AT THE FOREFRONT
UChicago Medicine | Piotr Witkowski Lab

Update on our pancreatic islet transplantation program

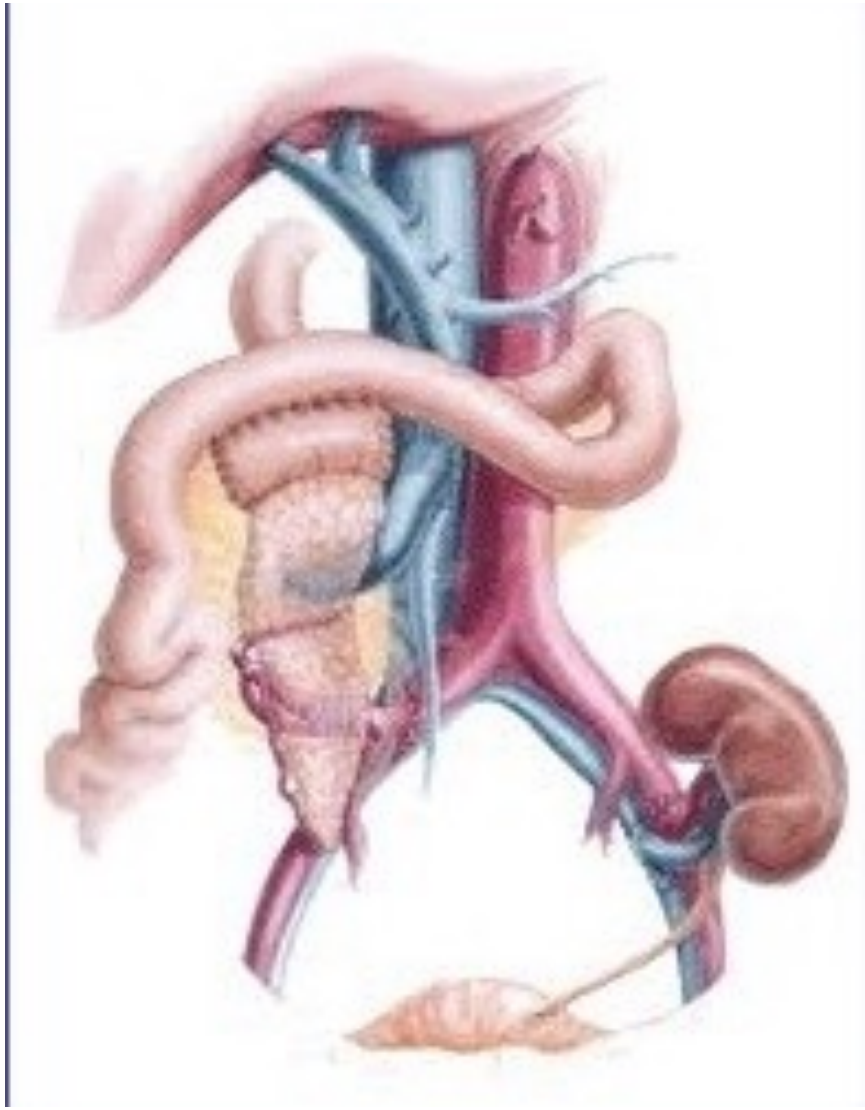
Pancreas Transplantation- standard of care

Main advantage:

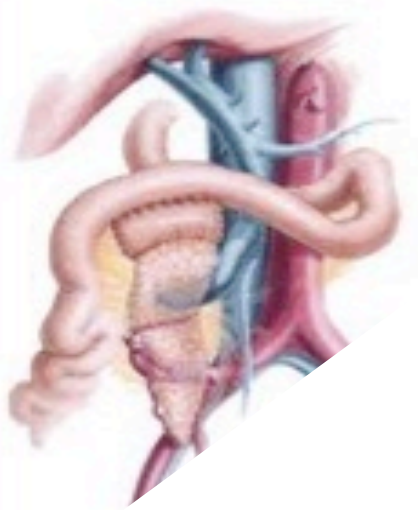
- Eliminates diabetes instantly

Main disadvantage:

- Requires major surgery, ICU, hospitalization, recovery
- Requires bowel anastomosis
- 10% risk of instant thrombosis (graft loss)
- 20% risk of re-operation due to bleeding, bowel leak



Pancreas Transplantation



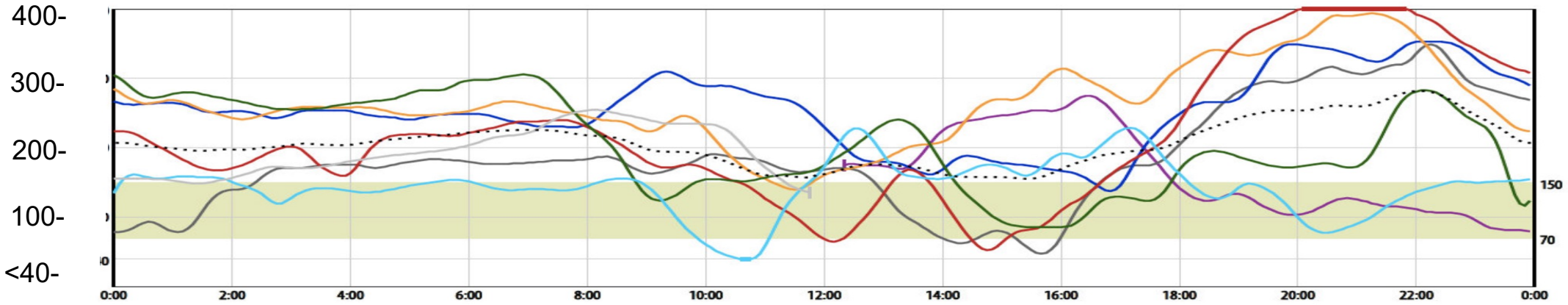
Highly selected type 1 diabetics:

1. those who **require a kidney transplant** (ESRD), so they would need anesthesia, major surgery, immunosuppression anyway.

or

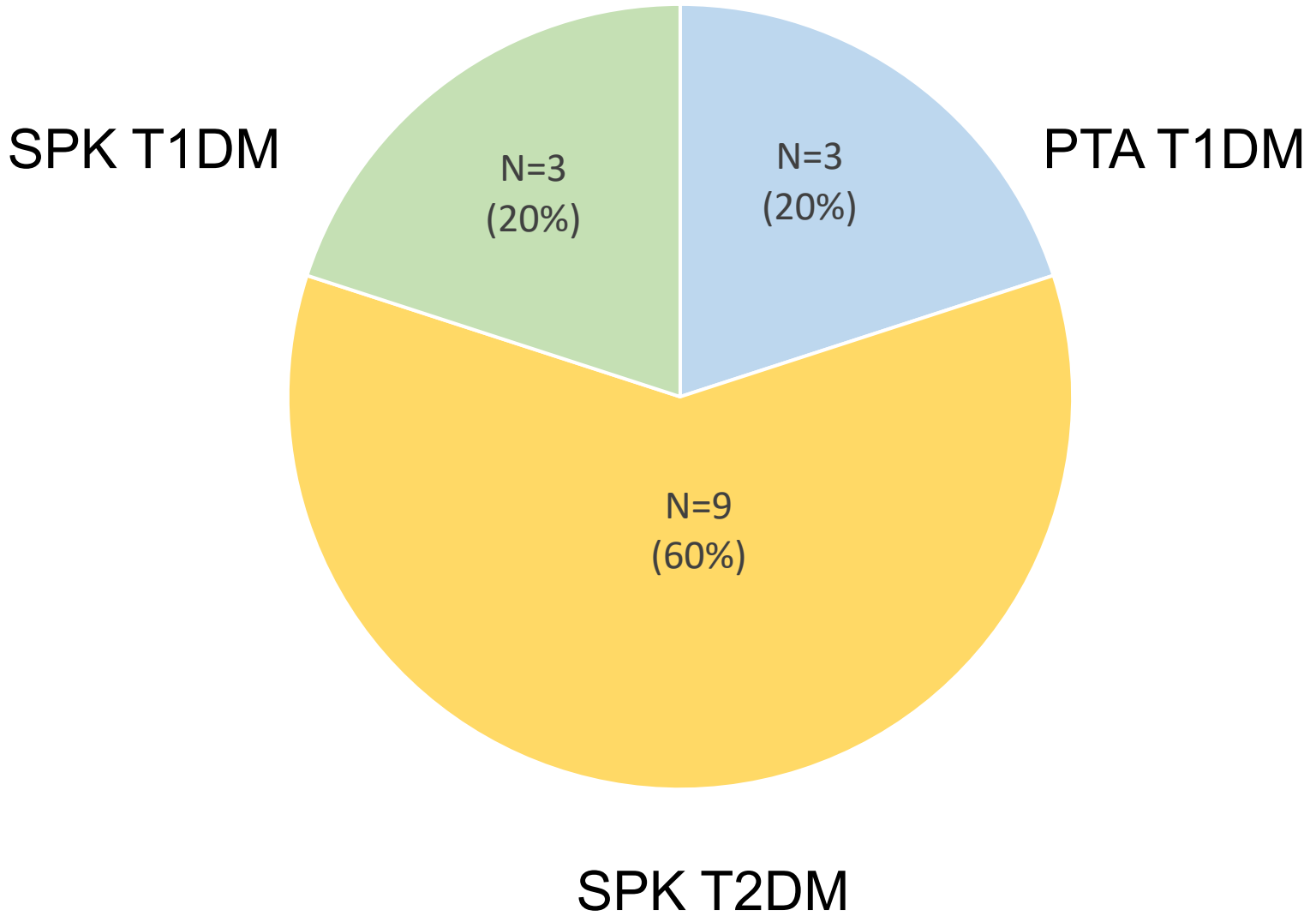
2. those with good kidney function who have a " brittle" T1DM, have **hypoglycemia unawareness with hypoglycemic episodes** despite the best, optimal insulin treatment.

Those patients have hypoglycemic **confusion, seizure, coma**, without any warning symptoms. It leads to **brain injury, car accidents.** Patients **develop anxiety, depression, can't work, drive, quality of live is severely compromised.**

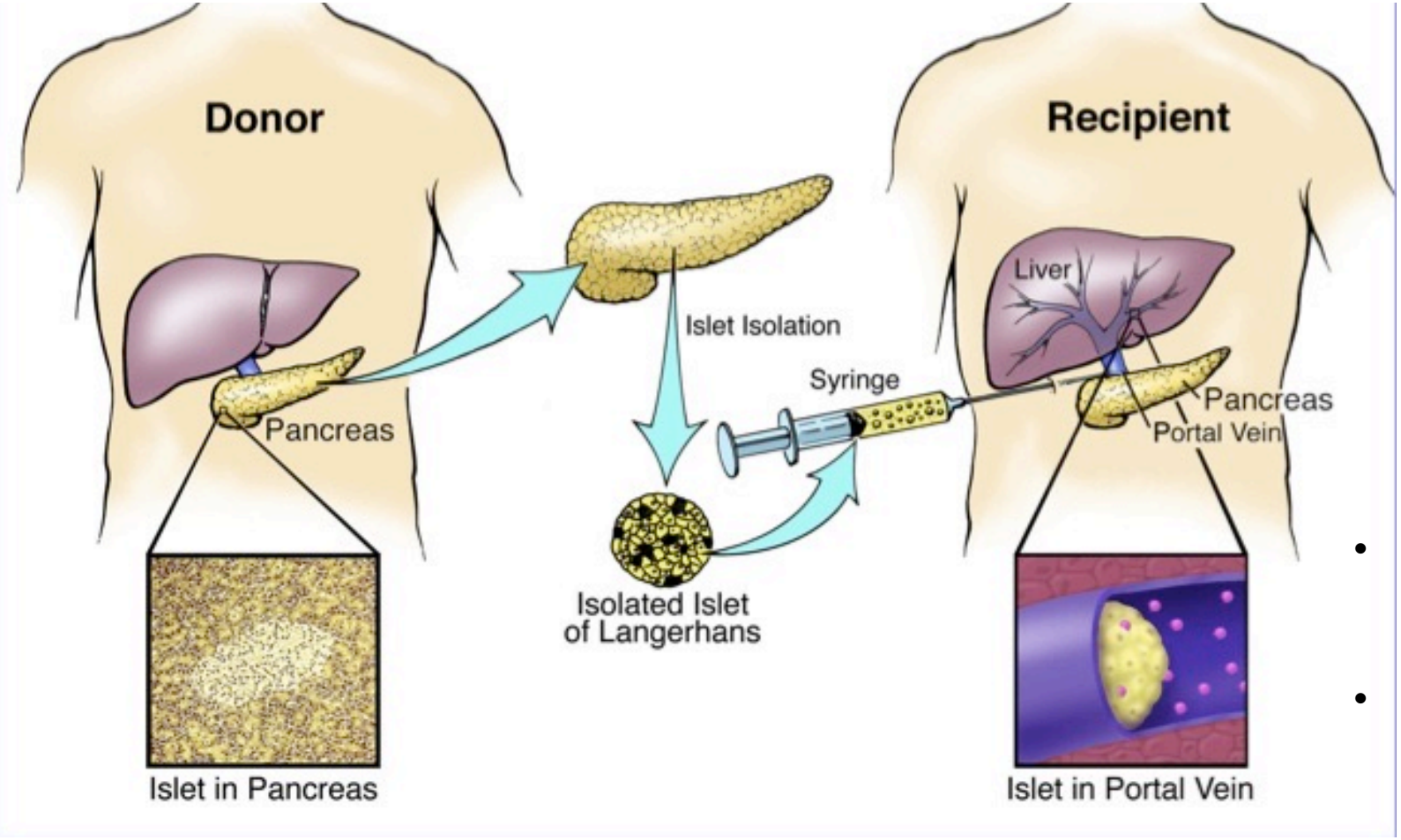


AT THE FOREFRONT
UChicago Medicine

2022 N=15 pancreas Tx

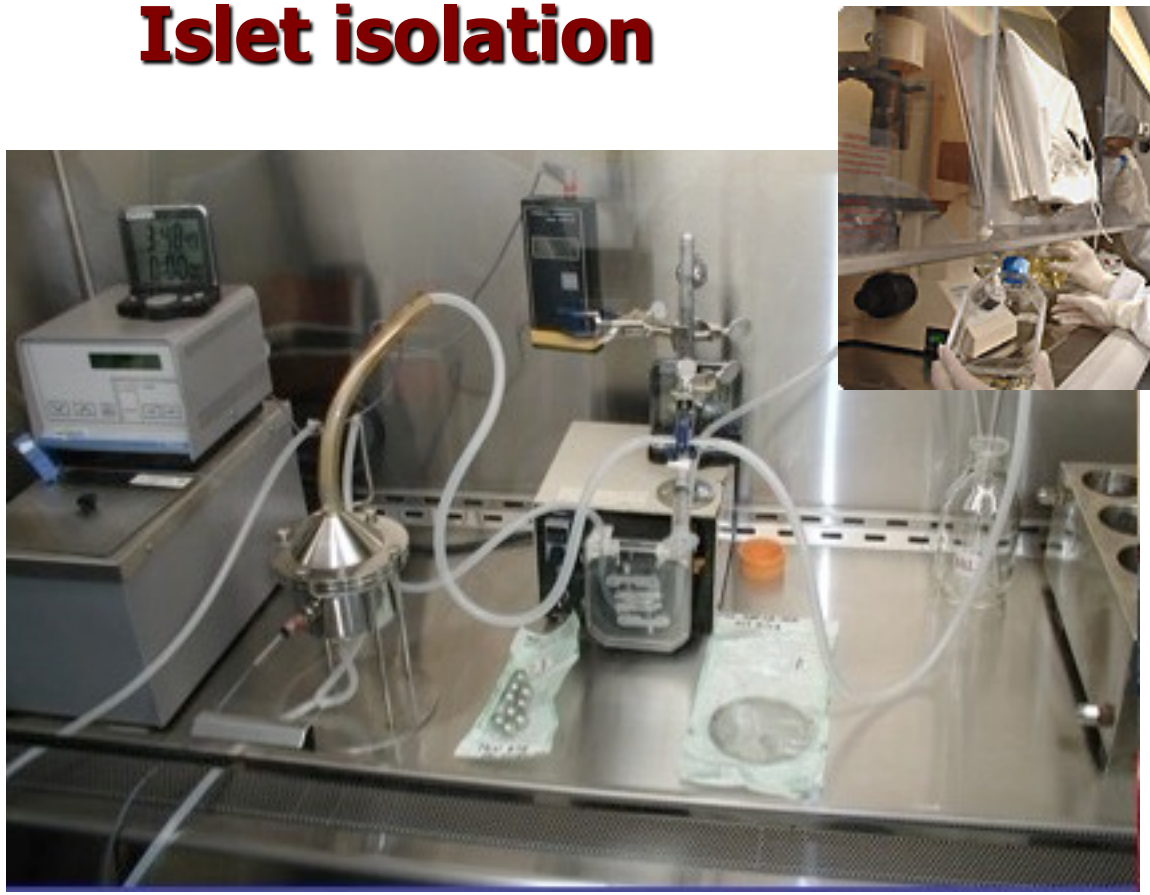


Islets allotransplantation-
as a minimally invasive alternative to whole pancreas transplantation



- The same peri-transplant testing for blood type compatibility and negative X-match
- The same immunosuppression to prevent allogenic rejection and recurrent auto-immunity

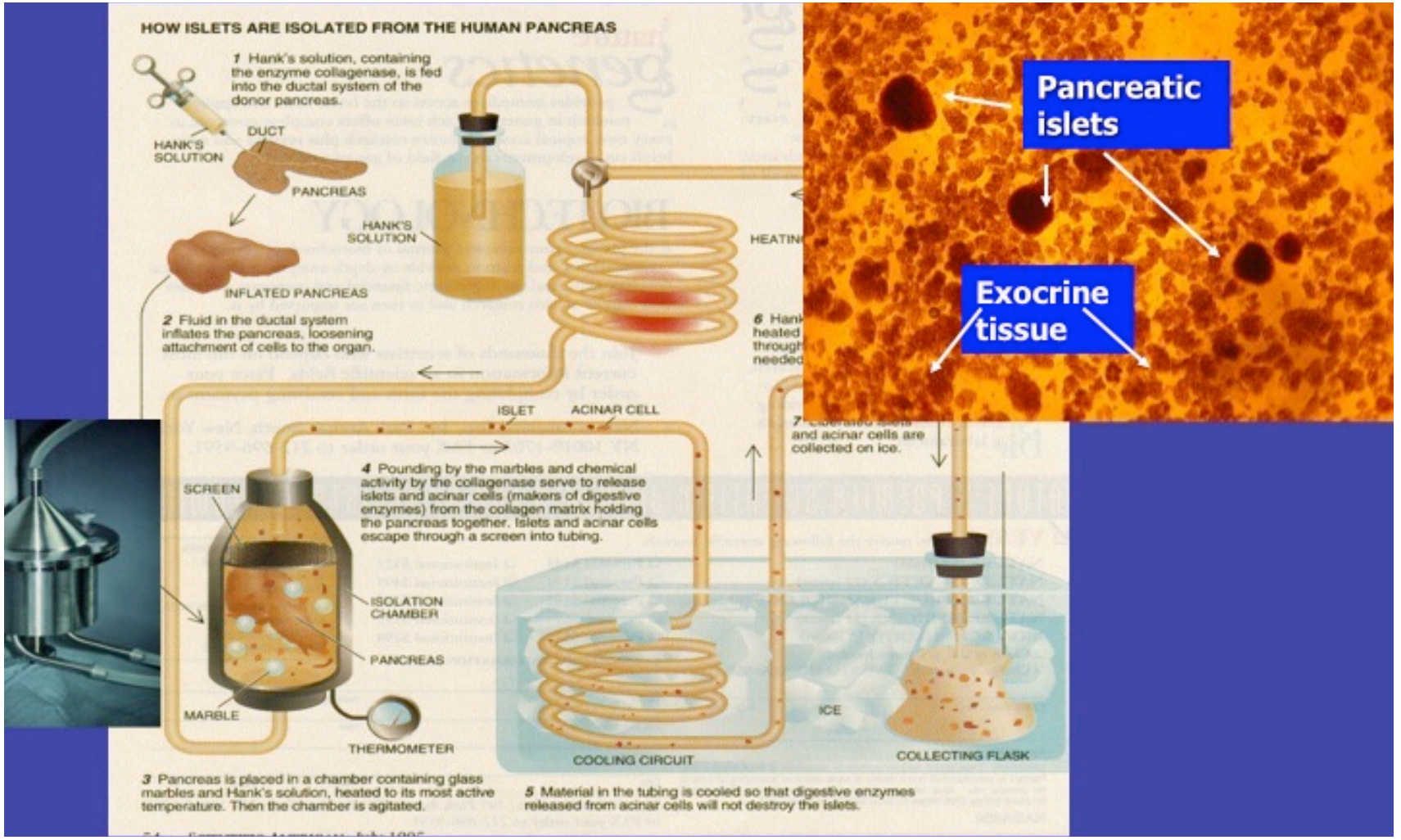
Islet isolation



- Certified cGMP Facility properly equipped with BSC, centrifuges, incubators etc.
- **Quality control system** assuring quality of the process and the final product.

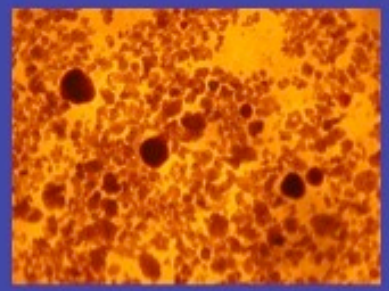
Steps of the islets isolation

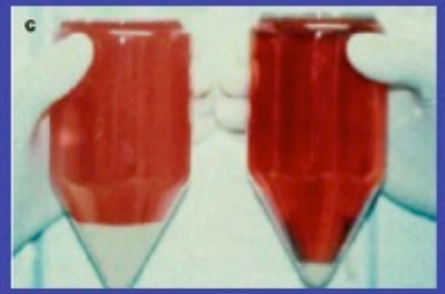
1. enzymatic digestion



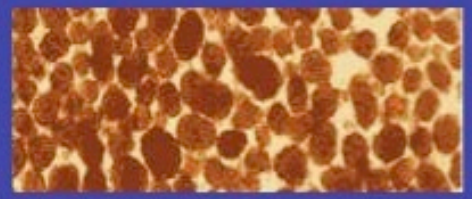
2. Separation of the islets from acinar tissue

20- 60 ml

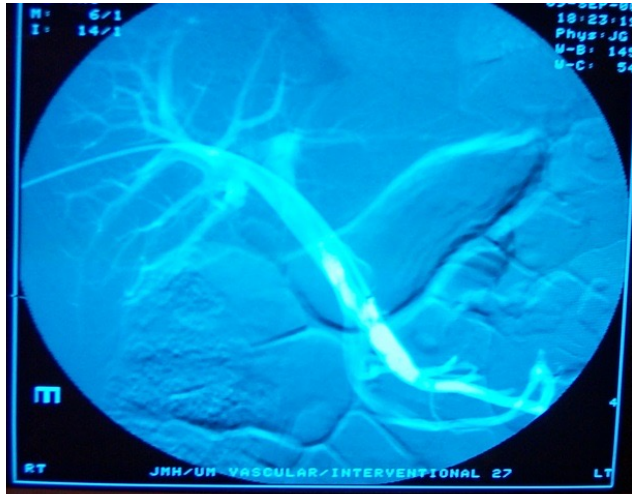


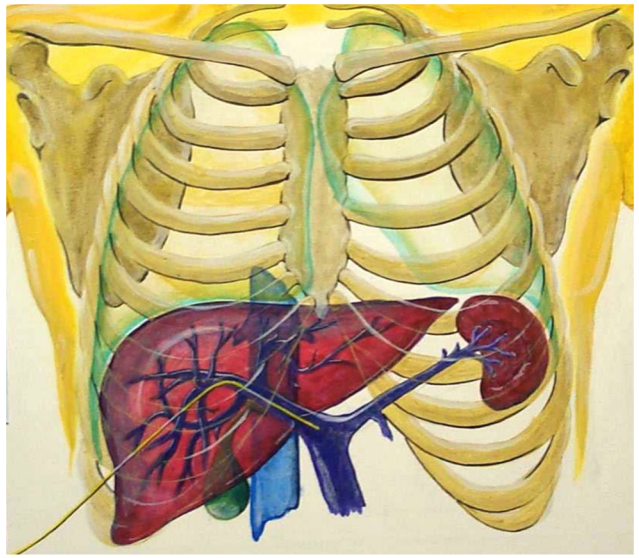


2-5 ml



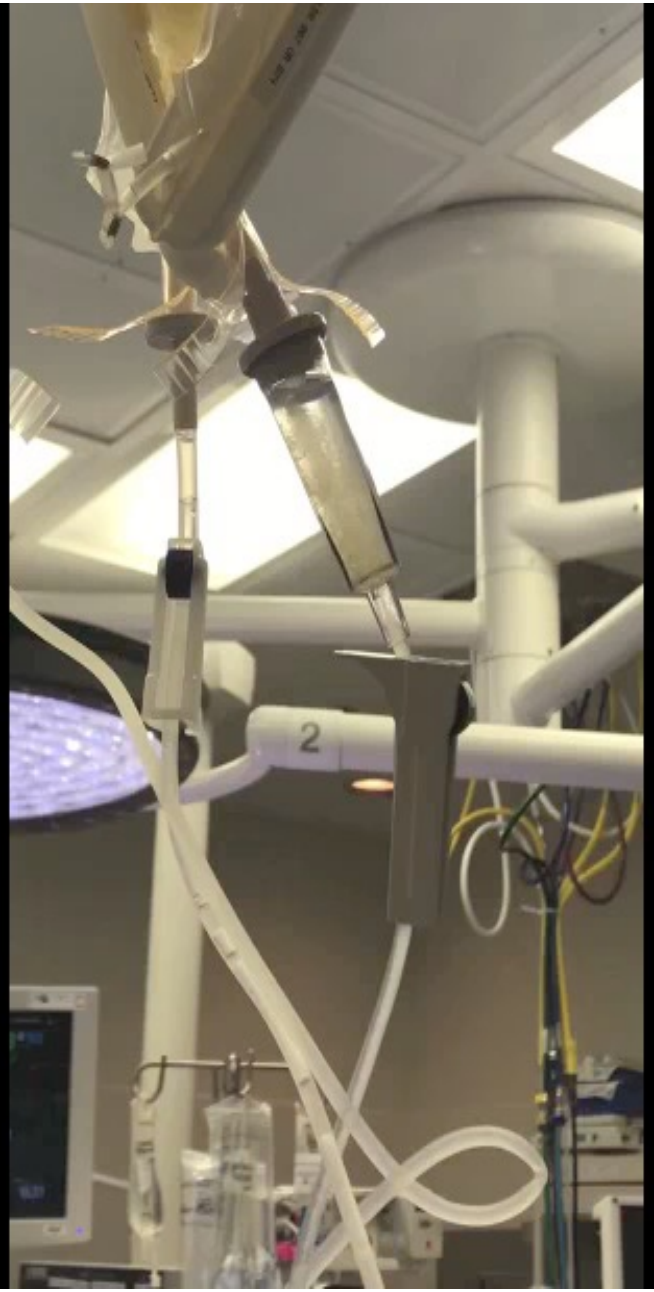
Islet transplantation- infusion into the portal vein





Interventional radiologist, percutaneous access, under local anesthesia,

Islets dripping into the portal vein in 200ml of media ~ 30- 45 min



Our clinical protocol

- **Evaluation:** liver function, portal vein flow, hypercoag work up

- **Immunosuppression meds-** Thymo, Tacrolimus/Myfortic (no steroids), starts 3-4 weeks prior to Tx (to optimize the dose without side effects)

- Activation on the list, waiting time ----> few days- few weeks (no completion in the US), we use fatty pancreas which are not good for whole pancreas tx

- ITx in IR, 2-3 days in hospital

- islets gradually recover, connect own blood vessels to liver-
  so protected from "work" by providing insulin ~ 50-70% during first few weeks, gradually weaning off as soon as seeing hypos

- But from day 1 BG is easy to control 80-180mg/ml

- we support patients till day 75, reassessment:

- if partial function (c-peptide present but still needs 50% insulin), we activate for 2nd ITx

In general

- If preTx insulin daily requirement <40u → 1 ITx might be enough

- If preTx insulin daily requirement >40u → usually 2-3 ITx

- if patient off insulin for some years and gradually needs some insulin- we can do subsequent ITx (4^{th} and 5^{th} still ok)

Risks and side effects

ITx procedure

- partial portal vein thrombosis- low 1-2%, since we give heparin drip for 48 hrs and Lovenox for 2 weeks
- bleeding/liver hematoma- 5% may required blood Tx (complications declines with experience 1/57 (1,7%) procedures in last 9 years)

Immunosuppression

- Tacro-
  - nephrotoxicity- prevention---stay well hydrated, keep tacrolimus level consistent- not too high (more affecting damaged kidneys with macroalbuminuria)
  - neurotoxicity (hand tremor)- minimal with dose adjustment and new once a day Envarsus
  - HTN- may be in long run in older patients
- CellCept- may cause N/V/diarrhea, leukopenia, but after dose adjustment- > none
- increased risk of skin cancer- easy to find and excise
- PTLD <2-4%- usually treatable

THE LANCET
Diabetes & Endocrinology
Volume 6, Issue 7, July 2018, Pages 527-537

Islet transplantation versus insulin therapy in patients with type 1 diabetes with severe hypoglycaemia or poorly controlled glycaemia after kidney transplantation (TRIMECO): a multicentre, randomised controlled trial

Sandrine Lablanche MD [a, g], Prof Marie-Christine Vantyghem MD [i, j], Prof Laurence Kessler MD [k], Prof Anne Wojtusciszyn MD [l, m], Sophie Borot MD [n], Prof Charles Thivolet MD [o], Sophie Girerd MD [s], Domenico Bosco PhD [t], Prof Jean-Luc Bosson MD [b, f, h], Prof Cyrille Colin MD [p, u], Rachel Tetaz MD [c], Sophie Logerot PharmD [d], Prof Julie Kerr-Conte PhD [i, j], Prof Eric Renard MD [l, m], Prof Alfred Penfornis MD [v, w], Prof Emmanuel Morelon MD [q], Fanny Buron MD [q], Kristina Skaare PhD [b, f, h] ... Thibault Bahoune

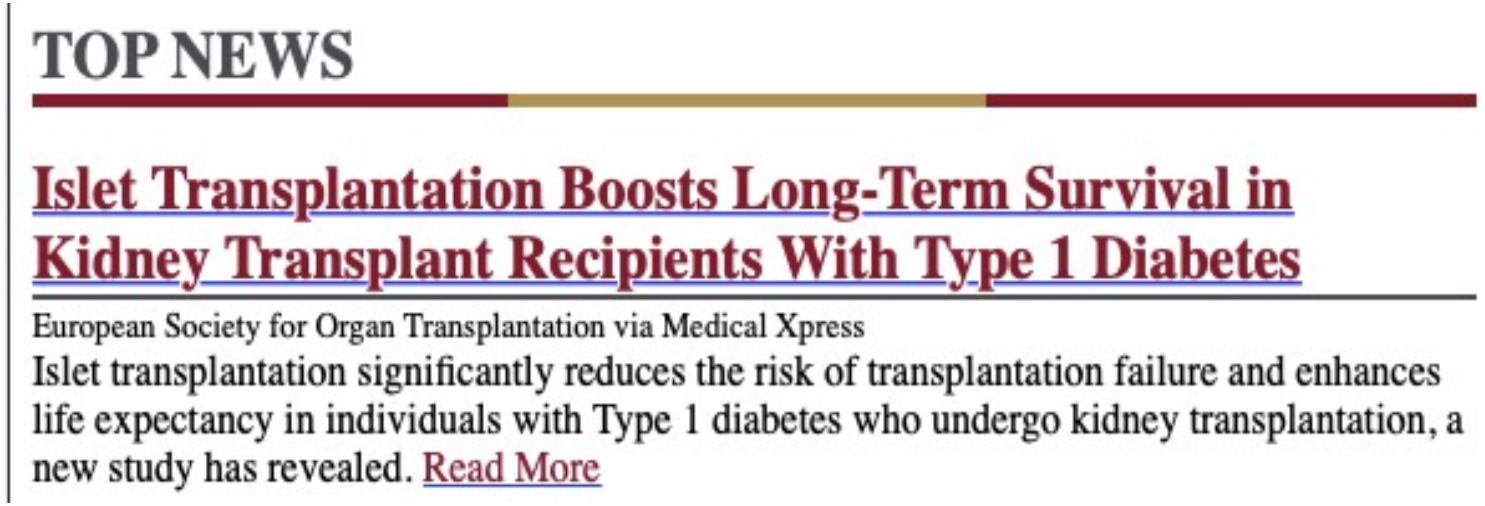
First randomized trial: insulin vs ITx
France, 15 academic centers
Brittle T1DM

N=22 optimized insulin treatment	N=24 Islet Tx
N=1 (4%) mortality died during the night severe hypoglycemia	No deaths
N=1 (4%) major complication severe head injury due to hypoglycemic seizure	No major complications, 7% bleeding -> blood tx
A1c 8 (6-10)	A1c 5.5 (4.8- 6.5)

A1c <7 and no severe hypoglycemic episodes

0	80%

- 60% insulin independent at 1 year
- hypoglycemic awareness was restored



TOP NEWS

Islet Transplantation Boosts Long-Term Survival in Kidney Transplant Recipients With Type 1 Diabetes

European Society for Organ Transplantation via Medical Xpress

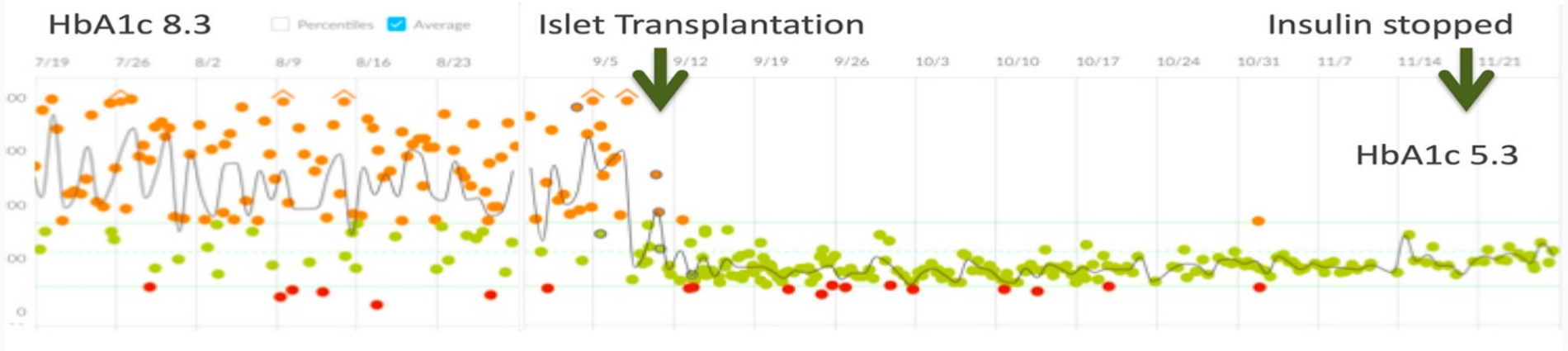
Islet transplantation significantly reduces the risk of transplantation failure and enhances life expectancy in individuals with Type 1 diabetes who undergo kidney transplantation, a new study has revealed. Read More

European Society for Organ Transplantation Congress; 17 September 2023; Athens, Greece.

The researchers investigated

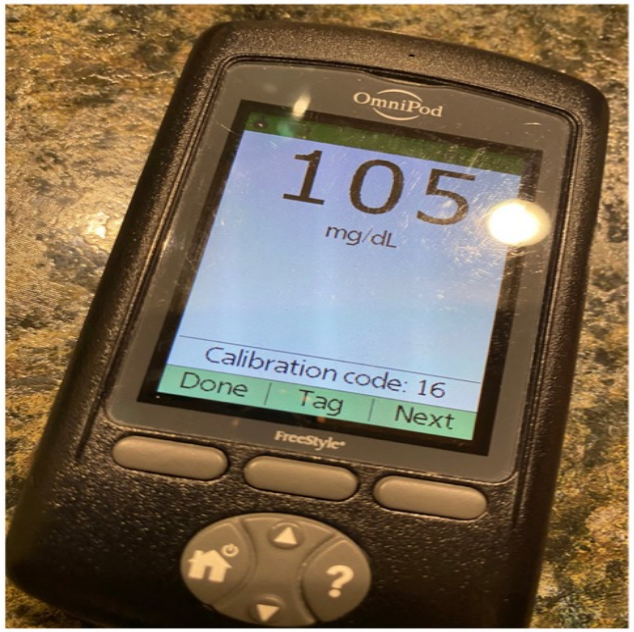
- every patient with type 1 diabetes in France who received a kidney transplant between 2000 and 2017.
- Among 2,393 patients, **327** were eligible for islet transplantation, including **47** that were actually transplanted with islets.

- The results showed a 0.47 hazard ratio for graft failure in the islet transplantation group, indicating a 53% lower risk of failure compared with the insulin-only group.
- had a higher estimated life expectancy for a 10-year follow-up (9.61 years vs 8.85 years for those on insulin alone).



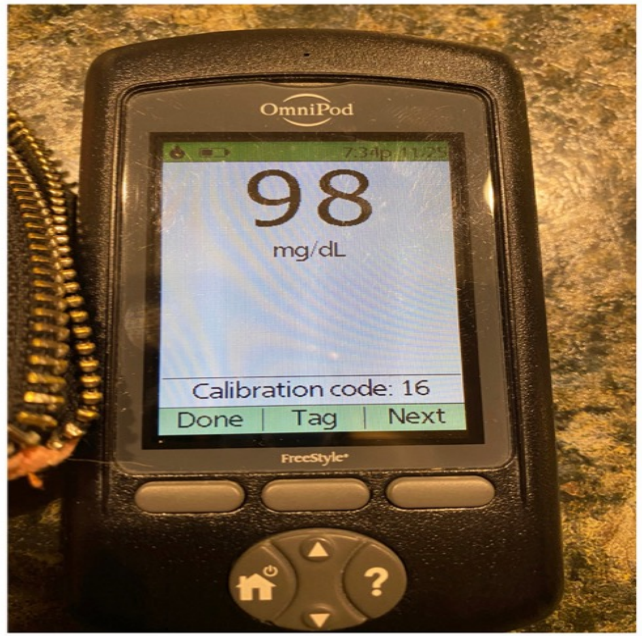
Thanksgiving Ultimate Turkey Test

Before dinner

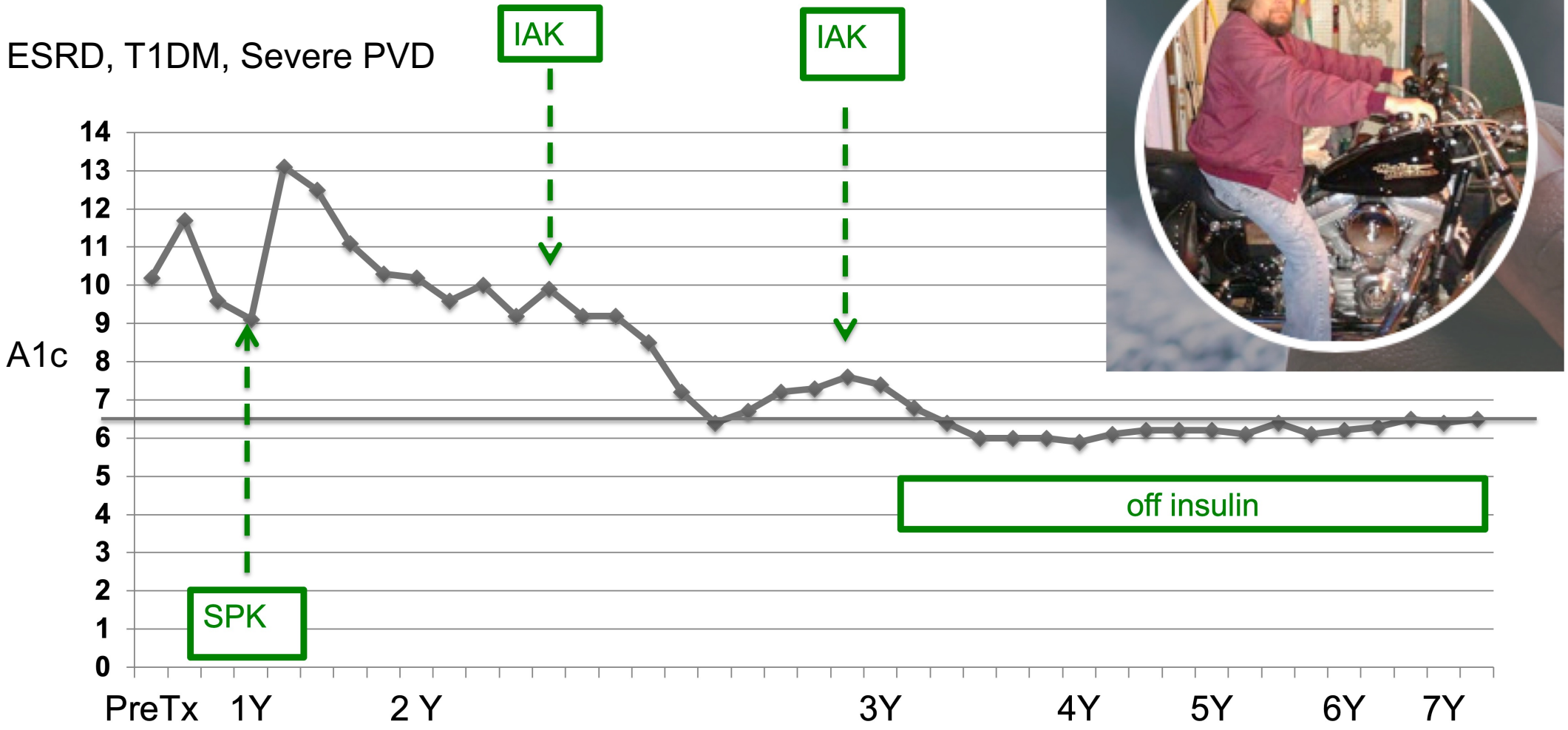


No insulin

After dinner



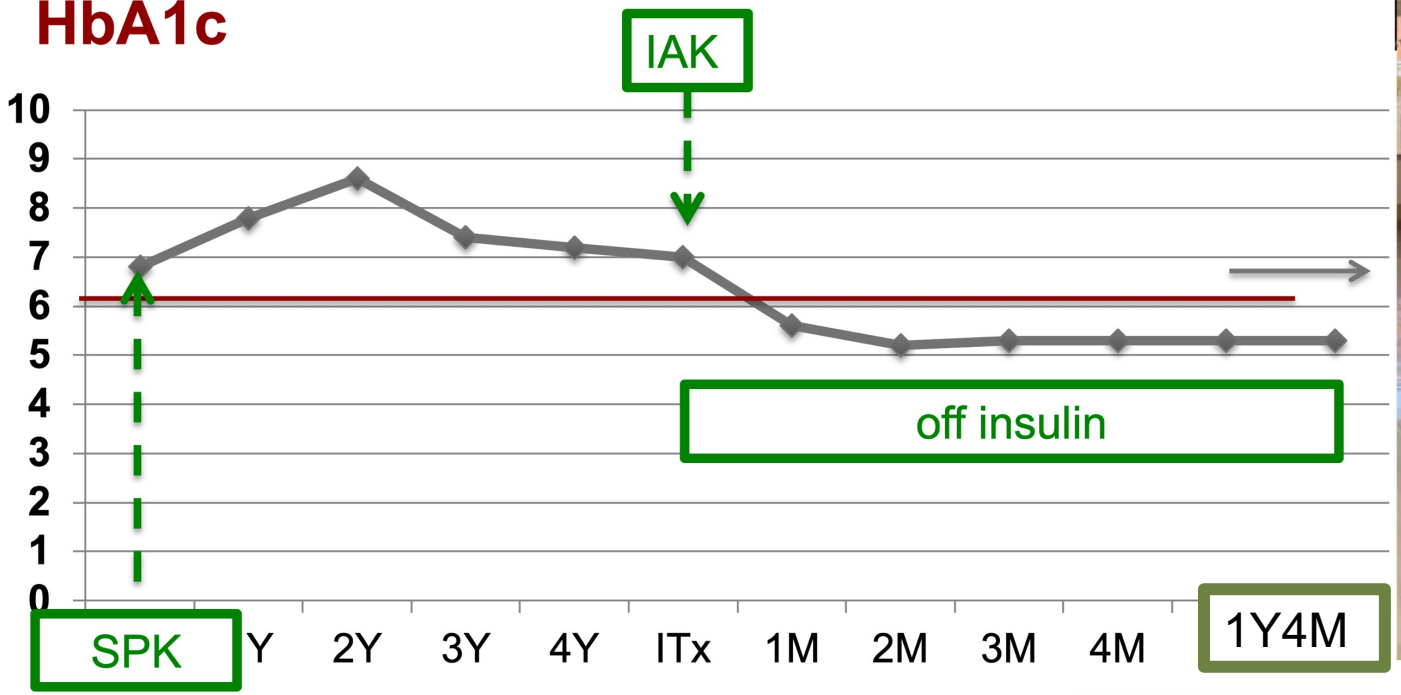
ESRD, T1DM, Severe PVD



Creatinine stable 1.0- 1.2
PRA=0

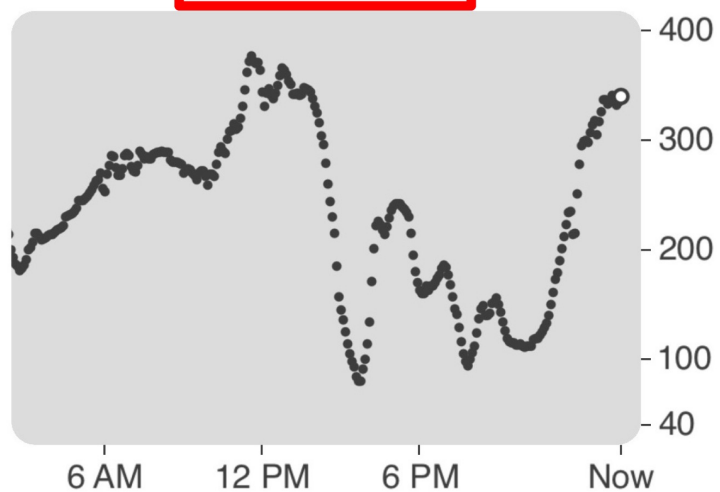
No exercise, gained 10 kg recently, has insulin resistance due steroids/prograf, needs a lot of insulin, a lot of islets (T2DM like)- > metformin

HbA1c

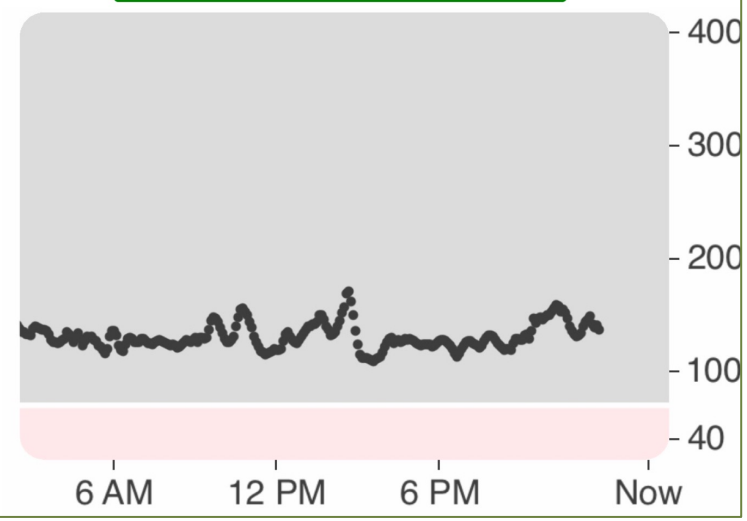


59 years old,
SPK (kidney and pancreas transplantation)
Lost pancreas Tx right away

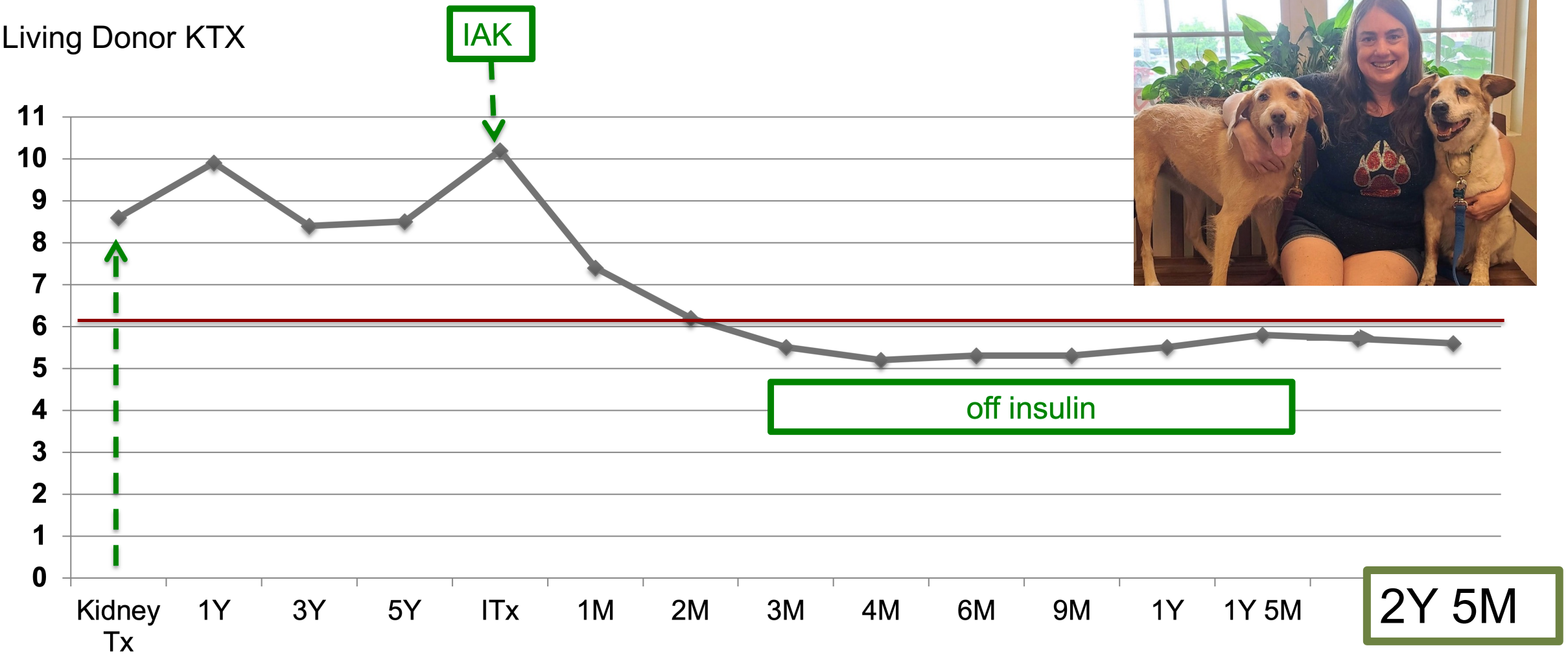
before ITx



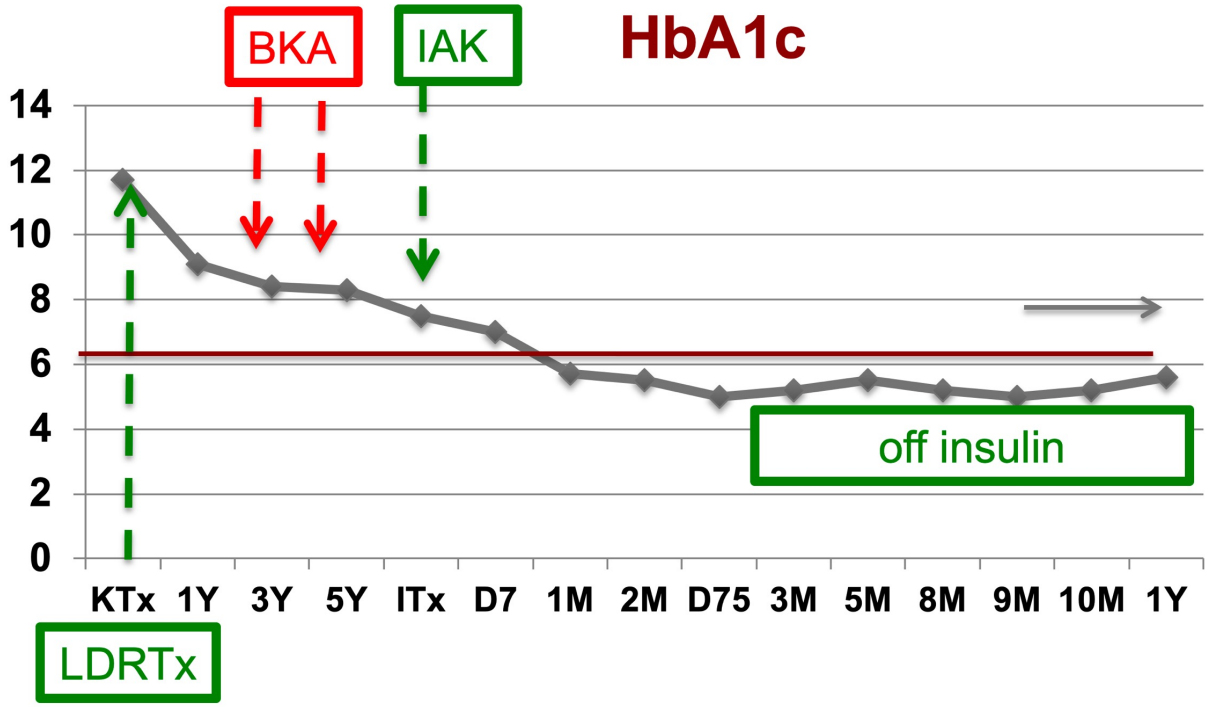
after ITx

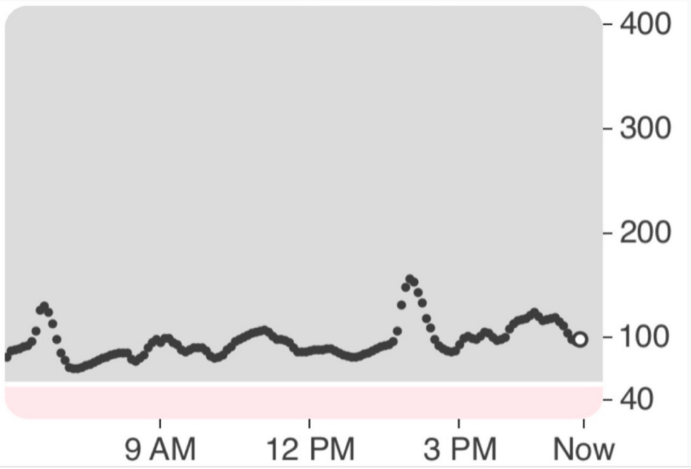


Living Donor KTX



Tac+ MPA+ Pred 5mg
Creatinine stable 1.2-1.4
PRA=0





Not SPK/PAK candidate- chronic hypotension, PVD,

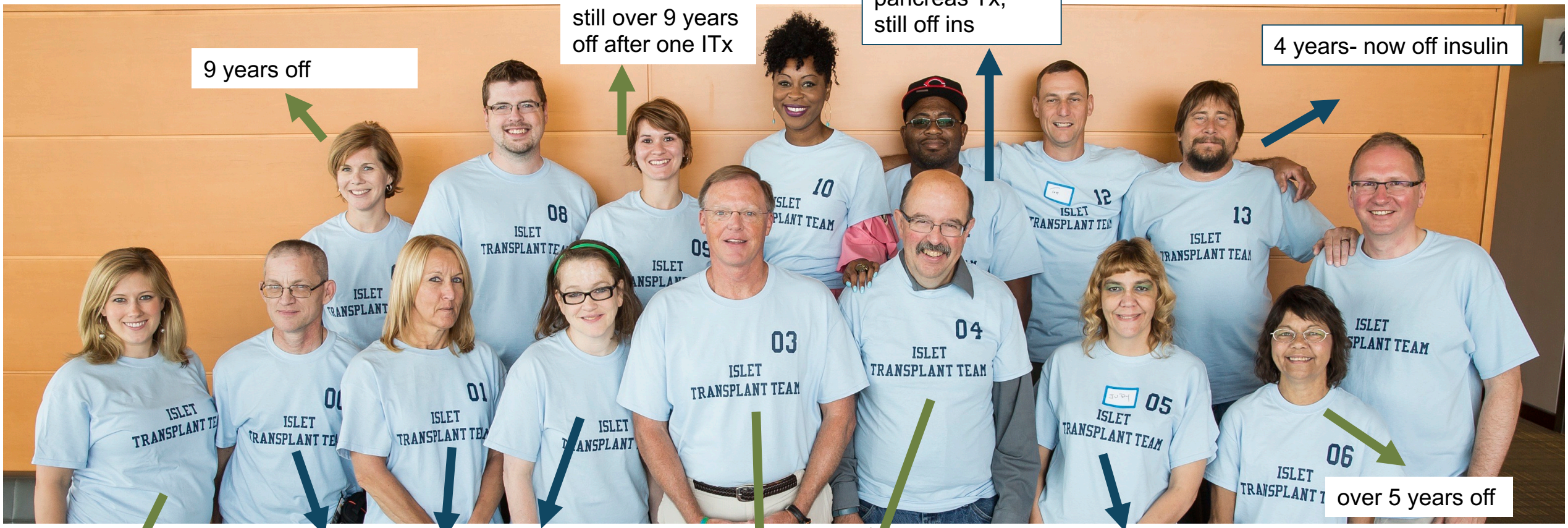
bilateral BKA

Tac+ MPA+ Pred 5mg
Creatinine stable 2.2- 2.5
PRA=0

bladder stimulator, recurrent pseudomonas UTI-> 1 year no UTI

Off insulin, 14 years after islet tx

Islet Tx Phase 3 Study, Patient Re-union, N=14 2015



- No drop out, No unexpected SAE,
- All -life changing improvement of QoL,
- 13/14 insulin independent

https://www.pwitkowski.org/islet-diabetes-patient-stories

Received: 28 December 2022 | Revised: 18 February 2023 | Accepted: 15 March 2023

DOI: 10.1111/ctr.14981

Clinical TRANSPLANTATION
The Journal of Clinical and Translational Research
WILEY

LETTER TO THE EDITOR

Peri-operative Reparixin therapy resulted in 50% 5-year insulin independence rate: The University of Chicago experience

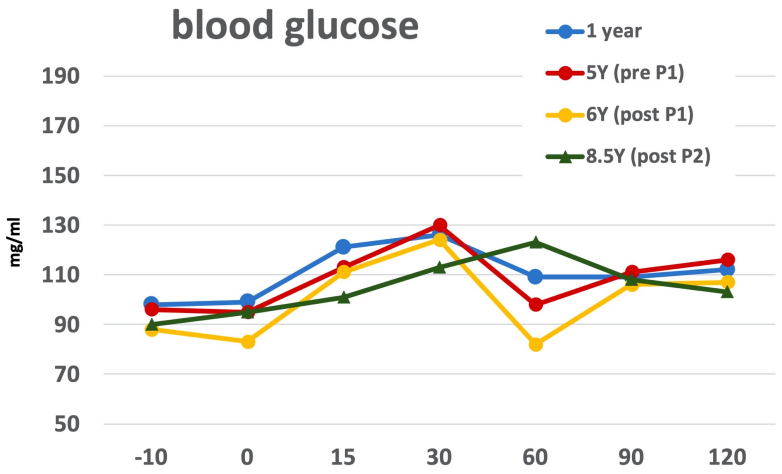
EUROPEAN JOURNAL OF TRANSLATIONAL
AND CLINICAL MEDICINE 2023;6(1):9-13

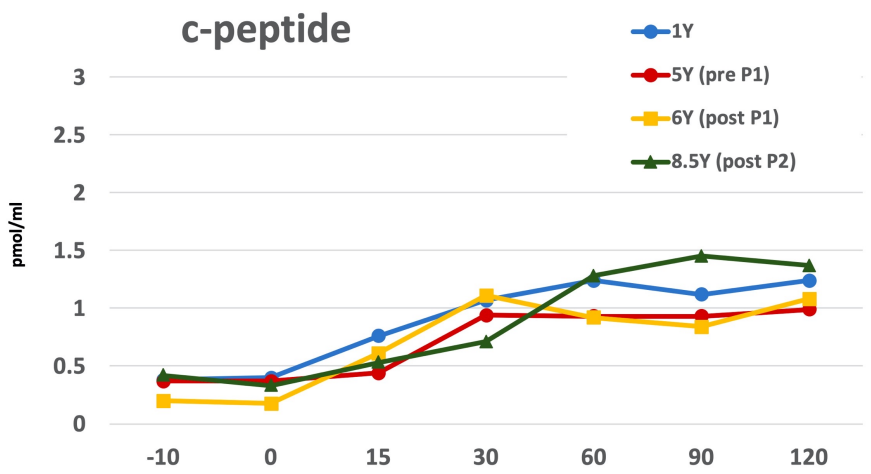
SHORT COMMUNICATION

Persistence of long-term insulin independence after islet transplantation and two subsequent pregnancies

Persistence of Long-term Insulin Independence After Islet Transplantation and **Two Subsequent Pregnancies**

- <u>Single donor islet infusion</u>
- >5 year insulin independence
- 1st pregnancy- insulin support up to 70u/day
- insulin independent after delivery
- 2nd pregnancy- insulin up to 35u/day
- Continue insulin independence >9 years after
- HbA1c <6.0 at any timepoint



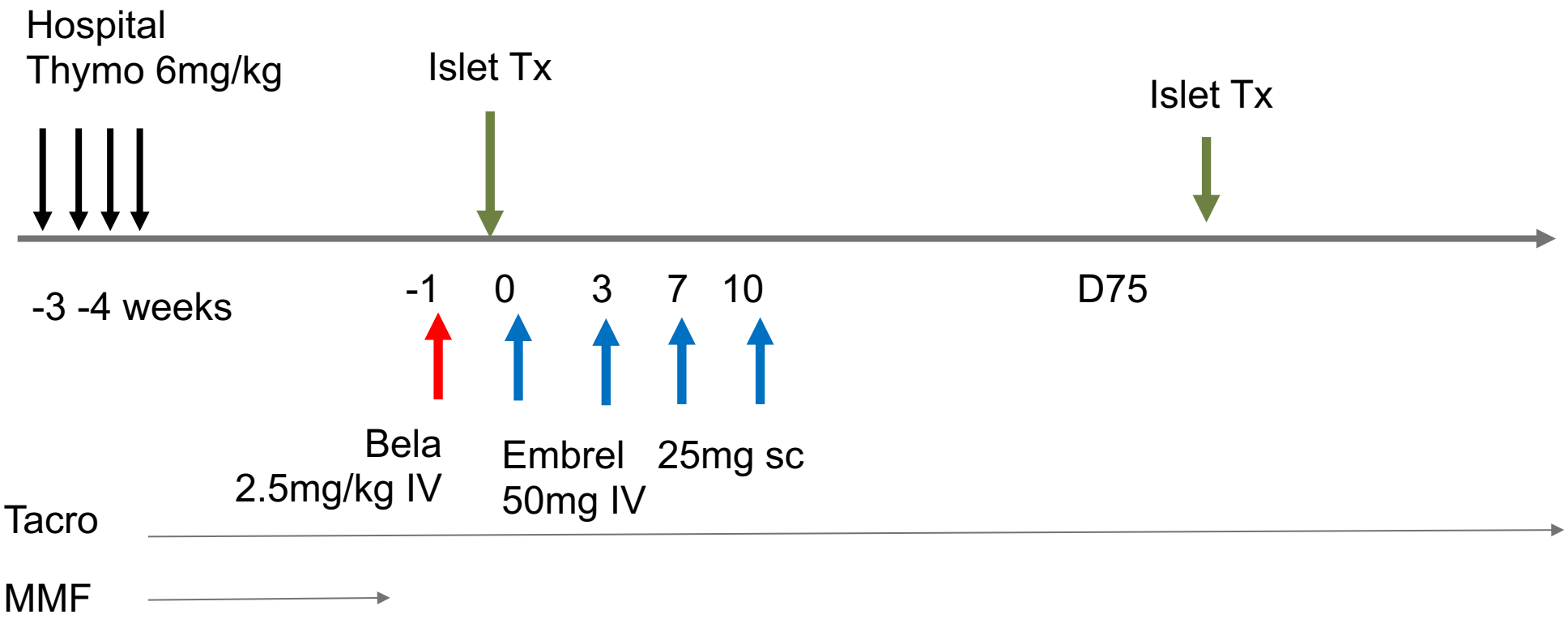


Diabetic Microangiopathy

Follow up (Years)	Time off insulin	Neuropathy	Diabetic Retinopathy
PLACEBO			
5	2.5Y	Stable	Stable (quiescent PDR)
5	2Y	Stable	Stable (quiescent PDR)
5	4.5	Stable	Stable(no DR)
4	3Y	Stable	**Improved** (mild NPDR--- None)
REPARIXIN			
2	2Y	Stable	Stable (no DR)
5	4.5Y	Stable	Stable (no DR)
4.5	4.5	Stable	Stable (no DR)
4	2.5Y	Stable	Stable (mild NPDR)
5	5Y	Stable	**Improved** (moderate—mild NPDR)
5	5Y	Stable	**Improved** (mild NPDR--- No DR)
4	9M	Stable	**Improved** (from PDR to quiescent)
3.5	**none**	**Improved**	Worsened within last year when A1c up, quiescent PDR –active OS,

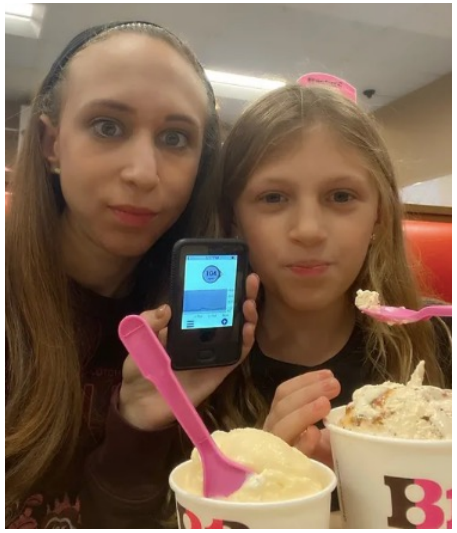
Intraportal islet transplantation

1. “traditional” ITx study (4-5 day admission) (also tx nr 3 in Sernova trial)



Ancef 1-2g IV 24hrs, after Tx Herparin drip PTT40-50, Levonox 30mg qd -> day 14

Nick
Insulin free 6Y



Aidel
insulin free 1Y3M

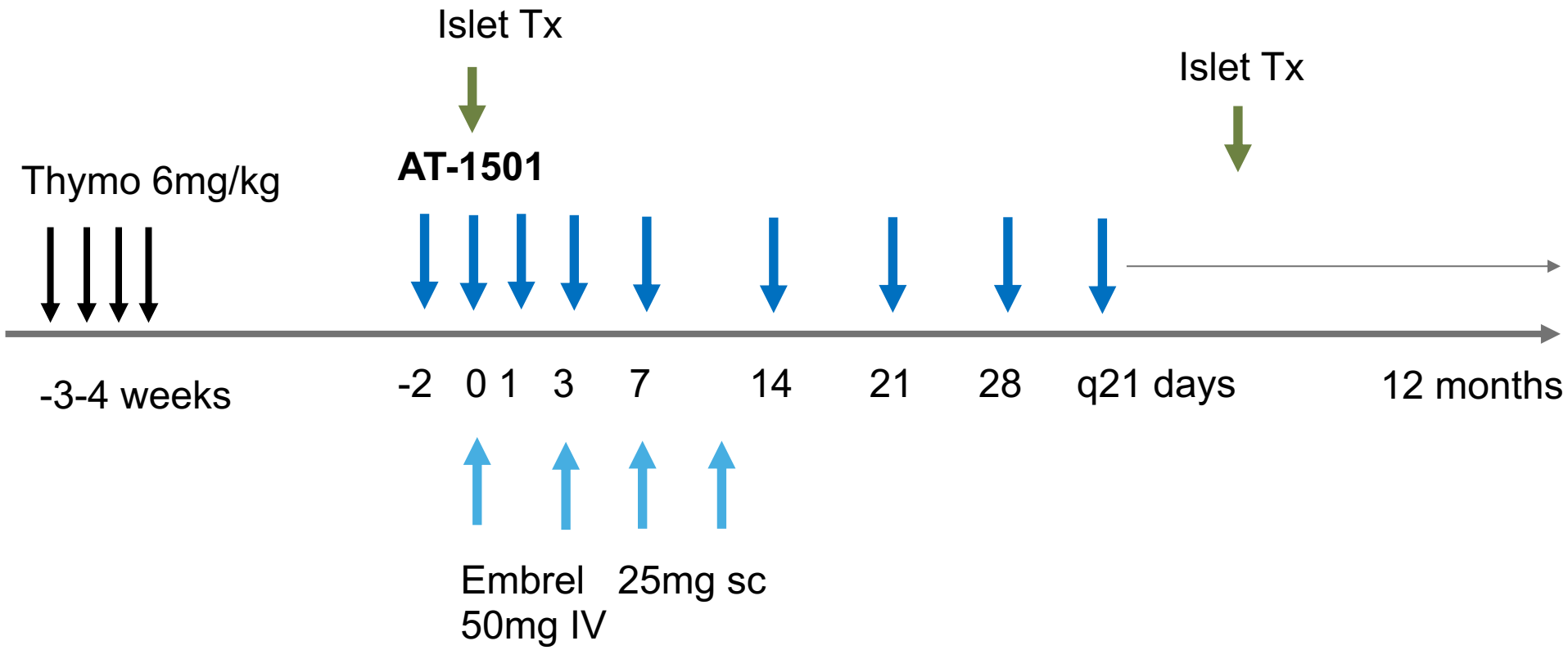
Ashley
Insulin free 1Y

Tawana
10 M

Whitney
Insulin free 10M

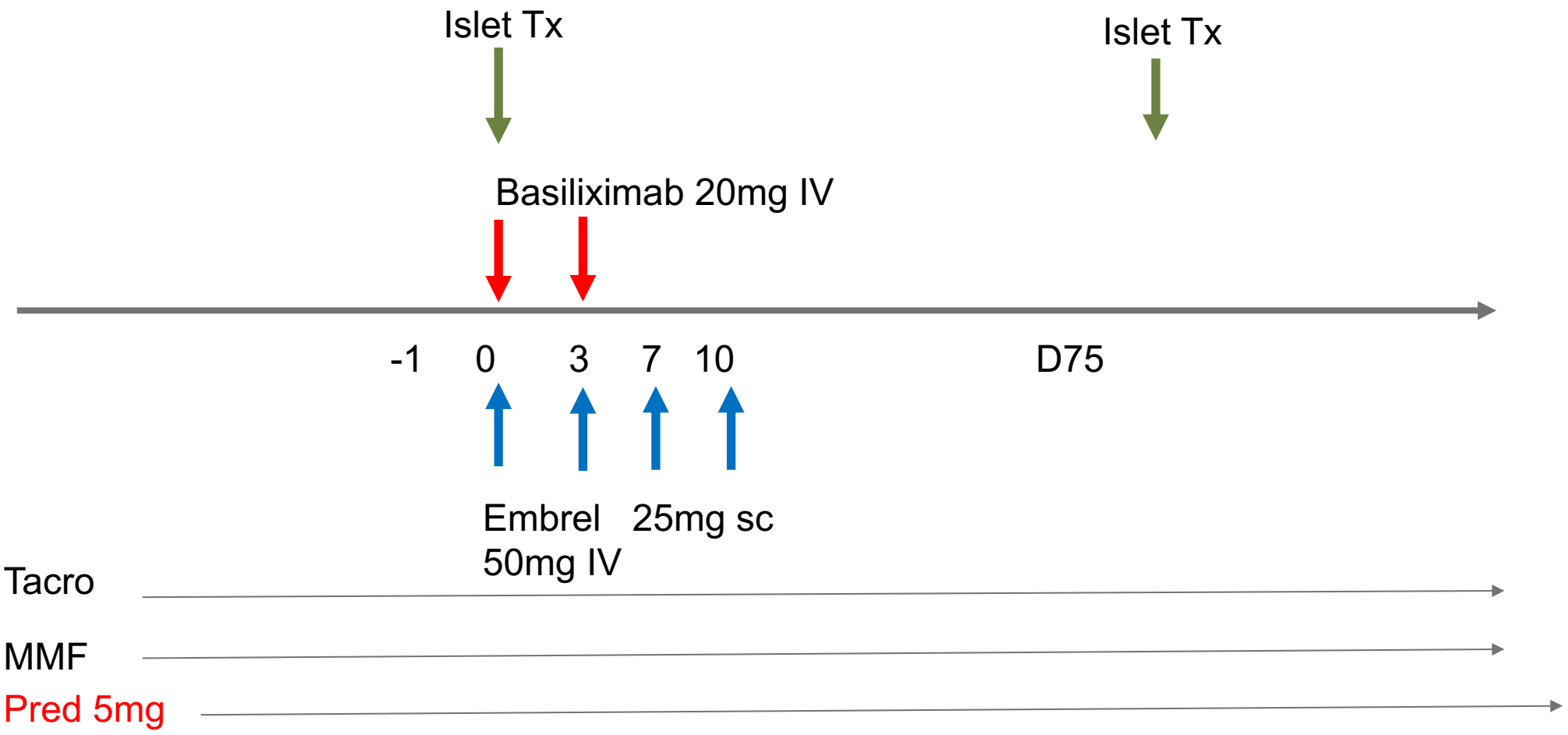
Intraportal islet transplantation

2. Eledon ITx study (5day admission)



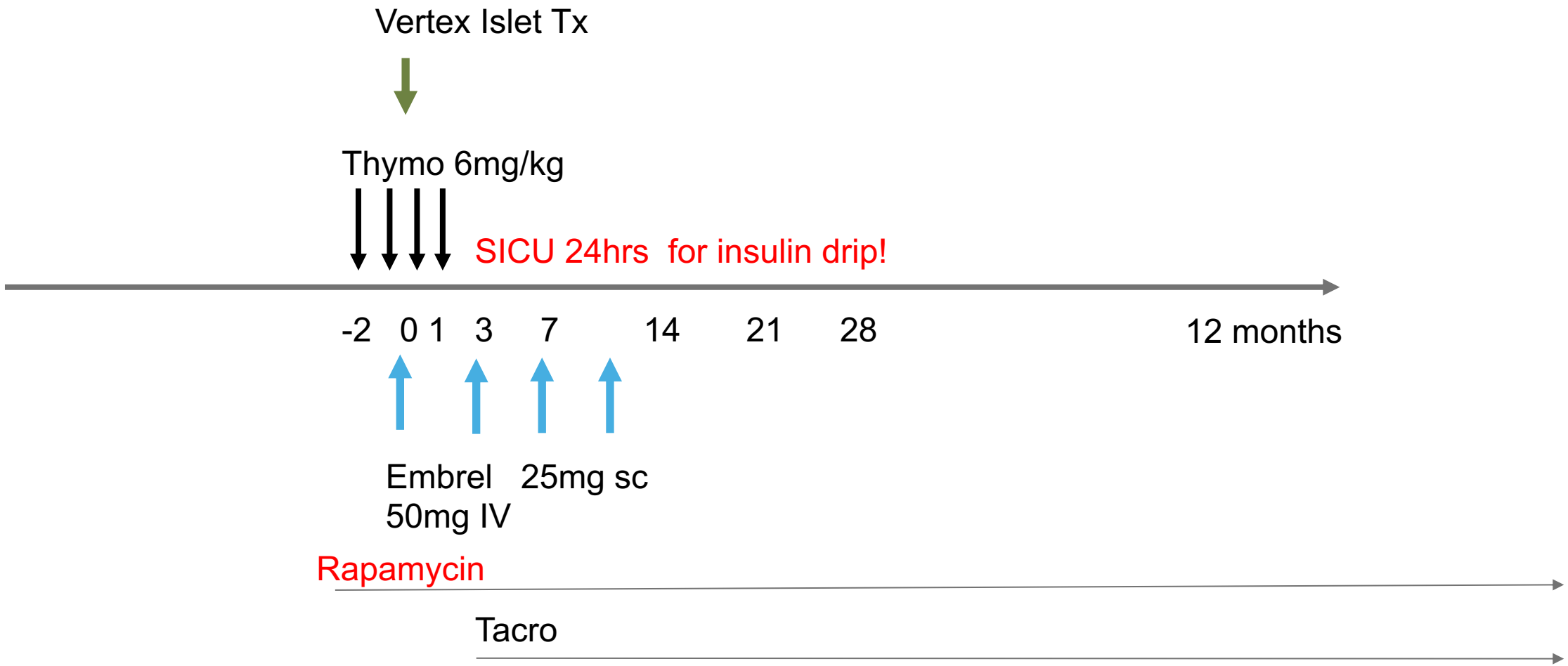
Intraportal islet transplantation

3. <u>islet after kidney</u> (4-5 day admission)



Intraportal islet transplantation

4. Vertex stem cell islets (VX-880) (8 day admission)



Ongoing clinical trials- stem cell- derived islet cell Tx

Vertex- VX 880

Single arm, open label, multicenter study testing safety, tolerability and effectiveness of the **embryonic stem cell derived islet cell Tx in patients with T1DM (VX-880)**

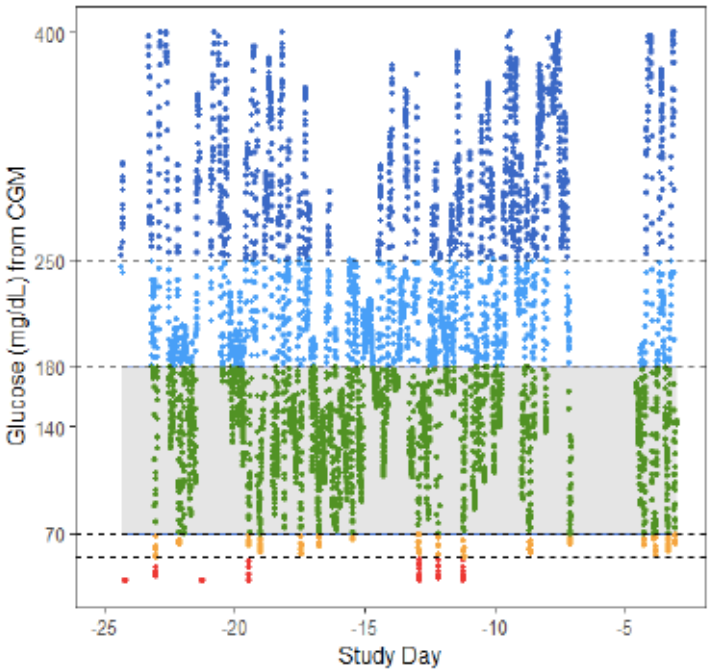
- In US: MGH , UPenn, UMiami, UChicago, NorthWestern, UWisconsin, UPittsburg, VCU
- In Canada: Montreal and Toronto

Methods

- fully differentiated stem cell derived islet cells
- Intraportal infusion
- Immunosuppression (CIT)- ATG + Embrel induction, rapamycin, low tacrolimus
- Cohort A- half cell dose, N=2,
- Cohort B- full cell dose, N=5, patient staggered, next patient over 90 days after previous patient infusion,
- Cohort C- full cell dose, N=10, non staggered- *on-going*

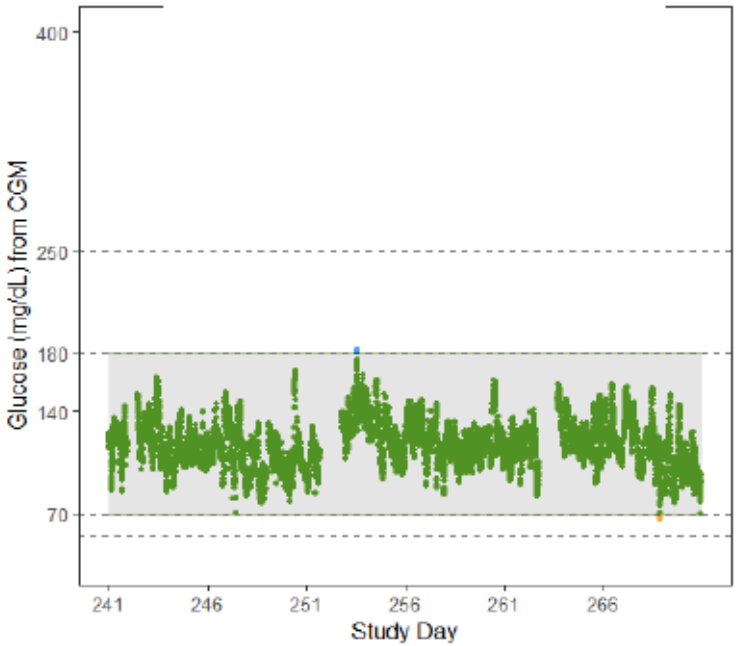
Patient 1 Achieved Insulin Independence with HbA1c of 5.2% and Time in Range 99.9% After Treatment with VX-880

Baseline



Exogenous Insulin : 34 units daily
TIR : 40.1%
HbA1c: 8.6%

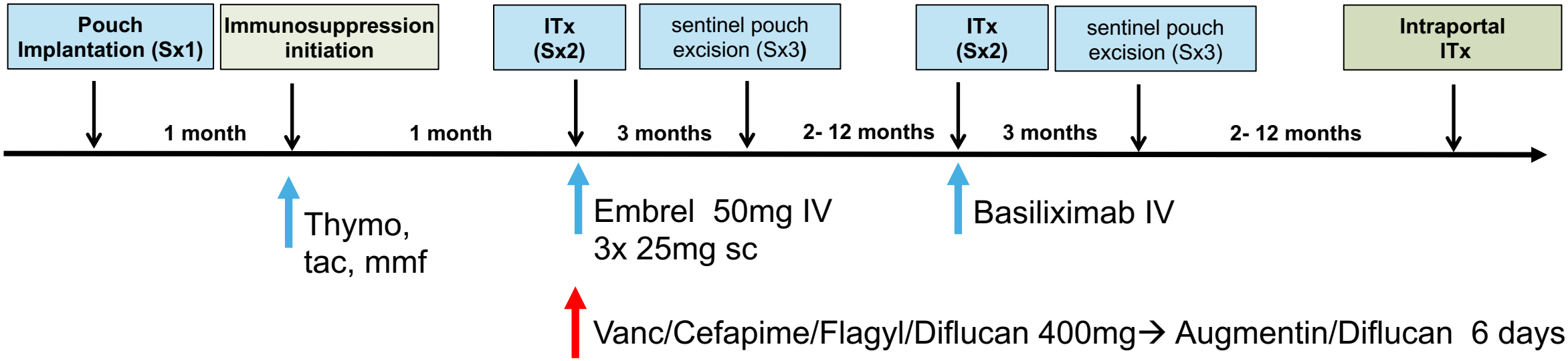
Day 241 – Day 270



Exogenous Insulin : 0 units daily
TIR: 99.9%
HbA1c: 5.2%

Glucose variability reduced from 41.8% at baseline to 13.5% at Day 270

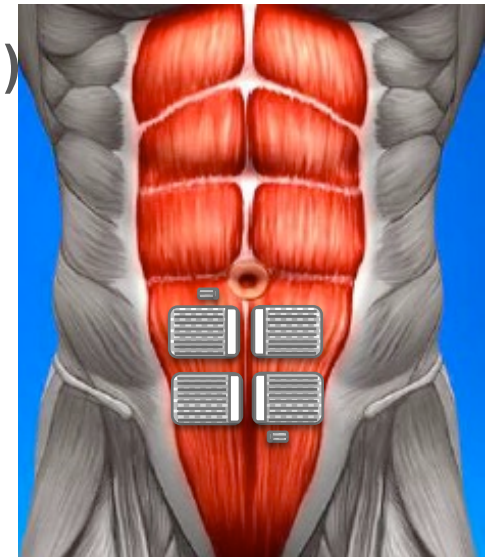
5. Sernova pouch study



Multi-Cohort Trial Design

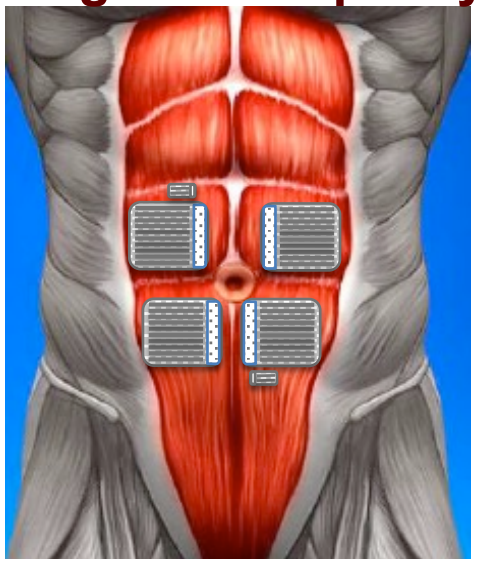
COHORT A *(n=6)*

- Enrolment completed
- 8-Channel Cell Pouch
- Mini (1-Channel Sentinel)
- Immunosuppression
  - Thymo ->
  - Tacrolimus
  - MMF
  - Etenarcept



COHORT B *(n=7)*

- 6 of 7 enrolled
- 10-Channel Cell Pouch (>50% greater capacity)
- 2-Channel Sentinel
- Immunosuppression
  - Thymo ->
  - Belatacept
  - ↓Tacro
  - Etenarcept



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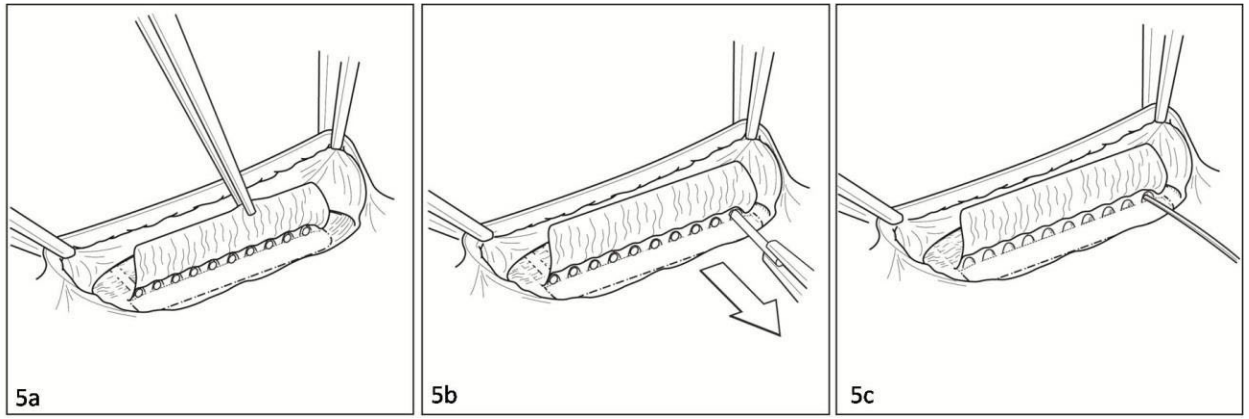
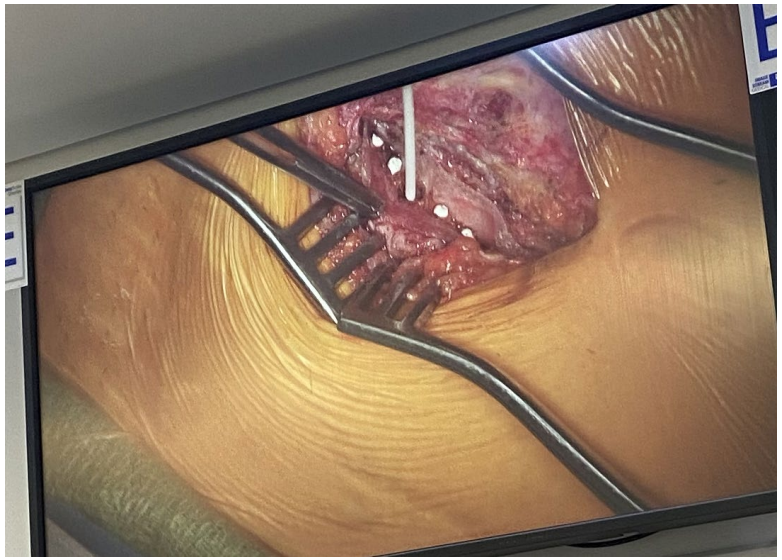
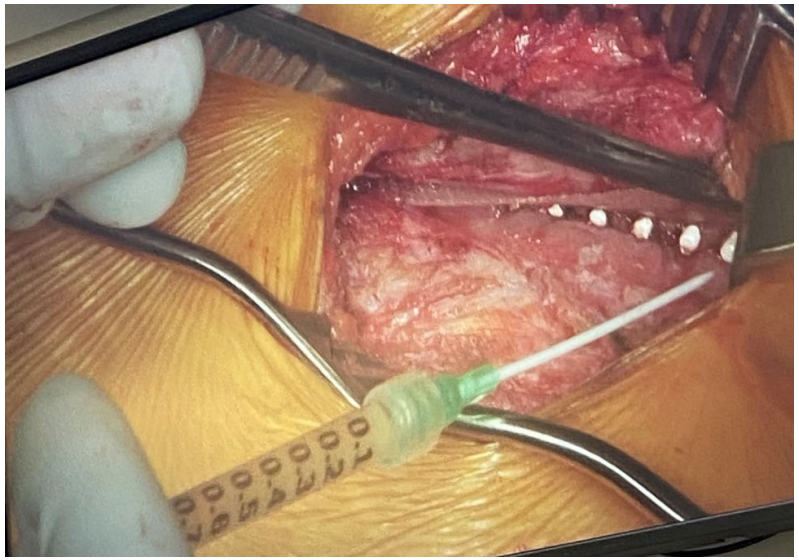
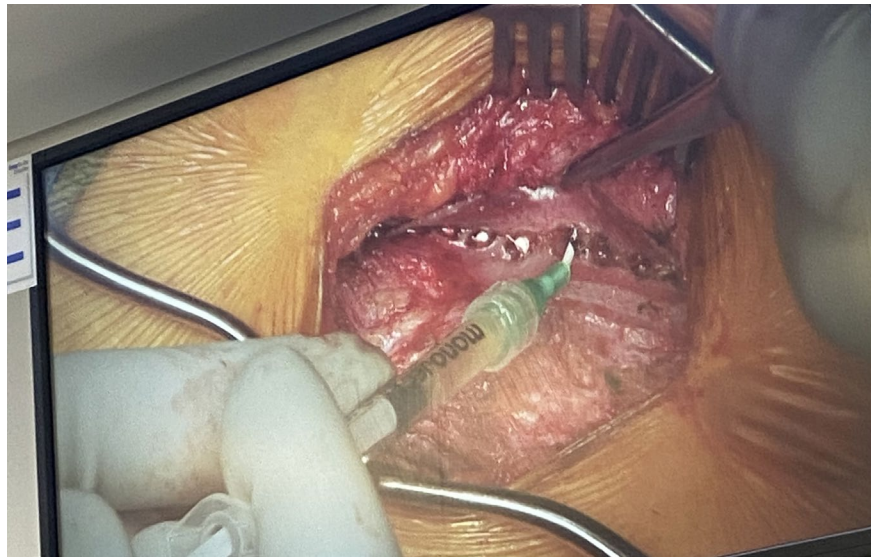
UChicago Medicine | Piotr Witkowski Lab

Islet Transplant to Cell Pouch

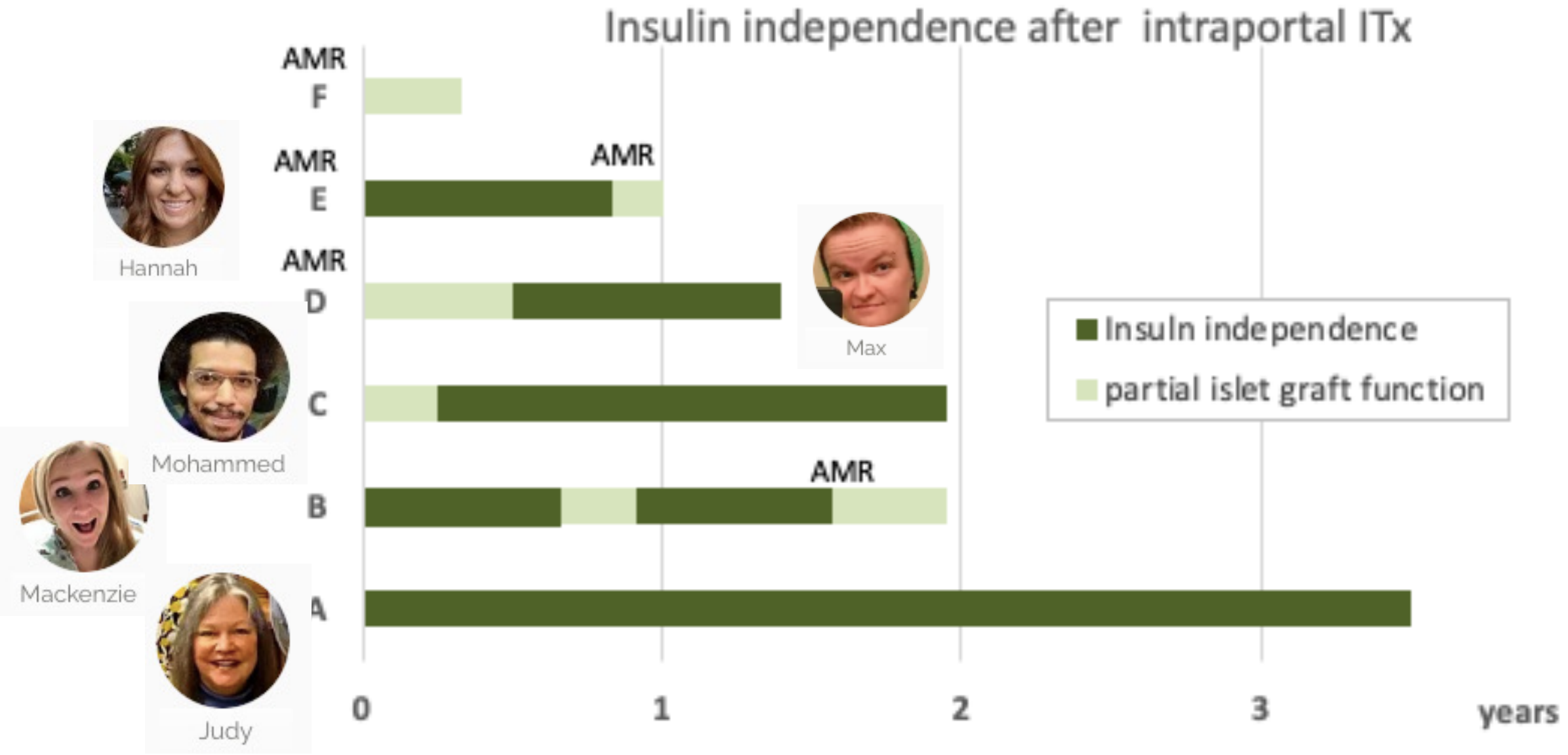








Sernova Pouch trial



Islet in pouch Tx

4. Vertex pouch study (VX-264)

- No immunosuppression
- Day -1 admission
- Day 0 transfer to the SICU for insulin drip and stay 24 hrs there after Sx
- PACU abd. ultrasound to assess location of the device
- Day 2-3 DC

Viacyte- VX 264

- Phase 1/2,
- T1DM without SHE,
- blood type A, AB
- US (U Miami, MGH, U Pittsburg, U Chicago), Canada (Edmonton, Toronto, Montreal), Europe (Netherlands)
- Islets in immuno-protective pouch
- Implanted in pre-peritoneal space

THANK YOU FOR YOUR CONTINOUS SUPPORT!