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**THE LONG-TERM EFFECTIVENESS OF DIALYSIS, KIDNEY
TRANSPLANTATION AND PANCREAS TRANSPLANTATION FOR
PATIENTS WITH DIABETES MELLITUS AND RENAL FAILURE: A
DECISION ANALYSIS**

by

Greg Knoll

Thesis submitted to
the School of Graduate Studies and Research
in partial fulfillment of the requirements for the
MSc degree in Epidemiology

University of Ottawa

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ABSTRACT

Background: Diabetics with renal failure have several treatment options including cadaveric (CKT) or living (LKT) kidney transplantation, simultaneous pancreas-kidney transplantation (SPKT), pancreas transplantation after kidney transplantation (PAKT) or dialysis. The objective was to determine the most effective treatment strategy.

Methods: Decision analysis comparing dialysis, CKT, LKT, PAKT and SPKT. Model probabilities were obtained from the medical literature and utilities were obtained using the standard gamble. The outcome measure was quality-adjusted life expectancy (quality-adjusted life years, QALYs).

Results: LKT was associated with 10.29 QALYs; PAKT, 10.00 QALYs; SPKT, 9.09 QALYs; CKT, 6.53 QALYs; dialysis, 4.52 QALYs. The results were sensitive to several key variables.

Conclusion: LKT is the most effective treatment strategy for diabetics with renal failure. However, PAKT is preferred for patients with severe metabolic complications of diabetes and for those patients who favor the kidney-pancreas health state over kidney transplantation alone.

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INTRODUCTION

End-stage renal disease (ESRD) is an important and growing health problem for Canadians. The incidence and prevalence of ESRD in Canada have increased every year since 1981 (1). In 1999, 4342 Canadians developed ESRD (142.4 cases/million population) (1). By the end of 1999, there were 10,275 Canadians receiving regular dialysis treatments and 8,322 were alive with a functioning renal transplant (1). The development of ESRD has a major impact because it leads to a poor quality of life (2,3) and premature death (4). For example, a 40 year old white female who develops ESRD would have an average life expectancy of 10.3 years compared to 41 years for a similar member of the general population (4). In addition, the financial impact of ESRD to Canadians is substantial. The average cost of keeping one patient on dialysis is \$66,782 per year (2). For renal transplant recipients the average first year costs are \$66,290; after the first year the annual costs are \$27,875 (2).

Diabetes mellitus (type 1 and type 2) is the leading cause of ESRD in Western countries (4). In Canada, nearly one third of new cases of ESRD is due to diabetes mellitus (1). From 1993 to 1997, 143,854 patients in the United States developed ESRD from diabetes mellitus (4). Twenty-nine percent of these had type 1 diabetes mellitus (4). Diabetics with ESRD have a higher prevalence of comorbid diseases compared to non-diabetics (1). Myocardial infarction, angina, cerebrovascular disease, lung disease, peripheral vascular disease and hypertension are all more common in diabetics with ESRD compared to non-diabetics (1). More importantly, these comorbid illnesses are frequently seen in diabetics less than 45 years of age (1). In addition, patient survival is

also substantially lower for diabetics with ESRD compared to non-diabetics (1). This excess burden of illness for diabetics with ESRD results in a diminished quality of life, more frequent hospitalizations and ultimately a greater cost to the health care system. Therefore, treatment strategies aimed at improving the outcome of diabetics with ESRD could have a significant impact on the health care system.

Type 1 diabetic patients with ESRD have several treatment options. They may stay on dialysis, undergo cadaveric kidney transplantation (CKT), undergo living kidney transplantation (LKT), undergo simultaneous pancreas-kidney transplantation (SPKT) or undergo pancreas transplantation after living kidney transplantation (PAKT) (5,6). Dialysis is a lifelong treatment process that replaces the function of the failed kidneys. Typically, patients undergo three treatments per week with each treatment lasting approximately four hours. This treatment modality requires the surgical creation of access to the circulation, usually in the form of an arteriovenous fistula or graft. Renal transplantation alone involves the surgical implantation of a cadaveric or live donor renal allograft into the iliac fossa of the recipient. Renal transplant recipients must first undergo an extensive medical assessment to determine if they are candidates for the operation (7). Post-operatively they receive high doses of immunosuppressive medication to prevent allograft rejection. The doses of the medications are decreased over time but they are never discontinued altogether. Pancreas transplantation can occur at the same time as a kidney transplant procedure (SPKT) or as a second operation following renal transplant surgery (PAKT). There are many surgical approaches to SPKT but all involve the implantation of a vascularized pancreas and kidney from the same cadaveric donor to one

recipient. With PAKT, the patient first undergoes solitary kidney transplantation as described above. The patient is given time to recover from the operation and then undergoes a second procedure to implant the cadaveric pancreas. This can occur anywhere from three months to several years after the original renal transplant operation. As with solitary renal transplantation, pancreas transplant recipients receive life-long immunosuppressive medications.

For type 1 diabetics with ESRD the best treatment strategy remains unknown. Each treatment option is associated with different risks and benefits. The main risks associated with dialysis are infection and malfunction of the vascular access (8). In addition, dialysis has a significant impact on lifestyle as the treatment schedule lasts a minimum of 12 hours per week. The main benefit of dialysis is that it prevents immediate death from pulmonary edema or hyperkalemia. The major disadvantages of renal transplantation are the increased short-term mortality risk and the adverse effects associated with immunosuppressive medication (9). These include an increased risk of serious infection, malignancy, hyperlipidemia and several cosmetic side-effects (10-12). The advantages of renal transplantation include an improvement in average long-term survival and quality of life when compared to dialysis (2,9). The main benefits of LKT over CKT include an improvement in allograft survival and the ability to schedule an elective transplant without prolonged waiting for a cadaveric kidney to become available(13). If planned properly, patients undergoing LKT may be able to avoid dialysis altogether. However, the relative benefit of each is unclear since there are no randomized controlled trials comparing each therapy.

The issues surrounding pancreas transplantation are slightly more complex. A successful pancreas transplant results in normal or near-normal blood glucose levels, glycosylated hemoglobin levels and independence from exogenous insulin (5,14). The main advantage for the patient is an improvement in quality of life as there is no need for daily insulin injections, frequent glucose monitoring or a strict diet (15,16). Despite the improvement in glucose control, pancreas transplantation has had a variable effect on the progression of diabetic complications (14,17,18). No beneficial effect has been demonstrated for established retinopathy (14,17,19) and it is unknown whether pancreas transplantation has any effect on macrovascular disease (5,14). In contrast, diabetic nephropathy can be prevented and even reversed with pancreas transplantation (20,21). However, the prevention of recurrent disease is not clinically relevant as renal allografts rarely fail because of diabetic nephropathy (17). Finally, improvement in nerve conduction velocity has been demonstrated in pancreas transplant recipients (5,22). Again, the relative benefit of pancreas transplantation is unclear because there are no randomized trials comparing this treatment option.

The main disadvantage of pancreas transplantation is the increase in patient morbidity. Pancreas transplant recipients have an increased rate of acute rejection (23,24), longer hospital stays (24,25), more readmissions (24,25), more reoperations (24), and more infections (24) when compared to renal transplant recipients. The main advantage of SPKT over PAKT is that only one transplant operation is required. However, the disadvantage of SPKT is that the patient must wait (usually while on

dialysis) for a suitable cadaveric donor to become available. With PAKT, the patient can undergo scheduled living renal transplant surgery and avoid dialysis while waiting for a cadaveric pancreas to become available.

Given the various risks and benefits associated with the treatment options it is not surprising that there is still no consensus as to the most appropriate treatment strategy for type 1 diabetics with ESRD. Since 1995 there have been over 40 review articles on pancreas transplantation and treatment options for diabetics with ESRD. In virtually all of these papers the authors subjectively describe their interpretation of the literature and give recommendations. For example, Becker et. al. recommend that type 1 diabetics undergo PAKT only if an *identically* matched living kidney donor is available (26); otherwise they recommend that all other appropriate candidates undergo SPKT (26). In a separate review, Hricik recommends that any type 1 diabetic with a living donor undergo LKT first rather than SPKT (18). Finally, Manske recommends SPKT only for type 1 diabetics under the age of 45 who do not have significant heart disease and for those patients with poor metabolic control (17). These examples of conflicting expert opinion highlight the confusion surrounding the management of type 1 diabetics with ESRD.

The lack of consensus regarding treatment options is because there have been no randomized controlled trials comparing the risks and benefits of pancreas transplantation to kidney transplantation alone. It is unlikely that such a trial will ever be performed since the success of pancreas transplantation has improved over the past few years, the number

of transplants performed at any one centre is small and immunosuppressive protocols are evolving rapidly(17,27).

Several decision models have been published evaluating dialysis, kidney transplantation and pancreas transplantation in type 1 diabetic patients (28-31). Each of these models focused on cost and had several limitations that will be reviewed. Holohan published two cost-effectiveness analyses on pancreas transplantation (30,31). The first analysis compared PAKT with kidney transplantation alone and the second analysis compared SPKT with kidney transplantation alone. The first model demonstrated that kidney transplantation alone was more cost-effective than PAKT (31). The second report demonstrated that SPKT was only cost-effective when the costs of treating diabetes were quite high (30). These analyses had a similar design and there were several limitations. In both reports, it was assumed that all pancreas transplants were technically successful and that no renal allograft loss occurred in the first three years post-transplantation. This is not accurate because at the time of the study the technical failure rate following transplant surgery was 12% (30) and the three-year renal allograft survival was approximately 80% (32). In addition, the utility scores for kidney-pancreas transplantation were only estimates and the model assumed that they would always be higher than kidney transplantation alone. Finally, both studies used a fixed time frame of three years rather than adopting a long-term time horizon to estimate life expectancy.

Douzdjian et. al. published a cost-effectiveness analysis that compared dialysis, CKT, LKT and SPKT in type 1 diabetics with ESRD (29). They demonstrated that SPKT

was the most cost-effective treatment strategy. The results of this analysis were sensitive to the utilities for kidney transplantation. However, no sensitivity analysis was performed on the utility for SPKT. In addition, the utility values used were not credible as they were obtained from only 17 patients who underwent successful SPKT and patients with early pancreatic failure were excluded. The exclusion of patients with graft failure would likely result in a falsely elevated utility score for SPKT (2). The utility score for kidney transplantation is also substantially lower than previously published reports (2,33). Other study limitations included a fixed time horizon of only five years, no adjustment for the additional short-term morbidity of SPKT and the exclusion of waiting time and death while waiting for transplantation. In addition, the patient and allograft survival rates used in these models are now out of date as the success of pancreas and kidney transplantation has improved significantly over the past few years (32,34).

Douzdjian et. al. published a second cost-effectiveness analysis that compared PAKT with SPKT (28). In this report they demonstrated that SPKT was more cost-effective than PAKT. The utility scores from their first analysis were used in this model but it was not clear if the utility for SPKT was varied in the sensitivity analysis. Other limitations such as a five-year time horizon, the exclusion of waiting time and the failure to account for short-term morbidity were also present in this model.

In summary, type 1 diabetic patients with ESRD have several treatment options with different advantages and disadvantages. There have been no randomized studies to help physicians and patients decide on the best treatment strategy. Published decision

models on this topic have several limitations. Accordingly, the objective of this study was to determine the optimal treatment strategy for type 1 diabetic patients with ESRD.

Specific objectives of this study include the following: 1) develop a decision analytic Markov model that evaluates all possible outcomes for the treatment options dialysis, CKT, LKT, PAKT and SPKT; 2) perform a literature search and synthesize the data on the outcome and complications of kidney transplantation alone and pancreas transplantation; 3) determine the utility for the health states dialysis, kidney transplantation and kidney-pancreas transplantation; 4) determine the average life expectancy, quality-adjusted life expectancy and discounted quality-adjusted life expectancy for the treatment options dialysis, CKT, LKT, PAKT and SPKT; and 5) determine, using sensitivity analysis, which variables had the most influence on the results of the model.

METHODS

1.0 Decision model

1.1 Model overview

A state-transition Markov model(35) was constructed to analyze the treatment options faced by a patient with type 1 diabetes mellitus and ESRD. Five treatment strategies were compared: remain on dialysis, undergo renal transplantation from a cadaveric donor (CKT), undergo renal transplantation from a living donor (LKT), undergo renal transplantation from a living donor followed by pancreas transplantation from a cadaveric donor (PAKT) and undergo simultaneous pancreas and kidney transplantation from a cadaveric donor (SPKT). For each of these strategies, the model considered a patient to be in one of the following health states: alive on dialysis requiring insulin therapy, alive with a functioning kidney transplant requiring insulin therapy, alive with functioning kidney and pancreas transplants not requiring insulin therapy and dead. The model calculated life expectancy, quality-adjusted life expectancy and discounted quality-adjusted life expectancy.

1.2 The Markov model

A Markov model is an analytical technique that tracks clinical events in a hypothetical cohort of patients (35). The model assumes that the patient is in one of a finite number of mutually exclusive health states known as Markov states (35,36). The

time horizon of the model is divided into equal increments known as Markov cycles (35). All clinical events are modeled as transitions from one Markov state to another. It is assumed that only one state transition can occur during a Markov cycle (35). The proportion of the cohort that moves from one state to another is based on clinical probabilities derived from the literature. Evaluation of the model yields the average amount of time spent in each Markov health state. Summing the time spent in each of the separate Markov states will yield the expected survival. Quality of life can be incorporated into the model by assigning a utility to each Markov state (35,36).

The model was analyzed using cohort simulation (35). A hypothetical group of patients was run through the cycles of the model in a probabilistic manner (35). For example, consider a simple two-state model (alive and dead) where the probability of death in each one-year cycle is 0.20. At the end of each cycle patients in the alive state are given a reward of 1 and patients in the dead state are given a reward of 0. If all patients in the cohort begin in the alive state then after one year 0.80 are alive and 0.20 are dead. After the second cycle 0.64 are alive ($0.80 - (0.8 \times 0.2)$) and 0.36 are dead. After three cycles 0.512 are alive ($0.64 - (0.64 \times 0.2)$) and 0.488 are dead. The simulation continues until most (i.e. >99.999%) members of the cohort are in the dead state. This will never be 100% because during each cycle there is a finite probability of a patient remaining alive (35). The simulation is stopped when the proportion of the cohort remaining alive falls below a certain amount (i.e., 0.001). The life expectancy is calculated by summing the rewards obtained in each cycle. These calculations were

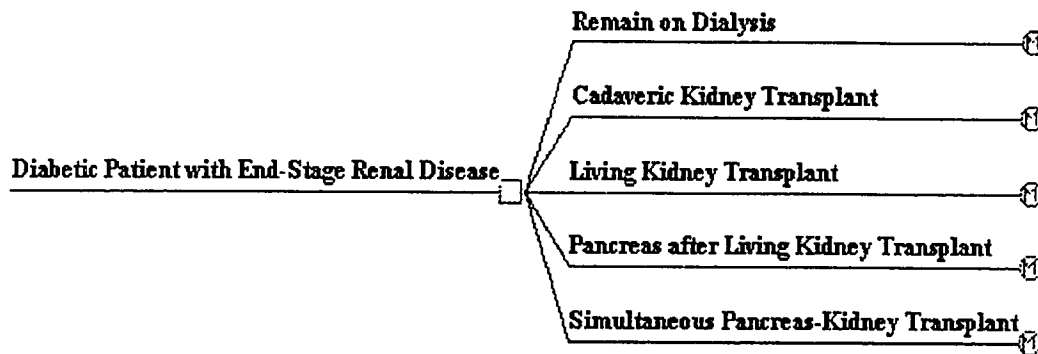
performed using the software program DATA 3.5 (Treeage Software, Williamstown, MA).

A Markov model was chosen over a conventional decision tree for three main reasons. First, the Markov model allows the transition probabilities to vary over time(35), which is clinically relevant to the field of transplantation. In the early post-transplant period the probability of allograft failure, infection or death is at its greatest (37,38). Several months after a transplant the probability that one of these events will occur is reduced but is never eliminated. Second, the Markov model allows for repetitive clinical events (35). Patients with diabetes mellitus are at constant risk for the development of hypoglycemia and ketoacidosis. With a Markov model the probability that an episode of hypoglycemia or ketoacidosis occurs can be incorporated into every cycle. Third, the Markov model does not require a fixed time horizon (35,36). This property is clinically important as life expectancies between patients vary according to events experienced and cannot easily be “fixed” as is required in conventional decision trees.

1.3 Model structure

A schematic representation of the Markov model is outlined in Figure 1. At the start of the first cycle all patients have ESRD and require insulin therapy. The decision node (open square) leads to five treatment options: dialysis, CKT, LKT, PAKT or SPKT.

Figure 1: Markov model of treatment options for type 1 diabetic patients with end-stage renal disease



Each treatment option leads to the possible Markov health states outlined in Figure 2. Each health state leads to a subtree. The subtrees (outlined in Figure 3) represent the clinically important events that may occur while a patient is in a particular health state. The face validity of the model was confirmed by having three experts in transplantation review and modify the tree structure and subtrees.

Figure 2: Markov health states for each treatment option (following page)

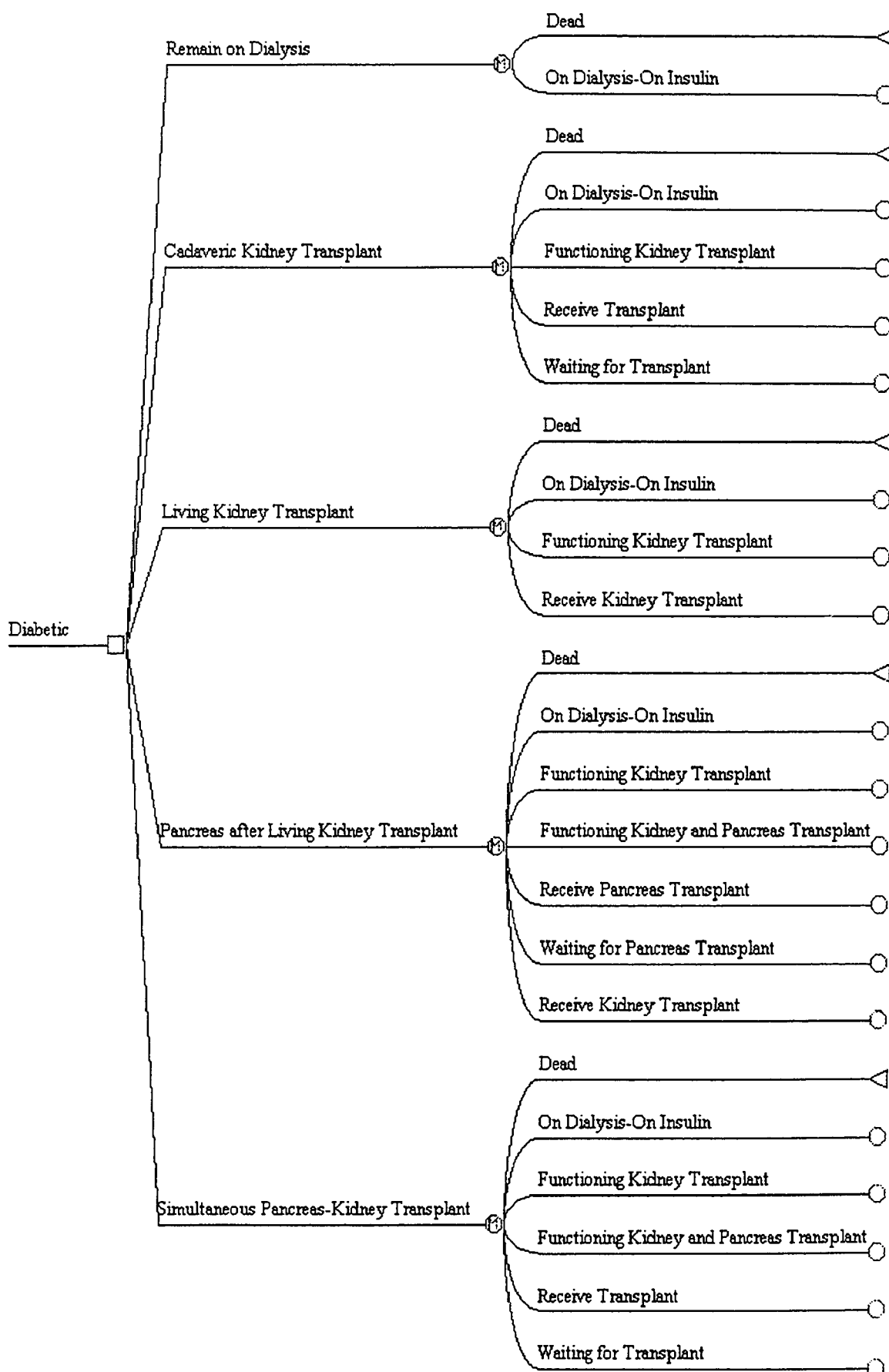
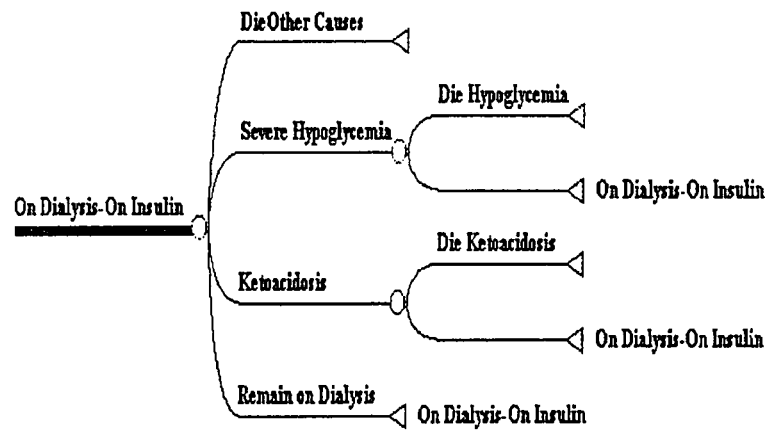
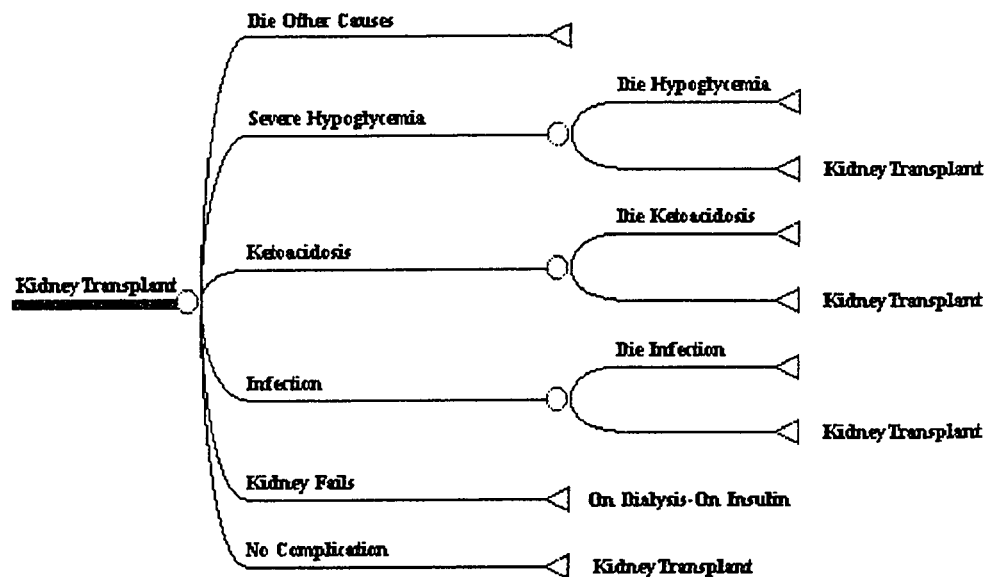


Figure 3: Health state subtrees

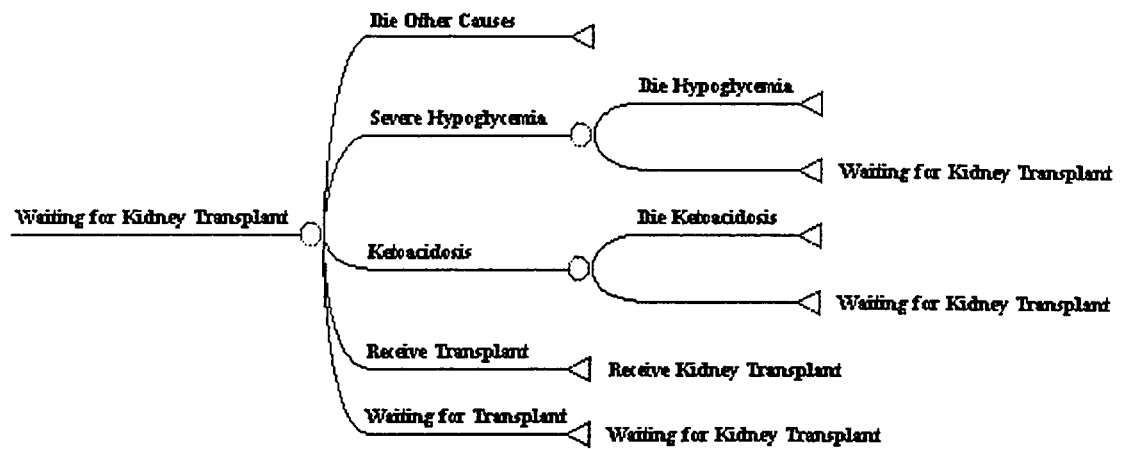
A: Subtree for the health state of being on dialysis and on insulin therapy



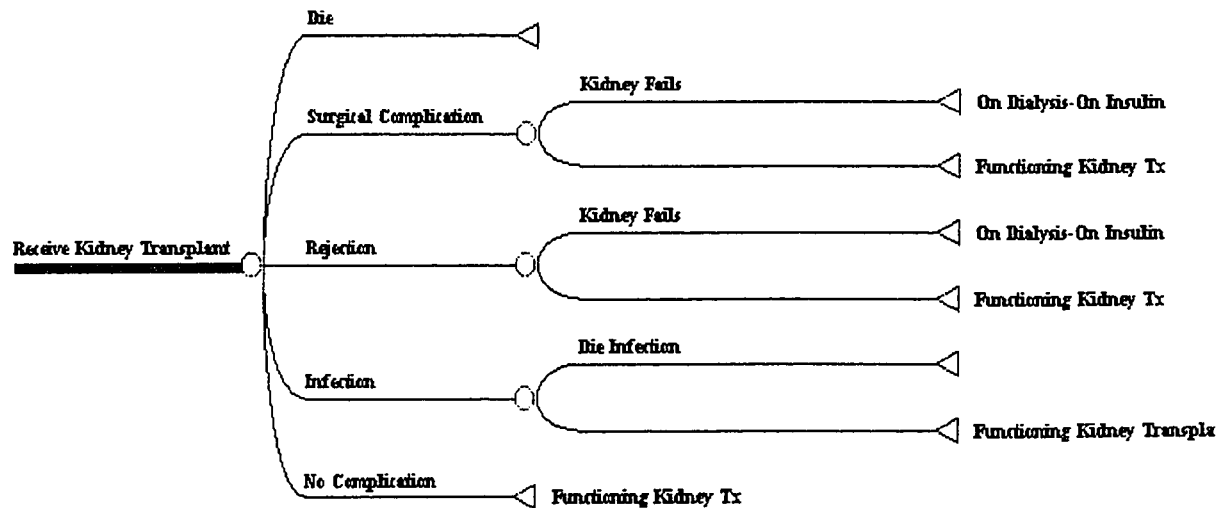
B: Subtree for the health state of having a functioning kidney transplant



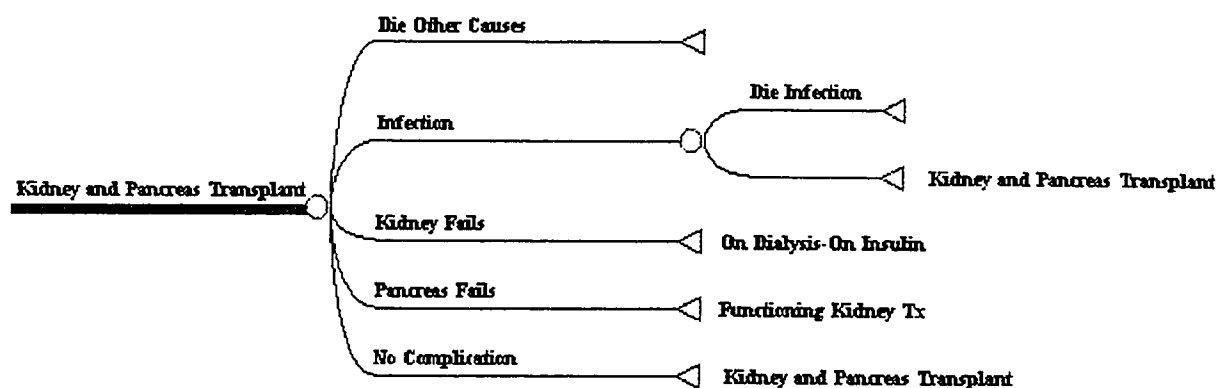
C: Subtree for the health state of waiting for a kidney transplant



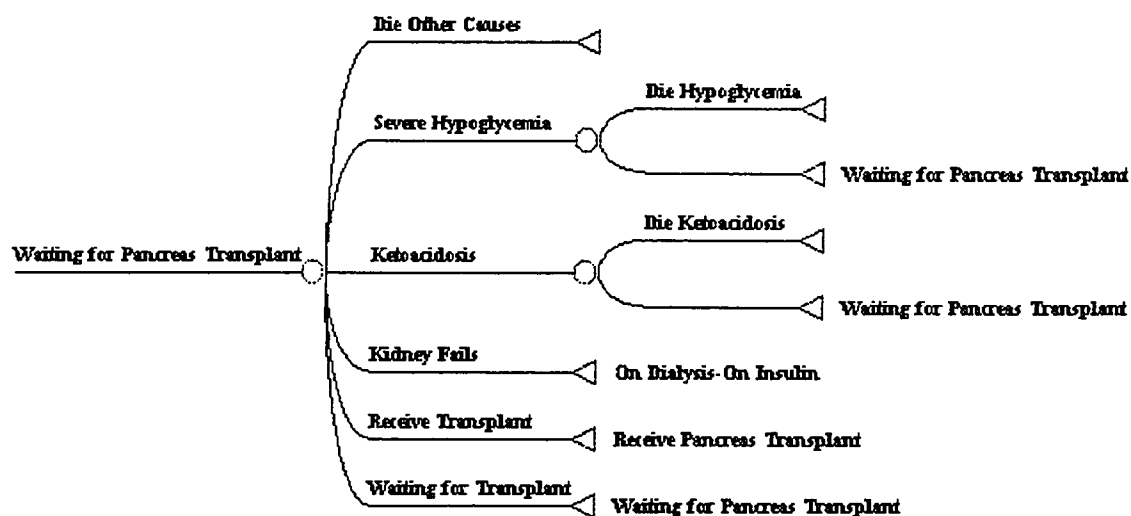
D: Subtree for the state of receiving a kidney transplant



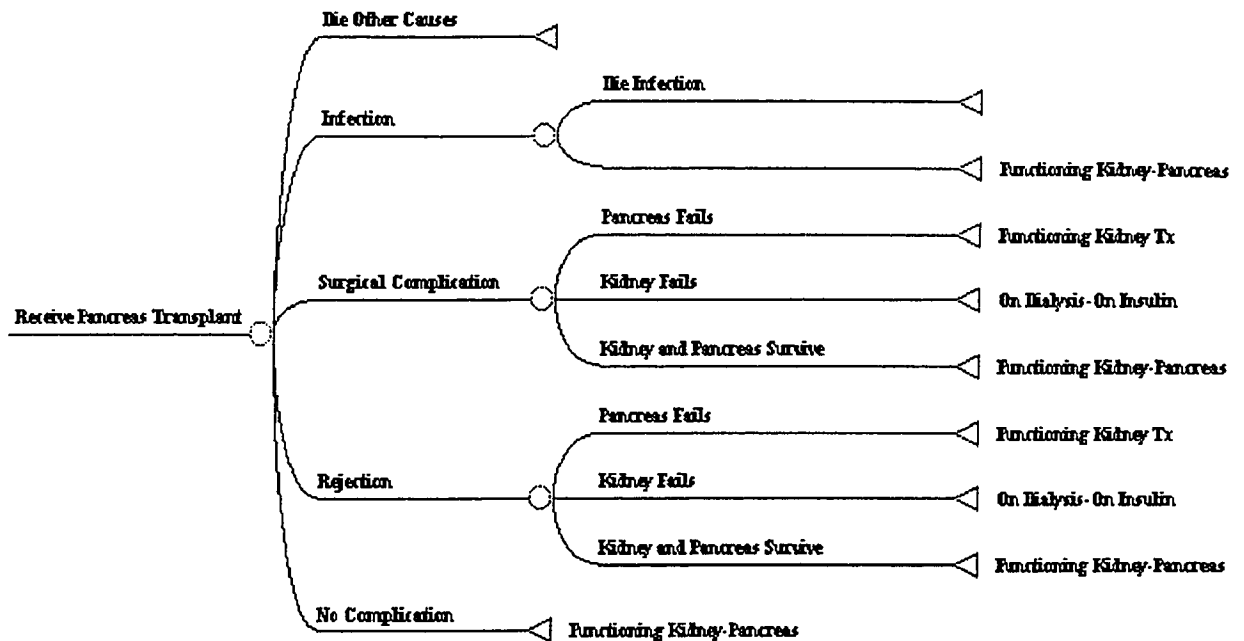
E: Subtree for the health state of having a functioning kidney and pancreas transplant



F: Subtree for the health state of waiting for a pancreas transplant



G: Subtree for the state of receiving a pancreas transplant



1.4 Study population

The hypothetical cohort consisted of patients with type 1 diabetes mellitus and ESRD. The patients were of either gender and ranged in age from 18 to 49 years. This age range was chosen because in the United States only three SPKT were performed in patients less than 18 years of age and only 97 were performed in patients greater than 49 years of age in 1999 (39).

1.5 Structural assumptions

Only the five treatment options outlined in Figure 1 were included in the model. Other surgical options such as combined living kidney and living pancreas transplantation (40) and simultaneous cadaveric pancreas living kidney transplantation

(41) were not considered as they are new techniques that have only been utilized by a few centers to date. Islet cell transplants were not included in the model as historically they have yielded poor results with less than 10% of patients achieving insulin independence (14). Newer immunosuppressive regimens have led to improvements in islet transplantation but none of these patients had ESRD (42).

The model was structured so that patients could only undergo one transplant procedure. If the pancreas allograft failed the patient resumed insulin therapy for the remainder of their lifetime. Similarly, if the renal allograft failed the patient remained on dialysis for the remainder of their lifetime. For kidney transplantation this was a simplifying assumption as many patients are listed for a second transplant (38) and in 1999, 12.6% of cadaveric renal transplants were performed in patients who had a previous transplant (39). However, for SPKT only 2% of all procedures performed from 1996 to 2000 were on patients who had a previous transplant (32).

The model assumed that when patients were in the first cycle they were medically suitable and ready to undergo transplantation immediately. This implies that their medical evaluation, which can be lengthy (7), was completed. As such, the model was structured so that patients undergoing LKT or PAKT received their kidney transplant within the first three-month cycle. The other transplant options, which used cadaveric donor organs, required that the patient enter a waiting period.

When pancreas transplantation occurs as a second operation after living renal transplantation there is no adverse impact on short-term or long-term renal allograft

survival (43). Therefore, the probability of losing the renal allograft from an early rejection or surgical complication was assumed to be zero following pancreas transplant surgery (for those patients that already had a living renal transplant). In addition, long-term renal allograft survival was assumed to be the same for patients who underwent LKT alone or PAKT (43).

2.0 Data for the model

2.1 Post-transplant complications

2.1.1 Literature search

A systematic review of the literature was performed to determine the complication rates following kidney and pancreas transplant surgery. Specific areas of interest included the rates of acute allograft rejection, cytomegalovirus infection, other major infections and technical complications. The surgical procedures of interest were CKT, LKT, SPKT and PAKT. The search strategy outlined in Appendix 1 was applied to English-language MEDLINE from 1995 to February 2001. The search was not extended beyond 1995 because the results of organ transplantation continue to improve each year (13). The use of older data would make the results of the model irrelevant today.

The search strategy yielded 11,670 references. Each title and abstract was reviewed and a hard copy was obtained for every study considered to have potentially relevant data. References were excluded from further review for the following reasons: animal study, human study but was investigating a basic science issue, pathology study, case report, involved pediatric patients only, involved non-heart beating donors, laboratory technique only, therapeutic drug monitoring study or involved combined

transplants such as heart-kidney transplants. After these exclusions, 1033 papers were retrieved and reviewed as full articles. Review of the reference lists from these papers yielded another 23 papers. Thus, a total of 1056 studies were reviewed as full articles. The literature review and data extraction was performed by the author alone and thus interobserver agreement was not evaluated.

2.1.2 *Data extraction*

Complication rates were extracted from the 1056 papers that were reviewed in detail. The inclusion and exclusion criteria for the specific complications will be outlined in the individual sub-sections that follow. Data was abstracted from several study types including single-center case series, case-control studies and randomized controlled trials. Non-randomized studies were included so that a wide range of data would be available to ensure the model reflected true clinical practice. Complication rates from multiple sources were combined using a weighted mean average to produce a best estimate. This average is weighted by the number of patients in each series. The lowest and highest complication rates were recorded for use in the sensitivity analysis.

Both rates and risks can be found in the medical literature. Rates represent the instantaneous potential to change over time and are usually measured in events per population-time (e.g. there were 40 deaths per 1000 patient-years) (44). Risks represent the probability that a person will move from one state to another in a specified time period (e.g. 5 years after surgery 40% of patients had died) (44). Risks are dimensionless and range from zero to one (44).

To be incorporated in the model, both rates and 'n'-year risks were converted to cycle-specific probabilities by using the following formulae (44).

For rates: cycle-specific probability = $1 - e^{(-\text{rate} \cdot \text{time})}$

where time = cycle length / duration of rate period

and both the numerator and denominator are in the same units

For risks: cycle-specific probability = $1 - (1 - p)^{1/t}$

where p = probability over time period t

t = number of cycles during time period

Certain probabilities in the model were linked when clinically appropriate. The use of probability linkage ensures that the model will produce logical results during sensitivity analysis (45). Relative risks were calculated so as to link probabilities to the reference group (CKT). If the event could only occur when a pancreas transplant was present the reference group was SPKT. For example, the probability of acute rejection in LKT was linked to CKT in the following manner:

$$p\text{Rej-Living} = (rr\text{Rej-Living}) (p\text{Rej-Cad})$$

where pRej-Living = probability of acute rejection in LKT

pRej-Cad = probability of acute rejection in CKT

rrRej-Living = relative risk of acute rejection in LKT

The best estimate, lower limit and upper limit for the relative risks were calculated in the following manner:

Best estimate:

Best estimate $\pi_{\text{Rej-Living}}$ = best estimate of $p_{\text{Rej-Living}}$ / best estimate of $p_{\text{Rej-Cad}}$

Lower limit:

Lower limit $\pi_{\text{Rej-Living}}$ = lower limit of $p_{\text{Rej-Living}}$ / upper limit of $p_{\text{Rej-Cad}}$

Upper limit:

Upper limit $\pi_{\text{Rej-Living}}$ = upper limit of $p_{\text{Rej-Living}}$ / lower limit of $p_{\text{Rej-Cad}}$

2.1.3 *Outcomes for post-transplant complications*

The probabilities for the post-transplant complications are outlined in Table 1. For each probability the best estimate and range of plausible values is presented. The data sources for each complication and assumptions are outlined in the individual sections below.

Table 1: Probabilities of events in the model**A: Events related to cadaveric renal transplantation**

Variable	Best Estimate	Range	References
Probability of death			(46)
First year post-transplantation	0.053	0.037-0.069	
After the first year post-transplantation	0.043	0.038-0.048	
Probability of allograft failure			(46)
First year post-transplantation	0.10	0.079-0.121	
After the first year post-transplantation	0.071	0.066-0.076	
Probability of acute rejection	0.171	0.081-0.27	(47-73)
Probability of cytomegalovirus infection	0.140	0.042-0.322	(25,47-51,53,57-59,61,62,73-86)
Probability of major infection	0.137	0.027-0.37	(48,54,76,77,82,83,87,88)
Probability of post-operative complication	0.086	0.004-0.161	(58,69,76,81-83,89-102)
Proportion transplanted within one year of placement on the waiting list	0.196	0.095-0.905	(73)
Probability of death on the waiting list	0.122	0.022-0.199	(9,46)

B: Events related to living renal transplantation

Variable	Best Estimate	Range	References
Probability of death			(46)
First year post-transplantation	0.038	0.023-0.053	
After the first year post-transplantation	0.024	0.018-0.029	
Probability of allograft failure			(46)
First year post-transplantation	0.063	0.044-0.082	
After the first year post-transplantation	0.044	0.038-0.05	
Probability of acute rejection	0.118	0.081-0.27	(47-73,103)
Probability of cytomegalovirus infection	0.140	0.042-0.322	(25,47-51,53,57-59,61,62,73-86)
Probability of major infection	0.137	0.027-0.37	(48,54,76,77,82,83,87,88)
Probability of post-operative complication	0.081	0.004-0.148	(58,69,76,81-83,89-93,104-112)

C: Events related to pancreas after living renal transplantation

Variable	Best Estimate	Range	References
Probability of death			(39)
First year post-transplantation	0.053	0.042-0.064	
After the first year post-transplantation	0.029	0.027-0.032	
Probability of renal allograft failure			(46)
First year post-transplantation	0.063	0.044-0.082	
After the first year post-transplantation	0.044	0.038-0.05	
Probability of pancreas allograft failure			(113)
First year post-transplantation	0.22	0.166-0.274	
After the first year post-transplantation	0.09	0.059-0.122	
Probability of acute rejection	0.287	0.20-0.50	(114-116)
Probability of cytomegalovirus infection	0.156	0.106-0.50	(114,115,117)
Probability of major infection	0.131	0.051-0.288	(117-123)
Probability of post-operative complication	0.289	0.05-0.525	(41,87,120,124-138)
Proportion transplanted within one year of placement on the waiting list	0.682	0.095-0.905	(73)
Probability of death on the waiting list	0.024	0.022-0.199	(9,46)

D: Events related to simultaneous-pancreas kidney transplantation

Variable	Best Estimate	Range	References
Probability of death			(39)
First year post-transplantation	0.053	0.042-0.064	
After the first year post-transplantation	0.029	0.027-0.032	
Probability of renal allograft failure			(39)
First year post-transplantation	0.079	0.066-0.092	
After the first year post-transplantation	0.053	0.049-0.056	
Probability of pancreas allograft failure			(39)
First year post-transplantation	0.16	0.142-0.178	
After the first year post-transplantation	0.041	0.038-0.044	
Probability of acute rejection	0.261	0.063-0.75	(41,115,116,120,122,123,135,139-156)
Probability of cytomegalovirus infection	0.176	0.083-0.37	(25,74,75,115,117,120,122,123,125,132,139,141-144,150,151,156-161)
Probability of major infection	0.118	0.051-0.288	(117-123)
Probability of post-operative complication	0.256	0.05-0.525	(41,87,120,124-129,131-138)
Proportion transplanted within one year of placement on the waiting list	0.42	0.095-0.905	(73)
Probability of death on the waiting list	0.079	0.022-0.199	(9,39)

E: Events related to diabetes mellitus

Variable	Best Estimate	Range	References
Diabetes-related complications			
Probability of hypoglycemia on dialysis	0.046	0-1.0	(162)
Probability of hypoglycemia with a kidney transplant	0.079	0-1.0	(162)
Probability of ketoacidosis	0.019	0-1.0	(163)
Probability of death from ketoacidosis	0.0055	0-0.15	(163)
Probability of death from hypoglycemia	0.00053	0-0.10	(163)

2.1.3.1 *Probability of acute rejection*

Biopsy-proven acute rejection and presumptive rejection episodes (patients that received anti-rejection therapy but did not undergo biopsy) were abstracted from the individual clinical studies. If the same group of patients had rejection rates reported at 3, 6 or 12 months the 12-month rate was used. Data was not used if patients received azathioprine as part of the immunosuppressive regimen since this no longer reflects current practice. The rejection rate from the placebo arm of randomized trials was excluded. Data was excluded if the patient received a dual immunosuppressive regimen (i.e. only cyclosporine and prednisone) since this is not standard practice in North America (164). Finally, the rejection rate was included only if the donor source was known for certain (i.e. cadaveric versus living donor). If the reported rejection rate was a combination of living and cadaveric transplants it was excluded.

There were 27 papers that had data on acute rejection rates for CKT (47-73). The reported acute rejection rates involved a total of 3603 patients. The probability of acute rejection following CKT varied between 0.081 and 0.27 (weighted mean average 0.171).

There were only a few studies involving a limited number of patients that reported separate acute rejection rates for LKT. However, there was a large registry study published involving 68,885 adult renal transplant recipients (103). In this study the relative risk of acute rejection for recipients of a living renal transplant was 0.69 (95% confidence interval, 0.66 to 0.73) compared to cadaveric renal transplant recipients (103). Using a relative risk of rejection for LKT of 0.69 and a probability of acute rejection of

0.171 for CKT, the probability of rejection for LKT was determined to be 0.118. The range for the sensitivity analysis was set at the same values as for CKT (0.081 to 0.27).

There were three studies that reported separate acute rejection rates for PAKT (114-116). These studies involved a total of 173 patients. The probability of acute rejection varied from 0.20 to 0.50 (weighted mean average 0.287).

There were 25 studies that reported acute rejection rates for SPKT (41,115,116,120,122,123,135,139-156). These studies involved 961 patients. The probability of acute rejection varied from 0.063 to 0.75 (weighted mean average 0.261).

2.1.3.2 *Probability of cytomegalovirus infection*

Cytomegalovirus (CMV) infection can occur as tissue invasive disease or as a syndrome of fever, leukopenia and thrombocytopenia following transplantation (165). Data on both types of CMV infection were abstracted. If the same patients had infection rates given at 3, 6 or 12 months the 12-month rate was recorded. Studies were excluded if no antiviral prophylaxis was given to high-risk patients as is currently recommended (166). Prophylaxis could be acyclovir, ganciclovir, valacyclovir or CMV hyperimmune globulin. The study was included if only low risk patients (both donor and recipient seronegative for CMV) did not receive antiviral prophylaxis (166).

There were 26 reports with data on CMV infection in renal transplantation (25,47-51,53,57-59,61,62,73-86). These studies involved 5154 patients. Most studies reported a combined CMV infection rate for recipients of cadaveric and living renal transplants. The

probability of CMV infection for living and cadaveric renal transplantation varied from 0.042 to 0.322 (weighted mean average 0.14).

There were three studies with data on CMV infection for PAKT (114,115,117). These studies involved 187 patients. The probability of CMV infection varied from 0.106 to 0.50 (weighted mean average 0.156).

For recipients of a simultaneous pancreas-kidney transplant there were 23 papers that provided data on CMV infection (25,74,75,115,117,120,122,123,125,132,139,141-144,150,151,156-161). These studies involved 1558 patients. The probability of CMV infection following SPKT varied from 0.083 to 0.37 (weighted mean average 0.176).

There was no data found on mortality related to CMV infection. This is likely due to the widespread use of effective antivirals such as ganciclovir . For the model it was assumed that the mortality following CMV infection was 0.001 and was varied from 0 to 0.10 in the sensitivity analysis.

2.1.3.3 *Probability of major infection*

A major infection was defined as any infection that would require hospitalization or prolongation of a hospitalization. This definition included bacteremia, fungemia, pneumonia, meningitis, fungal esophagitis, pyelonephritis, aspergillosis and toxoplasmosis. Local infections such as urinary tract infection (not resulting in pyelonephritis) and thrush were excluded. Also excluded from this definition was CMV infections as they were abstracted and reviewed separately. Major intra-abdominal infections were excluded as they often require surgical exploration or percutaneous

drainage under radiological guidance (124). These infections were included under post-operative complications and are reviewed in the following section.

There were eight reports with data on major infections following renal transplantation (48,54,76,77,82,83,87,88). These studies involved 1476 patients. As was the case with CMV infection, most studies only reported the combined infection rate for living and cadaveric renal transplant recipients. The probability of a major infection after CKT or LKT varied from 0.027 to 0.37 (weighted mean average 0.137).

There are several surgical techniques that can be used for SPKT (113). Each of these techniques may be associated with different infection rates. The most important aspect of the different techniques is the method by which the exocrine pancreas secretions are drained. The secretions can be drained through the bowel (enteric) or into the bladder (113). The majority of simultaneous pancreas-kidney transplants are performed using enteric-drainage(113). The model assumed that SPKT was performed using enteric-drainage. There were three studies that reported major infection rates following enteric-drained SPKT (120,122,123). These studies involved 102 patients. The probability of major infection following enteric-drained SPKT varied from 0.06 to 0.214 (weighted mean average 0.118).

There were five studies that reported major infections following bladder-drained SPKT (87,117,121,122,132). These studies involved 334 patients. The probability of major infection following bladder-drained SPKT varied from 0.051 to 0.288 (weighted mean average 0.131). The best estimate for the probability of major infection was set at 0.118 (enteric-drainage). The range for the sensitivity analysis included the lowest and

highest values from both the enteric-drained and bladder-drained simultaneous pancreas-kidney transplants (0.051 to 0.288).

There were no studies that had data on major infections following PAKT. The majority of pancreas after kidney transplants are performed using bladder drainage of the exocrine pancreas secretions (113). For patients undergoing PAKT it was assumed that the probability of major infection was the same as bladder-drained SPKT. Therefore, the best estimate for the probability of major infection following PAKT was set at 0.131. The range for the sensitivity analysis was set at the same values as for SPKT (0.051 to 0.288).

There were seven reports that had mortality data related to major infections following renal transplantation (47,69,81-83,88,167). These studies involved 1911 recipients of either a cadaveric or a living renal transplant. The probability of dying from a major infection varied from 0.021 to 0.19 (weighted mean average 0.066). The mortality data on major infection following pancreas transplantation could not be used as it contained death related to intra-abdominal infection. Therefore, in the model the probability of dying from a major infection following pancreas transplantation was set at the same value that was used for renal transplantation.

2.1.3.4 *Probability of post-operative complication*

A post-operative complication was defined as an event that required management with an invasive procedure. This definition included any major intra-abdominal infection that required relaparotomy or percutaneous drainage under radiological guidance. Repeat operation for any other reason such as allograft thrombosis (pancreas or kidney),

bleeding, ureteral leak, ureteral stricture, anastomotic leaks, wound dehiscence or lymphocele was also included. Invasive radiological management of ureteral strictures and lymphoceles was included. Asymptomatic lymphoceles that did not require any intervention were excluded. Similarly, mild urinary leaks that were managed by Foley catheter drainage were excluded. Finally, included in this definition were allografts that never functioned (primary non-function) which required operative removal.

The data on primary non-function, allograft thrombosis and wound dehiscence was usually reported as a combined rate for LKT and CKT. For the model it was assumed that these three post-operative complications occurred at the same rate in the cadaveric and living renal transplant patients. There were six articles with data on primary non-function in renal transplantation (69,76,81-83,89). These studies involved 2965 patients. The probability of primary non-function after CKT or LKT varied from 0.004 to 0.022 (weighted mean average 0.011). There were seven papers that reported allograft thrombosis rates (arterial or venous) following kidney transplantation (58,69,76,81,91-93). These studies involved 3334 patients. The probability of allograft thrombosis after CKT or LKT varied from 0.006 to 0.08 (weighted mean average 0.012). There were four papers reporting data on wound dehiscence after renal transplantation (90-93). These studies involved 1897 renal transplant patients. The probability of wound dehiscence after CKT or LKT varied from 0.007 to 0.036 (weighted mean average 0.013).

There were five papers that reported data on lymphoceles in CKT (92,94-96,100). These studies involved 4281 patients. The probability of developing a lymphocele

following CKT varied from 0.004 to 0.068 (weighted mean average 0.026). There were seven articles that reported the rate of urinary leak or obstruction in CKT (92,97-102). These studies involved 4217 patients. The probability of developing a urinary leak or obstruction following CKT varied from 0.017 to 0.057 (weighted mean average 0.024).

The best estimate of the probability of a post-operative complication in CKT was obtained by summing the weighted mean averages of the individual complications. Thus, the probability of developing a post-operative complication following CKT was 0.086 (the sum of 0.011, 0.012, 0.013, 0.026 and 0.024). The lower limit for the sensitivity analysis was set as the lowest probability of any single complication (primary non-function, 0.004). For the upper limit it was assumed that a patient could develop a wound dehiscence, lymphocele, urinary leak and urinary obstruction following renal transplantation. The highest probability of these individual complications was added to obtain the upper limit for the sensitivity analysis ($0.036 + 0.068 + 0.057 = 0.161$). Thus, for cadaveric renal transplantation the probability of developing any post-operative complication varied from 0.004 to 0.161 (best estimate 0.086).

There were six papers that had data on lymphoceles following LKT (91,92,104,107,109,110). These studies involved 2430 patients. The probability of developing a lymphocele following LKT varied from 0.01 to 0.047 (weighted mean average 0.016). There were 10 papers with data on urinary leaks or urinary obstruction following LKT (91,92,105-112). These studies involved 4643 patients. The probability of developing a urinary leak or obstruction following LKT varied from 0.013 to 0.065 (weighted mean average 0.029). The same method was used to obtain the best estimate

and range for the sensitivity analysis as was used above for cadaveric renal transplantation. Thus, the probability of developing a post-operative complication following LKT varied from 0.004 to 0.148 (best estimate 0.081).

As was mentioned in the section on major infections there are different surgical techniques for pancreas transplantation. In addition to the route of exocrine secretion, the surgeon must also decide which venous route to drain the insulin (either systemically or portally). For PAKT the majority of cases are performed with systemic-venous and bladder-exocrine drainage (113). For SPKT the majority are enterically drained. Of these, most have systemic drainage of insulin (113). As the technical failure rates of systemic-venous and portal-venous drainage are the same (113), studies using either technique were included in the calculation of post-operative complications.

There were ten articles with data on post-operative complications for bladder-drained SPKT (87,124-126,128,129,131-134). These studies involved 704 patients. The probability of a post-operative complication developing after bladder-drained SPKT varied from 0.05 to 0.525 (weighted mean average 0.291).

There were seven papers with data on post-operative complications following enteric-drained SPKT (41,120,127,135-138). These studies involved 227 patients. The probability of a post-operative complication after enteric-drained SPKT varied from 0.20 to 0.375 (weighted mean average 0.256). The best estimate for the probability of a post-operative complication was set at 0.256 (enteric-drainage). The range for the sensitivity

analysis included the lowest and highest values from both enteric-drained and bladder-drained SPKT (0.05 to 0.525).

There were two papers with data on post-operative complications for PAKT (128,130). These two studies involved 128 bladder-drained pancreas after kidney transplant patients. The probability of a post-operative complication varied from 0.25 to 0.50 (weighted mean average 0.289). The range of the sensitivity analysis was expanded to include the values used in SPKT (0.05 to 0.525).

2.2 Patient and allograft survival

2.2.1 Data sources

The United Network for Organ Sharing (UNOS) has required mandatory reporting of all solid organ transplant activity in the United States since 1998 (73). The UNOS database has compiled information on over 35,289 cadaveric kidney transplants and 16,288 living donor kidney transplants performed since 1994 (168). The UNOS database also has detailed information on 10,579 pancreas transplants performed since 1987 (113). The Canadian Organ Replacement Register maintains a voluntary database of transplant activity in Canada. The Canadian database reported patient and graft survival rates on only 107 pancreas transplants performed since 1987 (169). The Canadian database did not have any information on death while waiting for a transplant, PAKT or data stratified by the surgical procedure employed during pancreas transplant surgery (169). Due to these limitations as well as the small number of transplants reported to the Canadian database, the UNOS registry was used to obtain patient and allograft survival data.

The presence or absence of diabetes mellitus is one of the most important predictors of survival for patients with ESRD (9). The UNOS registry presents survival data stratified by the underlying renal disease. However, all diabetic patients (both type 1 and type 2) are categorized together (39). The use of this combined data may not be accurate as the survival of type 1 and type 2 diabetic patients is not the same (168). For this reason a special data request was submitted to UNOS in February 2001 (UNOS data request number 021201). The one-year and five-year patient and allograft survival rates for type 1 diabetic patients undergoing CKT and LKT was requested. In addition, information describing the incidence of death on the cadaveric waiting list for type 1 diabetic patients was also requested. Similar data was not required for pancreas transplant recipients as 97% of these recipients are listed as having type 1 diabetes mellitus (113).

Age is also a critical determinant of survival following transplantation (9). As the majority of pancreas transplant recipients are between 18 and 49 years old (39) only the patient and graft survival data from these strata were used in the model.

The risk of death or graft loss after renal transplantation is greatest in the first post-transplant year but remains constant thereafter (9,13,170,171). To account for this changing risk profile, the Markov model included a measure of short-term risk and long-term risk. Short-term risk was modeled as the probability of death or allograft failure in the first post-transplant year. The long-term risk was modeled as the average probability of death or allograft failure from year one to five post-transplantation. It was assumed that the rates of graft loss and patient death would remain the same after the fifth post-transplant year (9,13,170). To make the model as current as possible the most recent

patient cohort supplied by UNOS was used to determine the patient and allograft survival rates. The 95 percent confidence interval from the patient and allograft survival values was used as the range in the sensitivity analysis (172).

2.2.2 *Cadaveric renal transplantation*

For CKT the one-year survival rates are from the cohort of patients transplanted in 1997-1998. Five-year survival rates are from the cohort of patients transplanted 1992-1995. For type 1 diabetic patients undergoing CKT, the probability of survival at one-year and five-years was 0.947 and 0.775 respectively (46). Thus, the probability of death in the first post-transplant year (short-term risk of transplantation) was 0.053 and the annual probability of death after the first year (long-term risk) was 0.043 $((0.947 - 0.775)/4)$. The probability of allograft survival at one-year and five-years was 0.90 and 0.617 respectively (46). Thus, the probability of allograft loss in the first post-transplant year was 0.10 and the annual probability of allograft failure after the first year was 0.071 $((0.9 - 0.617)/4)$. As death also counts as an allograft loss (39) the probability of allograft loss unrelated to death was calculated by subtracting the patient survival from the allograft survival. Therefore, the probability of nonfatal allograft loss in the first post-transplant year was 0.047 $(0.10 - 0.053)$ and the annual probability of nonfatal allograft failure after the first year was 0.028 $(0.071 - 0.043)$.

For the sensitivity analysis the one-year patient survival ranged from 0.931 to 0.963 and the five-year patient survival ranged from 0.756 to 0.794. The one-year allograft survival ranged from 0.879 to 0.921 and the five-year allograft survival ranged from 0.597 to 0.637.

2.2.3 *Living renal transplantation*

For LKT the one-year survival rates are from the cohort of patients transplanted in 1997-1998. Five-year survival rates are from the cohort of patients transplanted 1992-1995. For type 1 diabetic patients undergoing LKT, the probability of survival at one-year and five-years was 0.962 and 0.868 respectively (46). Thus, the probability of death in the first post-transplant year was 0.038 and the annual probability of death after the first year was 0.024. The probability of allograft survival at one-year and five-years was 0.937 and 0.761 respectively (46). Thus, the probability of allograft loss in the first post-transplant year was 0.063 and the annual probability of allograft failure after the first year was 0.044. The probability of nonfatal allograft loss in the first post-transplant year was 0.025 and the annual probability of nonfatal allograft failure after the first year was 0.02.

For the sensitivity analysis the one-year patient survival ranged from 0.947 to 0.977 and the five-year patient survival ranged from 0.847 to 0.889. The one-year allograft survival ranged from 0.918 to 0.956 and the five-year allograft survival ranged from 0.736 to 0.786.

2.2.4 *Simultaneous pancreas-kidney transplantation*

For SPKT the one-year survival rates are from the cohort of patients transplanted in 1997-1998. Five-year survival rates are from the cohort of patients transplanted 1990-1998 for which a five-year survival time could be determined (39). For SPKT the probability of survival at one-year and five-years was 0.947 and 0.831 respectively (39). Thus, the probability of death in the first post-transplant year was 0.053 and the annual probability of death after the first year was 0.029. The probability of renal allograft

survival at one-year and five-years was 0.921 and 0.710 respectively (39). Thus, the probability of renal allograft loss in the first post-transplant year was 0.079 and the annual probability of renal allograft failure after the first year was 0.053. The probability of nonfatal renal allograft loss in the first post-transplant year was 0.026 and the annual probability of nonfatal renal allograft failure after the first year was 0.024. The probability of pancreas allograft survival at one-year and five-years was 0.84 and 0.678 respectively (39). Thus, the probability of pancreas allograft loss in the first post-transplant year was 0.16 and the annual probability of pancreas allograft failure after the first year was 0.041. The probability of nonfatal pancreas allograft loss in the first post-transplant year was 0.107 and the annual probability of nonfatal pancreas allograft failure after the first year was 0.012.

For the sensitivity analysis the one-year patient survival ranged from 0.936 to 0.958 and the five-year patient survival ranged from 0.821 to 0.841. The one-year renal allograft survival ranged from 0.908 to 0.934 and the five-year renal allograft survival ranged from 0.698 to 0.722. The one-year pancreas allograft survival ranged from 0.822 to 0.858 and the five-year pancreas allograft survival ranged from 0.666 to 0.69.

2.2.5 *Pancreas after living renal transplantation*

Short and long-term patient survival for PAKT is similar to that of SPKT (173). Therefore, the same patient survival rates were used in the model. As pancreas transplantation has no adverse effect on an existing renal transplant (43) short and long-term renal allograft survival was assumed to be the same as for patients undergoing LKT alone. The cohort of patients for the pancreas survival rates was transplanted from 1996-

2000 (113). The probability of pancreas allograft survival at one-year and three-years was 0.78 and 0.60 respectively (113). Thus, the probability of pancreas allograft loss in the first post-transplant year was 0.22 and the annual probability of pancreas allograft failure after the first year was 0.09.

For the sensitivity analysis the one-year patient survival ranged from 0.936 to 0.958 and the five-year patient survival ranged from 0.821 to 0.841. The one-year renal allograft survival ranged from 0.918 to 0.956 and the five-year renal allograft survival ranged from 0.736 to 0.786. The one-year pancreas allograft survival ranged from 0.726 to 0.834 and the three-year pancreas allograft survival ranged from 0.537 to 0.663.

2.2.6 *Remain on dialysis*

The mortality rate for diabetic patients on dialysis, who are not transplant candidates, is significantly higher than similar patients on the transplant waiting list (9). As the model assumed that patients entering the decision node were medically suitable for transplantation the use of the dialysis mortality rate would bias against the decision to remain on dialysis. For the model it was assumed that patients who remained on dialysis would have the same mortality rate as type 1 diabetic patients on the cadaveric renal transplant waiting list. The derivation of the waiting list mortality rate is outlined in the section to follow. For the sensitivity analysis, the highest mortality rate was assumed to be the mortality rate for diabetic patients who were not transplant candidates (19.9 deaths per 100 patient-years) (9). The lowest mortality rate was set at the same rate as Asians on the cadaveric waiting list (3.0 deaths per 100 patient-years) (9).

2.2.7 *Mortality while waiting for transplantation*

Patients with ESRD awaiting transplantation have a mortality rate that is lower than similar patients who are on dialysis but not transplant candidates and a rate that is higher than patients who have received a transplant (9). The attenuated mortality rate while awaiting transplantation was incorporated into the model.

The mortality rate for type 1 diabetic patients awaiting CKT was contained in the data obtained from UNOS (46). The mortality rate was calculated by taking the mean mortality rate for type 1 diabetic patients (age 18 to 49) from 1996-1999. The mortality rate was 0.122 per patient-year (46).

The mortality rate while waiting for SPKT was abstracted from the UNOS Annual Report (39). As was done for CKT, the mortality rate was calculated by taking the mean mortality rate (age 18 to 49) from 1996-1999. The mortality rate was 0.079 per patient-year (39). For patients awaiting PAKT it was assumed that the mortality rate would be the same as for patients with a functioning living kidney transplant.

For the sensitivity analysis of mortality while waiting for transplantation, the highest mortality rate was assumed to be the mortality rate for diabetic patients who were not transplant candidates (19.9 deaths per 100 patient-years) (9). The lowest mortality rate was set at the lowest mortality rate for recipients of a living kidney transplant (five-year survival 0.889).

2.3 **Waiting time to receive a transplant**

The waiting time to receive a cadaveric kidney or pancreas transplant varies considerably depending on clinical characteristics such as blood type and sensitization from a previous transplant (73). As the model assumes that each patient is undergoing their first transplant procedure the waiting time for first transplant recipients was used. For CKT the probability of receiving a transplant within one year was 0.196 (73). For SPKT the probability of receiving a transplant within one year was 0.42 (73). For PAKT the probability of receiving a transplant within one year was 0.682 (73).

For the sensitivity analysis the patient group that had the lowest and highest probability of being transplanted was used. Pancreas transplant recipients that were blood group AB had the highest probability of being transplanted within one year (0.905) (73). Asians waiting for a cadaveric renal transplant had the lowest probability of being transplanted within one year (0.095) (73).

2.4 Complications related to diabetes mellitus

2.4.1 *Hypoglycemia*

The most common acute metabolic complication of type 1 diabetes is hypoglycemia. The incidence of hypoglycemia is dependent on the degree of blood glucose normalization (162,174). When intensified insulin therapy is used to achieve near-normal glucose values, the risk of hypoglycemia is increased nearly threefold over conventional insulin therapy (162,174). However, intensive insulin therapy is recommended since it delays the progression of retinopathy, nephropathy and neuropathy (174). In the model we assumed that patients with a functioning renal transplant would receive intensive insulin therapy. For patients on dialysis, who already have many

complications of diabetes, strict glucose control is generally not recommended because of the risk of hypoglycemia (8). In the model we assumed that patients on dialysis would receive conventional insulin therapy. The model incorporated episodes of severe but not minor hypoglycemia. Severe hypoglycemia was defined as any episode of hypoglycemia in which the patient required assistance with treatment from another person (163).

Egger et. al. have published a meta-analysis that defined the risk associated with intensive glucose control in type 1 diabetes mellitus (162). In this study the median incidence of severe hypoglycemia was 7.9 episodes per 100 person-years among intensively treated patients and 4.6 episodes per 100 person-years in conventionally treated patients (162). In the model, the probability of severe hypoglycemia was 0.079 for patients with a functioning kidney transplant and 0.046 for patients on dialysis. Since pancreas transplantation is often recommended for the most labile diabetic patients (175) the probability of hypoglycemia was conservatively varied from 0 to 1.

2.4.2 *Ketoacidosis*

The incidence of ketoacidosis is not influenced by the intensity of glucose control (174). Therefore, we assumed that patients on dialysis (conventional insulin therapy) and patients with a functioning renal transplant (intensive insulin therapy) would have the same probability of developing ketoacidosis. An estimate of the risk of ketoacidosis could not be abstracted from the meta-analysis because of the way the data was presented. In the Diabetes Control and Complications Trial (n=1441), the largest randomized trial of intensive insulin therapy, there were 181 episodes of ketoacidosis in both treatment groups (probability of ketoacidosis of 0.019) (163). Since pancreas

transplantation is often recommended for the most labile diabetic patients (175) the probability of ketoacidosis was conservatively varied from 0 to 1.

2.4.3 *Mortality related to hypoglycemia and ketoacidosis*

In the Diabetes Control and Complications Trial there were two deaths directly related to hypoglycemia (163). As there were 3,788 episodes of severe hypoglycemia the probability of dying from an episode of hypoglycemia was set at 0.00053. Excluding the Diabetes Control and Complications Trial, there were two deaths directly related to hypoglycemia reported in the meta-analysis (162) and the probability of dying from an episode of hypoglycemia varied from 0 to 0.015. To account for the possibility that labile diabetics may be more likely to undergo pancreas transplantation the probability of dying from an episode of hypoglycemia was conservatively varied from 0 to 0.1.

In the Diabetes Control and Complications Trial there was one death directly related to ketoacidosis (163). Thus, the probability of dying from an episode of ketoacidosis was set at 0.0055. In the meta-analysis there were five deaths due to ketoacidosis, including the one death from the Diabetes Control and Complications Trial (162). If that one death is excluded, the probability of dying from an episode of ketoacidosis varied from 0 to 0.09. Once again, to account for the fact that labile diabetics may be more likely to undergo pancreas transplantation the probability of dying from an episode of ketoacidosis was conservatively varied from 0 to 0.15.

2.5 Utilities

2.5.1 *Overview*

The output from the model included life expectancy, quality-adjusted life expectancy and discounted quality-adjusted life expectancy. In order to determine the quality-adjusted life expectancy a subjective weight of time spent in the health states under consideration was required. Utilities, which reflect the strength of one's preference for a given health (33), were used as the subjective weight. Discounted quality-adjusted life expectancy was measured because individuals have a time preference for benefits today rather than in the future (176). Discount rates of both 3% and 5% have been used previously (177). A discount rate of 3% was chosen to reflect more recent trends as recommended by Lipscomb, Weinstein and Torrance (177). These authors also recommend that the discount rate be varied from 0 to 7% in the sensitivity analysis (177). The lower bound provides insight into the effect of no discounting; the upper bound represents a reasonable ceiling given current trends (177).

2.5.2 *Sources for health state preferences*

Utilities can be obtained from patients experiencing the health state, family members, health care professionals or members of the general public (178). The type of study often determines which group is most appropriate for obtaining preferences. For example, a cost-effectiveness study performed to determine resource allocation should obtain preferences from the general public (178). However, an analysis designed to evaluate different treatment choices of the same condition should use patient preferences (178). As this model was designed to evaluate alternative strategies of the same condition, the preferences were obtained from patients with type 1 diabetes mellitus.

Structured interviews were carried out on n=50 patients with type 1 diabetes to determine the utility score for the health states dialysis, functioning kidney transplant and functioning kidney-pancreas transplant. Potential participants were recruited from the General Medicine and Endocrinology clinics of The Ottawa Hospital. Participants were eligible to participate if they were greater than 17 years of age and had diabetes requiring insulin therapy. Patients were excluded if they had already received a kidney or pancreas transplant, had already started dialysis, were unable to understand English or they refused to consent. Patients who had already experienced one of the health states were excluded as the objective of the analysis was to determine the best treatment option at the onset of ESRD. The use of patients who already had a positive or negative experience with the health state under consideration would influence the measured utility value (178). For example, a patient who has an uncomplicated kidney transplant with a good outcome would assign a higher utility than someone who experienced a bad outcome with their transplant (2).

The study protocol to obtain utilities was reviewed and approved by The Ottawa Research Ethics Board (see Appendix 2). All participants had the study explained to them, were given an information sheet to read and were required to sign a consent form (see Appendix 3).

2.5.3 *Utility measurement*

The standard gamble technique was used to measure the health state utilities (33). The standard gamble is a paired comparison in which the participant must choose between two alternatives, one with a certain outcome and the other with a “gamble” (33).

Alternative 1 is a treatment with two possible outcomes: either the patient returns to perfect health (probability p) or dies immediately (probability $1-p$) (176). Alternative 2 is the certain outcome of remaining in the health state under consideration for the remainder of the patient's lifetime (176). The probability p is varied back and forth until the participant is indifferent between the alternatives. The utility score is equal to the indifference point and ranges from 0 (death) to 1 (perfect health) (176).

2.5.4 *Health state descriptions*

Hypothetical scenarios were developed to describe the health states under consideration: dialysis, functioning kidney transplant and functioning kidney-pancreas transplant. Each scenario consisted of a short narrative describing what one would experience in the health state followed by descriptors from the Health Utility Index Mark III (179). The Mark III is a generic, validated quality of life instrument that encompasses eight domains of health: vision, hearing, speech, ambulation, dexterity, emotion, cognition and pain (179). Each domain has five or six levels and the combination of levels from each domain make up a unique health state (180). The Health Utility Index Mark III format was used so that the measured utilities may be compared to utilities derived for other medical conditions.

The descriptions avoided the use of a disease label (such as “dialysis” or “cancer”) as it has been shown to bias utility measurement (180). As the utility for a health state is affected by its duration, the participants were told that they would remain in each health state for the remainder of their lives (180). Prognosis was not explicitly stated in the health state descriptions (33). The content of the scenarios was developed

and validated by six physicians with expertise in dialysis and transplantation. The health state descriptions are shown in Appendix 4.

2.5.5 *Patient interview process*

The utilities were generated using a computer-based interview. This allowed the interview to be carried out in a consistent manner at the pace of the subject. The computer program contained text descriptions of the health states with voice instructions. There was a graphical display of the standard gamble. The interviews were conducted by the author or a research coordinator.

To ensure that the subject understood the standard gamble a simple example was carried out before completing the three health states under consideration. The subjects were asked to perform the standard gamble on the health state of being blind in one eye and the health state of being completely blind. If the subject understood the standard gamble correctly the utility for complete blindness should be lower than the utility of being blind in one eye. If the subject gave a higher utility to complete blindness they were excluded from further analysis.

2.5.6 *Disutilities*

The impact of short-term health states on quality of life was accounted for by the use of disutilities. A disutility value represents the negative impact on quality of life associated with the health state (172). To calculate a disutility the period of time spent in the short-term state must first be determined. The disutility is then calculated assuming that the patient's utility during this time period was zero (172,181). Thus, the disutility

represents the proportion of the total cycle length (90 days) spent in a given short term health state.

Published data and a convenience sample of physicians were used to determine the period of time spent in the short-term health states (180). The transplant associated short-term health states were: major infection, CMV infection, acute rejection and post-operative complication. Six physicians with expertise in transplantation were asked to estimate the time that each of these health states would have a negative impact on the patient's quality of life. The mean value from the six physicians was used as the best estimate in the model. The mean (standard deviation) number of days spent in each health state was as follows: major infection 20 (9) days; CMV infection 29 (7) days; acute rejection 43 (32); and post-operative complication 43 (34). As these disutilities were only estimates, the sensitivity analysis was varied from 0 to 90 days (Table 2).

The diabetes-related short-term health states considered were severe hypoglycemia and ketoacidosis. Four internists with expertise in diabetes mellitus were asked to estimate the time period that a severe hypoglycemia episode would have a negative impact on quality of life. The mean (standard deviation) time was 6 (9) hours. Once again, the sensitivity analysis was varied from 0 to 90 days (Table 2). The time period of a ketoacidosis episode was set at 6 days. This value was used as it was the mean length of hospitalization derived from a study on ketoacidosis in type 1 diabetics (182). As no range in hospitalization could be found, the sensitivity analysis was varied from 1 to 90 days (Table 2).

Table 2: Disutility estimates of short-term health states

Short-Term Health State	Mean Duration (days)	Best Estimate of Disutility	Range for Sensitivity Analysis
Major infection	20	0.222	0-1.0
CMV infection	29	0.322	0-1.0
Acute rejection	43	0.478	0-1.0
Post-operative complication	43	0.478	0-1.0
Severe hypoglycemia	0.25	0.003	0-1.0
Ketoacidosis	6	0.067	0.011-1.0

3.0 Sensitivity Analysis

Sensitivity analysis was performed to correct any errors in the model and to assess the degree of uncertainty in the results (183). To determine if there were any structural errors, each variable in the model was changed over its entire range while holding all the other variables constant. The results were displayed graphically to determine if they made sense. For example, as the probability of dying post-kidney transplant is increased from 0 to 1, the life expectancy of kidney transplantation should decline. If this result did not occur then an error must be present in the model. Any errors were corrected and the process was repeated until all of the variables produced logical results.

The next step in the sensitivity analysis was to determine the robustness of the results. First, one-way sensitivity analyses were performed by changing the value of each variable over its plausible range while holding all the other variables constant (183). The results were displayed graphically to determine if a threshold value was present. The threshold is the value for the variable under consideration at which two treatment strategies have the same result. At any point beyond the threshold value a different treatment strategy will be preferred. If a threshold value falls within the plausible range, then the model is sensitive to that variable.

The final step in the sensitivity analysis was to perform two-way and three-way sensitivity analyses. In these analyses, two or three variables are simultaneously changed over their plausible range. Once again they are displayed graphically to determine if threshold values are present. Variables that appeared to be influential in one-way sensitivity analysis were evaluated by multi-way sensitivity analysis (183).

RESULTS

1.0 Utilities

1.1 *Patient Population*

Fifty patients with type 1 diabetes were interviewed. The mean (standard deviation) age of the patients was 30.6 (9.7) years and 68% were female. The mean duration of diabetes was 14.2 (9.9) years. One patient was excluded because he assigned a higher utility value to complete blindness compared to being blind in one eye.

1.2 *Utility estimates*

The mean (standard deviation) utility values for blind in one eye and complete blindness were 0.89 (0.11) and 0.77 (0.19) respectively. The mean utility values for dialysis, kidney transplantation and kidney pancreas transplantation were 0.70 (0.26), 0.80 (0.17) and 0.85 (0.12) respectively (Table 3).

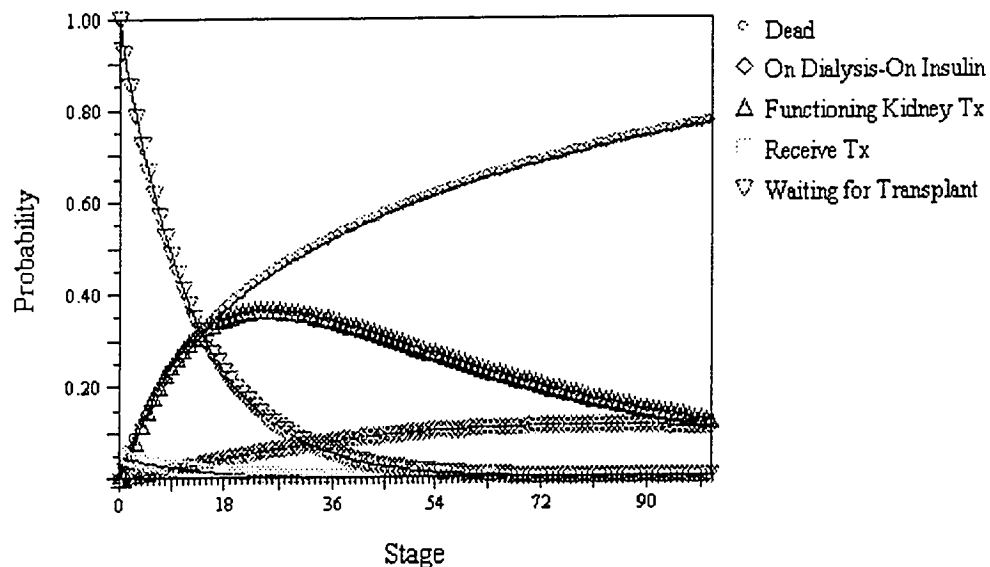
Table 3: Utility values for health states

Health State	Mean Utility	SD	Range
Dialysis	0.70	0.26	0.01-1.0
Kidney transplantation	0.80	0.17	0.01-1.0
Kidney-pancreas transplantation	0.85	0.12	0.5-1.0
Blind in one eye	0.89	0.11	0.5-0.99
Blind in both eyes	0.77	0.19	0.01-0.99

2.0 Model validation

To ensure that the patients progressed through the health states properly a Markov probability analysis was performed for each treatment option. The probability analysis for cadaveric renal transplantation is shown in Figure 4. As time progresses, patients leave the “waiting for transplant” state and move into the kidney transplantation, dialysis and death states. The Markov analyses for remain on dialysis, living kidney transplantation, pancreas after living kidney transplantation and simultaneous pancreas-kidney transplantation yielded similar results.

Figure 4: Markov probability analysis for cadaveric renal transplantation



The figure depicts how the cohort leaves the “waiting for transplant” state and enters the “kidney transplantation”, “dialysis” and “death” health states.

The survival estimates used in the model were derived from patients *after* they had received a transplant. However, the model included time spent in the pre-transplant state (waiting for a transplant) as well as time spent post-transplantation. To ensure that the survival estimates used in the model produced valid results, a Markov probability analysis was performed after revising the model so that all patients received a transplant immediately. The five-year patient survival values from the Markov probability analysis were nearly identical to the values entered into the model (Table 4).

Table 4: Validation of patient survival data from model

Treatment Option	Estimate Entered in Model (5-year survival)	Result from Model (5-year survival)
Cadaveric Renal Transplantation	77.5	77.2
Living Renal Transplantation	86.8	86.0
Pancreas after Living Renal Transplantation	83.1	83.0
Simultaneous Pancreas-Kidney Transplantation	83.1	83.7

3.0 Base case analysis

The life expectancy, gain in life expectancy, quality-adjusted life expectancy and discounted quality-adjusted life expectancy for each treatment option is presented in Table 5. Based on the best estimate of each variable in the model, LKT was the preferred treatment option for type 1 diabetic patients with ESRD.

Table 5: Results of base case analysis

Treatment Option	Life Expectancy (LY)	Gain in Life Expectancy (LY)	Quality-Adjusted Life Expectancy (QALY)	Discounted Quality-Adjusted Life Expectancy (QALY)	Gain in Discounted Quality-Adjusted Life Expectancy (QALY)
Dialysis	7.82	-	5.47	4.52	-
Cadaveric Renal Transplantation	11.44	3.62	8.54	6.53	2.01
Simultaneous Pancreas-Kidney Transplantation	15.74	4.3	12.32	9.09	2.56
Pancreas after Living Renal Transplantation	17.21	1.47	13.52	10.00	0.91
Living Renal Transplantation	18.30	1.09	14.03	10.29	0.29

LY denotes life year; QALY, quality-adjusted life year

4.0 Sensitivity analysis

4.1 One-way sensitivity analysis

The results of one-way sensitivity analysis on every variable in the model are displayed in Table 6. The results were sensitive to changes in the value of several variables that will be reviewed in the subsequent sections.

Table 6: Results of one-way sensitivity analysis

A: One-way sensitivity analysis on discount rate, utilities and disutilities

Variable	Baseline Value	Range	Threshold Value	Sensitive
Discount	0.03	0-0.07	-	No
Disutilities				
Ketoacidosis	0.067	0.011-1.0	-	No
Major infection	0.222	0-1.0	-	No
CMV Infection	0.322	0-1.0	-	No
Acute Rejection	0.478	0-1.0	-	No
Severe Hypoglycemia	0.003	0-1.0	-	No
Post-operative Complication	0.478	0-1.0	-	No
Utilities				
Dialysis	0.70	0.01-1.0	< 0.21: PAKT preferred > 0.21: LKT preferred	Yes
Kidney Transplantation	0.80	0.01-1.0	< 0.59: SPKT preferred 0.59-0.74: PAKT preferred >0.74: LKT preferred	Yes
Kidney-Pancreas Transplantation	0.85	0.5-1.0	< 0.91: LKT preferred > 0.91: PAKT preferred	Yes

PAKT denotes pancreas after kidney transplantation, LKT, living kidney transplantation
SPKT, simultaneous pancreas-kidney transplantation

B: One-way sensitivity analysis on variables related to diabetes

Variable	Baseline Value	Range	Threshold Value	Sensitive
Probability of hypoglycemia on dialysis	0.011	0-1.0	-	No
Probability of hypoglycemia with a kidney transplant	0.019	0-1.0	-	No
Probability of ketoacidosis	0.005	0-1.0	<0.23: LKT preferred > 0.23: PAKT preferred	Yes
Probability of death from ketoacidosis	0.0055	0-0.15	-	No
Probability of death from severe hypoglycemia	0.00053	0-0.10	< 0.09: LKT preferred > 0.09: PAKT preferred	Yes

PAKT denotes pancreas after kidney transplantation; LKT, living kidney transplantation

C: One-way sensitivity analysis on variables related to cadaveric renal transplantation and dialysis

Variable	Baseline Value	Range	Threshold Value	Sensitive
Remain on Dialysis				
Probability of death on dialysis	0.029	0.007-0.048	-	No
Cadaveric Renal Transplant				
Probability of death early post-transplant	0.044	0.028-0.06	-	No
Probability of death late post-transplant	0.011	0.009-0.012	-	No
Probability of death from CMV infection	0.001	0-0.10	-	No
Probability of death from major infection	0.066	0.021-0.19	-	No
Probability of death on waiting list	0.029	0.005-0.048	< 0.0069: SPKT preferred > 0.0069: LKT preferred	Yes
Probability of CMV infection	0.037	0.011-0.093	-	No
Probability of major infection	0.137	0.027-0.37	-	No
Probability of rejection	0.171	0.081-0.27	-	No
Probability of graft loss from rejection	0.134	0-1.0	-	No
Probability of post-operative complication	0.086	0.004-0.161	-	No
Probability of graft loss from post-operative complication	0.272	0-1.0	-	No
Probability of graft loss late post-transplant	0.007	0.006-0.01	-	No
Probability of receiving transplant	0.048	0.023-0.202	-	No

SPKT denotes simultaneous pancreas-kidney transplantation; LKT, living kidney transplantation

D: One-way sensitivity analysis on variables related to living kidney transplantation

Variable	Baseline Value	Range	Threshold Value	Sensitive
Relative risk of death early post-transplant	0.659	0.1-0.7	-	No
Relative risk of death late post-transplant	0.545	0.421-0.667	< 0.63: LKT preferred > 0.63: PAKT preferred	Yes
Relative risk of death from CMV infection	1	0-100	< 25.2: LKT preferred > 25.2: PAKT preferred	Yes
Relative risk of death from major infection	1	0.318-2.876	-	No
Relative risk of CMV infection	1	0.288-2.502	-	No
Relative risk of major infection	1	0.197-2.699	-	No
Relative risk of rejection	0.69	0.291-3.432	-	No
Relative risk of graft loss from rejection	0.771	0-7.253	-	No
Relative risk of post-operative complication	0.942	0.024-8.0	-	No
Relative risk of graft loss from post-operative complication	0.568	0-3.67	-	No
Relative risk of graft loss late post-transplant	0.743	0.516-0.968	-	No

PAKT denotes pancreas after kidney transplantation; LKT, living kidney transplantation

E: One-way sensitivity analysis on variables related to pancreas after living kidney transplantation

Variable	Baseline Value	Range	Threshold Value	Sensitive
Relative risk of death early post-transplant	0.258	0-0.395	-	No
Relative risk of death late post-transplant	0.67	0.59-0.734	-	No
Relative risk of death from CMV infection	1	0-100	-	No
Relative risk of death from major infection	1	0.318-2.876	-	No
Relative risk of death on waiting list	0.194	0.113-8.832	-	No
Relative risk of CMV infection	1.121	0.298-14.911	-	No
Relative risk of major infection	0.956	0.138-2.5	-	No
Relative risk of rejection	1.678	0.741-3.3	-	No
Relative risk of pancreas loss from rejection	4.257	0-12.189	-	No
Relative risk of post-operative complication	3.36	0.311-6.5	-	No
Relative risk of pancreas loss from post-operative complication	1.033	0-2.986	-	No
Relative risk of pancreas loss late post-transplant	5.274	6-12	-	No
Relative risk of kidney loss late post-transplant	0.544	0.317-0.769	-	No
Relative risk of receiving pancreas transplant	3.278	0.116-8.627	-	No

F: One-way sensitivity analysis on variables related to simultaneous pancreas-kidney transplantation

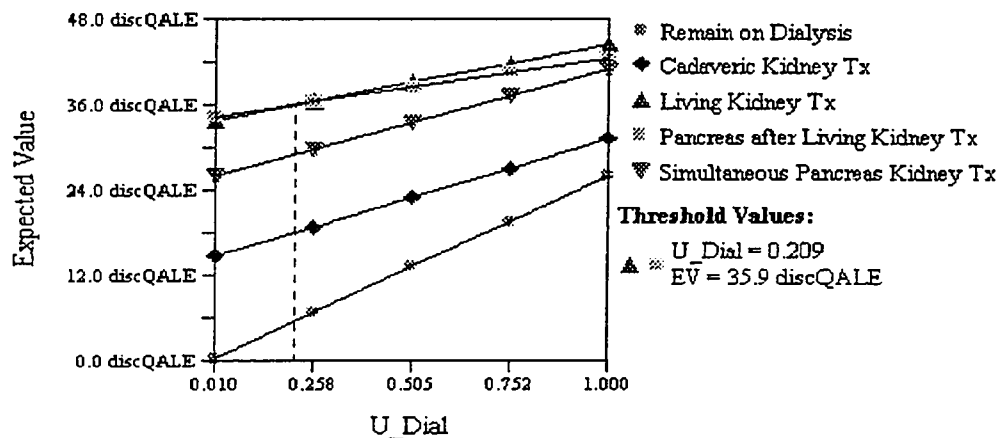
Variable	Baseline Value	Range	Threshold Value	Sensitive
Relative risk of death early post-transplant	1.029	0.779-1.279	-	No
Relative risk of death late post-transplant	0.67	0.59-0.734	-	No
Relative risk of death from CMV infection	1	0-100	-	No
Relative risk of death from major infection	1	0.318-2.876	-	No
Relative risk of death on waiting list	0.659	0.113-8.832	< 0.15: SPKT preferred > 0.15: LKT preferred	Yes
Relative risk of CMV infection	1.278	0.231-10.224	-	No
Relative risk of major infection	0.861	0.138-10.667	-	No
Relative risk of rejection	1.526	0.233-9.259	-	No
Relative risk of pancreas loss from rejection	1	0-12.189	-	No
Relative risk of kidney loss from rejection	0.361	0-7.253	-	No
Relative risk of post-operative complication	2.977	0.311-138.157	-	No
Relative risk of pancreas loss from post-operative complication	1	0-2.986	-	No
Relative risk of kidney loss from post-operative complication	0.187	0-3.672	-	No
Relative risk of pancreas loss late post-transplant	1	0.74-2.6	-	No
Relative risk of kidney loss late post-transplant	0.859	0.751-1.2	-	No
Relative risk of receiving kidney-pancreas transplant	2.084	0.116-8.627	-	No

SPKT denotes simultaneous pancreas-kidney transplantation; LKT, living kidney transplantation

4.1.1 One-way sensitivity analysis on utilities and disutilities

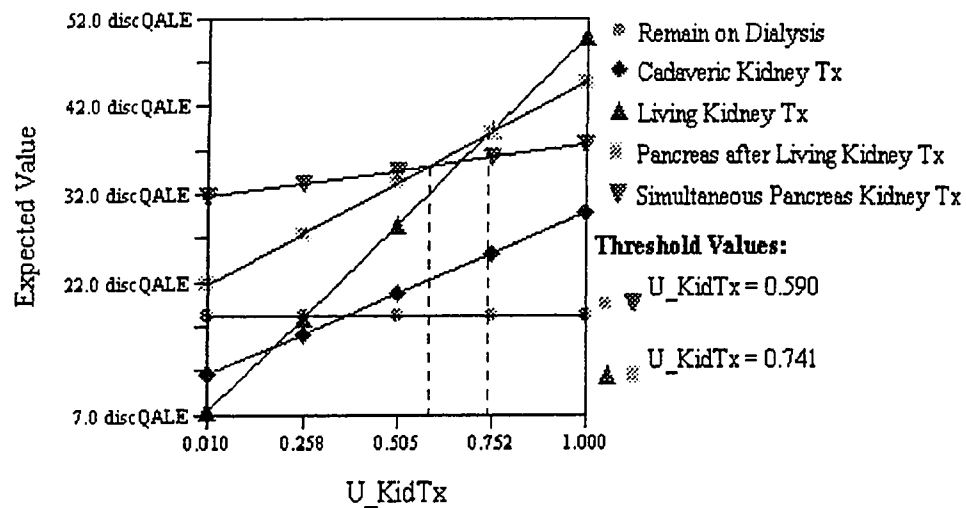
PAKT was the preferred treatment option when the utility for dialysis was less than 0.21 (Figure 5). Although this utility value was within the range considered plausible, only 8% of patients interviewed assigned the dialysis state a utility score less than 0.21.

Figure 5: One-way sensitivity analysis on the utility for dialysis



SPKT was preferred when the utility for kidney transplantation was less than 0.59 (Figure 6). Only 4.1% of patients interviewed assigned a utility score of less than 0.59 for kidney transplantation. PAKT was preferred when the utility for kidney transplantation was between 0.59 and 0.74. Above 0.74, LKT was the preferred strategy. Of all the patients interviewed, 77.6% assigned kidney transplantation a utility score above 0.74.

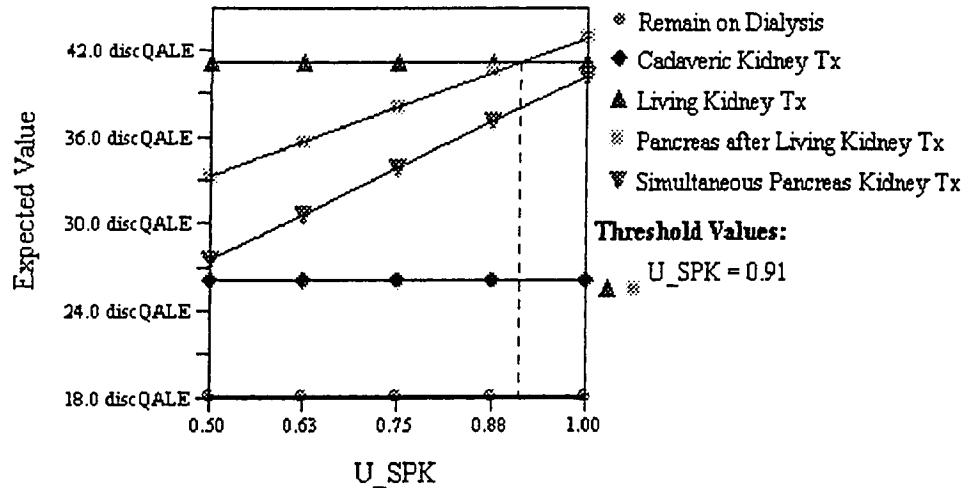
Figure 6: One-way sensitivity analysis on the utility for kidney transplantation



Living kidney transplantation was preferred over all other strategies when the utility for kidney transplantation was above 0.74.

When the utility for kidney-pancreas transplantation was below 0.91 LKT alone was the preferred option; above this value PAKT was preferred (Figure 7). Nearly one third of patients interviewed assigned kidney-pancreas transplantation a utility above 0.91.

Figure 7: One-way sensitivity analysis on the utility for kidney-pancreas transplantation

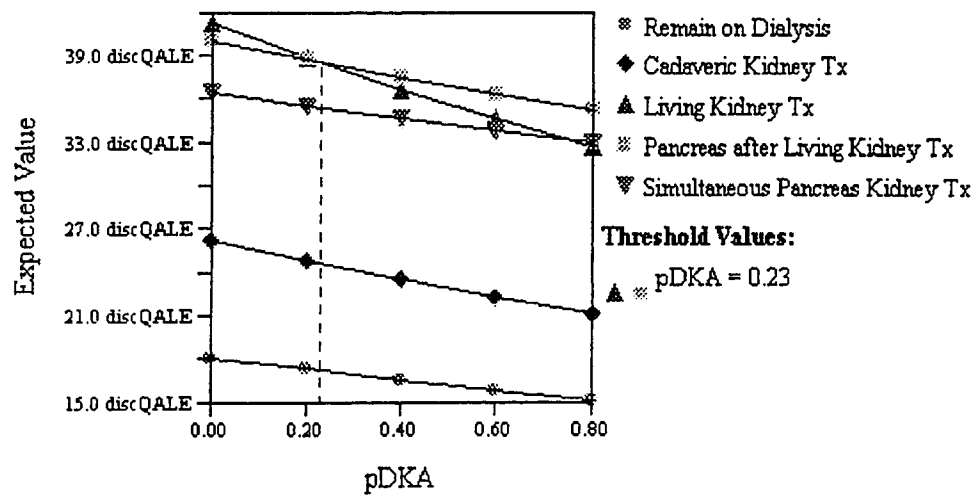


Pancreas after kidney transplantation was the preferred strategy when the utility for kidney-pancreas transplantation was above 0.91.

4.1.2 One-way sensitivity analysis on variables related to diabetes

When the cycle-specific probability of ketoacidosis was above 0.23, PAKT was preferred over LKT (Figure 8). This cycle-specific probability corresponds to a ketoacidosis rate of 104.5 episodes per 100 patient-years.

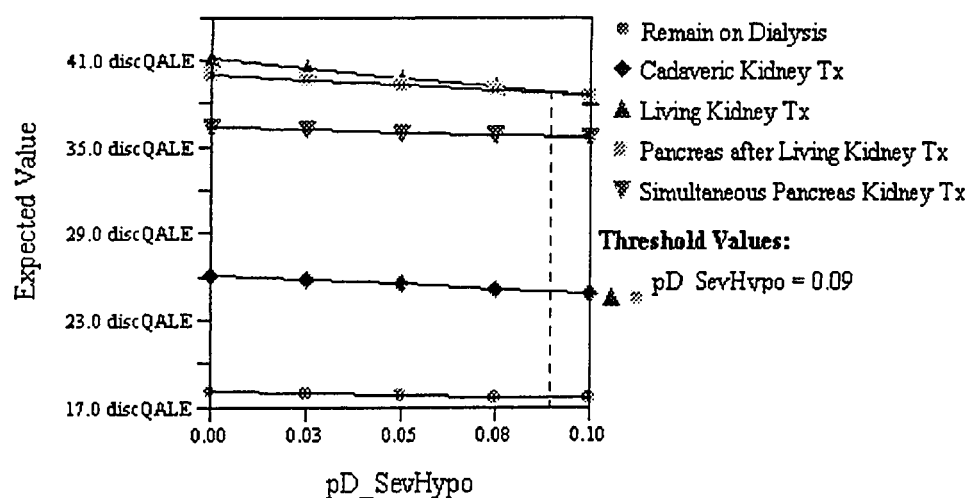
Figure 8: One-way sensitivity analysis on the probability of ketoacidosis



Pancreas after kidney transplantation was the preferred strategy when the cycle-specific probability of ketoacidosis was above 0.23.

When the probability of dying from an episode of hypoglycemia was above 9%, PAKT was preferred over LKT (Figure 9). This value was substantially higher than the best estimate used in the model.

Figure 9: One-way sensitivity analysis on the probability of death from hypoglycemia

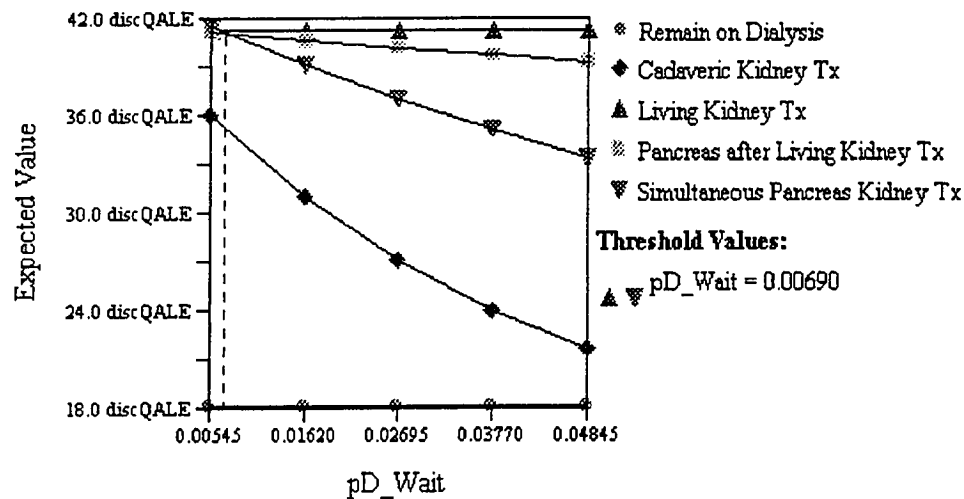


Pancreas after kidney transplantation was the preferred strategy when the probability of death from hypoglycemia was above 0.09.

4.1.3 One-way sensitivity analysis on probability of death on the waiting list

When the cycle-specific probability of death while awaiting transplantation was less than 0.0069, SPKT was the preferred treatment; above this value LKT was preferred (Figure 10). This cycle-specific probability of death corresponds to a mortality rate of 18.2 deaths per 1000 patient-years while awaiting SPKT.

Figure 10: One-way sensitivity analysis on the probability of death while waiting for transplantation

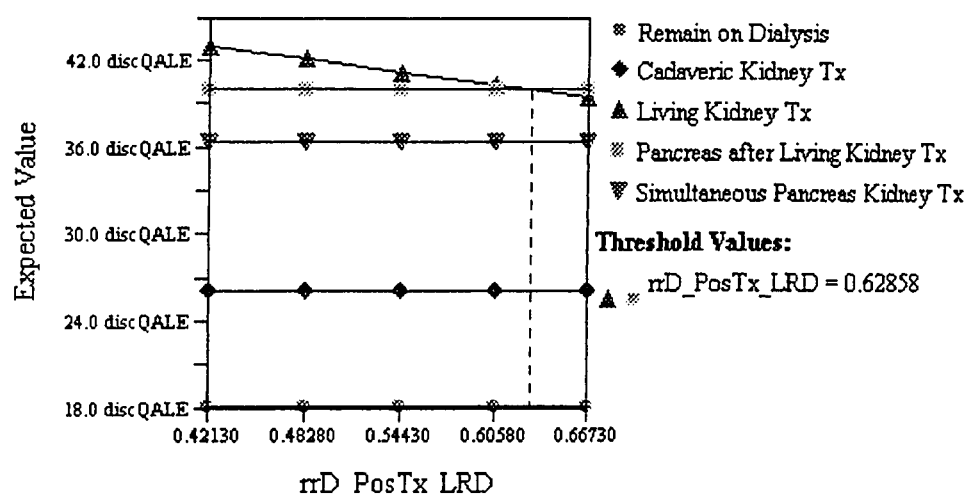


Living kidney transplantation was the preferred strategy when the cycle-specific probability of death on the waiting list was above 0.0069.

4.1.4 One-way sensitivity analysis on variables related to living kidney transplantation

When the relative risk of death after LKT was above 0.63, PAKT was preferred over LKT alone (Figure 11). This relative risk corresponds to a probability of survival of 84.7 at five-years. Thus, when all other variables were held constant LKT was the preferred strategy when the five-year patient survival was above 84.7.

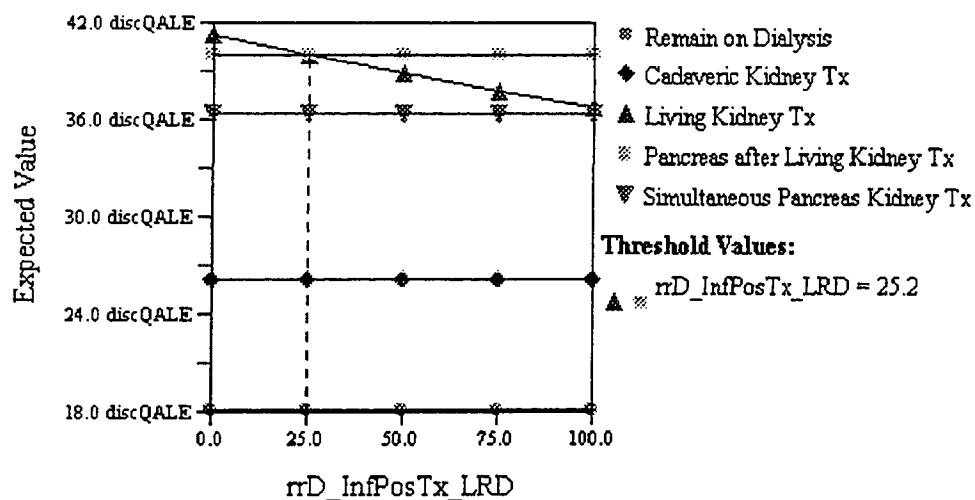
Figure 11: One-way sensitivity analysis on the relative risk of death post-living kidney transplantation



Pancreas after kidney transplantation was the preferred strategy when the relative risk of death after living kidney transplantation was above 0.63.

When the relative risk of death due to a CMV infection following LKT was below 25.2, LKT was preferred over PAKT (Figure 12). This relative risk corresponds to a probability of death of 0.025. As the probability of dying from CMV infection is very rare, this high mortality is unlikely to occur in the modern era of transplantation.

Figure 12: One-way sensitivity analysis on the relative risk of death from cytomegalovirus infection after living kidney transplantation



Pancreas after kidney transplantation was the preferred strategy when the relative risk of death due to a CMV infection following living kidney was above 25.2.

4.1.5 One-way sensitivity analysis on variables related to simultaneous pancreas-kidney transplantation

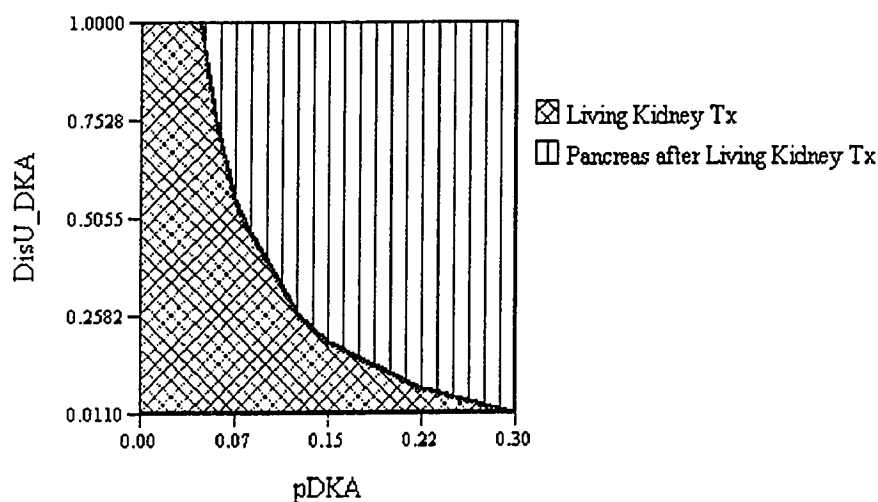
When the relative risk of death waiting for SPKT was below 0.15, SPKT was preferred over LKT. This relative risk corresponds to a mortality rate of 18.2 deaths per 1000 patient-years (graph not shown).

4.2 Two-way sensitivity analysis

The probability of ketoacidosis and the disutility for ketoacidosis were varied simultaneously (Figure 13). This analysis revealed that LKT was the preferred strategy

over a wide range of probabilities surrounding the base case estimates. However, PAKT was preferred over LKT as the probability of ketoacidosis and the disutility for ketoacidosis moved towards their extreme values.

Figure 13: Two-way sensitivity analysis on the probability of ketoacidosis and the disutility of ketoacidosis

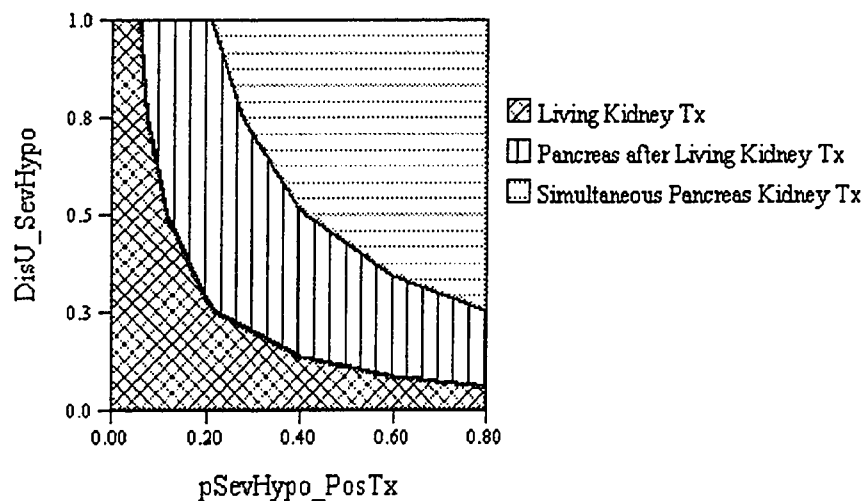


Living kidney transplantation was preferred over a wide range of probabilities surrounding the best case estimates. Pancreas after kidney transplantation was the preferred strategy as the probability and disutility of ketoacidosis approached the extreme values.

The probability of hypoglycemia post-transplantation and the disutility for hypoglycemia were varied simultaneously (Figure 14). LKT was the preferred strategy over a wide range of probabilities surrounding the base case estimates. As was seen with ketoacidosis, PAKT became the preferred strategy as the probability and disutility of hypoglycemia post-transplantation increased. When the value for these variables

approached their extreme, SPKT was the preferred treatment strategy. When the probability of hypoglycemia on dialysis and the disutility for hypoglycemia were varied simultaneously LKT was the preferred strategy throughout the entire range of both variables (data not shown).

Figure 14: Two-way sensitivity analysis on the probability of severe hypoglycemia post-transplantation and the disutility of severe hypoglycemia.

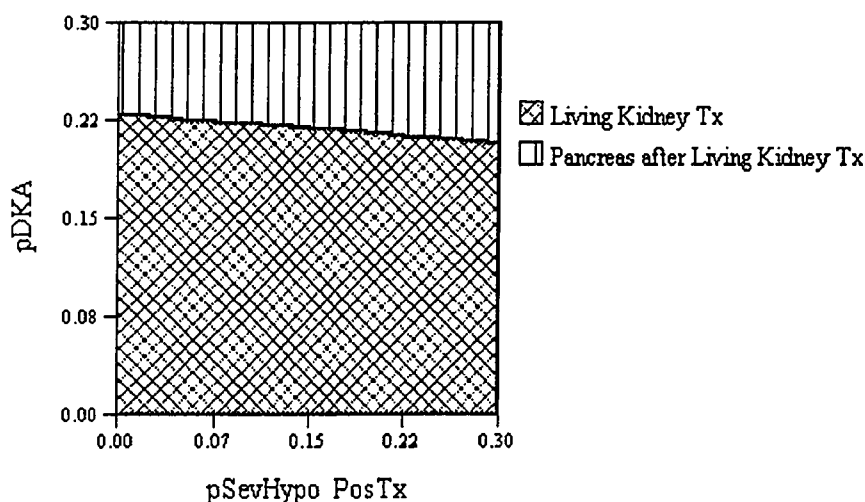


Living kidney transplantation was preferred over a wide range of probabilities surrounding the best case estimates. As the probability of hypoglycemia and disutility of hypoglycemia increased, pancreas after kidney transplantation was preferred. At the extreme values for these variables, simultaneous pancreas-kidney transplantation was the preferred treatment strategy.

The probability of hypoglycemia post-transplantation and the probability of ketoacidosis were varied simultaneously (Figure 15). LKT was preferred over a wide range probabilities of both variables. Only when the probability of ketoacidosis was

significantly elevated over its base case estimate was PAKT preferred. A nearly identical result was found when the probability of hypoglycemia on dialysis and the probability of ketoacidosis were varied simultaneously (data not shown).

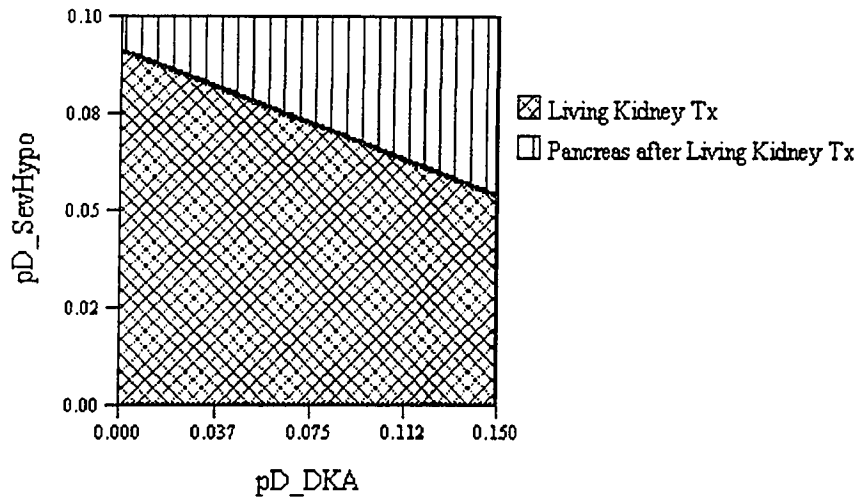
Figure 15: Two-way sensitivity analysis on the probability of severe hypoglycemia post-transplantation and the probability of ketoacidosis



Living kidney transplantation was the preferred treatment strategy over a wide range of probabilities. Only when the probability of ketoacidosis was significantly elevated did the option of pancreas after kidney transplantation become the preferred treatment strategy.

The probability of death from hypoglycemia and the probability of death from ketoacidosis were varied simultaneously (Figure 16). Once again, PAKT was the preferred strategy only when the variables were at their extreme values.

Figure 16: Two-way sensitivity analysis on the probability of death from hypoglycemia and the probability of death from ketoacidosis

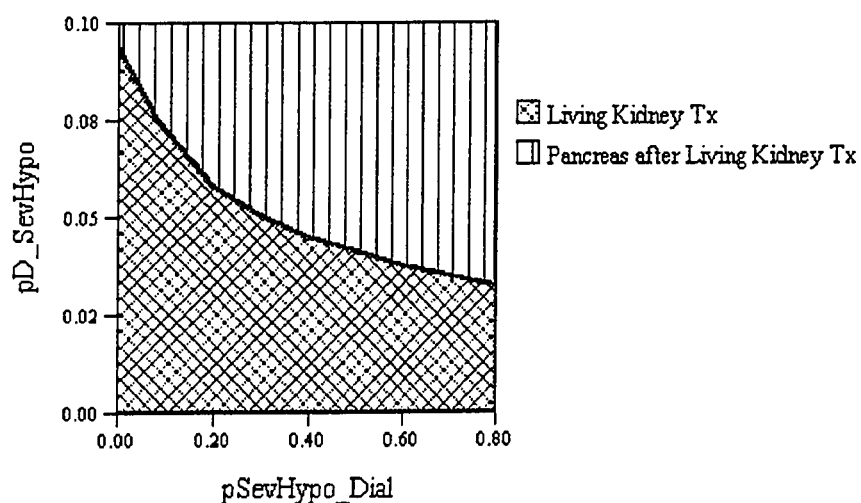


Living kidney transplantation was the preferred treatment strategy over a wide range of probabilities. Only when the probability of death from ketoacidosis and death from hypoglycemia were significantly elevated did the option of pancreas after kidney transplantation become the preferred treatment strategy.

The probability of hypoglycemia on dialysis and the probability of death from hypoglycemia were varied simultaneously (Figure 17). LKT was the preferred strategy over a wide range of probabilities around the base case estimates. PAKT was the preferred strategy as the variables became significantly elevated. The probability of hypoglycemia post-transplantation and the probability of death from hypoglycemia were varied simultaneously (Figure 18). Once again, PAKT was preferred as the values for these variables increased. At the extreme of these variables SPKT was the preferred

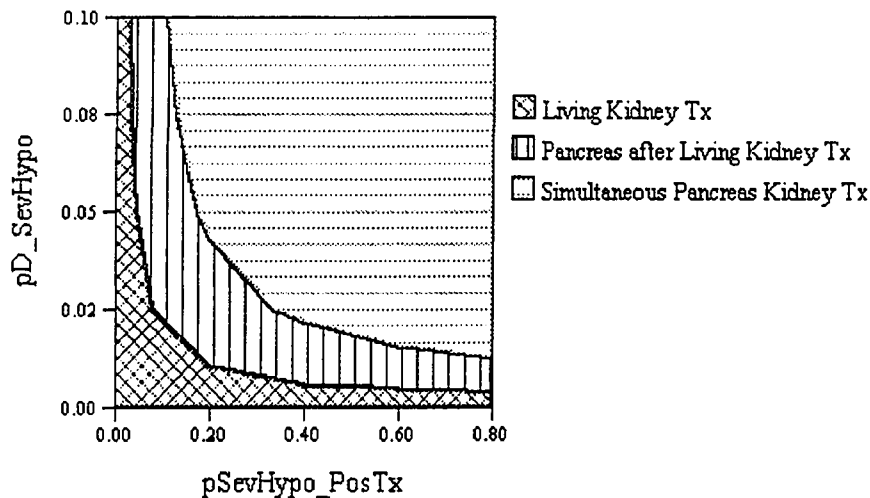
strategy. A nearly identical result was found when the probability of ketoacidosis and the probability of death from ketoacidosis were varied simultaneously (data not shown).

Figure 17: Two-way sensitivity analysis on the probability of severe hypoglycemia on dialysis and the probability of death from hypoglycemia



Living kidney transplantation was the preferred treatment strategy over a wide range of probabilities. Only when the probability of hypoglycemia and death from hypoglycemia were significantly elevated did the option of pancreas after kidney transplantation become the preferred treatment strategy.

Figure 18: Two-way sensitivity analysis on the probability of severe hypoglycemia post-transplantation and the probability of death from hypoglycemia

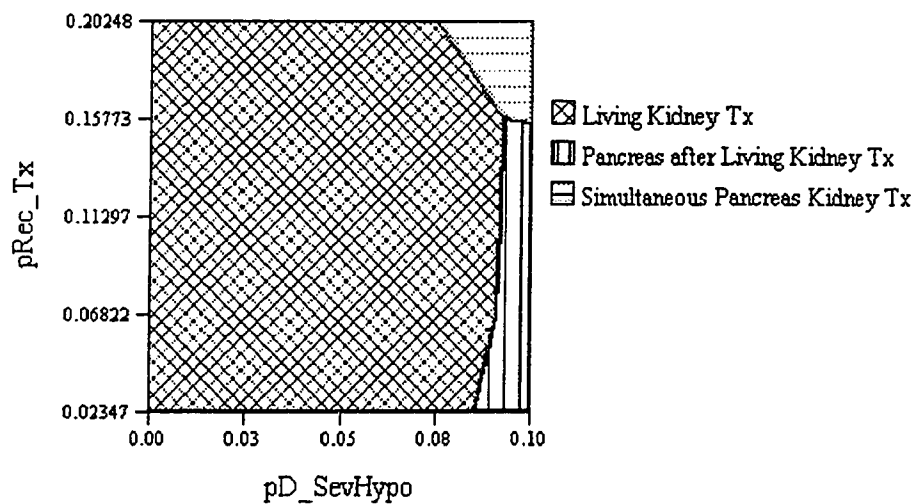


Living kidney transplantation was the preferred treatment strategy over a wide range of probabilities around the base case estimates. As the probability of hypoglycemia and death from hypoglycemia were increased, the option of pancreas after kidney transplantation was preferred. When these variables were at their extreme values simultaneous pancreas-kidney transplantation was the preferred treatment strategy.

The probability of death from hypoglycemia and the probability of receiving a transplant (which reflects the waiting time for a cadaveric transplant) were varied simultaneously (Figure 19). LKT was the preferred strategy over a wide range of probabilities. When the probability of death from hypoglycemia was significantly elevated, PAKT was preferred over a wide range of waiting times. When the probability of receiving a transplant and the probability of death from hypoglycemia were both very high, SPKT was the preferred treatment strategy. Similar results were found when the probability of ketoacidosis and the probability of receiving a transplant were varied simultaneously (data not shown). When the probability of death from ketoacidosis and

the probability of receiving a transplant were varied simultaneously LKT was preferred across the entire range of probabilities (data not shown). Similarly, when the probability of hypoglycemia on dialysis and the probability of receiving a transplant were varied simultaneously, LKT was preferred across the entire range of probabilities (data not shown).

Figure 19: Two-way sensitivity analysis on the probability of receiving a transplant and the probability of death from hypoglycemia



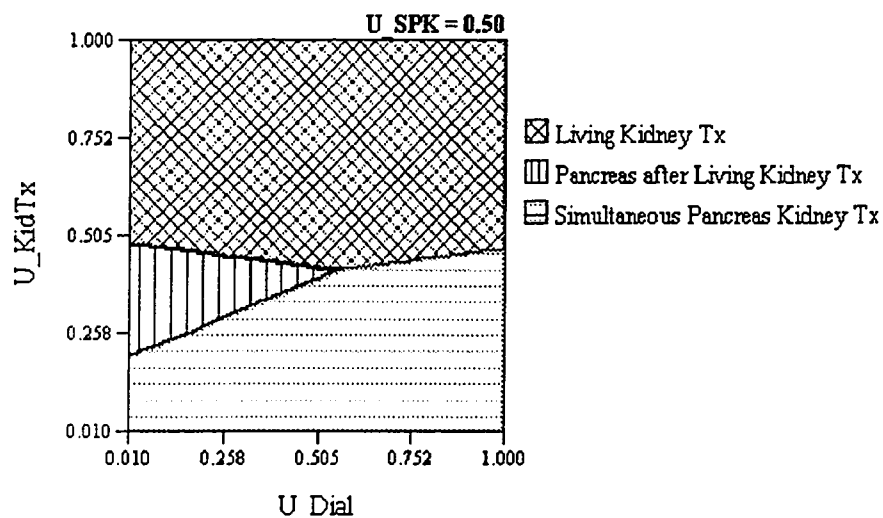
Living kidney transplantation was the preferred treatment strategy over a wide range of probabilities around the base case estimates. When the probability of death from hypoglycemia was significantly elevated, the option of pancreas after kidney transplantation was preferred. When the probability of death from hypoglycemia and the probability of receiving a transplant were both very high, simultaneous pancreas-kidney transplantation was the preferred treatment strategy.

4.3 Three-way sensitivity analysis

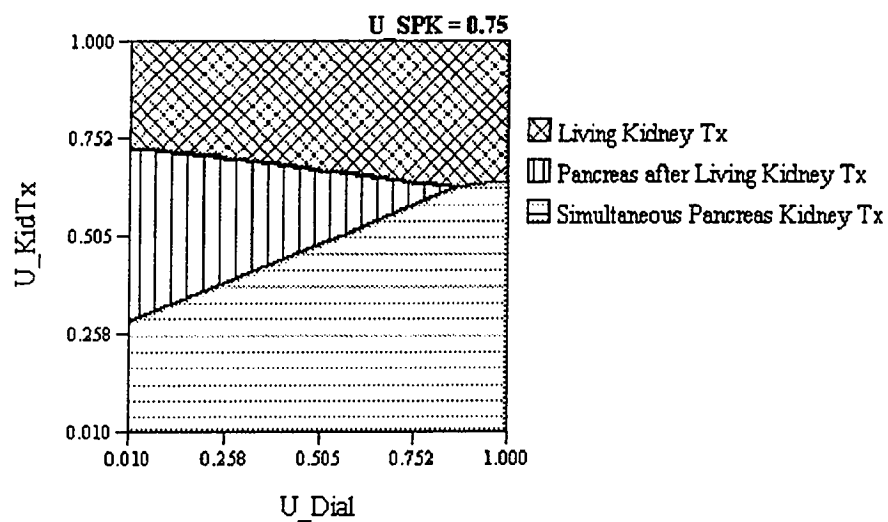
As the utilities for dialysis, kidney transplantation and kidney-pancreas transplantation were each influential on one-way sensitivity analysis they were simultaneously varied in a three-way sensitivity analysis (Figure 20). This demonstrated that when the utility for pancreas-kidney transplantation was low (0.50) LKT was preferred over a wide range of utility values for kidney transplantation and dialysis. As the utility score for pancreas-kidney transplantation was increased, LKT became less attractive and PAKT became a more attractive strategy. When the utility for pancreas-kidney transplantation was 1.0, PAKT was preferred over a wide range of utility scores for kidney transplantation and dialysis. However, when the utilities for both kidney and pancreas-kidney transplantation were both high, LKT remained the preferred strategy.

Figure 20: Three-way sensitivity analysis on the utility scores for dialysis, kidney transplantation and kidney-pancreas transplantation

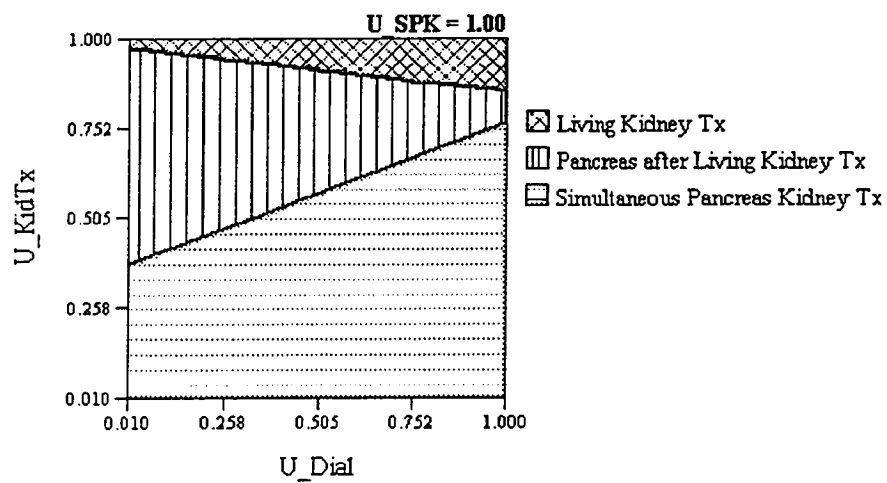
A: Utility for kidney-pancreas transplantation = 0.50



B: Utility for kidney-pancreas transplantation = 0.75



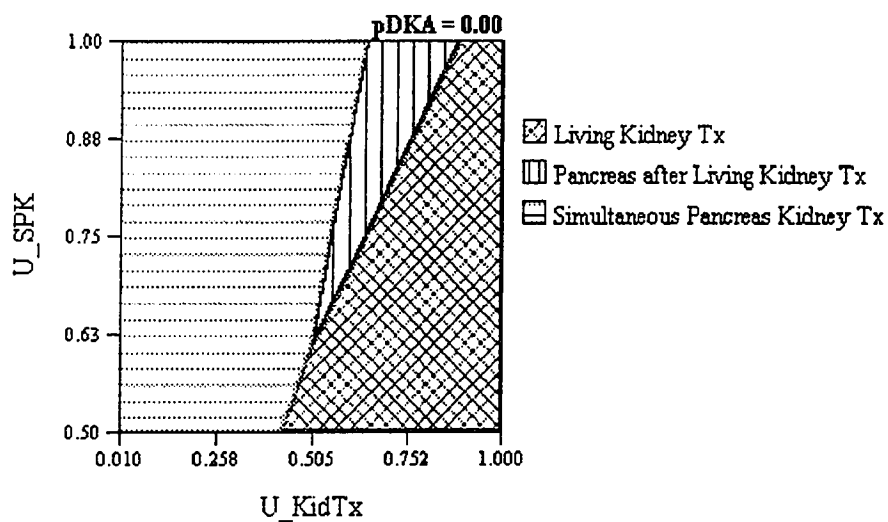
C: Utility for kidney-pancreas transplantation = 1.0



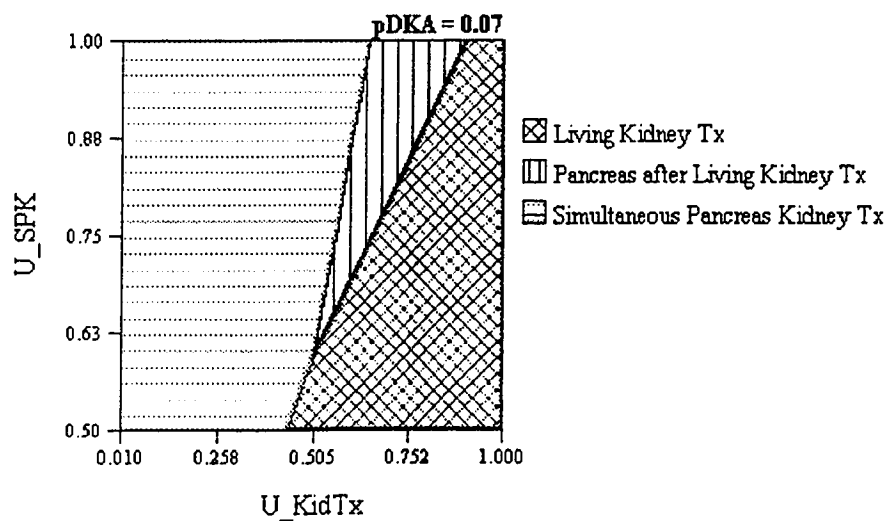
The utilities for kidney transplantation and pancreas-kidney transplantation were varied simultaneously with the probability of ketoacidosis (Figure 21). When the probability of ketoacidosis was zero, LKT was preferred over a wide range of utilities for kidney and pancreas-kidney transplantation. As the utility for kidney transplantation decreased and the utility for pancreas-kidney transplantation increased, PAKT was preferred. SPKT was preferred only when the utility for kidney transplantation was very low. As the probability of ketoacidosis increased, PAKT was preferred over a wider range of utility scores. Even when the probability of ketoacidosis was very high, SPKT was preferred only when the utility for kidney transplantation was very low. When the probability of death from hypoglycemia was varied simultaneously with the utility scores for kidney and kidney-pancreas transplantation a similar result was found (data not shown). However, the probability of hypoglycemia post-transplantation, the probability of hypoglycemia on dialysis and the probability of death from ketoacidosis did not influence the results when they were each examined in a three-way sensitivity analysis with the utilities for kidney and kidney-pancreas transplantation (data not shown).

Figure 21: Three-way sensitivity analysis on the utility for kidney transplantation, the utility for kidney-pancreas transplantation and the probability of ketoacidosis

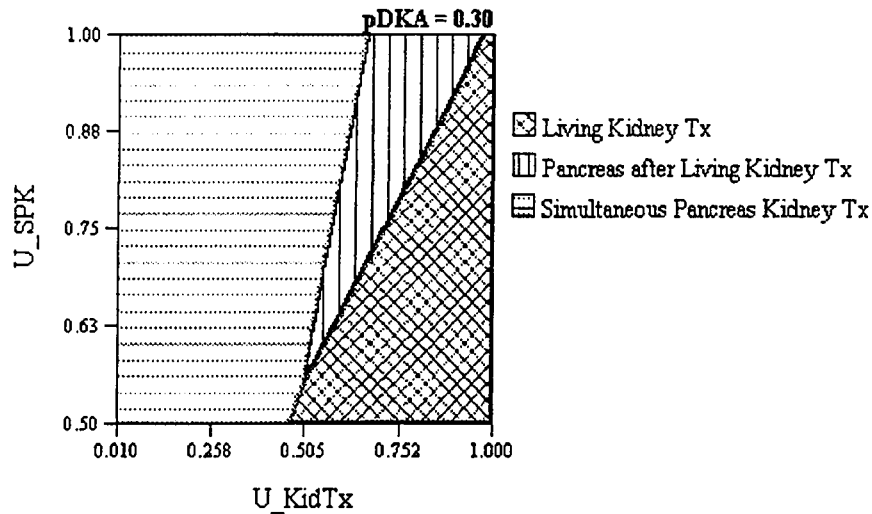
A: Probability of ketoacidosis = 0



B: Probability of ketoacidosis = 0.07



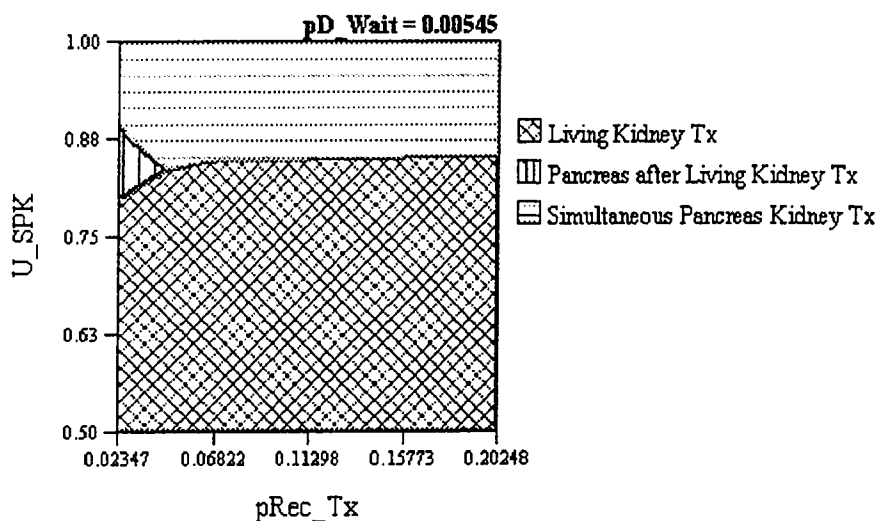
C: Probability of ketoacidosis = 0.30



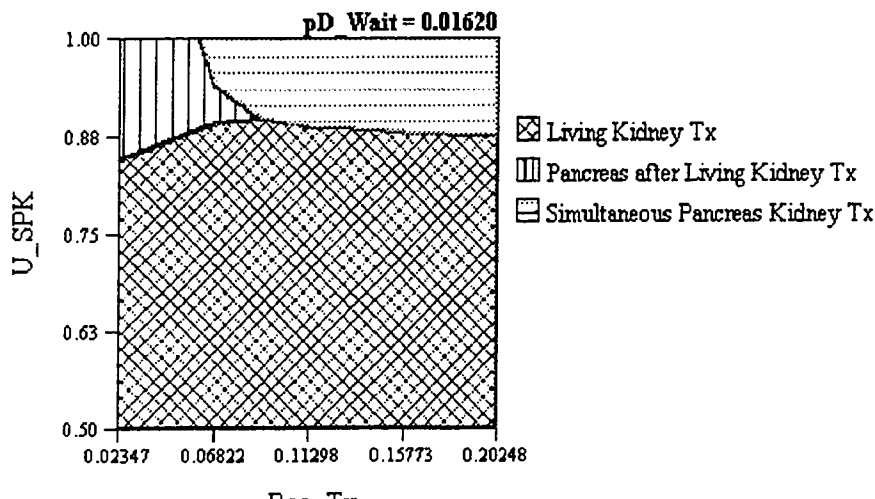
The probability of death while waiting, the probability of receiving a transplant and the utility of pancreas-kidney transplantation were examined in a three-way sensitivity analysis (Figure 22). When the probability of death on the waiting list was low and the utility for pancreas-kidney transplantation was low, LKT was preferred over a wide range of probabilities of receiving a transplant. As the probability of receiving a transplant increased and the utility for pancreas-kidney transplantation was high, SPKT was preferred. As the probability of death on the waiting list increased, LKT was preferred over a wider range of utility scores for pancreas-kidney transplantation. When the probability of death on the waiting list was very high, PAKT was preferred only when the utility for pancreas-kidney transplantation was also high. SPKT was not a preferred treatment option when the probability of death while waiting was high.

Figure 22: Three-way sensitivity analysis on the probability of death while waiting for a transplant, the probability of receiving a transplant and the utility for pancreas-kidney transplantation

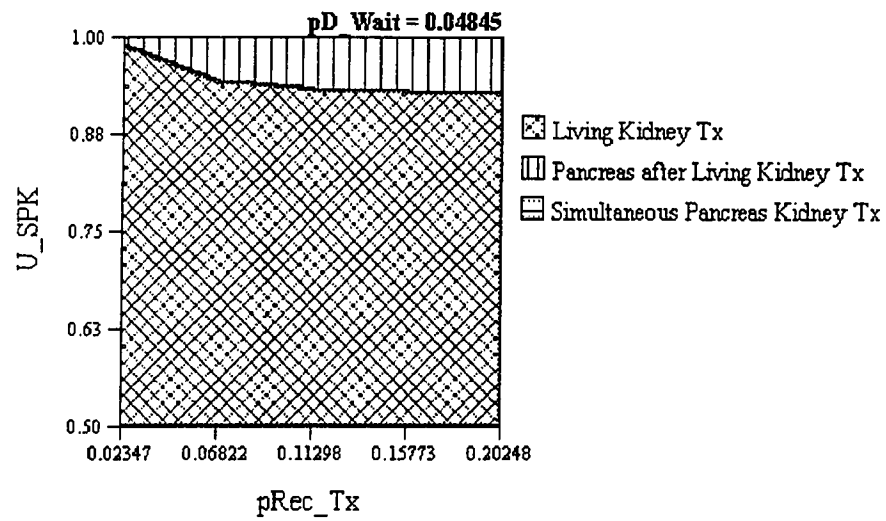
A: Probability of death while waiting = 0.00545 in each 3 month cycle



B: Probability of death while waiting = 0.0162 in each 3 month cycle



C: Probability of death while waiting = 0.04845 in each 3 month cycle



DISCUSSION

The decision to proceed with pancreas transplantation in a type 1 diabetic with ESRD is a tradeoff between the potential improvement in quality of life and the increased risk of post-transplant complications. This analysis demonstrated that based on the best available data LKT was associated with a greater life expectancy and quality-adjusted life expectancy compared to SPKT or PAKT. However, the results were sensitive to changes in several important variables.

Interpretation of sensitive variables

The preferred treatment strategy was sensitive to the utility values for dialysis, kidney transplantation and kidney-pancreas transplantation. In particular, the results were sensitive to the utility for kidney-pancreas transplantation. When this value was above 0.91 (base case 0.85), PAKT was the preferred strategy. This threshold value is likely clinically important since nearly one third of patients interviewed assigned kidney-pancreas transplantation a utility of 0.91 or higher. Also, a previous study found that the mean utility for the kidney-pancreas health state was similar to this value (184). When the utility scores for kidney and kidney-pancreas transplantation were varied simultaneously it was evident that pancreas transplant options would be preferred by patients who value kidney-pancreas transplantation over renal transplantation alone.

Extensive two-way sensitivity analyses were performed on the diabetes-related variables hypoglycemia, ketoacidosis, disutility of hypoglycemia or ketoacidosis and the

probability of death from hypoglycemia or ketoacidosis. In almost all of the variable combinations, PAKT was the preferred strategy as the probability or disutility of the diabetes-related complication increased. This suggests that diabetic patients with frequent metabolic complications, which are associated with a poor quality of life, would have a better quality-adjusted survival with PAKT. These results are in agreement with previous recommendations that patients with labile diabetes undergoing renal transplantation would likely benefit from a combined pancreas-kidney transplantation (175). These results are also consistent with the American Diabetes Association position statement on pancreas transplantation alone in nonuremic patients(185).

The analysis was sensitive to the probability of death while waiting for transplantation. This is clinically relevant as the death rates on the waiting list for CKT, pancreas transplantation and SPKT have increased over the past few years (39). In addition, the waiting time to transplant for these organs has also increased substantially (39). SPKT was the preferred treatment if the mortality rate while waiting for SPKT was less than 18.2 deaths per 1000 patient-years then. Unfortunately, the mortality rate on the waiting list for SPKT has not been under 30 deaths per 1000 patient-years since 1992 (39).

Interestingly, the results of the analysis were insensitive to the rate of infection, rejection and postoperative complications following pancreas transplantation. This is unlike most reviews on pancreas transplantation which have emphasized the importance of the complications when deciding on pancreas transplantation (17,175,186,187). It is

likely that the analysis was insensitive to these complications because of the relatively high utility value placed on kidney transplantation. This underscores the importance of health related quality of life and patient preferences in choosing treatment strategies for type 1 diabetics with ESRD.

Comparison to previous studies

There have been several other studies that have measured utilities in the setting of dialysis and transplantation. Russell et. al. prospectively measured quality of life in 27 patients on dialysis and again following renal transplantation (3). Using the time trade-off technique they found that the mean utility score for being on dialysis was 0.41. Following renal transplantation the mean utility score increased to 0.74. The mean utility score for dialysis in our study was significantly higher at 0.70 and the value for renal transplantation was also slightly higher at 0.80. There are several reasons why the utility scores could be different. First, the study by Russell was carried out from 1984 to 1988 and published in 1992 (3). Since that time there have been many technological advances, especially in dialysis delivery, that have resulted in fewer patients requiring hospitalization (4) and a significant reduction in mortality (4). It is conceivable that these improvements could translate into higher utility scores being obtained in a more modern era. Second, Russell's study only involved two patients with diabetes (3). It has been previously shown that diabetic patients experience the greatest gains in both quality and quantity of life following renal transplantation (2,9). Had Russell's study included more diabetic patients the relative gains after transplantation may have been greater leading to a higher mean utility score for renal transplantation. Finally, the study by Russell et. al.

used the time trade-off technique to measure utilities (3) while the standard gamble was used in our study. Although both techniques are acceptable for determining health state preferences, the standard gamble consistently produces utility scores that are higher than the time trade-off technique (178). The difference in utilities is likely due to the inherent risk aversion people have when dealing with death (178).

Laupacis et. al. measured quality of life in a cohort of renal transplant recipients using the Kidney Disease Questionnaire, the Kidney Transplant Questionnaire, the Sickness Impact Profile and the time trade-off (2). At twelve months post-transplantation they found that the mean utility score using the time trade-off was 0.74. However, in their subgroup of 27 diabetic patients the mean utility score was 0.82 (2) which was similar to the value obtained in our study.

The utility score for kidney-pancreas transplantation has been measured in only two studies to date (29,184). Douzajian et. al. measured the utility for renal transplantation and kidney-pancreas transplantation in 17 kidney-pancreas transplant recipients. Patients were excluded from the study if they had experienced failure of the pancreas allograft. They found that the mean utility for kidney transplantation was 0.6 and the value for kidney-pancreas transplantation was 1.0 (29). The utility for kidney-pancreas transplantation was significantly higher than our value of 0.85 and likely reflects the methodology that was used. Rather than anchoring the utility scores to 0 for death and 1 for perfect health as recommended (180), Douzajian et. al. asked the patients to choose the best and worst scenarios from the following options: (a) death (b) kidney

fails, pancreas works (c) pancreas fails, kidney works (d) both kidney and pancreas fail and (e) both kidney and pancreas work. The best scenario was given the utility of 1 and the worst was given the value of 0. Death was assigned a utility of 0 and kidney and pancreas both work was given a utility of 1 (29). The utilities for the other scenarios were determined using the standard gamble. By using this methodology they have equated the 'best scenario' (kidney-pancreas transplantation) with perfect health which has resulted in an unrealistic utility score.

Kiberd et. al. determined the utility for kidney-pancreas transplantation in a cohort of 16 type 1 diabetics with ESRD (184). They used the standard gamble technique and set death equal to 0 and perfect health equal to 1. The mean utility score for the kidney-pancreas health state was 0.95 and for kidney transplantation it was 0.72 (184). The utility for the kidney-pancreas health state was higher and the utility for kidney transplantation was lower than the values obtained in our study. These differences may be due to the number and type of patients studied. Kiberd et. al. interviewed only 16 patients while we interviewed 50 patients. Fifteen patients in our study assigned the kidney-pancreas health state a utility score of 0.95 or higher. Thus, had Kiberd et. al. interviewed additional patients they may have obtained more variation in the utility scores and a mean value that was lower than 0.95. In the Kiberd study three patients had functioning kidney-pancreas transplants and all had ESRD but no other details were given. The authors note that the kidney-pancreas transplant recipients provided utility scores that were "close to perfect health" although the actual values were not given. It has been previously demonstrated that utility scores post-transplantation are significantly higher from subjects

who have a functioning allograft compared to those who have suffered a graft loss (2). It is also possible that some of their patients had a kidney transplant that failed resulting in a utility score for renal transplantation that was lower than the value of 0.82 obtained by Laupacis (2) and the 0.80 obtained in our current study. Since it is known that past experience can influence the utility value elicited, we chose to obtain utility scores from diabetics who had not been on dialysis or had a previous transplant.

Four decision models have been published evaluating various options of kidney and kidney-pancreas transplantation in diabetics (28-31). Unfortunately, it is difficult to directly compare the results of these studies with our study, as the primary focus was cost rather than life expectancy and quality-adjusted life expectancy. All four studies used a fixed time horizon of either three or five years. Thus, the average life expectancy and quality-adjusted life expectancy of the various treatment options could not be extracted from the reports to compare with our results. The utility scores used in two of the studies have already been reviewed above (28,29) and the other two studies used only estimates provided by one author (30,31).

Strengths of current study

This analysis has several strengths. The use of a decision analytic model permitted the simultaneous comparison of all clinically relevant treatment options for a type 1 diabetic with ESRD. To perform this analysis using another study design, such as a randomized trial, would not be feasible due to the fact that the transplant volume at individual centers is small, patients may have to wait several years to receive a cadaveric

organ and these patients would then need to be followed for years before an outcome could be measured. During such a prolonged study the standards of care regarding immunosuppression, infection prophylaxis and surgical techniques would likely change so much that by the time the study was completed the results would be irrelevant to current practice.

The decision model used in this analysis included all relevant treatment options as well as all clinically important outcomes as recommended (188). The face validity of the model was verified by having experts in transplantation and nephrology review and modify the structure of the tree. In contrast to previous studies that describe health-related quality of life associated with ESRD, the present study considers the combined effect of morbidity and mortality. As well, the present analysis accounts for varying probability of short and long-term complications. Since patients value quantity and quality of life, the results of the present study have greater validity than those of the previous studies. The perspective of the outcome was long-term rather than a short time period of three or five years. This long-term analysis is more appropriate for ESRD and diabetes as patients with either of these conditions require lifetime therapy for their survival. The utilities employed in the model came from a credible source and were obtained using a validated approach (178). In addition, the utilities for kidney-pancreas transplantation were obtained from 50 subjects which is significantly larger than the sample size used in the two published articles to date (29,184).

Another strength of this study was the comprehensive literature search. Over 11,000 titles and abstracts were reviewed so that no important studies would be missed. The final data came from over 1000 articles that were reviewed in detail. In addition, the important data on patient and graft survival for type 1 diabetics was obtained from the UNOS database. This database includes information on *every* transplant performed in the United States, both successful cases and unsuccessful cases, thus avoiding any bias in reporting that may arise from single center reports. The end result was a more objective synthesis of the available data rather than a subjective review of the topic which has been published before (5,17,18,26).

The use of a Markov model rather than a simple decision tree also enhanced this study. The Markov model allowed us to vary probabilities over time, such as the CMV infection rate, to more accurately reflect clinical practice. Such variability cannot be incorporated into a simple decision tree, which only considers events at a single point in time or constant risk over time. The Markov model also allowed us to include repetitive clinical events, such as hypoglycemia, which more accurately reflects the risks faced by a diabetic. A simple decision tree would only permit one episode of hypoglycemia during a fixed time interval, which would not be realistic. Finally, the Markov model did not require a pre-defined fixed time horizon and thus life expectancy for each treatment strategy could be calculated.

Limitations of current study

This analysis has several limitations. First, the input data on post-transplant complications came from multiple sources. The data was abstracted from the individual studies by only one investigator and thus interobserver agreement could not be measured. Study quality was not formally measured; both randomized and nonrandomized studies were included. The use of single centre, nonrandomized data may have underestimated the complication rates, as centres with inferior outcomes would be less likely to publish their results. In addition, the use of data from multiple sources with different standards of care may be difficult to generalize to other centres. However, sensitivity analyses were carried out over a wide range of values to ensure that all clinically plausible event rates were included.

Second, we assumed that members of the cohort could undergo one treatment strategy and no repeat transplantation was permitted. Although this assumption may bias the analysis in favor of LKT, repeat transplantation is associated with an increased mortality risk in the PAKT category (113) and decreased allograft survival following CKT (34). In addition, repeat transplantation is rarely performed in the SPKT category (113).

Finally, we assumed that the quality of life was zero for the duration of the short-term health states and the duration of the short-term health states was estimated from expert opinion. Although this technique is the standard approach used to determine disutilities (181), patient-based preferences may have resulted in more accurate estimates.

However, considering a wide range of values for the short-term health states did not change which strategy is preferred.

Clinical relevance

This study has shown that LKT increased crude life expectancy by approximately 13 months and discounted quality-adjusted life expectancy by 3.5 months compared to PAKT. Although these gains do not seem large in the context of a person's entire lifespan, they are similar to or greater than life expectancy gains of other established medical practices (189). For example, coronary revascularization in men with triple vessel disease results in a gain in life expectancy of 4 to 14 months (189). Adjuvant chemotherapy in women with node-positive breast cancer results in a gain in life expectancy of 3.6 months (189). Therefore, the treatment strategy of LKT is associated with a clinically important improvement in average life expectancy that is similar to the results achieved by other commonly used interventions. This information can now be used by clinicians to make recommendations about treatment options for their patients with diabetes. Instead of reviewing the risks and benefits of each treatment option individually, the clinician can summarize that the average life expectancy and quality-adjusted life expectancy is greatest with LKT alone.

Since the study results were sensitive to the utility values, these preferences can now be incorporated in the discussion. For example, in a qualitative manner a physician could ask how their patient feels about glucose monitoring, insulin injections and other aspects about living with diabetes. If it is clear that the individual patient dreads injecting

themselves or having a hypoglycemic reaction then based on our results the clinician could recommend PAKT as the most appropriate option. By tailoring the results of this study to individual situations, the clinician can be more confident in the recommendations made to their own patients.

Using a more global perspective the results of this study, if adapted, could allow more Canadians with diabetes and ESRD to live longer and enjoy a greater quality of life. If more diabetics undergo LKT and PAKT rather than CKT and SPKT, as suggested by our results, then more cadaveric organs will be available for those patients without potential living donors. This would allow more Canadians with ESRD to stop dialysis and enjoy the benefits of transplantation. Such a strategy that maximizes transplantation rates would be cost-effective for Canada (2).

Summary and future recommendations

In conclusion, this analysis has demonstrated that LKT is associated with greater life expectancy and quality-adjusted life expectancy for type 1 diabetic patients with ESRD. However, PAKT is likely to be preferred by patients with frequent and severe metabolic complications of diabetes and by those patients who favor kidney-pancreas transplantation over kidney transplantation alone. The implications from this study are important since it is the patient preferences that are most relevant when choosing treatment strategies for diabetics with ESRD. An important area for further research arising from this study would be the development of a decision aid. Such an instrument

would facilitate shared decision making by matching patient preferences with appropriate treatment options (190).

As the experience with islet transplantation grows it is likely that the procedure will be extended to diabetics with ESRD. If the results are as good as in those patients without renal disease (42) then future studies will need to evaluate the option of renal transplantation (cadaveric and living donor) with simultaneous or sequential transplantation of pancreatic islet cells. Finally, as the methodology for determining cost in transplantation becomes more standardized then the decision model could be expanded to determine which treatment option is the most cost-effective.

APPENDICES

Appendix 1: Search Strategy

1. exp Pancreas Transplantation/
2. pancreas transplantation.tw.
3. pancreas transpl\$.mp.
4. spk.tw.
5. pak.tw.
6. kidney-pancreas transpl\$.tw.
7. (kidney and pancreas transpl\$.tw.
8. (kidney and pancreas transpl\$.tw.
9. pancreas-kidney transpl\$.tw.
10. pancreas after kidney transpl\$.tw.
11. 1 or 2 or 3 or 4 or 5 or 6 or 8 or 9 or 10
12. exp Kidney Transplantation/
13. kidney transplantation.tw.
14. renal transplantation.tw.
15. kidney trans\$.tw.
16. renal trans\$.tw.
17. renal allograft.mp.
18. kidney allograft.tw.
19. 12 or 13 or 14 or 15 or 16 or 17 or 18
20. 11 or 19
21. limit 20 to (english language and yr=1995-2001)
22. limit 21 to human

Appendix 2: Research Ethics Board Approval Letter

**The Ottawa
Hospital | L'Hôpital
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**Research Ethics Board
Conseil d'éthique en recherches
737-8930**

APPROVAL 1999

April 26, 1999

Dr. G. Knoll
Division of Nephrology
The Ottawa Hospital - General Campus

Dear Dr. Knoll:

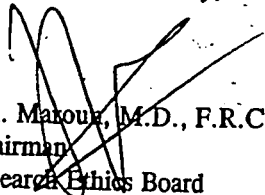
RE: OGH-99-028 Health-Related Quality of Life for Diabetics Undergoing Dialysis, Kidney Transplantation and Kidney-Pancreas Transplantation.

The Research Ethics Board has reviewed your response to a letter of concerns that you submitted on the above protocol.

I am pleased to inform you that the REB finds these revisions and the revised English Patient Information Sheets dated April 21, 1999 to be acceptable with respect to the ethics of research with human subjects and has therefore approved this protocol from April 1999 to April 2000.

The new guidelines of the Medical Research Council require a greater involvement of the REB in studies over the course of their execution. You must maintain, as part of your records, copies of the signed consent form. As well, you must inform the REB of adverse events encountered during the study, here or elsewhere, or of significant new information which becomes available after the REB review, either of which may impinge on the ethics of continuing the study. The REB will review the new information to determine if the protocol would be modified, discontinued, or should continue as originally approved.

Yours sincerely,


J.A. Marouk, M.D., F.R.C.P.C.
Chairman
Research Ethics Board

JAM/ac

Appendix 3: Patient Information Sheet**PATIENT INFORMATION SHEET AND INFORMED CONSENT FORM****Health-Related Quality of Life for Diabetics Undergoing Dialysis, Kidney Transplantation and Kidney-Pancreas Transplantation****PURPOSE**

You are being invited to participate in a research study to determine patient preferences for different treatment options in diabetes-related kidney failure. When people with diabetes develop kidney failure several options currently exist. They may receive dialysis treatments, receive a kidney transplant or receive a kidney and pancreas transplant together. At the present time, we do not know which treatment option is best for patients with diabetes. It is important to know what other patients with diabetes would do if they developed kidney failure. This knowledge (along with other patient input) will help us determine what is the best way to care for diabetic patients with kidney failure.

PROCEDURES

If you choose to participate in this study, you will be asked to read and sign a copy of this informed consent. Your involvement in the study will take approximately one hour. We will ask you to read three scenarios describing a person's life on dialysis, a person's life with a kidney transplant and a person's life with a kidney-pancreas transplant. We will then ask you to rank your preference for each of these scenarios on a scale. We will record your initials, date of birth, gender, number of years on insulin and any other significant medical conditions you may have. All bilingual patients may take part in this study. The interview will be carried out in English.

RISKS/BENEFITS

The study consists only of an interview. There will be no potential risks to participating in the study. Your participation will help us understand how patients with diabetes value the different treatment options for kidney failure.

Version: 21/04/99

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ALTERNATIVES TO PARTICIPATION

Your participation in this study is completely voluntary. If you choose not to participate, you will receive your standard care as prescribed by your regular physician.

CONFIDENTIALITY

All results of this study will be kept confidential. You will only be identified by your initials and date of birth. You will not be identifiable in any publication or presentation resulting from this study.

INDEPENDENT REVIEW

The Research Ethics Board of this hospital has reviewed and approved this research study.

QUESTIONS

You have the right to ask questions about the study and to have them answered fully. If you have any questions about the study you may call Dr. Greg Knoll at 737-8140 or the Chairperson of the Research Ethics Board at 737-8930.

Appendix 4: Health State Scenarios

A: Perfect Health

- Vision:** Able to see well enough to read ordinary newsprint and recognize a friend on the other side of the street, without glasses or contact lenses.
- Hearing:** Able to hear what is said in a group conversation with at least three other people, without a hearing aid.
- Speech:** Able to be understood completely when speaking to strangers or friends.
- Ambulation:** Able to walk around the neighborhood without difficulty, and without walking equipment.
- Dexterity:** Able to enjoy full use of two hands and ten fingers.
- Mood:** Happy and interested in life.
- Cognition:** Able to remember most things, think clearly and solve day to day problems.
- Pain:** Free of pain and discomfort.

B: Dialysis**Condition X**

You are attached to a machine three days a week for about four hours each time. The machine cleans your blood of waste products and excess water. You are attached to the machine by needles that are inserted into an enlarged vein on your arm.

You sometimes feel nauseated, sweaty, light-headed or have leg cramps while on the machine. You may feel pain as the needles are inserted or when you have leg cramps; you will not have pain for the remainder of the treatment. You sometimes get swollen legs and shortness of breath.

You carefully regulate the amount of fluid, salt, sugar and dairy products that you eat each day. You eat your meals at consistent times each day. You take pills with each meal that sometimes gives you gas, bloating or constipation.

You inject drugs under your skin twice a day. You prick your finger a few times each day for a drop of blood to check your sugar level.

You occasionally feel weak, sweaty, shaky or pass-out when your sugar level is low.

You only make a small amount of urine each day.

- Vision:** You are able to see well enough to read ordinary newsprint and recognize a friend on the other side of the street, without glasses or contact lenses.
- Hearing:** You are able to hear what is said in a group conversation with at least three other people, without a hearing aid.
- Speech:** You are able to be understood completely when speaking with strangers or friends.
- Ambulation:** You are able to walk around the neighborhood without difficulty, and without walking equipment.
- Dexterity:** You have the full use of two hands and ten fingers.
- Emotion:** You are **somewhat happy**.
- Cognition:** You are able to remember most things, think clearly and solve day to day problems.
- Pain:** You have **mild to moderate** pain that prevents no activities.

C: Kidney Transplantation

Condition Y

You have a long scar across your lower abdomen.

You take several pills every day. Some pills may cause infections or other serious illnesses. Some may cause excessive hair growth or weight gain; others may cause your bones to thin resulting in fractures.

You carefully regulate the amount of starches and sugars that you eat each day. You eat your meals at consistent times each day.

You inject drugs under your skin twice a day. You prick your finger a few times each day for a drop of blood to check your sugar level.

You occasionally feel weak, sweaty, shaky or pass-out when your sugar level is low.

You make a normal amount of urine each day.

You must visit the doctor and have blood samples taken several times per year.

Vision: You are able to see well enough to read ordinary newsprint and recognize a friend on the other side of the street, without glasses or contact lenses.

Hearing: You are able to hear what is said in a group conversation with at least three other people, without a hearing aid.

Speech: You are able to be understood completely when speaking with strangers or friends.

Ambulation: You are able to walk around the neighborhood without difficulty, and without walking equipment.

Dexterity: You have the full use of two hands and ten fingers.

Emotion: You are **somewhat happy**.

Cognition: You are able to remember most things, think clearly and solve day to day problems.

Pain: You are **free of pain** and discomfort.

D: Kidney-Pancreas Transplantation

Condition Z

You have a long scar across your abdomen.

You take several pills every day. Some pills may cause infections or other serious illnesses. Some may cause excessive hair growth or weight gain; others may cause your bones to thin resulting in fractures.

You are allowed to eat whatever you want.

You make a normal amount of urine each day.

You must visit the doctor and have blood samples taken several times per year.

Vision: You are able to see well enough to read ordinary newsprint and recognize a friend on the other side of the street, without glasses or contact lenses.

Hearing: You are able to hear what is said in a group conversation with at least three other people, without a hearing aid.

Speech: You are able to be understood completely when speaking with strangers or friends.

Ambulation: You are able to walk around the neighborhood without difficulty, and without walking equipment.

Dexterity: You have the full use of two hands and ten fingers.

Emotion: You are **somewhat happy**.

Cognition: You are able to remember most things, think clearly and solve day to day problems.

Pain: You are **free of pain** and discomfort.

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Ref Type: Report
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