




Ethics and Advocacy in the Modern Era of Pediatric Liver Transplantation in the United States

October 10, 2015
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Disclosure


- In the past 12 months, I have had no relevant financial relationships with the manufacturers of any commercial product(s) and/or provider(s) of commercial services discussed in this CME activity



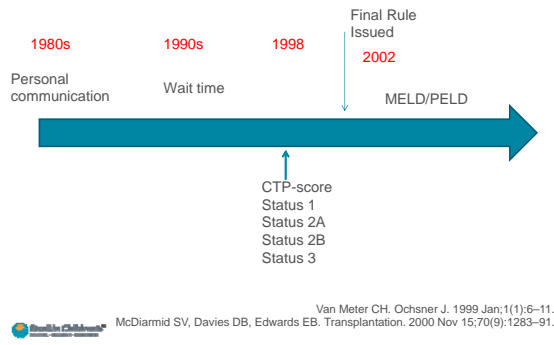
Learning Objectives

Upon completion of this session, the participants will:

- Have a better understanding of the ethical principles behind prioritizing children in deceased liver allocation
- Be able to employ potential strategies for advocating on behalf of children in the deceased liver allocation system
- Have a improved understanding of the ethical issues that surround anonymous altruistic living donor liver donation



History of Allocation in the United States



History of Allocation

- 1998—Final Rule
- **Mandate:**
 - Allocate in order of medical urgency
 - Minimize the role of waiting time
 - Avoid futile transplantation
 - Decrease inter-transplant center variance
 - Broader geographic distribution

Fed Regist. 1998 Apr 2;63(63):16296-338.

Figure X-1. Comparison of Original MELD and OPTN/UNOS MELD PELD Equations

Original MELD

$$\text{MELD} = (0.957 \times \text{LN}(\text{creatinine})) + 0.378 \times \text{LN}(\text{bilirubin}) + 1.12 \times \text{LN}(\text{INR}) + 0.643) + 0.643 \times (\text{cause of cirrhosis}^*)$$

OPTN/UNOS MELD

$$\text{MELD} = (0.957 \times \text{LN}(\text{creatinine}^{**})) + 0.378 \times \text{LN}(\text{bilirubin}^{**}) + 1.12 \times \text{LN}(\text{INR}^{**}) + 0.643)$$

PELD

$$\text{PELD} = (0.436 \times \text{age}^\dagger) - (0.687 \times \log(\text{albumin})) + (0.480 \times \log(\text{bilirubin})) + (1.857 \times \log(\text{INR})) + (0.687 \times \text{growth failure}^\ddagger)$$

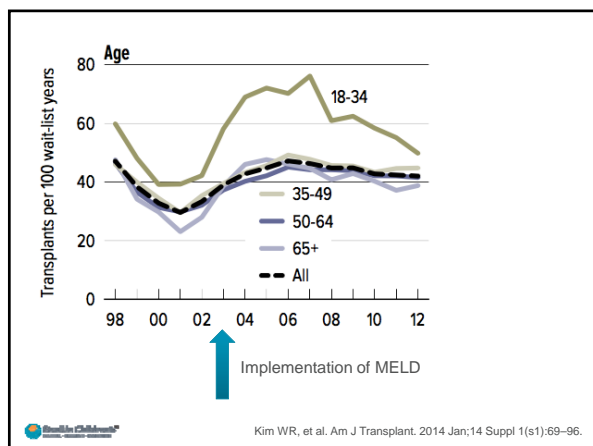
* Cholestatic liver disease = 0; all others = 1

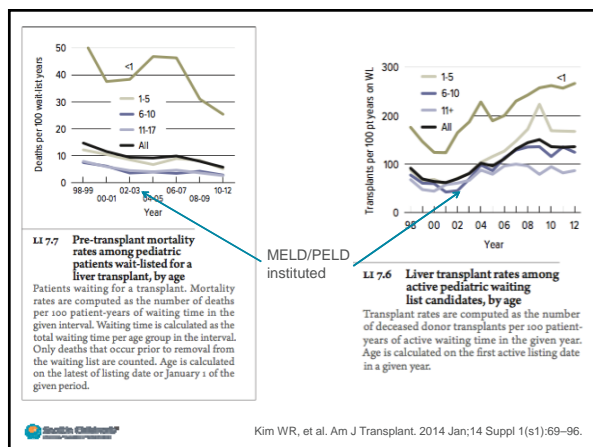
** Values < 1.0 rounded up to 1.0

† Age < 1 year = 1; all others = 0

‡ Values > 2 standard deviations from the norm = 1; all others = 0

Source: Wiesner et al, 2003. (14)





Adult Waitlist mortality

	2010	2011	2012
Patients at start of year	14956	15360	15428
Removed for Transplant	5659	5726	5660
Removed for death or deterioration	2820	2988	3002

*Mortality rates ranging 18-20% per year

Kim WR, et al. Am J Transplant. 2014 Jan;14 Suppl 1(s1):69-96.

Pediatric Waitlist mortality

	2010	2011	2012
Patients at start of year	701	666	655
Removed for Transplant	564	539	528
Removed for death or deterioration	75	45	54

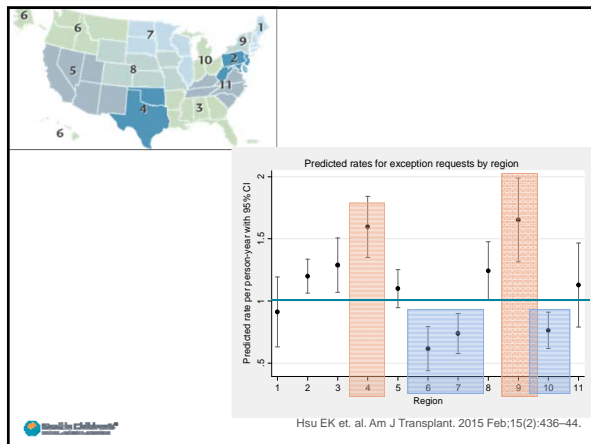
*Mortality rates ranging 7-11% per year



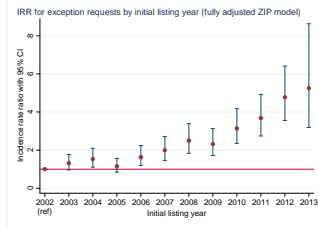
Kim WR, et al. Am J Transplant. 2014 Jan;14 Suppl 1(s1):69-96.

PELD Exception Scores

- Applications can be made by clinicians on behalf of their patients to the Regional Review Board (RRB) for additional exception points
- This is arbitrary and unstandardized
- Opens the system up to unfair application



US Exception Requests in pediatric pts with chronic liver disease



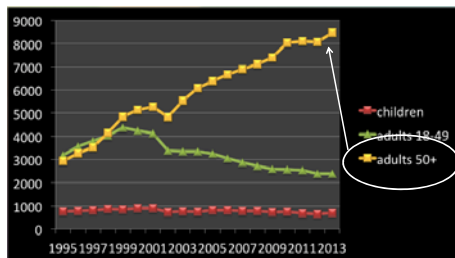
Exception requests were associated with **higher calculated MELD/PELD, younger age, and White race**

Exception status was associated with a **3-fold higher hazard ratio of transplantation**



Hsu EK et. al. Am J Transplant. 2015 Feb;15(2):436-44.

The Tragedy of the Commons



Number of patients added to the liver waitlist per year

UNOS OPTN Data
Simon Horslen, July 2014



Special Ethical Considerations in the Allocation of Human Organs to Pediatric Candidates

- UNOS Pediatric Transplantation and Ethics Committees
- Provide guidance about how organ allocation policies should address pediatric patient needs
- Justifications for pediatric priority in organ allocation

Ethical Principles of Pediatric Organ Allocation, OPTN
<http://optn.transplant.hrsa.gov/resources/ethics/ethical-principles-of-pediatric-organ-allocation/>



Declaration of the Rights of the Child

Whereas the child, by reason of his physical and mental immaturity,

needs special safeguards and care, including legal protection ...

Whereas mankind owes to the child the best it has to give ...

The child shall enjoy special protection, and shall be given opportunities and facilities, by law and by other means, to enable him to develop physically, mentally, morally, spiritually, and socially in a healthy and normal manner ...

In the enactment of laws for this purpose, the best interests of the child shall be the paramount consideration.

1959, United Nations General Assembly

Declaration of the Rights of the Child. Available from: <http://www.refworld.org/docid/3ae6b38e3.html>



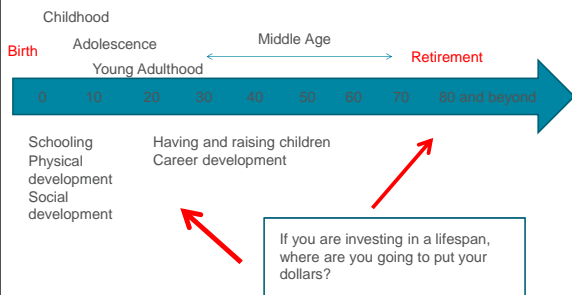
Prudential Lifespan Account

- Children with end-stage organ failure have time-limited opportunity for growth and development and may suffer lifelong consequences if not expeditiously transplanted
- How each individual would want to invest resources across one life with goal to make a life go as well as possible

Ethical Principles of Pediatric Organ Allocation, OPTN
<http://optn.transplant.hrsa.gov/resources/ethics/ethical-principles-of-pediatric-organ-allocation/>



Prudential Lifespan Account



Fair Innings

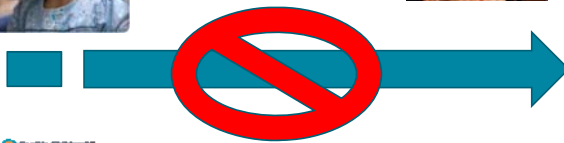
- Every individual deserves to experience a full life
- Children will die prematurely, denying opportunities in adulthood to complete education, establish career, have a family



Ethical Principles of Pediatric Organ Allocation, OPTN
<http://optn.transplant.hrsa.gov/resources/ethics/ethical-principles-of-pediatric-organ-allocation/>



Fair Innings



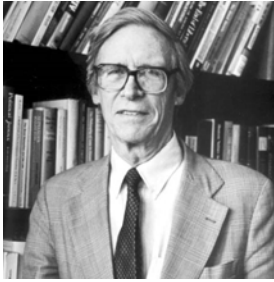
Maximin Principle

- **Maximizing the minimum benefit** to the least advantaged, or giving priority to the most disadvantaged groups
- Give the most benefit to the least-advantaged members of society

Ethical Principles of Pediatric Organ Allocation, OPTN
<http://optn.transplant.hrsa.gov/resources/ethics/ethical-principles-of-pediatric-organ-allocation/>



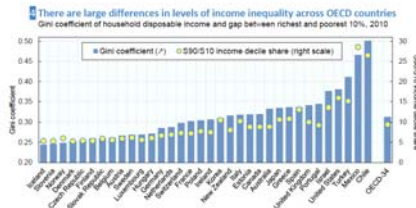
Maximin Principle



John Rawls
20th Century Philosopher
Social Contract Theorist



Maximin Principle



Society's institutional arrangement is **just** insofar as it **improves the lot of the worst-off group**

Priority in reducing the gaps between the **worst off** and the rest of the population



<https://www.washingtonpost.com/blogs/worldviews/wp/2013/05/16/report-income-inequality-rising-in-most-developed-countries/>

Maximin Principle

- Pediatric candidates are disadvantaged
 - small size
 - developing anatomy
 - lack of availability of life-sustaining therapies



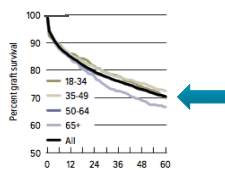
Utility Considerations

Pediatric liver recipients have a better patient and graft survival than adult recipients



Kim WR, et al. Am J Transplant. 2014 Jan;14 Suppl 1(s1):69-96.

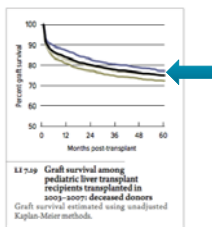
Utility Considerations



LI 6.4 Graft survival among adult liver transplant recipients transplanted in 2007: deceased donors
Graft survival estimated using unadjusted Kaplan-Meier methods.



Kim WR, et al. Am J Transplant. 2014 Jan;14 Suppl 1(s1):69-96.



LI 5.49 Graft survival among pediatric liver transplant recipients transplanted in 2007: deceased donors
Graft survival estimated using unadjusted Kaplan-Meier methods.

How do we invoke change on behalf of children?

- Alternatives should be fair, equitable, and improve pediatric waitlist outcomes without affecting the adult waitlist



How do we invoke change on behalf of children?

International experience

- Brazil
 - Pts < 12 years of age allocation score = {calculated PELD}x3
 - 6x increase in split liver transplantation and decreased waiting time
- Eurotransplant
 - "Pediatric MELD" score assigned < 12 years of age, point score corresponding to 35% 3-month wait-list mortality, upgraded by a 15% increase every 90 days
 - 12-16 yrs age given a score corresponding to a 15% 3 month waitlist mortality, upgraded by 10% every 90 days

Neto JS, et al. Liver Transplantation. 2010 Apr;16(4):426-30.



Herden U, et al. Clin Transplant. 2014 Jul 10



Discussion

Case #2

- Twins, adopted, both with end-stage liver disease from Alagille syndrome
- Only the father is a match/suitable candidate
- Desperate, they go to the media to plead for an anonymous altruistic living donor



Case #2



Twins need liver transplant, dad can only donate to one 02:04



CNN, Wednesday, Jan 28th, 2015

Overview: Living Donor Liver Transplantation

Pros

- Controlled setting, decreased ischemia time
- In related individuals, may improve tolerance of graft
- In areas facing critical shortage, may be the only choice

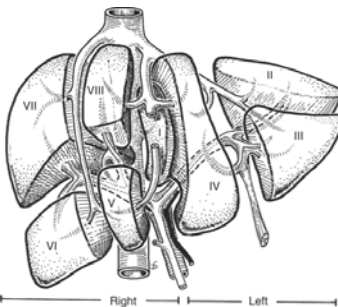
Cons

- Psychiatric complications
- Health related quality of life
- Physical complications (donor complication rate 40%, biliary complication rate 10.6%, incision infection rate 5.8%, 0.2% donor mortality)
- Psychosocial health: costs, family impact

Abecassis MM et al. Am J Transplant. 2012 May;12(5):1208-17.



Anonymous living liver donation



Living liver donation from genetically and emotionally related donors is effective and accepted life-saving therapy for escalating number of patients with end-stage liver disease

Donor complication rates ~40%, 10x risk of mortality (0.28%) of kidneys

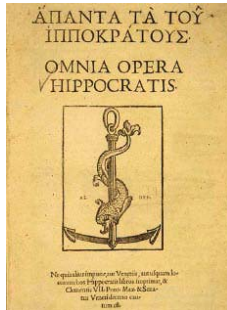
Couinaud, 1957.



Anonymous altruistic donation

In emotionally or genetically related donors, we expect, particularly in pediatrics, that the donor will be better off after surgery than before because of the benefit to the recipient

This assurance does not exist in anonymous donation



What do providers think about anonymous altruistic donation?

Most participants (caregivers, coordinators) were either wary of or opposed to altruistic stranger donation

"It's nice to be nice to other people but it's a strange thing. For me, it's difficult to understand... at this moment, I wouldn't consider it really."



Thomas EH, et al. Journal of medical ethics. 2014 Mar;40(3):157-62.

American Journal of Transplantation 2007; 7: 1032-1035
Blackwell Munksgaard

Journal compilation © 2007 The Authors
Transplantation and the American Society of Transplant Surgeons
doi: 10.1111/j.1600-6143.2006.01725.x

Case Report

Living and E

Table 1: Reasons for accepting LALDs

Table 2: LALD eligibility criteria

L. Wright^a
and D. Gra

1. History of altruistic behavior (i.e. must "walk the talk").
2. High level of motivation to donate.
3. Logical rationale for donation.
4. Altruistically motivated.
5. No expectation of secondary benefit (e.g. media or public attention, compensation, atonement).
6. Voluntary informed consent is obtained.
7. No evidence of increased risk of negative psychiatric or psychosocial outcomes.
8. Willingness to maintain confidentiality.
9. Family support of donor's decision to donate anonymously.
10. Understanding and acceptance of standard organ allocation criteria.



Wright L, et al. Am J Transplant. 2007 Apr;7(4):1032-5.

Altruistic Living Donor Kidney or Liver Donation

M.D. Jendrisak^{a,*}, B. Hong^b, S. Shenoy^c,
J. Lowell^a, N. Desai^a, W. Chapman^a, A. V.
R.D. Wetzel^d, M. Smith^e, J. Wagner^e,
S. Brennan^f, D. Brockmeier^g and D. Kapj

Table 1: Nondirected living donor evaluation

Phase	Activity
Phase I	Unidentified call to the transplant centers or the OPO
Phase II	<ul style="list-style-type: none"> Coordinator (OPO, CDC, UNOS) coordinates Review donor education materials and schedule Schedule physician with potential physician Review donor education materials Measure blood pressure, height and weight Review donor education materials Review donor education materials
Phase III	<ul style="list-style-type: none"> Laboratory tests Tests: CBC, BUN and B12 blood triglyceride Metabolic tests: CAC, normal function panel, PT, PTT Tests: HIV, Hepatitis, CMV, toxoplasma, 24-hr creatinine clearance Tests: HIV 1 & 2, HTLV 1 & 2, HIV RNA, EBV, Hg Abag, mg/dl, C-creatinine, mg/dl, P-creatinine, mg/dl Tests: HIV test (last blood test) within 12 months or over 40 years; HBsAg 1 within 12 months of last blood test
Phase IV	<ul style="list-style-type: none"> Psychosocial testing with family and TCI (2-3 days) Psychosocial testing with family and TCI (2-3 days) Additional interviews with family and other support system members Psychosocial testing (if applicable) Complete transplant center for receipt of organ (optional) Complete transplant center for receipt of organ (optional) Recipient selection Complete transplant center for receipt of organ (optional) Complete transplant center for receipt of organ (optional)
Phase V	<ul style="list-style-type: none"> Meet with transplant center coordinator and social worker Complete transplant center evaluation and acceptance Complete transplant center evaluation and acceptance Undergo donor surgery Undergo donor surgery
Phase VI	<ul style="list-style-type: none"> Postoperative recovery with transplant center Postoperative recovery with transplant center

*MMPI-2 = Minnesota multiphasic personality inventory-2; TCI = temperament and character inventory; OPO = organ procurement organization; SCSL = second chance St. Louis.



Jendrisak MD, et al. Am J Transplant. 2006 Jan;6(1):115-20.

How effective are media campaigns?

- Over 5 years-1000 potential donors initiated call, majority do not respond to calls or fail to complete required questionnaire
- Only 29 people submitted appropriate documentation, passed screening and underwent further eval in a 5 year period
- 17 terminated, leaving 12
 - 7 patient decisions
 - 5 medical concerns
 - 4 anatomical unsuitability
 - 2 breach of anonymity



Reichman TW, et al. Am J Transplant. 2010 Sep;10(9):2099–104.

Table 1: Demographics of anonymous donors

Donor	Age	Sex	Race	Marital status	Prior surgery	Donation type	Surgery	Psychological history
1	45	M	Caucasian	Married	Y	A	RLS	None
2	36	M	Caucasian	Divorced	Y	A	LLS	Job-related anxiety ~10 years ago
3	20	M	Caucasian	Single	Y	AD	LLS	None
4	48	F	Caucasian	Divorced	Y	A	RTM	None
6	52	M	Caucasian	Divorced	Y	A	RTM	None
8	38	M	Caucasian	Single	N	A	LLS	None
7	30	M	Caucasian	Divorced	Y	AD	RTM	Physical/mental abuse as child by parent
8	54	F	Caucasian	Married	Y	AD	RTM	Perimenopausal anxiety, abused by first husband
9	46	F	Caucasian	Married	Y	A	LLS	ADHD, death of twin sister at age 22
10	34	F	Caucasian	Married	Y	A	LLS	Postpartum depression
11	22	F	Caucasian	Single	Y	AD	RTM	None
12	66	F	Caucasian	Married	Y	A	LLS	None

A = anonymous; AD = anonymous-directed; ADHD = attention-deficit hyperactivity disorder; LLS = left lateral segmentectomy; RTH = right hepatectomy.

9	LLS	8	No	None	—	12	Hepatoclast	7	No	A
10	LLS	5	No	UTI	II	6	BA	25	No	A
11	RTH	5	No	None	—	3	PSC	16	Yes	A
12	RTH	6	No	None	—	12	ASH	19	No	A

LLS = left lateral segmentectomy; RTH = right hepatectomy; LOS = length of stay; PE = pulmonary embolus; UTI = urinary tract infection; RTW = return to work; LTx = liver transplantation; BA = biliary atresia; PBC = primary biliary cirrhosis; HCV = hepatitis C virus; HCC = hepatocellular carcinoma; ASH = alcohol-related steatohepatitis; PSC = primary sclerosing cholangitis; A = alive; D = deceased; CD = deceased donor.



Reichman TW, et al. Am J Transplant. 2010 Sep;10(9):2099-104.

Evaluation of anonymous living donors

- Need for protection of donor and recipient
- Rigorous requirements:
 - Past history of altruistic acts
 - Logical rationale for donation understandable to the team
 - No major psychiatric or psychosocial issues
 - Strong social supports
 - Must be willing to maintain confidentiality of patient information
 - No expectation of unacceptable secondary benefit such as media or public attention or illegal compensation
 - Must remain anonymous to recipient for at least 6 months
- Left lateral segment donation preferred due to surgical risk

