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Measuring the Efficiency of the Living Kidney Donor Candidate Evaluation Process

Steven Habbous, *The University of Western Ontario*

Supervisor: Garg, Amit X, *The University of Western Ontario*

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Abstract

Background: Living kidney donor transplantation is the ideal treatment for many patients with kidney failure. However, the living donor evaluation process has been criticized by patients and healthcare providers as inefficient. In the present research, we evaluated the inefficiency of the living donor evaluation process.

Methods: We conducted a scoping review of the literature and obtained data from large administrative datasets (1256 living donors) and medical chart review (849 prospectively recruited living donors across 12 transplant centres plus retrospective analysis of 1065 living donor candidates from a single centre).

Results: The median time to complete the entire evaluation was 9-11 months for donors and 4.3 months for candidates who were declined or withdrew from the evaluation. Up to 35% of recipients who could potentially have received a pre-emptive transplant (avoided dialysis entirely) started dialysis before transplantation, costing the healthcare system $8.1M for dialysis alone. Shortening the evaluation time by only 10% translated to an annual cost savings of at least $1.3M in Ontario due to averted dialysis costs and up to 38 intended recipients each year could have received a transplant they otherwise did not receive (17% increase in living donor transplantation). The cost to the healthcare system was $3,641 for the donor evaluation, $11,695 for the donor surgery (including perioperative costs), and $933 for the first year post-donation. There are many reasons that may contribute to a longer living donor evaluation. Donation through kidney paired donation prolonged the time until donation by 6 months. The evaluation time was doubled if the intended recipient started dialysis part-way through the donors' evaluation. Finally, every month delay in the recipient referral extended the time until donation by 0.4-0.9 months and increased the likelihood that the recipient would start dialysis before transplant. Between-centre differences were observed for evaluation times and donation costs.

Conclusions: The living donor evaluation is time-consuming, resulting in potentially avoidable unintended adverse consequences to donor candidates, their intended recipient,

and the healthcares system. Potential strategies to improve the efficiency of this process include eliminating unnecessary or redundant tests, evaluating multiple donor candidates simultaneously, performing 1-day evaluations, and promoting earlier recipient referrals.

Keywords

Living kidney donation; efficiency; evaluation; pre-emptive transplant; costs; living donor evaluation; transplantation; kidney

Co-Authorship Statement

For all work conducted through the Institute for Clinical Evaluative Sciences (ICES; Chapter 6, 7,8, and 9), Stephanie Dixon assisted with cohort creation and ensuring my access to the facility. Eric McArthur was the main point of contact for troubleshooting general coding, use of macros, and pulling data from various datasets held at ICES. Both also provided feedback on interpretation and writing. Carlos Ochoa-Garcia was responsible for independently validating the codes derived from the Ontario Health Insurance Plan database for categorizing them as "procedures".

For the work involving the Living Donor Network Study (Chapter 6), Jennifer Arnold, Dariusz Goździk, and Sebastian Przech were critical in organizing, collecting, and cleaning the data received from all participating centres. The following co-authors' main contribution was to organize and recruit participants from their respective transplant centres, including Drs. Neil Boudville, Christine Dipchand, Liane Feldman, Martin Karpinski, Scott Klarenbach, Greg Knoll, Ngan Lam, Charmaine Lok, Matthew Miller, Maurice Monroy-Cuadros, Chris Nguan, GV Prasad, Leroy Storsley, and Amit Garg.

For work involving the chart review (Chapter 7), the living donor nurse coordinators Beth Montesi, Peggy Allman, and Christy Masse were essential to obtaining the data, acquiring the charts, and understanding the living donor evaluation process at our centre and where differences may exist. Corinne Weernink provided data from the recipient database.

Drs. Sisira Sarma and Mehmet Begen offered keen insight on methodology, interpretation, future direction, and writing in all co-authored chapters.

Krista Lentine was supportive and provided keen insight on writing and interpretation of results. Moreover, the motivation for Chapter 2 and Chapter 3 was driven by her (these were invited reviews or chapters of a book).

Suzan McKenzie initiated some of this work (particularly Chapter 8), as it was her question that sparked interest in this area of research. From this, other outcomes followed, including those reported in Chapter 7.

Other co-authors served minor roles and restricted to interpretation and editing, including Matthew Cooper, Krista Lentine, Susan McKenzie, Marian Reich, and Kenneth Litchfield.

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Chapter 1

1 Background

The kidneys are mainly responsible for eliminating wastes and excess fluids through urine production. For a healthy adult, the kidneys filter more than 90 milliliters of blood every minute per 1.73 m^2 (normalized for body surface area), a feat that declines naturally with age.[1] Chronic kidney disease (CKD) is defined as a sustained filtration rate of less than 60mL/min/1.73 m^2, resulting in ionic imbalances that can lead to mineral bone disorders and cardiovascular complications that will ultimately result in kidney failure (e.g. a filtration rate <5 mL/min/1.73 m^2) and death if left untreated.[2–5] Filtering the blood through dialysis is currently the best technological means of mimicking the native kidney, but is associated with a variety of complications (morbidity and mortality is high) and is time and resource intensive for both patients and providers.[6–8] For some patients, their kidney disease can be managed and disease progression can be effectively slowed through medication (e.g. phosphate binders), dietary restrictions (e.g. limiting fluid intake; low-protein diet), lifestyle changes (e.g. smoking cessation), or early detection (e.g. through screening of high-risk patients).[9–11] For others, the progression to kidney failure is sudden and unpredictable, requiring rapid initiation of dialysis.[12] Adequately preparing patients for dialysis takes months of planning related to sustaining dialysis access and choosing the right modality for the patient that includes location (e.g. at home or in the clinic), type (e.g., hemodialysis or peritoneal dialysis), and the frequency and timing of dialysis sessions. Compared with dialysis, kidney transplantation is associated with increased longevity, improved quality of life, and results in substantial cost savings to the healthcare system beginning as early as 1 year after transplantation.[5,13–16] Among kidney transplants performed in the United States between 1996 and 2005, grafts remained viable for a median of 10-27 years depending on the type of donor.[17] Thus, kidney transplantation offers patients with end-stage kidney disease the best chance for dialysis-free survival. Despite this, the number of transplantable kidneys available from deceased donors does not meet the need, and there is opportunity to reduce this gap through living donor kidney transplantation.

1.1 Some statistics on kidney disease and transplantation*

The incidence of kidney failure in Ontario has risen steadily from 180 to 219 per million population between 2006 and 2015 (Figure 1).[18] As the risk factors for CKD continue to rise (particularly obesity, hypertension, and diabetes), the burden of CKD and kidney failure among Canadians is also expected to rise; the most common causes of CKD are diabetes (38%), renal vascular disease (14%), and glomerulonephritis (11%).[18,19]

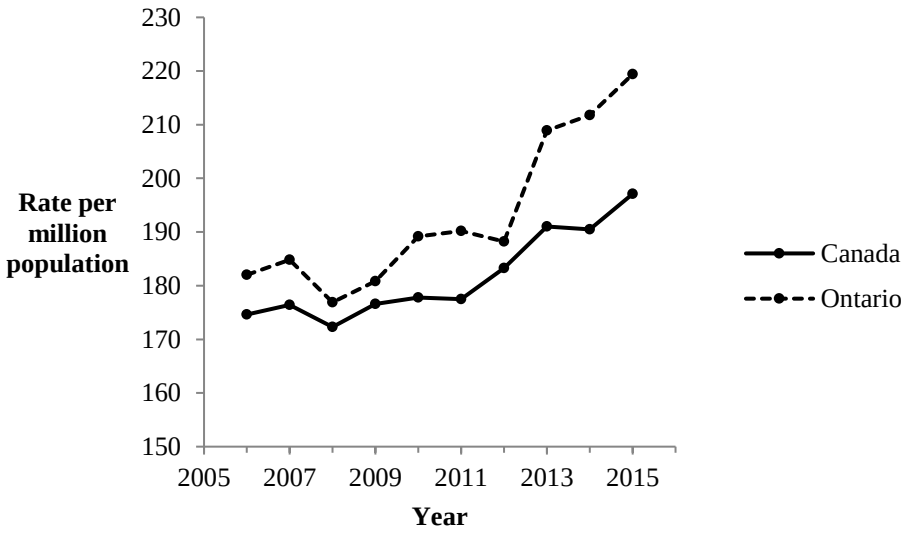

Figure 1: Incident end-stage kidney disease patients by province/territory, Canada (excluding Quebec), 2006 to 2015. Source: Canadian Organ Replacement Register, 2016, Canadian Institute for Health Information; Statistics Canada.

Despite the benefits of transplantation, dialysis is typically the first treatment given: 76% of patients with kidney failure received hemodialysis and 21% received peritoneal dialysis over the last decade (Figure 2).[18] In 2015, 41% (15,037/36,251) of Canadians living with end-stage kidney disease were living with a functioning transplant, which is only a modest rise from the 39% observed in 2006.[18]

* All statistics derived from the Canadian Organ Replacement Register (CORR) exclude Quebec because of significant underreporting from 2011-2015

Figure 2: Incident end-stage kidney disease patients by initial treatment, Canada (excluding Quebec), 2006 to 2015 (percentage of total). Source: Canadian Organ Replacement Register, 2016, Canadian Institute for Health Information; Statistics Canada.

Most kidney transplants across Canada are made possible by deceased donors (60%) (Figure 3).[18] The rate of living kidney donation has stagnated or even declined since 2006 and remains well below the rate of deceased donation.[20–23] This trend was observed across Canadian provinces, and by 2015 the proportion of all kidney transplants that were enabled by a living donor was 41% in Manitoba, 40% in British Columbia, 37% in Alberta, 37% in Ontario, and 26% in Nova Scotia.[18] On an international stage, Canada ranked below the United States and Norway on the number of living donor transplants per million population, but had a higher proportion of transplants from living donors.[22]

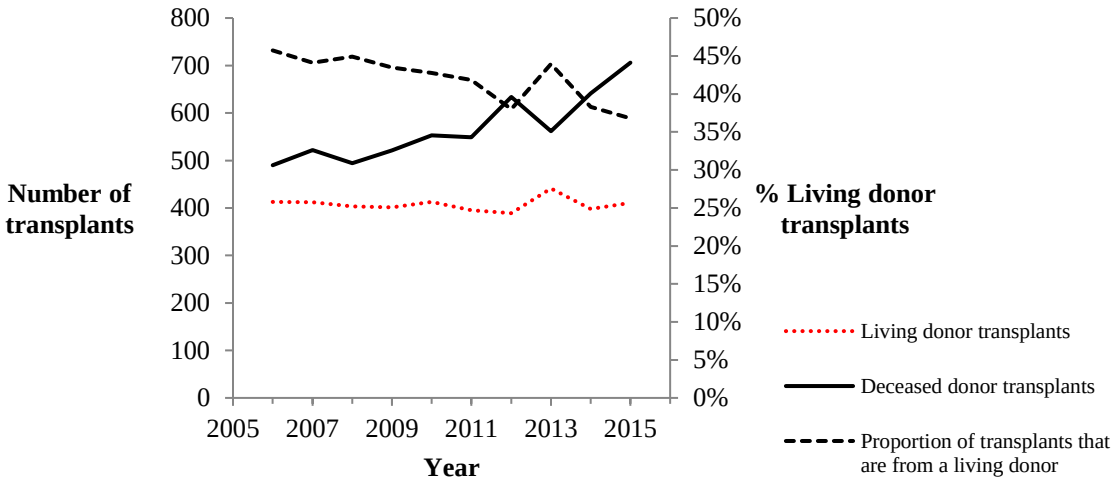

Figure 3: Number and proportion of kidney transplants enabled by living and deceased donors. Source: Canadian Organ Replacement Register, 2016, Canadian Institute for Health Information; Statistics Canada.

1.2 Living donor kidney transplantation

Living donation is preferred over deceased donation because it can be planned (i.e., scheduled), wait-time is reduced, and organ ischemic time† is reduced, leading to better recipient outcomes.[5,24,25] Between 2013 and 2015, the median time spent on dialysis until transplant was 4.0 years from a deceased donor and 1.6 years from a living donor (Figure 4).[18] Considering the potential for pre-emptive transplantation (transplant occurring before dialysis onset), this falls to 0.84 years for living donation (deceased donation remained at 4.0 years).[18]

Pre-emptive transplantation is recognized by many healthcare professionals as the ideal treatment for patients with kidney failure.[26] Pre-emptive transplantation avoids complications related to dialysis (e.g. infection of dialysis catheters) and promotes better survival as the time on dialysis is minimized.[7,27–30] Despite this, pre-emptive transplants

† The time spent without oxygen, usually due to removal of the organ from the body's blood supply (e.g. ligation of an artery, physical removal)

only occurred in 3% of Canadians, a proportion that has remained stable from 2006 through 2015 (Figure 2).[18] Pre-emptive transplants are mostly made possible by living donors due to deceased donor allocation systems that distribute organs and tissues by need (e.g. by time spent on the wait-list, and this generally only accrues after dialysis initiation).[31]

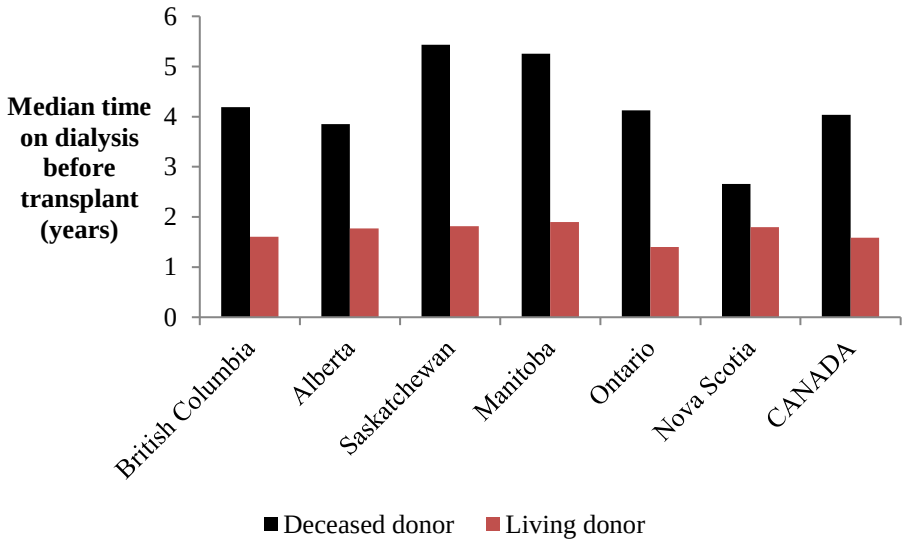

Figure 4: Median time on dialysis before transplant (years), excluding pre-emptive transplantation. Source: Canadian Organ Replacement Register, 2016, Canadian Institute for Health Information; Statistics Canada.

1.2.1 Barriers to living kidney donation

Several barriers to living kidney donation have been identified, including difficulties in identifying potential donors ("The Ask"), financial barriers associated with donation, a lack of knowledge of the long-term medical and psychological risks to donors, a lack of patient and provider education, socioeconomic and demographic factors leading to disparities in access to living donor transplantation (i.e., cultural, geographical, financial barriers), a lack of social support, and a lack of general knowledge about living kidney donation.[32–44] While these areas of research tackle critical barriers that may improve living kidney donation rates or the number of living donor candidate evaluations performed, the healthcare system seems to be presenting an additional barrier that has

received relatively little attention and is the focus of this research: the living kidney donor evaluation process is too long, difficult to complete, and is inefficient.[45]

1.2.2 Efficiency of the living donor candidate evaluation process

Prior donors and recipients have strongly advised that it is necessary to "be your own advocate", shedding light on the frustration and difficulty of navigating the healthcare system and completing the living donor evaluation process.[46,47] Several donors view the evaluation as the worst phase of the donation experience.[47,48] Recommendations from a recent international consensus conference cite the efficiency of the evaluation as a high-priority area for research.[49,50] These sentiments were further promulgated in the 2017 Kidney Disease: Improving Global Outcomes (KDIGO) Guideline on the Evaluation and Care of Living Kidney Donors and the United Kingdom's guidelines on Living Donor Kidney Transplantation.[51,52] Despite these recent advances, recommendations to improve the efficiency of the evaluation are not supported by evidence and are predominantly based on the ideas of key opinion leaders.[49] More work is needed to understand the current state of the evaluation process, the gaps in care created by an inefficient evaluation, and tractable solutions to improve the evaluation process.

1.2.3 Thesis breakdown

In Chapter 2, I briefly describe the main components that are required to complete a thorough living donor evaluation. Chapter 3 is a targeted discussion on various components of the evaluation where efficiency improvements have been recommended. Chapter 4 follows with a scoping review of the literature to understand the knowledge gaps and summarize the research conducted on the efficiency of the living donor work-up.

Chapter 5 describes the specific aims of the thesis. Chapter 6-10 follow with original work to satisfy these aims. Finally, Chapter 11 provides an overall discussion of the work and discusses its context for future developments.

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Chapter 2

2 Evaluation and Selection of the Living Kidney Donor Candidate‡

The purpose of this chapter is to describe the main components of the living donor evaluation. Although an efficient evaluation is not the subject matter, this chapter is a useful source of reference for the remainder of the thesis.

2.1 Introduction

The practice of living donor kidney transplantation is based on the principle that the benefits to the recipient outweigh the minimal risks to the carefully evaluated and selected living donor. Living kidney donors should undergo a rigorous evaluation and selection process to ensure that the short- and long-term risks to the donor are minimized. In addition to this, the benefits and risks to the intended recipient are also considered. From the recipient perspective, an aim is to select donors who will provide adequate graft function while minimizing the transmission of any donor-derived diseases, such as infections or malignancy. To mitigate potential conflict of interest, it is recommended that the evaluations of the donor candidate and the intended recipient be performed by separate, independent healthcare teams.[1–5]

Multiple guidelines assist clinicians in the complex process of donor evaluation and selection. A systematic review of these clinical practice guidelines found that while many recommendations were consistent, important variations exist and many appeared to lack methodological rigor.[6] The 2017 Kidney Disease: Improving Global Outcomes (KDIGO) 'Clinical Practice Guideline on the Evaluation and Care of Living Kidney Donors' provides a comprehensive set of best practice recommendations based on a systematic

‡ A version of this chapter has been accepted for publication as a subsection of a book chapter. Steven Habbous was responsible for completing this subsection of the book chapter: Lam NN, Habbous S, Garg AX, LentineKL. "Considerations in Living Kidney Donation". Transplantation.

evidence review, *de novo* evidence generation, and expert opinion when evidence was lacking.[1] When possible, the guideline recommends that transplant programs establish numeric thresholds for short- and long-term post-donation risks above which the program will not accept the candidate for donation. It also demonstrates how tools can be developed to help estimate a donor candidate's risk of long-term complications such as end-stage kidney disease based on their individualized set of pre-donation demographic and health characteristics.

A central goal of the KDIGO guideline is to promote "consistent, transparent and defensible decision-making" based on comparisons of individualized, quantitative estimates of donor risks "to a transplant program's acceptable risk threshold".[1] Risk threshold is defined as the upper limit of acceptable risk established by a program for donor candidate selection. Under this framework, when a candidate's estimated risk is above the acceptable threshold, the transplant program is justified in declining the candidate and can ground its decision in a quantitative framework. When a donor candidate's estimated risk is below the acceptable risk threshold, the transplant program should accept a donor candidate, and it should be the candidate's decision whether to proceed with living kidney donation after being informed of the risks. Once established, acceptable risk thresholds should be applied consistently and transparently for all donor candidates evaluated at a program. The KDIGO framework was informed by a systematic evidence review.[7] The KDIGO group also developed a tool to quantify a donor candidate's risk of post-donation complications such as end-stage kidney disease. This tool projects the 15-year and lifetime risk of renal failure based on level of predonation glomerular filtration rate (GFR) and other baseline demographic and health factors.[8] For practical applications, the resulting risk models were incorporated into an online risk prediction tool (http://www.transplantmodels.com/esrdrisk. The tool serves as an example, and can be improved with future research efforts for various types of living kidney donors worldwide.

The evaluation process should include a comprehensive history, physical exam, laboratory and radiological investigations, and specialist consultations. Aspects of the process may vary by region and transplant center, including the order and timing of the

components and what is considered required or additional testing. Depending on local resources and policies, transplant programs may also choose to evaluate multiple donors for an intended recipient either simultaneously or sequentially. The 2017 KDIGO living kidney donor guideline recommends that all donor candidates should be evaluated using the same criteria, regardless of who the intended recipient is.[1]

2.2 Kidney function

The purpose of evaluating GFR in kidney donor candidates is to detect kidney disease and to project long-term outcomes for the candidate and their recipient should they proceed with donation. Recommended methods for evaluating GFR in donor candidates are based on the 2012 KDIGO CKD guideline.[9,10] Considering practicality, test availability, and costs, the 2017 KDIGO living donor guideline recommends initial estimated GFR (eGFR) based on serum creatinine (eGFRcr) and confirmation using one or more of the following measurements according to their availability: measured GFR (mGFR) from clearance of exogenous radio-labeled filtration markers, measured creatinine clearance (mCrCl) based on collecting a timed (24-hour) urine specimen, eGFR based on serum creatinine and cystatin (eGFRcr-cys), or repeated eGFRcr; the latter being the least preferred approach.[1,9,10] Although mGFR or mCrCl is required for donor evaluation in the United States according to Organ Procurement and Transplantation Network (OPTN) policy, a timed urine collection for albumin excretion rate (AER) is not required (i.e., measurement of urine protein or albumin may be performed on a random "spot" urine sample). In countries where clearances are required for assessment of GFR, an efficient strategy may be to omit timed urine collections and rely on mGFR using clearance of an exogenous filtration marker and a random urine albumin-to-creatinine ratio (ACR). In countries where clearance measures are not required for assessment of GFR, transplant programs could obtain eGFRcr, eGFRcr-cys, and urine ACR prior to a candidate donors' visit to the center.[11]

The 2017 KDIGO living kidney donor guideline recommends a GFR ≥90 mL/min/1.73 m^2 as an acceptable level of kidney function for donation, while donor candidates with GFR <60 mL/min/1.73 m^2 should not donate. The decision to approve donor candidates

with GFR 60-89 mL/min/1.73 m^2 should be individualized based on demographic and health profiles.

2.3 Albuminuria

Elevated protein in the urine (proteinuria) may suggest the presence or risk of developing kidney disease due to increased permeability of the glomeruli to protein, and/or an inability of the renal tubules to reabsorb protein. Until acceptable standardization methods are available for quantifying deficiencies in tubular reabsorption, urine albumin remains the most reliable indicator of kidney disease, standardized to urinary creatinine as the ACR. The 2017 KDIGO living kidney donor guideline recommends initial evaluation using ACR in a random urine specimen with confirmation by AER (from a timed urine specimen) or otherwise a second random urinary ACR. Donor candidates with an AER >100 mg/d (or ACR >30 mg/mmol) should not donate. Such candidates have microalbuminuria and are at an elevated risk of developing chronic kidney disease in their lifetime.[12] Candidates with an AER <30 mg/d (or ACR <3 or below the detectable limit of the assay) may be acceptable for donation, while the decision to approve donor candidates with AER 30 to 100 mg/d should be individualized based on demographic and health profiles in relation to the transplant program's acceptable risk threshold.

2.4 Hematuria

The persistent presence of blood in the urine (hematuria) is another indicator for the presence or risk of developing kidney disease. Presence of hematuria is established by visualizing 2-5 red blood cells per high-powered field on microscopic evaluation. "Persistence" is established if hematuria is observed in more than 50% of urine samples obtained from 2-3 separate occasions. When hematuria is persistent, further investigation is warranted which many include a urine culture for bacterial or fungal infection (this may be treated without affecting candidacy), a 24-hour urine kidney stone panel, a cystoscopy, imaging to rule out a urinary tract malignancy, and a kidney biopsy to rule out underlying kidney disease (thin basement membrane disease may not be a contraindication to donation).[13,14]

2.5 Kidney stones

A renal calculus in the donor's remaining kidney may affect kidney function if it results in ureteral obstruction. Reassuringly, living kidney donors do not appear to have an increased risk of kidney stones requiring treatment with surgical intervention compared to healthy, matched non-donor controls (median follow-up of 8 years).[15] Evaluation of kidney stones in living kidney donor candidates includes a history from the candidate, laboratory investigations, including persistent microscopic hematuria, and renal imaging such as computed tomography. If suspected, further investigations may be performed, including parathyroid hormone measurements and 24-hour urine collections for metabolic testing. A history of previous stones does not necessarily rule out donation, particularly small, unilateral, non-recurrent stones.[1] There is also the option to remove small kidney stones at the time of procurement prior to transplantation.[16]

2.6 Hyperuricemia, gout, and metabolic bone disease

Compared to non-donor controls, living kidney donors have an increased risk of gout (3.4% versus 2.0% in non-donor controls, a median 8 years after donation).[17] This may be due to the reduced ability of a single kidney to excrete excess uric acid, a precursor to gout. Although a comprehensive gout assessment is not usually conducted for all candidates, pre-donation serum urate is frequently ordered alongside other biochemical indicators of metabolic kidney disease, including inorganic phosphate, calcium, and parathyroid hormone. Living kidney donor nephrectomy may lower the concentration of 1,25-dihydroxyvitamin D and phosphate and raise the concentration of parathyroid hormone, with no appreciable effect on the concentration of calcium. Whether these changes in bone mineral metabolism alter skeletal fracture risk in living kidney donors is an open question. To date, a single study of over 2,000 living kidney donors (median age 43 years) matched to a segment of the general population selected for good health has found that after a median follow-up of 6.6 years (maximum 17.7 years), the rate of fragility (osteoporotic) fractures is no higher in donors compared to non-donors.[18]

2.7 Blood pressure

Sustained elevated blood pressure is a common cause of kidney disease, and conversely, kidney disease may accelerate the development of high blood pressure. Candidates with hypertension are eligible for donation only if their blood pressure can be controlled with anti-hypertensive medications and that they are without end-organ damage related to their hypertension.[1] The systolic and/or diastolic blood pressure thresholds and the nature of the anti-hypertensive medications used (e.g. number of agents, class of drugs, and dosage used) to disqualify a candidate may vary across programs and according to other candidate characteristics. Blood pressure measurements should be performed on at least two separate occasions by trained personnel. An ambulatory (e.g. 24-hour) blood pressure monitor may be used if hypertension is suspected. Donor candidates with hypertension that can be controlled to less than 140/90 mmHg using 1 or 2 antihypertensive agents, and who do not have evidence of target organ damage, may be acceptable for donation. The decision to approve donation in persons with hypertension should be individualized based demographic and health profiles in relation to the transplant program's acceptance risk threshold.

2.8 Metabolic and lifestyle risk factors

Obesity is a strong risk factor for diabetes, cardiovascular disease, and kidney disease. Living donor nephrectomy is more difficult for patients with excess visceral fat, increasing the risk of perioperative complications including infection, blood loss, and delayed wound healing.[19] Various body mass index (BMI) cut-points have been reported in the literature as absolute or relative contraindications to donation. Elevated serum glucose or glucose intolerance are also strong risk factors for diabetes. Apart from personal and family history assessments of diabetes (childhood, adult-onset, gestational), glycosylated hemoglobin and serum and urinary glucose are typically measured early in the assessment of all candidates. Fasting glucose and glucose tolerance tests are recommended for high-risk candidates (e.g. high random glucose, positive family history). According to the 2017 KDIGO living kidney donor guideline, donor candidates with type 1 diabetes mellitus should not donate. The decision to approve donor candidates with prediabetes or type 2 diabetes should be individualized based on

demographic and health profiles in relation to the transplant program's acceptance threshold. Donor candidates with prediabetes and type 2 diabetes should be counseled that their condition may progress over time and may lead to end-organ complications.[1] Less evidence is available to comment on the influence of predonation lipids (e.g. cholesterol, triglycerides, and high-density and low-density lipoproteins) and smoking on donor candidacy, although notably, smoking was a strong risk factor for kidney failure in healthy persons.[8] While candidates should be educated and encouraged to modify their dietary and smoking habits, eligibility based on these factors may vary across programs. Smoking should be considered as part of comprehensive risk assessment.

2.9 Screening for transmissible infections

To minimize the risk of viral transmission from the donor to the recipient, the evaluation should include assessment of prior history of infections, recent travel history, and virology screens early in the evaluation and again within the 2-4 weeks of donation to minimize the window of infection.[20,21] The 2017 KDIGO living kidney donor guideline recommends screening for human immunodeficiency virus, hepatitis B and C, Epstein-Barr virus, cytomegalovirus, syphilis, urinary tract infection, and other potential infections based on geography and environmental exposures.[1] If a donor candidate is found to have a potentially transmissible infection, then the donor candidate, the intended recipient and transplant team should weigh the risks and benefits of proceeding with donation, and develop a management plan if the decision is to proceed with donation.

2.10 Cancer screening

All candidates should be up-to-date with local cancer screening guidelines according to age, sex, and family history. Donors with active cancer are generally not eligible to donate. Donors with a prior history of successfully treated cancer with a high risk of reoccurrence may be excluded from donation because anti-neoplastic agents may be nephrotoxic, and because transmission of cancer from the donor to the recipient can have serious consequences to the immunocompromised recipient.[22] Candidates with a prior history of cancer with a low risk of reoccurrence may be considered on a case-by-case basis. In some cases, candidates with small renal tumors (high-grade Bosniak renal cysts

(III or higher) or small (T1a) renal cell carcinoma curable by nephrectomy) may be acceptable for donation, and the donor and recipient provide consent for the cancer to be resected at the time of donor nephrectomy.[23,24]

2.11 Genetic kidney diseases

If the donor candidate is biologically related to the intended recipient, the cause of the recipients' kidney disease should be well understood before accepting the candidate. Candidates with a genetic kidney disease generally are not eligible to become donors. If a candidate has a family history of a genetic kidney disease, the candidate may be eligible to donate if the risk of developing kidney disease after donation is acceptably low and the risks are discussed with the candidate. Genetic diseases that may be assessed during the donor candidate evaluation include autosomal dominant polycystic kidney disease, APOL1-related kidney disease, atypical hemolytic uremic syndrome, Alport syndrome, Fabry disease, familial focal segmental glomerulosclerosis, and autosomal dominant tubulointerstitial kidney disease.

If a donor candidate is of sub-Saharan African ancestry, testing for APOL1 risk alleles may be offered.[25,26] The presence of two APOL1 risk alleles increases the lifetime chance of developing kidney failure even in the absence of donation. The effects of kidney donation on this risk are unknown, but are a topic of active research.

2.12 Pregnancy

While donation does not preclude future pregnancy and child-bearing, patients are not evaluated or do not donate while they are pregnant. A history of hypertensive disorders related to pregnancy (e.g. preeclampsia, gestational hypertension) increase the risk of developing kidney failure later in life, and the severity, timing, and frequency of these conditions should be considered before determining the potential donor's candidacy.

2.13 Psychosocial assessment

The 2017 KDIGO living kidney donor guideline recommends that a psychosocial assessment be conducted for all donors (regardless of relationship with the intended

recipient), in the absence of the intended recipient (to reliably assess voluntariness), and by a professional independent from the care of the intended recipient. A thorough psychosocial assessment should minimize the incidence of poor psychosocial outcomes postdonation by careful selection or treatment (e.g. counseling).[51] Quality of life is generally positive postdonation, but there have been instances of regret, depression, and financial hardships.[52,53]

2.14 Conclusion

This chapter summarized the main components of the living donor assessment, as well as quantitative and qualitative issues related to donor eligibility. With this background, concerns of efficiency can be discussed while completing a thorough evaluation.

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Chapter 3

3 Optimizing efficiency in the evaluation of living donor candidates: Best practices and implications[§]

3.1 Introduction

Compared with chronic dialysis, kidney transplantation is associated with increased survival, improved quality of life, and reduced costs to the healthcare system.[1–5] Living donor transplant is preferred over deceased donor transplant because the surgery can be scheduled when the recipient is in optimal health, without the wait for a deceased donor kidney to become available, potentially avoiding the need to start dialysis (pre-emptive transplantation), with a better graft survival than deceased donor kidney transplantation.[6,7] Despite these benefits to the recipient, in most regions the rate of living kidney donation has been stagnant over the last decade and remains well below the rate of deceased donation.[8–12] Thus, there is interest in safely increasing the number of living donor kidney transplants.

There are many recognized barriers to living kidney donation. One barrier that has received little attention, and is the focus of this review, is inefficiencies in the living kidney donor evaluation process.[13] A study in Ireland reported that the donor evaluation process can exceed 2 years, leading to donor fatigue and eventual dropout.[14] A multi-center Canadian and Australian study reported a median evaluation time (from evaluation start until donation) of 10.3 months (Chapter 6).[15] Notably, most donors feel that even 6 months is too long for this process.[16] The United Kingdom has set a target to complete the donor evaluation in under 5 months, but in current practice this target may not be

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achievable in many programs.[17] Although donor candidate withdrawal rates can reach 30% in some centers, it is difficult to quantify how many of these withdrawals are attributable to a prolonged evaluation process.[18,19] An international consensus conference highlighted the efficiency of the evaluation as a research priority.[20,21] The 2017 Kidney Disease: Improving Global Outcomes (KDIGO) Guideline on the Evaluation and Care of Living Kidney Donors recommends that transplant programs conduct efficient donor evaluations, meeting the needs of donor candidates, intended recipients, and the transplant program.[22] However, due to a lack of supporting evidence, this recommendation is ungraded.[22] In this review, we examine reasons why the living kidney donor evaluation may be inefficient, and make recommendations to optimize this process.

3.2 The Donor Candidate Evaluation

A thorough evaluation will result in donor selection that will optimize the medical and psychosocial outcomes of the donor candidate and their intended recipient. Minimizing donor risk is one of the main objectives of the living donor candidate evaluation and is the reason why donors and recipients often have different healthcare teams responsible for their care.[23,24]

A schematic of an overview of the evaluation process is shown in Figure 5. Typically, the donor candidate must contact the transplant program by phone, internet, or in person to express their interest in donation and initiate the evaluation process. Then, donor candidates complete a standard medical-social questionnaire and initial compatibility testing with an intended recipient (e.g. blood group). Following this, there is a more comprehensive set of laboratory and diagnostic investigations (Table 1). Candidates also meet with members of the transplant team in consultation, including nephrologists, surgeons, and psychosocial experts (e.g. social workers, psychologists). Candidates who meet the transplant center's eligibility criteria and make an informed decision to proceed will then be scheduled for nephrectomy.

For each of these steps, we offer recommendations that may lead to improved efficiencies with respect to reducing costs and/or the time to completion, drawing on the literature where possible (Figure 5). To improve economic efficiency, the process should perform

the minimal number of tests needed, use the least costly alternative, and avoid redundant or repeat testing. The living donor evaluation process is typically graded, organized to progress from less invasive and less costly tests to more invasive and costly tests, as needed.[25,26] To improve technical efficiency, the process should attempt to maximize the number of successful donations with respect to the number of donor candidates who start the evaluation process. The process should also attempt to maximize the number of completed evaluations with respect to the number of donor candidates who start the evaluation (regardless of donation).

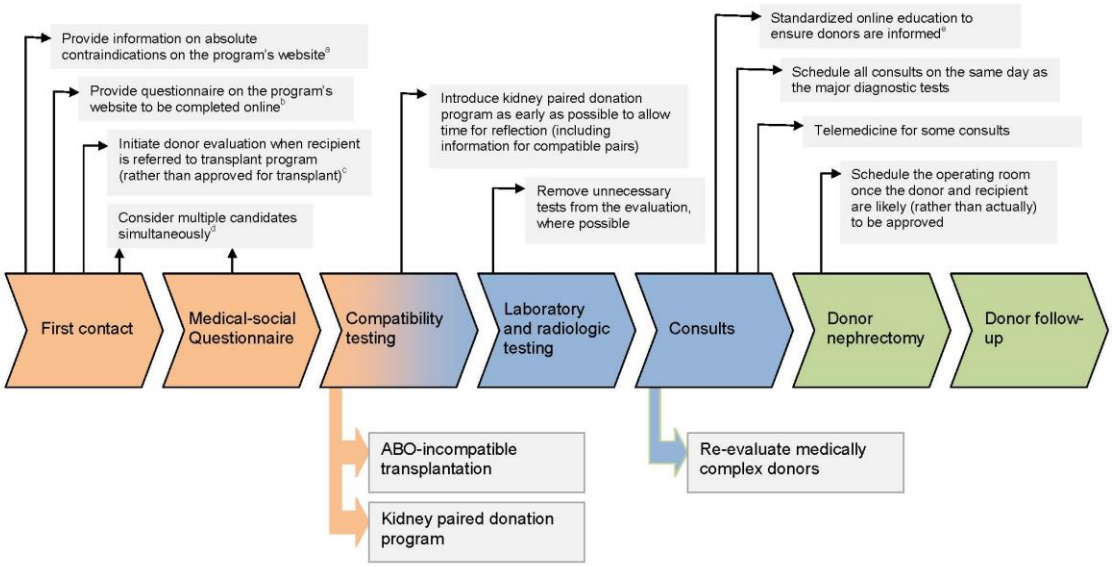

Figure 5: General flow of the living donor evaluation process with potential efficiency improvements

[a] Could also provide a living donor toolkit, with frequently asked questions, testimonials from previous donors, and details about the donation process
[b] Automated data quality checks to ensure it is filled out completely
[c] Care is needed to avoid evaluating the donor candidate too far ahead in case the recipient is never referred
[d] Encourage multiple candidates to initiate the process
[e] Can also have online tests to ensure the donor candidate understands the information provided to them

3.2.1 First contact

The donor candidate must self-refer to a living donor program. At first contact, the living donor coordinator can answer any initial questions the candidate may have and can

identify any absolute contraindications (e.g. type 1 diabetes mellitus) or issues that must be resolved before the evaluation can proceed (e.g. very high body mass index, uncontrolled hypertension). One strategy to improve the efficiency of the first contact stage is to provide information on absolute contraindications on a trusted website to reduce contacts from ineligible donor candidates and the associated workload on living donor coordinators.[27,28] Also, renal program staff working with patients with kidney failure and their families can provide basic education on absolute contraindications when discussing living kidney donation.

Table 1: Tests related to the living donor evaluation

Test	Indication	Pain[a]	Time to complete	Time to results (approximately)	Location of test
Initial screening					
First contact	all	0	various	immediately	digital
Medical-social questionnaire	all	0	various	7 days	digital or paper
Compatibility testing					
ABO blood typing	all	1	5 min	1 day	local lab
HLA typing	all	1	5 min	1 day	hospital
Biological crossmatching	all	1	5 min	5 days	hospital
Blood					
Blood chemistry	all	1	5min	1 day	local lab
Virology	all	1	5min	1 day	local lab
Oral glucose tolerance test	if indicated	1.5	2 hours	2 days	local lab
Urine					
Random urine test	all	1	5 min	1 days	local lab
24-hour urine test	program-specific[b]	2	24 hours	1 day	local lab
Imaging/other					
24-hour blood pressure monitor	if indicated	2	24 hours	1 day	home
Electrocardiogram	all	1	5 min	1 day	local lab
Chest x-ray	all	1	10 min	1 day	local lab
Echocardiogram	if indicated	1	1 hour	7 days	hospital
Renal ultrasound	all	1	45 min	2 days	local lab
Renal imaging (CT or MR)	all	2	1 hour	2 days	hospital
Nuclear renogram for split GFR	if indicated	2	1.5 hours	2 days	hospital
Nuclear GFR	if indicated	2	4.5 hours	2 days	hospital
Cystoscopy	if indicated	3	15 min	1 day	hospital
Biopsy	if indicated	3	6 hours	1-3 weeks	hospital

Cancer screening	if indicated	1-2	?	?	hospital or clinic
Consults					
Nephrology consult	all	1	1 hour	1 to 5 days	hospital
Surgical consult	all	1	45 min	1 to 5 days	hospital
Social worker consult	program-specific[b]	2	1.5 hours	5-6 days	hospital or phone (at least one in person)
Cardiology consult	if indicated	1	1 hour	7 days	hospital

GFR – glomerular filtration rate; CT – computed tomography; MR – magnetic resonance; HLA – human leukocyte antigen

[a] a subjective measure of invasiveness or pain based on our opinion (1 – least; 3 – most)

[b] all or if indicated, depending on the program's standard procedure

At this stage, there is also an opportunity to prioritize donor work-up when multiple donor candidates come forward for the same recipient. The donor candidate that is assessed first should be the one who is most likely to donate (i.e., has fewer comorbidities, has a closer relationship to the intended recipient, is biologically compatible). Most living donor programs perform sequential evaluations (i.e. work up one donor at a time). Although this is a cost-saving strategy with regard to donor evaluation costs, if the primary candidate does not donate, then the potential recipient will have consumed more healthcare resources related to their disease while waiting longer for the next donor to be approved. Currently, there is no evidence that sequential donor evaluations are more cost-effective than simultaneous donor evaluations.

3.2.2 Medical-social Questionnaire

A questionnaire is the most effective way to obtain information on the donor candidate's medical and psychosocial history, family history, and social habits (e.g. behaviour associated with transmissible infections, substance use). Results from the questionnaire can identify risk factors to both the donor and the recipient and inform the content of the evaluation or the order of tests. For example, some donors may require additional tests or consultations, while others may require a psychosocial assessment earlier than usually offered by the program.

The medical-social questionnaire can be done at the time of first contact or can be completed and received by the donor program after the first contact. At some donor

programs, a coordinator completes this questionnaire over the phone or in person with the donor candidate. While such a process can be time-consuming and resource intensive, it has the advantage of allowing coordinators to answer any initial questions the donor candidate may have, as well as gather further information on their medical history, if positive. Other programs provide this questionnaire on their website to be downloaded or completed online by the candidate; however, online submission may create a backlog of completed questionnaires that cannot be reviewed by healthcare staff in a reasonable amount of time. The length of the questionnaire varies across programs. For example, individual programs in Canada can modify a standardized questionnaire that includes at least 50 questions.[29] In contrast, a quality improvement initiative in Ireland developed a short (one-page) questionnaire with yes/no responses for ease of administration.[14] However, it is unclear whether the length of this questionnaire influences the time to complete the evaluation.

3.2.3 Compatibility Testing

Donor and recipient ABO blood typing, human leukocyte antigen typing, and cross-match testing are required to minimize the risk that the donor kidney will be rejected by the intended recipient.[30–32] If multiple donor candidates come forward for the same recipient, then it may be prudent to prioritize candidates who are more immunologically compatible.

For biologically incompatible pairs, alternatives include kidney paired donation (incompatible donor-recipient pairs exchange with each other) or performing incompatible transplants with desensitization protocols (a treatment option that removes antibodies from the recipient and aggressively suppresses the immune system).[33,34] Due to the costs and medical risks associated with desensitization, kidney paired donation is often the preferred option. However, kidney paired donation poses other challenges that may impact the efficiency of living donation, such as finding and organizing multiple exchanges with hard-to-match transplant candidates.[35–38] Matching cycles are conducted intermittently (e.g. every 3-4 months), which may prolong the time until donation can occur and impose a barrier for some donor candidates.[39] A recent study of 849 living kidney donors reported that the paired donation program prolonged the total time until

donation by 6.6 months (Chapter 6).[15] Furthermore, many donor candidates are unable or unwilling to travel to donate due to financial or time constraints or lack of family support. To address this barrier, one strategy is to transport the donor's kidney to the recipient's transplant hospital, recognizing that this may increase the cold ischemia time.[40,41] Medically suitable but biologically incompatible donors should be counseled early about the advantages and disadvantages of paired donation programs and be given the option to stop their evaluation early if they are not willing or able to proceed.

3.2.4 Laboratory and Radiologic Testing

For convenience, most initial blood and urine tests can be performed at local laboratories, rather than at the transplant center. These tests are typically performed before the donor candidate visits the transplant center for the first time, and the results can guide the remainder of the evaluation.[42] For example, if a donor candidate has persistent microscopic hematuria on multiple urinalyses, further work-up would be recommended to rule out infection, renal calculi, malignancy, and renal pathology. To rule out bladder malignancy, consultation with a urologist for consideration of cystoscopy is routine; however, for low-risk patients (i.e., <35 years of age), this step may be unnecessary given its low yield.[43] Moreover, cardiac evaluations (e.g., cardiology consultations, echocardiograms, nuclear stress tests) may not be necessary for donor candidates who have good exercise tolerance, yet guidelines are vague on this topic.[43]

A 24-hour urine collection is used to measure the donor candidate's creatinine clearance (an indicator of kidney function); however, results may be inaccurate in the setting of over- or under-collection.[44] Currently, there is no consensus on how many 24-hour urine tests should be performed (range 0-2 tests considered as part of the standard work-up).[15] Although there is no evidence that eliminating this test from the evaluation process results in more timely completion, it may reduce the burden on donor candidates.[15]

Due to its relatively low cost and high availability, renal ultrasound may provide the first image of the kidney in some regions. Renal ultrasound can identify cysts, kidney stones, and other anomalous findings in adjacent anatomy that require further investigation (i.e., liver, ovaries).[45–47] Advanced renal imaging, such as computed tomography (CT) or

magnetic resonance (MR) angiography, is a critical part of the living donor evaluation and may be reserved for a later phase of the evaluation because of its higher costs and wait times in some regions. CT or MR angiography provides higher resolution than renal ultrasound, enabling more accurate mapping of the renal vasculature, which is necessary to plan the donation surgery.[48,49] Nuclear renogram has been recommended to measure the split kidney function to determine which kidney should be donated, if indicated by differential kidney dimensions identified earlier in the evaluation. Due to the graded nature of the evaluation, advanced (and costly) imaging modalities are usually performed later. When donor candidates do not proceed to this stage of the evaluation (i.e., declined or withdrew), these tests would not be needed and fewer resources would be used to complete the evaluation. Even in the setting of a 1-day evaluation, the CT scan may be scheduled later in the day and subject to cancellation following review of earlier test results by the consulting nephrologist or surgeon.[14]

Other efforts to improve the efficiency of the living donor evaluation process have focused on eliminating the need for some tests, such as an assessment of split function with nuclear renogram. Some investigators have suggested using CT volumetry to estimate split kidney function instead of nuclear renogram.[50,51] Others have devised an algorithm to omit the measured glomerular filtration rate (GFR) test to assess the total kidney function: donor candidates whose estimated kidney function (based on serum creatinine and/or cystatin C) is sufficiently high or sufficiently low that the measured GFR will not change the decision on the candidate's eligibility may proceed or be declined without the need for measured GFR.[52,53]

3.2.5 Consults

All programs require donor candidates to receive consultation with a nephrologist and a surgeon, with less agreement on routine consultation with a psychosocial specialist.[54] Some programs have systems in place to permit all initial testing and imaging as well as consultations to be scheduled for the same visit. This is intended to reduce the travel burden for donor candidates, particularly for those who live far from the transplant center, but may also permit a one-day donor evaluation as a routine process for all donor candidates.[14,15] Despite this, the time between these three consultations is on average 3

months across Canada and Australia.[14] Another strategy to improve the efficiency of the consultations may be to delay the surgical consult in patients without a significant history of abdominal surgery, who have a healthy weight, and no abnormalities on initial testing. In this way, the surgeon would only see patients who are more likely to proceed with nephrectomy.

3.2.6 Donor Nephrectomy

CT angiography is generally regarded as one of the late-phase tests in the evaluation, and may further delay the evaluation as there may be a significant waiting time to book a CT angiogram in some regions. One potential solution is to negotiate dedicated time with radiology, and so the living donor program can expect a given number of spots for living donor assessments each week. The average time from CT until donation was reported to be 4.8 months across Canadian and Australian centers, ranging from 3-8 months.[15] If these delays are attributable to difficulties scheduling the operating room (OR), then efforts should be made to book the OR as early as possible, considering the needs of the donor candidate, the recipient, and the OR staff. Donor candidates often express times of the year when they can (or prefer to) donate so the recovery process will not greatly interfere with their work, dependent care, or other responsibilities. In situations where this leaves ample time for an evaluation, booking the OR should not be a factor delaying the time until donation. Conversely, if an expedited work-up is necessary, then the living donor program should work with the surgeons and the OR staff to book the ORs once the donor and recipient are likely to be approved (rather than waiting until the actual approval date). Alternatively, the living donor program could negotiate having a standing time in the OR schedule to accommodate the expected number of donations each year.

3.2.7 Other Aspects of the Evaluation

3.2.7.1 When does the living donor evaluation actually start?

Most programs do not start the living donor evaluation until the recipient has at least been referred to the transplant program. Some programs may additionally require that the recipient is approved for transplant. This latter strategy is a cost-conscious one, avoiding donor evaluations for those whose recipients will not be eligible for transplant. However,

this may delay the time until transplant, which will be particularly costly for recipients who are on dialysis. Although the optimal strategy to initiate the living donor work-up is unknown, the funding model and payer perspective are important considerations, as cost savings in one domain (fewer living donor evaluations) may not be reconciled by cost savings in another (less time on dialysis). In either case, earlier recipient referrals are expected to translate into earlier transplants.

3.2.7.2 Navigators as part of the evaluation

Donors are healthier than the general population, and may therefore be unfamiliar with healthcare systems. The use of prior recipients as navigators has been shown to be effective at increasing the number of steps completed as part of the evaluation for recipient candidates.[55] In Ontario, a pilot Transplant Ambassador Program is being launched: by connecting potential donor and recipient candidates with prior donors and recipients, candidates will be better positioned to make decisions about donation or transplantation and will be better informed about navigating the evaluation process. The Transplant Ambassador Program is expected to increase the number of living donor candidates contacting programs and the number of evaluation tests completed, but will also be positioned to assess the impact of donor ambassadors on the timeliness of donation.[56]

3.2.7.3 Cost to the living donor

The out-of-pocket costs to the donor to participate in and complete the evaluation have been recognized as a substantial barriers to living kidney donation.[57–59] Although reimbursement for at least some of these costs helps some donor candidates, others are still disadvantaged because reimbursement may occur some time after the evaluation is complete, be limited to only to those who complete an evaluation, or include only a portion of costs incurred (e.g., costs of travel and lodging, but not lost wages).[59–63] A pre-paid credit card for valid expenses or validated hospital parking may remove this barrier and allow candidates to complete the evaluation in a timely manner. Telemedicine is also a valid option for some consultations or educational sessions, particularly for donors who

live far from the transplant center. However, the effectiveness of such strategies has not yet been demonstrated.

3.2.7.4 Evaluating center is not the same as the center where donation is intended

The donor candidate is typically assessed at their home program, and if approved, their chart is sent to the intended donor recovery program for review. Differences in program-specific evaluation and selection criteria may result in inefficiencies, particularly when the home program may not perform tests routinely done by the recovery center. This may lead to additional or redundant testing after the candidate has already been approved by the home center. To ameliorate this, for donor candidates enrolled in the Canadian kidney paired donation program, a minimum set of required tests has been established by consensus.[29] However, for donor candidates who are not in the kidney paired donation program, this remains a potential source of inefficiency, and a uniform set of criteria for donor selection and evaluation should be adopted, regardless of donation strategy (direct donation, simple exchanges, national paired donation programs).

3.3 The intersection of efficiency and quality

Numerous quality indicators are reported by governmental health authorities each year that may be used to provide benchmarks or serve as indicators of quality, equity, or effectiveness. Common metrics include the number of deaths after an intended recipient has been approved for transplant but has not yet received one, the time spent on the wait-list, the number of patients on dialysis, the number of living and deceased donor kidney transplants performed, and the burden of disease on the healthcare budget.[64] A prolonged living donor evaluation will adversely affect most of these outcomes, but there are additional indicators that are important, yet not reported (Figure 6). If the intended recipient could receive a pre-emptive transplant, then this may avoid complications of kidney failure, reduce costs, and increase quality-adjusted life expectancy.[65–69] A new study at five centers in Ontario, Canada found that one-third of living donor transplant recipients initiated dialysis prior to receiving their living kidney donor transplant, despite their donor's evaluation being well underway (Chapter 8).[66] A faster donor evaluation

may increase the number of pre-emptive transplants.[14,70] In a similar vein, if the intended recipient dies while the living donor is being evaluated, this can also have long-term implications on the psychosocial health of the donor candidate. Finally, since most programs do not remove transplant candidates from the deceased donor wait-list because they have a living donor, deceased donor kidney transplantation is a competing treatment option that prevents another recipient from receiving that deceased donor organ, if the deceased donor organ is accepted in favor of living donation.[7] These outcomes are also not routinely reported.

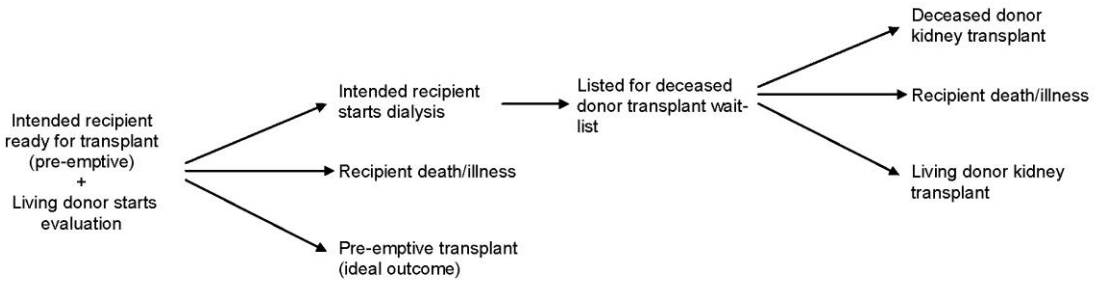

Figure 6 Potential implications of an inefficient living donor evaluation process. Once the living donor begins the evaluation and the intended recipient is approved for transplant, a prolonged evaluation may result in adverse consequences for the intended recipient, including dialysis initiation, transplantation from a deceased donor instead, or ineligibility resulting from death or illness.

3.4 Recommendations for future research

It is clear that an inefficient living donor evaluation can have substantive unintended consequences that have not yet been consistently measured and reported to date. The rather nebulous definition of "efficiency" complicates measurement using any single metric and likely requires multiple complementary indices.[15] However, we propose a working definition: an efficient evaluation is one that is completed in as little time as possible, results in optimal outcomes, and meets the expectations of patients and healthcare providers.

Quality indicators are needed for quality improvement projects.[14,71] Such indicators should be defined clearly and measured to enable comparisons between and within transplant programs. They should be measured retrospectively to provide an environmental scan and allow benchmarking, and also prospectively to facilitate monitoring in continuous audit-feedback loops. We recommend a few quality indicators, such as the total time until donation, among others[15,70], but a systematic approach is needed to generate a more complete list and define measures operationally (i.e., these metrics may require uniform definition of the evaluation start date, or a minimum time sufficient to complete an average donor's evaluation). We recommend that all stakeholders (patients, healthcare providers, insurers, and policy-makers) be involved in this process and remain engaged to identify, design, and implement solutions to improve the efficiency of the donor evaluation process. A more efficient living donor evaluation is expected to improve the living donor experience, increase the rate of living donor kidney transplants, improve recipient health, and reduce healthcare expenditures.

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Chapter 4

4 The efficiency of evaluating candidates for living kidney donation: a scoping review[**]

4.1 Introduction

An efficient living donor candidate evaluation is completed in as little time as possible and meets the needs of the donor candidate, the intended recipient, and the healthcare system. An inefficient evaluation process can result in missed opportunities for preemptive transplants if the intended recipient's kidney disease progresses.[1,2] If an intended recipient is approved for transplant but the evaluation of their living donor is delayed because of an inefficient healthcare process, this may cause anxiety and frustration for the recipient and the donor.[3] Finally, there may also be missed opportunities for living donor transplants if the intended recipient receives a deceased donor kidney transplant while their donor is being actively evaluated.[4]

A need to improve the efficiency of the living kidney donor candidate evaluation is featured in reports from patient advocacy groups, a recent consensus conference in the United States (U.S.), the 2017 Kidney Disease Improving Global Outcomes (KDIGO) international practice guideline, and a report from the National Health Services in the United Kingdom (U.K.) targeting an 18-week evaluation, where possible.[5–8] However, while advocating for efficiency, these reports do not provide any recommendations on how efficiency can be achieved.

[**] A version of this chapter has been accepted for publication: Habbous S, Woo J, Lam NN, Lentine KL, Cooper M, Garg, AX. "The efficiency of evaluating candidates for living kidney donation: a scoping review". *Transplantation Direct*. 2018:4(10):e394.

A review that summarizes existing information on the efficiency of the donor candidate evaluation can provide a necessary foundation for quality improvement.[9] As a multidimensional construct (including the time to complete the evaluation, patient outcomes, and resource use), an efficient evaluation process may not easily be summarized in a single systematic review of a focused question. Instead, we undertook a scoping review to map the available literature to themes related to an efficient living kidney donor candidate evaluation. We also reviewed the websites of living donor programs from four countries to describe the information provided to candidates about the nature and length of the evaluation process.

4.2 Methods

4.2.1 Literature review:

We followed the recommendations of the Joanna Briggs Institute for conducting and reporting scoping reviews.[10] On September 12, 2017, one author (S.H.) searched bibliographic databases using the search terms "living AND kidney AND donor AND (assessment OR evaluation OR practice OR screening OR selection OR efficient OR efficiency)" [Medline (n=2,801 citations via PubMed), PsychInfo (n=58), EMBASE (n=2,899 via OVID), and ABI Inform Collection (n=5)]. Search terms were chosen based on terms associated with known articles of interest. Articles were restricted to human studies published in English from 2000 onwards. Conference abstracts were excluded. Studies were not restricted by age or country. Google searches and reference lists of relevant articles were screened and manually added if appropriate, regardless of publication date. The title, abstract, or full-text of an article was used to sort the literature into themes related to the efficiency of living kidney donor evaluations. We then summarized the findings within each theme, focusing on how they could be used to guide future efficiency improvements. Articles only considering how accepting donors with certain characteristics influenced their postdonation outcomes were excluded.

4.2.2 Living donor program websites:

From May to August 2017, we searched the websites of living donor programs in Canada, U.S., U.K., and Australia for information related to an efficient evaluation process.

4.2.3 Statistical methods

Meta analysis was performed using the `metaprop` package in STATA v13.0 using a random-effects model. Confidence intervals were calculated using exact methods.

4.3 Results

A total of 4,706 articles were available for screening after duplicates were deleted. After applying the exclusion criteria, 273 articles were available for mapping (Figure 7). Five relevant themes emerged through the mapping process: 1) surveys of living donor program practices (eight studies); 2) renal imaging for the living donor assessment (159 studies); 3) kidney function assessment (56 studies); 4) the flow of living donor candidates through the evaluation process (38 studies); and 5) the living donor experience with the evaluation process (12 studies).

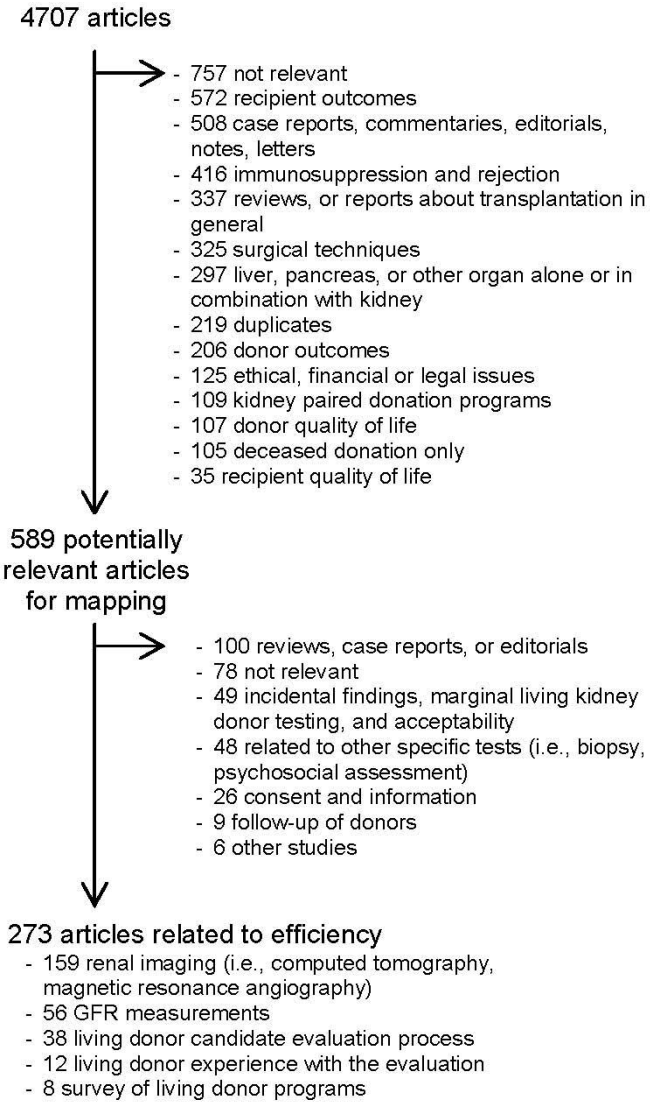


Figure 7: Summary of literature search, study inclusion and mapping for scoping review.

4.3.1 Studies surveying living donor programs

Eight surveys of multiple transplant programs were conducted in the U.S.[11–14], U.K.[15,16], France[17], and Europe[18] (Table 2). These surveys revealed some similarities in the evaluation and selection of living donor candidates, but also some notable differences in donor eligibility criteria and tests performed to evaluate a candidate.[12,19,20] Evaluating the

efficiency of the living donor evaluation process was not an objective of any of the surveys.

Table 2: Survey of living donor programs

Reference	Country	Number of centres responding	Average number of living donor transplants per centre each year
Bia 1995[12]	USA	173/231 (75%)	13
Lumsdaine 1999[16]	UK	29/31 (94%)	4.7
Gabolde 2001[18]	France	36/46 (78%)	1.6
Mandelbrot 2007[13] or Rodrigue 2007[14]	USA	132/205 (64%)	39
Lennerling 2012[19]	Europe	113 programs over 40 countries	median <50
Brar 2012[15]	USA	72/181 (40%)	median ~80
Arunachalam 2013[17]	UK	44/74 (59%) includes transplant and non-transplant centres	69

Table: Studies surveying living donor programs

4.3.1.1 Number of donors evaluated simultaneously

Several donor candidates may come forward at the same time for the same recipient. This may increase to dozens of candidates when recipients share their need for a living donor on social media, which is often public.[21] One survey from the U.K. reported that 50% of centres evaluate one donor candidate at a time, while 20% evaluate 2 or more simultaneously (although it was not reported what the policy is among the remaining 30%).[16] Detail on the relative rigor of the evaluations was not reported (e.g. one candidate evaluated quicker; full versus partial evaluation for one or all candidates). Further research is needed on the optimal use of resources in evaluating multiple donor candidates simultaneously versus sequentially.

4.3.1.2 Removal from the deceased donor wait-list

Some intended recipients are on a waitlist for a deceased donor kidney while the evaluation of their living donor candidate is underway. In such cases, a prolonged living donor evaluation may result in a deceased donor transplant and the loss of a kidney from a potential living donor at that time. A recent survey of 44 transplant centres from the U.K. reported that recipients are removed from the deceased donor waitlist when the

living donor kidney transplant date is scheduled (16 centres), when the candidate is approved for donation (eight centres), when the final crossmatch is complete (five centres), or on the actual day of the living donor transplant (one centre).[16] The U.S., Organ Procurement and Transplantation Network policy now requires potential recipients of all organ types (living or deceased) to be registered on the waiting list prior to their transplant, although listing status may be inactive to prevent offers of a deceased donor (policy 3 in reference).[22]

4.3.1.3 Receipt of a formal psychosocial evaluation

Survey responses suggest a formal psychosocial evaluation is required for all donor candidates by 74% of programs in the U.S. (survey from 2007), 60% in Europe (survey from 2001), and 53% in France (survey from 2013).[13,17,18] Whether these assessments were conducted by a psychiatrist, psychologist, or social worker varied. Programs that do not routinely conduct a formal psychosocial evaluation may do so if underlying problems were identified or suspected during the evaluation, or if the donor was unrelated to the intended recipient. The 2017 KDIGO guideline recommends that all candidates receive an in-person psychosocial evaluation (an ungraded recommendation due to insufficient evidence).[7] As of 2013, a psychosocial evaluation is required during the assessment of *donors* (rather than *candidates*) in the U.S., which can be conducted by any of the 3 aforementioned professionals (policy 14 in reference).[22] We are unaware of whether these policies impacted the efficiency of the living donor work-up.

4.3.1.4 Time for smoking cessation or abstinence

The requirements related to smoking have become less stringent over time. Most centres do not routinely exclude active smokers (36% of French centres exclude only heavy smokers; only 2% of U.S. centres require documentation of cessation), but instead urge donors to stop (or reduce) smoking for some period of time before donation.[13,17]

4.3.1.5 Time to complete evaluation

The time to complete the donor evaluation was mentioned briefly in two surveys from the U.K. Twenty programs did not have a targeted time period, but 3-6 months was seen as

an appropriate window by nine programs (although the start and end dates of the evaluation were not defined).[15,16]

4.3.1.6 Other differences

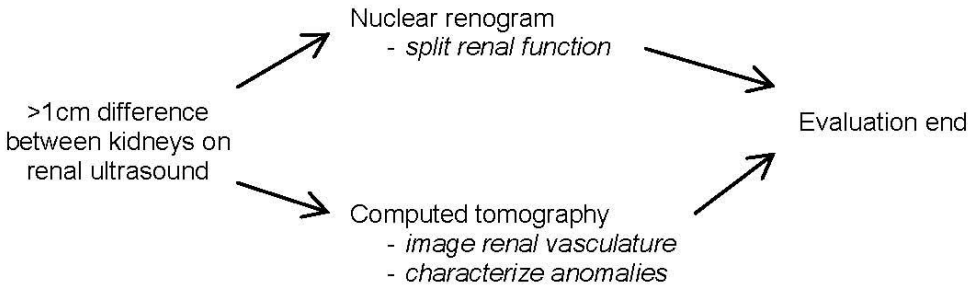
Living donor programs also varied on donor eligibility criteria. These issues relate to the age of an acceptable candidate, acceptable limits for hypertension, and other components of the evaluation. As these issues relate to the safety of the evaluation rather than efficiency, we describe these differences briefly in Appendix A.

4.3.2 Renal imaging studies

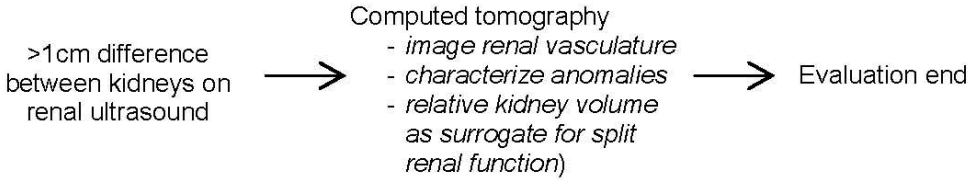
A total of 159 studies reported on renal imaging modalities in the candidate evaluation. Most of these studies considered the accuracy of computed tomography (CT) and magnetic resonance (MR) angiography to define the renal vasculature compared with the actual vascular findings observed during surgery (CT was more common than MR).[16,23] Correctly charting the vascular network and characterizing any abnormalities as benign (i.e., cysts, lesions, small excisable tumors or stones) is a critical function of CT or MR imaging in the living donor evaluation and is necessary to ensure donor and recipient safety.[24] Regarding efficiency, CT or MR imaging is generally performed later in the evaluation because these tests are costly and expose donor candidates to mild risks related to contrast media or ionizing radiation.[12,16,25,26] In some centres there may be a waiting time to receive such testing.

If a clinically important size discrepancy between the left and right kidney is observed (i.e., >1 cm or >10% difference from prior imaging), then a nuclear renogram may be performed to assess the relative function of each kidney, called the "split renal function" (if significantly different then the donor may be left with the higher-functioning kidney). All living donors complete a CT or MR scan as part of the evaluation (Figure 8A). Because of the expected relationship between kidney size and function (larger kidney = more nephrons = higher function), 18 studies assessed whether the relative kidney volume determined by CT can be used as a surrogate for relative function as determined by nuclear renography (Figure 8B). Most authors concluded that CT volumetry could replace split renal function measurement, eliminating this test from the evaluation process

for some candidates. Given such consistent reporting, a systematic review and meta-analysis was conducted separately (including these studies and more), which reported a moderate correlation between split renal volume by CT scan and split renal volume by nuclear renogram (Pearson's r=0.74, beta=0.76 by linear regression).[27] For predicting a clinically significant size difference between the two kidneys, CT had a specificity of 88% and negative predictive value of 86% (sensitivity 35%; positive predictive value 40%).[27]



A) current renal imaging protocol at many transplant centers.



B) proposed renal imaging protocol if relative renal volume by computed tomography can replace nuclear renography for the measurement of relative kidney function.

Figure 8 Improving the efficiency of the evaluation: The use of split renal volume measured by computed tomography to replace split renal function measurement by nuclear renogram. A) The current renal imaging protocol at many transplant centres, where the computed tomography (CT) scan and nuclear renogram are both performed for donor candidates. Both exams may be conducted on the same day, but this is not necessary. B) The proposed renal imaging protocol, where the nuclear renogram is replaced by CT scan for some donor candidates.

4.3.3 Studies measuring predonation kidney function

Acceptable living donor candidates must have sufficient predonation kidney function to minimize the risks associated with living with one kidney. Glomerular filtration rate (GFR) measured using a radionuclide (mGFR) is the current gold standard, but is a resource-intensive test, is not always readily available, exposes donor candidates to potentially harmful radioisotopes, and may be subject to systematic bias and measurement error.[28] Because of this, GFR is estimated (eGFR) early in the evaluation using serum creatinine (a biomarker that can be measured from a simple blood test).[7,29,30] Confirmation using another test can be performed later, including a second eGFR from creatinine with/without cystatin-c, measured creatinine clearance, or mGFR.[7,31]

Fifty-six studies focused on measuring or estimating GFR in kidney donor candidates. Most studies compared the accuracy of various equations to estimate kidney function or predict postdonation kidney function. In contrast, two studies were identified that directly addressed the role of GFR in an efficient living donor evaluation.[32,33] In the presence of imprecision and biases among existing methods, Huang *et al*.[32] developed an algorithm to determine whether mGFR could be unnecessary for some candidates based on high predictive value of eGFR, age, sex, and race for measuring kidney function. The rationale behind this algorithm is presented in Figure 9. The authors recommend that the second eGFR (the first confirmatory test, or "post-test probability 2" in Figure 9) be performed using both serum creatinine and cystatin-c. However, two validation studies used a second eGFR based only on serum creatinine since cystatin-c is not routinely available.[33,34] Huang *et al.* estimated that at least 53% of donors in the U.S. from 2009-2015 would not have required a mGFR based on an eGFR high enough to assure a mGFR ≥90 ml/min/1.73 m^2. In one validation study, 27% of mGFR could have been avoided, but a post-test probability cut-point >98% (rather than 95% in the original study) was required to achieve 100% sensitivity.[33] In a second validation study, 14% of mGFR could have been avoided, but a post-test probability cut-point >99.98% was required to achieve 100% sensitivity.[34] More work is needed to advance this prediction tool to clinical practice.

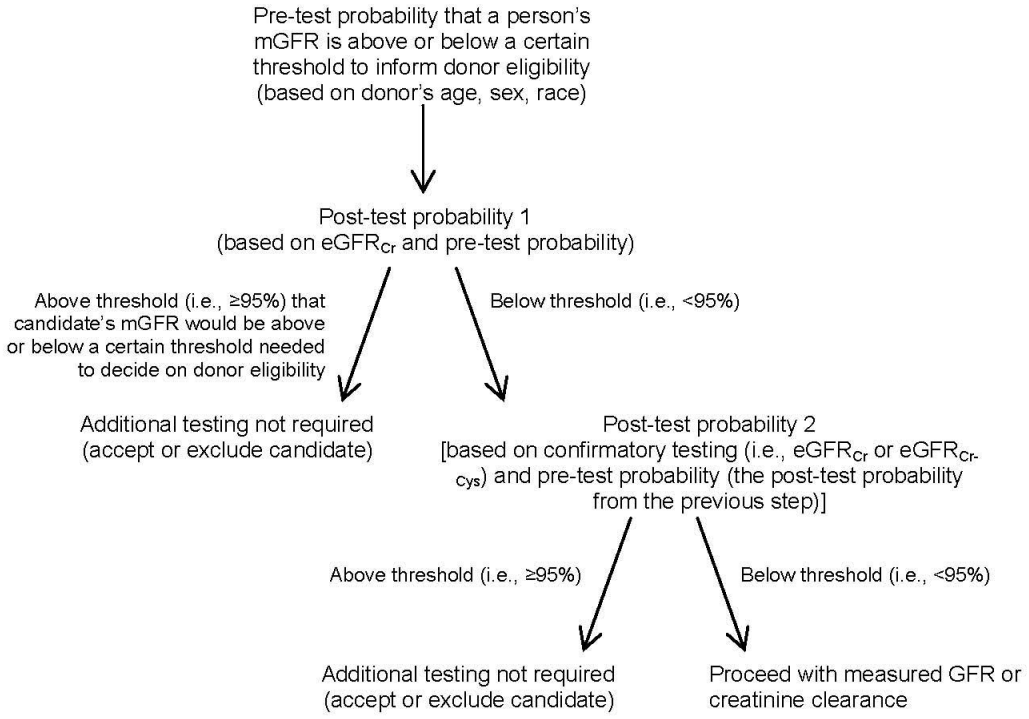


Figure 9: Algorithm to remove measured glomerular filtration rate (GFR) by radionuclide for some donor candidates. Threshold is an arbitrary cut-point generated by the data to permit 100% sensitivity. Algorithm described by Huang et al.[32] mGFR – measured GFR; eGFR – estimated glomerular filtration rate using serum creatinine ($eGFR_{Cr}$) or serum creatinine and cystatin c ($eGFR_{Cr-Cys}$). GFR – glomerular filtration rate; eGFR – estimated GFR; mGFR – measured GFR; Cr – serum creatinine; Cys – cystatin C; $eGFR_{Cr}$ – eGFR estimated using serum creatinine only; $eGFR_{Cr-Cys}$ – eGFR estimated using both serum creatinine and cystatin C

4.3.4 Studies describing the flow of living donors through the evaluation process

A total of 38 studies reported on the number of donor candidates evaluated by their programs.[2,3,35–73] We summarized these results, tabulating the proportion who donated, the number of potential donors lost because the intended recipient either received a

transplant from a deceased donor or died or became too ill to receive a transplant, and the time required to evaluate candidates.

The proportion of living donor candidates who ultimately donated ranged from 8% to 86%, averaging 37% across studies (Figure 10). Although the definition of the numerator and denominator varied, no difference was observed when we excluded any study.

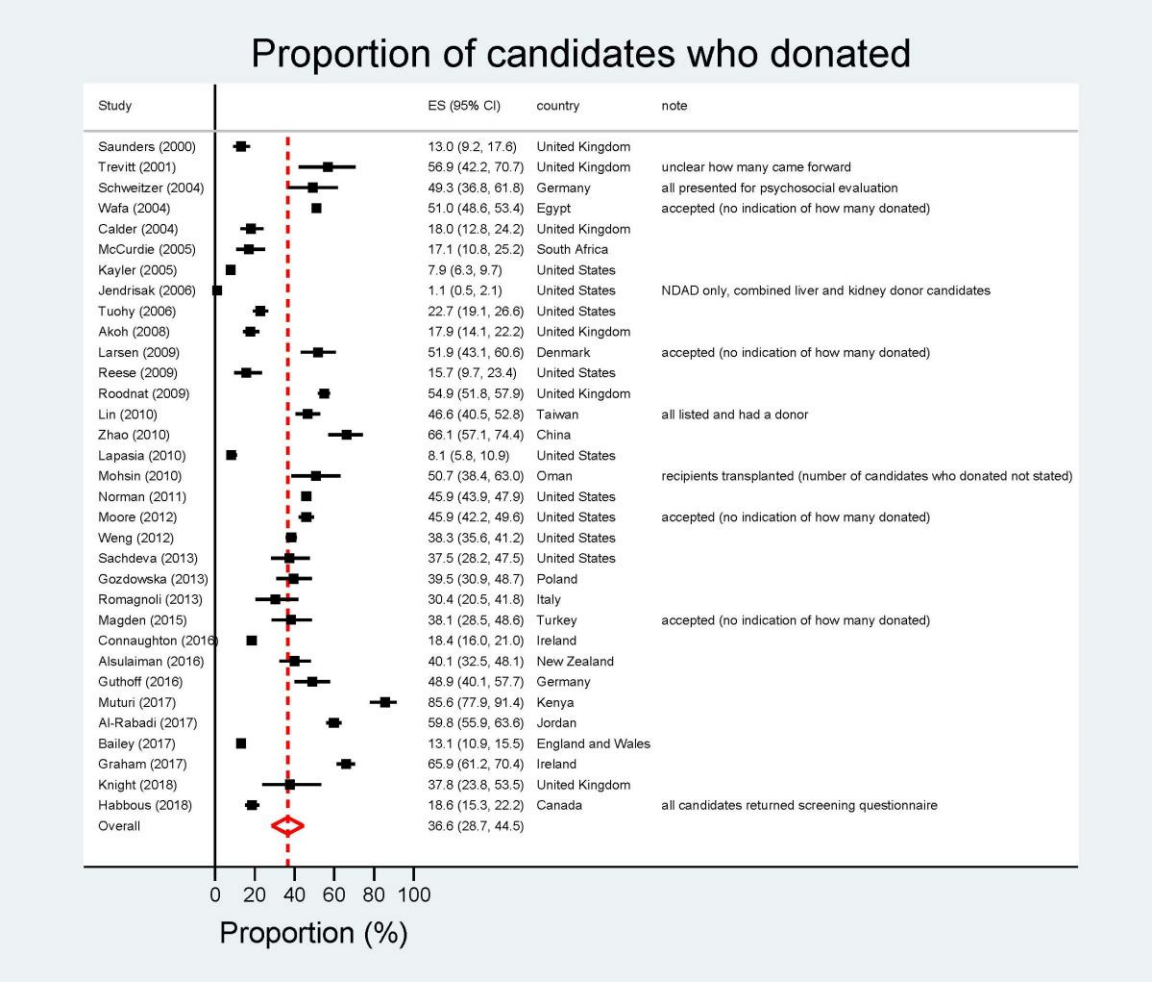


Figure 10: Forest plot with proportion of donor candidates who donated. Studies were pooled using a random effects model. There was significant variability (I2 = 99.5%, p<0.0001). ES – effect size (a proportion); CI – confidence interval.

Twenty-four (63%) studies reported a loss of intended recipients due to illness or death (range 1-7%) or receipt of a deceased donor kidney (1-21%) (Table 3). Although these recipients had a potential living donor, none of these studies evaluated whether a living

donor transplant was feasible (i.e., the donor candidate may have come forward only a few weeks before, which was not enough time to complete a thorough evaluation). It is possible that up to 21% of potential recipients could have received a living donor transplant if the evaluation was quicker. This is, however, an upper theoretical limit and the true loss of potential living donor transplants remains unknown without more data. A recent study projected that a more efficient living donor evaluation process (i.e., donor evaluation completed three months sooner) may result in a 20% increase in the total number of living donor kidney transplants performed, translating to substantial healthcare system cost savings through avoided dialysis.[4] These findings are supported by a recent quality improvement project that reduced the time to complete the living donor assessment using a one-day donor assessment model.[2]

Table 3: Summary of studies reporting on the loss of potential donor candidates due to recipient illness or death or competition from deceased donor transplantation

Reference	Transplant centre	Time period	Loss of potential donor candidates	
			due to recipient illness or death	due to deceased donor transplant
Saunders 2000[35]	Leicester General Hospital, Leicester UK	1994-1998	1 no longer eligible after surgeon consult (recipient cancer), but no indication of recipient death or loss before surgeon consult	25 (9%)
Schweitzer 2004[38]	University of Heidelberg Hospital, Germany	1997-2002	NR	3 (7%) (in subset of 45 candidates)
Calder 2004[40]	St. George's Hospital, UK	1997-2001	2 (1%) (death only)	13 (7%)
McCurdie 2005[41]	University of Cape Town and Groote Shuur Hospital, South Africa	Jan 2000-Mar 2003	4 (3%)	25 (21%)
Kayler 2005[42]	Thomas Jefferson University Hospital, PA	Jan 2000-April 2003	NR	64 (6%) (estimated)
Tuohy 2006[44]	Beth Israel Deaconess Medical Center, NY, USA	2000-2003	12 donors were approved but recipient too sick or died or received a transplant (unsure of donor source); for donors who did not initiate medical work-up (definition of this is unclear, n=120), 18 recipients died/too sick and 84 already transplanted (unsure of donor source)	
Akoh 2008[46]	South West Transplant Centre, UK	Jan 2003-Feb 2008	7 (2%) (death only)	34 (9%)
Larsen 2009[48]	Rigshospitalet, Denmark	Jan 2002-Dec 2006	NR (recipient unfit for transplant in 5 (4%), but no indication of deaths or loss due to illness)	NR
Reese 2009[49]	Hospital of the University of Pennsylvania	Dec 2006 – March 2008	NR	20 (17%) (but unclear if all had a live donor)

Roodnat 2009[50]	Erasmus Medical Center, University Hospital Rotterdam	Jan 2000-Dec 2007	59 (6%) recipient reasons including death, malignancy, cardiovascular disease (grouped)	15 (1%)
Lin 2010[51]	National Taiwan University Hospital, Taiwan	Jan 2005-Dec 2008	5 (2%) [illness only, no indication of death]	5 (2%)
Lapasia 2010[53]	Stanford, CA	Oct 2007-March 2009	28 (6%) (deaths)	not clear
*Sanner 2011[55]	Karolinska University Hospital, Stockholm Sweden	Jan 2004-July 2008	6/135 recipients	N/A (recipients only)
Norman 2011[56]	University of Michigan Transplant Center	Jan 1995-June 2006	14-20% of those excluded donors (death only)	23-28% of those excluded
Moore 2012[57]	Vanderbilt University Medical Center, TN, USA	Jan 2004-July 1 2009	35 (11%) (combined death, illness or incompatible)	NR
Weng 2012[59]	Saint Barnabas Medical Center in Livingston, N.J., USA	Jan 2000-Dec 2005	56 (5%)	36 (3%)
Gozdowska 2013[62]	Poland	2007-2011	NR (assume zero deaths)	17 (14%)
Romagnoli 2013[63]	Catholic University, Rome, Italy	Jan 2005-March 2012	5 (6%)	6 (8%)
Connaughton 2016[66]	Ireland	Jan 2000-Mar 2014	33 (3%)	75 (8%)
Alsulaiman 2016[67]	Christchurch Hospital, New Zealand	Jan 2004-Jun 2008	17 (10%) combined	
Muturi 2017[69]	Kenyatta National Hospital, Kenya	2010-2014	4/84 (5%) deaths (records available for only 84)	0 (no cadaveric donation in Kenya)
Al-Rabadi 2017[70]	King Hussein Medical Center, Jordan	Jan 2008-June 2016	42 (7%)	NR
Bailey 2017[71]	Multiple centres in England and Wales	Aug 8, 2014-Jan 31, 2016	32 (4%)	34 (4%)
Knight 2018[73]	Oxford Transplant Centre	Jan-Mar 2016	NR	2 (4%)
Habbous 2018 (unpublished data)	London Health Sciences Centre, London, Ontario Canada	Jan 2013 – Dec 2016	4 (1%) with a donor in the evaluation	13 (4%) with a donor in the evaluation

NR – not reported; N/A – not applicable
*these were studies primarily mapped to the living donor experience with the living donor evaluation

Seventeen studies (45%) reported evaluation times using various metrics, estimated using data or stated anecdotally. Common evaluation times included the time until approval to donate, donation, or rejection, although the definition of the starting point varied (Table 4).[35,47,48,65,72] The time until donation ranged from 4-14 months across studies and transplant programs. One report described a single recipient who received a kidney from her father (before) and her mother (after) the living donor evaluation process was redesigned to be completed in one day.[3] The results of this redesign were highly positive, showing a reduction in the evaluation time from 2 years to 3 months, an increase in the number of preemptive transplants from <10% to >50%, a rise in the number of living

donor kidney transplants per million population from <5 to >32, and a reduction in the prevalence of patients on dialysis.[2]

Table 4: Summary of studies reporting on the duration of the living donor evaluation

Reference	Transplant centre	Time period	Evaluation time
Saunders 2000[35]	Leicester General Hospital, Leicester UK	1994-1998	time until donation: mean 9.3 (SD 6.5) months
Trevitt 2001[37]	Barts and The London NHS Trust, London, UK	1997-1999	~4 months from the time of initial crossmatch until donation (estimated from graph)
Calder 2004[40]	St. George's Hospital, UK	1997-2001	process designed to take a minimum of 3 months (some with <3 months if coming from abroad and had testing done elsewhere already)
*Williams 2007[45]	Edith Cowan University and Sir Charles Gairdner Hospital	Not reported	most cases between 1-2 years, shortest was 6 months
Ferriman 2008[47]	Royal Free Hospital, London UK	~2007-2008	116 days
Larsen 2009[48]	Rigshospitalet, Denmark	Jan 2002-Dec 2006	median 4 (IQR 1-24) months time until approval; median 3 (IQR 0-9) months from approval to donation; median 3 (IQR 0-48) time until rejection
*Sanner 2011[55]	Karolinska University Hospital, Stockholm Sweden	Jan 2004-July 2008	11.0 (SD 8.6), range 1-48 months
Romagnoli 2013[63]	Catholic University, Rome, Italy	Jan 2005-March 2012	Not reported (but acknowledged it is time consuming and resource intensive)
Weng 2016[65]	Saint Barnabas Medical Center in Livingston, N.J., USA	2007-2010	163 days (time from referral to donation, but unclear what referral means)
Alsulaiman 2016[67]	Christchurch Hospital, New Zealand	Jan 2004-Jun 2008	3-9 months
*Bailey 2016[3]	Belfast City Hospital, UK	Not reported	9-10 months, down to <3 months for a healthy willing donor at the time of writing
Al-Rabadi 2017[70]	King Hussein Medical Center, Jordan	Jan 2008-June 2016	process designed to take a minimum of 2 months, but not measured
Bailey 2017[71]	Multiple centres in England and Wales	Aug 8, 2014-Jan 31, 2016	median 308 days for donors; median 61 days for non-donors
Graham 2017[2]	Ireland	2010-2015	2-3 months for work-up
Habbous 2018[72]	Multiple centres in Canada and Australia	Sept 2009-Jan 2015	median 10.3 months (total evaluation time), 7.9 months (time until approval), 0.7 months from approval until donation, 4.8 months from computed tomography angiogram until donation, and 3.0 months for time between consults
Knight 2018[73]	Oxford Transplant Centre	Jan-Mar 2016	median 132 days from first contact until decision; median 204 days from first contact until donation
Habbous 2018 (unpublished data)	London Health Sciences Centre, London, Ontario Canada	Jan 2013-Dec 2016	time from evaluation start until donation was a median 9.2 (6.1, 14.0) months; time until withdrawal or decline was a median 4.3 (1.4, 9.1) months

*these were studies primarily mapped to the living donor experience with the living donor evaluation
IQR – interquartile range (25th-75th percentile); SD – standard deviation

4.3.5 Studies describing the living donor experience

Twelve studies asked prior donors about their experience with donation.[3,45,55,74–82] One of the most common comments related to the evaluation process was that the evaluation was lengthy, and a prolonged evaluation was a source of strain on both the donor and the recipient:

> "It just has to be soon as possible because we are not able to do anything right now. X (the recipient) is so bad that we never know in advance if we can carry out the plans we've made but have to wait and see on the day."[74]

> "... it actually disrupted our whole life ... I had to keep taking time off work ... like each time we went for tests ... when ... they were going to have the first operation, I took holidays and then it was cancelled and then I tried to ring my boss and get back to work again so I could save my holidays. It was pretty hard ... you sort of have to try and switch off your family life to get on with the job."[45] (mother donating to her child)

> "At the first appointment, we were told that the process takes approximately 9 or 10 months, and all I could think of was whether we had this amount of time, as our daughter's kidney was failing and she was determined not to have dialysis if she could avoid it."[3]

> "I wish the process could be quicker, there are people dying and it shouldn't take so long to get checked out as a donor."[81]

The length of time needed to reconsider the act of donation (the 'cooling off' period) varies by donor, but three months may be sufficient for most.[76] Some donors have expressed wanting less time to think about the decision to donate because of the additional anxiety it produces: "the longer you wait, the longer you worry about it".[76] Once the decision is made, donors often want the surgical procedure as quickly as possible. Several donors blamed the healthcare system for conducting an inefficient and poorly executed evaluation process (concerning an evaluation time of six months or longer).[55,74] Moreover, the time between donor approval and donor surgery was prolonged for several donors, which injected an additional source of anxiety for both the donor and recipient.[45,74]

Some donors reported being frustrated that a prolonged evaluation resulted in their intended recipient spending an unnecessarily longer time on dialysis.[55] One study

reported donor responses in favor of preemptive transplant (i.e., better for recipient health), while others favoured transplant after some time on dialysis (i.e., more likely for the recipient to be compliant with medications and to better understand the value of a kidney).[76]

4.4 Information on living donor program websites

We reviewed the websites for 296 living donor programs in Canada, U.S., U.K., and Australia (Appendix B), focusing on issues related to an efficient living donor evaluation.

4.4.1.1 Time to complete the evaluation

9/296 (3%) of the websites provided information on the duration of the donor evaluation process, time until results are obtained, and the time to complete the evaluation (i.e., number of days of testing at the hospital). Most websites only provided a low level of information, stating either the number of days of testing required or the total evaluation time. Some representative examples are listed in Table 5. Twenty-one programs acknowledged the evaluation may take up to 6 months, sometimes providing very broad ranges (e.g. 6-12 months; 1-6 months; 3-18 months; up to 6 months). Others described evaluations <4 months. Although some of these may accurately represent the efficiency of the program, we are only aware of published data from one centre (2-3 months in Belfast City Hospital, Ireland, U.K.).[2] One website stated a time of two months from donor approval to surgery (Ohio State University Medical Center).

Ten transplant programs indicated that evaluation testing is completed in 1 day for most candidates (depending on the candidates' age; older candidates may require additional testing). Eleven programs indicated up to 2 days were required, and 6 programs indicated at least 3 days were required.

Table 5: Representative information from the websites of living kidney donor programs on the time to complete the evaluation process

Country	City, province	Hospital	Example	Quality[a]
Canada	London, Ontario	London Health Science Centre	2-3 days for tests; 3-6 months for results; 6+ months total from start to surgery date	moderate
USA	Portland, Oregon	Oregon Health and Science University	1 day for evaluation, 2-3 months plus a few weeks to schedule surgery	moderate
UK	Belfast, Ireland	Belfast City Hospital	1 day (1 full day, starts at 8am; the day's schedule provided); most results reported within a few days. While our priority is always to make sure donation is as safe as possible for the donor, we can actually complete all of this within 2-3 months if necessary. There may be an appropriate delay before you have the 1-day assessment process if we need additional information or blood tests. Other times it may be too early for you to have other investigations depending on the person that you are hope to give a kidney to	moderate
Canada	Toronto, Ontario	Toronto General Hospital	2-3 months, (3-6 months before surgery can be scheduled)	low
USA	Columbus, Ohio	Ohio State University Medical Center	1 day for evaluation, 2 months from donor approval to surgery	low
Canada	Vancouver, British Columbia	St. Paul's Hospital	3+ months	very low
USA	Hershey, Pennsylvania	Penn State Milton S Hershey Medical Center	4-6 months	very low
UK	Leeds, England	Leeds St James's University Hospital	3-6 months	very low

[a] the quality of reporting was subjective, based on the relative detail of information provided

4.4.1.2 Medical history form online

Seventy-two websites provided their medical history intake form online (71 from the U.S.). Of these, 49 (68%) could be completed and submitted directly to the program coordinators online. Twenty-two of these used the same third-party system (Breeze Transplant™) to facilitate collection of the online health history questionnaire.

4.4.1.3 Number of candidates evaluated simultaneously

Twenty-five websites stated their general procedure for assessing candidates when more than one comes forward at the same time. Most stated the preferred candidate is the one who is a better match (although the definition of "match" was not described), and few programs involve a joint decision by the healthcare team and the intended recipient. Most

programs stated only evaluating one candidate at a time, but screened up to 10 candidates at the outset.

4.5 Discussion

There is limited data on the efficiency of the living donor evaluation in the literature and the websites of living donor programs. Based on available information, we summarized several areas that have the potential to improve the living donor evaluation process, which may promote better recipient outcomes, improve donor satisfaction, and reduce costs to the healthcare system.

A prolonged living donor evaluation may cause anxiety for donor candidates who want to minimize the dialysis time for the intended recipient (including avoiding dialysis altogether).[55,76] There is a paucity of information on the duration of the living donor evaluation, but existing studies report evaluation times that are often long, used different definitions of the evaluation start and end date, and rarely report more than one indicator. For example, the time between donor approval and actual donation can take weeks in some programs and months in others.[48,72] Together with the time until approval, this can explain some of the differences between the total time until donation between different programs or can reveal hidden differences between programs who have similar total evaluation times.[72] Thus, more accurate estimates of the time to complete an evaluation (using multiple metrics) are needed to facilitate quality improvement. Moreover, the potential implications of a prolonged evaluation on recipient outcomes were infrequently reported or were reported with insufficient detail to draw conclusions or use as a reliable indicator for benchmarking. As a result, it remains only speculative whether the loss of potential living donor kidney transplants due to recipient illness or death, due to receipt of a deceased donor kidney transplant, or due to donor candidate withdrawal could have been avoided if the evaluation was completed earlier.[4] According to the websites of living donor programs, many programs can conduct the evaluation in a single visit to the transplant centre. However, whether they *can* do so and whether they *actually* do so is uncertain.

The necessity of measuring GFR in donor candidates with a radionuclide has been debated. By eliminating unnecessary tests, the burden on candidates, the cost to the healthcare system, and the timeliness of the evaluation process can all be improved. Nuclear renography is useful to measure the split (left versus right) renal function. However, CT volumetry can conceivably replace nuclear renography to measure the relative function.[27] Moreover, nuclear renography can be used to measure the GFR, which may be unnecessary if the candidate has an eGFR associated with a high post-test probability of having a level of GFR that permits or precludes donation.[32] In the case where a radionuclide is used to measure the total renal function, the split renal function can be measured with little additional effort and cost. However, for programs that use different contrast media for these two related tests, this may provide one strategy for improvement.[83,84] Better prediction of postdonation kidney function from predonation eGFR is needed, which may be enhanced by incorporating variables like predonation kidney volume.[85,86]

This scoping review has two main strengths. First, it highlights gaps in knowledge that require further research, including the potential implications of an inefficient evaluation process on health and cost outcomes. Second, it identifies areas for potential improvement that warrant additional testing. However, there are a few limitations that must be recognized. First, given the difficulty in performing a targeted search on this topic, we may have missed relevant studies that were not captured by the search terms chosen, or excluded some efficiency indicators. Future work is needed to establish important and actionable metrics for quality improvement. Second, we did not assess the quality of the included studies, as few studies had the primary objective of evaluating the efficiency of the living donor evaluation. Third, we were unable to estimate the true cost of an inefficient living donor evaluation on transplant activity. Although we found an upper limit of 21% lost opportunities for transplant, this represents an upper limit because we could never know if donor candidates: 1) would have completed their evaluation; 2) would have been deemed eligible for donation; and 3) would have donated. Finally, the cost of a more efficient living donor evaluation was unavailable. One study projected the cost savings associated with a shorter time until living donor kidney transplantation, but was based on hypothetical scenarios and only the costs due to recipient dialysis were

modeled (Chapter 9).[4] A second study used regression-based models to estimate the true cost of living kidney donation to the healthcare system for donors and potential candidates (Chapter 10).[87] However, the cost of the living donor evaluation due to real-world efficiency improvements remains to be estimated.

In conclusion, there are promising opportunities to improve the efficiency of the living donor evaluation process. Better efforts are needed to define, collect, and report indicators of an efficient living donor evaluation for accountability, benchmarking, quality improvement, and research.[9] Individual programs can learn from the processes used by other programs to improve their own practices (e.g. enable a 1-day evaluation), but this requires individual programs to be more transparent on their evaluation procedures. The evaluation should continue to focus on ensuring donor safety, including completing tests that are costly or time-consuming if they are necessary to complete a thorough evaluation for donor candidacy.

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Chapter 5

5 Research Objectives

The overarching goal of this thesis is to fill the gaps in the existing literature and to inform stakeholders (e.g. patients, providers, and decision-makers) on the efficiency of the living kidney donor evaluation process. We project that reducing the donor evaluation time to 3-4 months is feasible for at least highly motivated healthy donors (i.e., those who are essentially waiting for medical clearance).[1–3] We expect this to result in numerous benefits. First, a reduction in the donor evaluation time may result in fewer recipients starting dialysis before transplantation (e.g. more pre-emptive transplants), which will reduced the need for vascular access and the costs and complications associated with dialysis initiation.[4,5] Second, we expect less time on dialysis overall, which will improve the health outcomes of recipients and reduce costs associated with maintenance dialysis to the healthcare system.[6,7] Third, we expect fewer deaths on the transplant wait-list and increased living kidney donor transplantation rates, as fewer intended recipients are likely to receive a deceased donor transplant or lose eligibility for transplant entirely (e.g. through health deterioration).[2] For this overarching goal to be feasible, we propose three research objectives to provide an environmental scan of the current state of the living kidney donor evaluation in Ontario.

5.1 Objective 1: To understand and evaluate the living donor evaluation process

The first aim of Objective 1 is to measure how long it takes the complete the living donor evaluation using multiple metrics. Multiple metrics (process and outcome indicators) are needed to fully understand a process and identify any bottlenecks.[8,9] It is also critical to understand why different metrics vary across individuals and programs. Thus, the second aim of Objective 1 is to identify modifiable and non-modifiable factors associated with longer evaluation times.

5.2 Objective 2: Implications of a prolonged living donor evaluation

The process indicators used to measure the evaluation process should be linked to meaningful outcomes.[10,11] Moreover, any improvements in the quality indicators should result in improved outcomes. Healthcare agencies are moving towards such an evidence-based quality improvement strategy to improve the healthcare of its citizens.[12,13] A recent study has suggested that a longer evaluation time is related to fewer pre-emptive transplants and living donor transplants overall, but no such work has been done in a Canadian context and numerous outcomes remain to be measured.[2] Thus, for this Objective we will estimate some of the possible implications that a longer evaluation can have on transplant outcomes and financial outcomes. We will use real data to estimate how frequently the recipient starts dialysis despite having a living donor. To our knowledge, this is a metric that has not been reported before but has been asked of us by patients. We will also conduct scenario analyses to explore the potential implications of a quicker evaluation.

5.3 Objective 3: Cost of living donor evaluation

The cost of the living donor assessment is a key component to informing decisions on modifying the evaluation process. Examples include implementation of rapid assessments, which may result in more tests completed for candidates who do not donate or evaluating multiple candidates simultaneously rather than sequentially.[2] These potential process designs may increase costs due to donor evaluations, but may also reduce costs by increasing living donation and reducing time on dialysis. Thus, an accurate assessment of the cost of living donation is needed, and this will be the goal of Objective 3.

5.4 Future directions

Once these objectives are complete, possible solutions to improve the living kidney donor evaluation process can be proposed, prioritized, and ultimately tested. This research therefore follows the framework of Six Sigma – a quality improvement guide that is increasing being applied to a healthcare setting.[14,15] First, we identify and define the

problem (e.g. the living donor evaluation process is inefficient). Then we measure and analyze key indicators before and after improvements are made. Alongside interventions to address other barriers to living kidney donation as mentioned in the Introduction (1.2.1), successful quality improvement strategies following this research will result in increased transplantation rates and better transplant outcomes (health gains), substantial cost savings to the healthcare system (financial gains), and an improved living donor experience and overall quality of life (quality gains).[16,17]

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Chapter 6

6 Duration of Living Kidney Transplant Donor Evaluations: Findings From 2 Multicenter Cohort Studies††

6.1 Introduction

Kidney transplantation for patients with kidney failure is associated with improved survival and better quality of life at a fraction of the cost compared to dialysis.[1–4] Compared to deceased donor kidney transplantation, living donor kidney transplantation offers many advantages including superior rates of patient and graft survival and a shorter time until transplant.[5]

The evaluation of a living kidney donor candidate begins when they contact a transplant center. What follows is a series of screening tests (questionnaires, blood and urine tests), diagnostic tests (ultrasound, chest x-ray), and specialist consultations (nephrologist, surgeon, and an assessment of psychosocial health).[6–8] During the evaluation, a donor candidate often makes multiple trips to local clinics or the transplant center, and there may be frequent periods waiting for appointments or test results. We consider an efficient living donor candidate evaluation as one that is completed in as timely a manner as possible, is clinically appropriate, and promotes patient and provider satisfaction. At a recent international consensus conference, the efficiency of the donor evaluation was highlighted as a high-priority area for improvement.[8,9] Not surprisingly,

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several donors view the evaluation process as the worst phase of the donation experience.[10,11]

In response to such concerns, the 2017 Kidney Disease: Improving Global Outcomes Guideline on the Evaluation and Care of Living Kidney Donors recommends transplant programs conduct as efficient a donor evaluation as possible, to meet the needs of donor candidates, intended recipients, and transplant programs.[12] Guidelines from the United Kingdom set a more tangible goal: by the year 2020, all donor candidates should have the opportunity to complete their evaluation within 4-5 months whenever possible.[13] In order to put these recommendations into context we require knowledge of current performance. To date, the time to complete the living kidney donor evaluation has received limited attention as an outcome or as a focus for quality improvement.[14,15]

To address this knowledge gap and advance a patient-driven research priority,[16] we estimated the time to complete the donor evaluation process using data from multiple transplant centers in two cohorts. We also assessed the variability in donor evaluation times between transplant centres, and individual and transplant centre factors associated with longer evaluation times.

6.2 Methods

6.2.1 Data sources

Prospective cohort: Donors who donated between September 2009 and January 2015 were prospectively enrolled from 16 transplant centers in Canada and Australia (Appendix C). Participants were recruited prior to donation, spoke and read English or French, and were deemed good candidates for post-donation follow-up. Data were obtained from medical records (evaluation test results, consultation notes, operative records) and questionnaires. No data on recipient characteristics were used for this study. All records were de-identified and sent to a coordinating center for abstraction and analysis. All participants provided written informed consent and centers obtained ethics approval before starting recruitment (Appendix D; Table 6).

Table 6: Comparison of prospective and retrospective cohorts

Characteristic	Prospective Cohort	Retrospective Cohort
Overall characteristics:		
Sample size:	849	1140
Study design:	Observational cohort	Observational cohort
Population:	Prior living kidney donors	Prior living kidney donors
Time period:	September 2009 – January 2015	April 2004 – March 2014
Cohort ascertainment:	Identification by research personnel. Donors enrolled into the study prior to donation.	Identification through TGLN databases through ICES
Catchment area:	12 Canadian and 4 Australian transplant programs	5 Ontario transplant programs
Patient consent:	Required	Waived
Ethics approval:	#6056 (see Appendix D)	Not applicable
Observational period:	First contact with transplant centre (proxy) until donation	First contact with transplant centre (proxy) until donation
Strengths and limitations:		
center-to-center variability	16 transplant programs	5 transplant programs
Outcomes	total evaluation time, time until approval, time from approval until donation, time from CT until donation, time between consults	total evaluation time, time from CT until donation, time between consults
Key dates	Evaluation start and approval dates derived by proxy (limitation)	Evaluation start date derived by proxy; no approval date (limitation)
Scope of data	Individual-level factors available unique to this cohort, including smoking, BMI, blood pressure, kidney paired donation, marital status, education, employment (strength)	Individual-level factors available unique to this cohort, particularly recipient data including demographics, kidney function, cause of illness, date of referral (strength)
Data collection:	Convenient sample of medical records; self-reported questionnaires (limitation)	Comprehensive list of healthcare utilization in Ontario from ICES data holdings (TGLN, CORR, OHIP, CIHI) (strength)
Subgrouping by recipient dialysis status	Recipient data not available (limitation)	Stratification by pre-emptive transplant and dialysis-dependent status (strength)

TGLN – Trillium Gift of Life Network; ICES – Institute for Clinical Evaluative Sciences; CORR - Canadian Organ Replacement Register; CIHI – Canadian Institute for Health Information; BMI – body mass index

Retrospective cohort: We obtained linked healthcare administrative data for living donors who were evaluated and donated at one of Ontario's five transplant centers between March 2004 and April 2014. Data were obtained from Ontario's organ procurement organization Trillium Gift of Life Network[17] and multiple datasets available at the Institute for Clinical Evaluative Sciences (ICES). All recipients were Ontario residents who received a first-time kidney transplant (described previously).[18] This study was approved by the research ethics board at Sunnybrook Health Sciences Centre, Toronto, Canada (patient consent was waived; Table 6). A summary of each cohort is provided in Table 6.

6.2.2 Measures of evaluation time

Total evaluation time was defined as the time the donor started the evaluation until donation. *Total approval time* was defined as the time from evaluation start to the date the donor was approved to donate. Since the date the evaluation started and the date of approval were unavailable (and may not be well defined), we used tests relevant to the evaluation process to inform these dates (tests usually performed early or late in the evaluation; Table 7 for the prospective cohort; Habbous et al for the retrospective cohort – reproduced in Appendix E).[18] *Time to donation post-approval* was defined as the time from approval to donation. *Time from computed tomography (CT) until donation* was defined as the time from first CT angiogram (to assess kidney anatomy and vasculature) until donation. *Time between consults* was defined as the period between the first and last of the nephrologist, surgeon, and psychosocial assessments (restricted to donors with all three consults).

Table 7: Procedures for donors (N=849)

Procedure	N (%) with procedure	N (%) as first procedure (all tests)	N (%) as last procedure[c]
Consultations			
Surgery consult	804 (95%)	10 (1%)*	496 (58%)
Nephrologist consult	834 (98%)	14 (2%)*	132 (15%)
Psychosocial consult	753 (89%)	22 (3%)*	28 (3%)
Other health professional consult	323 (38%)	5 (<1%)*	93 (11%)
Cardiac evaluation	211 (25%)	5 (<1%)*	8 (1%)

Procedures			
Renal imaging	844 (99%)[a]	101 (12%)	9 (1%)
Nuclear medicine (GFR)	692 (82%)	20 (2%)	23 (3%)
24-hr blood pressure	227 (27%)	23 (3%)	16 (2%)
Renal biopsy	22 (3%)	0 (0%)*	1 (<1%)[d]
Cystoscopy	21 (2%)	0 (0%)*	2 (<1%)
Laboratory tests			
Histocompatibility test	839 (99%)	346 (41%)	–
Spot urine test	839 (99%)	23 (3%)	–
Biochemistry	829 (98%)	4 (<1%)	42 (4%)
Cholesterol (fasting)	702 (83%)	116 (14%)	–
24-hr urinalysis	708 (83%)[b]	96 (11%)	33 (4%)
Oral glucose tolerance test	379 (45%)	43 (5%)	8 (1%)
First contact date[e]	395 (46%)	21 (2%)	–

[a] any of renal/abdominal ultrasound (n=659) or CT angiogram (n=834)
[b] 289 had one and 419 had two 24-hr urinalysis tests documented
[c] only tests indicated in column without "–" were considered as a possible last procedure to define approval date
[d] exceeding 10 days prior to donation to ensure not an implant biopsy
[e] the date the donor first phoned or emailed the transplant program, restricted to Ontario donors. This was only considered as the first procedure if no other appropriate test was identified.
*not considered an appropriate start date (these donors were excluded from total evaluation time and time until approval)

6.2.3 Individual-level and center-level characteristics

We obtained individual-level donor, recipient, and transplant characteristics by abstracting medical records (prospective cohort) or linking across healthcare databases (retrospective cohort). Socio-demographic factors included age at donation, sex, marital status, race, and smoking status at the time of study recruitment. Individual-level socioeconomic factors included education, employment status, and rural residence. Neighbourhood-level median household income quintile was obtained from the 2006 Canada Census (Canada only). Other socioeconomic indicators were assessed, including the Canadian Marginalization Index (Can-MARG) and the Australian Socio-economic Index for Areas (SEIFA); both derived using several variables from each country's 2006 Census.[19,20] Pre-donation clinical factors included donor and recipient estimated glomerular filtration rate (eGFR) calculated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation.[21] Based on at least five systolic (SBP) and

diastolic (DBP) blood pressure measurements prior to donation, donors were considered normotensive if SBP <120 mmHg and DBP <80 mmHg, pre-hypertensive if SBP 120 to <140 mmHg or DBP 80 to <90 mmHg, and hypertensive if SBP ≥140 mmHg or DBP ≥90 mmHg. Other factors included the year of donation, distance to the transplant center (Euclidean distance between postal codes), the donors' relationship to the intended recipient (which may differ from the actual recipient if the donation occurred through paired donation), participation in kidney paired donation, the surgical technique, the recipient's referral date to a transplant centre for evaluation, and the recipient's primary cause of kidney failure.

Transplant center characteristics were obtained for the prospective cohort for the year 2012 (mid-year and peak of participant recruitment), including transplant center volume (number of living and deceased donor kidney transplants) and resources (number of full-time equivalent living donor nurse coordinators).

6.2.4 Statistical analysis

We present continuous data as mean (SD) or median (25^{th}, 75^{th} percentile). Differences between cohorts on categorical variables were compared using chi-squared tests from contingency tables. To evaluate individual-level predictors, we used generalized estimating equations to accommodate clustering by transplant center (identity link; normal distribution). Point estimates with 95% confidence intervals (CI) were presented. Multivariable models included all covariates yielding unadjusted p-values <0.2 (no selection algorithm was employed) or variables considered important. We used random-effects models to explore transplant center-level factors associated with evaluation times (random intercept for transplant center; center-level factors were treated as fixed effects). Random effects models without any individual-level or center-level covariates (unconditional means models) were used to compute the proportion of the total variability in evaluation times that could be accounted for by differences between transplant centers (the intracluster correlation coefficient, ICC). We evaluated model fit using a variety of indices, which showed use of linear regression was appropriate (Pregibon link test p=0.19; Hosmer-Lemeshow test p=0.9, Pearson's test p=1.0).[22] We used Statistical Analysis Software SAS v9.4 or SAS Enterprise Guide 6.1 (2013 SAS Institute Inc., Cary,

NC, USA) and STATA v13.0 (StataCorp LP, Texas, USA). This study was conducted and reported per recommended guidelines (Appendix F).

6.3 Results

From the prospective cohort, 849/851 (99%) donors were included (two donated outside of Canada or Australia). Donors were recruited a median (25^{th}, 75^{th} percentile) 2.3 (1.3, 7.5) weeks prior to donation. From the retrospective cohort, 1109/1140 (97%) living donors from Ontario were included (31 recipients could not be identified). The characteristics of the prospective and retrospective cohorts are presented in Table 8.

Table 8: Living Kidney Donor Characteristics

	Prospective cohort (N=849)	**Retrospective cohort (N=1140)**	
	Donors	**Donors**	**Recipients**
Demographic factors			
Mean age at donation, years	47.8 (11.4)	45.1 (11.0)	44.2 (14.4)
Sex			
Female	558 (66%)	716 (63%)	415 (36%)
Male	291 (34%)	424 (37%)	725 (64%)
Smoking status at recruitment (within last 30 days)*			
Not smoking	624 (80%)	na	na
Recently quit	47 (6%)	na	na
Still smoking	107 (14%)	na	na
Marital status			
Married/common-law	610 (78%)	na	na
Not married	168 (22%)	na	na
Race			
White	745 (88%)	428 (77%)	375 (75%)
Non-white**	101 (12%)	131 (23%)	124 (25%)
Socioeconomic factors			
Highest education			
University/college	451 (58%)	na	na
Trades/high school or less	326 (42%)	na	na
Employment status			
Full-time	499 (64%)	na	na
Other	280 (36%)	na	na
Residence[a]			
Urban	642 (81%)	959 (84%)	954 (87%)
Rural	151 (19%)	181 (16%)	148 (13%)
Median income quintile[b]			
5, highest	162 (26%)	257 (23%)	246 (22%)
4	152 (24%)	289 (25%)	255 (23%)
3	140 (23%)	239 (21%)	132 (21%)
2	91 (15%)	183 (16%)	193 (18%)
1, lowest	74 (12%)	172 (15%)	173 (16%)

Pre-donation clinical factors			
estimated GFR, mL/min/1.73m^{2c}			
≥90	548 (64%)	665 (62%)	na
80-89	177 (21%)	166 (15%)	na
<80	124 (15%)	251 (23%)	na
mean estimated GFR from serum creatinine, mL/min/1.73m^{2c}	96 (14.0)	97.3 (14.9)	16.2 (8.4)
mean measured (nuclear) GFR, mL/min/1.73m^{2c}	108 (21.2)	na	na
Recipient co-morbidities			
Cardiovascular disease	na	na	592 (53%)
Ischemic heart disease/ coronary artery disease	na	na	123 (11%)
Heart failure	na	na	86 (8%)
Diabetes	na	na	222 (20%)
Hypertension	na	na	925 (83%)
Body mass index, kg/m^2			
Underweight (<18.5)	9 (1%)	na	na
Normal (18.5-24.9)	321 (38%)	na	na
Pre-obese (25-29.9)	366 (43%)	na	na
Obese (30-34.9)	134 (16%)	na	na
Very obese (BMI ≥ 35)	16 (2%)	na	na
mean body mass index, kg/m^2	26.3 (3.90)	na	na
Blood pressure[d]			
Normal	420 (49%)	na	na
Pre-hypertensive	405 (48%)	na	na
Hypertensive	24 (3%)	na	na
Other factors			
Relation to intended recipient			
First degree relative	408 (48%)	571 (50%)	na
Spouse	166 (20%)	246 (22%)	na
Other (friend, other relative)	200 (24%)	323 (28%)	na
Non-directed anonymous donation	68 (8%)	na	na
Participated in Kidney Paired Donation			
No	748 (89%)	na	na
Yes	91 (11%)	na	na
Days until recipient referral[e]	na	na	26 (-81, 160)
Surgery type performed			
Laparoscopic	705 (84%)	na	na
Open	135 (16%)	na	na

Presented as number (percent) or mean (standard deviation).

[a] restricted to donors with a valid Canadian postal code. For donors in this table, rural status was derived from the second digit of the postal code (rural if zero, urban otherwise). Rural status is generally defined in the retrospective cohort as a municipality having <10,000 persons [990 (87%) of was urban with this definition].

[b] Median household income was obtained from the 2006 Canada Census

[c] GFR –glomerular filtration rate estimated using the CKD-EPI equation; recipient estimated GFR was measured a median 0 (-14, 17) days before the donor evaluation start date; measured GFR was restricted to donors with a radioisotope measurement (n=555)

[d] normal if systolic <120 mmHg or diastolic <80; pre-hypertensive if systolic 120-139 or diastolic 80-89; hypertensive if systolic ≥140 or diastolic ≥90

[e] calculated as the time from the donor evaluation start date until the recipient referral date. Negative values mean the recipient was referred to the transplant center before the donor evaluation started.

* donors were recruited a median (25th, 75th percentile) of 2.3 (1.3, 7.5) weeks prior to donation.

** in the prospective cohort, non-whites included 58 (7%) Asians, 20 Aboriginals (2%), 17 Blacks (2%), and 6 Hispanic/Latino (<1%). In the retrospective cohort, non-whites included 69 (12%) Asians, and 22 (4%) Blacks [the ethnicity of remaining donors was suppressed due to small cells (<6 individuals) to comply with privacy requirements to minimize the risk of re-identification.]

na – not available

For the prospective cohort, the mean (SD) age at donation was 47.8 (11.4) years, most donors were married (78%), white (88%), and female (66%). Many donors were educated (58% with a college or university degree), employed full time (64%), and were of high socioeconomic status (26% in the highest neighbourhood-income quintile). Most (87%) donors underwent a laparoscopic nephrectomy and 11% donated through kidney paired donation. In terms of health status indicators 18% were classified as obese (BMI ≥30 kg/m^2); and 2% were very obese (BMI ≥35 kg/m^2); 64% had a pre-donation eGFR ≥90 mL/min/1.73 m^2. Most intended recipients were first-degree relatives (48%), while 8% were non-directed (anonymous).

Donors from the retrospective cohort were similar to the prospective cohort with respect to age (mean 45.1 years), sex (63% female), residence (84% urban), income (23% in the highest neighbourhood-income quintile), pre-donation eGFR ≥90 mL/min/1.73 m^2 (64%), and relationship (50% were donations to a first-degree relative). However, Ontario donors were more likely to be non-white (23%) than donor participants in the prospective cohort (10%, p<0.001). Recipients in the retrospective cohort were similar to donors with respect to age, race, rural status, and neighbourhood-income quintile, but were more likely to be male (64% vs. 37%). Recipients were referred to a transplant centre a median (25th, 75th percentile) 26 (-81, 160) days after the start of their donor's evaluation (recipient referral date was available for 290/1256 (23%) of recipients).

6.3.1 Living kidney donor evaluation times

The distribution of evaluation times across transplant centres from the prospective cohort is presented in Figure 11 and Table 9.

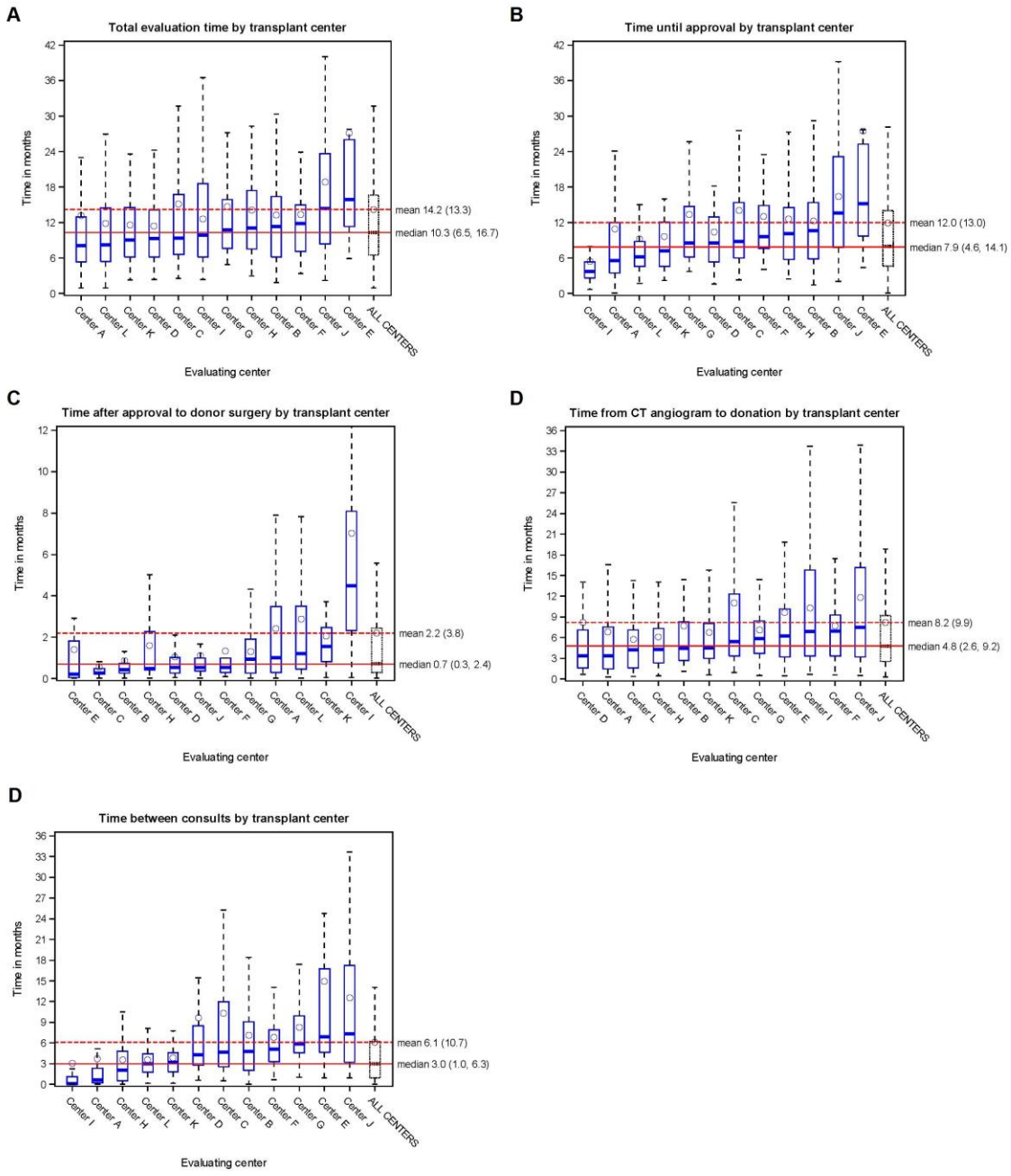

Figure 11: Evaluation times by transplant centre. Boxplots showing the distribution of evaluation times stratified by transplant center. A) The total wait time was defined as the time the donor completed the evaluation, from first contact until donation surgery; B) total approval time was calculated as the time from first contact until the donor was approved to donate; C) the time to donor surgery after approval was calculated as the difference in total wait time and total approval time; D) the time from CT (computed tomography) scan until donation; E) the time

between consults was defined as the period between the first and last nephrology, urology, and psychosocial consults (restricted to donors with all three consults). Vertical axis was truncated for readability. Box represents interquartile range (25th to 75th percentile). Horizontal line indicates median (50th percentile). Circle represents mean. Vertical lines represent the upper fence (75th percentile plus 1.5× interquartile range) and lower fence (25th percentile minus 1.5× interquartile range). Five Austrialian centers were combined and presented as a single center for this analysis.

The median (25^{th}, 75^{th} percentile) total evaluation time in the prospective cohort was 10.3 (6.5, 16.7) months (n=803) and varied across transplant centers (ICC=7.0%, p=0.04). Among the subgroup of Ontario participants, the median evaluation time was 10.7 (6.6, 16.7) months, similar to the evaluation time from the retrospective cohort [median 10.8 (7.3-19.4) months].

In the prospective cohort, the median time until approval was 7.9 (4.6-14.1) months (n=745, ICC 13.2%, p=0.02) and from approval to donation was 0.7 (0.3, 2.4) months (n=745, ICC 20.6%, p=0.01). The approval date was not available in the retrospective cohort.

The time from CT scan until donation was a median 4.8 (2.6, 9.2) months in the prospective cohort (n=839, ICC 2.9%, p=0.05), which was similar to the 4.9 (2.8, 8.8) months observed in the retrospective cohort (n=1054).

Among donors who completed a nephrology, surgery, and psychosocial assessment in the prospective cohort, the median time between the first and last consultation was 3.0 (1.0, 6.3) months (n=716, ICC 11.0%, p=0.03). In the retrospective cohort, the median time between consults was 3.3 months longer [median 6.3 (2.3-17.2) months (n=576)].

Table 9: Comparisons of the donor evaluation process between transplant centers in the prospective cohort

	Average time for different measures of the donor evaluation in months, median (25th, 75th percentile)[a]						Frequency of 24-hour urine tests in donors (%)		
	Total evaluation time, N=803	**Total approval time, N=745**	**Time after approval to donation, N=745**	**Time from CT scan to donation, N=839**	**Time between consults, N=716[b]**	**All consults completed ≤2 days, N=716[b]**	**0**	**1**	**2**
Center A	8.1 (5.4, 12.9)	5.6 (3.5, 12)	1.0 (0.3, 3.5)	3.4 (1.5, 7.6)	0.7 (0.3, 2.3)	15%	2	19	78
Center B	11.3 (6.2, 16.4)	10.7 (5.8, 15.4)	0.4 (0.3, 0.7)	4.5 (2.7, 8.3)	4.8 (2.1, 9.1)	1.3%	6	78	16
Center C	9.4 (6.6, 16.7)	8.8 (6.0, 15.4)	0.3 (0.2, 0.5)	5.5 (3.3, 12.3)	4.7 (2.5, 11.9)	0%	6	80	14
Center D	9.3 (6.1, 14.1)	8.6 (5.3, 12.9)	0.5 (0.3, 1.0)	3.3 (1.6, 7.1)	4.3 (2.8, 8.5)	0%	0	0	100
Center E	15.9 (11.4, 26.1)	15.2 (9.7, 25.3)	0.2 (0.1, 1.8)	6.2 (3.2, 10.2)	6.9 (4.6, 16.7)	0%	15	72	12
Center F	11.9 (7.1, 14.9)	9.6 (7.7, 14.9)	0.5 (0.3, 1.0)	7.0 (3.4, 9.3)	5.1 (3.3, 7.9)	0%	2	7	91
Center G	10.8 (7.6, 15.9)	8.5 (6.1, 14.7)	1.0 (0.3, 1.9)	5.9 (3.7, 8.4)	5.9 (4.6, 9.9)	0%	0	4	96
Center H	11.1 (7.6, 17.4)	10.2 (5.8, 14.6)	0.5 (0.4, 2.3)	4.3 (2.3, 7.3)	2.0 (0.6, 4.8)	10%	0	13	87
Center I	9.9 (6.2, 18.6)	3.8 (2.6, 5.3)	4.5 (2.3, 8.1)	6.9 (3.4, 15.8)	0.1 (0.0, 1.1)	50%	92	2	6
Center J	14.4 (8.4, 23.7)	13.6 (7.8, 23.1)	0.5 (0.4, 1.0)	7.5 (3.2, 16.1)	7.3 (3.2, 17.2)	0%	46	29	25
Center K	9.1 (6.1, 14.6)	7.2 (4.6, 12.1)	1.6 (0.8, 2.5)	4.5 (3.0, 8.1)	3.2 (1.8, 4.6)	0%	16	76	9
Center L	8.2 (5.5, 14.4)	6.2 (4.6, 8.8)	1.2 (0.5, 3.5)	4.2 (1.6, 7.1)	3.0 (1.8, 4.4)	0%	1	24	75
All centers	10.3 (6.5, 16.7)	7.9 (4.6, 14.1)	0.7 (0.3, 2.4)	4.8 (2.6, 9.2)	3.0 (1.0, 6.3)	–	–	–	–
ICC (p-value)	7.0% (p=0.04)	13.2% (p=0.02)	20.6% (p=0.01)	2.9% (p=0.05)	11.0% (p=0.03)	–	–	–	–

[a] Five Australian centers were combined and presented as a single center so that there were a meaningful number of participants for analysis.

[b] Time from first to last consults with either a nephrologist, a surgeon, and a professional performing a psychosocial evaluation (restricted to donors with all three consults)

ICC – intraclass correlation coefficient (proportion of the variance in the outcome explained by between-center differences); a p-vale <0.05 was interpreted as significant variability in the evaluation time between centers; CT – computed tomography

6.3.2 Transplant center characteristics associated with longer evaluation times

Associations of transplant center characteristics were only assessed in the prospective cohort. We found no association between the total evaluation time and the number of living-donor and deceased-donor transplants performed at the center, the number of full-time equivalent living donor coordinators, the number of 24-hour urine tests usually performed at the center, and whether centers routinely performed nephrology, surgery and psychosocial consults all within 24 hours of each other (p>0.2 for all). This did not change after adjustment for individual-level donor age, sex, relationship to the recipient, or whether the donation occurred through paired exchange (Table 10).

Table 10: Transplant center characteristics associated with donor evaluation times in the prospective cohort

	Average time for different measures of the donor evaluation in months, median (25th, 75th percentile)[a]				
	Total evaluation time, N=803	**Total approval time, N=745**	**Time after approval to donation, N=745**	**Time from CT to donation, N=839**	**Time between consults, N=716[b]**
#LD Tx[c,d]	-0.4 (-2.2, 1.4)	-0.3 (-2.6, 2.0)	-0.1 (-0.8, 0.6)	-0.4 (-0.4, 1.1)	-0.0 (-1.7, 1.7)
#DD Tx[c,d]	0.6 (-0.7, 1.9)	0.9 (-0.7, 2.6)	-0.2 (-0.7, 0.3)	0.1 (-0.5, 0.8)	0.4 (-0.8, 1.7)
FTE[c,e]	4.0 (-2.7, 10.7)	2.7 (-6.4, 11.8)	1.4 (-1.0, 3.8)	2.2 (-0.1, 4.4)	2.1 (-4.4, 8.7)
#LD Tx/FTE[c]	-0.1 (-0.2, 0.1)	-0.03 (-0.2, 0.2)	-0.03 (-0.1, 0.03)	-0.02 (-0.05, 0.1)	-0.01 (-0.1, 0.2)
# 24h urines[f]	-1.1 (-4.9, 2.7)	-0.1, (-5.0, 4.8)	-0.6 (-2.0, 0.8)	-1.6 (-2.9, -0.3)	-1.2 (-4.7, 2.4)
Same-day consults[g]	-2.5 (-8.8, 3.7)	-4.7 (-12.3, 2.8)	2.0 (-0.04, 4.1)	-1.1 (-3.9, 1.6)	-5.2 (-9.9, -0.6)

[a] Adjusted for donor age, sex, relationship to intended recipient, and donation through kidney paired donation. Five Australian centers were combined due to the number of participants recruited. A positive number means the characteristic is associated with a longer evaluation time, expressed in months of additional time. As an example of interpretation, transplant centers that differ by 10 transplants performed per year also differ by -0.4 months in the total evaluation time.
[b] Time from first to last consults with either a nephrologist, a surgeon, and a professional performing a psychosocial evaluation (restricted to donors with all three consults)
[c] Obtained from each institution in 2012 (the mid-year and most active year of study recruitment). The number of transplants performed serve as indicators of the transplant center volume. Variables were treated as a continuous.
[d] per 10 transplants
[e] per 0.5 FTE
[f] transplant centers were categorized as generally performing zero, one, or two 24-hour urine analyses based on the highest proportion in the three rightmost column of Table 9 and treated as a continuous variable (estimate is per 24-hour urine test).
[g] transplant centers were dichotomized as generally performing same-day consults if the nephrology, surgery, and psychosocial evaluation was performed within 2 days for at least 10% of the donors (Centers A, H, and I from Table 9). The reference group is "no".
CT – computed tomography; LD Tx – living donor kidney transplant; DD Tx – deceased donor kidney transplant FTE – full-time equivalent of living donor nurse coordinator

6.3.3 Individual donor factors associated with longer evaluation times

We explored whether individual-level factors were associated with the total evaluation time in unadjusted (Table 12) and adjusted (Table 13) analyses. The prospective cohort was adjusted for donor age, sex, and relationship to the recipient. The retrospective cohort was further adjusted for donor urban/rural status and median neighbourhood-income quintile. In the prospective cohort we did not have information on whether the recipient was receiving dialysis at the start of the donor evaluation. In the retrospective cohort, we separated the results by whether or not the recipient was on dialysis at the time the donor evaluation started, as this might influence the urgency of donation (if the goal was pre-emptive kidney transplantation). For these analyses we also focused on donors who received a pre-emptive kidney transplant (N=311), separating out those who started dialysis while the donor evaluation was underway, as for the latter many patients take some time to acclimatize to dialysis after it is initiated, which may delay the time to complete the transplant evaluation and confound associations measured in the present study.[18]

After adjustment, the evaluation took longer if the donor was older (by 0.7 to 2.0 months per 10-years of age). The evaluation time was shorter among rural versus urban donors [-2.7 (95% CI: -0.3, -5.1)] in the pre-emptive transplant cohort, with the trend of a shorter time in the dialysis-dependent cohort [-1.4 (-3.0, 0.2)]. There was a non-linear relationship between neighbourhood-household income and the time to complete the evaluation, and results varied in the cohorts: in the prospective cohort, the most and least affluent quintiles completed the evaluation in the shortest amount of time and the middle group took the longest. In the dialysis-dependent cohort, the least affluent group took the longest time to complete the evaluation [2.8 (0.8, 4.9) months longer than the most affluent], while in the pre-emptive transplant cohort results were qualitatively different. Sensitivity analysis in the prospective cohort using a deprivation index as a measure of socioeconomic status did not change these results (Table 11). For every mL/min/1.73 m^2 increase in recipient eGFR, the evaluation time was increased an average of 0.8 months ($p<0.001$). For every 30-day delay in recipient referral, the time of donor evaluation increased 0.4 (0.3, 0.5) months in the dialysis-dependent cohort and 0.9 (0.8, 1.0) months

in the pre-emptive transplant cohort (p<0.001). Other factors included the relationship to the intended recipient, the cause of kidney failure, and non-renal recipient co-morbidities, which differed qualitatively depending on the cohort of study. The most influential contributor was whether the donor participated in paired exchange, which prolonged the average time until donation by 6.6 (1.6, 9.7) months. Finally, and of weaker importance, was the association between female and non-white donors on longer evaluation times, which was only observed in the dialysis-dependent cohort (although point estimates for female donors were in a similar direction in all cohorts).

Table 11: Sensitivity analysis for neighbourhood-level deprivation index (prospective cohort)

	Canada only[a]	**Australia only[b]**	**Combined deprivation index (Canada and Australia)**		
	N (%)	N (%)	N (%)	beta	p-value
Deprivation					
1 (least deprived)	168 (27%)	21 (45%)	189 (28%)	0 (referent)	0.24
2	150 (24%)	9 (19%)	159 (24%)	-0.9 (-3.6, 1.7)	
3	127 (20%)	9 (19%)	136 (20%)	0.5 (-2.1, 3.1)	
4	98 (16%)	8 (17%)	106 (16%)	1.7 (-3.1, 6.5)	
5 (most deprived)	81 (13%)	0 (0%)	81 (12%)	-1.7 (-4.6, 1.3)	
Residential Instability[c]					
1 (least deprived)	126 (20%)	–	–	0 (referent)	0.02
2	150 (24%)	–	–	-1.2 (-3.8, 1.3)	
3	138 (22%)	–	–	1.2 (-0.8, 3.2)	
4	117 (19%)	–	–	2.5 (-1.3, 6.2)	
5 (most deprived)	93 (15%)	–	–	-0.4 (-3.0, 2.3)	

Deprivation quintiles derived at the national level from several socioeconomic variables from the 2006 national census

[a] Canadian Marginalization Index derived from Statistics Canada (Matheson et al[1]). Material deprivation included six variables related to family structure, income, and employment. Residential instability included seven variables primarily related to the home.

[b] Socio-economic Indexes for Areas (SEIFA) as an index of relative socioeconomic disadvantage[2]. Deprivation index included variables related to family structure, income, education, and various others.

For every 3-month increase in the time between consults, the time to complete the evaluation increased by 0.8 (0.5, 1.1) months in the pre-emptive transplant cohort (p<0.001), 1.1 (0.2, 2.0) months in the dialysis-dependent cohort (p=0.02), and 2.8 (2.5, 3.1) months in the prospective cohort (p<0.001). After adjustment, the time between consults was substantially shorter for rural donors in the pre-emptive cohort [-2.5 (-3.9, -

1.0)] and the dialysis-dependent cohort [-3.2 (-4.6, -1.8)], but not in the prospective cohort [4.2 (-1.5, 9.9)].

Table 12: Factors associated with total donor evaluation time, unadjusted estimates

	Prospective cohort 16 transplant centers in Canada and Australia		Retrospective cohort 5 transplant centers in the province of Ontario, Canada			
	Unknown if recipient was receiving dialysis at start of donor evaluation (n=849)		Recipient receiving dialysis at start of the donor evaluation (N=631)		Recipient was not receiving dialysis at the start of the donor evaluation, and a pre-emptive transplant was achieved (N=311)	
	beta (95% CI)[a]	p-value	beta (95% CI)[a]	p-value	beta (95% CI)[a]	p-value
Demographic factors						
Donor age, per 10 years	1.12 (0.34, 1.89)	0.005	0.33 (-0.17, 0.83)	0.20	2.19 (1.70, 2.68)	<0.001
Recipient age, per 10 years	na	na	0.66 (0.34, 0.99)	<0.001	-0.53 (-1.40, 0.35)	0.24
Female sex						
donor	0.91 (-0.24, 2.07)	0.12	1.33 (0.41, 2.24)	0.005	1.85 (-0.93, 4.64)	0.19
recipient	na	na	0.77 (-0.79, 2.32)	0.33	0.94 (-2.13, 4.01)	0.55
Donor smoking status at recruitment (within last 30 days)*						
Not smoking	0 (reference)	0.04	na	na	na	na
Recently quit	-1.32 (-2.94,0.31)					
Still smoking	-1.80 (-3.31, -0.29)					
Donor marital status						
e	0 (reference)	0.38	na	na	na	na
not married	-0.97 (-3.14, 1.20)					
Non-white Race						
donor	1.17 (-1.51, 3.85)	0.39	1.82 (0.16, 3.49)	0.03	0.20 (-4.45, 4.85)	0.9
recipient	na	na	0.59 (-0.47, 1.66)	0.27	-0.86 (-5.36, 3.63)	0.71
Rural residence						
donors	-0.27 (-2.02, 1.48)	0.76	-1.24 (-2.84, 0.36)	0.13	-2.14 (-4.09, -0.18)	0.03
recipients	na	na	-1.57 (-3.47, 0.32)	0.10	-1.69 (-2.16, -1.22)	<0.001
Socioeconomic factors						
Donor highest education						
University/college	0 (reference)	0.62	na	na	na	na
Trades/high school or less	0.44 (-1.32, 2.21)					
Donor employment status						
Full-time	0 (reference)	0.63	na	na	na	na
other	0.38 (-1.11, 1.88)					
Donor income quintile						
5, highest	0 (reference)	0.17	0 (reference)	0.10	0 (reference)	<0.001
4	1.96 (0.24, 3.67)		0.24 (-1.00, 1.49)		-3.28 (-4.92, -1.64)	
3	2.98 (0.33, 5.63)		0.36 (-0.65, 1.37)		-0.68 (-5.2, 3.83)	
2	1.92 (-0.69, 4.52)		0.12 (-1.35, 1.58)		0.85 (-0.84, 2.54)	
1, lowest	0.49 (-0.41, 1.38)		2.36 (0.28, 4.44)		-2.54 (-7.11, 2.02)	

Recipient income quintile)[b]						
5, highest	na	na	0 (reference)	0.07	0 (reference)	<0.001
4			0.26 (-1.80, 2.32)		-0.55 (-2.54, 1.44)	
3			1.57 (0.15, 2.98)		-0.95 (-5.63, 3.74)	
2			0.10 (-1.42, 1.62)		1.06 (-3.37, 5.5)	
1, lowest			2.89 (0.04, 5.73)		2.8 (-2.86, 8.47)	
Pre-donation clinical characteristics						
Donor eGFR[c]						
≥90 mL/min/1.73 m^2	0 (reference)	0.28	0 (reference)	0.75	0 (reference)	<0.001
80-89 mL/min/1.73 m^2	-1.52 (-3.81, 0.78)		-0.73 (-2.62, 1.16)		4.73 (1.30, 8.16)	
<80 mL/min/1.73 m^2	0.61 (-0.68, 1.91)		-0.07 (-1.46, 1.33)		2.87 (1.84, 3.90)	
Recipient eGFR at donor first contact, per mL/min/1.73 m^{2c}	na	na	na	na	0.79 (0.66, 0.93)	<0.001
Recipient co-morbidities						
Cardiovascular disease	na	na	0.50 (-0.17, 1.18)	0.14	-1.37 (-4.18, 1.43)	0.34
Ischemic heart disease/ coronary artery disease	na	na	1.85 (-0.91, 4.61)	0.19	5.16 (1.11, 9.20)	0.01
Heart failure	na	na	1.84 (-0.84, 4.51)	0.18	3.25 (-2.39, 8.89)	0.26
Diabetes	na	na	0.28 (-0.56, 1.13)	0.51	-3.95 (-5.78, -2.13)	<0.001
Hypertension	na	na	0.43 (-0.69, 1.54)	0.45	-4.74 (-6.83, -2.65)	<0.001
Donor body mass index, kg/m^2						
Underweight (<18.5)	-2.79 (-5.58, -0.01)					
Normal (18.5-24.9)	0 (reference)	0.05	na	na	na	na
Pre-obese (25-29.9)	0.85 (-1.47, 3.17)					
Obese (30-34.9)	0.46 (-0.82, 1.74)					
Very obese (≥ 35)	2.07 (-2.31, 6.45)					
Donor blood pressure						
Normal	0 (reference)	0.61	na	na	na	na
Pre-hypertensive	-0.01 (-1.41, 1.40)					
Hypertensive	3.28 (-3.39, 9.94)					
Time to recipient referral	na	na	0.39 (0.27, 0.50)	<00001	0.82 (0.71, 0.93)	<0.001
Other characteristics						
Relationship						
Spouse	0 (reference)	0.04	0 (reference)	0.03	0 (reference)	<0.001
Sibling	-2.07 (-5.71, 1.57)		-0.65 (-3.39, 2.09)		0.27 (-2.49, 3.03)	
Parent	-1.64 (-6.08, 2.81)		-1.22 (-3.0, 0.56)		1.52 (-3.73, 6.77)	
Child	-4.12 (-8.80, 0.56)		1.13 (-0.65, 2.9)		-4.1 (-8.39, 0.18)	
Other relation	-4.44 (-8.89, 0.01)		-0.07 (-3.85, 3.71)		-4.2 (-6.02, -2.38)	
Unrelated	0.74 (-4.47, 5.95)		1.35 (0.01, 2.69)		0.31 (-1.99, 2.62)	
Participated in kidney paired donation	7.00 (3.75, 10.3)	<0.001	na	na	na	na
Surgery type performed						
Laparoscopic	0 (reference)	0.19	na	na	na	na
Open	-1.23 (-3.07, 0.61)					
Cause of kidney failure						
GN/autoimmune	na	na	0 (reference)	<0.001	0 (reference)	<0.001
Polycystic			2.75 (-0.48, 5.97)		-0.95 (-4.76, 2.85)	
Diabetes			1.41 (-0.53, 3.35)		-6.59 (-9.61, -3.56)	

Other			1.53 (-0.28, 3.34)		0.03 (-4.16, 4.21)	
Unknown			1.94 (1.19, 2.69)		-1.55 (-11.02, 7.93)	
Year of transplant, per year	0.23 (-0.72, 1.17)	0.64	0.08 (-0.11, 0.27)	0.40	0.06 (-0.23, 0.36)	0.67
Distance to transplant program, per 50 km						
donor	0.05 (0.01, 0.10)	0.03	0.12 (0.02, 0.23)	0.02	-0.26 (-0.42, -0.11)	0.001
recipient	na	na	0.04 (-0.14, 0.21)	0.67	-0.20 (-0.36, -0.05)	0.009

The total evaluation time was defined as the time from the donor's evaluation start date until donation. A positive number means the factor was associated with a longer donor evaluation time, expressed in months of additional time. The median (25^{th}, 75^{th}) total donor evaluation time for the prospective cohort, dialysis-dependent cohort, and pre-emptive transplant cohort was 10.3 (6.5, 16.7), 10.6 (6.4, 21.6) and 9.5 (7.0, 14.3), respectively.[a] beta estimates with 95% confidence intervals (CI) obtained from linear regression accounting for clustering by transplant center (generalized estimating equations). The beta estimate corresponds to the average difference in total evaluation time for a change in category (compared to the reference category) or a 1-unit increment in a continuous variable (unless otherwise specified)

[b] neighbourhood-income quintile derived from the 2006 Canada Census (Canadian donors only)

[c] kidney function measured using CKD-EPI equation (mL/min/1.73 m^2) from serum creatinine identified at any point in the evaluation for donors and within 3 months of the donor's evaluation start date for recipients.

* donors were recruited a median (25th, 75th percentile) of 2.3 (1.3, 7.5) weeks prior to donation.

eGFR – estimated glomerular filtration rate; GN – glomerulonephritis; na – not available

Table 13: Factors associated with total donor evaluation time, adjusted estimates

	Prospective cohort 16 transplant centers Canada and Australia		**Retrospective cohort 5 transplant centers Ontario, Canada only**			
	Unknown if recipient was receiving dialysis at start of donor evaluation (n=849)		**Recipient receiving dialysis at start of the donor evaluation (N=631)**		**Recipient was not receiving dialysis at the start of the donor evaluation, and a pre-emptive transplant was achieved (N=311)**	
Variable	**beta (95% CI)[a,b]**	**p-value**	**beta (95% CI)[a,c]**	**p-value**	**beta (95% CI)[a,c]**	**p-value**
Demographic factors						
Donor age, per 10 years	0.81 (0.39, 1.57)	0.04	0.67 (0.31, 1.02)	<0.001	2.02 (1.72, 2.31)	<0.001
Female donor sex	0.72 (-0.54, 1.99)	0.26	1.22 (-0.07, 2.51)	0.06	1.51 (-1.04, 4.06)	0.25
Donor smoking status at recruitment (within last 30 days)*						
Not smoking	0 (reference)	0.18	na	na	na	na
Recently quit	-1.31 (-2.89, 0.28)					
Still smoking	-1.20 (-2.82, 0.41)					
Non-white donor race	–	–	2.07 (0.86. 3.29)	<0.001	–	–
Rural donor residence	–	–	-1.41 (-3.02, 0.20)	0.09	-2.71 (-5.10, -0.31)	0.03
Socioeconomic factors						
Donor income quintile[d]						
5, highest	0 (reference)	0.02	0 (reference)	0.05	0 (reference)	<0.001
4	2.17 (0.82, 3.52)		0.41 (-0.95, 1.78)		-2.90 (-4.09, -1.71)	
3	3.07 (0.47, 5.68)		0.65 (-0.11, 1.40)		-0.59 (-5.82, 4.64)	
2	2.64 (0.02, 5.26)		0.29 (-1.43, 2.01)		1.33 (-1.08, 3.75)	
1, lowest	0.88 (-0.42, 2.18)		2.84 (0.75, 4.93)		-1.06 (-5.21, 3.09)	

Pre-donation clinical characteristics						
Donor eGFR[f]						
≥90 mL/min/1.73 m^2	–	–	–	–	0 (reference)	0.002
80-89 mL/min/1.73 m^2					3.46 (1.48, 5.45)	
<80 mL/min/1.73 m^2					1.46 (0.36, 2.56)	
Recipient eGFR at donor first contact, per mL/min/1.73m^2[f]	na	na	na	na	0.83 (0.71, 0.95)	<0.001
Recipient co-morbidities						
Cardiovascular disease	na	na	0.18 (-0.37, 0.74)	0.52	–	–
Ischemic heart disease/ coronary artery disease	na	na	1.56 (-0.75, 3.88)	0.19	3.74 (-0.21, 7.70)	0.06
Heart failure	na	na	1.64 (-1.14, 4.41)	0.25	–	–
Diabetes	na	na	–	–	-4.17 (-6.98, -1.36)	0.004
Hypertension	na	na	–	–	-4.53 (-6.08, -2.98)	<0.001
Donor body mass index, kg/m^2						
Underweight (<18.5)	-3.74 (-7.59, 0.12)					
Normal (18.5-24.9)	0 (reference)	0.10	na	na	na	na
Pre-obese (25-29.9)	1.10 (-1.42, 3.62)					
Obese (30-34.9)	0.47 (-0.89, 1.83)					
Very obese (≥ 35)	2.05 (-2.67, 6.78)					
Time to recipient referral	na	na	0.38 (0.29, 0.51)	<0.001	0.86 (0.75, 0.97)	<0.001
Other characteristics						
Relationship						
Spouse	0 (reference)	0.14	0 (reference)	<0.001	0 (reference)	<0.001
Sibling	-1.63 (-5.20, 1.94)		-0.06 (-2.84, 2.71)		1.07 (-1.74, 3.88)	
Parent	-1.55 (-6.07, 2.97		-0.95 (-2.63, 0.72)		1.06 (-4.34, 6.45)	
Child	-2.71 (-7.00, 1.57)		2.17 (0.43, 3.92)		-1.45 (-4.68, 1.77)	
Other relation	-3.97 (-8.21, 0.27		0.55 (-3.38, 4.49)		-3.94 (-5.70, -2.18)	
Unrelated	1.06 (-4.02, 6.14)		1.87 (0.51, 3.24)		0.94 (-1.54, 3.43)	
Participated in kidney paired donation	6.59 (1.61, 9.74)	<0.001	na	na	na	na
Surgery type performed						
Laparoscopic	0 (reference)	0.46	na	na	na	na
Open	-0.84 (-3.06, 1.39)					
Cause of kidney failure						
GN/autoimmune	na	na	0 (reference)	<0.001	0 (reference)	<0.001
Polycystic			2.39 (-0.30, 5.07)		-2.45 (-5.79, 0.88)	
Diabetes			0.96 (-1.11, 3.03)		-7.18 (-10.9, -3.50)	
Other			1.58 (-0.27, 3.43)		-1.06 (-5.01, 2.88)	
Unknown			2.16 (1.40, 2.92)		-3.29 (-11.0, 4.42)	
Distance to transplant program, per 50 km	0.04 (-0.00, 0.08)	0.07	0.11 (-0.03, 0.25)	0.13	-0.19 (-0.46, 0.08)	0.17

The total evaluation time was defined as the time from the donor's evaluation start date until donation. A positive number means the factor was associated with a longer donor evaluation time, expressed in months of additional time.

[a] beta estimates with 95% confidence intervals (CI) obtained from linear regression accounting for clustering by transplant center (generalized estimating equations). The beta estimate corresponds to the average difference in total evaluation time for a change in category (compared to the reference category) or a 1-unit increment in a continuous variable (unless otherwise specified).

[b] adjusted for donor age, sex, and relationship to the recipient.

[c] adjusted for donor age, sex, urban/rural status, median neighbourhood-income quintile, and relationship to the recipient.

[d] neighbourhood-income quintile derived from the 2006 Canada Census (Canadian donors only).

[e] kidney function measured using CKD-EPI equation (mL/min) from serum creatinine identified at any point in the evaluation for donors and within 3 months of the donor's evaluation start date for recipients.
* donors were recruited a median (25th, 75th percentile) of 2.3 (1.3, 7.5) weeks prior to donation.
eGFR – estimated glomerular filtration rate; GN – glomerulonephritis; na – not available; analyses not done due to unadjusted p>0.2 (from Table 12) are shown by a dash (–)

6.4 Discussion

Using data available on living kidney donors from 16 transplant centers, we assessed living donor evaluation times using five different potential process indicators that can be used to assess the timeliness of a living donor evaluation.

We found the total time to complete the evaluation was a median 10 months, with 25% of donors experiencing an evaluation period of 16 months or more. Some of this time is appropriate and necessary to complete a quality evaluation. Sometimes there are findings that require additional examination for a comprehensive living donor work-up[23,24], but we believe that at least the most common additional tests should not prolong the evaluation by 3-9 months.[10] Other reasons for a longer evaluation time may be appropriate to reduce risks to the donor and recipient (e.g., weight loss, smoking cessation, blood pressure control).[25,26] However, some transplant programs may require these issues to be resolved before the evaluation begins, which may explain why we did not find any of our evaluation times to be associated with these factors. Other reasons that influence the donor evaluation time such as age, sex, ethnicity and geography may be non-modifiable, yet understanding why such factors lead to a longer evaluation may influence how the evaluation is organized. For example, transplant programs may perform multiple tests on the same day to respect the travel requirements of donors who live far away. This may explain the weak association between distance and evaluation times and the shorter total evaluation time and time between consults among rural donors in the present study.[27] Participating in kidney paired donation was the strongest predictor of longer evaluation times, which has some implications to the emerging practice of including compatible pairs.[28–30]

Recipient factors are also important. A delayed recipient referral significantly delayed the living donor evaluation time, a finding which emphasizes the importance of

improving patient education about living donor transplantation and increasing appropriate and timely transplant recipient referrals from kidney clinics.[31,32] A higher recipient eGFR increased the donor evaluation time in the subset of pre-emptive transplants, which is likely an appropriate pace to the living donor evaluation to extend use of the recipient's native kidneys until the transplant is needed. This was one reason why we presented some of our results stratified by whether the intended recipient was on dialysis at the time the donor evaluation started and whether the recipient received a pre-emptive transplant.[18]

There was considerable between-center variability for all measures. Those with the shortest time between consults (Centers I, A, and H) frequently performed these consultations on the same day (I>A>H; Figure 11 and Table 9). Although these centers may not have had the shortest total evaluation and approval times, there was a consistent ordering amongst them for both of these metrics (I<A<H). Despite this, these centers had the longest time between approval and donation (I>A>H). These results suggest that although combining tests on the same day may be a viable and donor-centric process improvement strategy, other factors are also important (e.g., the time needed to secure operating time after donor approval). How one center is performing compared to another must be interpreted cautiously given the centers may differ with respect to donor case-mix (e.g., proportion of donors donating through kidney paired donation, the proportion of donors who are obese), available resources (e.g., equipment and personnel), and the protocols they use to evaluate and select living donor candidates (e.g., how much they participate in kidney paired donation; their minimum requirements to evaluate a candidate). Adjustment for individual patient-level factors did not substantially change the point estimates, suggesting that center-level factors may be important drivers of evaluation times. A more detailed understanding of how different programs evaluate donor candidates is warranted. The living donor evaluation may be expedited under special circumstances that were not detailed in the present study, including urgency to avoid dialysis or to complete the evaluation before a deadline to enter a next matching cycle for kidney paired donation. Transplant centres should organize themselves to have the capacity to conduct a quicker donor evaluation when necessary.[15]

There are many negative implications of a prolonged living donor evaluation that remain to be reported. First, many donors report negative experiences that may be a barrier to living kidney donation.[10,11,15,16] Second, a prolonged living donor evaluation may increase the likelihood of competing events, including deceased donor kidney transplantation or the intended recipient becoming ineligible for transplant due to illness or death.[7,33,34] Finally, there are costs to the healthcare system related to a longer living donor evaluation as recipients continue to accrue costs attributable to kidney disease (e.g., dialysis).[35] Reducing the donor evaluation time when appropriate is a priority for patients, providers, and the healthcare system.

These two multi-centre studies provide new information not available elsewhere by reporting multiple measures of potentially meaningful process outcomes, examining factors associated with these outcomes, and demonstrating substantive center-to-center variability.[11,24,27,33,36,37] Many results are presented by transplant center, and other centers can collect and compare similar measures of performance. However, this study has several important limitations that should be addressed in future efforts. First, this study only included donors and the findings do not reflect the time to determine the candidacy of excluded donors, or the time to work-up donor candidates who were approved but ultimately did not donate. Second, we lacked information on program-level factors that may explain some variability in donor evaluation times (e.g., evaluation of multiple donor candidates simultaneously or sequentially[38]). Such data would be important to ascertain whether delays could be attributable to resources (i.e., human resources, wait-time for testing) or differences in living donor program processes. Third, we lacked some data on individual-level factors that may affect the living donor evaluation time (e.g., recipient illness that may have temporarily affected their transplant eligibility and their donor's evaluation process; various donor-driven reasons including financial or time constraints). Fourth, we used proxy dates to estimate several evaluation times, which may reduce the accuracy of some measures. Fifth, some of the center-to-center differences in donor evaluation times may be explained by differential data completeness rather than true differences. Finally, these results may not generalize to living donor programs in other countries with different healthcare systems and processes that may impact evaluation times.

This study was prompted by a consensus that an evaluation time of six months is too long for many donors.[11,16] The transplant community needs to further explore and define the reasons why some candidates experience prolonged evaluations and why some transplant centers have much longer evaluation times than others. A better understanding of these reasons can inform quality improvement initiatives to improve the experiences of candidates going through the evaluation process.

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Chapter 7

7 The flow of living kidney donor candidates through the evaluation process at a single centre

7.1 Introduction

There are several reasons why a transplant program may wish to assess the flow of living kidney donor candidates through its evaluation process. Knowledge of trends in the number of active open evaluations and the types of tests performed can be used to inform human resource planning and the required volume of specialized tests such as computed tomography (CT) angiography or nuclear renography.[1] Information on the length of the evaluation process for candidates who go on to donate as well as those who are deemed ineligible to donate can be shared with candidates at the beginning of the evaluation process as part of informed consent.[2] To guide quality improvement initiatives, it can be valuable to understand the reasons why the evaluation period is longer in some candidates than others, and the implications that this may have on the likelihood a candidate will complete their evaluation, or the length of time their intended recipient continues to receive dialysis (or needs to begin dialysis).[3–5] However, there is no accepted way to assess the flow of living kidney donor candidates in a donor evaluation program, and our detailed search of bibliographic databases in the form of a scoping review only identified a limited number of illustrative examples (Chapter 4).[6] These studies presented a few key metrics that can be used to compare the relative efficiency between programs, such as the time to complete the evaluation and the proportion of candidates who ultimately donated. However, the lack of consistent definitions of key dates renders many comparisons difficult, and lack of granularity of the data impairs interpretation.

With the paucity of available evidence to date, we conducted this case study of a single program in Ontario, Canada, where we provide an example of how a program can review 4-years of prior data to gain valuable insights on the flow of donor candidates through its evaluation process.

7.2 Methods

7.2.1 Data sources and variables

We retrospectively reviewed the medical records for all living donor candidates who contacted the London Health Sciences Living Donor program in Ontario, Canada between January 1, 2013 and December 31, 2016 (herein referred to as "the study period"). This included all evaluations which were open and ongoing at the beginning of the study period (January 1, 2013), as well as evaluations which began during the 4-year study period. Evaluations could be open and ongoing by the end of the study period (December 31, 2016).

We collected data on donor demographics, social habits, and medical factors from their medical records, which included clinic notes, diagnostic and lab test results, a preliminary screening checklist, living donor coordinator notes, and a self-reported medical-social questionnaire (MSQ). The preliminary screening checklist is conducted over the phone or email, which ascertains general information about prior cancer history, hypertension, diabetes, cardiovascular or cerebrovascular disease, body mass index (BMI), and history of renal stones. The MSQ is a detailed (11-page) paper or electronic questionnaire that ascertains a detailed account of the candidates' social, medical, travel, and family history. Many programs have some form of MSQ that may be paper-based, electronic, or available through some online submission portal.[6]

Blood pressure and BMI were ascertained early in the evaluation phase, as these would be most predictive of the trajectory of the evaluation. We used the BMI that was self-reported on the MSQ, and blood pressure readings were done at a clinic or local drug store and readings were submitted with the MSQ; these measures would be similarly reported for all candidates (donors and non-donors). Blood pressure was estimated from an average of up to five measurements. The second digit of the Canadian postal code was used as an indicator of rural or urban residence (rural if zero; urban otherwise). Persistent hematuria was defined as the presence of blood in the urine in at least 50% of a minimum of three random urine sample tests performed on different days (the presence of blood was defined as per Table 14 to accommodate variability in reporting).

Table 14: Classification of urine blood as positive, negative, or inconclusive

Positive		
trace blood	3-4 RBC	4-6 RBC
3-5 RBC	5-15 RBC	3+ RBC
blood (2)	1+ blood	13 RBC
3-10 RBC	mod blood	>10/uL RBC
moderate blood	16-50 RBC	11-20 RBC
<10 RBC	3 p/ul RBC	20-30 RBCs
large blood	5-20 RBC	5-30 RBC
6-10 RBC	3-5 microscopic RBC/HPF	blood (2+)
blood (1+)	0.3 blood	25-50% dysmorphic RBC
3+ blood	>10mg/L blood	10 blood
6-11 RBC	>50 RBC	11-25 RBC
3 RBC	2+ blood	20-30 RBC
small blood	16 RBC	trace-intact blood
Inconclusive		
1-5 RBC	small blood (menses started this day)	
0-5 RBC	2-5 RBC	
<5 RBC	large blood - patient on menses	
moderate blood (patient on menses)	small blood, rare RBC	
trace blood (patient had menses)	occasional RBC	
1-3 RBC		
Negative		
1-2 RBC		
trace blood (expected)		

Classification of results as positive, inconclusive, and negative was based on expert opinion. If 50% of a candidates' results were positive then the candidate was said to have persistent hematuria.
RBC – red blood cell; HPF – high-powered field

Recipient data were obtained from a local transplant database, which included the date an intended recipient started dialysis, the date transplant recipient candidates were referred for transplant evaluation, and the date transplant candidates were placed on the deceased donor wait-list. Information on intended recipients not referred to the program was unavailable. Unlike what occurs in some other countries including the United States, in Ontario a complete referral package is sent from the nephrologist managing the patient with kidney failure to a transplant centre for an assessment of transplant eligibility. This referral package includes the results of complete bloodwork, an electrocardiogram, an echocardiogram, cardiac perfusion testing (when a patient has cardiac risk factors), infectious disease and virology testing, complete cancer screening per Ontario guidelines, a chest x-ray, and an abdominal/renal ultrasound. The transplant centre acknowledges when they receive a complete referral package, which is the date a patient has been 'referred'.

7.2.2 The evaluation

The living donor evaluation was segmented into distinct phases. The evaluation began at the time the candidate made contact with the program (phoned, emailed, in-person visit). In this study, proceeding to the screening phase of the evaluation occurred if the program received the MSQ (complete or incomplete). Proceeding to the evaluation phase was defined as date the (completed) MSQ was reviewed by the program coordinators and a decision rendered about proceeding to the next phase of the evaluation. The evaluation phase started with the first laboratory test or consult after the screening phase, and ended with a definitive decision on ineligibility, candidate withdrawal, or donation (since the date of approval is not documented or defined).

Candidates were considered lost to follow-up if there was no progress with the evaluation for at least three months and there was no indication that their evaluation was placed on hold or was terminated because the candidate withdrew or was deemed ineligible. Thus, we assumed they were no longer interested in becoming a donor but did not wish to communicate this to the program explicitly. There was no system in place to attempt to contact these candidates, although gentle reminders were sometimes solicited.

Reasons for a delayed evaluation were abstracted from the clinical notes whenever encountered, although there was no systematic process for categorizing or documenting the duration of the delay.

7.2.3 Statistical methods

This study is largely descriptive, and results are reported as mean (standard deviation, SD) or median (25^{th}, 75^{th} percentile), where appropriate. Comparisons between donors and non-donor candidates were conducted using chi-square tests for categorical data and t-tests for continuous data.

7.3 Results

A total of 1,069 living donor candidates were active for some portion of the study period. Of these, 741 (69%) candidate evaluations were terminated without donation (e.g. candidates were deemed ineligible, indicated they wanted to withdraw, or were lost to follow-up); 138 (13%) were still undergoing evaluation by the end of the study period (although 20 ended up donating by January 2018); 103 (10%) candidates donated during the study period; and 87 (8%) candidate evaluations were on hold by the end of the study period, although the reason was unknown.

Mean (SD) candidate age was 46 (14) years, and BMI was 27.0 (5.2) kg/m^2. Candidates were predominantly women (66%), white (85%), and lived in an urban neighbourhood (76%) (Table 15). Most candidates wished to donate to a friend or non-relation (21%), a sibling (20%), or a distant relation (19%). Only 8% of candidates intended to donate anonymously (non-directed donation), two of whom had to have their kidney removed for their own health. During the study period, the program had 2.0 full-time equivalent living donor nurse coordinators, 1.0 full-time equivalent administrative assistant, and 2 nephrologists and 2 surgeons who were available to discuss open cases and see 8-10 new living kidney donor candidates in consultation each month.

Table 15: Donor candidate characteristics (n=1066)

Characteristic	Donor (n=123)	Non-donor (n=946)
Age, years	47.8 (11.1), n=121	45.3 (14.1), n=809
BMI, kg/m^2	26.6 (3.5), n=119	27.0 (5.5), n=475
SBP, mmHg	121 (9.9), n=115	122 (11.8), n=369
DBP, mmHg	76 (6.8), n=115	76 (8.4), n=369
Travel distance (km)		
Euclidean distance	91 (42, 168), n=118	94 (23, 165), n=552
Driving distance	110 (54, 193), n=118	115 (27, 189), n=552
Sex		
Male	39 (32%)	316 (34%)
Female	84 (68%)	607 (66%)
Race		
White	103 (89%)	383 (84%)
Arabic	3 (3%)	21 (4%)
South Asian	3 (3%)	12 (3%)
East Asian	1 (1%)	13 (3%)
Black/Indo-Caribbean	3 (3%)	9 (2%)
Other	3 (3%)	16 (4%)
Urban residence[a]		

Urban	90 (76%)	428 (76%)
Rural	28 (24%)	134 (24%)
Married	105 (85%)	463[b]
Intended recipient relation		
Friend or non-relation	10 (8%)	194 (22%)
Sibling	26 (22%)	169 (20%)
Distant relation	23 (19%)	168 (20%)
Spouse	27 (22%)	86 (10%)
Parent	10 (8%)	99 (11%)
Child	15 (13%)	80 (9%)
Non-directed (anonymous)[c]	10 (8%)	67 (8%)
Donor blood type		
O	66 (54%)	288 (47%)
A	38 (31%)	214 (35%)
B	14 (12%)	88 (15%)
AB	3 (3%)	20 (3%)
Recipient blood type		
O	49 (42%)	301 (44%)
A	44 (38%)	269 (39%)
B	18 (15%)	89 (13%)
AB	6 (5%)	25 (4%)
Enrolled in kidney paired donation	19 (23%)	29[b]
Anti-hypertensive medications	8 (7%)	84 (9%)
Type II diabetes	0 (0%)	10 (1%)
Smoking at screening		
current	15 (13%)	101 (21%)
former	35 (29%)	130 (28%)
never	69 (58%)	239 (51%)

Results are reported as mean (standard deviation), median (25th percentile, 75th percentile), or N (percent), where appropriate

[a] defined using second digit of Canadian postal code (rural if 0, urban otherwise)

[b] no denominator

[c] 1 in each group had to get their kidneys removed for their own health

7.3.1 Healthcare encounters over the study period

The annual number of new candidates who contacted the program doubled from 167 in 2013 to 348 in 2016, with a concomitant 45% increase in the number of donations (22 in 2013 to 32 in 2016) (Figure 12). The average number of candidates coming forward for the same recipient increased over time from a median of 2 (1, 7) (maximum 13) [mean 4.2 (SD 3.8)] in 2013 to 4 (2, 9) (maximum 24) [mean 7.0 (SD 7.3)] in 2016 (Figure 13).

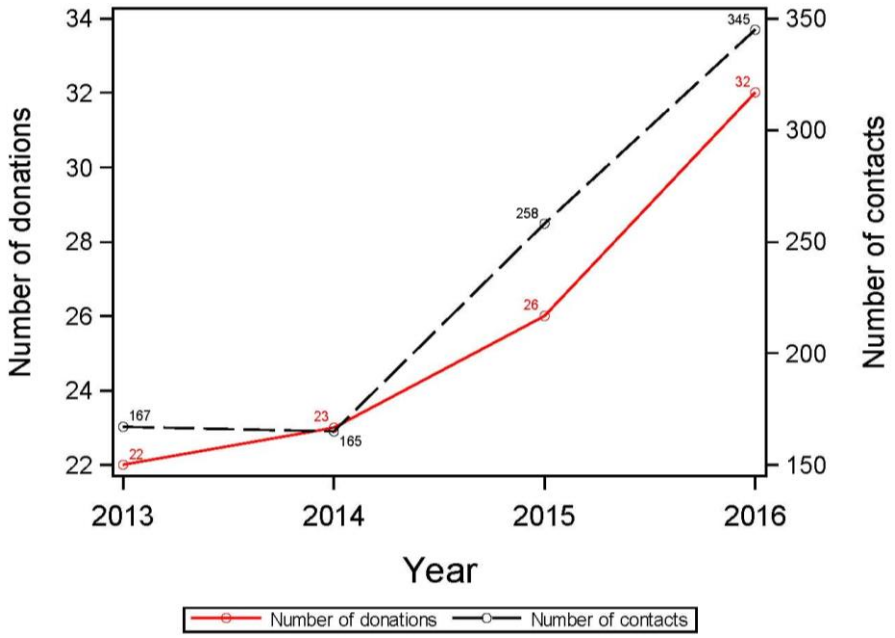

Figure 12: Number of contacts and donations that occurred between January 1, 2013 and December 31, 2016 at London Health Sciences Centre (N=935)

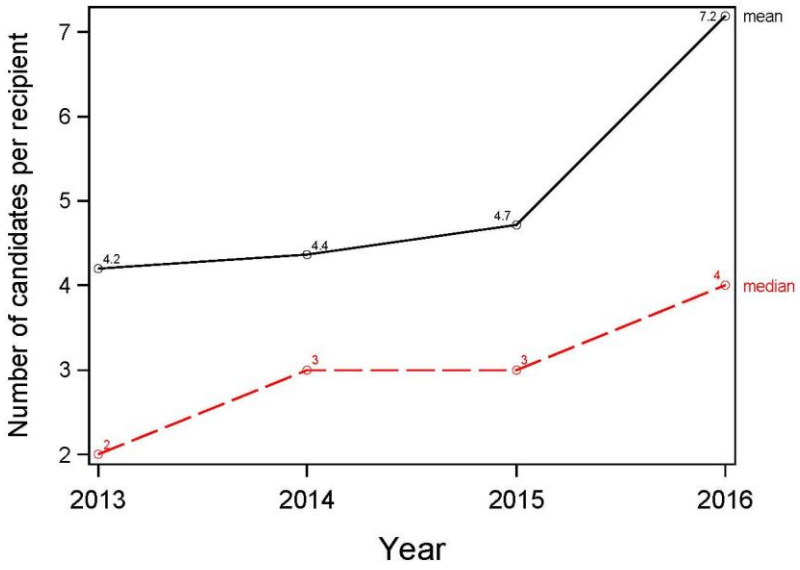

Figure 13: Number of contacts per recipient, restricted to candidates with a known recipient (N=860)

The number of specific healthcare encounters also increased during the study period, including the number of nephrology consults, psychosocial assessments, CT angiograms, and initial crossmatch tests (Figure 14). In contrast, the number of surgery consultations remained stable and the number of nuclear renograms decreased. The number of donors performing two or more 24-hour urine tests decreased over time: 19/22 (87%) in 2013, 20/23 (87%) in 2014, 12/26 (46%) in 2015, and 5/32 (16%) in 2016.

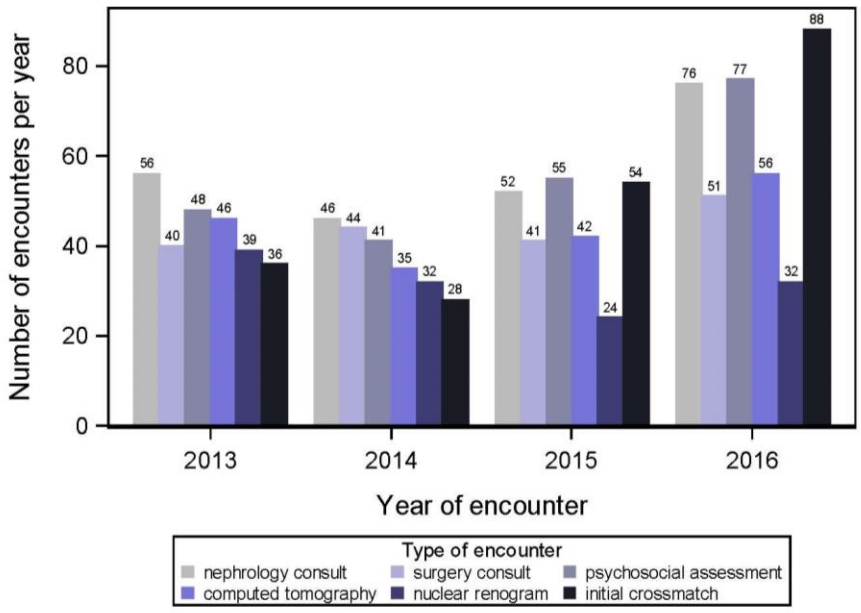

Figure 14: Annual number of healthcare encounters by year

7.3.1.1 Donor candidate attrition for all new contacts during the study period

We followed all candidates through their evaluation process, restricted to those with a first contact date during the study period (n=939). After contacting the program, 427 (45%) candidates did not proceed to the screening phase, 203 (22%) did not proceed to the evaluation, and 228 (24%) did not complete the evaluation (Figure 15). By January 2018, 95/939 (10%) donated. Loss of follow-up with the donor candidate was the most common reason for attrition, which usually occurred during screening (e.g. not screened out at initial contact, yet did not return the MSQ; Table 16). Based on medical or psychosocial grounds, 7% of candidates were deemed ineligible by the program during

the initial screening period (e.g. at initial contact), 15% were deemed ineligible following a more detailed screening (results from the MSQ), and 21% were deemed ineligible during the evaluation period. For candidates with an available date of withdrawal or decline (n=290, excluding those who were lost to follow-up), the total time of the evaluation was a mean 6.2 (SD 6.1) months and a median 4.3 (1.4, 9.1) months.

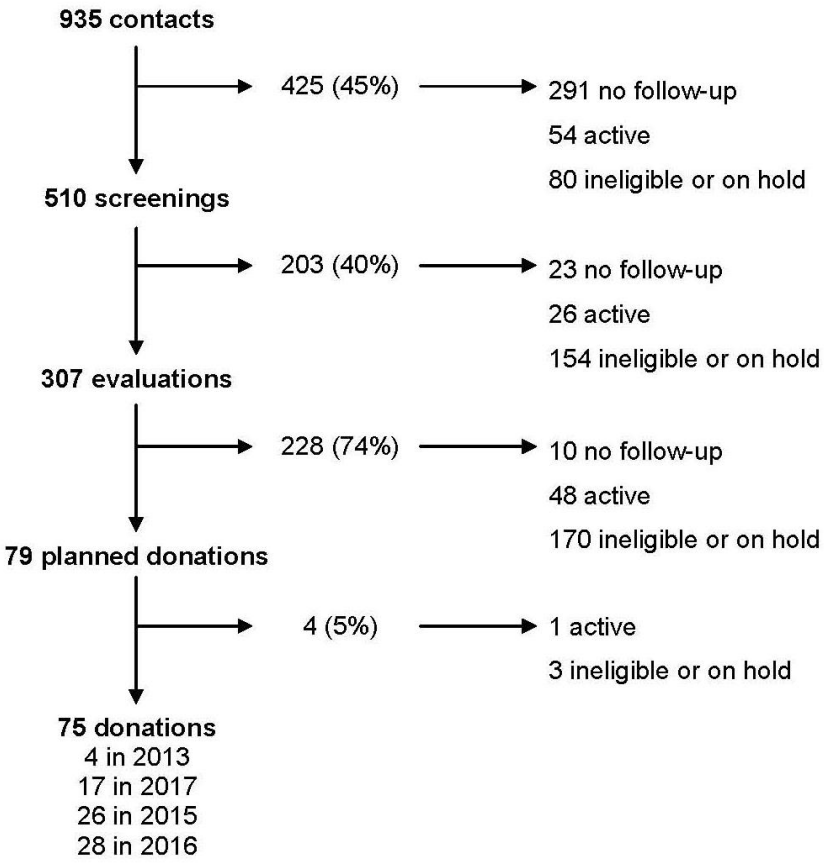

Figure 15: Flow of living donor candidates through the living donor program at London Health Sciences Centre. All candidates first contacted the program between January 1, 2013 and December 31, 2016. Candidates were considered *active* if they did not donate, were not declined, were not placed on hold, or were not lost to follow-up before December 31, 2016. Loss to follow-up was considered as 3 months without contact with the program.

Receipt of a deceased donor kidney transplant was recorded in the candidate's medical chart to be a reason for donor candidate attrition in 22 cases, 13 of whom had a candidate in the evaluation phase. Loss of recipients due to death or ineligibility occurred in only six instances, four of whom had a donor who had passed the screening phase (Table 16).

Table 16: Reasons for donor candidate attrition at different time-points in the evaluation

Reason for attrition	Initial screening period	Preliminary screening period	Evaluation period	After evaluation period
No donor follow-up	290 (68%)	24 (12%)	10 (4%)	0 (0%)
Active donor in period	55 (13%)	27 (13%)	47 (21%)	1 (25%)
Donor deemed medically unsuitable	30 (7%)	31 (15%)	49 (21%)	0 (0%)
Will work up other donors first	4 (1%)	25 (12%)	21 (9%)	0 (0%)
Recipient not ready/not assessed	2 (0%)	21 (10%)	6 (3%)	2 (50%)
Unknown reason	5 (1%)	10 (5%)	14 (6%)	0 (0%)
Donor changing lifestyle (i.e., smoking cessation, weight loss)	1 (0%)	21 (10%)	5 (2%)	0 (0%)
Donor no longer wants to continue with donation	11 (3%)	7 (3%)	7 (3%)	1 (25%)
Other reasons	4 (1%)	9 (4%)	10 (4%)	0 (0%)
Recipient received a deceased donor transplant	5 (1%)	4 (2%)	13 (6%)	0 (0%)
Recipient transplanted by other living donor	3 (1%)	4 (2%)	9 (4%)	0 (0%)
Incompatible (cross-matching) – not interested in kidney paired donation	0 (0%)	1 (0%)	13 (6%)	0 (0%)
Donor impaired by support, stressors, and responsibilities	2 (0%)	6 (3%)	5 (2%)	0 (0%)
Incompatible (ABO) – not interested in alternatives	4 (1%)	6 (3%)	2 (1%)	0 (0%)
Recipient to wait for deceased donor kidney with pancreas or liver	2 (0%)	2 (1%)	5 (2%)	0 (0%)
Recipient declined donor or transplant	3 (1%)	2 (1%)	2 (1%)	0 (0%)
Donor is to be worked up at another program	1 (0%)	3 (1%)	1 (0%)	0 (0%)
Recipient died or no longer eligible for transplant	1 (0%)	1 (0%)	4 (2%)	0 (0%)
Incidental finding during evaluation	0 (0%)	0 (0%)	4 (2%)	0 (0%)
Donor is an international non-directed anonymous donor (not accepted by our program)	3 (1%)	0 (0%)	0 (0%)	0 (0%)
Recipient too healthy for a transplant	1 (0%)	1 (0%)	1 (0%)	0 (0%)

Reasons for attrition were abstracted from clinic notes, whenever documented, and categorized as reported in this table.

7.3.1.2 Reasons for a delayed evaluation

The most frequently encountered reasons for a delayed donor evaluation occurred early in the process (Table 17). The most common reason was a delay in the referral of the intended recipient to the transplant centre (11% of candidates), as there was limited interest in evaluating some living donor candidates in too much detail until their intended recipient was referred to the transplant centre. The second most common reason was the requirement for the candidate to lose some weight (8% of candidates) or other candidates were prioritized when at least one other candidate contacted the program for the same intended recipient (4% of candidates).

Table 17: Reasons for a delayed evaluation process

Reason for delay	General timeline	All candidates (N=939)
Recipient was not assessed yet	early	99 (10.5%)
Candidate needed to lose weight	early	74 (7.9%)
Incidental finding during the evaluation	middle-late	37 (3.9%)
Other donors prioritized	throughout	35 (3.7%)
Other reason	throughout	31 (3.3%)
Smoking cessation	early	30 (3.2%)
Personal reasons	throughout	23 (2.4%)
Donor started the evaluation in another program	early	21 (2.2%)
Language barrier	throughout	21 (2.2%)
Donor coming from another country	throughout	19 (2.0%)
Recipient was not ready to proceed	middle-late	17 (1.8%)
Donor had to get blood pressure under control	early	14 (1.5%)
Donor intends to donate at another program	early	13 (1.4%)
Recipient's health had to improve	throughout	6 (0.6%)
Operating room time difficult to get	late	6 (0.6%)
Recipient kidney's still function so transplant surgery can be delayed	early	2 (0.2%)
Donor needed time to think or discuss with recipient	early	2 (0.2%)

7.3.1.3 Recipient dialysis status

Data were available from the transplant database for 860 (92%) intended recipients. Among these, 359 (42%) were on dialysis before their donor candidate started their evaluation, 316 (37%) were never on dialysis, and 185 (21%) started dialysis after this date (91 did so after their candidate's evaluation was completed and 58 within the first 3

months of their candidates' evaluation start date) (Figure 16). Among donors, 20% of their intended recipient started dialysis before donation (29% for non-donors). Omitting the 92-day buffer to complete the evaluation (a time sufficient to complete the evaluation) increased this estimate to 35% for donors (37% for non-donors). The proportion of living donor transplants that were pre-emptive increased over time: 18% (4/22) in 2013, 27% in 2014 (6/22), 38% in 2015 (9/24), and 34% (11/32) in 2016. Of the 36 recipients who started dialysis after the evaluation was underway for at least three months, this occurred a mean 356 (SD 197) days after the first contact date [median 351 (243, 419) days].

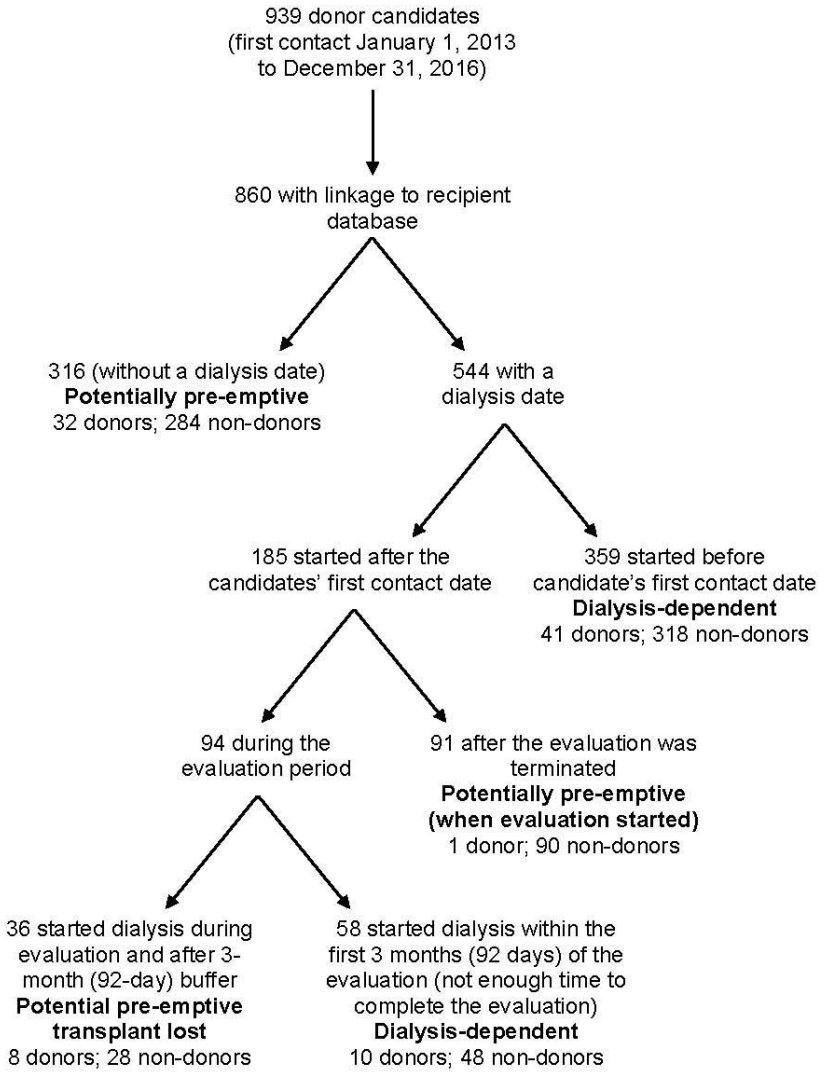

Figure 16: Classification of intended recipient by dialysis status

Recipients were referred to the transplant centre a median 9 (-108, 104) days (n=667) after their donor candidate first contacted the program, and were activated on the deceased donor wait list a median 175 (63, 306) [mean 127 (SD 572)] days (n=532) after their donor candidate first contacted the program.

7.3.2 The evaluation process

Among donors who donated during the study period who had a first contact date available (97/103, 94%), the time from first contact until donation was a mean 13.7 (15.7) months, median 9.2 (6.1, 14.0) months. The total evaluation time decreased over the study period from a median 12.8 (7.5, 14.9) in 2013 to 7.1 (4.8, 12.4) in 2016 (Spearman's rho=-0.24, p=0.02) (Figure 17).

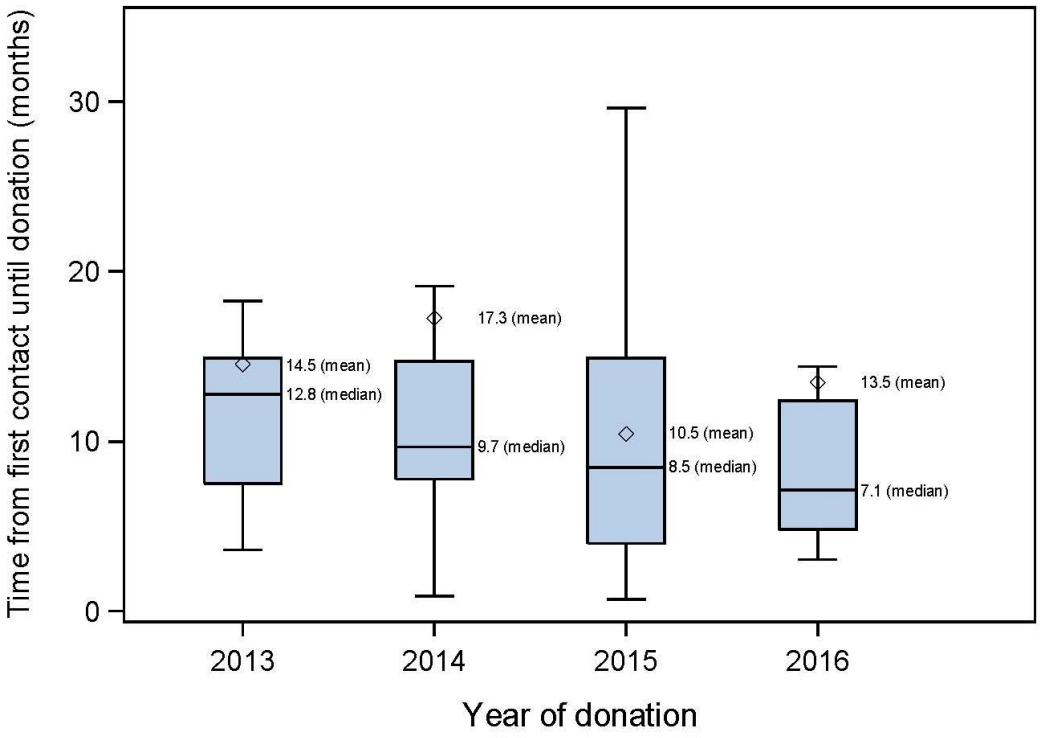

Figure 17: Average time from first contact until donation (n=97)

7.3.2.1 Timeliness of the evaluation

The candidate contacted the transplant program usually by phone (65%) or email (n=31%). Candidates completed the MSQ after a median 7 (IQR 1, 24) days (N=506) and

the program received the completed questionnaire a median 8 (3, 18) days later (Figure 18). The overall process from first contact until the MSQ was reviewed with the candidate took a median 40 (22, 90) days.

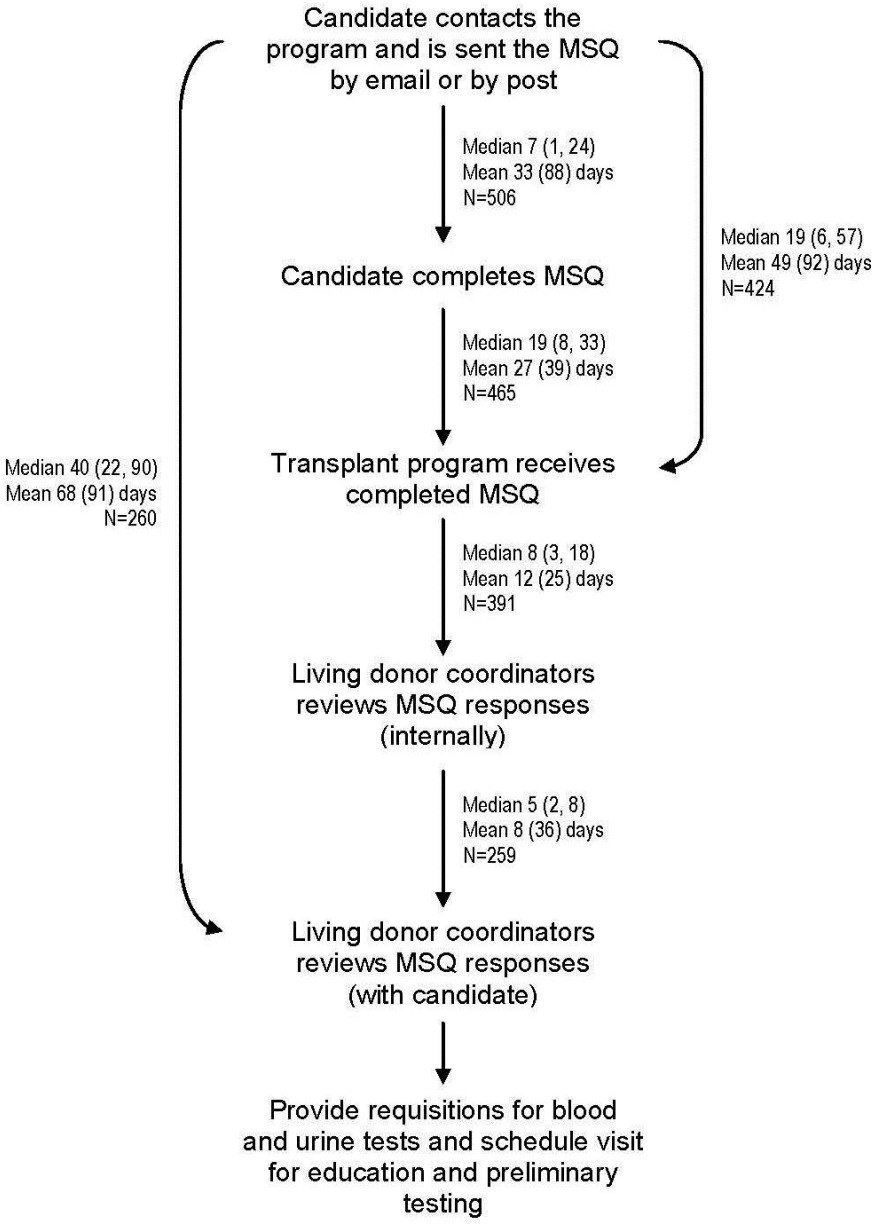

Figure 18: Overview of donor screening process

Since delays in this step may be predominantly donor-driven, we express the time to complete various components of the evaluation using the date the MSQ was received as the point of reference (Figure 19). The renal ultrasound, chest x-ray and electrocardiogram were completed a median 40 days after this time-point, the initial crossmatch, psychosocial evaluation, and nephrology consult after a median of 50-57 days, and the CT, nuclear renogram, and surgical consult after a median of 82-89 days. Donors completed these tests on a median 5 of different dates (range 2-9 days, mean 4.7 days, SD 1.4 days).

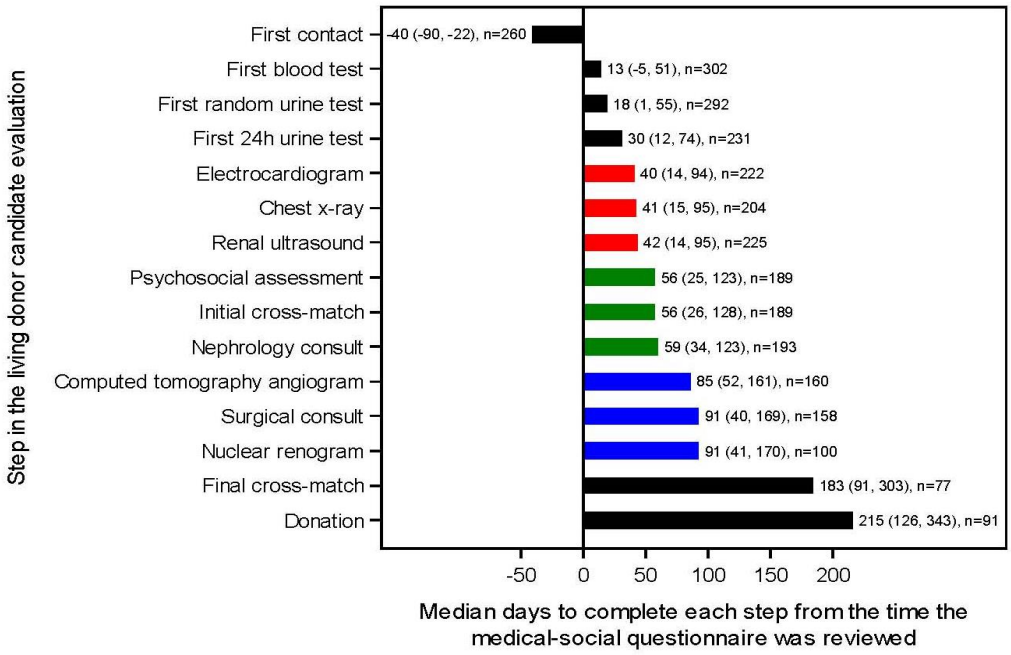

Figure 19: Time from receipt of the medical-social questionnaire (MSQ) until various tests in the living donor evaluation were completed

The initial cross-match was conducted a median 118 (63, 203) days after first contact (n=186), and the final cross-match was conducted a median 95 (56, 133) days afterwards. The first recipient serum that was used for cross-match testing was obtained from the recipient a median 19 (-43, 102) days after first contact. Since at least two samples collected at least two months apart is required, the initial cross-match could potentially

have been conducted 2 months after this date, a median of 48 (0, 115) days earlier than actually performed.

For candidates with a nephrology, urology, and psychosocial assessment, the time between consults was a mean 54 (74) days and a median 27 (4, 69) days (n=127) and was similar for donors (median 27 days) and non-donor candidates (median 28 days).

7.3.2.2 Laboratory, imaging, and consultations

There were no differences in select serum biochemical parameters between donors and non-donor candidates on their first blood test (Table 18). In contrast, donors had significantly less urinary albumin (2.6 g/L versus 6.2 g/L) and a lower random urinary albumin-to-creatinine ratio (0.16 mg/mmol versus 0.80 mg/mmol) than non-donors on their first urine test. Donors were less likely to have persistent hematuria (8/71, 11%) than non-donors (21/62, 34%) among those tested, but were more likely to continue with the evaluation and have a urine cytology exam (microscopic analysis of urine for evidence of malignancy), cystoscopy, or renal biopsy (Table 18).

There was no difference in 24-hour creatinine clearance (117 versus 114 mL/min/1.73m^2) or GFR measured by nuclear renogram (107 versus 92 mL/min/1.73 m^2) between donors and non-donors. The nuclear renogram was performed a median 0 (-35, 4) days from the time of the CT scan (if negative, renogram preceded the CT angiography). The time from CT until donation was a mean 127 (149) days [median 75 (36, 180) days] (n=74).

Other tests were required on an individual-level basis, including ambulatory blood pressure monitoring (n=54), echocardiography (n=20), stress tests (n=19), and 24-hour urine analysis for kidney stones (n=13). Consultation with other healthcare professionals were required on an individual basis, including dietitians (n=20), obstetricians or gynecologists (n=11), transplant infectious disease (n=11), cardiologists (n=9), hepatologists (n=5), gastroenterologists (n=5), and respirologists with or without a pulmonary function test (n=5).

Table 18: Test results for donor candidates

	Donor (N=95)	Non-donor candidate (N=844)	p-value
Lab finding (blood tests)			
Number of blood tests*			
1	2 (3%)	115 (59%)	<0.0001
2	30 (40%)	60 (31%)	
3	19 (25%)	12 (6%)	
4	9 (12%)	5 (2%)	
5	11 (15%)	1 (1%)	
6	4 (5%)	2 (1%)	
total protein (g/L)	71.0 (4.2)	71.5 (4.0)	0.47
albumin (g/L)	44.2 (3.1)	44.1 (2.7)	0.91
creatinine (μmol/L)	68.9 (11.3)	72.3 (13.9)	0.03
estimated GFR (mL/min/1.73 m^2)[a]	97.0 (13.8)	94.0 (16.9)	0.12
random glucose (mmol/L)	5.2 (0.7)	5.3 (1.3)	0.39
fasting glucose (mmol/L)	5.1 (0.5)	5.0 (0.7)	0.27
2-hour glucose (mmol/L)	5.1 (1.3)	5.8 (1.9)	0.32
hemo a1c (%)	5.4 (0.4)	5.4 (0.4)	0.38
cholesterol (mmol/L)	5.0 (0.9)	5.0 (1.0)	0.77
triglyceride (mmol/L)	1.4 (0.9)	1.3 (0.8)	0.54
HDL (mmol/L)	1.5 (0.5)	1.6 (0.5)	0.43
LDL (mmol/L)	2.8 (0.8)	2.8 (0.8)	0.96
Lab finding (urine tests)			
Number of urine tests*			
1	0 (0%)	74 (40%)	<.0001
2	4 (5%)	47 (26%)	
3	16 (21%)	31 (17%)	
4	16 (21%)	14 (8%)	
5	13 (18%)	9 (5%)	
6	15 (20%)	5 (3%)	
7+	11 (15%)	3 (2%)	
albumin (mg/L)	2.6 (4.7)	6.2 (12.4)	0.001
creatinine (mmol/L)	9.9 (7.6)	9.3 (6.6)	0.56
random albumin/creatine ratio (mg/mmol)	0.16 (0.26)	0.80 (2.46)	0.0007
Number with persistent hematuria[b]*	8 (11%)	21 (34%)	0.002
Number with urine cytology*	10 (13%)	17 (2%)	<.0001
Number with cystoscopy*	10 (13%)	10 (1%)	<.0001
Number with renal biopsy*	10 (13%)	4 (1%)	<.0001
Lab finding (24 hour urine tests)			
Number of 24h urine tests*			
0	2 (3%)	601 (82%)	<.0001
1	37 (49%)	78 (11%)	
2	28 (37%)	42 (6%)	
3+	8 (11%)	7 (1%)	
first measured creatinine clearance (mL/min/1.73 m^2)	117 (33.4)	114 (55.1)	0.59
Other investigations			
Number with renal ultrasound*	75 (100%)	129 (18%)	<.0001
Number with CT scan*	74 (99%)	57 (8%)	<.0001

Number with a nephrology consult*	75 (100%)	90 (12%)	<.0001
Number with a psychosocial consult*	73 (97%)	91(13%)	<.0001
Number with a urology consult*	67 (89%)	61 (8%)	<.0001
Lab finding (nuclear renogram)			
Number with nuclear GFR exam*	41 (55%)	51 (7%)	<.0001
Measured GFR (mL/min/1.73 m^2)	107 (50.2)	92.4 (23.1)	0.14
Left split renal function % (left)	51.7 (3.5)%	49.3 (3.7)%	0.004
Self-reported psychosocial history[c]			
Ever been treated, diagnosed with, or been prescribed medication for a mental, psychiatric, or emotional disorder			
no	64 (88%)	324 (80%)	0.13
yes	9 (12%)	80 (20%)	
In the past 5 years, have you ever been prescribed anti-depressants, anti-anxiety or other similar medications by a physician?			
no	63 (86%)	308 (75%)	0.04
yes	10 (14%)	100 (24%)	

[a] estimated using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula
[b] defined as at least 50% of urine samples positive for blood, restricted to those with at least 3 random urine tests (see Table 14 for details)
[c] self-reported on medical-social questionnaire
[F] p-value calculated using Fisher's exact test
[W] p-value calculated using non-parametric Wilcoxon rank sums test
*restricted to donors (n=75) and non-donors (n=728) with a completed evaluation (e.g. donation date and evaluation end-date within study period)
GFR – glomerular filtration rate

7.3.3 Living donor candidate expectations

Many donor candidates answered the MSQ question "Within what time frame are you hoping to complete this process (i.e., when will be the best time for you to donate if you are found suitable?)". Many candidates were keen to donate as soon as possible (n=158, 39%) while others did not express any urgency and were available whenever needed (n=246, 61%). Forty-four percent of candidates expressed that the ideal time to donate was as early as 1 month from the time the MSQ was completed, whereas 38% required at least 4 months and 18% preferred to donate anytime after 6 months. The ideal time to donate was less than 4 months by 41% of candidates, while 47% preferred a time >6 months from the date the MSQ was completed. There were no differences in expectations between donors and non-donor candidates (p>0.6).

7.4 Discussion

In the present study, we conducted a detailed chart audit to understand the flow of living donor candidates through our program. Although labor-intensive, the results are informative, enabling us to identify the most frequent reasons causing delay that are actionable or warrant further study.

One study reported a median (25^{th}-75^{th} percentile) time until approval of 4 (1-24) months, a median time from approval until donation of 3 (0-9) months, and a median time until rejection of 3 (0-48) months.[7] Another study reported a mean (standard deviation) time until donation of 9.3 (6.5) months.[8] One study reported a median time until donation of 5.9 (3.7-10.6) months from the time of referral (although the referral date was not clearly defined).[9] One study reported a time from screening bloodwork until donation of 4.3 months, down from 7.4 months following quality improvement efforts of implementing a clinical pathway.[10] Finally, one multi-centred study reported multiple metrics for evaluation times across multiple centres in Canada and Australia, demonstrating substantial variability across programs and estimating a median time until donation of 10.3 (6.5-16.7) months.[5]

We reported a median time until donation of 9.2 months, consistent with previous reports[5], but also identified a small reduction in the total time until donation over time. The number of living donor transplants increased over time, which may be explained either by the rise in the number of candidates coming forward for the same recipient, a reduction in the evaluation time, or both.[11] We expect further efficiencies in the evaluation process to result in a greater number of living donor transplants performed, which is of itself an important performance indicator. Comparable to other studies, the number of times the intended recipient started dialysis, died or became ineligible for transplant, or received a deceased donor transplant before their donor candidate completed their evaluation occurred often enough to warrant concern, and quality improvement efforts should attempt to reduce these occurrences whenever possible.[3,4,6]

There are many areas for efficiency improvements. One potential solution is to provide the MSQ on the program's website; a practice used by several programs in the United

States.[6] Most living donor programs only evaluate one candidate at a time, but it is unclear whether review of the completed MSQ is considered part of this evaluation. Review of the MSQ is labor-intensive, requiring at least one hour of living donor coordinator time (based on expert opinion). Although as many as 24 candidates came forward for one recipient in 2016, we do not expect all of them to complete the MSQ since many candidates do not follow up with the program after initial contact. Providing the MSQ online with the ability to complete it entirely electronically may ease the screening process and facilitate prioritization of candidates using pre-scored instruments and flags to enable coordinators to focus on key issues.

For donor candidates whose evaluation was delayed because their intended recipient was not assessed, their evaluation resumed 73% of the time (e.g. this was not a cause for termination of the candidate's evaluation). Nine percent of donors' evaluations were delayed for this reason – had the candidate's evaluation begun immediately, we would have expected some earlier living donor kidney transplants that may in turn improve outcomes (particularly if the recipient is on or approaching dialysis).[3] In addition to earlier recipient referrals, decisions should be made whether to begin (and when to pause) the donor candidate evaluation for candidates whose intended recipient was not yet evaluated. Other reasons for delay include the need for the candidate to lose weight, which is necessary for the safety of the donor and is largely non-modifiable.[12,13] Our program offers (but does not mandate) consultation with a dietitian in cases of obesity or elevated cardiovascular risk factors. Although BMI cut-points may vary between programs[6], the evaluation is often begun if it is clear that the candidate is making strides towards weight loss and the intended recipient has been approved for transplant. Finally, another reason for delay was the prioritization of other donor candidates. In some cases, it may be more cost-effective to evaluate multiple candidates simultaneously: in our population, only 2 donors' evaluations had a documented delay because other candidates were prioritized. Future research is needed to examine this scenario. Future efforts are needed to quantify periods of patient-driven and system-driven delay.

Strategies to improve the efficiency of the living donor evaluation process have been discussed in prior reports.[6,14] However, we believe the future of our program (and of

others) is to enable a 1-day evaluation for willing candidates. Several transplant centres already have such a strategy in place.[6,11] A step-wise evaluation is certainly cost-saving to the evaluation program, but from a broader perspective, the opportunity cost is high if the recipient starts dialysis or continues to accrue costs related to dialysis while waiting for their donor.[3] Following the screening phase, all candidates are required to complete random blood and urine tests. However, there is no consensus whether the requisitions for these tests should be provided at the same time as the MSQ or after the MSQ is reviewed by the living donor coordinators. Non-donors had significantly less favourable urine test results than donors, suggesting a greater emphasis for conducting this test as early as possible (perhaps during the initial screening phase). Following screening, all candidates could be scheduled for 1-day testing (Figure 20). Some time is then needed to establish candidacy, order additional tests on a second visit if needed, and schedule the operating room. In this scenario, the candidate is required to visit the transplant centre once or twice. Currently, candidates interacted with the healthcare system a median 5 times before the preoperative assessment (not including visits with a general practitioner or other *ad hoc* tests or consults). Scheduling the operating room as early as possible may help reduce the time until donation, which may be particularly important since the time from CT angiography (one of the last tests) until donation was the longest segment of the evaluation.[5,15] This may be due to a number of factors, including donor and recipient readiness in addition to scheduling challenges. If successful, a 1-day evaluation should result in a time until donation of approximately 4 months: a realistic and optimal target.[11,16]

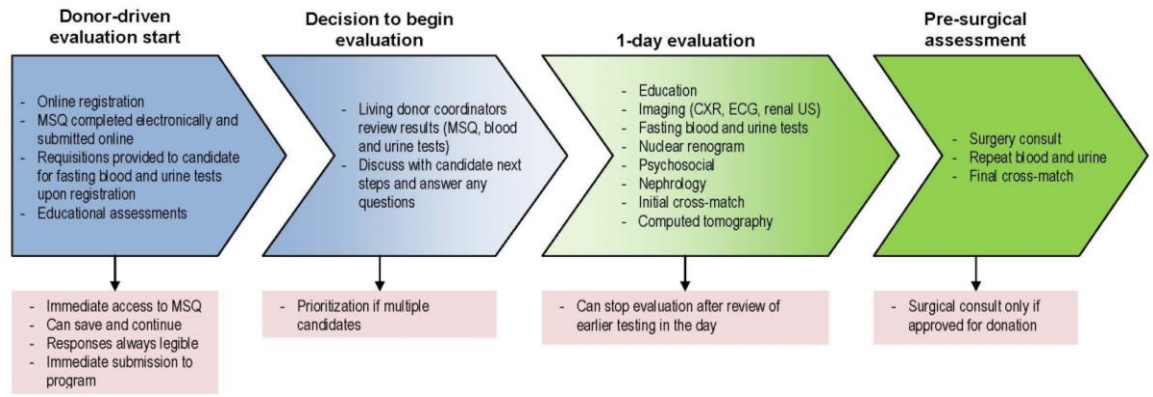

Figure 20: Proposed clinical pathway for a 1-day evaluation of living donor candidates

One of the limitations of this study is the underreporting of reasons for delay. At our centre, reporting reasons for delay became more routine over time as measures of evaluation time were increasingly requested. Another limitation is the lack of data on the date the donor candidate was approved. This is a critical date, as this separates delay due to the donor evaluation itself from other factors related to scheduling the transplant. These reasons are important for quality improvement efforts to streamline the evaluation process and reduce possible inefficiencies. A further limitation of this work is the unavailability of data regarding the donor candidate experience with the evaluation process.

In conclusion, the living donor evaluation process remains a challenging and resource-intensive process. A "one-stop shop" testing strategy is one solution to improve the efficiency of this process and improve recipient outcomes and the donor experience, while potentially reducing costs to the healthcare system. Synoptic reporting of key elements will enable future quality improvement efforts, and future work should focus on developing these methods.

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Chapter 8

8 Initiating maintenance dialysis prior to living kidney donor transplantation when a donor candidate evaluation is well underway‡‡

8.1 Introduction

A pre-emptive kidney transplant avoids the risks of initiating dialysis and results in better outcomes and patient experiences compared to other treatment options available to patients with kidney failure.[1,2] Deceased donor pre-emptive kidney transplants are rare, as most patients wait on a list for several years before an offer for a deceased donor kidney becomes available.[3] For this reason, pre-emptive kidney transplants are typically achieved from a living donor.

There are many challenges to receiving a pre-emptive living donor kidney transplant. First, the intended recipient needs to be referred to a transplant program, thoroughly evaluated, and approved to receive a kidney transplant. Second, the transplant should be timed such that the intended recipient's native kidneys have not failed to the extent of initiating dialysis urgently, but not too early so that the recipient can make use of any remaining native kidney function.[4] Third, a living donor has to be identified.[5] Finally, the living kidney donor candidate needs to be thoroughly evaluated and approved for kidney donation. For this last consideration, there is a growing appreciation that the living donor evaluation process for many motivated donor candidates is lengthy, difficult to navigate, and challenging.[6–8] The 2017 KDIGO 'Clinical Practice Guideline on the Evaluation and

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Care of Living Kidney Donors' recommends that transplant programs should conduct as efficient a donor evaluation as possible, meeting the needs of donor candidates, intended recipients and transplant programs.[9] Using data from a multi-centre study, the median estimated donor evaluation time (time from first contact to nephrectomy) was 10.3 months (Chapter 6). In some cases a prolonged donor evaluation process may prevent a pre-emptive transplant.

In this study, we focused on a cohort of patients with kidney failure, all who received a living donor kidney transplant. We studied persons not receiving dialysis when their donor candidate's evaluation was well underway and determined how often maintenance dialysis was initiated before receipt of the living kidney donor transplant. We assessed the cost of dialysis treatments, and whether dialysis was started urgently in a hospital setting. Finally, we explored whether some unmodifiable and modifiable factors were associated with dialysis initiation prior to transplant.

8.2 Methods

8.2.1 Design and setting

We conducted a retrospective analysis of living donor kidney transplants using linked databases for the entire province of Ontario, Canada. Ontario has a current population of 13.7 million people and residents receive access to publicly insured hospital and physician services. In 2016 there were approximately 10,000 patients receiving dialysis, and 20,000 patients followed in clinics for advanced chronic kidney disease; living kidney donor transplants took place in five transplant centres. This study was approved by the research ethics board at Sunnybrook Health Sciences Centre, Toronto, Canada. Datasets were linked using unique encoded identifiers and analyzed at the Institute for Clinical Evaluative Sciences (ICES). The study was conducted according to a pre-specified protocol and reporting of the study followed standardized guidelines (Appendix G).

8.2.2 Variables and data sources

We ascertained demographic characteristics, clinical factors, and outcomes using several linked databases. Information on all living kidney donors and recipients in Ontario were obtained from Trillium Gift of Life Network[10], chart abstraction, and the Canadian Organ Replacement Register databases, and included race, blood type, and donor-recipient relationship. Additional donor information included the donor's estimated glomerular filtration rate (eGFR) prior to donation. Additional recipient information included primary cause of kidney failure, prior transplant history, and serum creatinine, hemoglobin, and albumin at the time of dialysis initiation. Recipient referral dates were available for recipients transplanted after 2010. Demographic variables were obtained from the Registered Persons Database (age, sex, postal codes to calculate the Euclidean distance to the transplant centre and to obtain neighbourhood income quintiles from the 2006 Canada Census). The Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD) and the Ontario Health Insurance Plan (OHIP) datasets were used to determine if and when dialysis was initiated (and whether it was started in the hospital or outpatient setting), as well as to identify various non-renal comorbidities among recipients (Appendix H).[11] The ICES Physician Database and OHIP were used to determine the start date of the living donors' evaluation (Appendix I and Appendix J). Linked laboratory databases were used to obtain the most recent recipient serum creatinine at the time their donor initiated their evaluation (±3 months) and at the time of referral (±3 months) in a subset of patients. This database, the Ontario Laboratory Information System, includes inpatient and outpatient test values from hospital and commercial laboratories, together accounting for 91% of Ontario's lab results by 2016. eGFR was calculated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation (in mL/min per 1.73 m^2).[12] Dialysis costs were estimated for recipients who started dialysis after March 2006 (which was the first available date in our data sources when dialysis costs could be reliably ascertained). Costs were tabulated from the public payers' perspective using OHIP billing codes (Appendix H) plus resource intensity weights times the cost per weighted case to calculate the cost per case (i.e., consumable materials, nursing staff, machine costs).[13]

8.2.3 Selection

The selection of living donor kidney transplants for this study is presented in Figure 21. This study was restricted to patients who received a living kidney donor transplant, where the transplants occurred between April 1, 2004 and March 31, 2014. In this study, we focused on the subset of living donor transplants where the recipient was a first-time kidney transplant recipient and was not on dialysis when the evaluation process of the candidate who ultimately donated to them was well underway. Living donors were required to be Ontario residents for at least two years prior to donation to ensure that information on the donor evaluation process was complete and available in our data. We excluded donors who were missing a donation date, a nephrology consult, or a surgery consult (Figure 21), as these donors were likely from outside of Ontario or may have participated in a national kidney paired donation program. We also excluded donors with unreasonable patterns of procedures (i.e., nephrectomy codes before donation date) and those with a late-stage procedure captured as the first procedure (i.e., a living donor evaluation would not begin with a nephrology consultation).

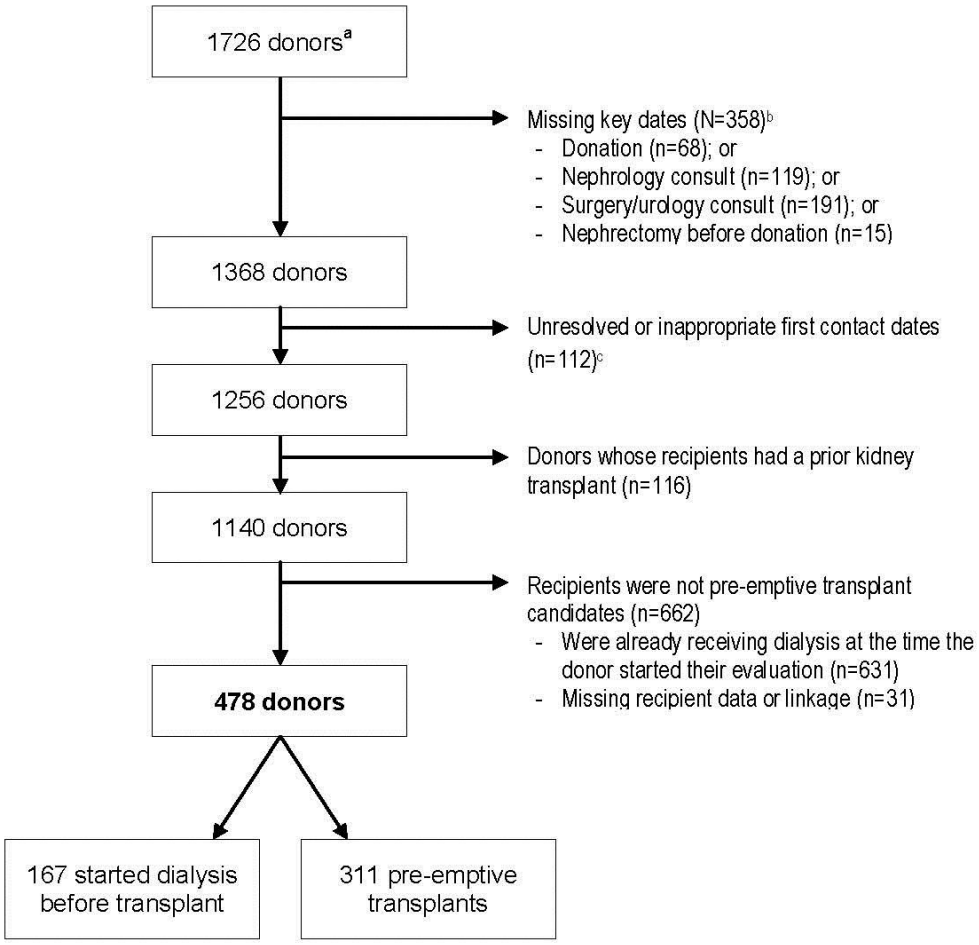

Figure 21: Overview of inclusion/exclusion criteria for living kidney donors in this study.

[a] Living kidney donors were identified through Trillium Gift of Life Network. All living donors have a unique identification number that allows linkage across datasets.

[b] These exclusions are not mutually exclusive so do not sum to 358; nephrology consults within two weeks of donation and surgical consults within two days of donation were not considered true consults (part of the pre-admission process).

[c] Healthcare procedures deemed appropriate start points for the living donor evaluation.

8.2.4 Measurements

In this study a pre-emptive transplant was defined as the absence of dialysis billing codes for the recipient prior to their transplant. We considered a pre-emptive transplant *potentially possible* if the recipient did not receive dialysis within 92 days following the donors' evaluation start date. For these recipients, if dialysis was initiated prior to transplant it was considered a "potential unrealized pre-emptive transplant". Our opinion is that 92 days (three months) is a reasonable buffer time to complete the evaluation (which would be the case if the donor was motivated and eligible to donate). In sensitivity analysis, we extended this period to four and six months; the United Kingdom 2020 strategy suggests all potential donors should be offered to complete the donor assessment within 4.5 months of referral (where appropriate).[14] With the data available to us we could not reliably assess how many unrealized pre-emptive kidney transplants were preventable [i.e., there were modifiable reasons (inappropriate waiting) that could be addressed to realize the pre-emptive kidney transplant]. For this reason we deliberately use the wording "potential" unrealized pre-emptive kidney transplant in this paper.

We defined the *total evaluation time* as the time when the donor started the evaluation (the earliest documented evaluation testing) until the nephrectomy. We defined the *total approval time* as the time from the donor evaluation start until the last specialist consult preceding nephrectomy. The procedures that defined the start of the evaluation and the consults that defined the approval date are presented in Appendix E. We defined the *time for consults* as the time from the first to the last nephrology, psychosocial, or surgical evaluation; this was restricted to donors who had all three consults and was limited to the most recent of the three consults. These three consults are a standard part of the donor candidate evaluation in all Ontario transplant programs. All times were expressed in months.

8.2.5 Statistical methods

Descriptive statistics included the mean (standard deviation, SD), median (25^{th}, 75^{th} percentile), and proportion (95% confidence intervals, CI), where appropriate.

We used a recommended approach to report risk ratios for the association between characteristics and dialysis initiation (i.e., a potential unrealized pre-emptive kidney transplant; yes/no) [estimates derived from modified Poisson regression models (`proc genmod` using a log link, a Poisson distribution, and a `repeated` statement (for individuals) for robust standard error estimation)].[15] To assess whether the results differed across the five Ontario transplant programs that performed living donor nephrectomies during the study period, we calculated the intraclass correlation coefficient using mixed models treating the transplant program as the clustering variable (as a measure of the proportion of the variance of the outcome accounted for by differences in transplant program).

To comply with privacy regulations for minimizing the chance of patient identification, five or fewer participants are reported as <6. For similar reasons the names of the transplant programs and the number of transplants per program were also suppressed. We used Statistical Analysis Software Enterprise Guide version 6.1 (2013 by SAS Institute Inc., Cary, NC, USA) for all analyses.

8.3 Results

8.3.1 Patient population

A total of 478 living kidney donor transplants were included in the primary analysis (Figure 21). Donors were a mean 46 (SD 11) years of age at the time of donation, most were white (79%), female (63%), lived in an urban area (87%), had higher neighbourhood income (24% were in the highest income quintile versus 13% in the lowest), and lived a median of 33 (16, 74) kilometers from the transplant centre where they donated (Table 19). The pre-donation eGFR was >80 mL/min per 1.73 m^2 in 79% of donors. Recipients were similar to donors with respect to age at transplant [mean 44 (SD 14) years], percent living in urban areas (87%), and neighbourhood income (24% in the highest income quintile), but were more likely to be male (63%).

Most transplants occurred between spouses (28%), siblings (24%), or unrelated donor-recipient pairs (17%) (Table 19). The proportion of living donor transplants performed in Ontario ranged from 6% to 31% across the five transplant programs.

Table 19: Donor, recipient, and transplant characteristics

	Donor (N=478)	**Recipient (N=478)**
Age at transplant (years), mean (SD)	46.3 (10.9)	44.0 (14.2)
Sex		
Female	301 (63%)	177 (37%)
Male	177 (37%)	301 (63%)
Race**		
White	197 (79%)	171 (81%)
Other	53 (21%)	39 (19%)
Income[a]		
5 (highest)	116 (24%)	116 (24%)
4	125 (26%)	126 (26%)
3	96 (20%)	95 (20%)*
2	78 (16%)	80 (17%)
1 (lowest)	63 (13%)	61 (13%)
Rural residence[b]		
Urban	415 (87%)	418 (87%)*
Rural	63 (13%)	60 (13%)
Blood type		
O	155 (60%)	160 (40%)
A	77 (30%)	167 (42%)
B	<6	51 (13%)
AB	<6	22 (5%)
Distance to transplant hospital		
<20 km	148 (31%)	124 (25%)*
20-39 km	115 (24%)	132 (28%)
40-89 km	118 (25%)	104 (22%)
>89 km	97 (20%)	118 (25%)
median (IQR)	33 (16-74)	29 (15-67)
mean (SD)	82 (142)	77 (145)
Donor eGFR at donation[c,]**		
>89 mL/min/1.73 m^2	281 (61%)	–
80-89 mL/min/1.73 m^2	80 (18%)	–
<80 mL/min/1.73 m^2	96 (21%)	–
mean (SD)	*96.5 (14.1)*	–
Recipient eGFR at beginning of donor evaluation[c,d,]**		
>19 mL/min/1.73 m^2	–	30 (21%)
15-19 mL/min/1.73 m^2	–	33 (23%)
10-14 mL/min/1.73 m^2	–	57 (39%)
<10 mL/min/1.73 m^2	–	24 (17%)
mean (SD)	–	*16.2 (8.4)*
Recipient referral (days after donor evaluation started)		

mean (SD)	–	178 (430)
median (25th, 75th percentile)	–	22 (-66, 322)
n (%)	–	136 (28%)
Recipient eGFR at time of recipient referral[c,d,**]		
>19 mL/min/1.73 m^2	–	18 (18%)
15-19 mL/min/1.73 m^2	–	24 (25%)
10-14 mL/min/1.73 m^2	–	37 (38%)
<10 mL/min/1.73 m^2	–	19 (19%)
mean (SD)	–	*14.3 (5.2)*
Recipient comorbidity		
Cardiovascular disease	–	186 (39%)
IHD/CAD	–	36 (8%)
Heart failure	–	17 (4%)
Cancer	–	104 (22%)
Diabetes	–	63 (13%)
Hypertension	–	384 (80%)
Anemia	–	29 (6%)
Anxiety/depression	–	51 (11%)
Relationship to recipient		
Sibling	115 (24%)	–
Unrelated	79 (17%)	–
Spousal	134 (28%)	–
Parent	60 (13%)	–
Child	59 (12%)	–
Other relation	31 (6%)	–
Cause of kidney failure**		
Glomerulonephritis/autoimmune	–	84 (26%)
Other	–	78 (24%)
Polycystic	–	75 (23%)
Diabetes	–	47 (14%)
Unknown etiology	–	42 (13%)
Year of transplant		
2004-2007	–	155 (33%)
2008-2010	–	145 (30%)
2011-2014	–	178 (37%)

[a] categorized into fifths of median neighbourhood income from the 2006 Canada Census
[b] defined as a municipality with <10,000 persons
[c] eGFR (estimated glomerular filtration rate) was calculated using CKD-EPI equation, in mL/min/1.73 m^2.
[d] recipient creatinine was measured ± 3 months of the evaluation start date or the recipient referral date
[e] codified for privacy
<6 – suppressed due to privacy (either <6 or another cell is <6 for the same variable)
*missing status assigned as 'urban', income quintile 3, or travel distance <20km
** highly missing variable
SD – standard deviation; IQR (interquartile range – 25th, 75th percentile); IHD/CAD – ischemic heart disease/coronary artery disease

8.3.2 Potential unrealized pre-emptive kidney transplant

A total of 478 persons (all who ultimately received a living kidney donor transplant) were not on dialysis when the donor candidate (who ultimately donated to them) was being evaluated for at least 3 months. Recipient eGFR at the start of their donors' evaluation was a mean (SD) of 16.2 (8.4) mL/min per 1.73 m^2, and in those with available data the recipient eGFR at recipient referral was 14.3 (5.3) mL/min per 1.73 m^2. For pairs with available data, the recipient referral predated the date the donor candidate first contacted the transplant program 55/136 (40%) of the time (a mean (SD) of -5.2 (4.8) months). Donor candidate first contact predated the recipient referral 80/136 (59%) of the time (a mean (SD) of 13.5 (13.9) months). The transplant programs in Ontario typically put the donor candidate evaluation on hold until the intended recipient is referred for transplant evaluation (Chapter 7).

A total of 167 of 478 recipients (35%) initiated dialysis prior to receipt of their transplant, which we consider potential unrealized pre-emptive kidney transplant. In sensitivity analyses, requiring the donor candidate to be evaluated for at least 4 or 6 months when their recipient (who was not on dialysis) entered the cohort, meant 144/451 (32%) and 111/412 (27%) of recipients, respectively, initiated dialysis before transplant.

The mean (SD) eGFR at the time of dialysis initiation was 8.5 (7.2) mL/min per 1.73 m^2, serum albumin was 35.2 (7.0) g/L, and serum hemoglobin was 105 (42) g/L. A total of 44 of the 167 recipients (26%) started dialysis as an inpatient in the hospital setting. Recipients who started dialysis during their donors' evaluation did so a median 9.7 (5.4, 18.7) months after their donor started the evaluation, were transplanted a median 8.8 (3.6, 16.9) months after starting dialysis, and accrued a mean of $48,717 (SD $55,249) in dialysis costs, totaling $8.1 million for the cohort of 167 recipients (2017 Canadian dollars). For recipients with available data, the transplant program received the referral for recipient evaluation a mean of 68 (SD 913) days [median 363 (198, 448) days] before dialysis started.

8.3.3 Characteristics associated with a potential unrealized pre-emptive kidney transplant

Associations between various characteristics and a potential unrealized pre-emptive transplant in an exploratory analysis are presented in Table 20. The recipient was more likely to start dialysis if their donor was female [RR 1.30 (0.99-1.70)], if either the donor or recipient was from a lower-income neighbourhood [respectively, RR 1.68 (1.16-2.43) and RR 1.96 (1.35-2.85) for the lowest quintile versus the highest], and if the donor was non-white [RR 1.53 (1.02-2.30)]. Recipient non-renal comorbidity was also a significant predictor of starting dialysis, particularly the presence of cardiovascular disease [RR 1.31 (1.03, 1.66)] and diabetes [RR 1.37 (1.03, 1.83)]. Non-significant associations were observed for anemia [RR 1.45 (0.98, 2.14)], ischemic heart disease or coronary artery disease [RR 1.35 (0.94, 1.95)], and anxiety or depression [RR 1.33 (0.95, 1.88)]. For recipients with available data, dialysis prior to transplant was more likely if there was a longer delay between the donor's evaluation start date and the date the transplant program subsequently received the referral to begin the intended recipient's evaluation [RR 1.03 (1.02-1.04) per 30-day delay]. Furthermore, a lower recipient eGFR at referral was associated with an increased likelihood of starting dialysis [RR 0.93 (0.86-1.00)], while no such association was observed for recipient eGFR at the donor's evaluation start date. There were significant differences across transplant programs (p=0.01), where one program was 29% less likely to have a potential unrealized pre-emptive transplant while another program was 47% more likely to do so when compared to a reference. However, between-centre variability only accounted for 2.8% of the total variability in potential unrealized pre-emptive transplant rates (p=0.16). After adjusting for donor sex, donor income, and clustering by transplant program, the strength of these associations changed very little (Table 20).

Table 20: Characteristics associated with an unrealized potential pre-emptive transplant

Variable	Pre-emptive transplant		Risk of an unrealized potential pre-emptive transplant			
	Yes	No	Unadjusted		Adjusted[b]	
	N=331	N=167	RR (95% CI)[a]	p-value	RR (95% CI)	p-value
Age at donation (years)[c]	46.0 (11.0)	46.8 (10.7)	1.04 (0.93-1.17)	0.44	–	–
Age at transplant (years)[c]	44.3 (13.7)	43.5 (15.1)	0.98 (0.90-1.06)	0.59	–	–
Sex (donor)						
Male	125 (40%)	52 (31%)	1.0 (ref)	0.06	1.0 (ref)	0.06
Female	186 (60%)	115 (69%)	1.30 (0.99-1.70)		1.29 (0.99-1.69)	
Sex (recipient)						
Male	196 (63%)	105 (63%)	1.0 (ref)	0.97	–	–
Female	115 (37%)	62 (37%)	1.00 (0.78-1.29)			
Race (donor)						
White	146 (82%)	51 (71%)	1.0 (ref)	0.04	1.0 (ref)	0.02
Other	32 (18%)	21 (29%)	1.53 (1.02-2.30)		1.58 (1.06-2.36)	
Race (recipient)						
White	123 (83%)	48 (77%)	1.0 (ref)	0.32	–	–
Other	25 (17%)	14 (23%)	1.28 (0.79-2.07)			
Income quintile (donor)[d]						
5 (highest)	81 (26%)	35 (21%)	1.0 (ref)	0.002	1.0 (ref)	0.002
4	95 (31%)	30 (18%)	0.80 (0.52-1.21)		0.79 (0.52-1.20)	
3	59 (19%)	37 (22%)	1.28 (0.88-1.86)		1.27 (0.87-1.84)	
2	45 (14%)	33 (20%)	1.40 (0.96-2.05)		1.41 (0.97-2.06)	
1 (lowest)	31 (10%)	32 (19%)	1.68 (1.16-2.43)		1.65 (1.15-2.39)	
Income quintile (recipient)[d]						
5 (highest)	84 (27%)	32 (19%)	1.0 (ref)	0.007	N/A	–
4	89 (29%)	37 (23%)	1.06 (0.71-1.59)			
3	60 (20%)	30 (18%)	1.21 (0.80-1.83)			
2	47 (15%)	33 (20%)	1.50 (1.01-2.22)			
1 (lowest)	28 (9%)	33 (20%)	1.96 (1.35-2.85)			
Residence (donor)						
Urban	268 (86%)	147 (88%)	1.0 (ref)	0.58	–	–
Rural	43 (14%)	20 (12%)	0.90 (0.61-1.32)			
Residence (recipient)						
Urban	266 (86%)	147 (89%)	1.0 (ref)	0.41	–	–
Rural	42 (14%)	18 (11%)	0.84 (0.56-1.27)			
eGFR of donor at time of donation[e]						
>89 mL/min/1.73 m^2	187 (62%)	94 (60%)	1.0 (ref)	0.51	–	–
80-90 mL/min/1.73 m^2	48 (16%)	32 (20%)	1.20 (0.87-1.64)			
<80 mL/min/1.73 m^2	65 (22%)	31 (20%)	0.97 (0.69-1.35)			
eGFR of recipient when…[f]						
donor evaluation started	16.1 (7.7)	16.4 (10.3)	1.00 (0.97-1.04)	0.84	–	–
recipient referred	15.1 (4.7)	12.6 (6.0)	0.93 (0.87-1.00)	0.06	0.93 (0.86-1.00)	0.05
Recipient comorbidity						
Cardiovascular disease	111 (36%)	75 (45%)	1.28 (1.00-1.63)	0.05	1.31 (1.03-1.66)	0.03
IHD/CAD	19 (6%)	17 (10%)	1.39 (0.96-2.01)	0.08	1.35 (0.94-1.95)	0.10
Heart failure	sup	sup	0.84 (0.40-1.77)	0.64	–	–
Cancer	72 (23%)	32 (19%)	0.85 (0.62-1.17)	0.33	–	–
Diabetes	34 (11%)	29 (17%)	1.38 (1.03-1.87)	0.03	1.37 (1.03-1.83)	0.03
Hypertension	252 (81%)	132 (79%)	0.92 (0.69-1.24)	0.60	–	–
Anemia	15 (5%)	14 (8%)	1.42 (0.95-2.11)	0.09	1.45 (0.98-2.14)	0.06
Anxiety/depression	29 (9%)	22 (13%)	1.27 (0.90-1.79)	0.17	1.33 (0.95-1.88)	0.10

Time from donor evaluation start until recipient referral[g]	-6 (-95, 67)	321 (40, 875)	1.03 (1.02-1.04)	<.0001	1.02 (1.02-1.04)	<.0001
Transplant centre[h]						
1	–	–	0.93 (0.67-1.31)			
2	–	–	1.0 (ref)	0.01	N/A	–
3	–	–	0.71 (0.46-1.10)			
4	–	–	1.47 (1.09-1.99)			
5	–	–	1.13 (0.66-1.93)			
Relationship						
Spouse	87 (28%)	47 (28%)	1.0 (ref)	0.60	–	–
Sibling	81 (26%)	34 (20%)	0.84 (0.59-1.21)			
Parent	38 (12%)	22 (13%)	1.05 (0.70-1.57)			
Child	33 (11%)	26 (16%)	1.26 (0.87-1.82)			
Other relation	21 (7%)	10 (6%)	0.92 (0.53-1.61)			
Unrelated	51 (16%)	28 (17%)	1.01 (0.69-1.47)			
Cause of kidney failure						
GN/autoimmune	45 (26%)	39 (25%)	1.0 (ref)	0.18	1.0 (ref)	0.21
Polycystic	41 (24%)	34 (22%)	0.98 (0.70-1.37)		0.97 (0.70-1.35)	
Diabetes	18 (10%)	29 (19%)	1.33 (0.96-1.83)		1.30 (0.96-1.77)	
Other	41 (24%)	38 (24%)	1.04 (0.75-1.43)		1.01 (0.73-1.39)	
Unknown etiology	27 (16%)	15 (10%)	0.77 (0.48-1.23)		0.78 (0.49-1.24)	
Year of transplant						
2004-2007	101 (32%)	54 (32%)	1.0 (ref)	0.54	–	–
2008-2010	99 (32%)	46 (28%)	0.91 (0.66-1.26)			
2011-2014	111 (36%)	67 (40%)	1.08 (0.81-1.44)			
Distance to transplant centre (donor)						
<20 km	93 (30%)	55 (33%)	1.0 (ref)	0.87	–	–
20-39 km	78 (25%)	37 (22%)	0.87 (0.62-1.21)			
40-89 km	77 (25%)	41 (25%)	0.94 (0.68-1.29)			
90+ km	63 (20%)	34 (20%)	0.94 (0.67-1.33)			
Distance to transplant centre (recipient)						
<20 km	83 (27%)	39 (23%)	1.0 (ref)	0.65	–	–
20-39 km	89 (29%)	43 (26%)	1.02 (0.71-1.46)			
40-89 km	64 (20%)	40 (24%)	1.20 (0.84-1.72)			
90+ km	74 (24%)	44 (27%)	1.17 (0.82-1.65)			

[a] RR (risk ratio) estimated using modified Poisson regression (Poisson distribution, log link, robust standard error estimation). A risk ratio greater than 1.0 refers to a higher risk of starting dialysis (a potential pre-emptive transplant lost).
[b] adjusted for donor sex and donor income quintile, and clustering by transplant centre
[c] risk ratio refers to 10-year increment
[d] categorized into fifths of median neighbourhood income from the 2006 Canada Census
[e] calculated using CKD-EPI equation (mL/min/1.73 m^2). Clinical cut-points used
[f] calculated using CKD-EPI equation (mL/min/1.73 m^2), creatinine was measured at the time the donors' evaluation started (±3 months) or at the time of recipient referral (±3 months). The RR corresponds to a 1 mL/min/1.73 m^2 increment in eGFR. Results were similar if categorized as 20+, 15-19, 10-14, and <10 mL/min/1.73 m^2 (p=0.45 for eGFR at donor evaluation start; p=0.06 for eGFR at recipient referral).
[g] calculated as the time from the donor evaluation start date until the recipient referral date. Negative values mean the recipient was referred to the transplant centre before the donor evaluation started. Risk ratio reflects a 30-day increment.
[h] transplant centre codified for privacy
CI – confidence interval; N/A – not applicable (for recipient income quintile this is due to collinearity with donor income quintile; for transplant centre, this variable is the clustering variable).; IHD/CAD – ischemic heart disease/coronary artery disease

8.3.4 Time to complete the living donor evaluation

The median total donor evaluation time among donors whose recipients were transplanted pre-emptively was 10.6 (6.4, 21.6) months [mean 15.3 (12.0) months]. For those who started dialysis during the evaluation, the median was twice as long: 22.4 (13.1, 38.7) months [mean 25.4 (14.0) months] ($p<0.0001$) (Figure 22). Similar results were observed for the time until approval: respectively, median 9.13 (5.9, 20.2) months [mean 14.3 (12.0) months] versus median 20.9 (11.7, 37.8) months [mean 24.2 (14.0) months] ($p<0.0001$). In contrast, we did not observe a relationship with a prolonged time to complete the major consultations with a higher likelihood of potential unrealized pre-emptive transplant: median 6.01 (1.77, 17.7) months [mean 11.0 (11.9) months] for pre-emptive transplants, median 6.47 (2.50, 15.8) months [mean 11.2 (11.4) months] for an unrealized potential pre-emptive transplant ($p=0.87$).

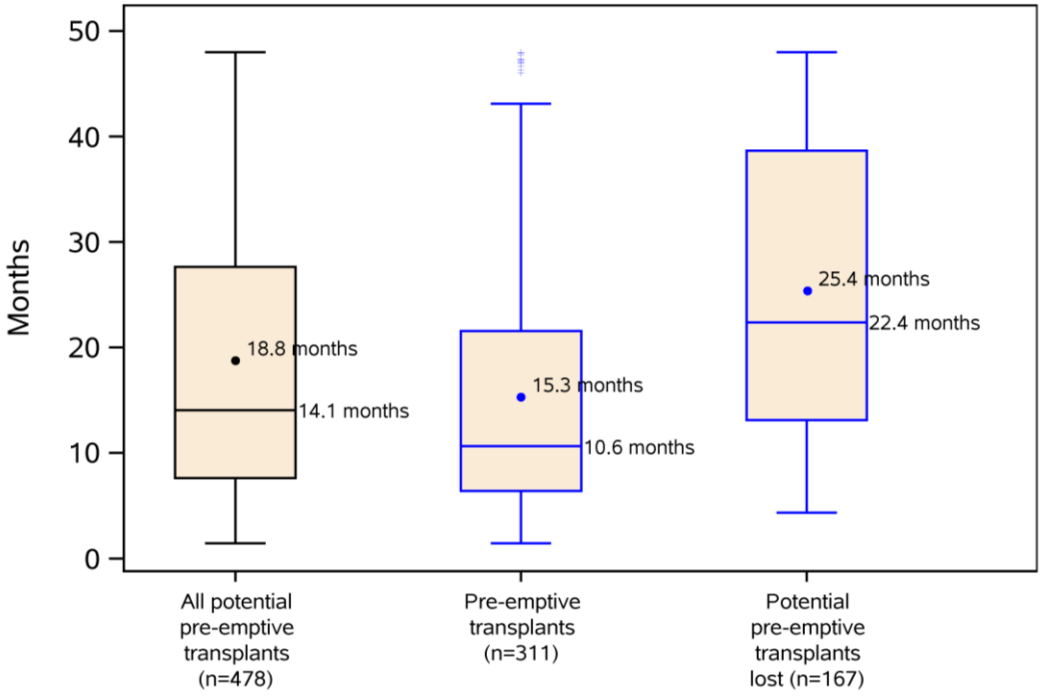

Figure 22: Boxplots showing the distribution of donor evaluation times. The time to complete the evaluation was defined as the period from evaluation start until nephrectomy. Boxes represents interquartile ranges (25th to 75th percentile). Horizontal lines indicate median (50th percentile). Circles represents means.

Horizontal lines represent the upper fence (75th percentile plus 1.5× interquartile range) and lower fence (25th percentile minus 1.5× interquartile range). Plus symbols indicate points that fall outside the fence.

8.4 Discussion

To our knowledge no prior study has described recipient outcomes in the context of the time to evaluate a living kidney donor candidate. To address this, we studied a group of people across five transplant programs in Ontario, Canada for the period 2004 to 2014, all who received living donor kidney transplants. We found that a third of persons not receiving dialysis when their donor's evaluation was well underway initiated dialysis prior to receiving their living donor kidney transplant. This dialysis cost was $8.1 million and 44/167 (26%) recipients initiated their dialysis urgently in hospital.

A recently published guideline in the United Kingdom has recommended that 50% of all eligible recipients are transplanted preemptively, and that all donors are able to complete their work-up in 18 weeks should they choose to do so.[14] We agree with this and believe that, for a healthy, motivated donor whose intended recipient has been cleared for transplant, 4 months is sufficient to complete a thorough evaluation while providing sufficient time for donor reflection. The time to complete the necessary nephrology, surgery and psychosocial consultations therefore should not be measured on the order of months and presents an opportunity for improvement. We are aware that some centers (including ours) have transitioned towards scheduling these consults on the same day or within 2 consecutive days of each other, particularly for donor candidates who live far from the transplant center. There is some evidence to suggest that centers that conduct same-day consults may have a faster time until approval (Chapter 6). There appeared to be a fair amount of consistency on how Ontario transplant programs evaluate living kidney donor candidates, which was evident when setting standards for the Canadian national kidney paired donation program.[16] However, operational decisions are made by individual living donor programs, and there is currently no recommendation on the timeliness of the evaluation.[9] Thus, we do expect variability in pre-emptive transplantation rates across transplant programs, much like variability in recipient referral rates observed across dialysis centres.[17] Some of this variability may be due to donor

evaluation protocols at each program, and determining how protocols affect the timeliness of the evaluation should be a focus of future work.

We believe these novel observations should be the focus of quality improvement efforts.[18] In the current study, we did not address the degree to which these dialysis starts could have been prevented, nor did we have information on reasons for the length of the evaluation for the donor or the intended recipient. Some of the delay in the donor candidate evaluation process may be due to the unpredictable nature of kidney failure. For example, it is possible the recipient's health suddenly deteriorated, placing the living donors' evaluation on hold until the recipient was well enough after receiving dialysis to receive a kidney transplant. This may avoid unnecessary donor work-up in case the recipient is no longer eligible for transplantation or avoid expiration of some donor's test results until the recipient is eligible again. Conversely, deterioration of the recipient's health may result in an expedited living donor evaluation to transplant the intended recipient before their health deteriorates further (i.e., before dialysis initiation, before potential transplant ineligibility). Although the donor and recipient evaluations are mostly independent, there is some communication that attempts to optimize coordination, outcomes, resource utilization, and donor burden. Other reasons for delay may result when more time is needed to complete a thorough evaluation, including initial test results that required further investigation, clearance of the donor related to any pre-existing comorbidity, or the requirement that some donor candidates change their lifestyle (e.g., lose weight or reduce their smoking).[19,20] Delays due to these reasons are appropriate and may be necessary to uphold the quality of the evaluation and the safety of donor candidate approval. However, in this study the living donor evaluation was underway for almost 10 months before 50% of the recipients in this group started dialysis, a sufficient amount of time to complete an evaluation even in the presence of some delay. Moreover, delays may stem from the donor or the intended recipient as they come to terms with living donor kidney transplantation.[21,22] Determining what factors are modifiable will be critical to be able to modify them and reduce the proportion of recipients starting dialysis.

This study also has other important limitations that should be addressed in future studies. First, the date of first contact and date of approval were obtained by proxy. While our

estimates of the total evaluation time (which includes all the time until nephrectomy) aligns with our clinical experience and is consistent with prior reports[23], the validity of this estimate needs to be substantiated using more accurate (and agreed-upon) start dates. The date the living donor first contacted the transplant program was unavailable, but is now being actively collected by Ontario transplant programs. The date of approval is important because many factors can influence the time until donation even after the donor has been approved to donate. Also, because evaluation practices in Ontario may differ from those used in other regions, the time until approval may allow additional comparisons to be made, and multiple metrics may be more informative than single metrics in isolation. Second, only patients who received a living kidney donor transplant were included in this study. It remains to be established whether improvements in the time to evaluate donor candidates can prevent lost opportunity for living donor transplants (e.g., due to competing events like intended recipient illness, death, or deceased donor kidney transplantation)[24,25] or influences candidates who drop out during the evaluation process.[18] Donor candidates who did not donate are not currently identifiable from administrative datasets alone. Further, many data on recipient referral dates were missing and we did not have information on when the intended recipient was approved for transplantation. Finally, among recipients who had no relation to their donors, we were unable to untangle the effects of non-directed anonymous donation versus kidney paired donation.[26,27]

In our exploratory analysis, several characteristics were associated with a greater likelihood of not realizing a potential pre-emptive living donor kidney transplant. Donors who were female, non-white and lived in a low-income neighborhood were all less likely to donate pre-emptively. These characteristics are all difficult or impossible to modify, but understanding the mechanism may suggest areas where potential modifications may be possible. We did find dialysis prior to transplant was more likely if the recipient was referred with a lower eGFR and if there was a longer delay between the donor's evaluation start date and the date the transplant program subsequently received the referral to begin the intended recipient's evaluation. These suggest earlier recipient referrals may prevent some recipients from starting dialysis. In Ontario, there is a guideline for intended recipients to undergo several tests, including cardiac assessment

organized by their nephrologist prior to submitting a referral package to a transplant program for evaluation.[28] Often, donor candidates contact transplant programs while this pre-transplant-referral testing for their recipient is underway, but the transplant programs usually do not advance the donor candidate evaluation until they receive a referral package for the intended recipient (as is the general approach in Ontario). From one perspective, it may not be worth while spending resources evaluating donors before their intended recipient is referred because many of these recipients may not be eligible for transplant or may never be referred, thereby wasting time and resources that could be spent on other donor evaluations. On the other hand, the potential implications of a late referral could at least partly be offset by a donor evaluation that is either quicker or starts before the recipient is referred. If the recipient is never referred or is not a transplant candidate, then this may result in some donor candidates pursuing non-directed donation instead. There is clearly a trade-off here that should be studied, as this is a potentially modifiable area for quality improvement. In this study we only reported data from five transplant programs in Ontario; our impression is these programs are similar to others throughout Canada, but we do not have data to corroborate this. We believe that this metric (the proportion of potential pre-emptive transplants that were unrealized) should be measured and reported by all programs nationally and internationally to facilitate comparisons and quality improvement efforts.

In conclusion, by linking donor evaluation times with recipient outcomes, this study raises the possibility of some modifiable adverse impact of a prolonged living donor evaluation process. These effects might not only be restricted to recipient health outcomes, but also may extend to the living donor's experience and to healthcare costs attributable to starting and/or maintaining dialysis until transplantation.[29,30] These findings inform future research and quality improvement activities that aim to help patients with kidney failure improve their chances of realizing a pre-emptive kidney transplant from a living donor.

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Chapter 9

9 Potential implications of a more timely living kidney donor evaluation[§§]

9.1 Introduction

For eligible patients with end-stage kidney disease, living donor kidney transplantation improves patient survival and quality of life and reduces healthcare costs compared to maintenance dialysis.[1–3] However, completing a living kidney donor evaluation according to current standards takes time and effort.[4] For many donor candidates and their intended recipients, the time to complete this evaluation is currently too long, which may have several unintended consequences for patients and the healthcare system. We have illustrated these consequences in Figure 23 for different types of recipients, where the black horizontal bars represent current living kidney donor candidate evaluation times from start (subscript *s*) to finish (donation; subscript *f*). First, the potential recipient may no longer be able to receive a transplant due to illness or death (Figure 23, patient a_f).[5–9] Second, the recipient may remain on dialysis longer than otherwise necessary, which may result in adverse outcomes following transplantation, reduced quality of life, ongoing risk of complications related to dialysis, and higher healthcare costs (Figure 23, patient b_f).[10,11] Third, the recipient may initiate dialysis before their donor is approved, potentially jeopardizing the benefits of pre-emptive transplantation, reducing quality of life, and increasing healthcare costs (Figure 23, patient c_f).[12] Finally, the recipient may receive a kidney from a deceased donor, an organ that could have gone to another recipient in need if the living donor transplant had been realized.[6,13] A poorly timed or

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prolonged living kidney donor evaluation can contribute to any of these adverse outcomes.

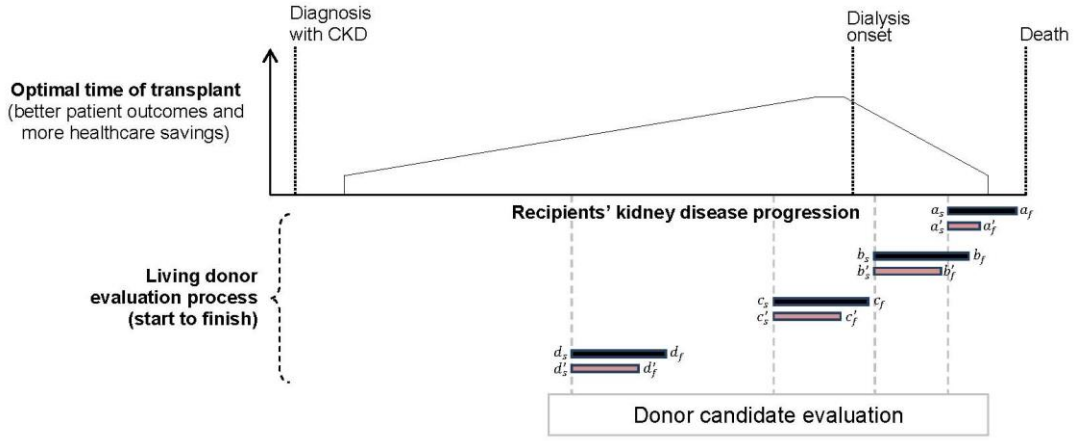

Figure 23: Potential effects of a more efficient living kidney donor evaluation process. Possible effects of a more efficient living donor evaluation (a'-d') for different types of potential recipients (a-d). Subscript *s* indicates the *start* of the living kidney donor candidate evaluation and subscript *f* indicates when the evaluation is *finished*. Recipient "a" is receiving maintenance dialysis when the living donor candidate evaluation begins and dies during the evaluation without receiving a transplant. Recipient "b" is receiving maintenance dialysis when the donor candidate evaluation begins and receives a living donor transplant. Recipient "c" is not receiving maintenance dialysis and has a low estimated glomerular filtration rate when the donor candidate evaluation begins, starts maintenance dialysis during the evaluation, and receives a living donor transplant. Recipient "d" is not receiving maintenance dialysis and has a low estimated glomerular filtration rate when the living donor candidate begins and receives a living donor transplant at a time when they could have lived longer with their native kidneys prior to initiating maintenance dialysis. For each of the potential recipients (a to d) the period from subscript "s" to subscript "f" represents a current donor candidate evaluation time (black horizontal bars); the period from subscript "s prime (s')" to "f prime (f')" represents a new shorter evaluative time (red horizontal bars). A more efficient living donor evaluation is completed in a shorter time and is better timed to promote optimal recipient outcomes (i.e., avoid dialysis or minimize the time spent on dialysis). Transplants occurring at time-point a_f' instead of a_f may prevent some deaths; transplants occurring at time-point b_f' compared with b_f will reduce the time the recipient spends on dialysis; transplants occurring at time-point c_f' instead of c_f may prevent some people from starting dialysis altogether; evaluation d_f' instead of d_f will reduce the amount of time the recipient lives with his/her native kidney prior to renal replacement therapy. Note: this diagram is a generalized simplification

by necessity. Individual recipients may progress differently and may die or receive dialysis (e.g. at a time of developing acute kidney injury) at any time throughout the recipient's kidney disease progression.

The 2017 Kidney Disease: Improving Global Outcomes Clinical Practice Guideline on the Evaluation and Care of Living Kidney Donors recommends that transplant programs "conduct as efficient a donor evaluation as possible, meeting the needs of donor candidates, intended recipients and transplant programs."[4] However, this recommendation remains ungraded because of insufficient evidence. In reality, the definition of an "efficient" evaluation is subject to interpretation. We believe that an efficient evaluation process is one that is completed in an appropriate time-frame (which may depend on the donor and recipient candidates' needs), achieves the best possible outcomes for donors and recipients, and prudently uses healthcare resources.

In this study, we explored the potential effects of an earlier living donor evaluation completion and donation date on recipient outcomes and healthcare costs attributable to potentially preventable dialysis. We used current observed outcomes from Ontario, Canada as the 'base case' scenario, and examined several "what if" scenarios for comparison had the living donor transplant occurred earlier.

9.2 Methods

9.2.1 Setting and databases

Ontario is Canada's largest province with a population of 13.6 million people; it has a single-payer universal publicly funded healthcare system where healthcare encounters, procedures and diagnoses are recorded for all Ontario citizens in large healthcare databases. We used information held at the Institute for Clinical Evaluative Sciences (ICES), which allowed linkage across multiple datasets in Ontario, Canada using a unique identifier. All living kidney donors in Ontario were identified through a database maintained by the provincial transplant agency Trillium Gift of Life Network.[14] Using physician billing codes from the Ontario Health Insurance Plan (OHIP) database, we

estimated the date the donor candidate started the evaluation using a healthcare test generally performed early in the living donor evaluation (described previously).[12] The physician claim database (OHIP) and the hospital-based Canadian Institute for Health Information (CIHI) Same-Day Surgery and Discharge Abstract databases were used to identify the date the recipient initiated dialysis.[12] The study was approved by the research ethics board at Sunnybrook Health Sciences Centre, Toronto, Canada.

9.2.2 Patient populations

All living donors in this study were Ontario residents for at least 2 years before donation, started the living donor evaluation on April 1, 2006 or later, and ultimately donated before April 1, 2014. They were divided into three mutually exclusive cohorts based on the following information at the time when the living donor evaluation started: 1) donors whose recipients were on dialysis (patient b_s in Figure 23); 2) recipients who theoretically could have been transplanted pre-emptively (were free from dialysis for at least 3 months after the donor started their evaluation) but started dialysis before transplant (patient c_s in Figure 23); and 3) recipients who were transplanted pre-emptively (patient d_s in Figure 23).[12,15] Classifying the cohort in this way enabled the outcomes to be evaluated separately for each cohort (outcomes described below).

We did not have data on donor candidates who did not ultimately donate to their intended recipient using administrative databases at ICES. Instead, we conducted detailed medical chart review for all living donor candidates who contacted the living donor program at the London Health Sciences Centre in London, Ontario between 2013 and 2016 (medical records were more complete during this time; Chapter 7). Donor candidate evaluation start date was defined as the date a detailed medical-social questionnaire completed by the candidate was reviewed by the program. If this date was unavailable, the date the candidate first contacted the program was used. The date the evaluation ended was the date the intended recipient died (patient a_s in Figure 23), was deemed no longer eligible for transplant, or received a deceased donor kidney transplant. To be included, the living donor candidate must have had at least 3 months of active evaluation (with any lab tests performed after review of the initial medical-social questionnaire). Institutional ethics

approval was obtained from Lawson Health Research Institute in London, Ontario (Appendix K).

9.2.3 Outcomes

This study was undertaken from the perspective of the Ontario government, which operates under a single-payer universal public healthcare system. Outcome data were based on four domains: time, pre-emptive transplantation, healthcare costs, and available additional kidneys for transplantation (summarized in Table 21 and described below). We defined the *total evaluation time* as the time the donor first started the evaluation until donation. We estimated the *proportion of potential pre-emptive transplants lost* as the proportion of recipients who were not on dialysis when the donor evaluation was underway for at least three months (the denominator) but started dialysis before transplant (the numerator). We estimated the *total recipient dialysis costs* for recipients from the time the donor started the evaluation until donation (costs described below). The *number of potential transplants lost* was calculated as the number of times the intended recipient died, became ineligible for transplant, or received a deceased donor kidney transplant despite having at least one living donor candidate whose evaluation was underway for at least three months. Since the number of potential transplants lost was obtained from the medical records of a subset of all donors in Ontario, we extrapolated these estimates to the entire Ontario population during the study period. Outcomes were presented using the mean (standard deviation, SD), median (25^{th}, 75^{th} percentile), and proportion (95% confidence interval), where appropriate.

Table 21: Definition of Outcomes

Term	Applied to	Definition
Domain: Time		
Total evaluation time	base case	the time the donor first started the evaluation until donation
total time recovered	scenario-specific	the difference in the total evaluation time between the scenario and the base case for all donors
total time lost	scenario-specific	the difference in the total evaluation time between the scenario and the base case for donors whose recipients were transplanted pre-emptively in the base case
dialysis time saved	scenario-specific	the difference in the total evaluation time between

		the scenario and the base case for donors whose recipients were already on dialysis when their living donor started the evaluation
Domain: Pre-emptive transplants		
Potential pre-emptive transplants	base case	recipients who were not on dialysis when the donor first started the evaluation for at least three months
proportion of potential pre-emptive transplants lost	scenario-specific	the proportion of potential pre-emptive transplants that did not occur (the recipient started dialysis before transplant)
number of recipients saved from starting dialysis	scenario-specific	the difference in the number of potential pre-emptive transplants and the number of potential pre-emptive transplants lost
Domain: Healthcare costs		
Total recipient dialysis costs	base case	the sum of all recipient dialysis-related costs to the healthcare system
total recipient dialysis costs saved	scenario-specific	the difference in the total recipient dialysis costs between the scenario and the base case
Domain: Number of transplants		
Number of living donor transplants lost	base case	the number of recipients who died or were no longer eligible to receive a transplant or who received a deceased donor kidney transplant despite having a living donor whose evaluation was underway for at least three months
number of living donor transplants gained	scenario-specific	the difference in the number of transplants lost

We devised 13 hypothetical scenarios (described below) where the transplant date would occur at an earlier date than the actual transplant date. Using Figure 23 to illustrate, a recipient who was actually transplanted at time-point b_f could instead have received a transplant at time-point b_f'. Using this new transplant date, we recalculated the outcomes and compared them to the base case. We calculated the *total time recovered* as the difference in the total evaluation time [$(b_f+c_f+d_f)-(b_f'+c_f'+d_f')$; the length of dark horizontal bars minus the length of light horizontal bars in Figure 23]. The *total time lost* was calculated as a subset of the total time recovered, restricted only to donors who donated pre-emptively (d_f-d_f' in Figure 23). This represents a lost period of survival only with native kidney function prior to initiating dialysis due to an earlier transplant. We calculated the *dialysis time saved* as a subset of the total time recovered, restricted only to donors who were already on dialysis when the evaluation started (b_f-b_f' in Figure 23). We determined the *number of recipients saved from starting dialysis* as the difference in the

number of pre-emptive transplant failures (patients whose evaluation times corresponded to category c_f-c_f' in Figure 23). We estimated the *total recipient dialysis costs saved* as the differences in accrued dialysis costs over the period [(b_f+c_f)-(b_f'+c_f')] in Figure 23. Finally, we estimated the *number of transplants gained* as the difference in the number of transplants lost due to intended recipient death, loss of transplant eligibility, or receipt of a deceased donor kidney transplant. For donor candidates who did not donate, we assumed their evaluation would have been completed and they would have donated in a time corresponding to each scenario's median total evaluation time.

9.2.4 Scenarios

In scenarios 1-5, the time between consecutive healthcare visits related to the living donor evaluation process were changed, which is shown pictorially in Figure 24. This was done using a longitudinal dataset with each healthcare visit for each donor on a separate row, sorted by date.[12] We used the 25th and 50th percentile of the distribution for all time-between-test transitions for Scenarios 1 and 2, respectively. For example, if the median (25th, 75th percentile) time to transition from a nephrology consult to a surgical consult was 23 (3, 66) days, then for all donors who had this specific chronological transition, we replaced their actual observed time with 25th and 50th percentile values (e.g., 3 days for scenario 1 and 23 days for scenario 2) and re-calculated the new (hypothetical) transplant date (Figure 24A). The distribution of some of these transition times is provided in Appendix L.

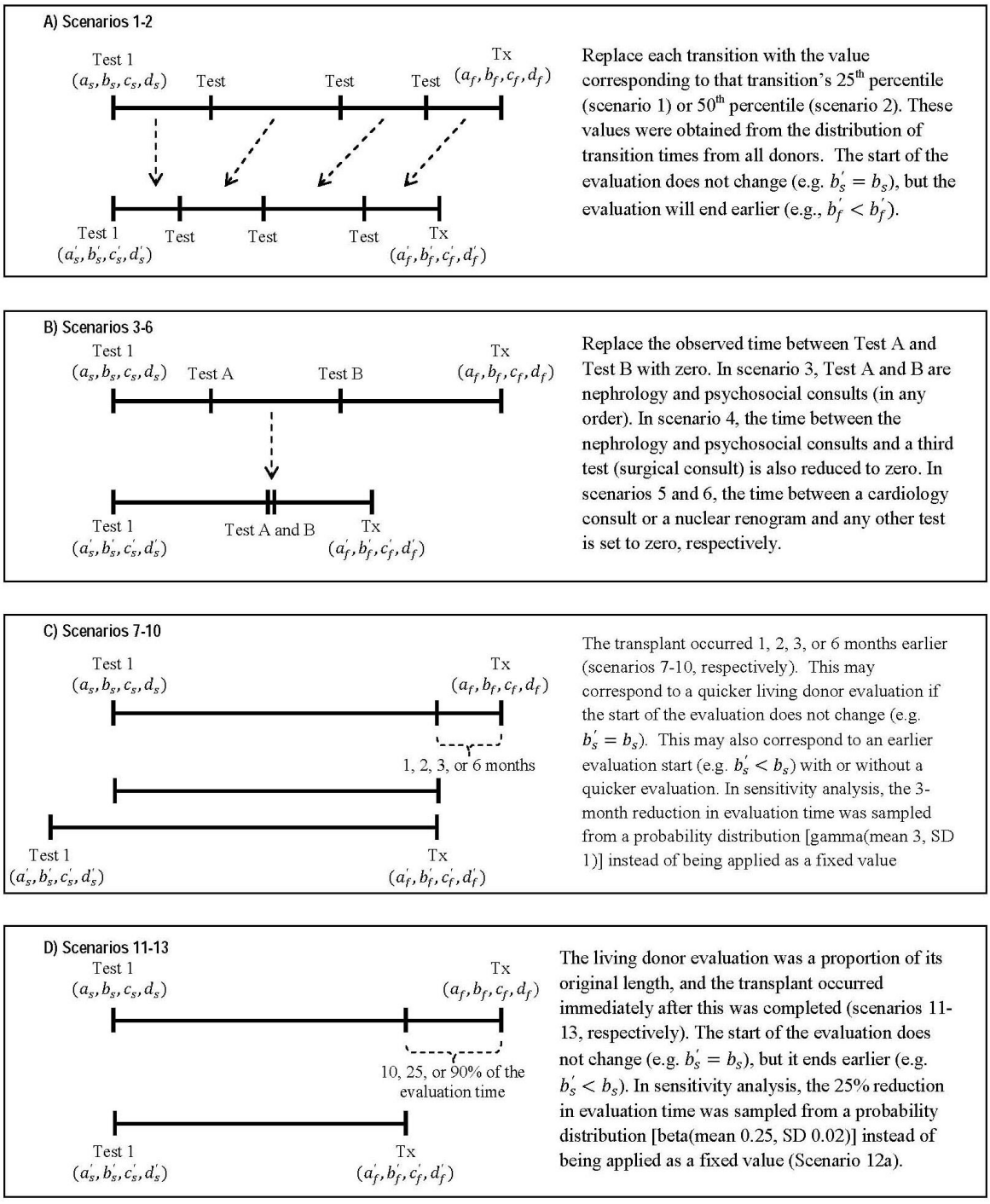

Figure 24: Altering the timeliness of the living kidney donor evaluation in hypothetical scenarios

We replaced the time between tests with a zero if two tests were to be modeled to occur on the same day (scenarios 3-5; Figure 24B). For example, if a psychosocial evaluation was modeled to occur on the same day as a nephrology consult, then the actual transition time for all donors who had these two visits in succession would be changed to zero (regardless of the order of tests). This occurred in 189+65=254 instances (Appendix L). If a test was completely removed (nuclear renogram in scenario 6), we replaced the time between this test and any other test (regardless of the order of tests) with a zero (Appendix L).

In scenarios 7-10, we shifted the transplant date to occur 1-, 2-, 3-, and 6-months earlier (Figure 24C). The resulting transplant dates reflect any combination of a quicker evaluation and/or an evaluation that simply started earlier. In a sensitivity analysis, the 3-month reduction in evaluation time was sampled from a gamma distribution (mean 3, SD 1) instead of being applied as a fixed value.

In Scenarios 11-13, we determined the hypothetical transplant date resulting from a proportionate reduction in the total time to complete the evaluation (10%, 25%, and 50% faster), setting a minimum evaluation time of three months (Figure 24D). In sensitivity analysis, the 25% reduction in evaluation time was sampled from a probability distribution [beta (mean 0.25, SD 0.02)] instead of being applied as a fixed value.

9.2.5 Costs

The ICES case-costing macro was used to tabulate recipient dialysis costs starting from April 1, 2006, which included various facility costs associated with dialysis treatment (i.e., dialysate, vascular access, nursing time) from the National Ambulatory Care Reporting System (NACRS).[16] The macro uses resource intensity weights multiplied by the cost per weighted case to derive the cost per case for all healthcare in a hospital setting.[16] We combined these estimates with physician claim codes and dialysis facility costs to obtain a final estimate of recipient dialysis costs.[12] Costs were estimated from the perspective of the provincial government and presented in $CAD 2016. We did not assess the costs related to the evaluation or transplant surgery, as we expect those to accrue to

all patients who receive a transplant (rather it is the timing of that transplant that affects the costs related to dialysis waiting for the transplant to occur).

9.3 Results

9.3.1 Patient population

We used data on 877 living donors who began their evaluation after March 2006: 497 (57%) of recipients were already on dialysis when the living donor started the evaluation (cohort b_s in Figure 23), 360 (41%) were potential pre-emptive transplants (cohorts c_s+d_s in Figure 23). We excluded 20 (2%) living donors who could not be classified (i.e., valid linkage to recipient was not available). A total of 19 potential transplants lost were identified from chart review over a 3-year period (6 corresponded to cohort a_s in Figure 23; 13 received a deceased donor kidney transplant).

9.3.2 The base case

The total time to complete the donor candidate evaluation was a median of 10.5 (6.93, 17.7) months [mean 14.2 (10.6) months], 122/360 (34%) recipients were potential pre-emptive transplants lost, and recipient dialysis costs were a median of $17,162 ($33, $66,054) per recipient [mean $44,065 (SD $61,990)] (Table 2). The 122 recipients who were potential pre-emptive transplants lost started dialysis a median 7.8 (5.0, 15.4) months [mean 11.9 (9.9); minimum 3.0 months] after their donor started the evaluation (Figure 25A) and were transplanted a median 8.7 (4.0, 16.3) months [mean 11.6 (10.1) months; minimum 5 days] after dialysis started (Figure 25B). Thirty percent (36/122) recipients started dialysis urgently in hospital. The total evaluation time for the 20 donor candidates who did not donate (one recipient had two candidates being evaluated) was a mean 4.8 (SD 7.9) and a median 8.0 (4.4, 11.3) months. Extrapolated to the whole province over the 8-year study period, 172 potential transplants were lost because the intended recipient died before receiving the transplant or lost transplant eligibility, and 372 potential recipients received a deceased donor kidney transplant.

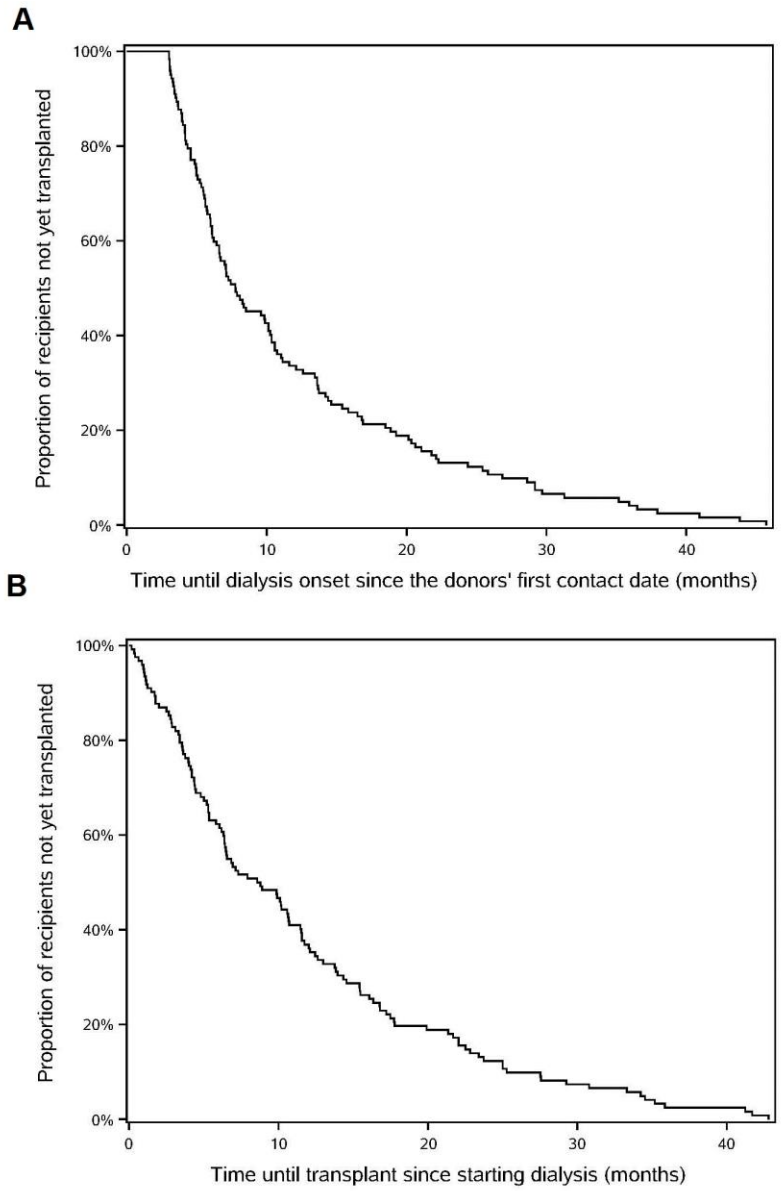

Figure 25: Time until dialysis since the donor started the evaluation (A); and time until transplant after dialysis started among recipients who could have been transplanted preemptively (B)

9.3.3 Scenarios

The mean time recovered, mean time lost, mean dialysis time saved, mean dialysis costs saved, and mean costs saved per month saved are presented in Table 22 for each scenario compared to the base case. The number of potential pre-emptive transplant failures saved

and number of living donor transplants gained are presented in Table 23 for each scenario compared to the base case.

The most effective scenario (from our list) in terms of absolute gains (differences in outcomes) resulted when the transition times between all tests took on the value of the 25th percentile. This resulted in a median total evaluation time of 2.2 months (a very optimistic scenario). More realistic scenarios reduced the total evaluation time by half (scenarios 2, 10, and 13). These scenarios saved a mean $22,000-$26,000 in recipient dialysis costs per recipient, prevented a minimum of 45 recipients from potentially starting dialysis altogether during the study period (>5 per year), could have given at least 86 intended recipients a transplant they otherwise did not receive (>11 per year), and introduced an additional 286 (>35 per year) kidneys to the organ donation pool.

The most effective scenarios in terms of relative gains (cost savings per month saved) resulted when the evaluation time was shortened towards the end of the evaluation time – the time during which more intended recipients are on dialysis. The mean intended recipient dialysis costs saved per month recovered was highest if the transplant occurred one month sooner ($4,116 per month recovered). This was associated with 0.27 (SD 0.45) months of native kidney time foregone, 0.58 (SD 0.50) months of dialysis time averted, seven recipients potentially avoiding dialysis altogether, and savings of $4,116 (SD $4,642) in dialysis costs per recipient. This could have given at least 58 intended recipients a transplant they otherwise did not receive (7.2 per year), and introduced an additional 172 kidneys to the organ donation pool (21.4 per year). This was followed by only slightly reduced marginal gains if the transplant occurred two months earlier ($4,011/month recovered) and three months earlier ($4,018/month recovered). A 10% reduction in the time to complete the evaluation was more effective than performing the transplant one month earlier since a greater absolute reduction took place for longer evaluation times (those that are more likely to accrue more costs). A 10% reduction in the time to complete the evaluation saved $5,689 (SD $8,636) in recipient dialysis costs, but was more wasteful than performing the transplant one month earlier in terms of performing a transplant when a patient's native kidney function was sufficient not to require dialysis initiation.

Table 22: Evaluation time, dialysis time, and cost savings by scenario

	Description of scenario	Total time (months) (n=877)				Recipient dialysis costs (2013 $CAD) (n=857)[2]		recipient dialysis costs saved per month recovered Mean (SD)
		Total time recovered Mean (SD)	Time lost Mean (SD)[1]	Dialysis time saved Mean (SD)[3]	Total time until transplant Median (IQR)	Cost saved Mean (SD)	Total Cost Median (IQR)	
	Corresponding cohort in Figure 23	b,c,d	d	b	b,c,d	b,c,d	b,c,d	b,c,d
–	Observed transition times (base case)	–	–	–	10.5 (6.93-17.7)	–	$17,162 ($332-$66,054)	–
1.	Reduce/increase all transition times to the first quartile (best-case scenario)	11.6 (9.71)	3.18 (7.56)	5.31 (7.08)	2.17 (1.54-3.24)	$37,092 ($54,764)	$1,079 ($0-$10,719)	$3,587 ($4,152)
2.	Reduce/increase all transition times to the median transition-specific transition time	7.84 (8.58)	2.24 (6.05)	3.35 (5.62)	5.13 (3.70-7.77)	$25,951 ($44,031)	$3,818 ($0-$29,163)	$3,420 ($4,319)
3.	Psychosocial and nephrology consults done on the same day	0.09 (0.85)	0.02 (0.23)	0.03 (0.24)	10.5 (6.93-17.7)	$241 ($2,266)	$17,038 ($262-$66,054)	$2,922 ($3,823)
4.	Psychosocial, nephrology, and surgical consults done on the same day	0.65 (1.65)	0.16 (0.74)	0.34 (1.08)	9.95 (6.14-17.2)	$2,534 ($8,739)	$15,307 ($0-$61,846)	$3,580 ($4,688)
5.	Reduce time to see a cardiologist to zero (if occurred after a nephrology consult)	0.06 (0.66)	0.03 (0.45)	0.03 (0.45)	10.5 (6.93-17.7)	$144 ($1,790)	$17,170 ($271-$65,571)	$3,063 ($4,314)
6.	Remove nuclear renograms from the evaluation process	0.55 (1.21)	0.12 (0.4)	0.29 (0.70)	10.2 (6.93-17.0)	$2,121 ($6,813)	$16,501 ($0-$61,846)	$3,451 ($4,389)
7.	Overall reduction by 1 month	1.02 (0)	0.27 (0.45)	0.58 (0.50)	9.49 (5.91-16.7)	$4,116 ($4,642)	$14,299 ($0-$58,890)	$4,116 ($4,642)
8.	Overall reduction by 2 months	2.00 (0)	0.54 (0.89)	1.14 (0.99)	8.51 (4.93-15.7)	$8,021 ($9,093)	$10,837 ($0-$50,764)	$4,011 ($4,547)
9.	Overall reduction by 3 months	3.02 (0)	0.81 (1.34)	1.71 (1.50)	7.49 (3.91-14.7)	$12,055 ($13,594)	$7,490 ($0-$43,310)	$4,018 ($4,531)
	9a. Average reduction by 3 months[4]	2.92 (1.94)	0.81 (1.66)	1.66 (2.05)	7.80 (4.06, 15.0)	$9,533 (14,094)	$10,609 ($0, $45,836)	$3,594 (4,209)
10.	Overall reduction by 6 months	6.01 (0)	1.62 (2.67)	3.41 (2.98)	4.50 (0.92-11.7)	$22,266 ($25,036)	$1,214 ($0-$22,006)	$3,711 ($4,173)
11	Reduction by 10%	1.41 (1.09)	0.38 (0.89)	0.67 (0.84)	9.46 (6.21-15.9)	$5,689 ($8,636)	$14,421 ($0-$56,364)	$3,954 ($4,657)
12.	Reduction by 25%	3.52 (2.69)	0.96 (2.21)	1.66 (2.09)	7.89 (5.19-13.2)	$13,617 ($20,377)	$8,648 ($0-$44,389)	$3,833 ($4,485)
	12a. Average reduction by 25%[4]	3.62 (3.94)	1.00 (2.76)	1.69 (2.57)	7.71 (5.05, 12.9)	$12,835 ($21,768)	$8,379 ($0-$43,201)	$3,795 ($4,430)
13	Reduction by 50%	6.97 (5.43)	1.90 (4.40)	3.26 (4.17)	5.26 (3.45-8.84)	$24,823 ($35,424)	$4,313 ($0-$28,546)	$3,680 ($4,568)

CI – confidence interval; NS – not stated to comply with privacy regulations that limit reporting a small number of observations; IQR – interquartile range (25^{th}-75^{th} percentile); time was measured in months, and costs presented in 2016 $CAD

[1] restricted to recipients who were not on dialysis within 3 months of when the donor began the evaluation

[2] restricted to recipients with valid identification number and complete costing data during the evaluation period

[3] restricted to those who were already on dialysis

[4] Reduction was modeled by randomly drawing from a distribution to allow for random variability. The 3 months reduction was sampled from a gamma distribution parametrized with a mean of 3 months and a standard deviation of 1 month; the 25% reduction was modeled using a beta distribution with a mean 0.25 and standard deviation 0.02. The number of living donor transplants gained was not calculated due to small sample for sampling and extrapolation

Table 23: Number of dialysis starts and missed opportunities for living donor transplant by scenario

	Description of scenario	Potential pre-emptive transplants lost (n=360)[1]		Number of living donor transplants gained (N=19)[2]	
		Number saved	Proportion lost (95% CI)	recipient death or illness (n=6)	deceased donor transplant (n=13)
	Corresponding cohort in Figure 23	c	c	a	a,b,c,d
–	Observed transition times (base case)	–	33.9% (29.0-38.8%)	–	–
1.	Reduce/increase all transition times to the first quartile (best-case scenario)	111	3.1% (1.3-4.8%)	172	372
2.	Reduce/increase all transition times to the median transition-specific transition time	75	13.1% (9.6-16.5%)	86	286
3.	Psychosocial and nephrology consults done on the same day	<6	NS	58	115
4.	Psychosocial, nephrology, and surgical consults done on the same day	8	31.7% (26.9-36.5%)	58	143
5.	Reduce time to see a cardiologist to zero (if occurred after a nephrology consult)	0	33.9% (29.0-38.8%)	58	115
6.	Remove nuclear renograms from the evaluation process	<6	NS	58	115
7.	Overall reduction by 1 month	7	31.9% (27.1-36.8%)	58	172
8.	Overall reduction by 2 months	15	29.7% (25.0-34.4%)	58	200
9.	Overall reduction by 3 months	21	28.1% (23.4-32.7%)	86	258
	9a. Average reduction by 3 months[3]	21	28.1% (23.4-32.7%)	–	–
10.	Overall reduction by 6 months	46	21.1% (16.9-25.3%)	115	286
11.	Reduction by 10%	12	30.6% (25.8-35.3%)	58	172
12.	Reduction by 25%	29	25.8% (21.3-30.4%)	86	200
	12a. Average reduction by 25%[3]	30	25.6% (21.0-30.1%)	–	–
13.	Reduction by 50%	62	16.7% (12.8-20.5%)	86	286

CI – confidence interval; NS – not stated to comply with privacy regulations that limit reporting a small number of observations; IQR – interquartile range (25^{th}-75^{th} percentile); time was measured in months, and costs presented in 2016 $CAD

[1] restricted to recipients who were not on dialysis within 3 months of when the donor began the evaluation

[2] between April 2004 and March 2014, LHSC performed 7% of the province's transplants. If X transplants were lost between 2013 and 2016 (4 years), then we expect X*8/4 transplants were lost over the 8-year study period. This was divided by 0.07 (7%) to extrapolate the total number of transplants lost over the study period in the entire province.

[3] Reduction was modeled by randomly drawing from a distribution to allow for random variability. The 3 months reduction was sampled from a gamma distribution parametrized with a mean of 3 months and a standard deviation of 1 month; the 25% reduction was modeled using a beta distribution with a mean 0.25 and standard deviation 0.02. The number of living donor transplants gained was not calculated due to small sample for sampling and extrapolation

9.4 Discussion

In this study, we project that a transplant occurring on average six weeks earlier (i.e., a 10% faster evaluation time) would result in average cost savings of $5,689 dialysis costs per recipient. Such an improvement would reduce the current median living kidney donor evaluation time from 10.5 to 9.5 months – a duration still believed by many to be too long.[17] For the approximately 220 living donor kidney transplants that occur every year in Ontario, shortening the evaluation time by 10% translates to an annual cost savings of at least $1.3M due to averted dialysis costs. In addition, up to 29 intended recipients each year [(58+172)/8] could have received a transplant they otherwise did not receive (a 29/220=13% increase), adding an average of $40,000 in cost savings each year over the lifetime of the transplant.[18] By starting the evaluation earlier, we would expect even greater gains. For instance, if a transplant occurred on average only three months sooner, we would expect at least $2.7M in cost savings in Ontario every year. Furthermore, avoiding or shortening dialysis time for recipients is expected to improve recipient health outcomes. Thus, there is much to be gained from improving the efficiency of the living kidney donor candidate evaluation process in beyond prompting earlier recipient referrals, both of which have been recognized as significant barriers to optimal living donor kidney transplantation.[3,12,15,19,20]

Where possible, pre-emptive kidney transplantation is the best treatment option for many patients with failing kidneys. Over the last decade, the proportion of kidney transplants that were pre-emptive increased to about one-third of all living donor transplants in the United States.[21,22] Despite this, pre-emptive transplantation only accounts for 3% of the initial renal replacement treatment modality for all new cases of end-stage kidney disease in Canada, an estimate that has remained stable over the last decade (Chapter 1).[23] Inefficiencies in pre-transplant living kidney donor evaluation processes (prolonged evaluation times, late recipient referrals) can result in wasted opportunities for pre-emptive transplantation, which may result in worse survival post-transplant and higher costs and complications due to dialysis initiation.[12,24,25] Evidence also suggests that dialysis onset further delays the living donor evaluation.[15] For patients with kidney failure who are already on dialysis, every additional month on dialysis increases the risk

of illness or death.[26,27] Moreover, patients live with a poorer quality of life.[28] Thus, an earlier transplant is better for patients, healthcare providers, and the healthcare system.

There are many barriers to living donor kidney transplantation. Inefficient living donor candidate and intended recipient evaluations should not be among them. These are often healthcare systems-level barriers that require healthcare systems-level solutions. For example, transplant education at dialysis centres or interdisciplinary chronic kidney disease clinics is not standardized and healthcare professionals are often uninformed on the benefits of living donor transplantation.[29–31] Although transplantation may not be the appropriate treatment option for all patients, all transplant-eligible patients should be provided the opportunity for high-quality ongoing education, and the nature of this education should be documented. Another issue is the possible incentive that some for-profit dialysis facilities may enjoy by continuing to treat patients with dialysis.[32–35] Although this situation is absent in a Canadian setting where there is universal healthcare, there are additional complexities that may exist even after a transplant referral occurs.[36,37] Finally, the wait time to see a nephrologist in Canada can range from 2-8 months.[38–40] This wait time may be longer for living donor candidates, who are essentially seeking an elective procedure (not urgent).

Although we used real data in our models and our conclusions are tenable, efforts to reduce the duration of living donor candidate evaluations may not translate to an earlier transplant for all recipients for a variety of reasons. The pace of the living donor evaluation may be titrated to correspond to the status of the intended recipient (i.e., the intended recipient must lose weight or clear an infection before being approved as a transplant candidate; the recipient's kidney function is sufficiently high to delay the donor candidate evaluation). Moreover, many donor candidates schedule a donation date to coincide with a time of the year when their responsibilities (i.e., workload, childcare) can be managed by others. Some donors may also appreciate the time to contemplate their decision and may not want a quicker evaluation for personal or health-related reasons. However, a quicker evaluation should nevertheless be an option for those who want one. Future efforts should focus on defining and capturing key dates in the evaluation process, including the evaluation start and approval dates for both donor and

recipient candidates, determining what factors are modifiable, and implementing changes at the health system level.

Given the nature of this study, we had to make several assumptions that may limit the accuracy of the estimates. First, the date the donor started the evaluation was obtained by proxy using healthcare services utilized over a 4-year time-frame before donation.[12] Second, the time between tests was used to model some scenarios, but the presence of a temporally intervening healthcare procedure would have prevented the scenario from being modeled accurately, thereby underestimating the effects of Scenarios 3-5. Third, only persons who participated in a living kidney donor transplant surgery were available in most of our databases. Until recently, most programs in Ontario did not systematically capture and report data on living donor candidates (i.e., those who do not donate). Thus, our provincial data sources did not capture donor candidate records for intended recipients who died prior to ever receiving their transplant or who became ill and ineligible to receive a transplant (patient a_s in Figure 23), or who received a deceased donor transplant after the living donors' evaluation started. To supplement our study data, we conducted a detailed medical chart review for all donor candidates who contacted one living donor transplant program in Ontario. Although we used medical chart review on all donor candidates at this centre to extrapolate the findings to the entire province, the number of events were small. We also assumed these estimates were generalizable, did not change over the study period, and that all candidates would have donated. Finally, the cost savings and improvement in outcomes presented in this report are likely underestimates because reductions in morbidity attributable to chronic kidney disease and dialysis are difficult to estimate (i.e., infection, hyperparathyroidism, anemia, hospitalizations, procedural related complications).

In conclusion, a more efficient living kidney donor evaluation process is expected to result in better recipient outcomes, more living donor transplants, and substantial cost savings to the healthcare system.[3,41] A small reduction in the waiting time to receive a transplant can have a large impact on the number of pre-emptive transplants gained and total recipient dialysis costs saved. This vitally important healthcare process will benefit from quality improvement efforts.

9.5 References

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Chapter 10

10 Health care costs for the evaluation, surgery, and follow-up care of living kidney donors***

10.1 Introduction

Patients with kidney failure live longer with a better quality of life after kidney transplantation when compared to maintenance dialysis.[1,2] Recipient outcomes are further improved when the transplant comes from a living rather than deceased donor.[3–5] As shown in modeling studies, an increase in the rate of living donor kidney transplantation is an effective strategy to ameliorate the burden of kidney disease, and remains cost-effective even if donors are paid.[6–17] Additional health care resources, however, are needed to evaluate, perform donor nephrectomy, and follow living kidney donors after donation.[18,19]

From a health system payer perspective, an accurate estimate of the costs of living kidney donation is important for several reasons. First, a better understanding of the true health care costs of donation would improve estimates regarding incremental costs and benefits of living donor kidney transplantation. Second, as countries across the globe seek to better address the demand for transplantable kidneys, a thorough understanding of donation-related health care costs will help project the anticipated expenses that could occur with initiatives aimed at increasing rates of living kidney donation. Third, detailed cost estimates would better inform the funding allocated to hospitals or clinics which provide the service. Finally, a better understanding of current costs may serve as an

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important baseline measure for future efforts to improve the efficiency and cost of the donor candidate evaluation.

Many prior studies only considered the surgical costs of donation and did not fully account for the additional costs of the evaluation and follow-up care of living kidney donors.[9,16] Studies that did include donor evaluation costs used pre-specified donor evaluation protocols of minimum required testing.[6,7,15] This method of costing underestimates the cost of donation because donors may require repeat tests, additional tests due to incidental findings, and tests that are not standard to donor evaluation protocols but are needed because of the donor's personal medical history.

To contribute to the literature, we conducted this detailed costing study in a universal health care system where most health care resource use and costs are incurred by a single payer. We investigated donor costs in three time-periods: the pre-donation evaluation period (beginning of the donor evaluation until donation), the perioperative period [the nephrectomy and the perioperative period (30 days post-donation)] and the follow-up period (after the perioperative period until one year following donation).

10.2 Methods

10.2.1 Design, population and setting

This was a retrospective analysis of living kidney donors who donated at one of Ontario's five transplant centres between April 1, 2004 and March 31, 2014.[20,21] Ontario residents have access to universal health insurance coverage through a public payer system, which includes all aspects of pre- and post-donation care. All living donors in this study were required to be Ontario residents for at least two years prior to donation. As per donor evaluation criteria, all donors had at least one nephrology consult and one surgery consult during the evaluation period (described in detail previously[21]).

10.2.2 Costing periods

The cost of living kidney donation was estimated separately for three time periods, corresponding to three phases of the donation process: 1) the evaluation period (from the date the donor started the evaluation until the day before donation), which captures costs associated with the living donor assessment; 2) the perioperative period (from the day of nephrectomy to 30 days post-donation), which captures costs related to the donor surgery, hospitalizations, and any possible perioperative complications (including early readmissions); and 3) the one-year follow-up period (from day 31 post-donation until 1-year post-donation), which includes costs related to longer-term or ongoing complications and any routine plus as-needed follow-up care.

10.2.3 Data collection and costing sources

All costs were measured from the perspective of the Canadian payer. Donors were identified from the Trillium Gift of Life Network (TGLN) database through the Institute for Clinical Evaluative Sciences (ICES).[20] Several health administrative datasets at ICES were used to link the data using unique encoded identifiers. These databases included the Ontario Health Insurance Plan (OHIP), which captures all primary care and specialist physician billings, Canadian Institute for Health Information (CIHI) Same-Day Surgery and Discharge Abstract Database (hospitalizations); National Ambulatory Care Reporting System (emergency visits); Ontario Drug Benefits (prescription drug costs for citizens 65 years of age and older or receiving social assistance); National Rehabilitation Services; Complex and Continuing Care; and Long-Term Care. The ICES-derived costing method was used to obtain all costs from the various linked databases for a specified time-period (inpatient and outpatient costs for the time periods described above). In addition to individual billing, this costing method uses resource intensity weights multiplied by the cost per weighted case to derive the cost per case.[22]

10.2.4 Cost estimation

We derived the frequency of each health care procedure received and calculated the cost of each procedure using the physician claims database codes deemed relevant to the donor evaluation.[21] These costs were totaled for each donor's evaluation period (we

restricted this to the evaluation period only as we could not pre-specify relevant health care use during the perioperative and follow-up periods). To estimate the total cost of donation, all costs (instead of pre-specified procedures) from the above databases were summed over each costing period. By including all costs accrued by the living donor, there is risk that some costs may have accrued for reasons unrelated to the evaluation (i.e., consulting the general physician for a non-specific viral illness). To account for this potential over-estimation of costs, a baseline non-donation-related health care cost was estimated using a cohort of matched healthy non-donor controls (i.e., individuals with similar indicators of baseline health as the donors; described in the Matching section below). To estimate the cost of donation with the baseline cost (the cost of the controls) removed, we developed a series of regression models (described in Statistical Methods below).

10.2.5 Matching

All Ontario residents were considered possible controls if they were alive, <80 years of age as of April 1, 2006, were not missing sex, and had no prior history of living kidney donation themselves. The eligible 17,092,895 control candidates were assigned a random date (a fake "donation date") to match the distribution of donation dates observed in the donors. Controls who were >79 years or died before their assigned donation date were excluded (ineligible to donate), resulting in 16,640,699 potential controls. Since donors are a highly selected healthy subset of the population, controls with any diagnostic, procedural, or intervention codes which suggested ill health or a contraindication to donation were excluded. These included codes related to dialysis, cancer, cardiovascular disease, human immunodeficiency virus, nephrectomy, renal biopsy, pulmonary disease, liver disease, systemic lupus erythematosus, rheumatoid arthritis, genitourinary disease, or alcoholism (full list of codes in Appendix M).

Potential controls were excluded if they were not Ontario residents for at least 2 years prior to their donation date or gave birth between 2 months prior and 6 months after the donation date (similar exclusions were previously applied to the donors). A total of 6,151,385 potential controls and 1,214 donors were available for matching (not missing matching covariates). Matching was done by donation date (±6 months), age at donation

date (±2 years), sex, rural/urban status, and neighbourhood-level income quintile. Four controls were matched to each donor.

10.2.6 Statistical methods

To estimate the cost of living donation, we used a series of multivariable regression models applied to the matched cohort and conducted various statistical tests to assess the fit of each model (described below). This approach is recommended for cost data because of its positive and skewed distribution.[23,24] Covariates included an indicator for donor/control status, age at the donation date, sex, urban/rural status, the year of donation (2003-2007, 2008-2010, and 2011-2014), neighbourhood-level income quintile, and the total evaluation time in months. The effect of a variable on costs was reported using the marginal effects post-estimation procedure in STATA, which uses the method of recycled predictions to provide estimates of mean cost. We were interested in the marginal effect of the dichotomous variable donor/control status, which represents the additional cost associated with living kidney donors (compared to controls). The marginal effect of any other covariate is interpreted as the incremental cost associated with a change in one unit of that covariate, holding the other factors constant. To assess whether the cost for donors was different from controls across levels of a covariate, we introduced an interaction term with the donor indicator in a separate model. A significant interaction term ($p_{int}<0.05$) means that the cost of the donor is significantly different from controls across levels of the covariate included in the interaction. In the case where the predictor is only present in donors (i.e., recipient's dialysis status[21,25], transplant centre), then the analysis is automatically restricted to donors only and the marginal effect is reported (p_{int} is not available).

We tested and compared the fit of ordinary least squares (OLS) regression on untransformed costs, log-transformed costs, and square-root-transformed costs. Non-linear models included the exponential conditional means model and Poisson regression with maximum likelihood estimation. We fit a variety of generalized linear models (GLMs) using a combination of link functions (identity, square-root, log) and distributional families (Gaussian, gamma, inverse Gaussian, and Poisson). We also attempted to fit the generalized gamma model assuming homoskedastic and

heteroskedastic versions, extended estimating equations, and two-component finite mixture models using gamma distributions.[24] If more than one GLM had similar indices of fit, we performed a Park test to choose the best fit model. We also explored various statistical indices of badness of fit, including the Pregibon link test, a modified Hosmer-Lemeshow test, and the Pearson's correlation p-value.[23,24] For each of these tests, a higher p-value is more desirable. We also considered statistics such as R^2, root mean square error (RMSE), and mean absolute percentage error (MAPE), where a lower value is desired. To guard against potential over-fitting, we assessed statistics following cross-validation, including RMSE and MAPE (lower is better), mean prediction error (MPE; zero is desirable), and the p-value for the Copas test (a test for over-fitting; higher is desirable).[23,24] Ultimately, GLMs were selected for each analysis: log-normal for the evaluation period, square-root-Poisson for the perioperative period, log-gamma for the follow-up period, and square-root-gamma for the entire duration period. Robust standard errors were calculated in all models to accommodate clustering by transplant centre where the donation occurred.

We reported mean (standard deviation, SD), median (25^{th}, 75^{th} percentile), and the mean difference (95% confidence interval, CI) from marginal effects, where appropriate. All costs are reported in 2017 Canadian dollars.

10.2.7 Sensitivity analysis

As of April 1, 2006, the ICES-derived costing method improved to accommodate primary care physician payments under capitation following primary care reform to the costing data, in addition to dialysis facility visit costs and cancer clinic visit costs.[22] We conducted sensitivity analysis in the subset of our cohort with an evaluation start date of April 1, 2006 or later using the updated costing method to accommodate these costs. Sensitivity analyses were also performed on the model chosen to estimate the donor costs since more than one model may fit the data for some analyses.

10.2.8 Software and privacy

We used Statistical Analysis Software SAS v9.4 or SAS Enterprise Guide 6.1 (2013 SAS Institute Inc., Cary, NC, USA) and STATA v13.0 (StataCorp LP, Texas, USA).

Procedures and consultations for 5 or fewer donors are not reported to comply with privacy requirements for minimizing the chance of patient identification. The study was approved by the research ethics board at Sunnybrook Health Sciences Centre, Toronto, Canada.

10.3 Results

We identified 1,256 living kidney donors who completed the evaluation and donated in Ontario during the study period (Figure 26). Donors had a median of 28 (20, 39) health care procedures (tests and consults) during the evaluation phase, performed during a median 16 (11, 24) separate visits (which meant the procedures/tests were performed on different dates). Donors were a mean 45 (SD 11) years of age, were mostly female (63%), white (78%), lived in urban areas (87%), and lived in higher-income neighbourhoods (23% in the highest quintile versus 15% in the lowest).

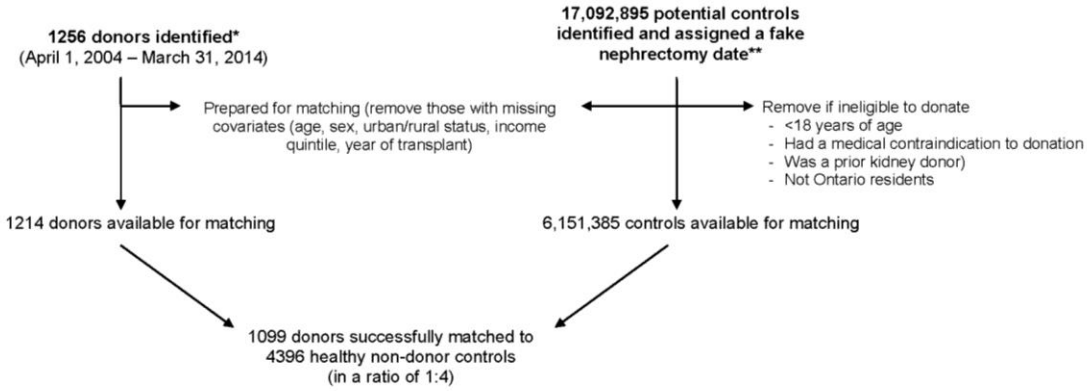

Figure 26: Donor selection and matching flow chart. *Using the Ontario Health Insurance Plan (OHIP) database, the health care utilization patterns for these donors were described for the evaluation period (n=1256), perioperative period (n=1240), and follow-up period (n=1223). **fake nephrectomy date was assigned to match the distribution of nephrectomy dates of the donors

10.3.1 Health care utilization patterns

Appendix N presents the list of procedures considered relevant to living kidney donation and the frequency of use during the evaluation (1256/1256, 100%), donation (1240/1256, 99%), and follow-up (1223/1256, 97%) periods. The most costly health care procedure during the evaluation was consultation with a nephrologist, with a mean 1.91 consultations per donor at a mean cost of $135 per consultation, accounting for 15% of the total evaluation cost (Appendix O and Appendix P). The second most costly test was computed tomography, which were performed a mean 1.08 times per donor, representing 10% of the total evaluation at mean a cost of $170 per exam. This was followed by nuclear medicine glomerular filtration rate test (9.0%), consultation with a surgeon or urologist (8.1%) and bloodwork (7.9%).

10.3.2 Cost of the living donor transplantation process

A total of 1099/1214 (91%) donors were successfully matched to 4396 controls (4 controls per donor; Figure 26). The matched donors were similar to the unmatched donors with respect to age (p=0.47), sex (p=0.27), urban status (p=0.82), and neighbourhood income quintile (p=0.13) (Table 24). The mean total health care costs during the evaluation period for donors and their matched controls were $4,522 (SD $1,073) and $881 (SD $3,061), respectively. The mean adjusted total cost attributable to the donor evaluation process was $3,596 (95% CI $3,350-$3,842) (Table 25). Similarly, the mean cost attributable to the perioperative period was $11,694 (95% CI $11,415-$11,973) and the mean cost attributable to follow-up in the first year after donation was $1,011 (95% CI $793-$1,230). The incremental cost of living donor-related care to the payer across all observation periods was $16,290 (95% CI $15,814-$16,767) (Table 25; Figure 27A-D). Using pre-specified health care procedures, the cost of the living donor evaluation was a mean $2,108 (SD $968) (n=1214).

Table 24: Living donor characteristics (n=1099)

	Donors (N=1099)
Age at donation	45.1 (11.1)
Sex	
Women	694 (63%)
Men	405 (37%)
Race	
White	480 (78%)
Non-white	135 (22%)
Income quintile[a]	
5, highest income	238 (22%)
4	275 (25%)
3	231 (21%)
2	182 (16%)
1, lowest income	173 (16%)
Urbanization	
Urban	959 (87%)
Rural	140 (13%)
Era	
2004-2007	286 (26%)
2008-2010	399 (36%)
2011-2014	414 (38%)

[a] rural was defined as having a population <10,000 persons

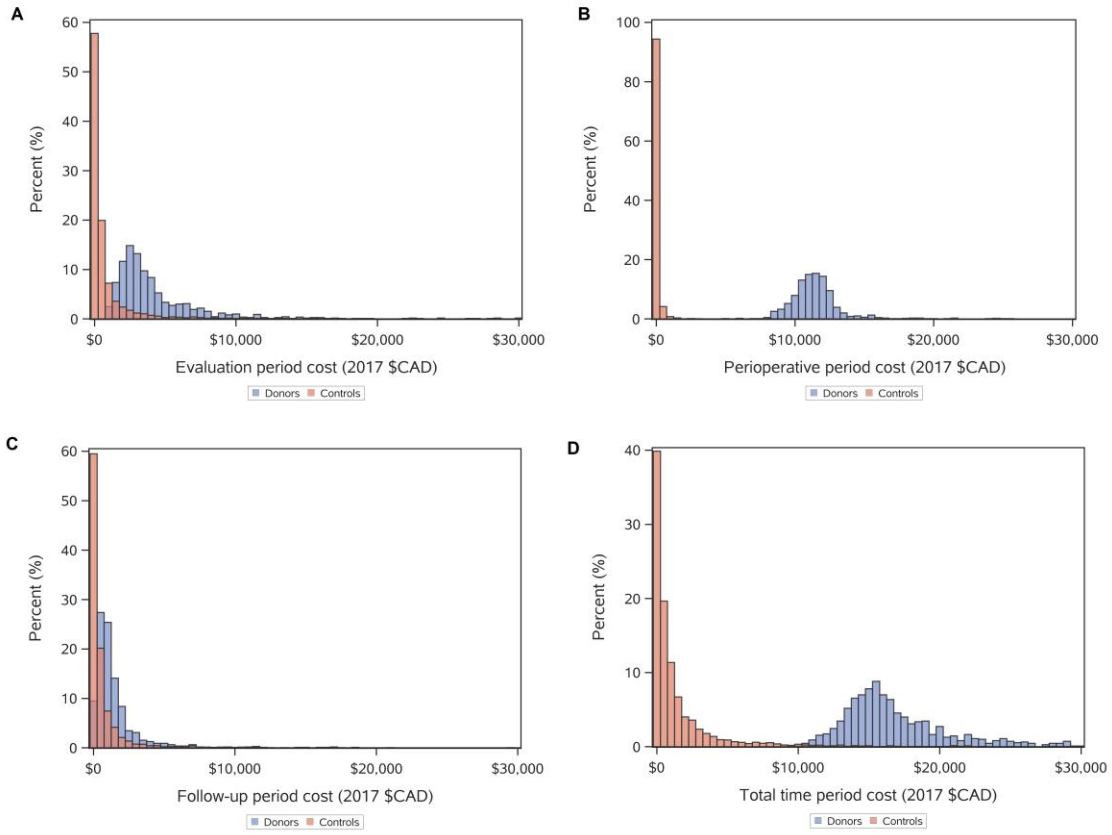

Figure 27: Distribution of health care costs for A) the pre-donation evaluation period (start of evaluation until the day before donation); B) perioperative period (day of donation until 30-days post-donation); C) one year of follow-up period (after perioperative period until 1-year post-donation); and D) the entire period from evaluation start until 1-year post-donation. Controls were matched to donors and were comprised of healthy non-donors with similar indicators of baseline health as donors.

Table 25: Cost of living kidney donation (n=4396 controls and 1099 donors)

	Mean (SD)	Median (25^{th}, 75^{th} percentile)	Mean difference (95% CI)
Pre-donation evaluation costs			
Control	$881 ($3,061)	$149 ($0, $634)	–
Donor	$4,270 ($3,846)	$3,115 ($2,305, $4,843)	–
t-test	–	–	$3,641 ($3,701-$3,898)
GLM-ME[a,b]	–	–	$3,596 ($3,350-$3,842)
Perioperative costs			
Control	$62 ($374)	$0 ($0, $0)	–
Donor	$11,757 ($4,869)	$11,427 ($10,542, $12,224	–
t-test	–	–	$11,695 ($11,407-$11,984)
GLM-ME [a,c]	–	–	$11,694 ($11,415-$11,973)
One-year follow-up costs			
Control	$753 ($2,421)	$139 ($0, $577)	–
Donor	$1,686 ($4,057)	$977 ($562, $1,683)	–
t-test	–	–	$933 ($682-$1,183)
GLM-ME [a,d]	–	–	$1,011 ($793-$1,230)
Total costs			
Control	$1,696 ($4,541)	$470 ($25, $1,550	–
Donor	$17,966 ($8,401)	$16,116 ($14,539, $19,026)	–
t-test	–	–	$16,268 ($15,754-$16,784)
GLM-ME [a,e]	–	–	$16,290 ($15,814-$16,767)

GLM-ME – generalized linear model, marginal effects of donor status; SD – standard deviation; CI – confidence interval.

Costs are presented in 2017 Canadian dollars.

Donors and their matched controls started the evaluation after March 31, 2003

[a] adjusted for age, sex, urban/rural status, income quintile, year of transplant, and total evaluation time (in months), $p<0.0001$ for all mean differences in the table.

[b] log-normal

[c] square-root Poisson

[d] log-gamma

[e] square-root gamma

10.3.3 Predictors of costs

Over the total donation period, health care costs were higher for women [$534 ($179, $890) higher than men], older persons [$316 ($172, $460) per 10-year increase in age], and over a longer pre-donation evaluation period [e.g. a longer window for health care utilization; $52 ($46, $58) per month] (Table 26). Health care costs were lower in more recent years [-$718 (-$1,217, -$218) in 2011-2014 compared with 2004-2007]. Health care costs did not differ by the person's neighbourhood income quintile (p=0.66) or urban versus rural residence (p=0.77). There was no significant difference in costs due to an interaction between the donor/control indicator and sex, age, or duration of the evaluation (p_{int}>0.1 for all). There was a significant interaction with era: in 2011-2014 the incremental cost of donation was $810 ($44, $1,577) higher than before 2008.

In the subset of donors (n=1,099), health care costs were higher if the recipient started dialysis during the donor's evaluation [$886 ($19, $1,752) compared with pre-emptive transplants], but this did not affect health care costs during the perioperative (p=0.82) or follow-up (p=0.68) periods (Table 26). There was a non-significant trend in different costs across transplant centres for the evaluation and follow-up periods (p=0.07 and p=0.09, respectively) (Table 26). Costs were significantly different across transplant centres during the perioperative period, ranging from -$1,318 (-$1,971, -$664) to $599 (-$502, $1,701) compared with one referent centre (p<0.0001).

Table 26: Predictors of cost by donation period

	Evaluation period[a]			Perioperative period[b]			Follow-up period[c]			All periods[d]		
	Incremental cost[e,f]	**p[e,f]**	**p_{int}[f,g]**	**Incremental cost[e,f]**	**p[e,f]**	**p_{int}[f,g]**	**Incremental cost[e,f]**	**p[e,f]**	**p_{int}[f,g]**	**Incremental cost[e,f]**	**p[e,f]**	**p_{int}[f,g]**
Female (vs. male) sex	$208 ($44, $372)	0.01	0.47	$39 (-$22, $100)	0.21	0.57	$220 ($81, $360)	0.002	0.38	$534 ($179, $890)	0.003	0.67
Age, per 10-years	$77 (-$7, $160)	0.07	0.67	$55 ($30, $80)	<.0001	0.86	$196 ($123, $269)	<.0001	0.91	$316 ($172, $460)	<.0001	0.82
Evaluation time per month	$52 ($46, $58)	<.0001	0.14	$1 (-$1, $4)	0.4	0.11	-$3 (-$9, $2)	0.24	0.45	$65 ($49, $81)	<.0001	0.21
Urban (vs. rural) residence	-$185 (-$467, $97)	0.20	0.36	-$77 (-$239, $85)	0.35	0.87	$152 (-$37, $341)	0.12	0.31	-$76 (-$576, $425)	0.77	0.98
Income quintile												
5, highest	0 (reference)	0.95	0.35	0 (reference)	0.51	0.16	0 (reference)	0.23	0.85	0 (reference)	0.66	0.67
4	$26 (-$200, $251)			-$13 (-$106, $79)			$95 (-$86, $276)			$22 (-$419, $463)		
3	$24 (-$221, $269)			-$20 (-$130, $90)			$124 (-$70, $318)			$233 (-$314, $779)		
2	-$64 (-$310, $182)			-$55 (-$155, $44)			$25 (-$173, $222)			-$215 (-$714, $284)		
1, lowest	$19 (-$264, $301)			-$61 (-$144, $23)			$272 ($6, $538)			$231 (-$350, $811)		
Era												
2004-2007	0 (reference)	0.60	0.01	0 (reference)	0.02	0.42	0 (reference)	0.005	0.02	0 (reference)	0.0003	0.15
2008-2010	$89 (-$133, $311)			$3 (-$75, $81)			$78 (-$116, $271)			$74 (-$469, $620)		
2011-2014	$106 (-$103, $316)			-$81 (-$150, -$12)			-$179 (-$353, -$4)			-$718 (-$1,217, -$218)		
Recipient dialysis status[h]												
pre-emptive	0 (reference)	0.06	N/A	0 (reference)	0.82	N/A	0 (reference)	0.68	N/A	0 (reference)	0.19	N/A
dialysis-dependent	$269 (-$233, $772)			-$224 (-$1,192, $743)			-$151 (-$521, $220)			-$44 (-$1,203, $1,115)		
started dialysis	$886 ($19, $1,752)			-$67 (-$825, $691)			$7 (-$454, $468)			$1,373 (-$175, $2,921)		
Transplant centre												
1	0 (reference)	0.07	N/A	0 (reference)	<.0001	N/A	0 (reference)	0.09	N/A	0 (reference)	0.004	N/A
2	$63 (-$613, $738)			-$631 (-$938, -$324)			-$13 (-$432, $406)			-$559 (-$1,408, $290)		
3	$390 (-$519, $1,300)			-$2,242 (-$2,746, -$1,739)			-$107 (-$685, $470)			-$1,997 (-$3,223, -$771)		
4	-$561 (-$1,147, $25)			$599 (-$502, $1,701)			-$325 (-$846, $197)			-$406 (-$1,899, $1,087)		
5	$236 (-$713, $1,185)			-$1,318 (-$1,971, -$664)			-$676 (-$1,143, -$209)			-$1,747 (-$2,878, -$616)		

[a-d] generalized linear model using a log link and normal distribution for the evaluation period (from the evaluation start until the day before donation); a square-root link and a Poisson distribution for the perioperative period (from the date of donation until 30 days post-donation); a log link and gamma distribution for the follow-up period (from day 31 post-donation until day 365 post-donation); and a square-root link and gamma distribution for the all periods (from the evaluation start until day 365 post-donation)

[e] incremental costs and p-values were obtained from a marginal effects analysis

[f] adjusted for donor/control indicator donor sex, age, time to complete the evaluation, urban/rural status, neighbourhood income quintile, and era of donation

[g] p-value from an interaction term with the donor/control indicator (p_{int})

[h] pre-emptive – recipients were not on dialysis before transplant; dialysis-dependent – recipients were on dialysis prior to (or within 3 months of) the time their donor starting their evaluation; started dialysis – recipient started dialysis at least 3 months after their donor's evaluation started.

N/A – not applicable (analysis restricted to donors only so interaction not possible)

10.3.4 Estimated cost of the evaluation process for candidates who did not donate

We estimated the cost of the evaluation assuming the donors were donor candidates who only completed a portion of their evaluation. The donor candidate evaluation cost was $1,633 ($1,452, $1,813) if the candidates completed 50% of the evaluation and $2,699 ($2,463, $2,936) if they completed 90% of the entire evaluation (Table 27). There was a nearly linear relationship between the proportion of the evaluation completed and the cost of the donor evaluation (Figure 28).

Table 27: Cost of living donor evaluation donors by proportion of evaluation completed (n=1099)

Proportion of evaluation completed	Median evaluation time (months)	Cost of evaluation[a]
0%	0 months	$0
10%	1.0 (0.66, 1.84)	$337 ($285, $388)
25%	2.7 (1.77, 4.76)	$865 ($773, $963)
50%	5.5 (3.61, 9.59)	$1,633 ($1,452, $1,813)
75%	8.2 (5.45, 14.4)	$2,320 ($2,102, $2,537)
90%	9.9 (6.54, 17.4)	$2,699 ($2,463, $2,936)
100%	11.0 (7.36, 19.4)	$3,596 ($3,350, $3,842)

[a] costs reported in 2017 Canadian dollars using the marginal effects post-estimation procedure following generalized linear regression with a log-link and normal distributional family.

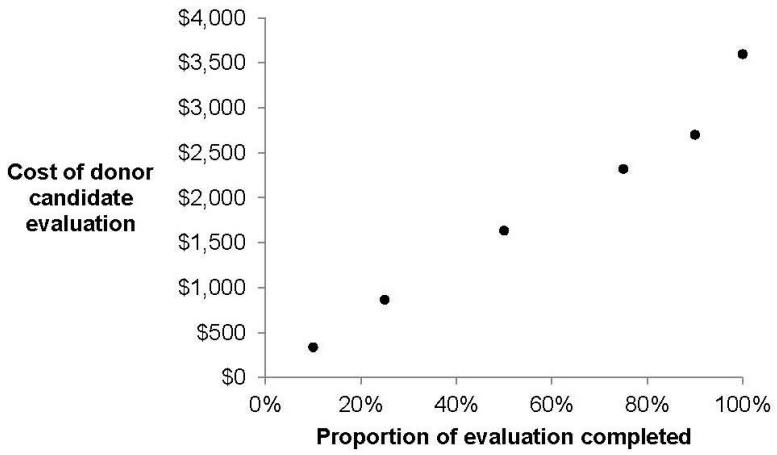

Figure 28: Cost of the living donor evaluation assuming the donors completed only a portion of their completed evaluation (n=1099). Costs are presented in 2017 Canadian dollars.

10.3.5 Sensitivity analysis

When we restricted the analysis to donations after April 1, 2006 to accommodate the cost of capitation, the total cost of health care for living donors was very similar [mean $16,666 (95% CI $15,799, $16,867)]. The cost of the evaluation, perioperative, and follow-up periods were also similar: $3,565 ($3,319, $3,810), $11,741 ($11,409, $12,073), and $989 ($747, $1,232), respectively.

In sensitivity analyses which altered the regression model selected, models that fit the data as well or only slightly worse than the base case did not change the marginal effect estimates for perioperative and follow-up donor costs, but the evaluation costs ranged from a mean $3,414 ($3,229, $3,599) with the square-root gamma model to $4,239 ($3,852, $4,626) with the log-gamma model.

10.4 Discussion

In this study from Ontario Canada, we found that the average cost to the health care system attributable to a living kidney donor was $16,290. Most of these costs were incurred in the perioperative period ($11,694), with costs also accrued during the

evaluation period ($3,596). The cost of the evaluation for potential donors who completed 25% of their evaluation was $865.

After adjusting for the donor/control indicator, higher health care consumption was observed during the evaluation period for women, older individuals, and those with a longer evaluation period. These observations were expected and consistent with the literature.[26] We did not find any evidence that the cost of donation was different concerning these factors (non-significant interaction terms). However, we found that the evaluation costs were significantly higher for donors if their intended recipient started dialysis partway through their evaluation. This may be due to incidental donor candidate findings that require further work-up (e.g. characterizing ovarian or hepatic lesions identified by renal ultrasound). In turn, a prolonged evaluation caused by the recipient initiating dialysis may result in some tests being repeated, which is additional to background health care consumption. While we did not observe any differences across transplant programs for the cost of the evaluation, there was significant variability in the cost of the perioperative period. As this is the most costly period of donation, understanding the reasons for these differences and any effects on outcomes may identify opportunities for cost-savings.

To the best of our knowledge, only one study attempted to describe the costs of the evaluation, donation, and follow-up periods separately for a small sample of living donor kidney transplants (n=130).[8] The cost of donor candidates (those who did not donate) were included in three studies.[8,10,27] However, the cost of a partial donor assessment may vary from centre-to-centre depending on their procedures for living donor work-up: transplant programs that perform multiple tests on the same day[28] or those that evaluate multiple candidates simultaneously may incur higher evaluation costs since donor candidates who did not donate will have a greater number of tests performed. We reported the cost of partial evaluations, assuming non-donors would be scheduled to receive the same evaluation process as donors. Individual programs can interpret these costs in a manner that most closely fits their current or prospective operations.

Previous studies have estimated the total cost of living donation-related care as $23,937 in Alberta Canada, $15,462 in France, and $15,850 in Spain (cf. $16,290 in this study, all in 2017 $CAD).[7,8,11] The donor evaluation period accounted for a significant proportion of the total cost of living donation: 11% in the Alberta study, 12% in the Spanish study, and 22% in this study (the periods differed in the French study). The estimated health care costs in the current study are lower than the Alberta study[8], particularly those related to the perioperative period ($11,644 vs. $18,482). Our study captured the health care utilization for donors more comprehensively, so it is unclear why the donation costs are much higher in Alberta. Although we did not include the cost of partial evaluations, the cost of the pre-donation phase was similar.

Having a non-donor control group and adjusting for covariates is a novel approach to estimate the incremental costs associated with living donation. This methodology (where all costs are included) guards against both underestimation (does not omit relevant costs since all costs are captured) and overestimation (does not include irrelevant costs since on average these are removed by the controls), and also provides a measure of precision. However, there are some limitations that should be acknowledged. First, the reimbursement costs for out-of-pocket expenses borne by the donors were not available.[29] These costs are often remunerated by government-funded organizations and should be included if a governmental perspective is desired.[30] Second, in this study we only considered persons who became donors. The health care utilization of donor candidates who did not donate should be described in future work. Several candidates may be evaluated to realize one kidney transplant, and some evaluations may not result in the identification of a suitable donor. Summating all these candidate evaluation costs may be important for some purposes. Third, the cost of running a living donor program was not measured. This includes the cost of personnel (e.g., living donor nurse coordinator, social work support, administrative assistant), equipment, and overhead. Fourth, we only looked at one-year follow-up costs. Some costs related to donation may take decades to manifest (i.e., possible donation-related kidney disease). Fortunately, the 15-year increase in the absolute risk of kidney failure attributable to donation appears to be small.[31] Finally, these estimates pertain to a universal health care system, where 78% of donors were of white race, and may not generalize well to other countries or health care systems.

We found that the cost of living kidney donation in Ontario, Canada is on average $16,290 per donor. The perioperative period is the largest component of the costs ($11,694 per donor) followed by the evaluation ($3,596 per donor) and follow-up periods ($1,011). While substantial costs of living donor care are related to the nephrectomy procedure, comprehensive assessment of costs must include evaluation and follow-up care. These estimates are informative for planning future work to support and expand living donation and transplantation, and directing efforts to improve the cost efficiency of living donor care.

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11 Discussion

11.1 Summary of the literature

The scoping review of the literature revealed a limited number of studies that reported on the efficiency of living donor evaluations. We also did not find reporting of efficiency metrics on the websites of living donor programs across Canada, the United States, the United Kingdom, or Australia. The total time to complete the evaluation was infrequently reported and measured using different time-points, some of which were only loosely defined (Table 4). In addition, the number of intended recipients who may have missed an opportunity for a living donor transplant (pre-emptive or otherwise) were sparsely reported (Table 3). Only more recently has evidence emerged suggesting that a faster evaluation process results in more living donor kidney transplants and more pre-emptive transplants.[1] Our results further support these claims. Following the consensus conference on living donor transplantation, Moore *et al* provided several recommendations to improve the efficiency of the living donor evaluation.[2] The authors discussed the role of the referring nephrologist in educating potential recipients and donor candidates on living kidney donation. Providing such education as early as possible may enable potential recipient candidates to pursue transplant evaluation and identify potential donors. This may also provide more information for potential living donor candidates to consider donation. However, the effect education has on the efficiency of the living donor work-up remains unknown (e.g., does a more informed donor candidate complete the evaluation quicker?). There is a trial underway to adapt the "Explore Transplant" and "Explore Living Donation" programs from the United States for use in Ontario (https://etontario.org/about-this-program/).[3,4] Moore *et al* also suggest that various blood tests and anthropometric assessments should be conducted before visiting the transplant centre, particularly for candidates who live far away.[2] In Chapter 3, we recognized that this process design deserves merit (regardless of distance), and while many programs already ask candidates to complete preliminary blood and urine tests at a local lab before visiting the transplant centre, there is little evidence about when this request should be made. For example, should laboratory requisitions be provided to all candidates at the

outset or only after they pass the preliminary screening phase? Finally, the authors recommended using community nephrologists, particularly for candidates who live far from the transplant centre.[2] Community nephrologists do not have the same experience with living donation as transplant nephrologists, which may produce variability in the selection and evaluation of living donor candidates (Appendix A).[5–9] Without evidence of the efficacy of placing more responsibility on community nephrologists in the work-up of living donor candidates, we cannot endorse this as efficiency-improving recommendation at this time, yet acknowledge this as a potential source of quality improvement. This specific area requires further investigation, as the use of community nephrologists may reduce wait times and travel burden for some candidates.

11.2 Summary of contributions to the field

Given the paucity of published data and the enthusiasm of patients surrounding this issue, we conducted a series of studies to inform the efficiency of the living donor evaluation.

First, we estimated the time to complete the evaluation. Using data from multiple sources, we established that the time until donation was a median 9-11 months across transplant centres. For many donors, this time is often overwhelming and fraught with uncertainty.[10] Although we explored individual-level (donor, recipient, and transplant) and some centre-level factors associated with longer evaluation times, the strongest predictors of a longer time until donation was participation in kidney paired donation. Some process improvements may help improve the timeliness of this process (e.g. shipping kidneys rather than donors; more frequent matching cycles).[11] However, this is also reflective of the fact that many recipients in paired donation programs are hard to match (e.g., AB blood types, presence of antibodies against antigens prevalent among potential donors).[11,12] The second most noteworthy factor associated with a longer evaluation time was a longer time until recipients were referred to the transplant centre. This suggests that dialysis centres and multidisciplinary chronic kidney disease clinics could be more proactive at educating and referring potential recipients for transplant evaluation.[13,14] This is consistent with the observation that recipient readiness (e.g. delayed recipient referrals) was one of the most frequently encountered reasons for a delayed living donor evaluation (Table 17). The time and effort for a donor candidate undergoing an evaluation may

result in some candidates abandoning the process, a suspected outcome that remains difficult to study.[1,15] Thus, measuring the evaluation time allows living donor programs to compare their performance with other programs and provides a starting point to guide improvement efforts.

Second, we estimated the potential undesirable consequences that can occur with a prolonged evaluation process. We found that the evaluation time was twice as long for donors whose recipient started dialysis while their evaluation was underway. Although poor recipient health may have prolonged the donor's evaluation (e.g. recipient may have become temporarily ineligible for transplant), we anticipate that a longer evaluation was frequently a cause of recipients starting dialysis for several reasons. First, the donor's evaluation is often completed by a different healthcare team than the recipient's healthcare team.[16,17] This is intended to ensure the donor healthcare team is focused on donor safety without the pressures of promoting recipient health (the donor is being harmed for the benefit of the recipient). Second, 50% of the recipients started dialysis at least 9 months after their donor started their evaluation, ample time to complete a donor assessment (Figure 25). All of these donors donated, meaning that they were all healthy enough and motivated enough to complete the evaluation and donate a kidney. It is therefore unclear why their evaluation wasn't completed before their recipient started dialysis. We also estimated the number of potential living donor transplants that could have occurred if the evaluation was quicker. Under these scenarios, we assumed the donor candidate was motivated and would have been deemed eligible to donate and therefore provide an upper limit of the number of missed opportunities. Altogether, this evidence suggests that a quicker evaluation is possible and would result in more living donor transplants, more pre-emptive transplants, less time on dialysis (and therefore better recipient outcomes), and reduced healthcare expenditures related to dialysis. These conclusions are consistent with the sole report linking efficiency improvements to some of these outcomes.[1]

Third, we estimated the cost to the healthcare system for a completed living donor evaluation as well as for partial evaluations. Accurate costing is needed to help programs project their budgetary requirements and their ability to cope with a more efficient living

donor evaluation. For example, if the evaluation process was streamlined and completed within 3-4 months, then more evaluations (completed or partial) would be conducted during a given fiscal year[1], thereby increasing costs. These projections may inform capital and capacity planning to ensure resources are available to continue to conduct timely evaluations and living donor transplants. These costs are also needed to inform decision models on whether donor candidates should be evaluated sequentially or simultaneously.

After summarizing the literature and generating novel results, we are able to explore additional avenues to improve the efficiency of living kidney donation (Figure 5). I briefly describe these efforts in the subsections below.

11.2.1 Sequential versus simultaneous evaluations

As demonstrated in Chapter 7, the number of living donor candidates coming forward for evaluation for the same recipient increased over time. As prospective recipients are increasingly advertising their need on social media, situations where multiple candidates are available will become more common. Living donor programs usually evaluate one candidate at a time and prioritize candidates who are considered more likely to donate (4.4.1.3). This is done to save resources and avoid unnecessary testing for candidates who ultimately would not donate. However, most candidates do not donate, and the evaluation time for non-donor candidates was estimated to take a median 3 to 4 months (Chapter 7). If the initial candidate does not donate, then the time until a true living donor is found will be prolonged by at least this amount. During this additional time, the intended recipient may start dialysis, will spend a longer time on dialysis, may lose eligibility for transplant due to their illness, or may instead receive a deceased donor kidney transplant (Chapter 8 and Chapter 9). Thus, the uncertainty of the outcome of living donor candidates (donation or non-donation) combined with a lengthy evaluation process may make simultaneous evaluations more cost-effective than sequential evaluations, especially when the recipient is on dialysis, the cost of which can exceed $1,000 every week.[18]

To explore this decision, I constructed a decision tree with a Markov model to follow donor candidate-recipient groups from the start of the first donors' evaluation until the intended or actual recipient dies (e.g. a lifetime time horizon). Quality-adjusted life-years (QALYs) gained was determined using utilities derived from the literature for chronic kidney disease (if not yet on dialysis), dialysis, and transplant. Costs included the cost of dialysis over time and the cost of the living donor evaluation (partial for non-donors, complete for donors), derived from the literature and the estimates from Chapter 10. The time to complete the evaluation for donors and non-donors were derived from estimates obtained in Chapter 6 and Chapter 7. We modeled several scenarios, varying the number of candidates coming forward from 2-4 and the number of donors (candidates who would donate upon completion of their evaluation) varied from 1-4 (versus non-donors, who would not donate upon completion of their evaluation). We also considered the scenario when the intended recipient was not on dialysis (potentially pre-emptive) when the first donor candidates' evaluation started, using data from Chapter 8 to inform the risk of starting dialysis over time. We also conducted probabilistic sensitivity analyses to accommodate parameter uncertainty.

The incremental cost-effectiveness ratio (ICER) was negative for all scenarios, driven by higher cost savings and more QALYs gained with simultaneous evaluations. For example, when 2 candidates came forward for the same candidate who was on dialysis and 1 candidate was a donor, there was a 50% probability that the donor would be selected first if they were evaluated sequentially. Simultaneous evaluations resulted in greater cost savings over the lifetime of the recipient than did sequential evaluations (Δcost = -$19,520) and also produced more QALYs (ΔQALY = 0.44). By breaking down some of the cost and effect components, the donor evaluation was more costly in the simultaneous strategy ($5,261 versus $4,192 due to the cost of evaluating the non-donor), but this was offset by the reduced dialysis cost ($56,290 versus $69,086) that resulted from a quicker evaluation time (0.63 versus 0.78 years). Moreover, this prolonged time until donation resulted in a greater proportion of recipients receiving a living donor transplant (92.6% vs. 89.1%) under the simultaneous method, which may be attributable to fewer recipients dying (5.9% versus 8.6%) or receiving a deceased donor transplant

instead (1.7% versus 2.4%). In the potentially pre-emptive scenarios, the added cost of dialysis in the sequential strategy may be exacerbated by the longer evaluation phase when the non-donor is evaluated first, resulting in more intended recipients starting dialysis before the donor evaluation was completed. The ICER was most sensitive to the donor and non-donor evaluation times, the cost of dialysis, and the cost savings associated with living donor transplantation. If the recipient was potentially preemptive at the outset of the evaluations, the ICER was also sensitive to the probability of starting dialysis. Regardless of the number of candidates coming forward, even if all candidates were donors, simultaneous evaluations were still cost-effective (under probabilistic sensitive analyses only) since the fastest donor was chosen.

11.2.2 Reducing the number of tests I – omit the nuclear renogram for split renal function†††

Several studies were identified by the scoping review (Chapter 4) that assessed replacing the split renal function assessment by nuclear renography with split kidney volume by computed tomography (CT) imaging (Figure 8). The rationale behind this logic is: 1) there is a relationship between kidney size and function; and 2) all donors must complete a CT scan to assess the renal vasculature. Since a scoping review is inappropriate to summarize the literature on this specific topic, we conducted a systematic review of the literature, identifying a total of 18 studies for inclusion after applying exclusions. We supplemented these studies with individual-level patient data from living donor candidates assessed at London Health Sciences Centre between 2013 and 2016. We measured the split renal volume from the actual CT images using the ellipsoid formula and abstracted the split renal function from the nuclear renogram reports.

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††† A complete manuscript is currently under review with *Canadian Journal of Kidney Health and Disease*

The Pearson's correlation coefficient (r) was the measure of association reported by most studies. For studies that did not report r yet presented a scatterplot or Bland-Altman plot, we digitized the datapoints from the published figures and generated r using the digitized (e.g., individual-level) data. We pooled this measure using Fisher's z-transformation using a random-effects model. For individual-level analyses (e.g., using digitized data), we performed linear regression to obtain a more interpretable estimate of the association between split renal volume and split renal function.

After pooling 19 studies (n=1,479), we obtained a pooled correlation of 0.74 (95% confidence interval 0.61, 0.82). By linear regression using individual-level data, we observed a 0.76 (95% CI 0.71, 0.81) percentage-point increase in split renal function (SRF) percent for every 1% increase in split renal volume (SRV) percent. SRV had a specificity of 88% for discriminating SRF% at a threshold that could influence the decision of which kidney is to be removed (between-kidney difference ≥10%). Predonation SRV% and SRF% similarly predicted kidney function 6-12 months postdonation: Δr=0.05 (-0.02, 0.13).

SRV has the potential to replace SRF for some candidates. However, it is uncertain whether it can do so reliably and routinely across different transplant centres. The impact on clinical decision-making also needs to be determined in a well-designed prospective study.

11.2.3 Reducing the number of tests II – omit the nuclear renogram for glomerular filtration rate for some candidates

The second process redesign involved omitting the nuclear renogram for measured glomerular filtration rate (mGFR) assessment among candidates with particular pre-test characteristics (Figure 9).[19] An algorithm was recently published online and tested in a French cohort of donors.[20] The rationale behind this algorithm is that a young donor candidate with a very high estimated GFR (eGFR) will have a very high probability of a mGFR exceeding the cut-point for acceptability, rendering this test superfluous. This probability (the "pre-test probability") is the probability of mGFR greater than a pre-

specified cut-point deemed acceptable to the living donor program (e.g. ≥80 mL/min/1.73 m^2). The pre-test probability is based on age, sex, race and eGFR, factors that are predictive of mGFR. Conversely, candidates with a very high pre-test probability of a very low mGFR (e.g. <60 mLmin/1.73 m^2, which is unacceptable for donation by all programs) could be excluded without confirmation by nuclear renography.

Using data from living donors across Canada and Australia (Chapter 6) and for candidates evaluated in London Ontario (Chapter 7), we determined the pre-test probability of a mGFR at various cut-points (<60, <70, ≥80, and ≥90 mL/min/1.73 m^2). To avoid false negatives (e.g. having a mGFR <80 mL/min/1.73 m^2 but confirmation by mGFR is deemed unnecessary), we selected a pre-test probability cut-point that would result in 100% sensitivity. Pre-donation eGFR and mGFR were weakly to moderately correlated in the cohort of donors (r=0.38, n=768) and the cohort of donor candidates (r=0.58, n=101). If the minimum mGFR threshold was 80 mL/min/1.73 m^2, a pre-test probability >99.94% was needed; only 7 donors had a pre-test probability above this cut-point and would therefore not have needed a mGFR. Addition of a second eGFR to improve the pre-test probability yielded slightly lower cut-point and could have prevented 14-15 candidates from requiring a mGFR test (e.g. 4 exams per year). Using the estimates from Appendix P (mean cost of $220 per nuclear medicine exam), this translates to up to $880 in direct cost savings each year at London Health Sciences (a medium-sized program).

Because the algorithm is based on categorization of key continuous variables (age and eGFR), the pre-test probabilities become ordinal. This results in poor discriminative ability and large "jumps" in the probabilities between categories. As a result, extremely high threshold probabilities are needed to obtain 100% sensitivity. Thus, the current prediction tool falls short of warranting its use in medical decision-making. Interpreting our findings with the original study and the French validation study, I do not support the widespread use of this online diagnostic tool to dictate the use of nuclear renography without improvement in its discriminatory ability.[19,20]

11.2.4 Time from referral to consultation or imaging

The time until a specialist is available for consult may differ across transplant centres and type of specialist. Also, the time until CT imaging is available may also vary. The time from referral until imaging or consultation is a common indicator used to measure quality of care in Ontario. We attempted to obtain the time of referral from the transplant department and the medical records at London Health Sciences, but data were unavailable. These wait times are necessary to identify bottlenecks in the evaluation process.[21,22] Health Quality Ontario provides an interactive online interface for users to look at various wait times across Ontario for surgeries and diagnostic imaging (http://www.hqontario.ca/System-Performance). Although kidney donation did not feature in these reports (e.g. time from referral until nephrectomy), priority-4 (lowest priority) patients who should have had a CT scan within 28 days waited a median 31 days. The median time ranged from a minimum of 5 days (Oxford Advanced Imaging Inc. – Ajax) to a maximum of 188 days (Ottawa Hospital).

11.3 Strengths and Limitations

11.3.1 Evaluation start date

One of the limitations of this research is the absence of a clear definition of the candidate evaluation start date used to estimate the total evaluation time. Some experts believe that the evaluation start date is the date the medical-social questionnaire (MSQ) is received by the program. Some candidates take months to complete and return the MSQ (we reported a median time of 40 days in Chapter 7), which may reflect the time required by candidates to reflect on their decision to donate, wait for other candidates (e.g. other family members) to proceed first, or complete their search for information about donation. In contrast, other experts believe that this questionnaire is indeed part of the evaluation process and the evaluation begins at the time the candidate first contacts the program. As part of the evaluation process, the time from first contact until the MSQ is received can therefore be subjected to quality improvement efforts by providing the MSQ online, reducing the number of questions, or referring candidates to a reliable and up-to-date source of information.

To estimate the total evaluation time, we were therefore required to make some assumptions since data on the first contact date or MSQ were rarely available. In one cohort derived using administrative data, we used an algorithm based on healthcare utilization patterns. This algorithm was based on expert opinion independent of the data. In the cohort comprised of 16 transplant centres across Canada and Australia, we used the earliest tests as a surrogate for the evaluation start date (typically blood or urine tests), supplemented with first contact dates obtained for many Ontario donors. Finally, in the single-centre cohort of living donor candidates in London, Ontario, we abstracted and used the actual date the candidate reached out to the program. Despite these differences, the estimated total evaluation time was consistent in all three cohorts. Furthermore, these estimates aligned with expert opinion (face validity). Finally, these estimates were corroborated using costing data, where the cost of partial evaluations approached zero as the evaluation time decreased to zero (Figure 28). Had the evaluation start date been estimated to be earlier or later than the true date, we would have expected the y-intercept to be negative or positive, respectively (concurrent validity).

11.3.2 Between-centre comparisons

The large (>1000) Canadian/Australian cohort of living donors was the most appropriate dataset to conduct between-centre comparisons because there were 12 transplant centres for comparison (compared with the five programs available from Ontario administrative data). Although we found statistically significant differences across transplant centres for evaluation times, the proportion of potential pre-emptive transplants lost, and the cost of living donor evaluations, we were unable to identify the drivers behind these differences.

Future research is needed, supported by more complete data on the program's evaluation practices and standardized collection and definition of key time-points. We propose one approach common to management operations and economics: a data envelopment analyses. This method uses linear programming to identify the technically efficient programs by simultaneously combining important inputs (e.g. resources + protocols + evaluation time) and outputs (e.g. number of transplants + number of pre-emptive transplants + number of candidates completing the evaluation).[23,24] Efforts are in place to obtain these data from multiple transplant programs, and the findings are expected to

identify the relatively inefficient programs and identify the inputs that should be targeted for improvement. For example, Program A may produce the same outputs as Program B, but may do so with fewer resources. In this case, Program A is more technically efficient than Program B because it uses fewer resources to produce the same amount of outputs. Program B can improve by either reducing its resources (e.g. personnel) while maintaining the same level of production, or increase its level of production (e.g. more transplants) while maintaining the same inputs.

11.3.3 Generalizability

The evaluation times estimated in this research may not be generalizable to other transplant programs (e.g. programs that perform a 1-day evaluation; programs in the United States where the CT scan is readily available and can be performed much earlier in the evaluation, according to expert opinion). The estimates also may not be consistent over time within the same program, as we anticipate all programs across Canada will modify their practices to become more efficient (as a result of this research plus ongoing engagement and collaboration).[25]

The potential cost savings of an earlier living donor transplant may also differ in other regions because the distribution of dialysis modalities [e.g. proportion of the population treated with peritoneal dialysis (less costly) versus in-centre hemodialysis (most costly)] differs.[18,26,27] This may also differ for countries where dialysis costs are not completely covered by the primary payer: in multiple countries, patients pay some portion of dialysis costs through an insurer or out-of pocket.[28,29]

11.4 Future directions

Throughout this thesis, I have argued that key quality indicators and definition of key terms are needed to improve the efficiency of the living donor evaluation process. To address this gap, we have launched a national Delphi study to identify and define key process and outcome indicators that should be measured, monitored, and used to compare performance between centres for accountability and quality improvement. [25,30–32] This is important because multiple metrics are needed to better understand any process,

participation in consensus-type methodology promotes buy-in across the country, and data collection cannot be centralized.

The total time to complete the evaluation is a rather simple and crude metric: it serves as a broad indicator of a programs' efficiency but offers little information on bottlenecks. Furthermore, because the definition of an efficient evaluation is so broad, multiple quality indicators are needed. For example, Program A may have a prolonged evaluation (longer time until approval), but once approved, the donor surgery can be scheduled quickly (Figure 29). In contrast, Program B has a quicker evaluation (faster time until approval), but has difficultly scheduling the operating theater. The total evaluation time does not distinguish these two programs and offers no suggests for quality improvement.

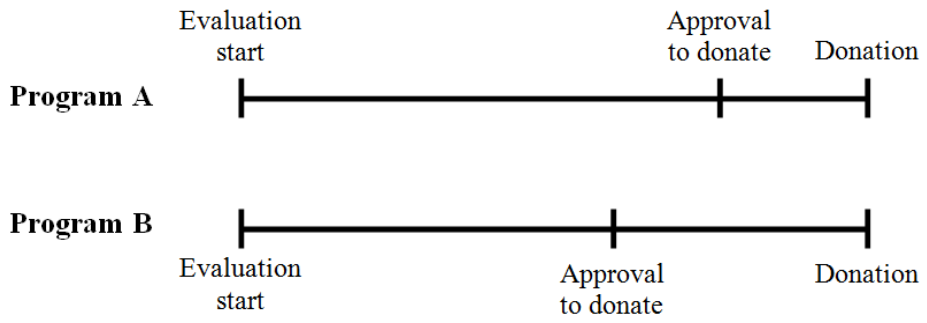

Figure 29: Comparison of two different hypothetical living donor programs with identical total evaluation times (defined as the time from evaluation start to donation)

Several process indicators have been suggested and we estimated these where possible, including the total time until donation, the time until approval, the time from approval until donation, the time from CT angiography until donation, and the time between consults. Most of the dates needed to measure process indicators are readily available and easily defined (e.g. date of CT). Others were not routinely captured until only recently (e.g. the donor candidate first contact date began to be recorded as of January 1, 2016 across Ontario). Others remain poorly defined (e.g. date of approval) and consensus is needed before these are used for quality improvement initiatives.

Outcome indicators (including those in Table 21) also require clear definitions to promote generalizability. One such definition is a "potential" preemptive transplant (e.g. could the donor candidate have completed their evaluation and donated before their intended recipient started dialysis?).

11.4.1 Implementing a 1-day evaluation

We believe that the future of living kidney donor evaluation processes in Canada should follow the 1-day evaluation in use by other programs. If a 1-day evaluation was implemented for all candidates, some of these metrics would become obsolete, yet others may weigh more heavily (e.g. time from CT until donation) or new metrics would be needed (e.g. time from 1-day evaluation until approval).

After screening the websites of living donor programs, several programs were identified that routinely conduct 1-day assessments, suggesting that this is a feasible process improvement strategy that may improve patient outcomes. One program (Belfast, Northern Ireland) provided a detailed schedule online.[1] We also contacted four programs from the United States for additional information, receiving a response from two: University of California, Davis and the University of Iowa. Information about these two programs were generously provided by the living donor coordinators.

11.4.1.1 Belfast

The day begins at 8am with a meeting with the living donor coordinators, blood tests and urine tests after a 12-hour (overnight) fast (http://www.donatelife.co.uk/?page_id=306). The candidate is then given breakfast and at 9am completes the renal ultrasound and is given an injection of a contrast agent for nuclear renographic assessment of split kidney function. At 9:30, an injection of another agent is given for total kidney function. Between 10am and noon, the nuclear testing for both split function and total kidney function are completed, along with a chest x-ray and an electrocardiogram. A nephrologist reviews the results in the afternoon and meets with the candidate. A CT scan may be performed, but is subject to cancellation if the nephrologist deems the candidate is ineligible based on results of tests completed earlier in the day. There appears to be quite a bit of movement between departments and floors (e.g. radiology on the first floor

of the hospital, meeting with the coordinators and performing blood draws on the eleventh floor, nuclear medicine in the cancer centre, and meeting the nephrologist in the dialysis unit in another building). No mention is made about their requirements to conduct routine psychosocial evaluations. The total evaluation time was reported to be 2-3 months.[1]

11.4.1.2 University of Iowa Organ Transplant Center:

During the course of the day, the candidate visits the living donor coordinator, social worker, psychologist, and surgeon, and conducts a CT scan, chest x-ray, and electrocardiogram. The candidate also visits with the independent living donor advocate (who happens to be a primary care physician). The advocates perform the medical examination, history and educate the potential donor about risk factors and issues related to donation, including the ability to back out and issues surrounding confidentiality.[33] The advocate assumes the role of the nephrologist. As with the Belfast program, the CT scan is subject to cancellation. The time from first contact until the 1-day evaluation was stated to be 4-6 weeks, and the time until donation varies after the 1-day assessment.

11.4.1.3 UC Davis Transplant Center:

The day begins at 7:30am with labs (blood and urine tests). The clinical research center registered nurse starts an intravenous line and injects the iohexol dose for nuclear renography. At 8:00am, the candidate completes an educational session with the living donor coordinators and at 9:00am meets with the nephrologist for a history and physical exam. At 10:00am, the candidate meets with the social worker and independent living donor advocate. This is followed by a nutritional evaluation and a 1-hour break for lunch. In the afternoon, a CT scan is scheduled (can also be canceled if needed) and the candidate completes “drop in” tests including chest x-ray and electrocardiogram. The morning is completed in the clinic and the afternoon is completed in the hospital. The total time from first contact until donation was stated to be approximately 3 months, but data were unavailable to support this.

11.4.1.4 Challenges to a 1-day evaluation

Some candidates may require additional testing (e.g. stress echo) that is not part of the 1-day evaluation. In such cases, some tests may be scheduled on a second day and the 1-day evaluation may be shortened to reduce the burden on the candidate (this is the case at UC Davis Transplant Centre for candidates aged 50 years or older).

Although we anticipate the cost of evaluating non-donor candidates to increase costs to the living donor program, such data were unavailable. If a 1-day evaluation does lead to more living donor transplants, then while these costs are likely to be recuperated from other departments (e.g. dialysis centres), the segmentation of operating costs and funding models may hinder such quality improvement projects. Thus, the funding model needs to be appropriately addressed to enable more living donor evaluations (e.g. for capital planning).

The wait time for specialists or specialized testing has to be addressed. Conducting more tests on candidates who ultimately do not donate represents not only a significant financial cost, but also prevents other patients from receiving these consultations or diagnostic exams. Thus, more work is needed to ensure healthcare resources are used efficiently (e.g. capacity planning).

Another consideration is the availability of the operating room. If the evaluation process was more efficient, we would anticipate more living donor transplants per year. The operating room must be able to accommodate this capacity.

11.4.2 Other quality improvement designs

There are likely other solutions to improve the efficiency of the living donor work-up, including partnering with local pharmacies to lease 24-hour ambulatory blood pressure machines free of charge to donor candidates, or running outpatient clinics on weekends. The final round of the aforementioned Delphi survey to is aimed to identify and prioritize solutions to improve the efficiency of the evaluation process.

11.5 Resource constraints

Unlike manufacturing processes, the flow of patients through a healthcare system is subject to individual heterogeneity (e.g. unlike cars on an assembly line, each patient is unique). Despite this challenge, multiple avenues for process improvement have been discussed in the context of our findings and those from the literature. From the experience of a single transplant centre (London Health Sciences Centre; Chapter 7), there was a rise in the number of living donor transplants, more pre-emptive transplants, and more living donor candidates contacting the program (e.g. more evaluations started). However, this was not associated with a longer time to complete the evaluation (e.g. due to resource constraints). In contrast, this was associated with a shorter time until donation. This suggests existing capacity and resource availability, which was somehow utilized to improve the efficiency of the evaluation. Without adding resources to the system (e.g. more human resources, additional CT scanners), there is an upper limit of efficiency that will preclude additional efficiency gains. Moreover, harm can be created in other areas because one more CT scan for a living donor may come at the expense of one less scan available for another patient. Although this was not in the scope of this thesis, future work will inform these issues. If additional resources are warranted, this will increase the overhead costs of running a living donor program. Thus, consideration of resource constraints in a specific setting is critical to eliminate system constraints and ensure the long-term success of a more efficient living donor evaluation process.

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Appendices

Appendix A: Variability on living donor eligibility criteria: summary of surveys of multiple living donor programs

Age: There has been an upward shift in the age range for donor acceptability across programs. Up to 58-59% of centres surveyed in the United States and Europe reported no upper age limit.[1–3] However, most living donor programs have a lower age limit for donor acceptance. Some programs have a cut-off of 25 years of age, while others are willing to accept minors under special circumstances.

Hypertension: Hypertension is a strong risk factor for kidney disease and cardiovascular disease, and donor candidates with uncontrolled hypertension are typically excluded. If hypertension is controlled (i.e., within normal limits while taking antihypertensive medication(s)), then some centres may accept this donor, particularly if the candidate is older. Variability exists regarding the number of anti-hypertensive medications permitted (ranging from zero to three), the highest acceptable blood-pressure (ranging from 120/80 to 140/90), and the use of a 24-hour ambulatory blood pressure monitor to rule out white-coat hypertension (hypertension in a doctor's office).

Diabetes: Diabetes is one of the more common absolute contraindications to kidney donation (72% across Europe and 64% across the United States[2,3]), as this is one of the leading causes of kidney disease. The presence of pre-donation risk factors (i.e., high blood glucose, family history of diabetes, donors of South Asian or Afro-Caribbean extraction) often mandates a fasting glucose measurement or an oral glucose tolerance test. The maximum glucose concentration used for donor exclusion varies across programs, but the upper limit across programs does not exceed 7.0 mmol/L (126 mg/dL).

Kidney function: kidney function is one of the strongest predictors of kidney disease. Kidney function is measured as the rate by which blood is filtered (the glomerular filtration rate, GFR) adjusted to body size, in mL/min/1.73 m^2. The minimum cut-point for donor acceptance generally ranges from 80-100 mL/min/1.73 m^2, but lower values may be acceptable by some programs under certain circumstances (i.e., advanced age

since GFR declines with age). There is little agreement on the best strategy to evaluate a donor candidate's kidney function. Some programs use measured GFR from urine collected over a continuous 24-hour period, estimated GFR (eGFR) using different equations, measured GFR using a nuclear renogram, or any combination of these.

Another indicator of kidney disease is proteinuria (protein in the urine), which may be measured using a random urine sample for semi-quantification (i.e., negative, trace, small, large) or quantification (g/L) using a dipstick or daily protein elimination using a 24-hour urine sample (g/day). Acceptance criteria vary across programs, but donors with ≥100mg/d albumin excretion or microalbuminuria (≥3 mg/mmol albumin-to-creatinine ratio) are generally excluded.

Another indicator of kidney disease is hematuria (blood in the urine), which may be measured using a random urine sample for semi-quantification using a dipstick (i.e., negative, trace, small, large) and confirmed using a microscopic analysis. Although reported only by the American surveys, the definition of hematuria based on the microscopic analysis ranges from a minimum of 2-10 red blood cells per high-powered microscopic field.[2,4] The definition of *persistent* hematuria may also vary, but presence of persistent hematuria generally mandates further testing using a cystocopy or a kidney biopsy to rule out underlying kidney disease.[5] Urine cytology (looking for cancerous cells in the urine) may be performed before cystoscopy or kidney biopsy.[6]

Obesity: obesity presents a surgical risk to the donor and also impacts the lifelong risk of developing diabetes and kidney disease. The BMI cut-point for acceptance ranges from 30-40 kg/m^2, but information was not provided on methods used by programs to help motivated candidates reach the cut-point.[3,4]

Cardiac testing: an electrocardiogram and cardiac stress testing is usually reserved for candidates with an indication for these tests (i.e., advanced age, cardiovascular risk factors). However, some centres perform these tests routinely for all donor candidates.

Stones: A history of renal stones is a strong risk factor for kidney disease and has typically been an exclusion criterion (for the safely of both the donor and the recipient).

Although none of the European surveys offered perspective on acceptance criteria, this has become less stringent over time in the United States. Many American centres (66%) accept donors with a history of a single stone, but other programs may relax this restriction based on absence of metabolic risk factors (i.e., hypercalciuria, hyperoxaluria, cystinuria, metabolic acidosis, and hyperuricemia).[2,4]

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Appendix B: List of Websites

Country	Province or State	Centre or agency	City	Website
Canada	British Columbia	St. Paul's Hospital	Vancouver	http://renal.providencehealthcare.org
Canada	British Columbia	Vancouver General Hospital	Vancouver	http://www.vch.ca
Canada	British Columbia	BC Transplant Society *	Vancouver	http://www.transplant.bc.ca
Canada	Alberta	Living Donor Services Program	Edmonton	http://www.albertahealthservices.ca
Canada	Alberta	Southern Alberta Renal Program	Calgary	http://www.albertahealthservices.ca
Canada	Alberta	Northern Alberta Renal Program *	Edmonton	https://www.kidney.ca
Canada	Saskatchewan	Saskatchewan Transplant Program	Saskatoon	https://www.saskatoonhealthregion.ca
Canada	Manitoba	Transplant Manitoba	Winnipeg	http://www.transplantmanitoba.ca
Canada	Manitoba	Health Sciences Centre *	Winnipeg	http://www.hsc.mb.ca
Canada	Ontario	London Health Sciences Centre	London	http://www.lhsc.on.ca
Canada	Ontario	St. Joseph's Health Care System	Hamilton	https://www.stjoes.ca
Canada	Ontario	St. Michael's Hospital	Toronto	http://www.stmichaelshospital.com
Canada	Ontario	Toronto General Hospital	Toronto	http://www.uhn.ca/MOT
Canada	Ontario	The Ottawa Hospital	Ottawa	http://www.ottawahospital.on.ca
Canada	Quebec	Hôpital Ste-Justine	Montreal	https://www.chusj.org
Canada	Quebec	Montreal Children's Hospital *	Montreal	http://www.thechildren.com
Canada	Quebec	Royal Victoria Hospital *	Montreal	https://muhc.ca
Canada	Quebec	C.H. Universitaire de Sherbrooke	Sherbrooke	http://www.chus.qc.ca
Canada	Quebec	Transplant Quebec *	agency	http://www.transplantquebec.ca
Canada	Nova Scotia/Prince Edward Island	Queen Elizabeth II Health Sciences Centre	Halifax (serves Nova Scotia, New Brunswick, PEI and Newfoundland	https://www.cdha.nshealth.ca
Canada	Nova Scotia/Prince Edward Island	Legacy of Life *	agency	http://www.legacyoflife.ns.ca
Canada	Nova Scotia/Prince Edward Island	Prince Edward Island Government Website *	agency	https://www.princeedwardisland.ca
Canada	New Brunswick	Réseau de santé Vitalité Health Network	New Brunswick	http://www.vitalitenb.ca
Canada	Newfoundland and Labrador	Western Memorial Regional Hospital	Corner Brook	http://westernhealth.nl.ca
Canada	KFOC	Kidney Foundation of Canada	agency	https://www.kidney.ca
Canada	KFOC	Canadian Blood Services	agency	https://blood.ca
Canada	KFOC	HealthLink BC	agency	https://www.healthlinkbc.ca
USA	Alabama	UAB Medicine	Birmingham	https://www.uabmedicine.org
USA	Alaska	Providence	Anchorage, Eagle River, Kodiak Island, Palmer, Seward, Valdez	http://alaska.providence.org
USA	Arizona	Phoenix Children's Hospital	Phoenix	http://www.phoenixchildrens.org
USA	Arizona	Banner - University Medical Center Phoenix and University Medical Center Tucson	Phoenix + Tucson	https://www.bannerhealth.com
USA	California	Scripps Center	La Jolla	https://www.scripps.org
USA	California	Loma Linda Medical Center	Loma Linda	http://medical-center.lomalindahealth.org
USA	California	Cedars-Sinai Medical Center	Los Angeles	https://www.cedars-sinai.edu
USA	California	University of California at Los Angeles Medical Center	Los Angeles	http://transplants.ucla.edu
USA	California	Keck Hospital of USC	Los Angeles	http://transplant.keckmedicine.org
USA	California	St. Vincent Medical Center	Los Angeles	https://stvincent.verity.org
USA	California	St. Joseph Hospital	Orange	https://www.sjo.org
USA	California	University of California Irvine Medical Center	Orange	http://www.ucirvinehealth.org
USA	California	Lucile Salter Packard Children's Hospital	Palo Alto	http://www.stanfordchildrens.org
USA	California	Stanford Health Care	Palo Alto	https://stanfordhealthcare.org
USA	California	Riverside Community Hospital	Riverside	http://riversidecom
USA	California	University of California Davis Transplant Center	Sacramento	http://www.ucdmc.ucdavis.edu
USA	California	Sharp Memorial Hospital Kidney Transplant	San Diego	https://www.sharp.com
USA	California	University of California San Diego Medical Center	San Diego	https://health.ucsd.edu

USA	California	Rady Children's Hospital and Health Center	San Diego	https://www.rchsd.org
USA	California	University of California San Francisco Medical Center	San Francisco	https://www.ucsfhealth.org
USA	California	California Pacific Medical Center	San Francisco	http://www.cpmc.org
USA	California	Living Donation California		http://livingdonationcalifornia.org
USA	Colorado	University of Colorado Hospital	Aurora	https://www.uchealth.org
USA	Colorado	University of Colorado Anschutz Medical Campus	Aurora	http://www.ucdenver.edu
USA	Colorado	Children's Hospital Colorado	Aurora	https://www.childrenscolorado.org
USA	Colorado	Centura Porter Adventist Hospital	Denver	http://www.porterhospital.org
USA	Colorado	Presbyterian/St. Luke's	Denver	http://pslmc.com
USA	Connecticut	Hartford Hospital Transplant Center	Hartford	https://hartfordhospital.org
USA	Connecticut	Yale New Haven Hospital	New Haven	https://www.ynhh.org
USA	Delaware	Christiana Care Health System	Newark	https://christianacare.org
USA	Delaware	Alfred I duPont Hospital for Children	Wilmington	https://www.nemours.org
USA	District of Colombia	Georgetown University Medical Center	Washington D.C.	https://www.medstargeorg
USA	District of Colombia	George Washington University Hospital	Washington D.C.	https://www.gwhospital.com
USA	Florida	Gulf Coast Medical Center	Ft. Myers	http://largomedical.com
USA	Florida	UF Health Shands Hospital	Gainesville	https://ufhealth.org
USA	Florida	Mayo Clinic Jacksonville	Jacksonville	http://www.mayoclinic.org
USA	Florida	Largo Medical Center	Largo	http://largomedical.com
USA	Florida	Jackson Memorial Hospital University of Miami School of Medicine	Miami	http://www.jacksonhealth.org
USA	Florida	Florida Hospital Medical Center	Orlando	https://www.fhtransplant.com
USA	Florida	Tampa General Hospital	Tampa	https://www.tgh.org
USA	Florida	Cleveland Clinic Florida Weston	Weston	https://my.clevelandclinic.org
USA	Georgia	Emory University Hospital	Atlanta	https://www.emoryhealthcare.org
USA	Georgia	Children's Healthcare of Atlanta at Egleston	Atlanta	https://www.choa.org
USA	Georgia	Piedmont Hospital	Atlanta	http://www.piedmont.org
USA	Georgia	AU Medical Center	Augusta	https://www.augustahealth.org
USA	Hawaii	The Queen's Medical Center	Honolulu	http://www.queenstransplantcenter.org
USA	Illinois	Rush University Medical Center	Chicago	https://www.rush.edu
USA	Illinois	University of Chicago Medical Center	Chicago	http://www.uchospitals.edu
USA	Illinois	Ann & Robert H. Lurie Children's Hospital of Chicago	Chicago	https://www.luriechildrens.org
USA	Illinois	University of Illinois Medical Center	Chicago	http://hospital.uillinois.edu
USA	Illinois	Northwestern Memorial Hospital	Chicago	https://www.nm.org
USA	Illinois	Loyola University Medical Center	Maywood	https://www.loyolamedicine.org
USA	Illinois	Advocate Christ Medical Center	Oak Lawn	http://www.advocatehealth.com
USA	Illinois	OSF Saint Francis Medical Center	Peoria	https://www.osfhealthcare.org
USA	Illinois	Memorial Medical Center	Springfield	https://www.memorialmedical.com
USA	Indiana	Lutheran Hospital of Fort Wayne	Ft Wayne	http://www.lutheranhospital.com
USA	Indiana	St. Vincent Hospital and Health Care Center	Indianapolis	https://www.stvincent.org
USA	Indiana	Indiana University Health	Indianapolis	http://iuhealth.org
USA	Iowa	Iowa Methodist Medical Center	Des Moines	http://www.unitypoint.org
USA	Iowa	Mercy Medical Center-Des Moines	Des Moines	https://www.mercydesmoines.org
USA	Iowa	University of Iowa Hospitals and Clinics and Iowa City VA Medical Center	Iowa City	https://uihc.org
USA	Kansas	University of Kansas Hospital	Kansas City	http://www.kumed.com
USA	Kansas	Saint Luke's Health System	Kansas City	https://www.saintlukeshealthsystem.org
USA	Kentucky	University of Kentucky Medical	Lexington	http://ukhealthcare.uky.edu

		Center		
USA	Kentucky	Jewish Hospital	Louisville	http://www.kentuckyonehealth.org
USA	Louisiana	Ochsner Foundation Hospital	New Orleans	https://www.ochsner.org
USA	Louisiana	Tulane Medical Center	New Orleans	http://tulanehealthcare.com
USA	Louisiana	Willis-Knighton Medical Center	Shreveport	http://www.wkhs.com
USA	Maine	Maine Medical Center Transplant Program	Portland	https://mainehealth.org
USA	Maryland	University of Maryland Medical System	Baltimore	http://www.umm.edu
USA	Maryland	Johns Hopkins Hospital	Baltimore	https://www.hopkinsmedicine.org
USA	Maryland	Walter Reed National Military Medical Center at Bethesda	Bethesda	http://www.wrnmmc.capmed.mil
USA	Massachusetts	Massachusetts General Hospital	Boston	http://www.massgeneral.org
USA	Massachusetts	Brigham and Women's Hospital	Boston	http://www.brighamandwomens.org
USA	Massachusetts	Boston Children's Hospital	Boston	http://www.childrenshospital.org
USA	Massachusetts	Beth Israel Deaconess Medical Center	Boston	http://www.bidmc.org
USA	Massachusetts	Boston Medical Center	Boston	https://www.bmc.org
USA	Massachusetts	Tufts Medical Center	Boston	https://www.tuftsmedicalcenter.org
USA	Massachusetts	Lahey Clinic Medical Center	Burlington	http://www.lahey.org
USA	Massachusetts	Baystate Medical Center	Springfield	https://www.baystatehealth.org
USA	Massachusetts	UMass Memorial Medical Center	Worcester	https://www.umassmemorialhealthcare.org
USA	Michigan	University of Michigan Medical Center	Ann Arbor	http://www.uofmhealth.org
USA	Michigan	Children's Hospital of Michigan	Detroit	https://www.dmc.org
USA	Michigan	Henry Ford Hospital	Detroit	https://www.henryford.com
USA	Michigan	Harper University Hospital Detroit Medical Center	Detroit	https://www.dmc.org
USA	Michigan	St. John Hospital and Medical Center	Detroit	http://www.stjohnprovidence.org
USA	Michigan	Helen DeVos Children's Hospital	Grand Rapids	https://www.spectrumhealth.org
USA	Michigan	Mercy Health Saint Mary's	Grand Rapids	http://www.smhealthcare.org
USA	Michigan	William Beaumont Hospital	Royal Oak	http://www.beaumont.edu
USA	Minnesota	University of Minnesota Medical Center, Fairview	Minneapolis	https://www.mhealth.org
USA	Minnesota	Abbott Northwestern Hospital	Minneapolis	https://www.allinahealth.org
USA	Minnesota	Hennepin County Medical Center	Minneapolis	http://www.hcmc.org
USA	Mississippi	The University of Mississippi Medical Center	Jackson	https://www.ummchealth.com
USA	Missouri	Children's Mercy Hospital	Kansas City	http://www.childrensmercy.org
USA	Missouri	St. Luke's Hospital of Kansas City	Kansas City	https://www.saintlukeshealthsystem.org
USA	Missouri	Research Medical Center	Kansas City	http://researchmedicalcenter.com
USA	Missouri	St. Louis Children's Hospital	St. Louis	http://www.stlouischildrens.org
USA	Missouri	Barnes-Jewish Hospital	St. Louis	https://www.barnesjewish.org
USA	Missouri	SSM Health Saint Louis University Hospital	St. Louis	http://www.ssmhealth.com
USA	Nebraska	The Nebraska Medical Center	Omaha	https://secure.nebraskamed.com
USA	Nevada	University Medical Center of Southern Nevada	Las Vegas	https://www.umcsn.com
USA	New Hampshire	Dartmouth-Hitchcock MC (Mary Hitchcock Memorial Hospital)	Lebanon	http://www.dartmouth-hitchcock.org
USA	New Jersey	Our Lady of Lourdes Medical Center	Camden	https://www.lourdesnet.org
USA	New Jersey	RWJ Barnabas Health	Edison, Rutherford	https://www.barnabashealth.org
USA	New Jersey	Hackensack University Medical Center	Hackensack	http://www.hackensackumc.org
USA	New Jersey	Saint Barnabas Medical Center	Livingston	https://www.barnabashealth.org
USA	New Jersey	Robert Wood Johnson	New Brunswick	http://www.rwjuh.edu
USA	New Mexico	UNM School of Medicine	Albuquerque	http://surgery.unm.edu
USA	New Mexico	Presbyterian Hospital	Albuquerque	https://www.phs.org
USA	New York	Albany Medical Center Hospital	Albany	http://www.amc.edu
USA	New York	Erie County Medical Center	Buffalo	http://www.ecmc.edu
USA	New York	North Shore University	Manhasset	https://www.northwell.edu

		Hospital/Northwell Health		
USA	New York	Westchester Medical Center	Mount Pleasant	http://westchestermedicalcenter.com
USA	New York	Mount Sinai Medical Center	New York City	http://www.mountsinai.org
USA	New York	New York-Presbyterian Hospital/Weill Cornell Medical Center	New York City	http://www.nyp.org
USA	New York	Montefiore Medical Center	New York City	http://www.montefiore.org
USA	New York	NY Presbyterian Hospital/Colombia Univ. Medical Center	New York City	http://www.nyp.org
USA	New York	New York University Medical Center	New York City	http://nyulangone.org
USA	New York	State University of New York, Downstate Medical Center	New York City	http://www.downstate.edu
USA	New York	Strong Memorial Hospital, University of Rochester Medical Center	Rochester	https://www.urmc.rochester.edu
USA	New York	University Hospital of State University of New York at Stony Brook	Stony Brook	https://www.stonybrookmedicine.edu
USA	New York	State University of New York, Upstate Medical University	Syracuse	http://www.upstate.edu
USA	North Carolina	University North Carolina Medical Center	Chapel Hill	http://www.uncmedicalcenter.org
USA	North Carolina	Carolinas Medical Center	Charlotte	http://www.carolinashealthcare.org
USA	North Carolina	Duke University Hospital	Durham	https://www.dukehealth.org
USA	North Carolina	Vidant Health	Greenville	https://www.vidanthealth.com
USA	North Carolina	Wake Forest Baptist Medical Center	Winston-Salem	http://www.wakehealth.edu
USA	North Dakota	Sanford Bismark Medical Center, Sanford Medical Center Fargo	Bismark, Fargo	http://www.sanfordhealth.org
USA	Ohio	University of Cincinnati Medical Center	Cincinnati	http://uchealth.com
USA	Ohio	The Christ Hospital	Cincinnati	https://www.thechristhospital.com
USA	Ohio	Children's Hospital Medical Center	Cincinnati	https://www.cincinnatichildrens.org
USA	Ohio	The Cleveland Clinic Foundation	Cleveland	https://my.clevelandclinic.org
USA	Ohio	University Hospitals of Cleveland	Cleveland	http://www.uhhospitals.org
USA	Ohio	Ohio State University Medical Center	Columbus	https://wexnermedical.osu.edu
USA	Ohio	University of Toledo Medical Center	Toledo	http://uthealth.utoledo.edu
USA	Oklahoma	Integris Baptist Medical Center	Oklahoma City	http://integrisok.com
USA	Oklahoma	OU Medical Center	Oklahoma City	https://www.oumedicine.com
USA	Oklahoma	Children's Hospital of Oklahoma	Oklahoma City	https://www.oumedicine.com
USA	Oklahoma	Saint Francis Hospital	Tulsa	https://www.saintfrancis.com
USA	Oklahoma	St John Medical Center	Tulsa	http://www.stjohnhealthsystem.com
USA	Oregon	Legacy Good Samaritan Hospital and Medical Center	Portland	http://www.legacyhealth.org
USA	Oregon	Oregon Health and Science University	Portland	http://www.ohsu.edu
USA	Pennsylvania	Lehigh Valley Hospital	Allentown	https://www.lvhn.org
USA	Pennsylvania	Geisinger Medical Center	Danville	https://www.geisinger.org
USA	Pennsylvania	UPMC Hamot	Erie	http://www.upmc.com
USA	Pennsylvania	Pinnacle Health System at Harrisburg Hospital	Harrisburg	http://www.pinnaclehealth.org
USA	Pennsylvania	Penn State Milton S Hershey Medical Center	Hershey	http://hmc.pennstatehealth.org
USA	Pennsylvania	Thomas Jefferson University Hospital	Philadelphia	http://hospitals.jefferson.edu
USA	Pennsylvania	Temple University Hospital	Philadelphia	http://kidney.templehealth.org
USA	Pennsylvania	Hospital of the University of Pennsylvania	Philadelphia	https://www.pennmedicine.org
USA	Pennsylvania	Albert Einstein Medical Center	Philadelphia	https://www.einstein.edu
USA	Pennsylvania	Children's Hospital of	Philadelphia	http://www.chop.edu

		Philadelphia		
USA	Pennsylvania	Hahnemann University Hospital	Philadelphia	https://www.hahnemannhospital.com
USA	Pennsylvania	Allegheny General Hospital	Pittsburg	https://www.ahn.org
USA	Pennsylvania	Children's Hospital of Pittsburgh of UPMC	Pittsburg	http://www.chp.edu
USA	Pennsylvania	University of Pittsburg Medical Center	Pittsburg	http://www.upmc.com
USA	Pennsylvania	Crozer-Chester Medical Center	Upland	http://www.crozerkeystone.org
USA	Pennsylvania	The Lankenau Hospital	Wynnewood	https://www.mainlinehealth.org
USA	Rhode Island	Rhode Island Hospital	Providence	https://www.lifespan.org
USA	South Carolina	Medical University of South Carolina	Charleston	http://www.muschealth.org
USA	South Dakota	Avera McKennan Hospital	Sioux Falls	http://www.avera.org
USA	Tennessee	Erlanger Medical Center	Chattanooga	http://www.erlanger.org
USA	Tennessee	University of Tennessee Medical Center at Knoxville	Knoxville	http://www.utmedicalcenter.org
USA	Tennessee	Methodist University Hospital	Memphis	http://www.methodisthealth.org
USA	Tennessee	Centennial Medical Center	Nashville	http://tristarcentennial.com
USA	Tennessee	St. Thomas Hospital	Nashville	https://www.sthealth.com
USA	Tennessee	Vanderbilt University Medical Center and Nashville VA Medical Center	Nashville	https://www.vanderbilthealth.com
USA	Texas	UT Southwestern Medical Center/William P. Clements Jr. University Hospital	Dallas	http://www.utswmedicine.org
USA	Texas	Children's Medical Center of Dallas	Dallas	https://www.childrens.com
USA	Texas	Medical City Dallas Hospital	Dallas	http://medicalcityhospital.com
USA	Texas	Methodist Dallas Medical Center	Dallas	http://www.methodisthealthsystem.org
USA	Texas	Baylor University Medical Center	Dallas	http://www.baylorhealth.com
USA	Texas	Las Palmas Medical Center	El Paso	http://laspalmasdelsolhealthcare.com
USA	Texas	Medical City Fort Worth	Fort Worth	http://medicalcityfortworth.com
USA	Texas	Baylor All Saints Medical Center	Fort Worth	http://www.baylorhealth.com
USA	Texas	Texas Health Harris Methodist Fort Worth Hospital	Fort Worth	https://www.texashealth.org
USA	Texas	University of Texas Medical Branch at Galveston	Galveston	https://www.utmbhealth.com
USA	Texas	Houston Methodist Hospital	Houston	http://www.houstonmethodist.org
USA	Texas	CHI St. Luke's Health Baylor College of Medicine Medical Center	Houston	http://www.chistlukeshealth.org
USA	Texas	Texas Children's Hospital	Houston	https://www.texaschildrens.org
USA	Texas	Memorial Hermann Hospital, University of Texas at Houston	Houston	http://www.memorialhermann.org
USA	Texas	University Hospital, University of Texas Health Science Center	San Antonio	http://www.universitytransplantcenter.com
USA	Texas	Methodist Specialty and Transplant Hospital	San Antonio	http://sahealth.com
USA	Texas	Christus Santa Rosa Hospital Medical Center	San Antonio	https://www.christushealth.org
USA	Texas	Scott and White Memorial Hospital	Temple	http://www.sw.org
USA	Texas	East Texas Medical Center	Tyler	https://www.etmc.org
USA	Utah	Intermountain Medical Center	Murray	https://intermountainhealthcare.org
USA	Utah	University of Utah Medical Center	Salt Lake City	https://healthcare.utah.edu
USA	Vermont	The University of Vermont Medical Center	Burlington	https://www.uvmhealth.org
USA	Virginia	University of Virginia Health Sciences Center	Charlottesville	https://uvahealth.com
USA	Virginia	Inova Fairfax Hospital	Falls Church	https://www.inova.org
USA	Virginia	Sentara Norfolk General Hospital	Norfolk	https://www.sentara.com
USA	Virginia	Children's Hospital of the King's Daughters	Norfolk	http://www.chkd.org

USA	Virginia	Medical College of Virginia Hospitals	Richmond	https://www.vcuhealth.org
USA	Virginia	Henrico Doctor's Hospital	Richmond	http://hcavirginia.com
USA	Washington	University of Washington Medical Center	Seattle	http://www.uwmedicine.org
USA	Washington	Seattle Children's Hospital	Seattle	http://www.seattlechildrens.org
USA	Washington	Swedish Medical Center	Seattle	http://www.swedish.org
USA	Washington	Virginia Mason Medical Center	Seattle	https://www.virginiamason.org
USA	Washington	Providence Sacred Heart Medical Center & Children's Hospital	Spokane	http://washington.providence.org
USA	West Virginia	Charleston Area Medical Center	Charleston	http://www.camc.org
USA	Wisconsin	University of Wisconsin Hospital and Clinics	Madison	http://www.uwhealth.org
USA	Wisconsin	Aurora St. Luke's Medical Center	Milwaukee	https://www.aurorahealthcare.org
USA	Wisconsin	Froedtert Memorial Lutheran Hospital	Milwaukee	http://www.froedtert.com
USA	Wisconsin	Children's Hospital of Wisconsin	Milwaukee	http://www.chw.org
USA	USA	National Kidney Foundation	agency	https://www.kidney.org
USA	USA	UNOS/Transplant Living	agency	https://www.unos.org
USA	USA	National Kidney Registry	agency	http://www.kidneyregistry.org
USA	USA	American Transplant Foundation	agency	http://www.americantransplantfoundation.org
USA	USA	Donate Life America	agency	https://www.donatelife.net
UK	Ireland	Belfast City Hospital	Belfast	http://www.belfasttrust.hscni.net
UK	England	Queen Elizabeth Hospital Birmingham	Birmingham	https://www.uhb.nhs.uk
UK	England	Bristol Southmead Hospital	Bristol	https://www.nbt.nhs.uk
UK	England	Cambridge Addenbrooke's Hospital	Cambridge	http://www.cuh.org.uk
UK	Wales	Cardiff University Hospital of Wales	Cardiff	http://www.cardiffandvaleuhb.wales.nhs.uk
UK	England	Coventry University Hospital	Coventry	http://www.uhcw.nhs.uk
UK	Scotland	Edinburgh Royal Infirmary	Edinburgh	http://www.nhslothian.scot.nhs.uk
UK	Scotland	Queen Elizabeth University Hospital Glasgow	Glasgow	http://www.nhsggc.org.uk
UK	England	Leeds St James's University Hospital	Leeds	http://www.leedsth.nhs.uk
UK	England	Royal Liverpool University Hospital	Liverpool	http://www.rlbuht.nhs.uk
UK	England	Guy's Hospital	London	http://www.guysandstthomas.nhs.uk
UK	England	St George's Hospital	London	https://www.stgeorges.nhs.uk
UK	England	The Royal Free Hospital	London	https://www.royalfree.nhs.uk
UK	England	The Royal London Hospital	London	http://bartshealth.nhs.uk
UK	England	West London Renal and Transplant Centre	London	https://www.imperial.nhs.uk
UK	England	Manchester Royal Infirmary	Manchester	http://www.cmft.nhs.uk
UK	England	Newcastle Freeman Hospital	Newcastle	http://www.newcastle-hospitals.org.uk
UK	England	Nottingham City Hospital	Nottingham	https://www.nuh.nhs.uk
UK	England	Oxford Churchill Hospital	Oxford	http://www.ouh.nhs.uk
UK	England	Plymouth Derriford Hospital	Plymouth	https://www.plymouthhospitals.nhs.uk
UK	England	Sheffield Northern General Hospital	Sheffield	http://www.sth.nhs.uk
UK	England	Other Leaflets from Sheffield Website		http://www.sth.nhs.uk
UK	England	Great Ormond Street Hospital	London	http://www.gosh.nhs.uk
UK	England	Evelina London Children's Hospital (Guy's)	London	http://www.evelinalondon.nhs.uk
UK	England	Leeds Children's Hospital	Leeds	http://www.leedsth.nhs.uk
UK	England	Nottingham Children's Hospuital	Nottingham	http://www.emeesykidney.nhs.uk
UK	agency	Organ Donation (part of NHS website)		https://www.organdonation.nhs.uk
UK	agency	The Renal Association (link to PDF)		http://www.renal.org
UK	agency	Give a Kidney		http://www.giveakidney.org
UK	agency	NHS Blood and Transport		https://www.nhsbt.nhs.uk

UK	agency	NHS Choices		http://www.nhs.uk
UK	agency	Kidney Research UK		https://www.kidneyresearchuk.org
UK	agency	Living Kidney Donation		http://livingkidneydonation.co.uk
UK	agency	Human Tissue Authority		https://www.hta.gov.uk
Australia	New South Wales	John Hunter Hospital	Newcastle	http://www.hnehealth.nsw.gov.au
Australia	New South Wales	Prince of Wales Hospital	Sydney	http://www.princeofwalesprivatehospital.com.au
Australia	New South Wales	Royal North Shore Hospital	Sydney	http://www.nslhd.health.nsw.gov.au
Australia	New South Wales	Statewide Renal Services	?	https://www.health.qld.gov.au
Australia	New South Wales	Sydney Childrens Hospital	Sydney	http://www.schn.health.nsw.gov.au
Australia	New South Wales	The Childrens Hospital Westmead	Sydney	http://www.schn.health.nsw.gov.au
Australia	New South Wales	Westmead Hospital	Sydney	http://www.wslhd.health.nsw.gov.au
Australia	Queensland	Queensland Renal Transplant Service		https://metrosouth.health.qld.gov.au
Australia	South Australia	Central Northern Adelaide Renal		http://www.sahealth.sa.gov.au
Australia	Victoria	Alfred Hospital	Melbourne	https://www.alfredhealth.org.au
Australia	Victoria	Austin Hospital	Melbourne	http://www.au
Australia	Victoria	Monash Medical (Adults)	Melbourne	http://www.monashhealth.org
Australia	Victoria	Monash Medical (Paediatric)	Melbourne	https://monashchildrenshospital.org
Australia	Victoria	Royal Childrens Hospital	Melbourne	http://www.rch.org.au
Australia	Victoria	Royal Melbourne Hospital	Melbourne	https://www.thermh.org.au
Australia	Western Australia	Fiona Stanley Hospital	Perth	http://www.fsh.health.wa.gov.au
Australia	Western Australia	Sir Charles Gairdner Hospital	Perth	http://www.scgh.health.wa.gov.au
Australia	agency	Kidney Health Australia		http://kidney.org.au
Australia	agency	Donate Life Australia		http://www.donatelife.gov.au
Australia	agency	Transplant Australia		https://transplant.org.au
Australia	agency	The Department of Health		http://www.health.gov.au
Australia	agency	Renal Resource Centre (ACI/Kidney Health Australia, PDF)		https://www.aci.health.nsw.gov.au
Australia	agency	ABC News (article)		http://www.abc.net.au
Australia	agency	The Conversation (article)		http://theconversation.com
Australia	agency	Organ Donation and Transplant Foundation of WA		http://www.odatwa.org
KFOC – Kidney Foundation of Canada; NHS – National Health Services				

Appendix C: List of Participating Centres

Canadian transplant centres

Dr. Amit X Garg
London Health Sciences Centre
London Ontario, N6A5W9

Dr. Liane Feldman
Royal Victoria Hospital
Montreal, Quebec, H4A 3J1

Dr. Darin Treleaven
St. Joseph's Hospital
Hamilton, Ontario, L8N 4A6

Dr. Charmaine Lok
University Health Network
Toronto, Ontario, M5G 2C4

Dr. Mauricio Monroy-Cuadros
Foothills Medical Centre
Calgary, Alberta, T2N 2T9

Dr. Chris Nguan
Vancouver General Hospital
Vancouver, British Columbia, V5Z 1M9

Dr. Christine Dipchand
Queen Elizabeth II
Halifax, Nova Scotia, B3H 2Y9

Dr. Greg Knoll
Ottawa General Hospital
Ottawa, Ontario, K1H 8L6

Dr. Ramesh Prasad
St. Michael's Hospital
Toronto, Ontario, M5B 1W8

Drs. Martin Karpinski and Leroy Storsley
Winnipeg Health Sciences Centre
Winnipeg, Manitoba, R3A 1R9

Dr. Scott Klarenbach
University of Alberta
Edmonton, Alberta, T6G 2R3

Australian transplant centres (these centres were combined due to sample size)

Dr. Neil Boudville
On behalf of
Monash Medical Centre Clayton, Clayton, Victoria, 3168
Fremantle Hospital, Fremantle, Western Australia, 6160
Royal Perth Hospital, Perth, Western Australia, 6000
Sir Charles Gairdner Hospital, Nedlands, Perth, Westeran Australia, 6009
Royal Adelaide Hospital, Adelaide, Southern Australia, 5000

Appendix D: Research Ethics Board approval for prospective cohort study

Office of Research Ethics

The University of Western Ontario
Room 4180 Support Services Building, London, ON, Canada N6A 5C1
Telephone: (519) 661-3036 Fax: (519) 850-2466 Email: ethics@uwo.ca
Website: www.uwo.ca/research/ethics

Use of Human Subjects - Ethics Approval Notice

Principal Investigator: Dr. A.X. Garg
Review Number: 15974E **Review Level:** Expedited
Review Date: June 09, 2009
Protocol Title: Long-term Effects of Becoming a Living Kidney Donor Study
Department and Institution: Nephrology, London Health Sciences Centre
Sponsor: CIHR-CANADIAN INSTITUTE OF HEALTH RESEARCH
Ethics Approval Date: June 09, 2009 **Expiry Date:** December 31, 2015
Documents Reviewed and Approved: UWO Protocol, Patient Letter of Information and Consent for Donors and Non-Donors (dated April 27, 2009), Patient Letter of Information and Consent for Donors and Non-Donors (3 Months) (dated April 27, 2009), Patient Letter of Information and Consent for Kidney Transplant Recipient (dated April 27, 2009), Genetic Sub-study Letter of Information and Consent (dated March 31, 2009), Sub-Study: Pregnancy Outcomes in Living Kidney Donors Patient Letter of Information and Consent (dated March 26, 2009), Pregnancy Sub-study Friendly Reminder Postcard. Release of Medical Information Form. Retention Cards.
Documents Received for Information: Protocol - February 9, 2009

This is to notify you that The University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects (HSREB) which is organized and operates according to the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans and the Health Canada/ICH Good Clinical Practice Practices: Consolidated Guidelines; and the applicable laws and regulations of Ontario has reviewed and granted approval to the above referenced study on the approval date noted above. The membership of this REB also complies with the membership requirements for REB's as defined in Division 5 of the Food and Drug Regulations.

The ethics approval for this study shall remain valid until the expiry date noted above assuming timely and acceptable responses to the HSREB's periodic requests for surveillance and monitoring information. If you require an updated approval notice prior to that time you must request it using the UWO Updated Approval Request Form.

During the course of the research, no deviations from, or changes to, the protocol or consent form may be initiated without prior written approval from the HSREB except when necessary to eliminate immediate hazards to the subject or when the change(s) involve only logistical or administrative aspects of the study (e.g. change of monitor, telephone number). Expedited review of minor change(s) in ongoing studies will be considered. Subjects must receive a copy of the signed information/consent documentation.

Investigators must promptly also report to the HSREB:

a) changes increasing the risk to the participant(s) and/or affecting significantly the conduct of the study;
b) all adverse and unexpected experiences or events that are both serious and unexpected;
c) new information that may adversely affect the safety of the subjects or the conduct of the study.

If these changes/adverse events require a change to the information/consent documentation, and/or recruitment advertisement, the newly revised information/consent documentation, and/or advertisement, must be submitted to this office for approval.

Members of the HSREB who are named as investigators in research studies, or declare a conflict of interest, do not participate in discussion related to, nor vote on, such studies when they are presented to the HSREB.

Appendix E: List of first and last procedures per donor

	Number (%)	
Procedure	**First contact***	**Approval***
Intermediate assessment	353 (28%)	90 (7%)
Biochemistry	175 (14%)	–
Cytology	152 (12%)	–
General consult	138 (11%)	–
Chest x-ray	109 (9%)	–
Electrocardiography	96 (8%)	–
Urinalysis	54 (4%)	–
Counselling/psychiatry	50 (4%)	74 (6%)
Immunohematology	43 (3%)	–
Ultrasound	35 (3%)	–
Nuclear medicine	27 (2%)	–
Surgery/urology consult	–	913 (73%)
Nephrology consult	–	129 (10%)
Computed tomography	24 (2%)	–
Cardiac evaluation	–	23 (2%)
General surgery consult	–	14 (1%)
Hematology consult	–	<6 (0%)
Pathology	–	<6 (0%)
Gastroenterology	–	<6 (0%)
Neurology	–	<6 (0%)
Respirology	–	<6 (0%)
Endocrinology	–	0 (0%)
Musculoskeletal consult	–	0 (0%)
Rheumatology	–	0 (0%)
Echocardiography	–	–
Stress test	–	–
Plastic surgery	–	–
Pulmonary function	–	–

*visits not allowed to be a first contact date or approval date are indicated by "–"

Appendix F: STROBE Checklist of items that should be included in reports of cohort studies

	Item #	Recommendation	Section
Title	1	(*a*) Indicate the study's design with a commonly used term in the title	Title page
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Background
Objectives	3	State specific objectives, including any prespecified hypotheses	Background
Methods			
Study design	4	Present key elements of study design early in the paper	Methods
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Methods
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Methods
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Methods
Bias	9	Describe any efforts to address potential sources of bias	Methods
Study size	10	Explain how the study size was arrived at	N/A
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Methods
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Methods
		(*b*) Describe any methods used to examine subgroups and interactions	Methods
		(*c*) Explain how missing data were addressed	Methods
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Methods

		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 8
		(b) Indicate number of participants with missing data for each variable of interest	Table 8, Results
		(c) Summarise follow-up time (eg, average and total amount)	Table 8, Results
Outcome data	15*	Report numbers of outcome events or summary measures over time	Table 9-Table 13
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 9-Table 13
		(*b*) Report category boundaries when continuous variables were categorized	Table 9-Table 13
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Table 11
Discussion			
Key results	18	Summarise key results with reference to study objectives	Discussion
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Discussion
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Discussion
Generalisability	21	Discuss the generalisability (external validity) of the study results	Discussion
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Title page

Appendix G: STROBE Checklist of items that should be included in reports of cohort studies

	Item	Recommendation	Section
Title	1	(*a*) Indicate the study's design with a commonly used term in the title	Title page
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Background
Objectives	3	State specific objectives, including any prespecified hypotheses	Background
Methods			
Study design	4	Present key elements of study design early in the paper	Methods
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Methods
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Methods, Appendix 3-4
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Methods
Bias	9	Describe any efforts to address potential sources of bias	N/A
Study size	10	Explain how the study size was arrived at	N/A
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Methods
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Methods
		(*b*) Describe any methods used to examine subgroups and interactions	Methods
		(*c*) Explain how missing data were addressed	Methods
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Methods and Figure 1
		(b) Give reasons for non-participation at each stage	N/A

		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
		(c) Summarise follow-up time (eg, average and total amount)	Figure 2, Tables 2-3
Outcome data	15	Report numbers of outcome events or summary measures over time	Tables 2-3, Appendix 6
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Tables 2-3, Appendix 6
		(*b*) Report category boundaries when continuous variables were categorized	Tables 1-3, Appendix 6
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Tables 1-3, Appendix 6
Discussion			
Key results	18	Summarise key results with reference to study objectives	Discussion
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Discussion
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Discussion
Generalisability	21	Discuss the generalisability (external validity) of the study results	Discussion
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Title page

Appendix H: List of OHIP and CIHI codes for dialysis status and comorbidity

Database	Type of code	Codes
Dialysis		
OHIP	Feecodes	"R849" "G323" "G336" "G325" "G326" "G860" "G862" "G863" "G865" "G866" "R825" "R826" "R827" "R833" "R840" "R851" "G330" "G331" "G332" "G861" "G864" "R852" "G082" "G083" "G085" "G090" "G091" "G092" "G093" "G094" "G095" "G096" "G294" "G295" "G333" "H540" "H740"
CIHI	ICD-9	"V451" "V560" "V568" "36104"
	ICD-10	"T824" "Y602" "Y612" "Y622" "Y841" "Z49" "Z992" "N180" "E1022" "E1023" "E1122" "E1123" "E1322" "E1323" "E1422" "E1423"
	procedure codes	"5127" "5195" "6698"
	intervention codes	"7SC59QD" "1KY76" "1PZ21"
Hypertension		
OHIP	diagnosis codes	"401" "402" "403" "404" "405"
CIHI	ICD-9	"401" "402" "403" "404" "405"
	ICD-10	"I10" "I11" "I12" "I13" "I15"
Cancer		
OHIP	diagnosis codes	"140" "141" "142" "143" "144" "145" "146" "147" "148" "149" "150" "151" "152" "153" "154" "155" "156" "157" "158" "159" "160" "161" "162" "163" "164" "165" "170" "171" "172" "173" "174" "175" "179" "180" "181" "182" "183" "184" "185" "186" "187" "188" "189" "190" "191" "192" "193" "194" "195" "196" "197" "198" "199" "200" "201" "202" "203" "204" "205" "206" "207" "208"
CIHI	ICD-9	"V10" "140" "141" "142" "143" "144" "145" "146" "147" "148" "149" "150" "151" "152" "153" "154" "155" "156" "157" "158" "159" "160" "161" "162" "163" "164" "165" "170" "171" "172" "173" "174" "175" "176" "179" "180" "181" "182" "183" "184" "185" "186" "187" "188" "189" "190" "191" "192" "193" "194" "1950" "1951" "1952" "1953" "1954" "1955" "1958" "196" "197" "198" "1990" "1991" "2000" "2001" "2002" "2008" "2010" "2011" "2012" "2014" "2015" "2016" "2017" "2019" "2020" "2026" "2028" "2029" "203" "204" "205" "206" "207" "208" "230" "231" "232" "233" "234"
	ICD-10	"80003" "80006" "80013" "80023" "80033" "80043" "80102" "80103" "80106" "80113" "80123" "80203" "80213" "83123" "87202" "87203" "959" "965" "966" "967" "968" "969" "970" "971" "980" "982" "984" "985" "986" "987" "988" "989" "990" "991" "993" "C00" "C01" "C02" "C03" "C04" "C05" "C06" "C07" "C08" "C09" "C10" "C11" "C12" "C13" "C14" "C15" "C16" "C17" "C18" "C19" "C20" "C21" "C22" "C23" "C24" "C25" "C26" "C30" "C31" "C32" "C33" "C34" "C37" "C38" "C39" "C40" "C41" "C43" "C44" "C45" "C46" "C47" "C48" "C49" "C50" "C51" "C52" "C53" "C54" "C55" "C56" "C57" "C58" "C60" "C61" "C62" "C63" "C64" "C65" "C66" "C67" "C68" "C69" "C70" "C71" "C72" "C73" "C74" "C75" "C76" "C77" "C78" "C79" "C80" "C81" "C82" "C83" "C84" "C85" "C90" "C91" "C92" "C93" "C94" "C95" "C96" "C97" "D00" "D01" "D02" "D03" "D04" "D05" "D06" "D07" "D09"
Cardiovascular disease		
OHIP	feecodes (procedure)	"Z434" "R742" "R743" "N220" "R792" "R802" "R816" "R817" "R783" "R784" "R785" "R814" "R787" "R780" "R797" "R804"
CIHI	ICD-9	"39" "40" "41" "42" "43" "44" "45"
	ICD-10	"I"
	procedural codes	"4802" "4803" "4809" "481" "5024" "5034" "5125"
	intervention	"1IJ50" "1IJ76" "1KA76" "1KG76"

	codes	
Anemia		
CIHI	ICD-9	"285"
	ICD-10	"D509"
Ischemic heart disease/coronary artery disease		
ICD-9	"414"	
ICD-10	"I120" "I121" "I122" "I123" "I124" "I125"	
Diabetes		
OHIP	fee codes	"K045" " K046" " K029" " K030" " Q040"
CIHI	ICD-9	"250"
	ICD-10	"E10" "E11" "E13" "E14"
Anxiety/depression		
OHIP	diagnostic codes	"311"
CIHI	ICD-9	"2962" "2963" "2966" "3000" "3002" "3003" "3004" "309" "311"
	ICD-10	"F063" "F064" "F204" "F313" "F314" "F315" "F32" "F33" "F341" "F400" "F401" "F402" "F408" "F409" "F410" "F411" "F412" "F413" "F418" "F419" "F420" "F421" "F422" "F428" "F429" "F430" "F431" "F432"
Heart failure		
OHIP	Fee codes	"R701" "R702" "Z429"
	diagnostic codes	"428"
CIHI	ICD-9	"425" "5184" "514" "428"
	ICD-10	"I099" "I420" "I425" "I426" "I427" "I428" "I429" "I43" "I500" "I501" "I509" "I255" "J81"
	procedure codes	"4961" "4962" "4963" "4964"
	intervention codes	"IHP53" "IHP55" "1HZ53GRFR" "1HZ53LAFR" "1HZ53SYFR"

OHIP – Ontario Health Insurance Plan; CIHI – Canadian Institute for Health Information (same-day surgery and discharge abstract database); ICD – International Statistical Classification of Diseases and Related Health Problems medical classification (ICD-9 before 2002; IHD/CAD – ischemic heart disease/coronary artery disease

Appendix I: Characterizing the living donor evaluation process

We captured all OHIP physician and laboratory billings for up to four years prior to donation (1826 unique billing codes) and obtained the description for each billing code. Based on these descriptions and prior validation studies, we grouped these codes into procedures based on *a priori* judgement (Step I in Table below). We categorized remaining billing codes (observed >5 times for privacy requirements) based on the descriptions (Step II in Table below). We then assigned general billing codes to a procedure based on the main speciality of the billing physician (obtained from the ICES Physician Database, IPDB) (Step III in Table below). We then assigned remaining general billing codes to a procedure based on other procedures performed on the same day (Step IV in Table below). Next, we combined similar procedures into a single category (Step V in Table below). Finally, we considered similar procedures performed on the same day to belong to a single category if we believed the procedures were related (i.e., we combined a billing code categorized as "pain management" on the same day as a billing code categorized as "anesthesia" as "anesthesia") (Step VI in Table below).

In order to identify the date of first contact (the date the donor started the evaluation), we set up specific rules independent of the data to decide which procedures would be considered part of the living donor evaluation process. For example, all nephrology consults and nuclear medicine exams were considered part of the evaluation since a healthy non-donor would be unlikely to have these billed if not part of the evaluation. Any procedure performed within 14 days of donation was considered part of the pre-admission visit and not a unique procedure in its own right (i.e., a nephrology consult during this time is likely not the main nephrology consult). The only exception to this rule is the surgical consult, which is allowed by some transplant programs to occur this late in the evaluation process. We provide the full list of rules in Appendix J.

Step I – procedures defined *a priori* (n=1726)	
Procedure	OHIP billing codes
Nephrectomy	'S411', 'S423', 'S413', 'S415', 'S416', 'S420', 'S421', 'S436', 'E694', 'E753', 'E766', 'E767', 'E768', 'E792', 'S412'
Stress test	'G315', 'G174', 'G111', 'G112', 'G319', 'G582', 'G583', 'G584', 'J607', 'J608', 'J807', 'J808', 'J809', 'J866', 'J609', 'J666'
Urinalysis	'L253', 'L254', 'L633', 'L641', 'G001', 'G002', 'G003', 'G004', 'G481', 'G006', 'G007', 'G008', 'G009', 'G010'
Biochemistry	'L065', 'L067', 'L068', 'L204', 'L226', 'L004', 'L005', 'L111', 'L112', 'L093', 'L634'

Renal biopsy	'Z601', 'E820'
Ultrasound	'J128', 'J135', 'J138', 'J162', 'J163', 'J428', 'J435', 'J438', 'J462', 'J463', 'J205', 'J505'
Nephrology consult	'A135', 'A136', 'A138', 'A435', 'C435', 'C135', 'C136', 'A133', 'A134', 'A131', 'C133', 'C134', 'C131', 'A161', 'A163', 'A164', 'A165', 'A166', 'A168', 'C132', 'C137', 'C139', 'C101', 'C138', 'G860', 'G323', 'G333', 'E083', 'H540'
Urology consult	'A355', 'A356', 'A935', 'A353', 'A354', 'C355', 'C356', 'C935', 'C353', 'C354'
Echocardiography	'G560', 'G561', 'G562', 'G566', 'G567', 'G568', 'G570', 'G571', 'G572', 'G574', 'G575', 'G576', 'G577', 'G578', 'G581'
Counselling	'K013', 'K014', 'K033', 'K040', 'K041'
Surgery consultation	'A095', 'A096', 'A935', 'A093', 'A094', 'C095', 'C096', 'C935', 'C093', 'C094', 'C033', 'C034', 'A033', 'A034', 'A036', 'C035', 'C036'
Glucose tolerance test	'G498', 'L104'
Immunohematology	'L471', 'L482', 'L473', 'L490', 'L492', 'L493', 'L494', 'L495'
Histocompatibility test	'L582', 'L581', 'L583', 'L580'
Chest x-ray	'X090', 'X091', 'X092'
CT	'X231', 'X232', 'X233', 'X126', 'X409', 'X410'
MRI	'X451', 'X461'
Pyelogram	'X129', 'X130', 'X138'
Cystoscopy	'Z606', 'Z607'
Cancer screen (pap)	'G365', 'G394', 'E430', 'L812', 'L713'
Cancer screen (breast)	'X184', 'X185', 'X186', 'X187', 'X172', 'X178','Z139','Z143'
Cancer screen (PSA)	'L354', 'L358'
Cancer screen (FOBT)	'Q150A', 'Q005A', 'Q118A', 'Q119A', 'Q120A', 'Q121A', 'Q122A' 'Q123A', 'Q152A', 'Q043A', 'L181', 'G004', 'L179', 'Q152', 'Z535', 'Z536', 'Z555', 'Z580'
Anaesthesiology consult	'A015', 'A016', 'C015', 'C016', 'A903'
SUBTOTALS	**1726 donors, 1826 unique billing codes, 215,363 rows**
Delete any feecodes that occur <6 times in the cohort	
SUBTOTALS	**1726 donors, 777 unique billing codes, 211,942 rows**

Step II – categorize remaining billing codes not yet assigned after Step I above (n=1726)	
Group A – billing codes that will be discarded later (not relevant to donation) but retained for the present (may be needed to explain other codes; for example, a biochemistry test performed on the same day as an emergency medicine visit is likely due to the emergency medicine visit, and not the donor evaluation)	
Procedure	**OHIP codes**
Allergies	'G196','G197','G200','G202','G209','G212'
Baby care	'A008','E411','G367','G378','J157','J158','J159','J160','J164','J168', 'J457','J458','J459','J460','J464','L103','L819','L820','P003','P004', 'P005','P006','P007','P008','P014','P016','P018','P023','P025','P030', 'P041'
STD counselling	'K028'
Biochemistry	'G871','G872','L718','L719'
Other CT	'X400','X401','X402','X404','X407','X412','X415'
Other surgical radiology	'X001','X004','X005','X007','X008','X016','X020','X025','X027','X028', 'X034','X035','X039','X045','X046','X048','X049','X050','X051','X052', 'X053','X054','X055','X056','X060','X063','X064','X065','X066','X067', 'X068','X069','X202','X203','X204','X205','X206','X207','X208','X210', 'X212','X215','X217','X218','X219','X220','X221','X224','X225','X226', 'X227','X228','X229','X230'
Emergency medicine	'K963','K996','Q090'
General eye care	'A111','A238','E140','E950','G219','Z847'
Fracture/casting	'F004','F008','F027','F061','Z203','Z204','Z213'

Diagnostic ultrasound of face	'J105','J108','J182','J183','J196','J200','J405','J482','J483','J496','J500'
Mandatory reporting to Ministry of Transportation	'K035'
MRI (other)	'X421','X425','X471','X475','X490','X492','X493','X495'
Some paediatric code	'A261','A263','A264','A265'
Sleep study	'J690','J889','J890','J895','J896'
Sports medicine or physical medicine	'A917','D016','E494','E552','E584','G370','G371'
Other/unknown	'H991','K037','K080','K683','M012','M060','N290','Q590','R110','R204','R205','R207','R302','R355','R416','R441','R495','R542','R687','G014','S120','S205','S247','S323','S738','S741','S745','S752','S754','S757','S772','S810','Z101','Z154','Z218','Z314','Z907'
Group B – lab tests referred to under the umbrella of "biochemistry"	
Procedure	**OHIP codes**
Radioassay	'L303','L309','L310','L315','L318','L319','L322','L325','L328','L329','L330','L331','L332','L334','L339','L340','L341','L345','L347','L606','L607','L608','L609'
Cholesterol	'L055','L117','L243'
Microbiology	'L622','L625','L626','L627','L628','L630','L636','L639','L643','L650','L653','L654','L655','L665','L668','L679','L683'
Immunology/virology	'L500','L501','L535','L544','L550','L551','L552','L553','L555','L575','L610','L842'
Hematology	'L393','L398','L419','L445','L451','L453','L462','L829'
General	'L018','L030','L031','L045','L046','L','L051','L053','L061','L066','L085','L107','L139','L146','L150','L157','L165','L169','L183','L191','L194','L208','L222','L223','L251','L252','L257','L266'
Cytology	'L700','L711','L733','L800','L810'
Group C – other codes deemed relevant and either started a new procedure category or merged in with Step I above	
Procedure	**OHIP codes**
Intermediate assessment	'A007'
Anesthesiology	'A013','A014','C012','C013','C014','C998','E001','E003','E004','E007','E010','E011','E017','E020','E022','E023','E400','E401'
Cardiac evaluation	'A605','A608','G268','G269','G297','G483','G489','J611','J613','J667','J804','J811','J813','J814','J867','Z440','Z442'
Counselling	'K002','K004','K005','K007','K016','K024','K025','K099','K190','K195','K197','K205'
CT	'X405','X406','X417'
Cholecystectomy	'E794','S287'
Some specialist consult	'A145'
Dermatology	'A023','A024','A025'
Electrocardiogram	'E451','G310','G313','G579','G650','G651','G652','G658','G682','G683','G690','G692','G693'
Diagnostic radiology	'A331','A335','J021','J022','X036','X037','X038','X100','X101','X103','X104','X106','X111','X113','X125','X181','X182','X189','X194','X200'
Endocrinology	'A154','A155','J817','J818','J820'
Gastroenterology consult	'A415','A418','C415','Z399','Z496','E702','J832','E705','E717','E719','E720','E740','E741','E746','E747','E749','Z499','Z527','Z543','Z570','Z571','Z787'
General consult	'A001','A003','A004','A005','C003','C004','C933','K131'
Hematology consult	'A615','A618'
Immunization	'A625','G538','G539','G590','G591','G842','G847','Q003','Q130'
Infectious disease consult	'A465,','L868'

Critical care	'G391','G395','G400','G401','G521','G523','G557'
MRI	'X455','X465','X487','X499'
Musculoskeletal consult	'J650','J651','J850','J851'
Nephrectomy	'E762','E769','G347','S435','S548'
Nephrology consult	'A160','C162','C165','C166'
Neurology evaluation	'A185','A188','G414','G418','G544','A044','A045'
Nuclear medicine	'J834','J835','J836','J838','J880','Y814','Y831'
Obstetrics/gynaecology	'A203','A204','A205','A206','C202','C203','G334','G399','X147','Z553','Z583','Z720','Z730','Z731','Z770'
Ophthamology	'A233','A234','A235','A253','G425','G432','G435','G436','G813','G818','G820','G853','G857','G858'
Orthopedic	'A063','A064','A065','A066','C062'
Otology/laryngology	'A243','A244','A245','G191','G403','G420','G440','G441','G442','G443','G451','G525','G526','G529','G530','G533','Z321'
Pain management	'C215','G220','G222','G223','G224','G227','G228','G231','G235','G238','G246','G247','G264'
Pathology	'A585','L720','L816','L817','L821','L840','L863','L864'
Physical medicine	'A315','A318','G455','G456','G457','G466','G999','H312'
Plastic surgery	'A083','A084','A085'
Pregnancy test	'G005'
Psychiatry	'A194','A195','C192','G478','K198','K199','K313','K623','Q020'
Pulmonary function	'E450','J301','J304','J306','J307','J310','J311','J313','J315','J318','J319','J322','J323','J327','J332','J333','J340','J860'
Skin lesion	'R031','R051','Z156','Z162','Z169','Z170'
Respirology	'A475','A478','Z296','Z299','Z327'
Rheumatology	'A485'
Sclerotherapy	'G536','G537'
Smoking cessation	'E079','K039','Q041','Q042'
General surgeon consult	'A035', 'A644','A645','C032'
Ultrasound	'J149','J161','J165','J193','J198','J201','J202','J203','J206','J425','J493','J498','J501','J502'
Urology consult	'C352','G193','G475','G476','G900'
Bone mineral density test	'X146','X153','X155'
Birth control surgery	'S626'
Home visit	'A901','B994'
Travel reimbursement	'K036'
Group D – cancer screening codes	
Procedure	**OHIP codes**
Colorectal	'Q005','Q133','Q142'
Fecal occult blood test	'Q150'
Breast	'Q002','Q131','R111','X201','J427','J127'
Papanicolaou test	'Q001','Q011','Q140'

Step III – categorize remaining billing codes not yet assigned after Step II using the main specialty associated with the usage of that code (n=1726)	
OHIP codes	**Procedure (using main specialty)**
'E082'	gastroenterology, urology, nephrology, respirology, orthopaedic, general surgery consult, general consult, internal medicine
'E078'	rheumatology, cardiac evaluation, nephrology, respirology,

	gastroenterology, internal medicine, neurology, hematology, endocrinology
'A473'	Respirology
'A183','A184'	Neurology
'H065','H101','H103','H123','H124','H131','H133','H153','H154','H151'	Emergency medicine
'Z611','Z113','Z116','Z117'	Dermatology
'Z611'	Ob/gyn, otolaryngology
'A888'	General consult
'A603','A604'	Cardiac evaluation
Any code	Nephrectomy (if on donation date)

Step IV – generic billing codes that will be assigned using any procedure already defined on the same day (i.e., a general code on the same day as a cardiac evaluation will be considered part of that cardiac evaluation) (n=1726)	
OHIP billing codes	**Procedure**
'Q012','G379','E409','E542','E545','E595','A613','C002','C109','C123','C124','C992','E005','Q016','C994','G118','G322','H103','H055','H123','H133','H134','H152','H153','H154','C122','H104','H132','Z153','J001','K070','A483','E078','K055','K992','K991','K994','K995','K998','K999','Q013','Q200','Q033','Z114','Z116','Z117','Z176','Z125','Z546','Z552','Z553','Z611', 'G700','G373','G372'	Various
'C122','Z176','R868','E595','A888'	Unknown/other
NOTE: the first part of this table was repeated in case there was >1 generic code on the same day	–

Step V – combining similar procedures (n=1726)	
Rule	**Procedure**
Nephrectomy codes the day before donation was assigned the donation date	Nephrectomy
Surgeon consult + urology consult	Surgeon/ urology consult
Counselling + psychiatry	Counselling/ psychiatry
NOTE: The same procedures on the same day are combined (rows are merged) and the total costs for the same procedure on the same day are summed	–
NOTE: Cancer screening tests are removed from dataset if they occurred >1 year before any other test	–

Step VI – combining similar procedures if done on the same day (n=1403)	
Procedure 1 (to be combined with [renamed as] Procedure 2)	**Procedure 2**
Pain management	Anesthesia
CT (discard)	CT
MRI (discard)	MRI
Dermatology	Skin lesion
Diagnostic ultrasound of face	Ultrasound
Pulmonary function	Allergies (discard)
Pulmonary function	Respirology
Pulmonary function	Smoking cessation
Pulmonary function	Sleep study (discard)

Smoking cessation	General consult
Smoking cessation	Intermediate assessment
Intermediate assessment	Gastroenterology
Intermediate assessment	Cardiac evaluation
Intermediate assessment	Pulmonary function
Intermediate assessment	Ophthalmology
Intermediate assessment	Obstetrics/gynaecology
Intermediate assessment	Otology/laryngology
Intermediate assessment	Sclerotherapy
Intermediate assessment	Pathology
Intermediate assessment	Sports medicine/physical medicine (discard)
Cytology	Obstetrics/gynaecology
Anaesthesiology	Cystoscopy
Obstetrics/gynaecology	Cancer screen (pap)
Plastic surgery	Skin lesion
Plastic surgery	Orthopaedic
Plastic surgery	Cancer screen (breast)
Diagnostic radiology	Ultrasound
Anaesthesiology	Sports medicine/physical medicine (discard)
Orthopaedic	Sports medicine/physical medicine (discard)
Physical medicine	Sports medicine/physical medicine (discard)
Plastic surgery	Sports medicine/physical medicine (discard)
Pain management	Sports medicine/physical medicine (discard)
Sleep study (discard)	Cardiac evaluation
Fecal occult blood test	Cancer screen (colorectal)
Gastroenterology	Cancer screen (colorectal)
Anaesthesiology	Cancer screen (colorectal)
Cytology	Cancer screen (colorectal)
Intermediate assessment	Cancer screen (colorectal)
Pathology	Infectious disease consult
Pathology	Cancer screen (pap)
Pathology	Cancer screen (breast)
Pathology	Cancer screen (colorectal)
Pathology	Fecal occult blood test
Pathology	Cytology
Pathology	Dermatology
Pathology	Gastroenterology
Pathology	Obstetrics/gynaecology
Pathology	Skin lesion
Respirology	Otology/laryngology
General consult	Cancer screen (pap)
Cytology	Cancer screen (pap)
General consult	Cancer screen (colorectal)
General consult	Cancer screen (breast)
General consult	Cancer screen (PSA)

General consult	Birth control surgery (discard)
Anaesthesiology	Birth control surgery (discard)
Intermediate assessment	Birth control surgery (discard)
Diagnostic radiology	Cancer screen (breast)
Diagnostic radiology	Cancer screen (colorectal)
Diagnostic radiology	Renal biopsy
Diagnostic radiology	Ultrasound
Diagnostic radiology	Chest x-ray
Diagnostic radiology	Diagnostic ultrasound of face (discard)
Diagnostic radiology	Other surgical radiology (discard)
Diagnostic radiology	Sports medicine (discard)
Diagnostic radiology	Emergency medicine (discard)
Diagnostic radiology	Bone mineral density test
Intermediate assessment	Cardiac evaluation
Intermediate assessment	Surgeon/urology consult
Intermediate assessment	Nephrology consult
Intermediate assessment	Counselling/psychiatry
Intermediate assessment	General surgery consult
Intermediate assessment	Neurology
Intermediate assessment	Anaesthesiology
Intermediate assessment	Orthopaedic
Intermediate assessment	Obstetrics/gynaecology
Intermediate assessment	Otology/laryngology
Intermediate assessment	Home visit
Intermediate assessment	Physical medicine
Intermediate assessment	Pain management
Intermediate assessment	Rheumatology
Intermediate assessment	Respirology
Any procedure <14 days prior to donation (except Surgeon/urology consult)	Pre-admission
Any procedure (verified through quality checks)	Fracture/casting
Any procedure (verified through quality checks)	Cholecystectomy
Any procedure (verified through quality checks)	General eye care (discard)
Any procedure (verified through quality checks)	Some paediatric code (discard)
Any biochemistry procedure	Biochemistry

Appendix J: Steps to identify donor's point of first contact

Rules to keep visit	**Procedures where rules are applied**
No rules (all are kept)	Nephrology consults
Last visit (i.e., most recent before nephrectomy)	Surgery/urology consult, preadmission
No rules (all are kept)	Nuclear medicine
4 months before nephrology consult or anytime thereafter	Cardiac evaluation
±6 months of any nephrology consult or surgeon/urology consult	- Lab tests *(urinalysis, biochemistry test, cytology, immunohematology)* - Diagnostic tests *(CT, ultrasound, echocardiography, ECG, MRI, chest x-ray, stress test, pulmonary function, pyelogram)* - Consults *(general consult, intermediate assessment, counselling/psychiatry, gastroenterology, surgery/urology consult, renal biopsy, cystoscopy, endocrinology, hematology, musculoskeletal, neurology, pathology, plastic surgery, respirology, rheumatology)*
±6 months of any nephrology consult or surgeon/urology consult AND associated with a physician who previously billed a code related to donation or a surgeon/urology consult	General surgeon consult
Within 30 days before a previously retained procedure	Counselling/psychiatry, cardiac evaluation
Within 1 year of nephrectomy	Cancer screen (pap, breast)
Within 3 years of nephrectomy	Cancer screen (colorectal)
Rules to delete visit	
No rules (all remaining are discarded)	All procedures not kept (as per the above rules)
If the first test is this procedure, this is deleted since this was likely done for another reason (i.e., the evaluation should not start with a cancer screen, a specialist consultation, etc) (repeated 8× until this was no longer observed)	Cancer screen (any)

Appendix K: Research Ethics Board approval for retrospective for retrospective chart review

LAWSON
HEALTH RESEARCH INSTITUTE

LAWSON FINAL APPROVAL NOTICE

LAWSON APPROVAL NUMBER: R-16-202

PROJECT TITLE: Evaluation of the Living Kidney Donor Assessment

PRINCIPAL INVESTIGATOR: Dr. Amit Garg

LAWSON APPROVAL DATE: September 6, 2016

Health Sciences REB#: 107847

Please be advised that the above project was reviewed by the Clinical Research Impact Committee and Lawson Administration and the project:

Was Approved

Please provide your Lawson Approval Number (R#) to the appropriate contact(s) in supporting departments (eg. Lab Services, Diagnostic Imaging, etc.) to inform them that your study is starting. The Lawson Approval Number must be provided each time services are requested.

Dr. David Hill
V.P. Research
Lawson Health Research Institute

All future correspondence concerning this study should include the Lawson Approval Number and should be directed to Sherry Paiva, Research Approval Officer, Lawson Health Research Institute, 750 Baseline Road, East, Suite 300.

cc: Administration

Appendix L: Specific transitions used in scenario analysis

				Transition time (days)	
			N	median (IQR)	mean (SD)
Transition times between major consults (nephrology, surgery, psychosocial) – for Scenarios 3 and 4[a]					
Nephrology	to	surgery	315	23 (3, 66)	45.0 (56.9)
Counselling	to	surgery	136	3 (0, 18)	13.8 (26.7)
Nephrology	to	counselling	189	0 (0, 14)	14.6 (53.0)
Surgery	to	nephrology	80	19 (7, 41)	45.6 (87.6)
Counselling	to	nephrology	65	13 (6, 23)	38.2 (99.9)
Surgery	to	counselling	36	12 (2, 22)	19.4 (26.8)
Transition times from various major medical consults (nephrology, surgery) to a cardiology consult – for Scenario 5[a]					
Nephrology			43	7 (0, 84)	66.7 (114)
Surgery			7	16 (3, 45)	69.4 (140)
Transition times from various procedures to a nuclear medicine exam – for Scenario 6[a,b]					
Biochemistry			147	21 (7, 41)	29.4 (28.9)
Computed tomography			102	7 (3, 13)	17.1 (73.8)
Chest x-ray			100	7 (2, 18)	14.8 (19.3)
Intermediate assessment			80	17 (8, 34)	42.7 (100)
Nephrology			65	20 (8, 29)	33.9 (61.5)
Stress test			46	0 (0, 0)	0.10 (0.70)
Electrocardiogram			43	12 (5, 36)	26.7 (48.9)
Ultrasound			41	0 (0, 6)	7.80 (20.3)
Cardiology consult			29	7 (6, 20)	29.5 (78.8)
Counselling			28	16 (5, 32)	23.9 (26.6)
Surgical consult			27	13 (1, 27)	16.0 (15.3)
General consult			26	20 (13, 40)	41.8 (60.5)
Pulmonary function test			25	0 (0, 0)	0.40 (1.70)
Echocardiography			20	7 (4, 11)	8.80 (8.60)
Cervical cancer screen			20	7 (4, 19)	14.3 (16.7)
Nuclear exam			13	22 (8, 49)	25.4 (22.1)
Colorectal cancer screen			11	18 (3, 130)	59.1 (71.5)
Cytology			10	33 (18, 41)	38.9 (29.2)
Breast cancer screen			9	8 (6, 11)	11.6 (10.2)

[a] also used for scenarios 1-2

[b] nuclear renogram not restricted to a test of total glomerular filtration rate or split function

Mean and median estimates of transition times were tabulated for all donors who donated a kidney after March 2004 (n=1256), using a list of procedures deemed relevant to the evaluation process.

SD – standard deviation; IQR – 25^{th}, 75^{th} percentile

Appendix M: Codes for exclusion of potential healthy non-donor controls for matching

Database	Type of code	Codes
Dialysis		
OHIP	Feecodes	"R849" "G323" "G336" "G325" "G326" "G860" "G862" "G863" "G865" "G866" "R825" "R826" "R827" "R833" "R840" "R851" "G330" "G331" "G332" "G861" "G864" "R852" "G082" "G083" "G085" "G090" "G091" "G092" "G093" "G094" "G095" "G096" "G294" "G295" "G333" "H540" "H740"
CIHI	ICD-9	"V451" "V560" "V568" "36104"
	ICD-10	"T824" "Y602" "Y612" "Y622" "Y841" "Z49" "Z992" "N180" "E1022" "E1023" "E1122" "E1123" "E1322" "E1323" "E1422" "E1423"
	procedure codes	"5127" "5195" "6698"
	intervention codes	"7SC59QD" "1KY76" "1PZ21"
Hypertension		
OHIP	diagnosis codes	"401" "402" "403" "404" "405"
CIHI	ICD-9	"401" "402" "403" "404" "405"
	ICD-10	"I10" "I11" "I12" "I13" "I15"
Cancer		
OHIP	diagnosis codes	"140" "141" "142" "143" "144" "145" "146" "147" "148" "149" "150" "151" "152" "153" "154" "155" "156" "157" "158" "159" "160" "161" "162" "163" "164" "165" "170" "171" "172" "173" "174" "175" "179" "180" "181" "182" "183" "184" "185" "186" "187" "188" "189" "190" "191" "192" "193" "194" "195" "196" "197" "198" "199" "200" "201" "202" "203" "204" "205" "206" "207" "208"
CIHI	ICD-9	"V10" "140" "141" "142" "143" "144" "145" "146" "147" "148" "149" "150" "151" "152" "153" "154" "155" "156" "157" "158" "159" "160" "161" "162" "163" "164" "165" "170" "171" "172" "173" "174" "175" "176" "179" "180" "181" "182" "183" "184" "185" "186" "187" "188" "189" "190" "191" "192" "193" "194" "1950" "1951" "1952" "1953" "1954" "1955" "1958" "196" "197" "198" "1990" "1991" "2000" "2001" "2002" "2008" "2010" "2011" "2012" "2014" "2015" "2016" "2017" "2019" "2020" "2026" "2028" "2029" "203" "204" "205" "206" "207" "208" "230" "231" "232" "233" "234"
	ICD-10	"80003" "80006" "80013" "80023" "80033" "80043" "80102" "80103" "80106" "80113" "80123" "80203" "80213" "83123" "87202" "87203" "959" "965" "966" "967" "968" "969" "970" "971" "980" "982" "984" "985" "986" "987" "988" "989" "990" "991" "993" "C00" "C01" "C02" "C03" "C04" "C05" "C06" "C07" "C08" "C09" "C10" "C11" "C12" "C13" "C14" "C15" "C16" "C17" "C18" "C19" "C20" "C21" "C22" "C23" "C24" "C25" "C26" "C30" "C31" "C32" "C33" "C34" "C37" "C38" "C39" "C40" "C41" "C43" "C44" "C45" "C46" "C47" "C48" "C49" "C50" "C51" "C52" "C53" "C54" "C55" "C56" "C57" "C58" "C60" "C61" "C62" "C63" "C64" "C65" "C66" "C67" "C68" "C69" "C70" "C71" "C72" "C73" "C74" "C75" "C76" "C77" "C78" "C79" "C80" "C81" "C82" "C83" "C84" "C85" "C90" "C91" "C92" "C93" "C94" "C95" "C96" "C97" "D00" "D01" "D02" "D03" "D04" "D05" "D06" "D07" "D09"
Cardiovascular disease		
OHIP	feecodes (procedure)	"Z434" "R742" "R743" "N220" "R792" "R802" "R816" "R817" "R783" "R784" "R785" "R814" "R787" "R780" "R797" "R804"
CIHI	ICD-9	"39" "40" "41" "42" "43" "44" "45"
	ICD-10	"I"
	procedural codes	"4802" "4803" "4809" "481" "5024" "5034" "5125"
	intervention codes	"1IJ50" "1IJ76" "1KA76" "1KG76"
Human immunodeficiency virus		
OHIP	diagnosis codes	"042" "043" "044"

CIHI	ICD-9	"042" "043" "044" "V08" "176"
	ICD-10	"B24" "C46" "Z21",
Nephrectomy		
OHIP	feecodes	"E762" "S435" "E769" "S434" "E771" "Z631" "G347" "G348" "G412" "G408" "G409"
CIHI	ICD-9	"V420" "99681"
	ICD-10	"T861" "N165" "Z940"
	procedural codes	"6743" "675"
	intervention codes	"1PC85"
Renal biopsy		
OHIP	feecodes	"Z601",
CIHI	procedural codes	"6781" "6782"
	intervention codes	"1PC87"
Gout		
OHIP	diagnosis codes	"274"
CIHI	ICD-9	"274"
	ICD-10	"M10"
Pulmonary disease		
CIHI	ICD-9	"46" "47" "48" "49" "50" "51"
	ICD-10	"J"
Liver disease		
CIHI	ICD-9	"57"
	ICD-10	"K7"
Systemic lupus erythematosus		
CIHI	ICD-9	"7100"
	ICD-10	"M32"
Rheumatoid arthritis		
CIHI	ICD-9	"714"
	ICD-10	"M05" "M06"
Genitourinary disease		
CIHI	ICD-9	"58" "59" "60" "61" "62"
	ICD-10	"N"
Alcoholism		
CIHI	ICD-9	"303" "3050"
	ICD-10	"E24" "E512" "F10" "G312" "G621" "G721" "I426" "K292" "K70" "K860" "T510" "X45" "X65" "Y15" "Y573" "Z502" "Z714" "Z721"

OHIP – Ontario Health Insurance Plan; CIHI – Canadian Institute for Health Information (same-day surgery and discharge abstract database); ICD – International Statistical Classification of Diseases and Related Health Problems medical classification (ICD-9 before 2002

Appendix N: Healthcare utilization patterns of the most common procedures determined from OHIP billing codes

Quantity utilized by living donors who started the evaluation as early as March 31, 2000 until 1-year follow-up post-donation, entire cohort

	Evaluation period		Perioperative period		Follow-up period	
Procedure	**N (%)**	**mean (SD)[a]**	**N**	**mean (SD)[a]**	**N**	**mean (SD)[a]**
Number of donors[b]	**1256 (100%)**	**–**	**1240 (99%)**	**–**	**1223 (97%)**	**–**
Nephrology consult	1256 (100%)	1.91 (1.74)	483 (40%)	4.17 (3.98)	935 (76%)	2.03 (1.70)
Surgery/urology consult	1256 (100%)	1.40 (1.00)	842 (70%)	2.80 (2.15)	790 (65%)	1.28 (0.76)
Chest x-ray	1210 (96%)	1.40 (0.70)	164 (14%)	2.24 (2.19)	119 (10%)	3.18 (2.71)
Electrocardiogram	1177 (94%)	1.61 (0.98)	88 (7%)	1.69 (1.08)	149 (12%)	3.38 (2.72)
Computed tomography	1163 (93%)	1.08 (0.30)	33 (3%)	2.76 (1.12)	50 (4%)	2.26 (1.10)
Biochemistry (bloodwork)	1038 (83%)	3.32 (2.20)	118 (10%)	5.11 (6.96)	921 (75%)	11.7 (11.3)
Cytology	1061 (84%)	3.34 (2.18)	228 (19%)	1.67 (1.43)	967 (79%)	3.51 (2.82)
Urinalysis	954 (76%)	2.55 (2.53)	103 (9%)	1.67 (0.96)	640 (52%)	2.47 (2.18)
Intermediate assessment	890 (71%)	3.44 (3.36)	434 (36%)	1.37 (0.67)	817 (67%)	3.25 (2.93)
Ultrasound	875 (70%)	1.42 (0.79)	91 (8%)	2.47 (1.70)	242 (20%)	4.28 (2.83)
Nuclear medicine	805 (64%)	1.12 (0.37)	0 (0%)	–	<6 (<1%)	–
General consult	646 (51%)	2.19 (2.09)	159 (13%)	1.20 (0.43)	524 (43%)	1.94 (1.70)
Echocardiogram	578 (46%)	1.09 (0.31)	<6 (<1%)	–	14 (1%)	4.36 (1.08)
Cardiology evaluation	527 (42%)	1.89 (1.43)	47 (4%)	1.53 (1.69)	186 (15%)	1.81 (1.33)
Stress test	498 (40%)	1.11 (0.33)	<6 (<1%)	–	13 (1%)	3.54 (2.96)
Counseling/psychiatry	486 (39%)	2.42 (4.81)	60 (5%)	1.23 (0.62)	193 (16%)	3.39 (6.97)
Cancer screen (pap)	401 (32%)	1.64 (0.64)	<6 (<1%)	–	235 (19%)	2.62 (1.18)
Immunohematology test	397 (32%)	1.07 (0.27)	0 (0%)	–	15 (1%)	2.73 (1.49)
Cancer screen (breast)	243 (19%)	1.23 (0.52)	<6 (<1%)	–	118 (10%)	2.57 (1.60)
Pulmonary function test	224 (18%)	1.09 (0.38)	<6 (<1%)	–	32 (3%)	6.66 (6.18)
Cancer screen (colorectal)	207 (16%)	1.51 (0.93)	<6 (<1%)	–	57 (5%)	1.18 (0.54)
General surgery consult	111 (9%)	1.22 (0.68)	52 (4%)	2.02 (1.32)	55 (4%)	1.67 (1.50)
Cystoscopy	78 (6%)	1.03 (0.16)	<6 (<1%)	–	10 (1%)	1.10 (0.32)
Magnetic resonance	67 (5%)	1.15 (0.40)	<6 (<1%)	–	29 (2%)	2.62 (2.27)
Gastroenterology consult	67 (5%)	1.28 (0.57)	29 (2%)	1.21 (0.49)	69 (6%)	3.96 (2.36)
Renal biopsy	54 (4%)	1.02 (0.14)	0 (0%)	–	0 (0%)	–
Pathology consult	39 (3%)	1.05 (0.22)	<6 (<1%)	–	57 (5%)	2.05 (0.93)
Pyelogram	31 (2%)	1.03 (0.18)	0 (0%)	–	0 (0%)	–
Hematology consult	30 (2%)	1.57 (1.04)	<6 (<1%)	–	<6 (<1%)	–
Neurology consult	27 (2%)	1.37 (0.84)	<6 (<1%)	–	15 (1%)	1.60 (1.55)
Plastic surgery consult	26 (2%)	2.15 (1.32)	<6 (<1%)	–	20 (2%)	2.40 (1.93)
Respirology consult	21 (2%)	1.57 (0.93)	<6 (<1%)	–	35 (3%)	1.60 (1.26)
Endocrinology consult	13 (1%)	1.08 (0.28)	0 (0%)	0 (–)	<6 (<1%)	–
Musculoskeletal consult	10 (1%)	1.10 (0.32)	0 (0%)	0 (–)	<6 (<1%)	–
Rheumatology consult	8 (1%)	1.38 (0.52)	0 (0%)	0 (–)	<6 (<1%)	–

costs presented only for more common procedures (present in >10% of donors)

[a] mean (standard deviation, SD) number of procedures per donor, restricted to those who had the procedure during the specified period of coverage.

[b] restricted to donors with an OHIP billing code in the specified period

[c] estimated (not measured) number of hours spend with a donor

Appendix O: Healthcare utilization patterns

Evaluation period

Common consultations: Several donors had more than one nephrology [mean 1.93 (SD 1.74)] and surgery [mean 1.40 (SD 1.00)] consultation. Other common consultations included intermediate assessments (a detailed donor examination performed by a physician in a family practice or pediatric services), which were utilized by 71% of donors during the evaluation period, general consultations (51%), cardiology consultations (42%), a psychosocial assessment (39%), and a general surgery consultation (9%).

Preliminary and diagnostic tests: Chest x-ray, electrocardiography and computed tomography (CT) exams were used by at least 93% of donors. With respect to laboratory tests, cytology, biochemistry and urinalysis was used by 76-83% of donors. A nuclear medicine exam was used by 64% of donors. CT and nuclear renograms were repeated infrequently: mean 1.08 (SD 0.30) and 1.12 (SD 0.37) exams per donor.

Other diagnostic tests and consultations: Cancer screening was used by 32% of donors for a pap smear, 19% for a breast exam, and 16% for a colorectal exam. Other procedures, including echocardiograms (46%), stress tests (40%), pulmonary function tests (18%), cystoscopy (6%), magnetic resonance (MR) exams (5%), renal biopsy (4%), and pyelography (2%), were also considered important parts of the donor evaluation and were infrequently used (mean 1.02-1.15 per donor). Other consultations, including gastroenterology (5%), pathology (3%), neurology (2%), hematology (2%), plastic surgery (2%), respirology (2%), endocrinology (1%), musculoskeletal (1%), and rheumatology (1%) were also retained since they may be necessary components of the evaluation (e.g., incidental findings, clearance from the perspective of pre-existing conditions).

Post-donation follow-up period

During the follow-up period, some healthcare procedures were utilized by most donors, including nephrology consultation (76%), surgery consultation (65%), blood and urine tests (52-79%), and intermediate assessments (67%). For small subgroups of donors, the frequency of certain healthcare procedures more than doubled after donation. For example, a mean 3.18 chest x-rays were conducted for 10% of donors during follow-up period compared with a mean 1.40 images among 96% of donors during the evaluation period. Similar observations were found for electrocardiograms, CT scans, renal ultrasound, echocardiograms, stress tests, immunohematological tests, breast cancer screening, pulmonary function tests, MR scans, and gasteroenterology consults.

Appendix P: Average cost of common procedures calculated from billing codes in Apr 1 2010 – Mar 31 2014

		Cost per unit for selected procedures (2017 Canadian dollars)*	
Procedure**	**N**	**Median (IQR)**	**Mean (SD)**
Number of donors	**589**	**–**	**–**
donation	511	$2,167 ($1,663-$2,839)	$2,168 ($835)
Nephrology consult	739	$165 ($83-$170)	$137 ($60)
Surgery/urology consult	642	$87 ($85-$161)	$102 ($47)
Chest x-ray	541	$36 ($34-$36)	$35 ($4)
Electrocardiogram	649	$18 ($12-$18)	$20 ($21)
Computed tomography	436	$149 ($126-$197)	$172 ($57)
Biochemistry test (bloodwork)	1069	$25 ($12-$76)	$51 ($53)
Cytology	1139	$8 ($8-$8)	$8 ($4)
Urinalysis	748	$3 ($3-$4)	$3 ($1)
Intermediate assessment	593	$38 ($37-$40)	$39 ($10)
Ultrasound	348	$89 ($84-$149)	$120 ($58)
Nuclear medicine	392	$253 ($203-$272)	$220 ($95)
General consult	261	$25 ($23-$32)	$38 ($29)
Echocardiogram	214	$254 ($244-$278)	$247 ($53)
Cardiology evaluation	304	$41 ($10-$88)	$72 ($82)
Stress test	198	$112 ($107-$115)	$158 ($138)
Counseling/psychiatry	262	$85 ($67-$205)	$128 ($69)
Cancer screen (pap)	212	$20 ($20-$49)	$42 ($40)
Immunohematology test	146	$11 ($11-$11)	$13 ($4)
Cancer screen (breast)	86	$71 ($67-$77)	$76 ($29)
Pulmonary function test	70	$4 ($4-$4)	$33 ($64)
Cancer screen (colorectal)	73	$44 ($14-$285)	$150 ($178)
General surgery consult	43	$98 ($95-$101)	$94 ($19)
Cystoscopy	27	$77 ($75-$78)	$84 ($28)
Magnetic resonance	28	$274 ($246-$329)	$267 ($82)
Gastroenterology consult	36	$169 ($133-$208)	$187 ($110)
Renal biopsy	21	$156 ($152-$156)	$155 ($6)
Pathology consult	7	$83 ($71-$138)	$100 ($33)
Pyelogram	<6	–	–
Hematology consult	13	$165 ($162-$168)	$140 ($53)
Neurology consult	13	$186 ($79-$193)	$144 ($64)
Plastic surgery consult	15	$29 ($28-$86)	$44 ($26)
Respirology consult	13	$165 ($85-$166)	$141 ($75)
Endocrinology consult	<6	–	–
Musculoskeletal consult	<6	–	–
Rheumatology consult	9	$126 ($37-$168)	$115 ($62)

costs presented only for more common procedures (present in >10% of donors), estimated from costs accrued from April 1, 2010 through March 31, 2014
IQR – interquartile range; SD – standard deviation
*costs calculated as of 2010 and later to account for any changes in cost over time
**the cost for a given procedure was calculated by summing the costs of all relevant Ontario Health Insurance Plan billings performed on the same day (see Appendix I).

12 Curriculum Vitae

Steven Habbous, MSc, PhD(c)
Toronto Ontario

Software expertise
- Microsoft Office
- SAS
- STATA
- TreeAge Pro
- R

Methodological expertise
- Cohort studies
- Case-control studies
- Randomized clinical trials
- Delphi survey
- Health economic evaluation
- Cost-effectiveness analysis
- Critical appraisal

Statistical expertise
- Linear and logistic regression
- Generalised linear models
- Regression of skewed data
- Multiple imputation
- Principal component analysis
- Survival analysis (censored data)
- Systematic review
- Meta analysis
- Multilevel (hierarchical) modeling
- Data envelopment analysis

Personal interests
- Sports (top 3: hockey, badminton, table tennis)
- Reading (top 3: The Count of Monte Cristo, Les Misérables, Captain Blood)

MISSION STATEMENT

I believe that health is more important than wealth. Society should strive to promote health equity through preventive medicine, improving the built environment, changing societal norms, and treating illness. This is everyone's responsibility and I will do my part to produce the greatest impact I can.

EDUCATION

2014-2018 **University of Western Ontario**

PhD – Epidemiology and Biostatistics

Experiences:
- Analytic epidemiology
- Biostatistics
- Clinical epidemiology
- Health economics
- Population health surveillance
- University Teaching and Learning (*certificate stream*)
- Dean's PhD Stipend for Graduate Research award in 2014 (maximum $25,000/year)
- Canadian Institutes for Health Research doctoral award – Frederick Banting and Charles Best Canada Graduate Scholarships ($35,000 over 3 years: May 2015 – April 2018)

2007-2010 **University of Toronto at St. George**

MSc – Institute of Medical Science

Experiences:
- Cardiovascular research
- Biomaterials and biomedical engineering
- Ethics of experimentation on animals
- Molecular biology
- Cytological and histological imaging
- Ontario Graduate Scholarship (OGS) scholarship awarded in 2008 ($15,000)

2003-2007 **University of Toronto at Scarborough**

Honors BSc – Specialist in Cell & Molecular Biology

PROFESSIONAL AND LEADERSHIP EXPERIENCE

2018- **Cancer Care Ontario**

Functional Lead – Quality, Measurement, and Evaluation

- Conduct current state analyses on how cancer patients are diagnosed and treated, with focus on regional and socioeconomic variability
- Develop algorithms to determine the date of suspicion of breast cancer
- Optimize methods to measure various cancer outcomes, including disease recurrence using administrative data
- Coach analysts on how to analyze, interpret, and report data

2014-2018 **University of Western Ontario**

Clinical researcher – Institute for Clinical Evaluative Sciences (ICES)

- Tasked with understanding the efficiency of the living kidney donor evaluation process
- Performed qualitative and quantitative research to understand the barriers and facilitators of an efficient evaluation; supervised junior researchers on projects; and engaged various stakeholders including patients, providers, and decision-makers.
- Prepared 10 manuscripts for publication and identified potential solutions to improve healthcare delivery.
- Member of the Canadian National Transplant Research Program

2010-2018 **University of Toronto & Western University**

Teaching assistant

- Taught seminars and labs for first-year and third-year undergraduate courses (30-50 students).
- Instructed students and created course material for health economics, a graduate-level course for 3-10 students. Taught students how to use the TreeAge program to conduct cost-effectiveness analyses.
- Provided ongoing support after the course was completed to students interested in pursuing publication of their economic evaluation.

2010-2016 **Princess Margaret Cancer Centre**

Clinical research data coordinator

- Tasked with better understand the epidemiology of human papillomavirus in head and neck cancer.
- Established a large head and neck cancer database, planned and executed a multi-centred Canada-wide study, collaborated with experts across disciplines, and mentored junior researchers.
- Advanced 14 reports for publication (8 as lead or co-lead author). The most recent publication (Habbous et al., *CMAJ* 2017) received substantial media (television, radio, online) attention due to its high-impact and potential to influence public health policy, including CTV, CBC, Global News Calgary and Toronto, the Canadian Press, and the Canadian Dental Association among others.

2000-2016 **City of Toronto – Parks, Forestry and Recreation**

Aquatic supervisor, trainer, instructor, and lifeguard

- Managed recreational and instructional swimming programs with the City of Toronto; facilitated the Toronto Sport Leadership Program, a program targeting at-risk youth in Toronto.
- Ensured facilities are up to standard, staff are certified and qualified to work, and liaised with Community Recreation Programmers on issues related to staff, public relations, and facility management.
- Delivered high-quality service to patrons and served as a role model for children and adolescents. Helped adolescents prepare resumes and apply for jobs with the City of Toronto and the YMCA through the Toronto Sport Leadership Program.

2007-2010 **Hospital for Sick Children**

Basic science researcher

- Challenged with elucidating part of the molecular mechanism behind ischemic and pharmacologic preconditioning
- Performed a series of molecular and biochemical assays to track the movement of a specific protein through the rabbit heart after oxygen starvation or drug treatment
- Characterised the spatiotemporal movement of this protein before and after the ischemic or pharmacologic stimuli

PUBLICATIONS

1. Lam NN, Garg AG, **Habbous S**, Lentine KL. “Brenner and Rector's The Kidney”. Elsevier Canada. 11th edition [*in press;* book chapter: “Considerations in living kidney donation”].
2. **Habbous S**, Garcia-Ochoa C, Brahm G, Nguan C, Garg AX. “Can split renal volume assessment by computed tomography replace nuclear split renal function in living kidney donor evaluations? A systematic review and meta analysis”. *Am J Kidney Dis* [*under review*].
3. **Habbous S**, Subnath M, Giblon R, Dasiewicz A, Wilk P. “Prevalence of food insecurity across Canada over time: analysis of nationally representative surveys” *Can J Pub Health* [*under review*].
4. Ren J, Xu W, Su J, Ren X, Cheng D, Chen Z, Bender N, Mirshams M, **Habbous S**, de Almeida J, Perez-Ordonez B, Goldstein D, Want J, Bratman S, Huang SH, Zhao Y, Waterboer T, Hung R, Liu G. “Multiple imputation and clinico-serological models to predict human papillomavirus (HPV) status in oropharyngeal carcinoma: An alternative when tissue is unavailable” *Int J Cancer* [*under review*].
5. Ren J, Yang W, Su J, Ren X, Fazelzad R, Tiong A, **Habbous S**, Goldstein D, de Almeida J, Hansen A, Jang R, Bratman S, Hope A, Chen Q, Wang J, Xu Y, Cheng D, Zhao Y, Xu W, Liu G. “Human Papillomavirus Prevalence and Prognosis of Squamous Carcinoma of Unknown Primary in the Head and Neck Region: A Systematic Review and Meta-Analysis” *Clinical Cancer Research* [*submitted*].
6. **Habbous S**, McArthur E, Sarma S, Begen MA, Lam NN, Manns B, Lentine KL, Dipchand C, Litchfield K, McKenzie S, Garg AX. “Potential implications of a more timely living kidney donor evaluation” *Am J Transplant*. 2018:18(11):2719-2729.
7. **Habbous S**, Sarma S, Barnieh L, McArthur E, Klarenbach S, Manns B, Begen MA, Lentine KL, Garg AX. “Healthcare costs for the evaluation, surgery, and follow-up care of living kidney donors” *Transplantation*. 2018:102(8):1367-1374.
8. **Habbous S**, Garg, AX, Lam, NN. “Optimizing efficiency in the evaluation of living donor candidates: Best practices and implications” *Curr Transplant Rep*. 2018;5(1):55-63.
9. **Habbous S**, Arnold A, Begen MA, Boudville N, Cooper M, Dipchand C, Dixon SN, Feldman LS, Goździk D, Karpinski M, Klarenbach S, Knoll GA, Lam NN, Lentine KL, Lok C, McArthur E, McKenzie S, Miller M, Monroy-Cuadros M, Nguan C, Prasad GVR, Przech S, Sarma S, Segev D, Storsley L, Garg AX. “Duration of Living Kidney Transplant Donor Evaluations: Findings From 2 Multicenter Cohort Studies” *Am J Kidney Dis*. *2018: 72(4):483-498.*
10. **Habbous S**, McArthur E, Dixon SN, McKenzie S, Garcia-Ochoa C, Lam NN, Lentine KL, Dipchand C, Litchfield K, Begen MA, Sarma S, Garg AX. “Initiating maintenance dialysis prior to living kidney donor transplantation when a donor candidate evaluation is well underway” *Transplantation*: 2018;102(7):e345-e353.

11. **Habbous S**, Przech S, Martin J, Garg AX, Sarma S. "Cost-effectiveness of first-line sevelamer and lanthanum versus calcium-based binders for hyperphosphatemia of chronic kidney disease". *Value Health*: *2018;21(3):318-325*.

12. **Habbous S**, Chu KP, Lau H, Schorr M, Belayneh M, Ha MN, Murray S, O'Sullivan B, Huang SH, Snow S, Parliament M, Hao D, Cheung WY, Xu W, Liu G. "The rise of human papillomavirus in head and neck cancers in Canada: analysis of five comprehensive cancer centres using multiple imputation". *CMAJ* (August 14, 2017) 189(32): E1030-E1040.

13. Gama RR, Song Y, Zhang Q, Brown MC, Want J, **Habbous S**, Tong L, Huang SH, O'Sullivan B, Waldron J, Xu W, Goldstein D, Liu G. "Body mass index and prognosis in patients with head and neck cancer". *Head Neck* (June 2017) 39(6): 1226-1233.

14. **Habbous S**, Przech S, Acedillo R, Sarma S, Garg AX, Martin J. The efficacy and safety of sevelamer and lanthanum versus calcium-containing and iron-based binders in treating hyperphosphatemia in patients with chronic kidney disease: a systematic review and meta-analysis. *Nephrol Dial Transplant* (January 1, 2017) 32(1): 111-125.
**This article was recommended by the Faculty of 1000.*

15. Chu KP*, **Habbous S***, Kuang Q, Boyd K, Mirshams M, Liu FF, Espin-Garcia O, Xu W, Goldstein D, Waldron MD, O'Sullivan B, Huang SH, Liu G. "Socioeconomic status, human papillomavirus, and overall survival in head and neck squamous cell carcinomas in Toronto, Canada". *Cancer Epidemiology*. (Dec 2015) 40:102-12.
*co-first authors

16. **Habbous S**, Garg AX, Martin J "Appraisal of a redundant report on lanthanum carbonate" *International Urology and Nephrology.* (Jan 2016) 48(1): 149-50.
(letter to the editor)

17. Garg AX, Nevis IF, McArthur E, Sontrop JM, Koval JJ, Lam NN, Hildebrand AM, Reese PP, Storsley L, Gill JS, Segev DL, **Habbous S**, Bugeja A, Knoll GA, Dipchand C, Monroy-Caudros M, Lentine KL, DONOR Network "Gestational Hypertension and Preeclampsia in Living Kidney Donors" *New England Journal of Medicine*. (Jan 2015) 372(2):124-133.

18. Graham DM, Isaranuwatchai W, **Habbous S**, de Oliveira C, Liu G, Siu LL, Hoch JS "A cost-effectiveness analysis of human papillomavirus vaccination of boys for the prevention of oropharyngeal cancer" *Cancer*. (Jun 2015) 121(11): 1785-1792.

19. Wang JR, **Habbous S**, Espin-Garcia O, Chen D, Huang SH, Simpson C, Xu W, Liu F-F, Brown DH, Gilbert RB, Gullane PJ, Irish JC, Goldstein DP, Liu G "Comorbidity and performance status as independent prognostic factors in head and neck squamous cell carcinoma patients" *Head Neck* (May 2016) 38(5): 736-742.

20. **Habbous S**, Pang V, Xu W, Amir E, Liu G "Human Papillomavirus and Host Genetic Polymorphisms in Carcinogenesis: A Systematic Review and Meta-Analysis" *Journal of Clinical Virology*. (Oct 2014) 61(2): 220-229.

21. Wong KM, Qiu X, Cheng D, Azad AK, **Habbous S**, Palepu PR, Mirshams M, Patel D, Chen Z, Roberts H, Knox J, Marquez S, Wong R, Darling G, Waldron J, Goldstein D, Leighl NB, Shepherd FA, Tsao M, Der S, Reisman D, Liu G **"**Two BRM promoter insertion polymorphisms increase the risk of early-stage upper aerodigestive tract cancers" *Cancer Medicine.* (Apr 2014) 3(2)**:** 426-33.

22. Eng L, Su J, Qiu X, Palepu PR, Hon H, Fadhel E, Harland LT, La Delfa A, **Habbous S**, Kashigar A, Cuffe S, Shepherd FA, Leighl NB, Pierre AF, Selby P, Goldstein DP, Xu W,

Liu G "Second-hand smoke as a predictor of smoking cessation among lung cancer survivors" *J Clin Oncol*. (Feb 2014) 32(6): 564-70.

23. **Habbous S**, Harland LT, La Delfa A, Fadhel E, Xu W, Liu F-F, Goldstein D, Waldron J, Huang SH, O'Sullivan B, Liu G "Comorbidity and prognosis in head and neck cancers: differences by subsite, stage, and human papillomavirus status" *Head and Neck* (June 2014) 36(6): 802-10.
24. **Habbous S**, Chu KP, Qiu X, La Delfa A, Harland LT, Fadhel E, Hui A, Perez-Ordonez B, Weinreb I, Liu F-F, Waldron J, O'Sullivan B, Goldstein D, Xu W, Huang SH, Liu G "The changing incidence of human papillomavirus-associated oropharyngeal cancer using multiple imputation from 2000-2010 at a comprehensive Cancer Centre" *Cancer Epidemiology* (Dec 2013) 37(6)**:** 820-9.
25. Kashigar A*, **Habbous S***, Eng L, Irish B, Bissada E, Irish J, Brown D, Gilbert R, Gullane P, Xu W, Huang S-H, Witterick I, Freeman J, O'Sullivan B, Waldron J, Liu G, Goldstein D "Social environment, secondary smoking exposure, and smoking cessation among head and neck cancer patients" *Cancer* (Aug 2013) 119(15): 2701-2709. *co-primary authors
26. **Habbous S**, Chu KP, Harland LT, La Delfa A, Fadhel E, Sun B, Xu W, Wong A, Howell D, Ringash J, Waldron J, O'Sullivan B, Goldstein D, Huang SH, Liu G "Validation of a one-page patient-reported Charlson comorbidity index questionnaire for upper aerodigestive tract cancer patients". *Oral Oncology* (May 2013) 49(5): 407-412.
27. **Habbous S,** Pang V, Eng L, Xu W, Kurtz G, Liu F-F, Mackay HJ, Amir E, Liu G "p53 Arg72Pro polymorphism, HPV status and initiation, progression, and development of cervical cancer: a systematic review and meta-analysis". *Clinical Cancer Research* (Dec 2012) 18(23): 6407-6415.
28. Eng L, Azad AK, **Habbous S**, Pang V, Xu W, van der Zee A-HM, Savas S, Mackay HJ, Amir E, Liu G "Vascular Endothelial Growth Factor Pathway Polymorphisms as Prognostic and Pharmacogenetic Factors in Cancer: A Systematic Review and Meta-analysis". *Clinical Cancer Research* (Sept 2012) 18(17): 4526-4537.

CONFERENCE PRESENTATIONS

1. **Habbous S**, Garg AX "Living Kidney Donor Evaluation Time and Pre-emptive Kidney Transplantation." Canadian National Transplant Research Program, November 8, 2017, Mont-Tremblant, Montreal Canada (poster presentation).

2. **Habbous S**, Garg AX "Living Kidney Donor Evaluation Time and Pre-emptive Kidney Transplantation." Society for Medical Decision Making, November 2, 2017, New Orleans, USA (poster presentation – Abstract #2788155).

3. Zhe L, **Habbous S**, Thain J, John-Baptiste A "Cost-effectiveness analysis of frailty assessment in older patients undergoing coronary artery bypass grafting surgery." Society for Medical Decision Making, October 23, 2017, Pittsburgh, USA (poster presentation).

4. **Habbous S**, Garg AX "A multi-centre retrospective study of evaluation times in prior living kidney donors." Canadian Society of Epidemiology and Biostatistics, May 31, 2017, Banff, Alberta (poster presentation).

5. Eng L, Alton D, Song Y, Farzanfar D, Krys O, Yoannidis T, Milne R, **Habbous S**, Brown CM, Vennettilli A, Shepherd F, Leighl N, Hope A, Howell D, Jones J, Selby P, Xu W, Goldstein DP, Giuliani ME, Liu G "Elimination of second-hand smoke (SHS) exposure after a lung or head and neck (HN) cancer diagnosis and subsequent patient smoking cessation." Cancer Survivorship Symposium: Advancing Care and Research, Jan 2016, San Francisco, CA (poster presentation; Abstract #183).

6. Seth P, Nicholson K, **Habbous S**, Ménard J "Implementation of a Hospitalist Medicine Model in a Community Hospital: Impact and Patient Satisfaction Two Years Post-Implementation." The Canadian Society of Hospitalist Medicine, Sept 24-27, 2015, Niagara Falls, ON (poster presentation).

7. Liu G, Song Y, Alton D, Yoannidis T, Milne R, Sarabia S, Merali Z, **Habbous S**, Brown C, Vinnettilli A, Hope A, Howell D, Jones J, Selby P, Goldstein DP, Giuliani ME, Xu W, Eng L "Prediction models of smoking cessation in lung and head and neck cancer patients: Role of second-hand smoke (SHS) exposure." American Society of Clinical Oncology, May 29-June 2, 2015, Chicago, IL (poster presentation).

8. Eng L, Alton D, Yoannidis T, Song Y, Milne, R, Sarabia S, Merali Z, **Habbous S**, Brown C, Vinnettilli A, Shepherd F, Leighl N, Hope A, Howell D, Jones J, Selby P, Xu W, Goldstein DP, Giuliani ME, Liu G "Change in second-hand smoke exposure after a lung and head and neck cancer diagnosis and subsequent patient smoking cessation" American Society of Clinical Oncology, May 29-June 2, 2015, Chicago, IL (poster presentation).

9. M Safi, **Habbous S**, A Fung, S Mital "Assessing the impact of early out-of-range tacrolimus levels on organ rejection after heart transplant" Canadian Society of Transplantation, Feb 28, 2014, Montréal, Canada (Oral presentation; Abstract# 54).

10. A Fung, T Marvasti, L D'Alessandro, AK Manickaraj, M Safi, **Habbous S**, S Mital "Influence of CYP3A Genetic Polymorphisms on Tacrolimus-Amlodipine Drug Interaction in Pediatric Heart Transplant Recipients" Canadian Society of Transplantation, Feb 28, 2014, Montréal, Canada (oral presentation; Abstract# 71).

11. **Habbous S**, M Safi M, A Fung, S Mital "Influence of concomitant medications on tacrolimus levels after pediatric solid organ transplantation" Canadian Society of Transplantation, Feb 28, 2014, Montréal, Canada (poster abstract# 45).

12. Eng L, **Habbous S**, X Qin, Prakruthi P, H Hon, D Pringle, CE Niu, V Ballarino, Liu G "Differences in use of pharmacologic smoking cessation aids between lung and other cancer patients" International Conference on Pharmacoepidemiology, August 28, 2013, Montréal, Canada (poster abstract #766).

13. **Habbous S**, Pang V, Eng L, E Amir, Liu G "Interactions of Human Papillomavirus and Host Genetic Polymorphisms in Carcinogenesis: A Systematic Review and Meta-

Analysis" International Conference on Pharmacoepidemiology, August 27, 2013, Montréal, Canada (poster abstract #870).

14. W Isaranuwatchai, DM Graham, Habbous S, C de Oliveira, Liu G, LL Siu, JS Hoch "A case study of human papillomavirus vaccination in males: Mixed messages from negative cost-effectiveness ratios" Canada's 2nd Applied Research in Cancer Control Conference, May 27, 2013, Vancouver, BC (poster abstract #038).

15. DM Graham, W Isaranuwatchai, **Habbous S**, C de Oliveira, Liu G, LL Siu, JS Hoch "A preliminary cost-effectiveness analysis of human papillomavirus vaccination in males for the prevention of oropharyngeal cancer" *Journal of Clinical Oncology*, (June 2013) **31** (suppl; poster abstract #6033), Chicago IL.

16. Eng L, J Su, X Qiu, PR Palepu, H Hon, E Fadhel, L Harland, La Delfa A, **Habbous S**, A Kashigar, S Cuffe, N B Leighl, A Pierre, P Selby, DP Goldstein, Liu G, Xu W "Developing a comprehensive smoking cessation program in lung cancer patients: the role of social smoking environments" American Society of Clinical Oncology Quality Care Symposium, San Diego, California, November 2012; J Clin Oncol 30, 2012 (suppl 34; abstract #75; poster).

17. **S. Habbous**, KP. Chu, A. La Delfa, L. Harland, X. Qiu, W. Xu, DaviGoldstein D, John Waldron, Brian O'Sullivan, S-H. Huang, G. Liu "The rise of Human Papillomavirus (HPV)-Associated Oropharyngeal Cancer (OPC) in Toronto, Canada: A Case for Vaccinating Males". International Society for Pharmacoepidemiology, Conference, Barcelona, Spain, August 24, 2012 (abstract #902, oral presentation #14).

18. E. Fadhel, YB Brhane, P Palepu, GP Joshi, H Hon, L Harland, La Delfa A, **S. Habbous**, S Cuffe, J Dong, A Pierre, A Brade, NB Leighl, FA Shepherd, Xu W, Liu G. "Socio-demographic factors influencing the rates of alcohol cessation and relapse in lung cancer survivors" Trillium Primary Health Care Research Day, Toronto CA, June 6, 2012 (poster presentation #21).

19. L. Eng, J. Su, P.R. Palepu, H. Hon, E. Fadhel, L. Harland, A. La Delfa, **S. Habbous**, A. Kashigar, S. Cuffe, N. B. Leighl, A. Pierre, D.P, Goldstein, G. Liu, W. Xu "Social Environment as Predictors of Smoking Cessation and Recidivism in Lung Cancer Survivors". American Society of Clinical Oncology, Conference, Chicago, June 4, 2012; J Clin Oncol 30, 2012 (suppl; abstract #9032; poster).

20. **S. Habbous**, V. Pang, L. Eng, H. Mackay, E. Amir, G. Liu "Association of p53 *Arg72Pro* Polymorphism and HPV Status in the Initiation, Progression, and Development of Cervical Cancer (CC): A Meta-Analysis". American Society of Clinical Oncology, Conference, Chicago, June 2, 2012; J Clin Oncol 30, 2012 (suppl; abstr 1597; poster).

21. A. Kashigar, D. Goldstein, C. Simpson, **S. Habbous**, S-H. Huang, J. Waldron, G. Liu, D. Goldstein "Smoking and Alcohol Cessation in Head and Neck Cancer Patients" Canadian Society of Otolaryngology, 66th Annual Meeting, Toronto, Ontario, May 20-22, 2012 (poster #H4).

22. **S. Habbous**, KP. Chu, J. Waldron, L. Harland, A. La Delfa, S. Su, W. Xu, A. Hui, F-F. Liu, D. Goldstein, B. O`Sullivan, S-H. Huang, G. Liu "The Effect of Comorbidity, Smoking and Alcohol on Survival of Head and Neck Cancer Anatomic Subsites: A Retrospective Analysis of 4689 Patients" American Association for Cancer Research, Conference, Chicago, April 2012 (abstract #666; poster).

23. L. Eng, E. Amir, A.K. Azad, **S. Habbous**, V. Pang, A.-H.M. van der Zee, S. Savas, H. Mackay, G. Liu "Polymorphisms in vascular endothelial growth factor (VEGF) and associated receptors as prognostic and predictive factors in advanced solid tumors". American Association for Cancer Research, Conference, Chicago, April 2012 (poster, abstract #4505).

24. JR Wang, **Habbous S**, O Espin-Garcia, Liu F-F, DP Goldstein, Liu G "Comorbidity and performance status are independent prognostic factors in head and neck squamous cell carcinoma patients" Triological Society 116th Annual Meeting at COSM, Orlando, Florida, April 12, 2012 (abstract # A229; 2nd place for best poster).

25. K. P. Chu, **S. Habbous**, S-H. Huang, L. Cheng, A. Hope, W. Xu, B. O'Sullivan, J. Waldron, E. T. Chang, G. Liu. "Impact of Socioeconomic Status (SES) on Head and Neck Cancer (HNC) Survival in an Equal Access Health Care System" *International Journal of Radiation Oncology*, (Oct 5, 2011), **81(2 Suppl 1):** S107-S108 (oral presentation #214, Miami FL).

26. **S. Habbous***, K. P. Chu[*], S-H. Huang, L. Cheng, W. Xu, G. Liu, A. Hope, F. Liu, J. Waldron, B. O'Sullivan. "Epidemiological Changes of Oropharyngeal Cancer and other Head and Neck Squamous Cell Carcinomas Treated from 2003-2010" *International Journal of Radiation Oncology* (Oct 3, 2011) **81(2 , Suppl 1):** S18 (oral presentation #35, Miami FL; *co-primary authors).

27. **S. Habbous**, Chu KP, HSH. Huang, W. Xu, B. Sun, L. Cheng, A. Tse, DP. Goldstein, J. Waldron, B. O'Sullivan, G. Liu. "Comparing Epidemiologic Survey Data To Abstracted Data From A Head And Neck Cancer (HNC) Radiation Oncology Administrative Database" *International Journal of Radiation Oncology* (Oct 1, 2011) **81(2, Suppl 1):** S501-S502 (Miami, FL; poster presentation).