



*George V. Mazariegos*

*UPMC Children's Hospital of Pittsburgh*

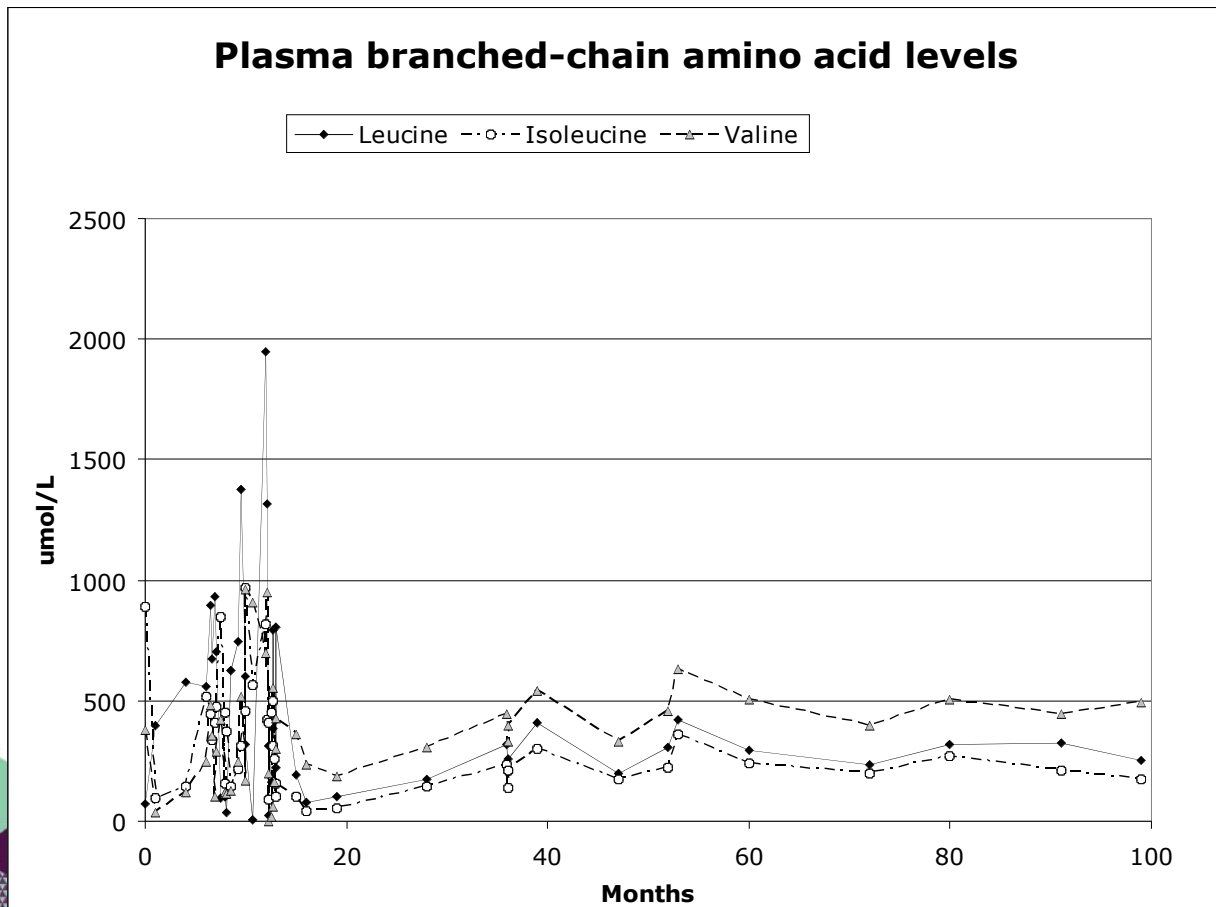
*June 28, 2024*

# LIVER TRANSPLANT FOR MSUD: LESSONS FROM THE FIRST 100+ CASES

# HOW DID WE GET HERE?



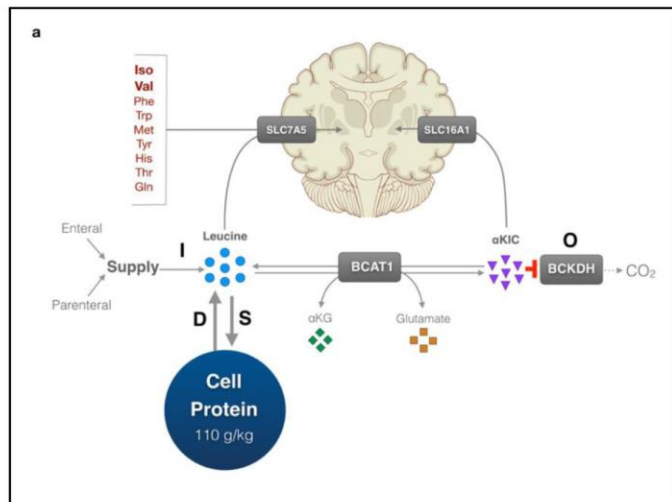
# MSUD: 1997 Learning from our patients



## Branched-chain $\alpha$ -ketoacid dehydrogenase deficiency (maple syrup urine disease): Treatment, biomarkers, and outcomes

Kevin A. Strauss <sup>a, b, c, d, e, f, g, h, i</sup>, Vincent J. Carson <sup>a, b</sup>, Kyle Soltys <sup>d</sup>, Millie E. Young <sup>a</sup>, Lauren E. Bowser <sup>a</sup>, Erik G. Puffenberger <sup>a</sup>, Karla W. Brigatti <sup>a</sup>, Katie B. Williams <sup>a</sup>, Donna L. Robinson <sup>a</sup>, Christine Hendrickson <sup>a</sup>, Keturah Beiler <sup>a</sup>, Cora M. Taylor <sup>a</sup>, Barbara Haas-Givler <sup>a</sup>, Stephanie Chopko <sup>f, g, h</sup>, Jennifer Hailey <sup>h</sup>, Emilie R. Muelly <sup>i</sup>, Diana A. Shellmer <sup>d</sup>, Zachary Radcliff <sup>f, g, h</sup>, ... D. Holmes Morton <sup>a, b, j</sup>

# Exceptional transplant outcomes were key to pushing the boundaries



Patient and Family  
Voice



Multidisciplinary teams



Multiple Safety points



1. Availability of MSUD TPN
2. Immediate turn around of amino acids
3. Collaboration with Metabolic team, CSC team, surgery teams



*American Journal of Transplantation* 2006; 6: 557–564  
Blackwell Munksgaard

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Journal compilation © 2006 The American Society of Transplantation and the American Society of Transplantation

doi: 10.1111/j.1600-6143

## Elective Liver Transplantation for the Treatment of Classical Maple Syrup Urine Disease

K. A. Strauss<sup>a</sup>, G. V. Mazariegos<sup>b,\*</sup>, R. Sindi<sup>b</sup>,

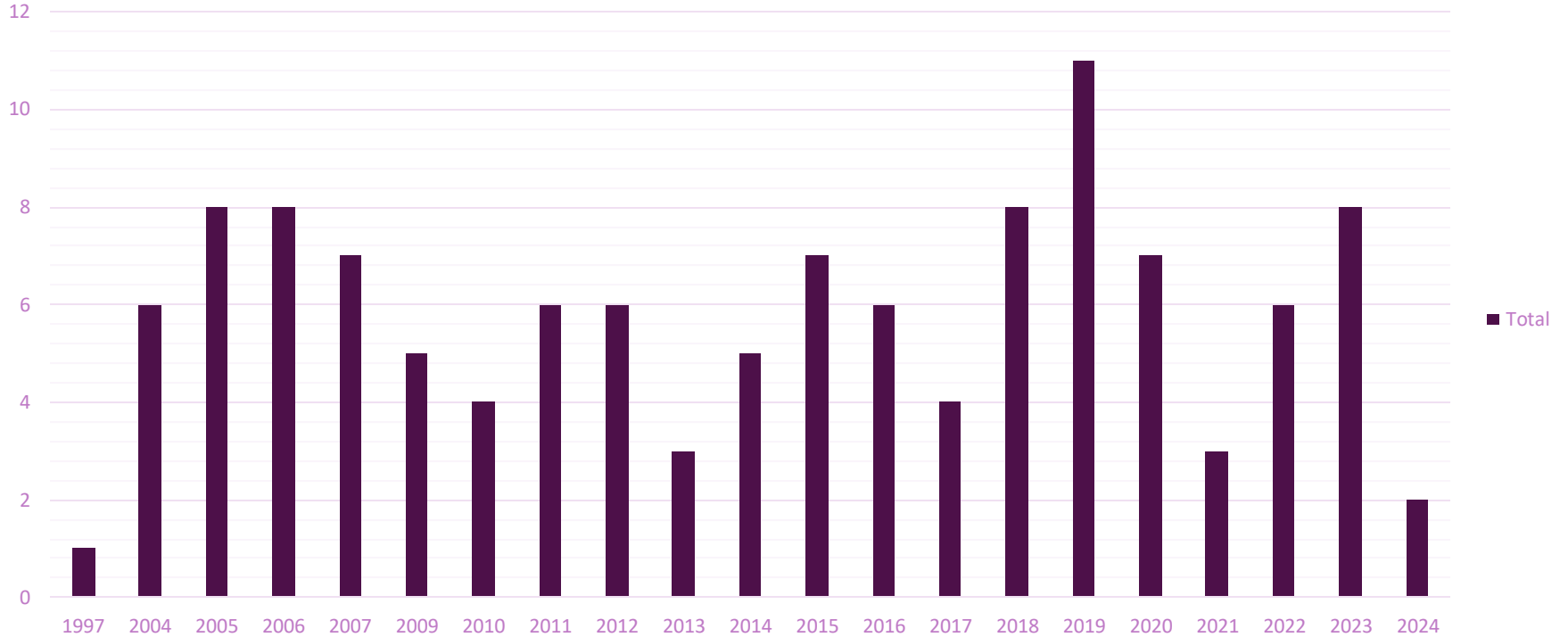
Introduction



# Objectives

- Current status and challenges in liver transplantation
- How to choose a transplant center
- Next steps/challenges
  - How to provide for a near normal lifetime of care?

# UPMC MSUD Experience (through 6/25/2024, n= 122)



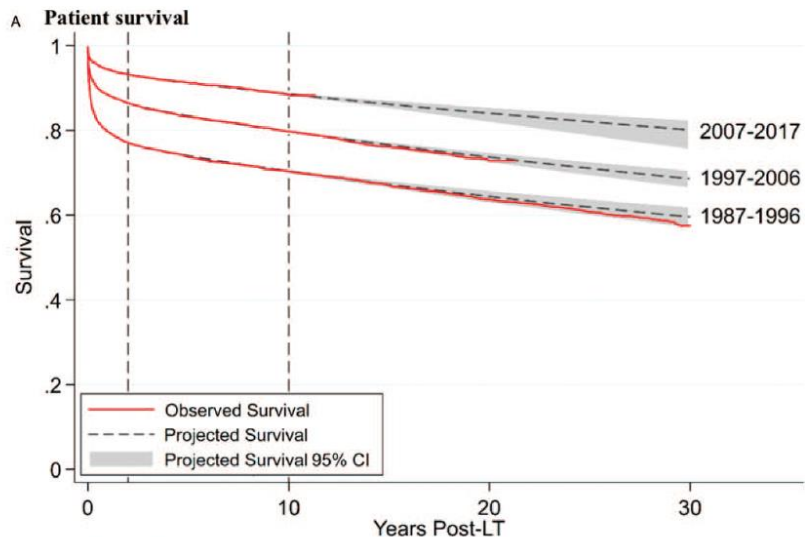
# What is the projected outcome for children transplanted today?

Bowring et al

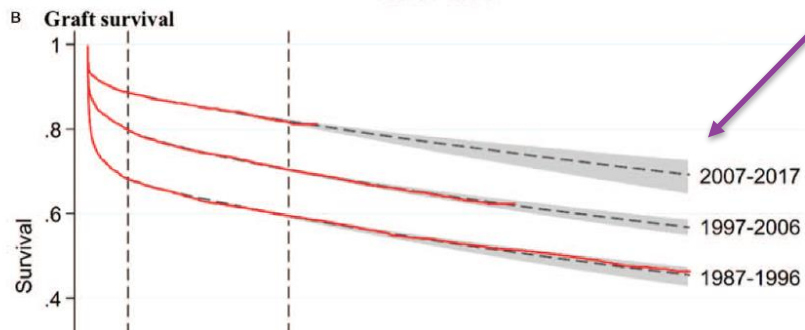
JPGN • Volume 70, Number 3, March 2020

## 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





# Overall outcomes

## Patient and graft survival

- Patient survival 98.4 %
- Graft survival 97.5 %
  - One ReTx
  - One relisted for transplant
- Current Followup (n=83)
  - Transferred to other center (n=28)
  - Lost to followup (n=6)

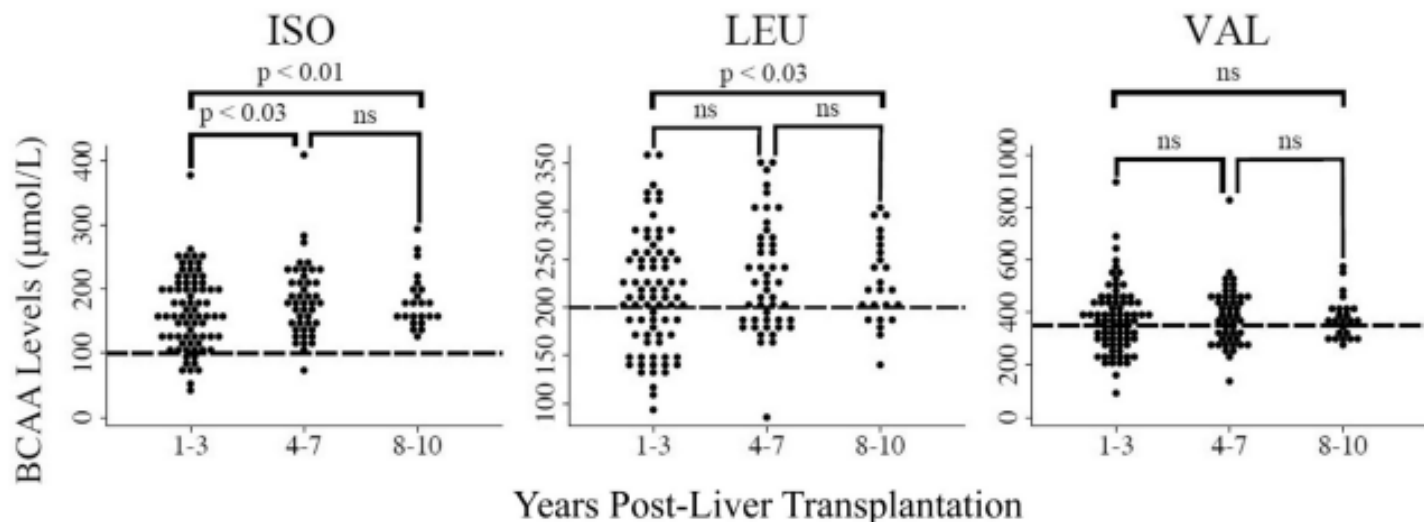
## Patient status

- Morbidity: 1 patient with biliary drainage catheter
- 100% unrestricted diet
- No metabolic crises



## Metabolic Control and “Ideal” Outcomes in Liver Transplantation for Maple Syrup Urine Disease

Caroline B. Ewing<sup>1</sup>, Kyle A. Soltys, MD<sup>2</sup>, Kevin A. Strauss, MD<sup>3</sup>, Rakesh Sindhi, MD<sup>2</sup>, Jerry Vockley, MD, PhD<sup>4</sup>, Patrick McKiernan, MD<sup>5</sup>, Robert H. Squires, MD<sup>5</sup>, Geoffrey Bond, MD<sup>2</sup>, Armando Ganoza, MD<sup>2</sup>, Ajai Khanna, MD, PhD, MBA,



**Figure 1.** Postliver transplant BCAA levels. BCAAs were recorded at 3 distinct time points at 1-3, 4-7, and 8-10 years. ULN for each BCAA is represented by the *dashed lines*. *P* values represent paired *t*-test of BCAA levels for each time point. ULN, upper limit of normal.

# Ideal outcome metrics, MSUD TX, J Peds 2021

**Table II. Results of health outcomes of 10-year survivors of pediatric liver transplantation**

Tests	n	Mean (SD)	Normal test value, No. (%)*
<b>Graft outcomes</b>			
TB, mg/dL	23	0.6 (0.3)	23 (100)
Albumin, g/L	23	4.3 (0.5)	22 (96)
ALT, IU/L	23	25.9 (9.7)	23 (100)
AST, IU/L	23	22.1 (6.0)	23 (100)
GGT, IU/L	23	32.8 (24.5)	14 (61)
<b>Renal function</b>			
Serum creatinine, mg/dL	23	0.7 (0.3)	22 (96)
BUN, mg/dL	23	12.3 (4.7)	23 (100)
GFR, mL/min/1.73 m <sup>2</sup>	23	102.1 (27.3)	22 (96)
<b>Cardiovascular risks</b>			
Cholesterol, mg/dL	21	140.4 (23.5)	21 (100)
Triglycerides, mg/dL	21	88.2 (44.5)	18 (86)
<b>Growth</b>			
Height/age, z score	23	-0.6 (1.2)	
>25th percentile			11 (48)
>10th percentile			15 (65)
>3rd percentile			22 (96)
BMI/age, z score	23	0.6 (0.9)	
>25th percentile			22 (96)
>10th percentile			23 (100)
>3rd percentile			23 (100)

**Table III. Ideal outcomes of 10-year survivors of liver transplantation**

Medical variables	No. (%)
<b>Health of allograft</b>	
1. No retransplantation	23 (100)
2. No chronic rejection	23 (100)
3. Serum ALT normal	23 (100)
4. Serum TB normal	23 (100)
5. Serum albumin normal	22 (96)
6. Serum GGT normal	14 (61)
<b>Absence of immunosuppression-induced conditions</b>	
7. No PTLD	23 (100)
8. No renal dysfunction; normal creatinine and BUN	22 (96)
9. Acceptable linear growth; height-for-age ≥5th percentile	20 (87)
10. No diabetes; no diabetes medications and normal glucose	23 (100)
<b>Absence of need for additional medications</b>	
11. On immunosuppression monotherapy	17 (74)
12. No use of antihypertensive agent	21 (91)
13. No use of antiseizure medication	20 (87)

PTLD, post-transplantation lymphoproliferative disease.

# Outcome metrics by time post Tx

Criteria	0-1 Yr post TX	1</=5 Yr	5</=10 Yr	>10 Yr
Followup (N)	6	26	19	29
Followup (YRS)	0.34	2.8	7.08	14.7
ALT	34.67(16-58)	23 (10-48)	23 (15-70)	25 (13-107)
GGT	25.33(10-77)	14 (8-55)	27 (10-113)	22 (4-176)
Tac Mono (n)	2	15	14	22
Tac Pred (n)	1	0	0	0
Tac Cellcept(n)	1	10	2	7
Tac/Cellcept/Pred (n)	2	1	3	0
GFR	89.42(80-100.5)	87.1 (50.84-648)	102.2 (75.7-361)	91.2 (59.7-154.5)
Leucine	235.5 (139-365)	207 (174-303)	248 (139-378)	264 (124-371)

## I want to consider liver transplant....

- What are the next steps in deciding on a transplant center?
- What type of transplant should my child get?
- What happens if I have to travel for my transplant?
- What's this option about 2<sup>nd</sup> listing?

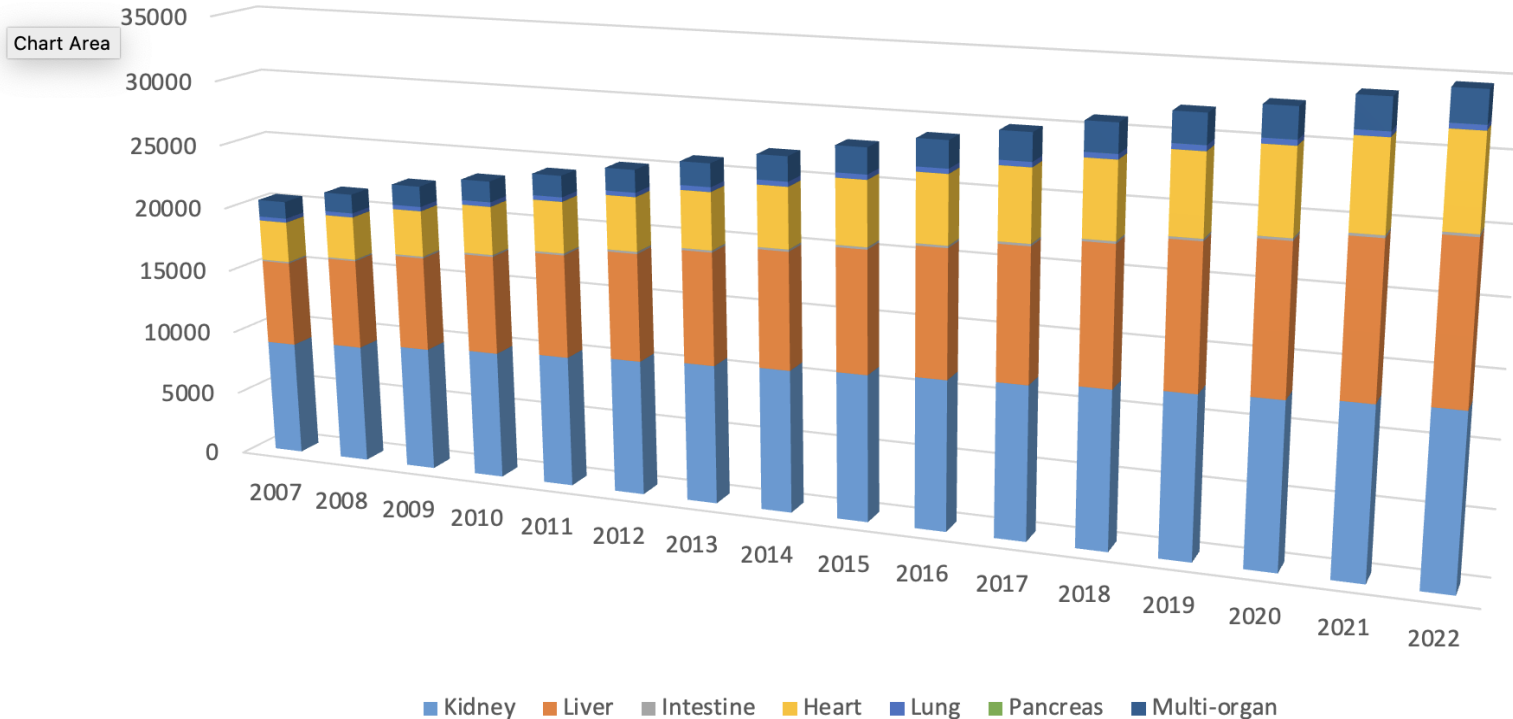


# You are NOT ALONE!



# If you pursue transplant, you become part of a growing community and family that will walk with you and your child....

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



## Resources to help you....

- MSUD Support group of course!
- Transplant Families
- Your physician team
- [www.starzlnetwork.org](http://www.starzlnetwork.org)
- [www.srtr.org](http://www.srtr.org)







# Organ Transplant Info for Patients, Families, & Donors



## Find & Compare Transplant Centers

Every day, transplants bring renewed life to patients and their families and communities. Learn more about the transplant centers near you by using the search bar below.

**Transplant Center Search**

Pediatric Recipient ▾

Liver ▾

Pittsburgh|

SEARCH

# SRTR.ORG



## The Organ Transplant Journey

Learn more about each step of the transplant journey. Choose any step to explore organ-specific information.

To see more about who plays a part in the journey,

[Explore the Interactive Transplant System](#)

Considering a Transplant ^

Find a Center ^

Getting Listed ^

Getting a Transplant ^

Recovery After Transplant ^



EXPLORE INTERACTIVE SYSTEM MAP



SRTR.ORG

- [Waiting List Overview](#)
- [Offer Acceptance Practices](#)
- [Transplant Procedures](#)
- [Posttransplant Outcomes](#)

### Posttransplant Outcomes

Transplants performed between 01/01/2018 - 03/12/2020, 06/13/2020 - 06/30/2020

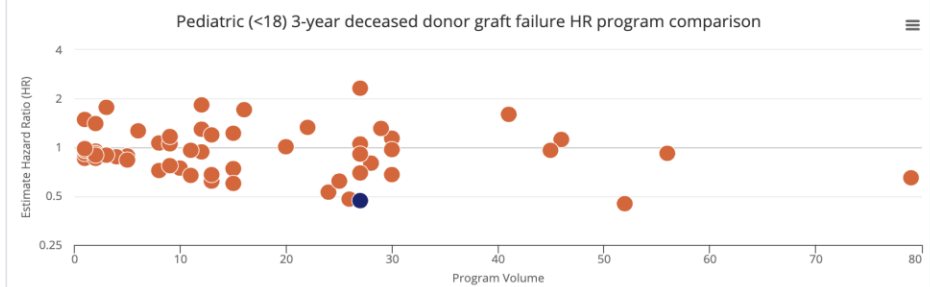
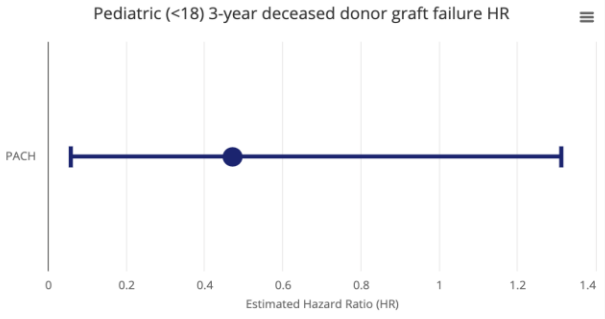
The Estimated Hazard Ratio shows whether the program has higher than expected (greater than 1.0) or lower than expected (less than 1.0) failure rates (graft failures or patient deaths).

Recipient: Pediatric (<18)

Time Frame: 3 Year

Donor Type: Deceased

Survival Results: Graft Survival Results



# <https://starzlnetwork.org/resource/family-resources-for-liver-diseases/>



## Resources

Info Sheet

### Family Resources for Liver Diseases

[VIEW NOW](#) →

Info Sheet

### Transplant-Specific Blood Tests

[VIEW NOW](#) →

Info Sheet

### Immunosuppression Medications & Levels

[VIEW NOW](#) →

Info Sheet

### Fundraising Resources

[VIEW NOW](#) →

## Family Resources for Liver Diseases

**Resource Category:** Emotional and Behavioral Support, Supported by American Legion Child Welfare Foundation Grant, Other Helpful Resources  
**Resource Type:** Info Sheet  
**Age of Child:** <5, 6-12, 13+  
**Years Since Transplant:** <2, 3-5, 5+

[Return to Resources >](#)

List of transplant and disease-specific resources for families

Families requested a list of disease-specific transplant resources that can help navigate the complexities of the disease and transplant processes and ensure that they are accessing the best possible support. The Starz Network is not affiliated with the organizations below and does not endorse any of the information provided therein. This information should not replace medical advice from your doctors or medical team.

#### Table of Contents:

1. Family Led Resources
2. Liver Disease-Specific Resources
3. Mental Health Resources
4. Other Helpful Resources
5. Professional Transplant Organizations

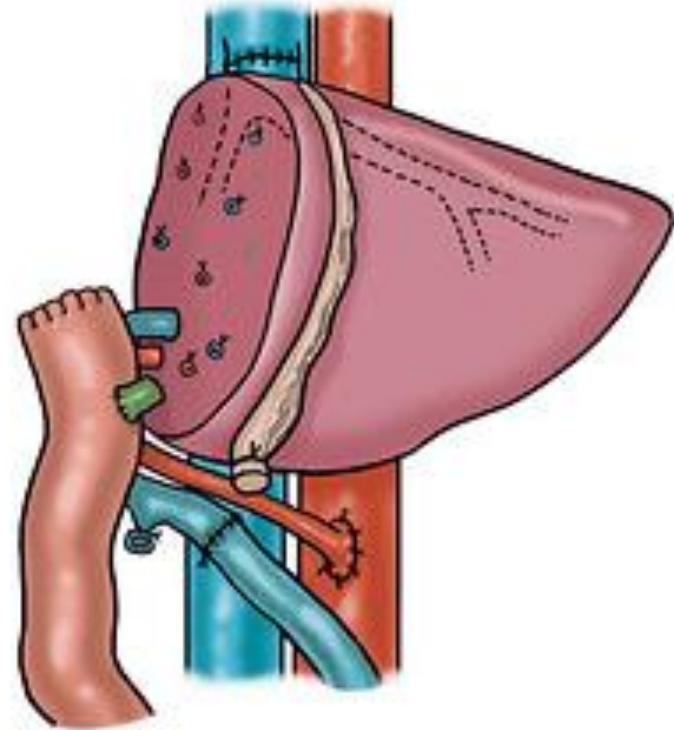
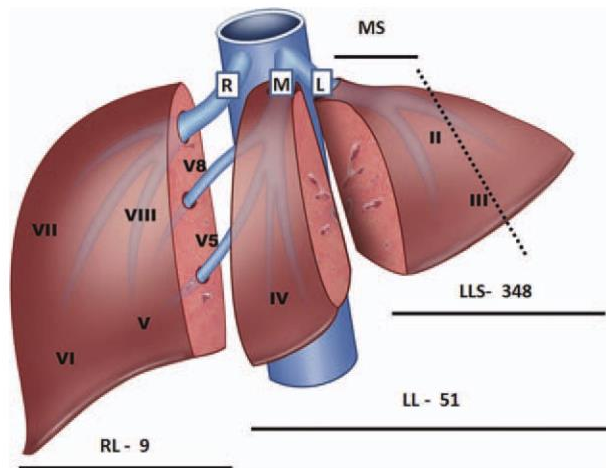
#### 1. Family Led Resources

##### Liver Mommas & Families

- We continue that support beyond the hospital, offering resources on our website for parents and families to help navigate some of the challenges presented by having a child with life-threatening liver disease and liver transplant. Our team members provide individual outreach to families through online support efforts and care packages.
- <https://www.livermommas.org>

# What type of transplant should my child get?

LIVER TRANSPLANTATION 18:577-584, 2012



# Children's 200th Living Donor Liver Transplant

HUMAN INTEREST

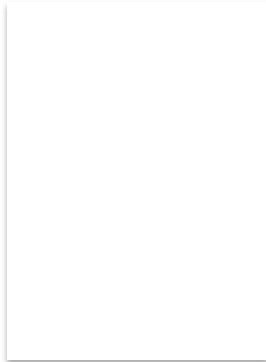
## Nurse Provides Life-Saving Transplant to 5-Year-Old Girl: Her Daughter: 'I Did What Any Mother Would Do'

"I'm so thankful," Haley Bice tells PEOPLE, adding that it means the world that her daughter "doesn't have the pain that she's been living with for years"

By [Wendy Grossman Kantor](#) Published on March 25, 2024 04:00PM EDT



From Left, Adleigh and Haley Bice. PHOTO: COURTESY OF THE BICE FAMILY



(L-R) Dr. George Mazariegos, Haley Bice, Adleigh Bice, Kendall Bice. PHOTO: COURTESY OF THE BICE FAMILY

# Traveling out of state and second listing

**OPTN** *Organ Procurement & Transplantation Network* U.S. Department of Health & Human Services **HRSA** Health Resources & Services Administration

About ▾ Policies & bylaws ▾ Patients ▾ Professionals ▾ Data & calculators ▾ News & events ▾

[Home](#) » [Patients](#) » [About transplantation](#) » Multiple listing

On this page: ^

How am I listed for a transplant?

Deceased organ donation

What is multiple listing?

Could multiple listing shorten my waiting time?

Restrictions

What is involved?

Waiting time

Transferring care

Additional resources

## Multiple listing

[Acceso en Español](#)

Print page

Frequently asked questions about multiple listing and waiting time transfer - OPTN (hrsa.gov)

Welcome to our question and answer page for multiple listing and waiting time transfer.

Below is commonly requested information to assist you. If you have other questions or comments, contact the Organ Procurement and Transplantation Network (OPTN) Patient Services line at [\(888\) 894-6361](tel:888-894-6361) or [submit them here](#).

### How am I listed for a transplant?

## Starting the conversation

- I understand second listing is an option....can you tell me about that?
- If I decide to do that, where would you recommend I go and who can help me in starting this process?





# What I hope you have heard

- Transplant- at an expert center- allows
  - Unrestricted diet
  - Lifelong metabolic control
  - Retransplant is very rare
  - Other “ideal outcome” metrics are good



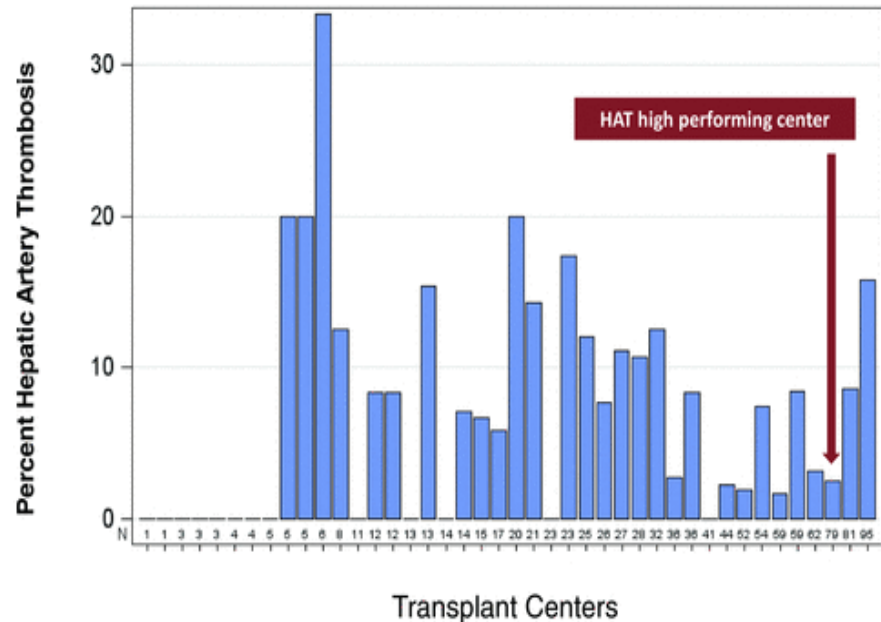
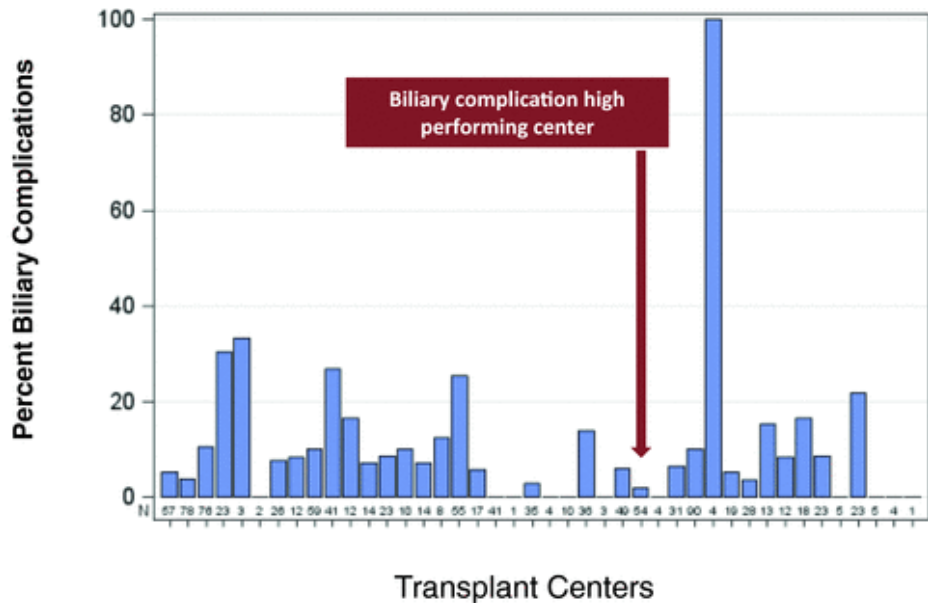
## 5 additional things you must know

- Advocacy for your loved one is always crucial
- Not all transplant centers are created equal
- Transplant is a commitment for life
- Life-long immunosuppression is the norm
- Lifelong liver graft and health surveillance is critical



# Knowledge gap and variation in critical outcomes

Reducing Pediatric Liver Transplant Complications: A Potential Roadmap for Transplant Quality Improvement Initiatives Within North America



Biliary complication ( LEFT) and Hepatic Artery Complication ( RIGHT) rates across North American pediatric liver transplant centers.

American Journal of Transplantation, Volume: 12, Issue: 9, Pages: 2301-2306, First published: 06 August 2012, DOI: (10.1111/j.1600-6143.2012.04204.x)

# Leaders of the largest pediatric liver transplant network in the U.S.

**UPMC** | **CHILDREN'S HOSPITAL OF PITTSBURGH**

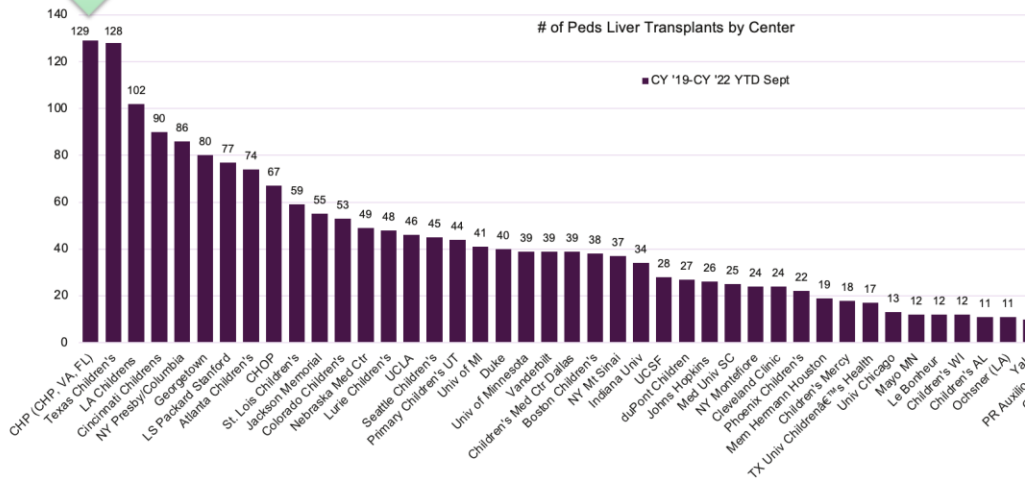
**UPMC Children's Pittsburgh**

**UVA Children's Charlottesville**

**AdventHealth for Children Orlando**

## National Pediatric Liver Transplant Volumes

The following table displays all pediatric liver transplants by center in the last 3 years & 9 months. CHP's transplant network led the country in pediatric liver transplants.

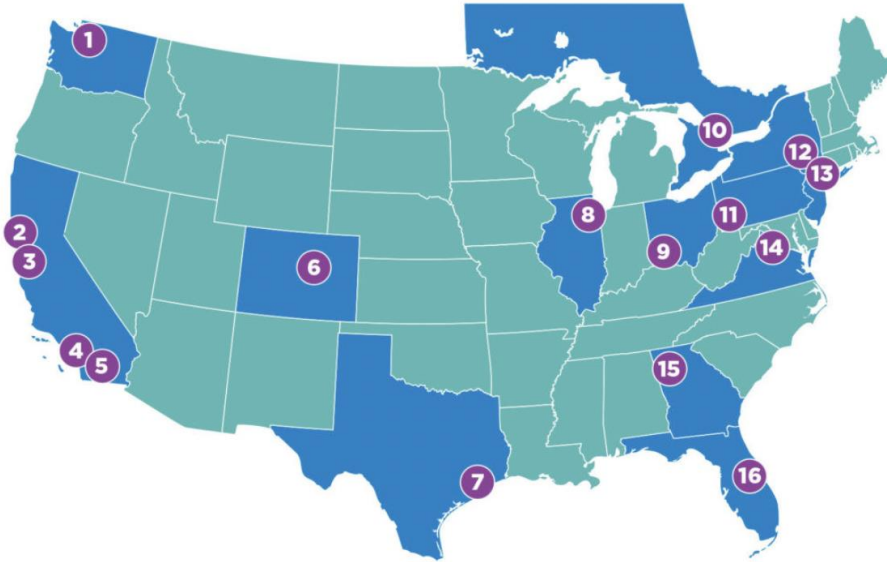


Source: UNOS

# 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

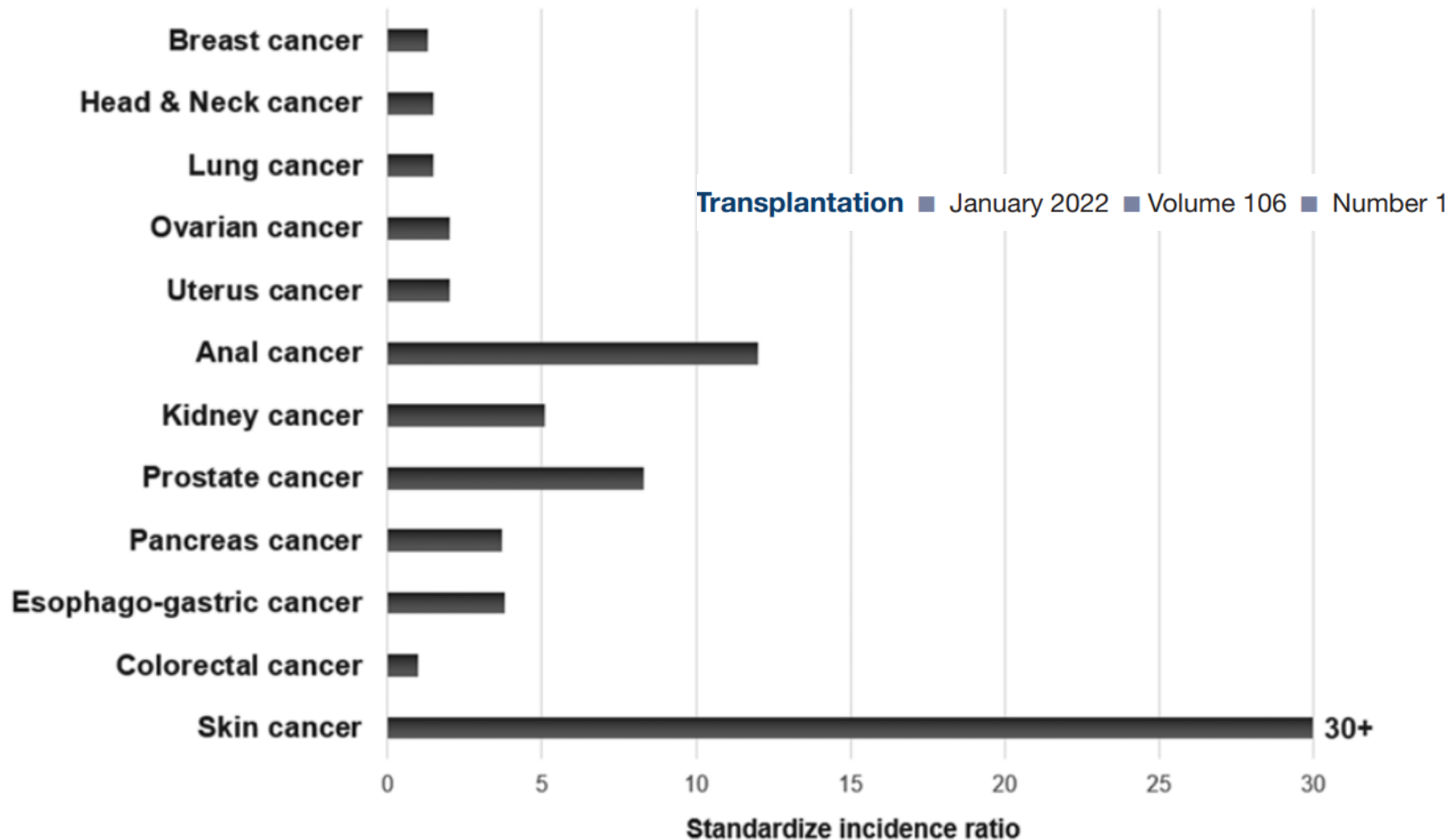


## STARZL NETWORK

for Excellence in Pediatric Transplantation

### Network Members

- |   |  |    |   |
|---|--|----|---|
| 1 | Seattle Children's<br>HOSPITAL • RESEARCH • FOUNDATION                       | 9  | Cincinnati<br>Children's                    |
| 2 | UCSF Benioff Children's<br>Hospitals   | 10 | SickKids                                    |
| 3 | Stanford Children's Health<br>Lucile Packard Children's Hospital<br>Stanford | 11 | UPMC   CHILDREN'S<br>HOSPITAL OF PITTSBURGH |
| 4 | UCLA Children's Hospital   | 12 | COLUMBIA UNIVERSITY<br>MEDICAL CENTER       |
| 5 | Children's Hospital<br>LOS ANGELES   | 13 | Mount<br>Sinai                              |
| 6 | Children's Hospital Colorado   | 14 | UNIVERSITY<br>VIRGINIA                      |
| 7 | Texas Children's<br>Hospital   | 15 | Children's<br>HOSPITAL OF ATLANTA           |
| 8 | Ann & Robert H. Lurie<br>Children's Hospital of Chicago                      | 16 | AdventHealth                                |



The overall incidence of de novo malignancies compiled from reported single-center and registry data.

**TABLE 2.****Screening recommendations specific to LT recipients**

<b>Cancer</b>	<b>Population at risk</b>	<b>Strategy</b>	<b>Frequency</b>	<b>Strength of recommendation and level of evidence<sup>a</sup></b>
Skin	All	Full-body skin exam	Annual	Strong/moderate
Colon	IBD	Colonoscopy	Annual	Strong/high
	PSC		Every 3–5 y	Strong/moderate
	NASH with HCC (>50 y)		At 5 y	Weak/low
	All others		Per Gen pop	Strong/high
Lung	Ex/smokers	Low-dose CT chest	Annual, per Gen pop	Strong/high
Oropharyngeal/head and neck	Ex/smokers, known oropharyngeal HPV	ENT exam	Annual	Strong/low
Cervical/vulvar/vaginal	Female	Pelvic exam, PAP with HPV testing	Annual; Annual × 3, HPV <sup>+</sup> continue annual; HPV- follow Gen pop	Strong/high; strong/high
Breast	Female	Mammography	Annual, per Gen pop	Strong/high
Prostate	Male	PSA	Per Gen pop	Strong/high
Renal	Previous RCC, PCKD, Von Hippel-Lindau disease	CT abdomen	Annual, per Gen pop	Strong/moderate

# Other life-long considerations

- Hypertension
- Renal insufficiency
- Dyslipidemias/ hypercholesterolemia
- Diabetes/ insulin insensitivity
- Fertility and prenatal care
- Management of pre-existing conditions
  - Mental health
  - Seizure disorders



# CLOSING PRINCIPLES



# The Puzzle People

- “...perhaps I could shed light on how advances occur in medicine, what goes on in the middle of the night in laboratories and hospital corridors, what the interactions are between the physicians, scientists, and patients; and ***how the patients themselves inevitably emerge as the heroes***” – Thomas Starzl



- Principle #1: The outcomes that really matter are measured in decades



Dr. Starzl would ask me- what are your 30 year outcomes?



*Todd McNeely, of Darien, Connecticut, now four years old, the first liver-transplant patient at Children's Hospital on May 11, 1981.*



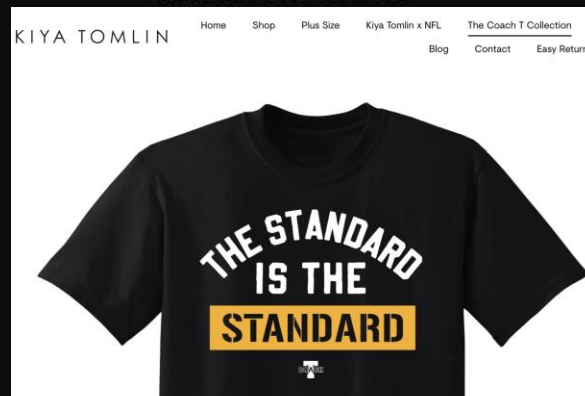
- Principle # 2: The Standard is the Standard





The Standard... is the standard.

— *Mike Tomlin* —



**CHILDREN'S**  
HOSPITAL OF PITTSBURGH



- Principle # 3: Children can't wait





- Principle #4 : Focus on outcomes that really matter to patients (help solve their problems)





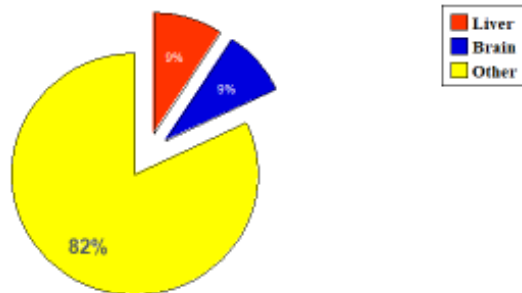
## Two for One

MSUD treats PKU (and MMA, and A1AT, etc.)



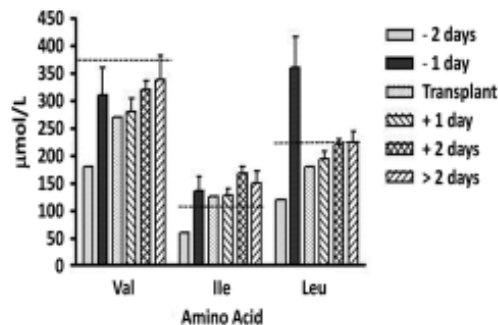
# MSUD: Domino Transplant

Relative Contribution of Various Organs to Whole Body Leucine Degradation

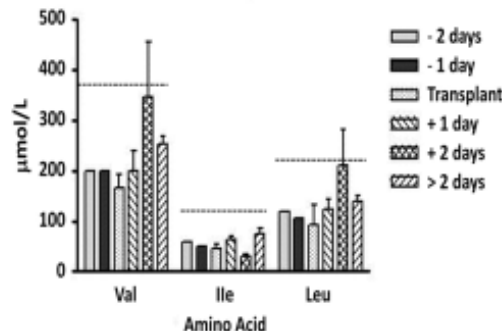


- 26 domino transplants
- Recipients 6 months – 64.59 (Y)
- HCV, PSC, PFIC, CF, CHF, PBC, Tumor, A1AT, PA, MMA, CPS, CN, PKU
- F/U 4.3 yrs median F/U

MSUD Patients



Domino Recipients



Received: 7 April 2021 | Revised: 23 June 2021 | Accepted: 27 July 2021  
DOI: 10.1111/ptr.14114

COMPREHENSIVE REVIEW

WILEY

## Domino transplantation for pediatric liver recipients: Obstacles, challenges, and successes

Vikram K. Raghu<sup>1</sup> | Peter D. Carr-Boyd<sup>2</sup> | James E. Squires<sup>1</sup> | Jerry Vockley<sup>3</sup> | Nicolas Goldaracena<sup>4</sup> | George V. Mazarigos<sup>2</sup>

UPMC | CHILDREN'S  
HOSPITAL OF PITTSBURGH



**Thank you!!**

