



Interventions in the Deceased Organ Donor to Improve Organ Quality and Quantity

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RESOLVING THE ORGAN SHORTAGE



PRACTICE |



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POLITICS

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Conflict of Interest Disclosure

I have no relevant financial relationships to disclose.

Objectives

- Why do we need donor intervention trials?
- Why are donor intervention trials complex?
- What is being done to facilitate more donor intervention trials?

What might be accomplished through deceased donor intervention?

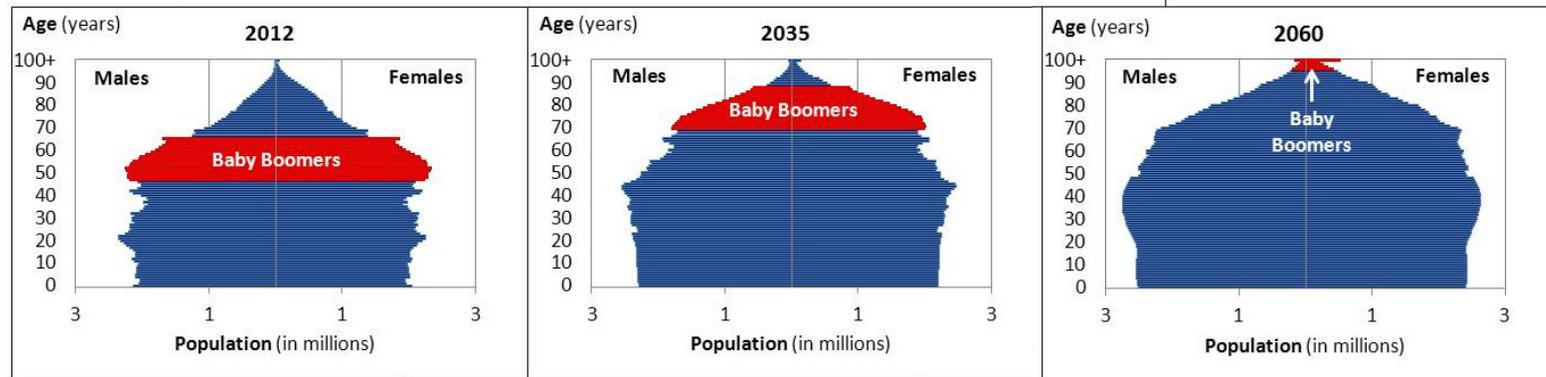
- Increase the quantity of organs available for transplantation.
 - Additional opportunities for transplant
- Increase the quality of the donor organs.
 - Additional years of graft survival

The Big Picture



- Demographics of the U.S. population project:
 - Increased demand for organs for transplantation
 - Decreased quality and low to modest increase of organs suitable for transplantation

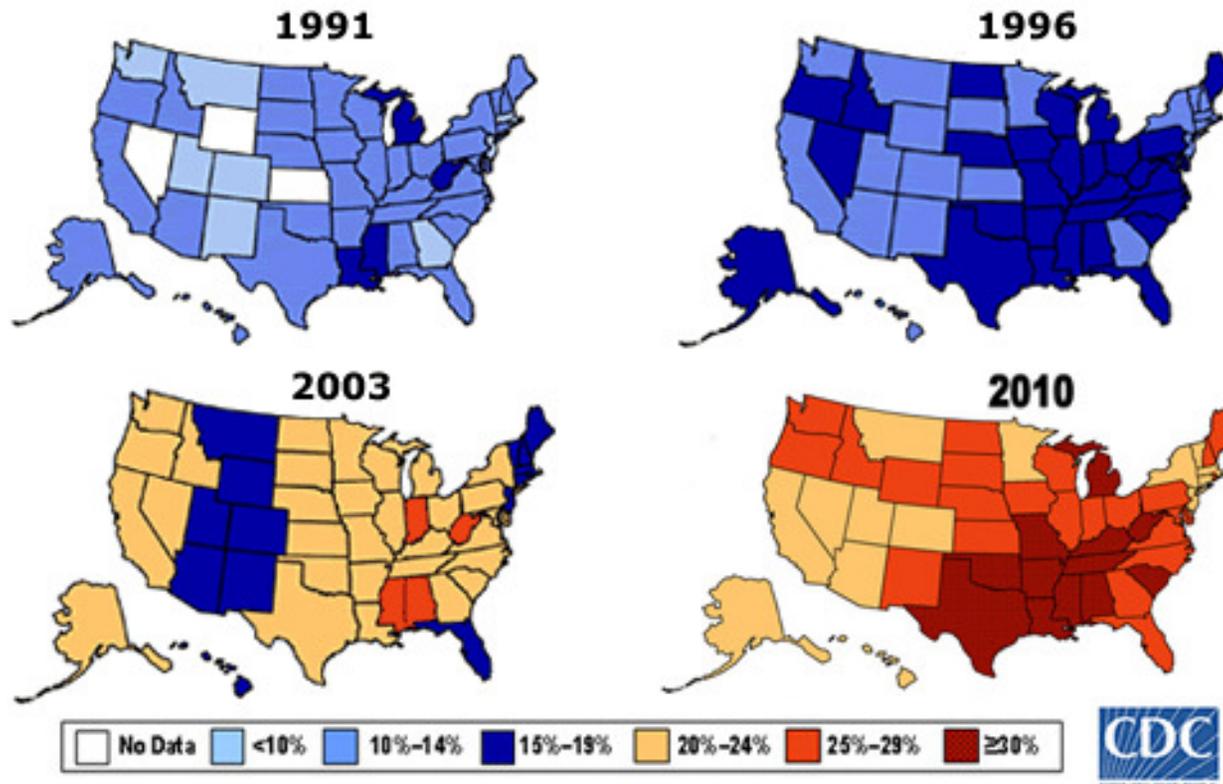
Aging of the U.S. Population



- Population age ≥ 65 years will more than double between 2012 and 2060
 - 43.1 million \rightarrow 92.0 million
 - 1 in 7 \rightarrow 1 in 5 US residents

United States[™]
Census
Bureau

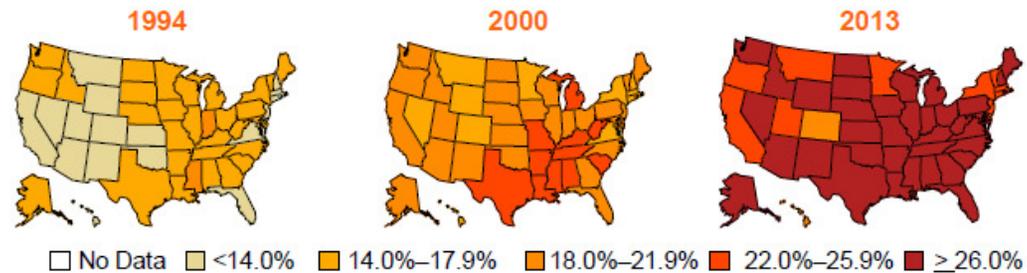
The Obesity Epidemic



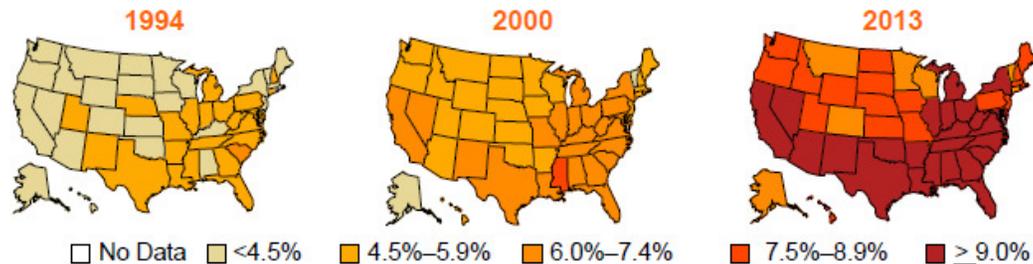
Obesity \leftrightarrow Diabetes

Age adjusted trends among US Adults

Obesity



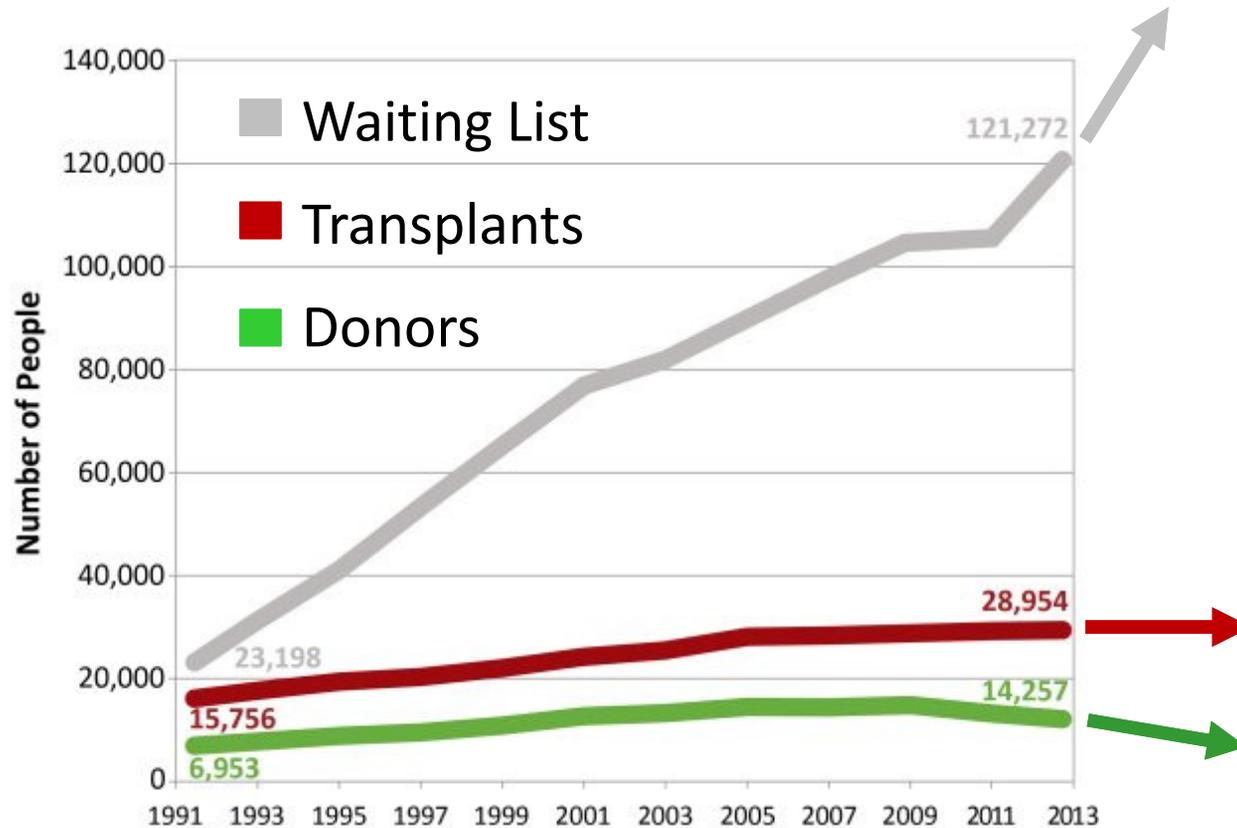
Diagnosed Diabetes



CDC's Division of Diabetes Translation. National Diabetes Surveillance System
available at <http://www.cdc.gov/diabetes/statistics>



The Wide / Ever Widening Gap



Organ Injury Secondary to Brain Death and Transplantation



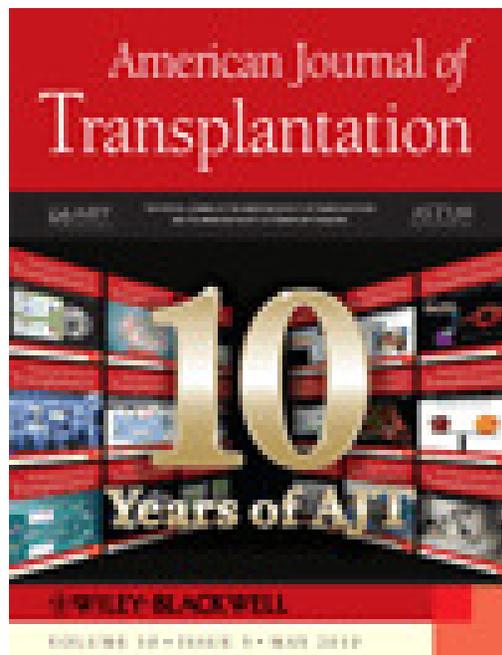
- Brain death is a physiologic, cellular, and molecular catastrophe that compromises organ viability and function
- The injury sustained in the donor is compounded by ischemia / reperfusion injury in the recipient
- Organs procured from older, less healthy donors are particularly vulnerable to injury

The Role of Research

- Population demographics impose severe limits on both the quantity and quality of suitable organs for transplantation
- Research is the **ONLY** approach that can mitigate the organ injury incurred as a result of brain death and transplantation
 - Improve the function organs that are utilized
 - Recruit additional organs for transplantation

Donor Intervention and Organ Preservation: Where Is the Science and What Are the Obstacles?

S. Feng



The organ shortage is widely acknowledged as the most critical factor hindering the full realization of success for solid organ transplantation. Innovation in the areas of donor management and organ preservation offers the most realistic hope to improve both the quality and size of the current organ supply. Although the basic science dissecting the complex processes of brain death and ischemia/reperfusion injury is replete with exciting discoveries, the clinical science investigating donor management and organ preservation is sparse in contrast. This review will survey the current landscape of trials to mitigate organ injury through interventions administered to donors *in vivo* or organs *ex vivo*. Consideration will then be given to the scientific, logistical and ethical obstacles that impede the transformation of laboratory breakthroughs into innovative treatments that simultaneously improve organ quality and supply.

NCT00245830	10/03	UNK	Ischemic Preconditioning of Liver in Deceased Donors	Completed	100	Treatment, Randomized, Single Blind, Active Control, Parallel Assignment, Efficacy Study
NCT00115115	3/04	12/07	Donor Dopar Initial Graft	Completed	100	Treatment, Randomized, Open Label, Active Control, Parallel Assignment, Efficacy Study
NCT00260676	9/04	(9/09)	Protective Ventilatory Strategy in Organ Donors	Recruiting	200	Treatment, Randomized, Open Label, Active Control, Parallel Group Assignment, Safety/Efficacy Study
NCT00238030	12/04	UNK	Thyroxine Replacement in Organ Donors	Recruiting	30	Treatment, Randomized, Double-Blind, Placebo Control, Single Group Assignment, Efficacy Study
NCT00998972	9/06	(1/10)	N-acetyl-cysteine (NAC) and Kidney Graft Function	Recruiting	236	Treatment, Randomized, Single Blind (Subject), Uncontrolled, Parallel Assignment, Efficacy Study
NCT00718575	8/08	(7/11)	The Effects of Glucose / Ischemic Preconditioning on Reperfusion Injury in Deceased Donor Liver Transplantation	Recruiting	(100)	Treatment, Randomized, Single Blind (Subject), Parallel Assignment, Safety/Efficacy Study
NCT00975702	4/09	(6/12)	Remote Ischemic Preconditioning in Abdominal Organ Transplantation (RIPCOT)	Enrolling by Invitation	580	Treatment, Randomized, Double Blind (Subject, Caregiver, Investigator), Active Control, Parallel Assignment, Safety/Efficacy Study
NCT00987714	8/09	(2/11)	Monitoring Organ Donors to Increase Transplantation Results (MOniToR)	Recruiting	(960)	Randomized, Open Label, Uncontrolled, Parallel Assignment

6 open trials

2010

Feng S.
AJT 2010

The Incredible Potential of Donor Intervention Trials



The NEW ENGLAND
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Therapeutic Hypothermia in Deceased Organ Donors and Kidney-Graft Function

Claus U. Niemann, M.D., John Feiner, M.D., Sharon Swain, M.S.N., R.N., Scott Bunting, R.R.T.,
Melissa Friedman, M.S.N., R.N., Megan Crutchfield, M.P.H., Kristine Broglio, M.S., Ryutaro Hirose, M.D.,
John P. Roberts, M.D., and Darren Malinoski, M.D.

Hypothermia Trial Design

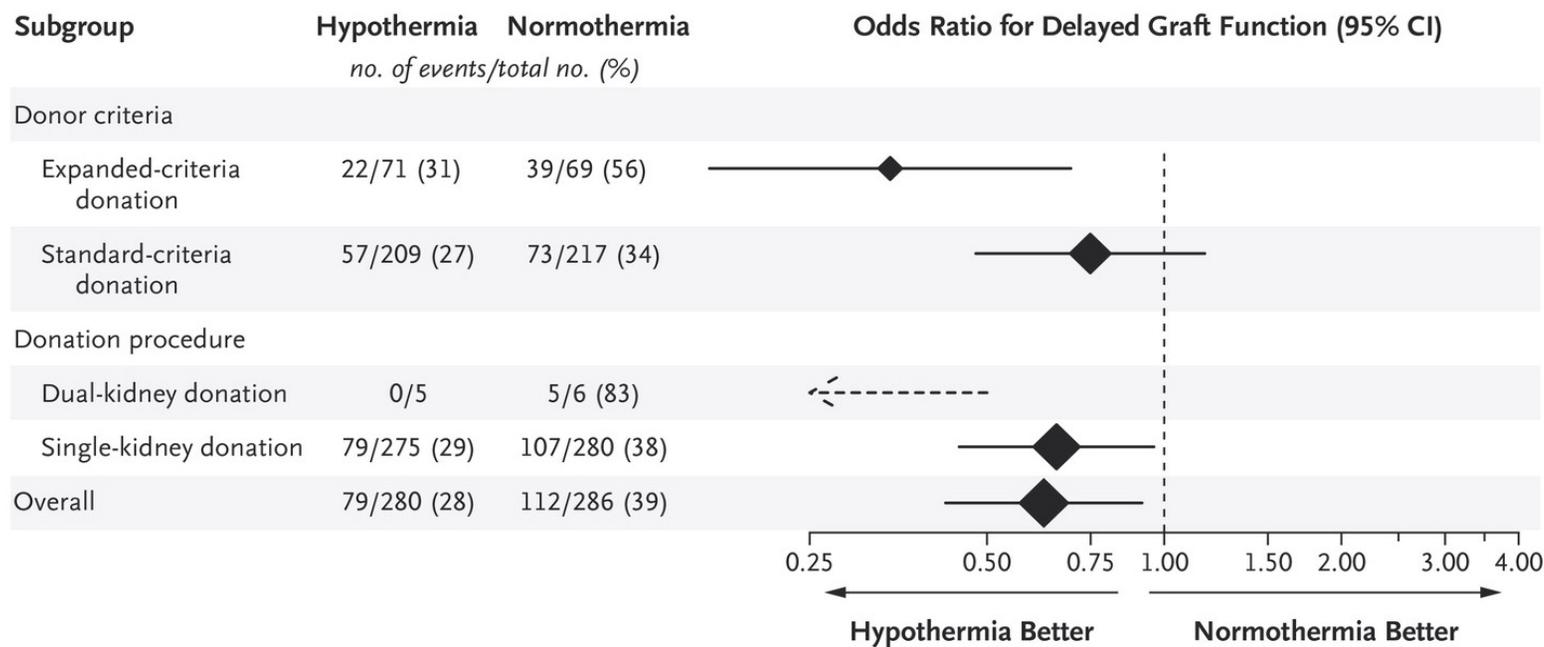
- After neurologic determination of death, deceased donors randomly assigned to two targeted temperatures
 - Hypothermia 34.0 – 35.0 C
 - Normothermia 36.5 – 37.5 C
- Non-invasive temperature management protocol began after authorization obtained and ended upon transfer to the operating room
- Primary endpoint: delayed graft function

Niemann et al., NEJM 2015

Hypothermia reduced incidence of delayed graft function

Normothermia = 39% vs. Hypothermia = 28%

OR = 0.62, P = 0.02



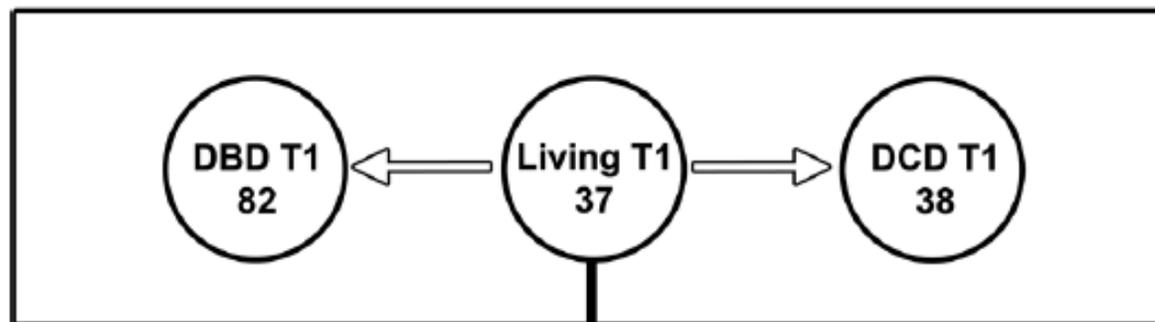
Niemann et al., NEJM 2015



Hypoxia and Complement-and-Coagulation Pathways in the Deceased Organ Donor as the Major Target for Intervention to Improve Renal Allograft Outcome

Jeffrey Damman,¹ Vincent W. Bloks,² Mohamed R. Daha,^{3,4} Peter J. van der Most,⁵ Bahram Sanjabi,⁶ Pieter van der Mies,⁶ Harold Snieder,⁵ Rutger J. Ploeg,⁷ Christina Krikke,⁸ Henri G.D. Leuvenink,⁸ and Marc A. Seelen⁴

Transcriptomics by whole genome microarray analyses followed by functional pathway analyses of biopsies from donation after brain death, donation after cardiac death, and living donor kidneys prior to donation



Renal Transcriptional Profile after Brain Death

- Changes comparable to DCD donor kidney **after** cessation of blood flow
 - Hypoxia
 - Enrichment of glycolysis or gluconeogenesis pathways
 - Induction of mitochondrial antioxidants
 - Up-regulation and enrichment of genes related to the proteasome
 - Pro-coagulable state
 - Up-regulation of all (classical, lectin, and alternative) complement pathways

Damman et al., Transplantation 2014

Bench to Bedside: Potential Interventions

- Inhibit complement
 - Soluble complement regulator proteins, complement receptor antagonists or antibodies against complement components or their split products
- Induce heme-oxygenase 1 / administer carbon monoxide
- Stabilize hypoxia inducible factor 1 subunit α
 - Prolyl hydroxylase domain inhibitors
- Administer tetrahydrobiopterin / nitric oxide

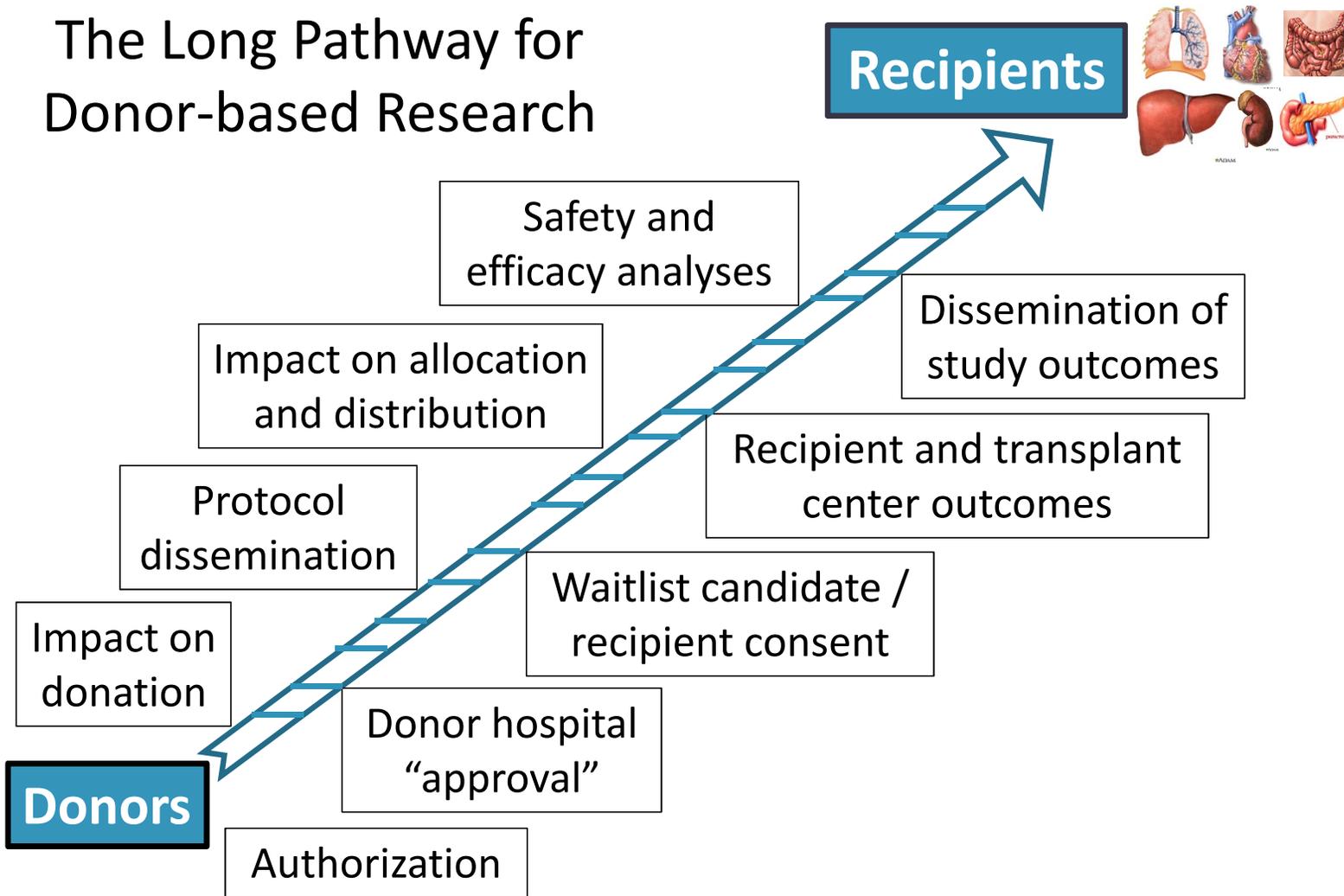


Why are there so few
donor intervention trials?

Current logistical, ethical, and regulatory infrastructure is inadequate to support effective donor intervention and treatment studies.

The *magnitude and complexity* of the challenges require guidelines to facilitate the optimal design and safe execution of clinical trials in deceased donors.

The Long Pathway for Donor-based Research



Donor Intervention Research is Unique

- Intervention occurs in a deceased donor
- Impact extends to multiple patient through the donor's organs
 - Organ under study and “bystander” organs
 - Waitlisted candidates and organ recipients
- Compressed and pressured timeframe
- Number and diversity of individual, group, and organizational stakeholders



The primary roadblock is the inability to map deceased donor research to existing federal regulatory requirements for review and approval of human subjects research.



A second obstacle is confusion among transplant surgeons, OPO professionals, and IRB members as to how the ethical, regulatory and legal framework for clinical trials apply to donor intervention research



I. Deceased donors are not human subjects, and therefore, not under the purview of an(y) IRB.

However, some level of ethical review is

- Expected
- Appropriate



Scenario Synopsis

Dr. Finnigan hypothesizes that an optimal dose of an FDA-approved thyroid hormone, a drug currently used in deceased donors, will increase procurement and utilization of hearts. Potential organ donors have documentation of donor designation, including authorization for research.

- Multi-site randomized controlled trial at 10 donor hospitals
- Brain dead donors will receive one of three different doses of the thyroid hormone
- Primary outcomes: heart procurement and utilization
 - No data collection on any organ recipients

Rodrigue et al., AJT 2016

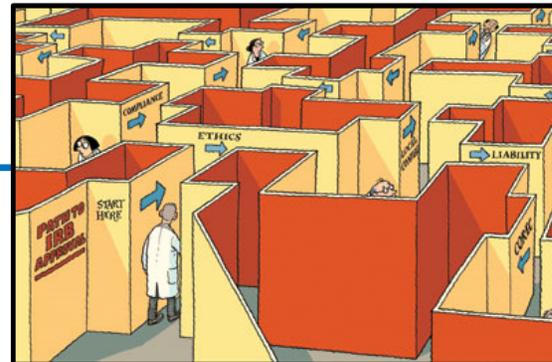
Tremendous Disparity in Perception

- Survey of transplant surgeons, OPO personnel, & IRB members
 - Is this human subjects research?
 - Yes : 19, 58, & 82%
 - Does the study require review by the donor hospital’s IRB?
 - Yes : 2, 16, & 61%
 - Does the study require review by Dr. Finnigan’s IRB?
 - Yes : 35, 73, & 93%

Rodrigue et al., AJT 2016

	Transplant surgeons (n = 294)	OPO professionals (n = 83)	IRB members (n = 317)	p-value
→	171 (58%)	16 (19%)	260 (82%)	<0.001
	156 (53%)	56 (68%)	193 (61%)	
	123 (42%)	26 (31%)	105 (33%)	
	9 (3%)	1 (1%)	10 (3%)	
	6 (2%)	0 (0%)	9 (3%)	0.12
	85 (29%)	52 (63%)	29 (9%)	
	176 (60%)	30 (36%)	139 (44%)	
	21 (7%)	1 (1%)	130 (41%)	
	11 (4%)	0 (0%)	19 (6%)	<0.001
	89 (30%)	58 (70%)	31 (10%)	
	183 (62%)	24 (29%)	144 (45%)	
	12 (4%)	1 (1%)	122 (38%)	
	7 (2%)	0 (0%)	18 (6%)	<0.001
→	215 (73%)	29 (35%)	294 (93%)	<0.001
→	47 (16%)	2 (2%)	193 (61%)	<0.001
	79 (27%)	11 (13%)	127 (40%)	<0.001
	58 (20%)	10 (12%)	125 (39%)	<0.001
	105 (36%)	7 (8%)	143 (45%)	<0.001
	129 (44%)	23 (28%)	291 (92%)	<0.001
	26 (20%)	2 (9%)	52 (18%)	
	45 (35%)	2 (9%)	44 (15%)	
	58 (45%)	19 (82%)	191 (66%)	<0.001
	117 (40%)	14 (17%)	250 (79%)	<0.001
	26 (22%)	1 (7%)	43 (17%)	
	44 (38%)	2 (14%)	33 (15%)	
	47 (40%)	11 (79%)	171 (68%)	<0.001

- II. Following standard research procedures is difficult → impossible because of the timing and processes of organ allocation and distribution
- Prospective informed consent from transplant candidates and recipients (human subjects)
 - Prospective IRB approval from all potentially involved transplant centers.



III. There is no mechanism to monitor whether and how donor intervention(s) may impact

- organ donation
- organ distribution / waitlist mortality
- recipient(s) of targeted (studied) organs
- recipient(s) of non-targeted (bystander) organs



But the hypothermia trial was done?!?

- Principal investigator's IRB stated that:
 - Trial was NOT human subjects research because donors were deceased
 - Minimal risk posed to organ recipients, negating need for informed consent to receive organs from enrolled donors
- No study-specific procedures
- Recipient outcome data obtained from SRTR
 - No need for informed consent from the kidney recipients
- Evaluation of impact on non-kidney organs limited to transplant rate

Niemann et al., NEJM 2015

What is being done?

- IOM



- Ethical issues regarding deceased donors, transplant candidates, recipients, and centers

- HRSA



- Regulatory and oversight issues

- ACOT



- Raise awareness; urge action by HRSA, CMS, SRTR, etc.

Why the IOM?

- IOM reports are respected by the public and healthcare professionals for being independent, objective, and evidence-based.
- Prior IOM reports have had a proven transformative impact on the field of organ transplantation.
 - 1997: Non-Heart-Beating Organ Transplantation: Medical and Ethical Issues in Procurement
 - 2000: Non-Heart-Beating Organ Transplantation: Practice and Protocols
 - 2006: Organ Donation: Opportunities for Action



HRSA: Recommendation for a National Oversight Mechanism

- Organs are a national resource.
- Recent changes to allocation policy have increased regional/national distribution of organs.
 - Anticipated future policy changes may further broaden organ distribution.
 - Need for a consistent approach for protocols that are executed at multiple sites
- The burden and impact of donor interventions trials on waitlisted patients and transplant recipients should be assessed at a national level.
- A single body would ensure a complete overview of all donor intervention trials.

Two Major Precedents

NCI Central Institutional Review Board Initiative

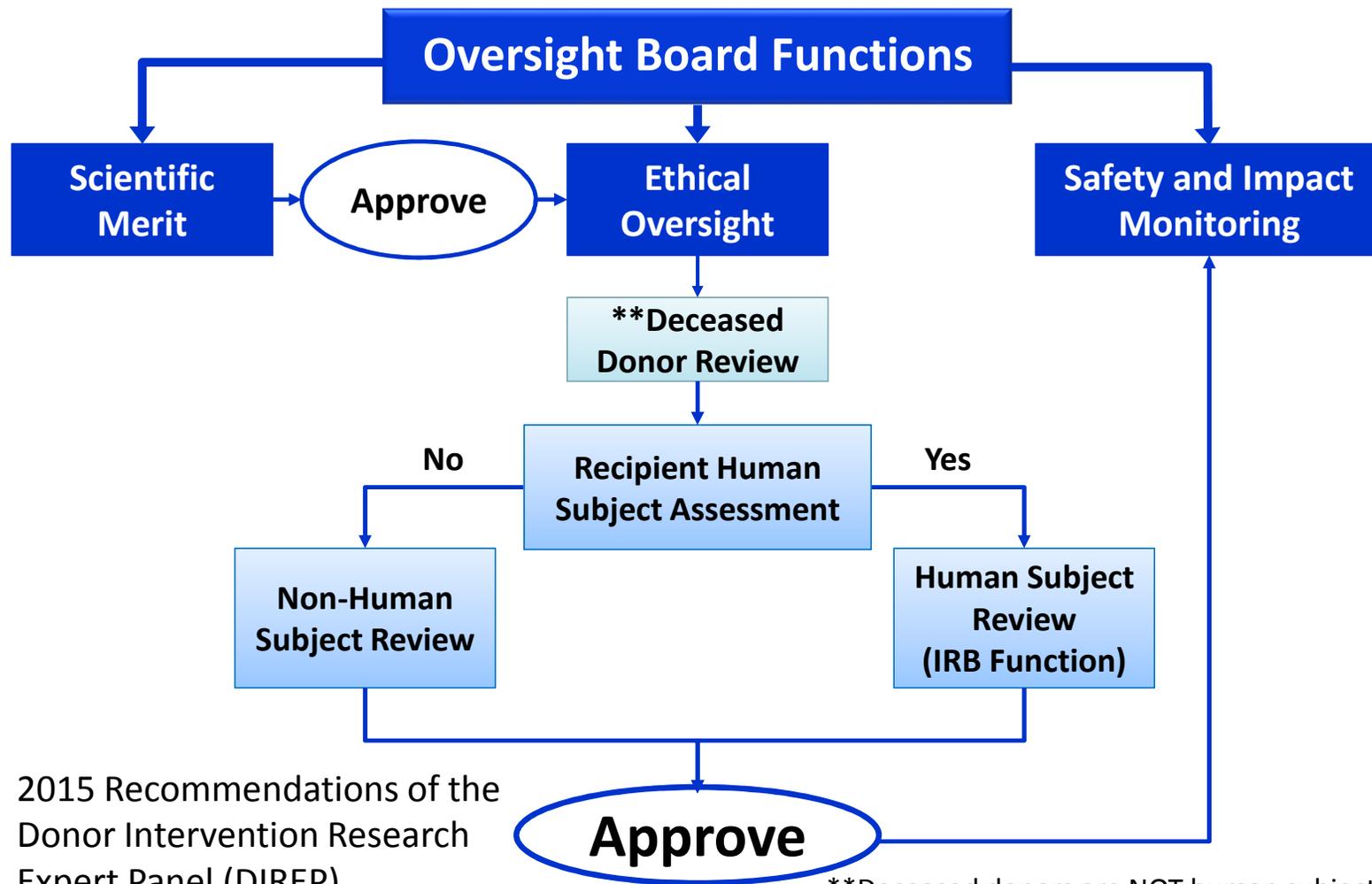
- Sponsored by NCI in conjunction with OHRP
- Reduce administrative burden on local IRBs and investigators
- Maintain high level of protection for research participants
- **Sole IRB of Record** responsible for both study and “local context” review

NIH NOT-OD-15-026 - Use of a Single Institutional Review Board for Multi-Site Research

- All NIH-funded, multi-site studies carried out in the United States should use a single IRB.

“By using single IRBs in multi-site studies, we reduce duplication of effort, speed the initiation of important research, and save time and taxpayer funds.”

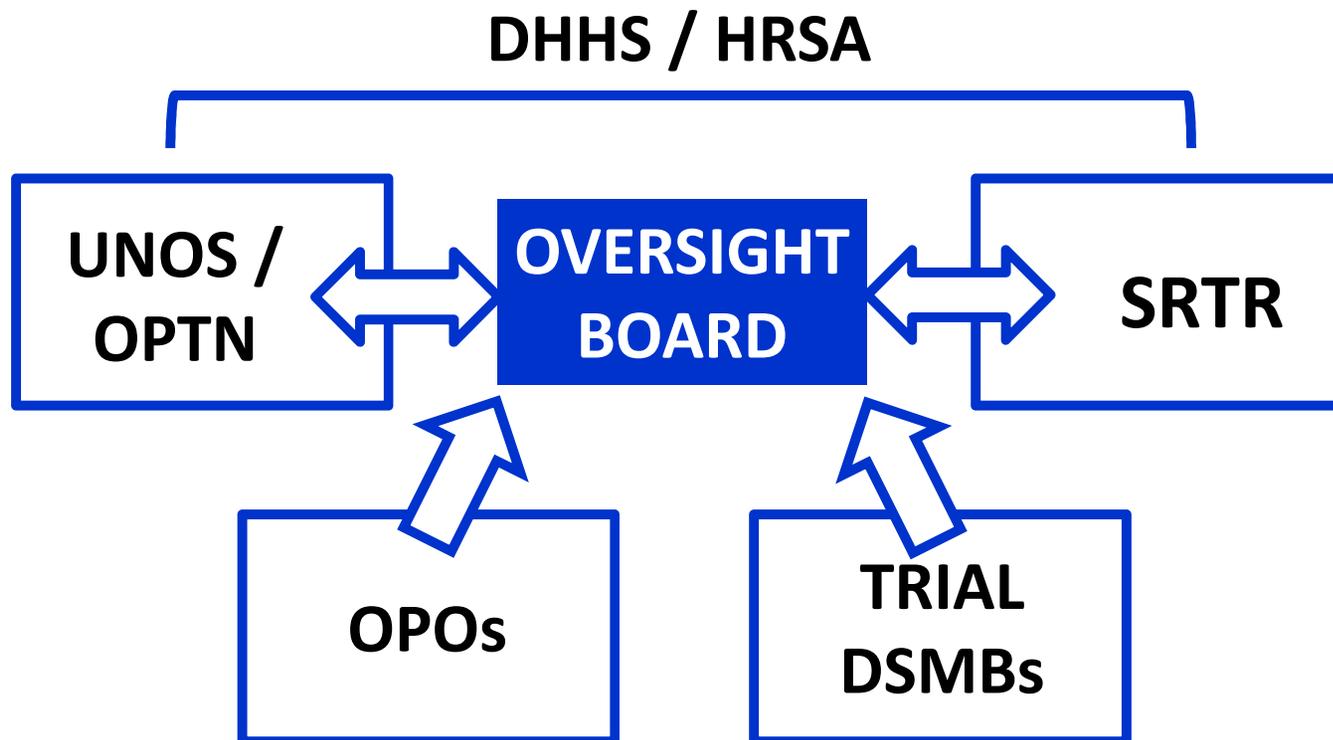
Francis Collins, MD, PhD



2015 Recommendations of the Donor Intervention Research Expert Panel (DIREP)

**Deceased donors are NOT human subjects

Formation of a National Oversight Board



2015 Recommendations of the Donor Intervention Research Expert Panel (DIREP)

ACOT Recommendations to the Secretary of HHS

- Take timely action to establish a nationwide centralized oversight mechanism to facilitate deceased donor (and organ) intervention research;
- Support and facilitate as appropriate the planned study by the Institute of Medicine on issues in deceased organ donor research; and
- Direct the relevant stakeholders (e.g. CMS, OPTN, SRTR, et al) to evaluate and implement mechanisms for risk-adjusting outcome measures and center-specific reports which would eliminate barriers for broader participation in donor intervention research thus potentially increasing both the quantity and quality of organs available for transplantation.

Summary

- Deceased donor intervention research has clear potential to substantially increase the quantity and quality of deceased organs.
- Multiple pathways to develop a framework for the safe and sound conduct of deceased donor research are being pursued.
- Funding agencies, both non-industry and industry, should be engaged to fund trials as soon as the path is paved.



Research
Grants
APPROVED

