National Urea Cycle Disorders Foundation

Legacy of HOPE
NUCDF FAMILY CONFERENCE
April 5-7, 2024 · Houston, TX

UPMC | CHILDREN'S HOSPITAL OF PITTSBURGH

A long term perspective on Liver Transplant Decision Making in Urea Cycle Disorders

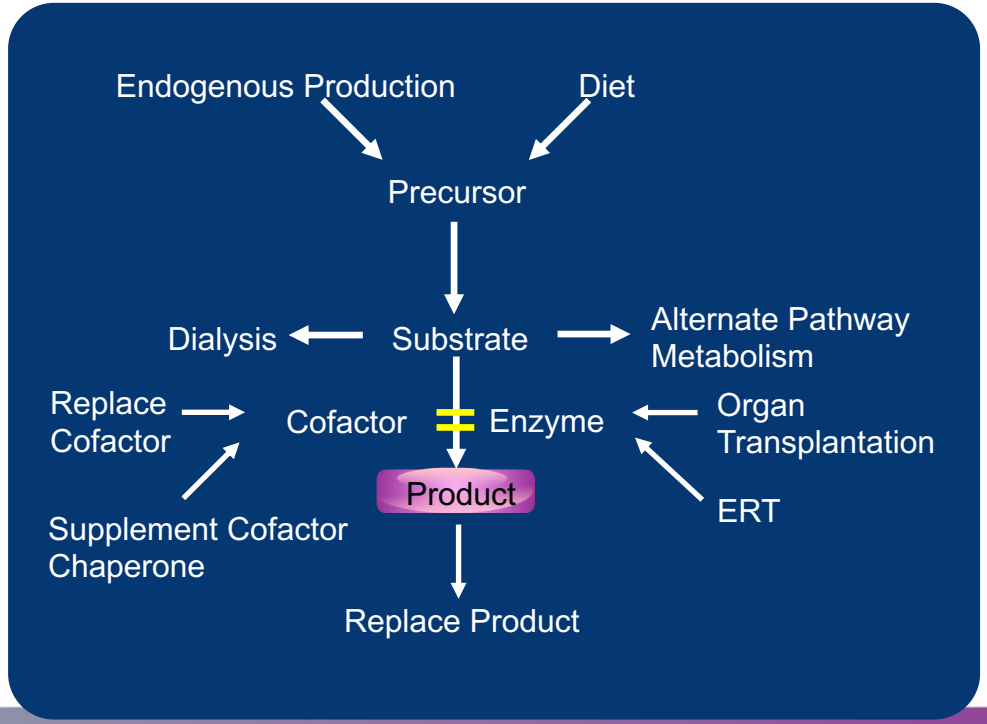
George Mazariegos @CHPTransplant

April 6, 2024

NO OTHER RELEVANT DISCLOSURES

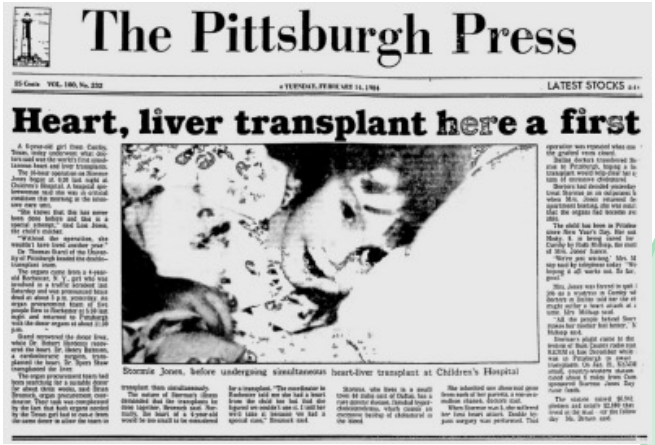
Strategies affecting protein level and function

- Substrate reduction
- Alternative substrates
- Toxin removal
- Cofactor supplementation
- Alternative pathways for metabolism
- Replace product
- Replace enzyme
  - **Transplant**
  - Gene therapy
  - mRNA therapy
  - Enzyme replacement



Courtesy, Dr Jerry Vockley

Metabolic disease: Connecting Surgeons/Physicians/Patients

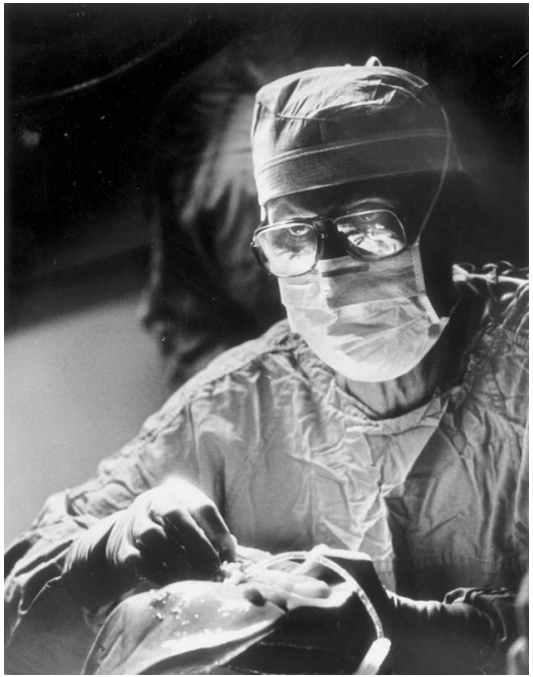


The Pittsburgh Press

LATEST STOCKS

Heart, liver transplant here a first

Stormie Jones, before undergoing simultaneous heart-liver transplant at Children's Hospital



Stormie's Story

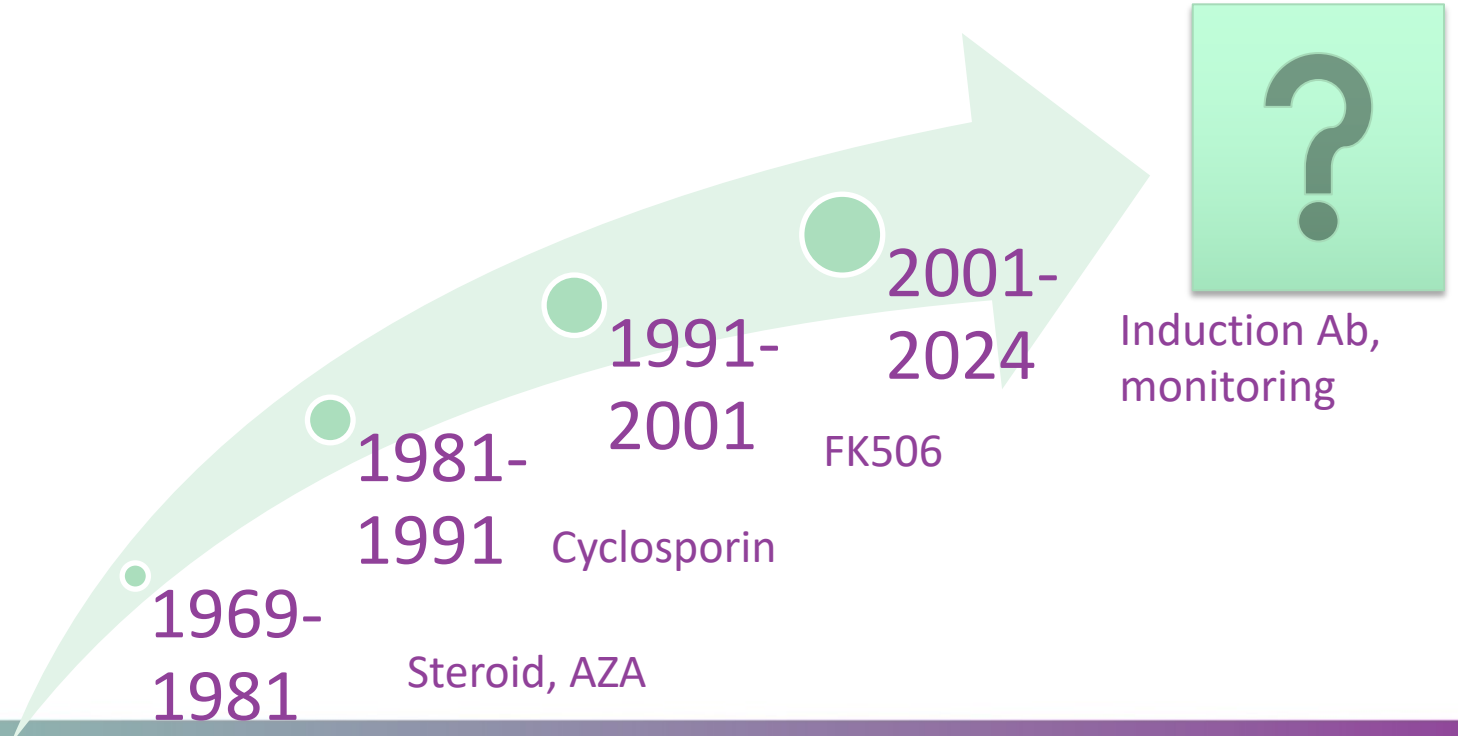
- Combined heart liver transplant, February 14, 1984 for familial hypercholesterolemia
- *" If the fundamental defect was exclusively or primarily in the liver, it was conceptually possible to correct the problem by replacing the liver"*

» – Thomas Starzl, The Puzzle People

The intersection of transplant and genetics

- *" armed with information from these dual lines of inquiry (pathology and biochemical genetics), more than a half dozen such inborn errors were "cured" metabolically between 1969 and 1983 by liver transplantation in Denver and Pittsburgh"* – The Puzzle People

The long journey of transplantation for metabolic disease



How much of a cure is achieved with transplant?

Disease specific outcomes and therapies

No Disease recurrence

Metabolic diagnoses for which liver transplant has been reported.

Conditions with liver injury	
Intrahepatic	**Extrahepatic**
Alpha-1-antitrypsin deficiency (*SERPINA1*)	• Wilson disease • Cystic fibrosis • FIC-1 deficiency • Glycogen storage disease types Ib, III and IV • Non-alcoholic steatohepatitis • Gaucher disease • Niemann–Pick disease • Cholesterol ester storage disease • Mitochondrial cytopathies • Cerebrotendinous xanthomatosis • Citrin deficiency • Erythropoietic porphyria
• Tyrosinemia type I • GSD Type IV (*GBE1* gene) • BSEP deficiency • MDR-3 deficiency • Primary bile acid synthesis disorders • Hepatic porphyrias o Acute intermittent porphyria o Variegate porphyria • Glycogen storage disease type Ia • Hereditary fructose intolerance • Indian childhood cirrhosis	

Conditions without liver injury	
Intrahepatic	**Extrahepatic**
• Crigler–Najjar syndrome type 1 • Primary hyperoxaluria • Urea cycle disorders • Familial hypercholesterolemia • Fatty acid oxidation defects • Coagulation defects o Hemophilia A o Factors V and VII deficiency o Proteins C and S deficiencies • Factor H deficiency • Afibrinogenemia • Amyloidosis type 1	• Citrulinemia • Cystinosis • Branched amino acids disorders (organic acidemias) o Propionic acidemia o Methylmalonic acidemia o Mevalonic acidemia o Maple syrup urine disease

Mazariegos et al , 2014, Molecular Genetics Metabolism,

Outcomes most well documented for Wilson Disease and CF. Other therapies now utilized for many of these systemic conditions

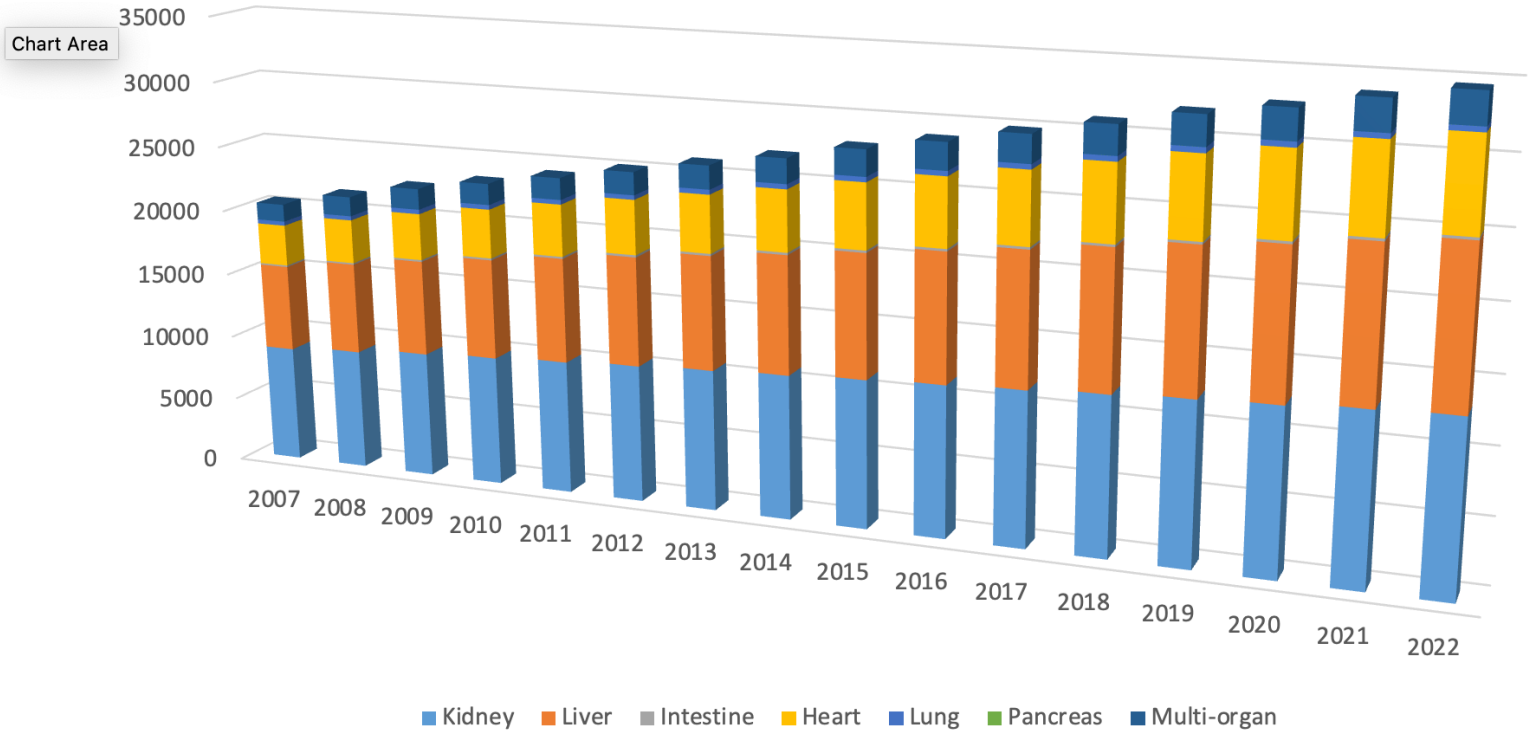
MSUD –phenotypic cure on normal diet
MMA, PA- improved metabolic status with improved but not normal protein intake

Objectives

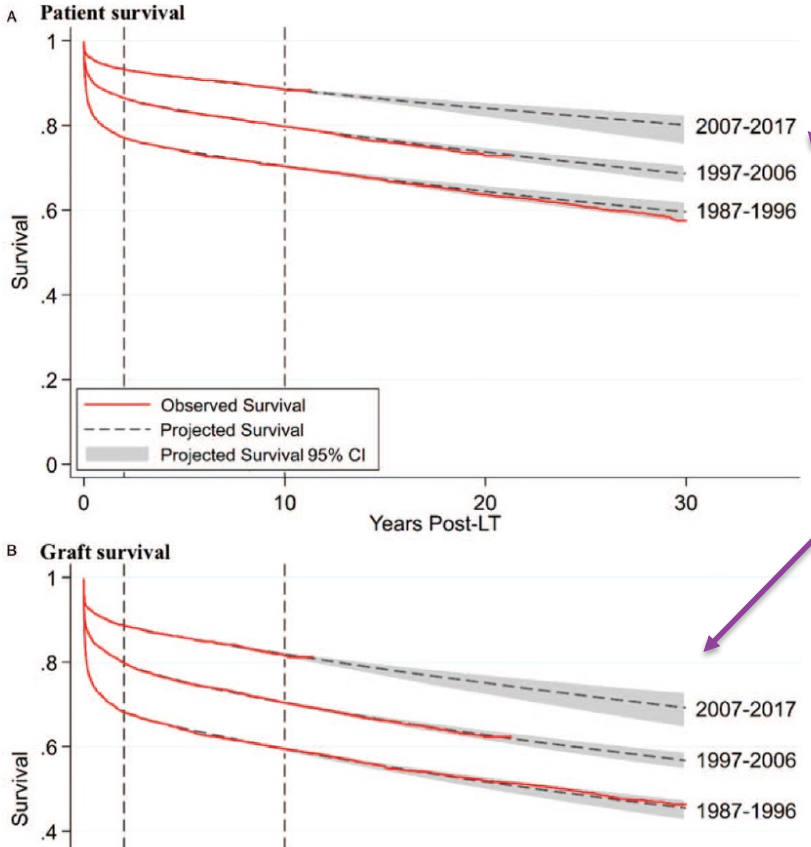
- Decision making in pediatric metabolic disease with focus on urea cycle disorders
- Perspectives on how we can improve in the long term
  - Location, location, location
  - Learning networks and working on long term care, transition, immunosuppression
- Supplementation after transplant

LONG TERM OUTCOMES IN TRANSPLANTATION TODAY

Number of pediatric recipients who are alive with graft function after organ transplants by year and organ type (SRTR, 2023)



What is the projected liver transplant outcome for children transplanted today?



Projected 20- and 30-Year Outcomes for Pediatric Liver Transplant Recipients in the United States

*Mary G. Bowring, *†Allan B. Massie, *Nadia M. Chu, *Sunjae Bae, ‡Kathleen B. Schwarz, *Andrew M. Cameron, §John F.P. Bridges, *†||Dorry L. Segev, and ‡Douglas B. Mogul

30 yr patient and graft survival projected at 80%/69.1%, respectively

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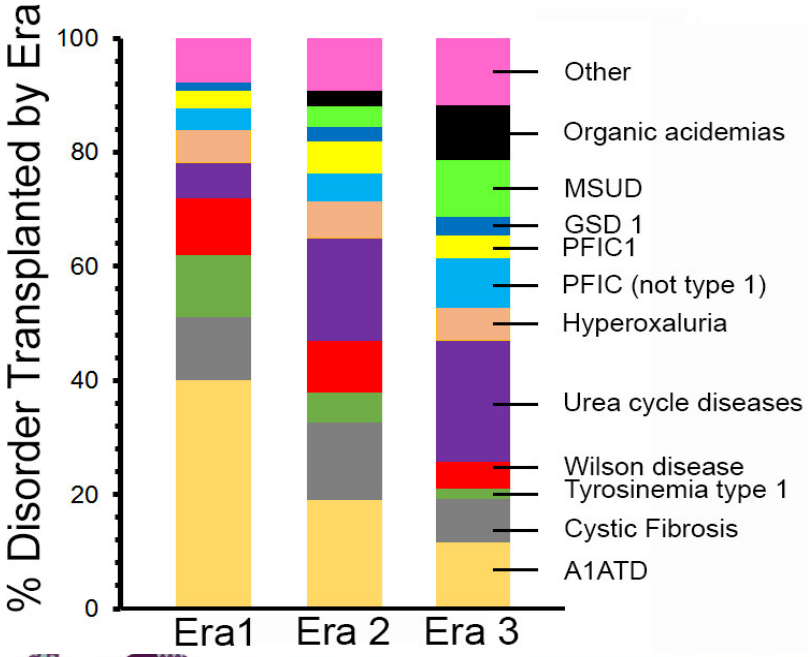
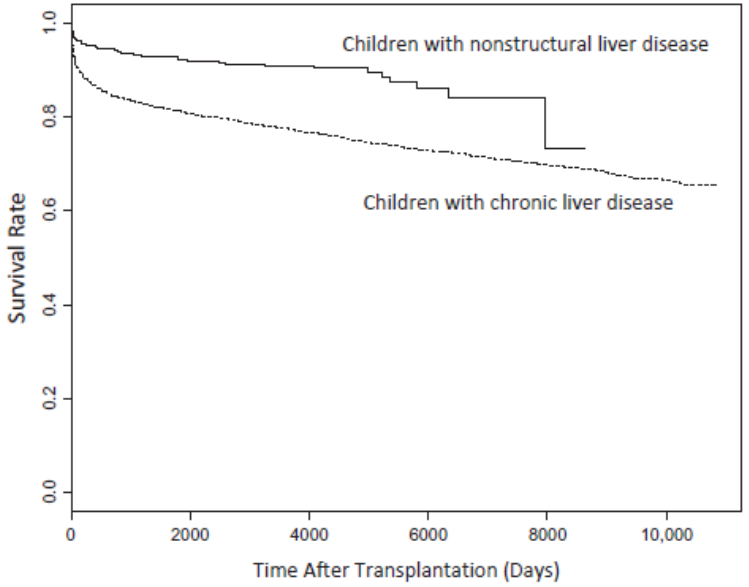
Evolving indication for liver transplant for metabolic disease in US over 30 years





McKiernan et al Liver Transpl 2019

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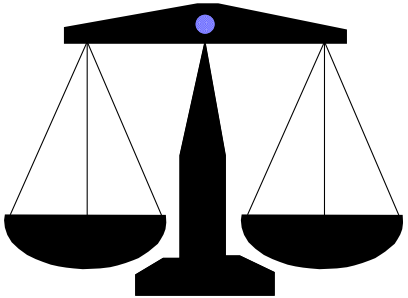
RISKS AND BENEFITS



Medical management

Natural history - phenotype

Frequency/severity of decompensations

Risks of end organ damage

Quality of life/adherence over time

Mortality

Liver transplant

Availability of expertise

Surgical complications

Early mortality

Degree of metabolic correction

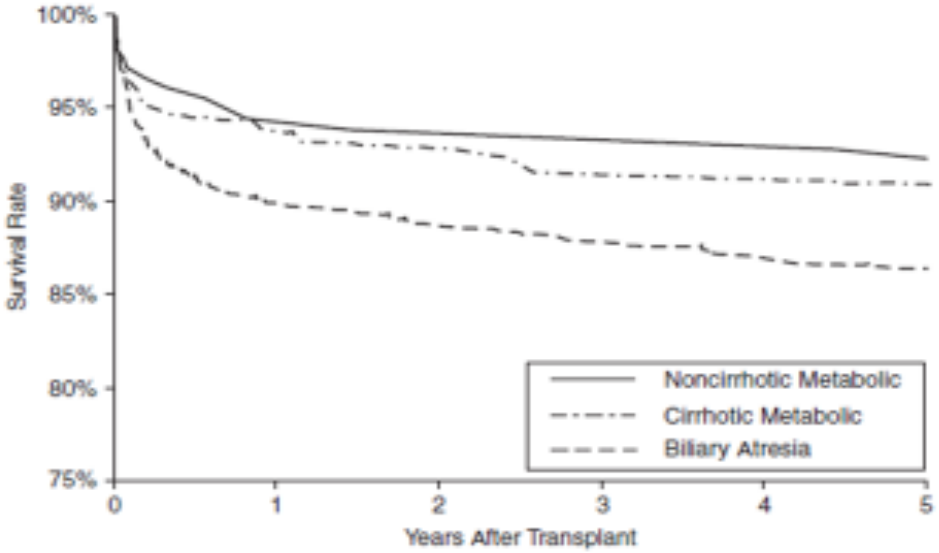
Life long immunosupression

Adherence

Impact of gene therapy and future therapies?

OUTCOMES: metabolic disease vs. chronic liver disease

Kayler, 2003



Arnon, 2010

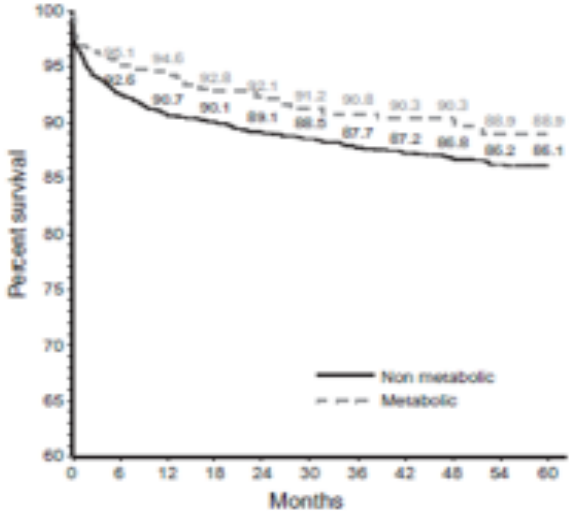
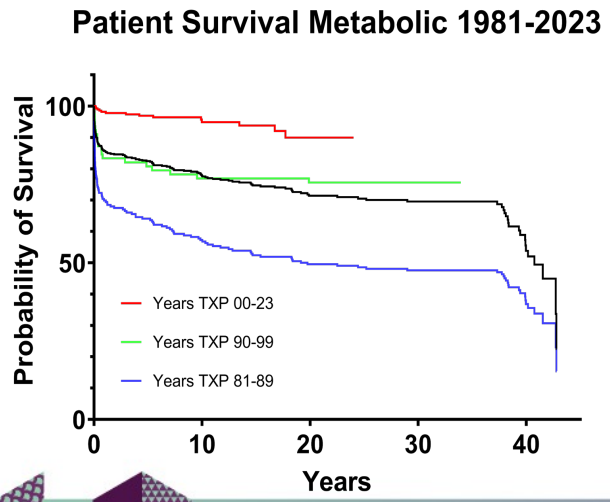


Fig. 1. Kaplan–Meier probability of survival after LT for metabolic vs. non-metabolic liver disease.

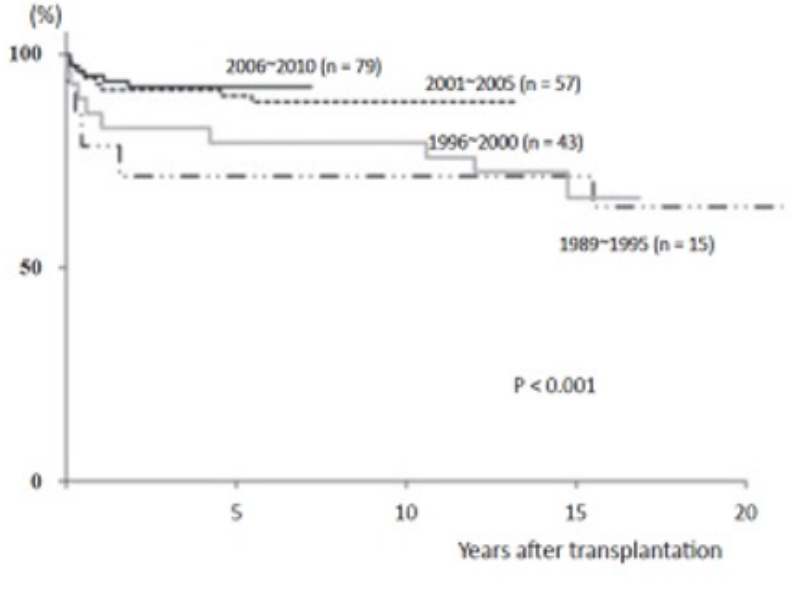
Liver transplant for metabolic disease by era

Pittsburgh series (n=404)

Overall Patient Survival By Decade Liver Transplant for Metabolic Disease (N=404), 1981- 12/31/2023



Japanese Registry (n=194)



Selected results

AUTHOR/YR	UCD CASES	PT SURVIVAL (1/5 YR)	GRAFT SURVIVAL (1/5 YR)	NOTES
Arnon, 2010	114	95.2/88.7%	91.8/83.7%	Data from SPLIT
Kim et al , 2013	23	Mean 5 yr survival was 100%	5 yr graft survival was 96%	Stanford data Mean age 3.4 yr;
Mazariegos et al, 2014. 2024	14/ 45	80% 20 year patient survival	80% 20 year graft survival	UPMC Children's Data
Kasahara et al, 2013	51	95.9/95.9	95.9% 15 yr patient survival	Japanese LTS Registry mandatory data
Kido et al , 2021	78	98.7% 5 year survival*		Survey questionnaire
Ziogas et al, 2021	403		90.4%/85.5%	Waitlist time associated with long term cognitive delay

Differences by sub groups of metabolic disease

Table 9 Demographics, procedure type, post-transplant complications, and outcome by primary diagnosis

	Urea cycle defects (N = 114)	Alpha 1 antitrypsin deficiency (N = 88)	Cystic fibrosis (N = 48)	Wilson disease (N = 34)	Tyrosinemia (N = 33)	Maple syrup urine disease (N = 29)	Crigler-Najjar (N = 21)	Neonatal hemochromatosis (N = 18)	p value
Age at transplant (mean ± SEM)	4.0 (0.4)	4.7 (0.5)	12.4 (0.6)	14.2 (0.5)	3.8 (0.7)	6.4 (0.8)	7.3 (1.2)	0.3 (0.1)	<0.0001
UNOS status 1*	35 (30.7)	6 (6.8)	4 (8.3)	15 (44.1)	6 (18.2)	0 (0)	2 (9.5)	7 (38.9)	<0.0001
Hospitalized in ICU	11 (9.6)	7 (8.0)	8 (16.7)	19 (55.9)	9 (27.3)	4 (13.8)	0 (0)	15 (83.3)	<0.0001
On dialysis/hemofiltration	7 (6.1)	1 (1.1)	0 (0)	4 (11.8)	0 (0)	0 (0)	1 (4.8)	0 (0)	0.0468
Cadaveric whole	67 (58.8)	58 (65.9)	34 (70.8)	28 (82.4)	14 (42.4)	28 (96.6)	15 (71.4)	6 (33.3)	<0.0001
Cadaveric split	18 (15.8)	10 (11.4)	3 (6.3)	2 (5.9)	5 (15.2)	1 (3.4)	0 (0)	2 (11.1)	
Cadaveric reduced	15 (13.2)	8 (9.1)	2 (4.2)	3 (8.8)	10 (30.3)	0 (0)	4 (19.0)	7 (38.9)	
Live donor (related and unrelated)	9 (7.9)	11 (12.5)	6 (12.5)	0 (0)	3 (9.1)	0 (0)	2 (9.5)	2 (11.1)	
Biliary complications	15 (13.2)	8 (9.1)	6 (12.5)	1 (2.9)	3 (9.1)	0 (0)	0 (0)	4 (22.2)	Not enough sample size to perform statistical test
Hepatic artery thrombosis	11 (9.6)	10 (11.4)	2 (4.2)	1 (2.9)	4 (12.1)	3 (10.3)	3 (14.3)	2 (11.1)	
Portal vein thrombosis	0 (0)	7 (8.0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (4.8)	2 (11.1)	
Gastrointestinal complication	9 (7.9)	3 (3.4)	1 (2.1)	2 (5.9)	1 (3)	3 (10.3)	1 (4.8)	1 (5.6)	
CNS complications	6 (5.3)	8 (9.1)	5 (10.4)	2 (5.9)	2 (6.1)	2 (6.9)	0 (0)	0 (0)	
Patient survival, one yr	95.2%	91.9%	91.5%	96.0%	100%	100%	94.7%	88.5%	0.80
Patient survival, five yr	88.7%	89.0%	88.0%	91.4%	92.4%	NA	94.7%	88.5%	
Graft survival, one yr	91.8%	86.0%	84.8%	96.0%	93.5%	100%	95.2%	82.1%	0.50
Graft survival, five yr	83.7%	80.7%	81.2%	91.4%	85.8%	NA	95.2%	82.1%	

Arnon et al, 2010

Differences by sub groups of metabolic disease: Living donor experience

Table 4. LDLT for each metabolic disorders

Diagnosis (n)	Wilson's disease (n = 59)	Urea cycle deficiency (n = 51)	Organic acidemia (n = 29)	Glycogen storage disease (n = 15)	Primary hyperoxaluria (n = 9)
Family history	4 (6.8%)	17 (33.3%)	2 (6.9%)	1 (6.6%)	3 (33.3%)
Donor age (yr)	41.7 ± 8.7 (22–68)	35.8 ± 6.8	33.6 ± 5.0	36.4 ± 9.2	39.9 ± 5.3
ABO incompatibility	5 (8.5%)	6 (11.8%)	5 (17.2%)	3 (20.0%)	1 (11.1%)
Age at onset (yr)	11.0 ± 4.4 (6–16)	1.1 ± 1.5 (0–2)	0.6 ± 1.7 (0–6)	0.1 ± 0.3 (0–1)	1.0 ± 0.8 (0.4–2)
Age at transplantation (yr)	11.4 ± 2.8 (6–17)	3.8 ± 4.6 (0.2–16)	2.2 ± 2.8 (0.4–12)	4.9 ± 4.3 (0.8–13)	7.7 ± 6.2 (1–17)
Indication of LTx	Chronic liver failure 42 Fulminant 17	Frequent hyperammonemia 51 Poor QOL 30	Metabolic decompensation 29 Poor QOL 29	Hypoglycemia 11 Chronic liver failure 3 Acute liver failure 2	Renal failure 9 Poor QOL 9
Transplantation score*	17.7 ± 3.2	19.3 ± 4.11	18.6 ± 3.0	14.0 ± 2.0	13.0 ± 2.0
Immunosuppression	Tac 66.0%, Tac+MMF 18.8% CyA 7.5%	Tac 72%, Tac+MMF20%, CyA 10%	Tac 86.2%, Tac+MMF3.4%, CyA 10.3%	Tac 80%, Tac+MMF 20%	Tac 77.8%, Tac+MMF 11.1%, CyA 11.1%
Acute and chronic rejection (%)	11.9, 3.4	9.8, 0	0, 0	6.6, 0	11.1, 0
Post LTx complication					
Hepatic artery thrombosis	1	0	0	0	1
Portal vein thrombosis	1	0	0	1	1
Biliary	1	1	0	0	0
Renal insufficiency	0	1	4	0	–
Seizure	4	4	3	3	0
Cause of death	*Pneumocystis* pneumonia Recurrent hepatitis C De novo autoimmune hepatitis Hypoxic–ischemic encephalopathy (epilepticus) Sepsis 2	Hemophagocytic syndrome Traffic accident	Sepsis 4	Sepsis 5 Liver failure after PV thrombus	Sepsis 3 Liver failure after HA/PV thrombus
Patient survival					
1 yr	98.4	96.1	89.7	80.0	55.6
5 yr	96.6	96.1	85.2	66.7	55.6
10 yr	94.7	96.1	85.2	66.7	55.6
15 yr	77.5	96.1	–	–	–

QOL, quality of life, LTx, liver transplantation, Tac, tacrolimus, MMF, mycophenolate mofetil, CyA, cyclosporine A, HA, hepatic artery, PV, portal vein.
*See Table 2.

Kasahara et al, 2014

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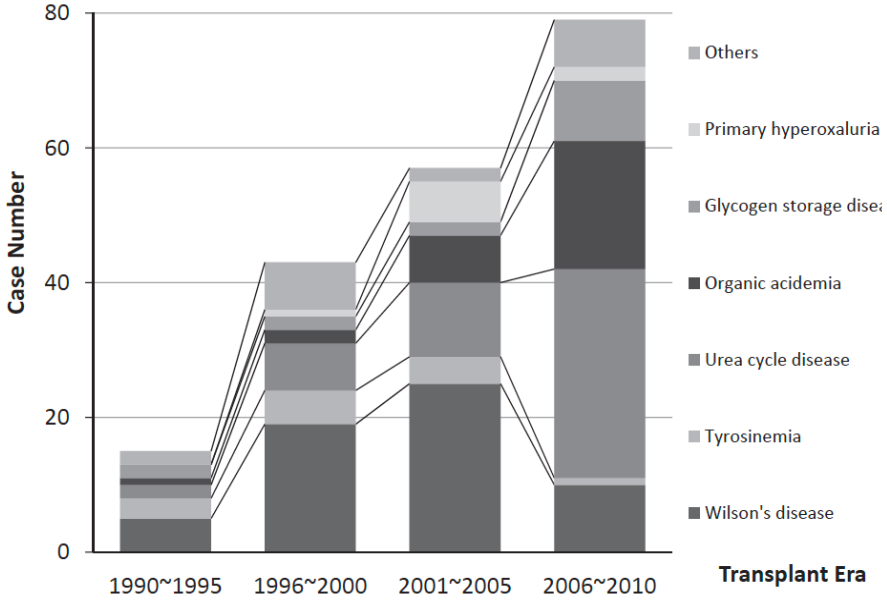
Pediatric Transplantation

Registry Report

Living donor liver transplantation for pediatric patients with metabolic disorders: The Japanese multicenter registry



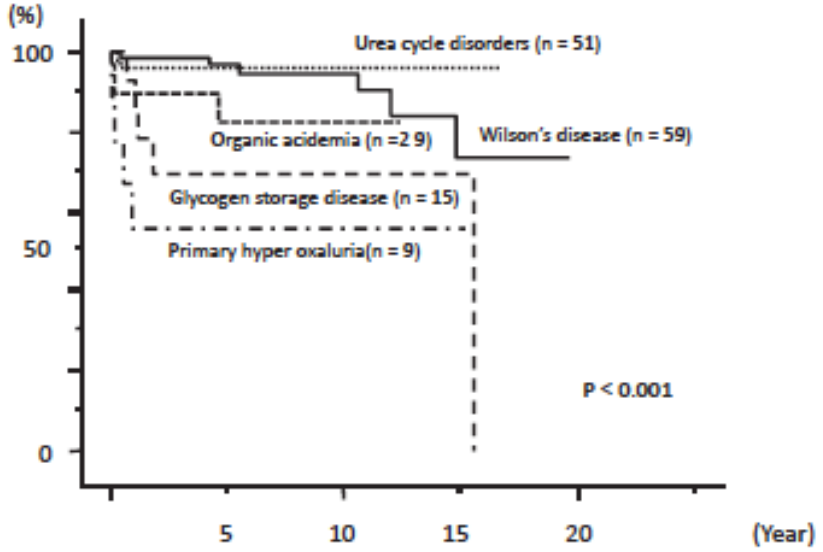
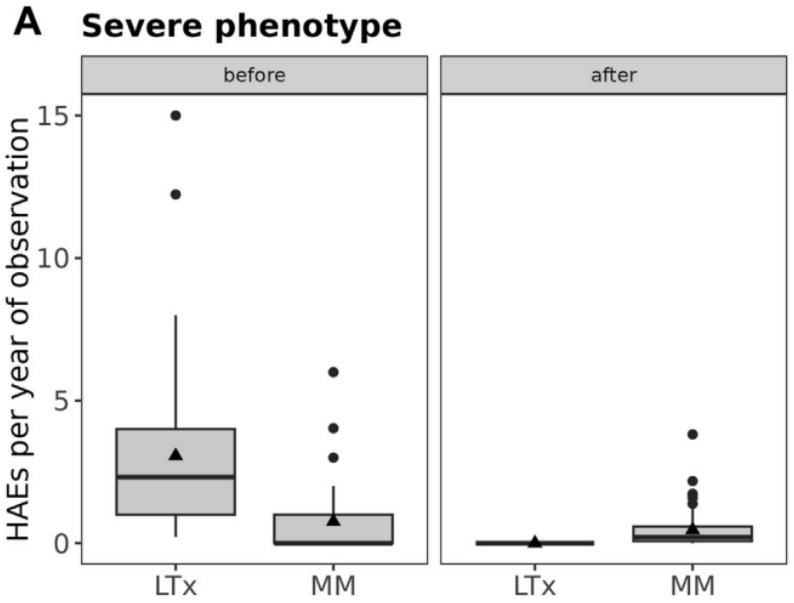


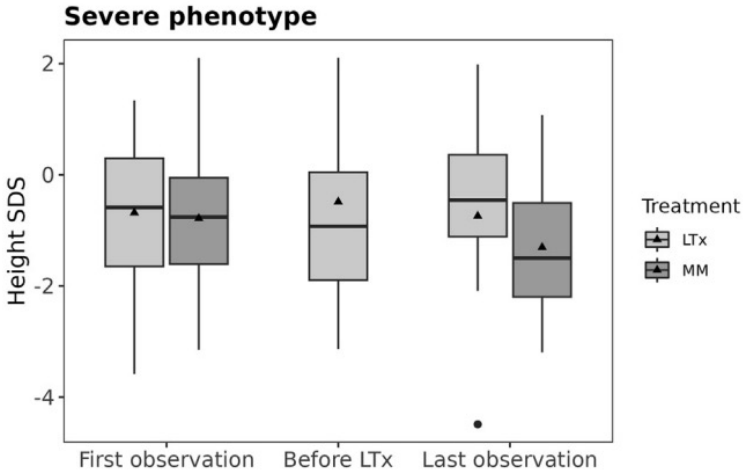
Fig. 3. Patient survival according to the original liver disease.

Metabolic and growth s/p LTx

Genetics in Medicine (2024)



Favorable growth outcome



Severity-adjusted evaluation of liver transplantation on health outcomes in urea cycle disorders

Roland Posset[1,*], Sven F. Garbade[1], Florian Gleich[1], Svenja Scharre[1], Jürgen G. Okun[1], Andrea L. Gropman[2], Sandesh C.S. Nagamani[3], Ann-Catrin Druck[1], Friederike Epp[1], Georg F. Hoffmann[1], Stefan Kölker[1], Matthias Zielonka[1,*]; on behalf of the Urea Cycle Disorders Consortium (UCDC) and the European registry and network for Intoxication type Metabolic Diseases (E-IMD) Consortia Study Group

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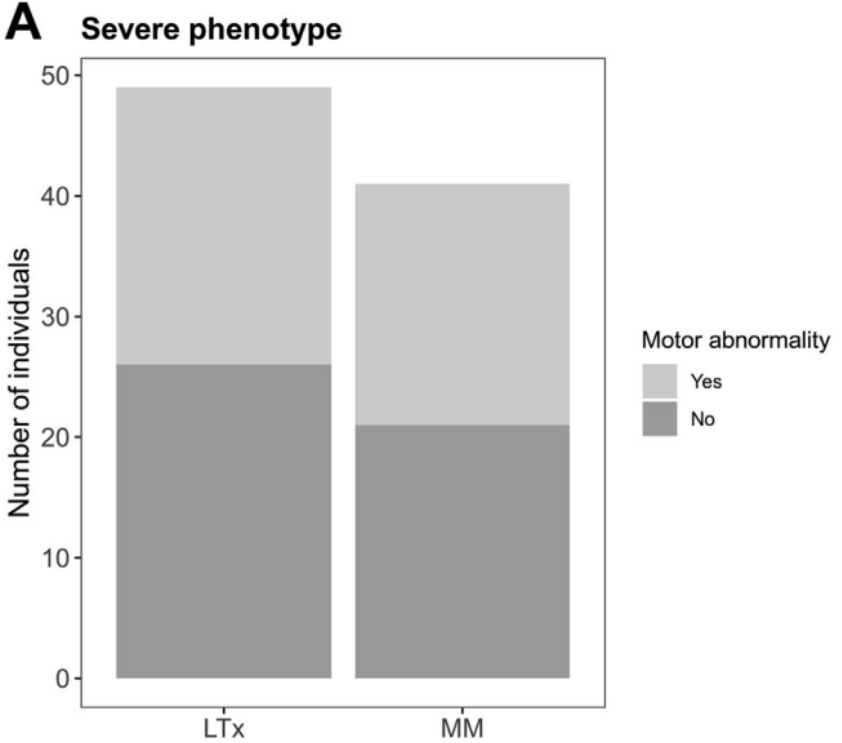
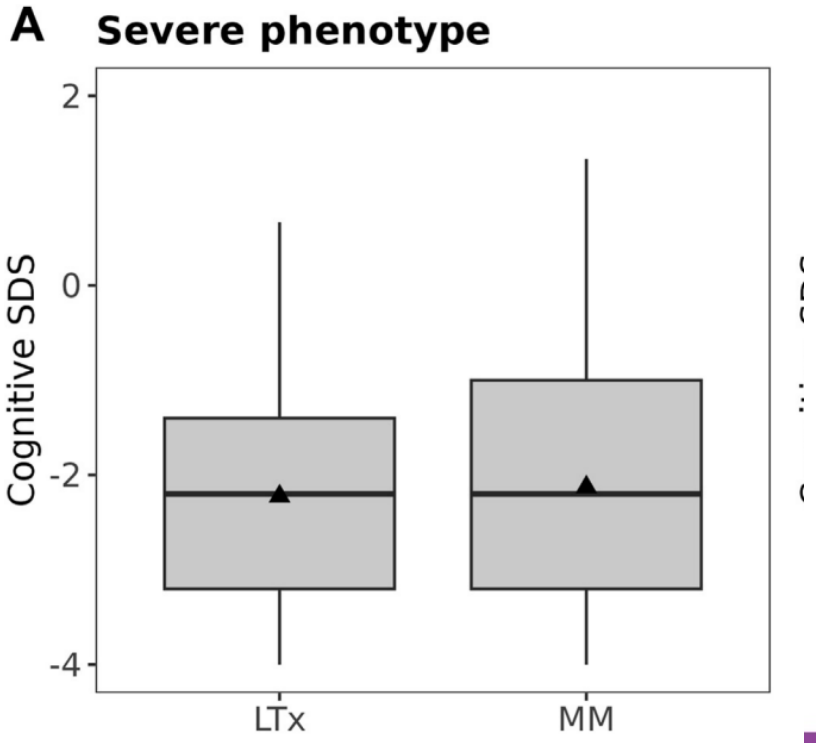
Motor and Cognitive Outcomes





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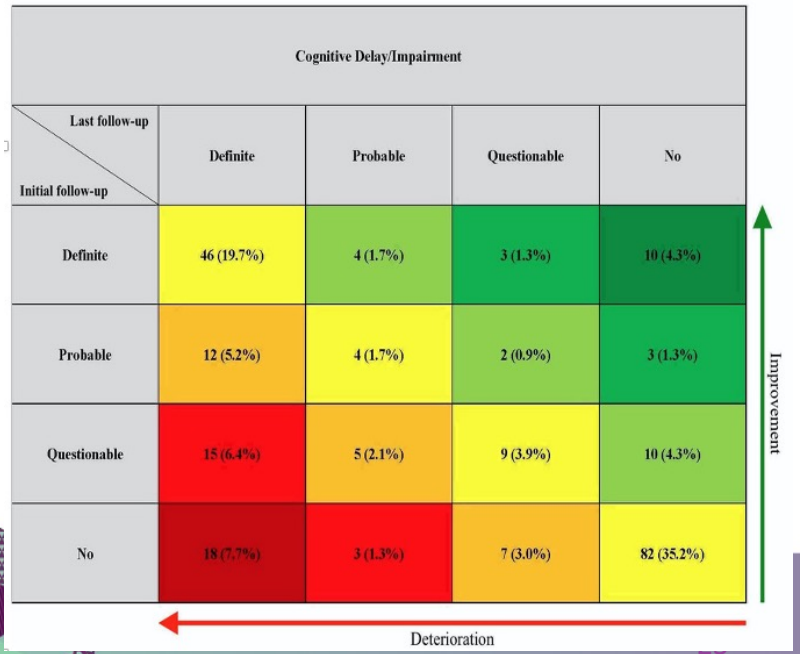
Ziogas et al Liver Transplantation, 31 May 2021, DOI: (10.1002/lt.26186)

Better to transplant early

Impact on cognitive delay



Cognitive Delay/Impairment				
Last follow-up / Initial follow-up	Definite	Probable	Questionable	No
Definite	46 (19.7%)	4 (1.7%)	3 (1.3%)	10 (4.3%)
Probable	12 (5.2%)	4 (1.7%)	2 (0.9%)	3 (1.3%)
Questionable	15 (6.4%)	5 (2.1%)	9 (3.9%)	10 (4.3%)
No	18 (7.7%)	3 (1.3%)	7 (3.0%)	82 (35.2%)

- 233 children with cognitive development data at initial and post transplant follow-up.
- Post LT cognitive status deteriorated over time in 60 (25.86%) and remained stable or improved in 74.2%
- In multivariable analysis, increasing waiting time and male sex associated with increased odds of having cognitive delay at last post tx follow-up
- Every month on waiting list increased odds of cognitive delay by 10%

Three additional perspectives to help

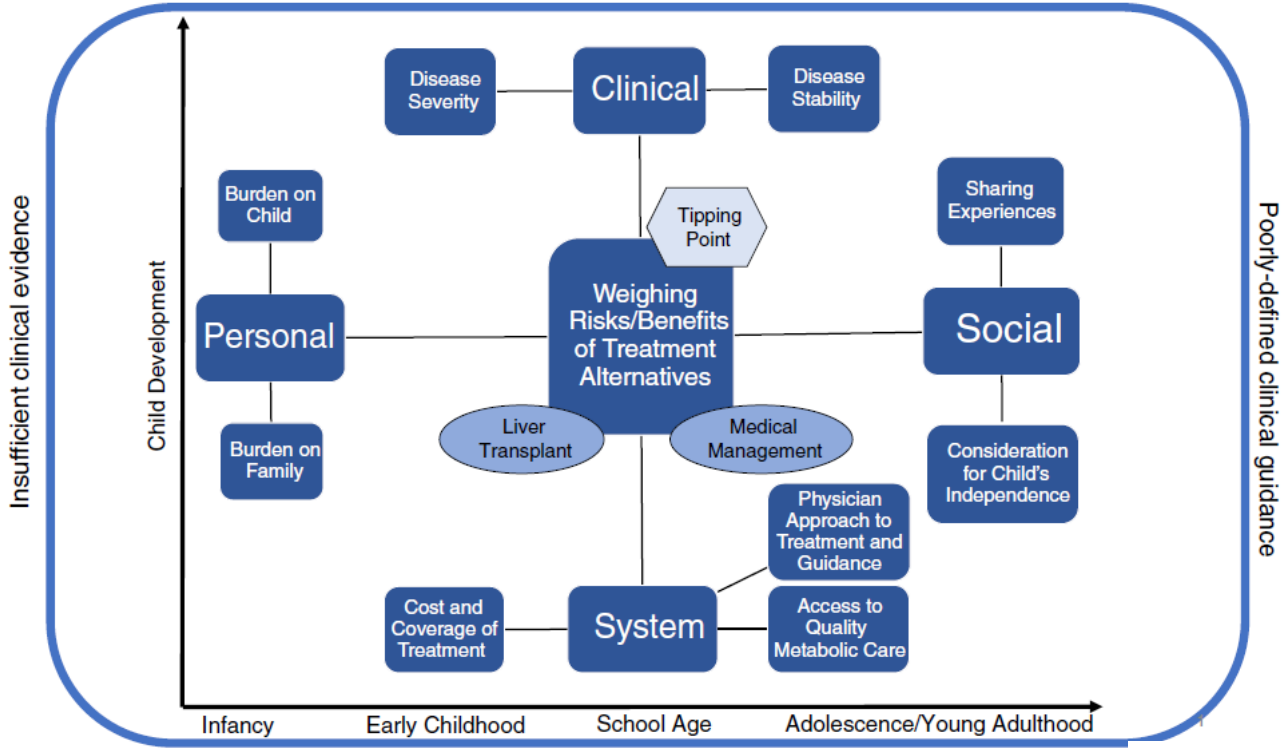
- Dynamic, life-cycle catalysts
- Outcome measures hierarchy
- Ideal outcome metrics

ORIGINAL ARTICLE

JIMD SSIEM WILEY

Choosing between medical management and liver transplant in urea cycle disorders: A conceptual framework for parental treatment decision-making in rare disease

Maya T. Gerstein[1] | Anne R. Markus[1] | Kan Z. Gianattasio[1] | Cynthia Le Mons[2] | Janice Bartos[2] | David M. Stevens[1] | Nicholas Ah Mew[3]

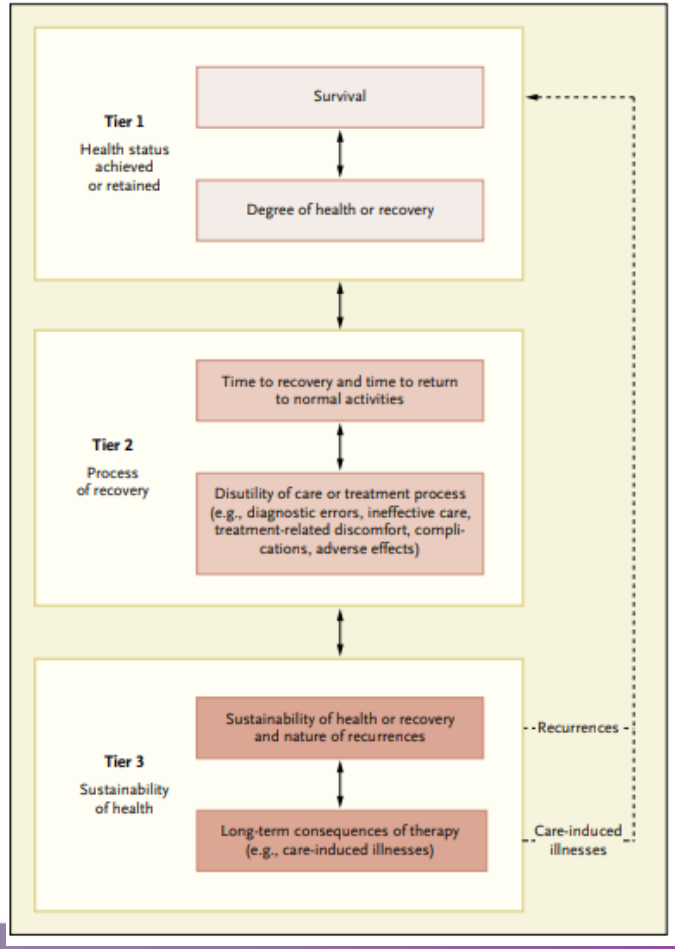


Cycle of care in children is much longer than for adults with resultant period of potential impact of care being measured in decades.

Outcome Measures Hierarchy

Porter, What is value in Health Care?

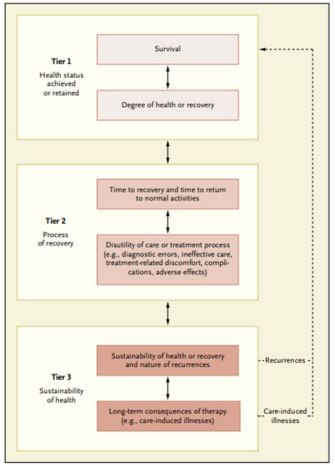
NEJM 12-23-2010, 2477-2481



Toward a more wholistic view: the “Ideal outcome” metric

Table IV. The ideal SPLIT 10-year survivor of pediatric LT

Medical variable: result reported at 10-year visit	Patient data available, n	Patients who answered “yes” to variable as phrased, n (%)	Patients missing data, n (%)
Sustainability of allograft			
1 No retransplantation	167	147 (88%)	0
2 No chronic rejection; confirmed diagnosis previously/presently	167	152 (91%)	0
3 Serum ALT normal	166	148 (89%)	1 (1%)
4 Serum TB normal	165	161 (98%)	2 (2%)
5 Serum albumin normal	162	160 (99%)	5 (3%)
6 Serum GGT normal	149	126 (85%)	18 (11%)
Absence of immunosuppression-induced comorbid conditions			
7 No PTLD; previous diagnosis of tissue-confirmed PTLD	167	158 (94%)	0
8 No renal dysfunction; cGFR <90 mL/min/1.73 m^2	118	107 (91%)	49 (29%)
9 Acceptable linear growth; >−2 SD for healthy population	121	112 (93%)	46 (27%)
10 No diabetes	167	165 (99%)	0
Absence of need for additional medications			
11 No ongoing use of prednisone	167	135 (81%)	0
12 No use of antihypertensive agent	167	146 (87%)	0
13 No use of antiseizure medication	167	167 (100%)	0



Vicky Ng et al : Health Status of Children Alive 10 years after Pediatric Liver Transplant J Pediatrics 2012: 160-820-6

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Objectives

- Decision making in pediatric metabolic disease with focus on urea cycle disorders
- Perspectives on how we can improve in the long term
  - Location, location, location
  - Learning networks and working on long term care, transition, immunosuppression
- Supplementation after transplant

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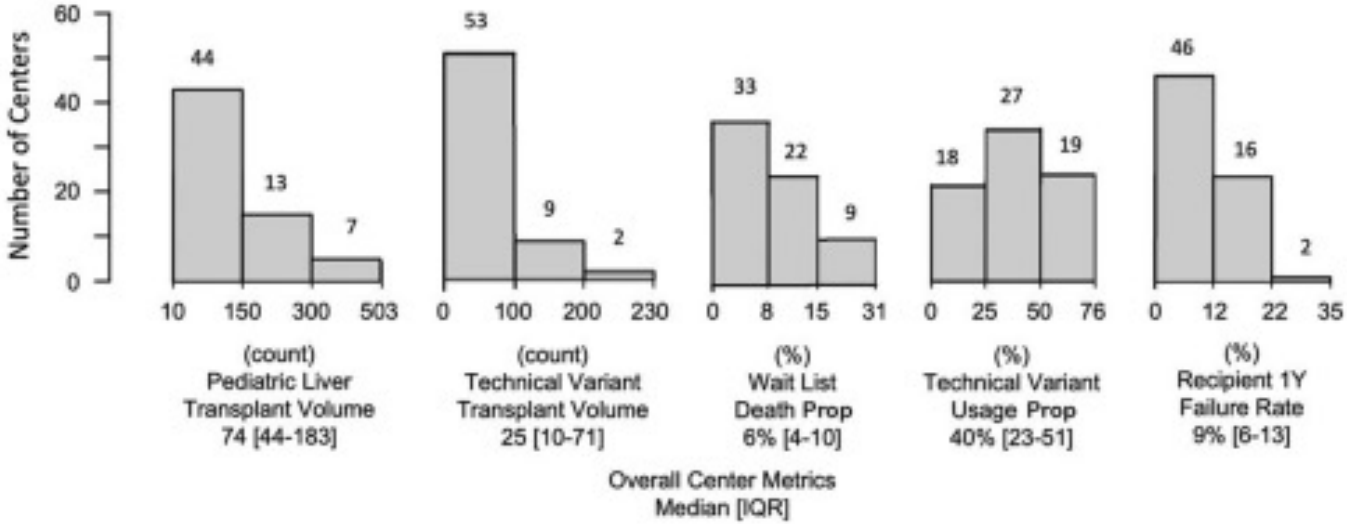
ORIGINAL ARTICLE

OPEN

Center use of technical variant grafts varies widely and impacts pediatric liver transplant waitlist and recipient outcomes in the United States

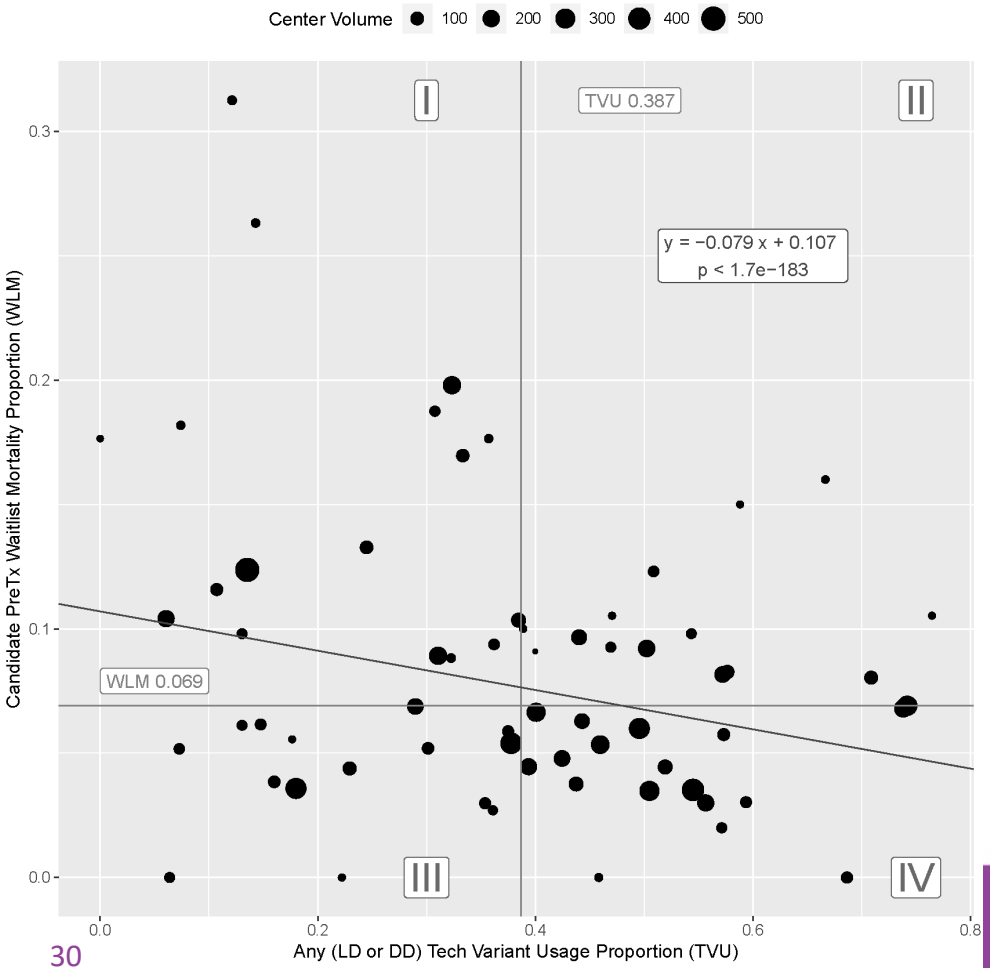
George V. Mazariegos[1] | Emily R. Perito[2] | James E. Squires[1] | Kyle A. Soltys[1] | Adam D. Griesemer[3] | Sarah A. Taylor[4] | Eric Pahl[5]



CHILDREN'S HOSPITAL OF PITTSBURGH

HOW DOES USE OF TECHNICAL VARIANT LIVERS AFFECT OUTCOMES?

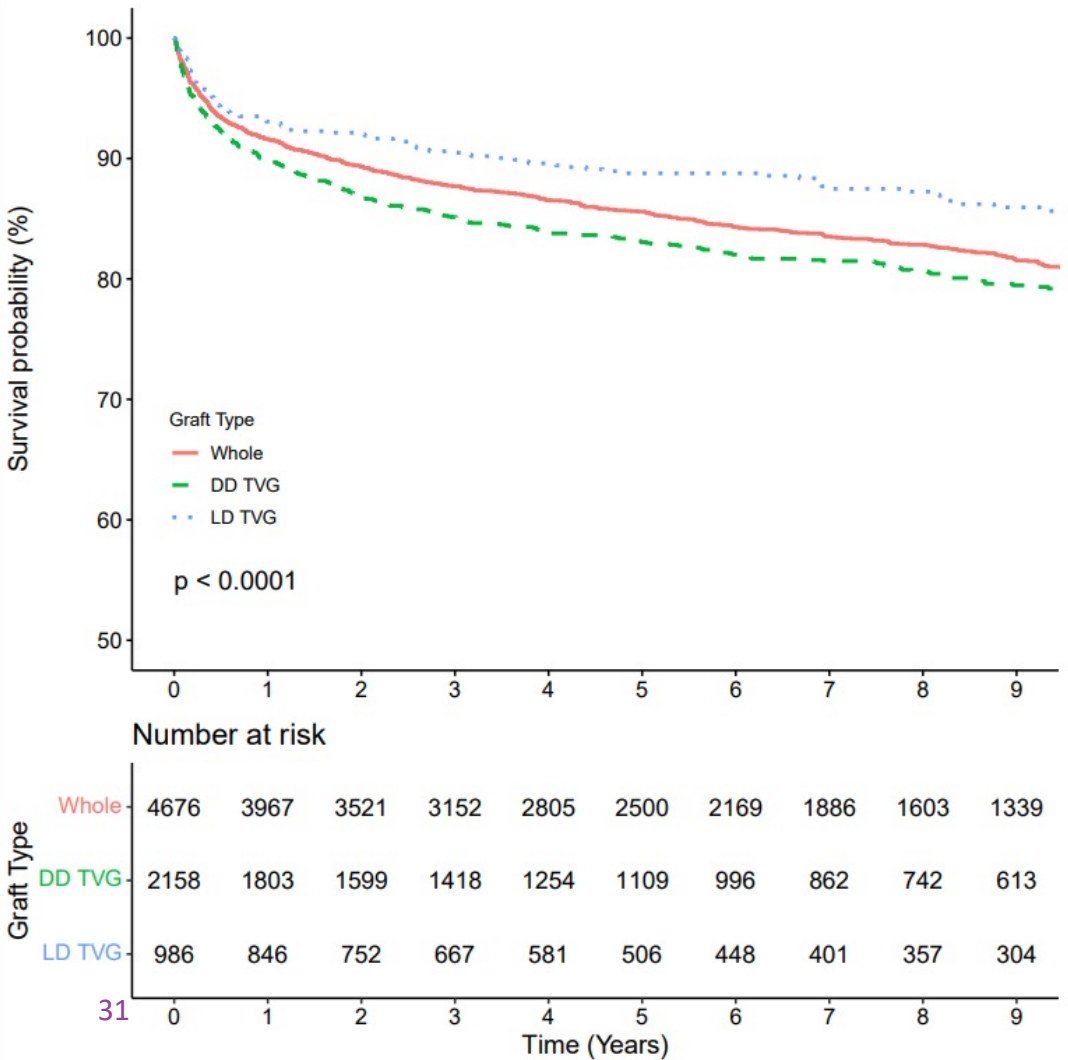
- WIDE VARIATION IN PRACTICE
- NOT DEPENDENT ON CENTER SIZE
- DID NOT SIGNIFICANTLY CHANGE OVER TIME
- TECHNICAL VARIANT DECEASED DONOR AND LIVING DONOR INDEPENDENTLY AND IN COMBINATION WERE ASSOCIATED WITH BETTER OUTCOMES



Liver Transplantation
Mazariegos et al, 2023

IMPACT OF LDLT

- **Recipients of Living Donor** transplants had significantly increased survival from transplant compared to other graft types (HR 0.611, CI (.40.92))
- **DD TV grafts** had equivalent outcomes to whole liver recipients (HR 1.066, CI (.93-1.22))



Objectives

- Decision making in pediatric metabolic disease with focus on urea cycle disorders
- Perspectives on how we can improve in the long term
  - Location, location, location
  - Learning networks and working on long term care, transition, immunosuppression
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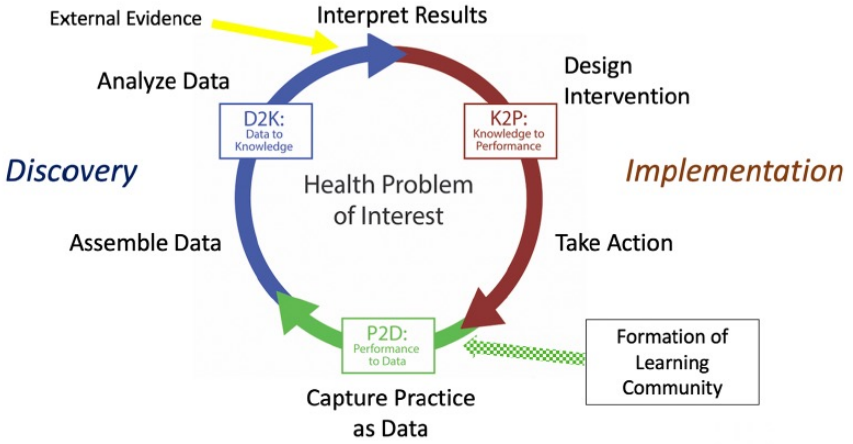
How do learning systems meet the current health care system needs?

Learning Health Systems: Learning Faster

Figure 1 Schematic of the health care system today. [From Best Care at Lower Cost: The Path to Continu America. Committee on the Learning Health Care System in America; Institute of Medicine; Smith M, S editors. Washington (DC): National Academies Press (US); 2013 May 10. With permission].



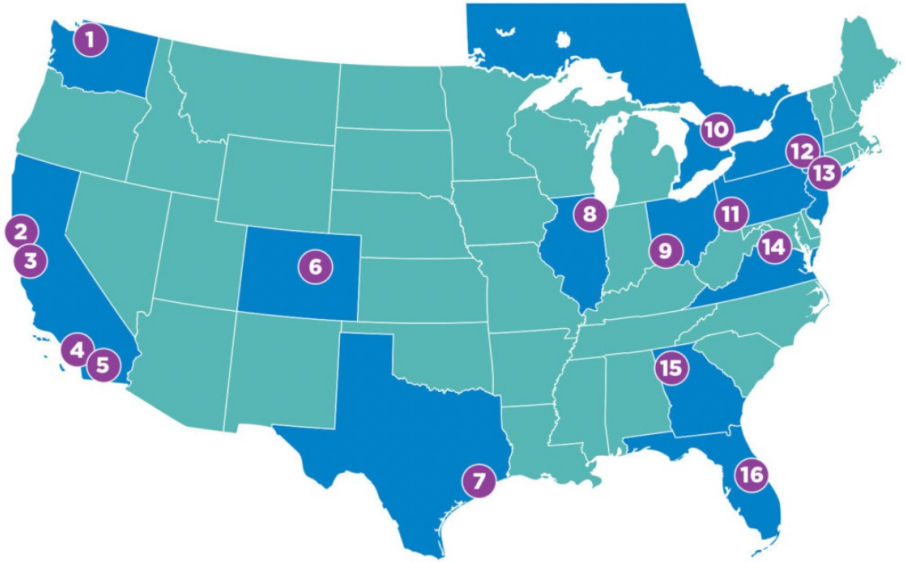
Learn Health Sys. 2022;6:e10328.
https://doi.org/10.1002/lrh2.10328

Peng, D, Rosenthal, D, Zafar F, et al. Collaboration and new data in ACTION: a learning health care system to improve pediatric heart failure and ventricular assist device outcomes. Translational Pediatrics, 2019 Oct; 8(4): 349–355.

Participating Centers

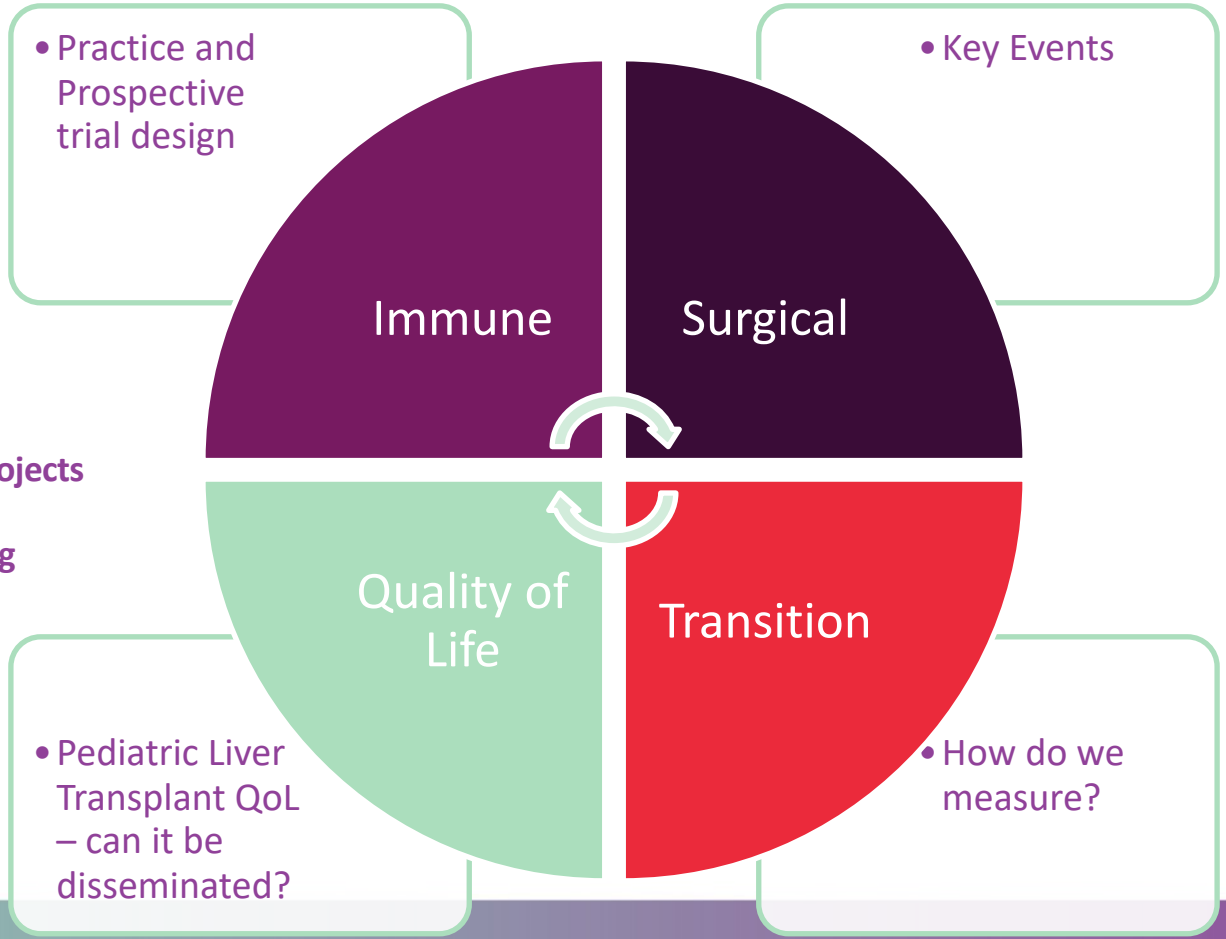
The Starzl Network for Excellence in Pediatric Transplantation aims to unite top children's liver transplant centers from around the world committed to:

- Improving outcomes and quality of life for each child who needs a transplant
- Creating and sharing best practices
- Solving the toughest problems in pediatric transplant



Network Members

1. Seattle Children's
2. UCSF Benioff Children's Hospitals
3. Stanford Children's Health | Lucile Packard Children's Hospital Stanford
4. UCLA Mattel Childrens Hospital
5. Children's Hospital Los Angeles
6. Children's Hospital Colorado
7. Texas Children's Hospital
8. Ann & Robert H. Lurie Children's Hospital of Chicago
9. Cincinnati Children's
10. SickKids
11. UPMC Children's Hospital of Pittsburgh
12. Columbia University Medical Center
13. Mount Sinai
14. University of Virginia
15. Children's Healthcare of Atlanta
16. AdventHealth



Prospective Priority Projects
Starzl Network
www.starzlnetwork.org

What do we need to truly optimize immunosuppression for pediatric liver transplant recipients?

- Strategies for "ensuring that the right care is provided to the right child at the right time, every time."
  - Evidence-based – or expert consensus
  - Feasible/achievable for the transplant center
  - Tailored to the child – pre-existing conditions, transplant, family priorities and preferences
  - Patient-centered – which outcomes are most important to patients and families? How do we balance protection of the graft and the child?

Forrest CB, Margolis P, Seid M, Colletti RB. PEDSnet: how a prototype pediatric learning health system is being expanded into a national network. Health Aff (Millwood). 2014 Jul;33(7):1171-7.

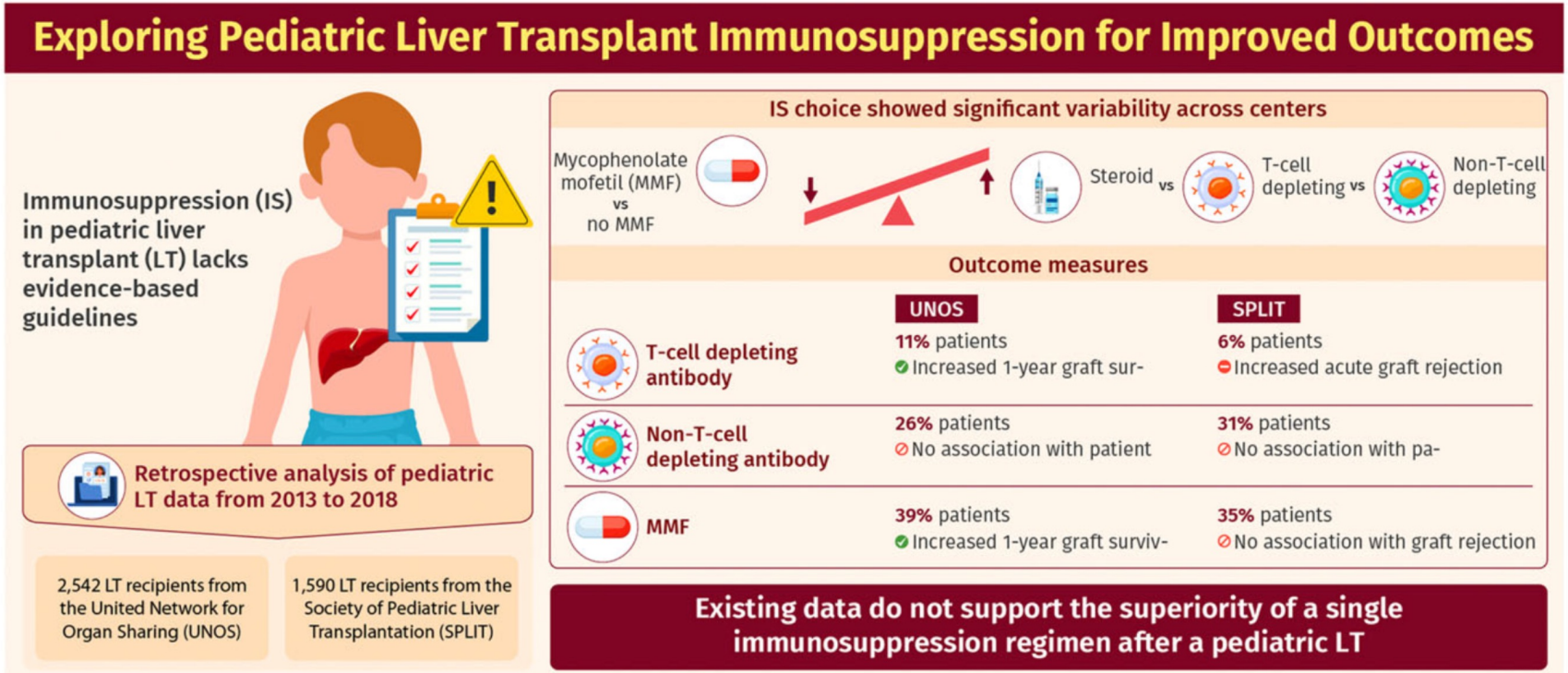
Received: 27 April 2023 | Accepted: 26 September 2023
DOI: 10.1002/jpn3.12112

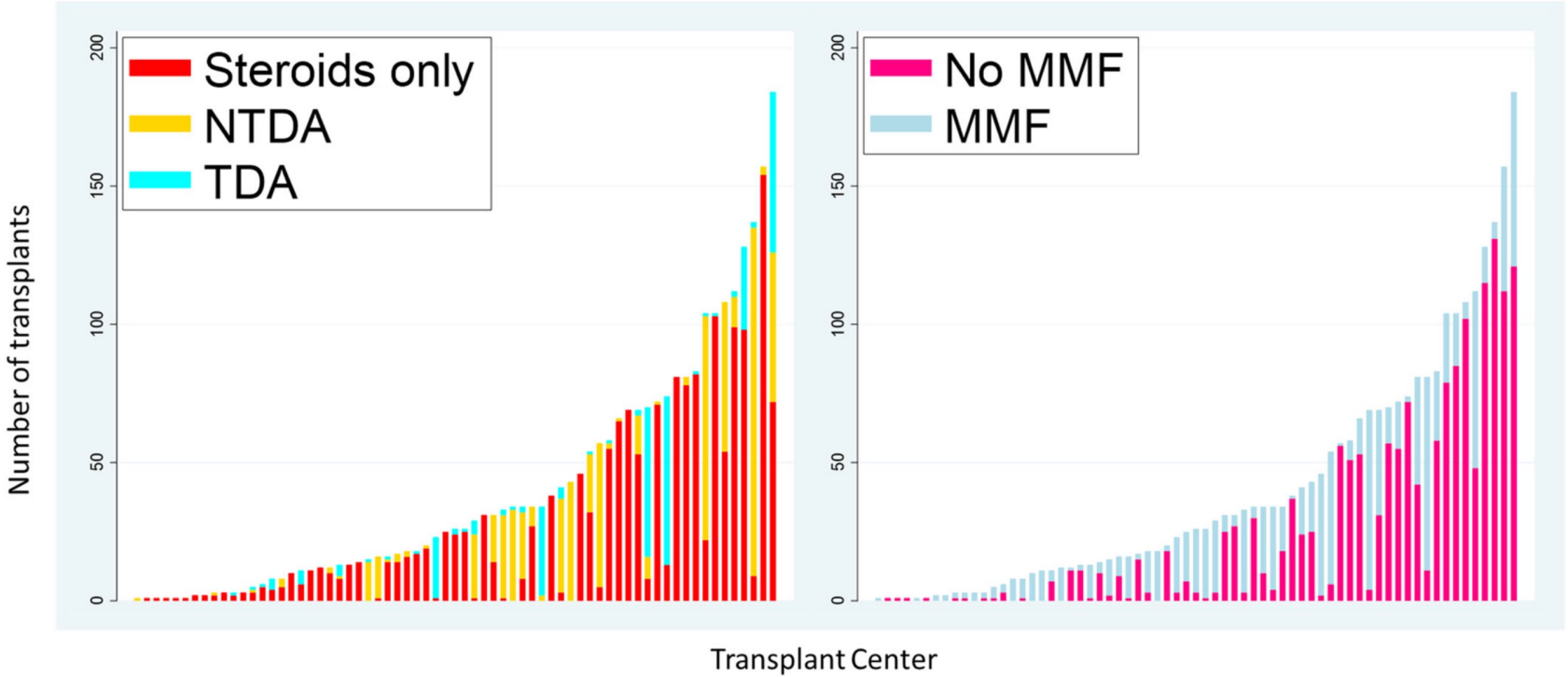
JPGN

ORIGINAL ARTICLE
Hepatology

Impact of early immunosuppression on pediatric liver transplant outcomes within 1 year

Vikram K. Raghu[1] | Xingyu Zhang[2] | James E. Squires[1] |





J Ped Gastro Nutr. 2024;1–11.

Consensus Protocol Development: reducing variability – so that we're all ordering off the same menu

Patient-centered outcomes research projects are usually comparative effectiveness studies.

- Comparative effectiveness studies compare the outcomes (benefits + harms) of 2 or more approaches to healthcare.
- These are often trials that compare 2 or more treatments that we already use in practice.
- PCOR focuses on trial outcomes that really matter to patients, family caregivers, clinicians, or other healthcare stakeholders.

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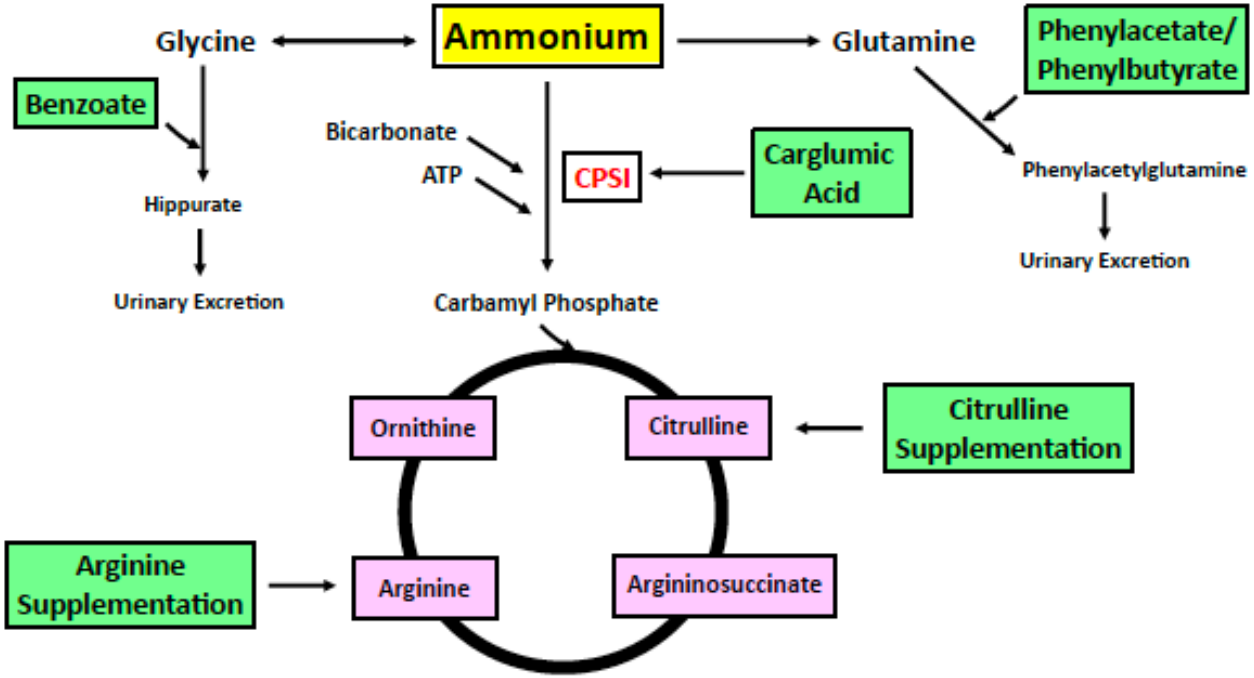
Do we need to keep giving citrulline and arginine?



Hearing from the Experts

Expert #1

- "You need Arginine or Citrulline for OTC, CPS1 and NAGS"
- You need Arginine for citrullilinemia and ASL
- Cirulline is better tolerated orally

Expert # 2

- In general, 100 mg/kg/day L-Citrulline divided BID is recommended post transplant for proximal disorders and arginine for distal disorders.

J Inherit Metab Dis. 2024;47:220–229.

Impact of citrulline substitution on clinical outcome after liver transplantation in carbamoyl phosphate synthetase 1 and ornithine transcarbamylase deficiency

Denise Aldrian[1] | Birgit Waldner[1] | Georg F. Vogel[1,2] | Areeg H. El-Gharbawy[3] | Patrick McKiernan[4] | Jerard Vockley[4] | Yuval E. Landau[5] | Fuad Al Mutairi[6,7] | Karolina M. Stepien[8] | Anne Mei-Kwun Kwok[9] | Yılmaz Yıldız[10] | Tomas Honzik[11] | Silvie Kelifova[11] | Carolyn Ellaway[12,13] | Allan M. Lund[14,15] | Mari Mori[16,17] | Sarah C. Grünert[18] | Sabine Scholl-Bürgi[1] | Thomas Zöggeler[1] | Rupert Oberhuber[19] | Stefan Schneeberger[19] | Thomas Müller[1] | Daniela Karall[1]

Molecular Genetics and Metabolism 141 (2024) 108112

Research Paper

Impact of supplementation with L-citrulline/arginine after liver transplantation in individuals with Urea Cycle Disorders

Roland Posset[a,*], Sven F. Garbade[a], Florian Gleich[a], Sandesh C.S. Nagamani[b], Andrea L. Gropman[c], Friederike Epp[a], Nesrine Ramdhouni[a], Ann-Catrin Druck[a], Georg F. Hoffmann[a], Stefan Kölker[a], Matthias Zielonka[a,*], on behalf of the Urea Cycle Disorders Consortium (UCDC) and the European registry and network for Intoxication type Metabolic Diseases (E-IMD) consortia study group

Synopsis

- Worldwide, transplantation for UCDs has increased and long term (>10yr) outcomes are >90% patient and transplant graft survival
- Optimal timing for neuro and motor development being studied but earlier transplant is favored
- Long term morbidities in both transplant and medical management need to be openly discussed
- Variability in surgical outcomes exist and should be reviewed with families and managing physicians

SOLVING PROBLEMS AND GIVING HOPE


WALK for
CHILDREN'S

Thomas E. Starzl, MD, PhD
1926-2017

UPMC | CHILDREN'S HOSPITAL OF PITTSBURGH

Thank you!!