Can MELD Be Improved: Implications of HCV Therapy and CKD

Russell H. Wiesner, MD
Professor of Medicine
Mayo Clinic College of Medicine
Rochester, Minnesota

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Outline

1) MELD historical background
2) MELD impact
3) Shortcomings of MELD model
4) Improving MELD model
5) Improving future MELD allocation policy

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Important Concepts from the Final Rule

OPTN/UNOS Allocation Performance Goals

- Allocation should be based upon **objective and measurable medical criteria**
- Allocation in the order of **medical urgency**
- Avoid **futile** transplants
- Promote patient **access to transplantation**

Important Concepts from the Final Rule

OPTN/UNOS Allocation Performance Goals

- **Minimize** role of waiting times
- Allocation **shall not** be based on the candidate's **place of residence** or place of listing
- Organs shall be distributed over as **broad a geographical area** as feasible

MELD Model

Developed in TIPS patient
Bilirubin, INR, Creatinine (etiology)
Validated in UNOS patients
Validated around the world—Europe, S. America, China
Accurately predicts survival in advanced liver disease
Used to allocate deceased donor livers since Feb. 27, 2002
Has held up to intense scrutiny

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Deceased Donor Liver Allocation

February 2002 Changes:

Child-Turcotte-Pugh Score	→ →	MELD Score
■ Ascites		— Creatinine
■ Encephalopathy		— Bilirubin
■ Bilirubin		— Protime INR
■ Protime INR		(sodium)
■ Albumin		

MELD Score = 0.957 x Log_e (creatinine mg/dL) + 0.378 x Log_e(bilirubin mg.dL) + 1.120 x Log_e(INR) + 0.643

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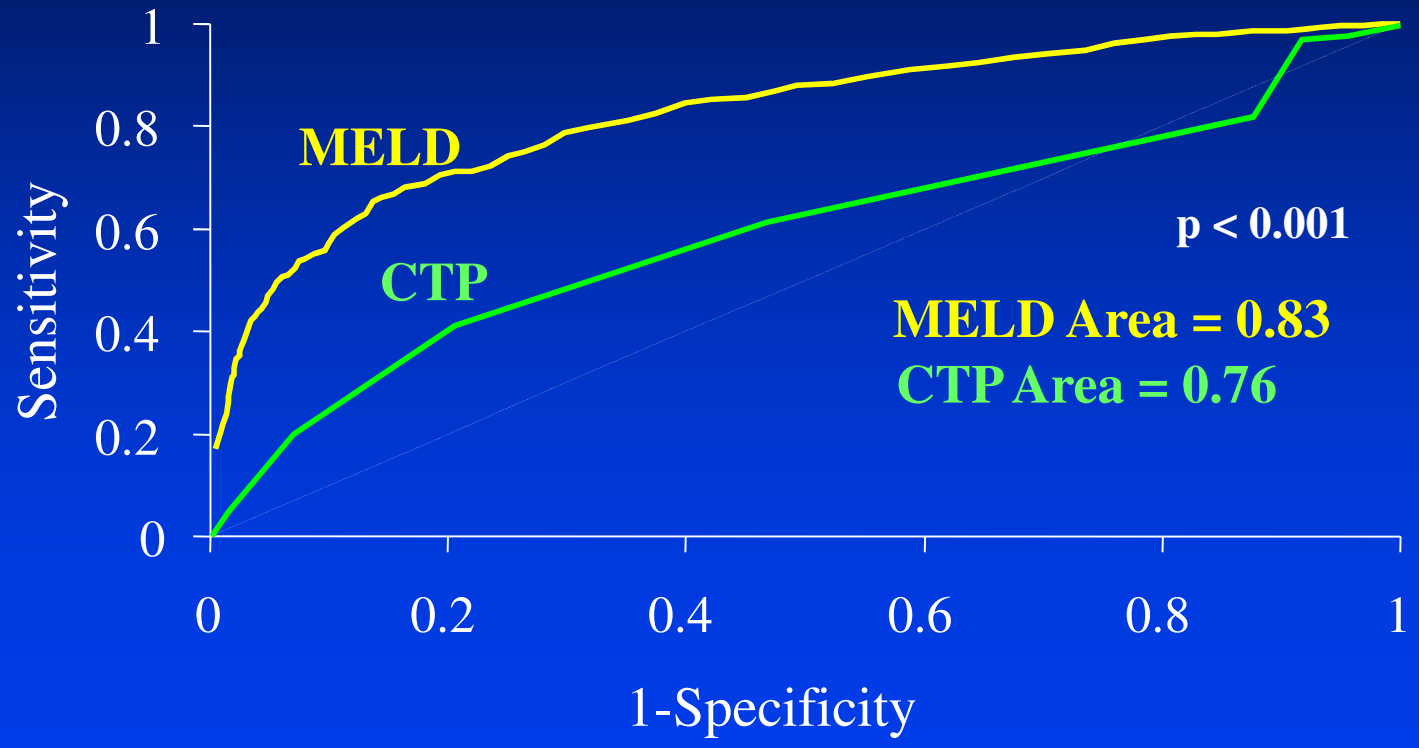
ROC Curve for 3-Month Mortality on UNOS Waiting List



MELD

What does it do?
Urgency Model

Estimates the probability of dying over time in patients with chronic liver disease

C-statistic 0.83 – 0.86

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Impact of MELD

- Decreased deaths on waiting list
- Transplanted sicker patients (higher MELD 17-21)
- Increase HCC patients transplanted
- Post-transplant survival unchanged/improved
- Better defines survival benefit
- Allowed evidence-based decision-making

Challenges

- Restricted by geography and exceptions
- 15% prioritized wrong
- Exception MELD scores – non standardized
- HCC over prioritized
- Regional Review Boards
- Geographic disparity
- Increasing female disadvantage
- Increasing number of liver/kidney transplants
- Increased cost – High MELD

Approach to Further Reducing Deaths on the Waiting List

1)Increase number of donors
2)Improve MELD Model
3)Improve MELD Allocation Policy

Can We Improve MELD Model?

- Variable not used, ascites, encephalopathy, objective
- Add sodium
- INR measurement
- Use direct bilirubin measurement
- Better measurement of renal function (females)
- Re-weigh and cap variable in MELD

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Significant Variables That Could NOT be Used in Model

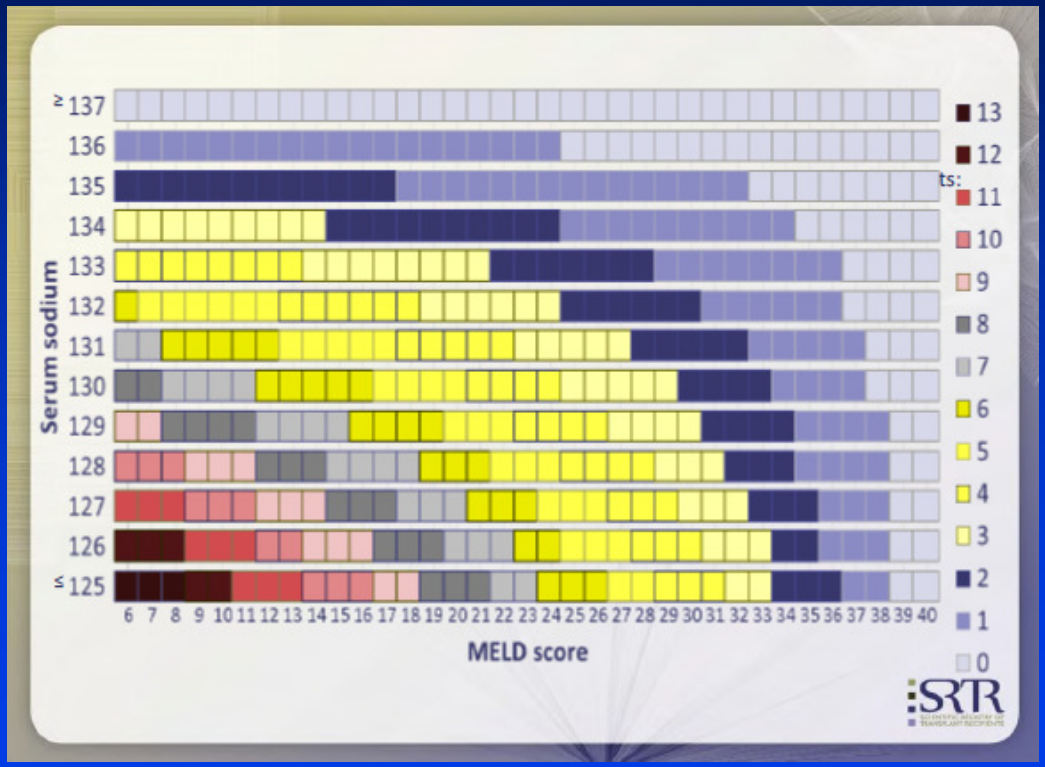
- Etiology
- Recipient age
- Race
- Gender
- Transplant Center

Final Model – Creatinine, INR, Bilirubin

Sodium

- Hyponatremia associated with ascites and independent predictor of 3-month survival
- MELD Na—would affected 23%
- 7% of deaths on waiting list might have been prevented using MELD Na
- More important at lower MELD level (12-23)

Additional MELD Points Using Updated MELD-Na Equation



INR

- Variability – laboratories
- Standardized for patients on Warfarin
- Need accurate, reproducible measure of coagulopathy in liver patients
- Costs of developing INR standard for liver disease
- Treating chronic PVT with Coumadin to increase MELD score

Direct Bilirubin

- Use of total bilirubin may overestimate degree of liver dysfunction
- 10% of population have Gilberts – indirect bilirubin
- Hemolysis not uncommon in liver disease

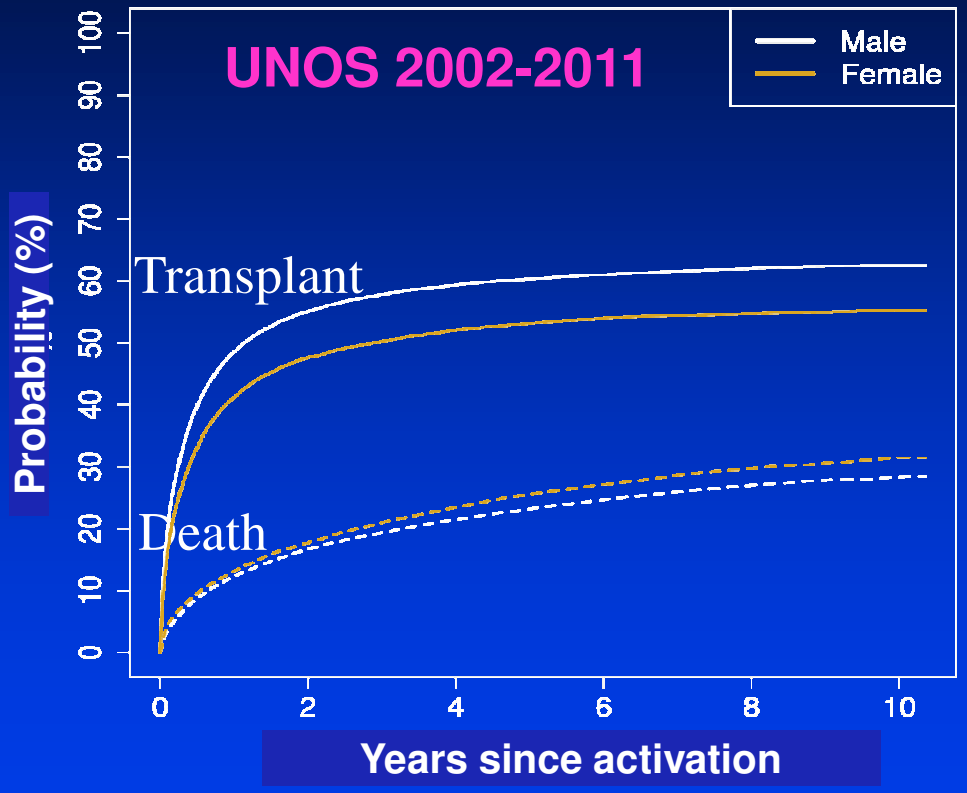
Creatinine

- Inpatients with high serum bilirubin, serum creatinine can be overestimated.
- In females – underestimated degree of renal dysfunction

Gender Disparity

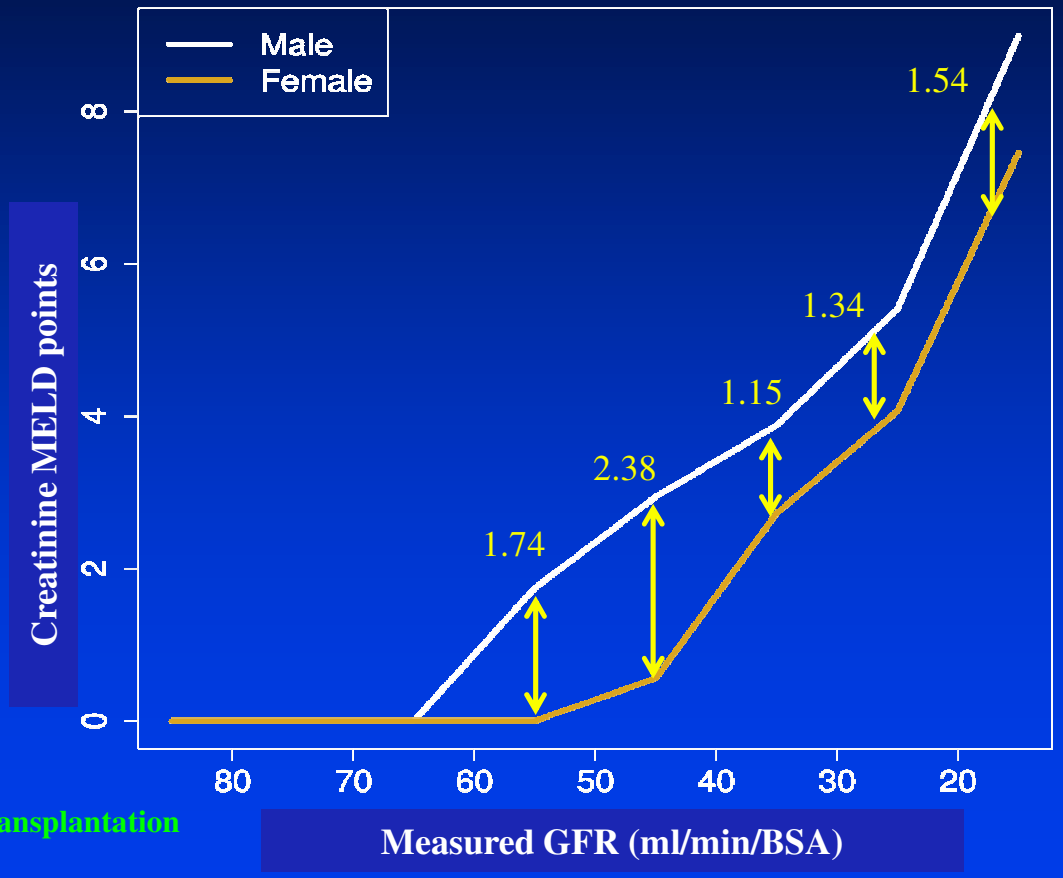
- Females associated with a 15% increased risk of death on the wait list and 20% decrease in probability of receiving a liver transplant
- Serum creatinine underestimates renal dysfunction in females
- Better measurement of renal function and addition of sodium may attenuate this difference

Waitlisted Women 20% Less Likely Than Men to Undergo Liver Transplantation



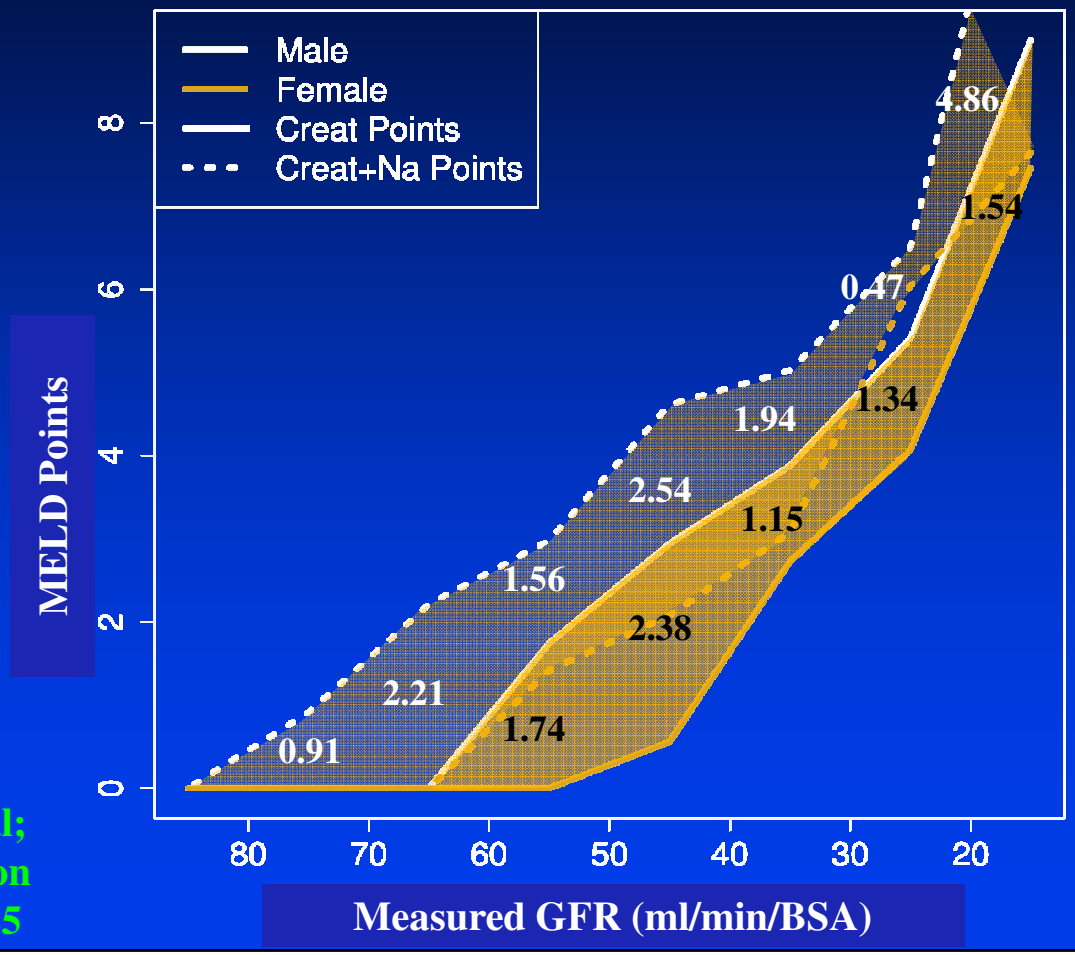
Allen AM, et al; Transplantation 2014 (98):S-725

Women Receive Fewer Creatinine-MELD Points Than Men With Similar Renal Function



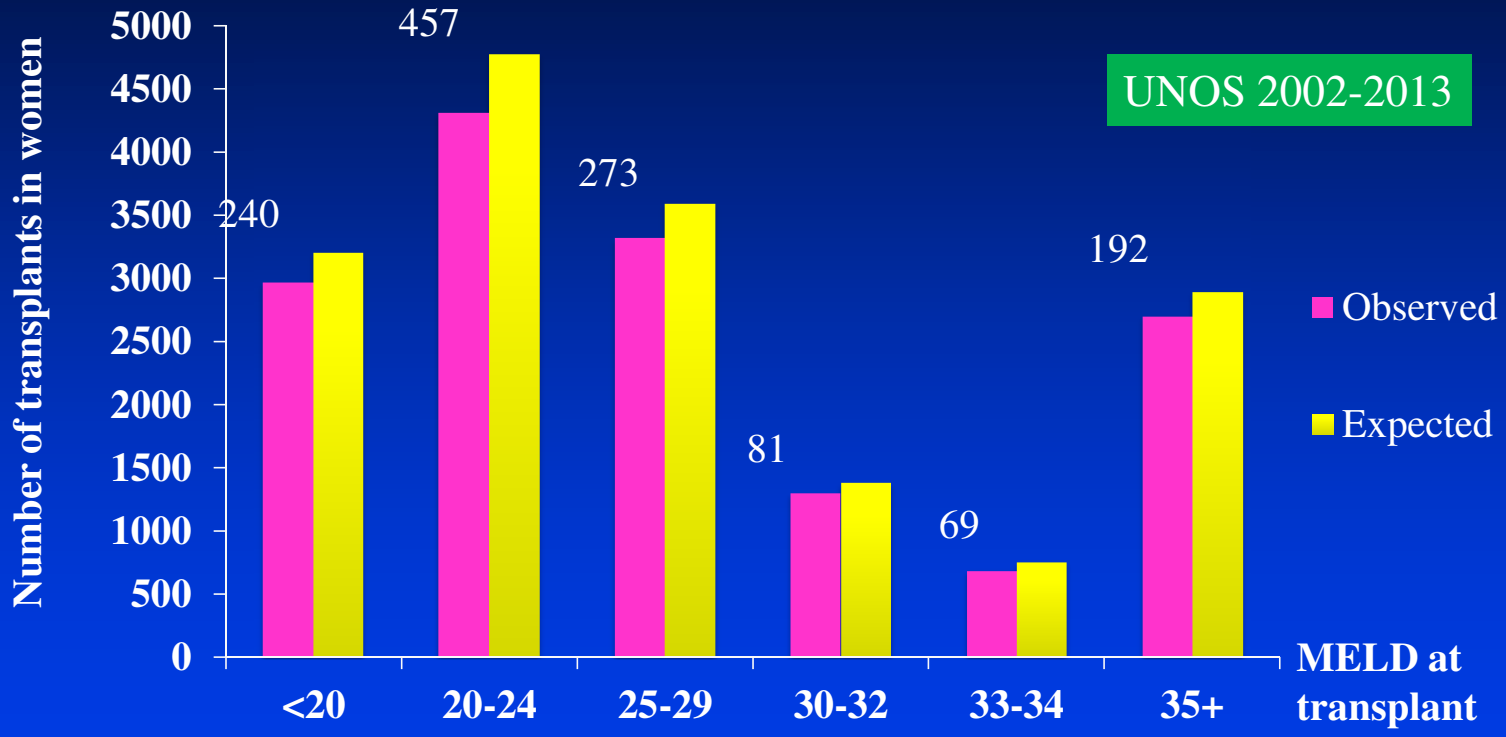
Allen AM, et al; Transplantation 2014 (98):S-725

MELD-Na Worsens The Disparity



Allen AM, et al; Transplantation 2014 (98):S-725

Women Receive fewer Than Expected Transplants at all MELD Scores



*adjusted for region, allocated MELD, recipient/donor height differences of ± 20 cm

Allen AM, et al; Transplantation 2014 (98):S-725

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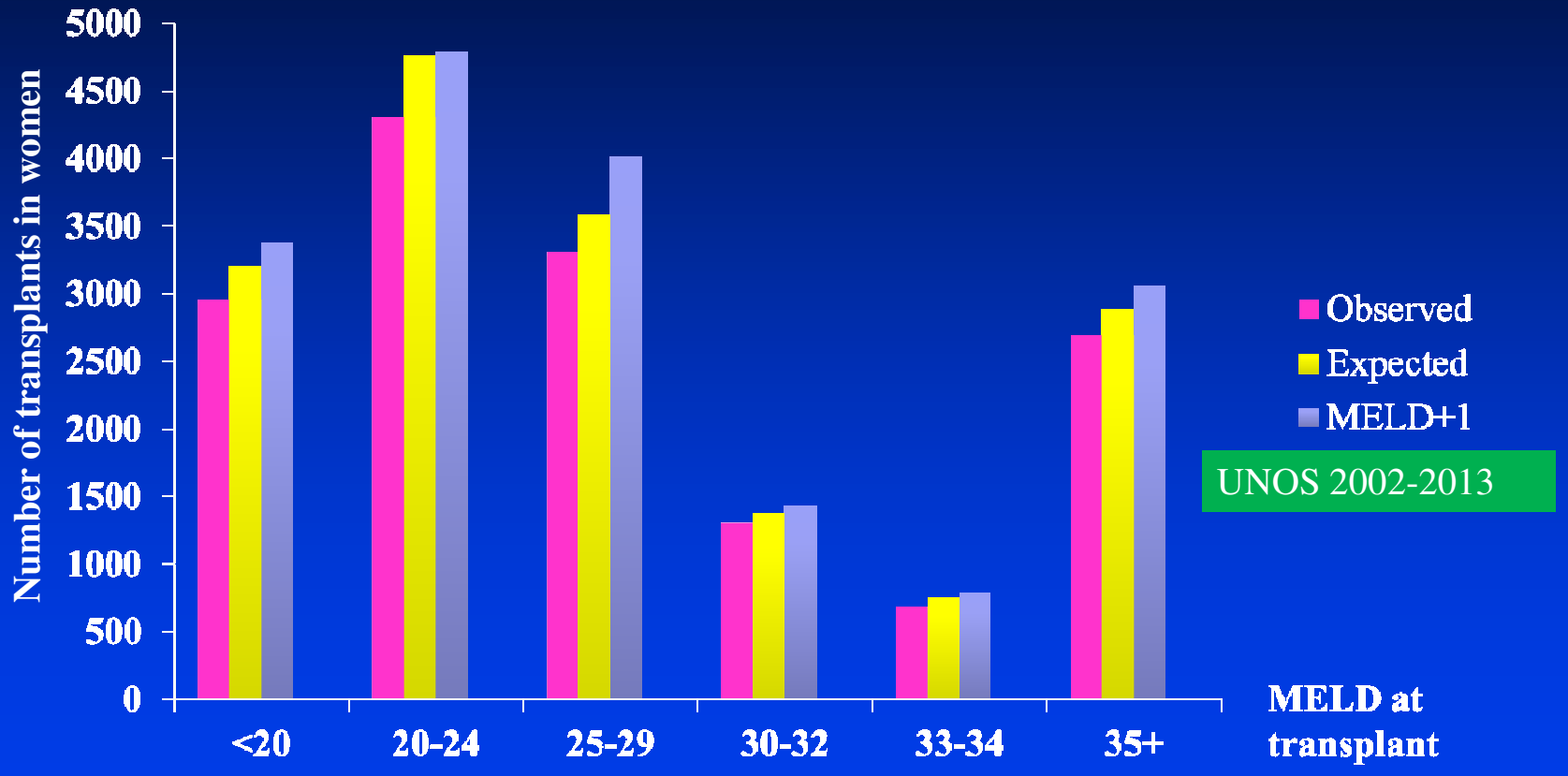
Adding 1 Point to Biological MELD in Women Corrects Disparity



Allen AM, et al;
Transplantation 2014 (98):S-725

*adjusted for region, allocated MELD, recipient/donor height differences of ± 20 cm

Summary

- Women are disadvantaged in the current allocation system
- Serum creatinine underestimates renal dysfunction in women, resulting in 1-2 fewer MELD points
- Addition of Na to MELD worsens the disparity
- 1 MELD point deficit has considerable impact on women's success to available livers, but the exact extent should be further assessed with simulation models

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Re-Weighing MELD Variables

- Changing boundaries for creatinine (0.8 – 3.0 mg/L and INR 1-3
- Weight of bilirubin increases
- Weight of INR and creatinine decreases
- Sodium is added

Results

Model	Concordance
Original MELD	0.8653
Refit MELD	0.8675
MELD Na	0.8758
Refit MELD Na	0.8778

Would affect ~ 12% of transplantations and 29 fewer deaths per year

Conclusion

- Changes only lead to a small improvement of MELD model C-statistic
- Expense to re-program
- Unlikely to get concordance greater than 0.9 given random events that occur on wait list

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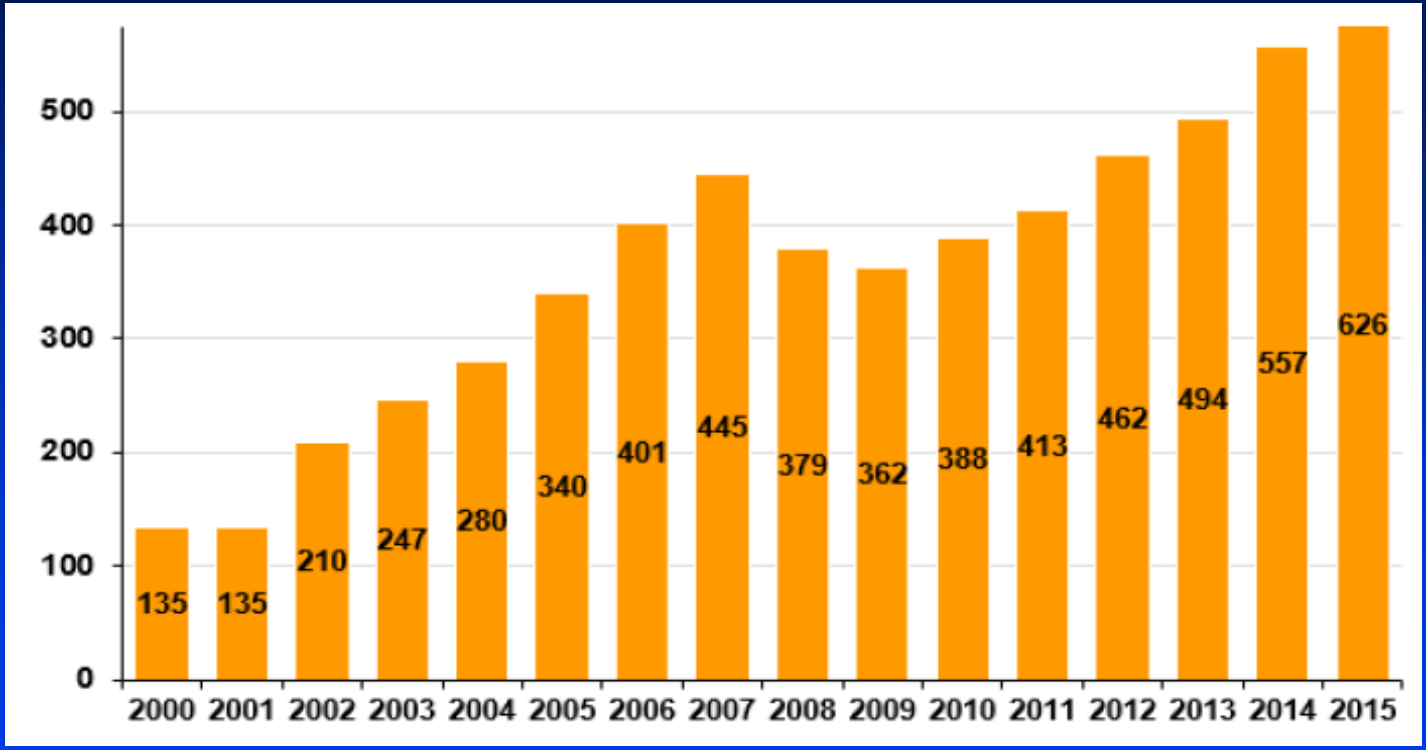
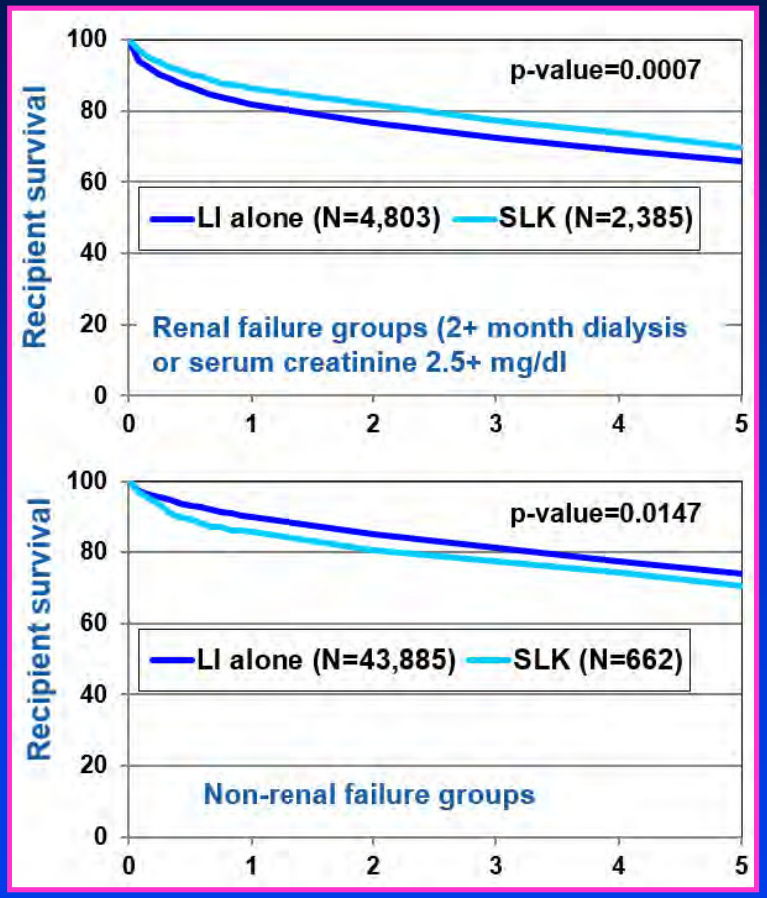
Number of SLK transplants by Year



Survival Advantage of Receiving an SLK vs. Liver Alone Transplant



OPTN/UNOS

New Criteria for SLK

1) On dialysis regularly administered
2) GFR $\leq$ 30 ml/min at listing and one of following for 6 wks or more:
    a) dialysis $\geq$ once per week
    b) Cr Cl $\leq$ 25 ml/min measured once per week

Need to confirm eligibility every 7 days for 6 weeks

New Criteria for SLK (cont.)

- Local recipient who meets MELD kidney criteria
- OPO is required to offer kidney along with liver

- Regional recipient who meets MELD kidney criteria and MELD is $\geq$ 35 or Status 1, Regional OPO required to offer kidney along with liver

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Safety Net

Chronic kidney disease 2-12 months after liver transplant

1) on kidney list or GFR ≤ 20
2) confirmed every 30 days
3) will receive additional priority for kidney transplant

Hepatitis C In DAA Era

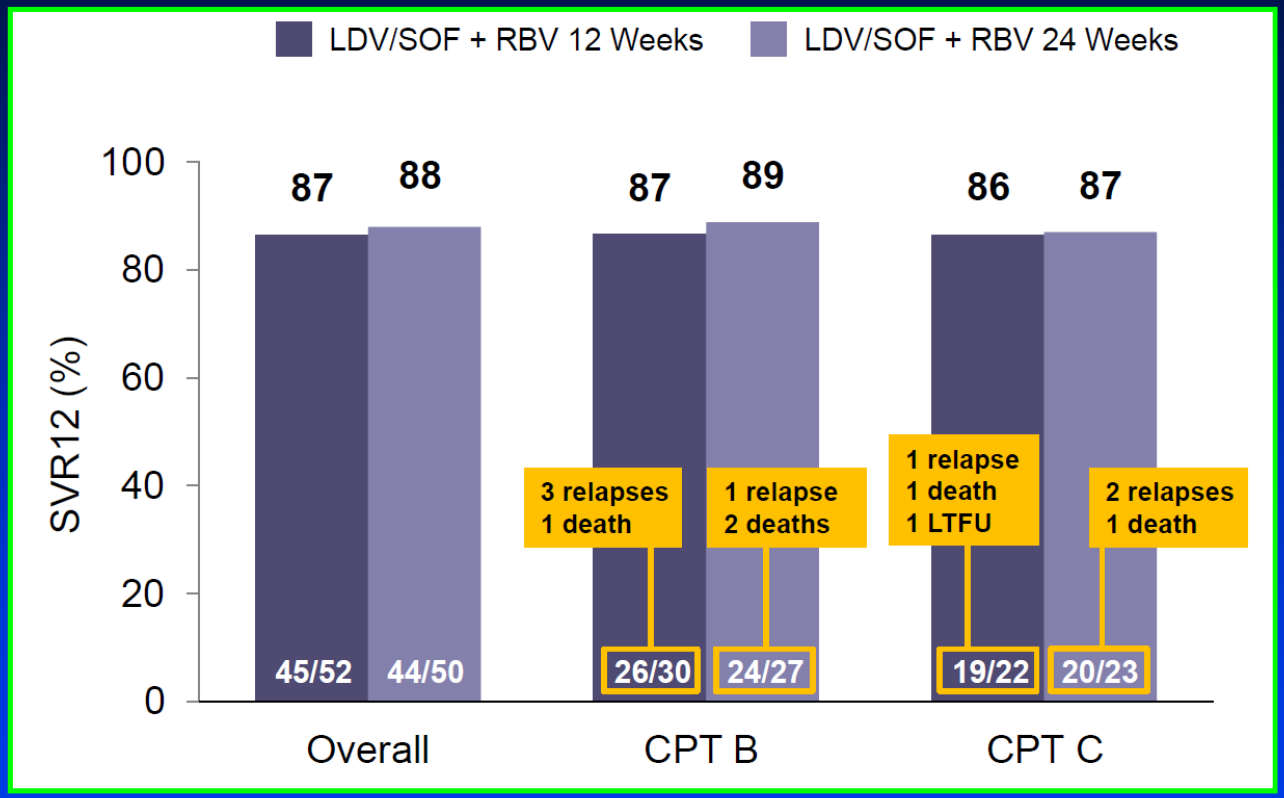
- Decreased indications for liver transplant in HCV
- Should HCV patients with decompensated disease be treated pre or post transplant?
- Using Hep C (+) donors
- Using older donors for HCV patients

SVR in Hepatitis C Patients

- Decreased all cause mortality
- Decreased liver-related mortality
- Decreased need for liver transplant in some
- Lowered portal pressures
- Lowered frequency of HCC

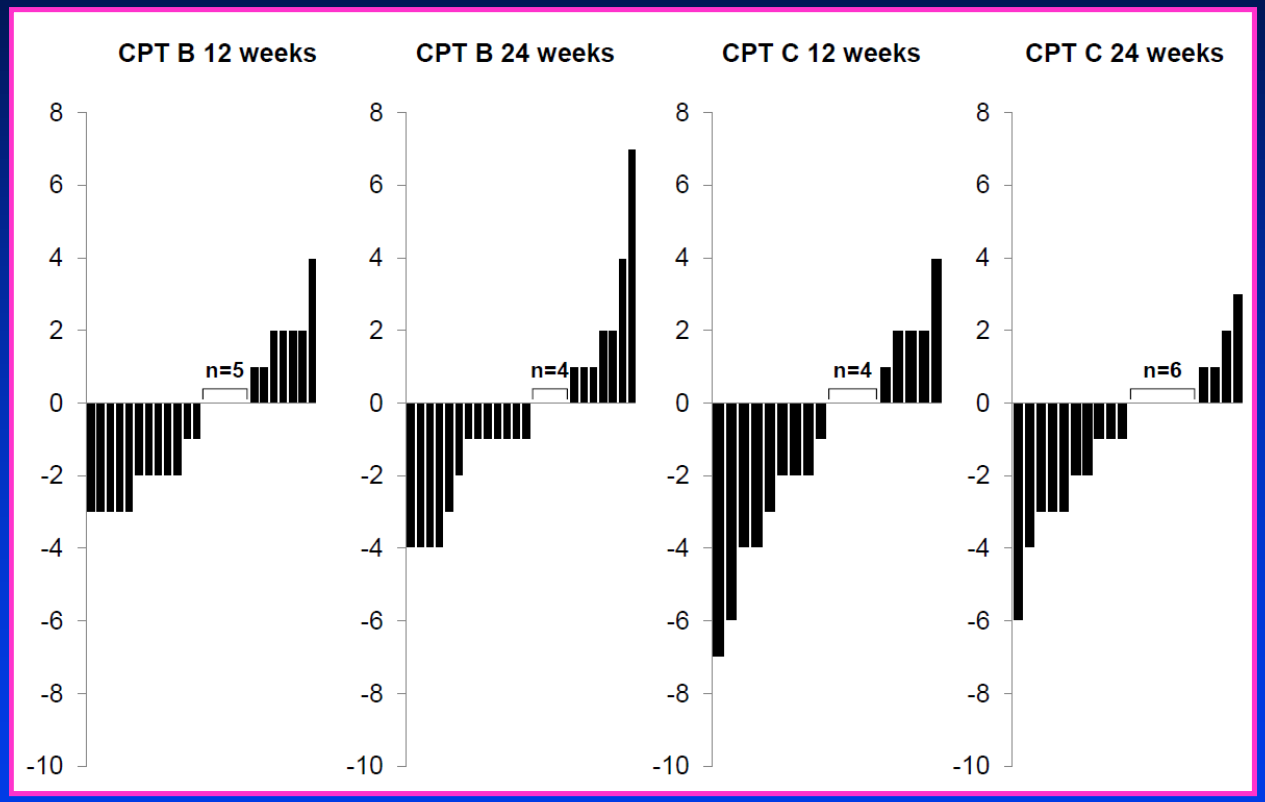
Which preliver transplant patients will benefit and which will not benefit from treatment with DAA

SVR in Decompensated Cirrhotic with Hepatitis C



Charlton, et al. Gastroenterology 2015 Sep; 149(3):649-659

Change in MELD Score from Baseline to Follow-up Wk 12 in CPT B & C Patients



Charlton, et al. Gastroenterology 2015 Sep; 149(3):649-659

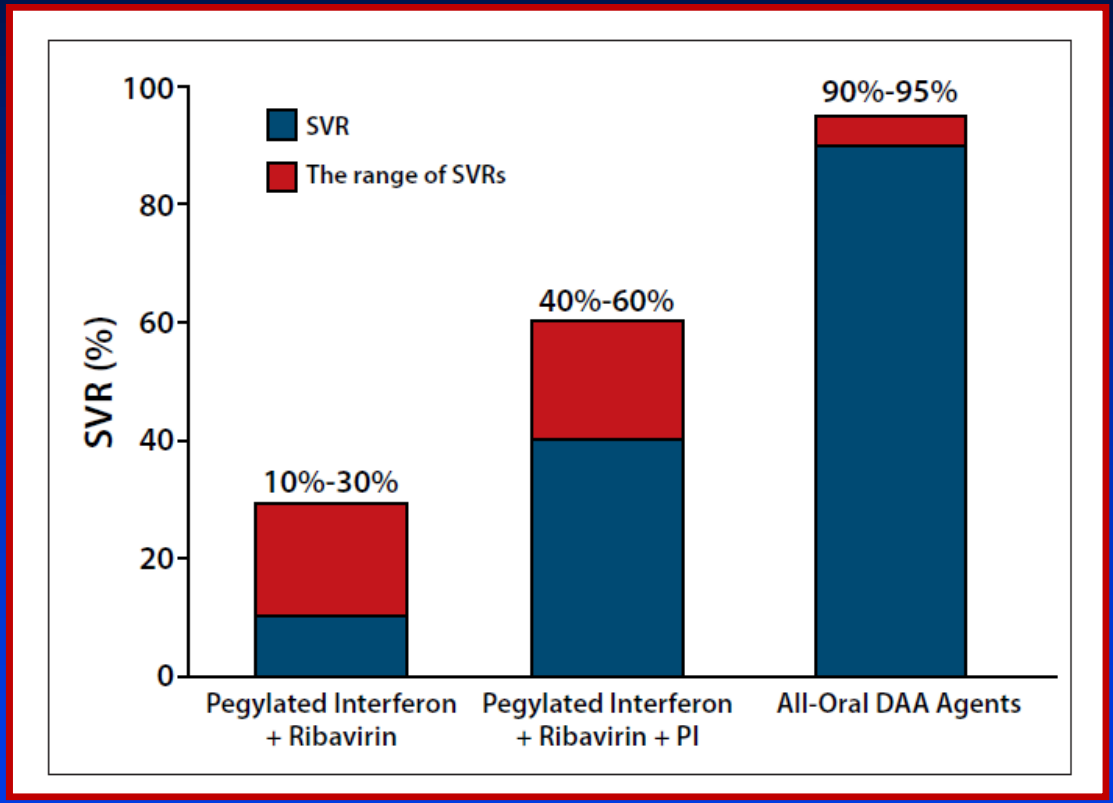

Improvement in
MELD Score…
Left with patients who are not
sick enough for liver transplant
(lower MELD Score),
but too sick
for life.

Transplant Purgatory

Treatment Considerations HCV MELD ≥ 20

1) Diminish threat of death on waiting list
2) Not much data on long-term followup ? prevent liver transplant
3) Decrease response in cirrhotics to DDA
4) Hepatitis C (+) donors
5) Good results with post-transplant treatment

Post Transplant SVR Rates



Suraweera et al. Gastro & Hepatol 2016 Jan 12(1):23-30

Use of Hepatitis C Positive Donor in DAA Era

HCV (+) Donors – Weighing Benefits vs Risks

1) Shorten waiting time
2) May prevent complications or death on waiting list
3) Good results in treating HCV post-transplant

Using Hepatitis C Positive Donor

No difference in outcomes vs Hep C negative donors

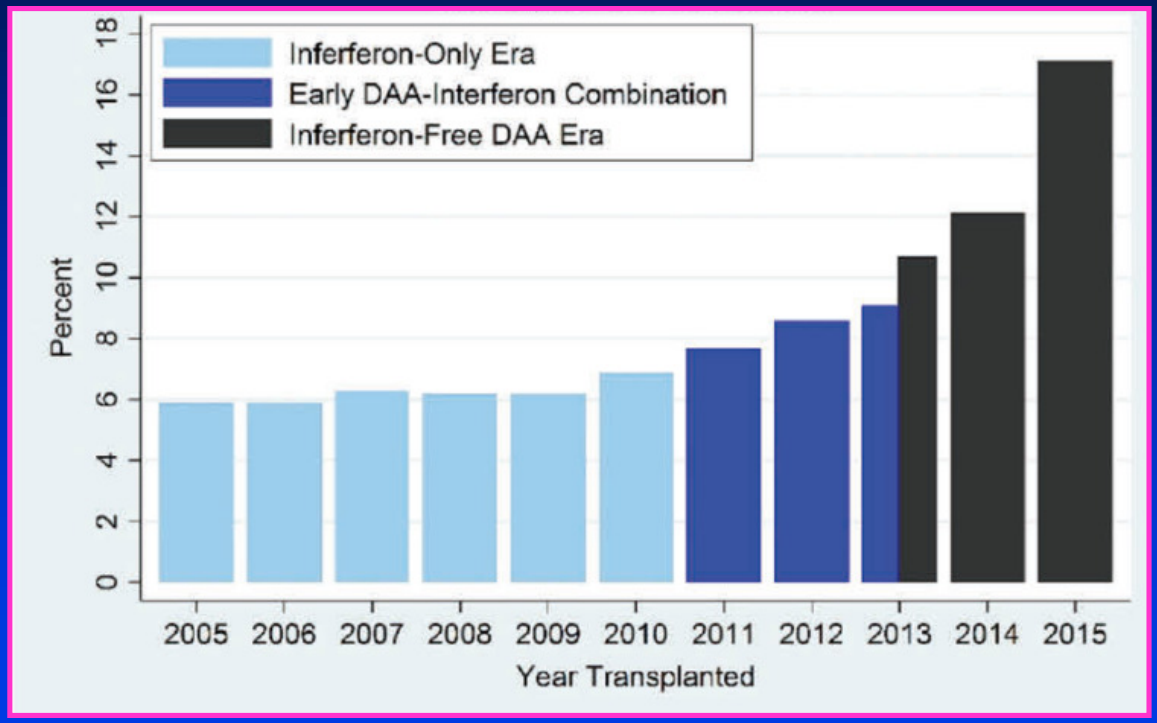
a) Graft survival

b) Severity of hepatitis recurrence

c) Fibrosis formation

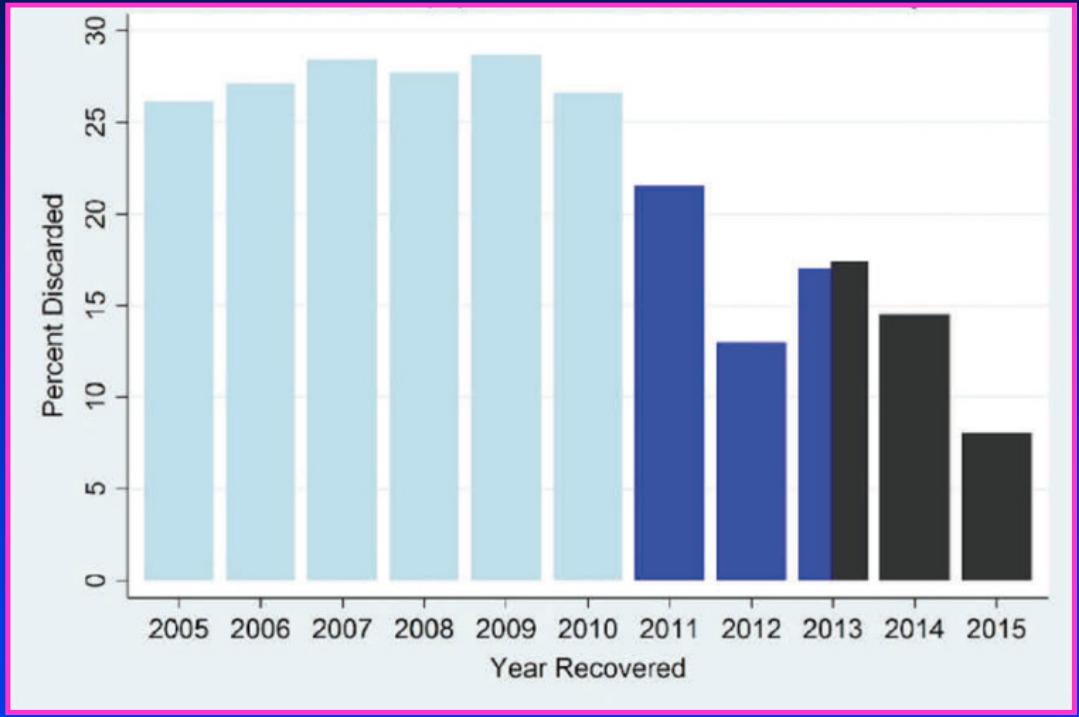
d) May be dominate genotype

Percent of HCV(+) Recipients Who Received an HCV(+) Donor By Year



Bowring M, et al. Am J Transpl 2016 Jan 16(S1):p73

Percent of HCV(+) Donor Livers Discarded By Year

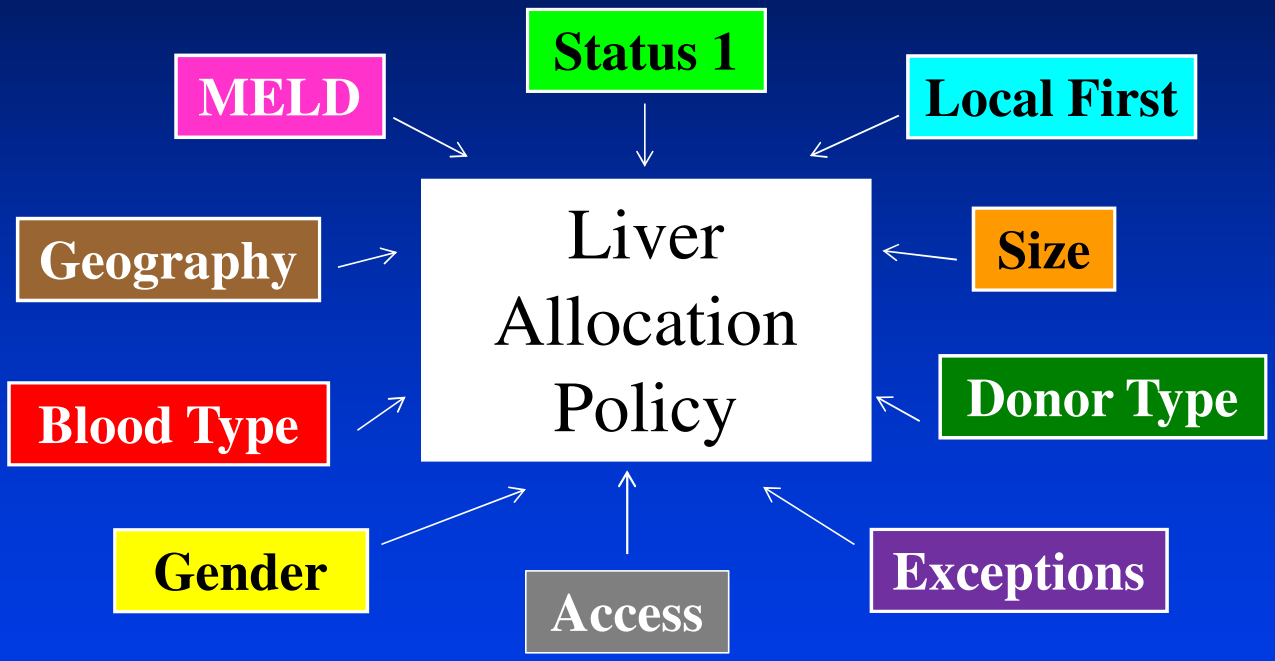


Improving Meld Allocation Policy

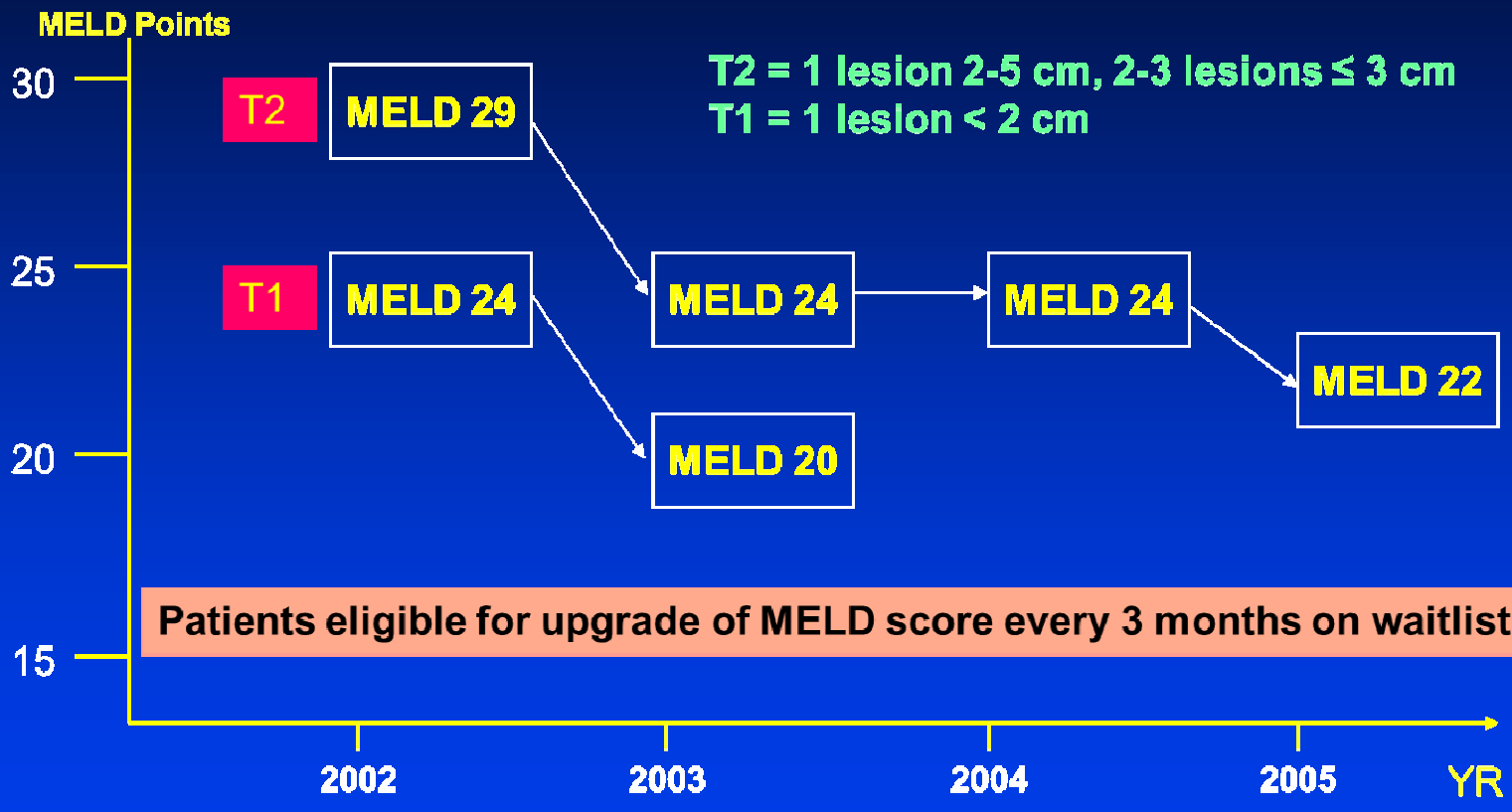
Evidence-based Modifications to MELD Allocation

1) HCC
2) Share 15
3) Share 35
4) Geographic disparity

Factors Involved in Allocation Policy

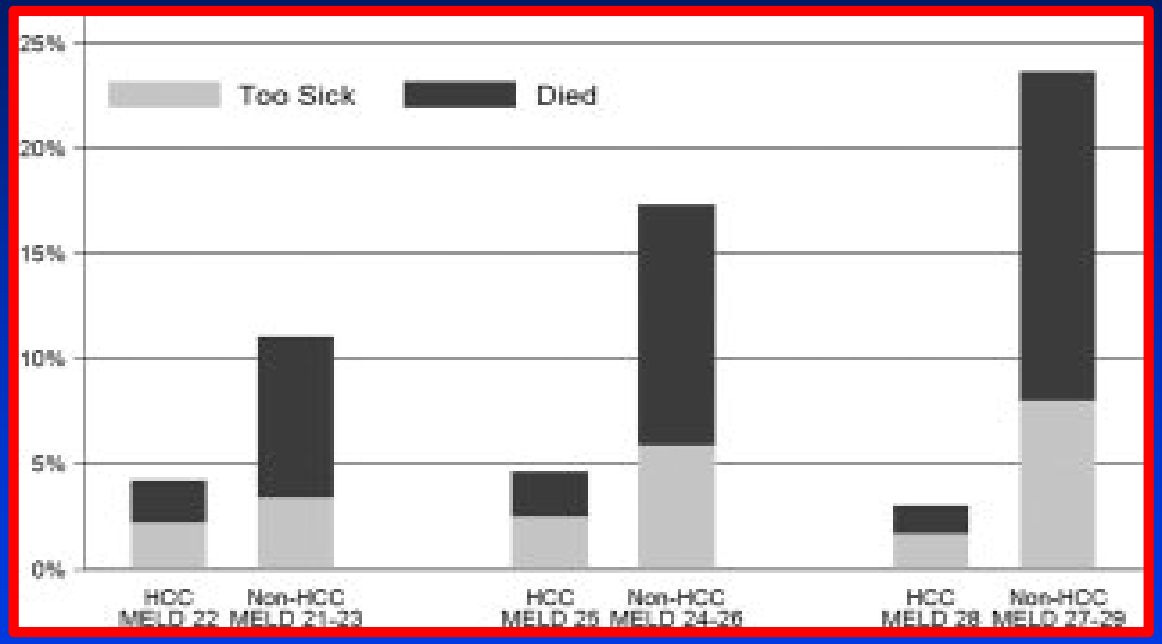


MELD ALLOCATION SYSTEM FOR HCC



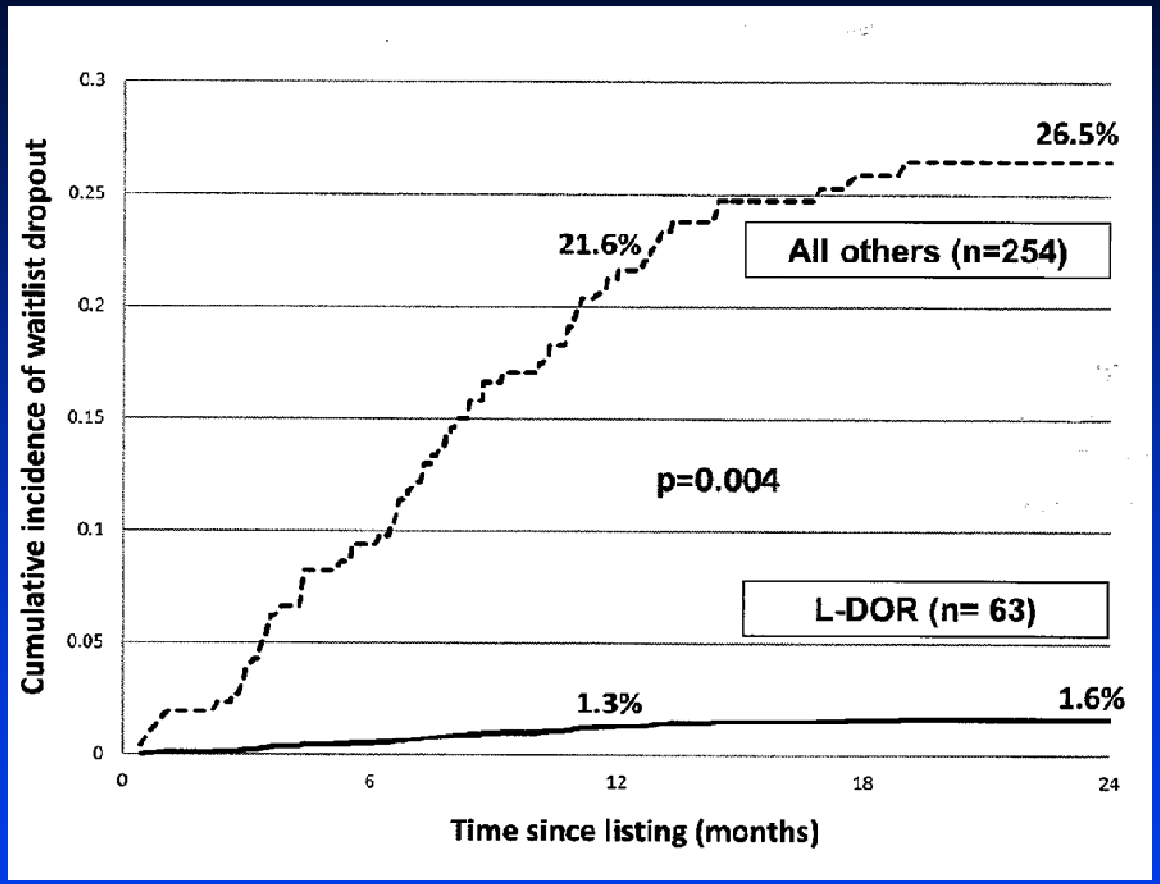
Yao, Mayo Clinic Transplant Grand Rounds: Sept 2010

Died or Removed From the List



Goldberg, et al. Liver Transplantation 2012; Volume 18, Issue 4, pages 434-443

Waitlist Dropout of HCC Patients



LDOR = 1 tumor <3 cm
Complete Response AFP < 20

Mehta, et al. Liver Transplantation: In press

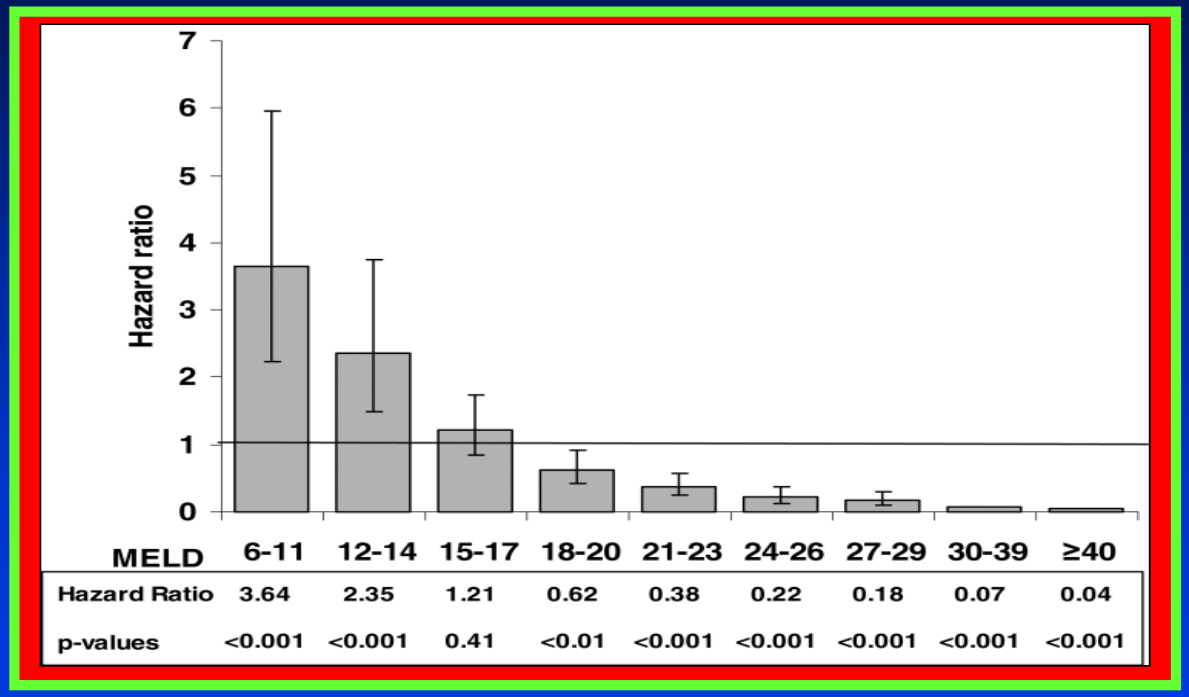
Recent HCC Consideration

Waiting period before activated
Cap Hep C at MELD 34

Share 15 Went Into Effect 2005

What was the impact?

Mortality Risk of Liver Transplantation Vs Waiting Based on MELD



MELD	6-11	12-14	15-17	18-20	21-23	24-26	27-29	30-39	≥40
Hazard Ratio	3.64	2.35	1.21	0.62	0.38	0.22	0.18	0.07	0.04
p-values	<0.001	<0.001	0.41	<0.01	<0.001	<0.001	<0.001	<0.001	<0.001

Merion R, Am J Transplantation 2005; 5: 307-313

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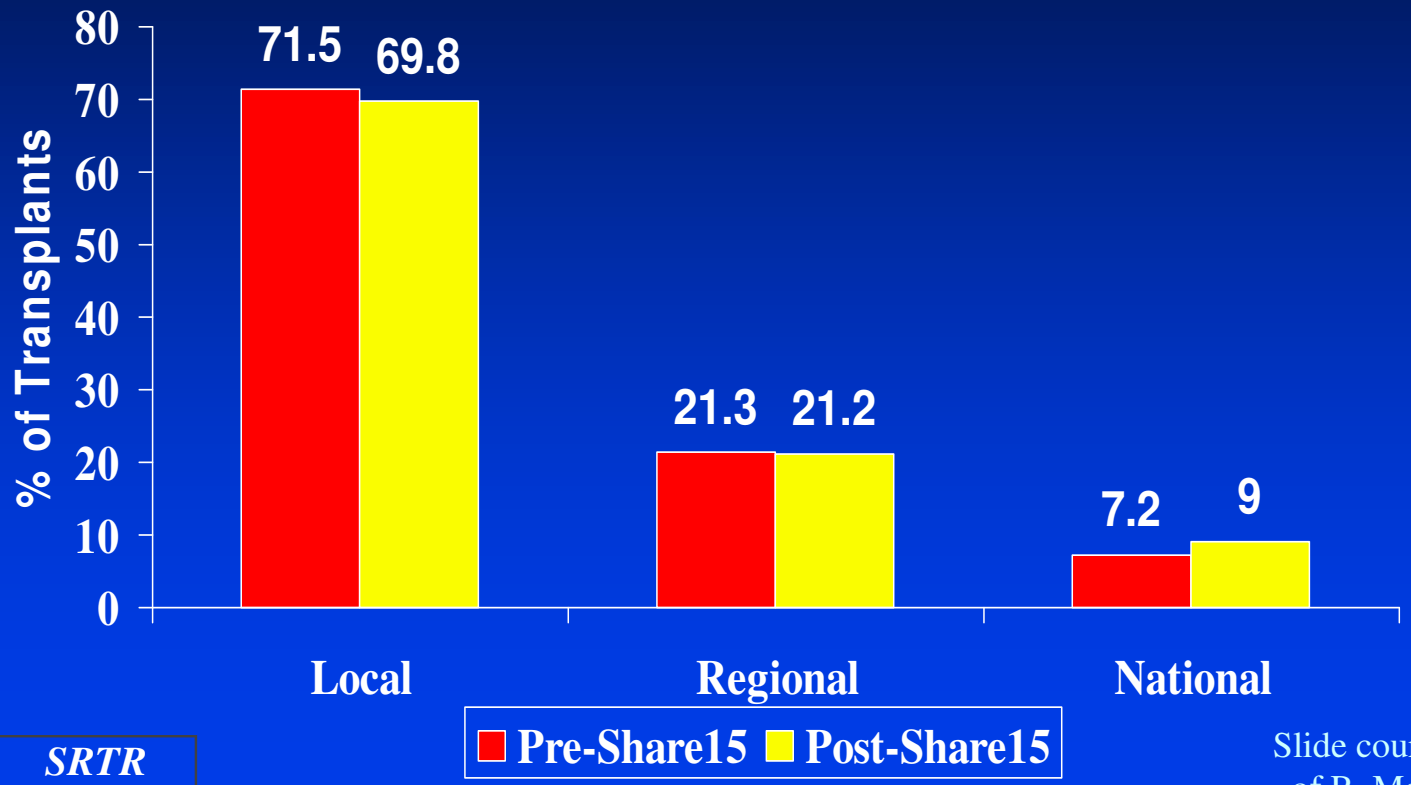
Distribution of Livers Post Share 15



SRTR

Slide courtesy
of R. Merion

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Why did Share 15 Not Increase Regional Sharing?

Applications for MELD 15 Exception

Before Share 15	5
After Share 15	452 (74% approved)

81% transplanted at MELD <15 (Median 11)

Bitterman et al., Liver Transplantation 2012; 18:1302

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Reason Applying for MELD 15 Exception

Ascites	57%
Encephalopathy	32%
Pruritus	3%
Cholangitis	3%
Hydrothorax	1%

All accountable in MELD Score

Regional Differences

Region 3	44%
Region 10	29%
Region 8	1.5%
Region 5	2.2%

53% were from single center OPO's

Conclusion

- Play-to-Keep local organs and prevent sharing for sicker patients
- Points to need for National Review Board to normalize criteria for MELD exceptions
- Single-center OPO's should be eliminated

Or is it more about the Benjamin??

Most Important Impediment to MELD Allocation Policy is Geography

Regional Share 35

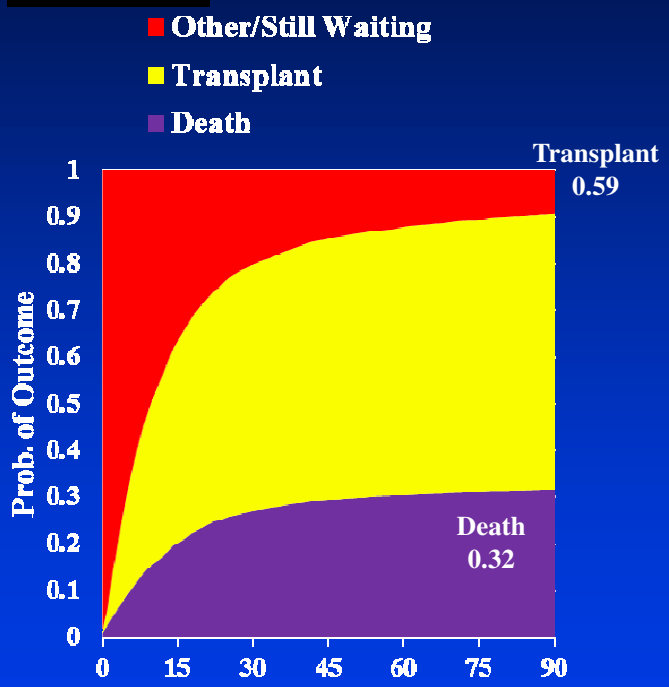
Started 6/18/2013

Help deal with geographic disparity

MELD/PELD 35+ Waiting List Outcomes: Competing Risks Analysis

Pre 35

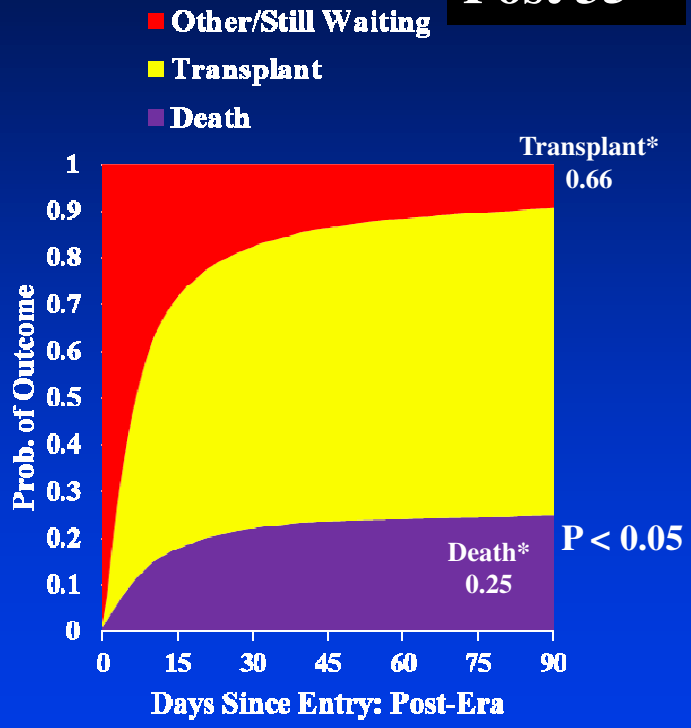
N = 3764



Pre: 6/18/2011-6/17/2013

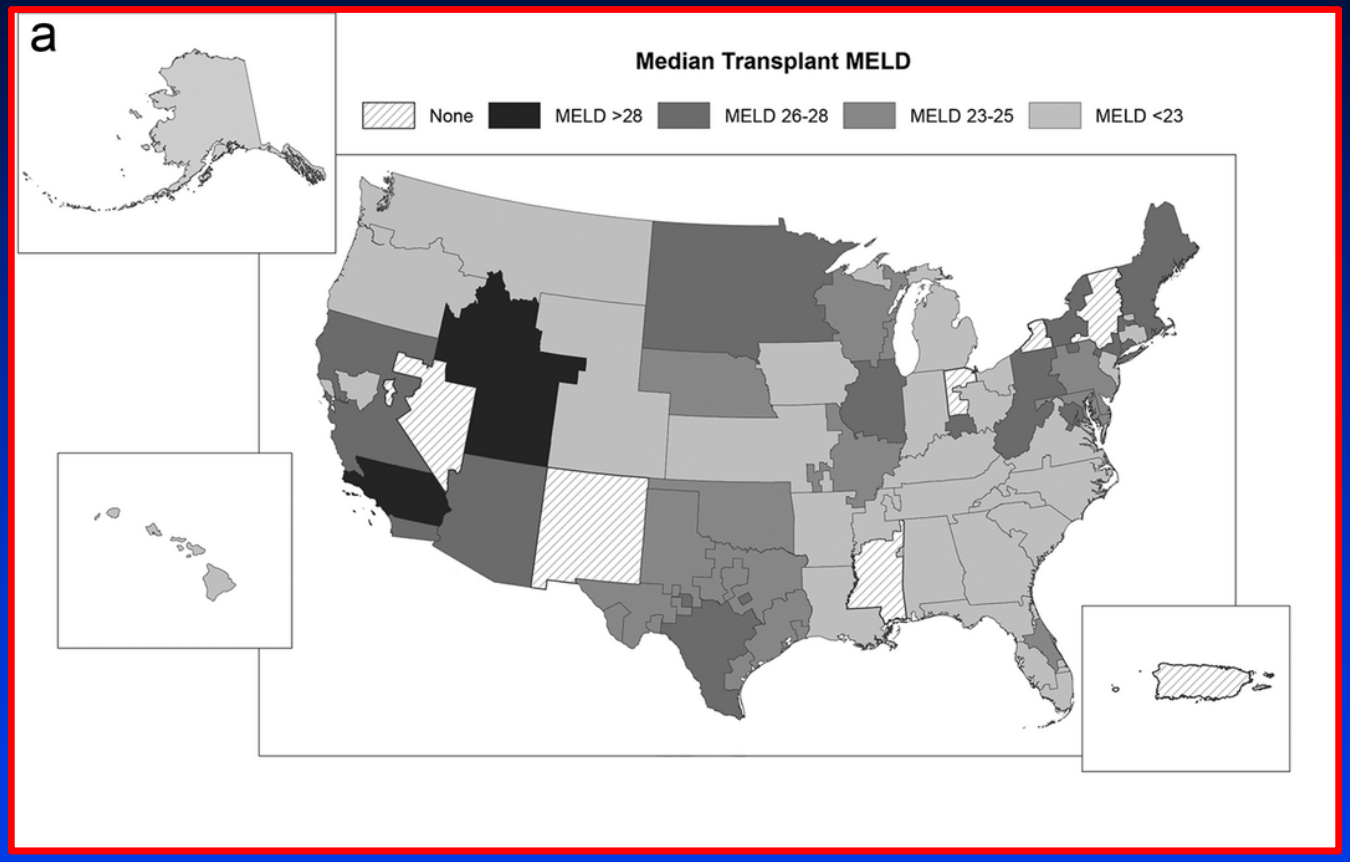
Post 35

N = 4796



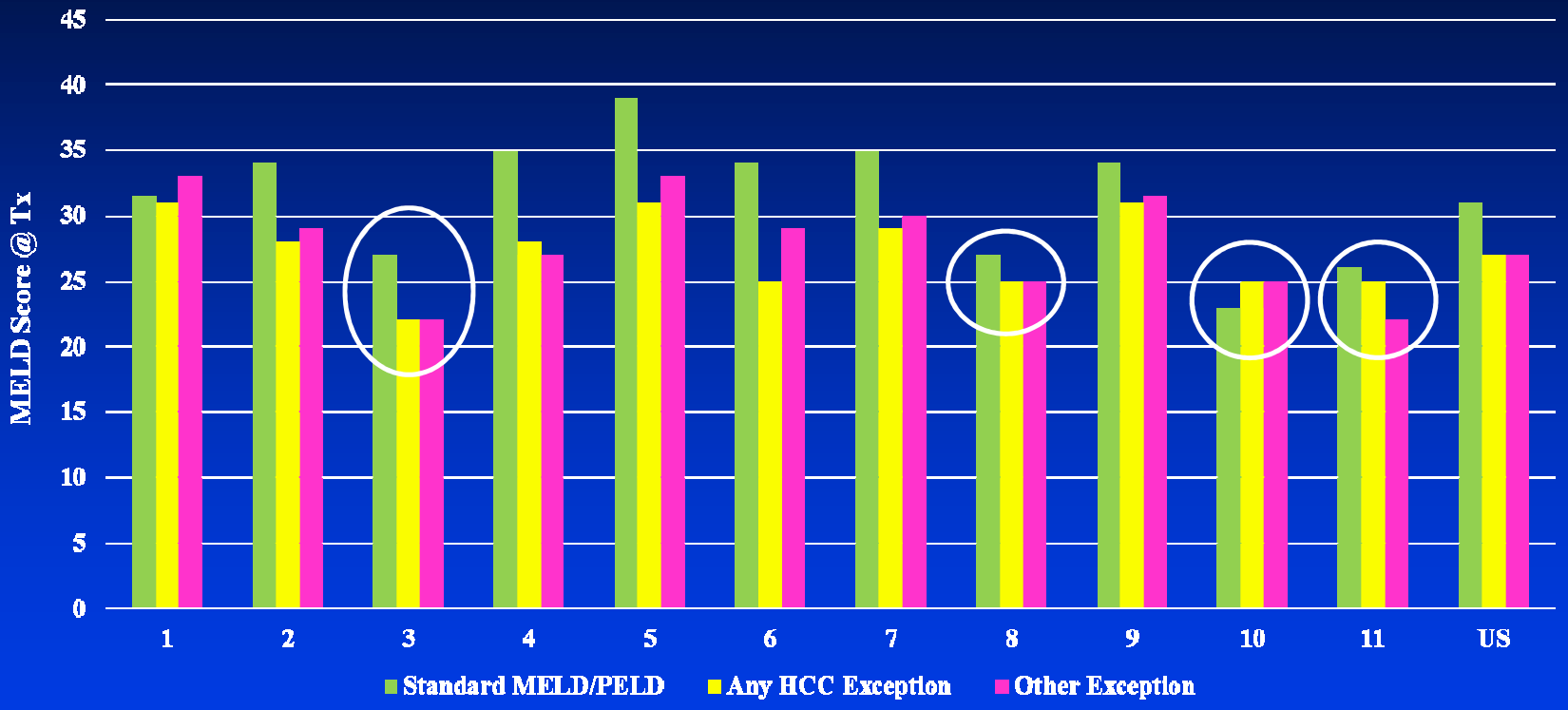
Post: 6/18/2013-6/18/2015

Share 35 Allocation

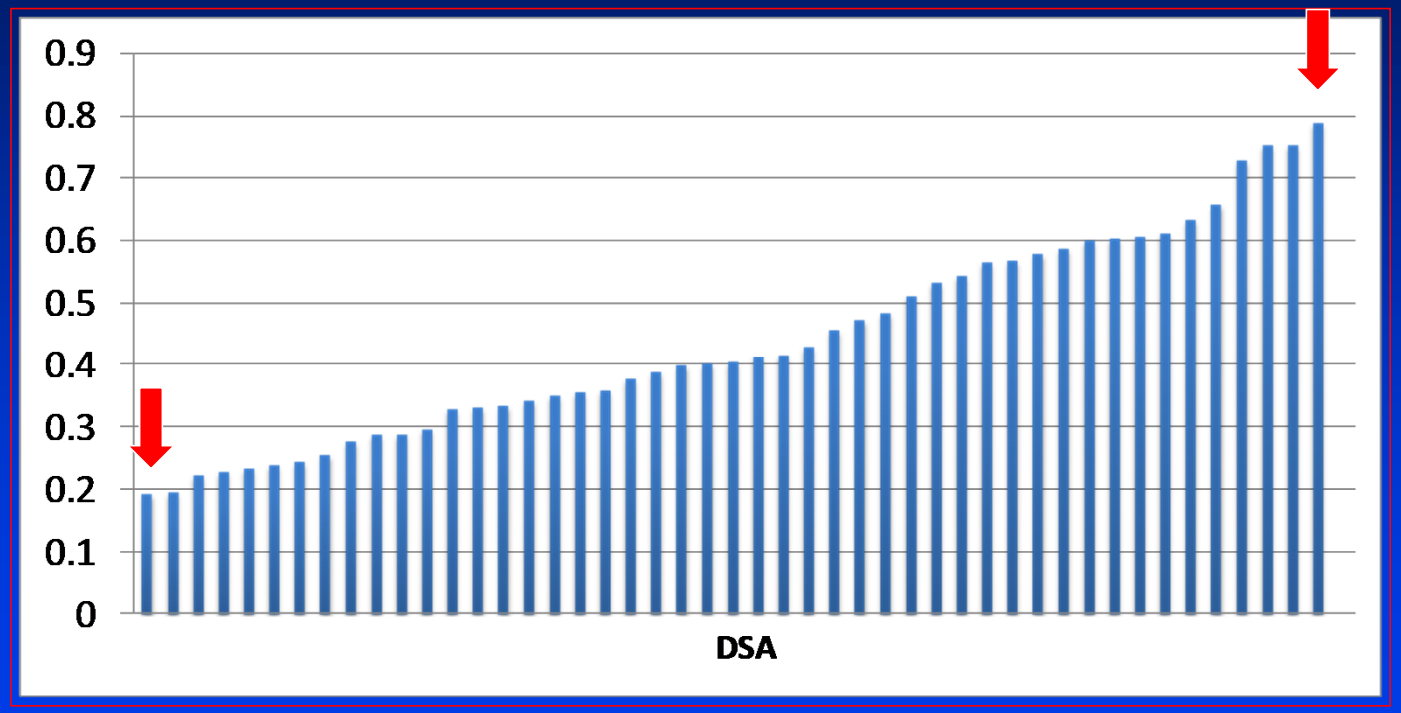


Gentry et al, Am J Transpl 2016 Jan

Adult Deceased Donor Liver Transplant Recipients, by Region and MELD Score at Transplant



Transplant Rates @ 365 Days
All Candidates Listed for a DD Liver Transplant
1/1/2007-6/30/09
Adults only, No Exceptions



*** DSAs with <10 Txs during 2008 excluded**

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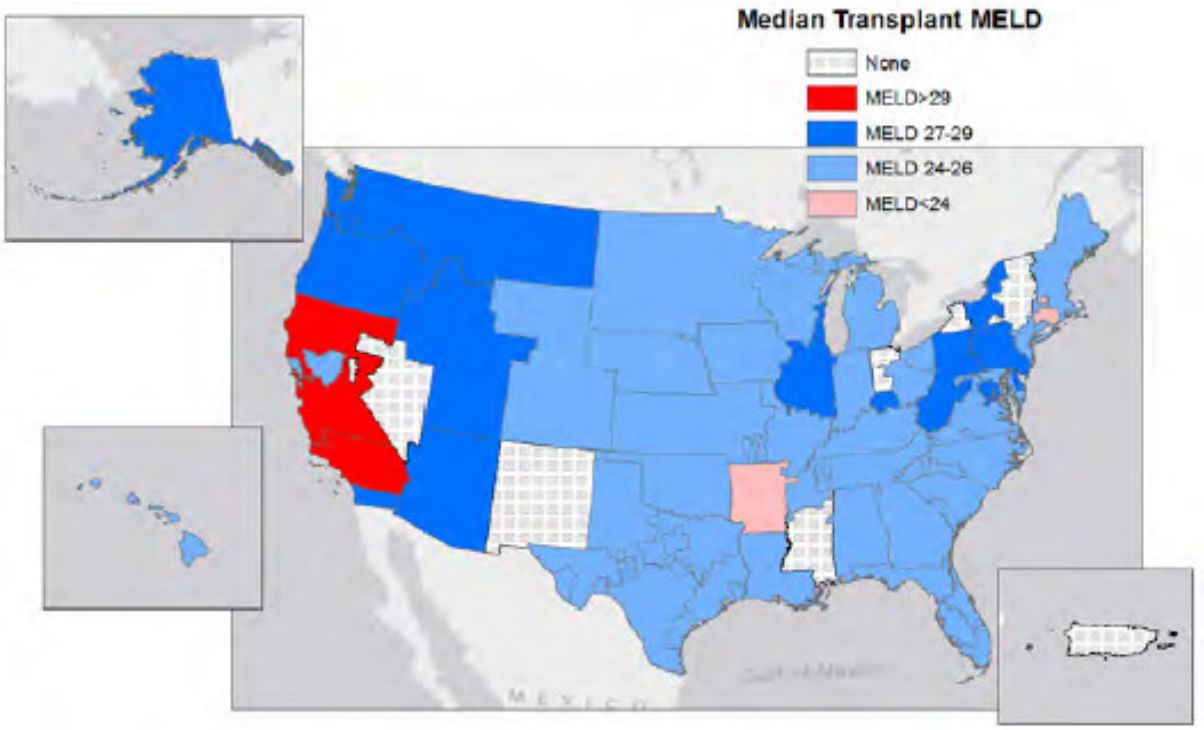
Proposal

- Broaden sharing
- 8 district model
- 4 district model

4 districts reduce disparity



Optimized redistricting plans

Districts	***Standard deviation of tx MELD***	% MELD <15	% MELD >25	% Pediatric	Net total deaths	***Net waitlist deaths***
4	***1.87***	2.5%	64.3%	8.7%	-553.8	***-581.1***
8	***2.08***	3.7%	59.6%	8.1%	-332.4	***-342.1***
Local first	***3.01***	5.8%	50.1%	7.5%	0	***0***
Regional	***3.26***	5.5%	54.3%	7.7%	-164.6	***-122.4***
National	***1.66***	1.9%	83.3%	10.4%	-343.6	***-509.9***

Financial Impact of Redistricting

	Share 35	8 District	4 District
Pre-Transplant (Per Month)	6,038	5,934	5,928
Transplant + 1 yr (Per Patient)	187,120	191,811	195,228
Transportation Costs (Per Patient)	8,988	11,874	14,552
Post-Trx Care (Patient / month)	1,214	1,235	1,248

Conclusion

- MELD Model is excellent at prioritization of patient on the wait list based on survival
- MELD can be tweaked – adding sodium, re-weighting variables, but impact would be minimal, expensive, and cumbersome
- Broad sharing and a National Review Board to standardized exceptions would have the largest impact in reducing deaths on the waiting list
- Better define who needs liver/kidney transplant
- HCC prioritization

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Ideal Model

Small number of variables
Objective parameters
Readily available
Standardized – Reproducible
Continuous score reflects disease severity
Applicable equally to all etiologies
Internal/External Validation
Evidence-based modification

Significant Variables That Could NOT be Used in Model

- Etiology
- Recipient age
- Race
- Gender
- Transplant Center

Final Model – Creatinine, INR, Bilirubin

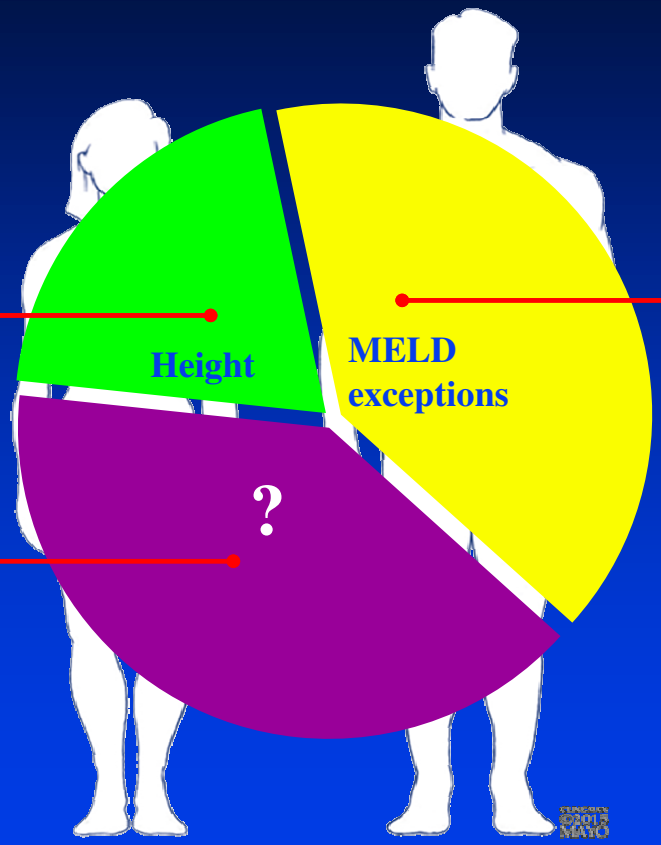
Factors That Disadvantage Women

WOMEN

MEN

Shorter
Small body ≠ big liver

Less muscle mass
Lower creatinine = lower MELD



More hepatocellular carcinoma =
MELD exception points

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Can MELD be Improved: Implications of HCV Therapy and CKD

Could Share 35 Disadvantage Women?

Alina M. Allen MD[1], Julie K. Heimbach MD[1],

Joseph J. Larson[1], W. Ray Kim MD[2], Patrick S. Kamath MD[1], Terry M. Therneau PhD[1]

[1]Mayo Clinic, Rochester, MN

[2]Stanford University, Stanford, CA

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Women Disadvantaged in MELD Era

- Equitable allocation for liver transplant framed on principles of utility and justice
- Organ allocation based on MELD/MELD-Na and exception scores
- Women less likely than men to undergo liver transplantation
- Disparities more obvious in MELD era

Moylan C. JAMA 2008

Lai J. AJT 2010

Mathur AK. AJT 2011

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Could Share 35 Disadvantage Women?

AIMS

To Determine

1. The difference in number of MELD points ("X") derived from serum creatinine in men and women with *similar measured glomerular filtration rate (GFR)*

2. Whether MELD-Na corrects the disparity between sexes

3. Whether addition of "X" number of MELD points improves women's deficit in liver transplantation

Aim 1

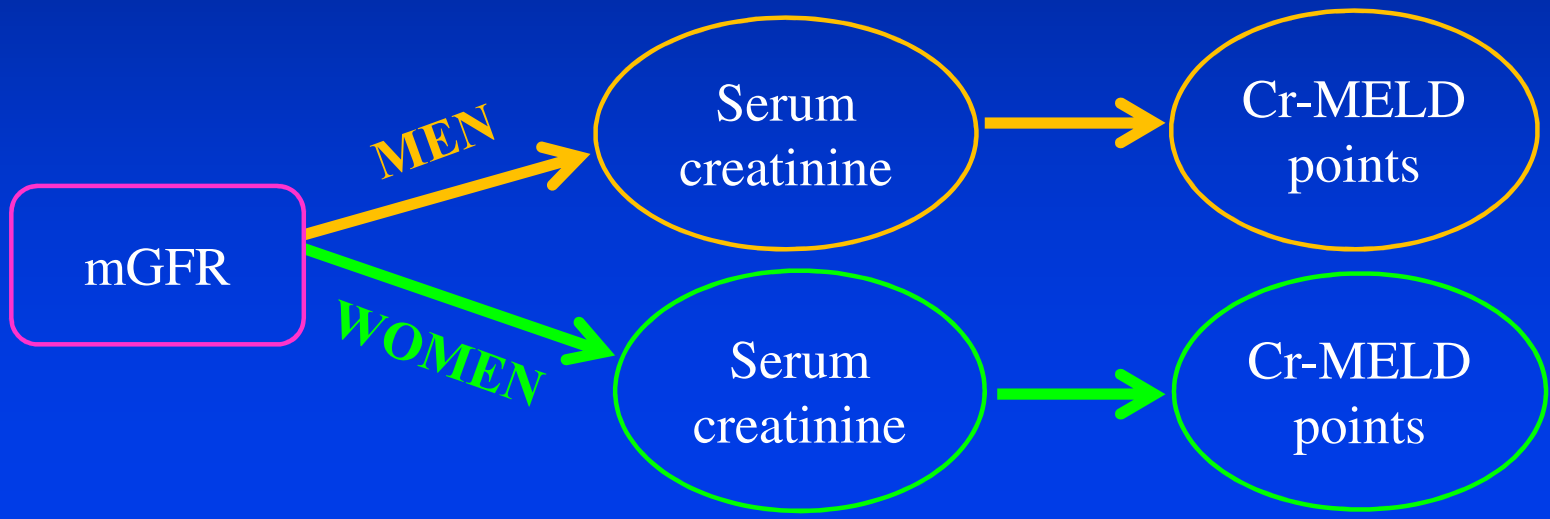
Creatinine-derived MELD points in men

versus

women with similar renal function

Methods

- Adults listed for LT at Mayo Clinic, Rochester MN 2002 - 2014
- GFR measured in all subjects by iothalamate clearance (gold standard)



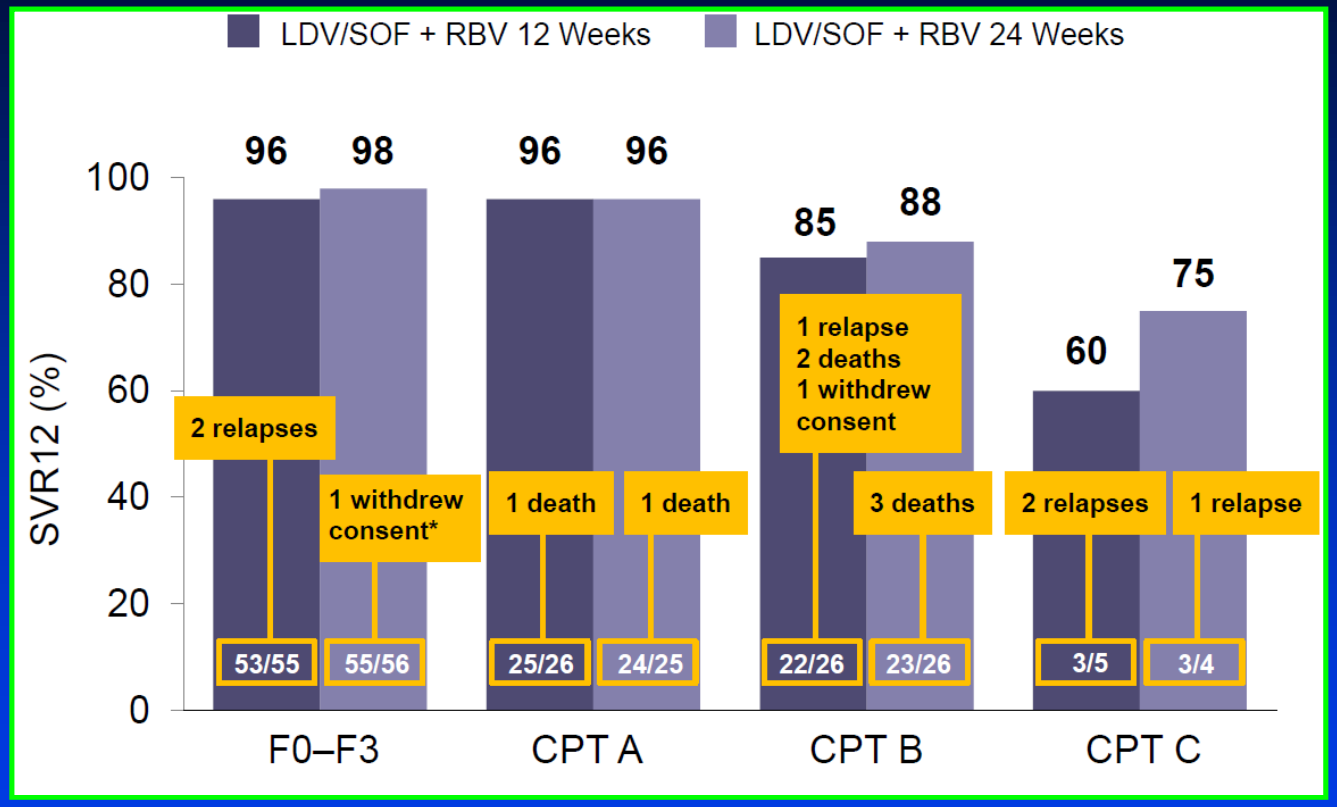
Could Share 35 Disadvantage Women?

RESULTS

Patient Characteristics at Listing

	Women N=262	Men N=349	Total N=611
Age (median, IQR)	55 (47-61)	54 (44-59)	54 (45-60)
Bilirubin (mg/dl)	2.5 (1.3-5.0)	2.6 (1.3-4.5)	2.5 (1.3-4.7)
INR	1.2 (1.1-1.4)	1.2 (1.1-1.5)	1.2 (1.1-1.5)
Creatinine (mg/dl)	0.8 (0.7-1.2)	1.0 (0.8-1.2)	0.9 (0.7-1.2)
Measured GFR (ml/min/BSA)	68 (45-97)	80 (55-103)	75 (50-101)
MELD	13 (9-18)	14 (10-19)	14 (10-18)
MELD-Na	16 (11-20)	16 (12-21)	16 (11-21)

SVR in Post Transplant Hepatitis C Cirrhotics



Charlton, et al. Gastroenterology 2015 Sep; 149(3):649-659

90-Day Mortality on Waiting List C-Statistics

MELD	0.896
MELD-Na	0.912*
MELD-Albumin	0.913*
MELD-Na-Albumin	0.922*

* $P < 0.01$

Myers, et al. PlusOne January 2013

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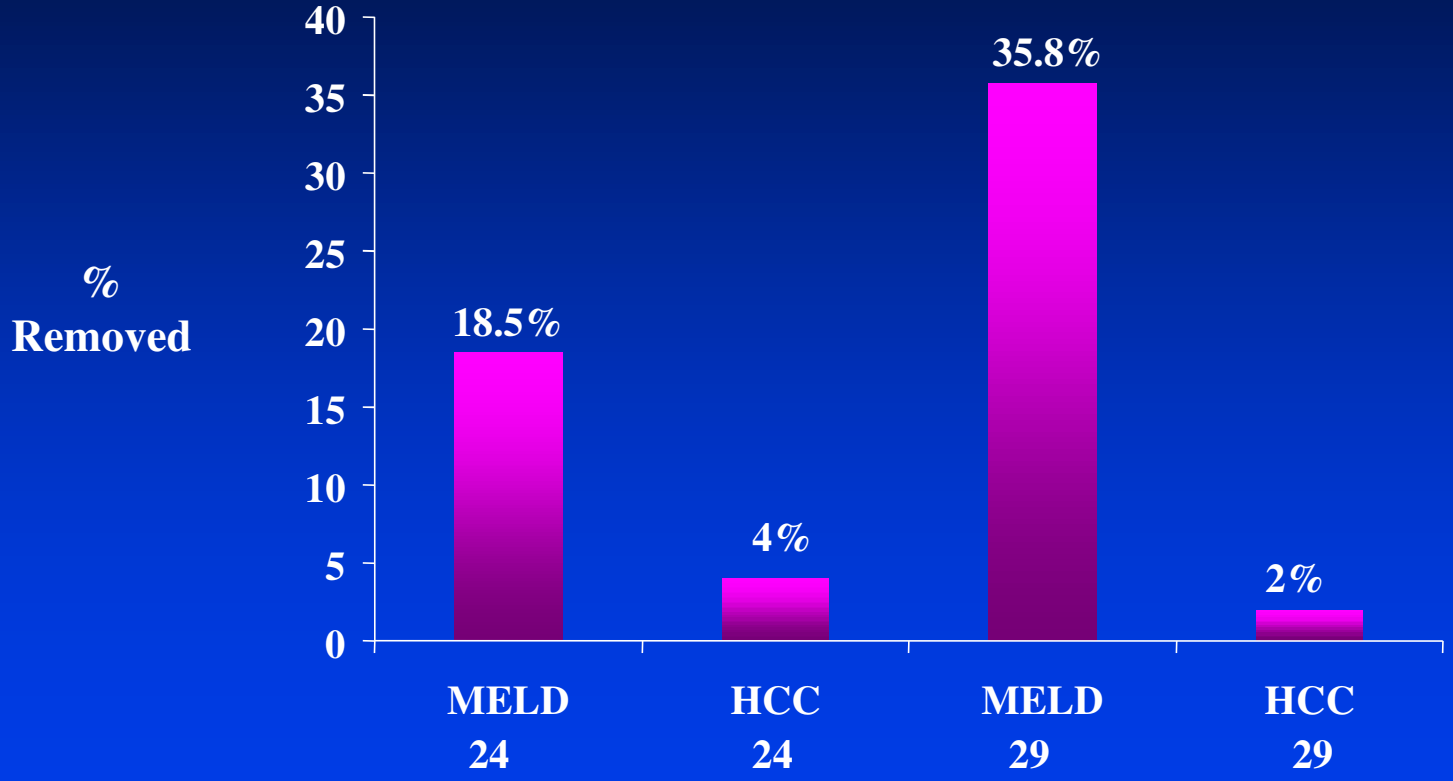
Removed Because Mortality / Too Sick on List

Chronic Liver Disease vs HCC (90 Days)



SRTR Analysis, Jan 2004

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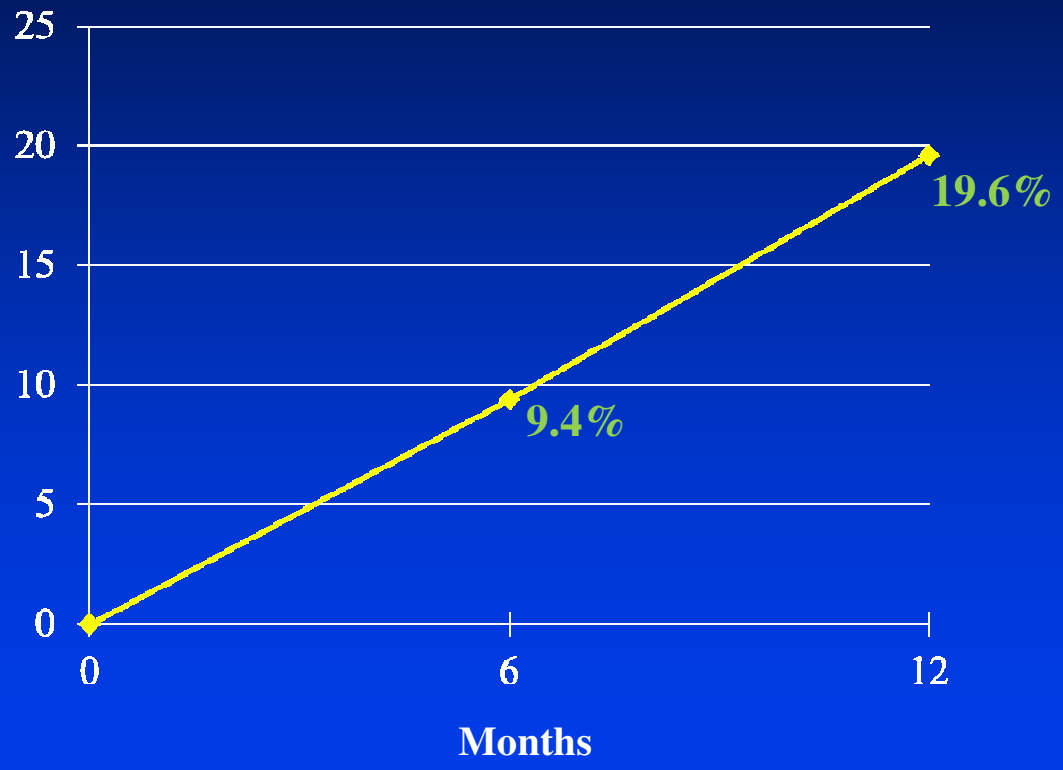
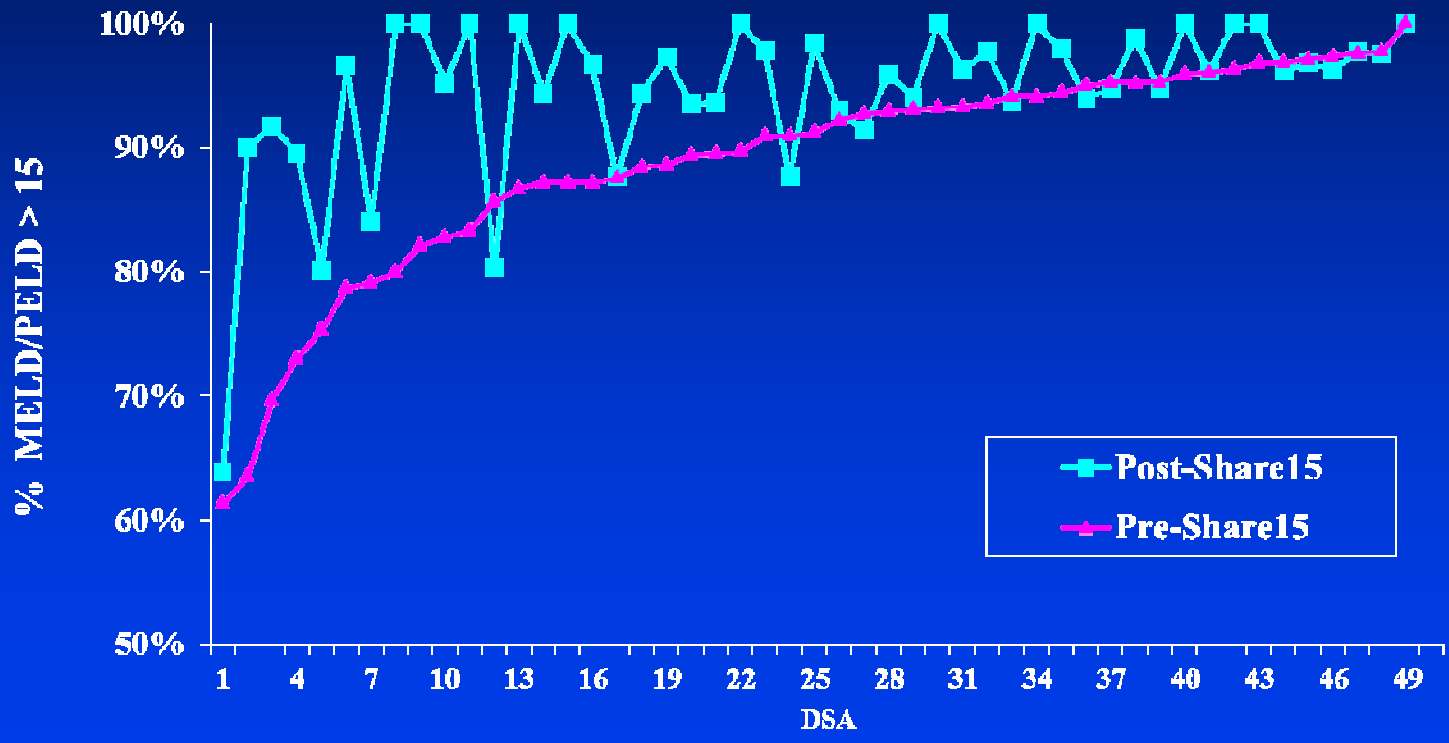
Dropout of HCC Patients with T_2 Lesion



Percent of Transplant Recipients with MELD/PELD ≥ 15 by DSA



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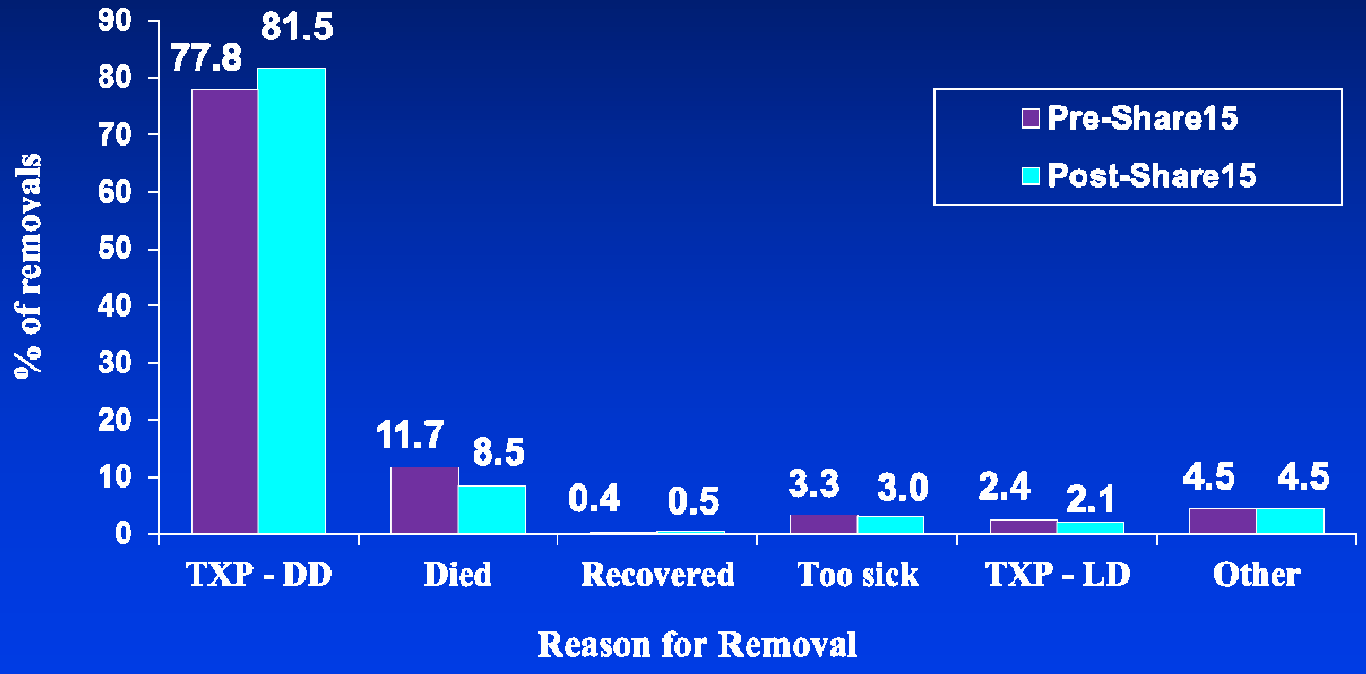
Reason for Removal from the Liver Wait List Among Candidates with MELD/PELD at Removal ≥ 15 Removal Date During Pre- or Post-Period



Summary: Post Share 35 Era Data

- Increased number / percent of MELD / 35+ transplants
- Increased regional sharing
- No impact of overall liver discard rate
- No impact to overall waiting list mortality
  - No impacts to waiting list mortality by age, ethnicity
- MELD / PELD 35+ waiting list candidates
  - Increased transplant rate
  - Decreased mortality rate
- Liver-Intestine candidates
  - Increased transplant rate
  - Mortality rate unchanged
- Post-transplant survival
  - No overall change
  - No change to outcomes for MELD/PELD 35+ recipients

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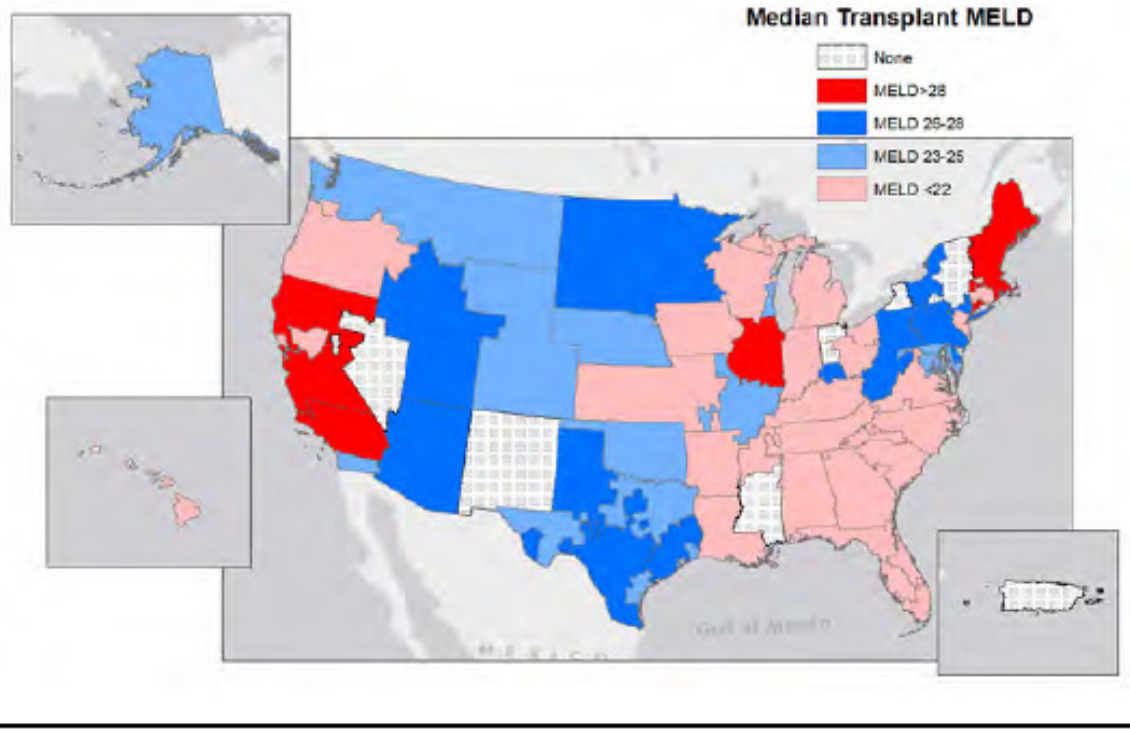
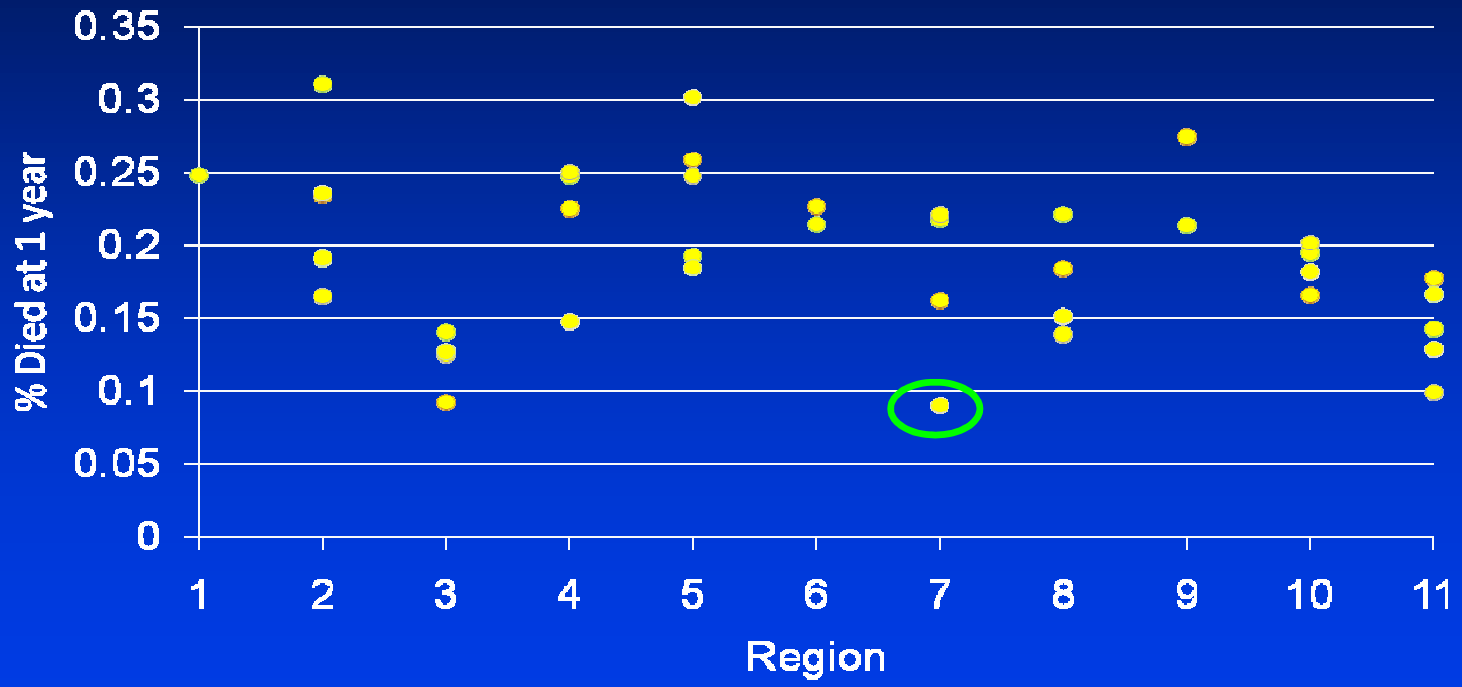
Existing geographic disparity



Death Rates* @ 365 Days
Candidates Listed for a DD Liver Transplant
By DSA within Region



*Adults only, No Exceptions, Initial MELD>=15, Candidates with an Initial Status of 1A/1B Excluded, DSAs with fewer than 10 events excluded

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MELD / PELD Allocation Summary

- Excellent predictor of pretransplant survival
- Decreased registrations (MELD < 10)
- Decreased death rate on waiting list
- Transplant sicker patients
- Increase transplant of HCC patients
- Post transplant survival unchanged
- Resource utilization correlates with MELD
- Better defining impact of donor-recipient matching
- Better defining survival benefit - optimal timing
- Evidence-based decision-making

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How to Improve Allocation Policy

1) Larger sharing area – eliminate single-center OPO's
2) Allow only recognized exceptions: HCC, HPS
3) National unbiased Review Board
4) Standardize INR for liver disease
5) Add sodium to MELD score
6) Better define those who need Liver/Kidney transplant
7) Better define Donor-Recipient matching to optimize outcomes
8) Pursue transplant – Benefit Model

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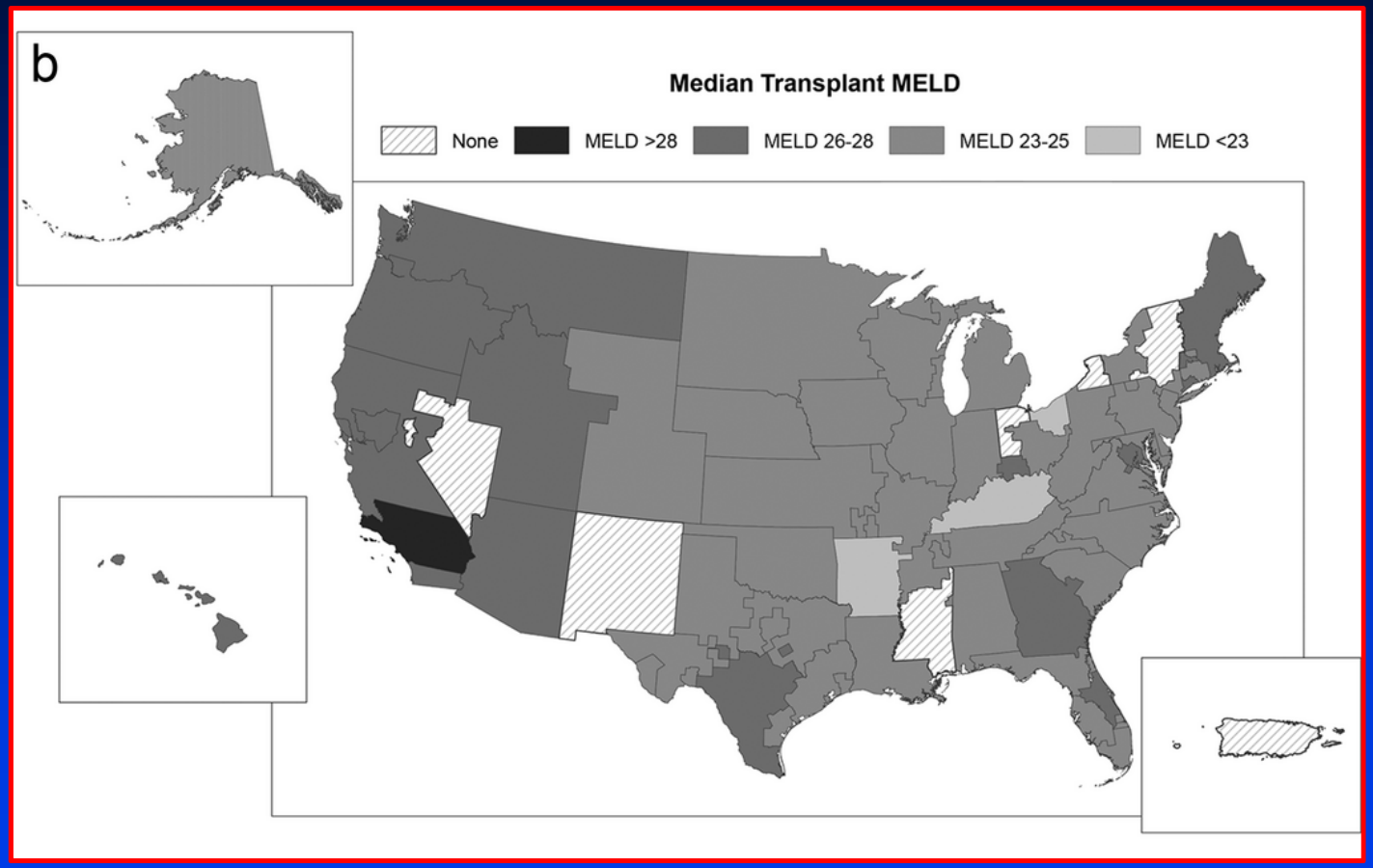
MELD ≥ 35: Pre 19% Post 29%

	Cost Difference Pre 35 - Post 35
Pre Tx Cost	7,076
Post Tx Cost	2,602

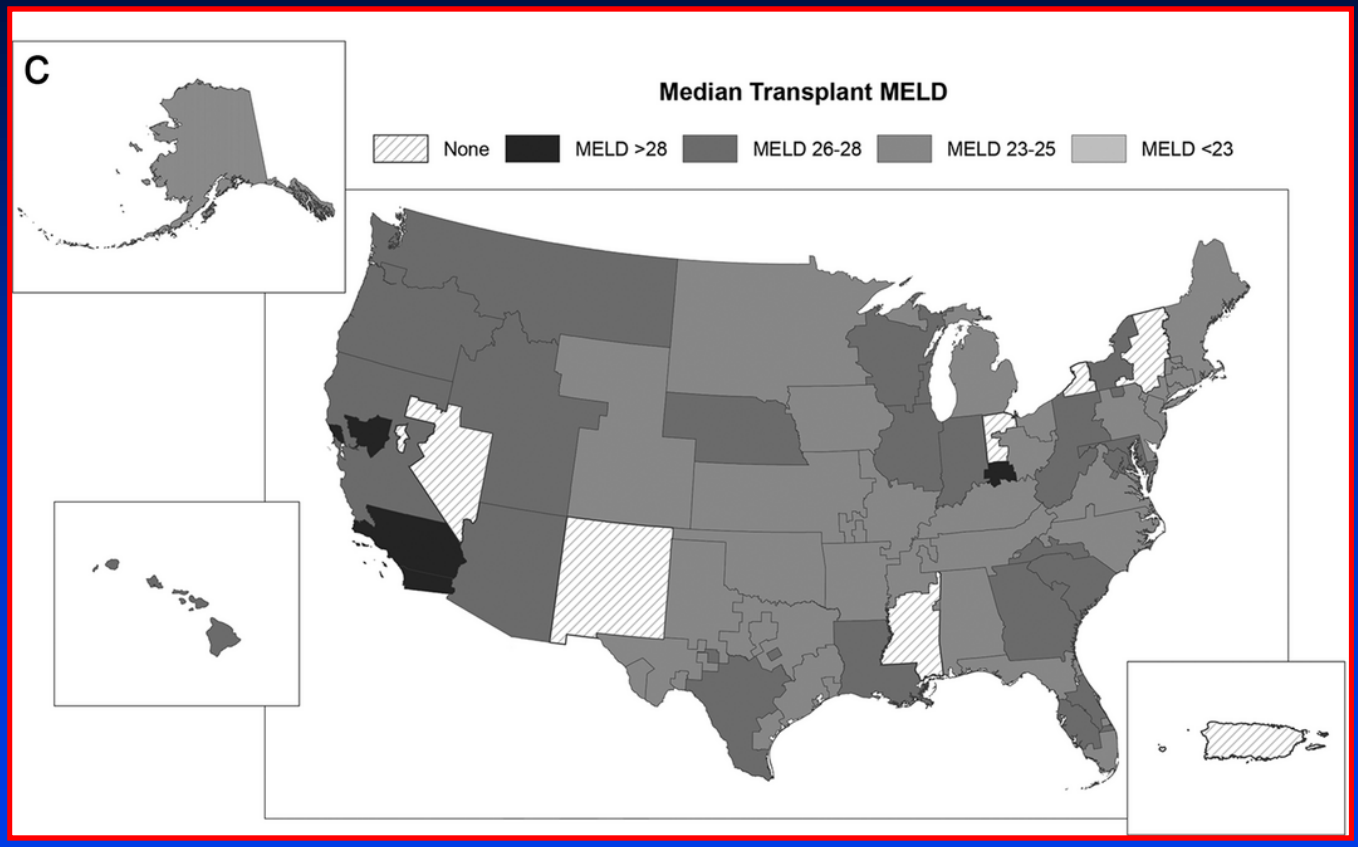
- Pre Tx cost reduction may offset increased cost of transplant patients with MELD ≥35 (19-28%)

Eight Districts



Gentry et al, Am J Transpl 2016 Jan

Four Districts



Gentry et al, Am J Transpl 2016 Jan

Share 35 Regional Percentage January 2013

New 35 List	9.2% - 9.7%
DAA ≥ 35	23.7% - 30.1%
Regional Share	18.9% - 30.4%

No change CPT
Mortality - $\downarrow$ 30% MELD > 30
Post-Trx loss, mortality
Few died

Acceptance Rate

	22.3%	10.3%
DAA	1.3	1.4

MELD Exceptions

- Liver "diseases" whose natural history is not quantified by MELD
  - Hepatocellular carcinoma
  - Cholangiocarcinoma
  - Neuroendocrine
- Complications of cirrhosis that change the natural history of the disease, independent of liver function
  - Hepatopulmonary syndrome
  - Portopulmonary hypertension
- Diseases expressed in the liver, that do not cause liver disease
  - Familial amyloidosis
  - Hereditary oxalosis
  - Polycystic liver disease

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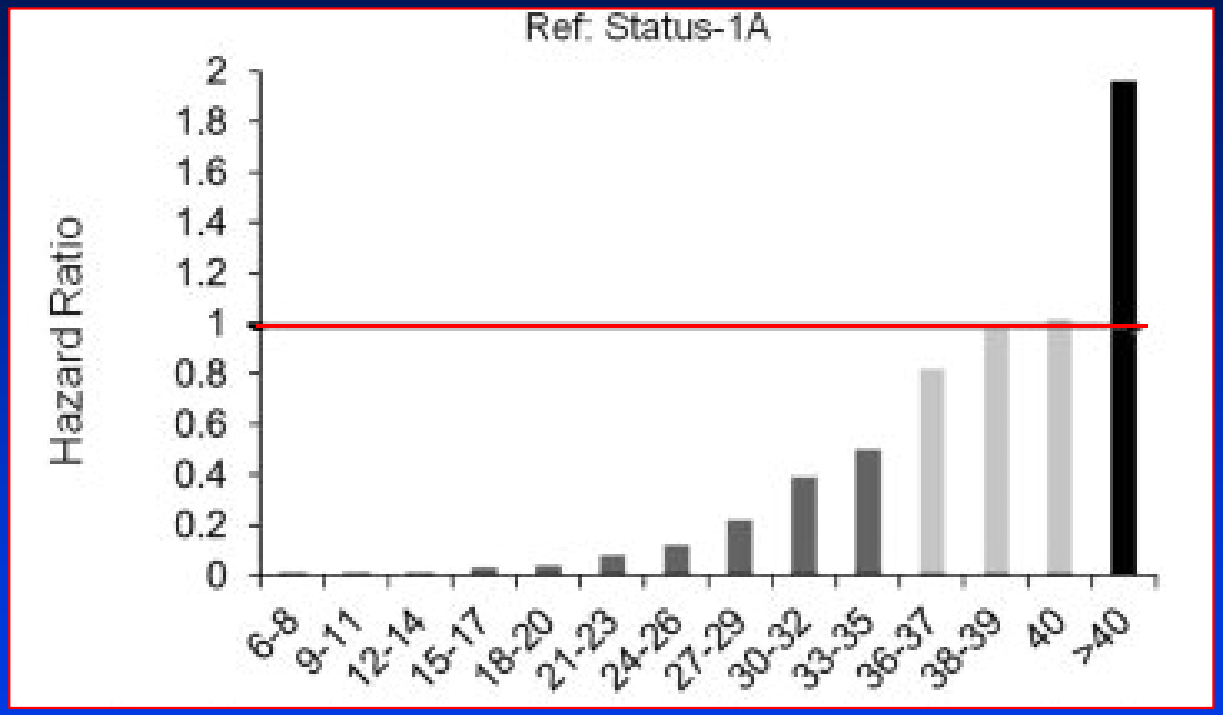
MELD Exceptions 2013

HCC – Not criteria	1185
Hepatopulmonary	249
Portopulmonary	81
Hepatic artery thrombosis	63
Metabolic disease	66
Primary oxaluria	23
Familial amyloid	22
Other	2098 (PSC, ascites, encephalopathy)

Risk of Waitlist Mortality



Sharm, et al. Hepatology 2012; 55:192-198.

Summary: Key Points

- Regional sharing increased from 19.4% to 30.4% of deceased donor transplants
- MELD/PELD 35+ transplants increased from 19.9% to 25.2%
- Liver-intestine transplants increased from 12 to 44
- Liver discards decreased
- Waiting list mortality decreased 7%
- Import/export dynamics by DSA was similar between eras

OPTN

UNOS DONATE LIFE

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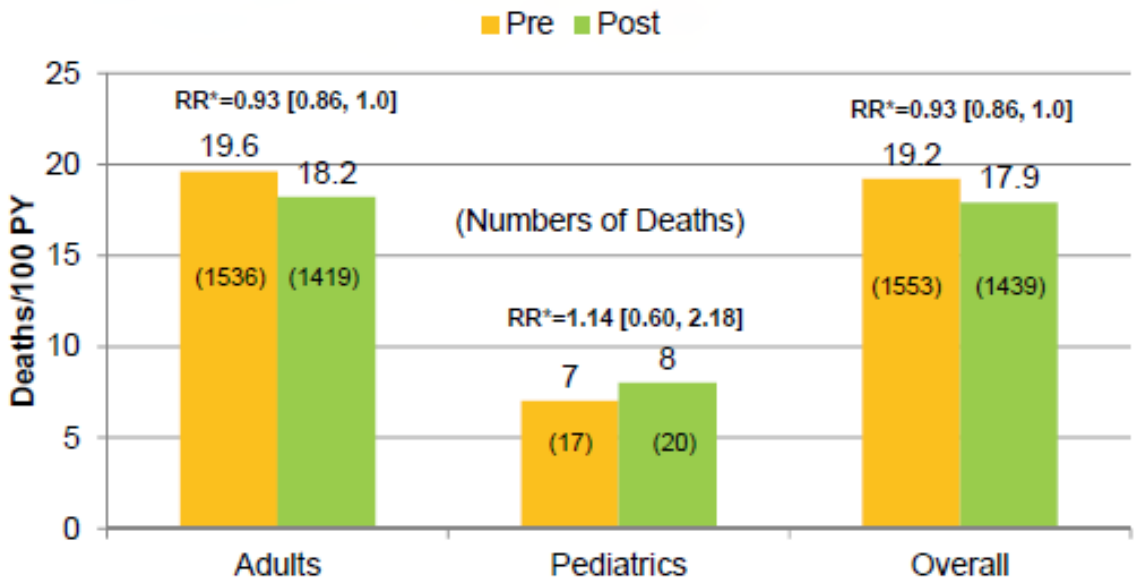
Liver Waiting List Death Rates: Deaths/100 Patient-Years



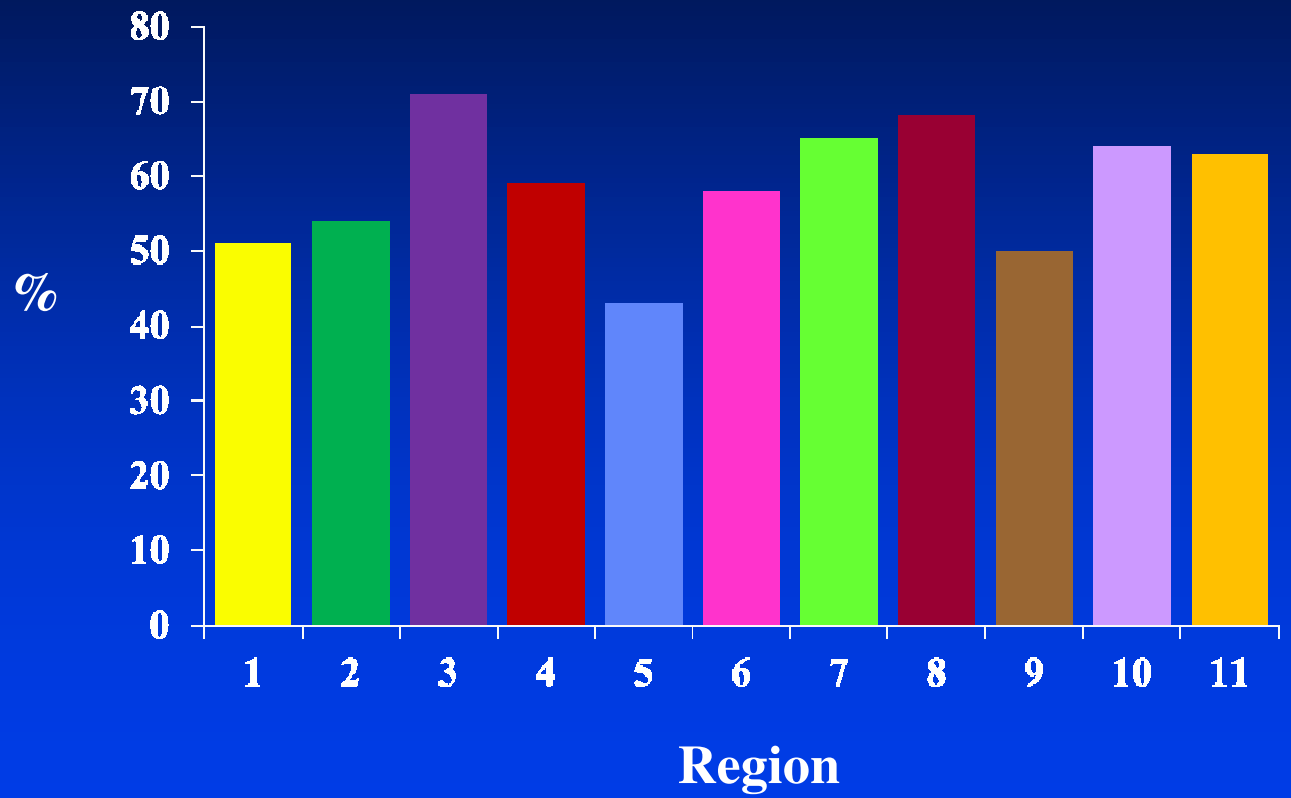
Pre: 12/17/2012 – 6/17/2013
Post: 6/18/2013 – 12/17/2013

OPTN

*Relative Risk: Post vs. Pre

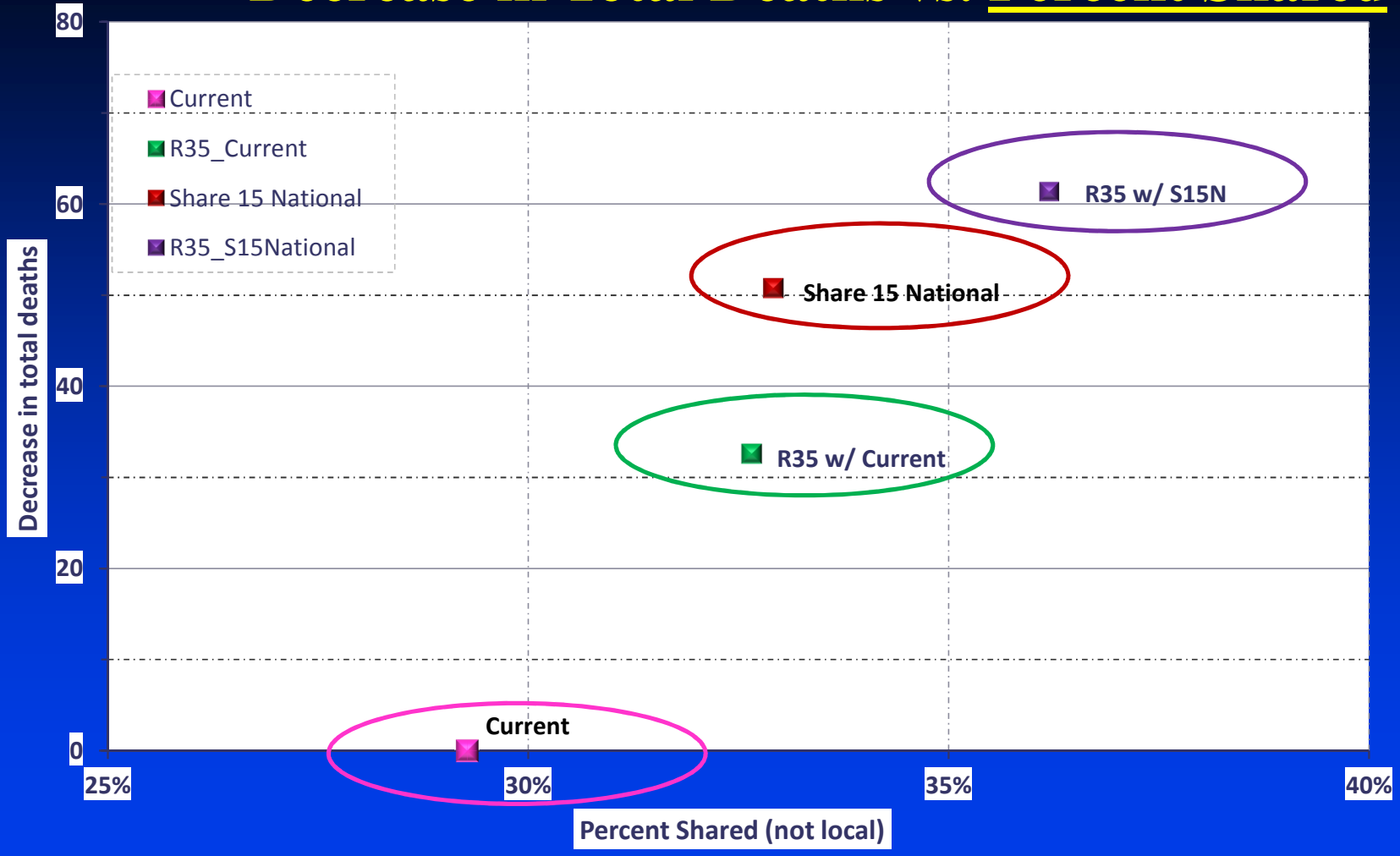
UNOS DONATE LIFE

Proportion of Liver Transplant Recipients with a Waiting Time of 90 Days or Less by Region



SRTR: Analysis Data as of May 2009

Decrease in Total Deaths vs. Percent Shared



Impact of MELD

- Reduction in waiting list registration (12%)
- Reduction in deaths on waiting list (3-5%)
- Decreased median waiting time (6-416 days)
- Transplanted within 30 days (23% 2001 to 37% 2008)

So is this really about looking out for the needs of John Q. Public?

Impact of Share 35

	Pre	Post
Allocated MELD ≥ 35	23.1%	30.1%
Regional Share	18.9%	30.4%
CIT (hours)	6.0%	6.0%
Waitlist Mortality MELD ≥ 30	17.6%	16.3%
Post Tx Mortality	Unchanged overall except 4, 10	
Post Tx Length of Stay	Unchanged	

8 districts reduce disparity