CANADIAN COUNCIL FOR DONATION AND TRANSPLANTATION

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CONSEIL CANADIEN POUR LE DON ET LA TRANSPLANTATION

Kidney Pancreas Allocation

October 2006

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Prepared for the CCDT by:
Bryce Kiberd

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Aim: To provide an evidence-based rationale to pancreas allocation that will increase overall outcomes without disadvantaging other patients needing an organ transplant.

In order to provide a framework for a discussion on allocation a review of candidate eligibility, transplant options, current activity status and current allocation practice is presented below.

I. The Candidate

Eligibility criteria for potential pancreas transplant candidates tends to be more stringent than for kidney transplant alone candidates. There is likely considerable center to center variation. In addition some centers perform pancreas transplantation in selected type 2 diabetes mellitus patients. Although C-peptide levels are not completely reliable, many centers will measure C-peptide levels. Low but detectable levels may be seen in some type 1 patients.

There is evidence that early morbidity is higher in patients receiving both organs and mortality increases in older patients. There is an age limit in some centers. With more experience the accepted age has drifted upwards from 45 to 55 as an upper limit. Some centers also have stricter cardiovascular disease guidelines. Some centers may insist that all have a cardiac catheterization and be free of significant vascular disease. Other recommended eligibility criteria include BMI <32, history of adherence to medical recommendations, and detailed informed consent.

Some centers allow for pre-emptive SKP so long as deterioration is progressive and GFR below 20 ml/min. Pancreas after kidney transplantation generally occurs in patients with very good renal allograft function.

Supporting Evidence:

Most of the evidence for the above recommendations was retrieved from review articles (1-4). There is little hard evidence for some recommendations such as BMI or compliance prior to transplantation as a predictor of later outcomes. There is some evidence for an upper age limit (see below). The use of pancreas transplantation in type 2 diabetes mellitus is being described in the literature (5-8). The practice in Canada is limited; however some Canadian centers do see this as an option (Appendix 1). The use of C-peptide to differentiate between type 1 and 2 has been examined and not found to be completely reliable as noted above (9-11). Consultation with an endocrinologist may be required. Although the cardiac evaluation of the potential kidney/pancreas recipient is of great interest and will impact on patient selection, its practice is not likely to have a large impact on allocation. In a survey of Canadian centers, routine cardiac catheterization is not practiced (Appendix 1).

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II. The Options:

Given the scarcity of organs for transplantation a review of the options and evidence is helpful. A uremic diabetic patient fit for transplantation has several options:

1. Simultaneous kidney pancreas (SKP): There is some evidence that combined kidney-pancreas transplantation results in improved quality and length of life over kidney-alone transplantation in uremic patients with type 1 DM. Unfortunately there are no randomized controlled trials and inevitably those receiving combined transplants are

younger with less co-morbidity than those receiving a kidney-alone transplant. In a multivariate analysis, better organs for SKP recipients also may explain superior outcomes. However, patients who are fortunate to receive both do better if both organs function compared to those where only the kidney functions (pancreas graft loss). There is softer evidence that better cardiac and metabolic control may explain better survival. Most patients will prefer both organs using standardized tests of preference or quality of life. Details of the evidence are provided in Appendices 2 and 3.

2. Kidney Alone Transplant (KA): Living kidney donation is an important option for uremic patients with type 1 diabetes mellitus. Some have argued that living donor KA may produce more quality adjusted life years (QALYs) at less cost than SKP especially if well matched and if performed pre-emptively. A direct comparison of these options is not possible given the lack of a randomized controlled trial. In general patients with a live donor have mortality rates that are significantly less than those receiving a deceased donor kidney.

3. Pancreas after kidney transplantation (PAK) is a growing approach to transplantation. Overall pancreas graft survival for PAK is improving but has not exceeded SKP. Furthermore, it requires a second operation. It may not improve overall length of life but may improve quality of life.

4. Perform a live kidney donor operation at the time of a deceased donor pancreas transplant operation as a means to eliminate the need for two operations.

5. Live pancreas and kidney donation is not widely practiced. Long-term donor safety has not been well described and the option will not be discussed further (1-2).

Islet transplantation, because of limited success, remains experimental (3). A recent consensus group of transplant physicians and surgeons was more positive about the future of this modality but agreed that its role was limited at the present time (4). However, widespread use of pancreas-alone transplantation in non-uremic patients will pose a stress to the supply of organs for uremic patients.

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III. Transplant Activity in Canada: 'Current Status'

CORR Report 2005 (http://secure.cihi.ca/cihiweb/) has data that are several years out of date. Table 1 shows transplant activity over the last decade. SKP was performed in 324, pancreas transplant alone (PTA) in 109, and PAK in only 13 (from a total of 446). SKP transplantation rates in the US are 3 per million population (pmp) compared to Canada at 1.2 pmp. PTA rates in the US are 0.5 pmp whereas in Canada they are higher at 0.8 pmp. PAK rates are 1.2 pmp in the US compared to <0.1 pmp in Canada. There is a clear difference in transplant activity in the US compared to Canada with more pancreas transplantation overall, mostly SKP and growing PAK. In Canada PTA appears to be more common than in the US, however, there may be significant misclassification. From a questionnaire sent to transplant centers in Canada there appears to be a significant discrepancy in the data (Appendix 1). It is probable that most of the PTA noted in the table were in fact PAK.

Table 1. Pancreas Transplant Activity, Canada 1994-2003 (CORR 2005 Report)

	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	**Total**
SKP	7	15	19	30	40	51	47	33	44	38	324
PAK	0	0	0	2	3	2	1	3	1	1	13
PTA	0	1	2	1	6	18	18	11	27	25	109
Total	7	16	21	33	49	71	66	47	72	64	446

In comparison to pancreas transplantation, there were 5468 deceased donor kidneys transplanted over the last decade. About 24.2% of patients transplanted have diabetes mellitus as a diagnosis or comorbidity. It is not clear how many are type 1 but <20% of all patients with DM are <40 years old. It is possible that the pool of patients that could be eligible for a SKP would be about 5% (24.2% *20%). There are about 120 patients awaiting an SKP compared to 2,845 adults awaiting KA on the list (4.2%). Although the comparisons and data are inexact, it would appear that no more than 5% of those on the transplant list are candidates for an SKP. The number of pancreas available for whole organ transplantation is at present unknown, but 64 pancreas organs were transplanted from 421 donors in 2003. Assuming that all viable organs were used, 15% of deceased donors were suitable for pancreas organ donation.

In 2003, there were 38 SKPs and 664 deceased donor kidney transplants (5.7%). From the above estimates, 4.2% of the list is for SKP. Acknowledging inaccuracies and assumptions, the numbers on the list for an SKP should not greatly exceed 5%. However if all pancreas donor organs were diverted to SKP recipients then patients on the list would be transplanted at almost twice the overall rate. Presumably, if the number of SKP transplants performed relative to the number of all kidney transplants performed was about the same as numbers

on the SKP waitlist relative to all waitlisted kidney recipients, there would be no great advantage or disadvantage.

V. International and Canadian Allocation Schemes

The following international sites were investigated by examining material on their website. Selected centers were contacted to confirm details of allocation practice.

United Network Organ Sharing (UNOS)

Source: http://www.unos.org/contact.asp

When a pancreas organ becomes available and there is a zero HLA-antigen mismatch candidate, that candidate receives the pancreas. It that recipient also needs a kidney, that recipient also receives the kidney.

When a pancreas organ becomes available the organ is offered first locally, then within the region and, then nationally. Priority is generally by wait time. Blood group O goes to blood group O. There are apparently 3 separate lists for SKP, PA, and Islet. If the highest recipient also needs a kidney, then the kidney is allocated along with the pancreas. There are internal variances that in general are not reported (D. Brennan personal communication).

Pancreas organs from donors age >50 years or BMI >30 go to islet programs. Kidneys that are shipped are paid back. Patients do not have to be on dialysis, can be on the list but cannot accrue wait time points if the GFR is > 20 ml/min. Table 2 shows that wait times are considerably less for SKP than KA transplants.

Table 2. Kaplan-Meier Median Wait Times (days) in UNOS 1999-2000 Registration

ABO	Kidney Alone	SKP	Pancreas Alone
O	1766	667	706
A	1084	471	367
B	1981	644	638

Australia

Source: Jeremy Chapman tsanz@racp.edu.au

Patients must be insulin-dependent. Whole pancreas has precedence over islet.
SKP overrides kidney allocation. Pancreas goes to patient with longest time on the list, such that a patient waiting for PAK may be transplanted ahead of SKP. Preference is based on wait time within blood group. Each state may allow some variance.

UKTransplant

Source: http://www.uktransplant.org.uk/ukt/default.jsp;
Maureen.Scargill@uktransplant.nhs.us

Similar to Australia, the country is divided into pancreas retrieval zones, with a pancreas transplant center in each zone; local use first, then by rotation to other zones. Center determines priority and use of kidney. In general kidney follows pancreas. Local center decides whether PAK or SKP (though, scheme suggests SKP priority). However, if there is a pediatric zero HLA antigen mismatched candidate, then the kidneys are given priority to these individuals. Payback is in effect

Scandinavia
Source: grunnet@scandiatransplant.org

Kidneys follow the pancreas; payback with kidney if within 6 months.

Eurotransplant
Source: Mayer G, Persijn GG. NDT 2006; 21:2-3; personal communication Bjorn Nashan

Combined have priority over kidney-alone. Payback in effect. Rare pre-emptive SKP performed.

Canada
Source: see Appendix 1

No uniform policy within transplant centers. Not all centers have the kidney follow the pancreas.

IV. Allocation Options

The options for allocation differ across around the world likely reflect a combination of negotiated practice and opinion. A series of "statement" and "at times" questions are appropriate.

1. Some believe that those with a live donor option should pursue this option, especially if it can be arranged pre-emptively. It is not clear how important HLA match should be. Some might insist that only the HLA identical should be 'mandated' over SKP. There is no evidence for SKP being superior (net life years) to any live KA over the first 10 years. Should patients with a live donor be strongly encouraged to pursue the live donor option first?

2. Some believe that giving priority to SKP is unjust by placing type 1 diabetic patients at the top of the list. However the number on the waitlist for SKP is probably low (<5%). Could mandating a soft ceiling on transplant SKP rates allay fears of injustice? Short median pancreas transplantation wait times as seen in the US (Table 2) will be a concern to some. Data from other countries and Canada are not available and could be different. Pancreas transplant rates in the US are almost 3 times the rate in Canada, so that the waitlists in Canada may actually be as long if not longer for SKP compared to those waiting for a kidney alone. Inevitably the organs received with SKP will be better and will have shorter cold ischemic times, however,

the SKP recipients will also in general be younger. Having some restriction on patient selection characteristics (age ceiling, absence of advanced disease, etc) for SKP would help reduce the numbers on the list.

3. Given the lack of evidence of improved life expectancy with a need for a second surgery, some could argue that PAK is not a viable option for most but could be offered to those who opted for a LRD transplant or had excellent graft function, were highly motivated and perceived marked improved quality of life with a pancreas transplant. With further improvements in graft outcomes this is becoming an excellent option and if all pancreas transplants were PAK then concerns about priority with SKP is avoided. Having PAK and SKP compete within the same list may also limit concerns about injustice if the kidney follows pancreas for SKP.

4. No donated pancreas organ should be wasted. Although those organs not used for whole organ transplantation can be used for islets, all attempts to use acceptable whole organs should be made. The allocation to a growing number of PTA recipients likely means that there will always be far more recipients that organs. PTA represents a 'threat' to the supply of organs for uremic candidates. Discussion of this option is beyond the scope of this review. The option appears justified in patients with hypoglycemic unawareness. Although this probably represents a relatively small proportion of patients with diabetes mellitus the absolute proportion could be considerable when compared to the eligible uremic candidate pool in the future.

VI. The Final Solution:

Flexibility and Priority: Every candidate will have different health perceptions, access to the live options, and access to the pancreas option.

1. Patients with living donors should strongly consider this option. Centers should strive for pre-emptive live kidney transplantation. However there will be patients who insist on SKP over a live donor and this may be difficult to argue against on an individual basis. Patients with high perceived benefits for combined transplant should probably be given the option even if a live donor is available, but the discussion should be detailed, especially if time waiting for an SKP is long.

2. Selected candidates that do not have live donors would benefit from an SKP. Since the numbers are relatively small and the numbers of suitable organs proportionately small, giving priority (kidney follow the pancreas) to this population when a pancreas graft is available could provide considerable net benefit without greatly disadvantaging the list. There probably should be some agreed upon patient selection criteria. The issue of whether SKP patients can be listed pre-emptive (before dialysis) is probably a regional issue and should occur if those waiting kidney-alone transplant are also given this option. Since some centers transplant for other regions allocation rules that ensure equity (payback) may be required.

3. PAK is an option for selected transplanted patients and this will undoubtedly reduce the SKP transplant rate. Patients should be very highly selected with high perceived improvement in QOL since there is little evidence of improved length of life. It seems reasonable to list those needing an SKP or PAK on one list and transplanting within ABO group by wait time.

Appendix 1: Pancreas Transplantation Questionnaire

Activity

1. *Does your center perform whole organ pancreas transplantation?*

Centres	SKPs Performed	PAKs Performed	PTAs Performed
A	5/yr	3/yr	n/a
B	4-5/yr	n/a	n/a
C	20	5	
D	4/yr	1/yr	1/yr
E	4/yr	1-2/yr	
F	10/yr	1/yr	n/a
G	No Response	No Repsonse	No Response

Eligibility Criteria

4. *Do you think the criteria for SKP/PAK transplantation should be more restricted than for kidney alone transplantation?*

Yes: 6 No: 0

5. *Do you think there should be an age limit for SKP? If so, what age?*

Yes: 4 No: 2
If yes what age? 50/50/50/60

6. *Do you think select type 2 patients should be eligible for a pancreas transplant?*

Yes: 4 No: 2

7. *For Pancreas after Kidney (PTA), what are the most common indications for selection?*

1. Hypo awareness
2. young/2-3 comp
3. Good kidney function/bridal

Not Done: 3

8. *For PTA, what is the requirement for level of kidney function?*

>50 GFR;
>40-50 GFR;
>50 an <1 g proteinuria

9. *Should potential SKP patients be listed prior to the need for dialysis?*

Yes: 4 No: 2
If yes, at what level of GFR should patients be listed? <30/20/12 (ml/min)

10. *Do you perform cardiac catheterization in all potential SKP recipients?*

Yes: 1 No: 5

11. *Do you allow patients to be transplanted with significant one or two vessel coronary artery disease?*

Yes: 6 No: 0

Allocation

12. *How do you select patients for SKP?*

a) *Do you have a separate list?*

Yes: 5 No: 1

b) *Do you have a single list but move the SKP to the top of the list when a pancreas and kidney are both available?*

Yes: 3 No: 2

c) *How do you decide between patients on the list if you have some waiting for PTA, SKP or PAK?*

SKP first;
NA: NC;
Waitlist, some SKP preference;
All equal by wait time;
SKP preference

d) *Do you perform pre-emptive SKP?*

Yes: 2 No: 2
If yes what is the level of GFR acceptable to list? <30/20 (ml/min)

13. *How do you prioritize the next pancreas if you have candidates eligible for PTA, PAK and SKP?*

Wait time: 3;
No comment: 3

14. *Do you think patients with a live donor should also be given the option of an SKP?*

Yes: 5 No: 1

Push for Live Donation

15. *If they take to live donor kidney should they be eligible for a PAK?*

Yes: 6 No: 0

16. *Do you believe giving priority to SKP will disadvantage non-diabetic patients on the waitlist for a kidney alone?*

Yes: 2 No: 3
Both disadvantaged: 1
Minor concerns in 2 centers

17. How do you think pancreas organs should be allocated? Other Comments?

Surgeon decides;
Center specific;
Priority to SKP;
All pancreas organs should be used

Transplant Centers Canada

ID	Facility Name	Province
20085	QUEEN ELIZABETH II HEALTH SCIENCES CENTRE*	NS
40003	ROYAL VICTORIA HOSP.-MCGILL UNIV. HLTH CENTRE	QC
40120	C.H. DE L'UNIVERSITÉ DE MONTRÉAL - NOTRE DAME	QC
53850	LONDON HLTH SCIENCES CTR	ON
53910	TORONTO HOSP - UNIVERSITY HEALTH NETWORK	ON
80016	CALGARY REGIONAL HLTH AUTH - FOOTHILLS	AB
80044	UNIVERSITY OF ALBERTA HOSPITAL SITE - EDMONTON	AB
90101	VANCOUVER HOSPITAL AND HEALTH SCIENCES CENTRE	BC

* *Queen Elizabeth II HSC is not active*

Appendix 2: Quality of Life

Overall assessment of quality of life has been difficult to determine with great precision. At issue is who should determine quality (medical profession, patient or community based) and how it should be measured (generic or disease specific instruments, or preference based measures). As with data on survival, ideally patients should be randomized to three treatment options (no transplant, kidney alone or SKP) and followed prospectively. There are no studies meeting this level of quality. What is available are a series of studies using preference based measures (Table 1, Refs. 1-5). The studies by Knoll were measured on Type 1 diabetes patients prior to transplantation using the standard gamble method (1). The studies by Kiberd (published and unpublished) used the standard gamble method (SG), time trade off (TTO) and visual analog scale (VAS) methods (2). Subjects included patients on the list with kidney alone transplant and with a functioning SKP. The results were not different by transplant status (data not shown). In a larger group of medical professionals (nurses and physicians) scores for these health states were ranked proportionately higher but ranked states similarly (data not shown).

Two groups used the SF-36 generic instrument (5, 6). Unfortunately many of the studies either are old (pre-1995), were duplicates or used instruments that were not standard(7-15). Although there is undoubtedly publication bias, most patients with diabetes mellitus and health professionals prefer to be insulin free.

Table 3. Quality of Life

3A. Utility/Preference Based Scores (Dialysis versus Kidney Alone versus SKP)

	Dialysis Mean (SD)	Kidney Alone Transplant	SKP	Method (n)
Knoll (1)	0.70 (0.26)	0.80 (0.26)	0.85 (0.12)	SG (n=50)
Kiberd (2)	0.70 (0.19)	0.78 (0.18)	0.87 (0.17)	SG (n=36)
Kiberd (2)	0.54 (0.21)	0.75 (0.17)	0.86 (0.15)	TTO (n=36)
Kiberd (2)	0.44 (0.18)	0.71 (0.16)	0.88 (0.11)	VAS (n=36)
Adang (3)*	0.50 (0.20)	0.60 (0.20)	0.80 (0.20)	VAS (n=20)
Boyd (4)**			0.74 (0.18)	VAS (n=23)
Boyd (4)			0.79 (0.24)	TTO (n=23)
Boyd (4)			0.84 (0.24)	SG (n=23)

**Scale 0=death to 1=perfect health*

***SG=standard gamble; TTO =time trade off; VAS=visual analog scale*

**** Extracted from figure and normalized to 0-1 scale.*

*** No comparison to diabetes mellitus with kidney alone transplant*

3B. Utility / Preference Based Scores *(Diabetes Mellitus versus Pancreas Transplant)*

	Diabetes Mellitus Alone	Pancreas Alone	Method (n)
Kiberd (2)	0.75 (0.20)	0.95 (0.04)	SG (n=16)
Kiberd (2)	0.82 (0.15)	0.92 (0.09)	TTO (n=16)
Kiberd (2)	0.76 (0.15)	0.91 (0.10)	VAS (n=16)

3C. Generic Quality of Life Measures

	Dialysis	Kidney Alone TX	SKP	Method (n)
Gross (5)	44 (25) n=26	49 (26) n=33	67 (24)** n=22	SF-36 GH Year 3
Sureshkumar(6)		55 (20)	63 (19) n=27	SF-36 GH

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Appendix 3: Patient Survival

The benefits of SKP compared to deceased donor kidney alone and live donor kidney alone are difficult to compare. There are a large number of studies comparing outcomes (1-16). Many of these studies are small, single center and will not be discussed further. Several of the larger series are robust but do not adjust for patient covariates that might impact on outcome such as age, comorbidity, donor quality, etc. All of the studies are performed at a time when pancreas-alone graft survival was lower. Since the real outcome of interest is overall patient survival this will be the emphasis.

Two studies analyzed the UNOS registry. Reddy and others collected data on patients from 1987 to 1996 and Ojo and others included patients from 1988 to 1997 (14, 15). The study by Reddy and others showed that SKP was superior to deceased donor KA alone transplantation yet SKP survival became equivalent to live donor KA transplantation at about eight years. The latter study found similar results with 10 year patient survival for SKP, live KA and deceased donor KA at 67%, 66% and 46%, respectively. This study also showed that SKP had a higher early mortality compared to the other modalities. Projected life expectancies for the modalities were 8 years for waitlisted dialysis, 12.9 years for deceased donor KA, 20.9 years for live donor KA, and 23.4 years for SKP. The study adjusted for delayed graft function and found no impact on the conclusions. The studies are interesting in that survival to time of follow-up (area under the curve) was superior for live donor kidney alone, but those survival projections beyond follow-up favoured SKP. Deceased donor KA was inferior in both studies compared to SKP and live KA. It is the long term projections that are most subject to error and overestimate benefit.

These two studies differ from an analysis published 2 years later on a UNOS cohort, of patients transplanted between 1994 to 1997 and followed to 2000 (16). After adjusting for significant covariates (donor age, donor cause of death, duration of dialysis, PRA, cold ischemia time and recipient age), deceased donor KA (HR 0.98, 95% CI 0.85-1.12) was not inferior to SKP. Patient survival in a low risk cohort of KA patients demonstrated nearly identical patient and kidney survival over a five year period. The most recent study of the UNOS database examined patients on the waitlist for an SKP but compared those who received an SKP (n=7458) compared to those who later opted for a KA (n=865) (17). SKP had lower graft loss compared to KA (HR 0.63, 95% CI 0.51-0.77) and lower combined kidney or patient loss (HR 0.66, 95% CI 0.55-0.78). There are several outstanding concerns. Patient survival alone was not presented and the model appears to only have only adjusted for year of transplant and center effect.

Several other issues are of interest. Some of the studies show that outcomes are significantly worse when the recipients are older (>45-50 age) with no obvious survival advantage compared to deceased donor KA (8, 9, 14, 15). In the study by Ojo and others, SKP in recipients >50 years old was not statistically different than waitlisted dialysis diabetic patients (15). Several studies have shown that pre-emptive transplantation is better in patients with diabetes mellitus (15, 17, and 18).

There is less information on the use of PAK, especially PTA. Schnitzler found no added years of survival gained for recipients of PAK (-0.3 years, 95% CI -4.8-5.8) but did find that

SKP (12.93, 95% CI 10.5-15.7) and deceased donor KA (7.7, 95% CI 6.4-8.1) improved patient survival (19). A study by Venstrom found that four year patient mortality was higher for PTA recipients (1.57, 95% CI 0.98-2.53, p=0.06) and PAK recipients (1.42, 95% CI 1.03-1.94, p=0.03) compared to patients remaining on the waitlist in a registry analysis of patients transplanted between 1995 and 2000 (20). A follow-up study found several methodological errors in the analysis and with longer follow-up to 2003, the increased risk in mortality was no longer apparent. However, there remained no clear survival advantage (21). The use of live donor pancreas transplantation has been described but the long term experience remains uncertain. Since this will not impact on allocation it will not be discussed further (22, 23).

Two medical decision analyses have been performed. The study of Knoll & Nicholl compared living and deceased donor KA, SKP and PAK (24). The baseline model projected outcomes in live KA>live KA with PAK> SKP>deceased donor KA. One issue with the study is that it may have favored live KA followed by PAK over SKP, was the very low mortality while waiting for the subsequent pancreas. The study also identifies the importance of quality of life preference and diabetic complications (e.g., hypoglycemic death) assumptions on overall outcomes. Patients perceiving vast improvements with pancreas function will be projected to have better outcomes with pancreas transplantation even without significant survival advantage. Those with brittle diabetes and hypoglycemic unawareness will also benefit most. A study by Kiberd & Larson strictly examined the benefits of PTA (25). Overall PTA met the criteria for being cost effective if the pancreas transplant had a graft survival at year 1 of 80% and a life expectancy of 10 years. Concerns about nephrotoxicity also limited the benefit of PTA.

There is a growing body of evidence that pancreas function will stabilize macro and micro-vascular disease progression. However, the data are often uncontrolled, single center, surrogate endpoints and are not based on an intention to treat (26-37). Patient survival is the most robust endpoint.

In summary, living KA may have distinct survival advantages with the ability to transplant pre-emptive, lower early morbidity mortality, and the ability to seek PAK at a later date, in patients who are well and have a strong desire. SKP may well be superior to deceased donor KA yet there are biases in selection that cannot always be adjusted for in cohort registry analyses. Patients with strong preferences and subsets with particular complications may benefit from PAK and PTA despite the lack of an early survival advantage for improved quality of life and possibility of long term survival.

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