The Cost-Effectiveness of Primary Screening for Chronic Kidney Disease in Manitoba's Rural and Remote First Nations

by

Thomas W. Ferguson

A Thesis submitted to the Faculty of Graduate Studies of

The University of Manitoba

in partial fulfillment of the requirements of the degree of

MASTER OF SCIENCE

Department of Community Health Sciences

University of Manitoba

Winnipeg, Manitoba, Canada

Abstract

Chronic Kidney Disease (CKD) is a risk factor for cardiovascular disease, early mortality, and kidney failure. There is a substantial burden of CKD in Manitoba's rural and remote First Nations. Early detection and treatment of CKD in this population may be cost-effective. We constructed a Markov model comparing screening for CKD, by both estimated glomerular filtration rate and albuminuria, to usual care using the perspective of the health care payer. Patients were classified into initial risk groups based on results from the First Nations Community Based Screening to Improve Kidney Health and Prevent Dialysis initiative. Screening in Manitoba's rural and remote First Nations was associated with a $33,500/QALY incremental cost-effectiveness ratio in comparison to usual care. Restricting to communities accessible primarily by air travel, this ratio fell to $16,180/QALY. In conclusion, at a willingness-to-pay threshold of $50,000/QALY, screening for CKD in Manitoba's rural and remote First Nations is likely cost-effective.

Acknowledgements

I would like to extend gratitude to everyone that has helped assist me with my studies and who have contributed to completion of this thesis project: Dr. Navdeep Tangri, Dr. Evelyn Forget, Dr. Paul Komenda, Dr. Rashid Ahmed, Dr. Claudio Rigatto, Dr. Barry Lavallee, Caroline Chartrand and the Diabetes Integration Project (DIP) Team, Dr. James Zacharias, Zhi Tan, Dr. Matthew James, Dr. Braden Manns, Dr. Fiona Clement, Dr. David Collister, Simon Walker, and the Research Team at Seven Oaks General Hospital.

In addition, I would like to thank all the participants in First Nations Community Based Screening to Improve Kidney Health and Prevent Dialysis (FINISHED) project, without whom none of this research would have been possible.

Furthermore, I would like to acknowledge the financial assistance that I have received throughout completion of my graduate studies in Community Health Sciences, which include the Western Regional Training Centre (WRTC) studentship, funding from Research Manitoba (formerly the Manitoba Health Research Council) through the University of Manitoba Graduate Fellowship, and the support of the Seven Oaks General Hospital Renal Program**.**

Table of Contents

List of Tables, Figures, and Appendices

Glossary of Acronyms

ACEI – Angiotensin-Converting Enzyme-Inhibitor

ACP – American College of Physicians

ACR – Albumin-to-Creatinine Ratio

ARB – Angiotensin Receptor Blocker

ASN – American Society of Nephrology

AUROC – Area Under the Receiver Operating Characteristic Curve

CADTH – Canadian Agency for Drugs and Technology in Health

CAPD – Continuous Ambulatory Peritoneal Dialysis

CCPD – Continuous Cycler Peritoneal Dialysis

CI – Confidence Interval

CKD – Chronic Kidney Disease

CORR – Canadian Organ Replacement Register

CSN – Canadian Society of Nephrology

DSM – Diagnostic Services of Manitoba

eGFR – Estimated Glomerular Filtration Rate

eKHR – Electronic Kidney Health Record

FINISHED – First Nations Community Based Screening to Improve Kidney Health and Prevent Dialysis

GFR – Glomerular Filtration Rate

HD - Hemodialysis

HHD – Home Hemodialysis

ICER – Incremental Cost-Effectiveness Ratio

KDIGO – Kidney Disease Improving Global Outcomes

KDOQI – Kidney Disease Outcomes Quality Initiative

KEEP – Kidney Early Evaluation Program

KEY – Kidney Evaluation for You

KFRE – Kidney Failure Risk Equation

LCDU – Local Centre Dialysis Units

MDRD – Modification of Diet in Renal Disease

mGFR – Measured Glomerular Filtration Rate

NHANES – National Health and Nutrition Examination Survey

NKF – National Kidney Foundation

PD – Peritoneal Dialysis

PREVEND – Prevention of Renal and Vascular End-Stage Disease

QALY – Quality-Adjusted Life-Year

SCr – Serum Creatinine

SHD – Satellite Hemodialysis

SLICK – Screening for Limb, I-Eye, Cardiovascular and Kidney

UAE – Urinary Albumin Excretion

USPTF – United States Preventative Task Force

1. Chapter 1: Introduction

1.1 Overview of Chronic Kidney Disease

Chronic kidney disease (CKD) is defined as the presence of persistent elevated urine albumin (proteinuria) and/or as decreased kidney function measured by glomerular filtration rate (GFR) less than 60 ml/min per $1.73m^2$[1]. Measured glomerular filtration rate (mGFR) is determined from the urinary plasma clearance of exogenous filtration markers such as inulin or iothalamate, but is rarely performed in clinical practice due to complexity of measurement and prohibitive costs[2]. As such, GFR is often estimated (eGFR) using validated equations. Often applied in clinical practice, these equations include the Modification of Diet in Renal Disease (MDRD) equation and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. This allows for a simplified calculation of GFR using routinely collected laboratory values such as age, sex, race, and measurement of serum creatinine (SCr)[3, 4].

CKD can be classified into stages of worsening severity and likelihood of progression to kidney failure based on a two-axis classification system comprised of both persistent albuminuria and eGFR. Individuals with normal kidney function, defined as eGFR > 60 ml/min per $1.73m^2$ and normal levels of persistent albuminuria (albumin-to-creatinine ratio (ACR) < 30 mg/g) are at negligible increased risk for kidney failure with a baseline rate of 0.04 per 1000 person-years in the healthy, general population. The overall risk of progression to kidney failure increases as eGFR declines below 60 ml/min per $1.73m^2$ and the ACR increases above 30 mg/g. Patients are then staged according to their level of eGFR across five stages of CKD. This two-axis risk staging system has been published as a guideline by the Kidney Disease – Improving Global Outcomes (KDIGO) organization, a worldwide initiative that provides guidelines for the management of patients with renal insufficiency[5].

1.2 Management of Patients with CKD and Kidney Failure

Current recommendations for the management of CKD suggest referral to inter-professional nephrology teams for patients who have an eGFR < 30 ml/min per 1.73m[26]. Earlier stages of CKD, which are often asymptomatic[7], can be managed with less intensive treatment by a primary care physician. Moreover, in its earliest stages, the primary focus would be on interventions to slow progression. These include the management of comorbid conditions, such as diabetes, hypertension, and proteinuria, as well as the mitigation of other risk factors using diet and pharmacological interventions such as statins and antihypertensives[6].

For those patients who reach kidney failure (eGFR < 15ml/min per 1.73m^2 who require renal replacement therapy) there are several treatment options available. Ideally, patients are offered kidney transplantation, the therapy that offers both the lowest overall cost and highest quality of life[8]. Unfortunately, kidneys are in short supply, organ wait lists are increasing[9], and some patients are frail and unsuitable for the demanding transplant procedure and required lifelong immunosuppressive regimens[10], and as such, other life sustaining therapies must be considered. There are two primary forms of dialysis therapy available: hemodialysis (through the blood), and peritoneal dialysis (through the abdomen). Hemodialysis (HD) is often done at a tertiary care hospital 3 times per week for 3-4 hours and is the primary modality prescribed in close to 80% of prevalent dialysis patients in Canada[11]. This therapy can also be done in a patient's home and has been associated with improved outcomes, costs, and quality of life[8]; however, in a Canadian setting, home hemodialysis (HHD) is only prevalent in 4% of patients receiving any form of dialysis[11]. The second available home therapy, peritoneal dialysis (PD) can be performed with multiple fluid exchanges through the abdomen per day (continuous ambulatory peritoneal dialysis (CAPD)) or as fluid exchanges overnight (continuous cycler peritoneal dialysis (CCPD))

and is the prevalent modality in 17.5% of the Canadian population[11]. PD offers considerable cost savings on a per-patient basis compared to conventional HD provided in-centre[12], however, due to the complicated nature of providing self-care dialysis, despite often offering improved outcomes, it is only prescribed in a minority of patients[13].

1.3 CKD and Kidney Failure Incidence and Prevalence Trends

A previous study evaluated the prevalence of Chronic Kidney Disease by determination of eGFR (CKD-EPI equation) and measurement of urine ACR (>2.0 mg/mmol for men and >2.8 mg/mmol for women in CKD stages 1 and 2 as a cut-off for microalbuminuria) based on previously established Canadian guidelines[14] using the Canadian Health Measures Survey[15, 16]. This study found a total prevalence of CKD in Canada to be 12.5%, or 2.5 million Canadians. However, awareness of this kidney dysfunction was low across all stages of CKD, with only 5.3% of those in Stages 1 in 2 aware of the condition, and 12% in Stages 3 and above[17]. Similarly, a study in Manitoba which evaluated screening in a single First Nations community found a kidney dysfunction awareness of 5% overall, with 17% of those with macroalbuminuria (urine ACR > 300 mg/g) and only 1% of those with microalbuminuria (urine ACR 30-299 mg/g) having awareness of their condition[18]. These findings highlight the magnitude of undetected CKD in the Canadian population, some of which that may benefit from targeted intervention.

Although most patients with CKD will not reach kidney failure requiring life-sustaining renal replacement therapy due to the competing risk of all-cause and cardiovascular mortality[19, 20], the prevalence of treated kidney failure has been increasing over the last twenty years in Canada. This proportion has increased from 26.2 cases per 100,000 population in 1992 to 67.9 per 100,000 in 2011 for patients receiving dialysis and from 20.9 per 100,000 to 49.2 per 100,000 for

patients surviving with a functioning transplant. In addition to this, the overall incidence of kidney failure in Canada has remained steady between 16.0 and 17.0 per 100,000 over the last decade. The epidemic of kidney failure is more alarming in Manitoba, where the total incidence of kidney failure reached a rate of 20.2 per 100,000 in 2011, one of the highest in the country[11]. This is particularly concerning in Manitoba's northern rural communities, having surpassed an incidence rate of 90.0 per 100,000 in recent years. In accordance with this, the prevalence of patients receiving chronic dialysis in Manitoba has markedly increased over the last twenty-five years from 24.8 cases per 100,000 population in 1984 to 152.3 per 100,000 in 2009 (Figures 1 and 2). This increase in dialysis prevalence puts a significant burden on available resources in the health care system, which has been demonstrated in increasing health care costs. Notably, 1.2% of all health expenditures in Canada are spent on dialysis therapy; a disproportionate ratio since only 0.092% of the population is classified as having kidney failure[21-24].

1.4 CKD in Canadian Rural and Remote First Nations

First Nations populations in Canada have shown a tremendous burden of diabetes that has been increasing and outpacing the general population[25]. Standardized for the difference in the age structure of those with First Nations status and the general Manitoba population, First Nations populations in Manitoba have a 3-fold increased risk of having diabetes. Older individuals in this population reach a nearly 40% crude prevalence of diabetes[26]. Consequently, this has led to an increased burden of CKD related to rising rates of diabetic nephropathy in this subpopulation, which is the leading cause of kidney failure in North America[11, 23].

In addition to the significant burden of CKD and kidney failure, Manitoba's First Nations often have poor access to both primary and specialist medical care[27]. In particular, they are

significantly less likely to receive care from a nephrologist when classified as having severe chronic kidney disease (eGFR < 30 ml/min per 1.73m^2, hazard ratio 0.57 (0.39 – 0.83 95% confidence interval (CI)))[28]., First Nations populations have been shown to have higher overall rates of progression to kidney failure for each respective classification of eGFR and persistent albuminuria, ranging from 1.5 times to over 3 times the risk experienced in a comparator general population[29]. Early identification of patients in this targeted high-risk group may offer improved outcomes if progression to kidney failure can be slowed or prevented alongside a reduction in all-cause mortality.

1.5 The FINISHED Screening Initiative

Mass screening of Manitoba's First Nations has been undertaken by the First Nations Community Based Screening to Improve Kidney Health and Prevent Dialysis (FINISHED) study, an initiative funded by Health Canada that has screened 11 communities across 2 tribal councils in Manitoba starting in March 2013 until January 2015. Seven of these rural communities are accessible by normal road access. The remaining four communities were only accessible by air throughout the majority of the year, with conditional access if weather permits on ice roads during the winter months. With only those over age 10 included for screening, the total eligible population totaled roughly 11,500 individuals[30]. Finding a particularly young population, there was only a potential 5860 adults (Age 18+) who were eligible for screening. From this pool, a total of 1346 individuals were screened, achieving a compliance rate of 23%[30].

1.6 Study Objectives and Thesis Statement

The cost-effectiveness of screening for CKD in the rural and remote northern First Nations populations of Manitoba has not been previously described. In addition to increased prevalence

of CKD and risk of progression to kidney failure, the rural and remote setting faced by many of the individuals residing in these communities presents challenging circumstances to providing adequate CKD care and renal replacement therapy[31]. In addition, the cost of providing satellite hemodialysis (SHD) in more remote smaller community clinics is much higher than care provided in dialysis centres in urban, densely populated regions (Ferguson T.W., Zacharias J., Walker S.R., et al. An Economic Assessment Model of Rural and Remote Satellite Hemodialysis Units. Pending Revisions).

In this thesis, datafrom the risk profile and costs obtained through the FINISHED screening initiative were used to develop a cost-utility model comparing one-off population based screening for CKD by eGFR and albuminuria to usual care in Manitoba's adult (age 18+) rural and remote First Nations. We hypothesized that due to increased rates of progression and higher prevalence of macroalbuminuria in First Nations populations[18, 29], an epidemic of kidney failure in Manitoba's rural and remote north (Figures 1 and 2), and particularly expensive dialysis therapy, that screening in this population would be cost-effective (<$50,000/quality-adjusted life-year (QALY)).

2. Chapter 2: Literature Review

In this chapter we will review relevant literature related to CKD screening in First Nations and subsequent treatment: (1) the types of screening tests used, (2) a review of previous screening initiatives, (3) the potential benefits of early screening, (4) the costs and consequences of progressive CKD, (5) an overview of current screening guidelines, (6) a review of existing cost-effectiveness literature with regards to CKD screening, and (7) a review of the burden of kidney disease in First Nations and other indigenous populations.

2.1 Screening Tests

There are two primary methods of screening for CKD reported in the literature. These include measurement of urine protein concentration through dipstick urinalysis, urinary albumin excretion (UAE), or measurement of urine ACR. This technique involves the patient submitting a random sample of urine, which can be assayed at the bedside qualitatively using a dipstick, and quantitatively using point of care instruments or laboratory testing. The second available screening method is assessment of eGFR through the measurement of standardized SCr using a routine blood test. Both tests used in combination can be used to more effectively diagnose the overall risk of progressive kidney failure[32]. Thresholds for kidney damage are assigned as microalbuminuria when urine ACR measures between 30 mg/g and 300 mg/g, and macroalbuminuria when urine ACR measures over 300 mg/g. Stages 1 and 2 CKD are defined as eGFR greater than 90 ml/min per $1.73m^2$ and between 60 and 90 ml/min per $1.73m^2$ respectively with either micro- or macroalbuminuria. Stage 3 CKD is defined as eGFR between 30 and 60 ml/min per $1.73m^2$, stage 4 as eGFR between 15 and 30 ml/min per $1.73m^2$, and stage 5 below

15 ml/min per 1.73m^2. As renal function declines further below 15 ml/min per 1.73m^2, patients eventually transition to renal replacement therapy (dialysis and transplantation).

2.2 Previous Screening Initiatives

There have been several previous initiatives that have explored screening for CKD with widely varying results dependent on the target population. In the general population, these include the National Health and Nutrition Examination Survey (NHANES) cycles in the United States, which found a prevalence of microalbuminuria of 7.1%, macroalbuminuria 1.1%, and reduced kidney function (eGFR < 60ml/min per 1.73m) of 5.6% during the 1988 to 1994 cycle across over 15,000 individuals. These rates increased to 8.2% for microalbuminuria, 1.3% for macroalbuminuria, and 8.1% for reduced kidney function in the subsequent cycle between 1999 and 2004 across over 13,000 individuals[33]. Similarly, the Prevention of Renal and Vascular Endstage Disease (PREVEND) study that screened over 8,500 patients in the Netherlands found a microalbuminuria prevalence of 7.2%, a macroalbuminuria prevalence of 0.7%, and a prevalence of reduced kidney function of 5.5%[34]. Lastly, an Australian initiative, KEY (Kidney Evaluation for You), found a microalbuminuria prevalence of 8% by urine ACR and 13% by protein dipstick in the general employed population[35].

Screening has also been performed in higher-risk populations. The KEEP (Kidney Early Evaluation Program) program in the United States also found an overall prevalence of CKD to be 11% in the general population, and when targeting high-risk individuals (those with diabetes, hypertension, and first-degree relatives of patients with CKD), found a prevalence of albuminuria to be 26% and found 16% of individuals with elevated levels of SCr[36, 37]. The KEEP initiative also had further studies that evaluated screening in other locales, with a Mexican study

finding 19% of the population with albuminuria defined as ACR > 30 mg/g[38], and a Japanese study finding 23.6% of the population with albuminuria defined ACR > 30 mg/g[39], and both studies found a prevalence of reduced kidney function by eGFR of 7% using the same criteria for high-risk participants as the KEEP program from the United States[37-39].

Indigenous and First Nations populations have also been explored in targeted screening initiatives, finding a considerable burden of proteinuric CKD. A screening program in Alberta, the Screening for Limb, I-Eye, Cardiovascular and Kidney (SLICK) study, screened individuals in First Nations communities with type 2 diabetes for proteinuria and found a microalbuminuria prevalence of 26% and a dipstick proteinuria prevalence of 13%, demonstrating a significantly elevated burden of CKD[40, 41]. In addition, the findings of the FINISHED project found similar results to a single-community screening initiative in a First Nations tribal council from Manitoba performed in 2003, which found a prevalence of macroalbuminuria of 5% (urine ACR > 30 mg/mmol (approx. 300mg/g))[18]. Screening has also been performed in several American indigenous populations, including the Zuni Indians, finding a microalbuminuria prevalence of 15% and a macroalbuminuria prevalence of 4.7%[42, 43], the Navajo Indians finding a microalbuminuria prevalence of 14.6% in those without diabetes and 36.1% in those with diabetes, and a macroalbuminuria prevalence of 2% in those without diabetes and 17.9% in those with diabetes[44], and the Pima Indians, who reached prevalence levels of microalbuminuria of 25.8% and macroalbuminuria of 20.8% in individuals with type 2 diabetes[45]. Lastly, screening in an isolated northern community of Australian aborigines found a microalbuminuria prevalence of 26% and macroalbuminuria prevalence of 24%[46].

A detailed summary of these screening initiatives is provided in Table 1.

2.3 Benefits of Early Screening

Late referral to nephrology has been associated with negative patient outcomes. Although early referral to nephrology is associated with increased initial costs, these are often offset with a reduction in hospitalizations over the following years[47]. In addition, early referral has been shown to prevent crash starts of dialysis, improve dialysis access planning, and allow for appropriate treatment modality education[48]. Consequently, it has been repeatedly shown that an earlier nephrologist referral is associated with a reduction in all-cause mortality compared to patients referred less than 90 days before starting dialysis[49, 50]. It is noteworthy, however, that this early referral may not imply causation and could be the product of a superior primary care structure[51]. Despite these potential benefits, many patients only receive first contact with a nephrologist within a month of beginning dialysis[52].

There have also been other benefits of early detection shown. Those who received earlier specialist care had lower blood pressure and received more aggressive antihypertensive therapy[7]. Antihypertensive treatment, in particular angiotensin-converting enzyme-inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), is often indicated in patients with detected albuminuria due to their antiproteinuric effects [53-56]. Both control of urinary protein excretion and blood pressure have been associated with a better preservation of eGFR and prevention of progression to kidney failure, having been extensively evaluated in multiple observational studies, randomized controlled trials, and meta-analyses, particularly in those with markedly increased albuminuria (> 300 mg/g) and diabetic kidney disease[57-64].

2.4 Costs and Consequences of Progressive CKD

CKD is associated with a significant burden of cardiovascular and all-cause mortality. In comparison to those with eGFR > 60ml/min per 1.73m^2, the hazard ratio of any cardiovascular event was 1.2 in patients with stage 3a CKD (eGFR between 45 and 59 ml/min per 1.73m^2), 1.8 in patients with stage 3b CKD (eGFR between 30 and 44 ml/min per 1.73m^2), 3.2 in patients with stage 4 CKD (eGFR between 15 and 29 ml/min per 1.73m^2), and 5.9 in patients with stage 5 CKD (eGFR below 15 ml/min per 1.73m^2). This trend is similar for all-cause mortality, ranging from a hazard ratio of 1.4 in those with stage 3a CKD to a hazard ratio of 3.4 in patients with stage 5 CKD in comparison to those with eGFR > 60ml/min per 1.73m^2. Likewise, hospitalization rates are shown to increase along the same trend, with stage 3a patients demonstrating a hazard ratio of 1.1 with respect to hospitalizations, and those with CKD stage 5 demonstrating a hazard ratio of 3.1[20]. Additionally, CKD has been shown to be associated with frailty[65] and cognitive impairment[66]. These health problems have a detrimental impact on the quality of life of those living with CKD[67].

Despite only few patients with CKD reaching kidney failure[19], the consequences of CKD that reaches the requirement for renal replacement therapy cause a substantial burden to health care payers. In Canada, the costs of renal replacement therapy total $1.8 billion per year, costing over $70,000 per patient[21]. In the United States these numbers are similar per-capita, with total expenditures in kidney failure) patients totaling over 30 billion US dollars in 2011 alone[23]. This is largely attributable to the expensive nature of chronic dialysis therapy, which oftentimes requires multiple hospital visits per week and extensive nursing expenditures. In addition, these patients are often affected by multiple comorbid conditions that require frequent hospitalizations, extensive pharmaceutical interventions, and frequent travel to and from clinical appointments[68].

The most common renal replacement modality, in-centre or facility HD, has remarkably similar costs across the developed world, costing between $60,000 and $70,000 per patient, per year in Canada[69], the United States[70], the United Kingdom[71], Australia[8, 72], and Japan[73, 74]. Canada's second most prevalent modality, PD costs roughly $27,000 per-patient, per-year[12]. Home hemodialysis offers some cost savings to facility HD, costing between $42,000 and $52,000 per-patient, per year after the initial year in which extra training and equipment setup costs are often experienced[69]. Transplantation is widely accepted to be the most cost-effective over the course of treatment, costing roughly $91,000 in the first year and $38,000 in subsequent years (2013 Canadian dollars) for maintenance immunosuppressive therapy, while offering the highest overall quality of life[75]. Cost-effectiveness analysis has shown that under widely varying assumptions that transplantation is the dominant treatment strategy compared with in-centre dialysis if organs are available and the patient is suitable for the procedure[8].

Oftentimes hemodialysis that is provided in-centre is relegated to smaller SHD units that are decentralized from primary tertiary care centres. In these circumstances, nephrology care is often provided remotely. This model of care[76, 77] has been met with conflicting findings on its potential benefits, with some studies finding mortality reduction[78], increased mortality[79], or no significant change in mortality[80, 81]. In addition to this, these units are often argued to increased patient quality of life[82-84] as a function of the decreased travel time required for patients[85, 86]. In the specific case of Manitoba's rural and remote First Nations, there may be potential benefits to quality of life associated with decreased relocation to urban centres that lack sensitivity to First Nation cultural considerations[87].

The cost-effectiveness of SHD units has been extensively explored in the literature and has been shown to be a cost-effective alternative to providing dialysis services in larger tertiary care

centres[12, 88-90]. When applying this model of care to the rural and remote SHD units in Manitoba there are other factors that require consideration that were not included in these previous analyses. In particular, there are premiums paid to nursing and other allied health care staff to accommodate differences in living arrangements between remote rural and urban living environments. Additionally, these units often function below optimal capacity, with previous findings suggesting that the break-even point for fixed costs is seven patients in a six-station unit[91]. Many SHD units in Manitoba fail to meet this threshold. Lastly, there are additional costs related to transportation for dialysis treatment, as well as transport for care only available in urban tertiary centres, oftentimes by air or road ambulance, that are incremental to the costs of a SHD unit in a more densely populated area (Ferguson T.W., Zacharias J., Walker S.R., et al. An Economic Assessment Model of Rural and Remote Satellite Hemodialysis Units. Pending Revisions).

2.5 Current Screening Recommendations

In general, screening for CKD in patients with hypertension and/or diabetes is universally supported by several nephrology collaborations, including the National Kidney Foundation (NKF – Kidney Disease Outcomes Quality Initiative (KDOQI)), the Canadian Society of Nephrology (CSN), the American Society of Nephrology (ASN), and the KDIGO group[6, 14, 92]. Both the American College of Physicians (ACP) and The U.S. Preventative Services Task Force (USPTF) argue that there is not sufficient evidence to warrant any screening in asymptomatic adults for CKD who do not have diabetes or hypertension. They further argue that false-positive results, subsequent unnecessary investigations and treatment, and potential complications from venipuncture could further introduce unnecessary harms in this population versus the potential benefits[93, 94]. Others argue that screening for Chronic Kidney disease should be extended to those

with cardiovascular disease and in first-degree relatives of those with a history of kidney disease. Screening in certain ethnic groups with observed increased risk has also been encouraged by the NKF, ASN, and CSN[6, 92].

2.6 Cost-Effectiveness of Population Based Screening

The cost-effectiveness of population based screening for CKD has been extensively evaluated by several studies. Primarily, these studies focused on the overall general population, patients with hypertension, patients with diabetes, and in high-risk minority groups. Screening in those with diabetes was found to be cost-effective in several health care settings (incremental cost-effectiveness ratio (ICER) $5,298/QALY - $54,943/QALY 2011 US dollars)[8, 95-100]. Similar findings were seen in screening those with hypertension, demonstrating marginally cost-effective ICERs ($23,028/QALY - $73,939/QALY 2011 US Dollars)[95-97, 101]. There was substantial variability in studies that considered screening in the general population, with reported cost-effectiveness ratios ranging from $14,063 to $160,018/QALY for proteinuria-based screening, and from $100,253 to $109,912/QALY ($2011 USD) for eGFR-based screening[73, 95, 97, 98, 102]. Targeted screening in African Americans by measurement of urine protein was also shown to be cost-effective (ICER $35,000/QALY when repeated annually and $9,000/QALY when repeated every 10 years)[103]. Additionally, increasing the age threshold of which patients would be screened and, in studies that considered repeated screening, increasing the length of time between subsequent screening events was shown to improve reported cost-effectiveness ratios[95, 101].

An evaluation of these existing studies found that several factors were consistently influential model drivers regardless of health care setting. Assumptions around treatment effectiveness, for

both reduction of all-cause mortality and reduction of progression to kidney failure, had a substantial effect on model results. Two studies in particular assumed considerable reductions in mortality as a result of preventing cardiovascular comorbidities in screened patients. One study, from the Netherlands, assumed a 40% reduction in cardiovascular mortality as a result of antihypertensive therapy in patients with microalbuminuria (urinary albumin excretion (UAE) ≥ 30 mg/d)) and found general population screening to be cost-effective (ICER $31,707/QALY 2011 US dollars)[102]. Similarly, a study evaluating the addition of CKD screening to mandatory annual checkups in Japan found proteinuria-based screening to be cost-effective (ICER $14,064/QALY 2011 US dollars) and had also assumed a substantial improvement in mortality from the addition of antihypertensive therapy (relative risk reduction of 42.1% to kidney failure, 71.0% to heart attack, and 69.3% to stroke with treatment)[73].

A further influential model driver was the progression assumptions from CKD to kidney failure. Increases in 50-100% of the rate of progression to kidney failure were shown to drastically reduce reported ICERs across several economic models[104]. In one Canadian study an increase in the risk of progression of 100% reduced the reported ICER from $104,900 to $80,200 CAD[98]. The transition rate from microalbuminuria to macroalbuminuria was also shown to be a powerful model driver in an American study evaluating the cost-effectiveness of microalbuminuria screening[95]. This finding is also analogous with the improved cost-effectiveness results in both diabetic and hypertensive subpopulations, with these groups showing increased progression to kidney failure, increased mortality, and increased cardiovascular events as levels of albuminuria increase in comparison to healthier individuals[105].

Baseline prevalence was also shown to be an influential model parameter. Many previously published cost-effectiveness analyses in North America used information from NHANES III to

determine prevalence of diabetes, hypertension, and CKD, and as such, these findings may not be generalizable to targeted screening in higher risk populations. For example, one study evaluating CKD screening in Japan found proteinuria based screening to be cost-effective and used prevalence and incidence estimates that were elevated compared to North American studies[73, 104]. Previous studies have shown that the prevalence of CKD in Japan is elevated compared to many western countries, likely attributable to differences in the age distribution, but nonetheless allowing a mass screening program to discover more potential cases[106, 107]. These cost-effectiveness findings may translate into other subpopulations with elevated prevalence of CKD and subsequent increased odds of case finding.

2.7 The Burden of Kidney Disease in Indigenous Populations

Indigenous populations have shown a significant burden of diabetes, CKD, and kidney failure, not only in Canada, but in many locales around the world. Canadian Aboriginal peoples have rates of kidney failure that are 2.5 to 3 times that of the general population, 60% of which is caused by diabetic nephropathy, comparable to 30 to 35% in the general population[11, 28, 108]. This burden has cemented itself strongly in the Prairie Provinces, particularly Saskatchewan and Manitoba, which have proportions of indigenous patients that encompass nearly 30% of all kidney failure cases despite making up only roughly 15% of the population[108, 109]. There have been similar findings with indigenous populations in the United States, with nearly 75% of primary diagnoses for kidney failure in this population attributable to type 2 diabetes[110], and incidence rates of kidney failure that are also 2-3 fold that of a comparator general population[111]. Additionally, indigenous populations in Australia and New Zealand have displayed similar disparities. Pacific Islanders, Maori, and Aboriginal and Torres Strait Islanders were all significantly ($p < 0.01$) more likely to have a primary kidney failure diagnosis of diabetic

nephropathy, ranging between 47 and 63% of kidney failure cases in each group, and had overall rates of kidney failure that ranged from 2-fold to 8-fold the Australian general population[112]. Lastly, the magnitude of the burden of CKD in these populations is often amplified since many of these indigenous or First Nations populations are located in isolated areas with reduced access to medical services or complex care only available in more densely populated regions[27, 113, 114].

3. Chapter 3: Materials and Methods

3.1 Overview

We performed an incremental cost utility analysis of one-off screening for CKD in Manitoba's rural and remote First Nations adult (age 18+) population in comparison to usual care, defined as no targeted screening with the allowance for incidental finding of CKD cases and referral to nephrology through existing routine clinical care pathways. The perspective of this analysis took that of the Canadian public health payer. All costs are presented in 2013 Canadian dollars and were inflated using the Canadian medical consumer price index[115], and all benefits are presented using quality-adjusted life-years (QALYs). All costs and benefits are discounted at 5% annually based on recommendations from published guidelines from the Canadian Agency for Drugs and Technologies in Health (CADTH)[116]. The model followed patients from age 45 (median and mean age of screening cohort) until age 90 or death.

3.2 Screening Initiative and Study Population

The FINISHED screening initiative screened 1346 adult patients between March 2013 and January 2015 across 11 communities within 2 tribal councils in the province of Manitoba, Canada. The methodology of the FINISHED study has been previously published[30]. Briefly, this includes 716 patients in communities accessible by road and 630 patients in communities accessible only by air or ice roads. Despite having similar eGFR profiles, the more remote air access communities experienced a significantly higher burden of CKD expressed as statistically significant differences in both urine ACR (median ACR of 16.8 mg/g (interquartile range 7.1 – 45.1) for individuals from air access communities and median ACR of 8.8 mg/g (interquartile range 4.4 – 16.8) for individuals from road-accessible communities; $p < 0.01$ using the Mann-

Whitney U-Test) and increased overall risk of kidney failure over five years as expressed by the Kidney Failure Risk Equation (KFRE) in air access communities ($p < 0.01$ using X^2 test). The KFRE is a multivariate model that predicts the risk of kidney failure at 2- 5- and 10- years (c-statistic > 0.90)[117]. Additionally, individuals from air access communities also experienced higher rates of glycated hemoglobin (HgB A1C) (median HgB A1C of 6.0% (interquartile range 5.4 – 8.0%) in air access communities and median HgB A1C of 5.6% (interquartile range 5.3 – 7.0%) in those from road-accessible communities; $p < 0.01$ using the Mann-Whitney U-Test) signifying an increased burden of uncontrolled diabetes. Demographic characteristics and comparisons between air access and road access communities are detailed in Table 2.

3.3 Simulation Model

We constructed a computer simulated Markov model using decision analysis software (TreeAge Pro 2014, Williamstown, MA). States were divided based on the KDIGO risk classification system. Patients were classified at the start of the model into normal kidney function (green in the KDIGO classification diagram), CKD with low risk of progression to kidney failure (yellow in the KDIGO classification diagram), CKD with intermediate risk of progression to kidney failure (orange in the KDIGO classification diagram), and CKD with high risk of progression to kidney failure (red in the KDIGO classification diagram)[32]. Patients with proteinuria (urine ACR > 300 mg/g) were assumed to receive a reduction in progression and all-cause mortality from prescription and use of an angiotensin-converting-enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) upon discovery of a CKD case through either screening or incidental presentation to primary care[101, 118]. We assumed that outcomes would be similar whether a patient was prescribed an ACEI or ARB[119]. From this, the model followed patients as they progressed or regressed between risk stages, through transplantation, dialysis, and death. The

model was executed using 1 year cycles and had a time horizon of 45 years. An overview diagram of the model is presented in Figure 3.

3.4 Data Inputs

The rates of initial kidney failure risk states were classified using screening results from the FINISHED study. eGFR was calculated using the MDRD study equation[3]. With a mean and median age of 45 years, there was an initial prevalence of 20.43% classified as low risk of kidney failure, 4.75% classified as intermediate risk, and 1.49% of classified as high risk. When considering measures of eGFR alone, this corresponded to 3.7% of individuals screened with eGFR between 30-60 ml/min per 1.73m^2 (stage 3 CKD), 0.3% of individuals screened with eGFR between 15-29 ml/min per 1.73m^2 (stage 4 CKD), and 0.1% of individuals screened with eGFR below 15 ml/min per 1.73m^2 (stage 5 CKD). Despite being similar to the general population when considering eGFR measurements, the FINISHED project found a substantially higher prevalence of proteinuria, with 24.4% of those screened having any elevated albuminuria in comparison to roughly 8.5% in the general population[5]. The initial kidney failure risk profile of the FINISHED population, by both road access communities and air access communities, is presented using the KDIGO two-axis stating system in Figure 4.

Since no longitudinal data were available from Manitoba for First Nations progression rates, CKD progression and regression rates for a First Nations population were sourced from the Alberta Kidney Disease Network (AKDN), a laboratory data repository for the province of Alberta, Canada[120]. The cohort selection criteria for individuals included in the progression and regression rate transitions ranged from Jan 1, 2005 to Dec 31, 2008. All First Nations individuals living in Alberta ≥ 18 years of age who had at least one outpatient serum creatinine (SCr)

measurement during this time were included. For patients with more than one SCr measurement, the first one was selected and defined as the index time. For patients with eGFR ≥ 30 ml/min per 1.73m^2 patients required a urine ACR measurement to adequately classify their level of risk with a 6 month window both prior and post index time. The follow up for transition ranged from Jan 1, 2009 to Dec 31, 2013. Patients who migrated from Alberta or died were treated as a censor case. To determine the follow-up risk classification stage, the last SCr measurement was chosen, with the associated urine ACR measurement allowed within 6 months of this time. Accordingly, the transition probability was taken over the median follow up time to ascertain transition rates between low, intermediate, high, and kidney failure (dialysis and transplantation) classifications. These progression and regression rates between risk categories and for kidney failure are outlined in Table 3.

Mortality rates were adapted from a baseline population using life tables from Statistics Canada[121]. To ascertain the risk of mortality in each respective CKD progression risk category, baseline mortality was modified using relative risk ratios from a previously published meta-analysis based on classification of both eGFR and urine ACR[5]. Mortality rates in both patients with a transplant and patients on dialysis, as well as the chance of a transplant failure requiring return to dialysis, were taken from the annual report of the Canadian Organ Replacement Register (CORR), a subset of the Canadian Institute for Health Information that tracks trends on organ replacement in Canada[11], as well as a previously published CKD screening study from Canada[98]. Annual mortality rates for each risk strata, those on dialysis, and those surviving with a transplant are provided in Table 4.

We applied general Canadian population rates for transplant mortality and graft failure as previous research has shown that First Nations who are selected for transplant do not have a

statistically significant difference in the rate of graft survival following a successful transplant[122]. Transition probabilities for both pre-emptive transplant (before initiating dialysis) and for those prevalent on dialysis were also taken from the CORR annual report. These rates were adjusted for the rate of First Nations receiving transplants using a hazard ratio of 0.43 (95% CI 0.35 – 0.53) from a previous Canadian study that evaluated the rates of transplantation in Canadian Aboriginals[123]. Transplantation rates, risk of mortality, and graft failure rates are also provided in Table 4.

Adherence to ACEI and ARB treatment was taken from a review of the existing literature and assumed to be 75% based on existing CKD screening models[98, 101, 103]. Rates of incidental presentation to medical care were taken from a previous Canadian study that evaluated screening for CKD and were estimated to be 5% annually[98]. Additionally, only patients who were of high risk (red on the KDIGO risk classification map) were given a consultation with a nephrologist following screening based on the guideline of referring patients with eGFR $\leq$ 30 ml/min per 1.73m^2 and those with highly elevated ACR (> 300 mg/g) and eGFR between 30 and 45 ml/in per 1.73m^2 for specialist treatment[5, 6].

Treatment effectiveness was taken from previous CKD screening models which applied findings from existing randomized controlled trials and meta-analyses regarding the benefit to both a reduction in all-cause mortality and progression of CKD from the use of ACEIs and ARBs[57-59, 95, 96, 101, 124-128]). ACEIs and ARBs were conservatively assumed to only offer a reduction benefit in individuals with macroalbuminuria, defined as urine ACR > 300 mg/g in the baseline scenario. With respect to mortality, we assumed treatment offered a relative risk reduction of 23%, and with respect to progression we assumed treatment offered a relative risk reduction of 33%[96, 101]. We assumed no increase in the relative risk of regression to less progressive CKD as a result of

ACEI or ARB therapy. In the baseline cohort (n = 1346, both air access and road access communities) the prevalence of macroalbuminuria (urine ACR > 300 mg/g) was 81% for those in the intermediate risk category (orange on the KDIGO classification map) and 75% for those in the high risk category (red on the KDIGO classification map). Healthy and low risk patients (green and yellow on the KDIGO classification map) do not have any presence of macroalbuminuria by advent of the structure of the classification system.

The prevalence of dialysis modality utilization was taken from the Electronic Kidney Health Record (eKHR). The eKHR is the Manitoba Renal Program's provincial electronic database that contains all dialysis patient scheduling data going back to 2011. The eKHR scheduling data has been extensively validated by independent chart review audits and is close to one hundred percent accurate for timing and location of dialysis runs. This prevalence rate was used to determine a weighted cost of dialysis based on the probability of receiving treatment with each respective modality. The prevalence of modality utilization was 25.7% for in-centre HD, 25.7% for PD, 1.4% for HHD, and the majority of patients in rural and remote communities received SHD (part of the Local Centre Dialysis Units (LCDUs), sixteen smaller clinical units in rural and remote communities throughout Manitoba) at a proportion of 47.2%. Table 5 provides a breakdown of the prevalence of modality utilization for all patients living in the areas considered for screening (Manitoba postal codes R0B, R0J, and R0L).

A summary of included model parameters is outlined in Table 6.

3.5 Costs

The cost of screening each patient was taken from the financial statements of the funding used to support the FINISHED screening initiative. This included all expenses related to the provision of

screening services, including transportation of equipment and personnel, staffing, administrative, laboratory, and testing device related costs. Adjusting for costs non-specific to the provision of screening, we had a total average per patient cost of $590. For incidental/inadvertent presentation to medical care for CKD treatment, costs were calculated based on the location in the KDIGO risk map. All inadvertently screened patients are attributed the cost of a general practitioner visit at $76.25 based on the Manitoba Physician's Manual[129] and the costs of a CKD screening test and resulting lab fees (electrolytes, urea, creatinine, urinalysis, and urine ACR) at a total cost of $30.43 based on provider quotes from Diagnostic Services Manitoba (DSM). For the highest risk patients who require referral to nephrology, an additional $175.25 was assessed for a specialist consultation based on the Manitoba Physician's Manual[129].

The cost of dialysis was assessed as a weighted average of the cost of PD, HHD, in-centre hospital HD, and SHD provided in LCDUs dependent on the prevalence of each modality's utilization previously described. The cost of PD was taken from an existing published Canadian costing study[12, 69], adjusted for additional costs of shipping consumables and travel expenses for returning to Winnipeg for medical care not available in remote communities, and totaled $43,500 ($29,603 modality + $13,897 shipping and transport costs). Likewise, the cost of HHD was taken from an existing Canadian microcosting study[69], adjusted for additional costs of shipping consumables and travel expenses for returning to Winnipeg for medical care, and totaled $61,305 ($47,408 + $13,897). Transport and shipping costs were taken from service provider quotes in Manitoba and ambulance costs from Manitoba Health, with the rate of acute returns to Winnipeg assumed to be 11% of all trips from a random sample of charts reviewed from patients in 9 of Manitoba's LCDUs (Ferguson T.W., Zacharias J., Walker S.R., et al. An Economic Assessment Model of Rural and Remote Satellite Hemodialysis Units. Pending Revisions). The cost of

patients who relocate to Winnipeg for regular dialysis using in-centre HD was taken from the same Canadian microcosting study and totaled $74,590 annually[69]. For the cost of SHD, we have performed a separate retrospective costing study quantifying the expenses of providing dialysis in Manitoba's LCDUs (Ferguson T.W., Zacharias J., Walker S.R., et al. An Economic Assessment Model of Rural and Remote Satellite Hemodialysis Units. Pending Revisions), from which we created a distribution of costs based on the proportion of patients receiving treatment across Manitoba's 16 available SHD units, with an expected value of $130,711 per-patient, per year (Table 7). The cost of receiving a transplant was taken as $94,987 in the first year and $39,942 in the following from a previously published Canadian study evaluating screening for CKD and a study evaluating the costs and benefits of renal transplantation[75, 98]. A detailed overview of the calculation of the weighted cost of dialysis is provided in Appendix 1.

The cost of treatment for CKD assumed that all patients with any elevated risk of progression (albuminuria > 30 mg/g and/or eGFR < 60ml/min per 1.73m^2) would be offered treatment with antihypertensives (ACEI or ARB) and that patients with stage 3 or higher CKD would receive increased care including specialist visits with nephrology when indicated, urine studies, hematology and serology, and the chance of a renal biopsy or renal ultrasonography. Additionally, patients with progressively worsening CKD would have a chance of receiving erythropoietin stimulating agents for treatment of anemia, and enrollment in a multidisciplinary CKD clinic in some cases. This costing was based on the CKD treatment structure in a previous Canadian CKD screening study by stage of CKD defined using eGFR[98]. Weighted to the KDIGO risk classifications of the screened FINISHED population, there was no assumed incremental cost for individuals identified as being of very low risk of progressive CKD (green in the KDIGO staging system). For individuals of low risk (yellow in the KDIGO staging system) the

average incremental annual cost was estimated to be $287, for those of intermediate risk (orange) the average incremental annual cost was estimated to be $545, and for those of high risk (red) the average incremental annual cost was estimated to be $2,291 when screened. Other than the additional cost of ACEIs in patients with albuminuria in those with CKD stages 1 and 2, the incremental health care cost of early stage CKD was considered to be $0[130].

An overview of cost inputs is provided in Table 8.

3.6 Valuing Health Benefits

All health benefits were presented using QALYs gained. Utilities were estimated from a review of the available literature for healthy individuals, patients with CKD, patients surviving with a transplant, and patients on dialysis. Reported using the time trade-off method, utility values were found to be 0.90 for patients with eGFR > 60 ml/min per 1.73m^2 and no albuminuria, 0.85 for patients with CKD, and 0.72 for patients on dialysis[67]. Since there is no conclusive randomized trial evidence comparing the differences in quality of life between individuals on PD and in-centre HD, and few patients living in the communities where screening was undertaken received HHD, we assumed equivalent utility estimates for all dialysis modalities[74, 131]. We assumed no difference in quality of life for undiagnosed and diagnosed CKD as per convention, since the addition of antihypertensive therapy has been suggested to have no statistically significant impact on quality of life[98, 132]. For patients surviving with a transplant, the utility value was assumed to be 0.816 using the time trade-off method from a previously published study on the cost and benefits of renal transplantation, as well as having been conventionally used in other CKD screening studies[75, 98]. The values of health benefits are summarized in Table 8.

3.7 One-Way Sensitivity Analyses

We performed one-way sensitivity analysis on model variables based on thresholds from previous cost-effectiveness analyses[73, 98]. The initial CKD risk strata prevalence (low, intermediate, high – yellow, orange, red on the KDIGO heat map) were varied +/- 50%. Treatment adherence was evaluated if increased to 100% or decreased to 50%. The risk of progression between any health state and kidney failure was varied +/- 50%. Relative risk reduction for both progression and all-cause mortality afforded by antihypertensive treatment in patients with macroalbuminuria was also varied +/- 50%. Utility values were varied across plausible ranges, from 0.75 to 0.90 for people with CKD, and 0.60 to 0.85 for people on dialysis. Costs of treatment for each risk strata and the cost of dialysis were varied at a range of +/- 50%. The cost of screening was evaluated when decreased 50%, and increased to the maximum possible threshold of $683.25 (Baseline $590), which included all costs spent during the FINISHED project including those that would not be routinely expensed from the perspective of the health care spender. Transplantation rates, the relative risk of transplantation, cost of transplantation, utility of living with a transplant, mortality risk in transplant patients, and the pre-emptive transplant rate were also varied across plausible ranges. Finally, we varied the annual chance of incidental presentation to primary care from 2.5% to 10% (Baseline 5%). Sensitivity analysis was performed on discount rates using values of 0% and 3%[116].

3.8 Scenario Analyses

Due to statistically significant differences in the overall risk profile of road accessible and road inaccessible communities, including a higher prevalence of progressive CKD, increased levels of uncontrolled blood sugar, and increased risk of progression to kidney failure (Table 2), we performed a sensitivity analyses on the baseline estimates by running the model for both air accessible and road accessible community subsets. Communities accessible by air experienced a

significantly higher burden of CKD, with 26.98% of those screened with low risk CKD, 7.46% of those screened with intermediate risk CKD, and 1.59% of those screened with high risk CKD (Baseline 20.43%, 4.75%, and 1.49% respectively). In addition, the expected cost of dialysis in air access communities for patients who receive care in satellite dialysis units was $158,506 per patient based on the available distribution of patients receiving satellite treatment in the eKHR (Baseline $130,711). Accordingly, the cost of transportation for returns to tertiary care centres in Winnipeg for care not available in remote communities was much higher in air access communities, at $27,530 per patient (Baseline $13,897). The prevalence of macroalbuminuria in the intermediate and high CKD risk categories was also elevated in air access communities, coming in at 81% in those with intermediate CKD (Baseline 81%), and 90% in those with high risk CKD (Baseline 75%). Just as well, these numbers varied in road accessible communities. The cost of SHD was expected to be $90,563 per patient in these communities based on the patient distribution (Baseline $130,711), with transportation and shipping costs substantially lower at $1375 per patient (Baseline $13,897). The prevalence of elevated risk CKD was also lower, with 14.7% of those screened with low risk CKD, 2.4% with intermediate risk CKD, and 1.4% with high risk CKD (Baseline 20.43%, 4.75%, and 1.49% respectively). The prevalence of macroalbuminuria in the intermediate and high CKD risk categories was lower in road accessible communities, coming in at 82% in those with intermediate CKD (Baseline 81%), and 60% in those with high risk CKD (Baseline 75%).

The threshold for relative risk reduction afforded by treatment was also varied. To test the robustness of the model to treatment effectiveness and due to the arbitrary discrete cut-off in urine ACR for treatment effectiveness, we extended the risk threshold for which treatment was effective from macroalbuminuria in the baseline (urine ACR > 300 mg/g) to microalbuminuria

(urine ACR > 30 mg/g). Recent research in indigenous populations with type 2 diabetes has demonstrated a potential reduction in disease progression even in patients with microalbuminuria (ACR 30 – 300 mg/g) and not only in those with overt proteinuria[133]. We also considered the impact of dialysis modality distributions on our results to consider the impact of increasing home modality uptake. In the screening arm, we considered increasing the prevalence of home modalities (PD and HHD) by 25, 50, and 100% through earlier identification and nephrology intervention.

4. Chapter 4: Results

4.1 Baseline Findings

In Manitoba's rural and remote First Nations communities, a strategy of screening for CKD by both eGFR and albuminuria was associated with a per-person cost of $14,172 and an effectiveness of 13.0006 QALYs. The usual care scenario was associated with a per-person cost of $13,322 and an effectiveness of 12.9752 QALYs. The incremental cost between the two alternatives was $850 and incremental gain of QALYs totaled 0.0254, resulting in an ICER of $33,500/QALY. These results are outlined in Table 9. Model validity was evaluated by constructing life expectancy tables. In the usual care arm life expectancy at age 45 was an additional 28.95 years, whereas the screening arm afforded an additional life expectancy at age 45 of 29.03 years. Detailed life tables for both the screening and usual care arms are provided in Tables 10 and 11.

4.2 One-Way Sensitivity Analyses

One-way sensitivity analysis of transition probabilities and modifiers showed some moderate variability in results. Increasing the initial risk strata prevalence (baseline 20.4% low, 4.8% intermediate, and 1.5% high risk of progression) by 50% would decrease the ICER to $25,760/QALY. A decrease in initial risk strata prevalence of 50% would result in an ICER of $56,720/QALY. Increasing the treatment adherence assumed in the model to 100% (baseline 75%) resulted in a drop of the ICER to $17,090. A decrease of adherence to 50% resulted in an ICER of $66,320/QALY. Increase of the risk of progression from CKD to kidney failure by 50% resulted in a decrease of the ICER to $19,070/QALY, whereas a 50% decrease produced an ICER of $52,970/QALY. Treatment effectiveness was also considered, with an increase in

ACEI/ARB therapy effectiveness with respect to mortality by 50% resulting in an ICER of $26,720/QALY, and an increase of ACEI/ARB effectiveness with respect to progression by 50% resulted in an ICER of $11,800/QALY. Reducing the effectiveness of ACEI/ARB therapy by 50% with respect to mortality resulted in an ICER of $45,760/QALY and reducing effectiveness of ACEI/ARB therapy by 50% with respect to progression resulted in an ICER of $66,660/QALY. Finally, we considered the chance of incidental contact with the health system resulting in CKD screening. Increasing this rate to 10% per person, per year, (baseline 5%) resulted in an increase in the reported ICER to $45,060/QALY, and decreasing the rate to 2.5% per person, per year resulted in a decrease to the reported ICER to $11,820/QALY. The results of this one-way sensitivity analyses are presented in Table 12.

Modification of cost and utility parameters were also considered in one-way sensitivity analysis. Utility values were robust when varied over a plausible range. Increasing the utility value associated with the CKD state (low, intermediate, and high risk) to 0.90 (baseline 0.85) resulted in a change of the ICER to $31,380/QALY. Reduction of the utility value to 0.75 resulted in a change of the ICER to $38,750/QALY. Increasing the utility value associated with dialysis to 0.85 (baseline 0.72) resulted in an increase of the ICER to $34,880/QALY. Reducing the utility value associated with dialysis to 0.60 decreased the reported ICER to $32,320/QALY. Varying cost inputs had more of a substantial impact on results. An increase of 50% in the assumed cost of dialysis resulted in a reported ICER of $19,340/QALY, whereas reducing the cost of dialysis by 50% resulted in a reported ICER of $47,660/QALY. Increasing treatment costs associated with CKD by 50% increased the ICER to $55,180/QALY and reducing them by 50% resulted in a reported ICER of $21,890/QALY. When considering the entire potential pool of available funds for the FINISHED project, including research and dissemination overhead, we reached a

total screening cost of $683 (baseline $590), which resulted in an ICER of $37,200/QALY. Reducing the cost of screening from baseline by 50% decreased the reported ICER to $21,890/QALY. Using a discount rate of 3% resulted in an ICER of $22,300/QALY and using a discount rate of 0% resulted in an ICER of $10,490/QALY. The results of this one-way sensitivity analyses are presented in Table 12.

Likely due to the relatively low percentage of individuals who transition to transplantation in the kidney failure population, in particular the First Nations kidney failure population, the baseline model showed a robust ICER when considering changes in transplant related model parameters. The cost of transplant, when varied from 0$ to $200,000 in the first year varied the ICER between roughly $22,000/QALY and $36,000/QALY and was the most influential transplant-related model variable. Utility of living with a transplant, relative risk of transplant in First Nations, annual transplant mortality, the annual transplant rate on dialysis, and the pre-emptive transplant rate all changed the ICER between $30,000/QALY and $35,000/QALY even when varied to estimates that are likely implausible to observe in reality. This sensitivity analysis is detailed in Figure 5.

A detailed tornado plot of influential model drivers considered in one-way sensitivity analyses is presented in Figure 6.

4.3 Comparison of Road Access and Air Access Communities

Due to the increased costs of dialysis therapy attributable to transportation, capital costs, and extra nursing expenses, an increased prevalence of progressive CKD by both KDIGO classification category and total overall proteinuria, the incremental cost of screening in air access communities totaled $611 with a gain of 0.0378 QALYs per patient, at a cost per QALY

of $16,180. Conversely, due to a lower burden of CKD and lower SHD costs in road accessible communities, the model demonstrated an incremental cost of $973 with an associated incremental effectiveness of 0.0152 QALYs per patient, at a cost per QALY of $63,870 with the screening strategy. These results are also outlined in Table 9.

4.4 Scenario Analyses

If the benefits of treatment to both progression and mortality were extended to those with microalbuminuria as well as macroalbuminuria, screening for CKD was associated with an incremental cost of $176 and incremental effectiveness of 0.0657 QALYs in the entire FINISHED population, resulting in an ICER of $2,680/QALY. In communities accessed primarily by air, screening was associated with incremental savings of $360 and incremental effectiveness of 0.0903 QALYs and was the dominant treatment choice. In road accessible communities screening was associated with an incremental cost of $556 and an incremental effectiveness of 0.0469 QALYs, resulting in an ICER of $11,870/QALY.

If earlier detection of kidney disease is able to allow for a 25% increase in home dialysis modality uptake (PD and HHD), the incremental cost of screening would be $349 and the incremental effectiveness 0.0254 QALYs (ICER $13,760/QALY). Increasing home modality uptake by 50% resulted in an incremental savings of $218 and incremental effectiveness of 0.0254 QALYs and was dominant. Increasing home modality uptake by 100% resulted in an incremental savings of $1,170 and incremental effectiveness of 0.0254 QALYs and was also dominant.

A summary of scenario analyses is provided in Table 13.

Chapter 5: Discussion

5.1 Summary of Findings

Our cost-utility model found that a screening initiative for CKD in comparison to no screening with allowance for incidental case finding (usual care) in Manitoba's rural and remote First Nations is cost-effective (ICER $33,500/QALY). Furthermore, in the most remote communities accessible primarily through air travel, the reported ICER was reduced to $16,180/QALY. Targeted screening in less remote, road accessible communities was less favourable but still had a reasonably low ICER at $63,870/QALY. The most influential model drivers were the cost of dialysis, effectiveness of treatment with respect to reducing progression to kidney failure, adherence to treatment, the incremental cost of managing detected CKD patients, the baseline rates of progression to kidney failure, and the cost of screening. These model drivers, when varied over a plausible range in one-way sensitivity analyses, despite showing the largest changes in the reported ICER, still demonstrated robust results and did not produce a reported ICER above $70,000/QALY in the baseline scenario (Figure 6). These findings suggest that CKD screening in this high risk indigenous group with low access to health care and high costs of treatment would likely be cost-effective.

5.2 Comparison with Previous Studies

We found our model to be comparable to previous studies that examined the cost-effectiveness of screening in high risk populations: those with diabetes and hypertension[72, 95, 97-101]. This is likely driven by the high rate of diabetes in the First Nations populations of Manitoba[26], contributing to an excess burden of diabetic nephropathy and high rates of overt proteinuria. Our baseline prevalence in the screened cohort demonstrated 20.43% of the population as being low

risk of kidney failure, 4.75% being classified as intermediate risk, and 1.49% classified as high risk with a mean adult population age of 45. These risk categories had been previously broken down in the general population, with 9.2% of the general population demonstrating low risk of progressive kidney failure, 2% demonstrating intermediate risk, and 0.7% demonstrating high risk[5]. The prevalence of any kidney damage was over 2-fold higher in the FINISHED population. Even more alarmingly, the prevalence of macroalbuminuria (urine ACR > 300 mg/g) was equal to 5% in the FINISHED population, which was substantially higher than the prevalence of 1.1% seen in a comparator general population, and comparable to estimates of 5.4% used for a wholly diabetic population applied in previously published CKD screening models[5, 101]. However, the higher odds of diabetic and proteinuric CKD allowed for an increased treatment effectiveness potential with ACEI and ARB therapy, and subsequently improved the estimated cost-effectiveness of the screening initiative, with previous general population screening models using eGFR alone demonstrating a lack of cost-effectiveness when identifying patients without determination of proteinuria despite having a low eGFR[98].

5.3 Cost of Screening

The per-patient cost of screening was also an influential driver in our cost-effectiveness model. As previously mentioned, a reduction in cost of 50% per patient screened would result in a reduction of the reported ICER from $33,500/QALY to $21,890/QALY. Operational inefficiencies at the start of the screening program resulted in increased costs for human resources and transportation, many of which were resolved or improved upon as the program progressed. Continued screening would likely experience lower average per-patient screening costs. In addition, many of the costs revolved around establishing protocols and screening procedures would be avoided in continued or repeated screening scenarios as operational

efficiencies are established. Moreover, if screening is able to be introduced as part of routine care in clinics within communities these costs could be substantially improved without requiring mobile assessment clinics to travel, often experiencing high costs related to air transport for staff and shipping equipment. Total screening costs ranged from $85 - $158 in other studies that evaluated primary CKD screening when extra transportation and staffing costs did not require consideration, substantially lower than the $590 per-patient assumed in our model[104]. As such, integration of screening into routine clinical practice could further improve cost-effectiveness outcomes.

5.4 Access to Care and Incidental Screening

The rate at which the health care system manages to identify patients with CKD at baseline is an important factor in considering the cost-effectiveness of any screening initiative. Incidental case finding was assumed to be 5% annually using a previously published Canadian study that considered general population and diabetic population screening for CKD using rates of presentation to medical care from the Alberta Kidney Disease Network[98]. There are potential limitations to using this figure that include the reduced access to primary care and specialist care in Manitoba's First Nations communities[27, 134], as well as the difference in rates of lower stage (Stages 1 and 2) CKD with macroalbuminuria in the FINISHED screened population. Accordingly, any reduction in the assumed rate of incidental case finding under the usual care scenario results in a reduction of the ICER. Future research linking the individuals in the FINISHED cohort to databases available through Manitoba Health would allow for a more detailed evaluation of health care use patterns in these individuals, which due to the remote nature of many of the communities may have a lower incidental presentation rate for CKD screening than the Canadian general population.

5.5 Risk Prediction, Early Identification, and Clinical Care Planning

The classification of patients within the KDIGO risk classification grid can be further improved with the application of readily available risk prediction tools that have been found to have a improved diagnostic accuracy to referral or eGFR alone (area under the receiver operating characteristic curve (AUROC) = 0.9 for the KFRE compared with AUROC = 0.78 for corresponding eGFR cut-offs) (Whitlock, R. H., Komenda, P. Hingwala, J., et al. Validation of the Kidney Failure Risk Equation in Manitoba. Manuscript in Progress). This equation uses lab values that are routinely collected, namely age, sex, urine ACR, and eGFR[117]. Tools such as this may potentially contribute to a more favourable cost-effectiveness outlook when patients are able to be appropriate assigned to more costly nephrology interventions and multidisciplinary CKD clinics, with low risk patients being referred to a primary care practitioner. For example, A 40 year old male patient with an eGFR of 45 ml/min per 1.73m^2 and urine ACR of 30 mg/g would have an estimated kidney failure risk of 20.2% over five years. A patient with the same lab characteristics aged 85 would have an estimated 5-year risk of kidney failure totaling 8.8%[117, 135]. The recommended treatment path for these two patients would differ significantly, with the younger patient likely requiring specialist intervention, and the elderly patient likely reaching a clinical endpoint outside of renal failure due to the competing risk of all-cause mortality[20]. One-way sensitivity analysis demonstrated that reducing the costs of CKD treatment by 50% resulted in a reduction of the reported ICER to $11,820/QALY (Baseline $33,500).

Each patient in the FINISHED cohort was assigned a percentage and category of kidney failure risk based on this algorithm (Table 2). Likely due to the younger age distribution of those screened in comparison to a general, primarily Caucasian population, there was a total burden of any kidney failure risk of 34% across the entire cohort (23.4% in road accessible and 46.1% in

air accessible communities), whereas the KDIGO risk classification system found 26.7% having kidney damage in the entire cohort based on eGFR and urine ACR alone (18.4% in road accessible and 36% in air accessible communities). As such, more intensive nephrology interventions may be considered in younger individuals who have a lower competing risk of all-cause mortality which has cost implications that were not captured in this analysis.

When screening, a 2-fold prevalence of CKD with a high risk of progression was found (red on the KDIGO heat map), which includes individuals that have up to a 9.1% annual chance of kidney failure, unadjusted for age[5]. There are several benefits to the early identification of these individuals that may require further evaluation in future research. Namely, when these patients are poorly prepared for the transition to kidney failure, there are worse clinical outcomes. These include higher hospitalization rates, lower chance of arteriovenous fistula preparation, less home modality uptake, and overall increased mortality[136-138]. For example, patients who progress to kidney failure requiring hemodialysis experience costs for vascular access care that are nearly fivefold higher in individuals who begin with a central venous catheter or synthetic graft as opposed to patients who are able to be prepared pre-dialysis with an arteriovenous fistula[12].

Previous screening models were often robust to changes of the cost of dialysis in sensitivity analyses[104]. Our model, by contrast, was more sensitive due to the high number of patients who receive treatment at costly remote SHD units. As such, if there is an increase in home modality uptake as a result of earlier identification in place of facility based hemodialysis crash starts, early intervention would appear more cost-effective. A previously published meta-analyses of 14 studies found that patients who were referred earlier to a nephrologist had a 2-fold chance of being selected for home peritoneal dialysis (OR 2.1 95% CI 1.9-2.3)[139] and suggests that early intervention may offer this benefit. Our scenario analysis showed that with improvements in

home modality uptake as a result of early identification that screening may become a dominant treatment strategy.

Although our model only evaluated the addition of antihypertensive therapy (ACEIs and ARBs), there are other potential benefits to the early identification and treatment of CKD. For example, recommendations exist prescribing the use of statins to improve cardiovascular and all-cause mortality in CKD patients. One study that pooled the results of three randomized controlled trials of the drug pravastatin in individuals with moderate CKD (stage 3 as defined by eGFR 30 – 59.99 ml/min per 1.73m^2) found an overall reduction in cardiovascular events of 23% and a reduction in all-cause mortality of 14%[140]. The additional costs of incremental pravastatin therapy would also need to be considered in any future economic evaluation, and we are unaware of baseline statin use in the FINISHED population. The implications of this were considered in a previous Canadian CKD screening study that performed a sensitivity analysis including the addition of statins as well as angiotensin blockade and found that the ICER ratio decreased from $104,900/QALY at baseline for screening in the general population to $53,700/QALY[98].

5.6 Generalizability of Findings

These findings may also help inform health policy in other high risk groups and indigenous populations. As previously mentioned, an existing cost study has found screening in African Americans to be cost-effective[103]. African Americans have a rate of CKD that is over 2.5 fold higher than the general population[141], similar to rates experienced in the FINISHED screening cohort. Several other ethnic groups have demonstrated an elevated burden of diabetes and CKD. This includes the Pima Indians of Arizona who have the world's highest incidence of non-insulin dependent diabetes and have a rate of kidney failure that is over twenty times that of the general

population[142, 143]. There is also an elevated burden of kidney disease in the United States Hispanic population, showing nearly a 2-fold increased risk of end stage kidney failure[144]. Additionally, elevated prevalence of CKD has also been seen in Australian aborigines[145], and Navajo and Zuni Indians in the United States[43, 44]. Evaluation of the cost-effectiveness of screening initiatives in these high risk ethnic groups warrants consideration in future research and findings from the FINISHED project may indicate investment in other screening initiatives that target similar populations.

There are also implications for care provided in rural and remote areas. Previously research has shown that patients with non-dialysis dependent CKD who live more than 50km for the nearest nephrologist experience reduced rates of care. These patients were less likely to visit a nephrologist, be involved in multidisciplinary CKD clinics, or received appropriate laboratory testing. In addition, they experienced increased mortality and hospitalizations[134]. These findings are not unique to the CKD population. Rural and remote communities often demonstrate a shortage of physicians and other health care professionals[87, 146]. In addition, some health care procedures are more expensive in rural and remote settings, or are not available and require a patient to relocate for adequate treatment. We observed increasing cost-effectiveness as those screened became more remote in our model, influenced not only by worsening health status from lack of care, but also by increasing health care expenditures.

5.7 Strengths and Limitations

This study had several strengths. Primarily, previous cost-effectiveness models focused on the measurement of either proteinuria (dipstick proteinuria or urine ACR), or eGFR in isolation[104]. Our analysis combined both measurements, performed concurrently, to assess risk of progression

to kidney failure using the two-axis KDIGO classification system[32]. This allows for a more comprehensive risk assessment and triage to appropriate clinical care. In addition, our model was the first to explore the cost-effectiveness of screening for CKD in a rural and/or remote area that has limited access to regular medical care, whereas previous studies did not focus on location, allowing us to evaluate a model not only with an elevated burden of CKD in a high risk indigenous population, but with higher overall costs of dialysis therapy in those who reach kidney failure and higher costs of per-patient screening.

There were also several limitations to our model. We applied only a single measurement of urine ACR to classify persistent albuminuria. Ideally, risk would be evaluated longitudinally with several urine ACR measurements to fully ascertain a consistent level of raised albuminuria. However, the study used to classify the risk of mortality by albuminuria and eGFR category used only a single ACR measurement as well[5], as did the retrospective database analysis of Alberta Kidney Disease Network First Nations patients used to determine progression and regression transition probabilities, and as such, progression and mortality rates relate to individuals with only a single ACR measurement.

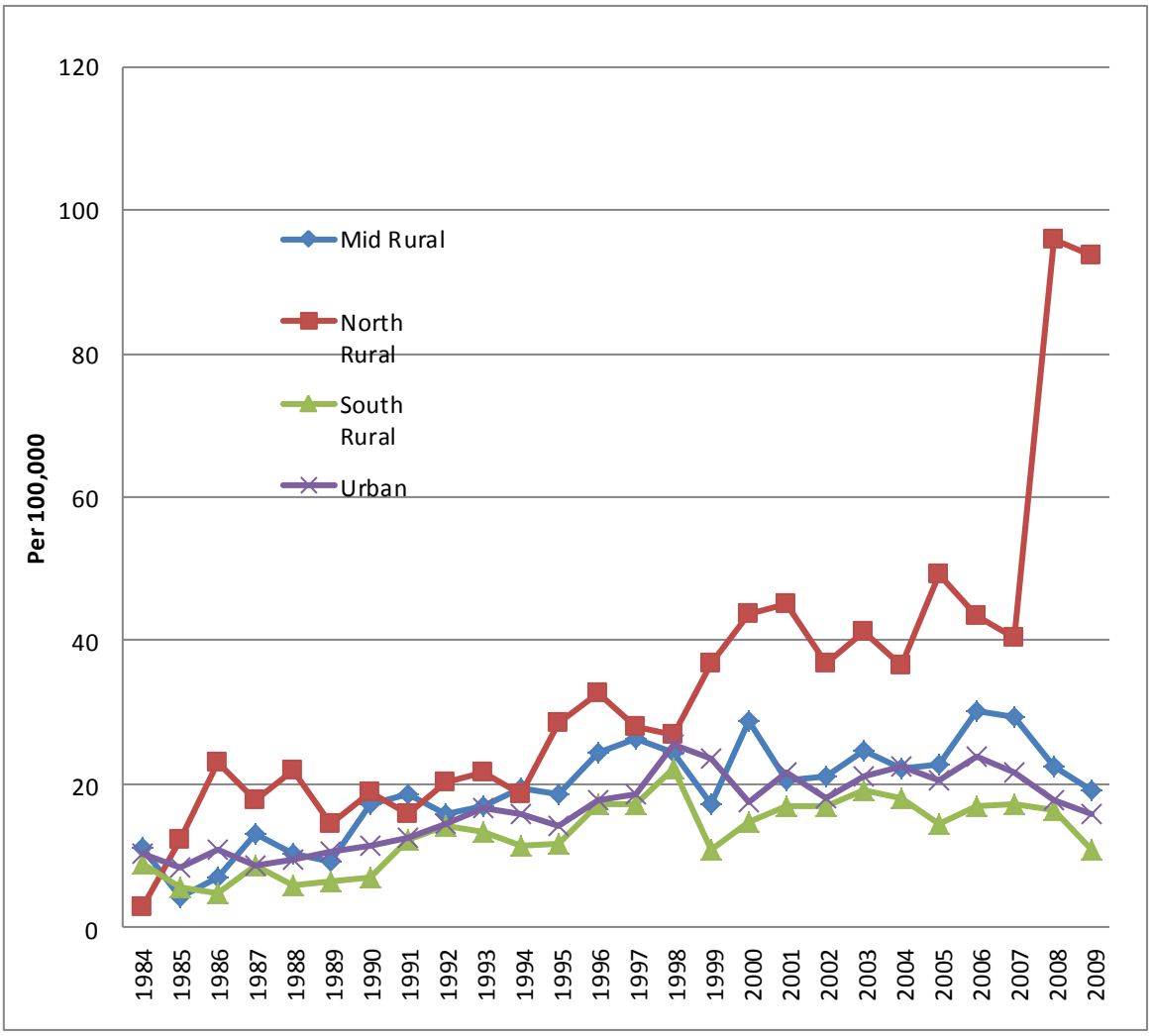
A further limitation is the lack of randomized controlled trial evidence that explores screening for CKD. A previous systematic review explored the effectiveness of early stage CKD screening but found uncertain benefit with respect to clinical end points (kidney failure and morality) in those with early stage CKD; however, agreed that evidence was strong for the adoption of ACEIs and ARBs in reducing mortality and progression[93]. Despite being the gold standard of treatment efficacy, a RCT of screening for CKD would be particularly costly and require many years to perform. As such, there would be a cost of inaction if this is used as the only form of policy discourse.

Lastly, the model was unable to be extensively validated using longitudinal clinical outcomes from a First Nations population in Manitoba due to a lack of available data. However, we applied real progression rates from the Alberta Kidney Disease Network, which has been used in previous cost-effectiveness analysis for CKD screening and was found to be related ($R^2 > 0.97$) to both kidney failure and mortality at the five year time point[98]. Furthermore, to verify mortality rates in our model, we computed life expectancy rates and life tables for both the usual care and screening arms. We found that the FINISHED population (60.7% female) had a remaining life expectancy of nearly 28.95 years at age 45 (Table 10), which represents a sex-weighted gap of roughly 8.5 years from the general Manitoba population[147]. This number closely relates to previous research that has shown an 8 year life expectancy gap between registered First Nations and the general Manitoba population[148].

5.8 Conclusions

In summary, we found that a targeted primary screening initiative for CKD in Manitoba's high risk rural and remote First Nations populations may be a cost-effective strategy (< $50,000/QALY). Similar to previous studies, progression rates, treatment effectiveness, and the incidence of CKD were shown to be substantial model modifiers in one-way sensitivity analyses. These findings could potentially be extended to other Canadian First Nations populations, indigenous populations who exhibit heightened risk of CKD progression, other high-risk ethnic populations, and in providing other rural and remote care. Our findings demonstrated that even those First Nations in road accessible communities that were less remote demonstrated an ICER that was likely cost-effective ($63,870/QALY). Moving towards the future, we feel that the investment required for a cluster randomized controlled trial[149] of screening for CKD in other communities to ascertain the overall efficacy of targeted screening programs may be warranted.

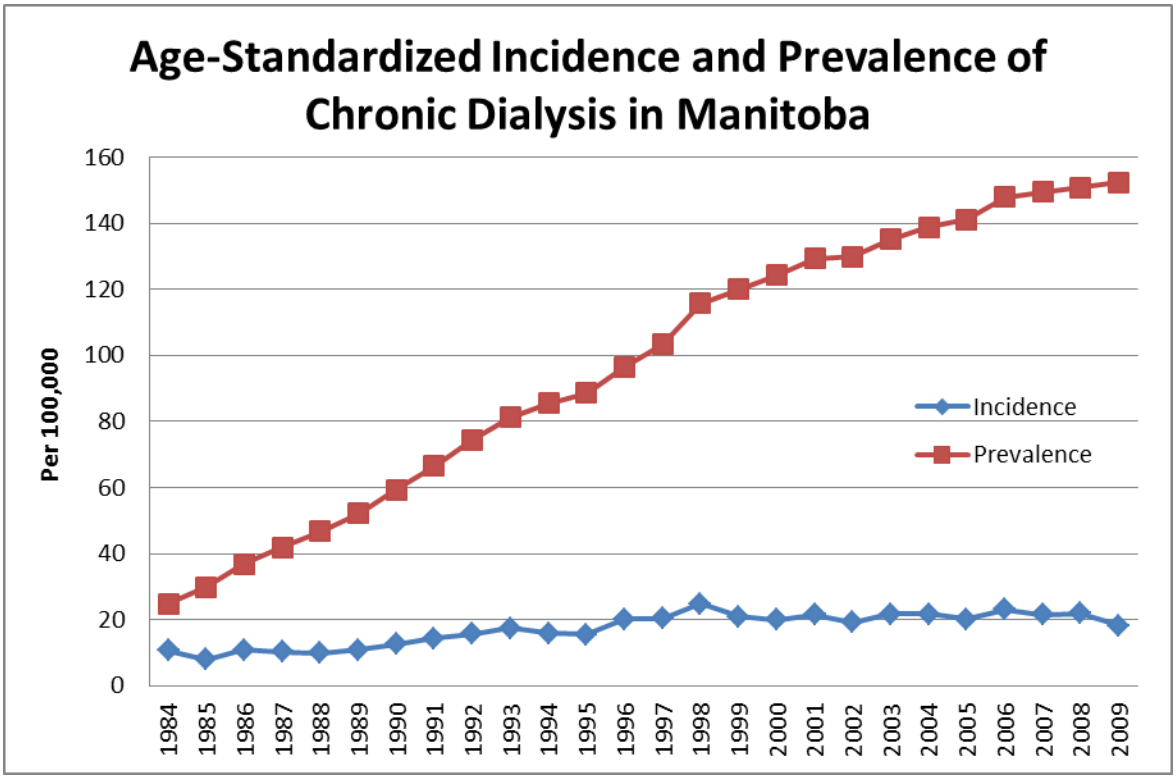
Figure 1. Incidence of Kidney Failure in Manitoba



Accelerated growth in Rural North of Manitoba

Growth rates of kidney failure in Manitoba have plateaued in the populated, urban and highly healthcare-resourced South, but are reaching epidemic proportions in remote, under-resourced, and primarily First Nations (Aboriginal) northern communities.

Figure 2. Prevalence of Chronic Dialysis in Manitoba



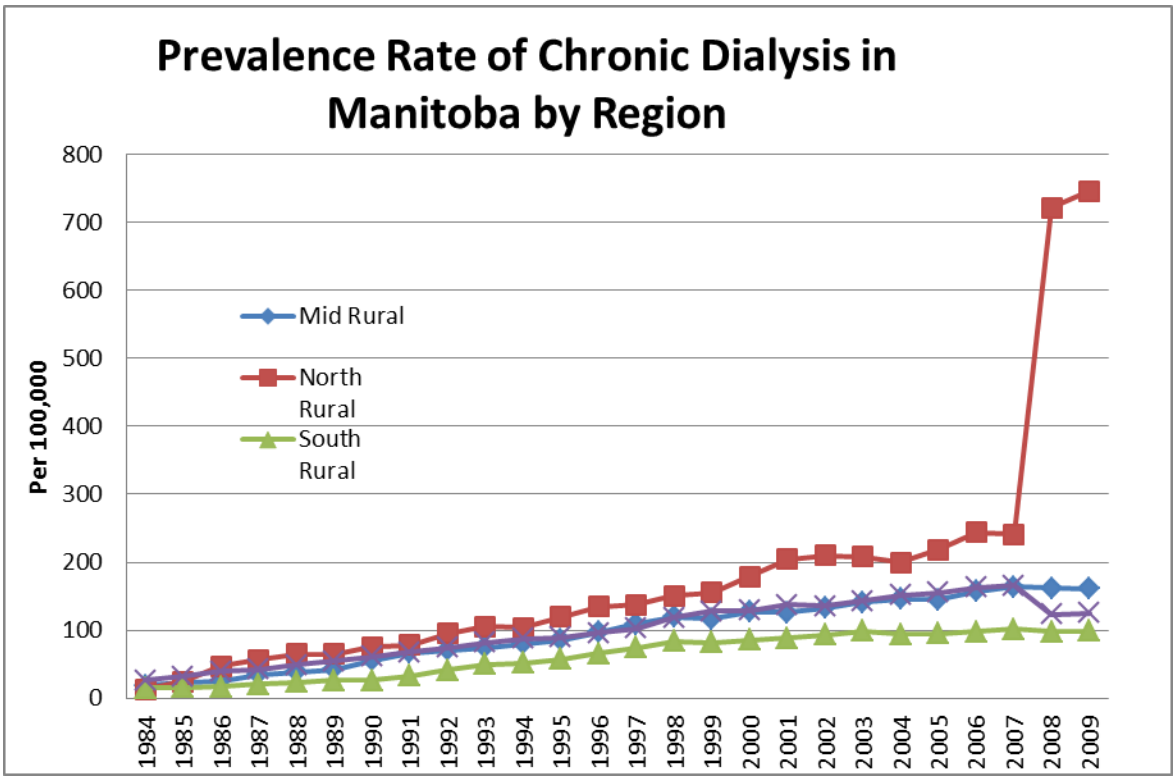


Table 1. Comparison of Chronic Kidney Disease Screening Studies

Comparison of Chronic Kidney Disease Screening Studies							
			Albuminuria				Kidney Function
Study	**Population**	**n**	**Micro Definition**	**Micro (%)**	**Macro Definition**	**Macro (%)**	**eGFR < 60 ml/min per m^2 (%)**
NHANES (1988-94)[33]	US, Age 20+	15488	ACR 30 - 299 mg/g	7.1%	ACR > 299 mg/g	1.1%	5.6%
NHANES (1999-04)[33]	US, Age 20+	13233	ACR 30 - 299 mg/g	8.2%	ACR > 299 mg/g	1.3%	8.1%
PREVEND[34]	Netherlands, Aged 28-75	8592	UAC 20 - 200 mg/L	7.2%	UAC > 200 mg/L	0.7%	5.5%
KEEP US[36,37]	US, Age 18+, high-risk	22000+	26% Albuminuria defined as UAC > 20mg/L				N/A
KEEP Japan[39]	Japan, Age 18+, high-risk	1065	23.6% Albuminuria defined as ACR > 30mg/g				7.0%
KEEP Mexico[38]	Mexico, Age 18+, high-risk	1519	19.0% Albuminuria defined as ACR > 30 mg/g				7.0%
KEY Australia[35]	Australian, Age 18+, high-risk	402	ACR > 30 mg/g	8.0%	N/A	N/A	10.0%
SLICK Study[40,41]	Canada, First Nations, Age 18+	743	ACR > 2.74 mg/mmol (Female) ACR > 1.94 mg/mmol (Male)	26.0%	Protein Dipstick	13.0%	N/A
Zacharias et al.[18]	Manitoba, First Nations (Ojibway), Age 18+	483	ACR > 2.8 mg/mmol (Female) ACR > 2.0 mg/mmol (Male)	15%	ACR > 30 mg/mmol	5%	N/A
Zuni Kidney Project[42,43]	US, Zuni Indians, Age 5+	1483	ACR 30 – 299 mg/g	15%	ACR > 300 mg/g	4.3%	N/A

Hoy et al. (1996)[44]	US, Navajo Indians, Age 18+	366 (nondiabetic) 400 (diabetic)	ACR 30 – 299 mg/g	14.6% (nondiabetic) 36.1% (diabetic)	ACR > 300 mg/g	2.0% (nondiabetic) 17.9% (diabetic)	N/A
Hoy et al. (1998)[46]	Australian Aboriginals, Age 18+	487	ACR 30 – 299 mg/g	26%	ACR > 300 mg/g	24%	N/A
Nelson et al. (1989)[45]	US, Pima Indians, Age 15+	2728	ACR 30 – 299 mg/g	25.8% (type 2 diabetics) 14.7% (impaired glucose tolerance) 6.7% (normal glucose tolerance)	ACR > 300 mg/g	20.8% (type 2 diabetics) 2.0% (impaired glucose tolerance) 1.2% (normal glucose tolerance)	N/A
FINISHED	**Canada, First Nations, Age 18+**	**1346**	**ACR 30 - 299 mg/g**	**19.5%**	**ACR > 299 mg/g**	**5.0%**	**4.2%**
FINISHED (road)	**Canada, First Nations, Age 18+**	**716**	**ACR 30 - 299 mg/g**	**13.7%**	**ACR > 299 mg/g**	**2.8%**	**3.6%**
FINISHED (air)	**Canada, First Nations, Age 18+**	**630**	**ACR 30 - 299 mg/g**	**26.0%**	**ACR > 299 mg/g**	**7.5%**	**4.8%**

High-risk defined as those with diabetes, hypertension, or a family history of diabetes, hypertension, and/or kidney disease. ACR is albumin-to-creatinine ratio, UAC is urinary albumin clearance, UAE is urinary albumin excretion, eGFR is estimated glomerular filtration rate.

Table 2. Demographic Characteristics of Screened Cohort

Table 2. Demographic Characteristics of Screened Cohort					
		Total Cohort	Road	Air	*p-value*
		n = 1346	n = 630	n = 716	
Age (years)		44.9 (± 14.5)	45.2 (± 14.4)	44.6 (± 14.6)	*0.4731*
Sex (% female)		60.7%	59.3%	62.2%	*0.2737*
HgbA1C (%)		5.8 (5.4 -7.4)	5.6 (5.3 – 7.0)	6.0 (5.4 – 8.0)	*<0.01*
eGFR (ml/min per 1.73 m2)	≥ 60	95.8%	96.4%	95.2%	*0.891*
	45 - 59	2.5%	2.1%	2.9%	
	30 - 44	1.3%	1.1%	1.4%	
	15 - 29	0.3%	0.3%	0.3%	
	< 15	0.2%	0.1%	0.2%	
Urine ACR (mg/g)		12.4 (5.3 - 28.3)	8.8 (4.4 - 16.8)	16.8 (7.1 - 45.1)	*<0.01*
Kidney Failure Risk	No Risk	66.0%	76.6%	53.9%	*<0.01*
	Low Risk	31.4%	21.6%	42.6%	
	Int. Risk	1.6%	1.0%	2.4%	
	High Risk	1.0%	0.8%	1.1%	

Continuous variables expressed as mean (± standard deviation) or median (interquartile range) for HgbA1C and Urine ACR. Categorical variables expressed as percentages.

Figure 3. Markov Simulation Model

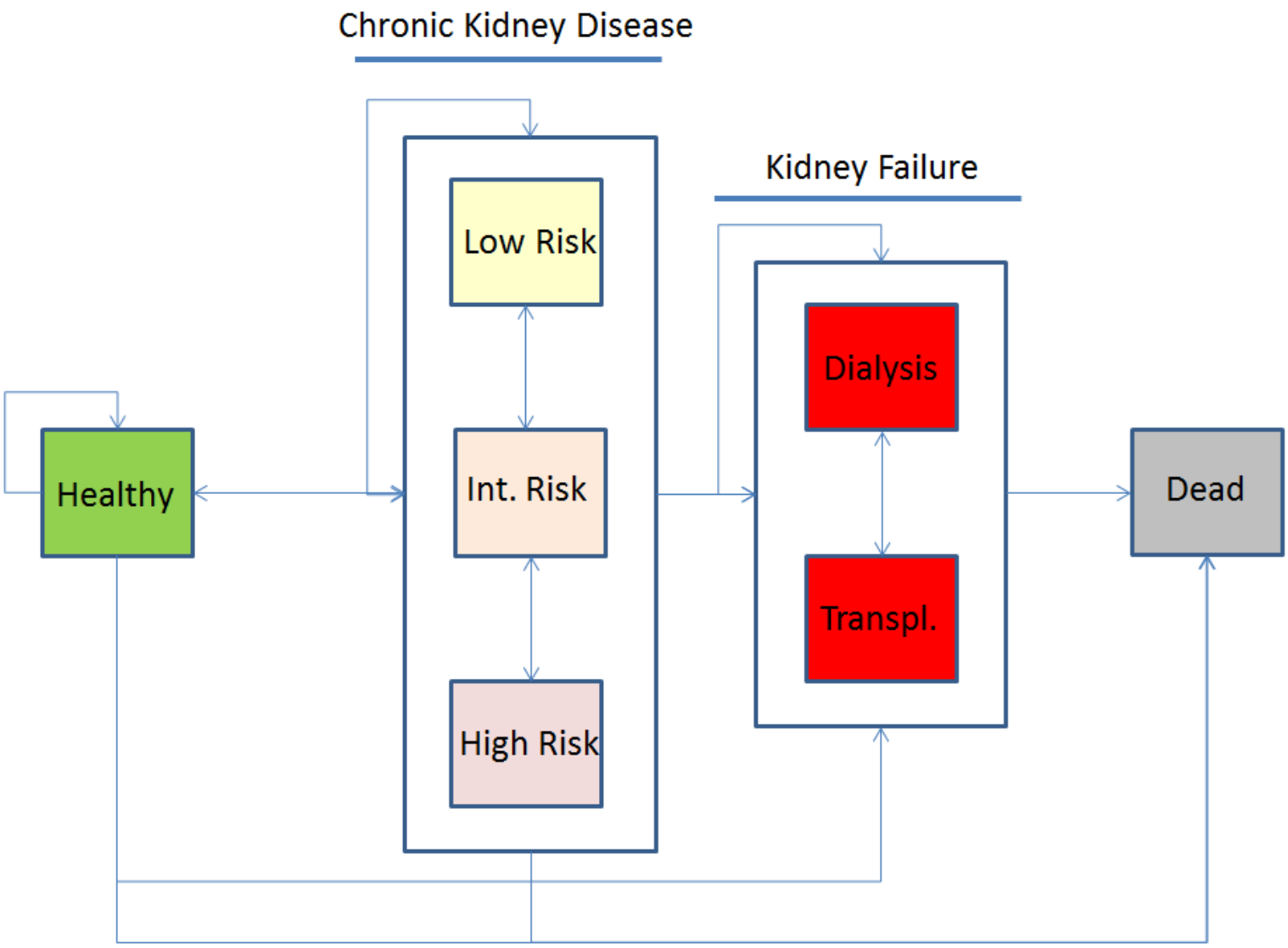


Figure 4. Initial Risk Classification of Screened Population – KDIGO Classification System[32]

Entire Screened Population – See Figure 7 for Cell Counts

			Albuminuria (mg/g)			
			A1		A2	A3
			Optimal to high-normal		High	Very high to nephrotic
			<10	10-29	30-299	>300
eGFR ml/min per 1.73m^2	G1a	>105	20.36%	17.01%	10.77%	1.86%
	G1b	90-104	10.62%	5.94%	3.79%	0.59%
	G2a	75-89	8.54%	5.50%	2.01%	0.67%
	G2b	60-74	3.49%	1.86%	2.08%	0.74%
	G3a	45-59	0.82%	0.97%	0.45%	0.22%
	G3b	30-44	0.15%	0.30%	0.37%	0.45%
	G4	15-29	0.00%	0.00%	0.00%	0.30%
	G5	<15	0.00%	0.00%	0.00%	0.15%

Air Access Communities – See Figure 7for Cell Counts

			Albuminuria (mg/g)			
			A1		A2	A3
			Optimal to high-normal		High	Very high to nephrotic
			<10	10-29	30-299	>300
eGFR ml/min per 1.73m^2	G1a	>105	16.51%	18.89%	15.56%	2.86%
	G1b	90-104	6.35%	5.71%	4.44%	0.63%
	G2a	75-89	6.67%	5.08%	2.54%	1.11%
	G2b	60-74	2.86%	1.90%	2.70%	1.43%
	G3a	45-59	0.48%	1.27%	0.63%	0.48%
	G3b	30-44	0.32%	0.48%	0.16%	0.48%
	G4	15-29	0.00%	0.00%	0.00%	0.32%
	G5	<15	0.00%	0.00%	0.00%	0.16%

Road Access Communities – See Figure 7 for Cell Counts

			Albuminuria (mg/g)			
			A1		A2	A3
			Optimal to high-normal		High	Very high to nephrotic
			<10	10-29	30-299	>300
eGFR ml/min per 1.73m^2	G1a	>105	23.74%	15.36%	6.56%	0.98%
	G1b	90-104	14.39%	6.15%	3.21%	0.56%
	G2a	75-89	10.20%	5.87%	1.54%	0.28%
	G2b	60-74	4.05%	1.82%	1.54%	0.14%
	G3a	45-59	1.12%	0.70%	0.28%	0.00%
	G3b	30-44	0.00%	0.14%	0.56%	0.42%
	G4	15-29	0.00%	0.00%	0.00%	0.28%
	G5	<15	0.00%	0.00%	0.00%	0.14%

Table 3. Chronic Kidney Disease Risk Stratum Transition Probabilities for First Nations

State Transition	Annual Transition Probability
Green → Yellow	0.011815
Green → Orange	0.002383
Green → Red	0.001004
Green → Kidney Failure	0.000154
Yellow → Orange	0.012439
Yellow → Red	0.007932
Yellow → Kidney Failure	0.001717
Yellow → Green	0.023976
Orange → Red	0.028740
Orange → Kidney Failure	0.013357
Orange → Yellow	0.015379
Orange → Green	0.005516
Red → Kidney Failure	0.017711
Red → Orange	0.003342
Red → Yellow	0.001683
Red → Green	0.001955

Yellow defined as low risk of progression to kidney failure on the KDIGO heat map; Orange intermediate risk; Red high risk. Data derived from the Alberta Kidney Disease Network (AKDN).

Table 4. Annual Mortality and Transplant Probabilities

	Annual Mortality - CKD			
Age	**Healthy**	**Low Risk**	**Int. Risk**	**High Risk**
45-49	0.0033	0.0052	0.0094	0.0130
50-54	0.0050	0.0079	0.0143	0.0197
55-59	0.0070	0.0111	0.0203	0.0279
60-64	0.0112	0.0179	0.0325	0.0448
65-69	0.0191	0.0303	0.0552	0.0761
70-74	0.0311	0.0494	0.0898	0.1237
75-79	0.0475	0.0755	0.1374	0.1892
80-84	0.0741	0.1177	0.2143	0.2952
85-89	0.1273	0.2023	0.3681	0.5070
90+	0.2479	0.3939	0.7069	0.8800
Age	**Annual Mortality - Dialysis (First Year)**			
45-55	0.0780			
55-65	0.1280			
65-75	0.1800			
75+	0.2500			
Age	**Annual Mortality - Dialysis (Year 2+)**			
45-46	0.0680			
47-54	0.0860			
55-56	0.1040			
57-64	0.1190			
65-66	0.1330			
67-74	0.1520			
75-76	0.1800			
77+	0.1940			
Age	**Transplant - Failure; Return to Dialysis**			
All	0.0400			
Age	**Transplant - Mortality**			
45-64	0.0120			
65+	0.0710			
Age	**Transplant Chance - Pre-Emptive**			
45-64	0.0194			
65-74	0.0039			
75+	0.0000			
Age	**Transplant Chance - Patient on Dialysis**			
45-64	0.0046			
65+	0.0003			

Table 5. Prevalence of Dialysis Modality Utilization in Manitoba

Modality	Proportion
Satellite Hemodialysis	47.20%
In-centre Hemodialysis	25.70%
Peritoneal Dialysis	25.70%
Home Hemodialysis	1.40%

Table 6. Model Probability Parameters

Overview of Model Probability Parameters		
	Estimate	**Reference**
Initial Risk Probability (Healthy)	0.7333	FINISHED
Initial Risk Probability (Low)	0.2043	FINISHED
Initial Risk Probability (Intermediate)	0.0475	FINISHED
Initial Risk Probability (High)	0.0149	FINISHED
Proportion of patients with macroalbuminuria (Healthy)	0	FINISHED
Proportion of patients with macroalbuminuria (Low Risk)	0	FINISHED
Proportion of patients with macroalbuminuria (Intermediate Risk)	0.81	FINISHED
Proportion of patients with macroalbuminuria (High Risk)	0.75	FINISHED
Annual Inadvertent Screening Rate	0.05	Manns et al.[98]
Treatment adherence	0.75	Boulware et al.[101]
Relative risk of receiving a transplant in First Nations	0.43	Tonelli et al.[123]
Relative risk, mortality reduction from ACEI or ARB in patients with macroalbuminuria	0.77	Hoerger et al.[95,96] Boulware et al.[101]
Relative risk, progression reduction from ACEI or ARB in patients with macroalbuminuria	0.67	Hoerger et al.[95,96] Boulware et al.[101]

Table 7. Distribution of Satellite Hemodialysis Costs

Satellite Hemodialysis Cost Distribution (All)	
Probability	**Cost**
0.164	$83,060
0.132	$86,920
0.088	$103,390
0.132	$110,900
0.022	$114,420
0.198	$138,100
0.077	$156,150
0.033	$204,640
0.154	$215,850

Satellite Hemodialysis Cost Distribution (Air Access Communities)	
Probability	**Cost**
0.184	$110,900
0.037	$114,420
0.333	$138,100
0.130	$156,150
0.056	$204,640
0.260	$215,850

Satellite Hemodialysis Cost Distribution (Road Access Communities)	
Probability	**Cost**
0.405	$83,060
0.324	$86,920
0.216	$103,390
0.055	$116,900

All costs provided in 2013 Canadian dollars.

Table 8. Model Cost and Utility Parameters

Overview of Model Cost and Utility Parameters		
Costs	**Amount**	**Reference**
Screening	$589	FINISHED
In-Centre Dialysis (Annual)	$74,590	Klarenbach et al.[69]
Peritoneal Dialysis (Annual)	$43,500	Klarenbach et al.[69]
Home Hemodialysis (Annual)	$61,300	Klarenbach et al.[69]
Transplant (First Year)	$94,987	Laupacis et al.[75]
Transplant (Year 2+)	$39,942	Laupacis et al.[75]
Annual CKD Treatment (High Risk)	$2,291	Manns et al.[98]
Annual CKD Treatment (Intermediate Risk)	$545	Manns et al.[98]
Annual CKD Treatment (Low Risk)	$287	Manns et al.[98]
Inadvertent Screening (High Risk)	$814	Manitoba Physician's Manual[129] & Provider Quote
Inadvertent Screening (Intermediate Risk)	$207	Manitoba Physician's Manual[129] & Provider Quote
Inadvertent Screening (Low Risk)	$153	Manitoba Physician's Manual[129] & Provider Quote
Inadvertent Screening (Healthy)	$107	Manitoba Physician's Manual[129] & Provider Quote
Utilities (0 - 1)		
Healthy	0.9	Gorodetskaya[67] et al.
CKD	0.85	Gorodetskaya[67] et al.
Dialysis	0.72	Gorodetskaya[67] et al.
Transplant	0.816	Laupacis[75] et al.
Discount Rate		
Costs	0.05	CADTH[116]
Utilities	0.05	CADTH[116]

Table 9. Cost-Effectiveness of Targeted Screening in the FINISHED Project

Population	Incremental Cost ($C)	Incremental QALYs	Cost/QALY
All FINISHED	850	0.0254	33,500
Air Access Communities	611	0.0378	16,180
Road Access Communities	973	0.0152	63,870

Table 10. Life Expectancy – Usual Care Arm

Age	Survivors	Deaths	Probability of Death	Probability of Survival	Years Lived	Years Remaining	**Life Expectancy**
45	1000.00	4.26	0.0043	0.9957	997.87	28951.29	**28.95**
46	995.74	4.79	0.0048	0.9952	993.35	27953.42	**28.07**
47	990.95	5.32	0.0054	0.9946	988.29	26960.07	**27.21**
48	985.63	5.85	0.0059	0.9941	982.70	25971.78	**26.35**
49	979.78	6.37	0.0065	0.9935	976.59	24989.07	**25.50**
50	973.40	6.88	0.0071	0.9929	969.96	24012.48	**24.67**
51	966.52	7.46	0.0077	0.9923	962.80	23042.52	**23.84**
52	959.07	8.02	0.0084	0.9916	955.06	22079.72	**23.02**
53	951.05	8.57	0.0090	0.9910	946.76	21124.66	**22.21**
54	942.48	9.10	0.0097	0.9903	937.93	20177.90	**21.41**
55	933.38	9.90	0.0106	0.9894	928.43	19239.97	**20.61**
56	923.48	10.93	0.0118	0.9882	918.01	18311.54	**19.83**
57	912.55	11.92	0.0131	0.9869	906.59	17393.52	**19.06**
58	900.63	12.87	0.0143	0.9857	894.20	16486.93	**18.31**
59	887.77	13.77	0.0155	0.9845	880.88	15592.73	**17.56**
60	873.99	14.63	0.0167	0.9833	866.68	14711.85	**16.83**
61	859.37	16.27	0.0189	0.9811	851.23	13845.17	**16.11**
62	843.09	17.81	0.0211	0.9789	834.19	12993.94	**15.41**
63	825.28	19.24	0.0233	0.9767	815.66	12159.76	**14.73**
64	806.04	20.54	0.0255	0.9745	795.77	11344.10	**14.07**
65	785.51	22.11	0.0281	0.9719	774.45	10548.32	**13.43**
66	763.40	23.92	0.0313	0.9687	751.44	9773.87	**12.80**
67	739.47	25.51	0.0345	0.9655	726.72	9022.43	**12.20**
68	713.96	26.86	0.0376	0.9624	700.53	8295.72	**11.62**
69	687.10	27.97	0.0407	0.9593	673.11	7595.19	**11.05**
70	659.13	28.82	0.0437	0.9563	644.72	6922.07	**10.50**
71	630.31	30.17	0.0479	0.9521	615.22	6277.35	**9.96**
72	600.14	31.16	0.0519	0.9481	584.56	5662.13	**9.43**
73	568.98	31.79	0.0559	0.9441	553.08	5077.57	**8.92**
74	537.19	32.10	0.0597	0.9403	521.14	4524.48	**8.42**
75	505.09	32.39	0.0641	0.9359	488.90	4003.34	**7.93**
76	472.71	33.23	0.0703	0.9297	456.09	3514.44	**7.43**
77	439.47	33.54	0.0763	0.9237	422.70	3058.36	**6.96**
78	405.93	33.36	0.0822	0.9178	389.25	2635.65	**6.49**
79	372.57	32.74	0.0879	0.9121	356.20	2246.41	**6.03**
80	339.82	31.75	0.0934	0.9066	323.95	1890.21	**5.56**
81	308.07	32.44	0.1053	0.8947	291.85	1566.26	**5.08**
82	275.63	32.18	0.1167	0.8833	259.54	1274.41	**4.62**
83	243.45	31.11	0.1278	0.8722	227.90	1014.87	**4.17**
84	212.34	29.40	0.1385	0.8615	197.64	786.97	**3.71**
85	182.94	27.24	0.1489	0.8511	169.32	589.34	**3.22**
86	155.70	27.11	0.1741	0.8259	142.15	420.02	**2.70**
87	128.59	25.52	0.1984	0.8016	115.84	277.87	**2.16**
88	103.08	22.87	0.2219	0.7781	91.64	162.03	**1.57**
89	80.20	19.62	0.2447	0.7553	70.39	70.39	**0.88**
90	60.58						

Table 11. Life Expectancy – Screening Arm

Age	Survivors	Deaths	Probability of Death	Probability of Survival	Years Lived	Years Remaining	**Life Expectancy**
45	1000.00	4.16	0.0042	0.9958	997.92	29028.93	**29.03**
46	995.84	4.67	0.0047	0.9953	993.51	28031.01	**28.15**
47	991.17	5.19	0.0052	0.9948	988.57	27037.50	**27.28**
48	985.98	5.71	0.0058	0.9942	983.13	26048.93	**26.42**
49	980.27	6.22	0.0063	0.9937	977.16	25065.80	**25.57**
50	974.05	6.72	0.0069	0.9931	970.69	24088.64	**24.73**
51	967.34	7.29	0.0075	0.9925	963.69	23117.95	**23.90**
52	960.05	7.85	0.0082	0.9918	956.12	22154.26	**23.08**
53	952.20	8.39	0.0088	0.9912	948.00	21198.13	**22.26**
54	943.81	8.92	0.0095	0.9905	939.35	20250.13	**21.46**
55	934.88	9.71	0.0104	0.9896	930.03	19310.78	**20.66**
56	925.17	10.74	0.0116	0.9884	919.81	18380.75	**19.87**
57	914.44	11.73	0.0128	0.9872	908.57	17460.95	**19.09**
58	902.71	12.69	0.0141	0.9859	896.36	16552.38	**18.34**
59	890.02	13.60	0.0153	0.9847	883.22	15656.01	**17.59**
60	876.42	14.47	0.0165	0.9835	869.18	14772.79	**16.86**
61	861.94	16.13	0.0187	0.9813	853.88	13903.61	**16.13**
62	845.81	17.69	0.0209	0.9791	836.97	13049.73	**15.43**
63	828.13	19.13	0.0231	0.9769	818.57	12212.76	**14.75**
64	809.00	20.45	0.0253	0.9747	798.78	11394.20	**14.08**
65	788.55	22.02	0.0279	0.9721	777.54	10595.42	**13.44**
66	766.53	23.87	0.0311	0.9689	754.60	9817.88	**12.81**
67	742.66	25.49	0.0343	0.9657	729.92	9063.28	**12.20**
68	717.17	26.87	0.0375	0.9625	703.74	8333.36	**11.62**
69	690.30	28.01	0.0406	0.9594	676.30	7629.63	**11.05**
70	662.29	28.89	0.0436	0.9564	647.85	6953.33	**10.50**
71	633.40	30.27	0.0478	0.9522	618.27	6305.48	**9.95**
72	603.13	31.29	0.0519	0.9481	587.49	5687.22	**9.43**
73	571.84	31.95	0.0559	0.9441	555.87	5099.73	**8.92**
74	539.90	32.27	0.0598	0.9402	523.76	4543.86	**8.42**
75	507.63	32.57	0.0642	0.9358	491.34	4020.10	**7.92**
76	475.06	33.43	0.0704	0.9296	458.34	3528.76	**7.43**
77	441.62	33.76	0.0764	0.9236	424.75	3070.41	**6.95**
78	407.87	33.58	0.0823	0.9177	391.08	2645.67	**6.49**
79	374.29	32.96	0.0881	0.9119	357.81	2254.59	**6.02**
80	341.33	31.96	0.0936	0.9064	325.35	1896.78	**5.56**
81	309.37	32.64	0.1055	0.8945	293.05	1571.43	**5.08**
82	276.73	32.37	0.1170	0.8830	260.54	1278.38	**4.62**
83	244.36	31.29	0.1280	0.8720	228.71	1017.83	**4.17**
84	213.07	29.56	0.1387	0.8613	198.29	789.12	**3.70**
85	183.51	27.37	0.1491	0.8509	169.83	590.83	**3.22**
86	156.14	27.22	0.1743	0.8257	142.53	421.00	**2.70**
87	128.92	25.61	0.1987	0.8013	116.11	278.47	**2.16**
88	103.31	22.95	0.2221	0.7779	91.83	162.35	**1.57**
89	80.36	19.68	0.2449	0.7551	70.52	70.52	**0.88**
90	60.68						

Table 12. One-way Sensitivity Analysis of Model Variables

Variable	Incremental Cost ($C)	Incremental QALYs	Cost/QALY
Baseline	**850**	**0.0254**	**33,500**
Initial CKD risk strata prevalence (Baseline Low = 20.4%, Intermediate = 4.8%, High = 1.5%)			
Initial CKD risk strata prevalence increased 50%	980	0.0381	25,760
Initial CKD risk strata prevalence decreased 50%	719	0.0127	56,720
Discount rate (Baseline = 5%)			
Discount rate decreased to 0%	721	0.0687	10,490
Discount rate decreased to 3%	819	0.0367	22,300
Treatment adherence (Baseline = 75%)			
Treatment adherence increased to 100%	578	0.0338	17,090
Treatment adherence decreased to 50%	1,122	0.0169	66,320
Annual risk of progression to Kidney Failure (Baseline Table 3)			
Risk of progression increased 50%	512	0.0268	19,070
Risk of progression decreased 50%	1,248	0.0236	52,970
ACEI/ARB treatment effectiveness - Progression reduction (Baseline = 33% progression reduction)			
Relative risk reduction increased 50%	368	0.0312	11,800
Relative risk reduction decreased 50%	1,322	0.0198	66,660
ACEI/ARB treatment effectiveness - Mortality reduction (Baseline = 23% mortality reduction)			
Relative risk reduction increased 50%	901	0.0337	26,720

Relative risk reduction decreased 50%	801	0.0175	45,760
Utility value associated with CKD (Baseline = 0.85)			
Utility value increased to 0.90	850	0.0271	31,380
Utility value decreased to 0.75	850	0.0219	38,750
Utility value associated with dialysis (Baseline = 0.72)			
Utility value increased to 0.85	850	0.0244	34,880
Utility value decreased to 0.60	850	0.0263	32,320
Expected cost of dialysis (Baseline = $92,900)			
Cost of dialysis increased 50%	491	0.0254	19,340
Cost of dialysis decreased 50%	1,209	0.0254	47,660
Cost of screening (Baseline = $590)			
Cost of screening includes research and dissemination overhead ($683)	944	0.0254	37,200
Cost of screening decreased 50%	555	0.0254	21,890
Average incremental CKD treatment costs - (Baseline for high risk = $2,291, intermediate risk = $545, low risk = $287)			
Incremental CKD treatment costs increased 50%	1,400	0.0254	55,180
Incremental CKD treatment costs decreased 50%	300	0.0254	11,820
Annual incidental screening rate (Baseline = 5%)			
Incidental screening rate increased to 10%/year	737	0.0164	45,060
Incidental screening rate decreased to 2.5%/year	954	0.0329	28,970

Table 13. Scenario Analyses

Variable	Incremental Cost ($C)	Incremental QALYs	Cost/QALY
Baseline	**850**	**0.0254**	**33,500**
Threshold for relative risk reduction afford by treatment extended to patients with microalbuminuria (urine ACR > 30 m/g) (Baseline urine ACR threshold of > 300 mg/g)			
All communities	176	0.0657	2,680
Air access	-360	0.0903	Dominant
Road access	556	0.0469	11,870
Increase in home modality uptake			
Increased PD and HHD use by 25%	349	0.0254	13,760
Increased PD and HHD use by 50%	-218	0.0254	Dominant
Increased PD and HHD use by 100%	-1170	0.0254	Dominant

Figure 5. Sensitivity Analysis of Transplantation Related Model Inputs

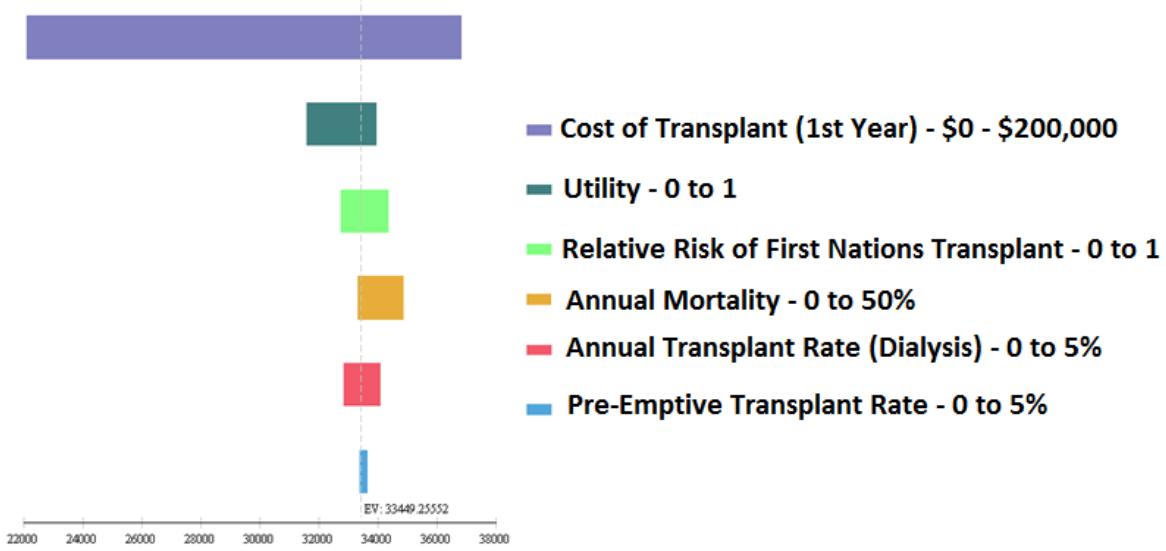


Figure 6. Sensitivity Analysis of Influential Model Estimates

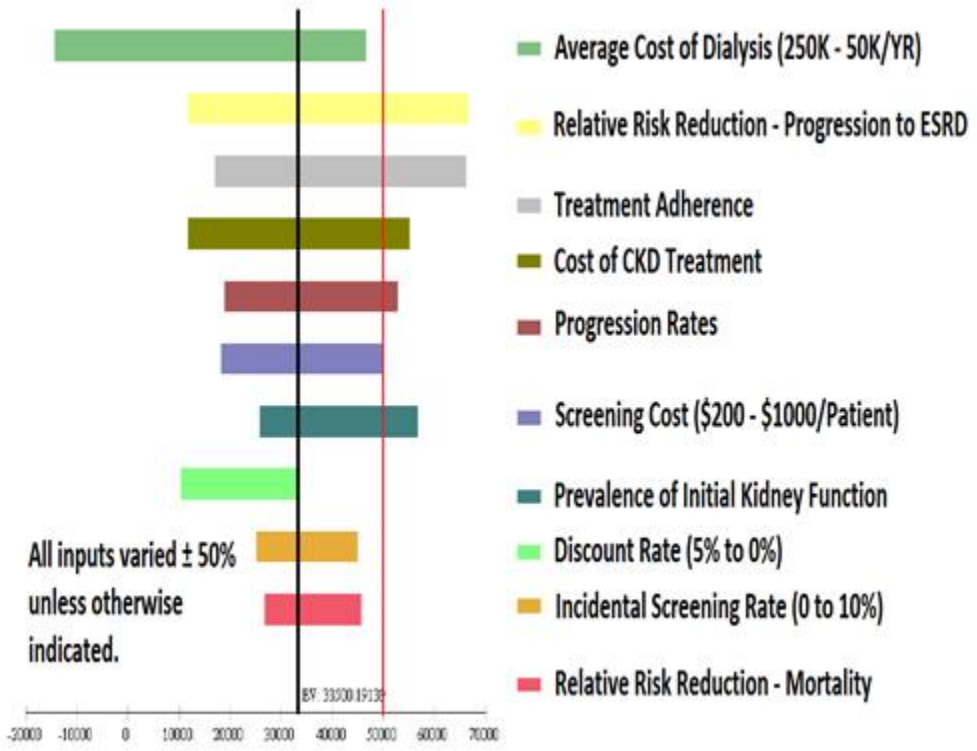


Figure 7. Cell Counts for Initial Risk Stratum – KDIGO Heat Map

Entire Screened Population

			Albuminuria (mg/g)			
			A1		A2	A3
			Optimal to high-normal		High	Very high to nephrotic
			<10	10-29	30-299	>300
eGFR ml/min per 1.73m^2	G1a	>105	274	229	145	25
	G1b	90-104	143	80	51	8
	G2a	75-89	115	74	27	9
	G2b	60-74	47	25	28	10
	G3a	45-59	11	13	6	3
	G3b	30-44	2	4	5	6
	G4	15-29	0	0	0	4
	G5	<15	0	0	0	2

Air Access Communities

			Albuminuria (mg/g)			
			A1		A2	A3
			Optimal to high-normal		High	Very high to nephrotic
			<10	10-29	30-299	>300
eGFR ml/min per 1.73m^2	G1a	>105	104	119	98	18
	G1b	90-104	40	36	28	4
	G2a	75-89	42	32	16	7
	G2b	60-74	18	12	17	9
	G3a	45-59	3	8	4	3
	G3b	30-44	2	3	1	3
	G4	15-29	0	0	0	2
	G5	<15	0	0	0	1

Road Access Communities

			Albuminuria (mg/g)			
			A1		A2	A3
			Optimal to high-normal		High	Very high to nephrotic
			<10	10-29	30-299	>300
eGFR ml/min per 1.73m^2	G1a	>105	170	110	47	7
	G1b	90-104	103	44	23	4
	G2a	75-89	73	42	11	2
	G2b	60-74	29	13	11	1
	G3a	45-59	8	5	2	0
	G3b	30-44	0	1	4	3
	G4	15-29	0	0	0	2
	G5	<15	0	0	0	1

Appendix 1. Calculation of Weighted Cost of Dialysis

Calculation of weighted SHD cost – all communities (See Table 8 for input variables):

0.164 x (83,060) + 0.132 x (86,920) + 0.088 x (103,390) + 0.132 x (110,900) + 0.022 x (114,420) + 0.198 x (138,100) + 0.077 x (156,150) + 0.033 x (204,640) + 0.154 x (215,850) = **$130,711**

Calculation of weighted SHD cost – air access communities (See Table 8 for input variables):

0.184 x (110,900) + 0.037 x (114,420) + 0.333 x (138,100) + 0.130 x (156,150) + 0.056 x (204,640) + 0.260 x (215,850) **= $158,500**

Calculation of weighted SHD cost – road access communities (See Table 8 for input variables):

0.405 x (83,060) + 0.324 x (86,920) + 0.216 x (103,390) + 0.055 (116,900) = **$90,560**

Calculation of weighted dialysis cost (See Tables 5, 7, and 8 for input variables):

Proportion SHD x Cost SHD + Proportion HD x Cost HD + Proportion PD x Cost PD + Proportion HHD x Cost HHD = 0.472 x (130,711) + 0.257 x (74,590) + 0.257 x (43,500) + 0.014 x (61,300) = **$92,900**

Where HD is hemodialysis, SHD is satellite hemodialysis, PD is peritoneal dialysis, and HHD is home hemodialysis.

References

1. Levey AS, Coresh J: Chronic kidney disease. Lancet 379(9811):165-180, 2012

2. Stevens LA, Levey AS: Measured GFR as a confirmatory test for estimated GFR. J Am Soc Nephrol 20(11):2305-2313, 2009

3. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D: A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation. modification of diet in renal disease study group. Ann Intern Med 130(6):461-470, 1999

4. Levey AS, Stevens LA, Schmid CH, et al: A new equation to estimate glomerular filtration rate. Ann Intern Med 150(9):604-612, 2009

5. Levey AS, de Jong PE, Coresh J, et al: The definition, classification, and prognosis of chronic kidney disease: A KDIGO controversies conference report. Kidney Int 80(1):17-28, 2011

6. Levey AS, Coresh J, Balk E, et al: National kidney foundation practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. Ann Intern Med 139(2):137-147, 2003

7. Black C, Sharma P, Scotland G, et al: Early referral strategies for management of people with markers of renal disease: A systematic review of the evidence of clinical effectiveness, cost-effectiveness and economic analysis. Health Technol Assess 14(21):1-184, 2010

8. Howard K, Salkeld G, White S, et al: The cost-effectiveness of increasing kidney transplantation and home-based dialysis. Nephrology (Carlton) 14(1):123-132, 2009

9. Knoll G: Trends in kidney transplantation over the past decade. Drugs 68 Suppl 1:3-10, 2008

10. Knoll G, Cockfield S, Blydt-Hansen T, et al: Canadian society of transplantation consensus guidelines on eligibility for kidney transplantation. Cmaj 173(10):1181-1184, 2005

11. Canadian Institute for Health Information: 2014 CORR report: Treatment of end-stage organ failure in Canada, 2003 to 2012. Accessed 2015(1/1). 2014. Accessed at https://secure.cihi.ca/free_products/2014_CORR_Annual_Report_EN.pdf.

12. Lee H, Manns B, Taub K, et al: Cost analysis of ongoing care of patients with end-stage renal disease: The impact of dialysis modality and dialysis access. Am J Kidney Dis 40(3):611-622, 2002

13. McLaughlin K, Manns B, Mortis G, Hons R, Taub K: Why patients with ESRD do not select self-care dialysis as a treatment option. Am J Kidney Dis 41(2):380-385, 2003

14. Levin A, Hemmelgarn B, Culleton B, et al: Guidelines for the management of chronic kidney disease. Cmaj 179(11):1154-1162, 2008

15. Giroux S: Canadian health measures survey: Sampling strategy overview. Health Rep 18 Suppl:31-36, 2007

16. Tremblay M, Wolfson M, Connor Gorber S: Canadian health measures survey: Rationale, background and overview. Health Rep 18 Suppl:7-20, 2007

17. Arora P, Vasa P, Brenner D, et al: Prevalence estimates of chronic kidney disease in canada: Results of a nationally representative survey. Cmaj 185(9):E417-23, 2013

18. Zacharias JM, Young TK, Riediger ND, Roulette J, Bruce SG: Prevalence, risk factors and awareness of albuminuria on a Canadian first nation: A community-based screening study. BMC Public Health 12:290-2458-12-290, 2012

19. Dalrymple LS, Katz R, Kestenbaum B, et al: Chronic kidney disease and the risk of end-stage renal disease versus death. J Gen Intern Med 26(4):379-385, 2011

20. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY: Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 351(13):1296-1305, 2004

21. Klarenbach SW, Tonelli M, Chui B, Manns BJ: Economic evaluation of dialysis therapies. Nat Rev Nephrol 10(11):644-652, 2014

22. Manns BJ, Mendelssohn DC, Taub KJ: The economics of end-stage renal disease care in Canada: Incentives and impact on delivery of care. Int J Health Care Finance Econ 7(2-3):149-169, 2007

23. U.S. Renal Data System: USRDS 2013 annual data report: Atlas of chronic kidney disease and end-stage renal disease in the United States. 2013

24. Mallick NP: The costs of renal services in Britain. Nephrol Dial Transplant 12 Suppl 1:25-28, 1997

25. Young TK, Reading J, Elias B, O'Neil JD: Type 2 diabetes mellitus in Canada's first nations: Status of an epidemic in progress. Cmaj 163(5):561-566, 2000

26. Jacobs P, Blanchard JF, James RC, Depew N: Excess costs of diabetes in the aboriginal population of Manitoba, Canada. Can J Public Health 91(4):298-301, 2000

27. Martens P, Martin B, O'Neil J, MacKinnon M: Diabetes and adverse outcomes in a first nations population: Associations with healthcare access, socioeconomic, and geographical factors. Canadian Journal of Diabetes 31(3):223-232, 2007

28. Gao S, Manns BJ, Culleton BF, et al: Access to health care among status aboriginal people with chronic kidney disease. Cmaj 179(10):1007-1012, 2008

29. Samuel SM, Palacios-Derflingher L, Tonelli M, et al: Association between first nations ethnicity and progression to kidney failure by presence and severity of albuminuria. Cmaj 186(2):E86-94, 2014

30. Lavallee B, Chartrand C, McLeod L, et al: Mass screening for chronic kidney disease in rural and remote Canadian first nations people: Methodology and demographic characteristics. Cjkhd 2(9) 2015

31. Zacharias J, Komenda P, Olson J, Bourne A, Franklin D, Bernstein K: Home hemodialysis in the remote Canadian north: Treatment in Manitoba fly-in communities. Semin Dial 24(6):653-657, 2011

32. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group: KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney International Supplement 3:1-150, 2013

33. Coresh J, Selvin E, Stevens LA, et al: Prevalence of chronic kidney disease in the United States. Jama 298(17):2038-2047, 2007

34. Hillege HL, Janssen WM, Bak AA, et al: Microalbuminuria is common, also in a nondiabetic, nonhypertensive population, and an independent indicator of cardiovascular risk factors and cardiovascular morbidity. J Intern Med 249(6):519-526, 2001

35. Mathew TH, Corso O, Ludlow M, et al: Screening for chronic kidney disease in Australia: A pilot study in the community and workplace. Kidney Int Suppl (116):S9-16. doi(116):S9-16, 2010

36. Brown WW, Peters RM, Ohmit SE, et al: Early detection of kidney disease in community settings: The kidney early evaluation program (KEEP). Am J Kidney Dis 42(1):22-35, 2003

37. Bello AK, Nwankwo E, El Nahas AM: Prevention of chronic kidney disease: A global challenge. Kidney Int Suppl (98)(98):S11-7, 2005

38. Obrador GT, Garcia-Garcia G, Villa AR, et al: Prevalence of chronic kidney disease in the kidney early evaluation program (KEEP) Mexico and comparison with KEEP US. Kidney Int Suppl (116):S2-8. doi(116):S2-8, 2010

39. Takahashi S, Okada K, Yanai M: The kidney early evaluation program (KEEP) of Japan: Results from the initial screening period. Kidney Int Suppl (116):S17-23. doi(116):S17-23, 2010

40. Oster RT, Virani S, Strong D, Shade S, Toth EL: Diabetes care and health status of first nations individuals with type 2 diabetes in Alberta. Can Fam Physician 55(4):386-393, 2009

41. Virani S, Strong D, Tennant M, et al: Rationale and implementation of the SLICK project: Screening for limb, I-eye, cardiovascular and kidney (SLICK) complications in individuals with type 2 diabetes in Alberta's first nations communities. Can J Public Health 97(3):241-247, 2006

42. Stidley CA, Shah VO, Scavini M, et al: The Zuni kidney project: A collaborative approach to an epidemic of kidney disease. J Am Soc Nephrol 14(7 Suppl 2):S139-43, 2003

43. Shah VO, Scavini M, Stidley CA, et al: Epidemic of diabetic and nondiabetic renal disease among the Zuni Indians: The Zuni kidney project. J Am Soc Nephrol 14(5):1320-1329, 2003

44. Hoy W, Jim S, Warrington W, Light A, Megill D: Urinary findings and renal function in adult Navajo Indians and associations with type 2 diabetes. Am J Kidney Dis 28(3):339-349, 1996

45. Nelson RG, Kunzelman CL, Pettitt DJ, Saad MF, Bennett PH, Knowler WC: Albuminuria in type 2 (non-insulin-dependent) diabetes mellitus and impaired glucose tolerance in Pima Indians. Diabetologia 32(12):870-876, 1989

46. Hoy WE, Mathews JD, McCredie DA, et al: The multidimensional nature of renal disease: Rates and associations of albuminuria in an Australian aboriginal community. Kidney Int 54(4):1296-1304, 1998

47. Obrador GT, Pereira BJ: Early referral to the nephrologist and timely initiation of renal replacement therapy: A paradigm shift in the management of patients with chronic renal failure. Am J Kidney Dis 31(3):398-417, 1998

48. Diaz-Buxo JA: Early referral and selection of peritoneal dialysis as a treatment modality. Nephrol Dial Transplant 15(2):147-149, 2000

49. Avorn J, Bohn RL, Levy E, et al: Nephrologist care and mortality in patients with chronic renal insufficiency. Arch Intern Med 162(17):2002-2006, 2002

50. Winkelmayer WC, Owen WF,Jr, Levin R, Avorn J: A propensity analysis of late versus early nephrologist referral and mortality on dialysis. J Am Soc Nephrol 14(2):486-492, 2003

51. Levinsky NG: Specialist evaluation in chronic kidney disease: Too little, too late. Ann Intern Med 137(6):542-543, 2002

52. Kinchen KS, Sadler J, Fink N, et al: The timing of specialist evaluation in chronic kidney disease and mortality. Ann Intern Med 137(6):479-486, 2002

53. Taal MW, Brenner BM: Renoprotective benefits of RAS inhibition: From ACEI to angiotensin II antagonists. Kidney Int 57(5):1803-1817, 2000

54. Remuzzi G, Ruggenenti P, Perico N: Chronic renal diseases: Renoprotective benefits of renin-angiotensin system inhibition. Ann Intern Med 136(8):604-615, 2002

55. Remuzzi G, Perico N, Macia M, Ruggenenti P: The role of renin-angiotensin-aldosterone system in the progression of chronic kidney disease. Kidney Int Suppl (99)(99):S57-65, 2005

56. Weir MR: Progressive renal and cardiovascular disease: Optimal treatment strategies. Kidney Int 62(4):1482-1492, 2002

57. Jafar TH, Schmid CH, Landa M, et al: Angiotensin-converting enzyme inhibitors and progression of nondiabetic renal disease. A meta-analysis of patient-level data. Ann Intern Med 135(2):73-87, 2001

58. Jafar TH, Stark PC, Schmid CH, et al: Progression of chronic kidney disease: The role of blood pressure control, proteinuria, and angiotensin-converting enzyme inhibition: A patient-level meta-analysis. Ann Intern Med 139(4):244-252, 2003

59. Ruggenenti P, Perna A, Gherardi G, et al: Renoprotective properties of ACE-inhibition in non-diabetic nephropathies with non-nephrotic proteinuria. Lancet 354(9176):359-364, 1999

60. Ruggenenti P, Perna A, Gherardi G, Benini R, Remuzzi G: Chronic proteinuric nephropathies: Outcomes and response to treatment in a prospective cohort of 352 patients with different patterns of renal injury. Am J Kidney Dis 35(6):1155-1165, 2000

61. Gansevoort RT, de Zeeuw D, de Jong PE: Long-term benefits of the antiproteinuric effect of angiotensin-converting enzyme inhibition in nondiabetic renal disease. Am J Kidney Dis 22(1):202-206, 1993

62. Praga M, Hernandez E, Montoyo C, Andres A, Ruilope LM, Rodicio JL: Long-term beneficial effects of angiotensin-converting enzyme inhibition in patients with nephrotic proteinuria. Am J Kidney Dis 20(3):240-248, 1992

63. Sarnak MJ, Greene T, Wang X, et al: The effect of a lower target blood pressure on the progression of kidney disease: Long-term follow-up of the modification of diet in renal disease study. Ann Intern Med 142(5):342-351, 2005

64. Peterson JC, Adler S, Burkart JM, et al: Blood pressure control, proteinuria, and the progression of renal disease. the modification of diet in renal disease study. Ann Intern Med 123(10):754-762, 1995

65. Walker SR, Gill K, Macdonald K, et al: Association of frailty and physical function in patients with non-dialysis CKD: A systematic review. BMC Nephrol 14:228-2369-14-228, 2013

66. Etgen T, Chonchol M, Forstl H, Sander D: Chronic kidney disease and cognitive impairment: A systematic review and meta-analysis. Am J Nephrol 35(5):474-482, 2012

67. Gorodetskaya I, Zenios S, McCulloch CE, et al: Health-related quality of life and estimates of utility in chronic kidney disease. Kidney Int 68(6):2801-2808, 2005

68. Komenda P, Gavaghan MB, Garfield SS, Poret AW, Sood MM: An economic assessment model for in-center, conventional home, and more frequent home hemodialysis. Kidney Int 81(3):307-313, 2012

69. Klarenbach S, Tonelli M, Pauly R, et al: Economic evaluation of frequent home nocturnal hemodialysis based on a randomized controlled trial. J Am Soc Nephrol 25(3):587-594, 2014

70. Foley RN, Collins AJ: End-stage renal disease in the united states: An update from the united states renal data system. J Am Soc Nephrol 18(10):2644-2648, 2007

71. Baboolal K, McEwan P, Sondhi S, Spiewanowski P, Wechowski J, Wilson K: The cost of renal dialysis in a UK setting--a multicentre study. Nephrol Dial Transplant 23(6):1982-1989, 2008

72. Howard K, White S, Salkeld G, et al: Cost-effectiveness of screening and optimal management for diabetes, hypertension, and chronic kidney disease: A modeled analysis. Value Health 13(2):196-208, 2010

73. Kondo M, Yamagata K, Hoshi SL, et al: Cost-effectiveness of chronic kidney disease mass screening test in Japan. Clin Exp Nephrol 16(2):279-291, 2012

74. Ferguson TW, Tangri N, Rigatto C, Komenda P: Cost-effective treatment modalities for reducing morbidity associated with chronic kidney disease. Expert Rev Pharmacoecon Outcomes Res 15(2):243-252, 2015

75. Laupacis A, Keown P, Pus N, et al: A study of the quality of life and cost-utility of renal transplantation. Kidney Int 50(1):235-242, 1996

76. Cambi V, Christopher TG: The satellite dialysis center. Lancet 2(7734):1158-1159, 1971

77. Shapiro FL, Messner RP, Smith HT: Satellite hemodialysis. Ann Intern Med 69(4):673-684, 1968

78. Bernstein K, Zacharias J, Blanchard JF, Yu BN, Shaw SY: Model for equitable care and outcomes for remote full care hemodialysis units. Clin J Am Soc Nephrol 5(4):645-651, 2010

79. Tonelli M, Manns B, Culleton B, et al: Association between proximity to the attending nephrologist and mortality among patients receiving hemodialysis. Cmaj 177(9):1039-1044, 2007

80. Maripuri S, Arbogast P, Ikizler TA, Cavanaugh KL: Rural and micropolitan residence and mortality in patients on dialysis. Clin J Am Soc Nephrol 7(7):1121-1129, 2012

81. O'Hare AM, Johansen KL, Rodriguez RA: Dialysis and kidney transplantation among patients living in rural areas of the United States. Kidney Int 69(2):343-349, 2006

82. Diamant MJ, Harwood L, Movva S, et al: A comparison of quality of life and travel-related factors between in-center and satellite-based hemodialysis patients. Clin J Am Soc Nephrol 5(2):268-274, 2010

83. Diamant MJ, Young A, Gallo K, et al: Hemodialysis in a satellite unit: Clinical performance target attainment and health-related quality of life. Clin J Am Soc Nephrol 6(7):1692-1699, 2011

84. Roderick P, Nicholson T, Armitage A, et al: An evaluation of the costs, effectiveness and quality of renal replacement therapy provision in renal satellite units in England and Wales. Health Technol Assess 9(24):1-178, 2005

85. Prakash S, Austin PC, Oliver MJ, Garg AX, Blake PG, Hux JE: Regional effects of satellite haemodialysis units on renal replacement therapy in non-urban Ontario, Canada. Nephrol Dial Transplant 22(8):2297-2303, 2007

86. Moist LM, Bragg-Gresham JL, Pisoni RL, et al: Travel time to dialysis as a predictor of health-related quality of life, adherence, and mortality: The dialysis outcomes and practice patterns study (DOPPS). Am J Kidney Dis 51(4):641-650, 2008

87. Wilson R, Krefting L, Sutcliffe P, Van Bussel L: Native Canadians relocating for renal dialysis. psychosocial and cultural issues. Can Fam Physician 40:1934-1941, 1994

88. Bilinsky RT, Morris AJ, Klein HR: Satellite dialysis. An economic approach to the delivery of hemodialysis care. Jama 218(12):1809-1813, 1971

89. Gonzalez-Perez JG, Vale L, Stearns SC, Wordsworth S: Hemodialysis for end-stage renal disease: A cost-effectiveness analysis of treatment-options. Int J Technol Assess Health Care 21(1):32-39, 2005

90. Mowatt G, Vale L, MacLeod A: Systematic review of the effectiveness of home versus hospital or satellite unit hemodialysis for people with end-stage renal failure. Int J Technol Assess Health Care 20(3):258-268, 2004

91. Soroka SD, Kiberd BA, Jacobs P: The marginal cost of satellite versus in-center hemodialysis. Hemodial Int 9(2):196-201, 2005

92. Vassalotti JA, Stevens LA, Levey AS: Testing for chronic kidney disease: A position statement from the National Kidney Foundation. Am J Kidney Dis 50(2):169-180, 2007

93. Fink HA, Ishani A, Taylor BC, et al: Screening for, monitoring, and treatment of chronic kidney disease stages 1 to 3: A systematic review for the U.S. preventive services task force and for an American College of Physicians clinical practice guideline. Ann Intern Med 156(8):570-581, 2012

94. Moyer VA, U.S. Preventive Services Task Force: Screening for chronic kidney disease: U.S. preventive services task force recommendation statement. Ann Intern Med 157(8):567-570, 2012

95. Hoerger TJ, Wittenborn JS, Segel JE, et al: A health policy model of CKD: 2. the cost-effectiveness of microalbuminuria screening. Am J Kidney Dis 55(3):463-473, 2010

96. Hoerger TJ, Wittenborn JS, Segel JE, et al: A health policy model of CKD: 1. model construction, assumptions, and validation of health consequences. Am J Kidney Dis 55(3):452-462, 2010

97. Kessler R, Keusch G, Szucs TD, et al: Health economic modeling of the cost-effectiveness of microalbuminuria screening in Switzerland. Swiss Med Wkly 142:w13508, 2012

98. Manns B, Hemmelgarn B, Tonelli M, et al: Population based screening for chronic kidney disease: Cost effectiveness study. Bmj 341:c5869, 2010

99. Palmer AJ, Valentine WJ, Chen R, et al: A health economic analysis of screening and optimal treatment of nephropathy in patients with type 2 diabetes and hypertension in the USA. Nephrol Dial Transplant 23(4):1216-1223, 2008

100. Siegel JE, Krolewski AS, Warram JH, Weinstein MC: Cost-effectiveness of screening and early treatment of nephropathy in patients with insulin-dependent diabetes mellitus. J Am Soc Nephrol 3(4 Suppl):S111-9, 1992

101. Boulware LE, Jaar BG, Tarver-Carr ME, Brancati FL, Powe NR: Screening for proteinuria in US adults: A cost-effectiveness analysis. Jama 290(23):3101-3114, 2003

102. Boersma C, Gansevoort RT, Pechlivanoglou P, et al: Screen-and-treat strategies for albuminuria to prevent cardiovascular and renal disease: Cost-effectiveness of nationwide and targeted interventions based on analysis of cohort data from the Netherlands. Clin Ther 32(6):1103-1121, 2010

103. Hoerger TJ, Wittenborn JS, Zhuo X, et al: Cost-effectiveness of screening for microalbuminuria among African Americans. J Am Soc Nephrol 23(12):2035-2041, 2012

104. Komenda P, Ferguson TW, Macdonald K, et al: Cost-effectiveness of primary screening for CKD: A systematic review. Am J Kidney Dis 63(5):789-797, 2014

105. Gerstein HC, Mann JF, Yi Q, et al: Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. Jama 286(4):421-426, 2001

106. Imai E, Horio M, Iseki K, et al: Prevalence of chronic kidney disease (CKD) in the Japanese general population predicted by the MDRD equation modified by a Japanese coefficient. Clin Exp Nephrol 11(2):156-163, 2007

107. Imai E, Horio M, Watanabe T, et al: Prevalence of chronic kidney disease in the Japanese general population. Clin Exp Nephrol 13(6):621-630, 2009

108. Dyck RF: Mechanisms of renal disease in indigenous populations: Influences at work in canadian indigenous peoples. Nephrology (Carlton) 6:3-7, 2001

109. Statistics Canada: Percentage of aboriginal people in the population, Canada, provinces and territories, 2006. Accessed 2015(4/29). 2009. Accessed at http://www12.statcan.gc.ca/nhs-enm/2011/as-sa/99-011-x/2011001/tbl/tbl02-eng.cfm.

110. Garcia-Garcia G, Jha V, World Kidney Day Steering Committee: CKD in disadvantaged populations. Kidney Int 87(2):251-253, 2015

111. Nicholas SB, Tareen N, Zadshir A, Martins D, Pan D, Norris KC: Management of early chronic kidney disease in indigenous populations and ethnic minorities. Kidney Int Suppl (97)(97):S78-81, 2005

112. McDonald SP, Russ GR: Current incidence, treatment patterns and outcome of end-stage renal disease among indigenous groups in Australia and New Zealand. Nephrology (Carlton) 8(1):42-48, 2003

113. Anderson I, Crengle S, Kamaka ML, Chen TH, Palafox N, Jackson-Pulver L: Indigenous health in australia, new zealand, and the pacific. Lancet 367(9524):1775-1785, 2006

114. Castor ML, Smyser MS, Taualii MM, Park AN, Lawson SA, Forquera RA: A nationwide population-based study identifying health disparities between american Indians/Alaska natives and the general populations living in select urban counties. Am J Public Health 96(8):1478-1484, 2006

115. Statistics Canada: Consumer price index, health and personal care, by province (Canada). Accessed 2015(4/15). 2015. Accessed at http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/econ161a-eng.htm.

116. Canadian Agency for Drugs and Technologies in Health: Guidelines for the economic evaluation of health technologies. Accessed 2015(4/15). 2006. Accessed at https://www.cadth.ca/media/pdf/186_EconomicGuidelines_e.pdf.

117. Tangri N, Stevens LA, Griffith J, et al: A predictive model for progression of chronic kidney disease to kidney failure. Jama 305(15):1553-1559, 2011

118. Kent DM, Jafar TH, Hayward RA, et al: Progression risk, urinary protein excretion, and treatment effects of angiotensin-converting enzyme inhibitors in nondiabetic kidney disease. J Am Soc Nephrol 18(6):1959-1965, 2007

119. Li EC, Heran BS, Wright JM: Angiotensin converting enzyme (ACE) inhibitors versus angiotensin receptor blockers for primary hypertension. Cochrane Database Syst Rev 8:CD009096, 2014

120. Hemmelgarn BR, Clement F, Manns BJ, et al: Overview of the Alberta Kidney Disease Network. BMC Nephrol 10:30-2369-10-30, 2009

121. Statistics Canada: Deaths by age group and geography - both sexes. Accessed 2015(4/15) 2008. Accessed at http://www.statcan.gc.ca/pub/84f0211x/2009000/t003-eng.htm.

122. Weber CL, Rush DN, Jeffery JR, Cheang M, Karpinski ME: Kidney transplantation outcomes in canadian aboriginals. Am J Transplant 6(8):1875-1881, 2006

123. Tonelli M, Hemmelgarn B, Manns B, et al: Death and renal transplantation among aboriginal people undergoing dialysis. Cmaj 171(6):577-582, 2004

124. Agodoa LY, Appel L, Bakris GL, et al: Effect of ramipril vs amlodipine on renal outcomes in hypertensive nephrosclerosis: A randomized controlled trial. Jama 285(21):2719-2728, 2001

125. Brenner BM, Cooper ME, de Zeeuw D, et al: Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 345(12):861-869, 2001

126. Gerstein HC, Mann JF, Yi Q, et al: Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. Jama 286(4):421-426, 2001

127. Lewis EJ, Hunsicker LG, Clarke WR, et al: Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 345(12):851-860, 2001

128. Lindholm LH, Ibsen H, Dahlof B, et al: Cardiovascular morbidity and mortality in patients with diabetes in the losartan intervention for endpoint reduction in hypertension study (LIFE): A randomised trial against atenolol. Lancet 359(9311):1004-1010, 2002

129. Manitoba Health: Manitoba physician's manual. Accessed 2015(4/15). 2014. Accessed at http://www.gov.mb.ca/health/manual/.

130. Honeycutt AA, Segel JE, Zhuo X, Hoerger TJ, Imai K, Williams D: Medical costs of CKD in the medicare population. J Am Soc Nephrol 24(9):1478-1483, 2013

131. Korevaar JC, Feith GW, Dekker FW, et al: Effect of starting with hemodialysis compared with peritoneal dialysis in patients new on dialysis treatment: A randomized controlled trial. Kidney Int 64(6):2222-2228, 2003

132. Okano Y, Tamura K, Masuda S, Ozawa M, Tochikubo O, Umemura S: Effects of angiotensin II receptor blockers on the relationships between ambulatory blood pressure and anti-hypertensive effects, autonomic function, and health-related quality of life. Clin Exp Hypertens 31(8):680-689, 2009

133. Weil EJ, Fufaa G, Jones LI, et al: Effect of losartan on prevention and progression of early diabetic nephropathy in American Indians with type 2 diabetes. Diabetes 62(9):3224-3231, 2013

134. Rucker D, Hemmelgarn BR, Lin M, et al: Quality of care and mortality are worse in chronic kidney disease patients living in remote areas. Kidney Int 79(2):210-217, 2011

135. QxMD: Use kidney failure risk equation to predict progression to kidney failure. Acessed 2015(4/16). 2011. Accessed at http://www.qxmd.com/calculate-online/nephrology/kidney-failure-risk-equation.

136. Bradbury BD, Fissell RB, Albert JM, et al: Predictors of early mortality among incident US hemodialysis patients in the dialysis outcomes and practice patterns study (DOPPS). Clin J Am Soc Nephrol 2(1):89-99, 2007

137. Mendelssohn DC, Curtis B, Yeates K, et al: Suboptimal initiation of dialysis with and without early referral to a nephrologist. Nephrol Dial Transplant 26(9):2959-2965, 2011

138. Soucie JM, McClellan WM: Early death in dialysis patients: Risk factors and impact on incidence and mortality rates. J Am Soc Nephrol 7(10):2169-2175, 1996

139. Smart NA, Titus TT: Outcomes of early versus late nephrology referral in chronic kidney disease: A systematic review. Am J Med 124(11):1073-80.e2, 2011

140. Tonelli M, Isles C, Curhan GC, et al: Effect of pravastatin on cardiovascular events in people with chronic kidney disease. Circulation 110(12):1557-1563, 2004

141. Tarver-Carr ME, Powe NR, Eberhardt MS, et al: Excess risk of chronic kidney disease among african-american versus white subjects in the united states: A population-based study of potential explanatory factors. J Am Soc Nephrol 13(9):2363-2370, 2002

142. Nelson RG, Newman JM, Knowler WC, et al: Incidence of end-stage renal disease in type 2 (non-insulin-dependent) diabetes mellitus in pima indians. Diabetologia 31(10):730-736, 1988

143. Nelson RG, Bennett PH, Beck GJ, et al: Development and progression of renal disease in pima indians with non-insulin-dependent diabetes mellitus. diabetic renal disease study group. N Engl J Med 335(22):1636-1642, 1996

144. Peralta CA, Shlipak MG, Fan D, et al: Risks for end-stage renal disease, cardiovascular events, and death in hispanic versus non-hispanic white adults with chronic kidney disease. J Am Soc Nephrol 17(10):2892-2899, 2006

145. Hoy WE, Hughson MD, Singh GR, Douglas-Denton R, Bertram JF: Reduced nephron number and glomerulomegaly in australian aborigines: A group at high risk for renal disease and hypertension. Kidney Int 70(1):104-110, 2006

146. Dussault G, Franceschini MC: Not enough there, too many here: Understanding geographical imbalances in the distribution of the health workforce. Hum Resour Health 4:12, 2006

147. Statistics Canada: Life tables, Canada, provinces and territories, 2009 to 2011. Accessed 2015(04/22). 2011. Accessed at http://www.statcan.gc.ca/pub/84-537-x/84-537-x2013005-eng.htm.

148. Martens PJ, Sanderson D, Jebamani LS: Mortality comparisons of first nations to all other manitobans: A provincial population-based look at health inequalities by region and gender. Can J Public Health 96 Suppl 1:S33-8, 2005

149. Puffer S, Torgerson DJ, Watson J: Cluster randomized controlled trials. J Eval Clin Pract 11(5):479-483, 2005