

**Total pancreatectomy and islet cell
autotransplantation: A look into the
crystal ball**

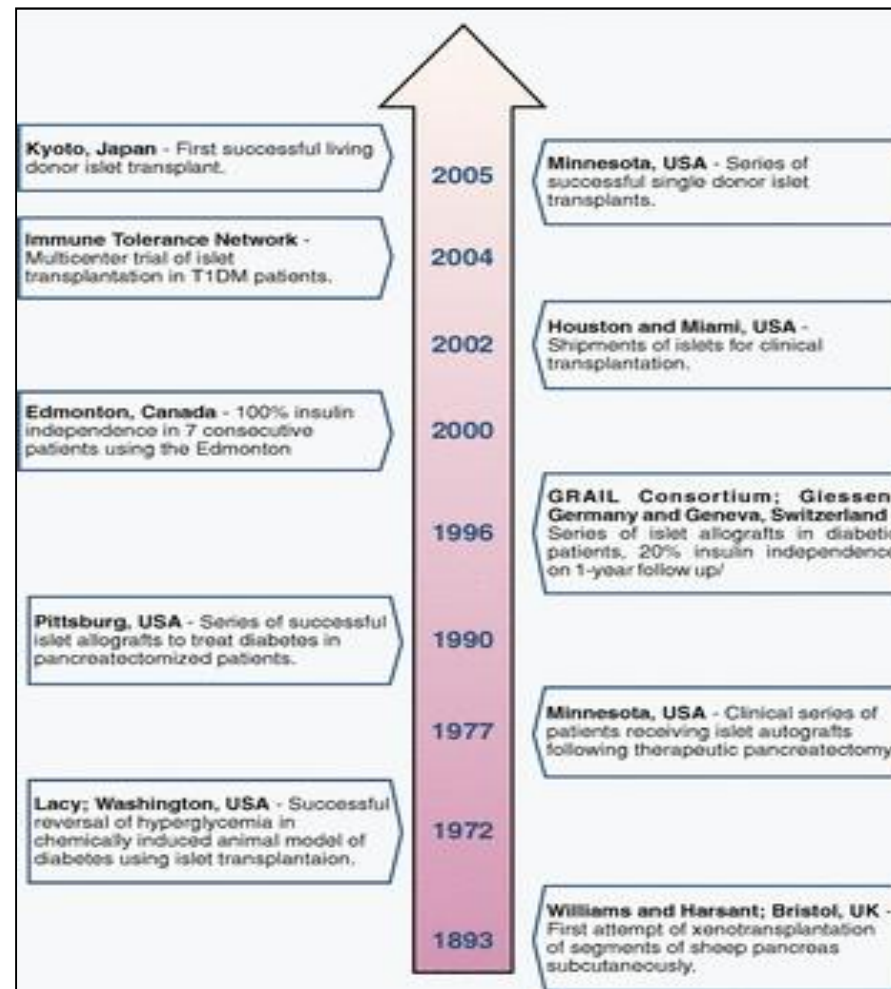
Ashley Dennison

The Association of British Clinical Diabetologists

Spring Meeting

April 2013

Islet isolation and transplantation



Leicester experience

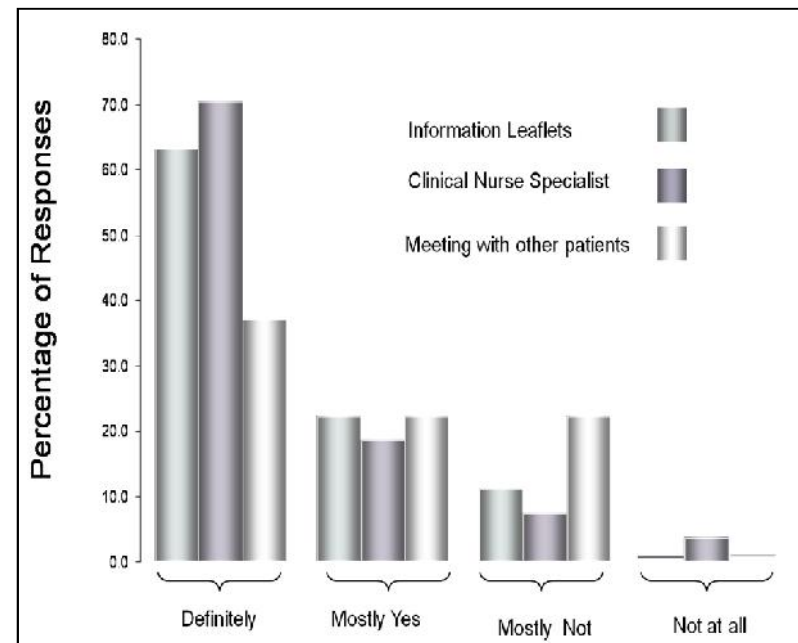
- Total pancreatectomy and simultaneous islet autotransplantation for chronic pancreatitis
- 60 patients since Sept 1994
- Follow up at 3, 6, and 12 months and annually for a minimum of 10 years
- Two prospectively maintained databases (reliable data for >10 years)
- Telephone interview Feb 2011 (40/46)

Patient details

Parameter	Patients (n=60)
Age	44 ± 11
Sex	Female 38 (63%)
Height (m)	1.7 ± 0.9
Weight (kg)	63 ± 14
BMI	22.7 ± 4.5
Aetiology of pancreatitis	Alcohol 28.8%, Idiopathic 71.2% (previous gallstone pancreatitis in 3 [8.5%], pancreas divisum in 3 [5.1%])
Type of surgery	Total pancreatectomy 57, near total 3
Mean length of operation (HRS)	9 (7.5-12)
Blood loss (litres)	0.7 (0.2-2.5)
ITU stay (days)	3 (1-14)
Hospital stay (days)	21.5 (8-52)
Mortality	1.6% (1 patient 64 years old CVA at day 36)

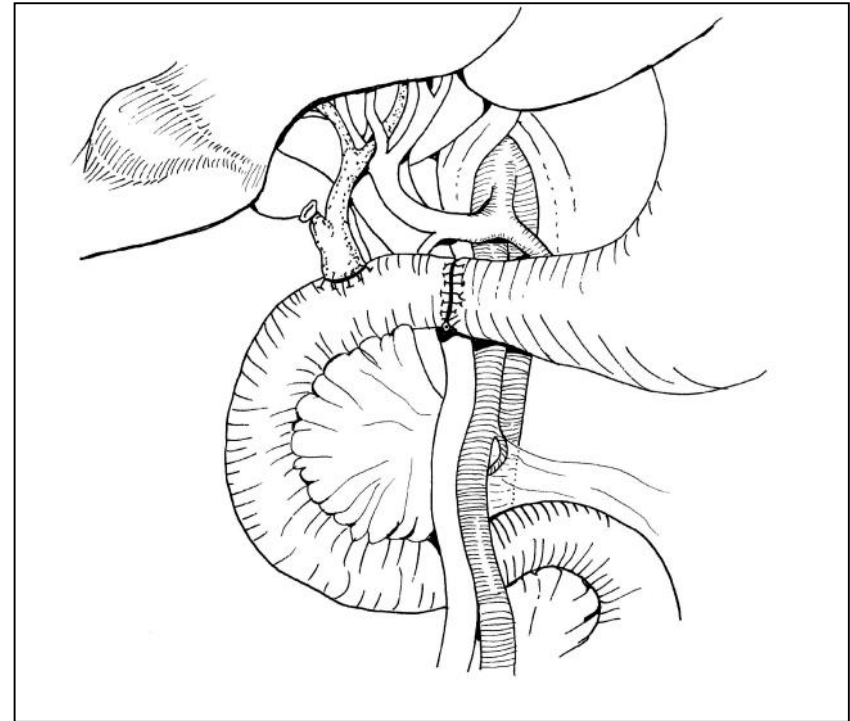
Assessment (Nurse Specialist)

- Glucose tolerance test
- Butterfat test, fecal elastase
- ERCP, CT/MRI/MRCP
- Independent clinical assessment (gastroenterologist, diabetologist, pain specialist (anaesthetist), anaesthetist and medical psychologist)
- Introduced to 2 patients who have had the procedure (recently and >1year ago)
- Discuss consent 1 month later (with family) at formal clinic appointment

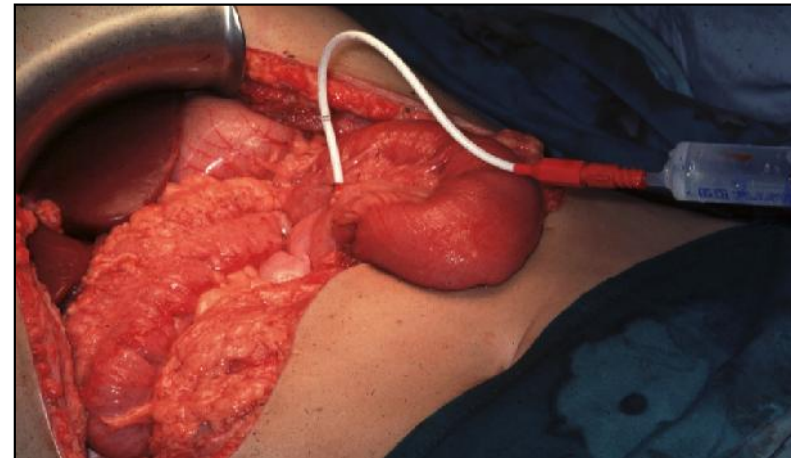
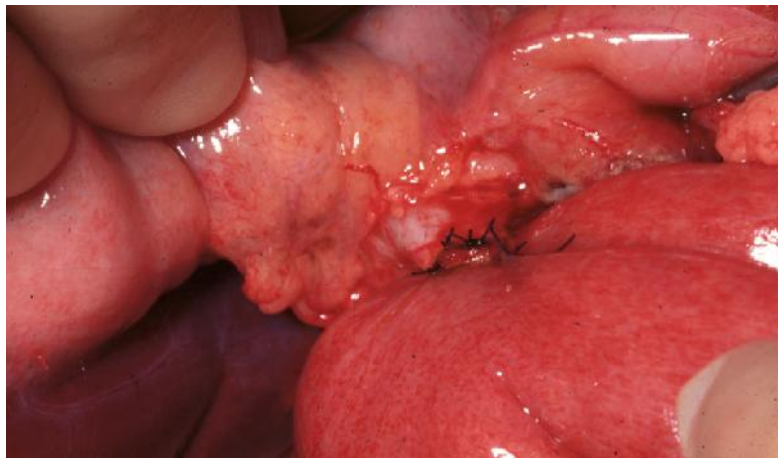
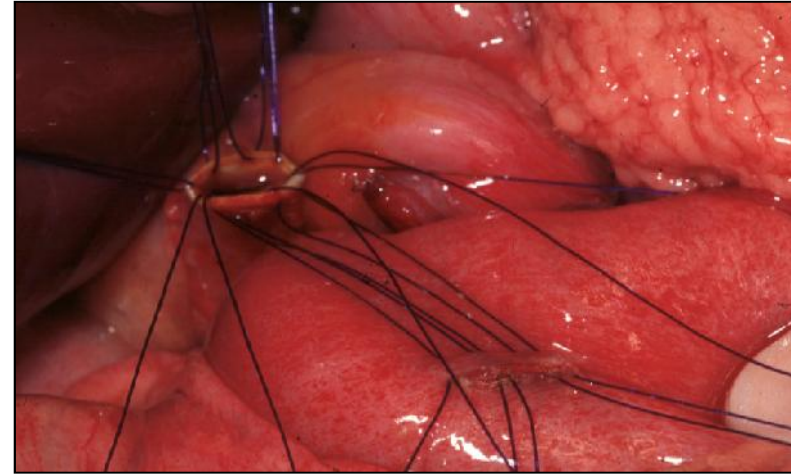
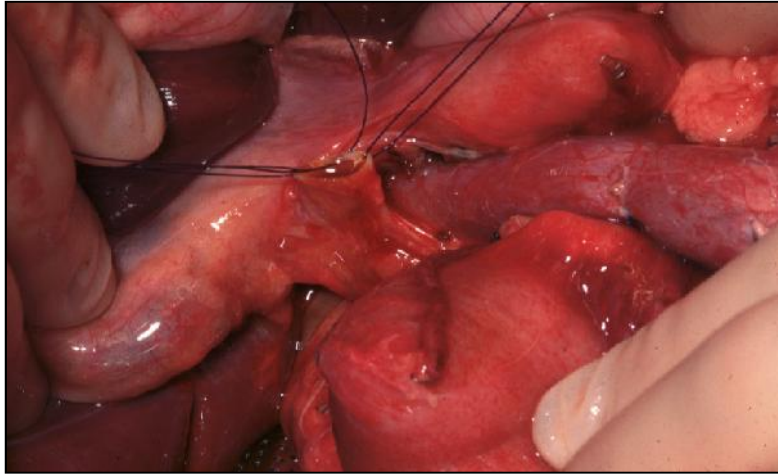


Surgical technique

- Total pancreatectomy and excision of the duodenum
- Duodenal preservation first 6 patients
- Pylorus and spleen preserving

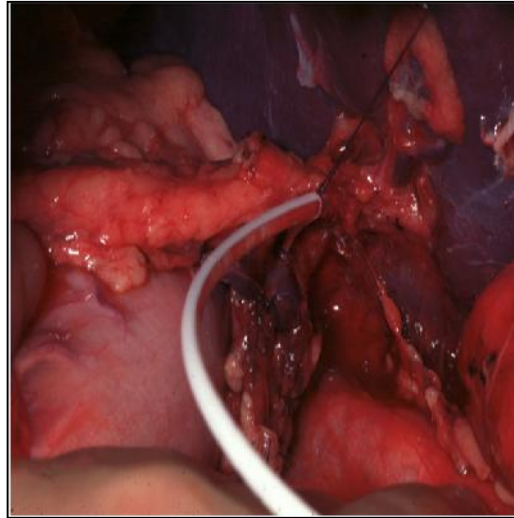
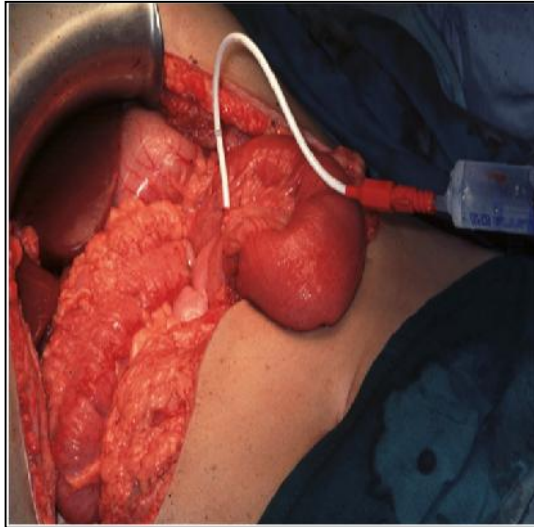


Biliary anastomosis and portal access



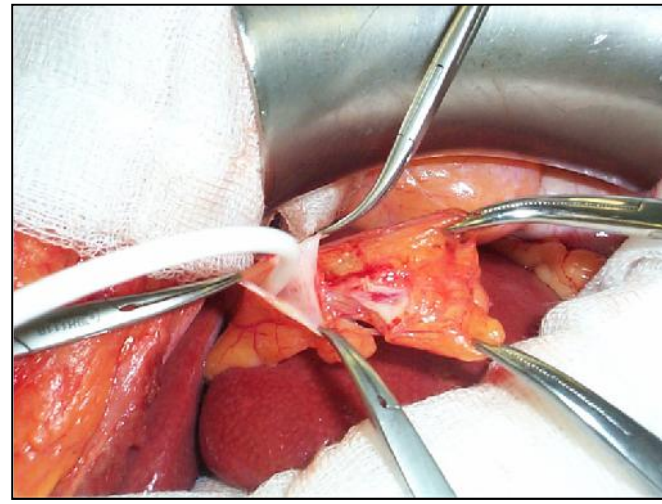
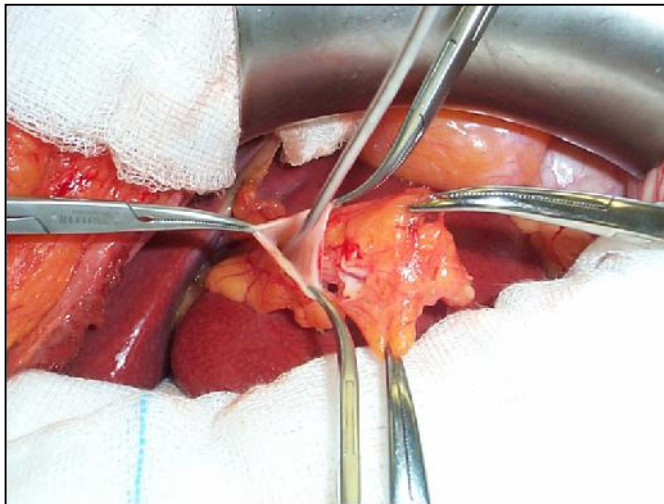
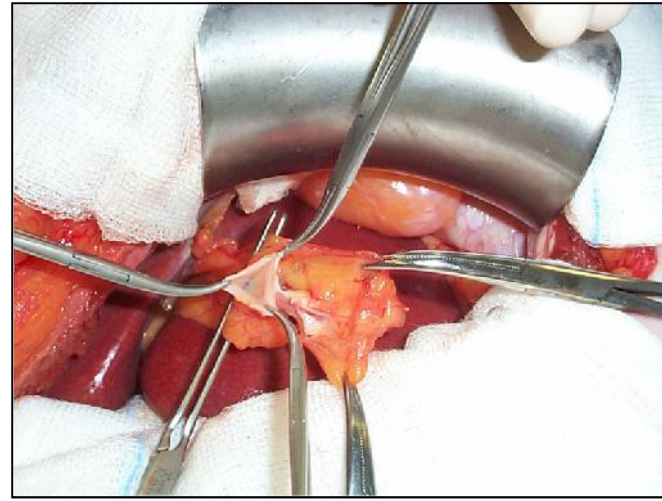
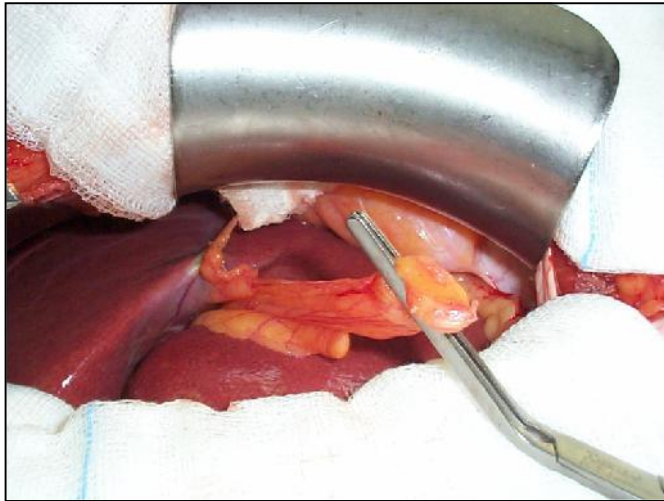
Initially portal venous access was via the middle colic vein and infusion into the left side of the liver (+/- spleen)

Islet infusion

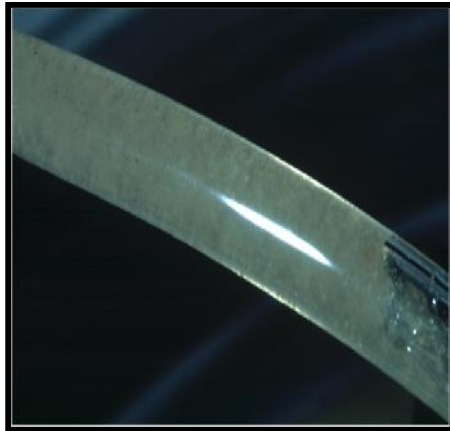


Islet autotransplantation into portal vein via mesenteric or recannalated umbilical vein (since 2005: 18 patients) to the left side of the liver (liver plus spleen in 3 and spleen alone [1996] in 2: liver only since 12/05/98)

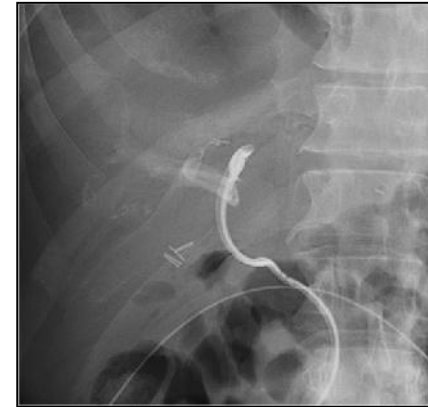
Recannalated umbilical vein for islet infusion



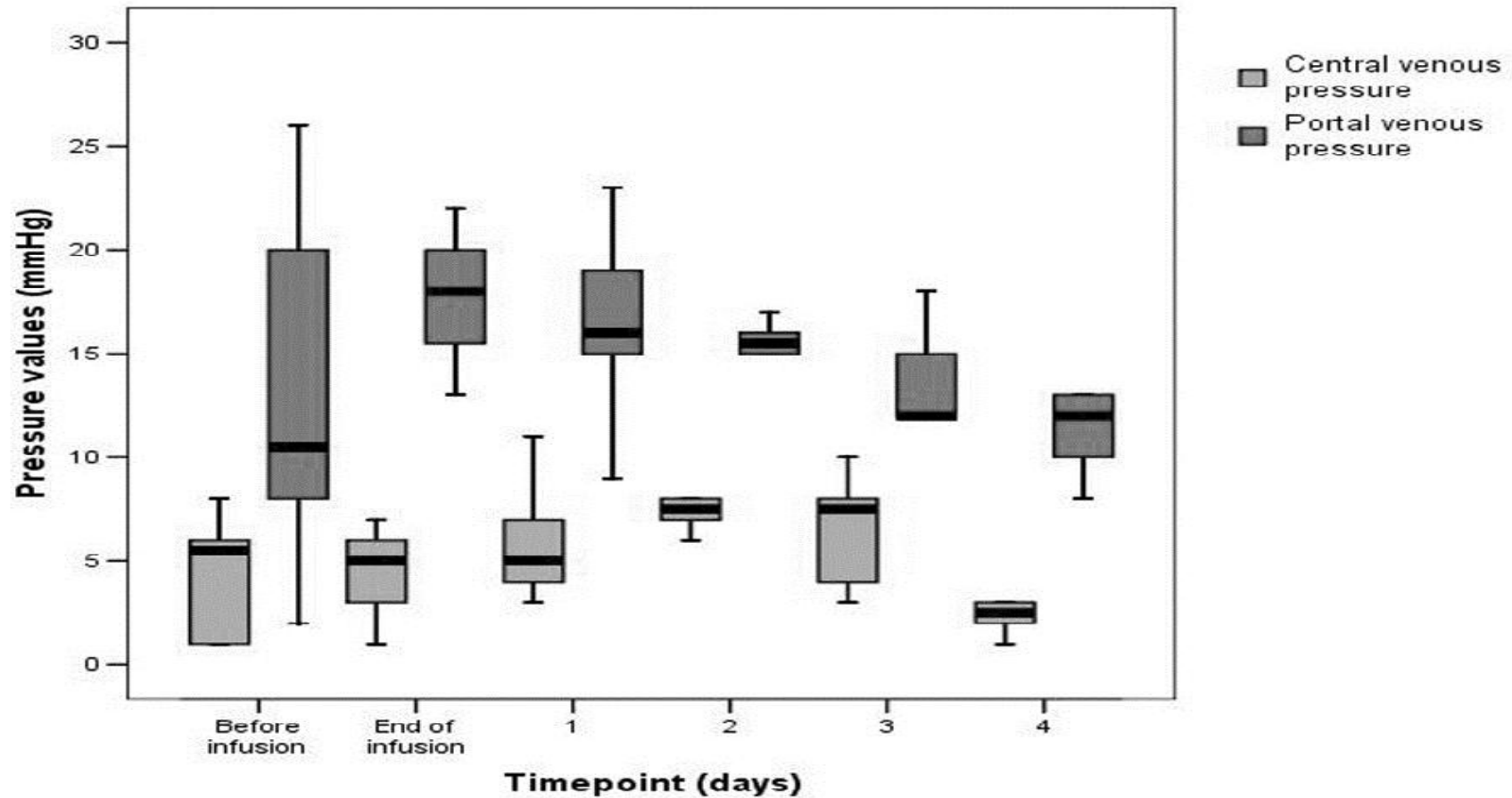
Venograms



Concerns about
portal venous
embolisation of
unpurified digest

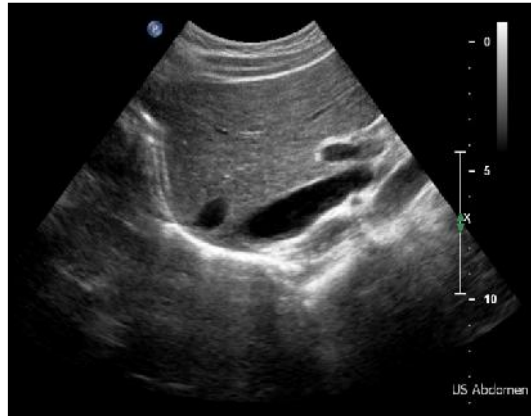


Portal pressures

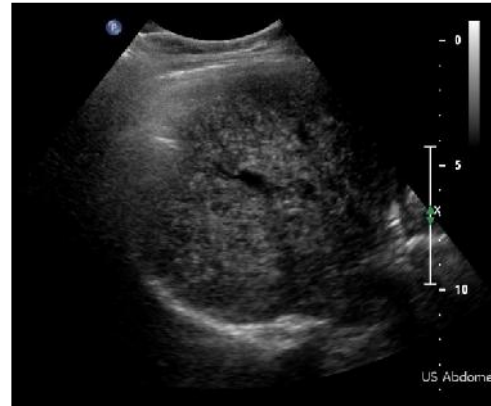


Central and portal venous pressures pre-infusion, immediately following infusion and from day 1-7

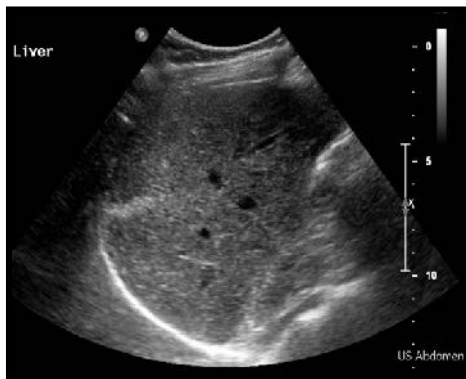
Ultrasound appearances



Normal ultrasound



> 1 year following islet autotransplantation



Non-progressive;
transplant patient
over 24 months

Islet transplants result in a nodular appearance within 6 months which is ubiquitous, non-progressive and does not affect liver function

(Ong SL et al Transplantation 2008;85(12);1773-77)

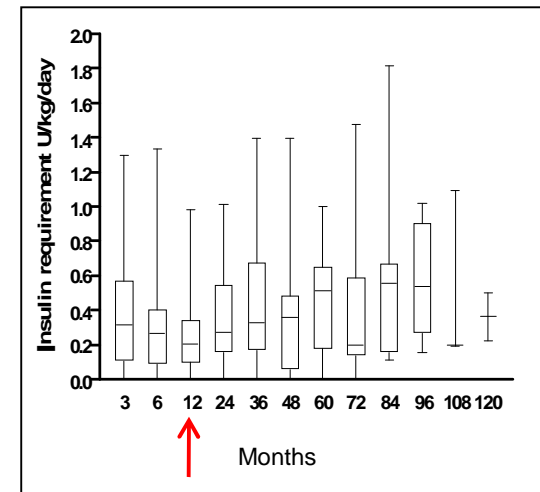
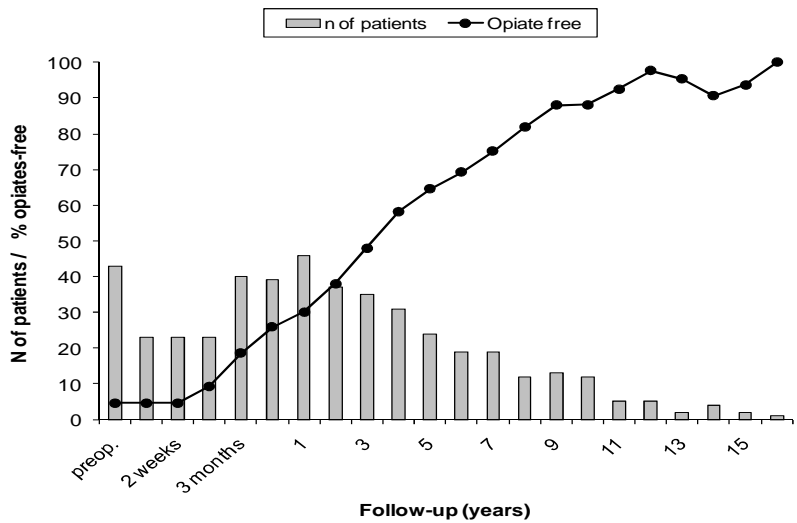
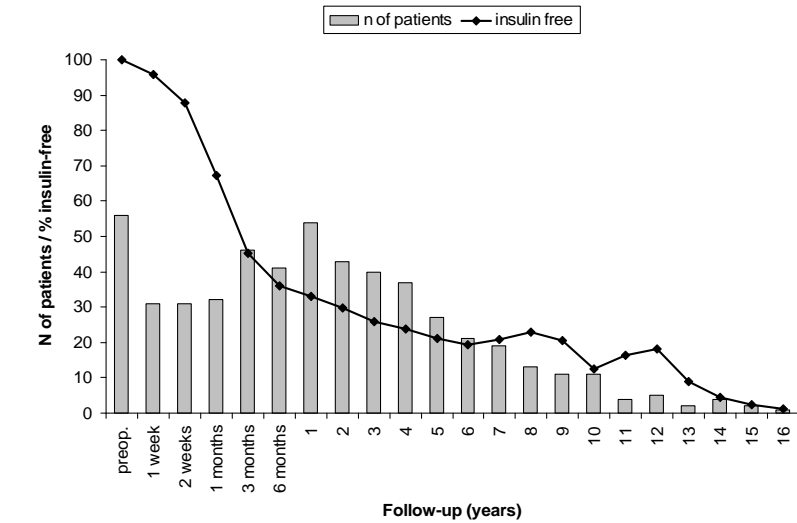
Islet details

Pancreas weight (g)	68±22
Volume transplanted (ml)	14±8
Total islet counts	260 450 (33 500-879 000)
Total IEq's	142 935 (24 322-1 057 488)
IEQ/kg	2 166 (305-20 385)
IEQ/g pancreas	2 349 (249-17 015)
Mean islet volume (mm ³ x10 ⁻⁴)	4.4 (0.3-27)
Total islet volumes (ml)	0.25 (0.03-1.9)
Purification	14/60: Last patient 12/05/98 (median purity 50)

Insulin and opiate requirements

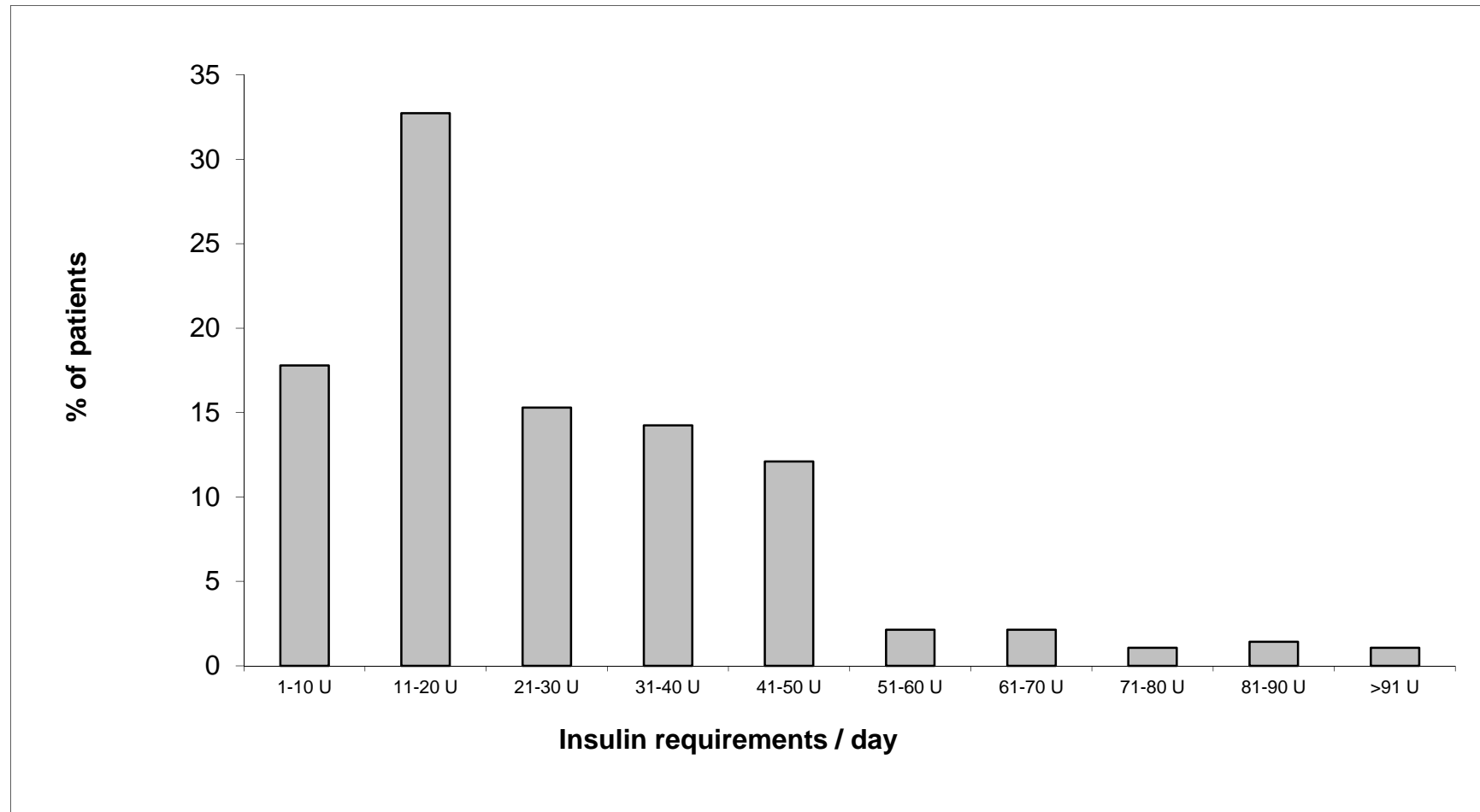
- No patients require insulin at the time of transplantation
- 22/60 (37%) patients have a period of insulin independence
- Between the 6th month and 10th year the % of non-diabetic patients falls from 30-8%
- Insulin requirements in 36 (60%) of diabetic patients is very low (0.1-0.35 IU/Kg/day)
- Opiate usage demonstrated progressive weaning after the 3rd post-operative month with 56% opiate free at 5 years and 89% at 10 years

Results

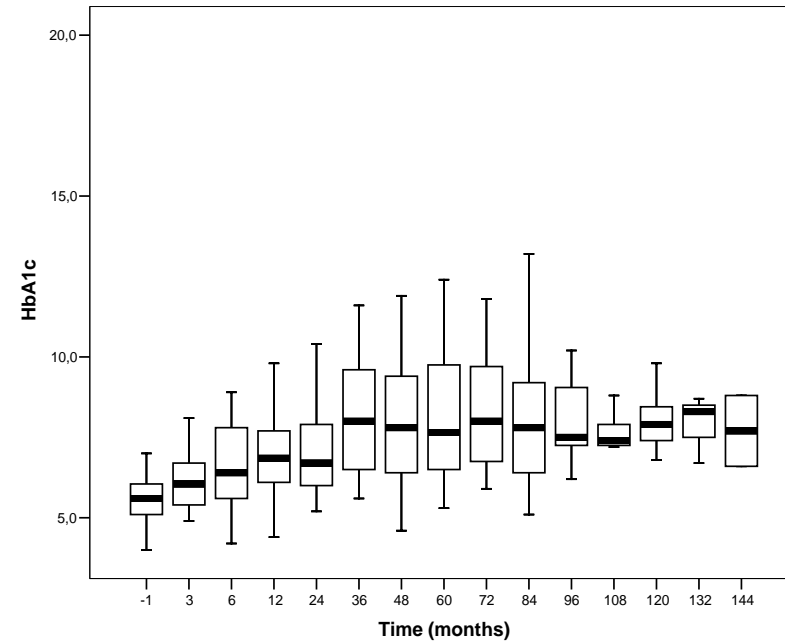
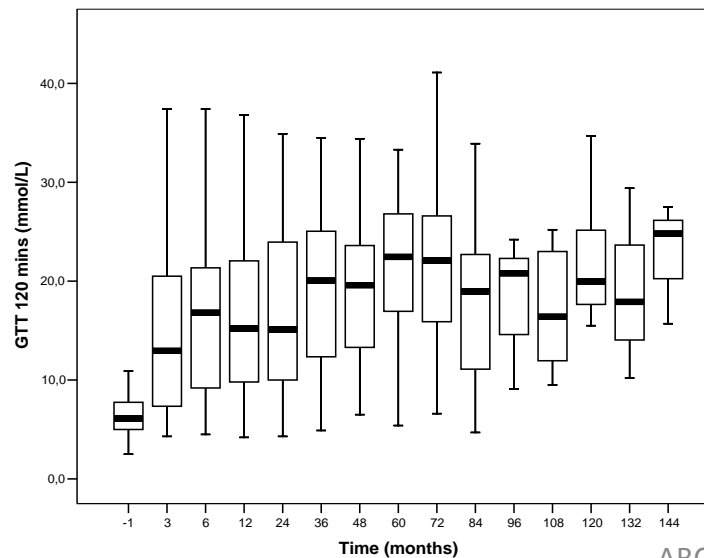
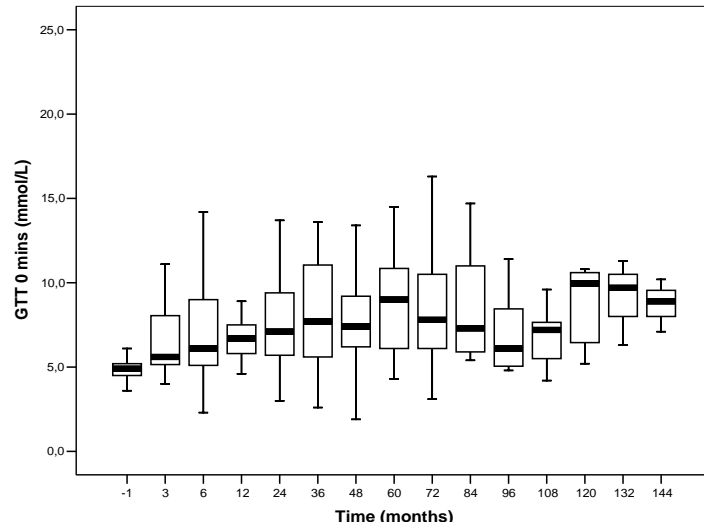


Insulin requirements are lowest at 1 year post-transplant

Overall insulin requirements are low



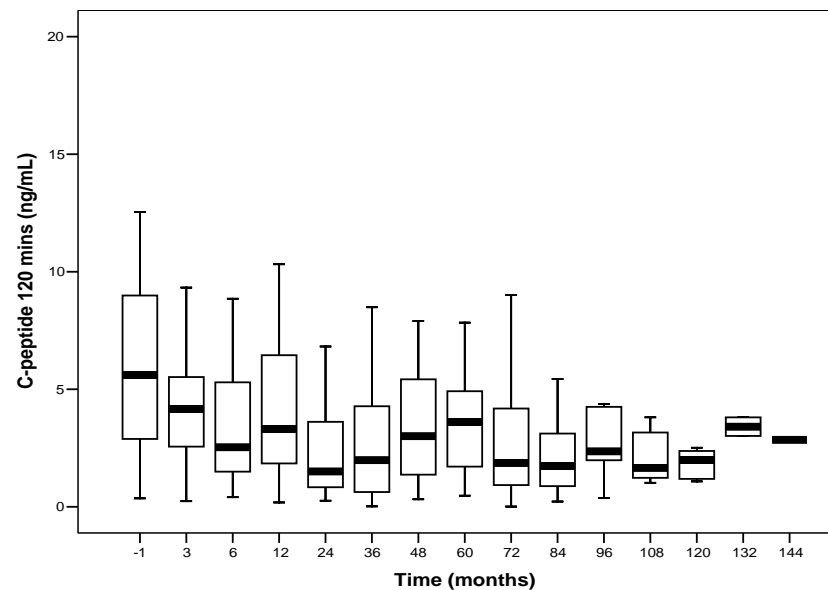
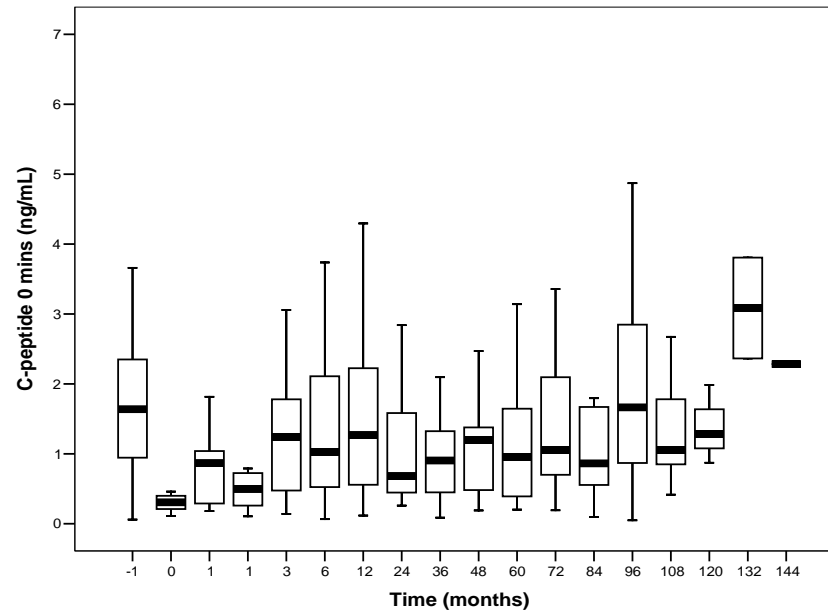
Glucose tolerance and HbA1c



GTT 0 and 120 deteriorate with time and are mirrored by HbA1c levels

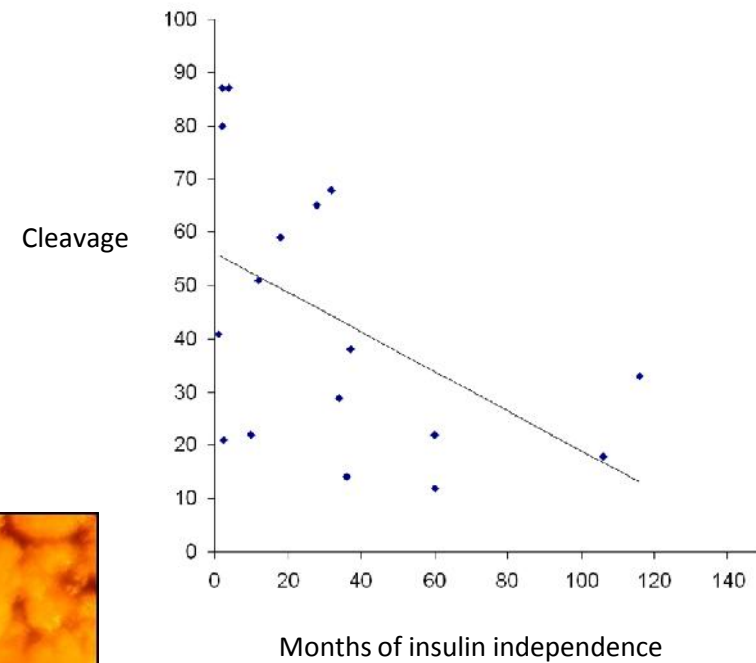
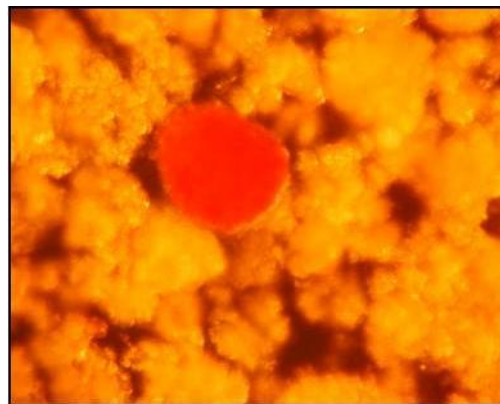
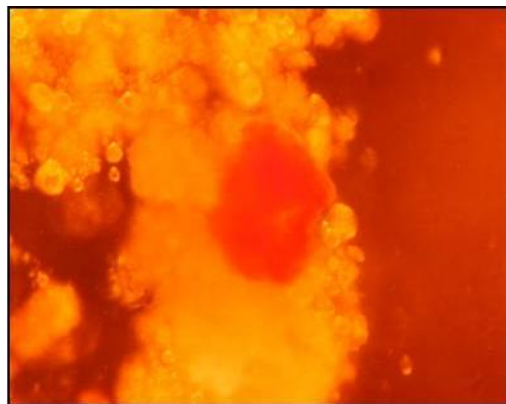
C-peptide

- No significant change in basal C-peptide
- Stimulated (120 min) demonstrates a steady decline with time
- All patients continue to produce C-peptide

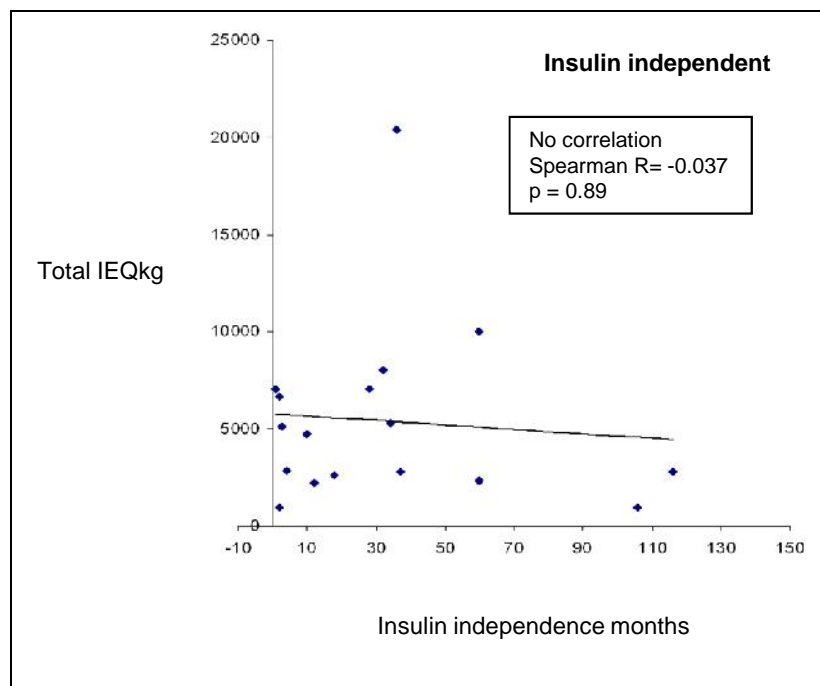


Factors associated with the duration of insulin independence

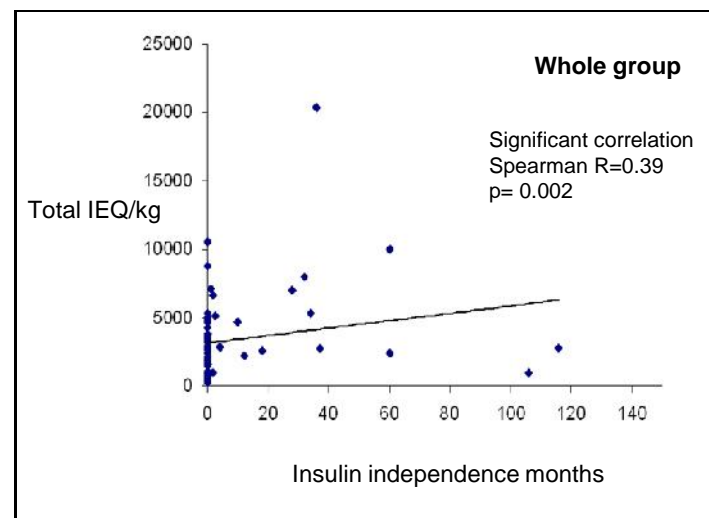
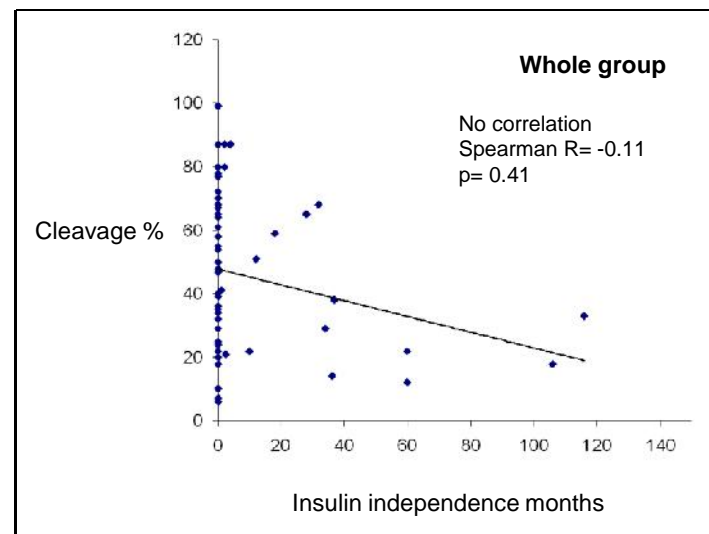
Factor	p Value
Cleavage if insulin independent	0.026
IEQ [different for patients who are insulin independent]	
Age	NS
Gender	NS
Length of operation	NS
BMI	NS
C-peptide basal	NS
C-peptide stimulated	NS



Insulin independent patients



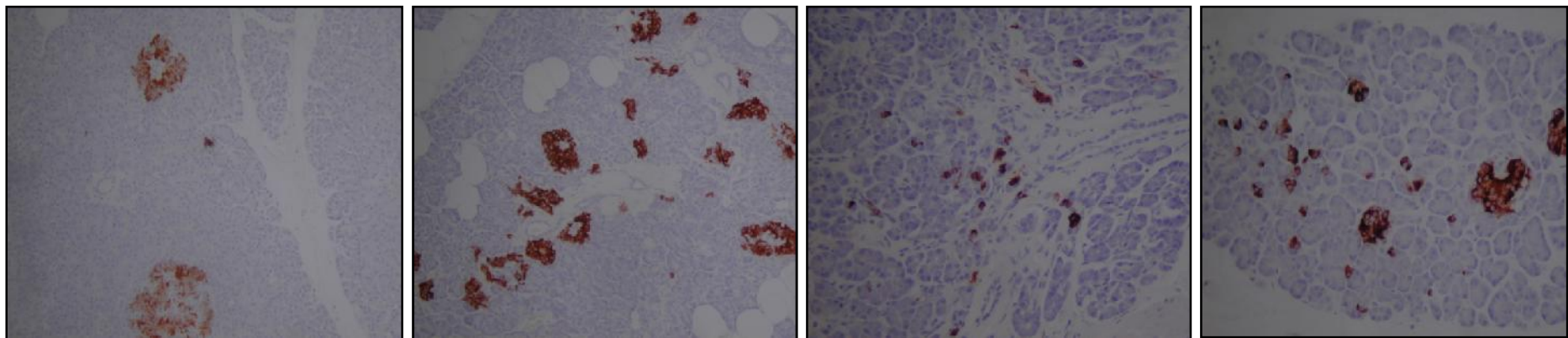
- No relationship between duration of insulin independence and total IEQ's in patients off insulin
- Whole group displays a strong correlation between duration of insulin independence and IEQ's transplanted but not the % cleavage



Intermediate cells

surgery	Total PX
age	43
BMI at TX (kg/m ²)	22.6
IEQ/kg	954.93
Cleavage %	18
Insulin free period post-TX	>8 years

- Female patient with long term insulin independence with very low original number IEq's
- Some patients C-peptide increases with time
- Two patients have stopped insulin ~2 years

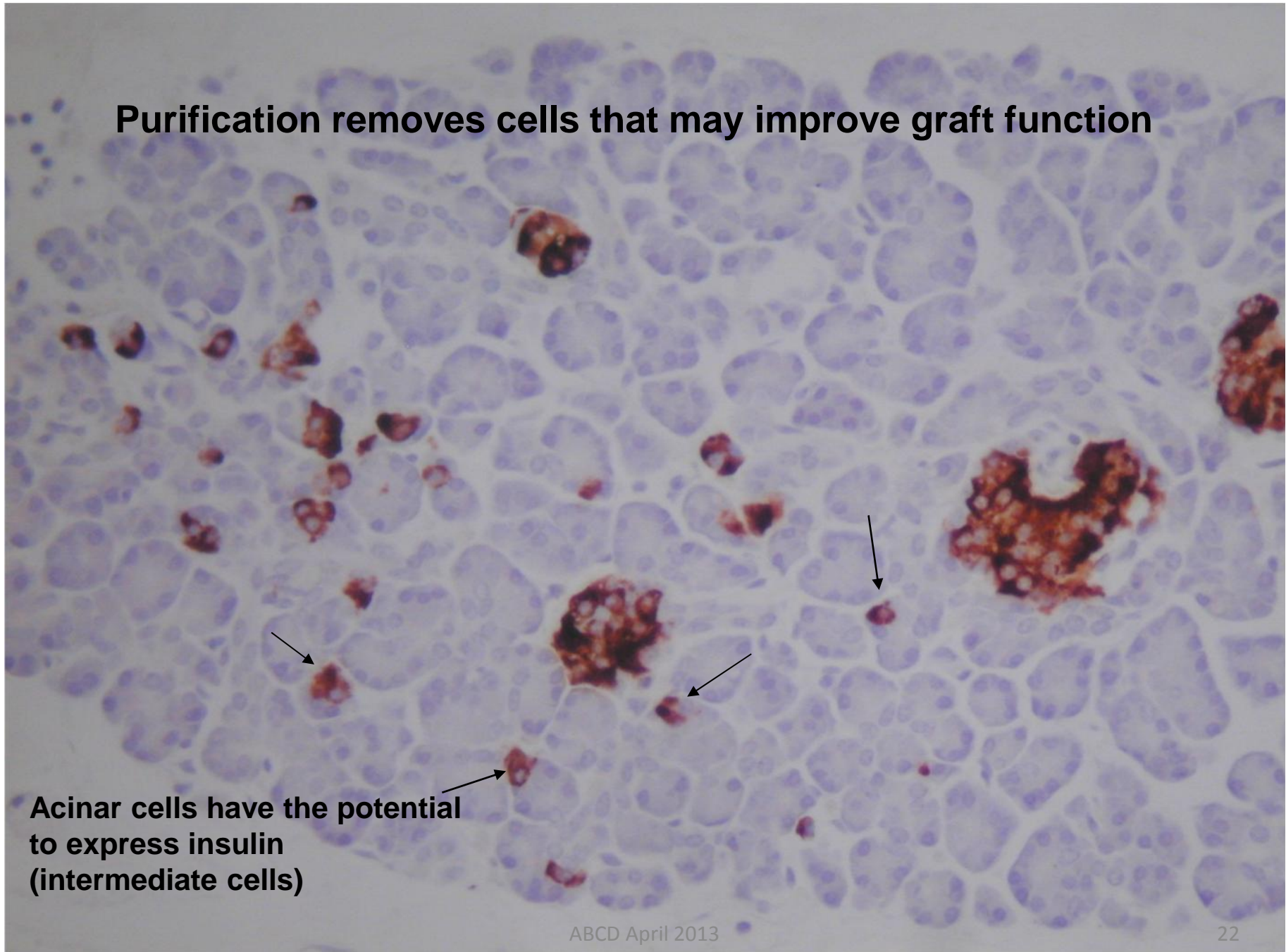


Normal

CP

Intermediate cells (IC'S)

Purification removes cells that may improve graft function



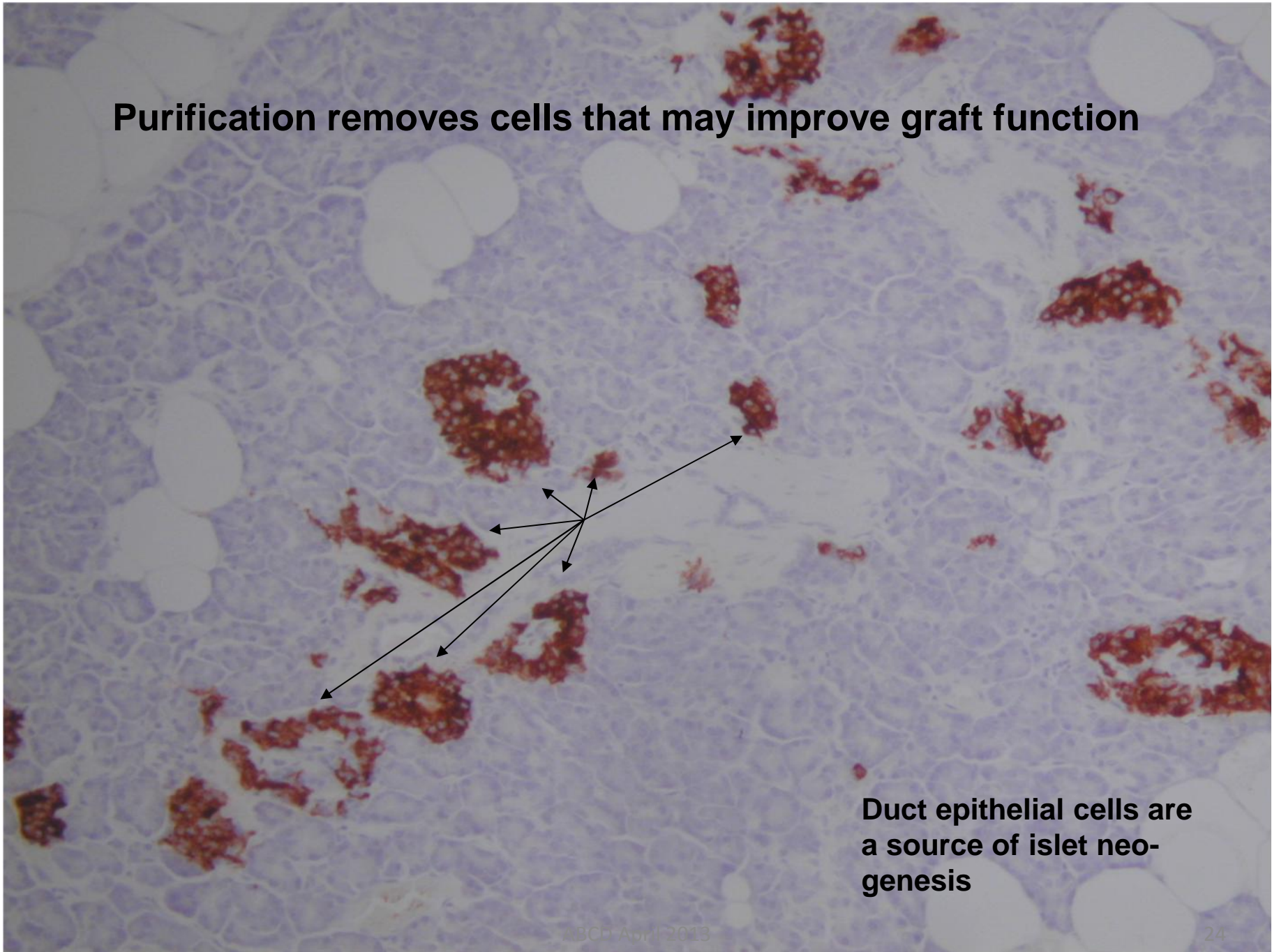
Acinar cells have the potential to express insulin (intermediate cells)

Purification removes cells that may improve graft function

Duct cells have the potential to express insulin

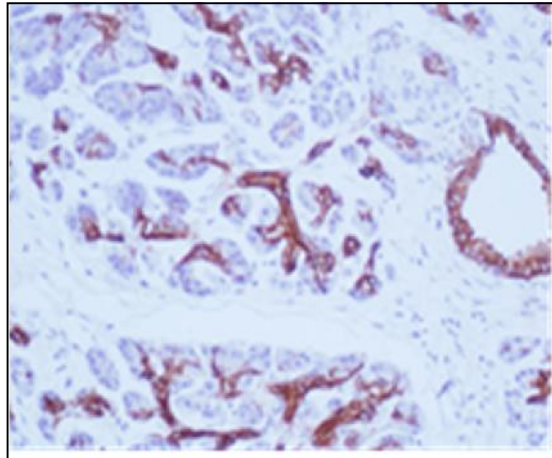


Purification removes cells that may improve graft function

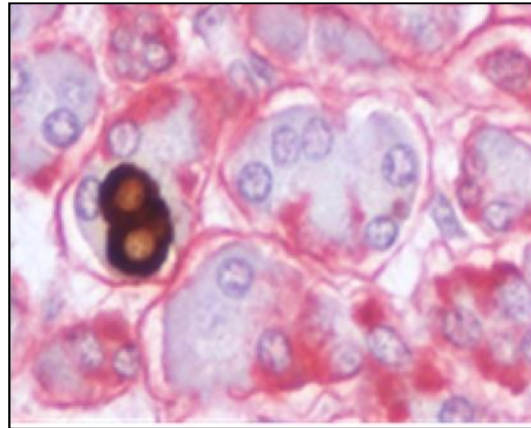


Duct epithelial cells are a source of islet neogenesis

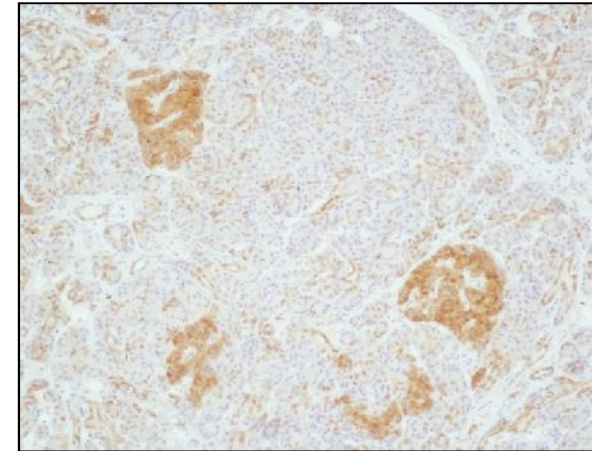
The potential role of non-islet cells on islet autograft function



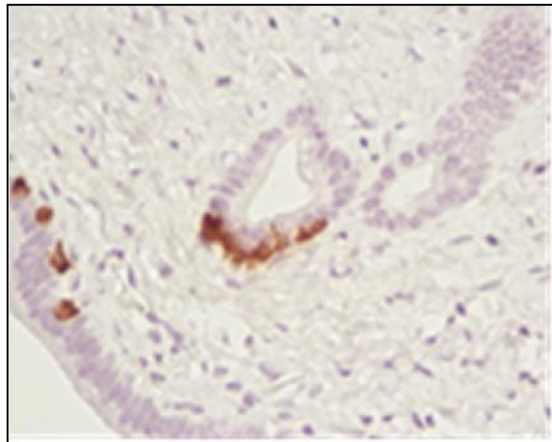
Ductal cells?



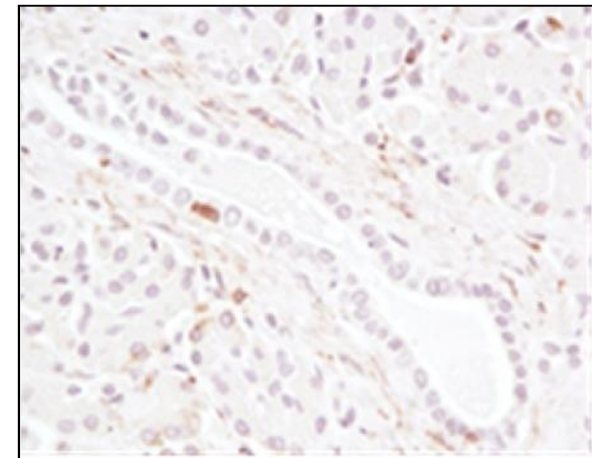
Insulin positive intermediate cells?



PDX-1 positive cells?

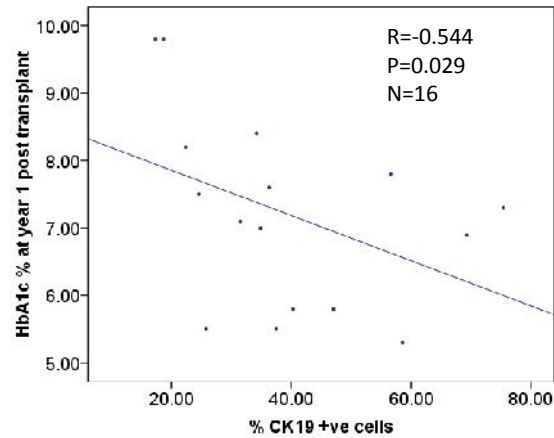
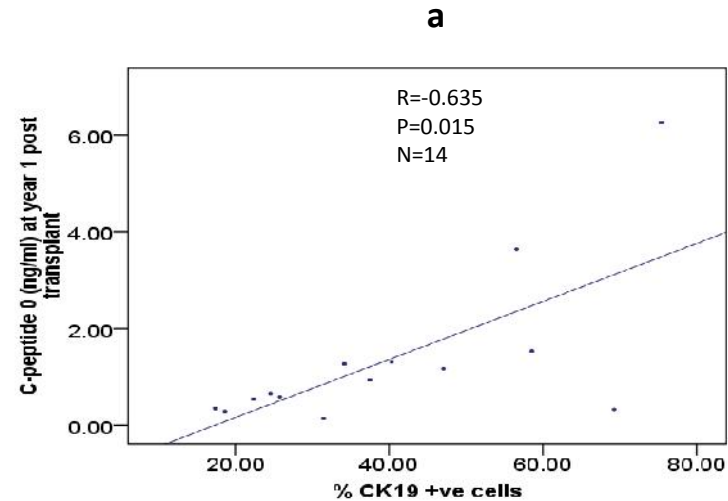
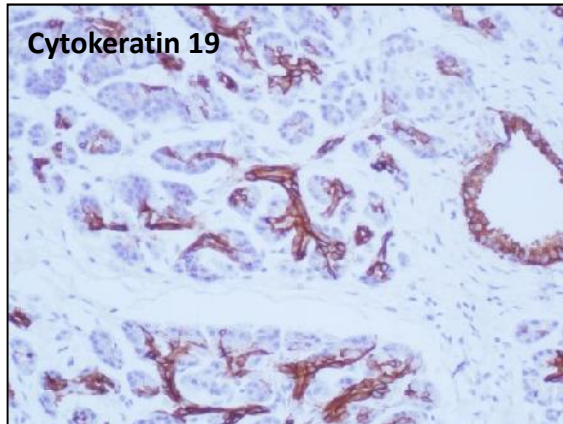


Glucagon positive ductal cells?



Vimentin positive ductal cells?

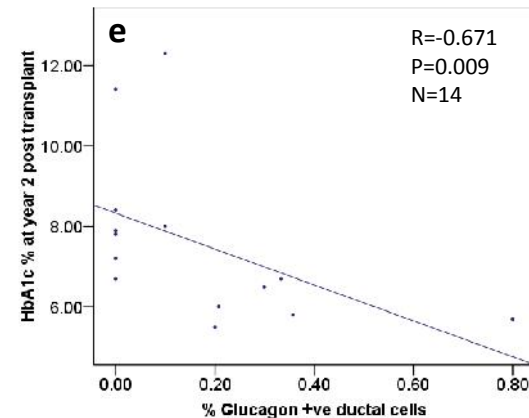
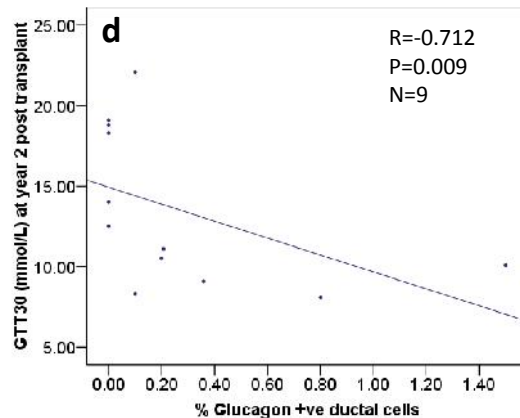
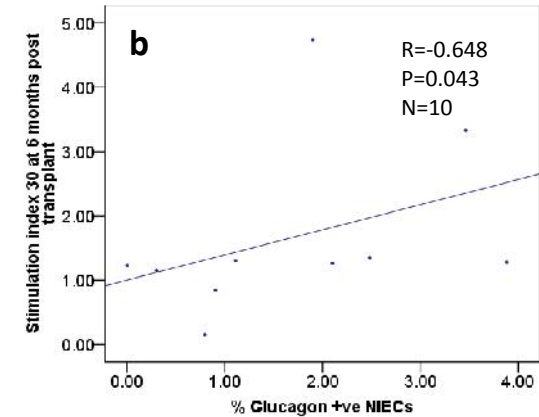
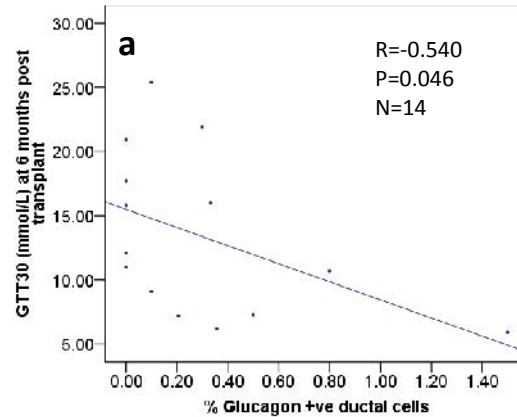
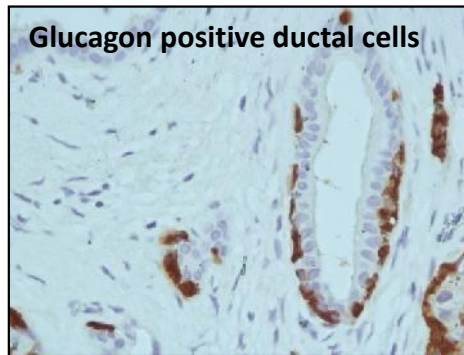
Ductal Cells



b

CK19 was observed to be correlated with significantly high fasting C-peptide (a) values and low HbA1c (b) at 1 year post transplant.

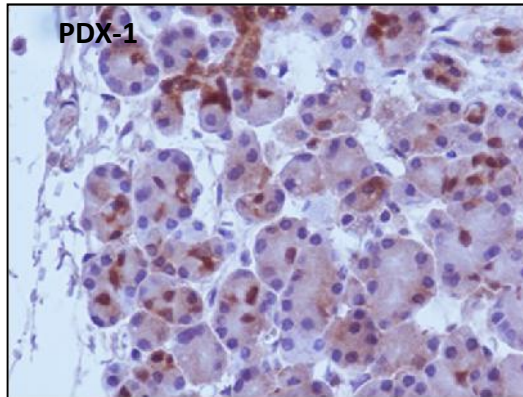
Glucagon-positive ductal cells



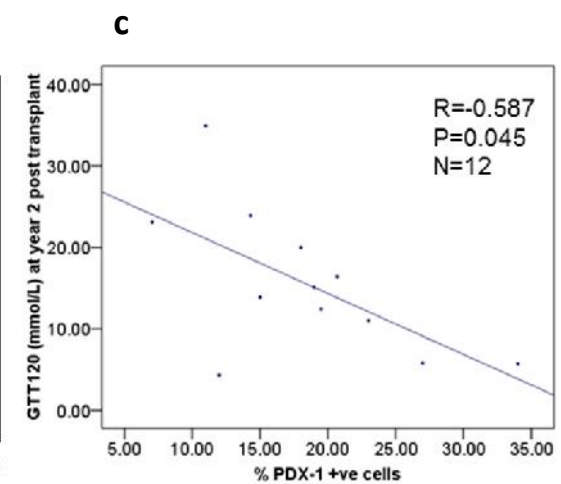
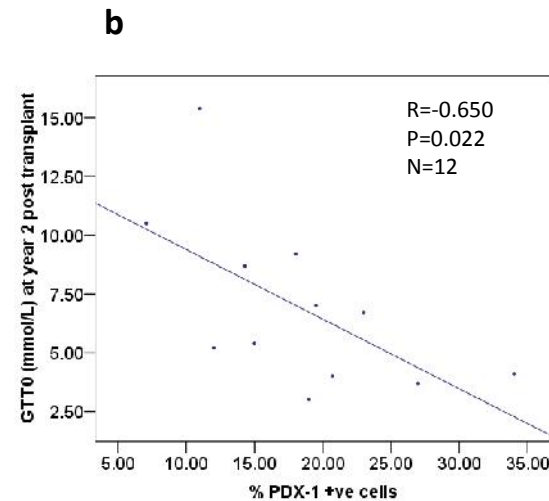
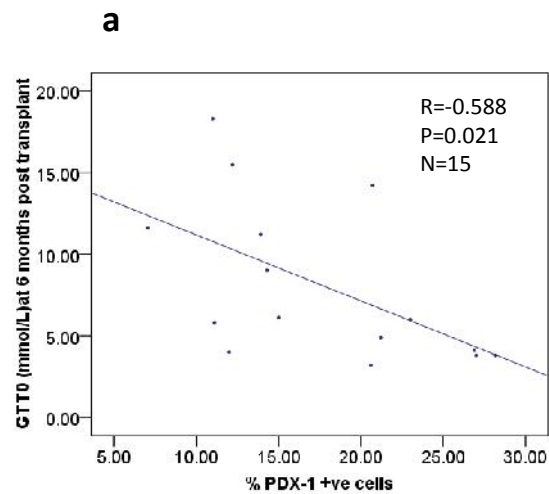
Glucagon positive ducts were shown to significantly correlate with lower stimulated glucose levels (a) and an increased SI 30 at 6 months post-transplant (b&c) and lower stimulated glucose (d) and lower HbA1c % (e) at 2 years post-transplant.

Stimulation index = Stimulated C-peptide levels divided by basal C-peptide levels

Non-islet PDX-1 (pancreatic and duodenal homeobox-1) positive cells



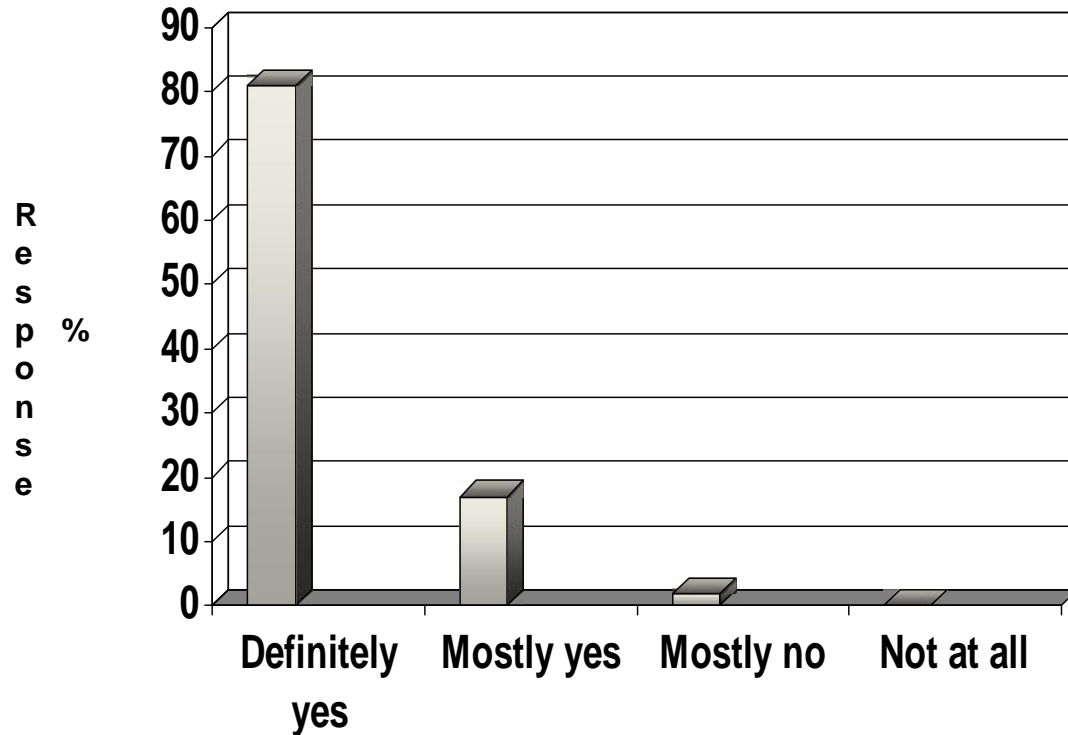
PDX-1 was observed to be significantly correlated with lower fasting glucose (mmol/L) at both 6 months and 2 years (a & b) and stimulated glucose at 2 years post transplant (c).



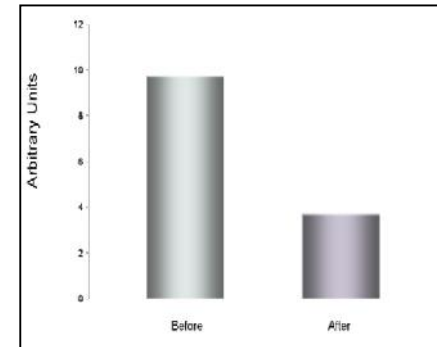
Patient survey following total pancreatectomy

- Questionnaire posted out to all patients (still alive following total pancreatectomy; with or without islets)
- Questions kept simple and brief, detailing patient satisfaction with their surgery, pain control before and after surgery
- Second round of questionnaires posted to non-responders to ensure maximum capture of all patients
- 80% response rate for TP/IAT patients and 65% for TP alone

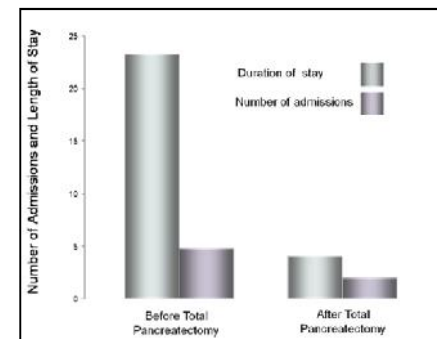
Response to patient questionnaire: *“Do you think you have benefited from your total pancreatectomy.”*



At 1 year 78% reduction in visual analogue pain scores, 60% reduction in the number of hospital admissions and an 80% reduction in their duration

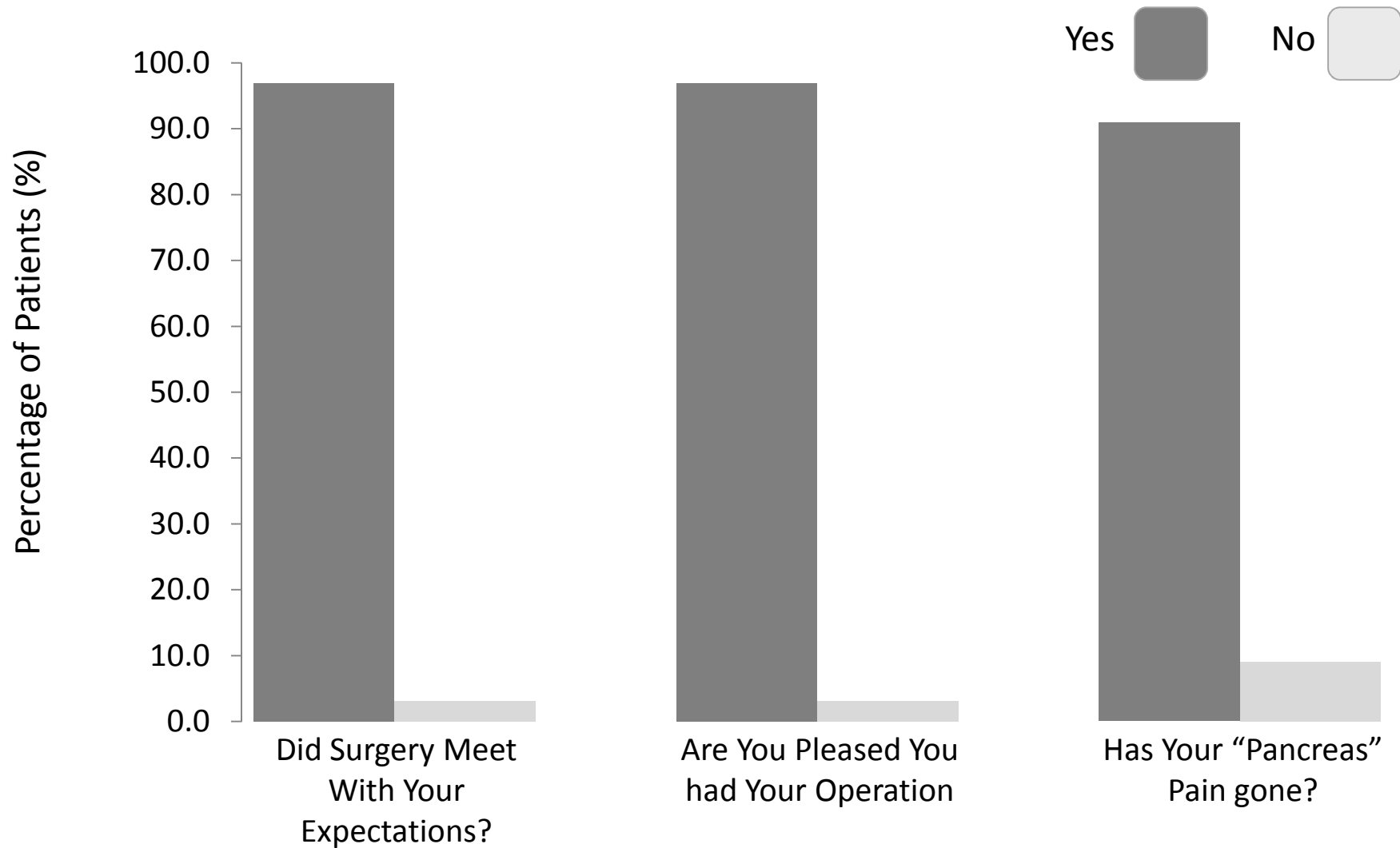


Reduction in pain scores

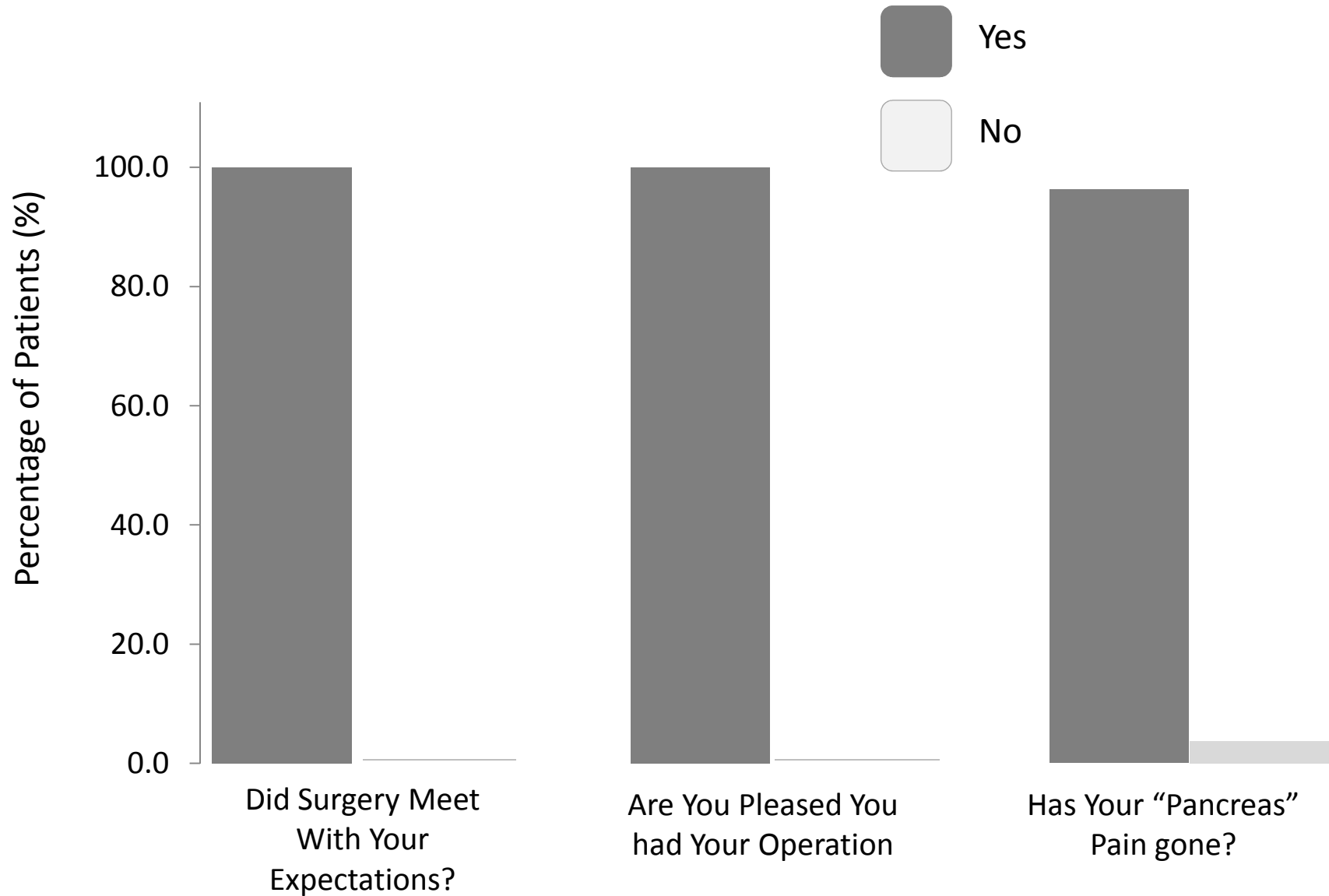


Reduced hospital admissions and duration

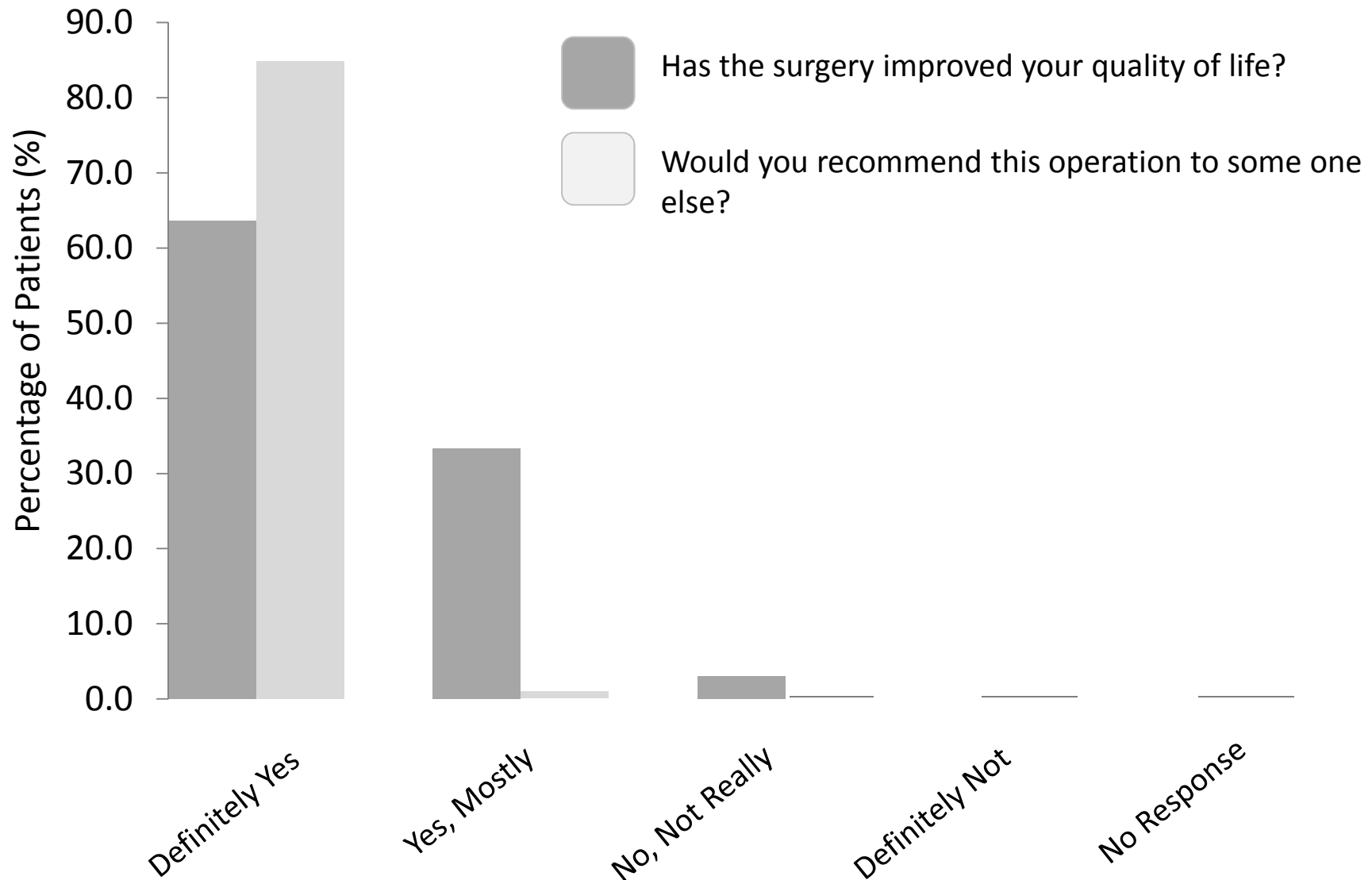
Patient Satisfaction Following Surgery (All Patients)



Patient Satisfaction Following Surgery (Islets Only)



Patient Post-Operative Satisfaction Responses (all patients)



Improvements in quality of life following total pancreatectomy and islet autotransplantation for CP

	Pre-operative state	Post-operative state
Family/home responsibilities	12 (61%)	2 (10%)
Recreation	16 (80%)	4 (20%)
Social activities	13 (66%)	3 (15%)
Occupation	14 (70%)	3 (20%)
Sexual behavior	11 (55%)	2 (10%)
Self care	6 (39%)	0 (0%)
Life support activity	9 (45%)	1 (10%)
Depression	4 (19%)	0 (0%)
Anxiety	1 (4%)	1 (4%)
Pain scale	11 (55%)	2 (10%)

Aguilar-Saavedra et al 2011 "TP-IAT significantly improves pain, depression, anxiety and QoL in appropriately selected patients with CP"

Overall results of large series are similar

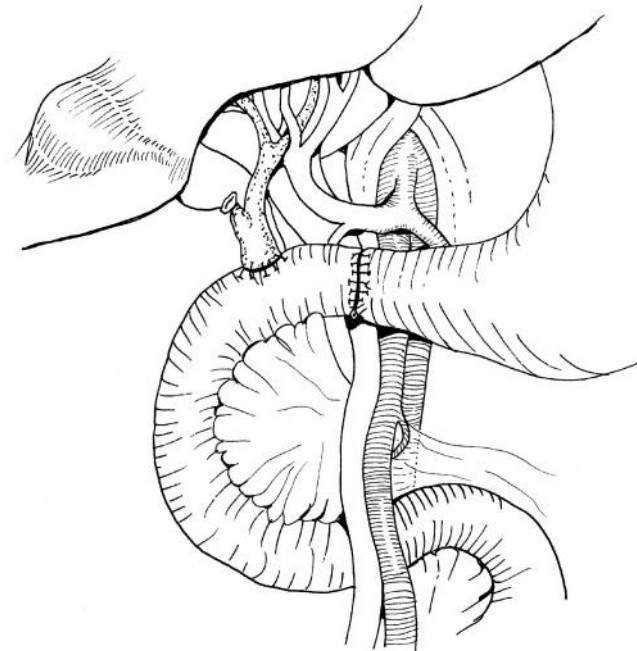
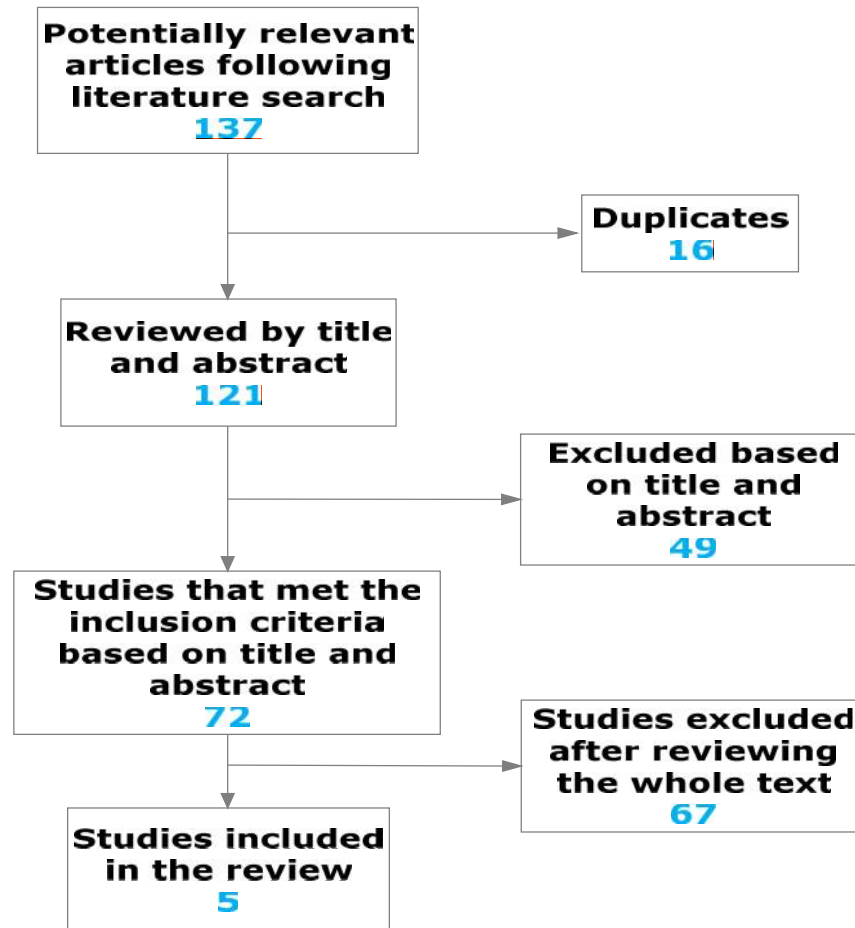
	Number of procedures	Alive at 1 year %	Alive at 10 years %	Off insulin %	C-peptide positive %	Operation length (hrs)	Blood loss	Hospital stay (days)
Minnesota 2006	188	98	73	33	<100	10±1.7	1.5L 50ml-30L	22 (1-89)
2011	279			36	88			
Cincinnati 2004	45	ND	ND	40	ND	ND	ND	ND
2009	118							
Leicester 2011	60	98	84	37.5	100	9 (7.5-12)	0.7L (200ml-2.5L)	21.5 (8-52)

Data in blue presented at IPITA 2011 (Pollard et al 2011, Bellin et al 2011).

Minnesota 2006 data published by Blondet et al 2007 and the Cincinnati data by Ahmed et al 2006 and Sutton et al 2010

Review of total pancreatectomy ± islet autotransplantation (TP/IAT) results

Bramis K, Gordon-Weeks AN, Friend PJ, Bastin E, Burls A, Silva MA and Dennison AR *Br J Surg* 2012;99(6):761-766



Study demographics

Author	Publication date	Country	Design	Number of patients	Mean age (range)	Male (%)	Mean Weight (range)	Idiopathic (%)	Alcohol (%)
Toledo-Pereyra	1983	USA	Case series	6	(28-41)	83	*	50	50
Valente	1985	Italy	Case series	22	*	*	*	*	*
Ahmad	2005	USA	Case series	45	38 (16-62)	33	74 (39-110)	87	4
Sutherland	2008	USA	Case series	173	*	*	*	*	*
Garcea	2009	England	Retrospective Cohort	50	43 (21-65)	46	58.5 (40.4-103)	48	36

Summary of TP/IAT results

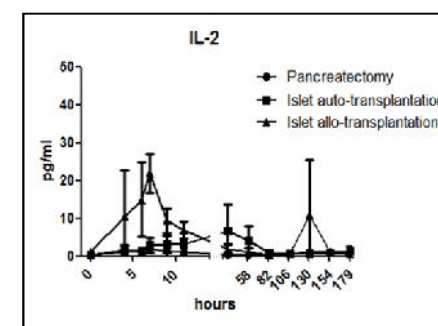
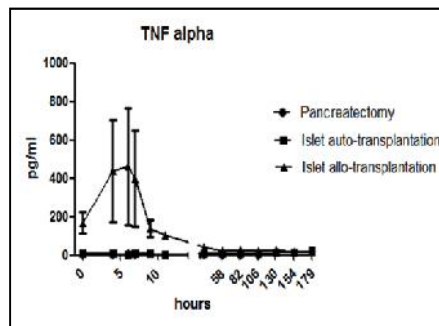
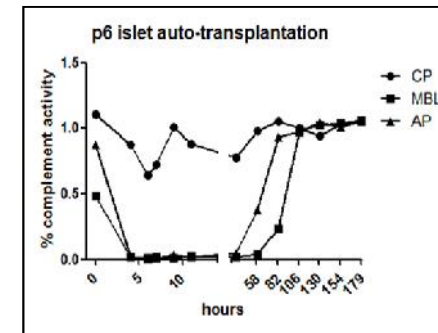
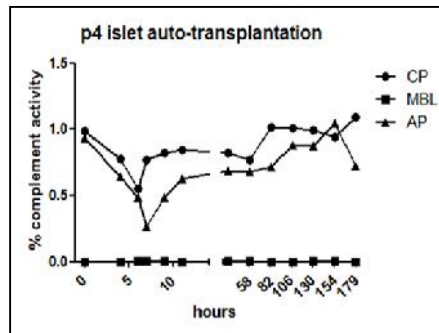
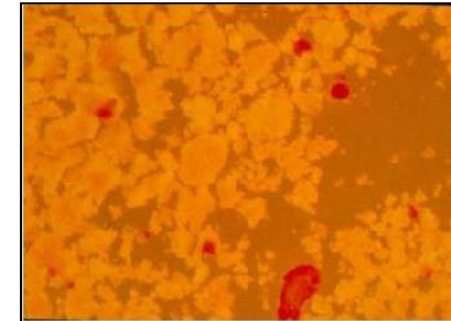
- Pancreatectomy and islet autotransplantation has a low mortality
- Patient satisfaction and quality of life is good
- Purification is not necessary and may be harmful
- Insulin independence is achieved in a significant number of patients but insulin production falls with time
- Weaning from opiates is prolonged but successful
- Use of the umbilical vein for access to the portal circulation is safe and facilitates examination (and potentially manipulation) in the post-operative period

The future

Use of the umbilical vein allows routine portal venous sampling for the measurement of cytokines and complement

Ex-vivo autologously perfused porcine model allows very studies of islet implantation

FUNDING



Funding

Depends on the country

Availability of national funding

Insurance status

13 Insurance companies in the USA
support TP/IAT

European and UK experience different
UK funding previously from Health
Authorities

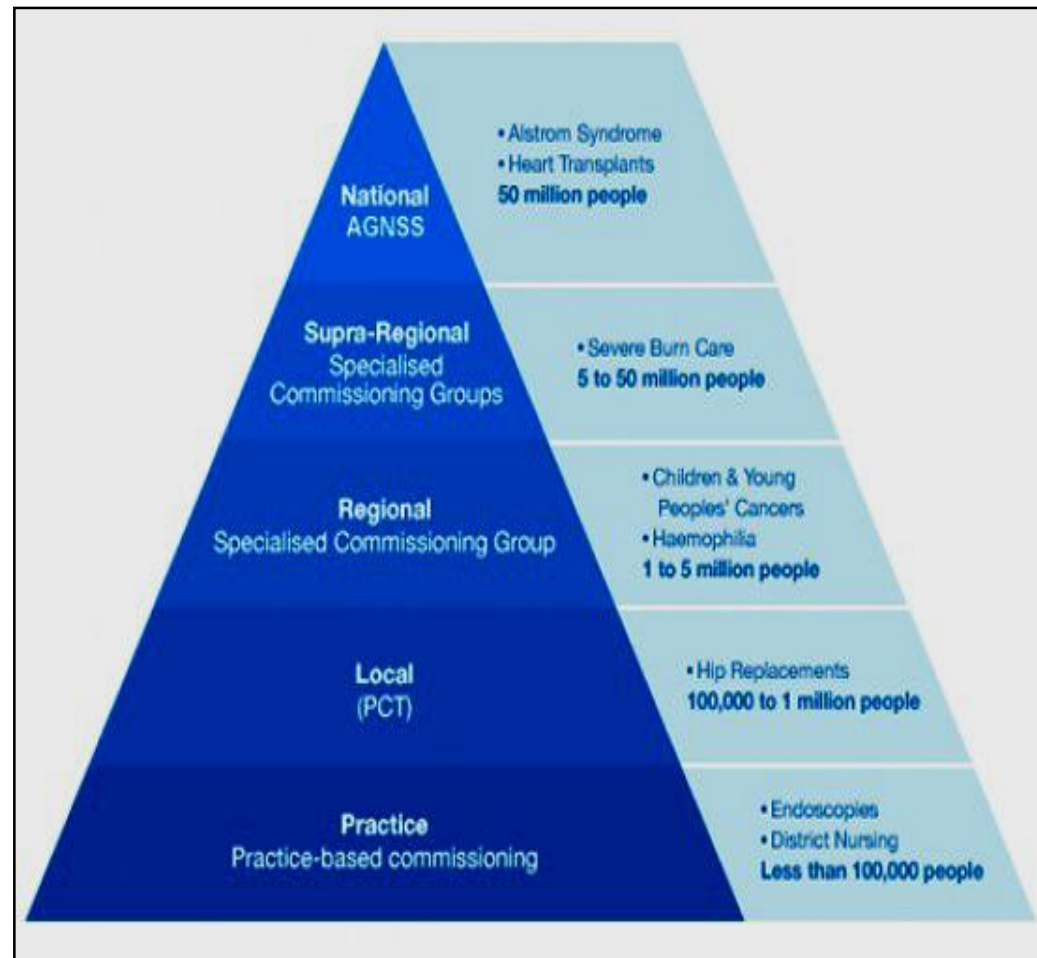
Much more difficult with primary care
trusts

Application to NCG (AGNSS)



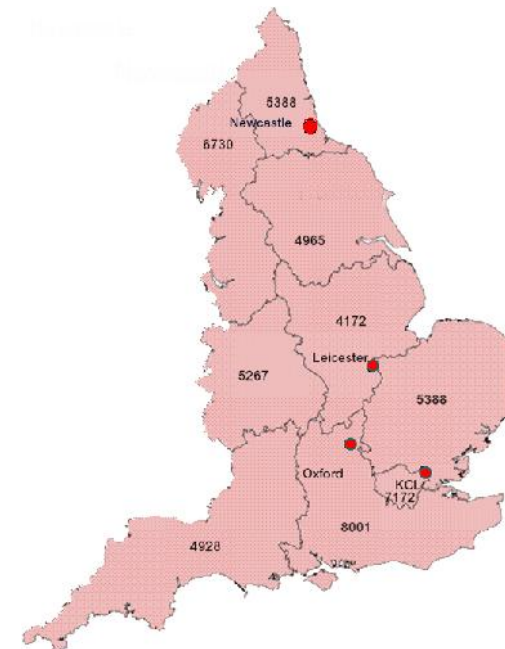
Advisory Group for National specialised Services (AGNSS nee NCG)

- AGNSS funds highly specialised services performing less than 500 procedures/year
- 60 services supported
- Alström Syndrome, eye cancer, xeroderma pigmentosa, heart, lung, liver, pancreas and small bowel transplantation and children's gender identity issues

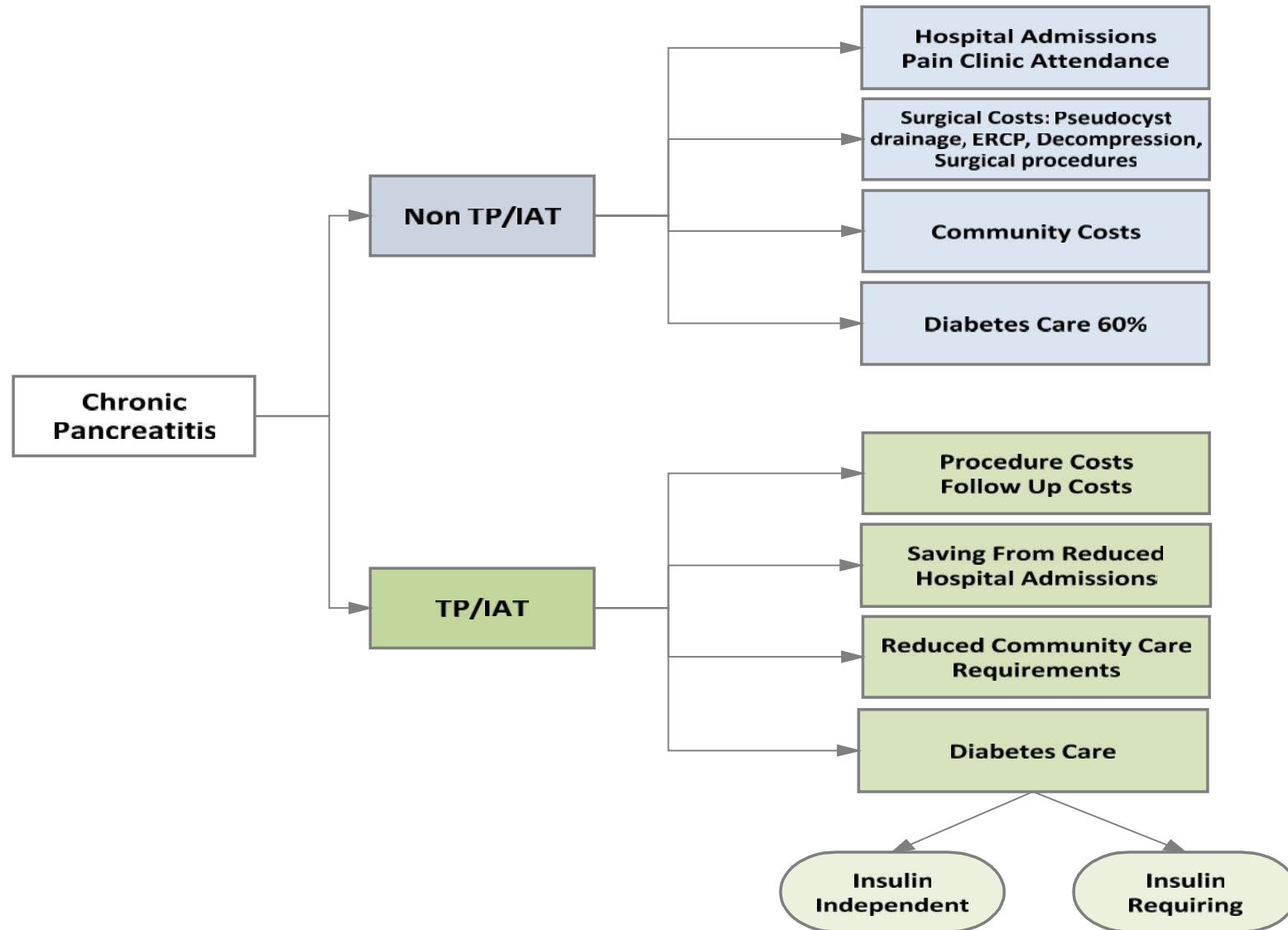


AGNSS application

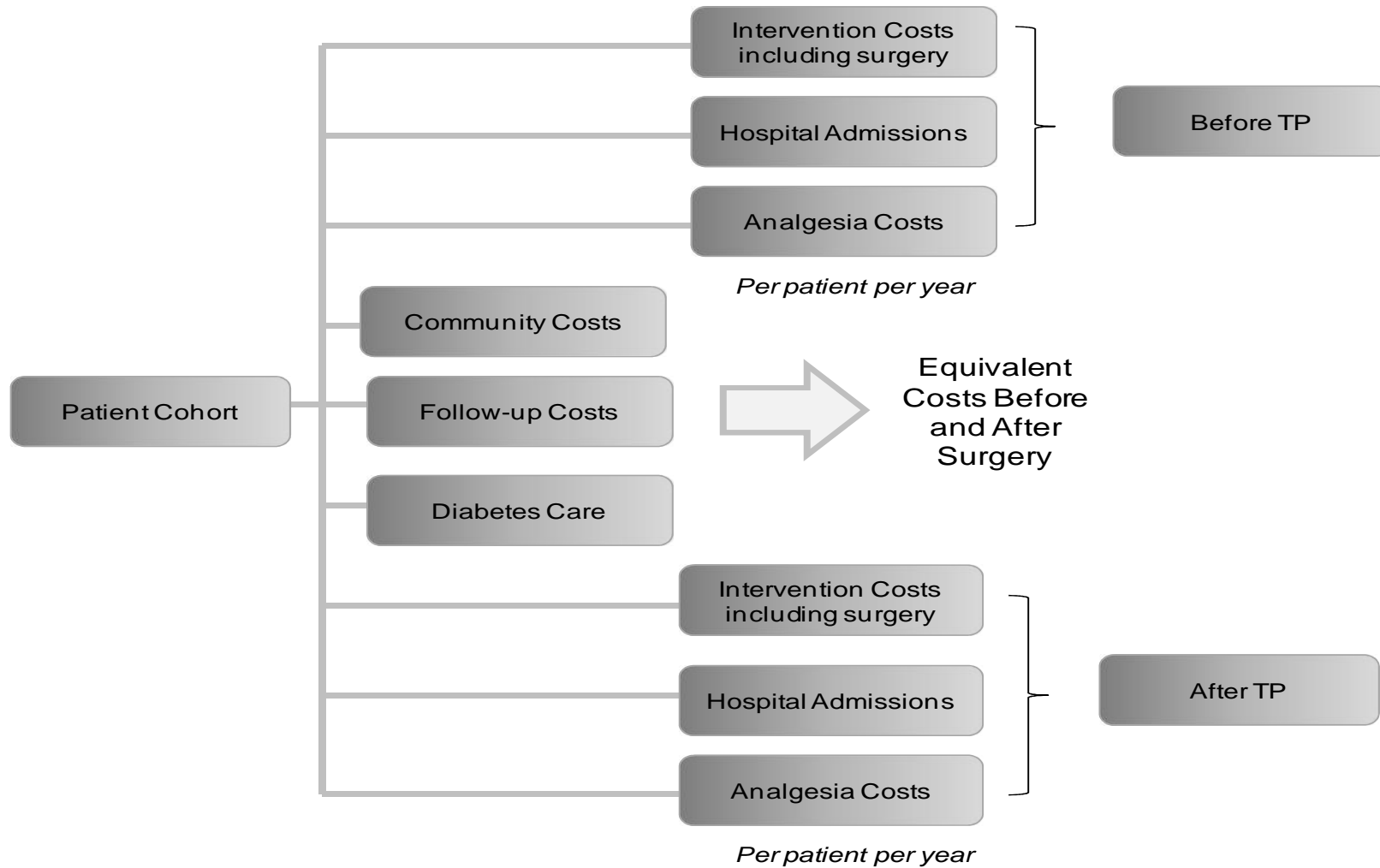
- Consortium application
- Leicester, Oxford, Kings Hospital London and Newcastle
- **Hopefully to start 2013**
- Only other source of funding insurance companies
[*pancreatectomy with autologous islet cell transplantation J5711*]



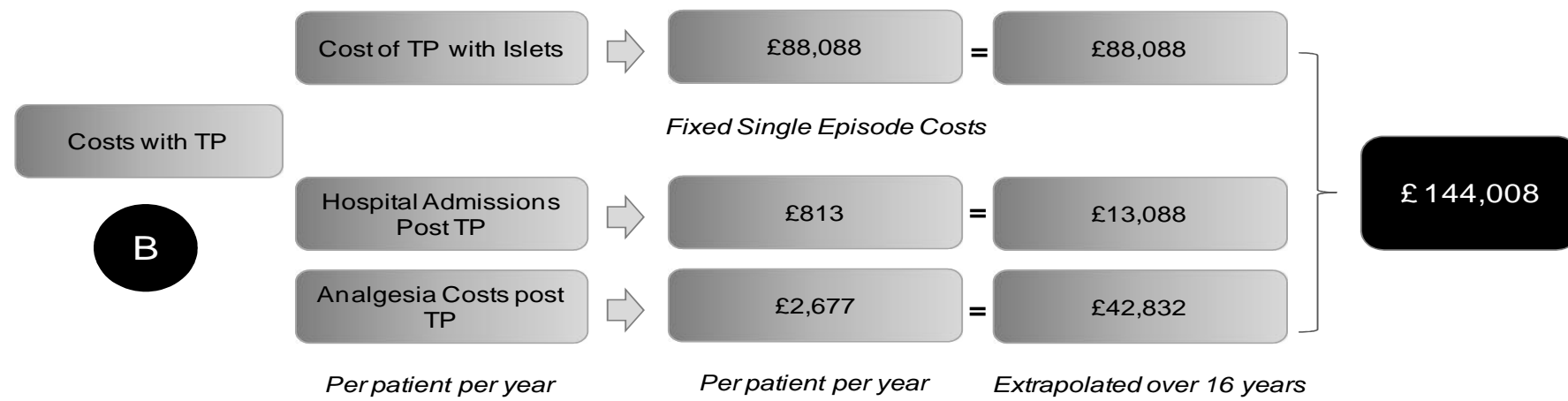
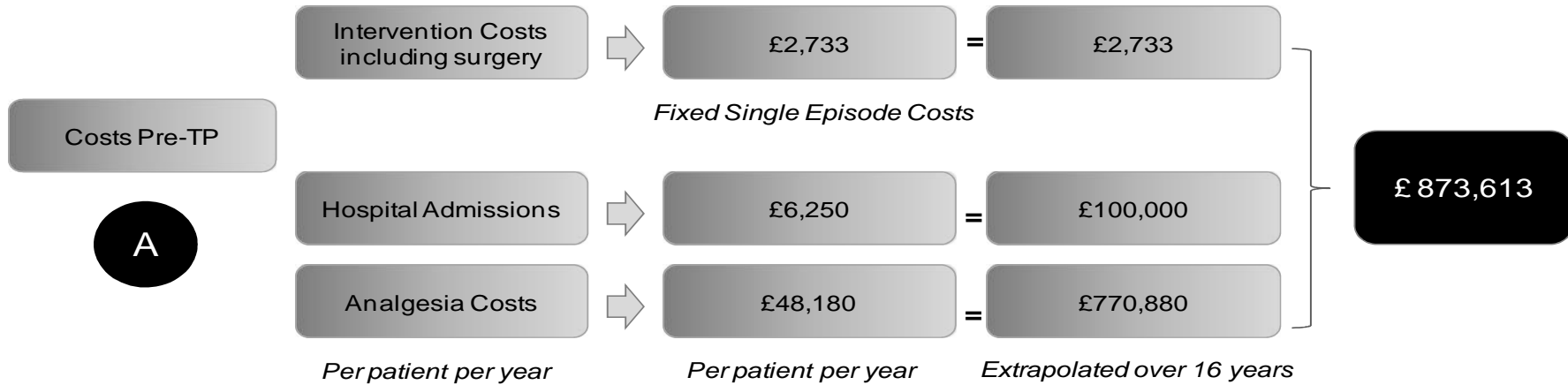
Approach to health economics analysis



Health economics following TP/IAT



Cost with and without TP/IAT



Conclusions

- Pancreatectomy and islet autotransplantation has a low mortality
- Patient satisfaction and quality of life is good
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Many thanks to

- Cris Pollard patient workup, program supervision, portal pressure recording and venograms
- M'Balu Webb for the intermediate cell work
- M'Balu Webb and Severine Illouz for islet preparation and data analysis
- Gianpiero Gravante for database analysis and statistical support
- Wen Chung for complement, cytokine and portal pressure analysis
- Patrick Musto anaesthetic support
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- Ling Ong and Jane Chen
- Lyn Power and theatre team at LGH