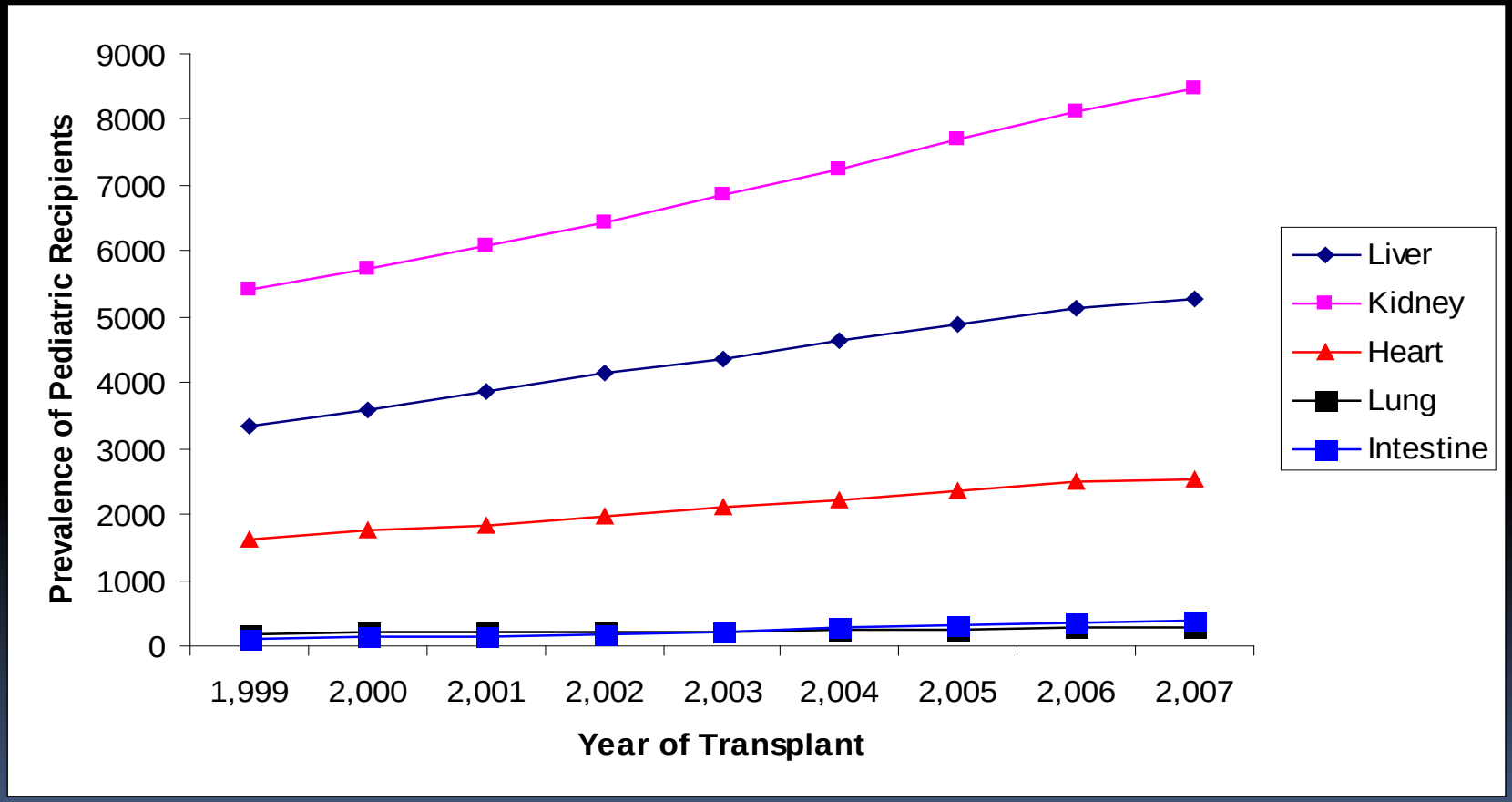
LONG TERM OUTCOMES IN PEDIATRIC LIVER TRANSPLANT

GEORGE V. MAZARIEGOS
Children's Hospital of Pittsburgh of UPMC

April 27, 2013

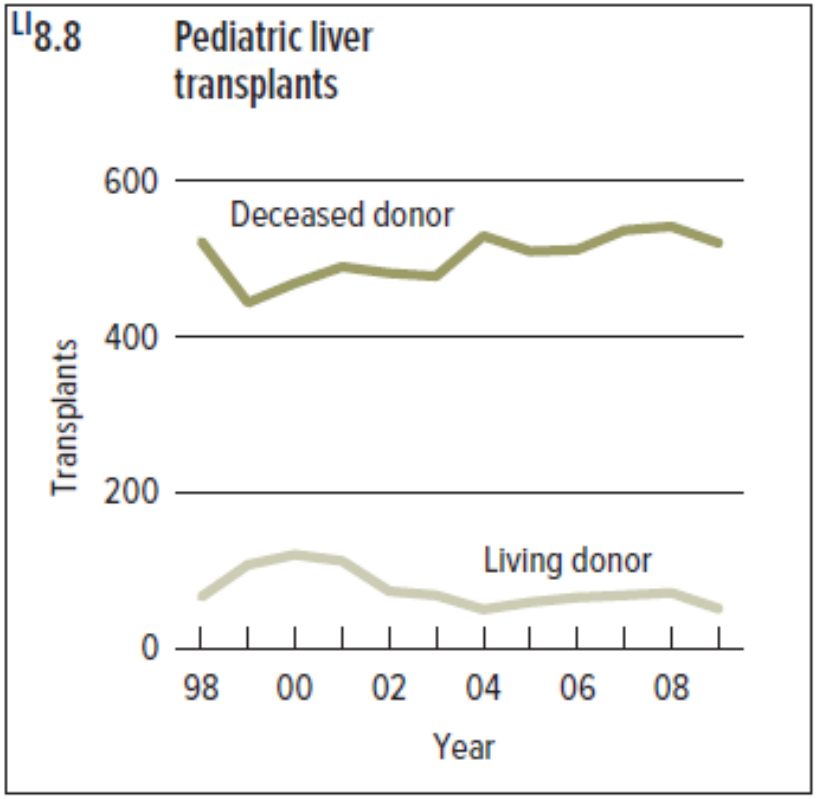
PSC PARTNERS SEEKING A CURE

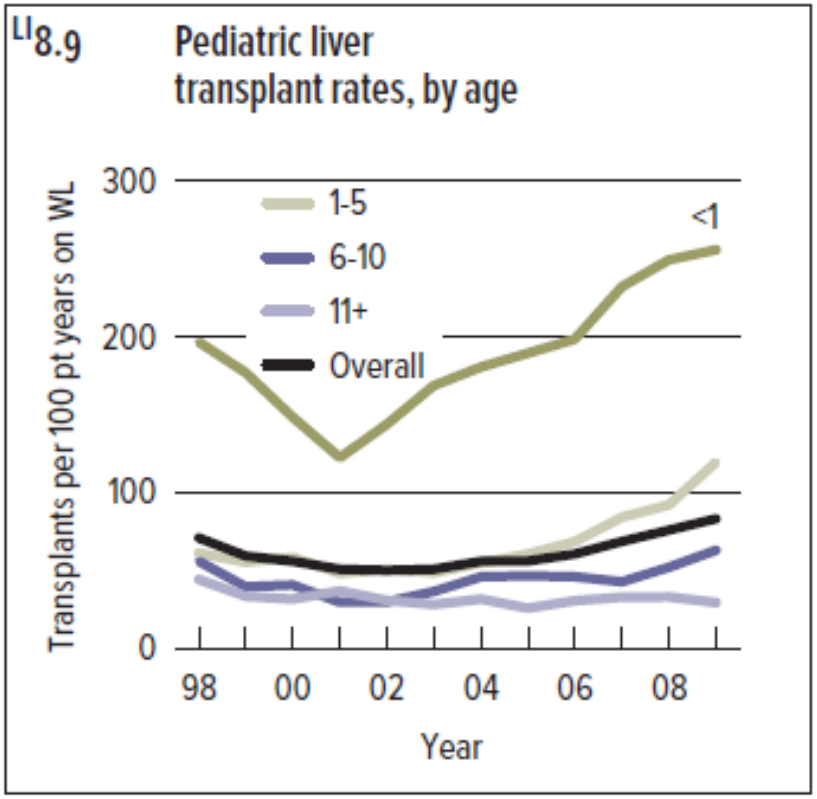
Normal life post transplant: How close are we? Children with functioning allografts (1999-2007)



OPTN/SRTR Data as of May 4, 2009

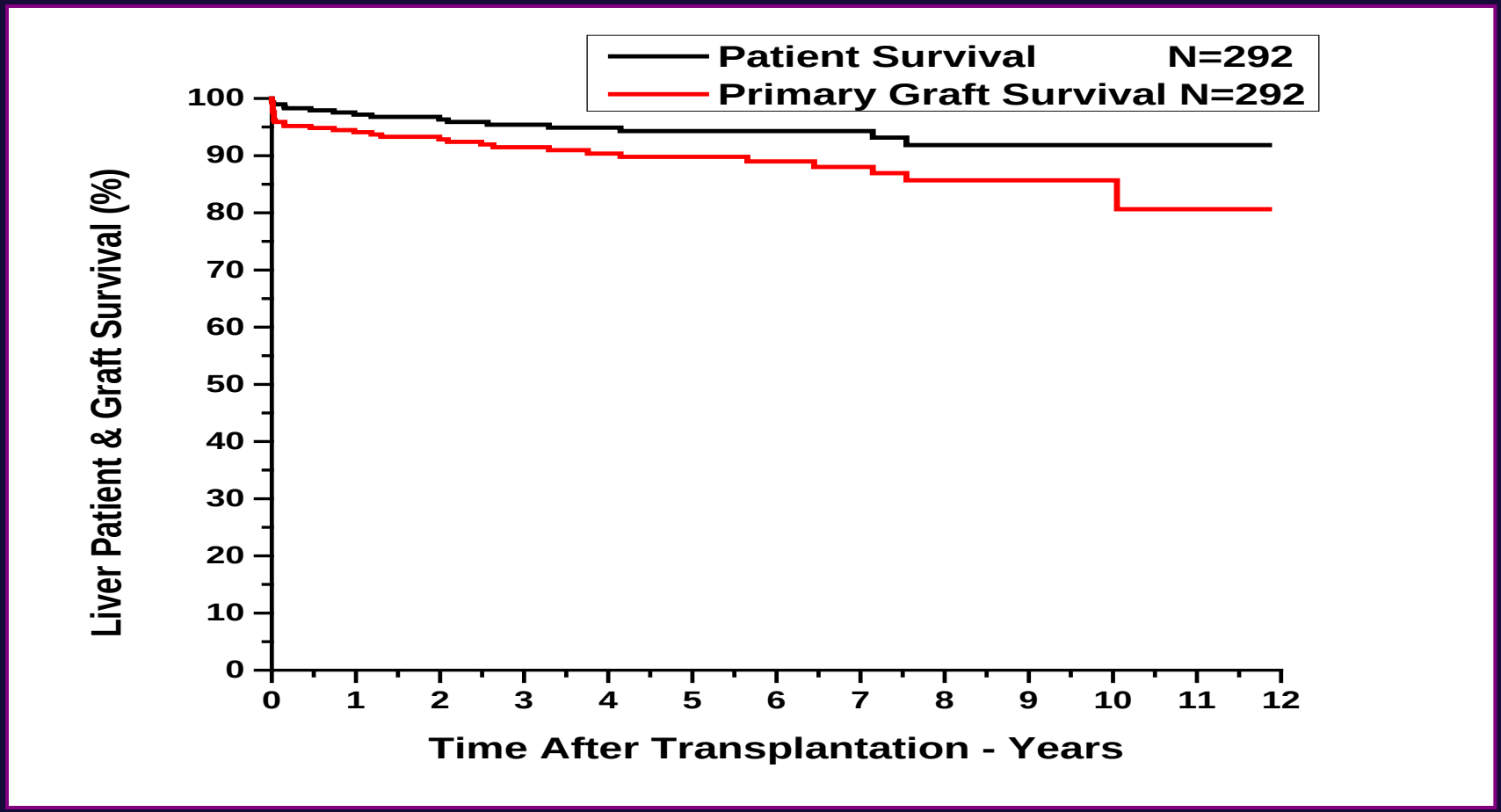
Pediatric liver transplant/year 1998-2009





Organ Procurement and Transplantation Network (OPTN) and Scientific Registry of Transplant Recipients (SRTR). OPTN/SRTR 2010 Annual Data Report. Department of Health and Human Services, Health Resources and Services Administration, Healthcare Systems Bureau, Division of Transplantation. Am J Transplant 2012;12(Suppl1).

CHP Liver Transplant (2001-Present): Post-transplant Patient & Graft Survival



Outcomes after Tx for PSC

(Miloh et al Liver Transplantation 17:925-933, 2011)

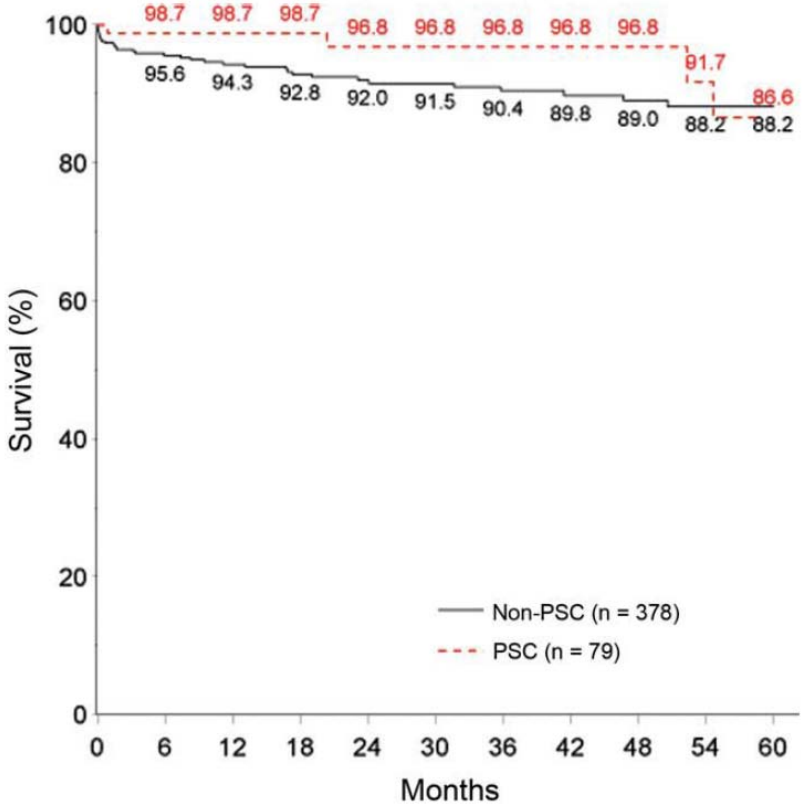
TABLE 1. Demographics and Clinical Data for Children With PSC and an Age-Matched Group at the Time of LT

	PSC Group (n = 79)	Non-PSC Group (n = 378)	*P* Value
Age (years)*	12.6 ± 3.9	12.6 ± 3.9	0.96
Male sex (%)	58.2	45.5	0.04
Caucasian (%)	67.1	61.6	0.01
Calculated PELD score*	6.1 ± 11.3	6.6 ± 11.3	0.6
Hospitalization (%)	7.6	16.1	0.05
Intensive care unit admission (%)	13.9	17.2	0.6
z score for height*	−1 ± 1.5	−0.7 ± 1.6	0.05
z score for weight*	−0.6 ± 1.5	−0.2 ± 1.5	0.008
History of gastrointestinal bleeding (%)	27.8	27.0	0.9
Ascites (%)	40.5	40.7	0.9
Intractable pruritus (%)	24.1	20.1	0.4
Hepatic encephalopathy (%)	7.6	19	0.01
Full-time school attendance (%)	Not available	Not available	Not available
Mean time on the waiting list (months)*	10.2 ± 12.9	8.7 ± 14.9	0.002

TABLE 3. Graft Types and Surgical and Posttransplant Courses for Children With PSC and an Age-Matched Group

	PSC Group (n = 79)	Non-PSC Group (n = 378)	*P* Value
Graft type [n (%)]*			
Whole	56 (70.9)	299 (79.1)	0.05
Reduced	5 (6.3)	23 (6.1)	
Split	3 (3.8)	24 (6.3)	
Living related donor	12 (15.2)	22 (5.8)	
Roux-en-Y [n (%)]	71 (89.9)	195 (51.6)	<0.0001
Biliary stent [n (%)]	37 (46.8)	173 (45.8)	0.3
Warm ischemia time (minutes)†	43 ± 15	49 ± 22	0.2
Cold ischemia time (hours)†	6.3 ± 3.1	7.6 ± 3.1	0.007
Primary nonfunction [n (%)]	2 (2.5)	7 (1.9)	0.7
Initial time in the pediatric intensive care unit post-LT (days)†	5.7 ± 6.3	5.9 ± 5.3	0.2
Total initial hospitalization post-LT (days)†	18.1 ± 14.2	31 ± 200	0.8
Biliary leak/other biliary complications in the first 6 months post-LT [n (%)]	4 (5.1)	34 (9.0)	0.2
Anastomotic strictures in the first 6 months post-LT [n (%)]	2 (2.5)	20 (5.3)	0.3
Intrahepatic strictures in the first 6 months post-LT [n (%)]	3 (3.8)	3 (0.8)	0.03
Intrahepatic strictures in the first 5 years post-LT [n (%)]	7 (8.9)	10 (2.6)	0.01
Cholangitis in the first 30 days post-LT [n (%)]	4 (5.1)	4 (1.1)	0.01
Vascular complications in the first 6 months post-LT [n (%)]	13 (16.5)	44 (11.6)	0.2
1-year patient survival (%)	98.7	94.3	0.1
5-year patient survival (%)	86.6	88.2	0.3
1-year graft survival (%)	93.0	90.0	0.4
5-year graft survival (%)	76.1	79.5	0.6
Retransplantation within 1 month of primary LT [n (%)]	1 (1.3)	11 (2.9)	0.3
Retransplantation more than 1 month after primary LT [n (%)]	6 (7.6)	22 (5.8)	

Patient and Graft Survival after LTx in PSC



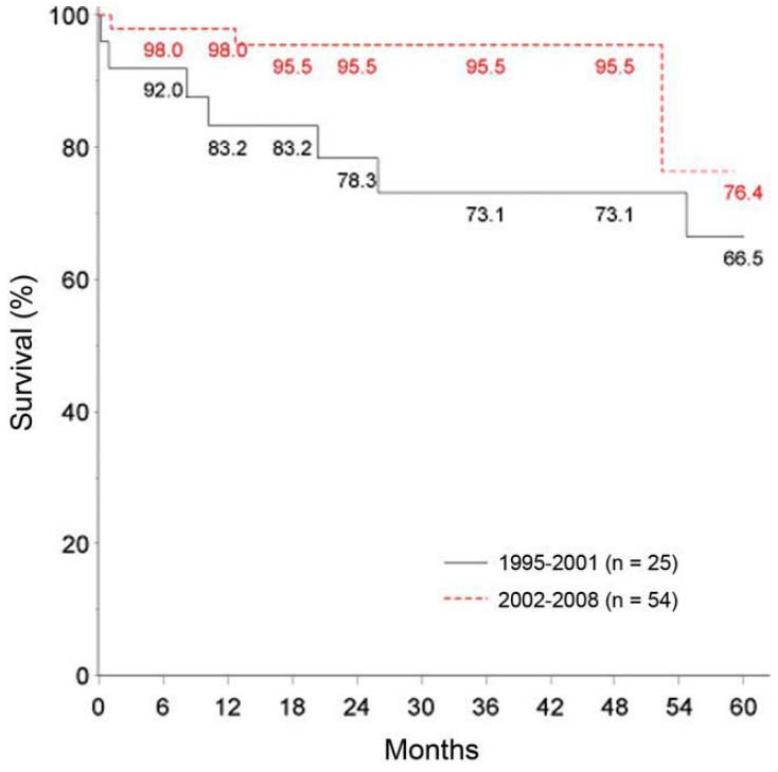


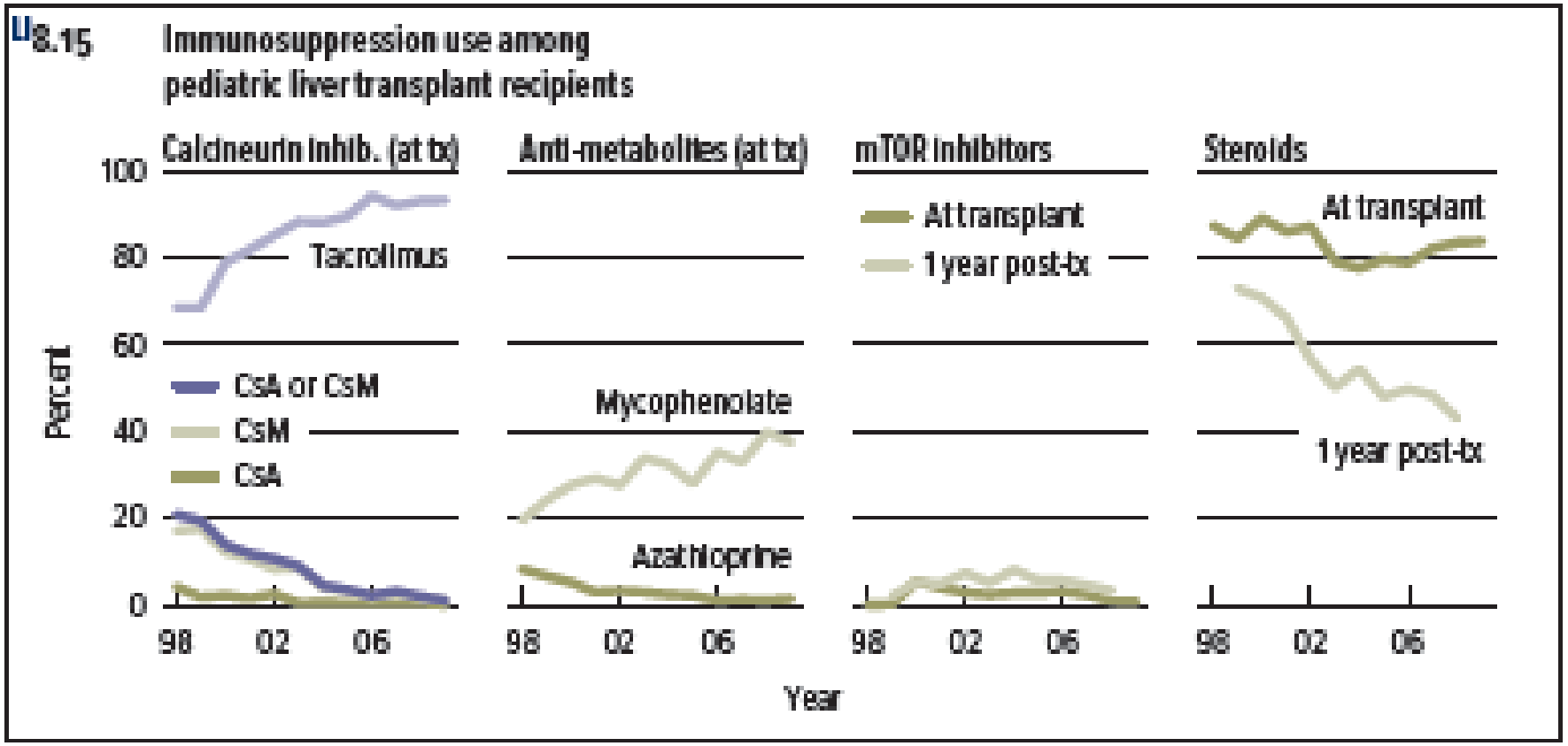
Figure 1. Kaplan-Meier probability of patient survival over time

Critical areas in long term pediatric transplantation

- Long term outcomes
  - Allograft outcomes over the long term
  - Non-allograft related outcomes
  - What do we mean by an "ideal" outcome
- Barriers to overcome
  - Better immune monitoring
  - Investigating tolerance

Late Challenges After Transplant

- **Long term management of Immunosuppression**
- **Assessment and management of late surgical and medical issues**
  - Late graft pathology
  - PTLD
  - Renal Insufficiency
  - Recurrent Disease
- **Neurodevelopmental Issues**
- **Non-adherence**



Organ Procurement and Transplantation Network (OPTN) and Scientific Registry of Transplant Recipients (SRTR). OPTN/SRTR 2010 Annual Data Report. Department of Health and Human Services, Health Resources and Services Administration, Healthcare Systems Bureau, Division of Transplantation. Am J Transplant 2012;12(Suppl1).

Long term outcomes: what do we know?

Author	Year	# Patients (adults/children)	Transplant years (Follow-up period)	Notes
Soltys	2007	872 children	>1 year	
Ng	2008	461 children 167 children	➢5 years ➢10 years	Graft survival 88%
Duffy	2010	179/114	1984-1988 (20 year)	
Jain	2011	834/166	1989-1992 (17-20 year)	20 year survival rate for children= 77.1%

Impact of technical and immune complications on long term outcome *Duffy et al: Annals of Surgery 2010*

Long-Term Patient Outcome and Quality of Life After Liver Transplantation

Analysis of 20-Year Survivors

John P. Duffy, MD, Kenneth Kao, MD, Clifford Y. Ko, MD, MPH, Douglas G. Farmer, MD, Sue V. McDiarmid, MD, Johnny C. Hong, MD, Robert S. Venick, MD, Susan Feist, RN, BSN, Leonard Goldstein, MD, Sammy Saab, MD, MPH, Jonathan R. Hiatt, MD, and Ronald W. Busuttil, MD, PhD

Objective: To evaluate patient survival and allograft function and health-related quality of life (HRQOL) 20 years after orthotopic liver transplantation (LT).

Summary of Background Data: Although LT is the established treatment of choice for acute and chronic liver failure, allograft function and recipient HRQOL 20 years after LT remain undefined.

Methods: We performed a prospective, cross-sectional study of LT recipients surviving 20 years or more. Clinical data were reviewed to identify factors associated with 20-year survival. Survivors were directly contacted and offered a survey to assess HRQOL (SF-36; Liver Disease Quality of Life), social support, and cognition (Neuropsychological Impairment Scale). Logistic regression analysis was performed to identify clinical factors influencing HRQOL 20 years after LT.

Results: Between February 1, 1984 and December 31, 1988, a total of 293 patients (179 adults, 114 children) received 348 LTs. Of the 293 patients, 168 (56%) survived for 20 years or more. Actuarial 20-year survival was 52% (patient) and 42% (graft). Factors associated with 20-year survival included recipient age <18 ($P = 0.01$), nonurgent LT ($P = 0.01$), no retransplantation (0.02), female gender (0.03), absence of biliary complications ($P = 0.04$),

Since the first successful orthotopic liver transplant (LT) was performed in 1967, the procedure has been established as the only effective and durable therapy for end-stage liver disease (ESLD) in pediatric and adult patients.[1–4] A review of the early experience of more than 500 LT recipients led to the consensus statement issued in 1983 by the National Institutes of Health, which confirmed LT as appropriate therapy in select patients with ESLD.[5] Since the consensus conference, advances in organ preservation,[6] surgical technique,[6] intraoperative and perioperative care, immunosuppression,[7–9] and graft monitoring have further improved the outcome and utilization of LT.

Clinical outcomes in the past 25 years have been consistently excellent. In 2008, the US Department of Health and Human Services reported patient and graft survival rates at 1, 5, and 10 years after deceased donor transplantation of 87%, 73%, and 59%, and 83%, 68%, and 53%, respectively.[10] Survival data from the largest transplant centers in the US compare favorably with these national data.[3,4]

Impact of biliary complications

TABLE 2. Clinical Characteristics of All Patients Undergoing LT From 1984–1988

	All Patients (n = 293)	20-yr Survivors (n = 163)	Non-20-yr Survivors (n = 130)	*P*
Age (yr)	28 ± 21	23.9 ± 19	31 ± 22	0.06
Age <18 yr, (%)	129 (44)	86 (53)	43 (33)	0.01
Gender, % F	169 (58)	101 (62)	68 (53)	0.03
Urgent LT, n (%)	146 (49)	41 (25)	105 (46)	0.01
Total ischemia time, h	7.7 ± 2.1	6.2 ± 1.5	8.7 ± 2.3	0.05
Complex arterial reconstruction, n (%)	12 (4)	4 (3)	8 (4)	0.97
Biliary complication, n (%)	29 (10)	11 (7)	18 (11)	0.04
Retransplantation, n (%)	48 (16)	11 (9)	37 (19)	0.02
Rejection, n (%)	88 (30)	57 (35)	31 (27)	0.03

LT indicates liver transplantation.

Impact of immune complications

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Duffy et al, Annals of Surgery, 2010

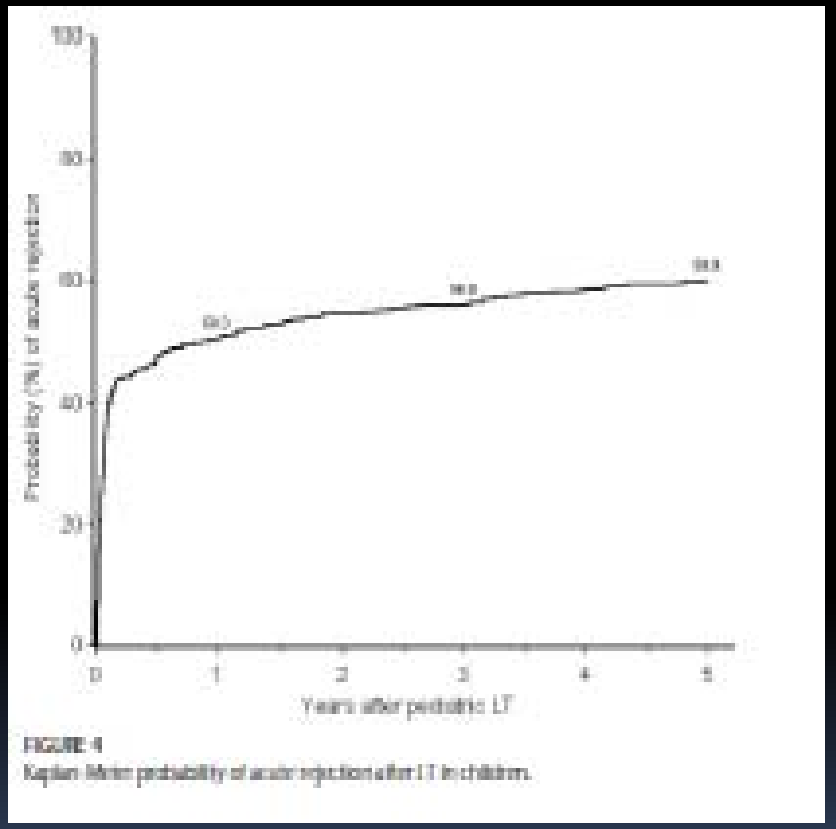


FIGURE 4

Ng et al, Pediatrics, 2009

Etiology of late mortality and graft loss (Soltys et al, 2007)

Table 6: Etiology of late mortality after LT (n = 34)

	n	%
Malignancy	7	20.6
Recurrence/metastasis	6	
Denovo malignancy	1	
Sepsis/infection	5	14.7
MSOF	5	14.7
PTLD	4	14.7
Other	3	8.8
Cardiomyopathy	1	
Cystic fibrosis	1	
Aplastic anemia	1	
Cardiopulmonary	3	8.8
Cerebral edema/infarct	3	8.8
Portal vein thrombosis	1	2.9
Pancreatitis	1	2.9
Liver failure	1	2.9
Chronic rejection	1	2.9

Table 3: Etiology of late graft loss after LT (n = 35)*

	n	%
Chronic rejection	13	37.1
Other	5	14.3
Venoocclusive disease	1	
Parenteral nutrition	1	
Regenerative nodular hyperplasia	1	
Fulminant liver failure	1	
Chronic cholangitis	1	
Acute rejection	4	11.4
HAT	4	11.4
Biliary	3	8.6
Missing	3	8.6
HCV	1	2.9
Recurrent disease	1	2.9
Stopped immunosupression	1	2.9

EVIDENCE OF OVER IMMUNOSUPPRESSION (INFECTION) AS WELL AS UNDER IMMUNOSUPPRESSION (IMMUNE INJURY)

Outcomes of 5-Year Survivors of Pediatric Liver Transplantation: Report on 461 Children From a North American Multicenter Registry

TABLE 3 Immunosuppression Medications Taken by Survivors at the 5-Year Anniversary Visit

Drug	Patients Receiving the Drug, *n* (%)	Daily Dose, Mean ± SD, mg
Cyclosporine	107 (24)	128.9 ± 81.5
Tacrolimus	332 (74)	3.4 ± 2.6
Prednisone	114 (26)	6.5 ± 8.1
Mycophenolate mofetil	63 (14)	782.5 ± 562.8
Azathioprine	16 (4)	45.8 ± 44.5
Sirolimus	17 (4)	2.4 ± 3.1
Single-drug therapy	285 (64)	—
Double-drug therapy	111 (25)	—
Triple-drug therapy	51 (11)	—

Data are for 447 out of 461 five-year survivors; information regarding immunosuppression at 60-month visit was missing for 14 survivors.

ARTICLE

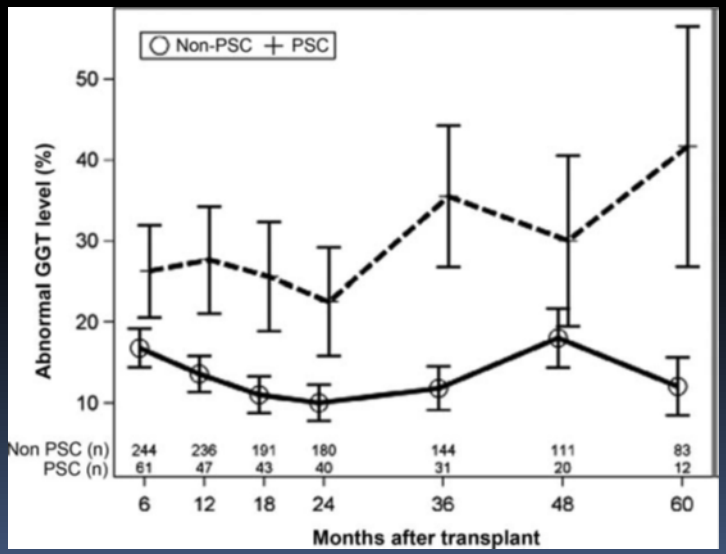
Outcomes of 5-Year Survivors of Pediatric Liver Transplantation: Report on 461 Children From a North American Multicenter Registry

Vicky Lee Ng, MD, FRCPC[a,b], Annie Fecteau, MD, FRCSC[a,c], Ross Shepherd, MD[d,e], John Magee, MD[f], John Bucuvalas, MD[g], Estella Alonso, MD[h], Suzanne McDiarmid, MD[i], Geoff Cohen, PhD[j], Ravinder Anand, PhD[j], and the Studies of Pediatric Liver Transplantation Research Group

[c]SickKids Transplant Center, [a]Division of Paediatric Gastroenterology, Hepatology, and Nutrition, and [b]Division of Paediatric General Surgery, Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada; [d]Washington University School of Medicine, St Louis, Missouri; [e]St Louis Children's Hospital, St Louis, Missouri; [f]Division of Transplant Surgery, University of Michigan, Ann Arbor, Michigan; [g]Division of Pediatric Gastroenterology, Hepatology, and Nutrition, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio; [h]Siragusa Transplant Center, Children's Memorial Hospital, Chicago, Illinois; [i]Dumont-University of California Los Angeles Liver Transplant Center, Los Angeles, California; [j]Studies of Pediatric Liver Transplantation, EMMES Corporation, Rockville, Maryland

TABLE 2 Liver Tests, Biochemistry Results, and Outcomes 5 Years After LN

Test	*N*	Mean ± SD	% With Abnormal Test[a]
Alanine aminotransferase, IU/L	424	44 ± 61	31
Aspartate aminotransferase, IU/L	424	47 ± 38	33
γ -Glutamyltransferase, IU/L	380	65 ± 130	46
Total bilirubin, μmol/L	448	11.8 ± 27.8	9
Albumin, g/L	435	43 ± 30	6
Serum creatinine, μmol/L	440	58 ± 76	5
cGFR, mL/min per 1.73 m²	352	135 ± 61	13
Cholesterol, mmol/L[b]	173	3.60 ± 0.98	47
Triglycerides, mmol/L[b]	167	1.01 ± 0.56	25
Hemoglobin, g/L[b]	74	130 ± 16	38
Height/age, *z* score	361	−0.72 ± 1.43	
<25th percentile	—	—	47
<10th percentile	—	—	29
<3rd percentile	—	—	18
Weight/age, *z* score	364	−0.16 ± 1.38	
<25th percentile	—	—	29
<10th percentile	—	—	18
<3rd percentile	—	—	10



Miloh et al (2011), above

Critical areas in long term pediatric transplantation

- Long term outcomes
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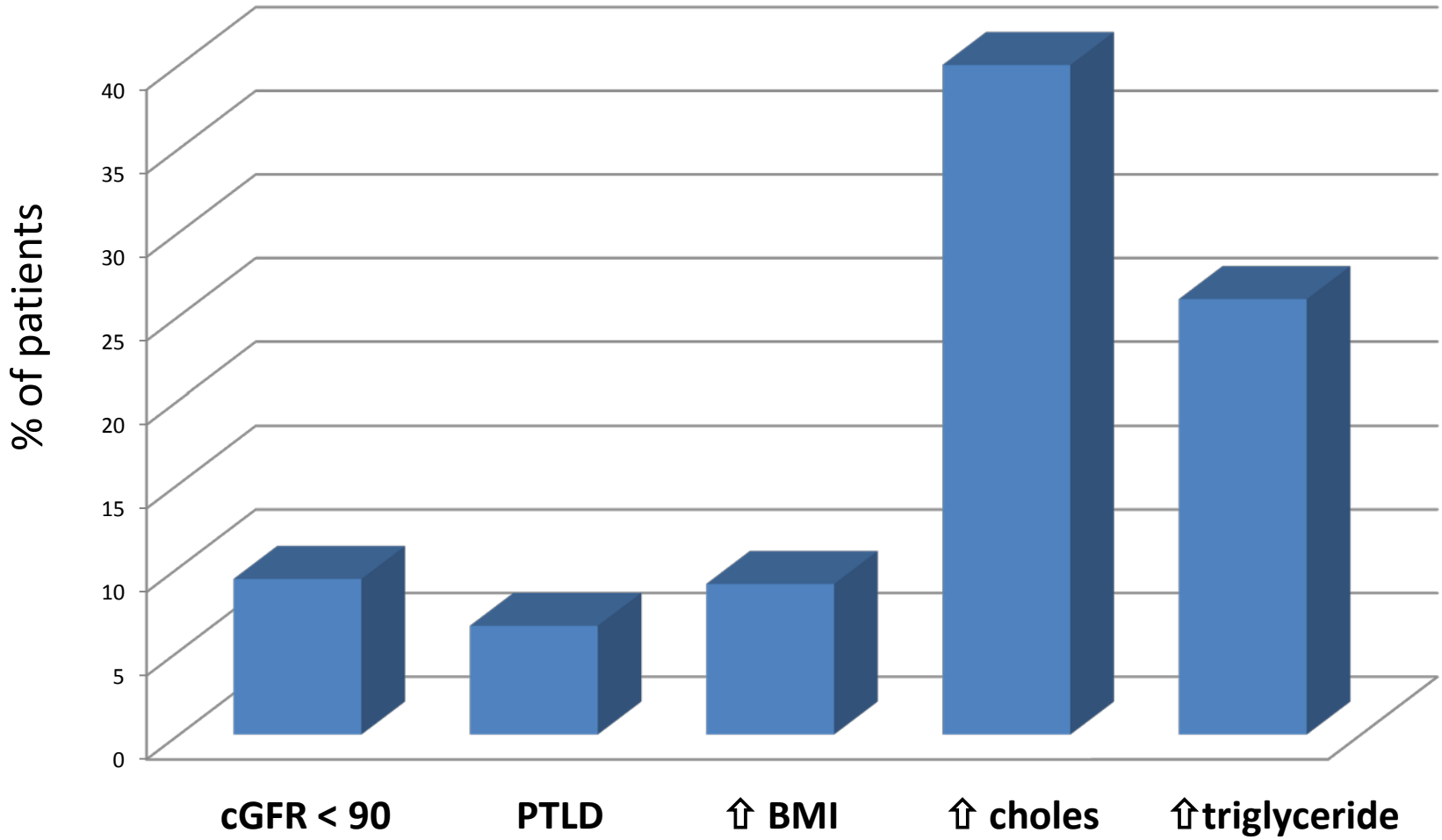
Extra-Hepatic Morbidity at the 10-Year Anniversary Clinic Visit



Health Status of Children Alive 10 Years after Pediatric Liver Transplantation Performed in the US and Canada: Report of the Studies of Pediatric Liver Transplantation Experience

Vicky L. Ng, MD, FRCP(C)[1], Estella M. Alonso, MD[2], John C. Bucuvalas, MD[3], Geoff Cohen, PhD[4], Christine A. Limbers, PhD[5], James W. Varni, PhD[6], George Mazariegos, MD[7], John Magee, MD[8], Susan V. McDiarmid, MD[9], and Ravinder Anand, PhD[4], for the Studies of Pediatric Liver Transplantation (SPLIT) Research Group*

Objectives To determine clinical and health-related quality of life outcomes, and to derive an "ideal" composite profile of children alive 10 years after pediatric liver transplantation (LT) performed in the US and Canada.

Study design This was a multicenter cross-sectional analysis characterizing patients enrolled in the Studies of Pediatric Liver Transplantation database registry who have survived >10 years from LT.

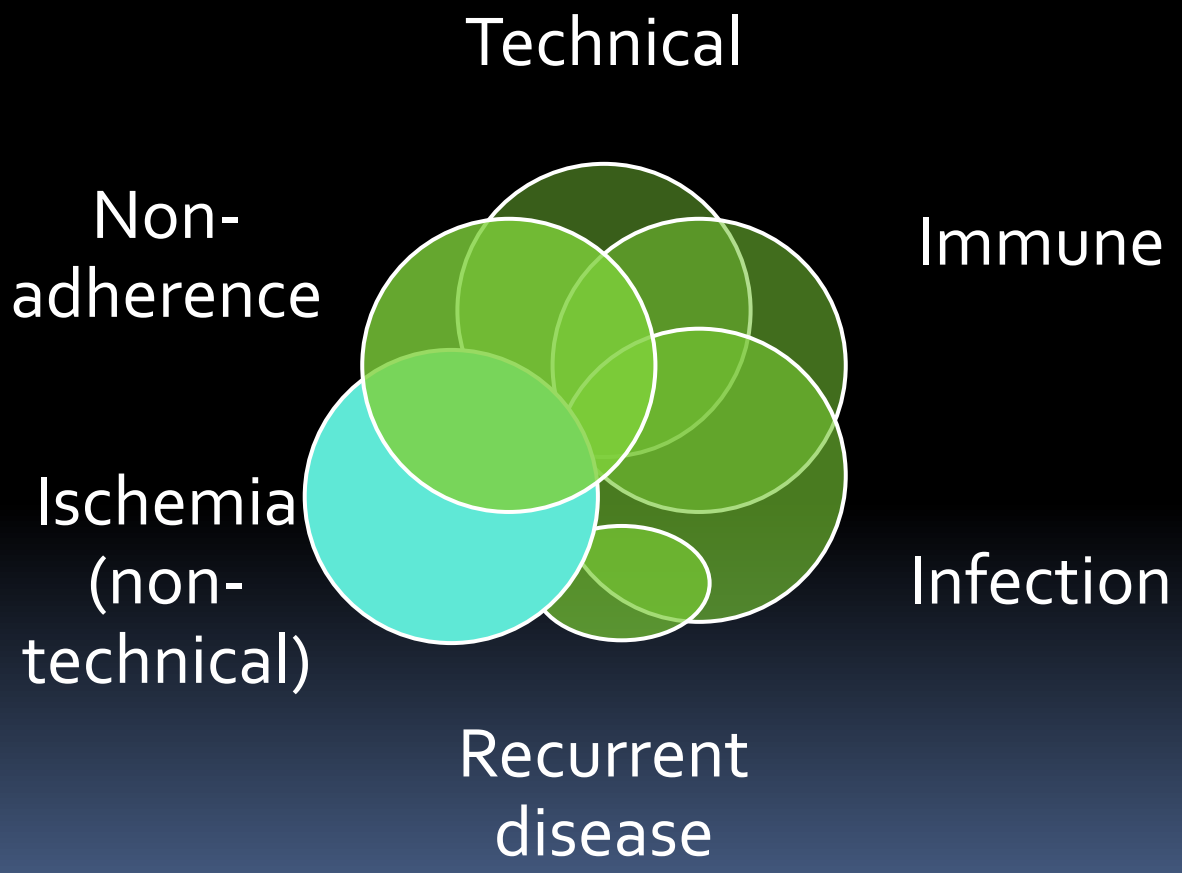
Results A total of 167 10-year survivors were identified, all of whom received daily immunosuppression therapy. Comorbidities associated with the post-LT course included post-transplantation lymphoproliferative disease (in 5% of patients), renal dysfunction (9%), and impaired linear growth (23%). Health-related quality of life, as assessed by the PedsQL 4.0 Generic Core Scales, revealed lower patient self-reported total scale scores for 10-year survivors compared with matched healthy children (77.2 ± 12.9 vs 84.9 ± 11.7; $P < .001$). At 10 years post-LT, only 32% of patients achieved an ideal profile of a first allograft stable on immunosuppression monotherapy, normal growth, and absence of common immunosuppression-induced sequelae.

Conclusion Success after pediatric LT has moved beyond patient survival. Availability of an ideal composite profile at follow-up provides opportunities for patients, families, and healthcare providers to identify broader sets of outcomes at earlier stages, ultimately contributing to improved outcomes after pediatric LT. *(J Pediatr 2011;*■

The “ideal” survivor?

- Allograft related criteria
  - Normal ALT, t bili, albumin, ggt
  - No CR, no Re-Tx,
  - Monotherapy immunosuppression
- Absence of immune suppression morbidity
  - PTLD, diabetes, growth deficit, renal dysfunction, hypertension, anti-seizure medication

Contributors to late allograft dysfunction



Critical areas in long term pediatric transplantation

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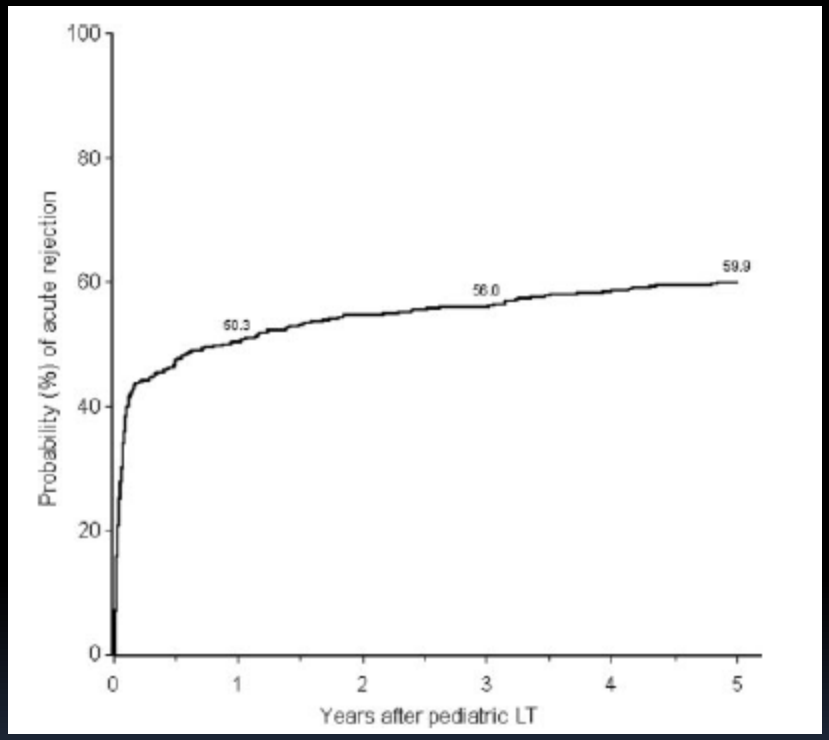
Need for improved immune monitoring



KM Probability of rejection in 5 year survivors Ng et al, Pediatrics, 2008

American Journal of Transplantation 2008; 8: 1–12
Wiley Periodicals Inc.

doi: 10.1111/j.1600-6143.2008.02459.x

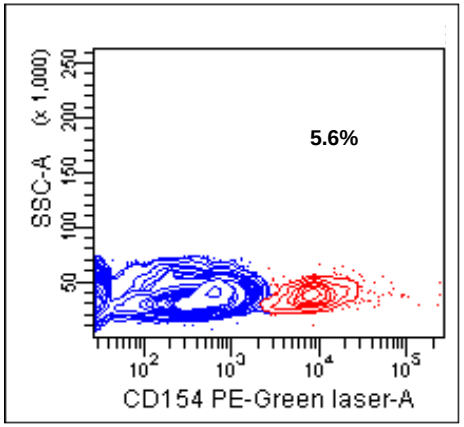
Allospecific CD154+ T Cells Associate with Rejection Risk After Pediatric Liver Transplantation

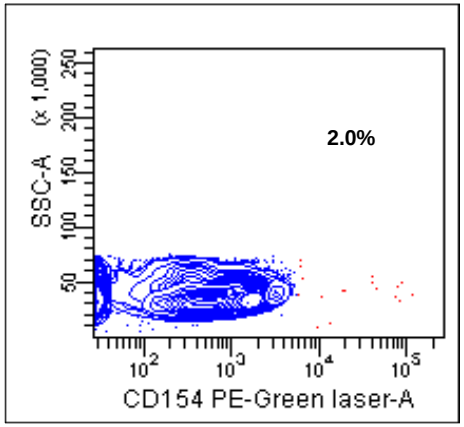
C. Ashokkumar[a], A. Talukdar[a], Q. Sun[a], B. W. Higgs[a], J. Janosky[a], P. Wilson[a], G. Mazariegos[a], R. Jaffe[b], A. Demetris[b], J. Dobberstein[a], K. Soltys[a], G. Bond[a], A. W. Thomson[a], A. Zeevi[b] and R. Sindhi[a,*]

Received 30 April 2008, revised 13 August 2008 and accepted for publication 09 September 2008

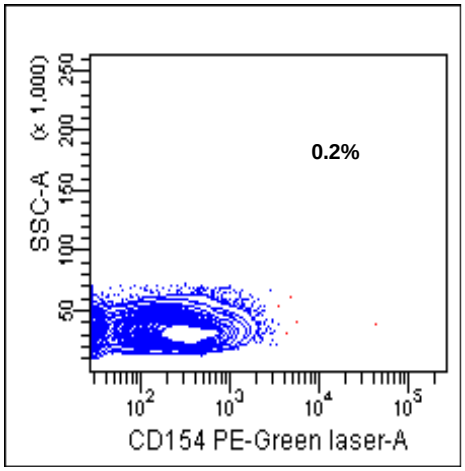
Introduction

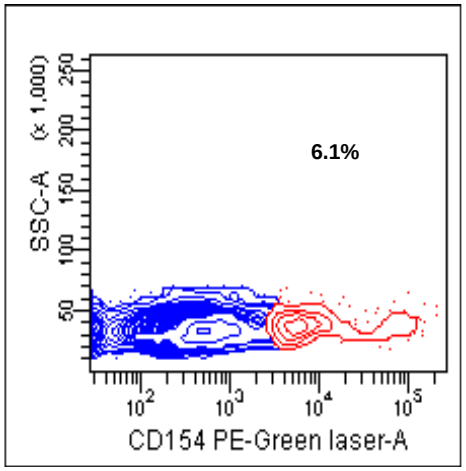
With Donor | **With Third Party**





Rejector: Donor response **>** third-party response

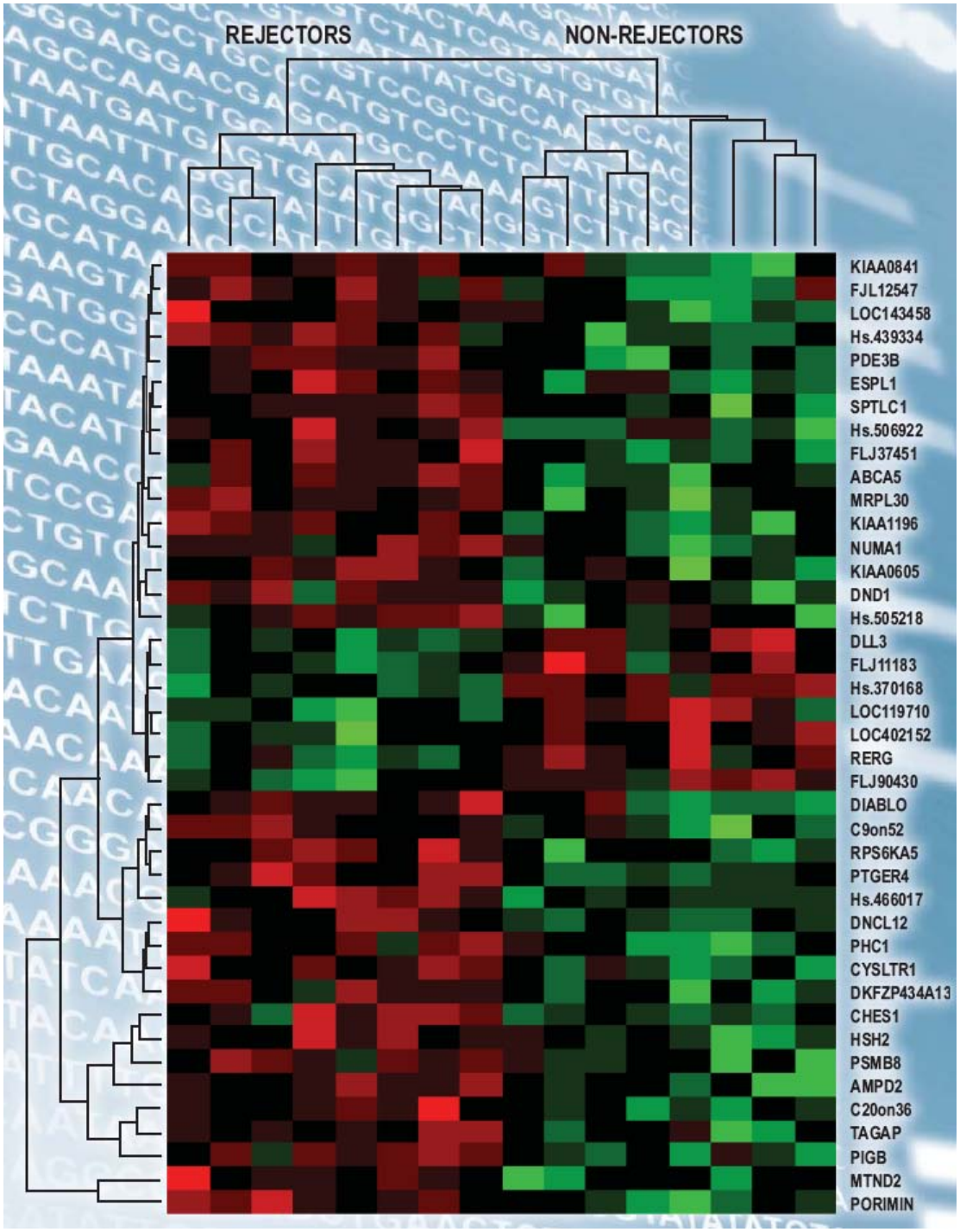




Non-rejector: Donor response **<** third-party response

AJT, 2009

Molecular signatures- rejection-free outcomes after liver transplantation



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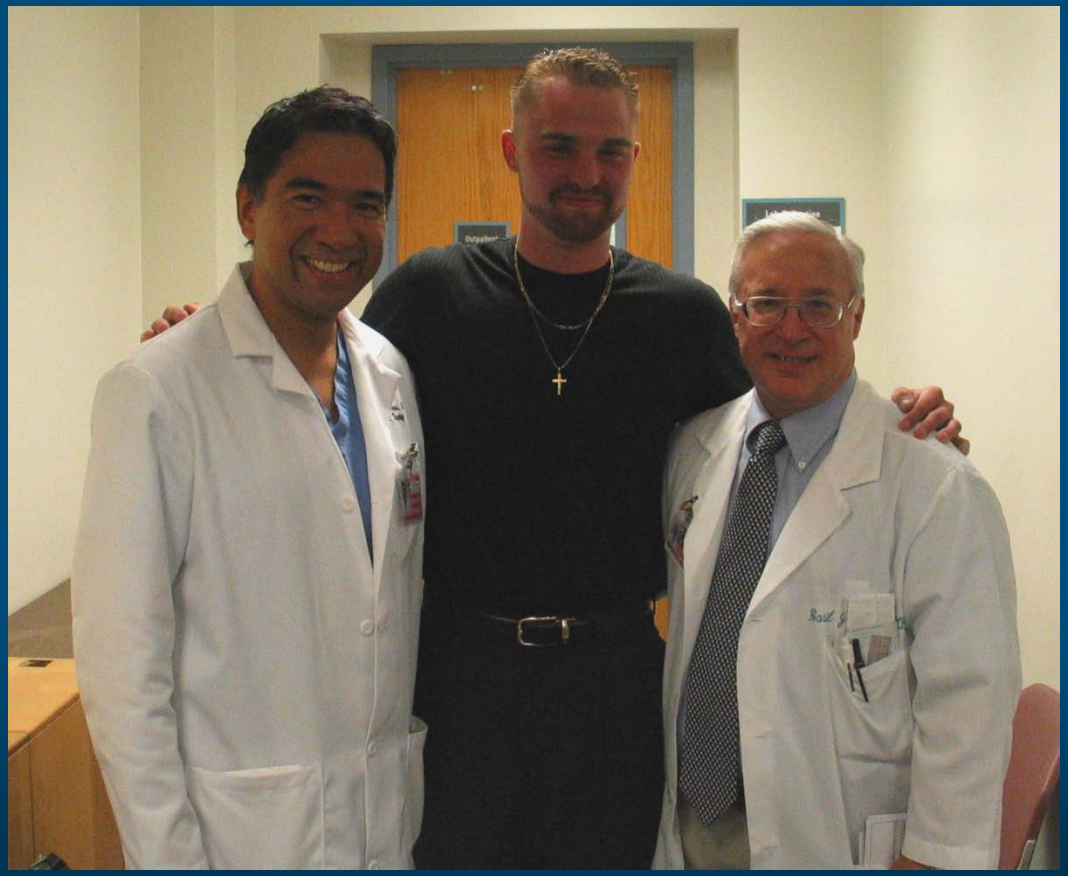
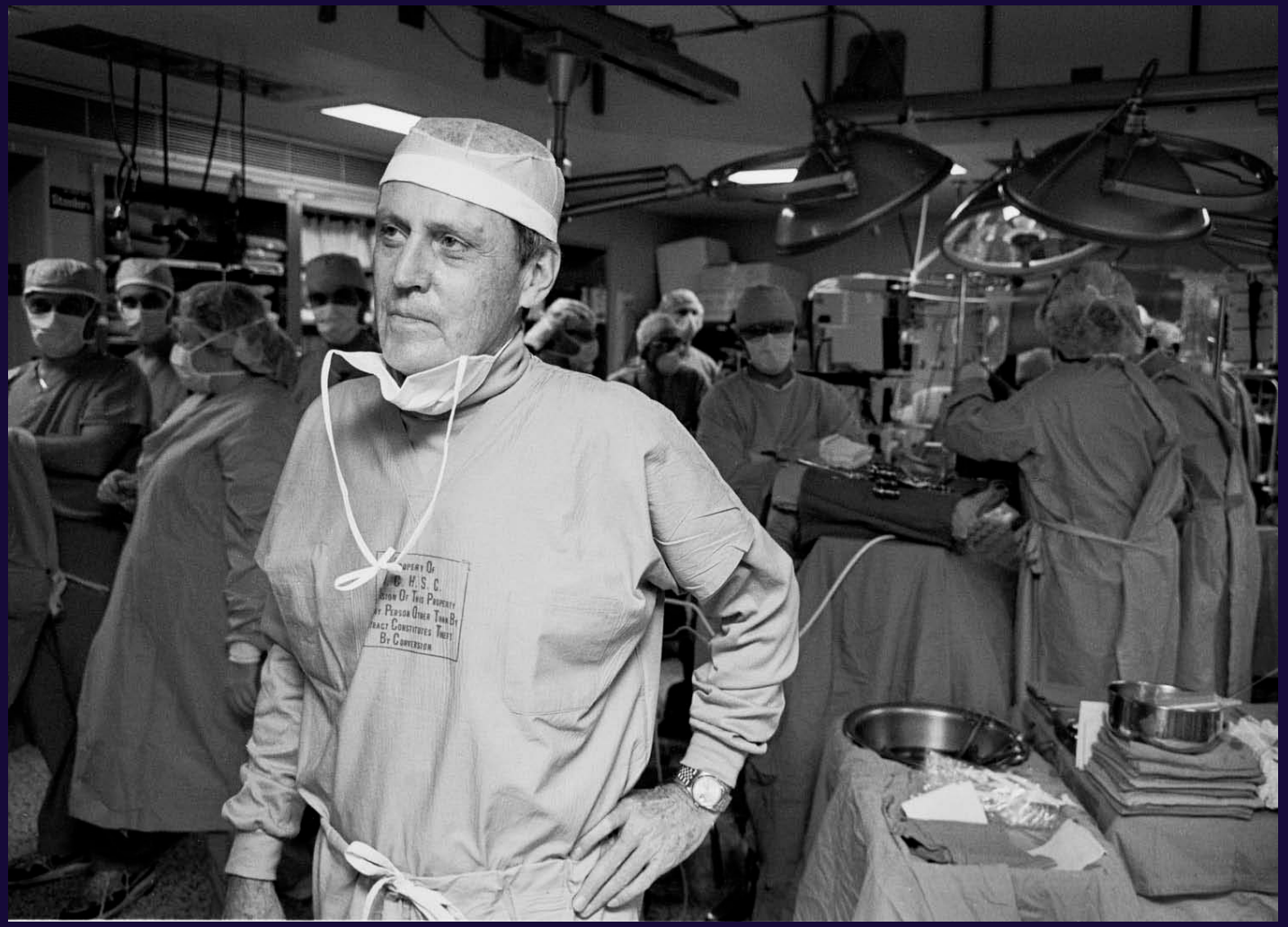
Operational transplant tolerance



“Children are the trailblazers”...Dr Starzl



Thank you!