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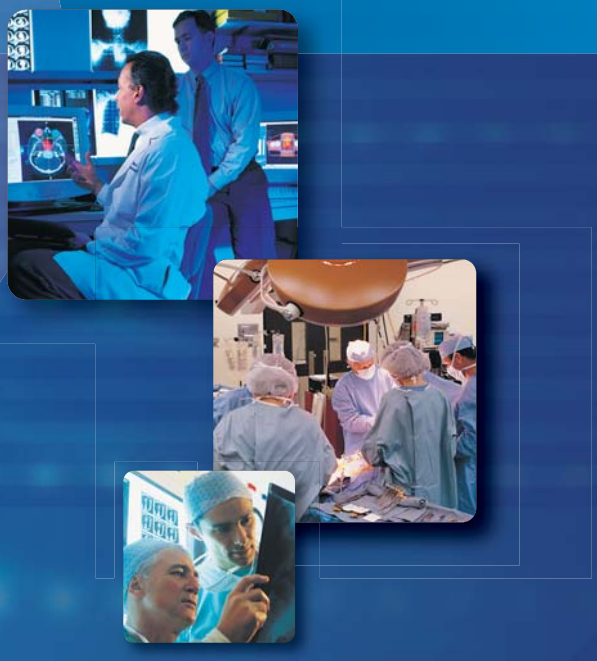
Pancreas Transplantation to Restore Glucose Control: Review of Clinical and Economic Evidence



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Canadian Agency for Drugs and Technologies in Health

Pancreas Transplantation to Restore Glucose Control: Review of Clinical and Economic Evidence

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March 2007

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Health technology assessment (HTA) agencies face the challenge of providing quality assessments of medical technologies in a timely manner to support decision making. Ideally, all important deliberations would be supported by comprehensive health technology assessment reports, but the urgency of some decisions often requires a more immediate response.

The Health Technology Inquiry Service (HTIS) provides Canadian health care decision makers with health technology assessment information, based on the best available evidence, in a quick and efficient manner. Inquiries related to the assessment of health care technologies (drugs, devices, diagnostic tests, and surgical procedures) are accepted by the service. Information provided by the HTIS is tailored to meet the needs of decision makers, taking into account the urgency, importance, and potential impact of the request.

Consultations with the requestor of this HTIS assessment indicated that a review of the literature would be beneficial. The research question and selection criteria were developed in consultation with the requestor. The literature search was carried out by an information specialist using a standardized search strategy. The review of evidence was conducted by one internal HTIS reviewer. The draft report was internally reviewed and externally peer-reviewed by two or more peer reviewers. All comments were reviewed internally to ensure they were addressed appropriately.

Reviewers

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Reviewers who agreed to be acknowledged include:

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ABBREVIATIONS

AHCPR	Agency for Health Care Policy and Research
AETMIS	L'Agence d'évaluation des technologies et des modes d'intervention en santé
AETSA	La Agencia Andaluza de Evaluación de Tecnologías Sanitarias
CHAMPVA	Civilian Health and Medical Program of the Department of Veterans Affairs
CIHI	Canadian Institute for Health Information
DKT	deceased-donor kidney transplantation
ESRD	end-stage renal disease
HbA1c	hemoglobin A1c
HTA	health technology assessment
IAK	islet transplantation after kidney
ICSI	Institute for Clinical Systems Improvement
KA	kidney alone
LKT	living-donor kidney transplantation
OPTN	Organ Procurement and Transplantation Network
PAK	pancreas after kidney
PTA	pancreas transplant alone
QALY	quality-adjusted life-year
QOL	quality of life
RCT	randomized controlled trial
SPK	simultaneous pancreas kidney
UNOS	United Network for Organ Sharing

Title: Pancreas transplantation to restore glucose control: review of clinical and economic evidence

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1 CONTEXT AND POLICY ISSUES

More than 1,000 pancreas transplantations are performed every year worldwide at approximately 200 institutions.[1] In Canada, 446 pancreas transplantations have occurred between 1994 and 2003, with Québec and Ontario performing nearly 60% of them.[2] Pancreas transplantation is usually performed for patients with type 1 diabetes who have end-stage renal disease (ESRD).[3]

The purpose of a pancreas transplant is to establish glucose control. The new pancreas will restore endogenous insulin secretion. Glucose regulation should translate into improved quality of life (QOL) through elimination of the acute complications of insulin-dependent diabetes and halting or reversing the long-term secondary complications (retinopathy, nephropathy, neuropathy, and coronary artery disease).[4]

The three types of pancreas transplantations are categorized by when they occur in relation to a kidney transplantation:[4] simultaneous pancreas kidney (SPK) transplantation, pancreas after kidney (PAK) transplantation, and pancreas transplant alone (PTA). In this report, pancreas transplantation refers to SPK, PAK, and PTA, unless otherwise stated.[1,4]

- SPK patients generally have type 1 diabetes with ESRD and other diabetic complications. Both organs usually come from the same deceased donor, or they may come from a living-donor.
- PAK is usually the option of choice for patients who have a living donor for the kidney. Two operations are required.
- PTA patients usually have hypoglycemic unawareness or labile diabetes (including patients with frequent episodes of ketoacidosis), without ESRD.

As with other organ transplants, there is an early high risk period (of death or re-transplantation) followed by a lower, constant risk.[5] Therefore, the risk of surgery and immunosuppression must be weighed against the new organ's potential benefits.[4] Patients with organ transplants require lifelong immunosuppression to prevent rejection of the transplant and the recurrence of the autoimmune process.

With the advances in techniques, pancreas transplant is perceived to be a viable surgical option for patients with type 1 diabetes and ESRD. It is important to use the available evidence regarding the efficacy, safety, and costs of all three types of pancreas transplantations to determine which is the best to provide in which circumstances. Because many countries, including Canada, have had experience with determining the criteria for funding, it is valuable to review the eligibility and funding guidelines for pancreas transplants.

2 RESEARCH QUESTIONS

1. What are the safety, efficacy, and cost-effectiveness of SPK, PAK, and PTA?
2. How is pancreas transplantation funded in Canada, US, UK, and Australia?
3. Who (and in what settings) is eligible for pancreas transplantation in Canada, US, UK, and Australia?

3 METHODS

Published literature was obtained by searching PubMed and OVID multi-file databases including PREMEDLINE®, MEDLINE®, EMBASE®, and BIOSIS Previews®. Filters were applied to limit the retrieval to systematic reviews, health technology assessments (HTAs), randomized controlled trials (RCTs), guidelines, and economic studies. Systematic reviews and HTAs were searched from 1990 to the present, and results for RCTs, guidelines, and economic studies were searched from 2001 to the present. No language limits were applied, but search results were restricted to human studies. Weekly

alerts were established on these databases in October 2006, and information that is retrieved through alerts is current to November 13, 2006. A parallel search was performed on the Cochrane Library 2006, Issue 3, and results updated to Issue 4.

Grey literature was identified by searching the web sites of regulatory and HTA agencies, such as the University of York Centre for Reviews and Dissemination databases, ECRI (formerly Emergency Care Research Institute)'s HTA Information Service, and EuroScan. The Google™ search engine was used to find information on the Internet, including international funding and coverage information. These searches were supplemented by manual searches of the bibliographies of selected publications.

By request, this report includes studies that span multiple eras when various immunosuppressants and surgical techniques were used, so that the findings may not apply in today's environment.

4 SUMMARY OF FINDINGS

4.1 HTA Reports

ECRI: ECRI, a non-profit health services research agency, has produced a report on living-donor pancreas transplantation.[6] The report addressed four questions, two of which focused on the effectiveness and costs of living-donor pancreas transplantation compared with deceased-donor pancreas transplantation. The report included five studies (Table 1). All were case series occurring between 1998 and 2001. Four were based at the University of Minnesota. Living-donor SPK, PAK, and PTA patient and graft survival rates, at one- and five-year marks, were equal or greater than those of deceased-donor pancreas transplantations. Not all five studies addressed all these end points. No statistical analyses were reported.

There are a few limitations in the interpretation of the results in Table 1. First, the results of living-donor pancreas transplantation come from small sample sizes (the SPK survival rates are based on slightly more than 30 patients, and the PAK or PTA survival rates are based on 83 patients).

Second, only two centres reported on living-donor pancreas transplantation, with nearly all based at the University of Minnesota. Third, the living-donor PTA graft survival rates may be inflated because the percentages exclude technical failures (i.e., failed operations). Fourth, it is difficult to compare the survival rates of living-donor SPK to those of living-donor PAK and PTA, because PAK and PTA were mainly conducted between approximately 1978 and 1983, whereas SPK was mainly performed more recently. This comparison is complicated because there have been differences in the surgical techniques and immunosuppressants that have been used in pancreas transplantations over time.

There have been no living-donor mortalities reported.[6] There are living-donor morbidities including intra-operative morbidity and longer-term pancreas-function morbidities. Up to a quarter of living donors require splenectomy because of inadvertent damage to the spleen during transplantation.[6] Long-term living-donor outcomes are uncertain.

At the time of the ECRI report, living-donor pancreas transplantation was in its early phase of diffusion. It was offered at a few tertiary care transplant centres in the US and Europe; and it was projected that this would remain the status.[6] Given the lack of living-donor data in the Canadian Organ Replacement Register[2] and the US Organ Procurement and Transplantation Network (OPTN),[7] it can be deduced that living-donor pancreas transplantation is not yet a common practice.

An earlier ECRI report on pancreas transplantation was published in 1994.[4] This report did not mention the exclusion of studies based on living-donor pancreas transplantations, but no breakdown of living- versus deceased-donors was provided. It is likely that most of the data were based on deceased-donor pancreas transplantations, because that was common practice at that time. The report noted that the clearest benefit of SPK was the protection of the

kidney from diabetes-related deterioration, but it may also double the risk for kidney-rejection episodes. PTA is more controversial than SPK and PAK, because it requires the recipient to receive the immunosuppression that may have been unnecessary otherwise, whereas SPK and PAK recipients are committing to lifelong immunosuppression after their kidney transplant. In PAK, it is more difficult to diagnose pancreas rejection, which may account, at least partially, for the lower graft survival rates compared with those after SPK. The report found that all types of pancreas transplantation improved aspects of QOL that were related to diabetes.

It is difficult to assess the effect of pancreas transplantation on secondary diabetic complications because there are no RCTs and no direct comparison studies of its effects compared with those of insulin therapy.[4] The studies that look at nephropathy and retinopathy after pancreas transplantation are inconclusive. While there is evidence supporting the idea that SPK can halt the progression of neuropathy, the effect may also be explained by the resolution of uremia after the kidney transplant.[4]

This report[4] looked at survival rates from United Network for Organ Sharing (UNOS) and OPTN, between 1987 and 1992. The one- and three-year graft and patient survival rates appear in Table 2.

While the one- and three-year patient survival rates were similar across pancreas transplantations, SPK graft survival rates at the one- and three-year marks were higher than the PAK and PTA graft survival rates. No statistical analyses were reported, so it is unknown whether the differences were statistically significant.

A common morbidity associated with pancreas transplantation is graft failure. The incidence of pancreas graft failure due to non-immunologic factors (e.g., thrombosis, pancreatitis, infection) is 10.4% for SPK, 19.9% for PAK, and 16.5% for PTA. This reported incidence applies for bladder-drained, deceased-donor pancreas transplants.[4] Complications from surgical techniques can also occur. For example, metabolic acidosis, dehydration, urinary tract infections, or hyperkalemia may occur as a result of bladder drainage.[4] Some researchers note that kidney-rejection episodes may double as a result of SPK.[4] Immunosuppression complications such as infections, neoplasms (e.g., non-Hodgkin's lymphoma), neurotoxicity, hyperglycemia, and hypertension may also occur.[4]

The adjusted costs (used interchangeably with charges) for SPK were estimated in five studies, with amounts ranging between US$54,599 and US$91,177. The cost is what the hospital spends to provide the transplantation. The charge is what the patient or third-party payer is billed. For pancreas transplantation, the two terms are often used interchangeably because the data are incomplete.[4]

The costs were adjusted through 1993 with an assumed 5.0% annual inflation rate. Three studies did not specify the costs or charges included in the assessments. One study included hospital charges, professional fees, and donor-organ acquisition charges, but excluded physician fees and organ-procurement charges. One study looked at the total initial hospitalization charges. The study years ranged between 1988 and 1993.

The authors of the 1994 ECRI report performed a cost-effectiveness evaluation of SPK compared with kidney transplantation. They concluded that the cost of 10 SPK transplantations equalled the cost of 17 kidney transplantations. The authors, however, did not use the five primary studies found in their literature search to determine the values in the cost-effectiveness model. Instead, they used the median values from two studies. One study estimated that the initial cost of one SPK in 1988 was US$67,415 (includes hospital charges, physician's fees, and donor-acquisition costs). Another study estimated the cost for one renal transplant to be US$39,625 (no specifics were provided on what this estimate included). The estimated costs at one year that were used in the model were US$89,887 for one functional SPK compared with US$52,833 for one functional kidney transplant. The authors do not specify whether these numbers included living- or deceased-donor pancreas and kidney transplantations. There was no adjustment for inflation, and no sensitivity analyses were reported.

Table 1: Patient and graft survival rates for living- and deceased-donor pancreas transplantations[6]				
Type Of Pancreas Transplantation	**Living- Or Deceased-Donor**	**Pancreas Graft (Organ) Or Patient Survival**	**1-Year Survival (%)**	**5-Year Survival (%)**
SPK	living	patient	100.0	100.0
SPK	deceased	patient	92.0 to 95.0	88.0
SPK	living	graft	86.0	77.0
SPK	deceased	graft	77.0 to 86.0	73.0
PAK and PTA	living	patient	no data	90.0
PAK and PTA	deceased	patient	no data	78.0 to 89.0
PTA	living	graft	68.0	50.0
PAK and PTA	deceased	graft	no data	57.0 to 62.0

Table 2: One- and three-year graft and patient survival rates after pancreas transplantation[4]			
Type of Pancreas Transplantation	**Pancreas Graft (organ) or Patient Survival**	**1-Year Survival (%)**	**3-Year Survival (%)**
SPK	patient	91.0	84.0
PAK	patient	92.0	82.0
PTA	patient	91.0	84.0
SPK	graft	76.0	68.0
PAK	graft	47.0	30.0
PTA	graft	48.0	31.0

Institute for Clinical Systems Improvement (ICSI): The ICSI has released a report[1] on pancreas transplantation among patients with insulin-dependent diabetes. The report states that 94.0% of patients with diabetes receiving pancreas transplants have type 1 diabetes. After >7,000 pancreas transplantations were performed from 1996 to 2002, the one-year survival rates were similar for SPK (95.0%), PAK (94.0%), and PTA (98.0%). There was a significant difference in the one-year pancreas graft rejection rates (excluding technical failures) between SPK and PAK (2.0% versus 7.0%, p=0.0001) and between SPK and PTA (2.0% versus 8.0%, p=0.0001). One-year graft survival rates were significantly different between SPK and PAK (84.0% versus 76.0%, p=0.0001), and between SPK and PTA (84.0% versus 77.0%, p=0.0001).

The authors of the report provide four conclusions:

- Nearly all uremic diabetic patients are candidates for a kidney transplant. Most should be considered for a pancreas transplant simultaneously or sequentially with a kidney transplant. For those patients who have a living kidney donor, PAK is preferable to SPK.
- Long-term patient survival is higher after SPK and PAK compared with a kidney alone (KA) transplant. There is evidence supporting the assertion that SPK and PAK transplants prevent the recurrence of diabetic nephropathy in the transplanted kidney and stabilize neuropathy.
- PTA is usually done in patients with hypoglycemic unawareness or labile diabetes (including patients with frequent episodes of ketoacidosis). These patients undergoing failed insulin-based management may have incapacitating clinical or emotional problems with exogenous insulin therapy. Any gains that result from insulin independence must be weighed against the side effects of immunosuppression. PTA has been shown to stabilize neuropathy.
- Pancreas transplants can be performed at any hospital with an accredited transplant program (UNOS accredited) and appropriately trained surgeons.

Agency for Health Care Policy and Research (AHCPR): The Agency for Health Care Policy and Research (now the Agency for Healthcare Research and Quality) has released two reports on pancreas transplantation. One focused

on isolated pancreas transplantation[8] (PAK or PTA), and the other focused on SPK and PAK.[9]

The first report[8] based its findings on UNOS/OPTN (1987 and 1993) data and published literature (Table 3). The numbers are similar to the ECRI data (Table 2).[4] This is not surprising because both reports relied on UNOS/OPTN data from similar years. It is reported that smaller centres (performing <11 pancreas transplants over 27 months) experienced double the risk of graft failure of the centres performing >18 pancreas transplants over the same timeframe.

The second report[9] focused on SPK and PAK in patients with insulin-dependent diabetes and ESRD. This report concluded that while SPK and PAK have a low mortality rate, the morbidity rate exceeds that of kidney transplant alone. One- and three-year pancreas graft survival rates averaged 74.0% and 64.0% respectively. Approximately 16.0% of transplant recipients experienced complications, including wound infection; venous and arterial thrombosis of the graft; pancreatitis; intra-abdominal bleeding; and urinary tract infection. There were approximately three hospital admissions, on average, per transplant recipient. Re-transplant grafts have lower survival rates compared with those of the patients who had originally received SPK or PAK. The authors did not find evidence that SPK and PAK prevent or improve the secondary complications associated with diabetes.

The authors[9] built a cost-effectiveness model of SPK, PAK, and KA, based on a range of QOL estimates. They note that there is evidence of a wide variation in reported transplantation charges. Table 4 summarizes some of the costs that they used. The model was based on 100 patients receiving SPK and 100 patients receiving KA. The QOL preference weights (1=perfect health and 0=death) for SPK were 0.95 and 0.90. The authors deemed this to be moderately optimistic. Conversely, the authors assigned KA pessimistic QOL weights at 0.70, 0.75, and 0.80. The model included a three-year post-transplant observation period when no deaths or renal graft failure occurred.

With SPK given a QOL preference weight of 0.90, and KA given a QOL weight of 0.80 (a plausible scenario), SPK becomes as cost-effective as KA only when the annual costs of treating hyperglycemia or hypoglycemia are US$28,000 (for a KA payment of US$77,000) and US$40,000 (for a KA payment of US$50,000).

Table 3: One- and three-year graft and patient survival rates after pancreas transplantation[8]

Type Of Pancreas Transplantation	Pancreas Graft (Organ) Or Patient Survival	1-Year Survival (%)	3-Year Survival (%)
SPK	patient	90.3	80.8
isolated (PAK or PTA)	patient	91.3	80.1
SPK	graft	75.0	65.0
isolated (PAK or PTA)	graft	50.0	30.0

Table 4: Costs used in cost-effectiveness model[9]

Transplant	Variable	Cost (US$)	Source
SPK	hospitalization (year not reported)	73,000	University of Rochester
	average payment by third party (1993)	153,000	Health Insurance Association of America
	total 1-year charge selected (assumed to be contemporary to 1993)	150,000	Mayo Clinic
KA	hospitalization (1993)	50,000	Medicare
	average payment by third party (1993)	77,000	Health Insurance Association of America
	total 1-year payments (1993)	98,000	Medicare

PAK was not as cost-effective as KA even at annual costs of $40,000 for the treatment of hyperglycemia and hypoglycemia. This result was calculated under the most optimistic quality-adjusted life-year (QALY) scenario, with preference weights of 0.90 for PAK and 0.75 for KA.

A sensitivity analysis using various costs and QALY preference weights was conducted. No significantly different conclusions resulted. The authors note that the costs of SPK may have been underestimated because of the assumptions made in constructing the model. For example, the out-of-pocket costs were excluded in the model; it is unlikely that there were no graft failures in the three years post-transplant, but this assumption is made; and the QALY preference weights may have been too optimistic for SPK and PAK, and too pessimistic for KA.

The authors reviewed several studies but found limited evidence of improved QOL resulting from pancreas transplantation. The studies had methodological shortcomings including retrospective design, use of non-validated instruments, and comparison of groups that were assessed at different post-transplant intervals.

HTA summaries and updates: Three reports from health technology agencies were identified: two from Europe, and one from Québec.

Te AETSA, a health technology agency in Andalucia, Spain, assessed PTA.[10] The report states that isolated pancreas transplantation is considered to be an investigational phase III procedure, because of controversy about the mortality benefits. This assessment focuses on patients with frequent episodes of unconsciousness due to hypoglycemia or patients with unstable diabetes (including frequent episodes of ketoacidosis) in which insulin therapy is failing, and clinical incapacity or emotional problems are expected.

The Medical Technology Unit (of the Federal Social Insurance Office of Switzerland) has also assessed isolated pancreas transplantation.[11] The authors state that this procedure is considered to be a therapeutic procedure that should be performed in a specialized hospital. They conclude that there is a low morbidity associated with isolated pancreas transplantation. There were post-operative bleeding complications in 20% to 30% of the transplantations. Most patients were home and free of insulin use and further complications. The 10-year survival rate was 65.0%, and the procedure was deemed to provide insulin independence and normalization of hemoglobin A1c (HbA_{1c}) without hypoglycemia.

The Agence d'évaluation des technologies et des modes d'intervention en santé (AETMIS) has released a report examining SPK.[12] According to this report, pancreas transplantation was considered to be an innovative technology (not experimental). It was noted that SPK should only be practised in authorized centres. Preliminary results showed that patient survival was between 90.0% and 100.0%. At the end of the first year, organ survival was approximately 85.0%. It was noted that transplant patients experienced an improved QOL, and it is likely that the secondary effects of diabetes are reduced, if not halted. The costs of pancreas transplantation in the first year are approximately C$25,000. While supplementary costs are unavailable, the AETMIS report suggested that these costs are unlikely to be >C$15,000 in the first year (and do not significantly increase over subsequent years).

4.2 Systematic Reviews

Demartines *et al.* have systematically reviewed the literature on SPK and PTA.[13] The focus of this review was to compare the surgical (e.g., drainage techniques) and immunosuppressive aspects for SPK and PTA. They also assessed the cost-effectiveness of SPK and PTA. The range for one-year graft survival was between 70.0% and 100.0%. The range for one-year patient survival was between 82.0% and 100.0%. This is based on a literature search spanning 1992 to 2004.

In a five-year model, the cost per QALY for SPK was US$102,422 compared with US$156,042 for a deceased-kidney transplant and US$317,746 for dialysis. Using the same five-year model to compare PAK to SPK, the costs were comparable between groups. When adjusted for utility, PAK costs US$153,911 per QALY while SPK costs US$110,828 per QALY. The authors stated that they performed plausible variations in survival, costs, and utilities through a one-way sensitivity analysis, and found SPK to be the optimal procedure. No other details were provided.

Based on the UNOS/OPTN data between 1995 and 2000, the authors of this systematic review report that a patient's overall risk of death after SPK ranged between 0.29 and 0.43 compared with patients on a wait list for transplantation ($p<0.001$). Based on the evidence, the authors conclude that successful SPK is cost-effective and is superior to insulin therapy with dialysis or KA. The authors conclude that SPK is the gold standard for therapy.

From this systematic review, the four-year survival rate in the PTA group was 90.5%, which was comparable to 87.4% among patients in the wait-list group. When compared with standard insulin therapy, PTA may provide 0.42 more life-years and 2.2 more QALYs. The incremental costs (or charges) for PTA compared with those of standard therapy were about US$56,600 per QALY for the baseline case. The authors state that PTA may be cost-effective in labile non-uremic diabetic patients (grade C evidence). The authors conclude that PTA is an emerging therapy, and that an RCT would likely reveal its value in controlling diabetic complications. While no prospective PTA studies exist, the authors conclude that the evidence shows PTA is a viable alternative for diabetes patients without nephropathy.

Dew *et al.*[14] reviewed 19 studies on pancreas transplantation and QOL: 15 of these studies had a comparison group in their design, and 12 were cross-sectional (assessed QOL once after transplantation, and this could include what the patients recollected of their QOL before transplantation). The study sizes ranged between four and 65. Pancreas transplantation studies found evidence for improved QOL in terms of physical function, compared with similarly ill comparison samples (mostly KA transplant wait-list patients). No studies provided evidence to support the statement that transplant recipients experience an overall QOL equal to that of healthy persons. Every study that evaluated pancreas transplantation or pancreas and kidney transplantation, found evidence of improved QOL in physical function.

This systematic review had at least five limitations. First, there was no mention of a second reviewer. This may limit the credibility of the included research because there is a potential for the introduction of unchecked bias. Second, it is unclear how much time had passed between the time of transplantation and when the final QOL was assessed. Third, the research encompasses different immunosuppressant and surgical techniques, each of which may have an independent effect on QOL. Fourth, there were no RCTs, so the role of systematic patient differences (e.g., demographic and psychological) cannot be excluded. This could affect the QOL ratings. Fifth, patients who have not been received a transplant may assess their QOL differently from those who have undergone organ transplantation. This is central to the debate over the preferred source of utility measures.

Joseph *et al.*,[15] who reviewed the QOL after SPK, found 17 studies, mostly from the US. The years ranged between 1989 and 2001, with the study size ranging between seven and 1,138. Most studies were cross-sectional. Joseph *et al.* concluded that the QOL after SPK significantly improved, especially in easing the secondary complications of diabetes. Several limitations existed in this article. First, no statistics were presented to support the author's conclusions that there was a significant improvement in QOL after SPK. Second, comparing QOL studies across centres is problematic because the QOL instrument can be biased by individual investigators. Third, there were variations in sample sizes and duration of follow-up. Fourth, the authors report that there was a poor response rate, although no range was reported. Fifth, the responders to the QOL survey may have

systematically differed from the non-responders. This may have introduced a potential for the estimates of the outcomes to be biased.

4.3 Guidelines and Recommendations

Canadian Diabetes Association: The Canadian Diabetes Association has provided clinical guidelines for pancreas transplantation.[16] These recommendations are based on a consensus of expert opinions.

- In centres with personnel who are appropriately skilled in the technical aspects of surgery, pancreas transplantation is a preferred option for patients whose type 1 diabetes has been difficult to control and who are undergoing kidney transplantation for diabetic nephropathy.
- Whole-organ pancreas transplant for non-uremic patients remains a high risk procedure, and should be considered only for the patient with persistent major problems in diabetes control causing lifestyle disruptions despite efforts at intensive insulin therapy.

American Diabetes Association: The American Diabetes Association considers pancreas transplantation to be an acceptable therapy compared with continued insulin therapy in patients with type 1 diabetes.[17] They have two assertions.

- Pancreas transplantation should be considered in type 1 diabetic patients with imminent or established ESRD, or who have had or will have a kidney transplant (i.e., PAK or SPK). Additional criteria include meeting the medical indications and an absence of excessive surgical risk of the transplant procedures. It is also suggested that Medicare and other third-party payers should cover pancreas transplant procedures.
- If a patient does not present with indications for kidney transplantation, then pancreas transplantation should be considered for the patient with a history of frequent, acute, and severe metabolic complications such as hyperglycemia and ketoacidosis requiring medical attention, clinical and emotional problems with exogenous insulin therapy that render the patient incapacitated, and a history of consistent insulin-based management failures in preventing acute complications. If the facility has program guidelines to ensure the patient's condition and eligibility are established and followed, then third-party coverage should apply.

Capital Health (Alberta): Capital Health in Alberta has published the eligibility criteria for pancreas transplantation on their web site.[18]

- For SPK, the patient has type 1 diabetes and as a result, poor kidney function.
- For PAK, the patient has had a successful kidney transplant and has type 1 diabetes.
- For PTA, the patient has adequate kidney function and type 1 diabetes.
- The patient wants to have a transplant and understands his or her responsibilities after the transplant.
- The patient can safely tolerate receiving an anesthetic and undergoing surgery, and does not have other active medical problems.
- The patient is free of active infection.
- The patient does not have cancer.

UNOS: According to the UNOS, to be eligible for a living-donor or deceased-donor pancreas transplantation, the recipient must have one of the following:[19]

- re-transplant or graft failure
- type 1 or type 2 diabetes
- diabetes secondary to chronic pancreatitis without pancreatectomy
- diabetes secondary to cystic fibrosis without pancreatectomy
- pancreas, bile duct, or other cancers
- pancreatectomy before pancreas transplantation.

Aetna: Aetna has published recipient candidate eligibility criteria.[20]

A SPK or PAK candidate must have:

- ESRD and require, or is expected to require, dialysis within 12 months

- creatinine clearance <20 mL per minute (using the Cockcroft-Gault formula) or a glomerular filtration rate <30 mL per minute.

In addition, the patient must not have:

- malignant neoplasm with a significant risk for recurrence
- poorly controlled HIV infection
- persistent substance abuse
- unresolvable psychosocial problems
- inability to adhere to the regimen required to preserve the transplant
- ongoing or recurrent infections that are inadequately treated.

4.4 Cohort studies

Coppell *et al.* prospectively studied the beneficial effects of PTA in 32 patients with type 1 diabetes compared with 30 matched patients who did not receive a transplant.[21] Patients were matched by age, gender, insulin dose, and duration of diabetes. Data were collected at baseline and one-year post transplantation. Patients who had the transplantation experienced significantly improved fasting plasma glucose (pre-transplant 250±105 mg/dL compared with post-transplant 85±10 mg/dL, $p<0.01$) and C-peptide levels (pre-transplant 0.01±0.00 ng/mL, post-transplant 2.7±1.1 ng/mL, $p<0.01$). (Unless otherwise noted, data are means±standard deviation.)

Patients who did not have the transplantation did not see a significant change in any of the metabolic parameters. There were no significant differences in blood pressure and urinary protein levels between the two patient groups at baseline. At follow-up, the patients who underwent the transplantation had significantly lower blood pressure than the matched cohort. The clinical significance of this is unclear. One limitation of interpreting the study's results is the fact that there was no explanation of why the matched control patients were not selected for transplantation. There may have been systematic differences between these two groups that could account for any benefits seen in the transplant group. The authors state that there were no baseline differences between the two groups, but no data were presented on patient characteristics to verify this statement.

Kessler *et al.*[22] prospectively compared glucose levels and hypoglycemic events over a three-day period across three groups of patients (n=26). One group received insulin infusion through an implantable pump (IPII), the second group had SPK transplant, and the third group had pancreas islet transplantation after kidney grafting (IAK). The recruitment spanned 1999 to 2002. The mean glucose concentration of the SPK and IAK groups were significantly lower than that of the IPII group (5.38±1.12, 5.83±1.12, 7.81±2.55, $p<0.001$). The IPII group experienced 4.12±1.66 hypoglycemic events, whereas the IAK group experienced 0.66±0.57 ($p<0.0001$), and the SPK group did not experience any such events. Patients in the three groups did not differ in gender, age, BMI, or diabetes duration. There were differences in graft duration years and HBA_{1c} percentages. Thus, the authors conclude that insulin infusion through an IPII does not provide superior glucose control. However, there was a small number of patients in each group, and glucose was measured for only three days.

Venstrom *et al.*[23] retrospectively evaluated the four-year mortality rate of 5,990 patients with preserved kidney function who had PTA, PAK, or SPK transplants compared with 5,582 patients with diabetes on the wait list for three types of pancreas transplants. The data, which came from the UNOS/OPTN, were gathered between 1995 and 2000. Patients on the wait list did not differ in diabetic severity, but were selected primarily based on blood type, and time on the wait list. The overall risk of death and one- and four-year survival rates appear in Table 5. There were no statistically significant differences in the overall risk of death between the PTA transplant group and the patients on the wait list. Thus, compared with the patients on the wait list, the overall PTA survival does not differ, PAK transplantation patients have significantly worse overall survival, and SPK transplant patients have significantly better overall survival.

Table 5: Survival of patients with pancreas and pancreas-kidney transplant versus patients on wait list for same transplant[23]							
Transplant	**Number of Patients**		**Overall Risk of Death**	**1-Year Survival Rate (%)**		**4-Year Survival Rate (%)**	
	Transplant	Wait List	Transplant versus Wait List	Transplant	Wait List	Transplant	Wait List
PTA	361	311	1.57 (CI 95%: 0.98 to 1.94, p=0.06);	96.5	97.6	85.2	92.1
PAK	753	645	1.42 (CI 95%: 1.03 to 1.94, p=0.03);	95.3	97.1	84.5	88.1
SPK	4,876	4,626	0.43 (CI 95%: 0.39 to 0.48, p<0.001).	94.4	92.8	87.5	63.8

Venstrom's study was not a RCT. Therefore, there could be systematic differences between the patients who receive transplants and those who remain on the wait lists. Chi square tests revealed that PAK and PTA recipients were similar in age, coronary artery disease, and diabetes duration, with one difference being that non-Caucasian wait-list patients received fewer transplants. In the SPK group, the same ethnicity difference emerged in addition to slight differences in age, gender, and duration of diabetes. No statistics were presented on patient characteristics, so the magnitude of any differences could not be judged. This study did not address morbidity or QOL, which would have given a more complete picture of the relative success of PTA, PAK, and SPK.

A retrospective, case-controlled study published by Rerolle *et al.*, evaluated renal graft failure in 26 SPK patients and 67 KA transplant recipients between 1992 and 1998.[24] Actuarial patient survival in the SPK and KA groups were comparable at one and four years (100.0% versus 97.1%, and 100.0% versus 94.1%, p=ns). No kidney graft survival differences emerged between SPK and KA transplant groups (3.8% versus 7.5%, p=ns) after the numbers were adjusted for patient death. In the SPK group, pancreas graft survival rates at one and four years were 88.5% and 80.2%. The only demographic information that was presented was that SPK recipients were significantly younger than the KA group (39.9±7.1 years versus 43.1±11.3 years, p=0.0006). The SPK group experienced a significantly shorter mean waiting time and duration of dialysis.

Israni *et al.*[25] assessed the impact of SPK transplant on kidney graft survival in patients with type 1 diabetes. The study included SPK wait-list patients from the UNOS/OPTN between 1990 and 2002. They compared 7,458 recipients of a SPK transplant to 865 recipients of a KA transplant. SPK recipients had fewer kidney graft failures (15.0% versus 34.0%, p<0.001). Kidney graft failure or patient death occurred in 23% of SPK recipients compared with 43.0% in the KA group (p<0.001). If SPK occurred before the initiation of chronic dialysis, there was a 17.0% hazard ratio (HR) reduction (HR=0.83, CI 95%: 0.69 to 0.99, p=0.042) in kidney graft failure. It was not stated when the kidney graft survival was assessed. It is implied that it occurred from immediately post-transplant up to five years, for which 80.0% of transplant recipients' data were available. The most notable limitation is that the investigators assessed databases, not patients. Therefore, patients could have been on wait lists for SPK and KA, and had their kidney transplant done before the pancreas procedure, which means that some patients received PAK and not SPK. There were differences in the baseline characteristics between the two groups, for example, SPK recipients were more likely to be younger, be Caucasian, have shorter ischemia time, have less delayed allograft function, and have >0 HLA mismatch.

Whiting *et al.*[26] compared the Medicare payments after a SPK (n=3,342) to those after a KA (n=5,178) in type 1 diabetic patients, using the UNOS/OPTN renal-transplant data between 1990 and 1997. The authors found that a SPK is more expensive (US$72,617 versus US$67,446, p<0.0001) in the first year but the differences are not significant by five years (US$125,947

versus US$125,757, p=ns). This includes payments at a 5.0% discount rate, in 1998, dollars with a $25,000 organ-acquisition charge added to all payments. When the charges to Medicare are considered, a SPK has significantly more charges than a KA at one and five years (US$189,019 versus US$145,421 for the first year, and US$310,109 versus US$276,827 for the fifth year, p<0.0001).

4.5 Organ Transplant Registries

The Canadian Institute for Health Information (CIHI) has released a report that summarizes the Canadian Organ Replacement Register data on pancreas transplantation between 1994 and 2003.[2] During this period, 446 pancreas transplantations occurred. Nearly 60.0% of these were performed in Québec and Ontario. American data on pancreas transplantation are gathered by the OPTN, which presents data on SPK, PAK, and PTA.[7] Table 6 describes the one- and five-year patient and graft survival rates. The Canadian data are presented as unadjusted rates whereas the American data are presented as adjusted rates.

4.6 Modelling studies

Knoll and Nichol[33] constructed a decision-analytic Markov model to evaluate life-years gained and QALY gained across five treatment strategies for a hypothetical cohort of patients with type 1 diabetes and renal failure. (A Markov model is used to determine QALYs and cumulative health costs after a utility score, i.e., the score on the QOL scale, and a cost for each health state are assigned.) These groups were dialysis, deceased-donor kidney transplantation (DKT), living-donor kidney transplantation (LKT), SPK, and PAK. The typical patient in this model had type 1 diabetes, was between the ages of 18 and 49, had recent onset of permanent kidney failure, and had not previously received a renal transplant. The model included the wait-list risks such as death, hypoglycemia, ketoacidosis, and transplant risks. Five transplant risks were a technically successful transplant without complications; a post-transplant infection (fatal or nonfatal); a post-transplant complication that may result in graft failure; acute graft rejection; or patient death. The lowest gains in life expectancy and QALY compared with dialysis were in the DKT group and the most gains were seen in the LKT group. The transplant comparisons are made in relation to 7.82 life-years on dialysis with a QALY of 4.52 (Table 7).

This model included wait times for pancreas transplant in the PAK, DKT, and SPK groups, the possibility of illness and mortality occurring during the wait times, and five outcomes from the transplant (death, post-operative complication, major infection, acute rejection, or no complication). Several assumptions were made, including DKT and LKT groups having the same major infection rate, the mortality rate for dialysis patients being the same as that of type 1 diabetic patients on the deceased-donor renal wait list, dialysis patients receiving conventional insulin, DKT and LKT groups receiving intensive insulin therapy, PAK and SPK groups having the same patient survival rate, and the PAK group having the same mortality rate while waiting for a pancreas as that of patients with functioning LKT.

Kiberd *et al.*[34] developed a Markov model, based on information gathered from the literature, to estimate the benefit of PTA compared with insulin therapy in type 1 diabetic patients before ESRD. The purpose of this study was to provide evidence to support an RCT in this patient group. Assuming a baseline graft life expectancy for the pancreas of 10 years, they found that early PTA could give 0.42 more life-years and 2.2 additional QALY, discounted at 3.0%. The incremental cost for early PTA compared with standard insulin therapy was US$56,600 per QALY for the baseline case. The utility scores were based on 16 patients with type 1 diabetes and ESRD. In this model, the utility score for a functioning pancreas was given 0.95. The QALY gains for PTA varied depending on the patient: early microalbuminuria resulted in a gain of 1.7 QALY; more advanced nephropathy (mildly elevated serum creatinine) resulted in a gain of 1.1 QALY; and a more rapid deterioration of renal function resulted in a gain of 2.7 QALY. The

authors conclude that these results provide support for an RCT of PTA in patients before ESRD. A few of the model's assumptions were that normal pancreas function would halt the progression of diabetic retinopathy and nephropathy; the risk of cardiovascular events was similar in the pancreas and insulin groups; the mortality increased with age and duration of diabetes, and varied with health states such as ESRD; and patients with ESRD received kidney or pancreas-kidney transplant and dialysis.

Table 6: Patient and graft survival data from Canadian and American organ registries

Type Of Pancreas Transplantation	Graft (Organ) or Patient Survival	Survival			
CIHI		**1-Year Survival Unadjusted (1994 to 1998) (%)**		**5-Year Survival Unadjusted (1994 to 1998) (%)**	
SPK[2]	patient	96.4		94.6	
SPK[2]	graft	91.9		82.9	
OPTN		**1-Year Adjusted (1999 to 2000 cohort)**		**5-Year-Adjusted (1997 to 1998 cohort)**	
		%	SE (%)	%	SE (%)
PTA[27]	graft	81.3	2.5	52.2	4.8
PTA[28]	patient	98.3	1.0	86.5	3.8
PAK[29]	graft	81.3	1.5	52.4	3.0
PAK[30]	patient	96.0	0.9	87.2	3.0
SPK[31]	graft	no data	no data	no data	no data
SPK[32]	patient	95.9	0.5	89.5	0.8

SE=standard error; CIHI=Canadian Institute for Health Information; OPTN=US Organ Procurement and Transplantation Network.

Table 7: Gains in life-years and QALY for transplant procedures, compared with dialysis[33]

Type Of Transplantation Compared with Dialysis	Gain in Life-Years	Gain in QALY
DKT	3.62	2.01
SPK	7.92	4.57
PAK	9.39	5.48
LKT	10.48	5.77

4.7 Funding and Setting

No information detailing the Canadian or Australian funding status of SPK, PAK, or PTA was available.

Five sources in the US were found (Medicare,[6] Bluecross Blueshield of Tennessee,[35] Excellus Health Inc., Bluecross Blueshield Association,[36] CHAMPVA,[37] and Aetna[20]). All fund the three types of pancreas transplantation. Details about the eligibility criteria for pancreas transplantation and the amount of immunosuppressant therapy covered by each plan appear in each of the cited references. In the US, Medicare does not restrict which hospitals or physicians perform pancreas transplantations, as long as they are Medicare-approved institutions.[38]

In 2003, UK Transplant began operating a national scheme for retrieving and sharing pancreata for transplantation. The National Specialist Commissioning Advisory Group designated seven centres that could provide pancreas transplantation.[39] Pancreas transplantation in Scotland is performed in a treatment facility in Edinburgh. Residents from Wales are treated in England.

In the UK, the National Specialist Commissioning Advisory Group stated that it funds the cost of the SPK of citizens of England (not citizens of Wales or Northern Ireland who can undergo the procedure in England).[39]

4.8 Limitations

One limitation of this report is the absence of RCTs assessing the clinical effectiveness,

including mortality and morbidity, associated with pancreas transplantation versus no transplantation (or standard therapy). In the absence of such trials, this review included systematic reviews of non-randomized trials, cohort studies, modelling studies, and registry data. Non-randomized trials are vulnerable to several sources of bias. For example, in the studies included in this report, there were significant patient differences between transplant and wait-list groups, including ethnicity, age, ischemia time, and incidence of cerebrovascular disease. This limits the comparability between studies.

Given that pancreas transplantation has been widely disseminated for years, it is unlikely that well-designed RCTs that examine pancreas transplantation will occur because ethical and logical complications will prevent this. These may include the possibility that patients will not consent to a RCT because there is a chance that they will not receive the pancreas transplant; the difficulty of blinding patients; and the improbability of assessing the effects of immunosuppression agents alone, without the operation.

Another limitation of this report is that most of the literature on which it is based is derived from UNOS/OPTN data. In addition, pancreas transplantation, while done worldwide, is mostly localized to a few centres. This is especially the case of living-donor pancreas transplantation where the data come solely from the University of Minnesota and have been collected over a long time.

In addition, most studies did not provide details on the morbidity associated with pancreas transplantation. Understanding the adverse events associated with a health technology is necessary to evaluate its clinical effectiveness.

The interpretation of the costs and benefits of pancreas transplantation is complicated by the fact that the literature search included studies that encompassed different surgical techniques and immunosuppressant therapy eras. The fact that pancreas transplantation has changed over time undermines the ability to effectively evaluate the data, because the changes have affected mortality and morbidity. Since tacrolimus and mycophenolate mofetil became standard immunosuppressive agents, and enteric drainage replaced bladder drainage in most transplants (approximately 1998 and onward), graft and patient survival rates have improved while complications have been reduced. This complicates the comparison of today's results with those of procedures performed before 1998. Several RCTs address the efficacy of immunosuppressant therapies and surgical techniques, but it is beyond this report's scope to address this facet of pancreas transplantation.

It is also beyond the scope of this report to seek input from transplant centres in Canada and other countries. This produces a gap in information, especially in describing clinical and other issues that are involved in the decision-making processes.

5 CONCLUSIONS AND IMPLICATIONS FOR DECISIONS FOR POLICY MAKING

Pancreas transplantation is an accepted treatment for patients with type 1 diabetes and ESRD. This has occurred despite the absence of high quality, robust evidence (i.e., RCTs) on which to base such a decision. As pancreas transplantation has been integrated into the health care system with acceptable clinical benefits, it is unlikely that RCTs will be started, because of ethical considerations.

Evidence exists of increased graft and patient survival, and reduction of complications. It comes mainly from the transplant registries. The most recent published literature (data from 1990 and onward) report one-year graft survival rates between 70.0% and 100.0%, and one-year patient survival rates between 82.0% and 100.0%. These numbers may provide a sense that pancreas transplantation will yield positive results for the patient. However, there is a lack of published RCTs to establish its value

compared with lifelong insulin or dialysis treatments.

The morbidity associated with pancreas transplantation is an important consideration because it affects health outcomes, cost of care, and resource utilization, all of which contribute to policy decisions. Studies that address the rates of transplant morbidities (e.g., metabolic acidosis and urinary tract infections), immunosuppression complications (e.g., neurotoxicity and hypertension), or the prevention of secondary diabetic complications (e.g., retinopathy and nephropathy) were scarce. One HTA reported that approximately 15% of PAK or SPK patients experienced complications.

It is difficult to determine whether pancreas transplantation is cost-effective, because there is little evidence comparing it with lifelong insulin treatment or lifelong dialysis. In this report, one modelling study estimated that compared with dialysis, a simultaneous pancreas and kidney transplant provided 7.92 additional life-years and a gain of 4.57 QALYs. The same study reported that a PAK transplant provided an additional 9.39 life-years and a gain of 5.48 QALYs. A different modelling study compared a pancreas transplant alone with dialysis and estimated that there were an additional 0.42 life-years and 2.2 more QALYs when compared with insulin therapy. One systematic review estimated the cost per QALY for a SPK transplant to be approximately US$100,000 compared with approximately US$315,000 for dialysis.

Pancreas transplantation is performed in several countries including Canada, US, Australia, and UK. In the UK, there are designated centres where the pancreas transplantation can occur, whereas in the US, it can be done in any hospital that fulfils UNOS accreditation criteria. While pancreas transplantation can be a covered service, there are eligibility criteria that must be met. These can differ across hospitals and jurisdictions, and the issue of how many years the immunosuppressant therapy is covered can be resolved in different ways across funding bodies.

While some of the studies that were evaluated mentioned the use of pancreas transplantation for patients who have type 2 diabetes, no studies assessed this patient population. No other patient population for pancreas transplantation was evaluated.

While there is a paucity of rigorous data regarding the clinical effectiveness and cost-effectiveness of pancreas, there is access to Canadian and US registry data. These registry data are invaluable in providing long-term graft and patient survival rates; which are required to understand the risk and benefits of pancreas transplantation.

6 REFERENCES

1. *Pancreas transplant*. Bloomington (MN): Institute for Clinical Systems Improvement; 2003.
2. Canadian Institute for Health Information. *Treatment of end-stage organ failure in Canada, 2002 and 2003* [CORR report]. Ottawa: The Institute; 2005. Available: http://secure.cihi.ca/cihiweb/products/CORR_Annual_Report_0203_e.pdf (accessed 2006 Nov 7).
3. Meier-Kriesche HU, Stegall MD. Should we be performing pancreas transplants? *American Journal of Transplantation* 2004;4(12):1935-6.
4. *Pancreas transplantation*. [ECRI health technology assessment report]. Plymouth Meeting (PA): ECRI; 1994.
5. Schnitzler MA, Whiting JF, Brennan DC, Lentine KL, Desai NM, Chapman W, et al. The life-years saved by a deceased organ donor. *Am J Transplant* 2005;5(9):2289-96.
6. *Living-donor pancreas transplantation*. [Windows on medical technology no.90]. Plymouth Meeting (PA): ECRI; 2003.
7. *Welcome to the 2004 OPTN/SRTR annual report. The U.S. Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients*. Rockville (MD): Department of Health and Human Services; 2004. Available: http://www.optn.org/AR2004/default.htm (accessed 2006 Nov 7).

8. Hotta S. Isolated pancreas transplantation. In: *Health services/technology assessment text (HSTAT)* [database online]. Bethesda (MD): National Library of Medicine; 1995. Available: http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hstat6.chapter.44230 (accessed 2006 Oct 13).

9. Holohan TV. Simultaneous pancreas-kidney and sequential pancreas-after-kidney transplantation. *Health Technol Assess (Rockv)* 1995;(4):1-53. Available: http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hstat6.chapter.42926 (accessed 2006 Oct 13).

10. Isolated pancreas transplantation. In: *EUROSCAN* [database online]. Birmingham (UK): University of Birmingham; 2004.

11. Isolated pancreas transplantation. In: *EUROSCAN* [database online]. Birmingham (UK): University of Birmingham; 2001.

12. *Sommaire: la transplantation au Quebec. Rapport preliminaire sur l'efficacite, les couts et les caracteristiques organisationnelles (documents d'appui 1 a 7) [Rapport no.12]*. Montreal: CETS; 1991. Available: http://www.aetmis.gouv.qc.ca/site/download.php?f=865489c8f5b4e715624160817125b0e3 (accessed 2006 Oct 13).

13. Demartines N, Schiesser M, Clavien PA. An evidence-based analysis of simultaneous pancreas-kidney and pancreas transplantation alone. *Am J Transplant* 2005;5(11):2688-97.

14. Dew MA, Switzer GE, Goycoolea JM, Allen AS, DiMartini A, Kormos RL, et al. Does transplantation produce quality of life benefits? A quantitative analysis of the literature. *Transplantation* 1997;64(9):1261-73.

15. Joseph JT, Baines LS, Morris MC, Jindal RM. Quality of life after kidney and pancreas transplantation: a review. *Am J Kidney Dis* 2003;42(3):431-45.

16. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. *Canadian Diabetes Association 2003 clinical practice guidelines for the prevention and management of diabetes in Canada: pancreas and islet transplantation*. Toronto: Canadian Diabetes Association; 2003. Available: http://www.diabetes.ca/cpg2003/chapters.aspx?pancreasandislettransplantation.htm (accessed 2006 Oct 13).

17. American Diabetes Association. Pancreas and islet transplantation in type 1 diabetes. *Diabetes Care* 2006;29(4):935.

18. *Who needs a pancreas transplant?* Edmonton: Capital Health; 2006. Available: http://www.capitalhealth.ca/YourHealth/BrowseByTopic/content.asp?guid=B9B754AB-21A3-43F0-B69C-CC26F033A52B&NavType=Topic&Level_1_ID=70&Level_2_ID=1807&Level_3_ID=4634&Level_4_ID (accessed 2006 Oct 19).

19. Barr ML, Belghiti J, Villamil FG, Pomfret EA, Sutherland DS, Gruessner RW, et al. A report of the Vancouver Forum on the care of the live organ donor: lung, liver, pancreas, and intestine data and medical guidelines. *Transplantation* 2006;81(10):1373-85.

20. *Pancreas kidney transplantation*. Hartford (CT): Aetna; 2006. Available: http://www.aetna.com/cpb/medical/data/500_599/0587.html (accessed 2006 Oct 16).

21. Coppelli A, Giannarelli R, Vistoli F, Del Prato S, Rizzo G, Mosca F, et al. The beneficial effects of pancreas transplant alone on diabetic nephropathy. *Diabetes Care* 2005;28(6):1366-70.

22. Kessler L, Passemard R, Oberholzer J, Benhamou PY, Bucher P, Toso C, et al. Reduction of blood glucose variability in type 1 diabetic patients treated by pancreatic islet transplantation: interest of continuous glucose monitoring. *Diabetes Care* 2002;25(12):2256-62. Available: http://care.diabetesjournals.org/cgi/reprint/25/12/2256 (accessed 2006 Oct 26).

23. Venstrom JM, McBride MA, Rother KI, Hirshberg B, Orchard TJ, Harlan DM. Survival after pancreas transplantation in patients with diabetes and preserved kidney function. *JAMA* 2003;290(21):2817-23.

24. Rerolle JP, Thervet E, Anglicheau D, Desgrandchamps F, Nochy D, Janin A, et al. Long-term renal allograft outcome after simultaneous kidney and pancreas transplantation. *Nephrol Dial Transplant* 2002;17(5):905-9.

25. Israni AK, Feldman HI, Propert KJ, Leonard M, Mange KC. Impact of simultaneous kidney-pancreas transplant and timing of transplant on kidney allograft survival. *American Journal of Transplantation* 2005;5(2):374-82.

26. Whiting JF, Martin JE, Cohen D, Woodward R, Singer G, Lowell J, et al. Economic outcome of simultaneous pancreas kidney transplantation compared with kidney transplantation alone. *Transplant Proc* 2001;33(1-2):1923.

27. Table 6.8. Adjusted graft survival, pancreas transplant alone (PTA) transplants. Survival at 3 months, 1 year, 3 years, and 5 years. In: *2004 annual report of the U.S. Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients: transplant data 1994-2003*. Rockville (MD): Department of Health and Human Services; 2004. Available: http://www.optn.org/AR2004/608_pta.pdf (accessed 2006 Nov 7).

28. Table 6.12. Unadjusted patient survival, pancreas transplant alone (PTA) transplants. Survival at 3 months, 1 year, 3 years, and 5 years. In: *2004 annual report of the U.S. Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients: transplant data 1994-2003*. Rockville (MD): Department of Health and Human Services; 2004. Available: http://www.optn.org/AR2004/612_pta.pdf (accessed 2006 Nov 7).

29. Table 7.8. Adjusted graft survival, pancreas after kidney (PAK) transplants. Survival at 3 months, 1 year, 3 years, and 5 years. In: *2004 annual report of the U.S. Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients: transplant data 1994-2003*. Rockville (MD): Department of Health and Human Services; 2004. Available: http://www.optn.org/AR2004/708_pak.pdf (accessed 2006 Nov 7).

30. Table 7.11. Adjusted patient survival, pancreas after kidney (PAK) transplants. Survival at 3 months, 1 year, 3 years, and 5 years. In: *2004 annual report of the U.S. Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients: transplant data 1994-2003*. Rockville (MD): Department of Health and Human Services; 2004. Available: http://www.optn.org/AR2004/711_pak.pdf (accessed 2006 Nov 7).

31. Table 8.8. Adjusted kidney graft survival, pancreas-kidney transplants. Survival at 3 months, 1 year, 3 years, and 5 years. In: *2004 annual report of the U.S. Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients: transplant data 1994-2003*. Rockville (MD): Department of Health and Human Services; 2004. Available: http://www.optn.org/AR2004/808_kp.pdf (accessed 2006 Nov 7).

32. Table 8.11. Adjusted patient survival, kidney-pancreas transplants. Survival at 3 months, 1 year, 3 years, and 5 years. In: *2004 annual report of the U.S. Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients: transplant data 1994-2003*. Rockville (MD): Department of Health and Human Services; 2004. Available: http://www.optn.org/AR2004/811_kp.pdf (accessed 2006 Nov 7).

33. Knoll GA, Nichol G. Dialysis, kidney transplantation, or pancreas transplantation for patients with diabetes mellitus and renal failure: a decision analysis of treatment options. *J Am Soc Nephrol* 2003;14(2):500-15.

34. Kiberd BA, Larson T. Estimating the benefits of solitary pancreas transplantation in nonuremic patients with type 1 diabetes mellitus: a theoretical analysis. *Transplantation* 2000;70(7):1121-7.

35. *Bluecross Blueshield of Tennessee medical policy manual: pancreas/pancreas-kidney/pancreatic islet cell transplantation*. Chattanooga (TN): Bluecross Blueshield of Tennessee; 2005. Available: http://www.bcbst.com/MPManual/Pancreas_Transplantation__48160.htm (accessed 2006 Oct 16).

36. *Pancreas transplant (pancreas transplant alone, pancreas after kidney transplant, simultaneous pancreas kidney transplant) [medical policy]*. Rochester (NY): Excellus Bluecross Blueshield; 2006. Available: https://www.excellusbcbs.com/download/files/med_policies/panc_tsplt_0306.pdf (accessed 2006 Oct 16).

37. SPK (simultaneous pancreas-kidney), PAK (pancreas after kidney), and PTA (pancreas transplant alone). In: *CHAMPVA policy manual*. Washington: Department of Veterans Affairs; 2005. Available: http://www.va.gov/hac/forbeneficiaries/champva/policymanual/cvapmchap2/1c2s31.5.pdf (accessed 2006 Oct 13).

38. Pancreas transplants alone (PA). In: *CMS manual system*. Washington: Department of Health & Human Services; 2006. Available: http://www.cms.hhs.gov/transmittals/downloads/R957CP.pdf (accessed 2006 Oct 16).

39. *Pancreas transplants*. [Chief executive bulletin]. London: Department of Health; 2004. Available: http://www.dh.gov.uk/PublicationsAndStatistics/Bulletins/ChiefExecutiveBulletin/ChiefExecutiveBulletinArticle/fs/en?CONTENT_ID=4074642&chk=hHkzeq (accessed 2006 Oct 16).