

Key Principles for Organ Allocation

***Canadian Blood Services Organ Expert Committee
January 11, 2010***

Alan Leichtman, MD

**Division of Nephrology
Kidney Epidemiology and Cost Center
University of Michigan**

**Scientific Registry of Transplant Recipients
Arbor Research Collaborative for Health
Ann Arbor, MI**

**Gift of Life Michigan
Ann Arbor, MI**

Disclosure Information

I have no financial relationships to disclose beyond my affiliations.

I will not discuss off label or investigational uses of pharmaceutical agents or medical devices during this presentation

Disclaimers

- I am not here today as a representative of the Scientific Registry of Transplant Recipients
- I do not know the “right way” to allocate organs, but I suspect that optimal systems will vary by
 - organ type
 - location
 - available data

Scientific Registry of Transplant Recipients Co-investigators

- Robert Wolfe
- Jack Kalbfleisch
- Keith McCullough
- Ann Rodgers
- Mary Guidinger
- Kathryn Meyers

CBS Organ Expert Committee: 6 Key Principles for Organ Allocation

- **Equity**
- **Utility**
- **Urgency**
- **Transparency**
- **Medical evidence**
- **Accountability**

Clearly the principles of Equity, Utility, and Medical Urgency can interact in opposition or in concert, depending on the specific allocation attribute under consideration.

CBS Would Like To Understand

- Are these broad principles sufficient and useful in guiding the development of priority ranking systems for organ allocation?
 - No
- What implications do specific priority organ allocation systems have for system design requirements?
 - Let's discuss

“Consequences of Allocation” versus “Principles of Allocation”

- **EQUITY:**
 - Includes utility and justice and encompasses urgency
- ~~UTILITY~~
- ~~URGENCY~~
- **TRANSPARENCY**
- **MEDICAL EVIDENCE**
- **ACCOUNTABILITY**
- **Allocation Trade-offs:**
 - Allocation to maximize a specific transplant outcome: waitlist survival, post-transplant survival, or incremental survival; or
 - Allocation based on non-outcome-based considerations: waiting time, lottery, “social worth”, one chance, children first, etc.
- **Opportunity Trade-offs**
 - Who owns the organ, i.e. will the administrative/geographic unit of organ allocation be the same as the unit of recovery
 - What and when to share
- **Transition from old system to new**

Examples of the Consequences of Allocation Trade-Offs

Candidate	60 y/o DM	20 y/o non DM	20 y/o DM
Lifespan Without Transplant*	4 years	16 years	9 years
Lifespan With Transplant*	9 years	22 years	16 years
Incremental Survival (LYFT)	5 years	6 years	7 years

- 60 y/o DM: allocate to maximize waitlist survival
- 20 y/o non DM: allocate to maximize post-transplant survival
- 20 y/o DM: allocate to improve incremental survival

**median US survival for these specific populations*

Organ Allocation to Adults in the United States

- **Liver – MELD – 90 day waitlist survival**
- **Lung – LAS – one-year waitlist and one-year post-transplant survival**
 - weighted towards waitlist survival
- **Heart – Status – waitlist survival**
- **Pancreas – local preference**
- **Kidney – waiting time, tissue match, sensitization**

Current U.S. Deceased Donor Kidney Allocation Algorithm

- **15% - ECD kidneys allocated based upon waiting time alone**
- **Allocates SCD kidneys**
 - **5% - kidney plus life saving organ**
 - **15% - zero HLA-A,B,DR mismatched kidney or simultaneous kidney pancreas candidates (projected to decrease to 8%)**
 - **65% - HLA mismatched candidates based upon a menu of priorities**

Current U.S. Allocation Priorities for Mismatched Deceased Donor Kidney

- Prior living donors
- Paybacks
- Pediatric candidates have first priority for donors under the age of 35 years
- Point System
 - Time waiting (1 point per year, fraction of a point for partial year)
 - Prior sensitization (4 points for Panel Reactive Antibody level $\geq 80\%$)
 - HLA-DR Similarity (2 points zero HLA-DR MM, 1 point for a one HLA-DR MM)

Ongoing Criticisms of the Current National Kidney Allocation Algorithm

- Weights assigned to the existing allocation priorities are not objective, i.e. they do not reflect the biological effect of these priorities on outcomes
 - one year of waiting time is assigned the same allocation priority as a one HLA-DR mismatch
 - 4 points for PRA 80, zero points for PRA 79.9
- Does not (with the exception of ECD) account for differences in potential survival of recipients and donated organs
 - consequently, 10,000-15,000 years of potential future recipient survival are lost from each year of deceased donor kidney allocation
 - contributes to high rates of repeat transplantation

Ongoing Criticisms of the Current National Kidney Allocation Algorithm

Contributes to system-wide inequities in access

- Race, ethnicity, socioeconomic status
- Geography
- Does not account for special medical needs of candidates (except for pediatric, and combined organ transplant candidates)
- Time consuming, contributes to inefficient allocation, prolonged cold ischemic injury, and discard

Ongoing Criticisms of the Current National Kidney Allocation Algorithm

- **Inconsistent allocation rules across Donor Service Areas (variances)**
 - Alternative local allocation systems
 - Alternative local allocation units
- **Does not provide uniform access to sensitized patients**
 - 4 points provides a different advantage in each DSA depending on DSA waiting time and candidate blood type
 - No priority for moderately sensitized candidates

Ongoing Criticisms of the Current National Kidney Allocation Algorithm

- Median time to kidney transplant in U.S. varies markedly by DSA
 - 25th percentile among adult kidney transplant programs varies from 3 months to 55 months
- Waiting times for individual patients are unpredictable
- Waiting time favors younger and healthier candidates
- Does not accommodate medical urgency

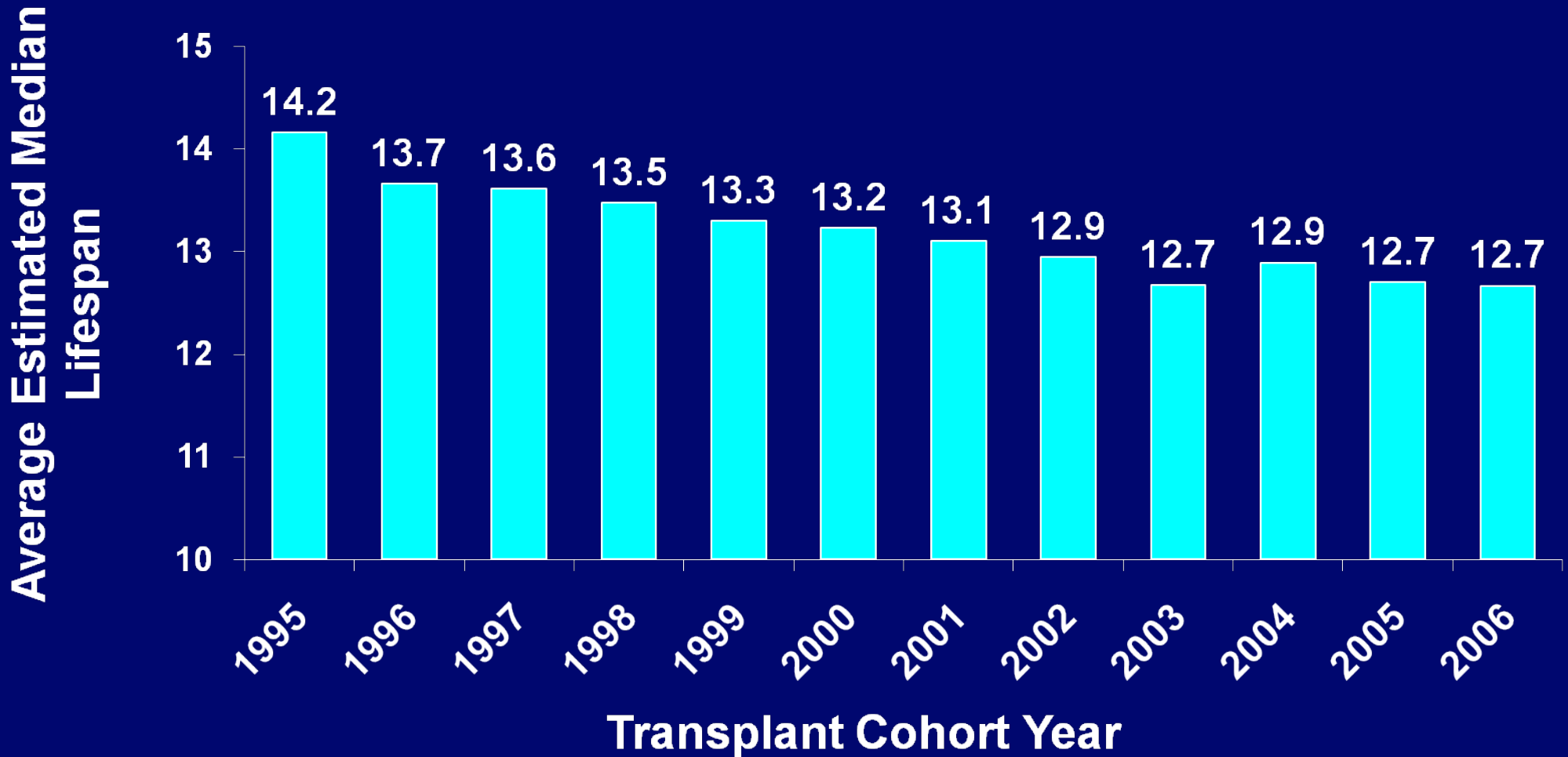
Ongoing Criticisms of the Current National Kidney Allocation Algorithm

- Does not link access to care with progression of disease
- Does not link access to care with measures of benefit
- Unbalanced in terms of allocation priority in favor of HLA match and waiting time
- Does not serve patient autonomy
 - ECD versus SCD
 - Inadequate information on donor quality
- Does not conform to final rule

OPTN Final Rule

- Sets requirements for all organ allocation systems
- Allocation systems must:
 - Be based on sound medical judgment
 - Seek to achieve the best use of donated organs
 - Be designed to avoid wasting organs, to avoid futile transplants, to promote patient access to transplantation, and to promote the efficient management of organ placement
 - Set priority rankings...through objective and measurable medical criteria
 - Deemphasize waiting time

Decline in Average Post-Transplant Lifespan Among SCD Kidney Transplant Recipients



***Concepts and data from Recent
US Initiatives to Redesign its
National Kidney Allocation
System***

Life Years from Transplant (LYFT)

- May, 2004 OPTN Kidney Committee was charged with performing a 360° review of the existing kidney allocation algorithm
- June, 2005 reported to the OPTN Board of Directors three principal areas of concern
 - Allocation system (inequitable, inefficient, suboptimal utility)
 - Donor organ supply (HRSA Collaboratives)
 - Effects of geography on allocation equity
- OPTN Board charged the Kidney Committee with revising the kidney allocation system
- OPTN Kidney Committee began to explore integrating a measure of incremental survival (LYFT) into the kidney allocation system.

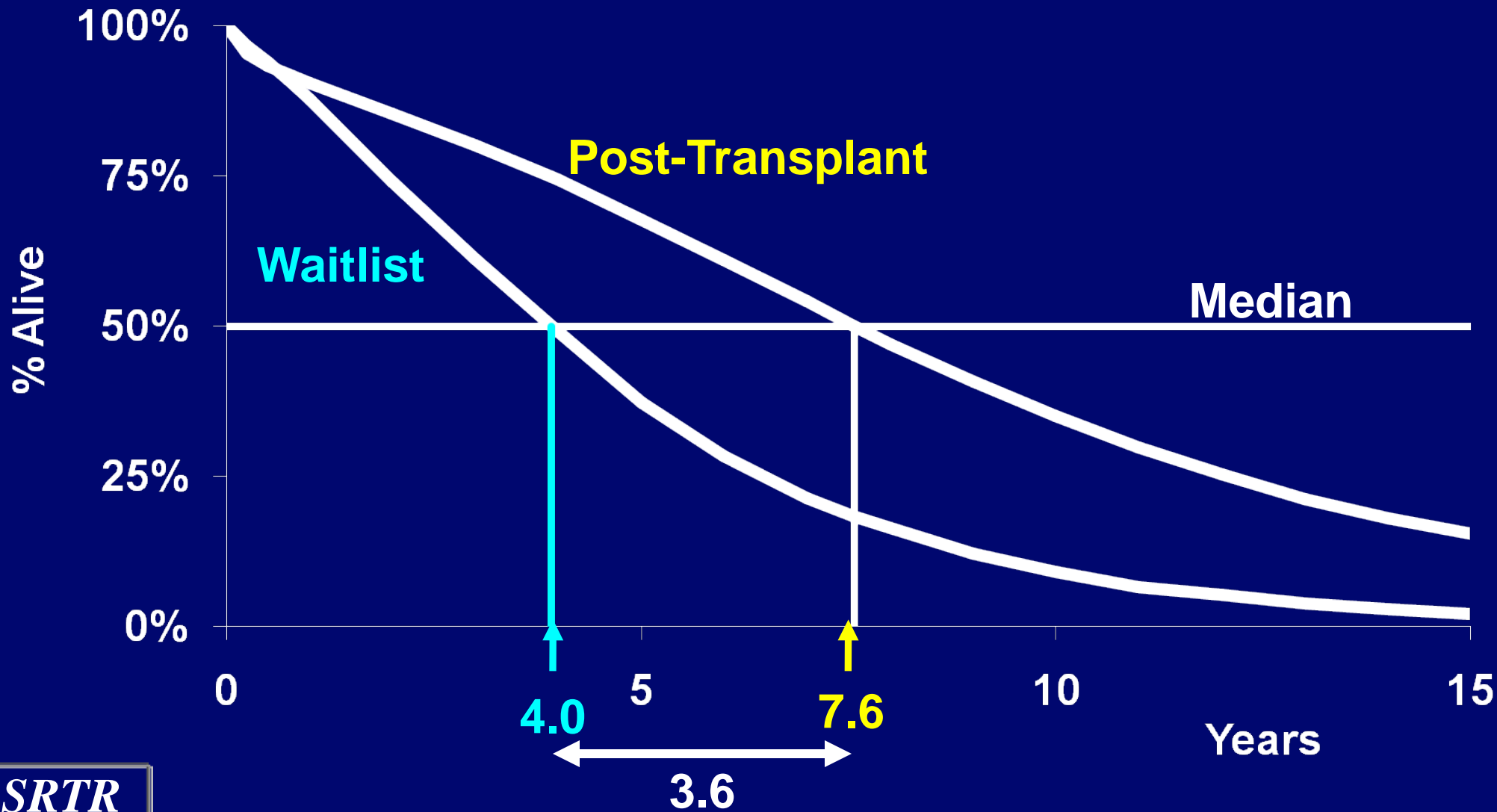
Life Years From Transplant (LYFT)

- LYFT is the difference between two predicted lifetimes:
 - Expected lifetime without a transplant
 - Expected lifetime with a transplant from a specific donor
- Example, a hypothetical 30 year old (otherwise average) candidate's remaining life might be:
 - 18 years with a deceased donor kidney transplant
 - 12 years with dialysis
 - LYFT = 6 extra years of life with transplant
- This hypothetical candidate's LYFT would be greater if his or her expected survival
 - on dialysis would be shorter, or
 - post-transplant would be longer

LYFT Combines Two Major Approaches to Organ Allocation

- **Prioritize medical urgency**
 - Higher priority if waitlist lifetime is shorter
- **Prioritize post-transplant survival**
 - Higher priority if post-transplant lifetimes are longer
- **LYFT prioritizes both by using the common metric of expected future years of life**
- **LYFT can be used**
 - as an element in organ allocation
 - as a metric
 - to assess trends in outcomes of existing allocation systems
 - to compare the current allocation system to proposed alternative allocation systems

Median Survival And LYFT Age 55, Diabetic, Kidney Candidate



SRTR

Accuracy of LYFT Depends on Accuracy of Component Models

- In the LYFT calculation, there are separate statistical models for each component:
 - patient survival without a transplant,
 - patient survival with a transplant, and
 - graft survival
- Models are based on historical data from actual transplant candidates, recipients and organs
- The predictive value of each model can be evaluated in a number of ways

Overall C-Statistics for Models Related to Organ Allocation

- **For the LYFT models**

C-Statistics for:	0-15 year Survival
Patient survival without transplant	0.68
Patient survival with transplant	0.68
Graft survival	0.61

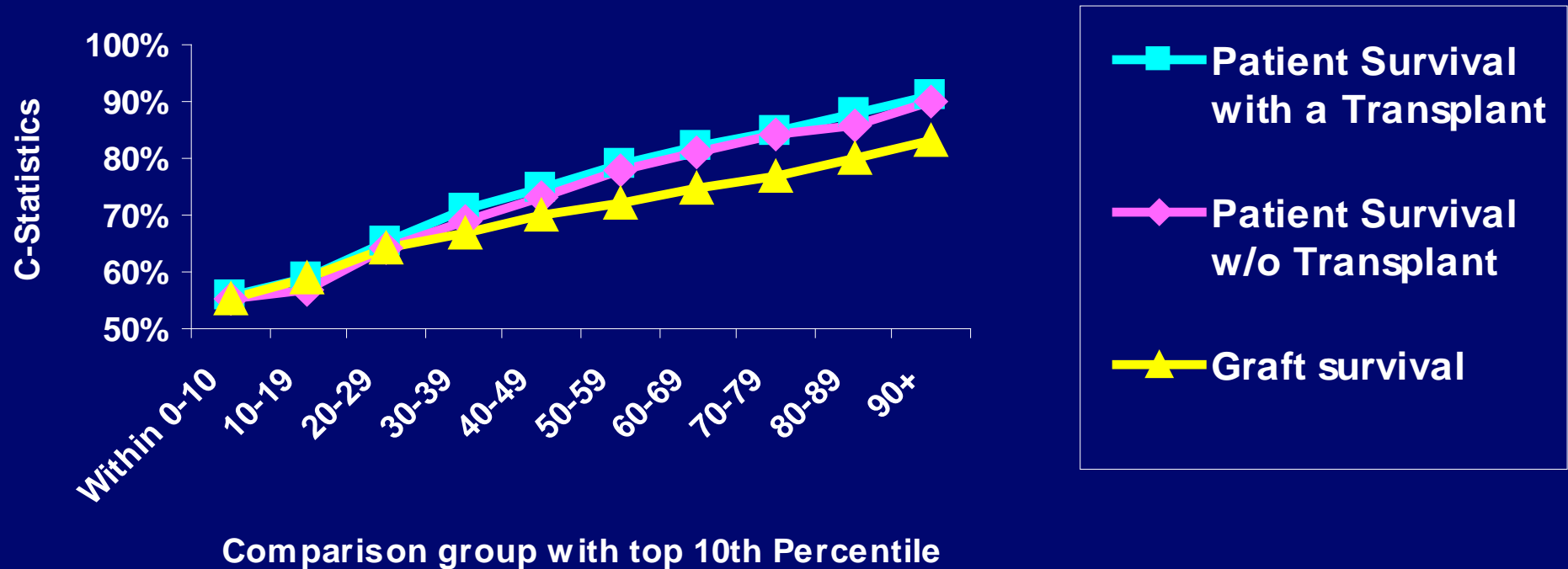
- **MELD (used in liver allocation): 0.75 for 90-day waitlist survival, 0.64 for overall waitlist survival**
- **LAS (used in lung allocation): 0.76 for waitlist, 0.59 for post-transplant**
- **HLA-alone kidney models (HLA is used in kidney allocation): 0.52 for patient survival, 0.53 for graft survival**

Validation using C-Statistics

- Comparisons of these C-statistic values indicate that the predictive value of the LYFT components are comparable to those currently used in the allocation of livers, hearts and kidneys
- C-statistics assess overall goodness of fit, assigning equal importance to the comparison between patients 1 and 500 as to the comparison between patients 249 and 250 on the list

C-Statistics of LYFT Models: Topmost 10-Percentile Group v. Descending 10-Percentile Groups

LYFT Component Models



Validation using C-Statistics

- LYFT can be used to distinguish patients with long expected lifespans from those with short expected lifespans
- In allocation, distinguishing very different patients is more relevant than the rank ordering of similar candidates
- Ideally allocation metrics should assign similar scores to similar candidates and dissimilar scores to dissimilar candidates
- The survival models used in LYFT are highly accurate at distinguishing patients from the extremes of the predicted lifetime distributions

Validation Using Split-Half Models

- The split-half approach uses half of a dataset for model building and the other half for validation
- When the analysis from the previous slide was repeated using split half models, all but 2 of the thirty decile comparisons resulted in c-statistics within +/- 0.01 (the remaining two deciles were within 0.02 and 0.03)
- $R^2 \geq 0.994$ between split half median lifespans
- $R^2 = 0.988$ for split-half LYFT

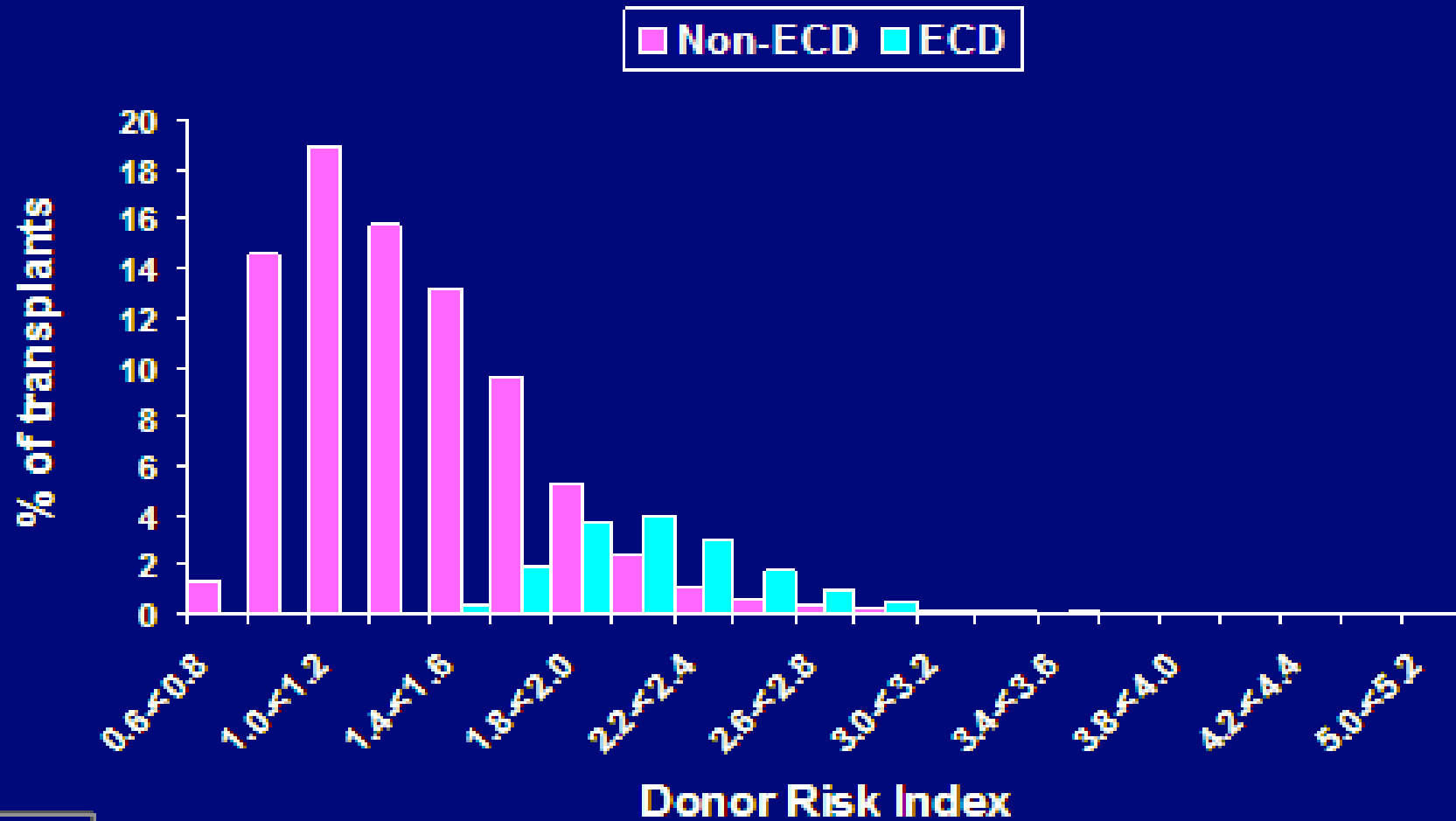
The Kidney Allocation Score (KAS)

- It is important to distinguish LYFT, (a metric), from the Kidney Allocation Score (KAS) which is an allocation model that includes, among several components, LYFT
- KAS Components
 - Time on Dialysis
 - LYFT
 - PRA
 - DPI

For KAS, Life Years From Transplant (LYFT) Was Adjusted for QoL

- LYFT is the extra years of life a candidate could expect to achieve with a kidney transplant compared to never receiving a kidney transplant
- For KAS, LYFT was adjusted for QoL
- Years spent without a functioning graft were weighted by 0.8* to account for reduced quality of life
- $\text{QoL-LYFT} = \text{Lifetime of functioning graft} + 0.8 \times \text{lifetime after graft failure} - 0.8 \times \text{lifetime without a transplant}$

Histogram of KDRI by ECD Status

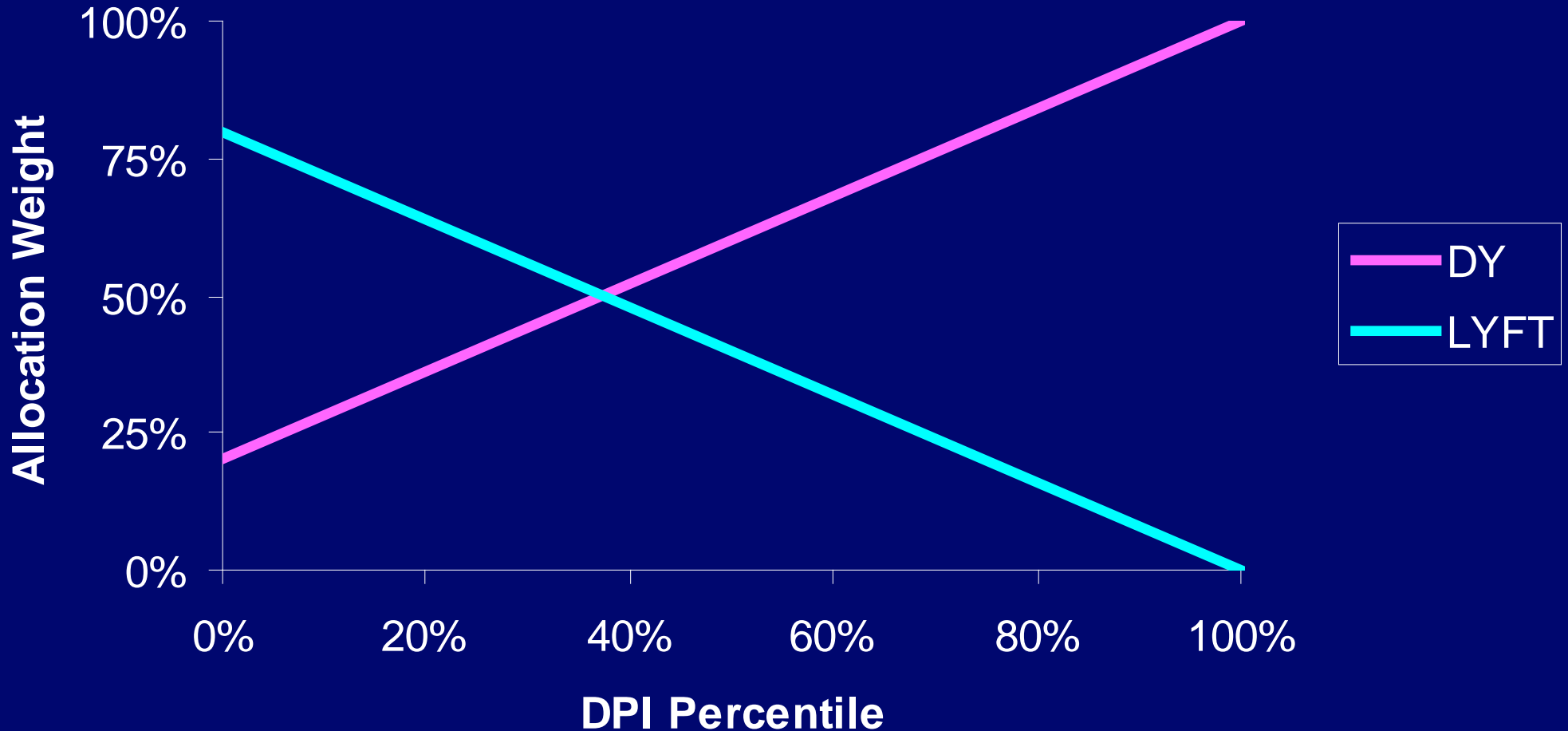


SRTR

SRTR

Capped LYFT and DY 28

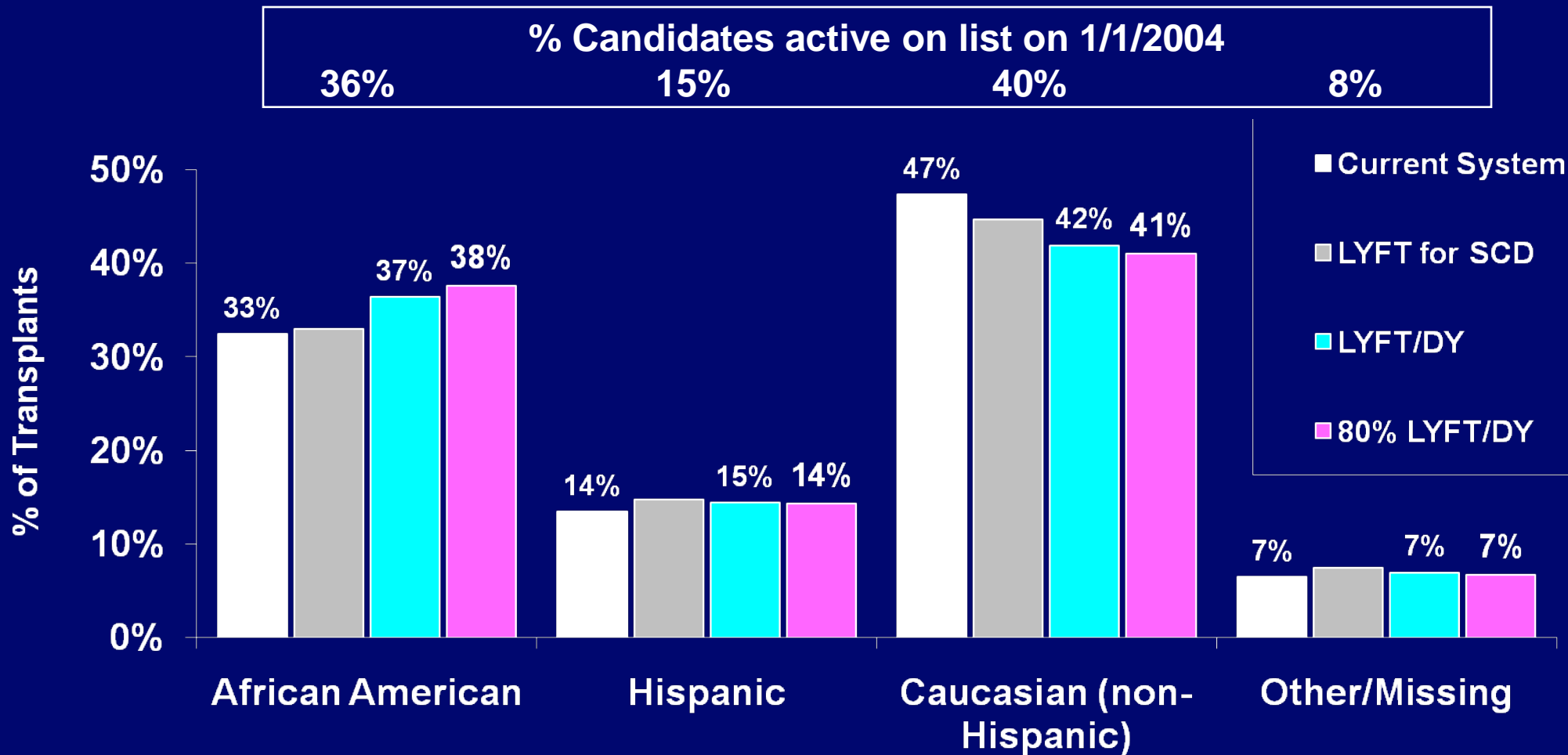
$$\text{LYFT} * 0.8 * (1 - \text{DPI}) + \text{DY} * (0.8 * \text{DPI} + 0.2) + \text{PRA} * 4$$



Expected Years of Life Per Year of Allocation

	Current System	Simulation 16a LYFT For SCD	Simulation 18f LYFT/DY	Simulation 28 80% LYFT/DY
Years after tx	107,865	143,505	122,140	118,133
Total graft yrs	72,814	86,614	75,600	73,772
Total extra life yrs	48,187	59,691	52,947	51,589
Δ years after tx		35,640	14,275	10,268
Δ graft yrs		13,800	2,786	958
Δ extra life yrs		11,504	4,760	3,402

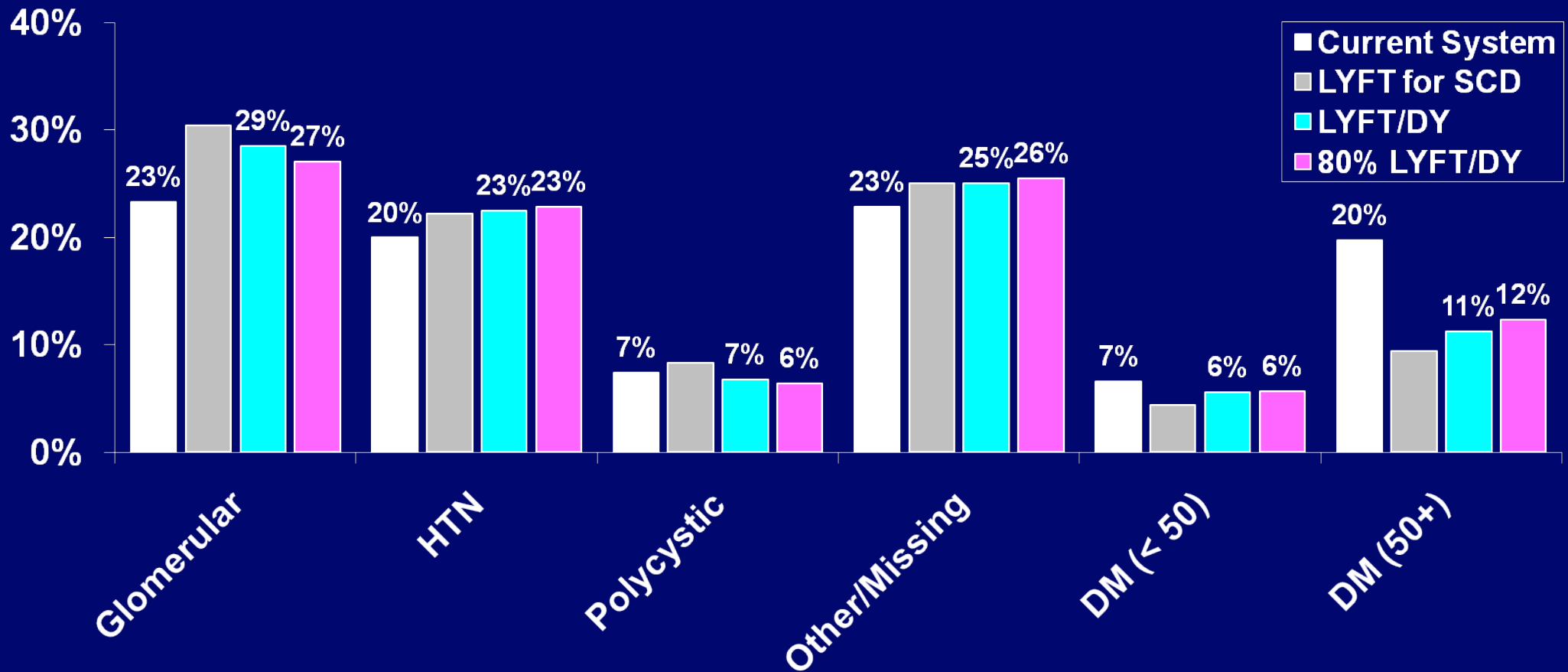
Racial Distributions of Kidney Recipients



Diagnosis Distributions of Kidney Recipients

% Candidates active on list on 1/1/2004

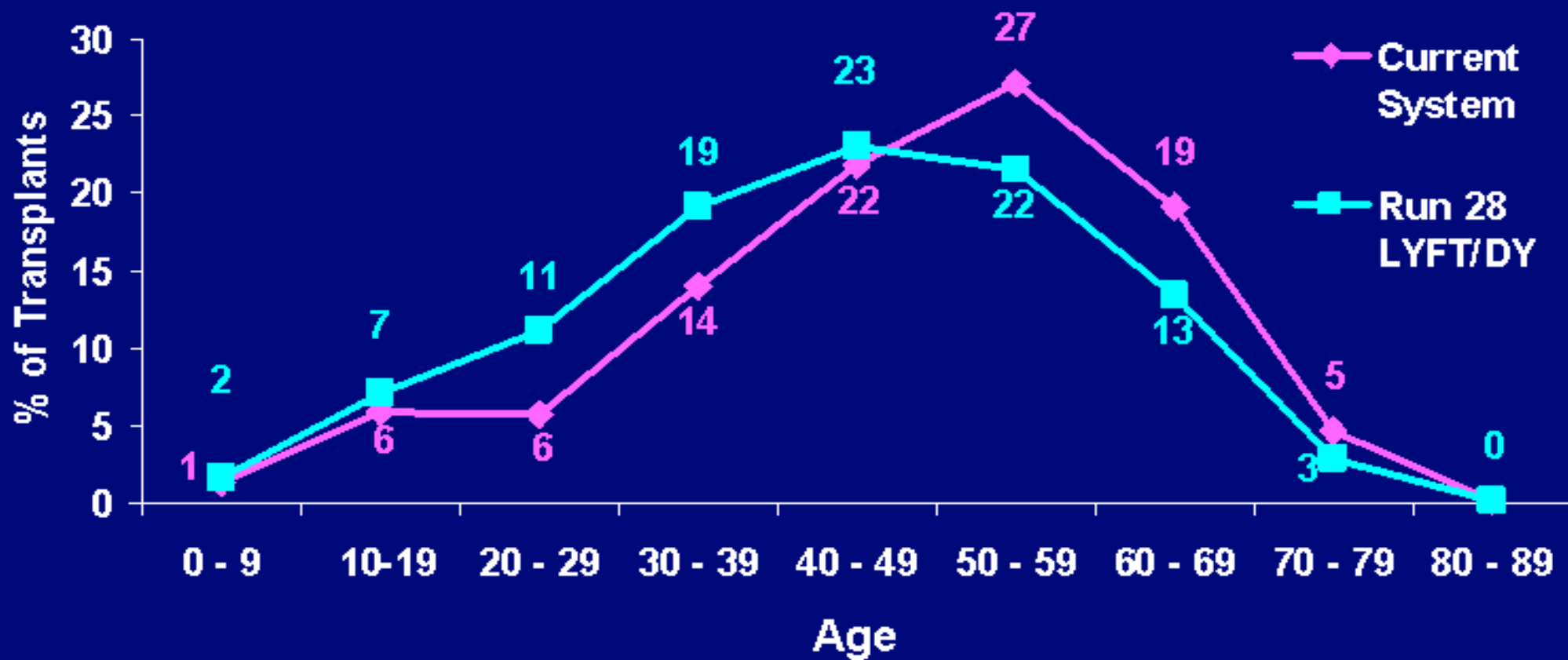
20% 16% 6% 23% 12% 23%



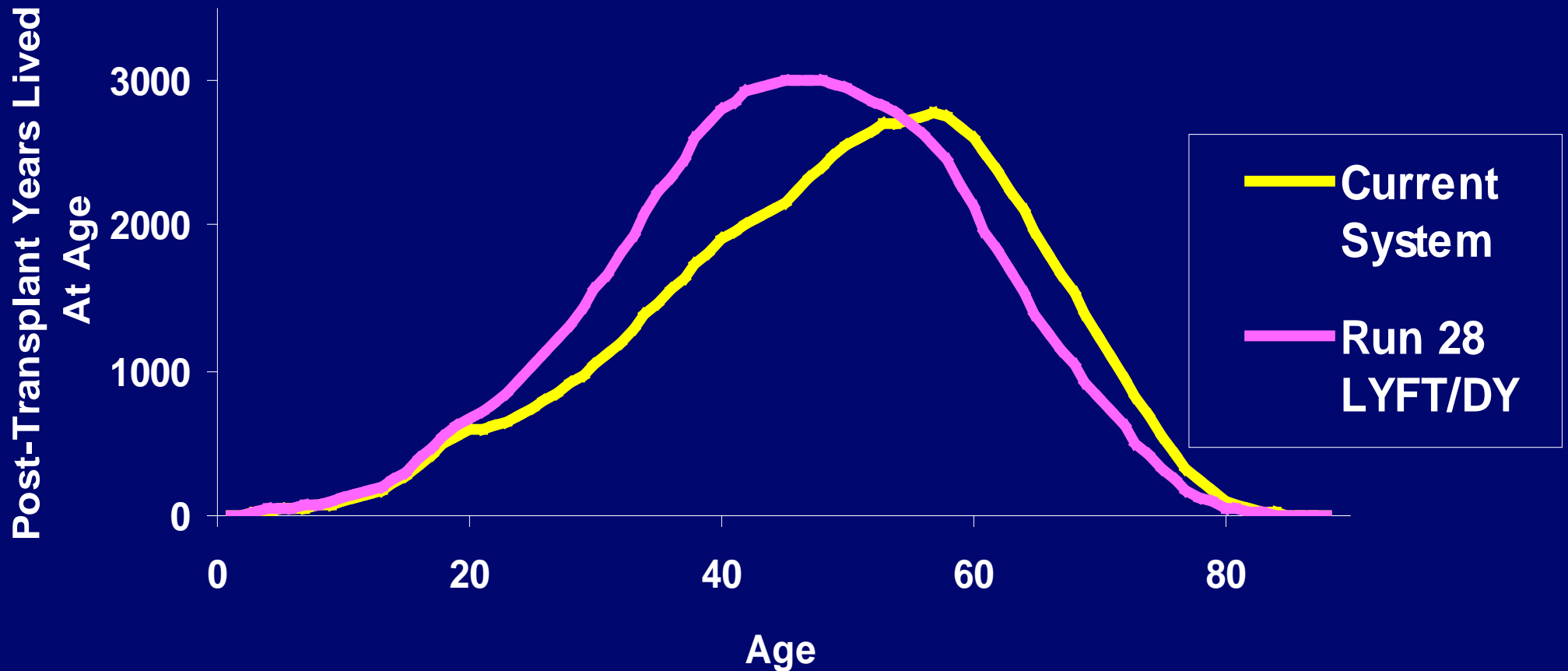
Age Distribution of All Kidney Alone Recipients Changes When Allocation Incorporates LYFT

% Candidates active on list on 1/1/2004

0% 2% 7% 15% 24% 29% 19% 4% 0%



Distribution of Recipients' Post-Transplant Years Lived At Each Age



Examples of the Consequences of Allocation Trade-Offs

Candidate	60 y/o DM	20 y/o non DM	20 y/o DM
Lifespan Without Transplant*	4 years	16 years	9 years
Lifespan With Transplant*	9 years	22 years	16 years
Incremental Survival (LYFT)	5 years	6 years	7 years

- 60 y/o DM: allocate to maximize waitlist survival
- 20 y/o non DM: allocate to maximize post-transplant survival
- 20 y/o DM: allocate to improve incremental survival

**median US survival for these specific populations*

Other Allocation Strategies Under Consideration

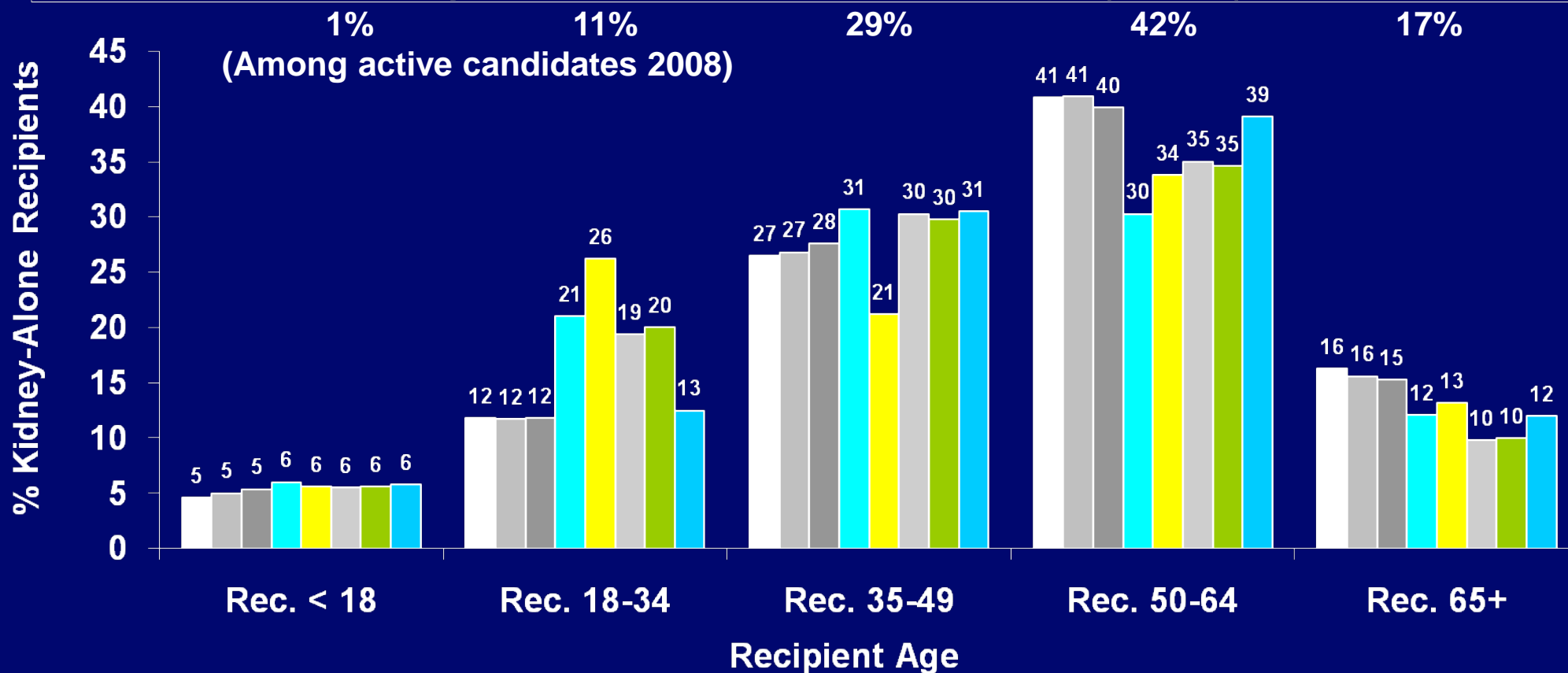
- **KPSAM Data Request**

- **Eight runs:**

- 34 Current rules prior to January, 2009
- 35 Current rules after January, 2009 (without OMM PRA < 20 sharing)
- 36 Run 35 + A2-B, kidney follows pancreas locally, no paybacks, and dialysis time in addition to wait time
- 37 Top 20% of candidates have priority for top 20% of donors
- 38 Candidates under 35 have priority for donors under 35
- 39a Candidates within 10 years of donor age have priority
- 39b Candidates within 15 years of donor age have priority
- 40 Top 80% of candidates have priority for top 20% of donors

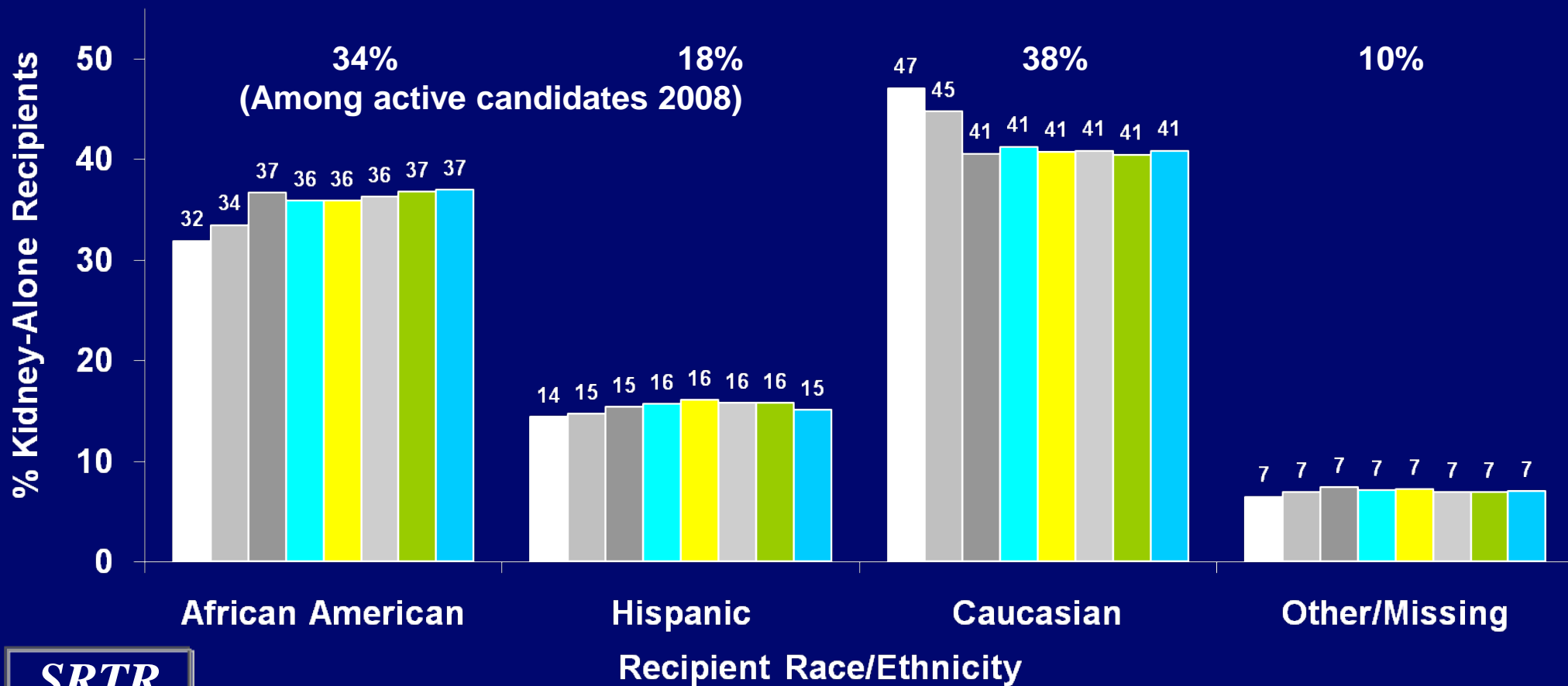
Age Distribution by Allocation Rule

- Run 34: current rules pre 2009
- Run 35: 2009 rules no PRA <20 0mm
- Run 36: 2009 rules + extras
- Run 37: top 20%-top 20%
- Run 38 <35 to <35
- Run 39a Within 10 years
- Run 39b Within 15 years
- Run 40: top 20%-top 80%



Race Distribution by Allocation Rule

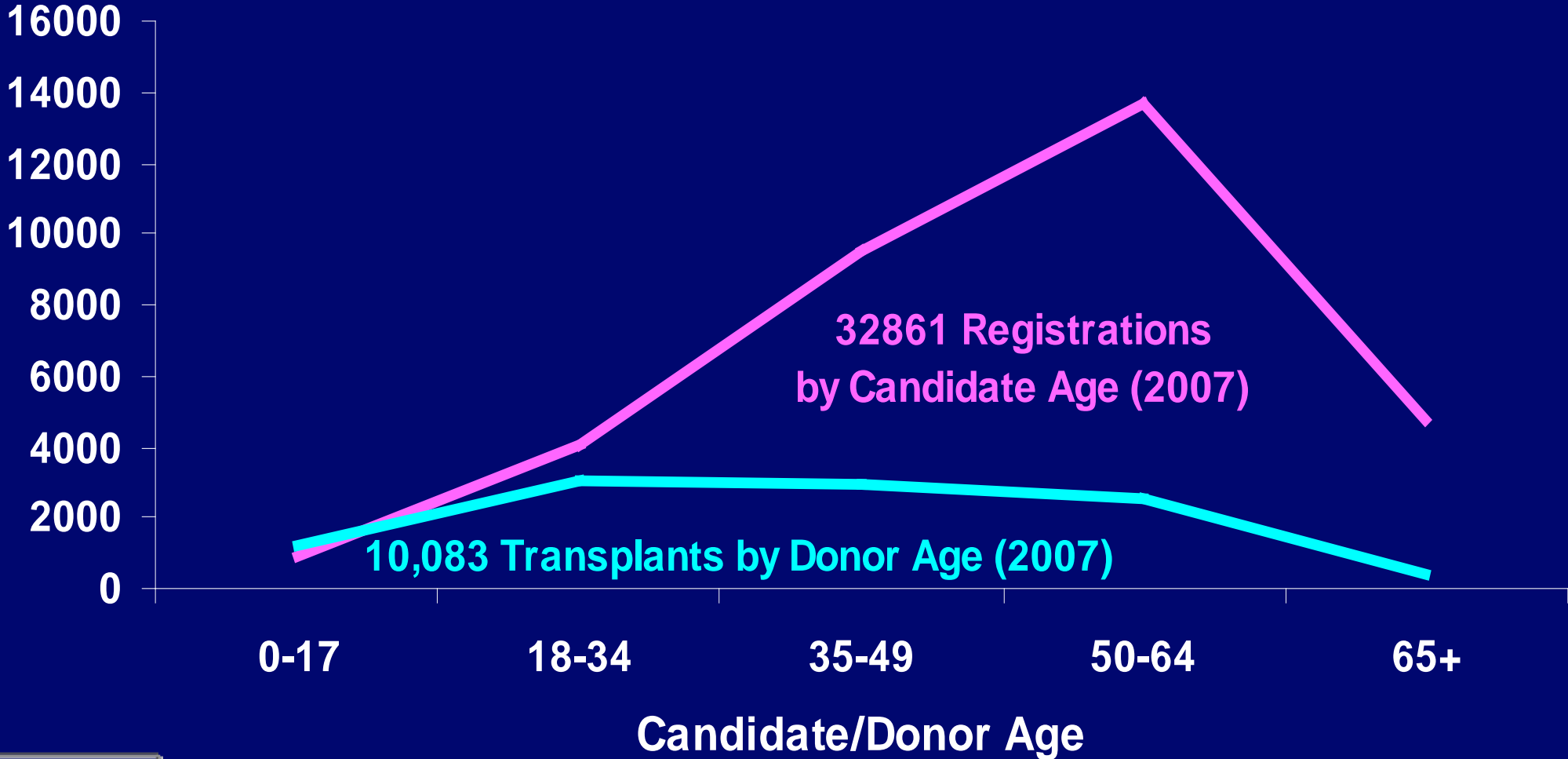
- Run 34: current rules pre 2009
- Run 35: 2009 rules no PRA <20 0mm
- Run 36: 2009 rules + extras
- Run 37: top 20%-top 20%
- Run 38 <35 to <35
- Run 39a Within 10 years
- Run 39b Within 15 years
- Run 40: top 20%-top 80%



Life Years by Allocation Rule

Years	Run34: curr rules pre 2009	Run 35: 2009 rules no PRA<20 0mm	Run 36: 2009 rules + extras	Run 37: top 20 to top 20%	Run 38: <35 to <35	Run 39a: within 10 years	Run 39b: within 15 years	Run 40: top 20% to top 80%
Number of transplant recipients	10764	10788	10652	10608	10676	10789	10708	10718
Total lifespan after transplant	121153	121707	119392	137931	133418	135305	134184	126532
Total graft years of life	84158	83700	81600	87677	85845	87175	86306	84370
Total extra years*	51311	51682	50834	57124	54717	56366	56056	54023
Change in lifespan after transplant	1,762	2,315	(ref)	18,540	14,026	15,913	14,792	7,141
Change in graft years of life	2,558	2,100	(ref)	6,077	4,245	5,575	4,706	2,770
Change in extra years	476	848	(ref)	6,290	3,882	5,532	5,221	3,189
Lifespan benefit per transplant*	4.77	4.79	4.77	5.39	5.13	5.22	5.23	5.04

Numbers of Transplants and Registrants in 2007 by Candidate/Donor Age



Comparison of the Current and Simulated Kidney Allocation Systems

Current Kidney Allocation System		KAS Simulations	Newer Simulations
HLA Match - Increase allograft survival	Medical Criteria	Life Years From Transplant (LYFT) - Increase candidate survival	Age or Post-Transplant Survival - Increases recipient survival
Wait time - Starts at listing or GFR < 20	Time	Dialysis Years (DY) - Starts at initiation of dialysis	
4 points for % PRA > 80	Sensitization	4 * % PRA/100	
SCD/ECD	Donor Quality	Donor Profile Index (DPI)	

Alan's Personal Opinions on Allocation Priorities

- Allocation elements should be measurable and clinically meaningful
- Weighting of allocation priorities such as waiting time, tissue match or sensitization should reflect the actual biological effects of these variables on survival
- Allocation algorithm should avoid arbitrary or unreliable cutoffs such as 4 points for PRA > 79, or top 20% of organs to top 20% of candidates, or organs from donors under the age of 35 years to candidates under the age of 35 years
- Allocation priorities should discriminate unlike from unlike, and assign similar scores to similar patients

Key Principles for Organ Allocation

***Canadian Blood Services Organ Expert Committee
January 11, 2010***

Alan Leichtman, MD

**Division of Nephrology
Kidney Epidemiology and Cost Center
University of Michigan**

**Scientific Registry of Transplant Recipients
Arbor Research Collaborative for Health
Ann Arbor, MI**

**Gift of Life Michigan
Ann Arbor, MI**