MedStar Georgetown Transplant Institute

Knowledge and Compassion
Focused on You

November 13, 2020

Advances in Organ Transplantation

Matthew Cooper, MD
Director, Kidney and Pancreas Transplantation
Medstar Georgetown Transplant Institute
Professor of Surgery
Georgetown University School of Medicine

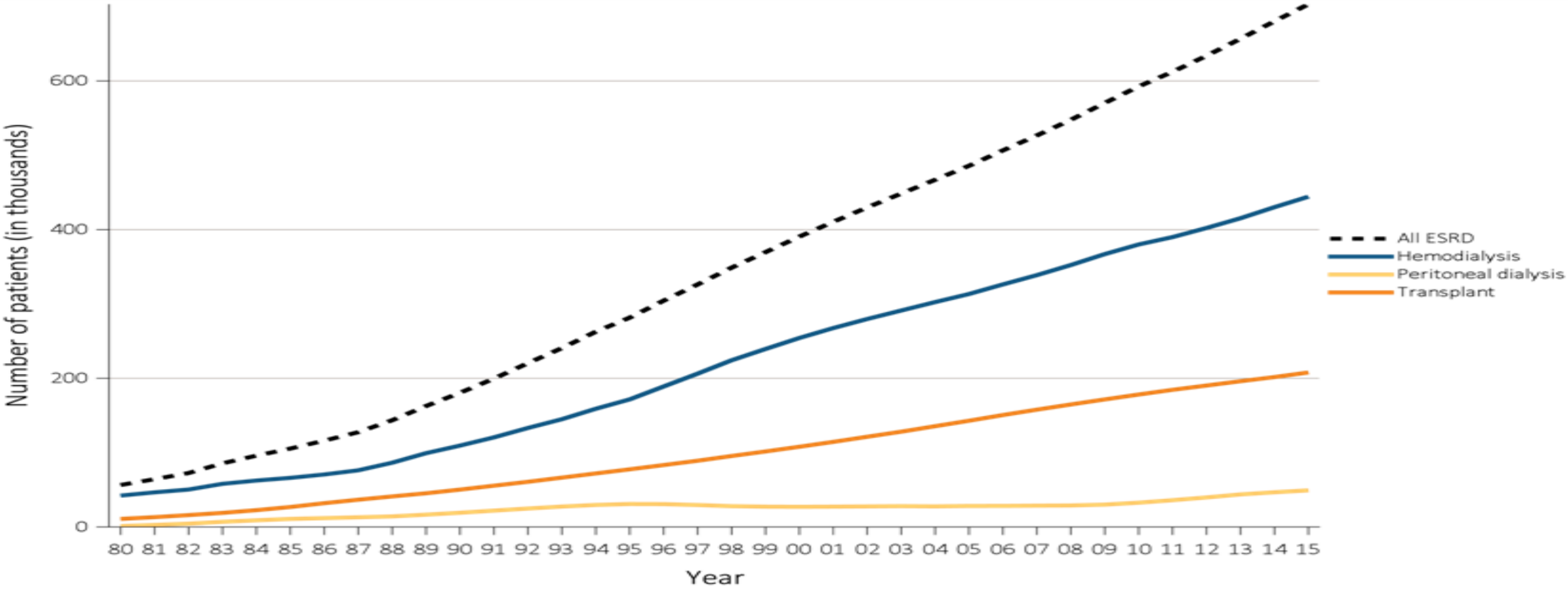
Learning Objectives

- Explore advances and current innovations in abdominal transplantation.
- Review the most current guidelines released by the PHS on assessing donors to increase utilization of increased risk organ donors.
- Review the upcoming change in allocation of kidney and pancreata toward elimination of geographic disparities in organ allocation.
- Identify technologies for increasing donor organs outside of the conventional allograft paradigm, such as organogenesis, biologic scaffolding, and cloning.

HOW ABOUT THE PRESENT!

…Why do we always seem to be talking about the future???

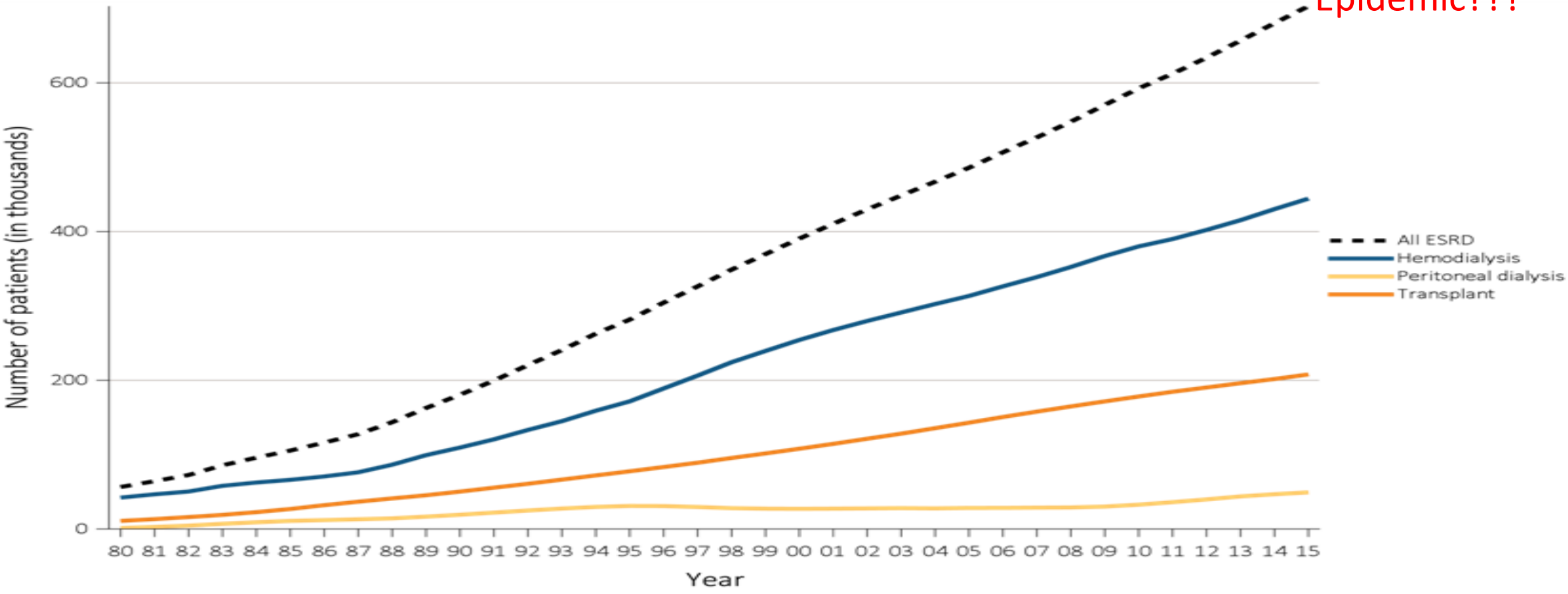
Growing Incidence of ESRD



Data Source: Reference Table D.1. Abbreviation: ESRD, end-stage renal disease.

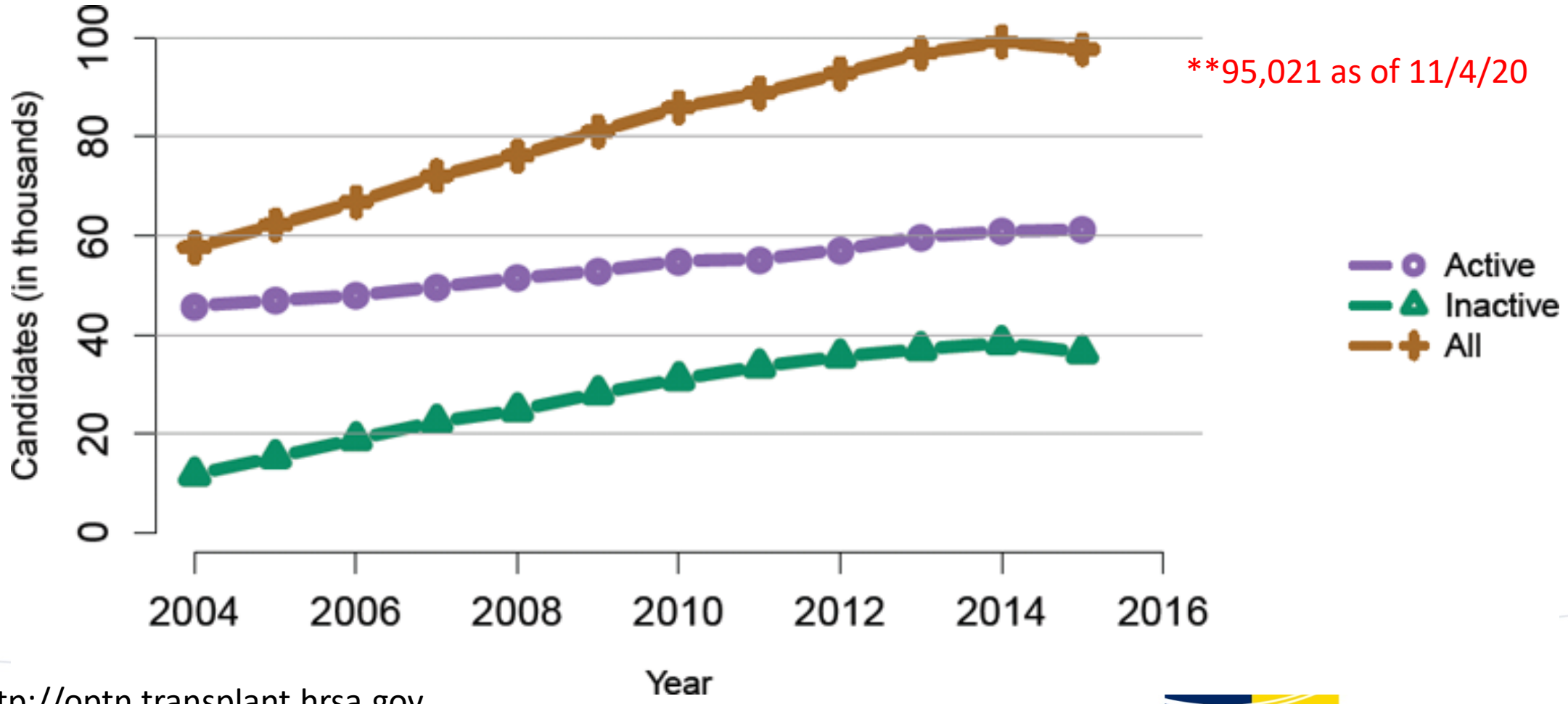
Growing Incidence of ESRD

Epidemic???



Data Source: Reference Table D.1. Abbreviation: ESRD, end-stage renal disease.

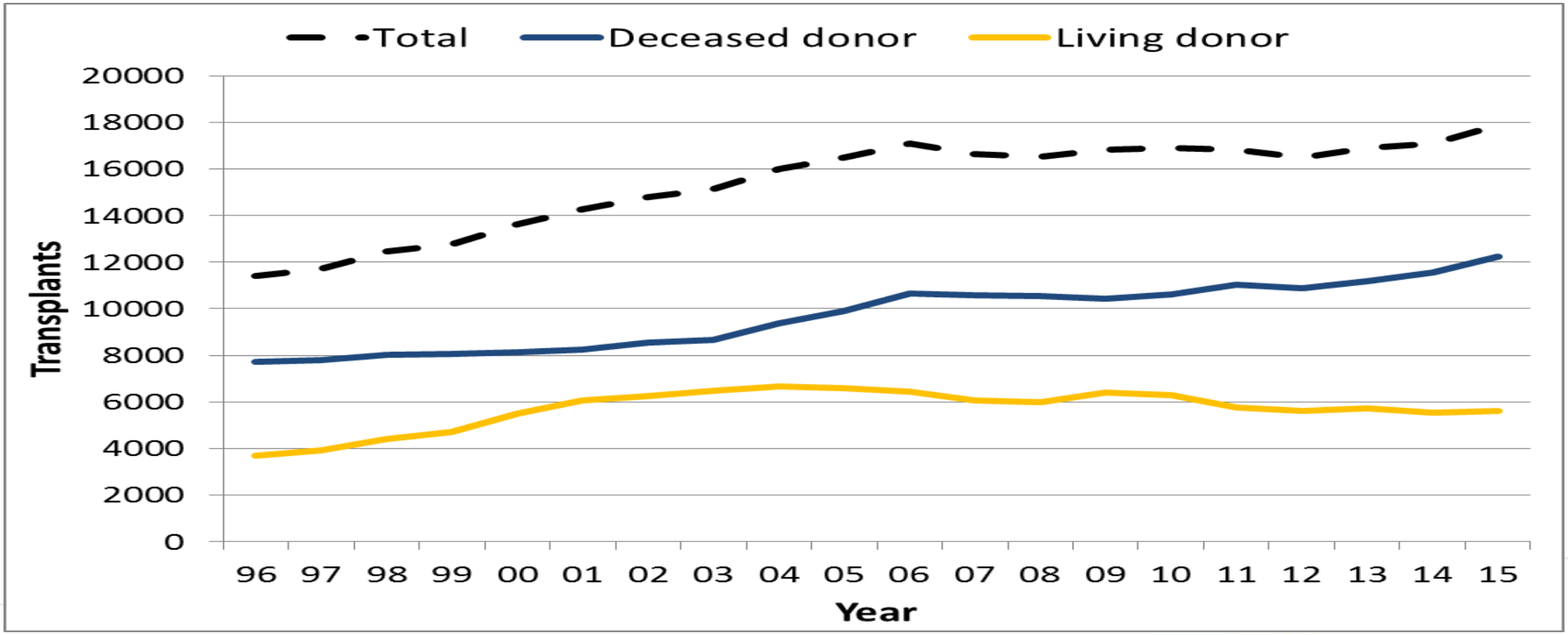
The Growing Waiting List



**95,021 as of 11/4/20

Ref: http://optn.transplant.hrsa.gov

Kidney Transplant Totals



Ref: http://optn.transplant.hrsa.gov/

WHAT SEEMS LIKE THE FUTURE??

HIV Organ Policy Equity Act

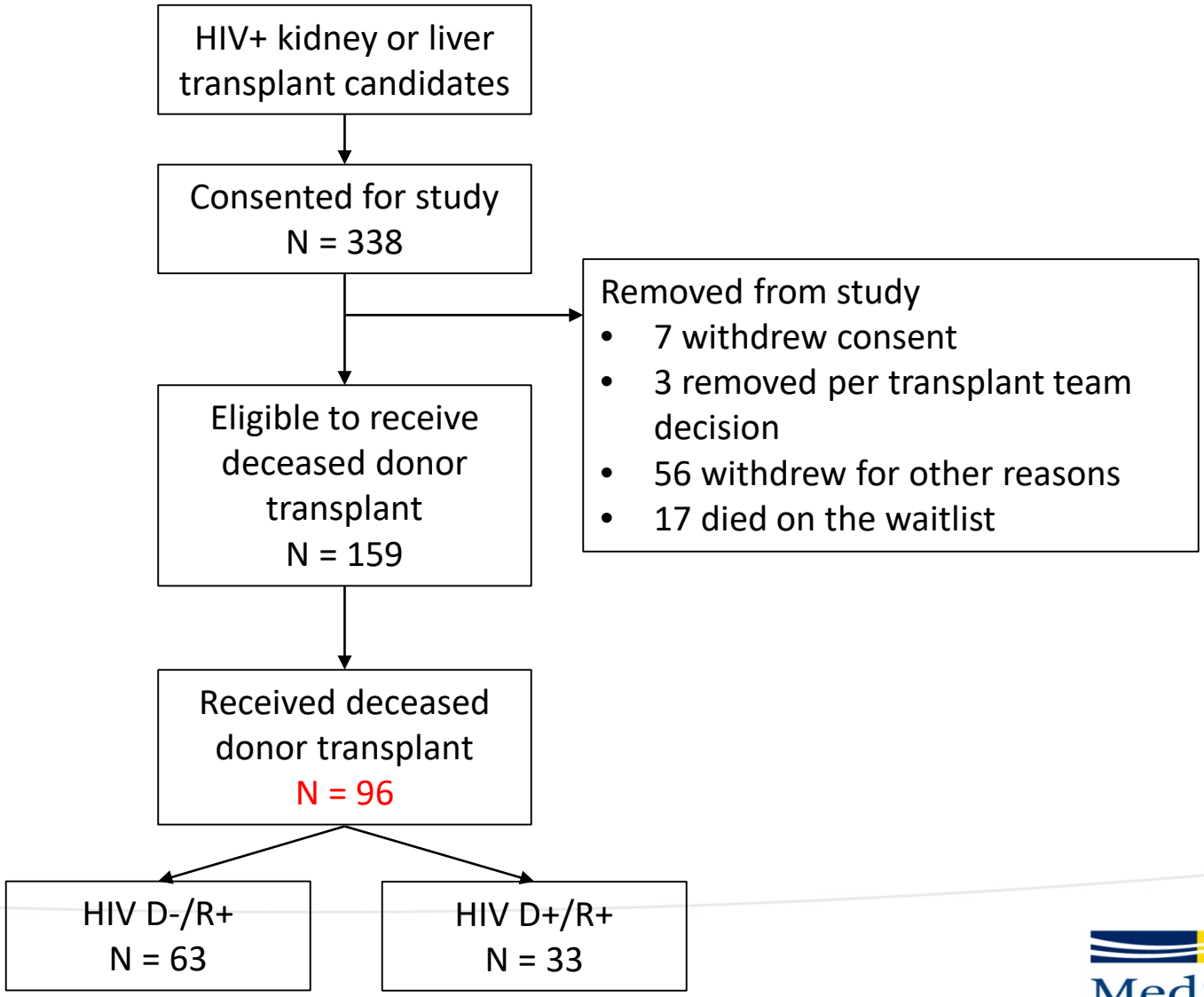
HIV Organ Policy Equity (HOPE) Act is Now Law

NOVEMBER 21, 2013 AT 7:25 PM ET BY DR. GRANT COLFAX

Summary: President Obama signs into law the HIV Organ Policy Equity (HOPE) Act, bipartisan legislation that updates regulations from 1988 to reflect our advances in understanding and treating HIV

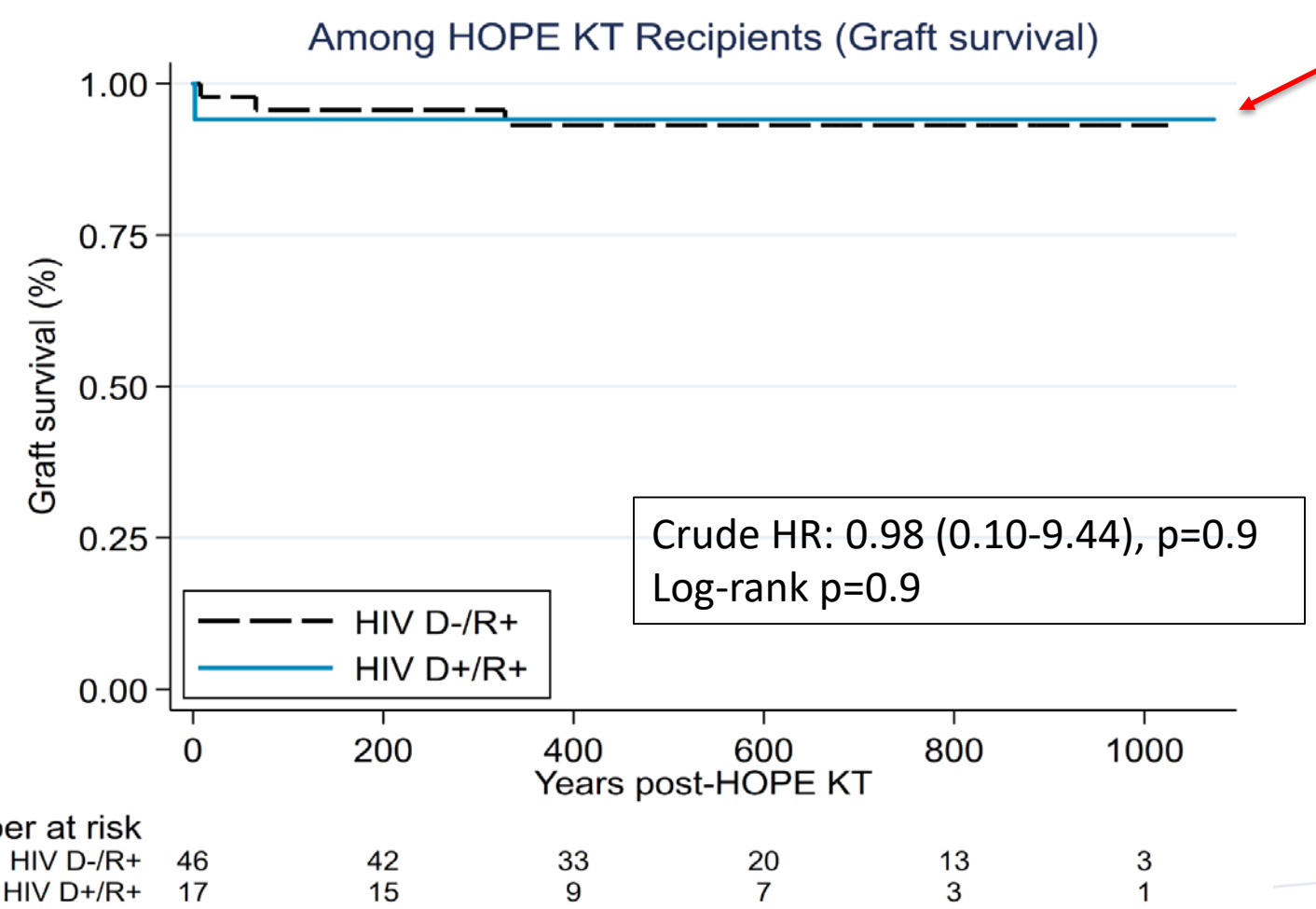
President Barack Obama signs S. 330: HIV Organ Policy Equity Act during a signing ceremony in the Oval Office, Nov. 21, 2013. (Official White House Photo by Lawrence Jackson)

U.S. Enrollment



HIV+ kidney-only transplant recipients

Return to dialysis or re-transplant



indistinguishable

HOPE deceased kidney donors (N=71)

Factor	HIVD-	HIVFP	HIVD+	p-value
	36	14	21	
Organs used				<0.001
Kidney(s)-only	27 (75%)	6 (43%)	4 (19%)	
Liver-only	5 (14%)	2 (14%)	6 (29%)	
Both	4 (11%)	6 (43%)	11 (52%)	
Age, median (IQR)	31.5 (27, 39.5)	29.5 (20, 41)	32 (27, 42)	0.7
Male sex	22 (61%)	9 (64%)	15 (71%)	0.8
Race				0.5
White/Caucasian	20 (56%)	7 (50%)	8 (38%)	
Black/African American	12 (33%)	4 (29%)	11 (52%)	
Asian	1 (3%)	0 (0%)	0 (0%)	
Hawaiian	1 (3%)	0 (0%)	0 (0%)	
Other	2 (6%)	3 (21%)	2 (10%)	
Ethnicity				0.2
Hispanic/Latino	2 (6%)	3 (21%)	2 (10%)	
Not Specified/Unknown	34 (94%)	11 (79%)	19 (90%)	

EDITORIAL

AJT

HIV-positive deceased donor–to–HIV-positive recipient kidney transplantation: The HOPE must go on

Nuria Montero[1,2]
Francesc Moreso[3]
Josep M. Cruzado[1,2,4]

Considering the mortality of HIV+ patients on the waitlist and the benefits and risks shown in the HOPE Act of the United States, the use of HIV+ donors provides a valuable pathway to expand the donor pool. Thus, in resemblance with the Queen rock band song "The Show Must Go On," we could claim that "The HOPE must go on."

HCV + → HCV- Transplantation

HCV- Participant Inclusion Criteria

- On deceased donor transplant waitlist at JHU
- On dialysis or GFR < 15 ml/min
- ≥ 50 years old
- HCV-

HCV+ Donor Inclusion Criteria

- Age 13-50
- Creatinine < 3.0 mg/dL, normal renal biopsy
- **Qualitative** HCV NAT+, UNOS screening test
- HCV genotype sent to commercial lab

HCV D+/R- Transplant N =10

GZR EBR on call to OR
Daily for 12 weeks

GT1a

NS5a resistant variants

Yes

Add ribavirin
Treat for 16 weeks

No

GT1b, 4

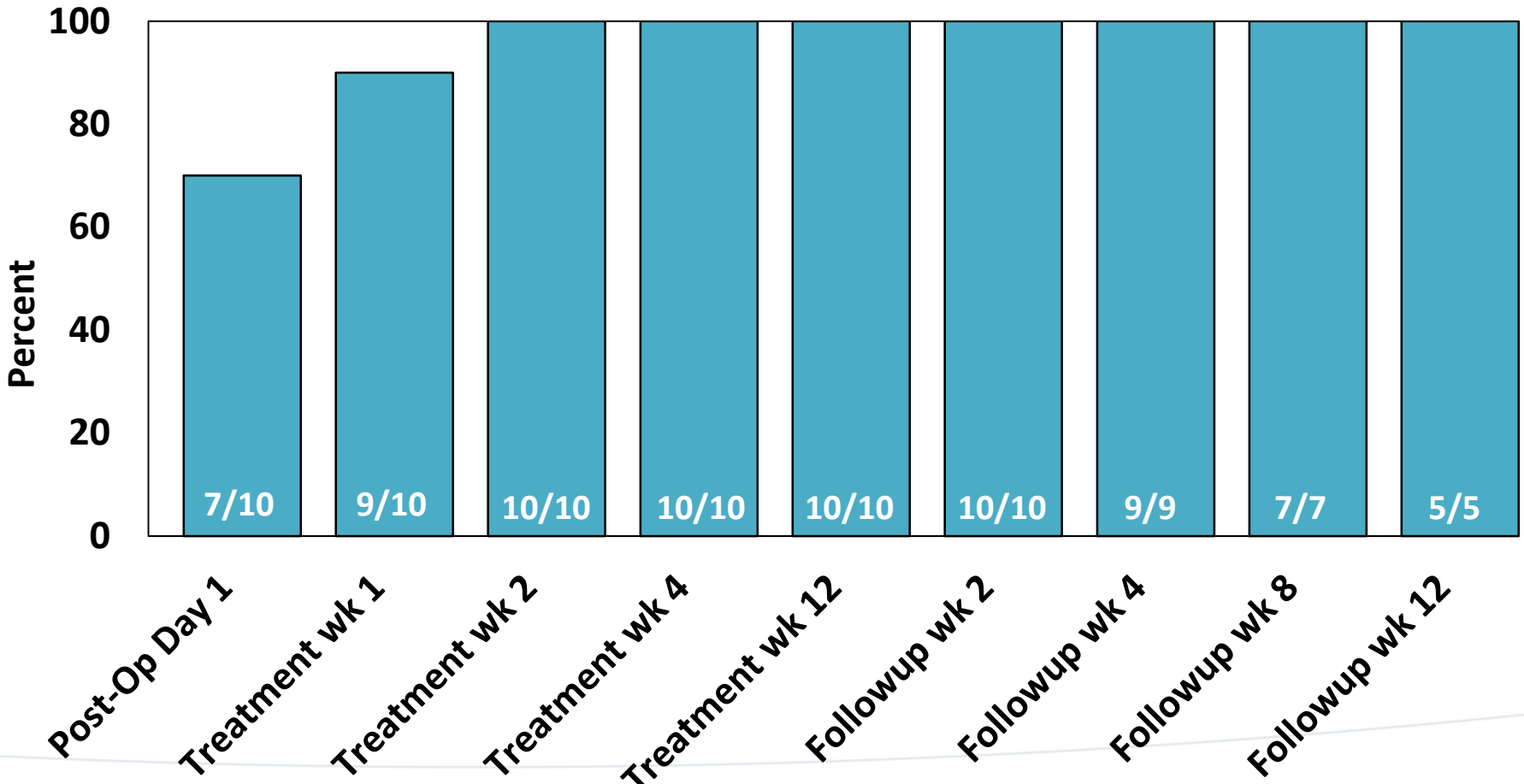
No change

GT2, 3

Add sofosbuvir
Treat for 12 weeks

Excellent Patient Results

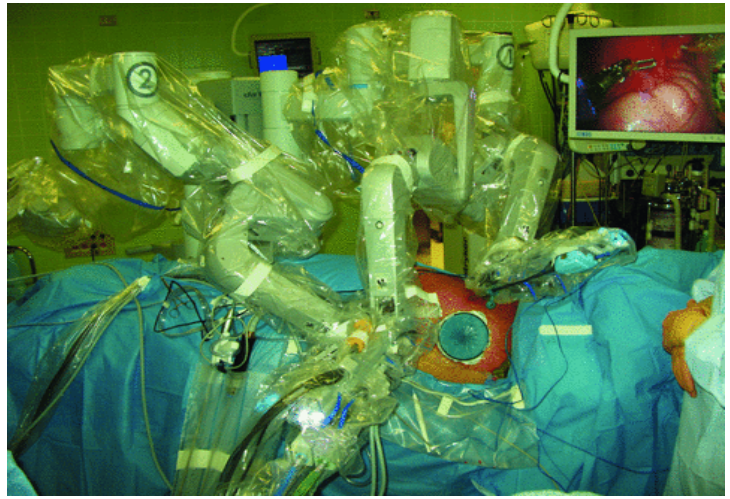
Percent with undetectable HCV RNA at each visit

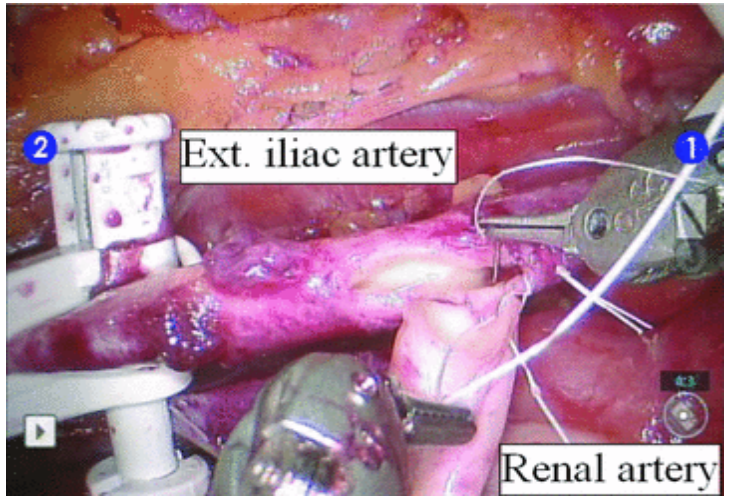


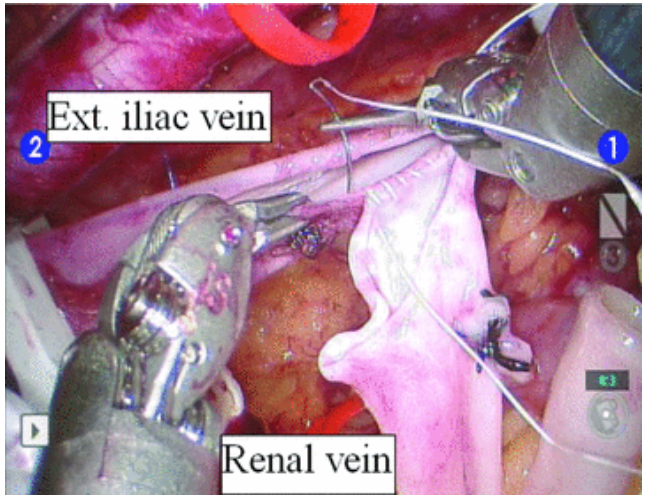
Robotics – Donors and Recipients

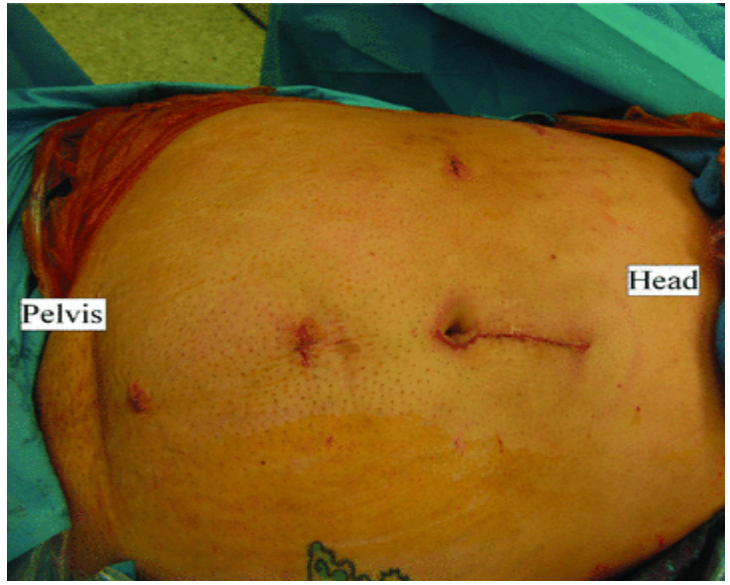
Robotic Trans-abdominal Kidney Transplantation

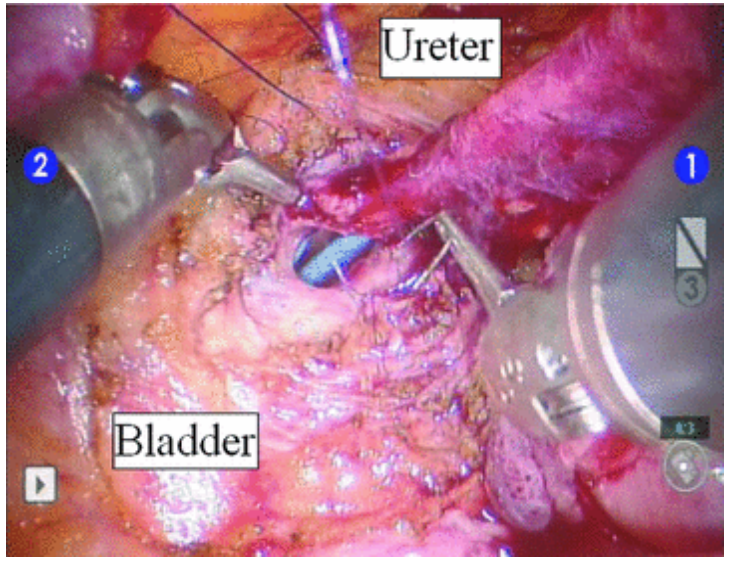
Robotic Transabdominal Kidney Transplantation











Giulianotti et al: AJT 2010, 10(6):1478-1482

Face Transplant Research

Vascularized Composite Allotransplantation (VCA)

EXPERIMENTAL

Facial Subunit Composite Tissue Allografts in Nonhuman Primates: I. Technical and Immunosuppressive Requirements for Prolonged Graft Survival

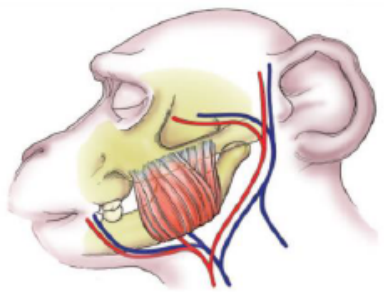


Fig. 1. Donor composite facial graft (*above*) and schematic (*below*) outlines. The osteomyocutaneous facial segment was based on the common carotid artery and both jugular veins, and included the facial, transverse facial, and superficial temporal arteries.

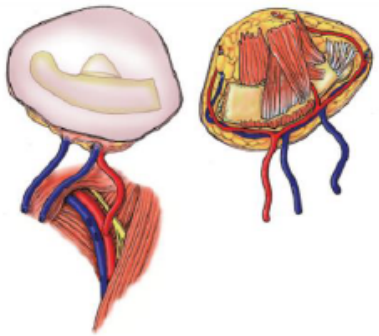


Fig. 2. Intraoperative photographs (*above*) and schematic drawings (*below*) of facial subunit depicting bone, muscle, and skin; the common carotid artery; and the internal and external jugular veins.

Barth *et al*, Plast. Reconstr. Surg. 123: 493, 2009.

- $12M Funding over 12 yrs
- Active grants
  - Consortium with Duke, Penn, Louisville
  - Collaboration with Walter Reed
- Trained 13 fellows (2-YR)
  - 4 academic surgeons
- Trained 8 students
  - All enrolled/headed to medical school/surgical careers
- Two new faculty recruits experienced in abdominal wall and GU VCA

CDMRP

VCA^{ci} Vascularized Composite Allotransplantation Collaborative Initiative

USU Uniformed Services University

Face Transplant Research

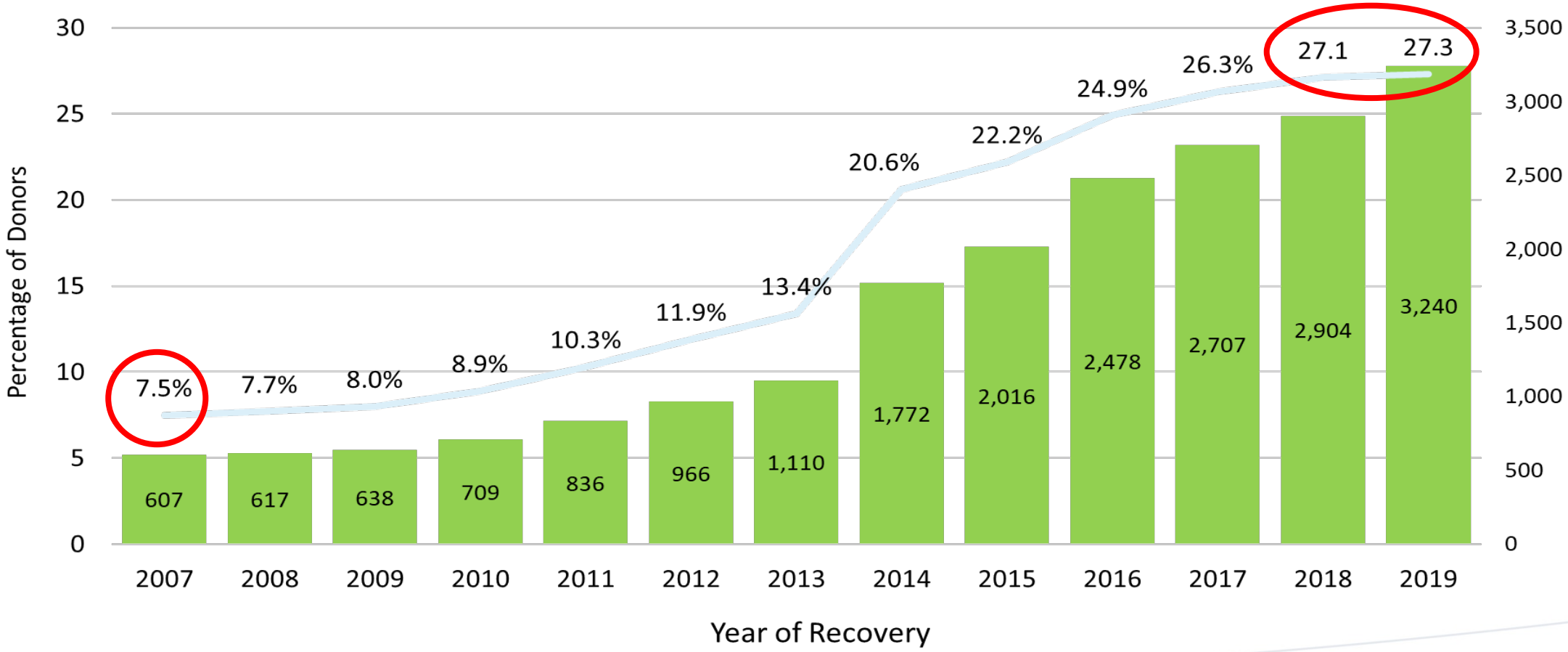
Vascularized Composite Allotransplantation (VCA)

ALIGN OPTN POLICY WITH U.S. PUBLIC HEALTH SERVICE GUIDELINE, 2020

Align OPTN Policy with U.S. Public Health Service Guideline, 2020

- Aligns policy language to PHS Guideline, as required by the Final Rule
- Changes risk criteria to be less restrictive, however additional testing is added as a safety measure
- Changes prompted from community request; unexpected disease transmission of HIV, HBV, HCV is very low
- Goal is to increase number of transplants

PHS Increased Risk Donor: 2007-2019



Proposal

- Remove label “increased risk donor”
- Shorten timeframe for donor risk criteria assessment from 12 months to one month
- Remove hemodilution as infectious disease risk criteria in policy
- Require deceased donor testing specimens drawn within 96 hours of procurement
- Require living donor recovery hospitals to arrange storage of pre-transplant samples for 10 years

Proposal

- Remove requirement for a separate informed consent when donors meet risk criteria
- Require assessment of need for HBV vaccination during candidate medical evaluation and report vaccination status
- Add required testing:
  - Candidate pre-transplant for HIV, HBV, and HCV during transplant hospital admission but before transplant occurs
  - Universal NAT for HIV, HBV, HCV on all transplant recipients 4-8 weeks after transplant
  - Liver recipient testing between 11-13 months post-transplant for HBV NAT

ELIMINATE THE USE OF DSA AND REGION IN KIDNEY (AND PANCREAS) ALLOCATION POLICY

What is Problem with Current Allocation?

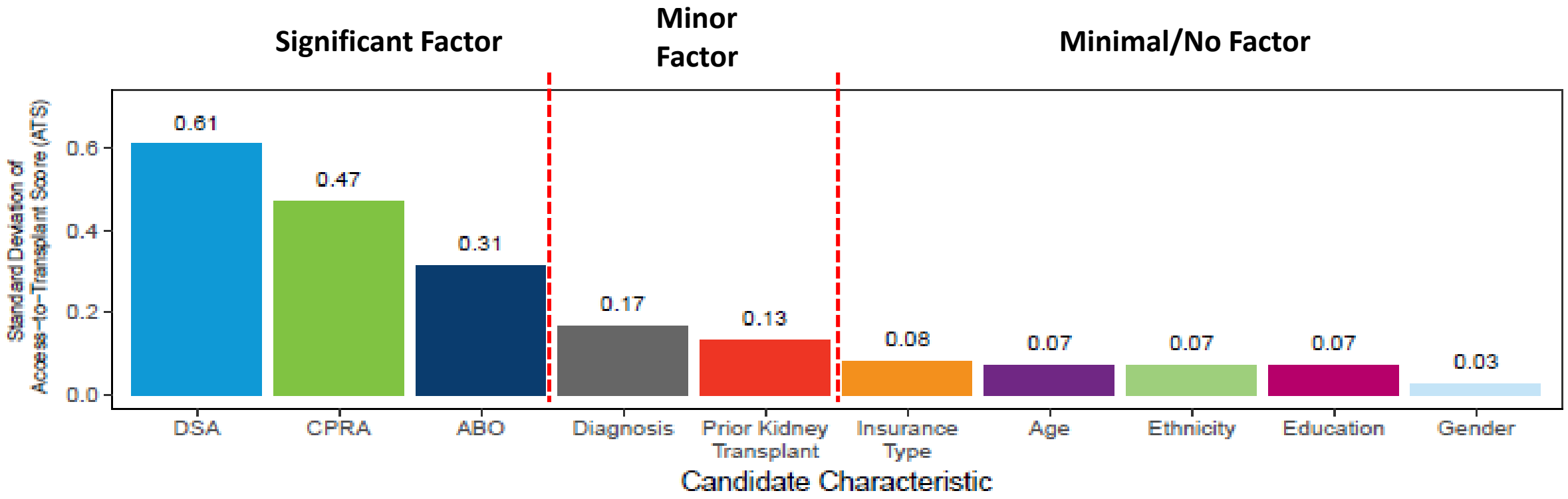
- DSA and Region not optimized for organ distribution

  Final Rule: geography shall not impact candidate access to transplant, except to the extent necessary (e.g. avoid unnecessary organ loss / promote efficient management of organ placement)

- Geographic disparity in access to transplant

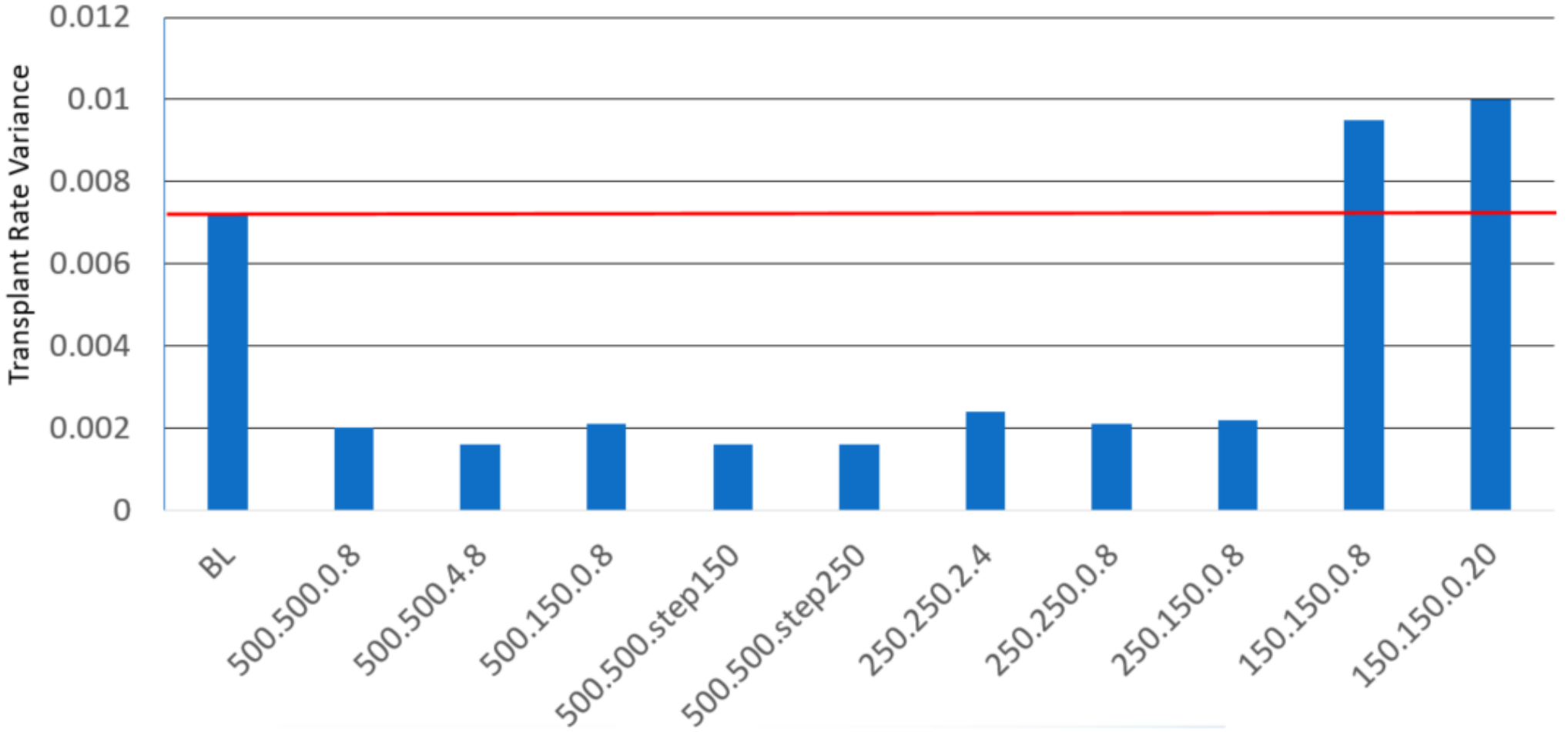
  DSA → largest factor related to disparity in kidney allocation

Location is the single biggest contributor to access



DSA= Donor Service Area

Variation in Kidney Transplant Rates by Donor Service Area



Overview of New Allocation Policy

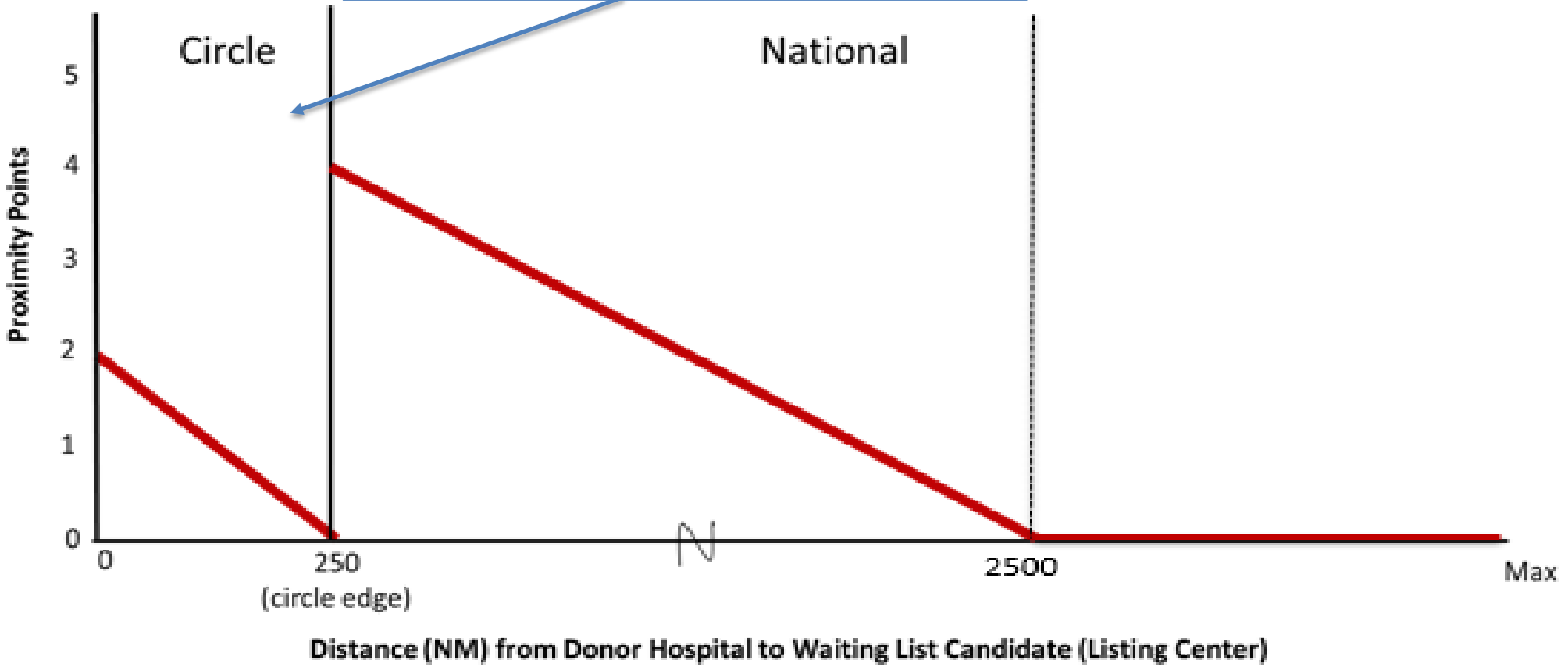
- Hybrid Framework with proximity points
- 250 NM fixed circle around the donor hospital
- Maximum of two proximity points inside the circle
- Maximum of four proximity points outside of the circle
- Medical urgency classification and review process
- Import match run following declination

Hybrid Framework

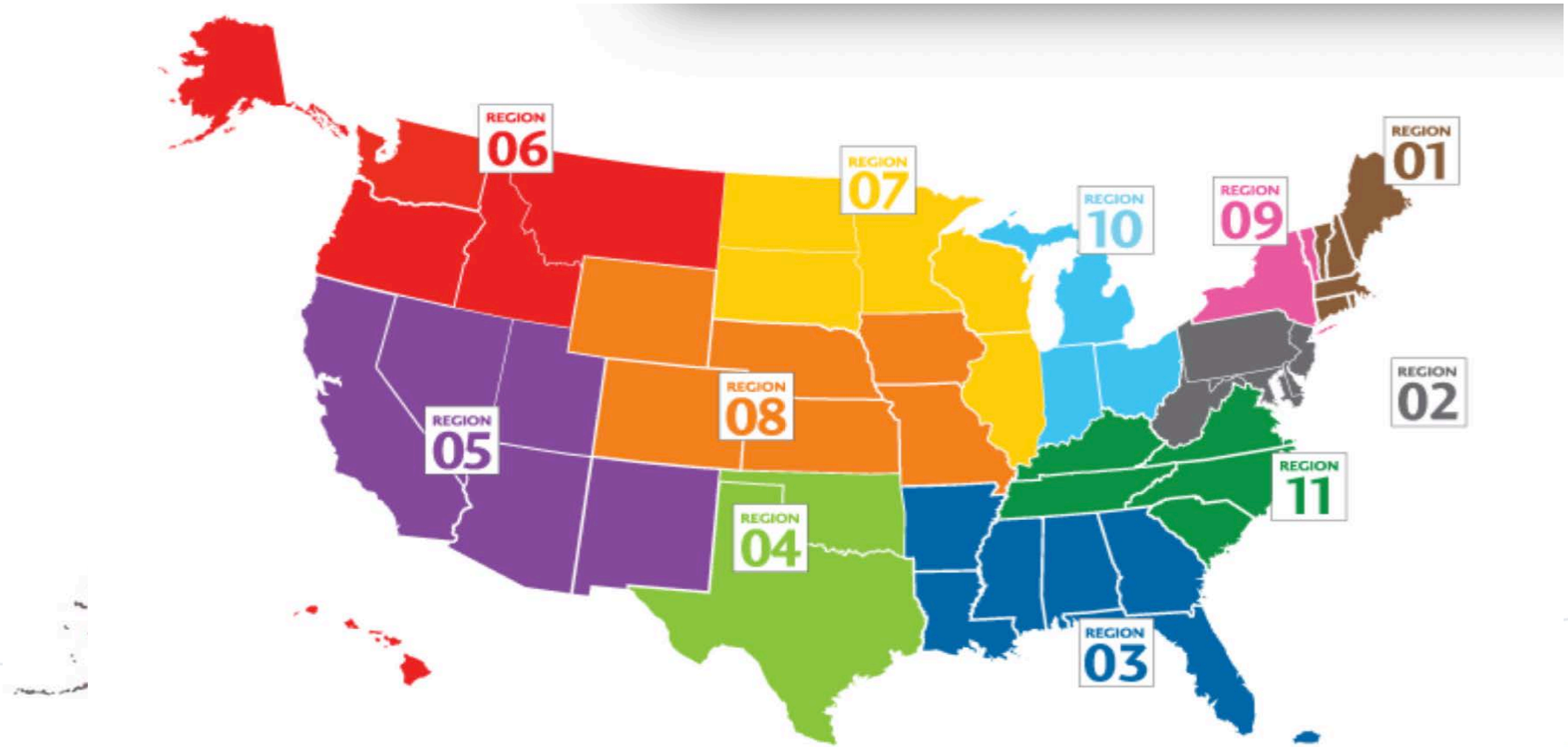
- What is the “hybrid” framework?
  - Single fixed-distance circles with proximity points
  - The single fixed-distance circle is based on the distance from the donor hospital to the candidate’s place of listing
  - One proximity point is equivalent to one year of waiting time
  - Proximity points only affect rank-ordering of candidates *within* classifications

Illustration of Proximity Points Allocation

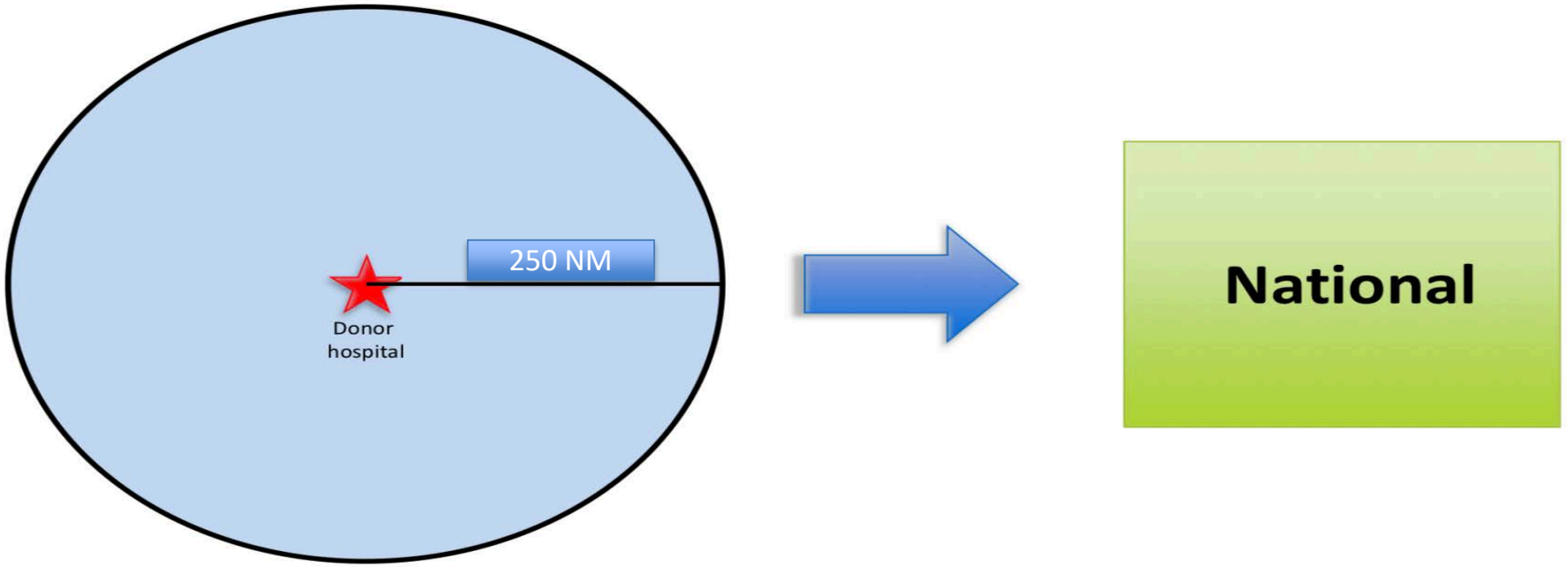
Candidates in classifications at the top remain at the top, and cannot be surpassed by candidates below them <u>even with the inclusion of proximity points</u>



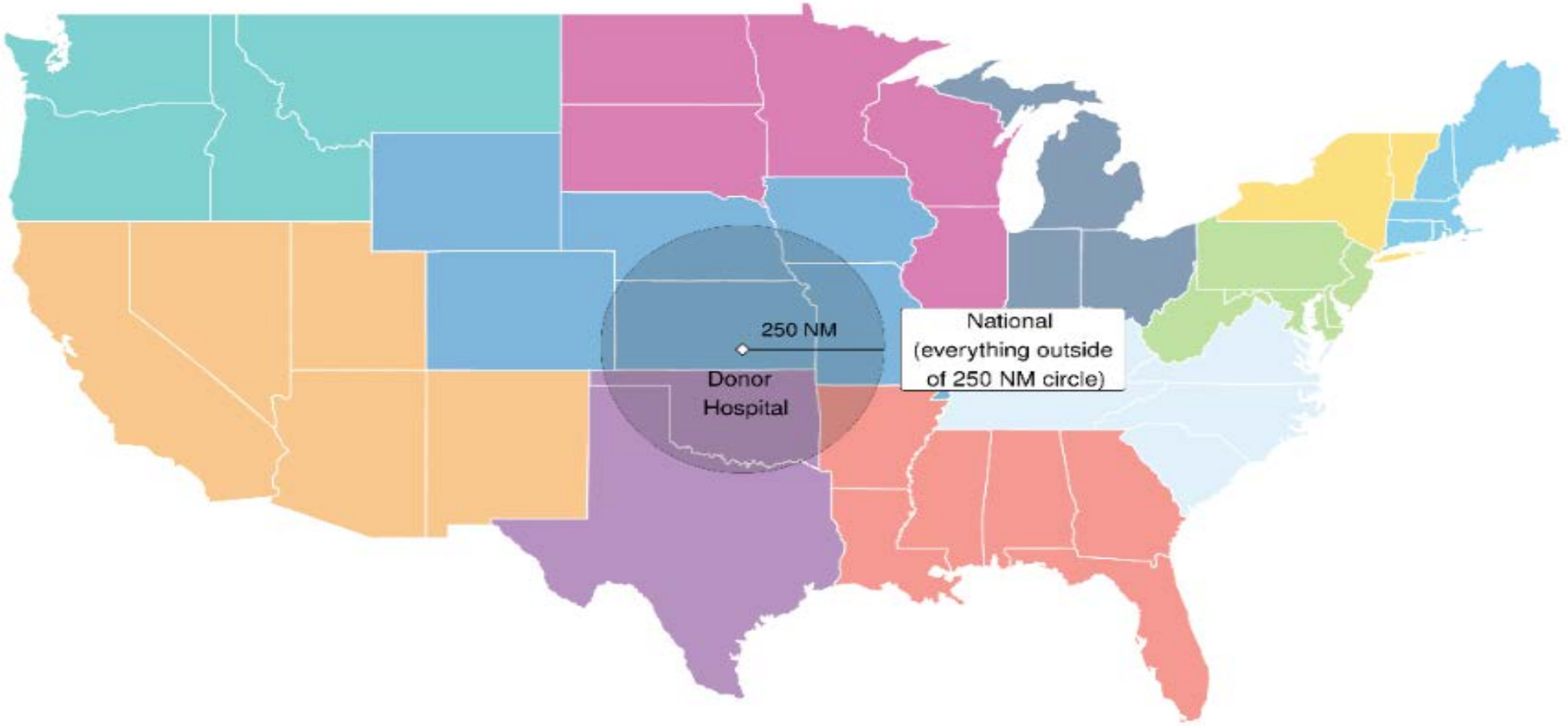
Donation Service Area (DSA) → **Region** → **National**



New Allocation System



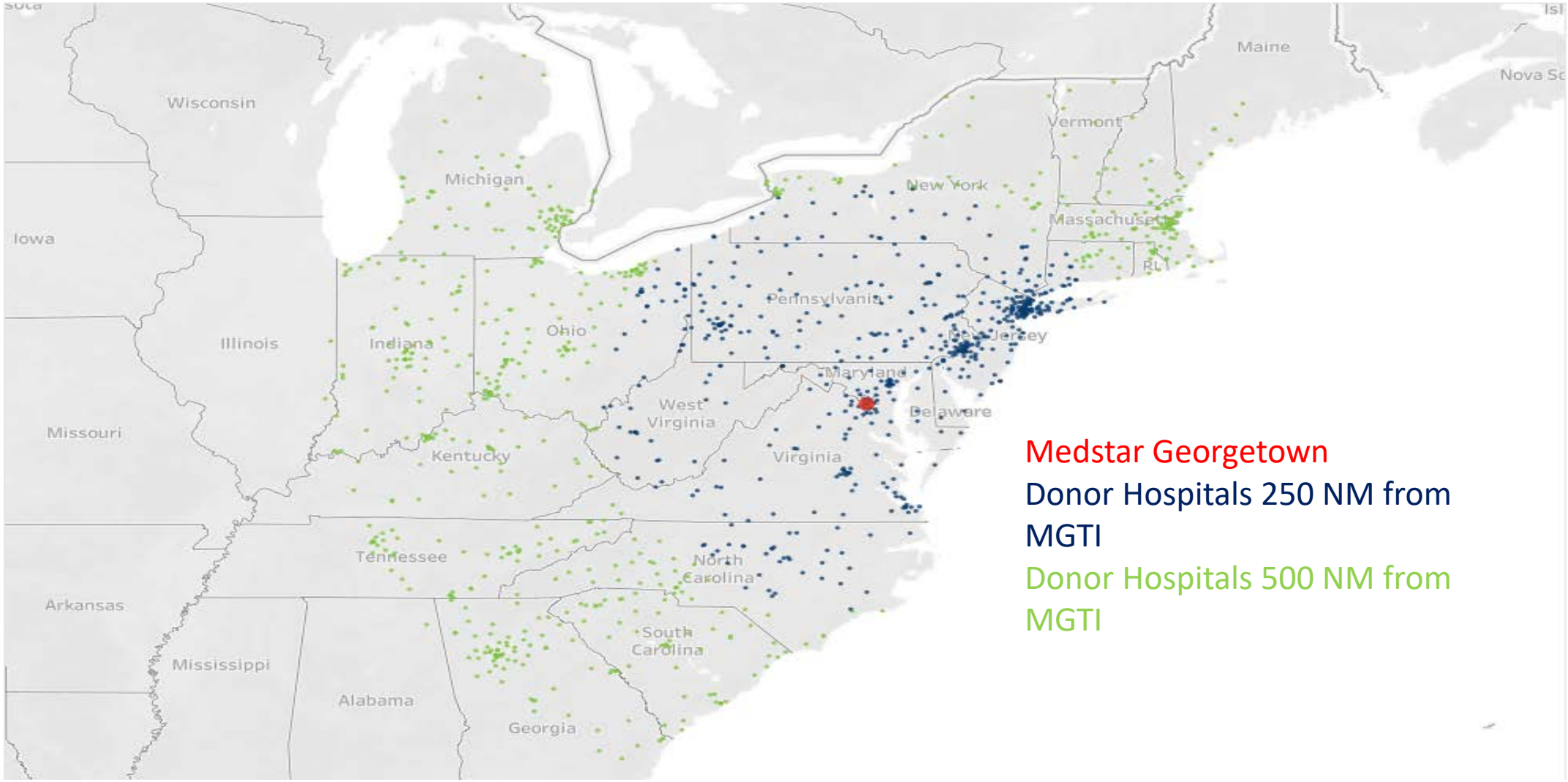
New Allocation



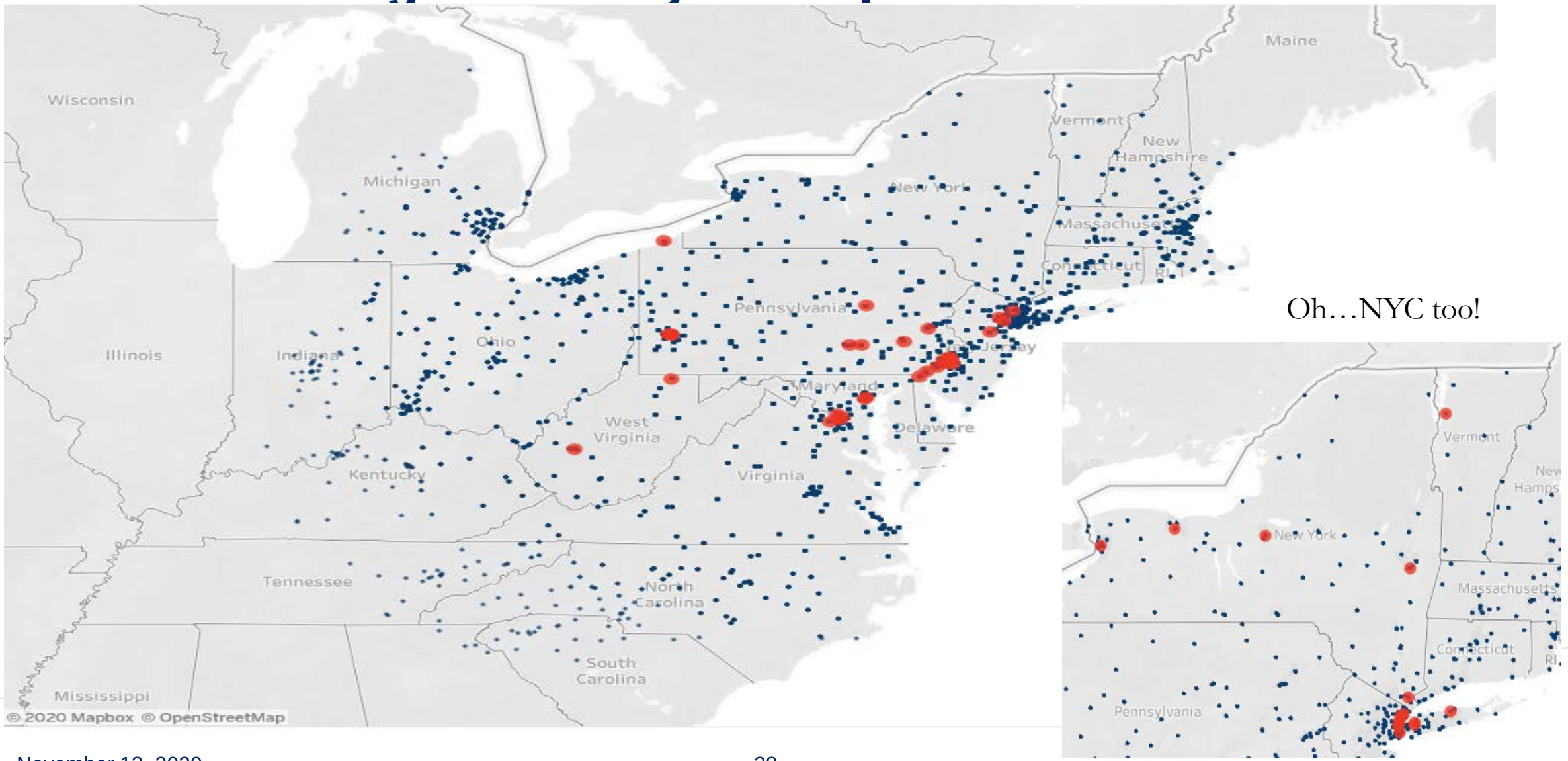
New Classifications

Sequence A KDPI 0 – 20%	Sequence B KDPI 20 – 34%	Sequence C KDPI 35 – 85%	Sequence D KDPI 86 – 100%
100% Highly Sensitized Inside Circle Prior LD Inside Circle Pediatrics Inside Circle Med Urgent 98% - 99% High Sensitized 0-ABDRmm Inside Circle Top 20% EPTS 0-ABDRmm (All) Inside Circle (All) National Pediatrics National (Top 20%) National (All)	100% Highly Sensitized Inside Circle Prior LD Inside Circle Pediatrics Inside Circle Med Urgent 98% - 99% High Sensitized 0-ABDRmm Inside Circle Safety Net Inside Circle (All) National Pediatrics National (All)	100% Highly Sensitized Inside Circle Prior LD Inside Circle Med Urgent 98% - 99% High Sensitized 0-ABDRmm Inside Circle Safety Net Inside Circle (All) National (All) Inside Circle (dual) National (dual)	100% Highly Sensitized Inside Circle Med Urgent 98% - 99% High Sensitized 0-ADBRmm Inside Circle Safety Net Inside Circle Inside Circle (dual) National National (dual)

Why I don’t sleep at night!



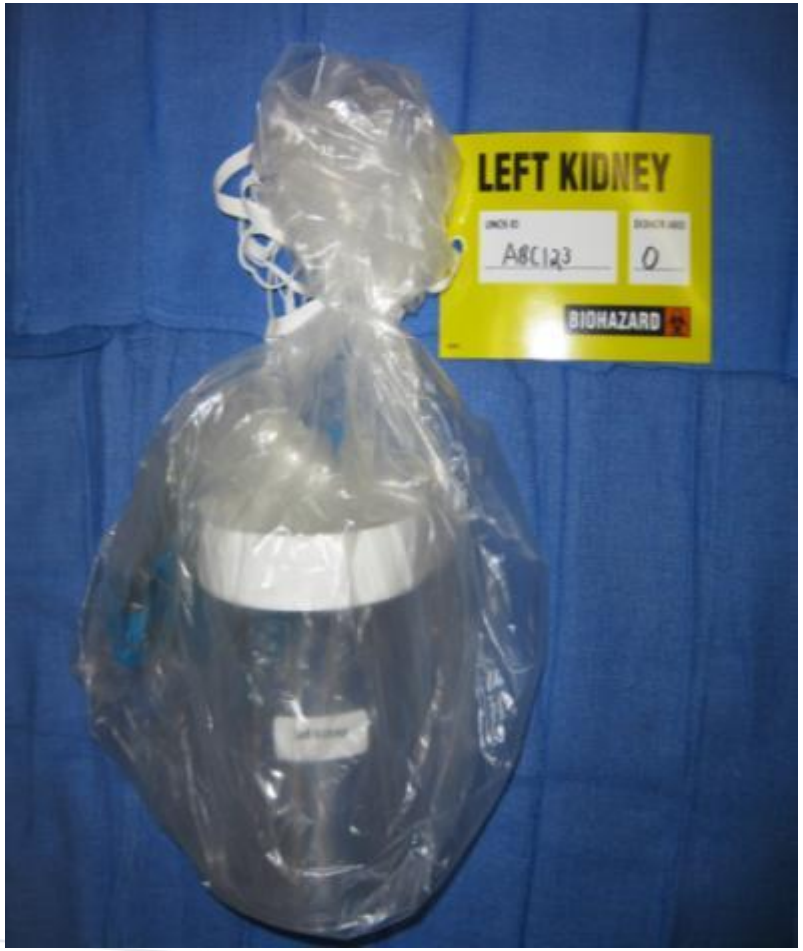
Region 2 Only Transplant Centers



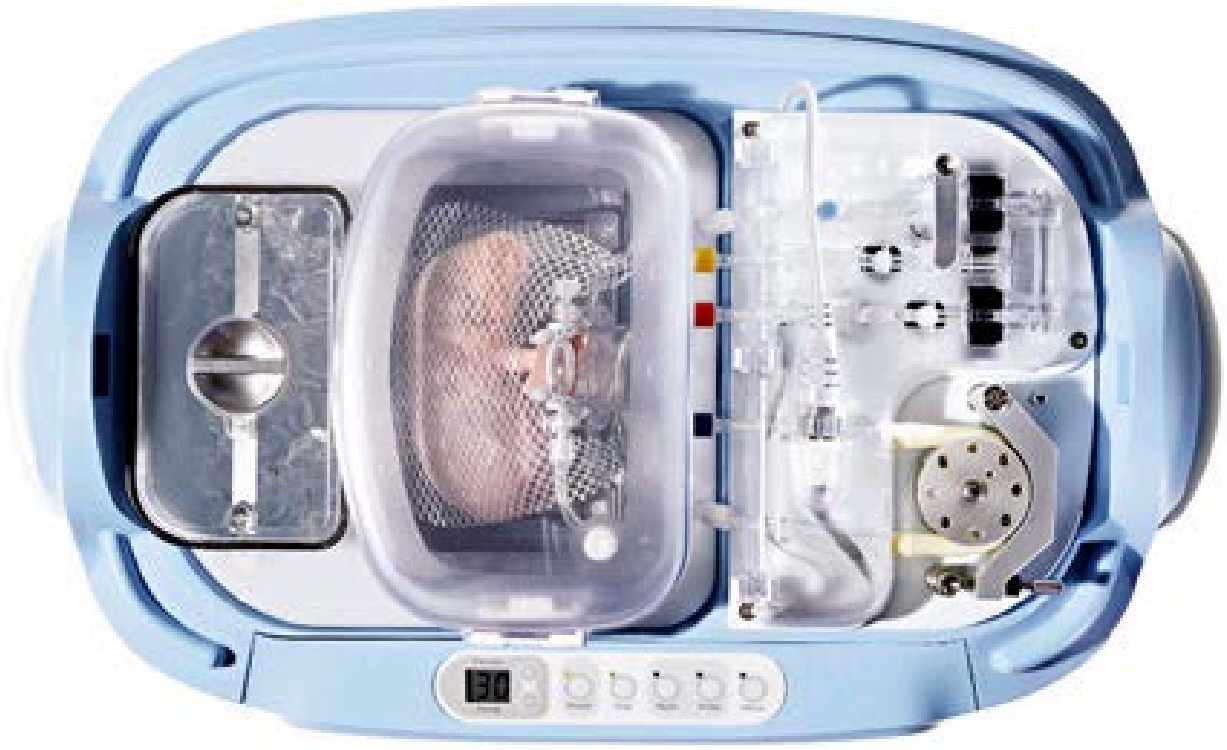
Oh…NYC too!

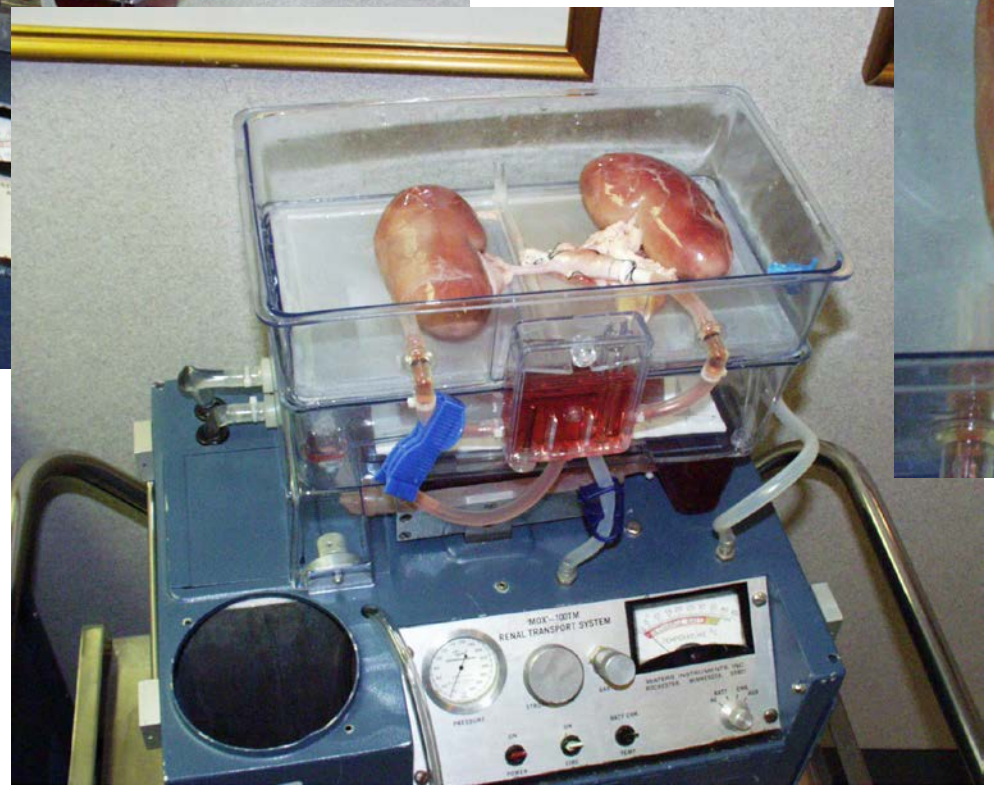
ORGAN PRESERVATION

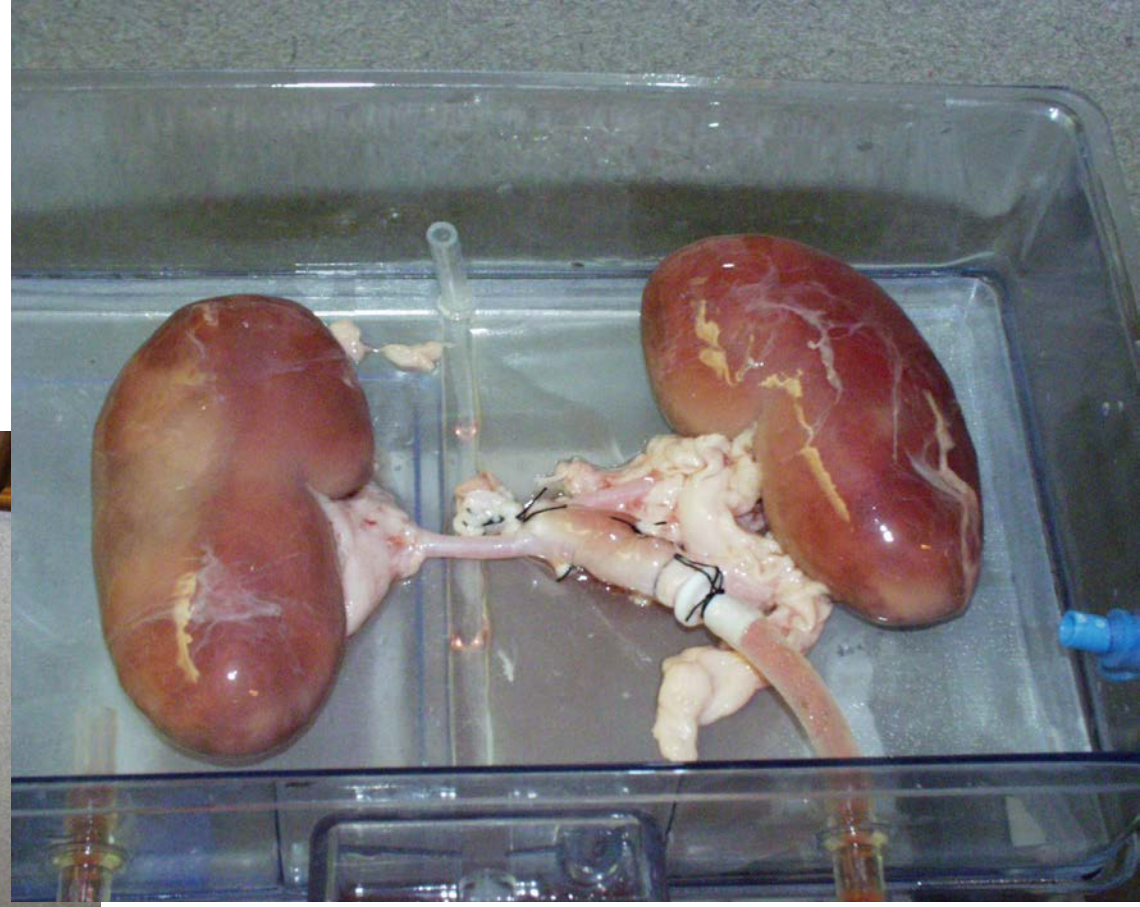
Cold Storage Organ Preservation



Organ Preservation - LifePort System




RENAL TRANSPORT SYSTEM

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Normothermic Liver Preservation

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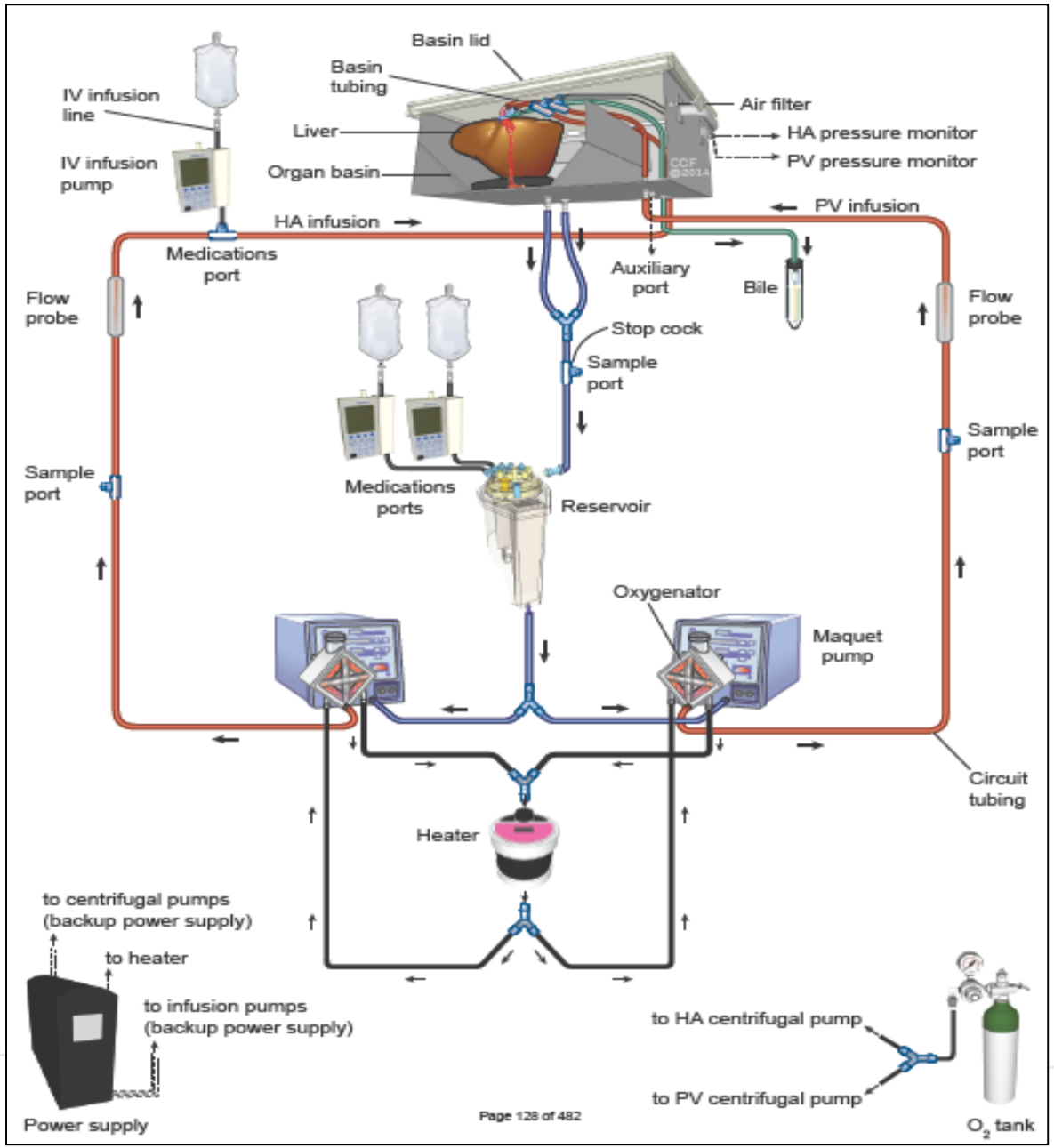
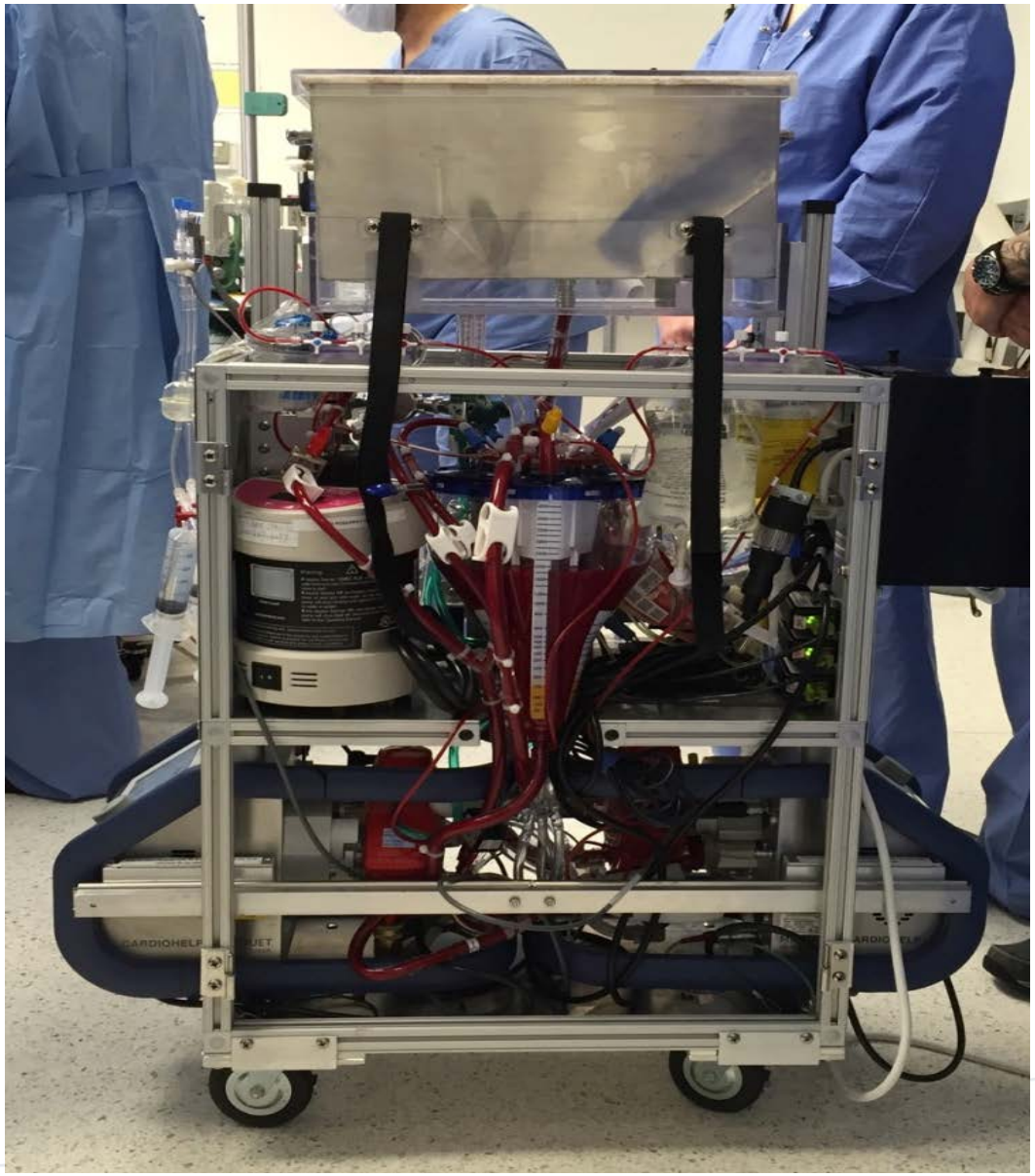
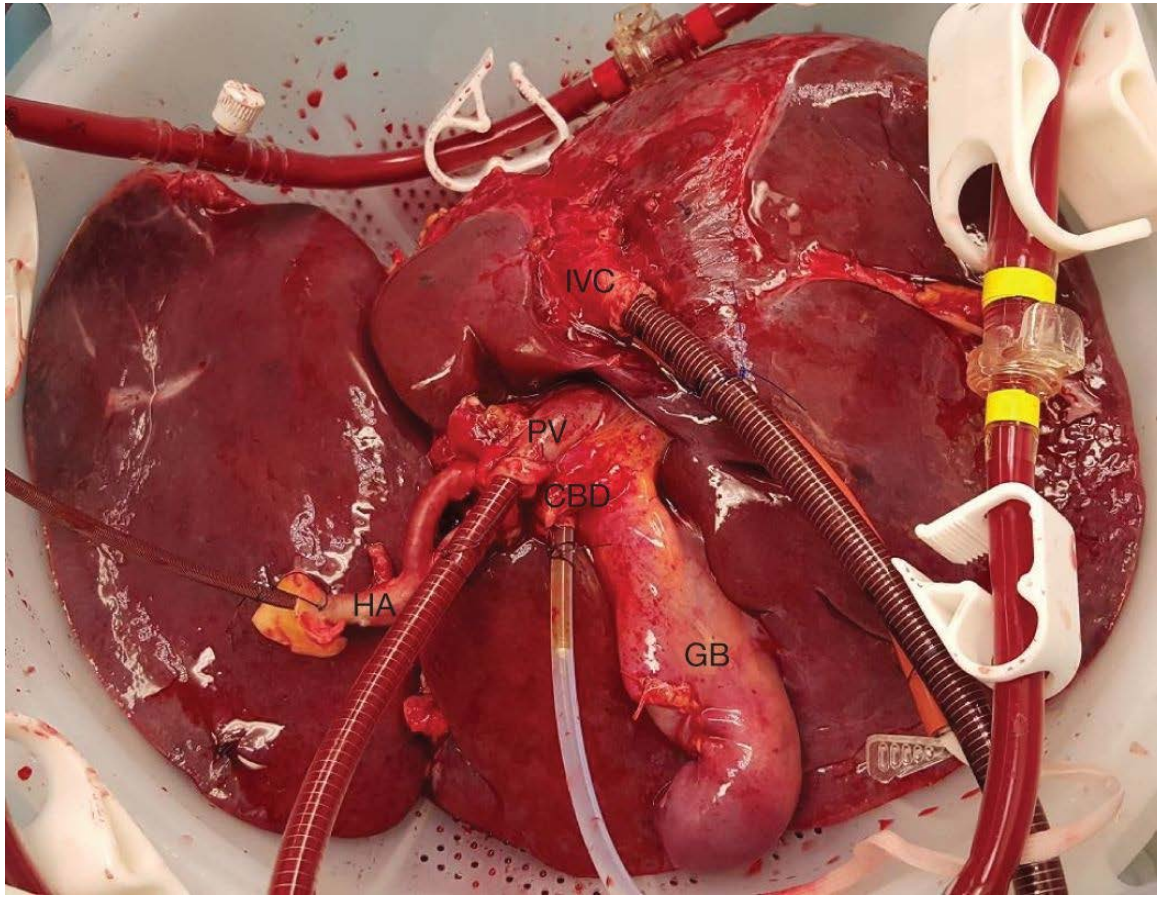




Knowledge and Compassion **Focused on You**

MedStar Georgetown Transplant Institute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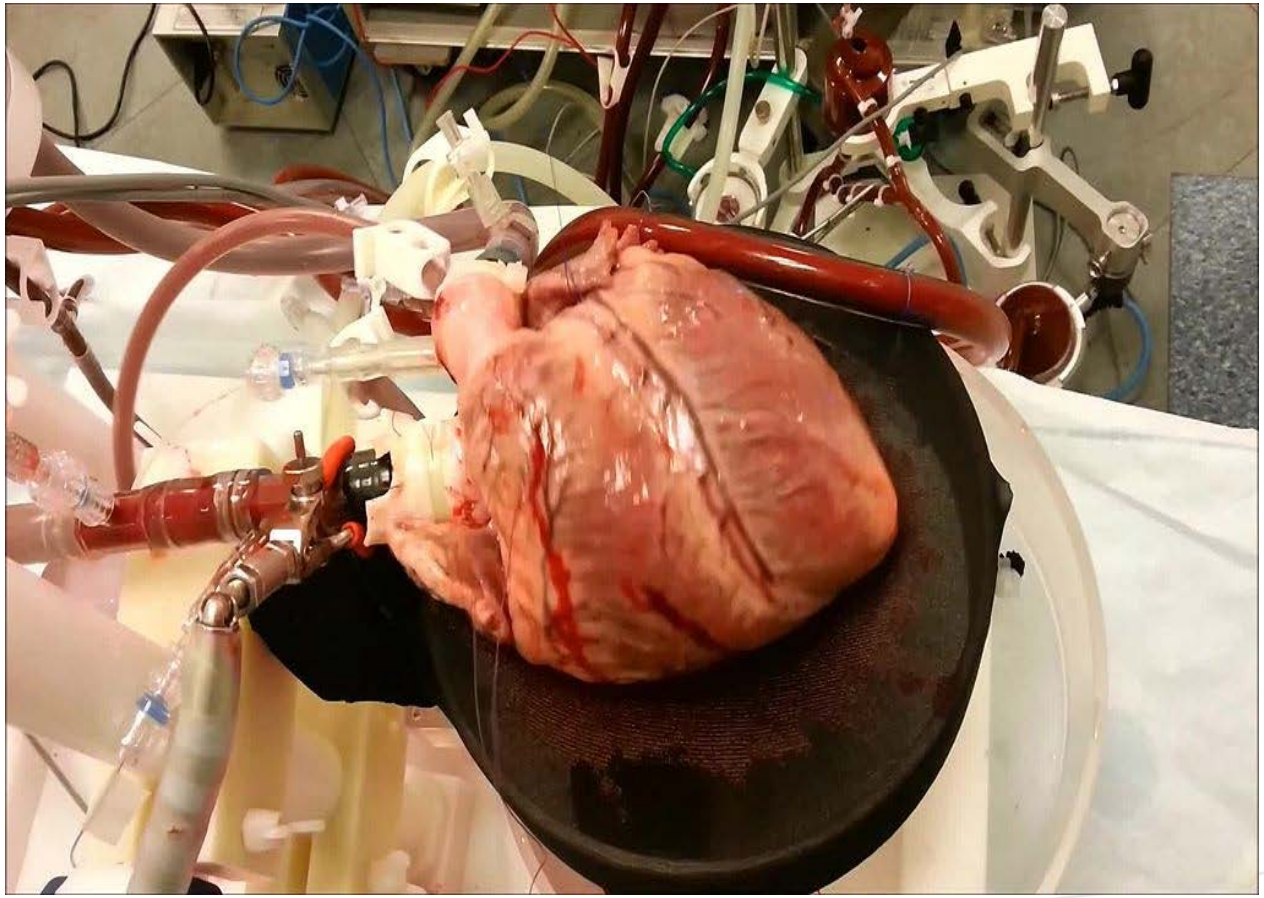
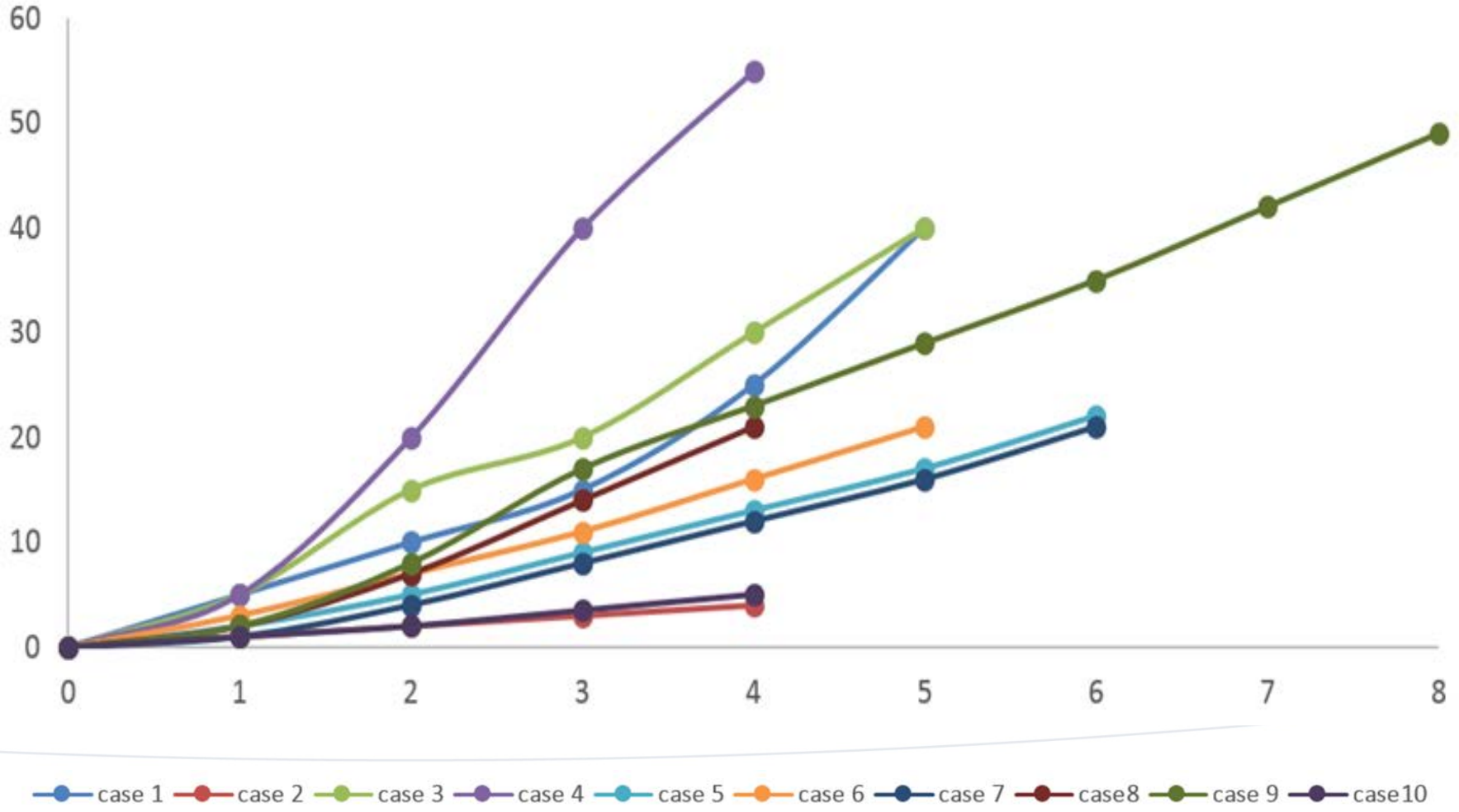


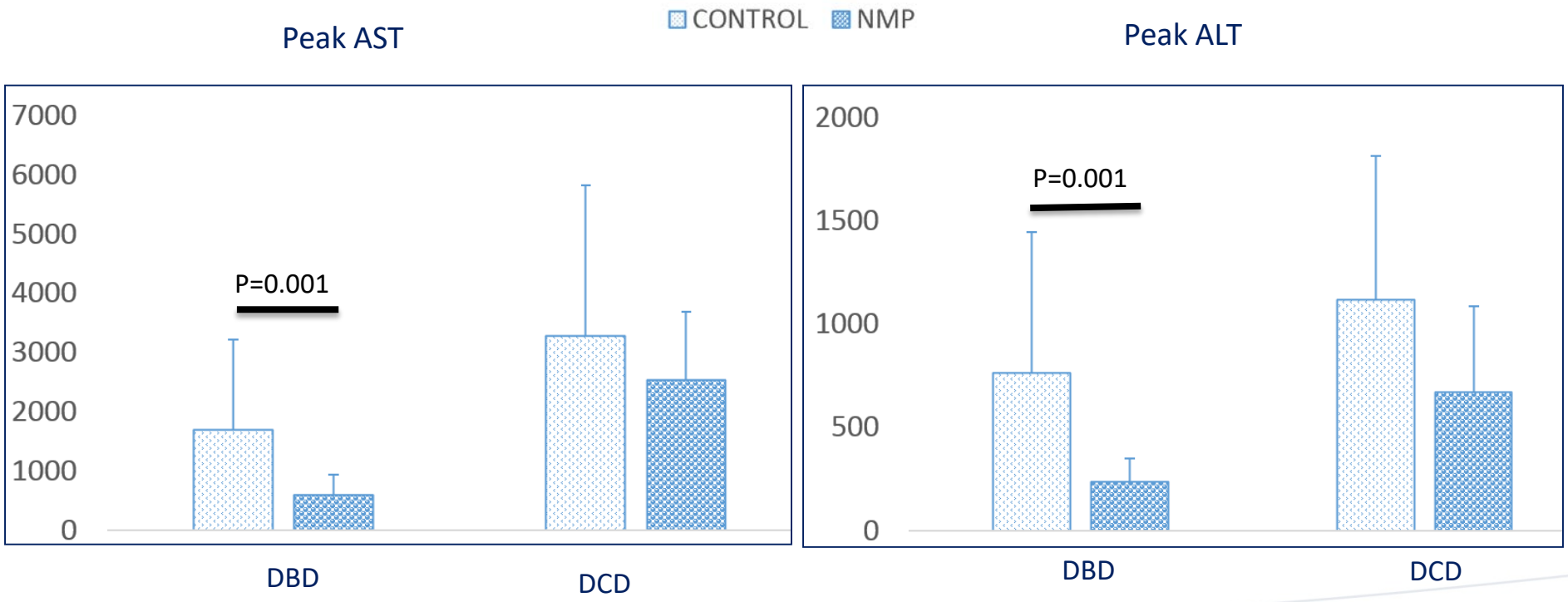
Ex vivo liver normothermic machine perfusion (NMP)

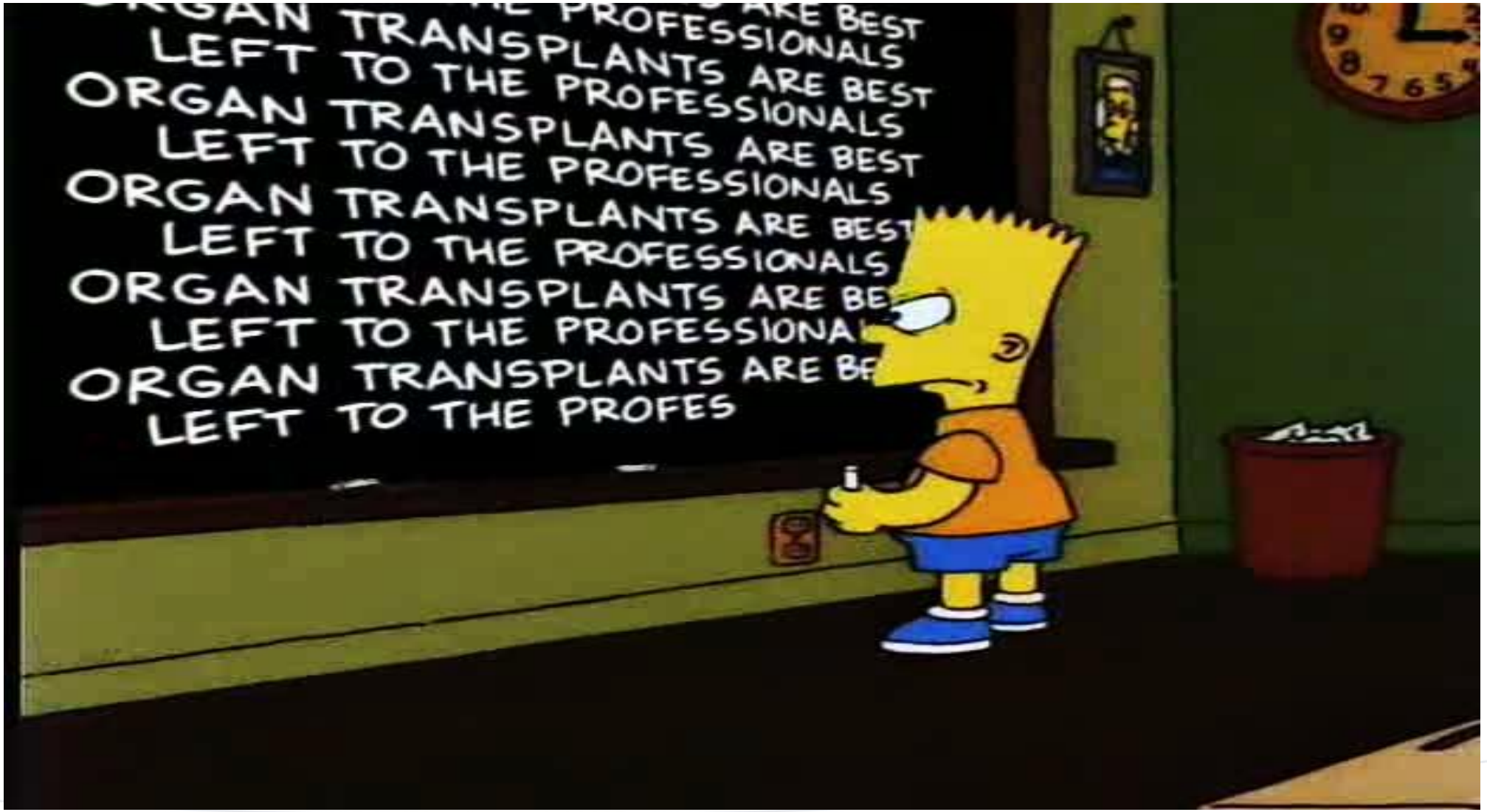
Cumulative bile production (ml)



Comparison between Control and Perfusion group

- Control group had more EAD (35%) but not significant (p=0.24).
- significant higher peak AST & ALT in control cases than NMP group.

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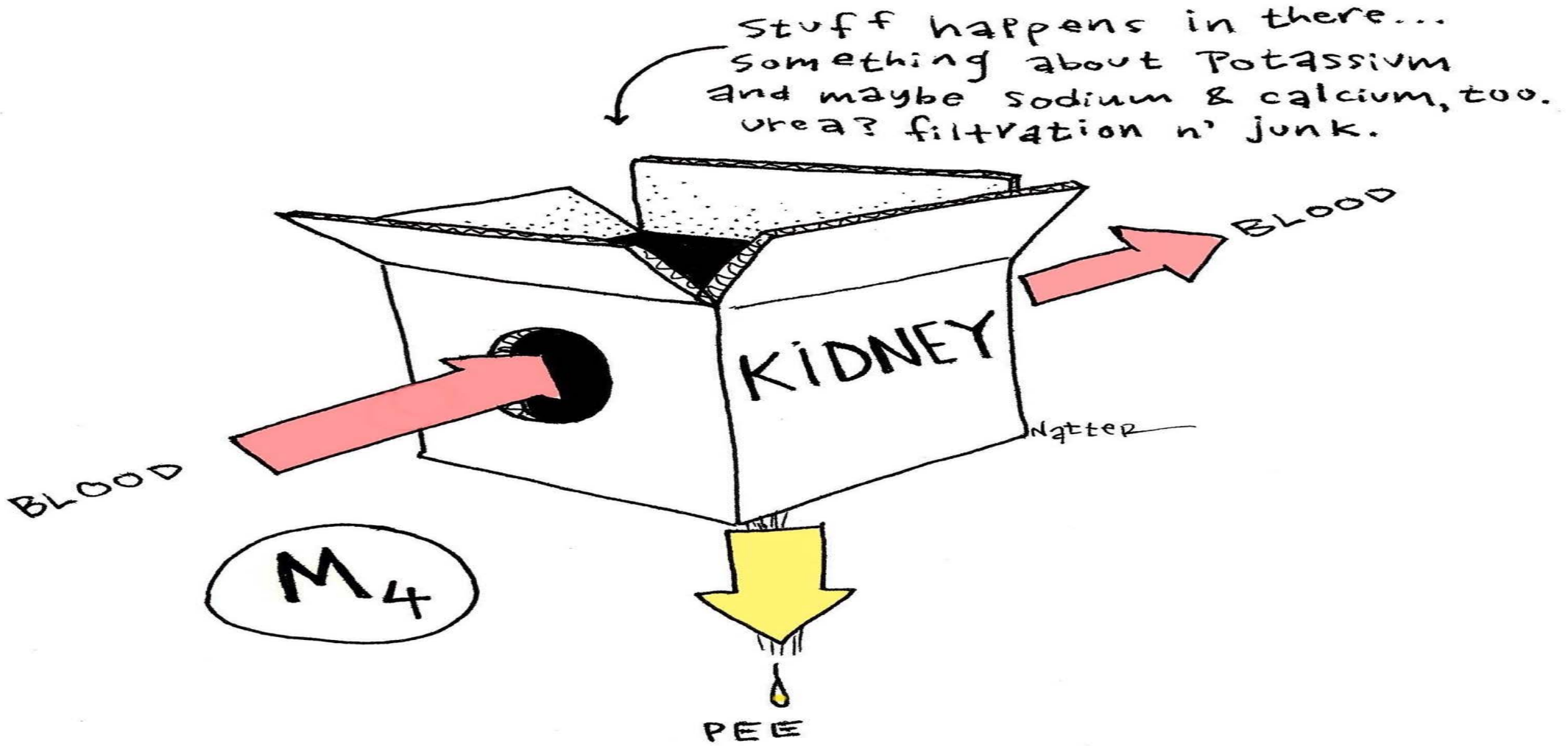
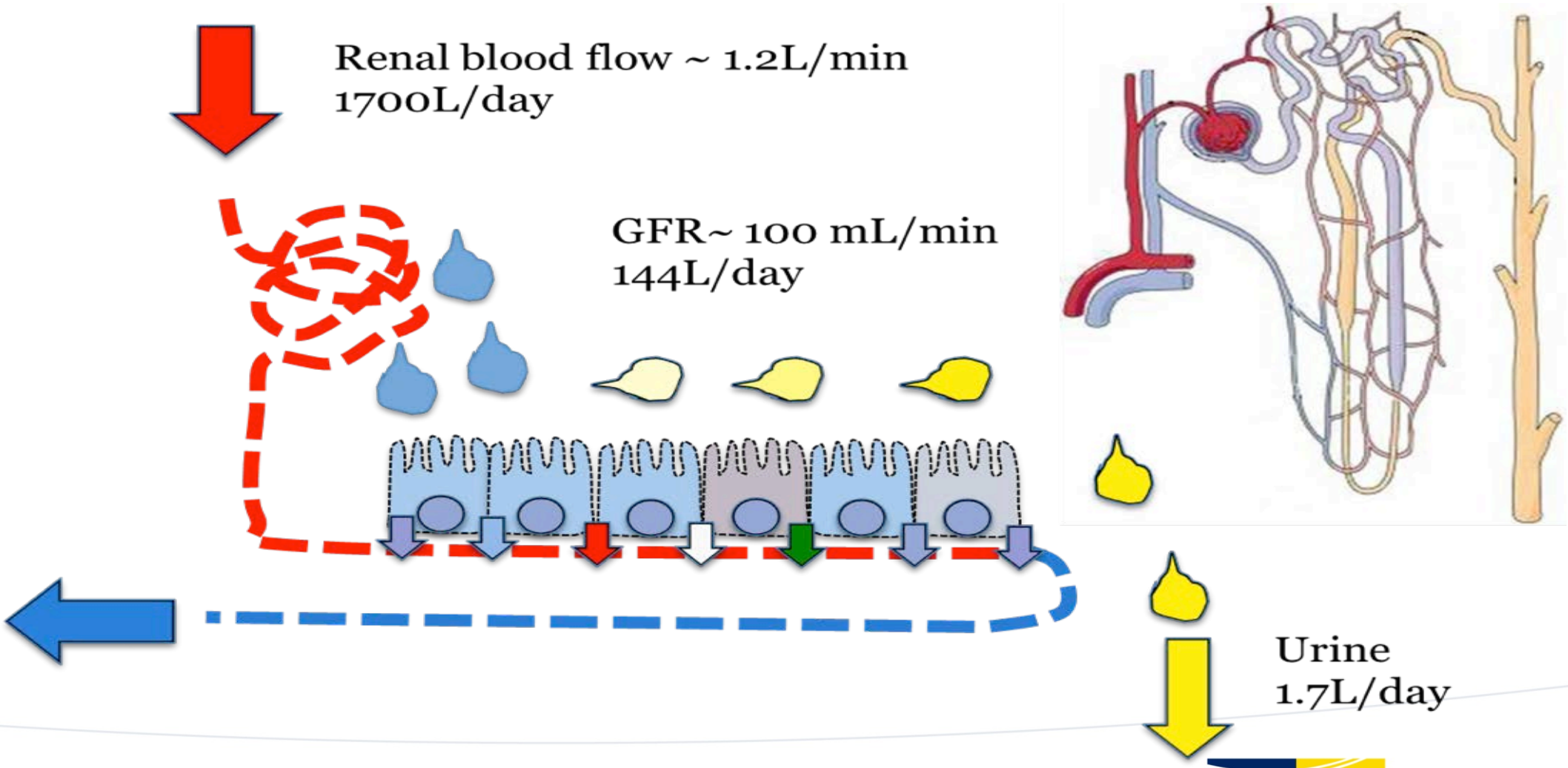
The Future of Organ Transplantation

Surgeon's View Toward Kidney Function



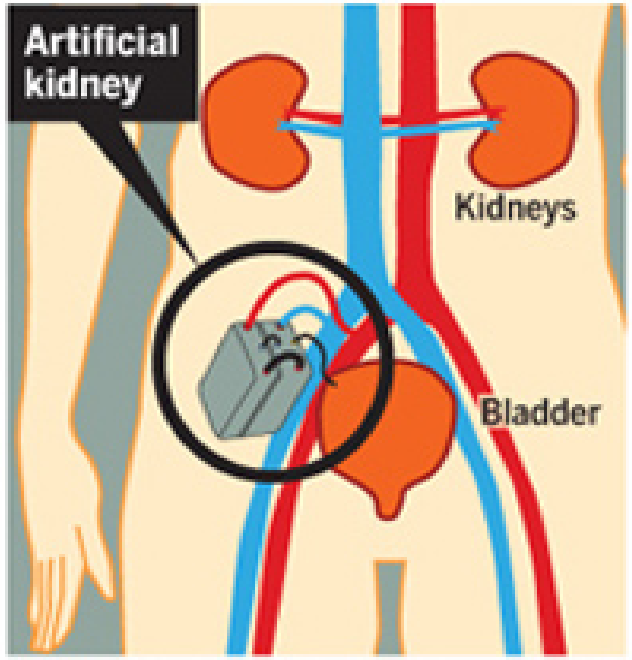
Kidney – Continuous, High Efficiency



Building the Artificial Kidney?

Implantable artificial kidney

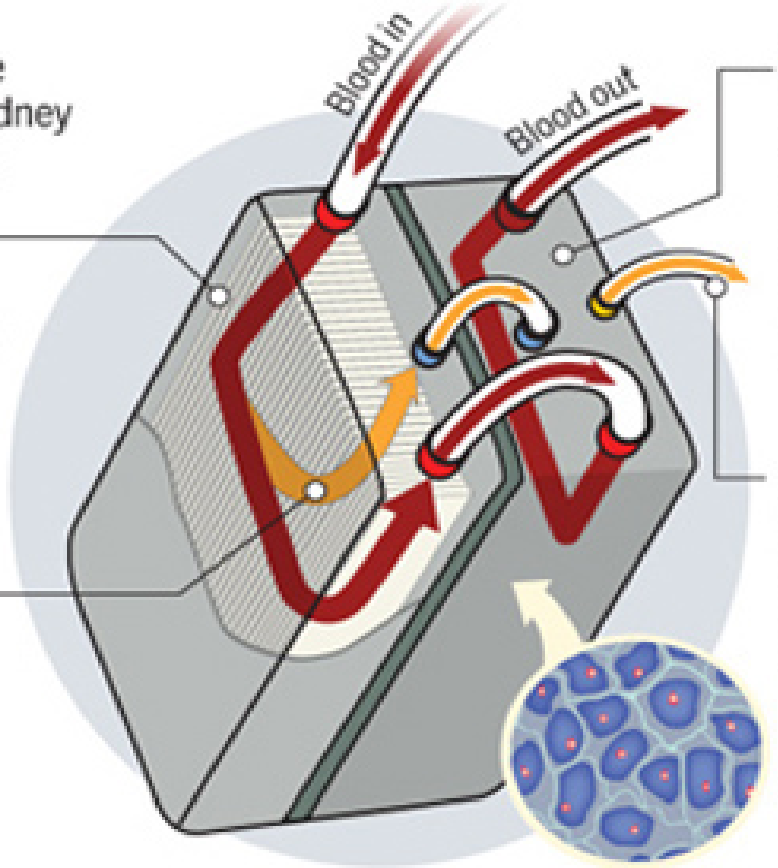
UC San Francisco is heading a team of researchers around the country who are working to create an implantable, artificial kidney the size of a coffee cup. The device consists of two chambers:



1 Hemofilter

The left chamber filters incoming blood with super-efficient membranes made with silicon nanotechnology.

Ultrafiltrate, separated from the blood, contains dissolved toxins, as well as water, sugars and salts.



2 Cell bioreactor

The right chamber contains live kidney cells that reabsorb much of the water, sugars and salts into the bloodstream.

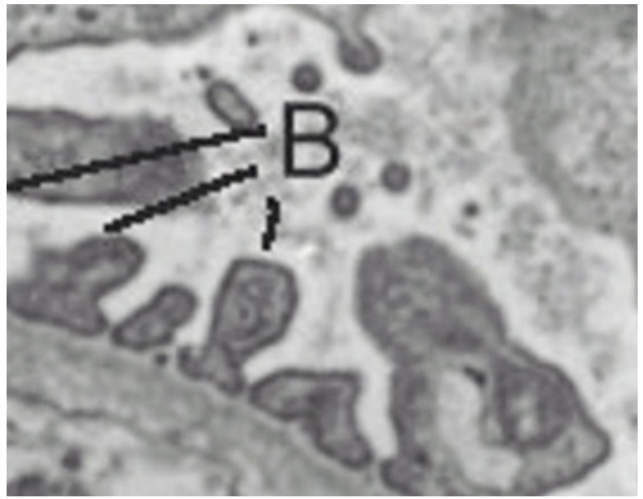
The toxins and excess water are passed into the waste outlet connected to the bladder.

Kidney cells

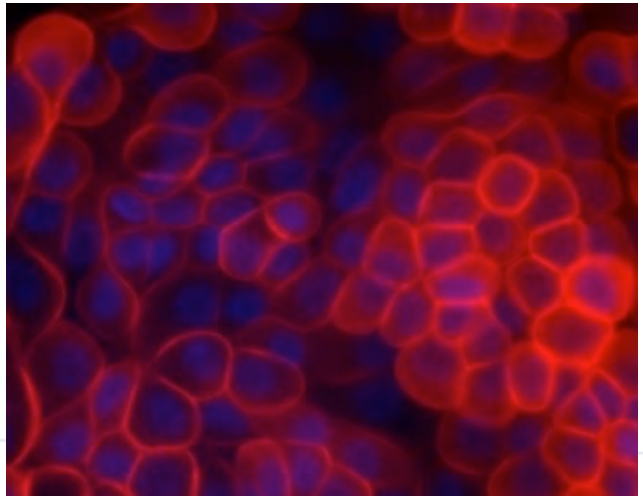
Source: UC San Francisco

BAY AREA NEWS GROUP

Implantable Artificial Kidney

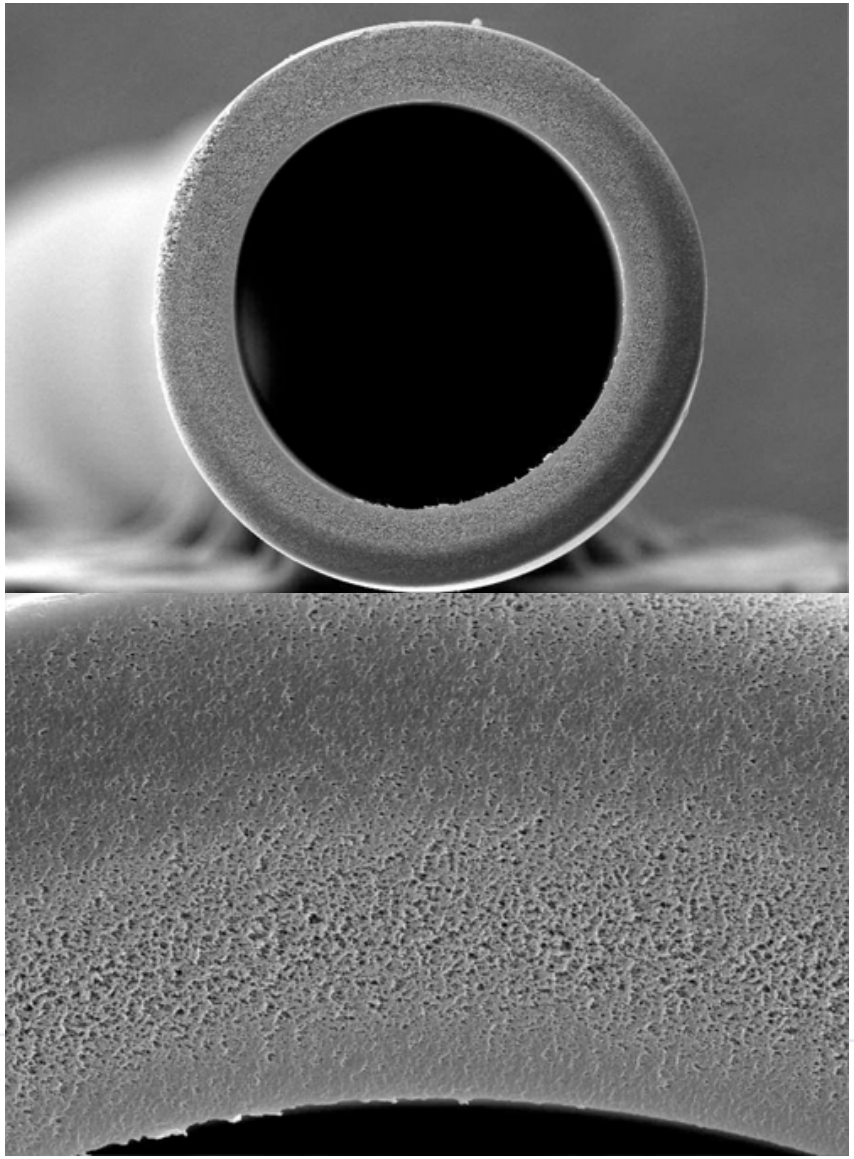


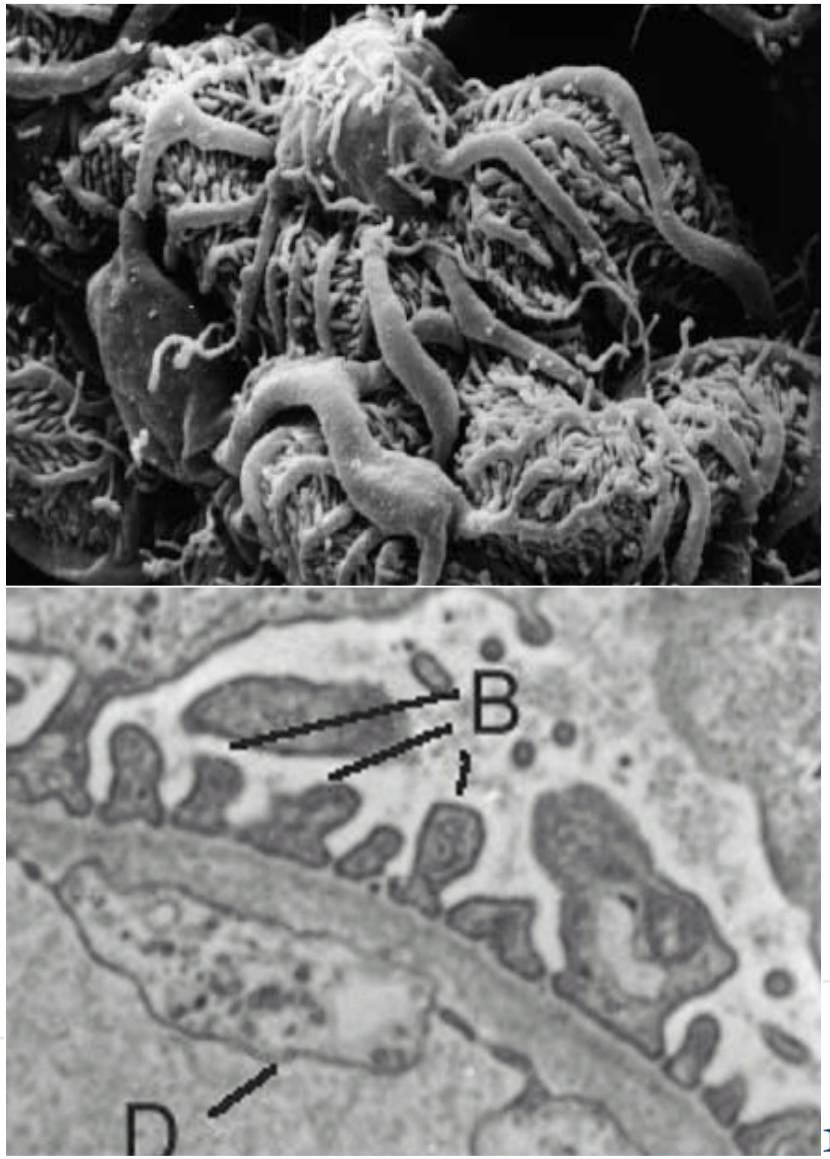
FILTER → ***BUILD*** *what we cannot* ***GROW***



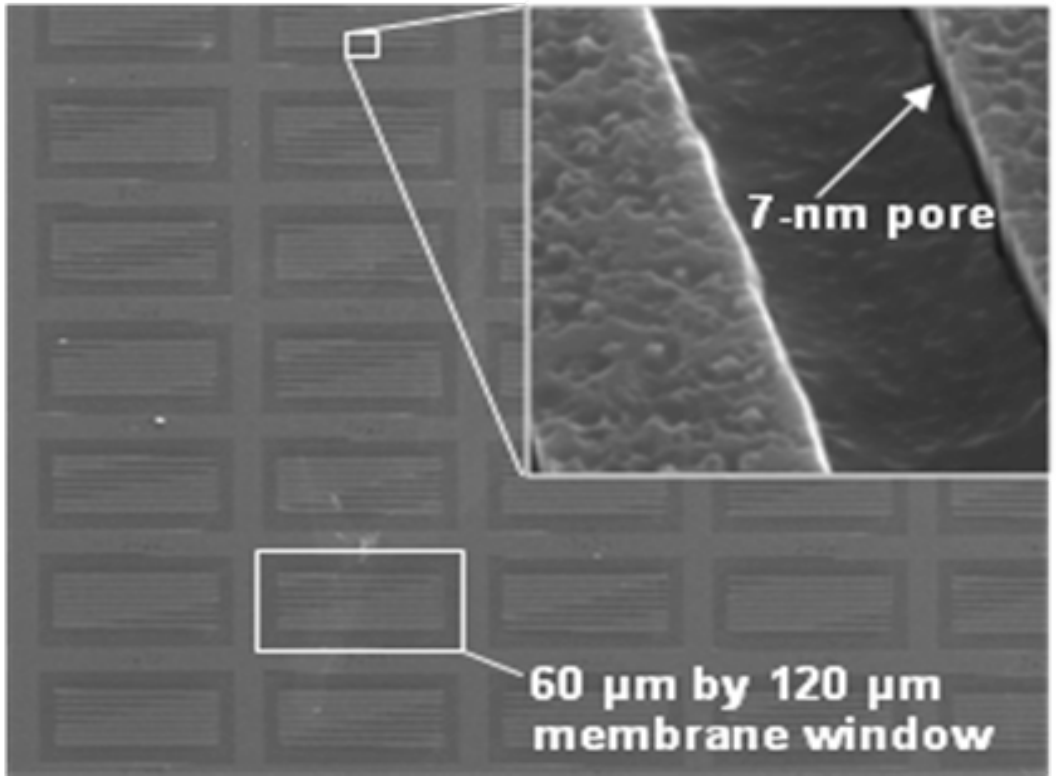
TUBULE → ***GROW*** *what we do not know how to* ***BUILD***

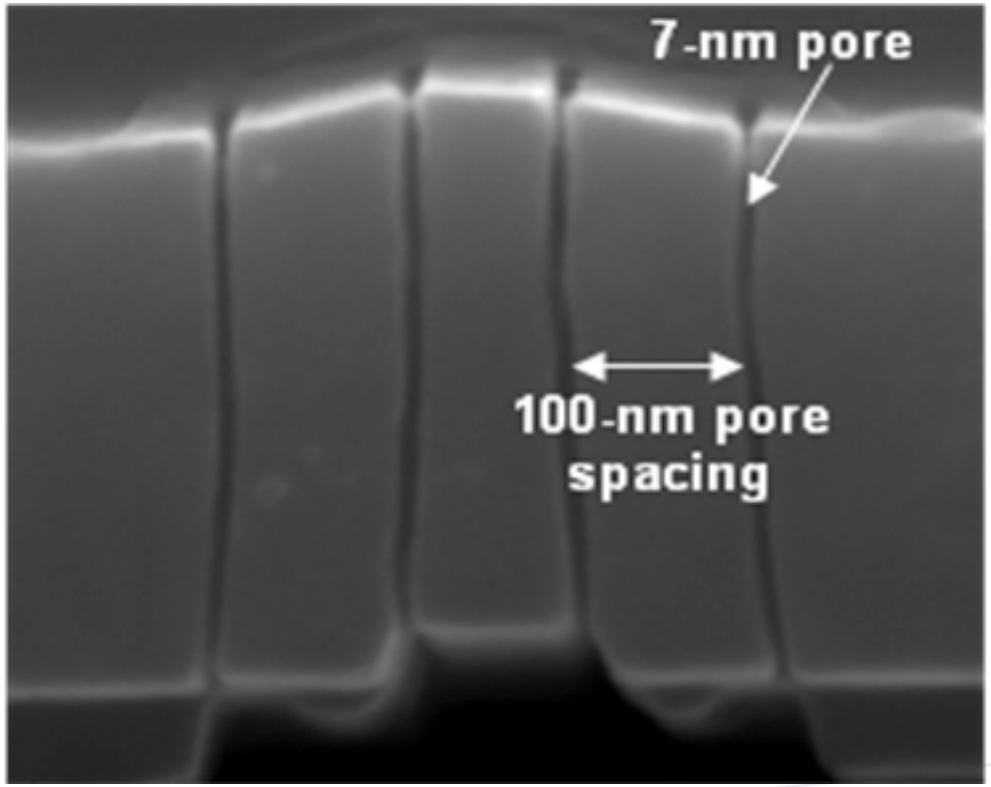
Artificial versus Natural Hemofilter





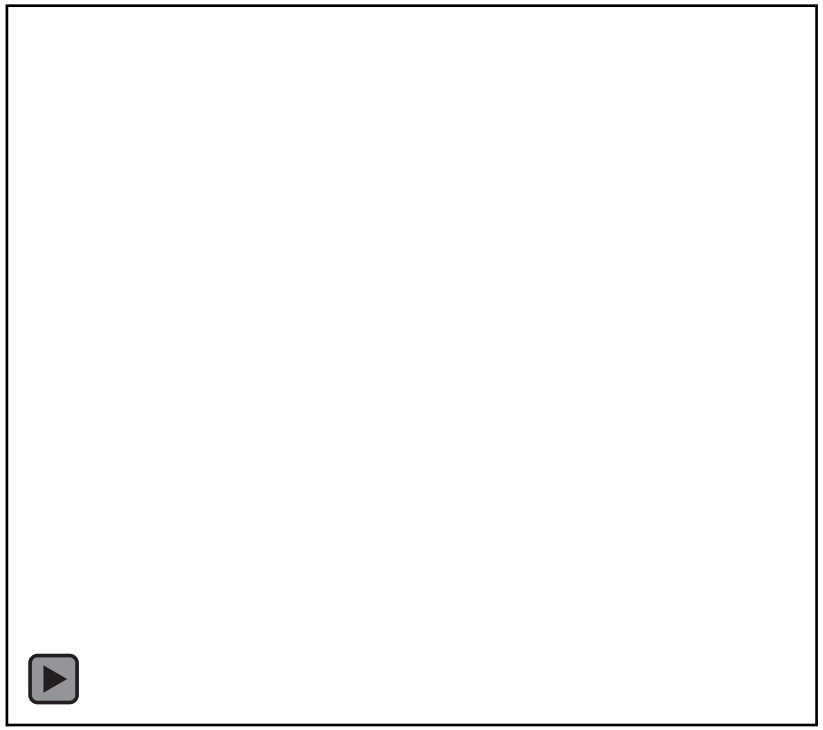
Silicon Nanopore Membrane



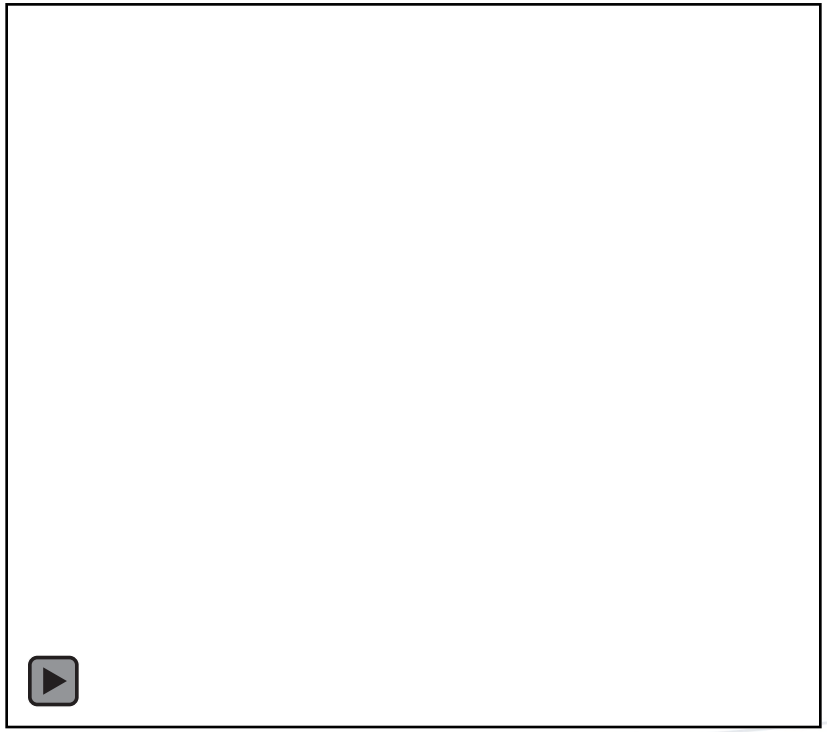


Wall Shear Stress Over Cardiac Cycle

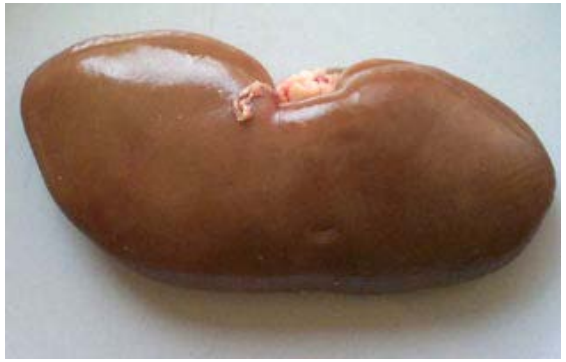
Original Flat Design



New Helical Design



Cells *in vivo* vs Cells *in vitro*



?!

- 1 kPa stiffness
- 1-5 dyn/cm^2 shear
- Insulin ~75 pmol
- Glucose ~ 80 mg/dL
- Gluconeogenic

megaPa stiffness

Static

Insulin ~ 1mmol

Glucose 300 mg/dL

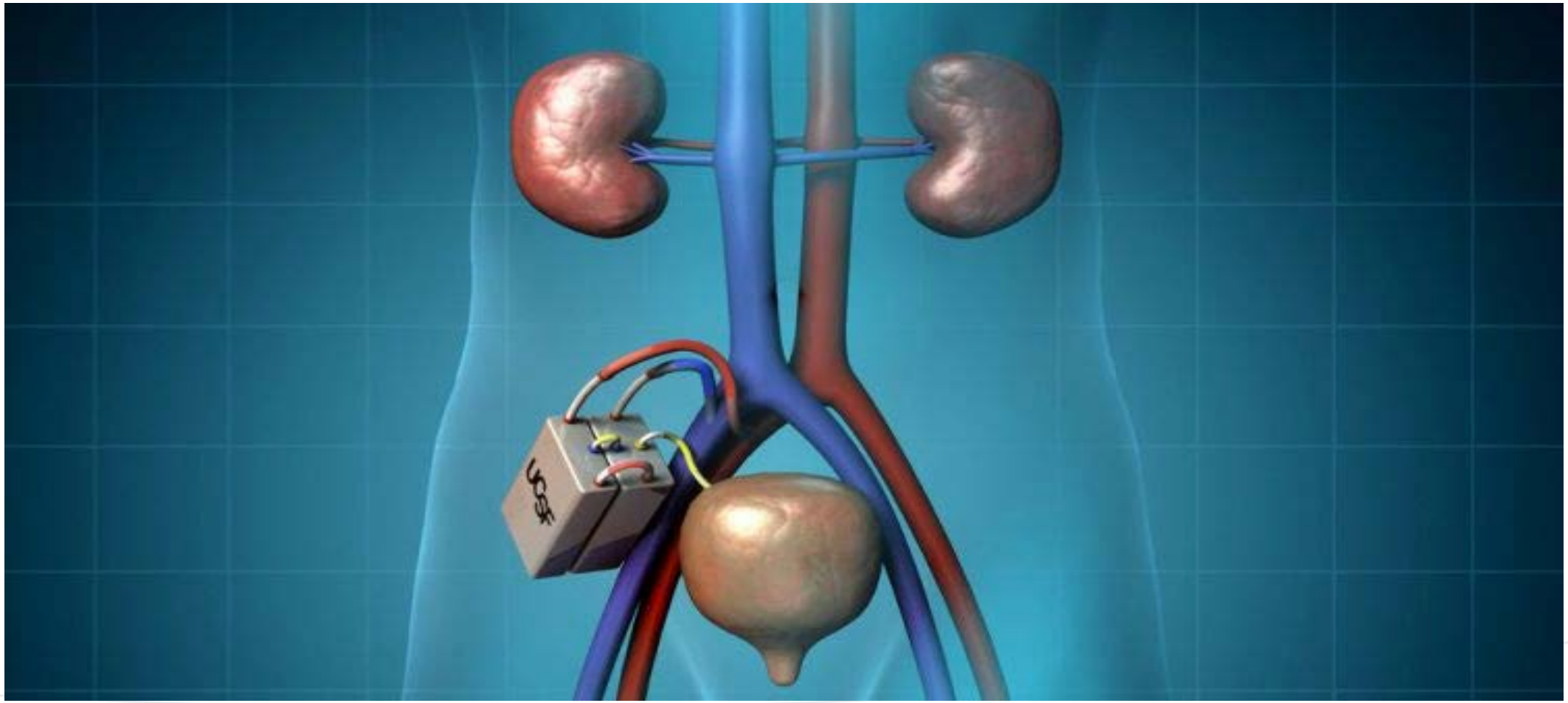
Glycolytic

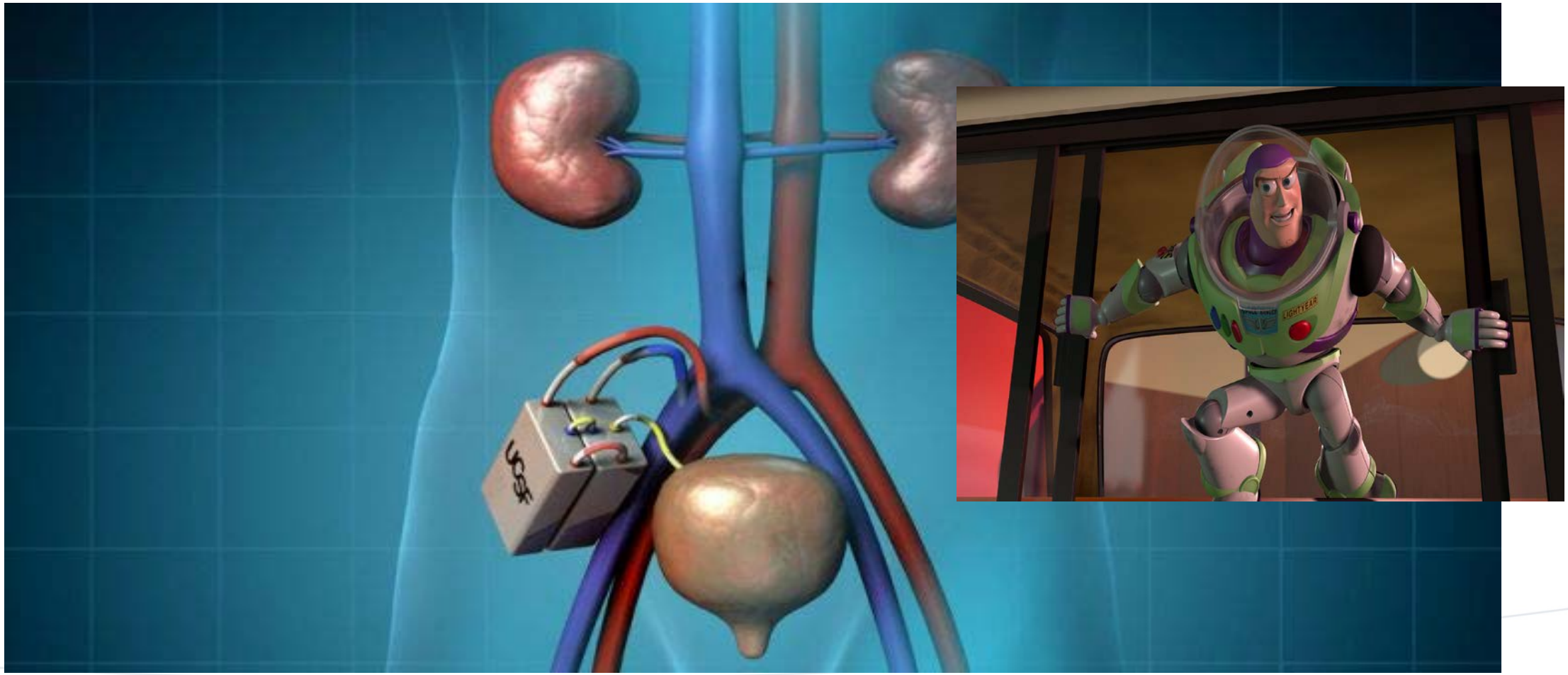
Bioartificial Kidney

The bioartificial kidney is a compact, surgically implanted, free-standing device to treat end stage renal disease (ESRD). It performs the vast majority of the biological functions of the natural kidney.

Beginning Human Clinical Trials in 2021

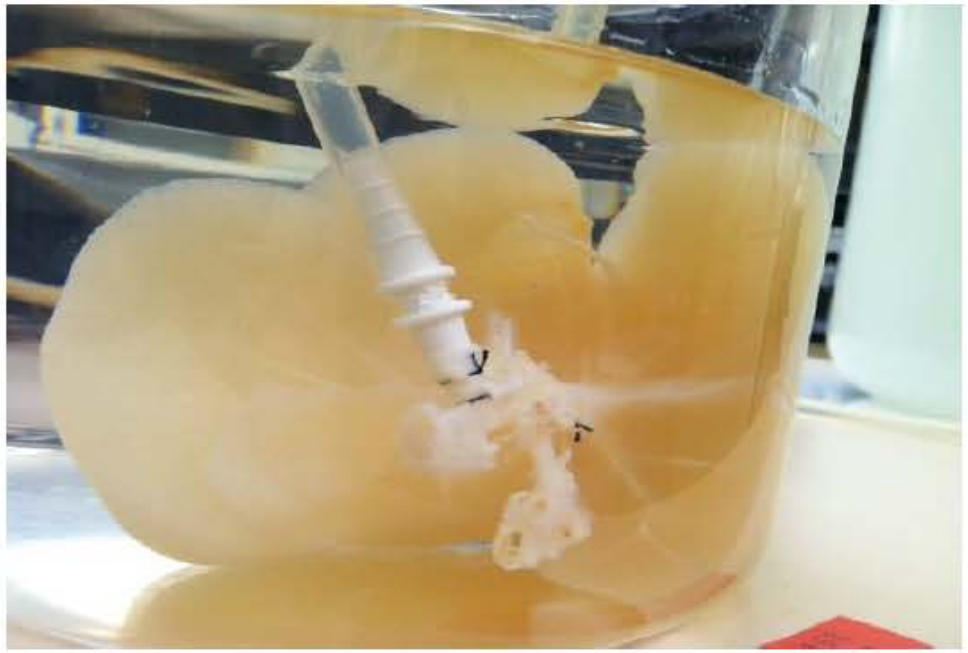
https://pharm.ucsf.edu/kidney

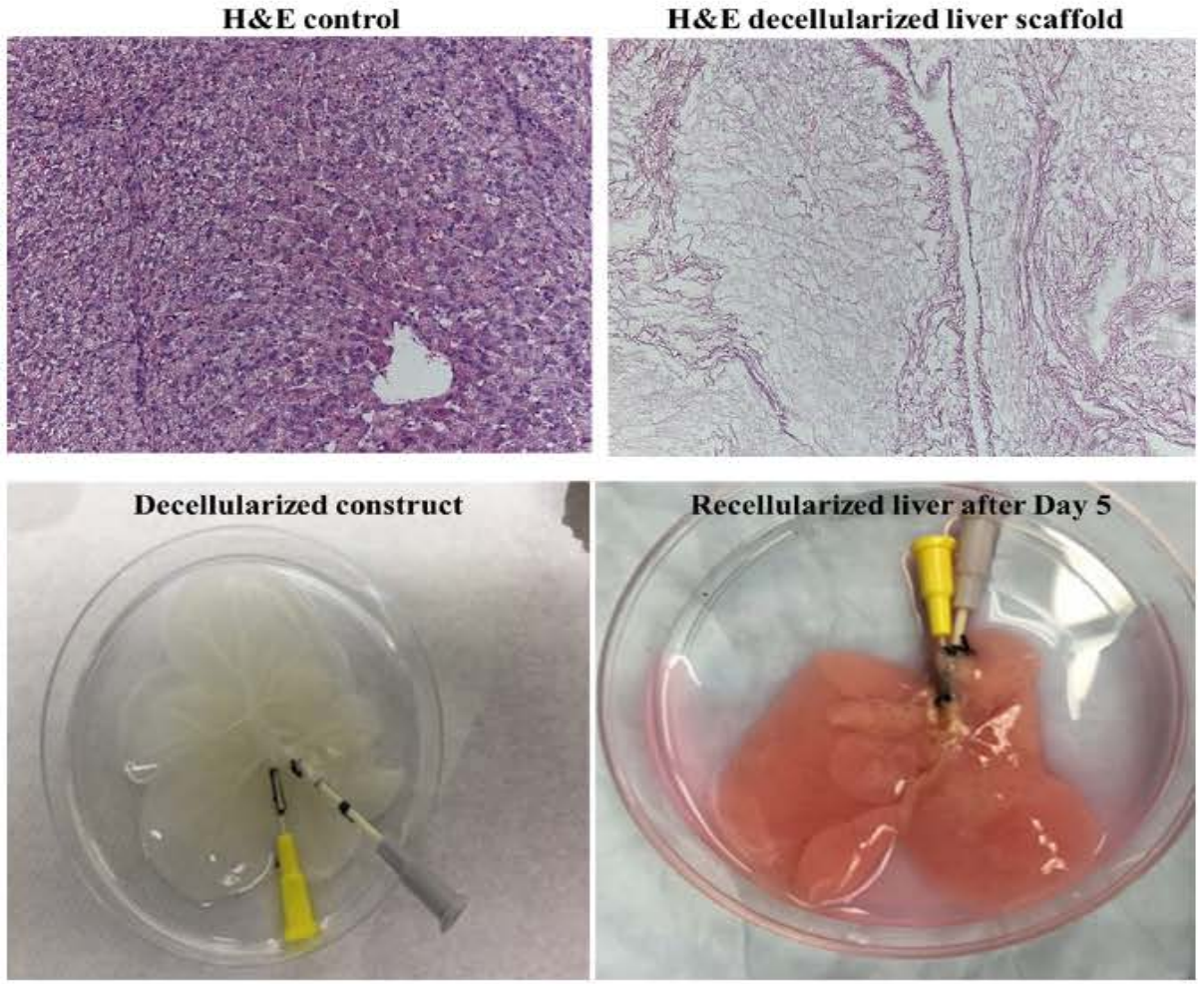




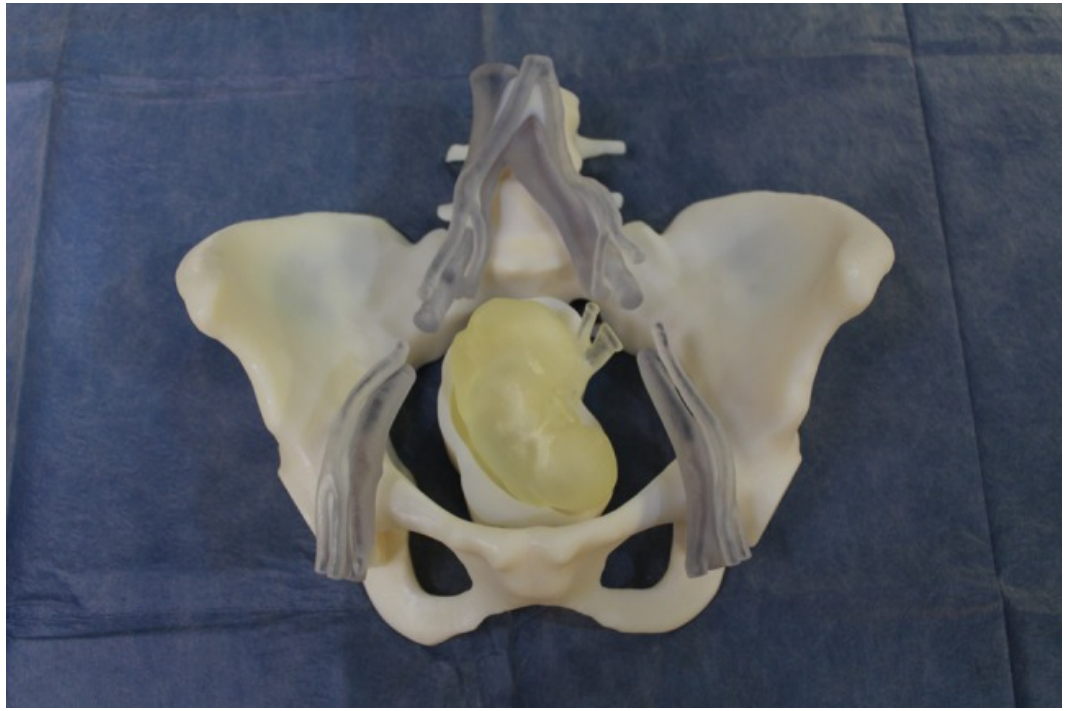
Liver Bioengineering – Biologic Scaffolds

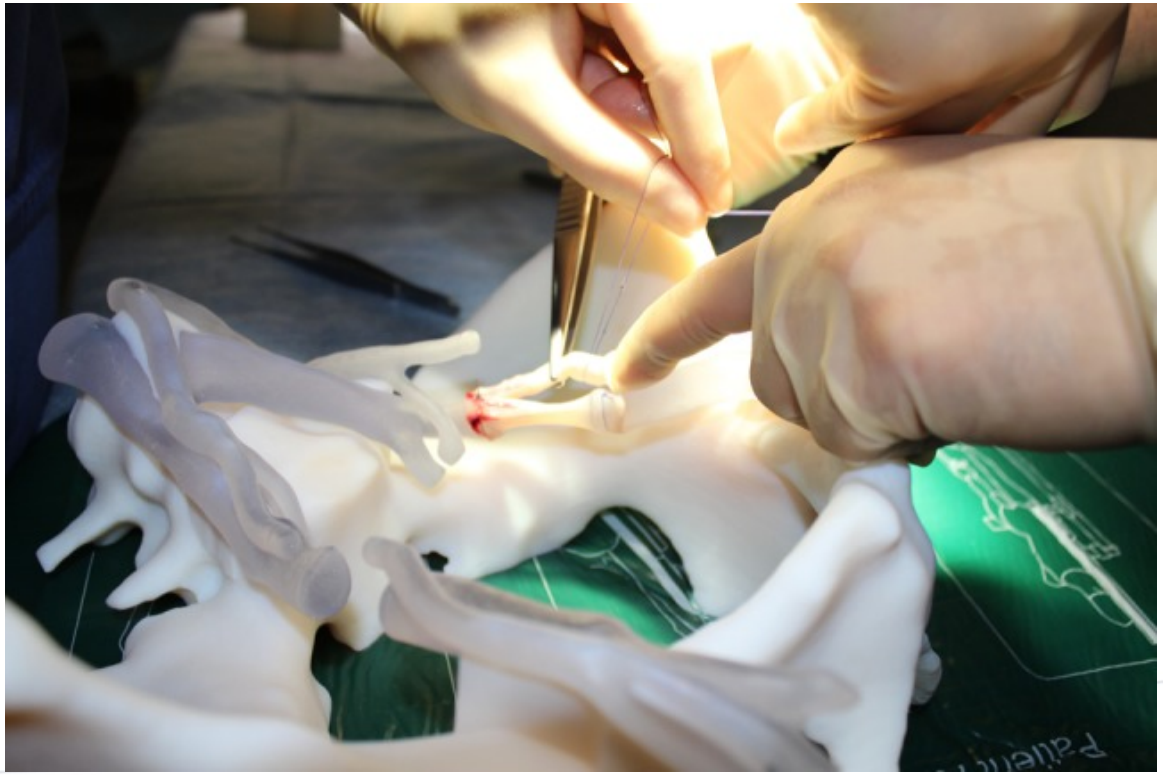
Detergent perfusion of porcine liver

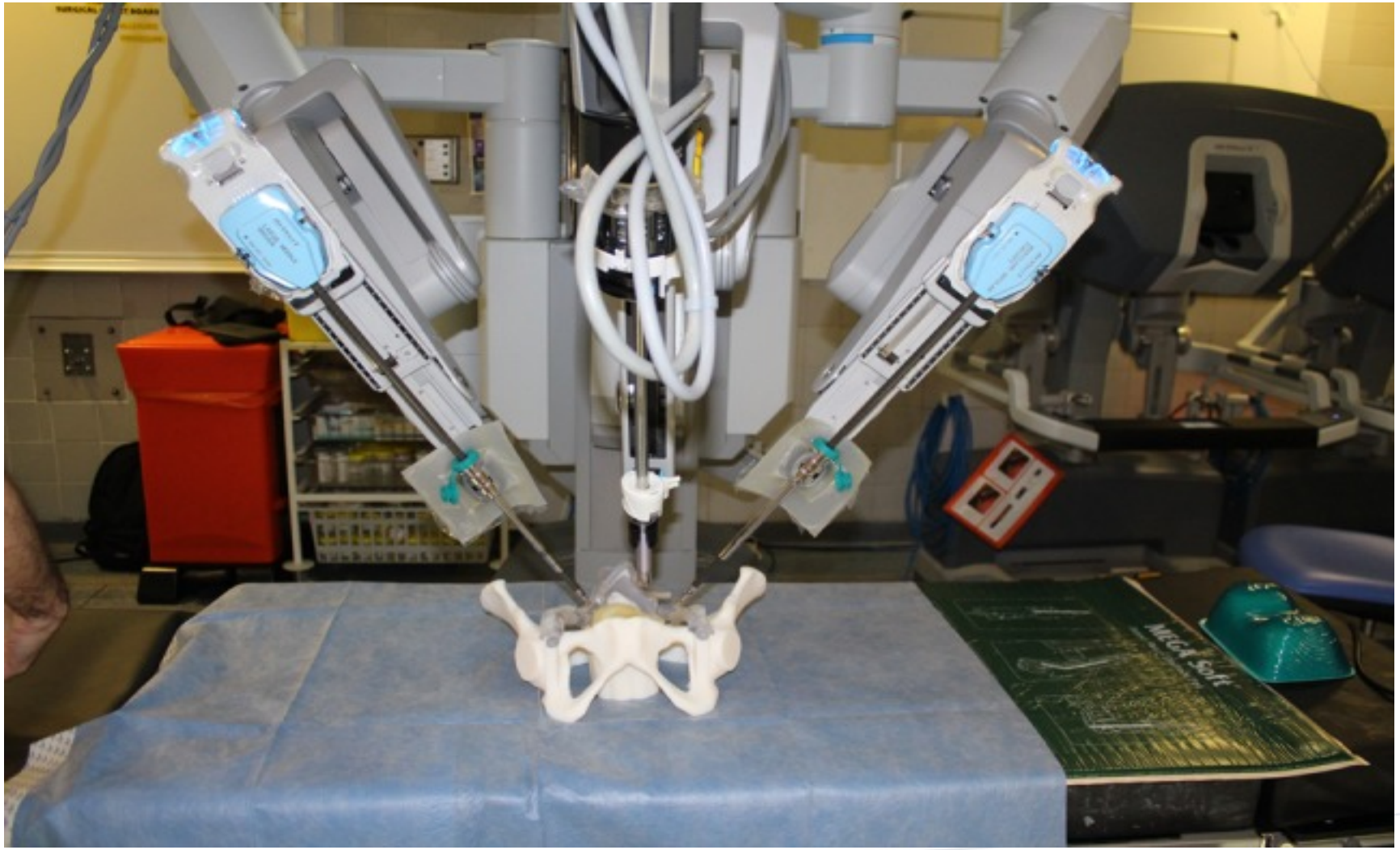


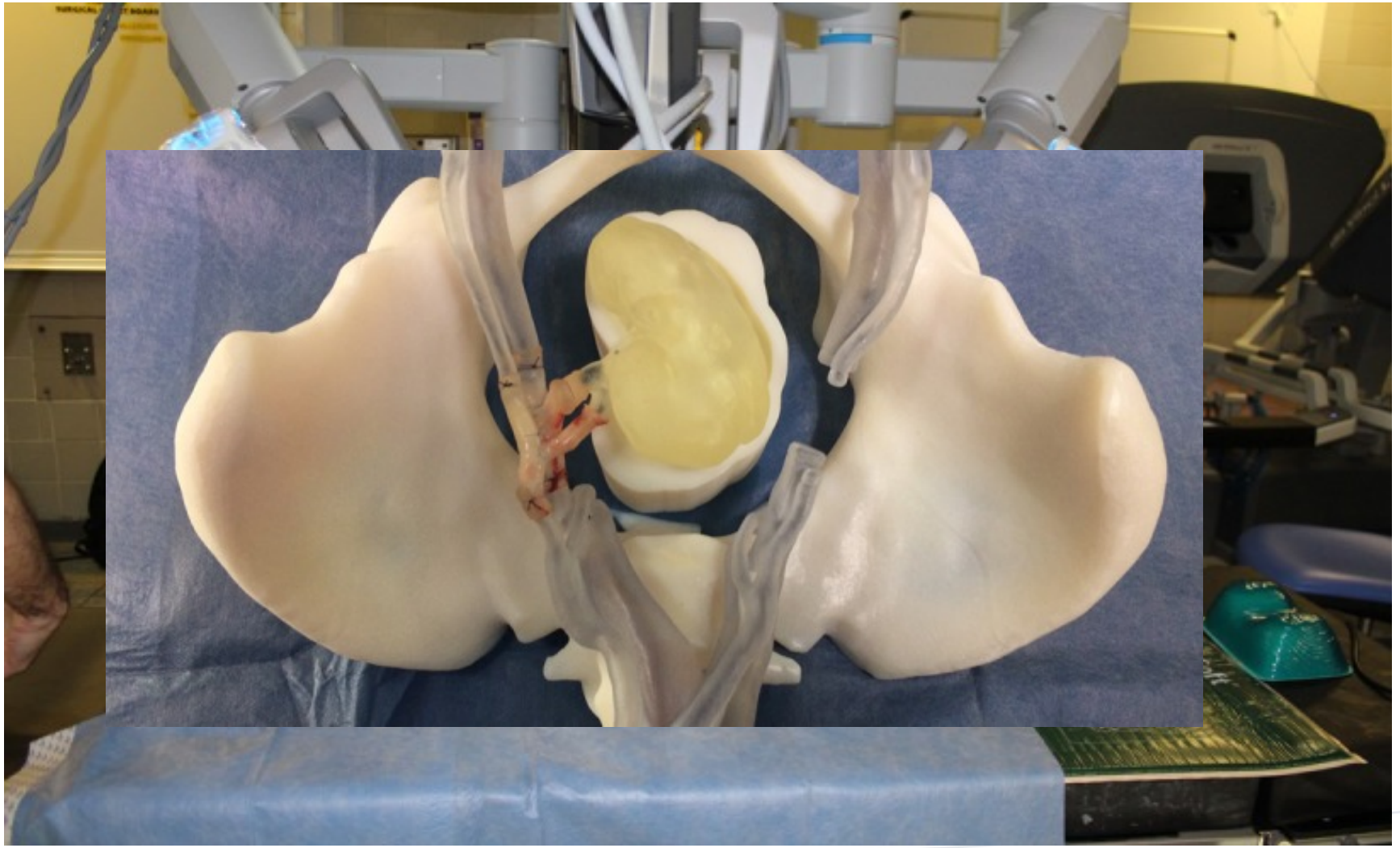


3D PRINTING

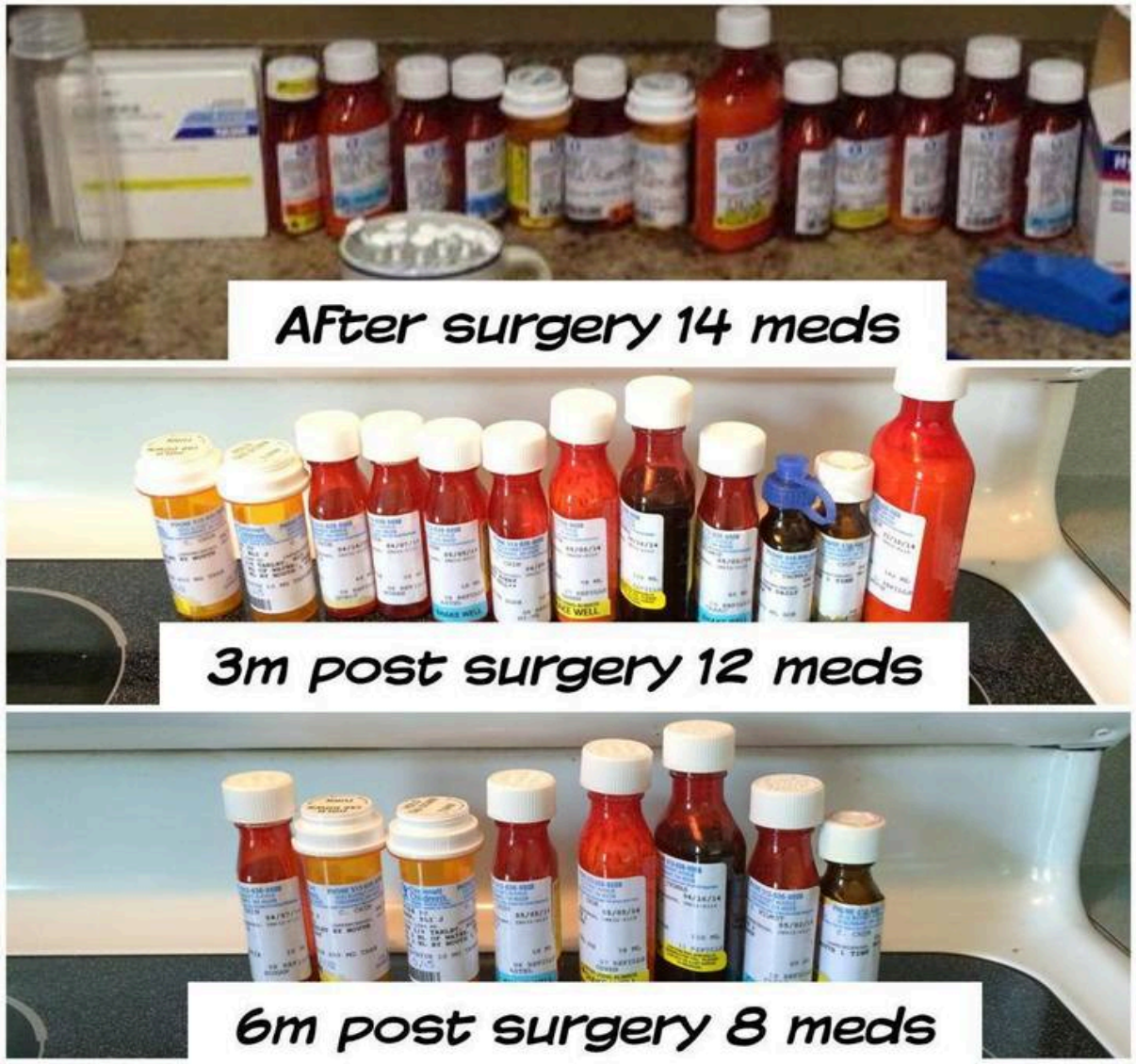


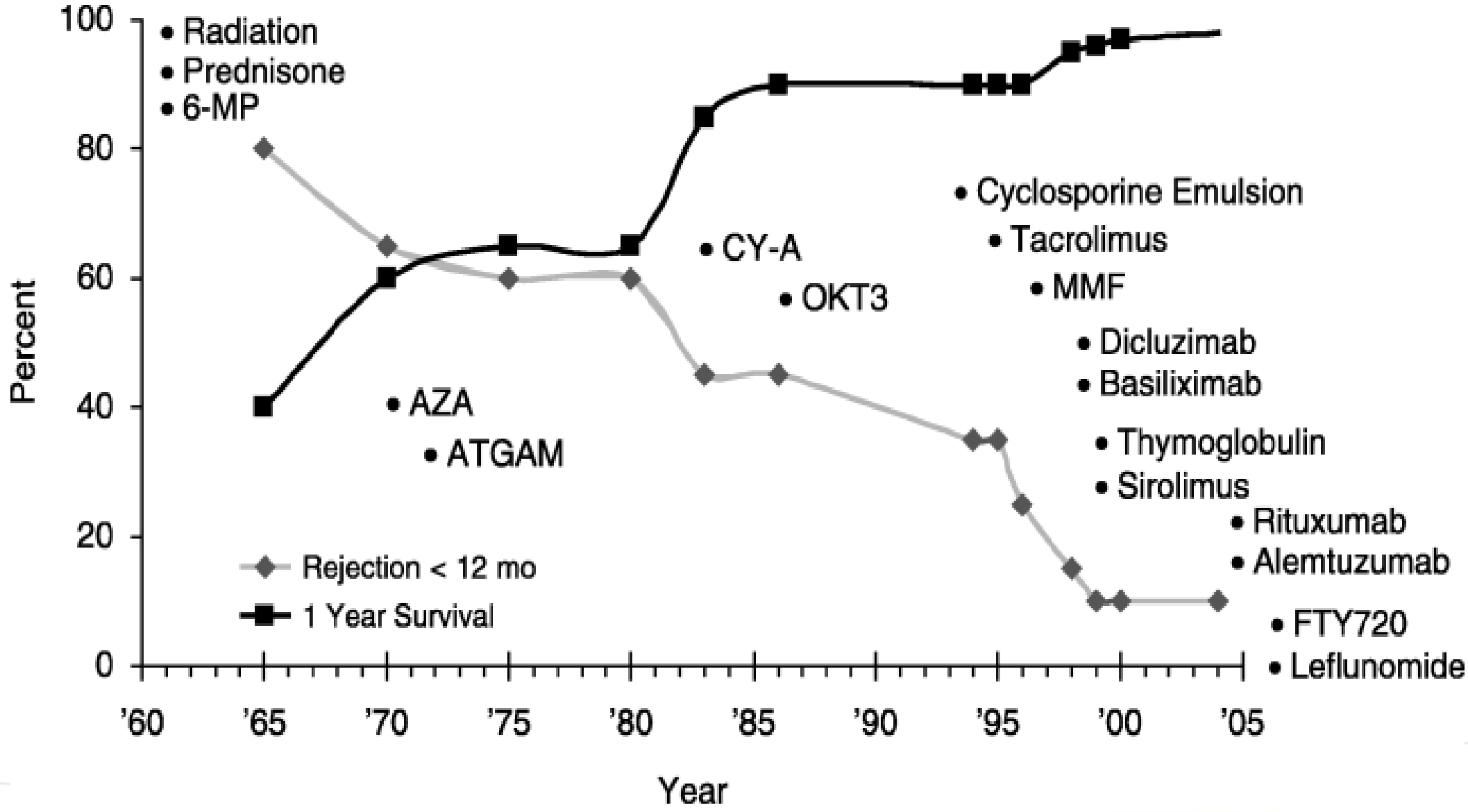



MEGA Soft

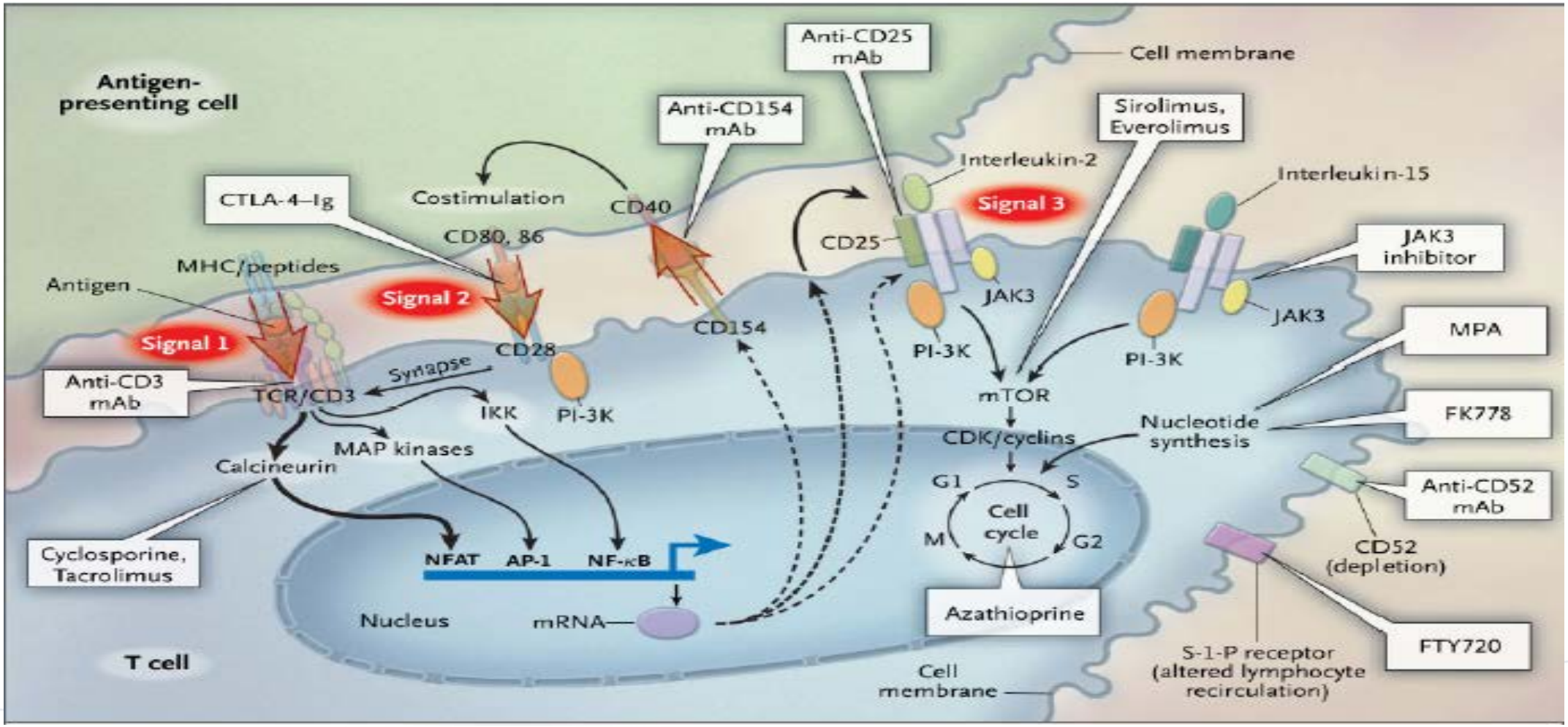


Transplant Medications




100
80
60
40
20
0
Percent
• Radiation
• Prednisone
• 6-MP
• AZA
• ATGAM
• CY-A
• OKT3
• Cyclosporine Emulsion
• Tacrolimus
• MMF
• Dicluzimab
• Basiliximab
• Thymoglobulin
• Sirolimus
• Rituxumab
• Alemtuzumab
• FTY720
• Leflunomide
Rejection < 12 mo
1 Year Survival
'60
'65
'70
'75
'80
'85
'90
'95
'00
'05
Year

Sites of Action of Immunosuppressive Medications



The Graveyard of Transplant Drugs

Inducing Tolerance??

Human Immunology 79 (2018) 272–276

Contents lists available at ScienceDirect

Human Immunology

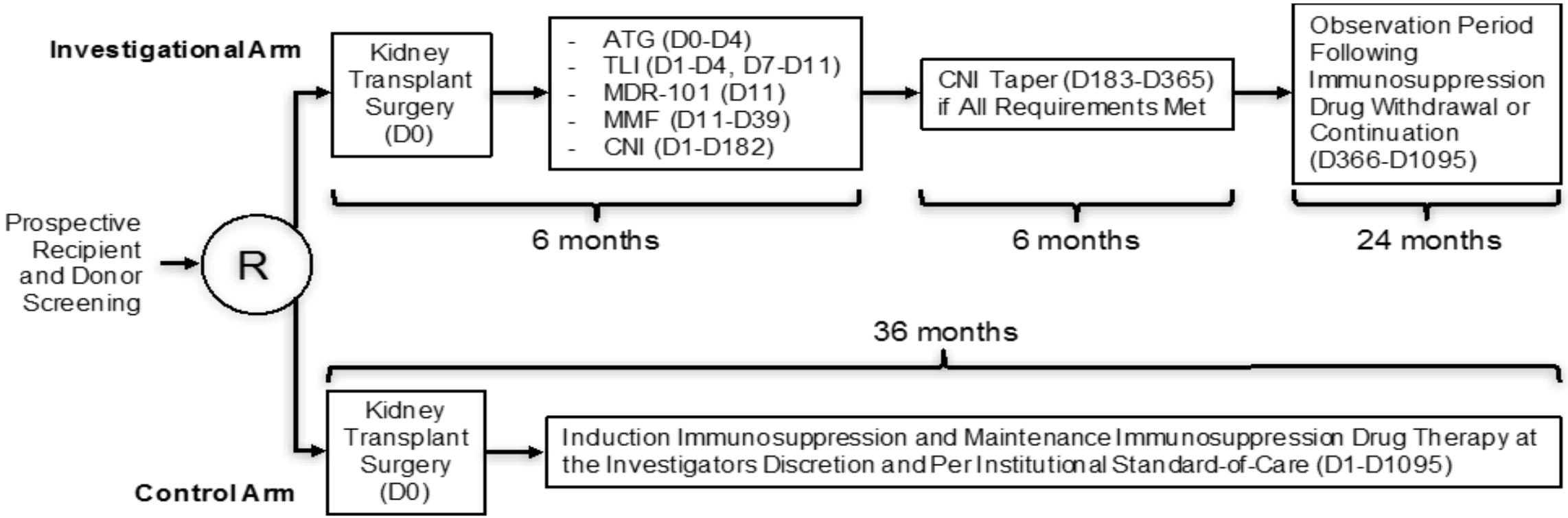
journal homepage: www.elsevier.com/locate/humimm

Tolerance induction in HLA disparate living donor kidney transplantation by facilitating cell-enriched donor stem cell Infusion: The importance of durable chimerism

Joseph R. Leventhal[a,*], Suzanne T. Ildstad[b]

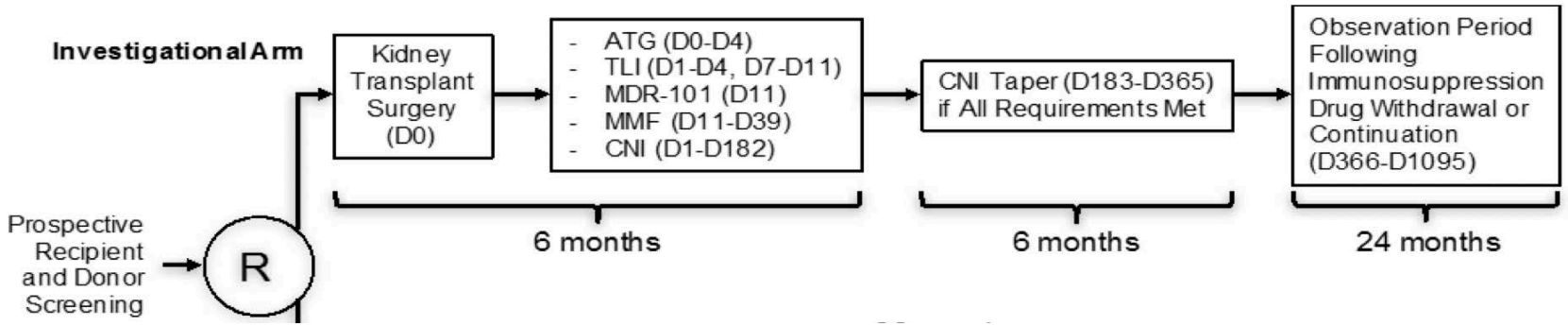
[a] Department of Surgery – Comprehensive Transplant Center, Northwestern University, Chicago, IL, USA
[b] Institute for Cellular Therapeutics, University of Louisville, Louisville, KY, USA

Common Study Treatment Schema



ATG = anti-thymocyte globulin; CNI = calcineurin inhibitor; MMF = mycophenolate mofetil; TLI = total lymphoid irradiation

Study Treatment - Investigational Arm

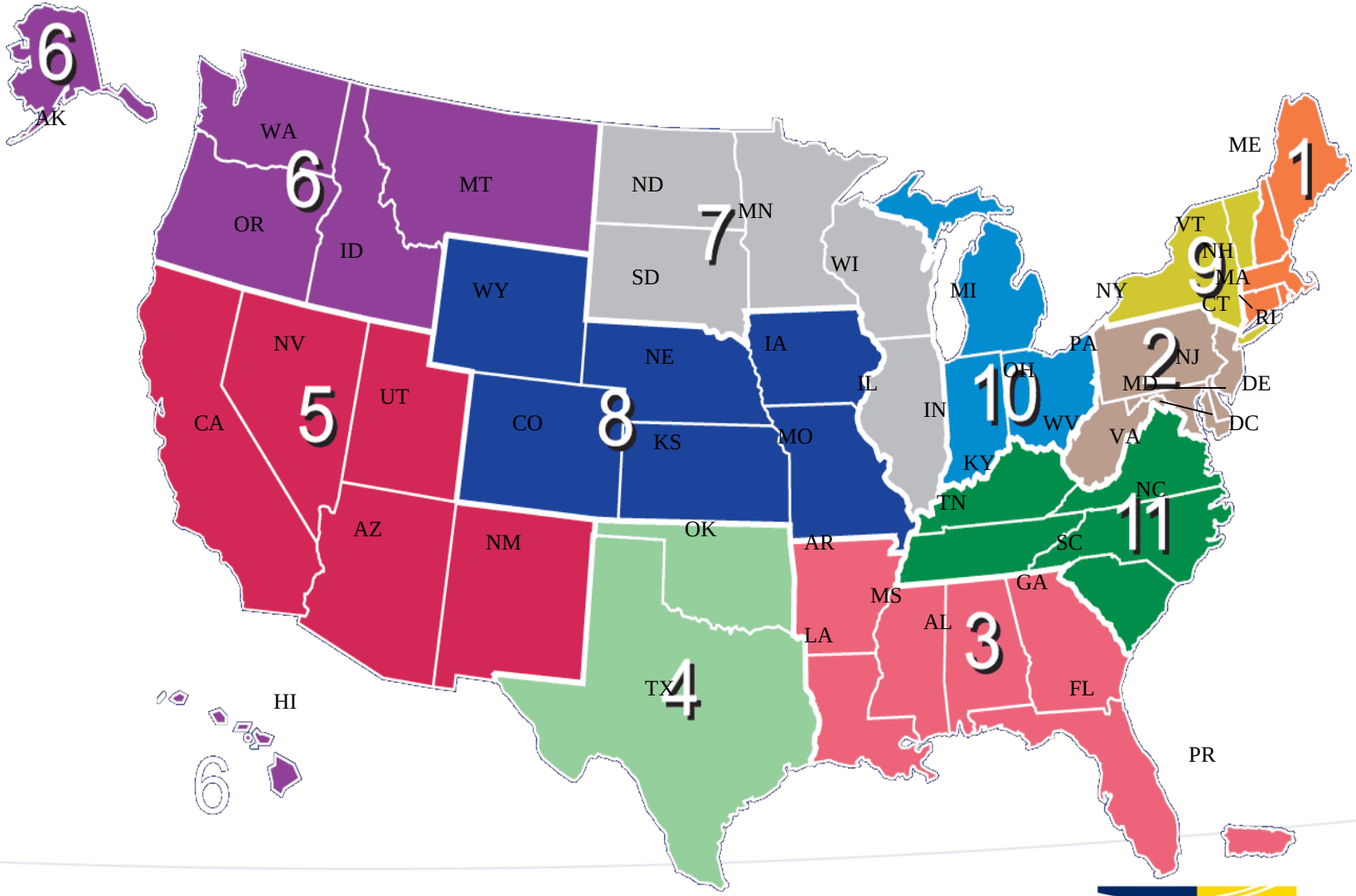


CNI= Calcineurin Inhibitor
MMF= Mycophenolate Mofetil

- **MDR-101 IV infusion**
  - D11 follows completion of TLI conditioning regimen
- **Conventional IS Therapy**
  - CNI* beginning on D1
    - Subjects eligible for CNI taper with at least 180d of persistent mixed chimerism & negative protocol biopsy; CNI will be tapered after 180d.
  - MMF for 28d beginning on the day of MDR-101 infusion (D11).
    - Chimerism check D30; if positive:
    - MMF will be discontinued without a taper

ORGAN TRANSPORTATION

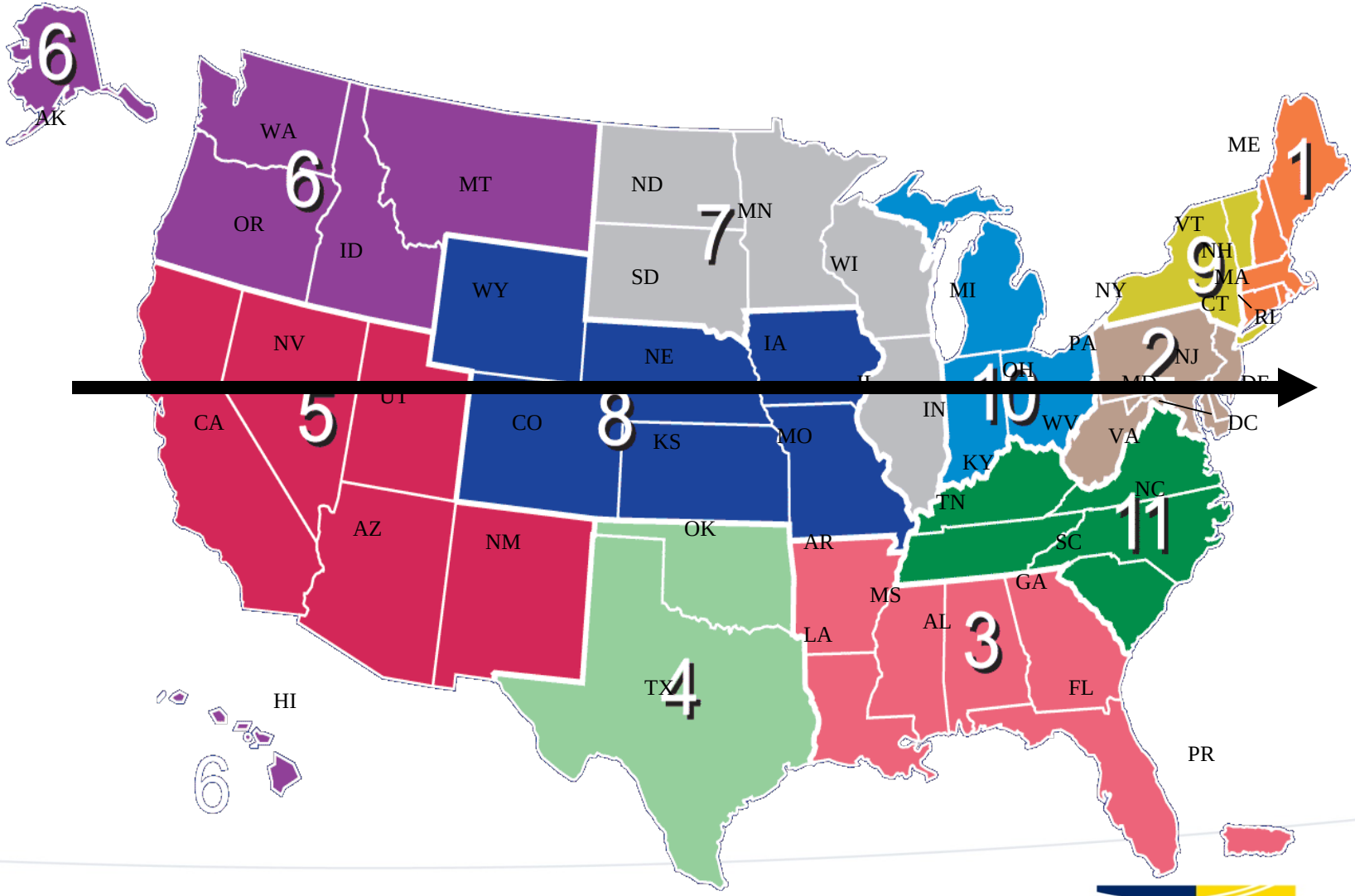
OPTN/UNOS REGIONAL MAP



Knowledge and Compassion **Focused on You**

MedStar Georgetown Transplant Institute

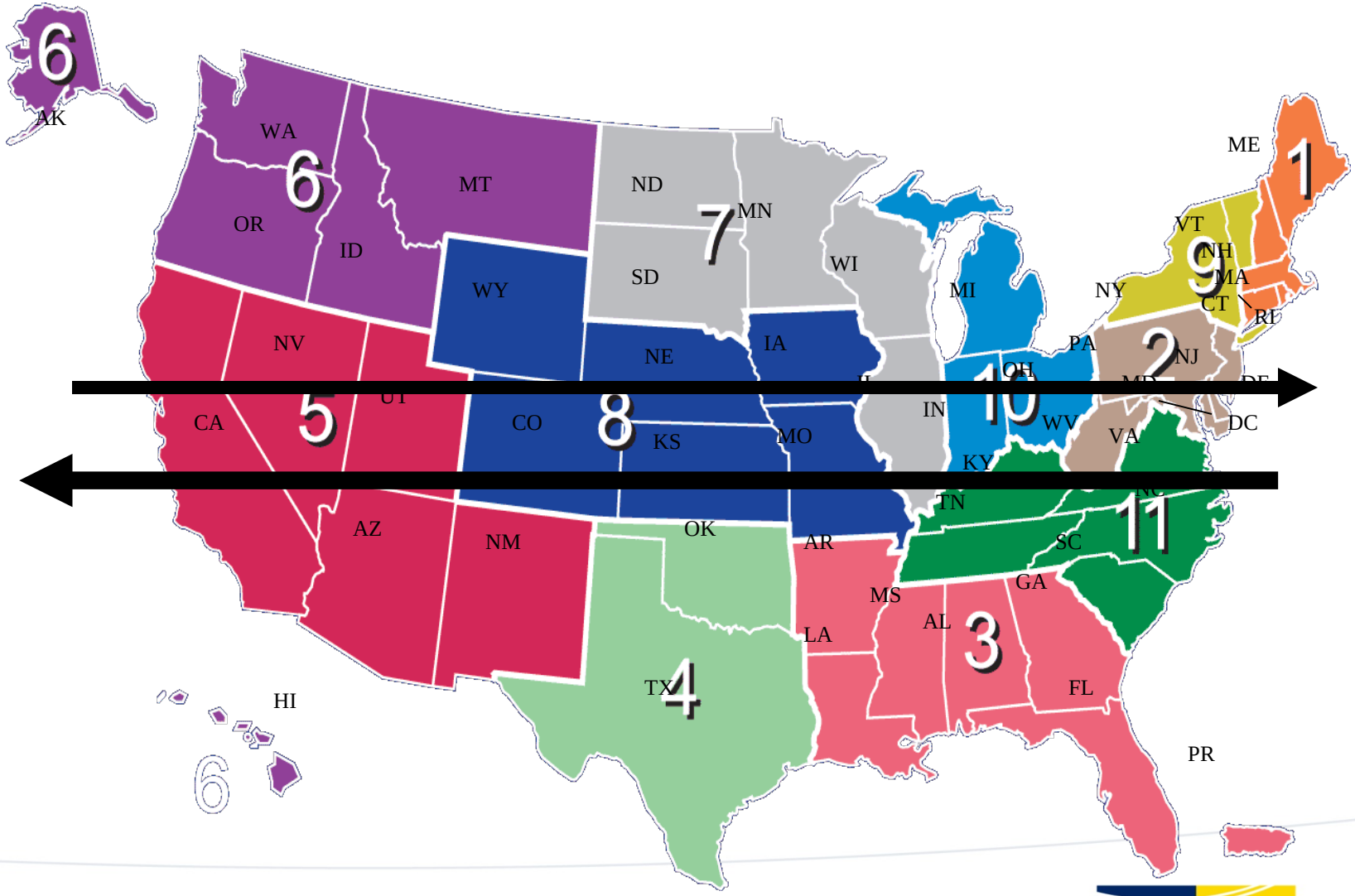
OPTN/UNOS REGIONAL MAP



Knowledge and Compassion **Focused on You**

MedStar Georgetown Transplant Institute

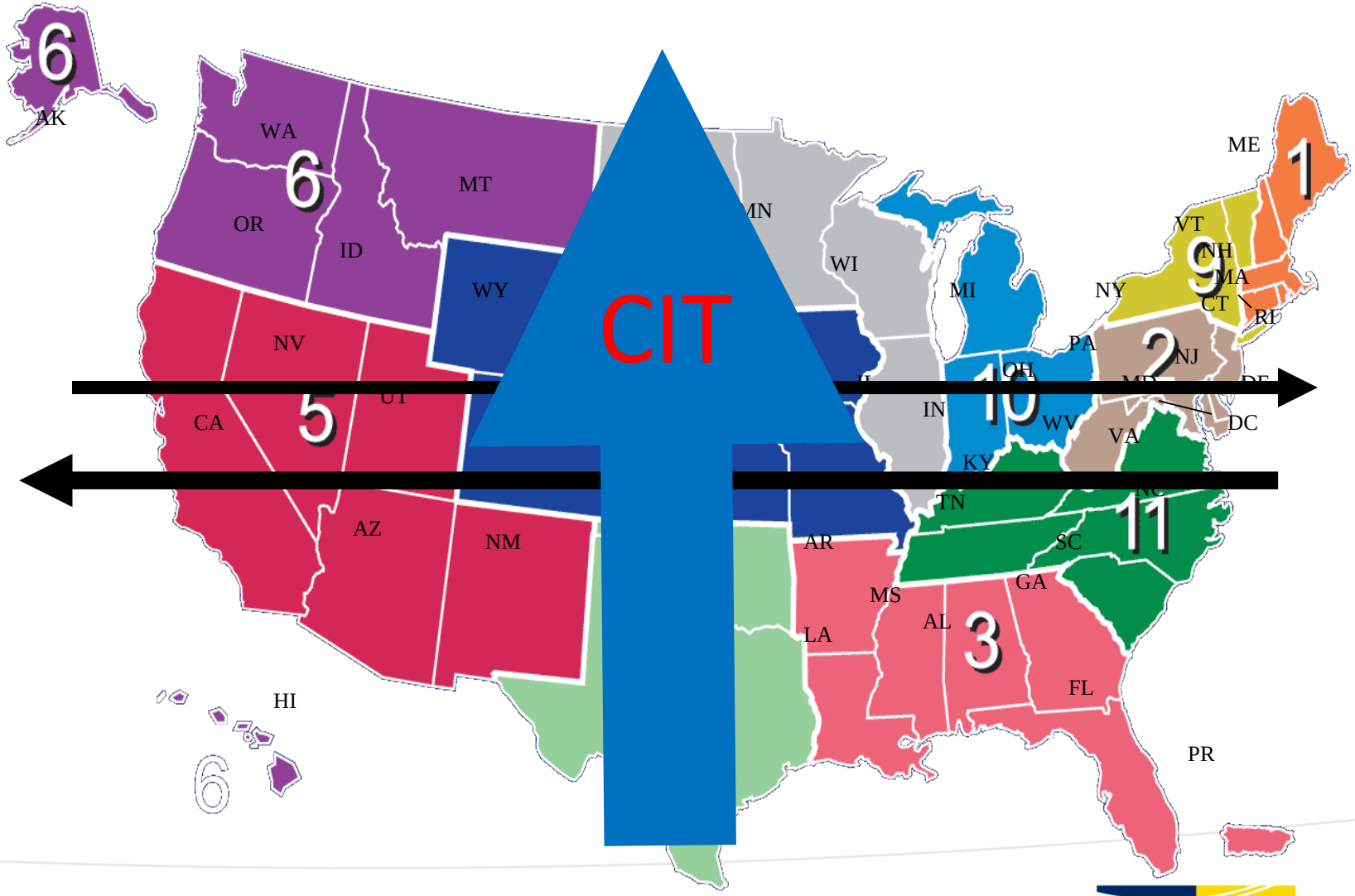
OPTN/UNOS REGIONAL MAP



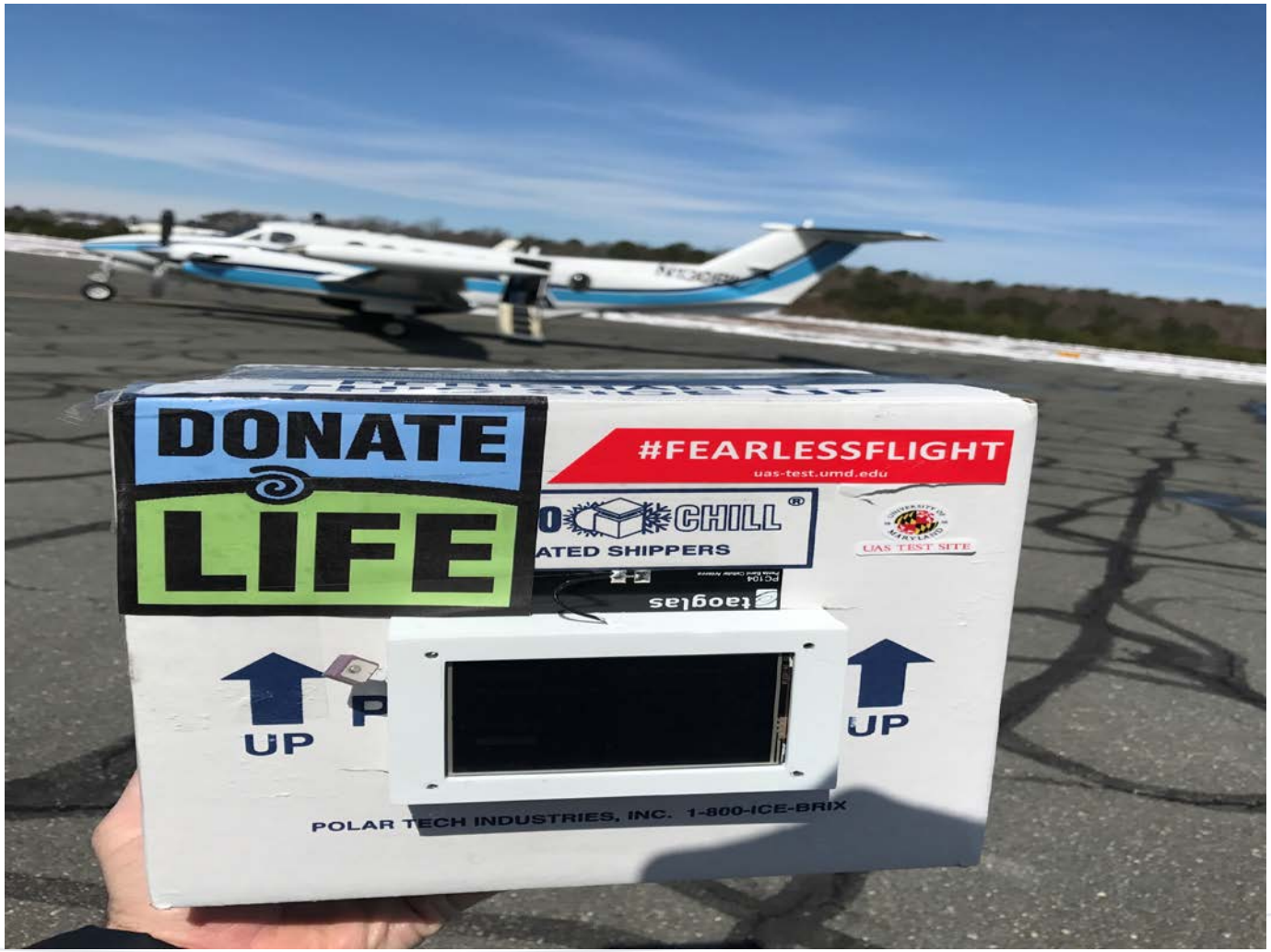
Knowledge and Compassion **Focused on You**

MedStar Georgetown Transplant Institute

OPTN/UNOS REGIONAL MAP



The Secret of Organ Transport



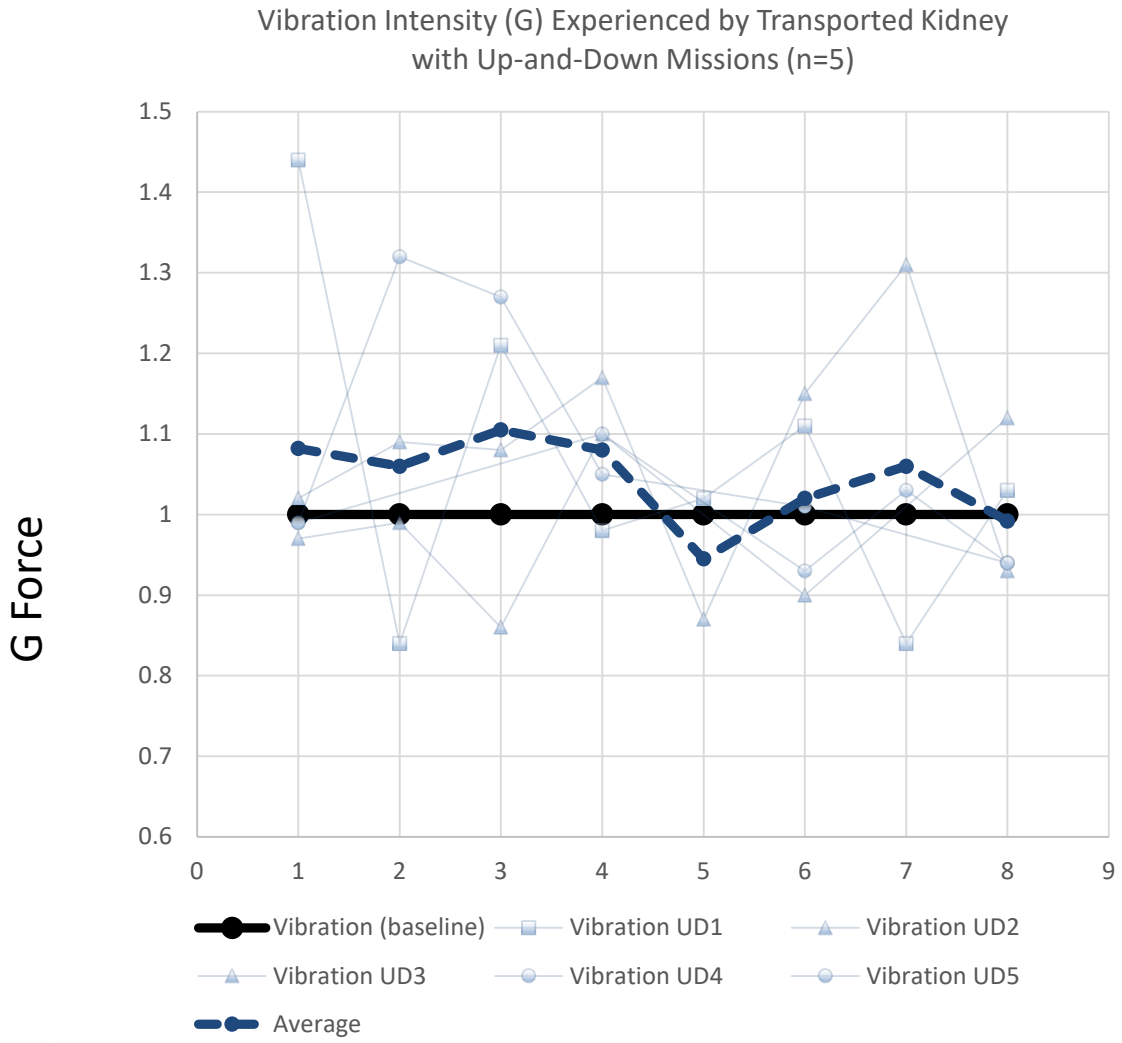
After losing 20 percent of its air cargo volume over the last decade due to a lack of infrastructure on and off the airport, JFK will undergo a $13 billion revitalization. Photo credit: Shutterstock.com.

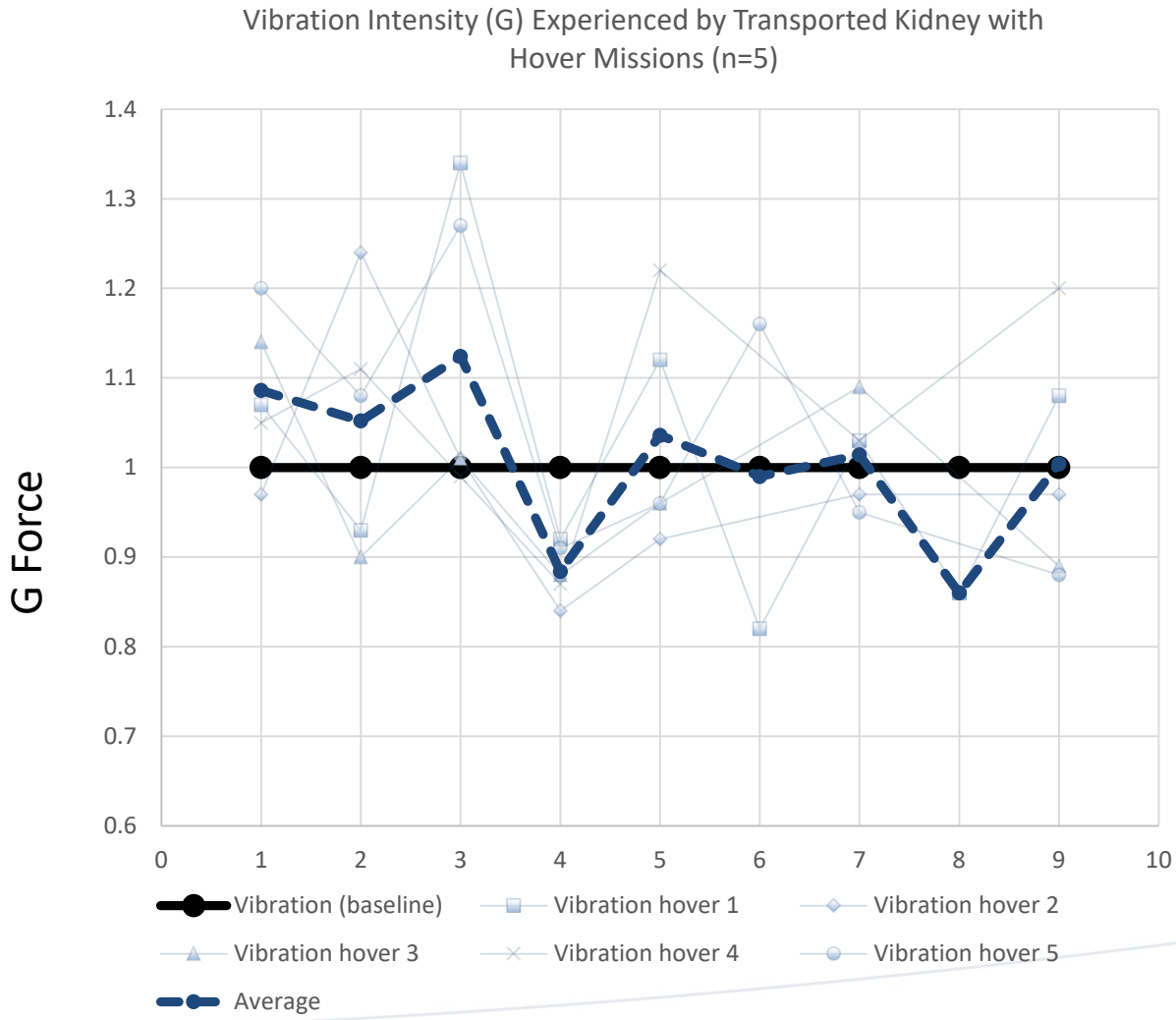
Drones!!

Drones!!

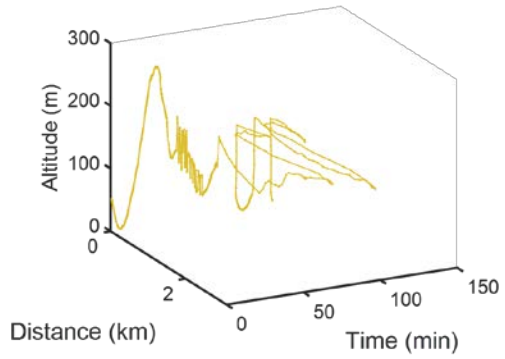
November 13, 2020

Vibration during UAS missions



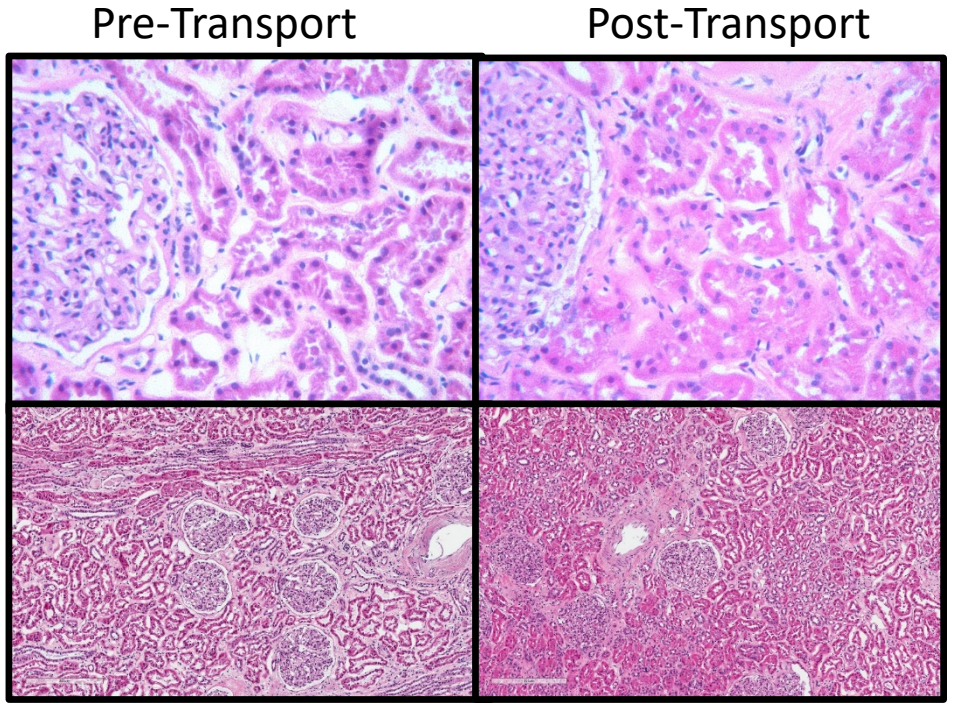


Payload tracking and organ quality status



High-magnification

Low-magnification



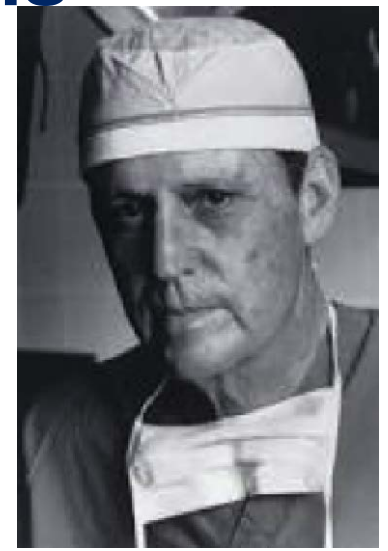
Xenotransplantation – Why???

- Need for organs

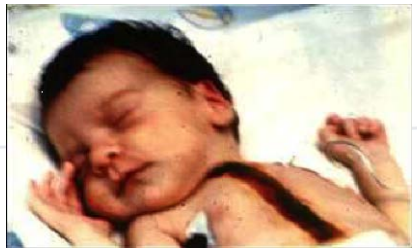
- Xenotransplantation
  - Fulfills organ supply
  - Avoidance of human donation ethical questions
  - Ability to plan transplants around conditioning regimens
  - Manipulation of donor animals (knockout, transgenic, etc.)

UNOS website, accessed 4/13/15

Early Xenotransplantation Attempts in Humans



- Starzl
  - Baboon kidneys 1964 (19-60 day survival)
  - Chimpanzee liver 1966-1974 (<14 day survival)
  - Baboon liver 1992-1993 (survival up to 70 days)
- Reemtsma: 13 baboon kidneys 1963 (9 month survival)
- Hardy: chimpanzee heart 1963 (90 min survival)
- Others: Barnard, Ross, Cooley, Bailey (Baby Fae 1984)



Early Troubleshooting

- Heavy immunosuppression
  - Could not ultimately prevent rejection
  - Major infectious complications

- Genetic engineering
  - hDaf pigs with human cell marker limiting complement cascade
  - Gal-knockout pigs lacking Gal cell surface epitope causing hyperacute rejection
  - Multiple knockouts
  - Cloning
  - CRISPR

- Conditioning regimens
  - Tregs + organ
  - Bone marrow + organ
  - Thymus + organ → T cell tolerance

Goldie: First genetically engineered Gal knockout pig

Emerging Strategy: Treg Therapy

- Infusion of purified Tregs prevents rejection

(Juvet et al. AJT. 2014;14: 750-763)

- Shown to suppress B cell response

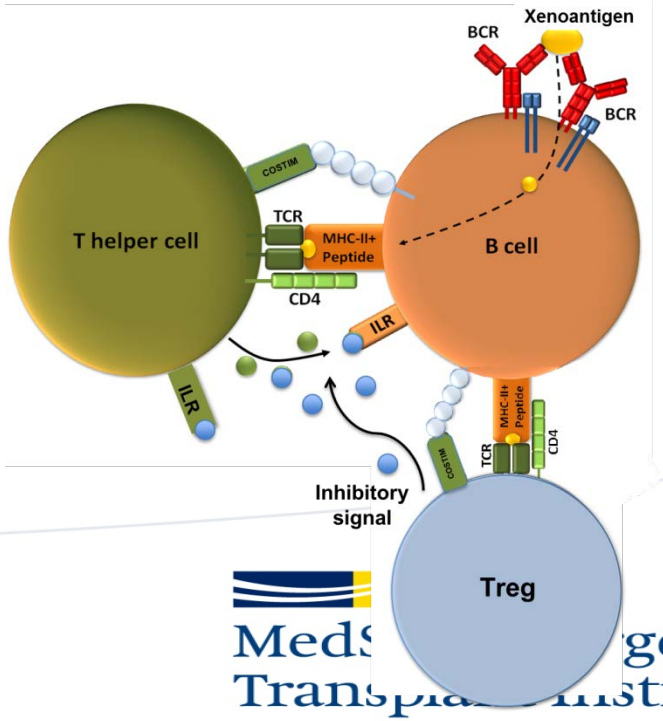
(Singh et al. Xenotransplantation. 2012;19(2): 102-11)

- Protocols for massive Treg expansion

(Hippen et al. Science Trans Med. 2011;3(83); Riley et al. Immunity. 2009: 30;656-665)

1971	•Suppressor cell concept (6)
1985	•CD4⁺ suppressor cells (8)
1990	•CD4⁺CD25⁺ suppressor cells (9)
1993	•CD4⁺ T cell-mediated infectious tolerance (1)
1995	•Tolerance induction generates regulatory CD4⁺ cells (14) •CD4⁺CD25⁺ cells control autoimmunity and graft rejection (15)
2001	•Characterization of human Tregs (24-25) •First expansion of human CD4⁺CD25⁺ Tregs from PB (93)
2002	•CD4⁺CD25⁺ cells control GVHD in mice (20-22)
2003	•Role of Foxp3 in nTregs (16-18) and iTregs (19)
2006	•Human Tregs are mainly CD127^{lo} (96)
2009	•First-in-human report of Treg therapy in GVHD (84)
2010	•Expansion of human CD127^{lo} Tregs (3)
2011	•Large-scale Treg expansion protocols (80, 82, 85, 86) •First clinical trials of Tregs in GVHD (26, 82)
2013	•The ONE study of regulatory cell therapy in kidney transplantation (30)

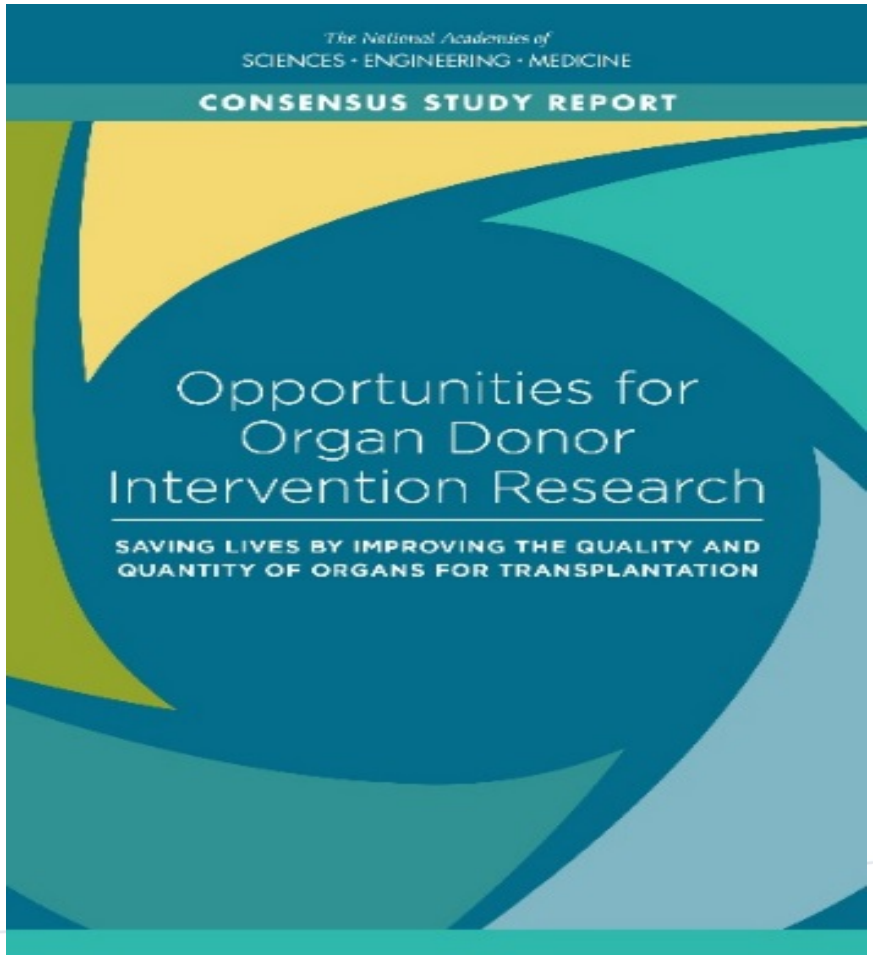
Juvet 2014



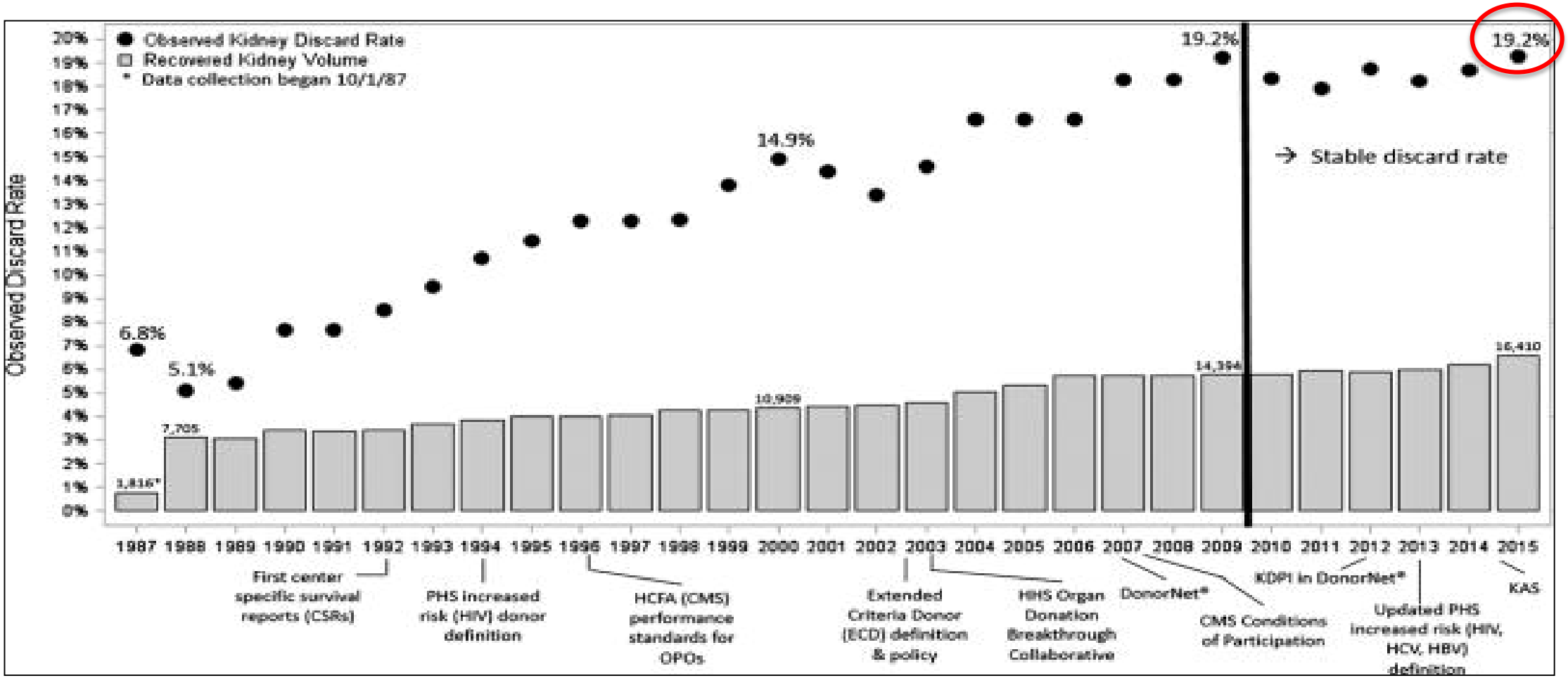
National Academy of Medicine Organ Donor Intervention Research

- Increase the quantity of organs available for transplantation
  - Additional opportunities for transplant

- Improve the quality of the donor organs
  - Additional years of graft survival



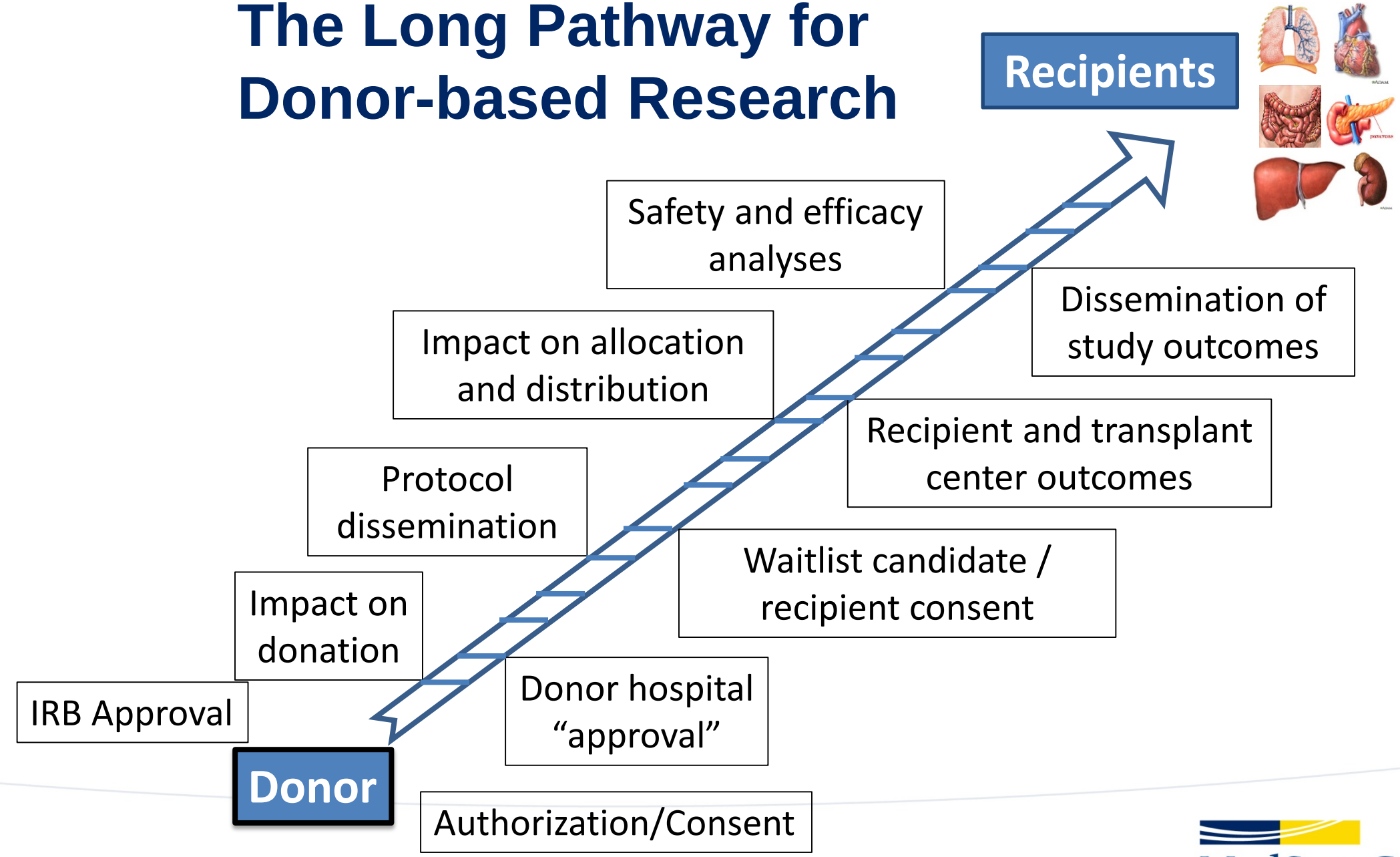
The Rising Deceased Donor Kidney Discard Rate in the U.S.



3159 kidneys were discarded in 2015

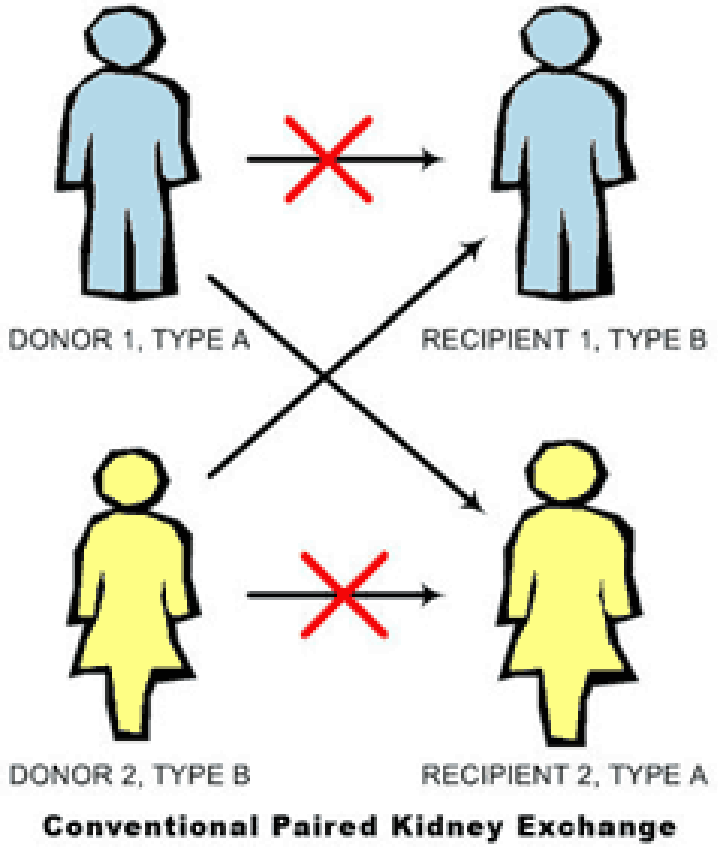
Stewart, D. Transplantation 2017; 101(3):575-587

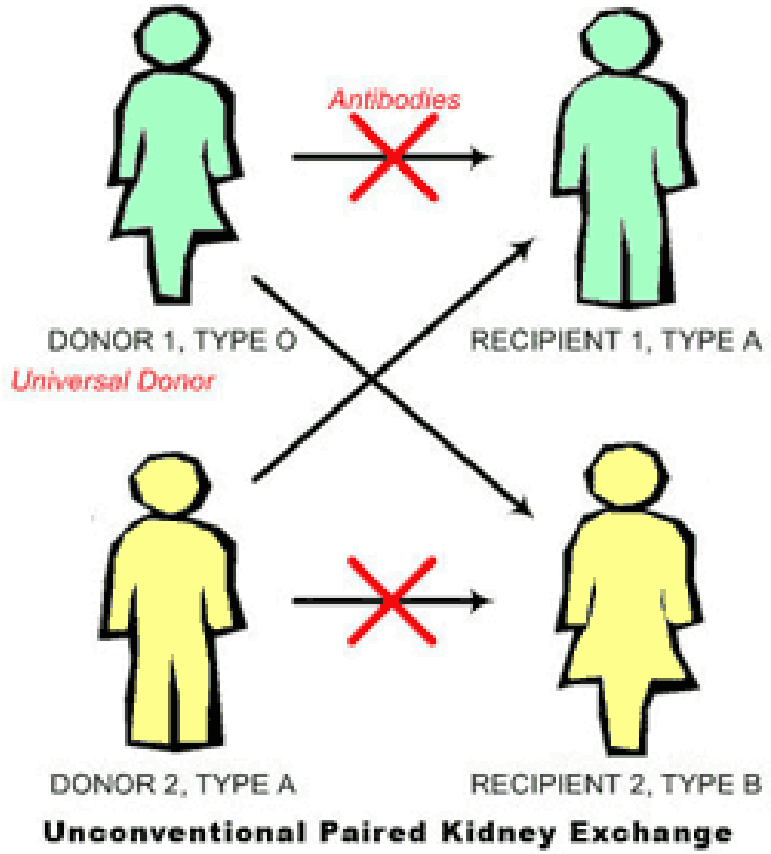
The Long Pathway for Donor-based Research



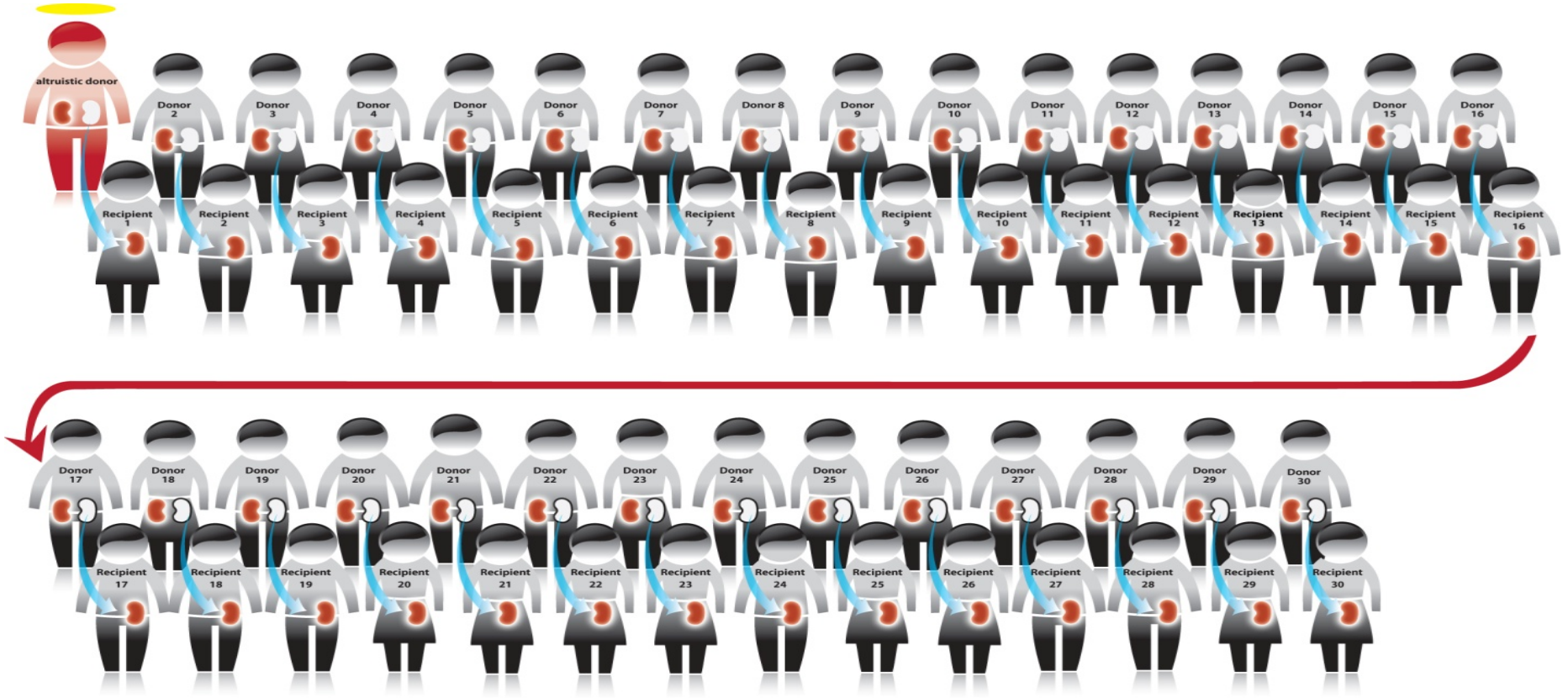
LIVING DONOR AND PKE

Rationale for paired exchange





Non-Directed Donors and Never Ending Donor Chains



Doctor, If you believe so much in living donation, why don’t you donate yourself??

The NKF Voucher Program

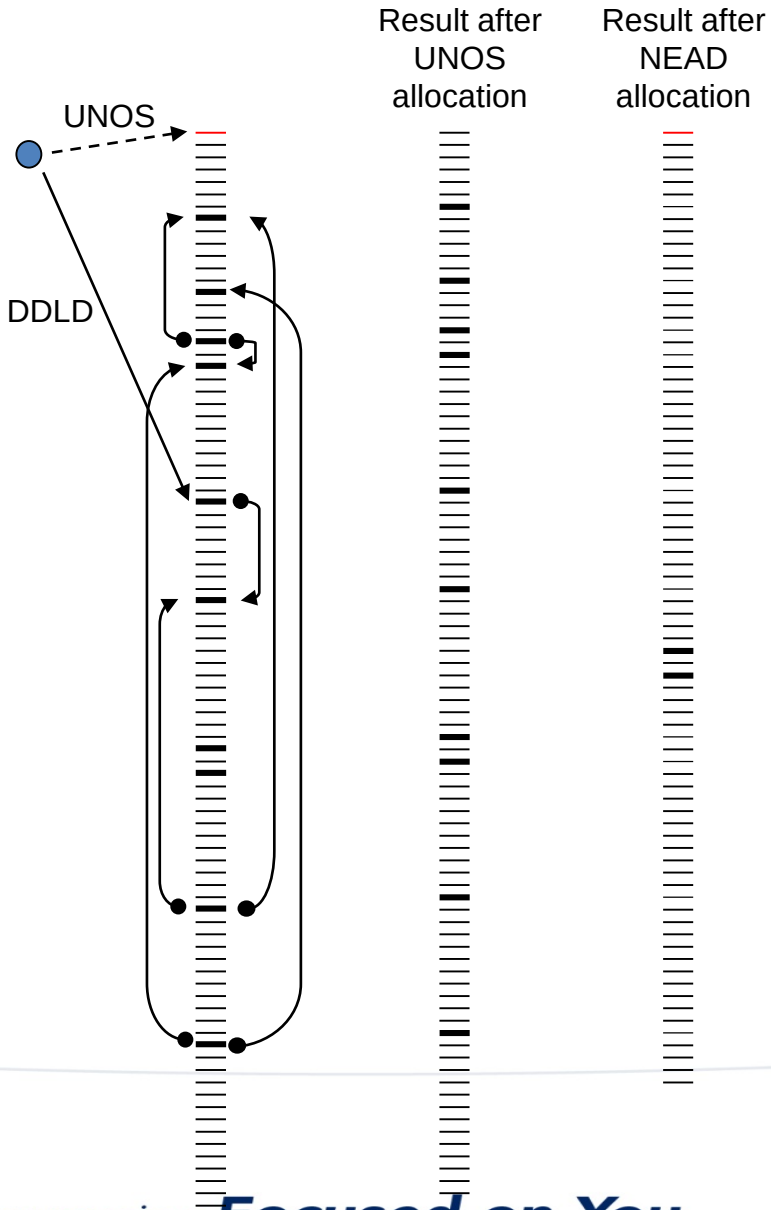
- Potential donors could be incompatible with their intended recipient based on:

- Blood Type
- DSA
- Anatomy
- Time

First 'voucher donor' Judge Broadman and first 'voucher holder' his grandson Quinn (UCLA 2014)

- **Family Voucher** allows identification of up to 5 immediate family members to hold vouchers if EVER needing kidney!

Deceased Donor →LD Chain



Patient at top of the Deceased Donor Waiting List
As determined by UNOS allocation algorithm

Allocation of altruistic donor kidney according to UNOS deceased donor allocation algorithm

Allocation of altruistic donor kidney according to NEAD chain allocation algorithm

Altruistic Donor

Patient on Deceased Donor Waiting List without an incompatible, but willing living donor

*Estimated Distribution by Ethnicity**

Caucasian	38.4%
African American	34.0%
Hispanic	18.1%
Asian	8.1%
Other	1.4%

Patient on Deceased Donor Waiting List with an incompatible, but willing living donor

*Estimated Distribution by Ethnicity**

Caucasian	70.3%
African American	12.5%
Hispanic	13.0%
Asian	2.9%
Other	1.2%

Future of Transplant?

- Human organs for the foreseeable future
- Increased sharing and transportation with organ shortage
- Demanded an improved allocation policy
- Removal of disincentives to living donation
- Reduced regulatory oversight →Increased innovation
- Ongoing research into Tolerance
- Support for other sources of organs
- Coordinated advocacy