Improving Utilization of Organs from Increased Risk Donors

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CDC

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RESOLVING THE ORGAN SHORTAGE
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Office of Blood, Organ, and Other Tissue Safety

AST Cutting Edge of Transplantation

Resolving the Organ Shortage: Practice, Policy, Politics

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Phoenix, AZ

National Center for Emerging and Zoonotic Infectious Diseases

Division of Healthcare Quality Promotion

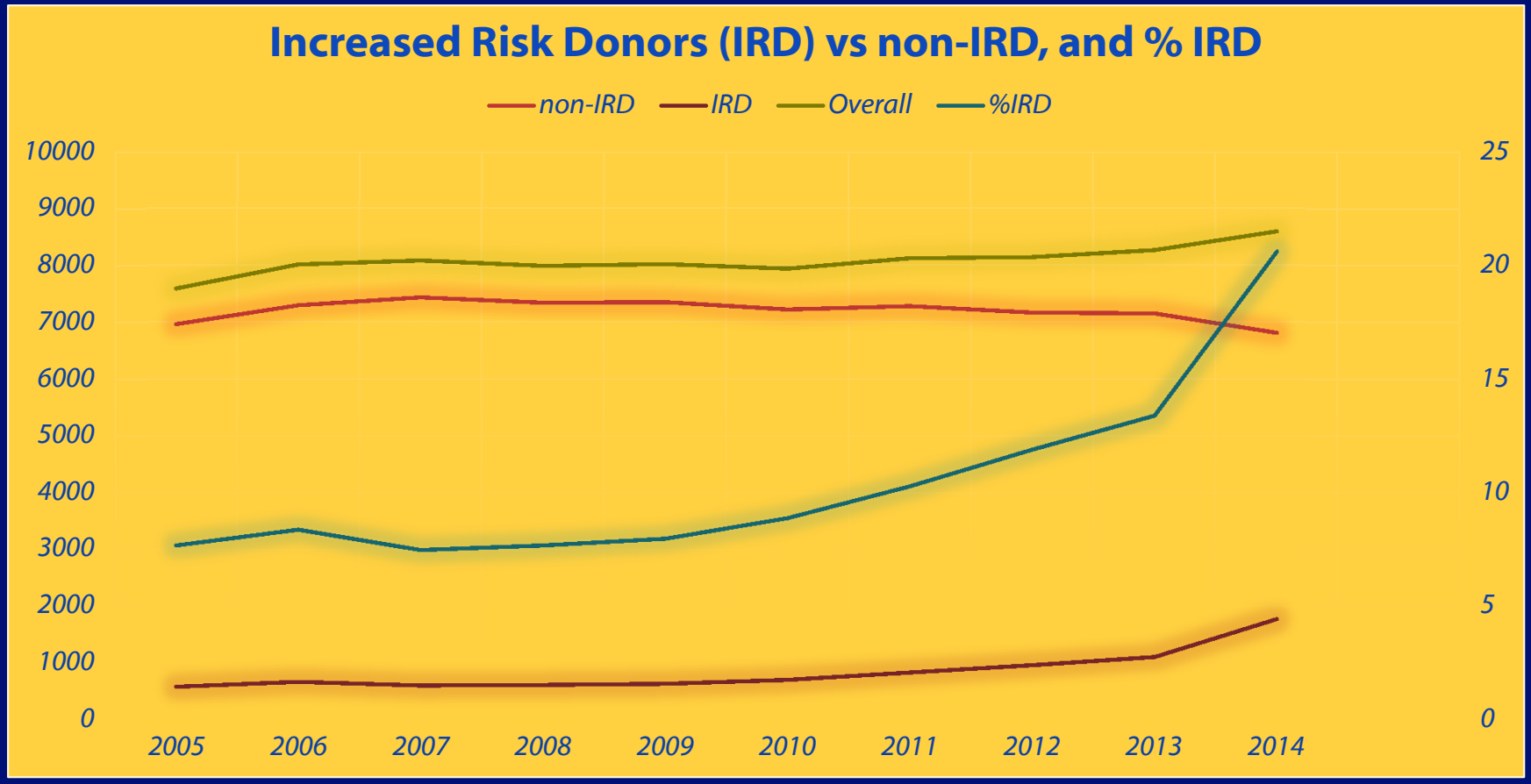
"What we've got here is failure to communicate"

Martin S. *Cool Hand Luke*, Warner Bros.-Seven Arts, 1967.

Outline

- Why are increased risk donor (IRD) numbers going up?
- Why does IRD status matter for organ placement?
- What is being done to increase availability of organs from donors at increased risk of infection?
- How can we better communicate the true risk?

Deceased Donors Recovered in the US, Jan 2005-Dec 2014



OPTN data; accessed Nov 13, 2015

Why are IRD Numbers Going Up?
Some Possibilities

- PHS Guideline revision?
- Donors engaging in more increased risk behavior?
- Changes in donor selection by OPOs?

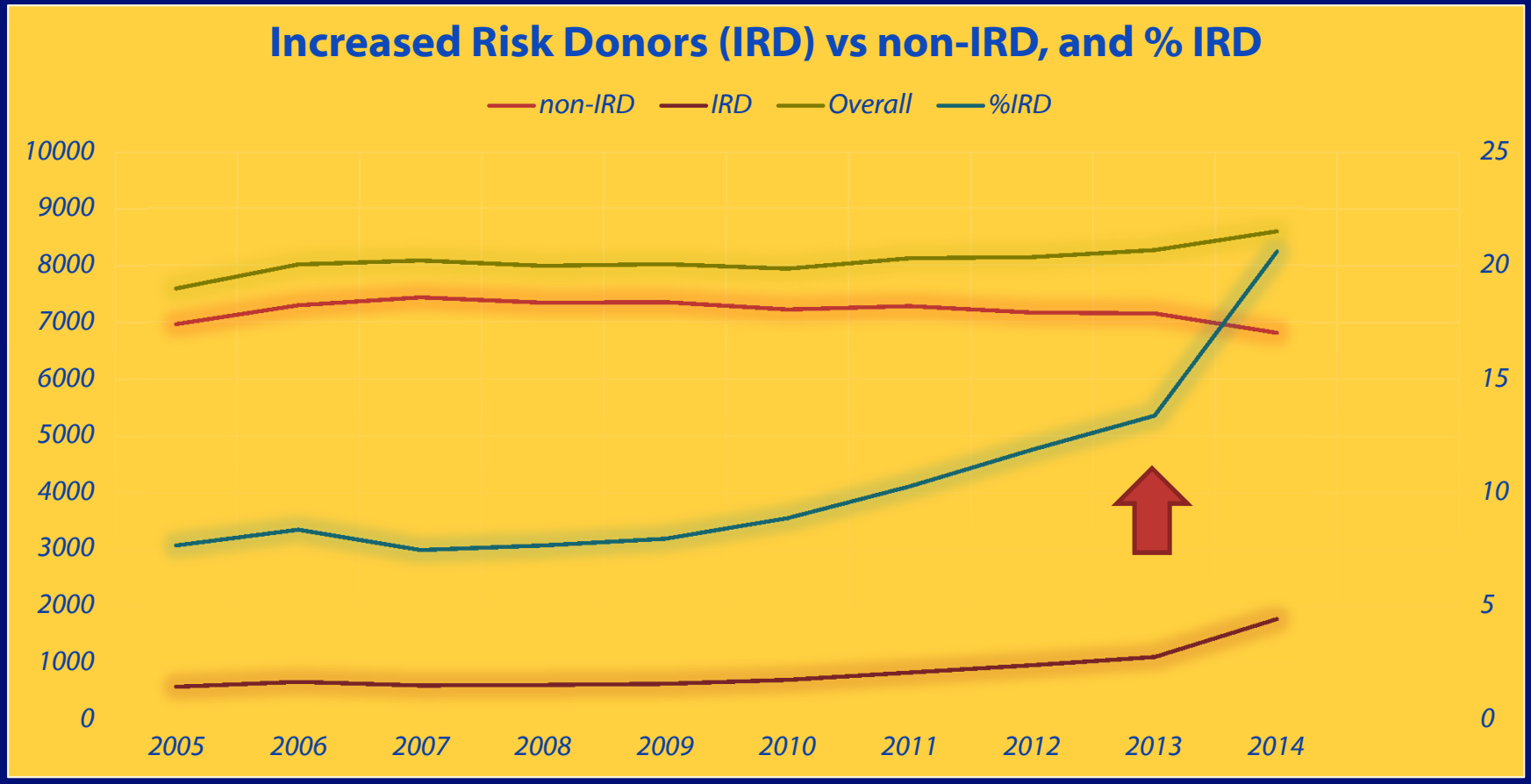
Possibility #1: PHS Guideline Revision?

PHS Guideline Revision

- **Released 2013 by HHS**
- **Guideline implemented into OPTN policy Feb 1, 2015**

- **Changed criteria for increased risk donors (IRDs)**
  - Addition of HBV and HCV
  - 11 criteria result in a donor being designated as an IRD
    - Hemodialysis exposure (HCV) added
    - Correctional facility exposure clarified
    - Shortened relevant risk history time frame to 12 months
    - Remained dichotomous classification (yes or no) based on risk factor
  - Specific recommendations on testing (e.g., NAT for all donors for HCV, and for increased risk donors only for HIV)

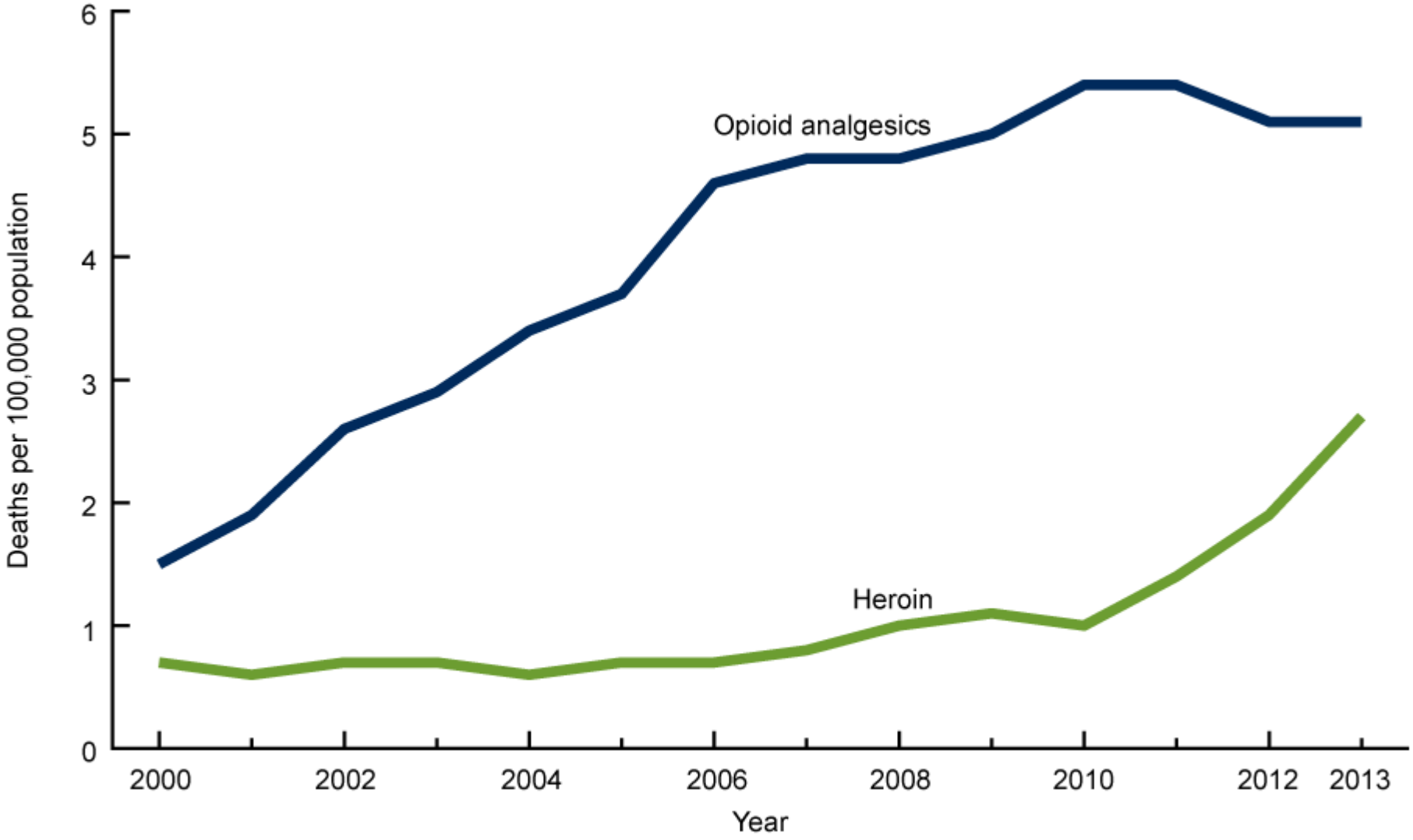
Deceased Donors Recovered in the US, Jan 2005-Dec 2014



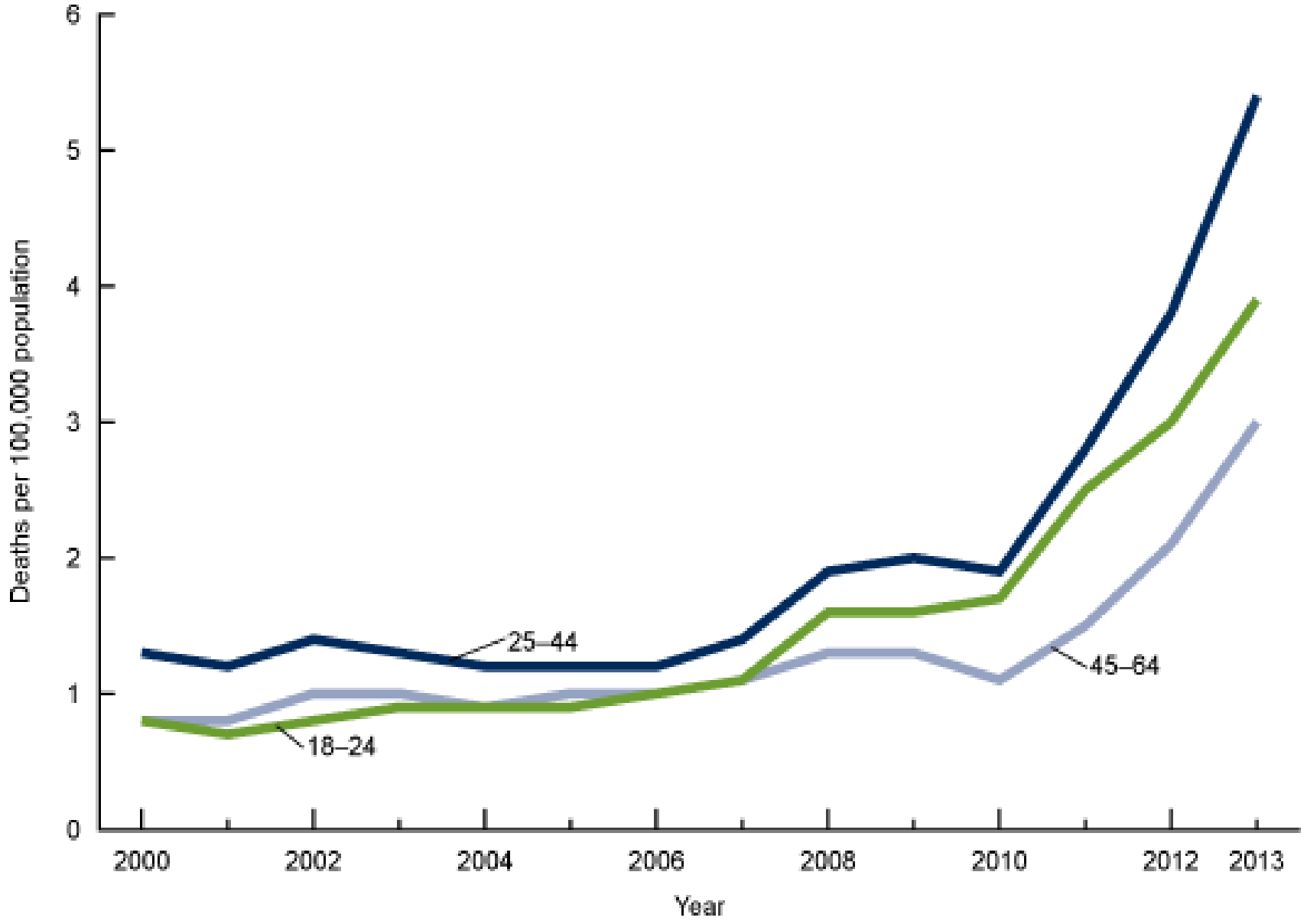
OPTN data; accessed Nov 13, 2015

Possibility #2: Changes in donor increased risk behavior?

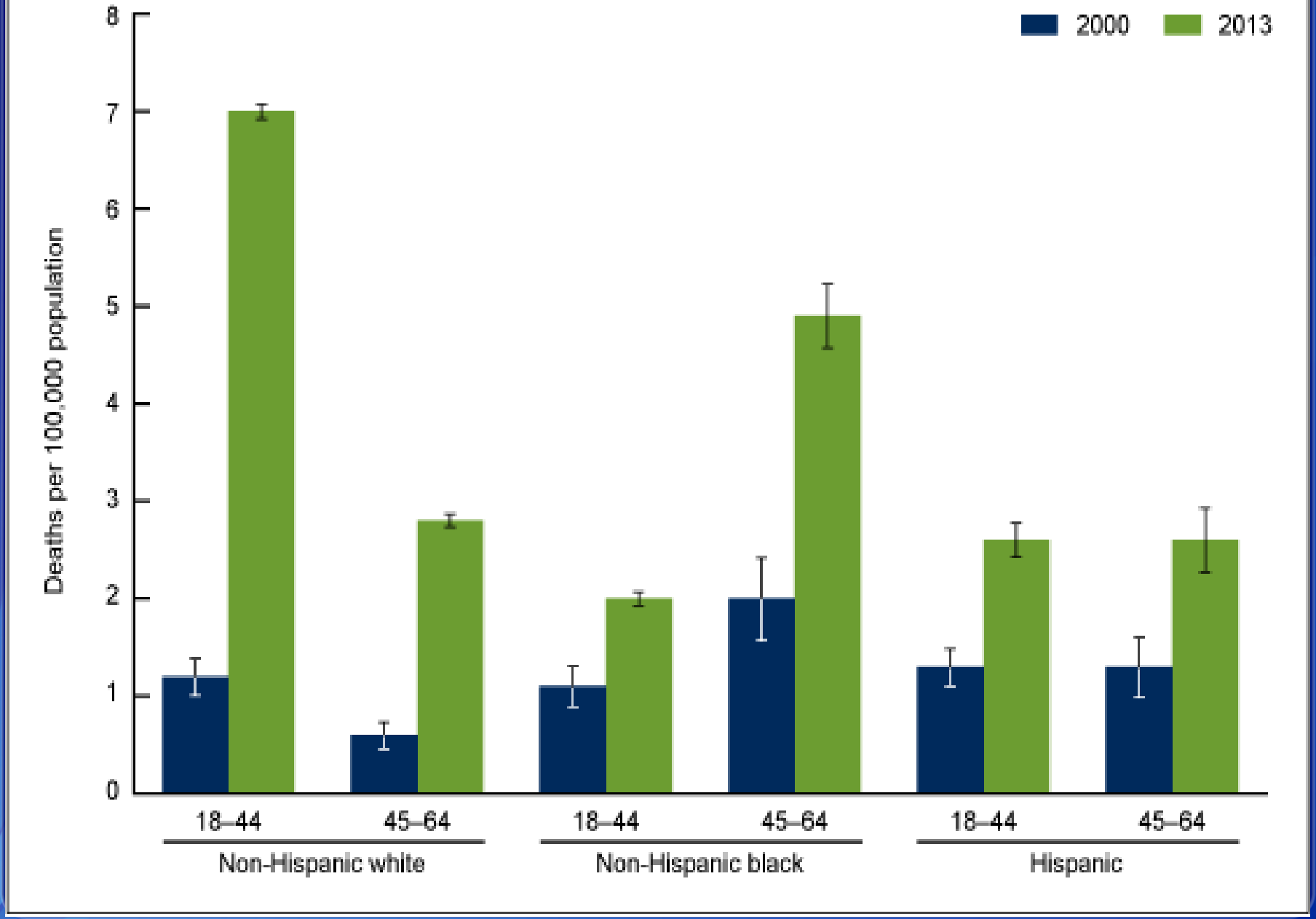
Figure 1. Age-adjusted rates for drug-poisoning deaths, by type of drug: United States, 2000–2013



NOTES: The number of drug-poisoning deaths in 2013 was 43,982, the number of drug-poisoning deaths involving opioid analgesics was 16,235, and the number of drug-poisoning deaths involving heroin was 8,257. A small subset of 1,342 deaths involved both opioid analgesics and heroin. Deaths involving both opioid analgesics and heroin are included in both the rate of deaths involving opioid analgesics and the rate of deaths involving heroin. Access data table for Figure 1 at: http://www.cdc.gov/nchs/data/databriefs/db190_table.pdf#1.
SOURCE: CDC/NCHS, National Vital Statistics System, Mortality.



CDC/NCHS: National Vital Statistics System, Drug-poisoning deaths involving Heroin



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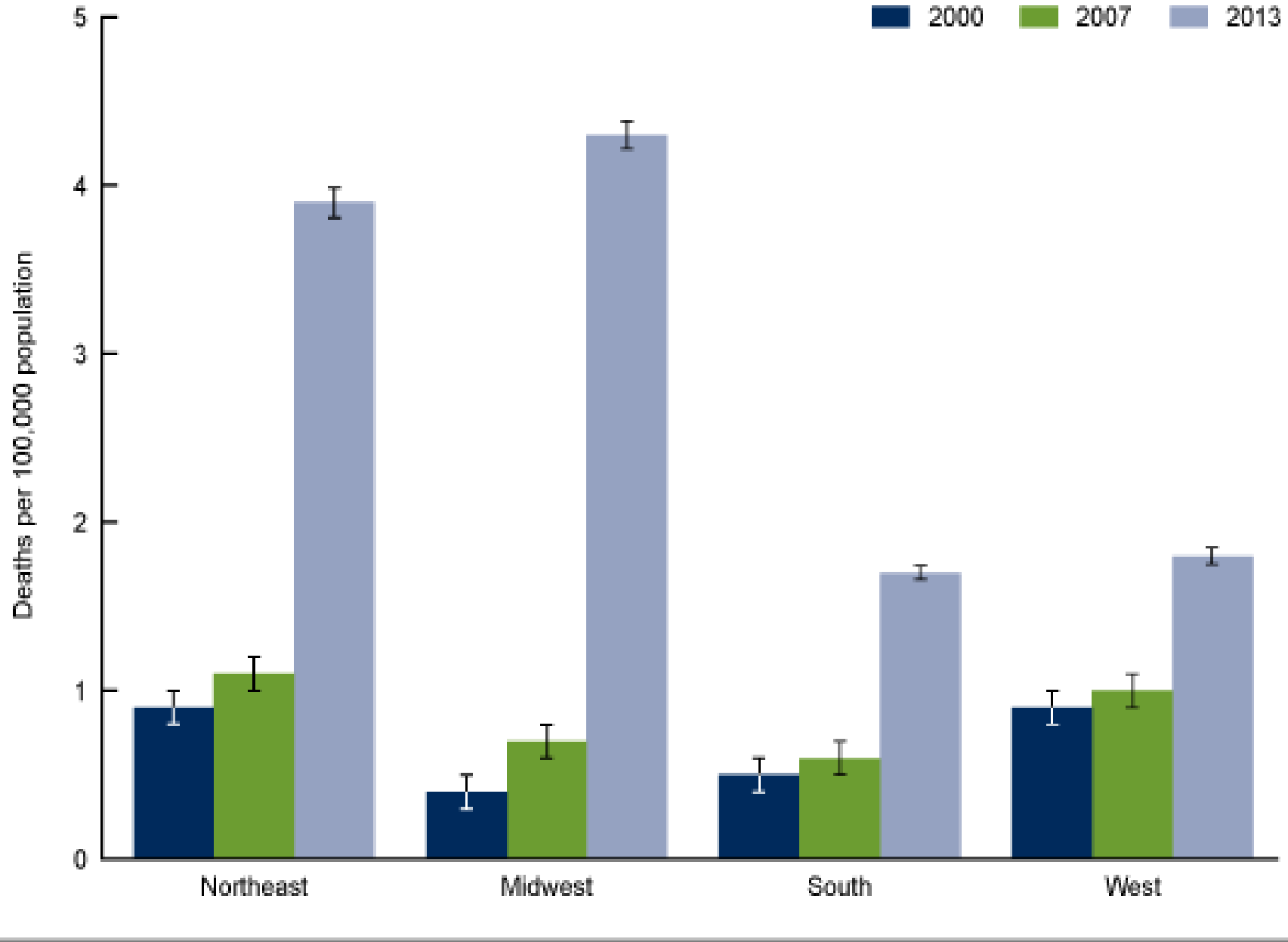
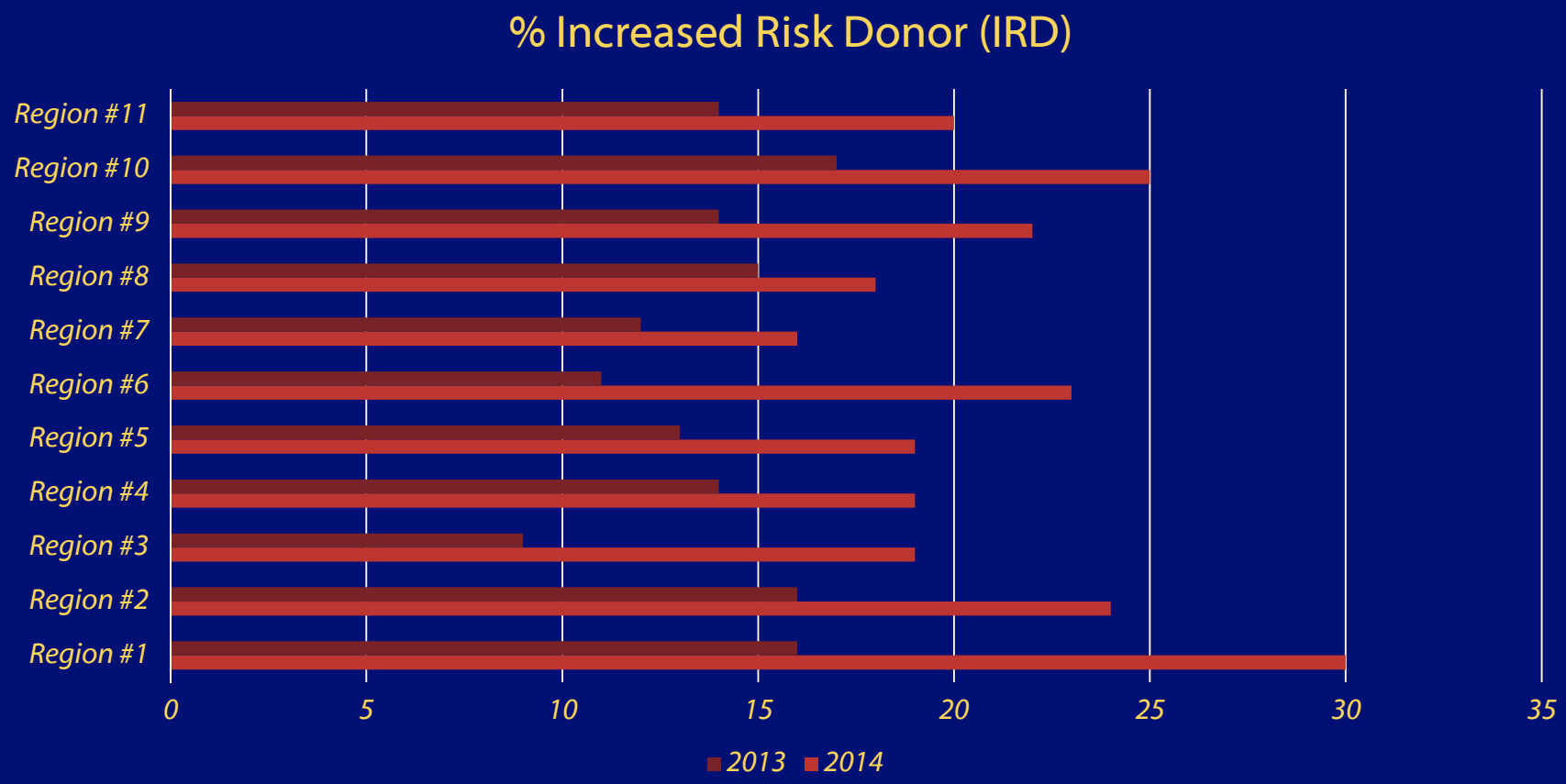


CDC/NCHS: National Vital Statistics System, Drug-poisoning deaths involving Heroin

Possibility #3: Changes in OPO Donor Selection?

Deceased Donors Recovered in the U.S., 2013 vs 2014, by OPTN Region



OPTN data; accessed Nov 13, 2015

Why does IRD status matter?

- Perception by clinicians and patient, leading to decreased utilization of IRD organs
- Requirement for specific informed consent
- Some quantifiable increased risk of transmission

Why does IRD status matter?

- **Kucirka LM et al AJT 2009; 9:629-635**

  Duan KI et al AJT 2010; 10:416-420

  Use and attitudes toward organs from IRDs by **transplant surgeons**

  - Surgeons more likely to accept organs from donors with certain behavioral risks (in order): **MSM, IDU**, sex for money, hemophilia, known HIV exposure, **incarceration**
  - Use of NAT associated with higher organ acceptance rates
  - Disincentives included concern over recipient complications from HIV or HCV infection and poor organ quality

  - IRD Kidneys 8.2% less likely to be used (OR of utilization of 0.67), despite similar transplant survival compared with non-IRD kidneys

Why does IRD status matter?

- **Gordon EJ et al Clin Transplant 2012; 26: 359-368**
  Ros RL 2012 et al Clin Transplant 2012; 26:247-253

  Assessed **kidney candidate perceptions** on organs from IRDs

  - Most patients assumed IRDs must have been in "poor health", from older persons, and associated with organs "not of good quality"
  - Were more interested in how long the organ would last and their survival, rather than disease that can be transmitted and treated

  - Impression that risk of HIV and HCV transmission was higher through dialysis
  - Most communication on risk is with organ clinician (i.e., nephrologist), not surgeon or infectious disease consult

Why does IRD status matter?

- **Chow EKH et al AJT 2013; 13:1227-1234**
  Turgeon N et al AJT 2013; 13: 1121-1122
  Kucirka LM et al AJT 2009; 9: 1197-1204
  Challenges of **informed consent**

  - Since HIV-HCV transmission in 2007, trepidation about accepting organs from IRDs
  - In 2008, new UNOS policy requiring transplant teams to obtain "special informed consent (SIC)" but not specified
  - A defined IRD policy for SIC associated with higher utilization of livers (trend of increased utilization for kidneys)

  - **Challenge is that the risk for each individual organ offer is dichotomous and is poorly quantified**

CDC is working with partners to better quantify the risk of infectious disease transmission through organ transplantation

- **Pathogens modeled**
  - Bloodborne pathogens (HIV completed; HCV being planned)
  - Infectious encephalitis-causing agents
- **Techniques to estimate risk**
  - Mathematical modeling
- **Techniques to communicate risk**
  - Clinical decision aid tools

Objective: HIV Quantified Risk Model

- Develop a mathematical model to estimate the probability of undetected HIV in an IRD
- The model results in estimated undetected HIV transmission based on:
  - Type of Increased Risk Behavior
    - MSM1 and MSM2 (two different data sources)
    - IVDU
    - Sero-discordant Sex
    - Sex with a commercial sex worker
  - Time from increased risk behavior relative to organ donor screening
  - Negative NAT on donor screening
- Provide quantitative estimates of risk to improve organ utilization and informed consent.

CDC, unpublished data 2016

Table: Per-act risk of acquiring HIV by exposure route

Exposure Route	Risk per 10,000 exposures	95% CI	Reference
Needle Sharing Injection Drug Use	63	(41-92)	(Hudgens, 2002)
Sero-discordant Couples	82	(39-150)	(Wawer, 2005)
Commercial Sex	6.3	(5.55-7.05)	(Kimani, 2008)
MSM1/MSM2: Receptive Anal Intercourse			
----- regardless of ejaculation (MSM2)	82	(24-276)	(Vittinghoff,1999)
----- with ejaculation inside rectum (MSM1)	143	(48-285)	(Jin, 2010)

CDC, unpublished data 2016

Methods: Monte Carlo Simulation

- Estimation of the upper end probability of undetected HIV infection by day following each increased risk exposure
  - Negative NAT
  - Single and multiple (combined) exposures
  - Per-act transmission risk at the reported 95% CI
- Risk computation based on
  - Log-normal distribution per act viral inoculum & NAT detection threshold
  - Normally distributed viral exponential growth rate
- Simulated 1000x per behavior
  - Mean initial viral inoculum assumed to be proportional to per act infection risk

CDC, unpublished data 2016

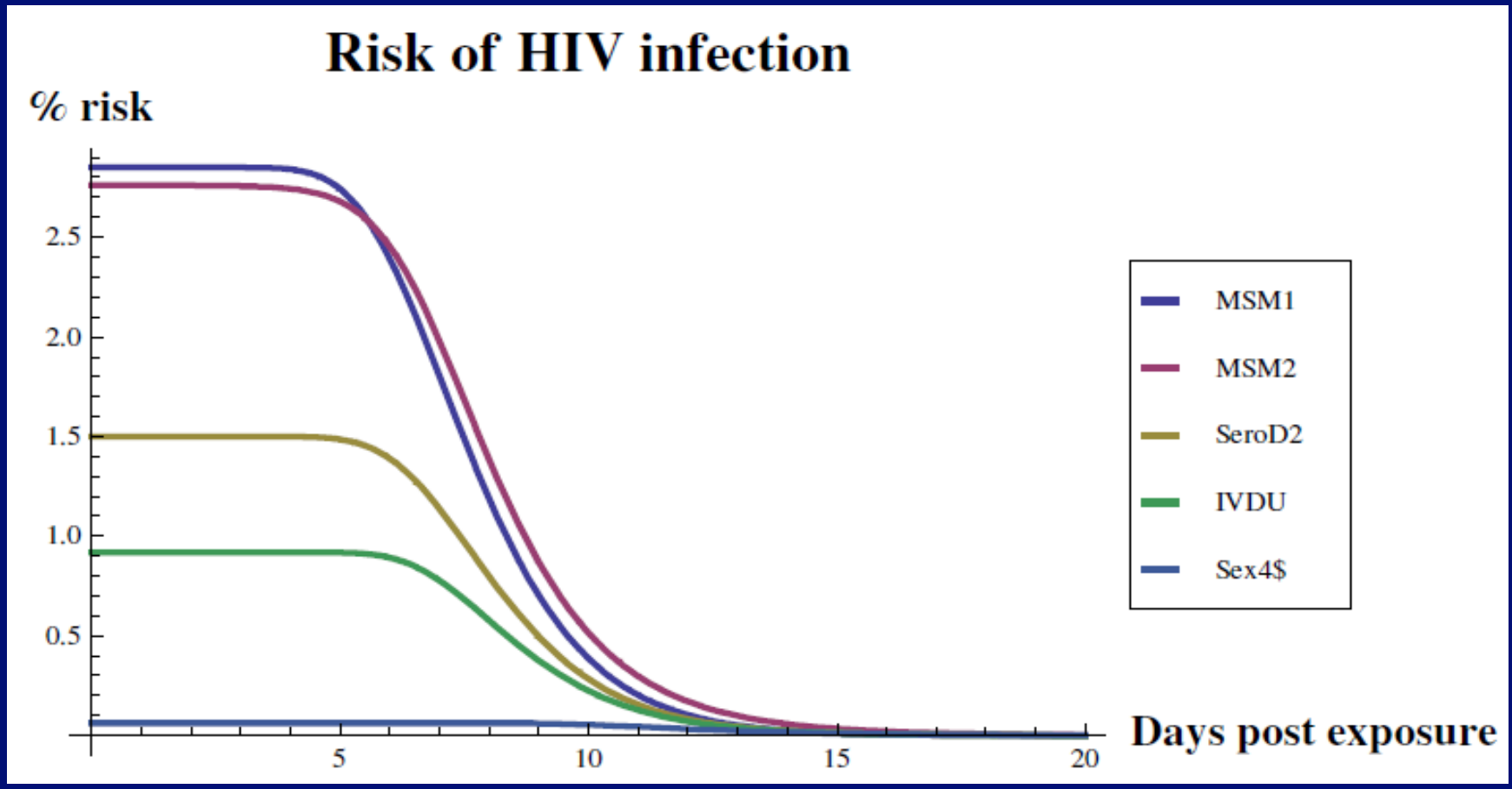
Results
Risks as a function of time since exposure for each risk type

Days Since Exposure (%)

Risk Behavior	1	5	10	28	91	182	365
IDU	0.92	0.92	0.22	1.38×10^{-5}	1.27×10^{-13}	0	0
MSM1	2.85	2.74	0.39	2.70×10^{-6}	0	0	0
MSM2	2.76	2.68	0.52	1.33×10^{-4}	1.24×10^{-10}	4.29×10^{-15}	0
Sex with CSW	0.06	0.06	0.05	1.07×10^{-4}	2.84×10^{-10}	1.58×10^{-14}	0
Serodiscordant couple	1.50	1.49	0.28	7.05×10^{-6}	6.00×10^{-15}	0	0

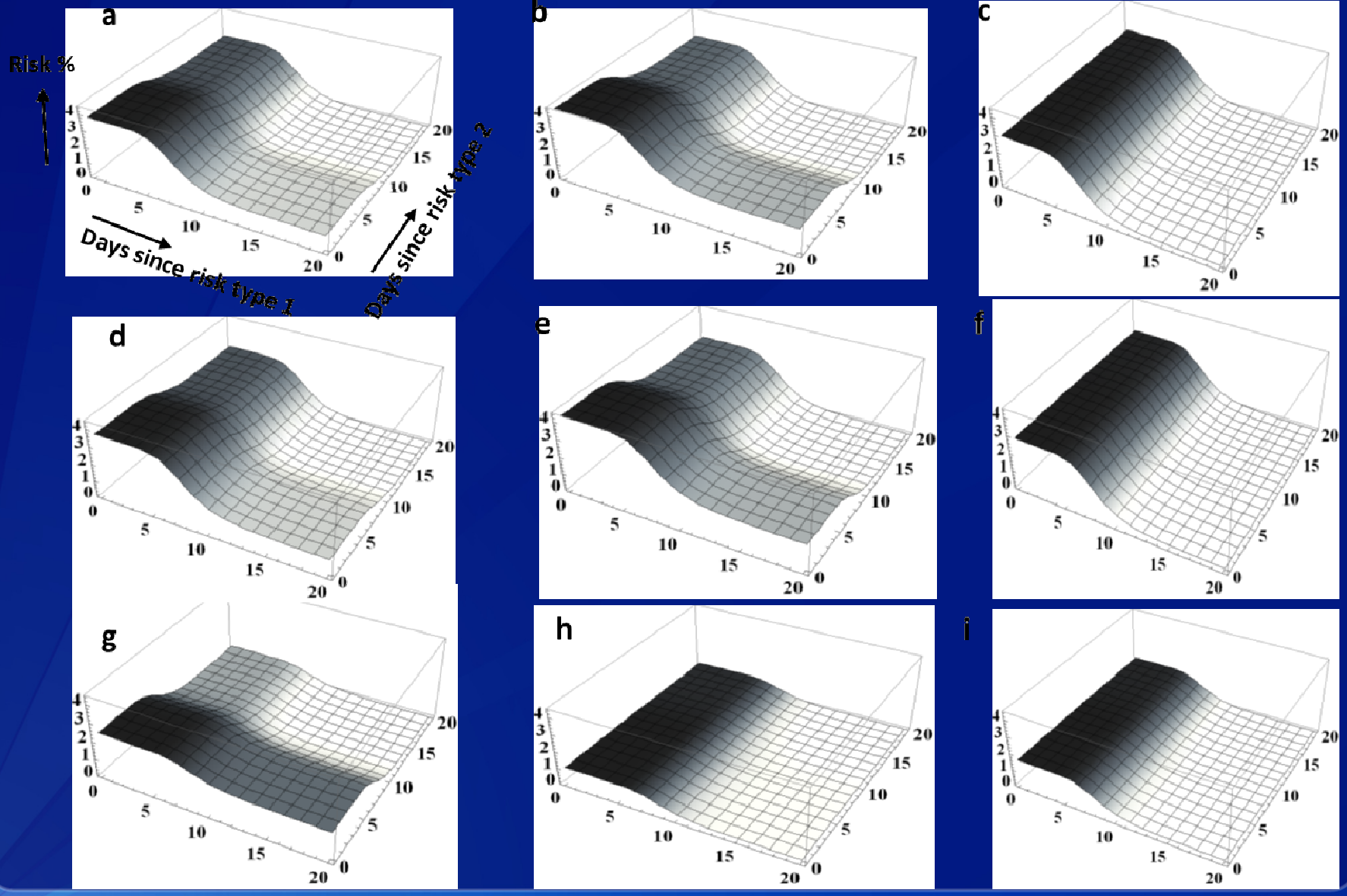
CDC, unpublished data 2016

Results



CDC, unpublished data 2016

Results



CDC, unpublished data 2016

Discussion

- Risk of HIV infection among increased risk organ donors with negative NAT
  - Highest within 5 days of engaging in the behavior (up to ~4%)
  - Significantly decreased 10 days following exposure (< 0.5%)
  - **Approaches zero >182 days (< 4.29 X 10^{-15} %)**
- Donor risk in quantified order: 1) MSM behavior, 2) known HIV+ serodiscordant partner of opposite gender, 3) IVDU, 4) sex with a commercial sex worker of opposite gender
- Risk of undetected HIV infection remains small with NAT
  - < 5% even with history of combined behaviors (e.g., MSM and HIV+ sero-discordant sexual exposure)

CDC, unpublished data 2016

What are the next steps?

- Development of clinical decision aid tools
  - Probability of undetected HIV infection
  - Risk of infectious encephalitis in organ donors
  - Identifying the recipients with maximal survival benefit to improve matching and informed consent
- Leveraging collaborations with academia via private philanthropy (Carlos and Marguerite Mason Trust)
  - Georgia Institute of Technology, Industrial Engineering Department
- Coordination with other projects quantifying and describing risks to clinicians and patients (e.g., OPTN/DTAC, HRSA IDEASpring IT projects)

Unusual Transplant-transmitted Infectious Encephalitis Clusters

Clusters in the United States, Reported to CDC, 2002-2014			
Infectious Agent	Total donors and clusters	Total Recipients	Total Deaths
West Nile virus	6	16	4
LCMV	4	13	10
Rabies	2	8	5*
Balamuthia mandrillaris	2	7	3**
Microsporidia	1	3	1
Total	15	47	23

* Three recipients received rabies post-exposure prophylaxis and survived.
** Four recipients received prophylatic treatment.

LCMV: Lymphocytic choriomeningitis virus
Basavaraju SV, et al. *Emerg Infect Dis* 2014.

What is CDC working on?
Risk Stratification Model Identifying Donors with Infectious Encephalitis

1. **Clinical tool to identify donors with infectious encephalitis**
   - Must distinguish infectious from non-infectious encephalitis
   - Use available clinical data including
     - Fever and other symptoms
     - Cerebrospinal fluid analysis
     - Imaging results (e.g., CT, MRI and x-rays)
   - Incorporate donor history questionnaire

2. **Properly allocate organs from donors with infectious encephalitis**
   - Maximize survival benefit for recipients

Infectious encephalitis identification

Encephalitis

- Infectious
- Non-Infectious

Other conditions
(Bacterial meningitis, trauma, etc.)

Case reports of infectious and non-infectious encephalitis

Case data (370 records):
Infectious encephalitis caused by four viruses:

- West Nile Virus
- Rabies
- Balamuthia Mandrillaris
- Lymphocytic Choriomeningitis

Control data (96 records):
Non-infectious encephalitis causes:

- Autoimmune
- Bickerstaff
- Optic Neuritis
- 12 more causes

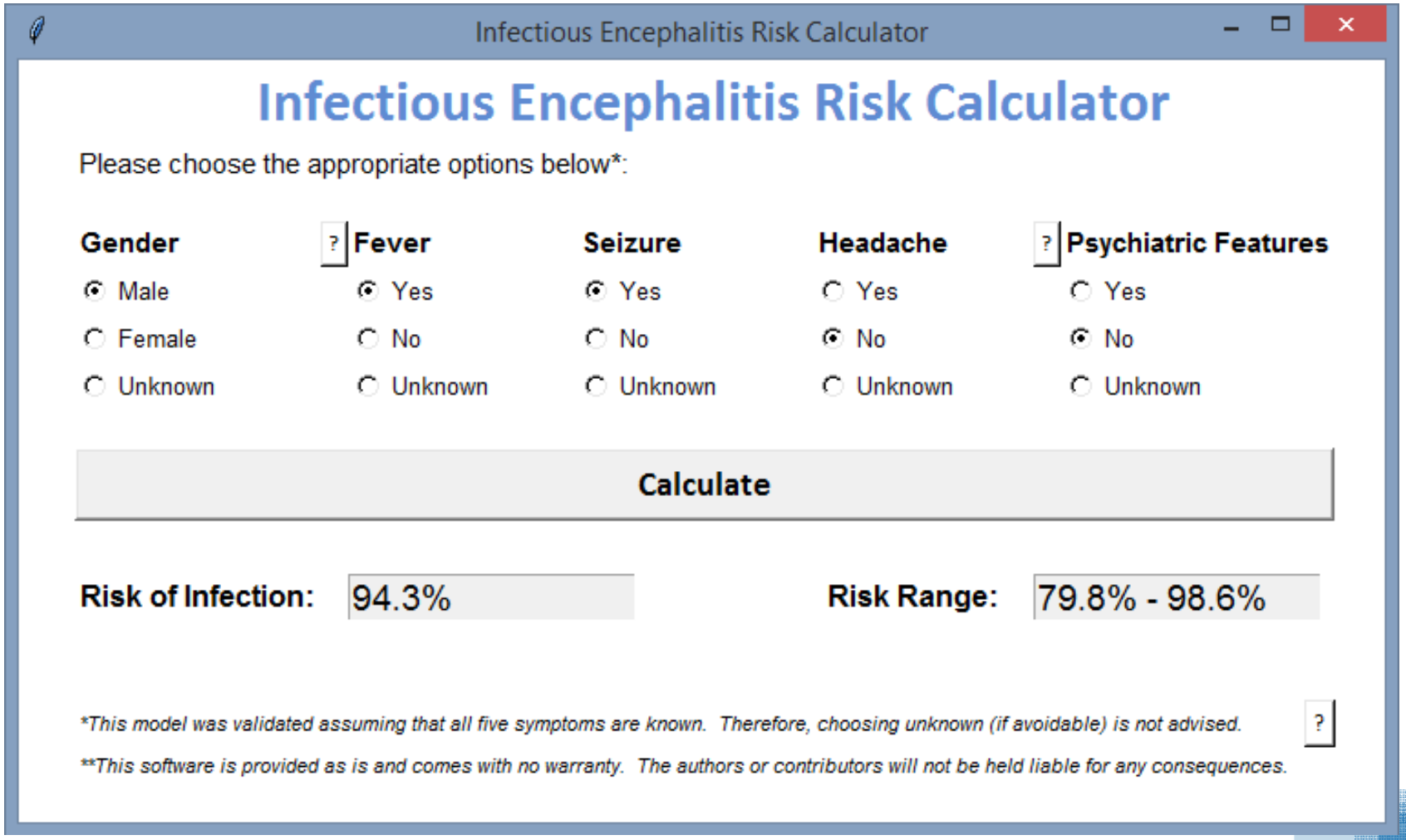
Limitations:

Small sample size
Missing data fields
Unknown true population ratio of case to control

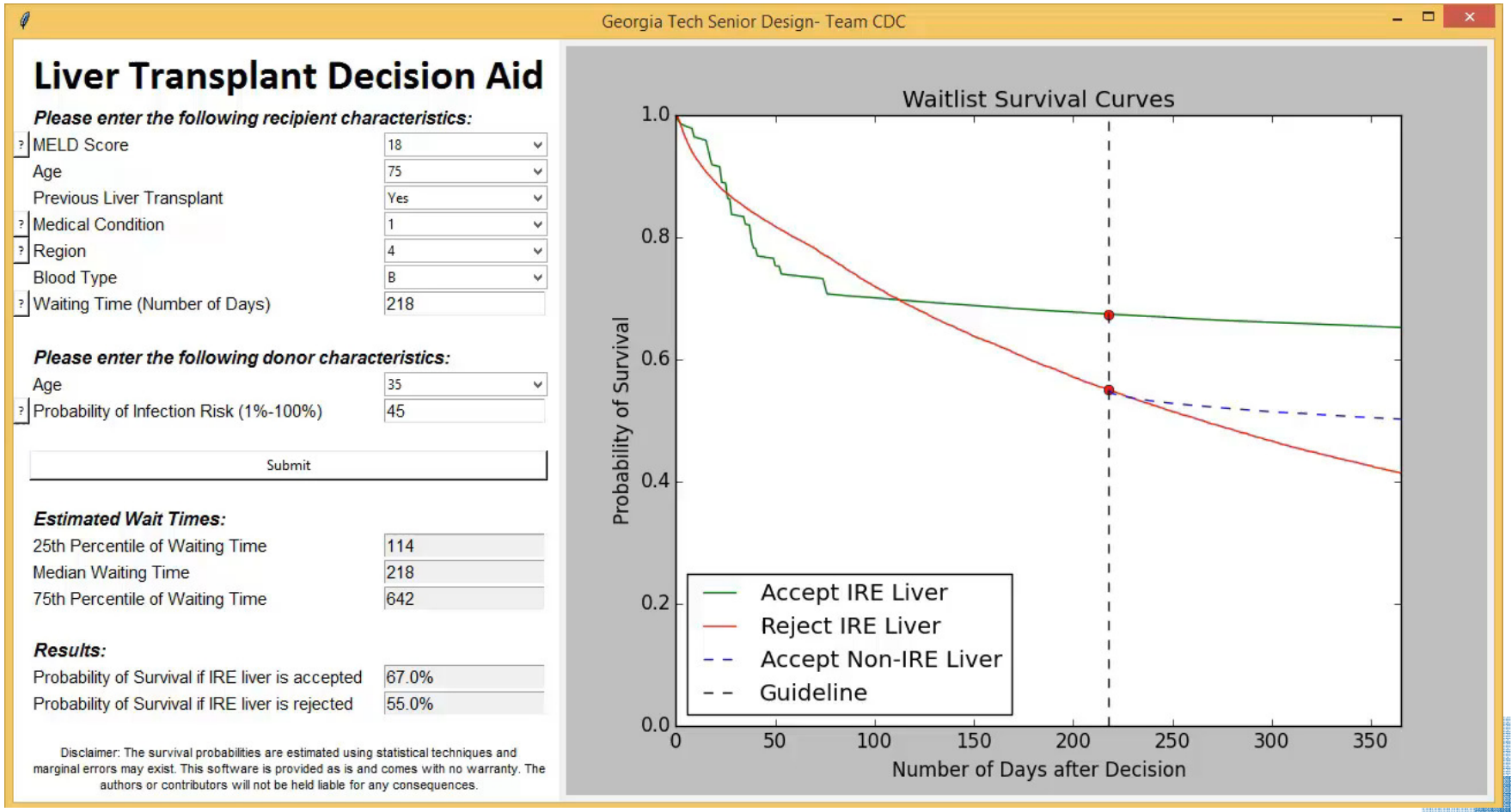
Variable selection to determine infection risk

Method	Gender (98%)	Fever (93%)	CSF Protein (72%)	Seizure (71%)	Headache (71%)	Psychiatric (95%)	Abnormal MRI (62%)	Altered Mental State (87%)	CSF WBC (75%)
CART	x	x	x	x	x				
Sequential		x		x	x	x			
Binary	x	x	x	x	x	x	x		
Forward	x	x		x	x	x			
Backward		x		x	x	x	x		
Best Subset	x	x	x	x	x	x	x	x	

Infectious Encephalitis Risk Calculator



IRE Liver Transplant Decision Aid



Conclusions

- IRD designation is increasing, most likely due to a number of factors
- The understanding of the implication of IRD status on disease transmission and recipient outcome could be improved for both transplant clinicians and patients
- CDC Risk models are being developed for bloodborne pathogens and in aggregate for infectious encephalitis
- Translational applications needed to animate the individual risk, leading to better informed consent and decision making
- Risk data exist, but communication is the challenge

Acknowledgements

- **UNOS**
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- **CDC**
  - Pallavi Annambhotla
  - Brian Gurbaxani
  - Sridhar Basavaraju

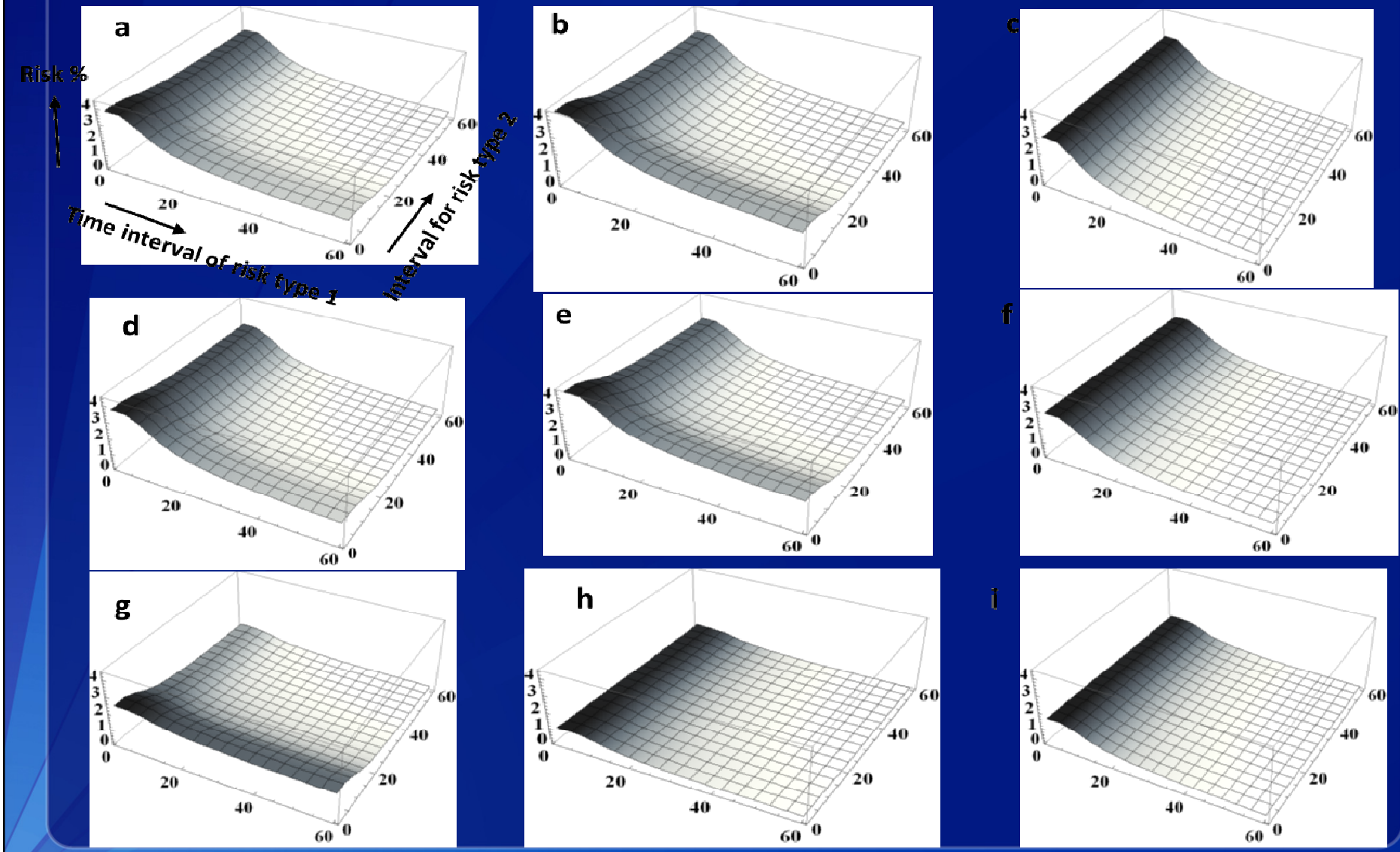
QUESTIONS?

Martin S. *Cool Hand Luke*, Warner Bros.-Seven Arts, 1967.

Methods: Literature Search and Review

- PubMed Literature Review
  - PubMed search to quantify the per-act HIV transmission risk for the four selected increased risk behaviors
    - Search terms: HIV, HIV infection, human immunodeficiency virus, AIDS and disease transmission, per-contact, per-act (coupled with heterosexual, homosexual, coital, anal) or needle sharing
  - PubMed search to quantify performance characteristics of HIV NAT screening assays and the dynamics of HIV infection
    - Search terms: :HIV screening, NAT assay, mathematical models
  - PubMed search to understand the time course of HIV viral load following acute infection
    - Search terms using the following search terms: viral load of HIV, and HIV NAT

Results



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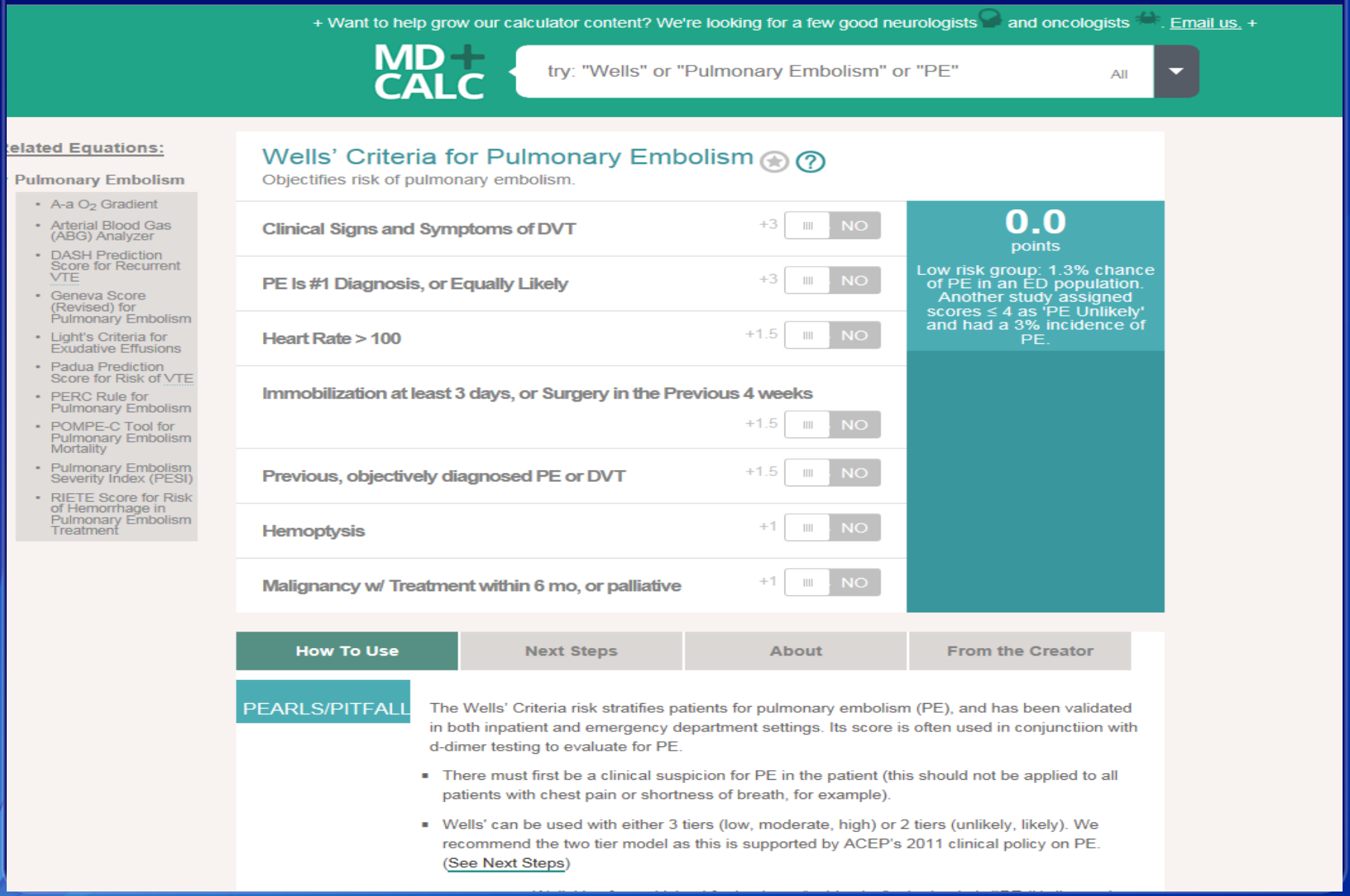
What could a decision tool look like?