan, **IRMA-2:** Irbesartan in Microalbuminuria, Type 2 Diabetic Nephropathy Trial, **KPNW:** Kaiser Permanente North-west Division, **LYG:** Life years gained, **Macro:** Macroalbuminuria, **Micro:** Microalbuminuria, **N/A:** Not Available, **NIH:** National Institute of Health, **NLG:** Dutch Guilder, **Normo:** Normoalbuminuria, **ODBF**: Ontario Drug Benefit Formulary, **ORIENT:** Olmesartan Reducing Incidence of End-Stage Renal Disease in Diabetic Nephropathy Trial, **QALY:** Quality Adjusted Life Year, **RENAAL:** Reduction of Endpoints in Non-insulin dependent diabetes with the Angiotensin II Antagonist Losartan), **ROADMAP:** Randomized Olmesartan and Diabetes Microalbuminuria Prevention, **SD:** Standard Deviation, **Steno-2:** Intensified Multifactorial Intervention in Patients with Type 2 Diabetes and Microalbuminuria, **SVK:** Swiss Association for Shared Responsibilities of Health Insurance Providers, **T1D:** Type-1 diabetes mellitus, **T2D:** Type-2 diabetes mellitus, **TL:** Turkish Lira, **TURDEP-1:** Turkish Diabetes Epidemiology Study-1, **TURDEP-2:** Turkish Diabetes Epidemiology Study-2,**Tx:** Treatment, **UK:** Unites Kingdom, **UKPDS:** United Kingdom Prospective Diabetes Study, **US:** United-States, **USD:** Unites States Dollar, **USRDS:** US Renal Data System, **WHO:** World Health Organization, **y:** years

Table B.2 Extraction Data for COIs

First Author (year)	Country	Study population	Model of analysis	Time horizon	Costs included	Data source	Results (currency year)	2019$C Adjusted Results
Brandle, M., et al. (2003). [134]	US	>18-y with T2D (n = 1,364) Mean age: 66y Micro: 2% Proteinuria: 15% ESRD: 0.4% Missing: 18% Male: 49.9%	N/A	1-y	Healthcare System perspective Direct medical costs	-Costs inputs: Michigan HMO -Clinical inputs: Patient survey (Telephone or written) and medical records	**Median annual direct medical costs associated with nephropathy** Micro: $1,970 Macro: $2,189 ESRD with dialysis: $17,733 Cost were calculated by multiplying the annual direct cost for a diet-controlled white male without microvascular complications by a multiplicative factor (USD 2000)	**Median annual direct medical costs associated with nephropathy** Micro: $3,770 Macro: $4,189 ESRD with dialysis: $33,938

First Author (year)	Country	Study population	Model of analysis	Time horizon	Costs included	Data source	Results (currency year)	2019$C Adjusted Results
Brown et al.; (1999) [135]	US	T2D and at least 12 months of health plan eligibility (n = 11,768) **Age** 30-49y: 17% 50-69y: 52% ≥70y: 32% **Renal complication by sex** <u>Male (51%)</u> None: 75% Abnormal: 13% Advanced: 11% ESRD: 1% <u>Female (49%)</u> None: 80% Abnormal: 11% Advanced: 8% ESRD: 1%	N/A	9y	Healthcare system perspective Outpatient costs (office visits, imaging, testing) and inpatient costs (direct hospital services)	<u>-Costs inputs:</u> KPNW	**Average total medical cost by renal complication stage** <u>Female</u> None: $4,663 Abnormal: $7,535 Advanced: $12,551 ESRD: $27,991 <u>Male</u> None: $4,226 Abnormal: $5,691 Advanced: $9,597 ESRD: $17,762 (USD 1993)	**Average total medical cost by renal complication stage** <u>Female</u> None: $8,419 Abnormal: $13,604 Advanced: $22,660 ESRD: $50,536 <u>Male</u> None: $7,630 Abnormal: $10,275 Advanced: $17,327 ESRD: $32,068

First Author (year)	Country	Study population	Model of analysis	Time horizon	Costs included	Data source	Results (currency year)	2019$C Adjusted Results
Caro JJ et al.; (2002) [136]	US	T2D Age range: 25 to 74-y Male: 45%	N/A	Lifetime (30-y)	Healthcare system perspective Direct medical costs (acute and sub-acute inpatient care, home health care, outpatient therapy, physician visits, diagnostic and therapeutic procedures)	-Costs inputs: Literature (O'Brien, 1998), 2000 Medicare Fee Schedules -Clinical inputs: UKPDS	The cost for managing complications over 30 years is approximately $47,240 per patient. Nephropathy accounts for 21% of these managing complications cost. ($9,826) (US 2000)	The cost for managing complications over 30 years is approximately $90,410 per patient. Nephropathy accounts for 21% of these managing complications cost. ($18,805)

Gordois, A., et al. (2004). [137]	US and UK	T1D or T2D with DN	Prevalence based model	1-y	US- Health Care Payer perspective UK- National Health Services perspective Includes only direct costs of treatment	-Costs inputs: US- Literature (Rodby, 1996), Drug topics 2002, National Kidney foundation 2002, British medical association RPSoGB 2002 and Agency for Health Research and Quality 2002 UK- British medical association RPSoGB 2002 and Department of Health 2002a -Clinical inputs: US- Literature (Rodby, 1996), NIH 1995, CDC 1998, DARTS 2001 and USRSD 2001 UK- Literature (Harvey, 2001; McIntosh, 2002), DARTS 2001 and UK transplant 2002	**Total annual cost for managing DN for T2D patients** US: $15 billion UK: $613,8 Million **Annual cost by health state severity** US Micro: $3,185 billion Overt nephropathy: $8,287 Billion ESRD: $3,006 Billion UK Micro: £25,7 million Overt nephropathy: £449,6 million ESRD: £137,8 million Total annual cost of DN is 13 times greater in the US than in the UK *Also presented cost for T1D (USD/GBP 2001)	**Total annual cost for managing DN for T2D patients** US: $29 Billion UK: $1,71 Billion **Annual cost by health state severity** US Micro: $6,098 Billion Overt nephropathy: $15,867 Billion ESRD: $5,755 Billion UK Micro: $71,6 million Overt nephropathy: $1,253 Billion ESRD: $384 million
Happich et al.;	Germany	T1D and T2D with DN	N/A	1-year	Societal perspective and health	-Costs inputs: N/A	**Average total estimated cost related to nephropathy (patient/year)**	**Average total estimated cost related to**

First Author (year)	Country	Study population	Model of analysis	Time horizon	Costs included	Data source	Results (currency year)	2019$C Adjusted Results
(2008) [138]		(n = 200) Micro: 33.9% Macro: 30.5% ESRD: 35.6% T1D: 27.6% T2D: 72.4% Mean age: 64.6y (range 31-93) Male: 63%			insurance perspective Direct costs Inpatient costs (hospitalization, rehabilitation) and outpatient costs (physician visit, diagnostic and laboratory costs), medication, home help services and transportation Indirect costs Cost of temporary disabilities and early retirement	-Clinical inputs: DIMICO Study -Utility inputs: N/A	Health insurance perspective: €1,332 Societal perspective: €2,019 **Average cost per patient/year by complication stage** Societal Perspective Micro: €684 Macro: €683 ESRD: €10,223 Health Insurance Perspective Micro: €221 Macro: €398 ESRD: €7,862 (Euro 2002)	**nephropathy (patient/year)** Health insurance perspective: €2,353 Societal perspective: €3,566 **Average cost per patient/year by complication stage** Societal Perspective Micro: €1,208 Macro: €1,206 ESRD: €18,057 Health Insurance Perspective Micro: €390 Macro: €703 ESRD: €13,887

First Author (year)	Country	Study population	Model of analysis	Time horizon	Costs included	Data source	Results (currency year)	2019$C Adjusted Results
Kumpatla, S., et al. (2013). [139]	India	T2D patients hospitalized with or without severe long-term diabetic complications <u>CKD (n = 67)</u> Stage I (n = 16) Stage II (n = 20) Stage 3 (n = 19) Stage IV (n = 12) Mean age: 59y Male: 75% <u>No complication</u> (n = 86) Mean age: 51y Male: 57%	Cross-sectional study	1-y	Societal perspective Direct medical costs (medical consultations, laboratory test, drugs, surgery, inpatient costs) and non-medical costs (accompanying attendant and transportation charges)	<u>-Costs inputs:</u> Questionnaire, hospital and patients' expenditures	**Total annual expenditure per patient** CKD: $12,690 No complication: $4,493 *(INR 2013)	**Total annual expenditure per patient** CKD: $229 No complication: $81

First Author (year)	Country	Study population	Model of analysis	Time horizon	Costs included	Data source	Results (currency year)	2019$C Adjusted Results
Malhan, S., et al. (2014). [140]	Turkey	T2D with history of diabetes related complications Micro: 23.4% Macro: 6.1%	N/A	1-y	Third-party payer perspective Direct medical costs (Hospital inpatient and outpatient costs, screening and laboratory test costs, prescription drugs and medical supplies expenses)	-Costs inputs: Baskent University Hospital patient records -Clinical inputs: TURDEP-1, TURDEP-2, Registry of Nephrology, Dialysis, and Transplantation in Turkey 2009	**Annual cost of renal complication** Micro: $383 Macro: $2,017 Hemodialysis: $21,936 Peritoneal dialysis: $1,939 **Cost of T2D renal complications in Turkey** $3,219 Million *25% to 28% of the total costs of T2D *Also presented, acute event costs (hospital admission to discharge) (TL 2010)	-

First Author (year)	Country	Study population	Model of analysis	Time horizon	Costs included	Data source	Results (currency year)	2019$C Adjusted Results
Nichols et al.; (2011) [141]	US	Hypertensive patients with T2D (n = 7,758) Mean age: 61y Normo: 67.3% Micro: 27.5% Macro: 5.2%	N/A	1-y	Healthcare system Perspective Direct medical care costs (inpatient, outpatient, pharmacy)	-Costs inputs: Literature (Hornbrook, 1998)	**Mean Adjusted Baseline Total Costs** **Normo at baseline** Progressed: $7,134 Not progressed: $6,346 **Micro at baseline** Progressed: $8,275 Not progressed: $7,539 **Macro at baseline** Progressed: $7,085 Not progressed: $8,575 (USD 2009)	**Mean Adjusted Baseline Total Costs** **Normo at baseline** Progressed: $8,548 Not progressed: $7,604 **Micro at baseline** Progressed: $9,915 Not progressed: $9,033 **Macro at baseline** Progressed: $8,489 Not progressed: $10,274
O'Brien, J. A., et al. (2003). [142]	Canada	T2D	N/A	1-y	Healthcare system perspective Direct medical costs (laboratory tests on urine and physician visits)	-Costs inputs: Literature (Health Resourcing Branch, 1999) Ontario Case Cost Project database, Physician and laboratory fee schedule, formularies, reports and literature, Ontario Drug Benefit Formulary and Statistics Canada	**Costs of a typical event (within the first year)** Micro: $62 Proteinuria: $54 ESRD: N/A **State costs (subsequent annual cost)** Micro: $10 Proteinuria: $18 ESRD: $63,045 (CND 2000)	**Costs of a typical event (within the first year)** Micro: $80 Proteinuria: $69 ESRD: N/A **State costs (subsequent annual cost)** Micro: $13 Proteinuria: $23 ESRD: $80,937

First Author (year)	Country	Study population	Model of analysis	Time horizon	Costs included	Data source	Results (currency year)	2019$C Adjusted Results
O'Brien, J. A., et al. (1998). [143]	US	T2D	N/A	1-y	Healthcare system perspective Direct medical costs (laboratory tests on urine and physician visits)	-Costs inputs: State discharge databases, Medicare fee schedule 1996, 1994 Medicare data	**Costs of a typical event (within the first year)** Micro: $62 Proteinuria: $69 ESRD: N/A **State costs (subsequent annual cost)** Micro: $14 Proteinuria: $23 ESRD: $53,659 (USD 1996)	**Costs of a typical event (within the first year)** Micro: $117 Proteinuria: $130 ESRD: N/A **State costs (subsequent annual cost)** Micro: $26 Proteinuria: $43 ESRD: $101,041
O'Brien, J. A., et al. (2003). [144]	US	T2D	N/A	1-y	Healthcare system perspective Direct medical cost (Physician visits, urine tests and ESRD related costs)	-Costs inputs: US Renal Data system, Medicare and Medicaid Statistics 1999 -Clinical inputs: Literature (Manton, 1995) and American Diabetes Association	**Event costs of a typical event (within the first year)** Gross proteinuria: $67 Microalbuminuria: $63 **State costs (subsequent annual cost)** Gross proteinuria: $22 Microalbuminuria: $15 ESRD: $37,022 *The cost of other diabetic complications are also provided **(US 2000)**	**Event costs of a typical event (within the first year)** Gross proteinuria: $191 Microalbuminuria: $180 **State costs (subsequent annual cost)** Gross proteinuria: $63 Microalbuminuria: $43 ESRD: $105,675

First Author (year)	Country	Study population	Model of analysis	Time horizon	Costs included	Data source	Results (currency year)	2019$C Adjusted Results
Zhou, Z., et al. (2017). [145]	US	>18-y with T2D and at least two urine albumin test Mean age: Normo: 54y Micro: 55y Macro: 56y Male: Normo: 53% Micro: 60% Macro: 63% Normo: 18,409 Micro: 3,863 Macro: 963	Retrospective health care claims database	2-y	Thirds party payer perspective All cause and nephropathy-related healthcare costs resulting from medical services (inpatient, ER, outpatient and other medical services) and pharmacy prescriptions	-Costs inputs: Truven Health Analytics MarketScan database -Clinical inputs: Truven Health Analytics MarketScan database	**All cause total health care costs** Normo: $12,353 Micro: $15,893 Macro: $25,424 **Nephropathy related total health care costs** Normo:$368 Micro: $780 Macro: $4,427 (USD 2016)	**All cause total health care costs** Normo: $23,693 Micro: $30,483 Macro: $48,763 **Nephropathy related total health care costs** Normo:$706 Micro: $1,496 Macro: $8,491

Abbreviations: **CDC:** Center for Disease Control and Prevention, **CKD:** Chronic Kidney Disease, **CND:** Canadian Dollar, **DIMICO:** Diabetic Microvascular Complications, **DN:** Diabetic Nephropathy, **ESRD:** End-Stage-Renal-Disease, **Euro:** European Monetary Unit, **HbA1c:** Hemoglobin A1c, **HMO:** Health Maintenance Organization, **GBP:** Great Britain Pound, **INR:** Indian Rupee, **IR:** Irbesartan, **KPNW:** Kaiser Permanente North-west Division, **Macro:** Macroalbuminuria, **Micro:** Microalbuminuria, **N/A:** Not Available, **NIH:** National Institute of Health, **Normo:** Normoalbuminuria, **ODBF**: Ontario Drug Benefit Formulary, **SD:** Standard Deviation, **T1D:** Type-1 diabetes mellitus, **T2D:** Type-2 diabetes mellitus, **TL:** Turkish Lira, **TURDEP-1:** Turkish Diabetes Epidemiology Study-1, **TURDEP-2:** Turkish Diabetes Epidemiology Study-2,**Tx:** Treatment, **UK:** Unites Kingdom, **UKPDS:** United Kingdom Prospective Diabetes Study, **US:** United-States, **USD:** Unites States Dollar, **y:** years

Appendix 2: Appendix of Article #2

Appendix A

Table A. Characteristics of the ADVANCE Genotyped Participants at baseline in Comparison with the Whole ADVANCE cohort

Characteristic	Genotyped ADVANCE (n=4098)	Whole ADVANCE (n=11,140)*
Age — yr; Mean (SD)	67 (7)	66 (6)
Female sex — no (%)	1524 (37.2)	4735 (43)
Diagnosis age — yr; Mean (SD)	60 (9)	58 (9)
Diabetes duration — yr; Median (SD)	5 (2–10)	7 (3–11)
BMI — kg/m^2; Mean (SD)	30 (5)	28 (5)
HbA_{1c}— %; Mean (SD)	7.31 (1.36)	7.50 (1.6)
SBP — mmHg; Mean (SD)	147 (21)	145 (21)
DBP — mmHg; Mean (SD)	82 (11)	81 (11)
History of currently treated hypertension — n (%)	2635 (64)	7655 (69)
eGFR — ml/min/1.73 m^2; Median (IQR)	72.9 (61.0–85.7)	75.9 (63.6–89.7)
eGFR ≥ 90; no (%)	653 (16)	2611 (25)
eGFR 60 to 89; no (%)	2465 (61)	5996 (56)
eGFR < 60; no (%)	956 (23)	2033 (19)
UACR — µg/mg; Median (IQR)	13.7 (6.2–39.7)	15.0 (7.1–39.8)
UACR < 30; no (%)	2702 (70)	7377 (69)
UACR 30 to 300; no (%)	996 (26)	2862 (27)
UACR > 300; no (%)	178 (4)	401 (4)

*The values of all characteristics for whole ADVANCE are reported and extracted from Patel et al.[71] except for eGFR & UACR, extracted from Ninomiya T. et al.[72]

Abbreviation: **n**: Number of patients, **Yr**: Years, **SD**: Standard deviation, **IQR**: Interquartile range. **BMI**: Body mass index, **HbA_{1c}**: Glycated hemoglobin, **SBP**: Systolic blood pressure, **DBP**: Diastolic blood pressure, **eGFR**: Estimated glomerular filtration rate based on CKD-EPI formula, **UACR**: Urinary albumin creatinine ratio.

Source: Tremblay J, H.M., Harvey F, Tahir R, Marois-Blanchet F-C, Long C, et al., *Polygenetic Risk Scores Predict Diabetic Complications and Their Response to Therapy.* MedRxiv - The Preprint Server for Health Sciences, 2019. Supplementary material.

Appendix B

Table B.1 Cost-effectiveness results – scenario analysis (10-year time horizon)

	Usual screening	PRS
Total QALYs	6.53	6.58
Incremental QALYs [a]		0.054
Total costs, $CA MoH perspective	12,453	9,741
Incremental total costs, $CA MoH perspective		2,711
Total costs, $CA Societal perspective	13,594	10,371
Incremental total costs, $CA Societal perspective		3,223
Incremental cost/QALY, $CA MoH perspective		Dominant
Incremental cost/QALY, $CA Societal perspective		Dominant

[a]May not sum to total because of rounding

CA: Canadian Dollars, *MoH:* Ministry of Health, *PRS*: Polygenic Risk Score, *QALY:* Quality-adjusted life years

Over a 10-year time horizon, the PRS was associated with an average of 6.58 QALYs, compared to an average of 6.53 QALYs with usual screening methods for DN, for a QALY gain of 0.054. From a MoH perspective, PRS and usual screening tests were associated with total costs of $CA9,741 and $CA12,453, respectively (difference of -$CA2,711), which resulted in a dominant ICER. From a societal perspective, PRS and usual screening tests were associated with total costs of $CA10,371 and $CA13,594, respectively (difference -$CA3,223), which once again resulted in a dominant ICER.

Table B.2 Cost-effectiveness results – scenario analysis (lifetime horizon)

	Usual screening	PRS
Total QALYs	8.75	8.88
Incremental QALYs [a]		0.126
Total costs, $CA MoH perspective	19,874	16,950
Incremental total costs, $CA MoH perspective		2,924
Total costs, $CA Societal perspective	21,482	17,984
Incremental total costs, $CA Societal perspective		3,498
Incremental cost/QALY, $CA MoH perspective		Dominant
Incremental cost/QALY, $CA Societal perspective		Dominant

[a]May not sum to total because of rounding

CA: Canadian Dollars, *MoH:* Ministry of Health, *PRS*: Polygenic Risk Score, *QALY:* Quality-adjusted life years

Over a lifetime horizon, the PRS was associated with an average of 8.88 QALYs, compared to an average of 8.75 QALYs with usual screening methods for DN, for a QALY gain of 0.126. From a MoH perspective, PRS and usual screening tests were associated with total costs of $CA16,950 and $CA19,874, respectively (difference of -$CA2,924), which resulted in a dominant ICER. From a societal perspective, PRS and usual screening tests were associated with total costs of $CA17,984 and $CA21,482, respectively (difference -$CA3,498), which once again resulted in a dominant ICER.