IMPROVING OUTCOMES FOR INFANTS WITH BILIARY ATRESIA: TOWARDS UNIVERSAL NEWBORN SCREENING

Ryan Himes, MD

Section Head, Gastroenterology, Hepatology, & Nutrition

Medical Director, Pediatric Liver Transplant Program

Associate Chair, Pediatrics-Subspecialties

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ALIGNMENT

Creating SpACE Specialty Access for Children Everywhere

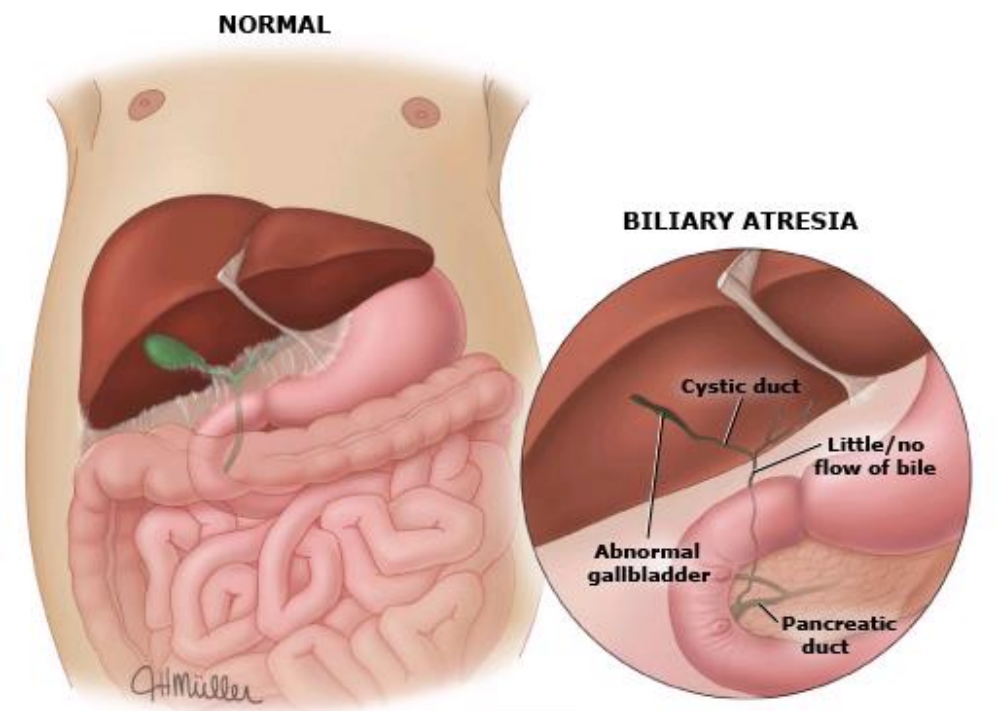
We are committed to eliminating uneven care and health outcomes disparities in the way:

> Children are referred to us

> We diagnose children

> We treat children

BILIARY ATRESIA

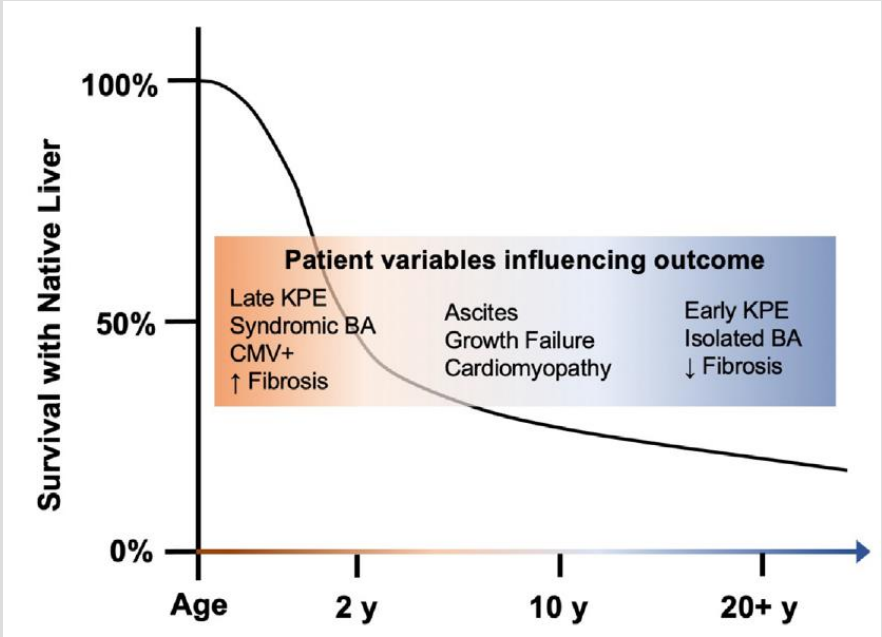


- Rapidly progressive fibro-obliterative process affecting extrahepatic biliary tree
- 1:10,000-1:15,000 births in US
- Pathophysiology
  - Viral, immune, environmental?
- Treatment is surgical
  - Kasai portoenterostomy
  - Liver transplantation
- Untreated, children succumb in first 2 years of life

BILIARY ATRESIA

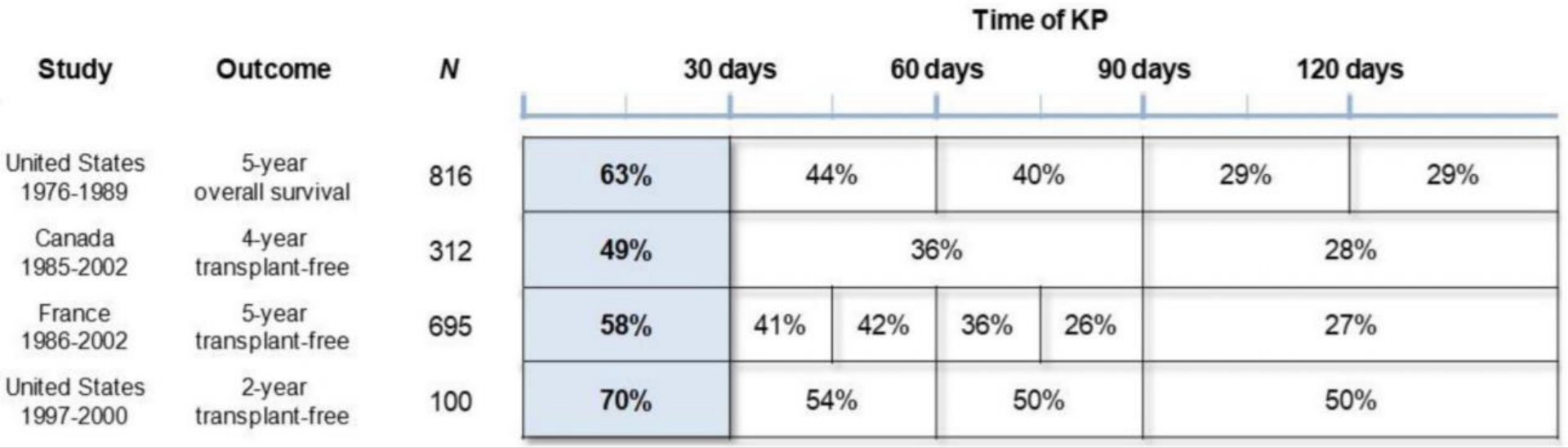
Early surgical intervention is unequivocally associated with <u>better patient outcomes</u>

- Survival
- Avoiding/delaying liver transplant



Clin Liver Dis 26 (2022) 341–354

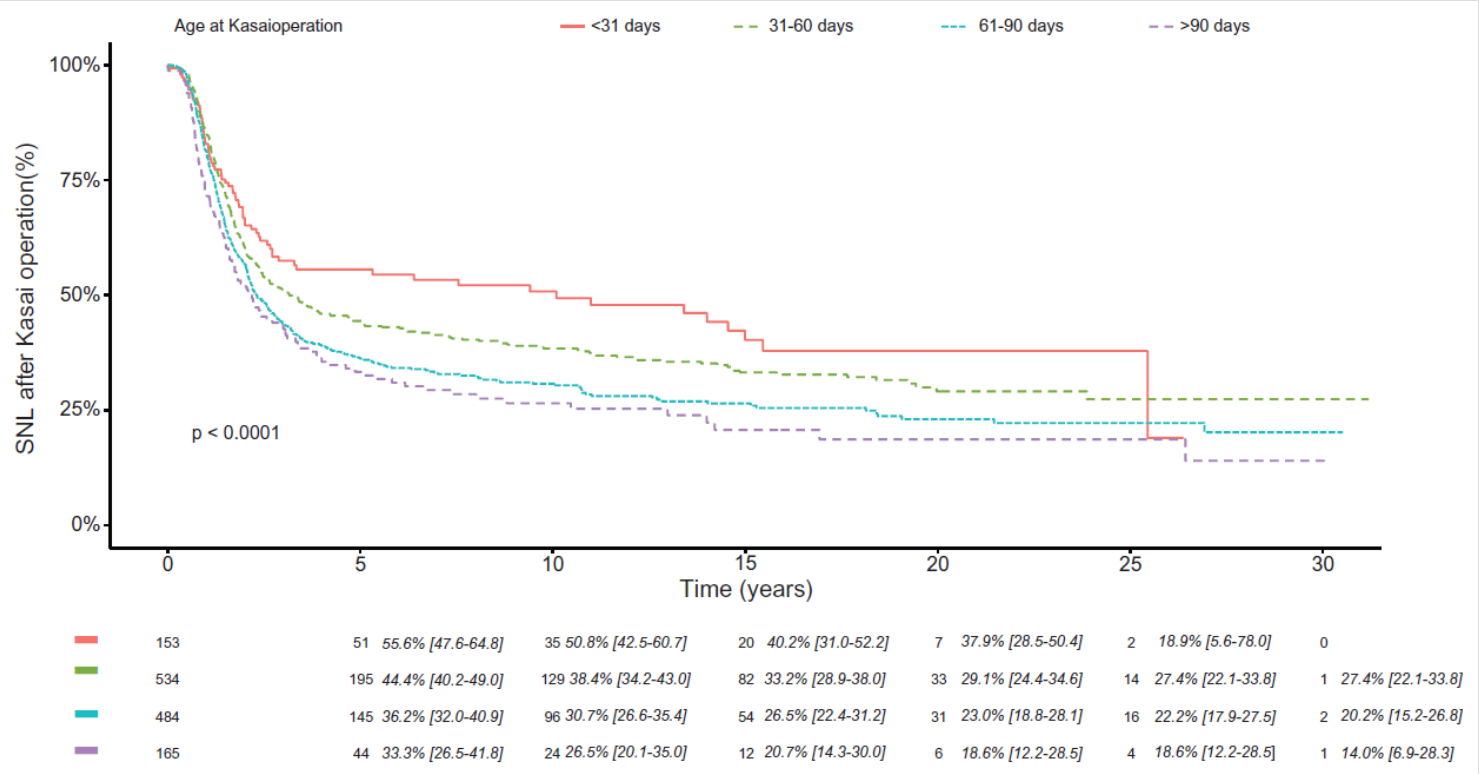
EARLY KASAI IMPROVES OUTCOMES



Mysore et al, *JPGN*, 2019

FRANCE

- n=1,336
- 1986-2015
- Median age at KP 59 days; no era effect



DAYS MATTER

The need for early Kasai portoenterostomy: a Western Pediatric Surgery Research Consortium study

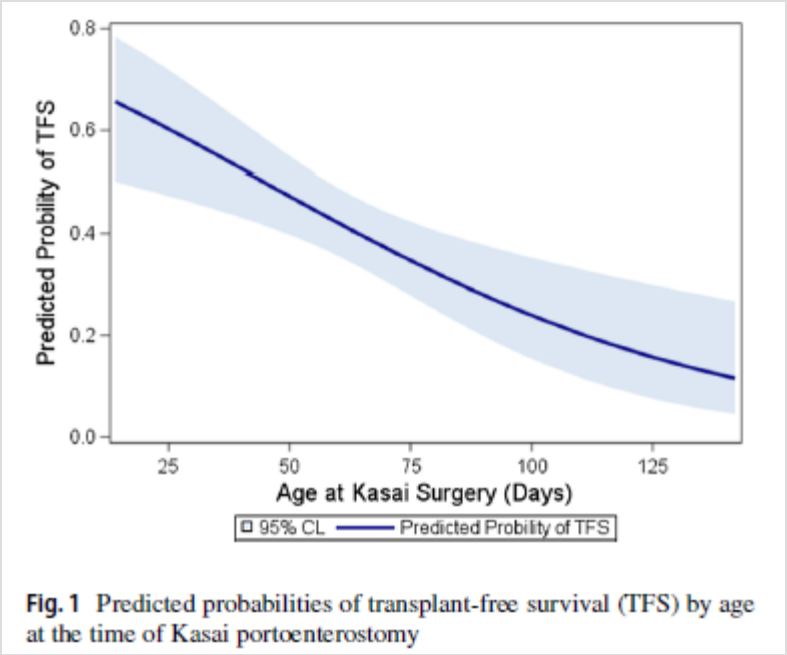


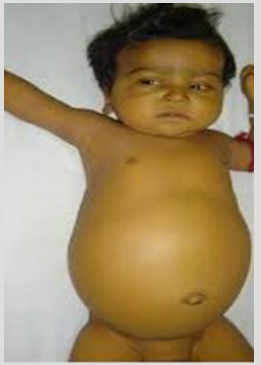
Fig. 1 Predicted probabilities of transplant-free survival (TFS) by age at the time of Kasai portoenterostomy

"Controlling for patient and surgeon-level factors, **each additional day of age toward operation was associated with a 2% decrease in likelihood of TFS** (OR 0.98, 95% CI 0.97–0.99)".

Pediatric Surgery International (2022) 38:193–199

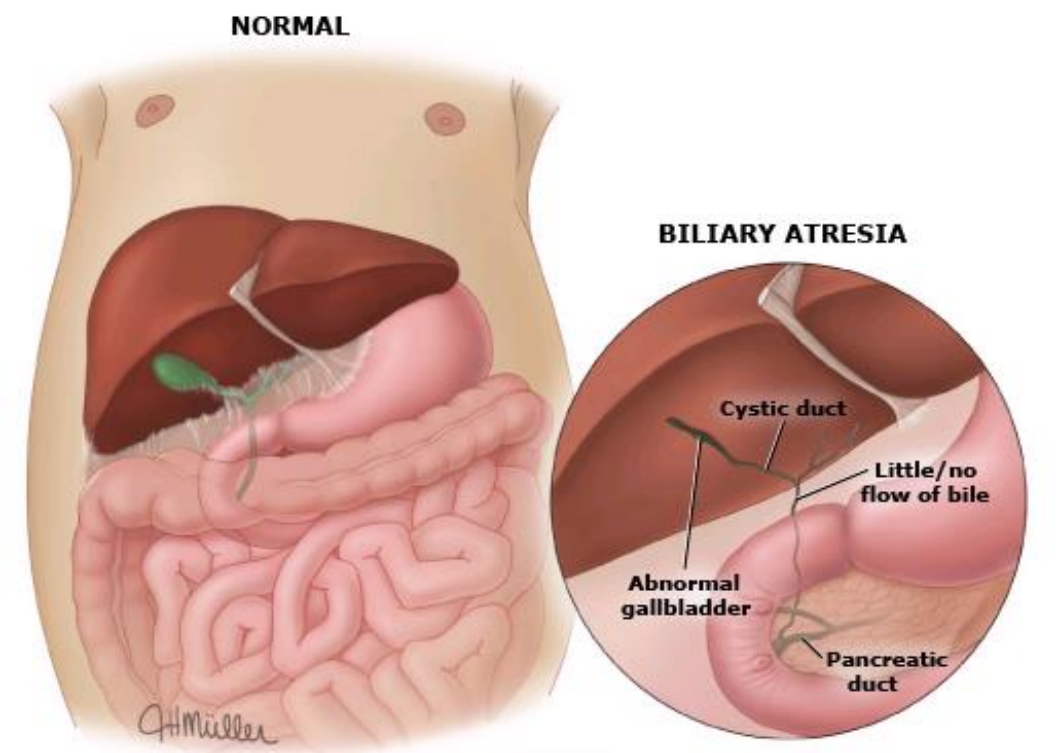
A DIAGNOSTIC PROBLEM

2-3 months



Usually term gestation
Normal birth weight
Not visibly/mildly jaundiced
No organomegaly
Stools pigmented
AST/ALT normal
Direct bilirubin elevated

Weight falters
Jaundice fails to improve
Hepatomegaly develops
Stools become acholic
AST/ALT/GGT elevated
Direct bilirubin continues to rise



- Relatively common
- #1 reason for pediatric liver transplantation worldwide
- Early intervention = better outcomes
- <u>Lack of timely diagnosis</u> is THE chief barrier to early intervention

NEWBORN SCREENING IS A LEVER FOR EARLIER DX

Box 1. **Wilson and Jungner classic screening criteria**[1]

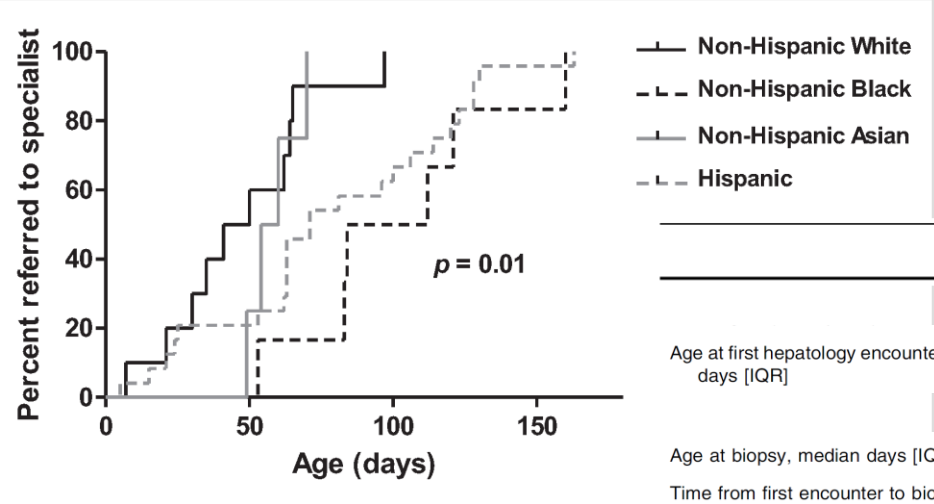
1. The condition sought should be an important health problem.
2. There should be an accepted treatment for patients with recognized disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognizable latent or early symptomatic stage.
5. There should be a suitable test or examination.
6. The test should be acceptable to the population.
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8. There should be an agreed policy on whom to treat as patients.
9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case-finding should be a continuing process and not a "once and for all" project.

TABLE. Estimated number of U.S. children who would have been identified with disorders in 2006 using the American College of Medical Genetics recommended newborn screening panel,* based on incidence of these disorders in four state newborn screening programs during 2001–2006, by disorder

Disorder	California, Massachusetts, North Carolina, and Wisconsin (2001–2006)† Observed no. of cases	No. of births	Rate per 100,000	(95% CI§)	United States (2006) Estimated no. of cases¶	(95% CI)
Amino acid disorders						
Phenylketonuria (includes clinically significant hyperphenylalaninemia variants)	254	4,884,217	5.20	(4.76–5.68)	215	(197–235)
Maple syrup urine disease	14	2,214,329	0.63	(0.42–0.94)	26	(17–39)
Homocystinuria	6	2,214,329	0.27	(0.14–0.50)	11	(6–21)
Citrullinemia I	13	2,214,329	0.59	(0.38–0.89)	24	(16–37)
Argininosuccinic acidemia	4	2,214,329	0.18	(0.08–0.39)	7	(3–16)
Organic acid metabolism disorders						
Isovaleric acidemia	19	2,474,313	0.77	(0.54–1.08)	32	(22–45)
Glutaric acidemia type I	23	2,474,313	0.93	(0.68–1.26)	38	(28–52)
Hydroxymethylglutaric aciduria	2	2,474,313	0.08	(0.02–0.24)	3	(1–10)
Multiple carboxylase deficiency	2	2,474,313	0.08	(0.02–0.24)	3	(1–10)
Methylmalonic acidemia (mutase deficiency)	30	2,474,313	1.21	(0.93–1.58)	50	(38–66)
Methylmalonic acidemia CblA,B	7	2,474,313	0.28	(0.16–0.50)	12	(6–21)
3-Methylcrotonyl-CoA carboxylase deficiency	60	2,474,313	2.43	(2.01–2.92)	100	(83–121)
Propionic acidemia	9	2,474,313	0.36	(0.22–0.60)	15	(9–25)
Beta-ketothiolase deficiency	4	2,474,313	0.16	(0.07–0.35)	7	(3–14)
Fatty acid oxidation disorders						
Medium-chain acyl-CoA dehydrogenase deficiency	143	2,460,473	5.81	(4.90–6.85)	239	(212–269)
Very long-chain acyl-CoA dehydrogenase deficiency	41	2,460,473	1.67	(1.20–2.26)	69	(55–86)
Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency	8	2,460,473	0.33	(0.14–0.64)	13	(8–23)
Trifunctional protein deficiency	1	2,460,473	0.04	(0.00–0.23)	2	(0–7)
Carnitine uptake defect	26	1,256,869	2.07	(1.35–3.03)	85	(63–113)
Hemoglobinopathies**						
Hb SS	777	4,403,132	17.65	(16.78–18.56)	1,128	(1,063–1,200)
Hb SC	326	4,403,132	7.40	(6.65–8.01)	484	(442–532)
Hb S/β thalassemia	74	3,673,283	2.02	(1.70–2.38)	163	(131–205)
Other disorders						
Primary congenital hypothyroidism (excluding secondary, transient, or other)	2,544	4,884,217	52.09	(50.67–53.55)	2,156	(2,097–2,216)
Biotinidase deficiency (including partial)	19	1,268,943	1.50	(1.06–2.10)	62	(44–87)
Congenital adrenal hyperplasia (excluding non 21-hydroxylase deficiency)	121	2,474,313	4.89	(4.29–5.57)	202	(178–230)
Classical galactosemia variant (excluding GALK and GALE)	264	4,884,217	5.41	(4.96–5.90)	224	(205–244)
Cystic fibrosis (including nonclassical)	270	895,410	30.15	(27.66–32.87)	1,248	(1,145–1,360)
Total (all disorders)					6,439	(6,282–6,596)

* Available at http://www.acmg.net/resources/policies/nbs/nbs-sections.htm. Two of the 29 disorders listed in the screening panel are not included: tyrosinemia type I and hearing loss.
† Not all states screened for all disorders during this period. Number of births varies based on period in which the disorder was screened for in each state.
§ Confidence interval.
¶ Based on live birth occurrence data for 2006 (n = 4,138,349).
** Estimated number of cases was calculated based on race- and ethnicity-specific prevalence rates using the following categories: non-Hispanic white, non-Hispanic black, other (i.e., American Indian/Alaskan Native, Asian/Pacific Islander, and Hispanic), and unknown race/ethnicity.

SCREENING CAN ELIMINATE UNEVEN CARE



Creating SpACE *Specialty Access for Children Everywhere*

	Cohort (*N* = 69)	White patients (*N* = 50)	Non-White patients (*N* = 19)	*p* Value[a]
Age at first hepatology encounter, median days [IQR]	43 [20–72]	34 [17–65]	67 [42-133]	0.001
Age at biopsy, median days [IQR]	53 [31–73]	43 [28–70]	68 [44–111]	0.02
Time from first encounter to biopsy, median days [IQR]	2 [1–8]	4 [1–10]	1.5 [–43]	0.02
HPE, *n* (%)	52 (75%)	42 (84%)	10 (53%)	0.01

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Harpavat et al. (2018) *JPGN* 66:850-6.
Bonn et al. (2024) JPGN April 3

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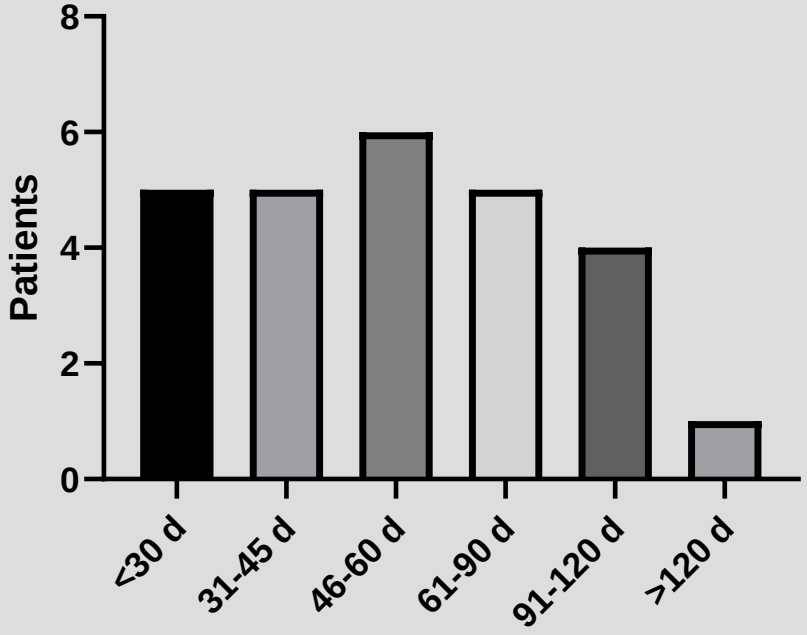
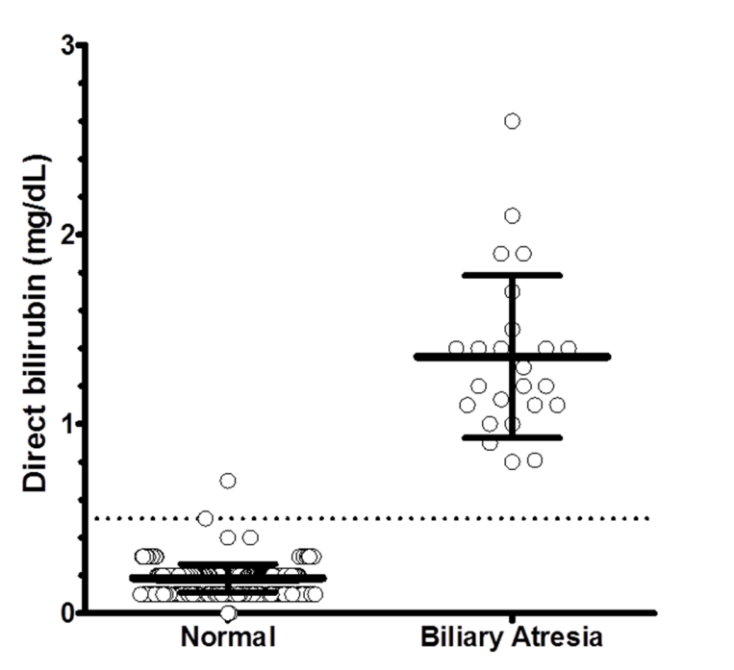
HOW IS LOUISIANA DOING?



- Average age at Kasai: 58 days (median 55)
- 81% done after 30 DOL

n=26 patients, 2007-2020

EARLY DB LEVEL IDENTIFIES NEONATES WITH BA



- Retrospective assessment of patients with BA in Texas
- All 24 patients with BA had elevated Db in nursery
- Tb alone or Db/Tb ratio missed patients with BA

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Harpavat S, Finegold MJ, and Karpen SJ (2011) Pediatrics 128: e1428-33.

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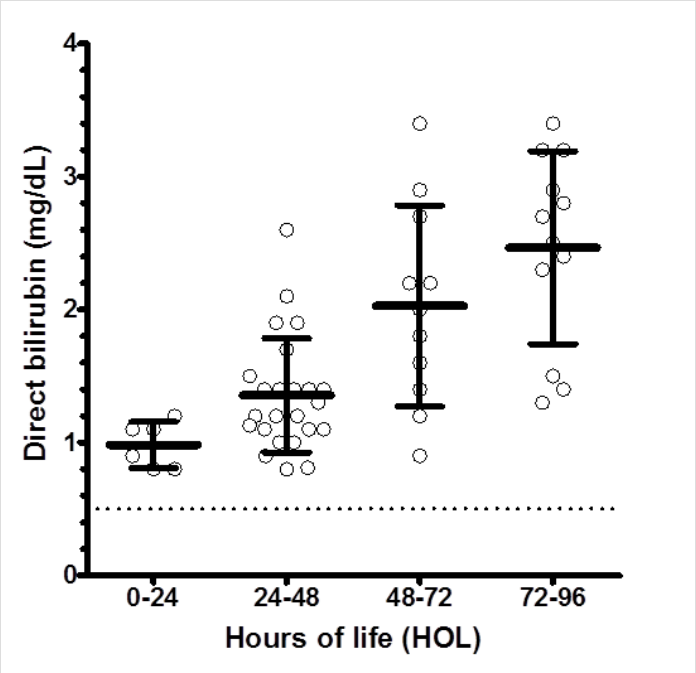
DB LEVELS RISE OVER TIME IN BABIES WITH BA



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Harpavat S, Finegold MJ, and Karpen SJ (2011) Pediatrics 128: e1428-33.

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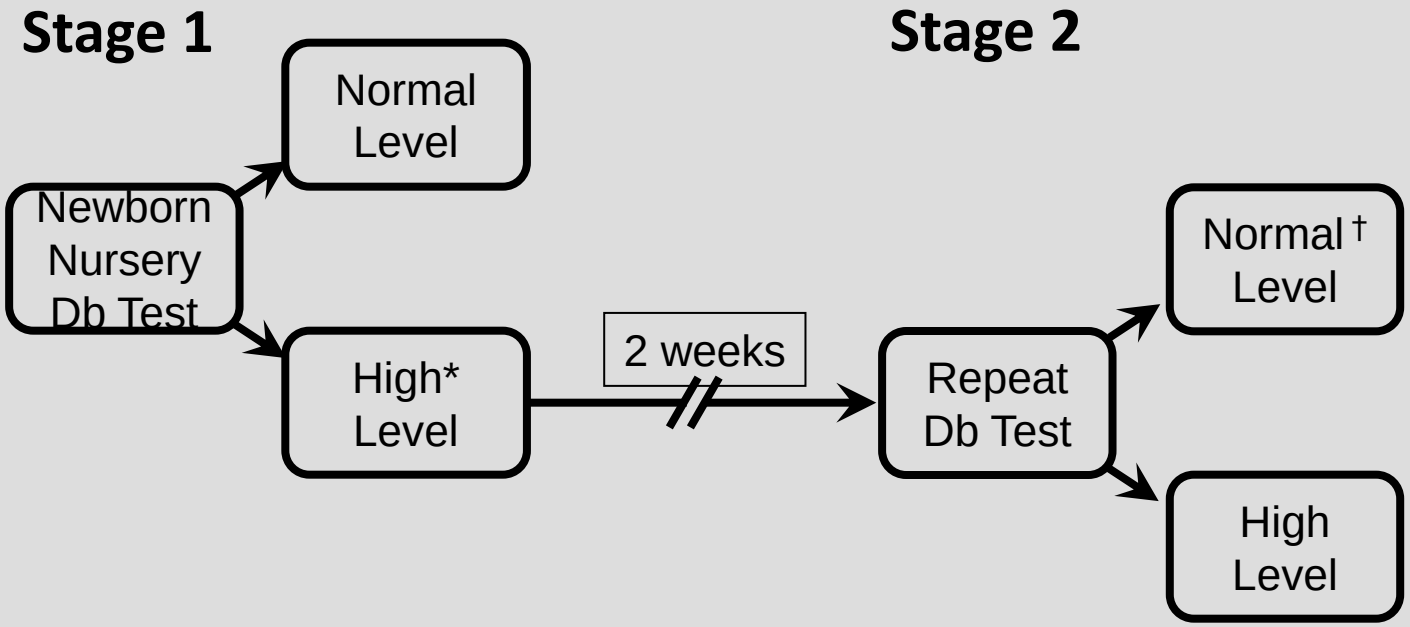
TWO-STAGE DB SCREENING SCHEMA



*high = anything over the ULN for that laboratory

† normal = ≤ stage 1 measure AND ≤ 1 mg/dL

- **Prospective study 11,636 neonates**
- **Test 1: Db/Cb ≤60 hours-of-life**
- **Test 2: Db/Cb at or before 1st well-child visit**

Newborn Bilirubin Screening for Biliary Atresia

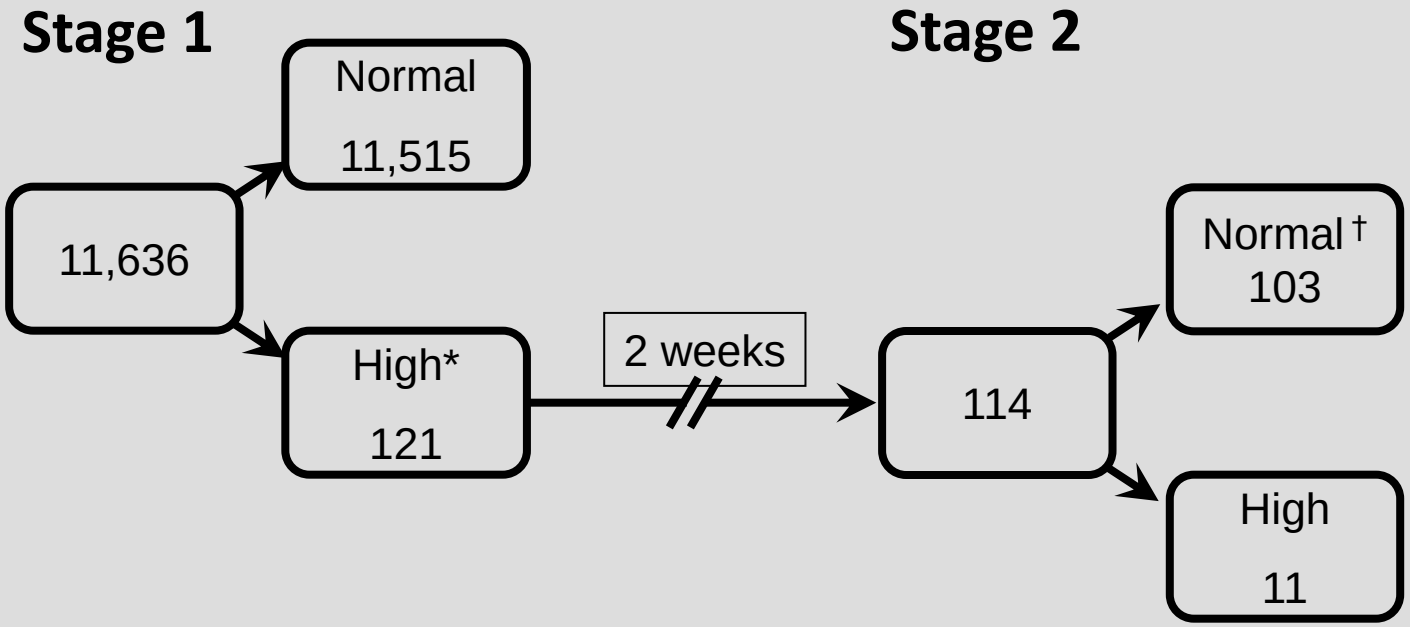
TO THE EDITORS: Biliary atresia accounts for approximately 60% of the liver transplantations in infants younger than 1 year of age. These complicated early transplantations can be prevented only with the use of the Kasai hepatoportoenterostomy. The success of the Kasai procedure is varied, but a good outcome is more likely if the operation is performed before 30 to 45 days of life.[1] Unfortunately, in the United States, infants with biliary atresia are usually identified later and the average age at surgery is 60 to 70 days.[2]

95th percentile reference interval in their laboratory. In stage 2, infants were considered to be positive if they had rising concentrations on retesting at (or before) the first well-child visit. All cases of biliary atresia were identified by tracking infants who were undergoing liver evaluation at the two subspecialty-care pediatric hospitals in Houston.

A total of 11 infants retested positive (median age, 14 days), of whom 3 required an invasive

Harpavat S *et al*, 2016, *NEJM*

PROSPECTIVE STUDY #1

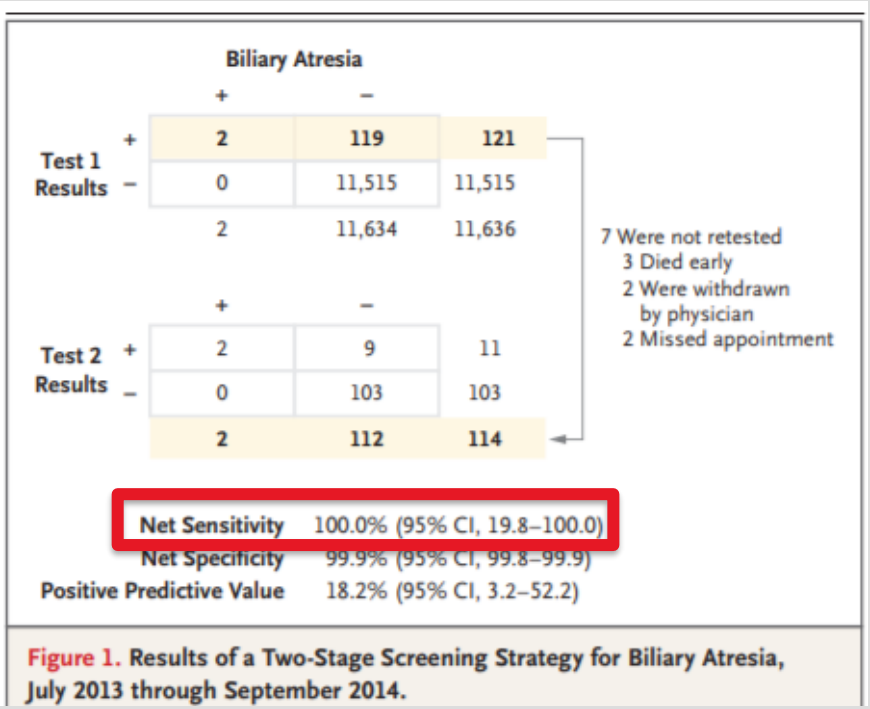


*high = anything over the ULN for that laboratory

† normal = ≤ stage 1 measure AND ≤ 1 mg/dL

11 Stage 2 Positive Tests

- Biliary atresia (2)
- Alpha-1 AT MZ (1)
- Rh-incompatibility (1)
- Prematurity, infection (1)
- Resolved w/ follow-up (6)



		Biliary Atresia +	Biliary Atresia −	
Test 1 Results	+	2	119	121
	−	0	11,515	11,515
		2	11,634	11,636

7 Were not retested
3 Died early
2 Were withdrawn by physician
2 Missed appointment

		Biliary Atresia +	Biliary Atresia −	
Test 2 Results	+	2	9	11
	−	0	103	103
		2	112	114

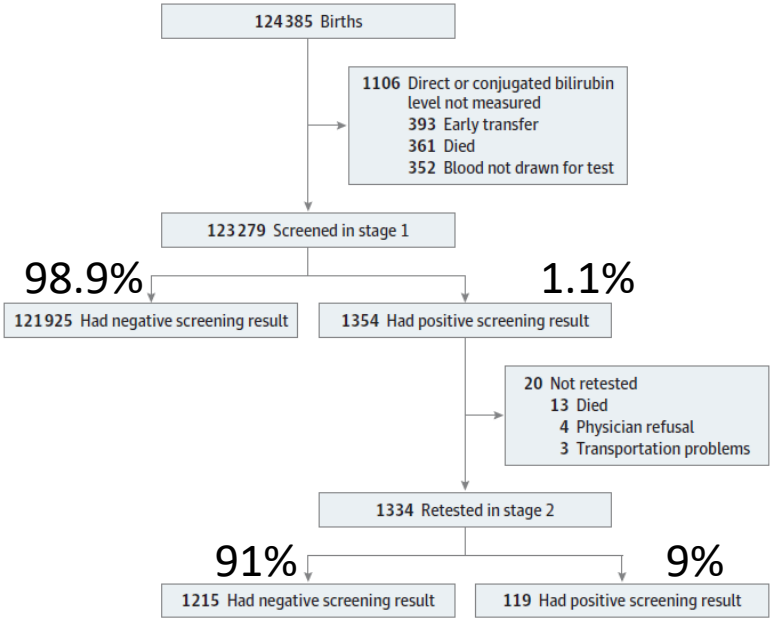
Net Sensitivity	100.0% (95% CI, 19.8–100.0)
Net Specificity	99.9% (95% CI, 99.8–99.9)
Positive Predictive Value	18.2% (95% CI, 3.2–52.2)

Figure 1. Results of a Two-Stage Screening Strategy for Biliary Atresia, July 2013 through September 2014.

Harpavat S *et al*, 2016, *NEJM*

PROSPECTIVE STUDY #2

Figure 1. Patient Flow for the 2-Stage Screening Study for Biliary Atresia



Stage 1 testing occurred within the first 60 hours of life. Stage 2 testing occurred at or before the 2-week well-child visit.

Harpavat S *et al*, 2020, *JAMA*

119 positive stage 2

7 biliary atresia

Figure 2. Newborn Direct or Conjugated Bilirubin Screening for Biliary Atresia

Stage 1	Positive screening result	Negative screening result	Total No.
Positive	7	1347	1354
Negative	0	121925	121925
Total	7	123272	123279

Stage 2	Positive screening result	Negative screening result	Total No.
Positive	7	112	119
Negative	0	1215	1215
Total	7	1327	1334[a]

Total	Positive screening result	Negative screening result	Total No.
Positive	7	112	119
Negative	0	123140	123140
Total	7	123252	123259

	% (95% CI)
Sensitivity	100.0 (56.1-100.0)
Specificity	99.9 (99.9-99.9)
PPV	5.9 (2.6-12.2)
NPV	100.0 (100.0-100.0)

NPV indicates negative predictive value; PPV, positive predictive value.

[a] There were 20 newborns who were not retested in stage 2 because 13 died, the physician refused to test in 4, and there were transportation problems for 3.

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Harpavat S *et al*, 2020, *JAMA*

Table 2. Diagnoses and Evaluation for False-Positive Screening Results (n = 112)

Description of diagnosis and evaluation	No. (%)
Type of diagnosis	
Not determined	59 (52.7)
Cholestasis-associated conditions[a]	17 (15.2)
Heterozygosity in cholestasis-related genes[b]	12 (10.7)
Cholestatic liver diseases[c]	9 (8.0)
Congenital infections[d]	8 (7.1)
Excessive red blood cell clearance	7 (6.3)
Type of evaluation performed	
Additional direct or conjugated bilirubin testing only	28 (25.0)
Additional laboratory testing	25 (22.3)
Additional noninvasive imaging	38 (33.9)
Liver biopsy with or without percutaneous transhepatic cholangiogram	20 (17.9)
Intraoperative cholangiogram	1 (0.9)

[a] Included trisomy 21 (5 cases), gastroschisis (4 cases), trisomy 18 (3 cases), portosystemic shunt (2 cases), maternal lupus (1 case), omphalocele (1 case), and panhypopituitarism (1 case).

[b] The gene names appear in eTable 7 in the Supplement.

[c] Included Alagille syndrome (4 cases), α_1 antitrypsin deficiency (3 cases), *ABCB11* deficiency (1 case), and choledochal cyst (1 case).

[d] Included cytomegalovirus (3 cases), syphilis (3 cases), coxsackievirus (1 case), and rubella (1 case).

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Harpavat S *et al*, 2020, *JAMA*

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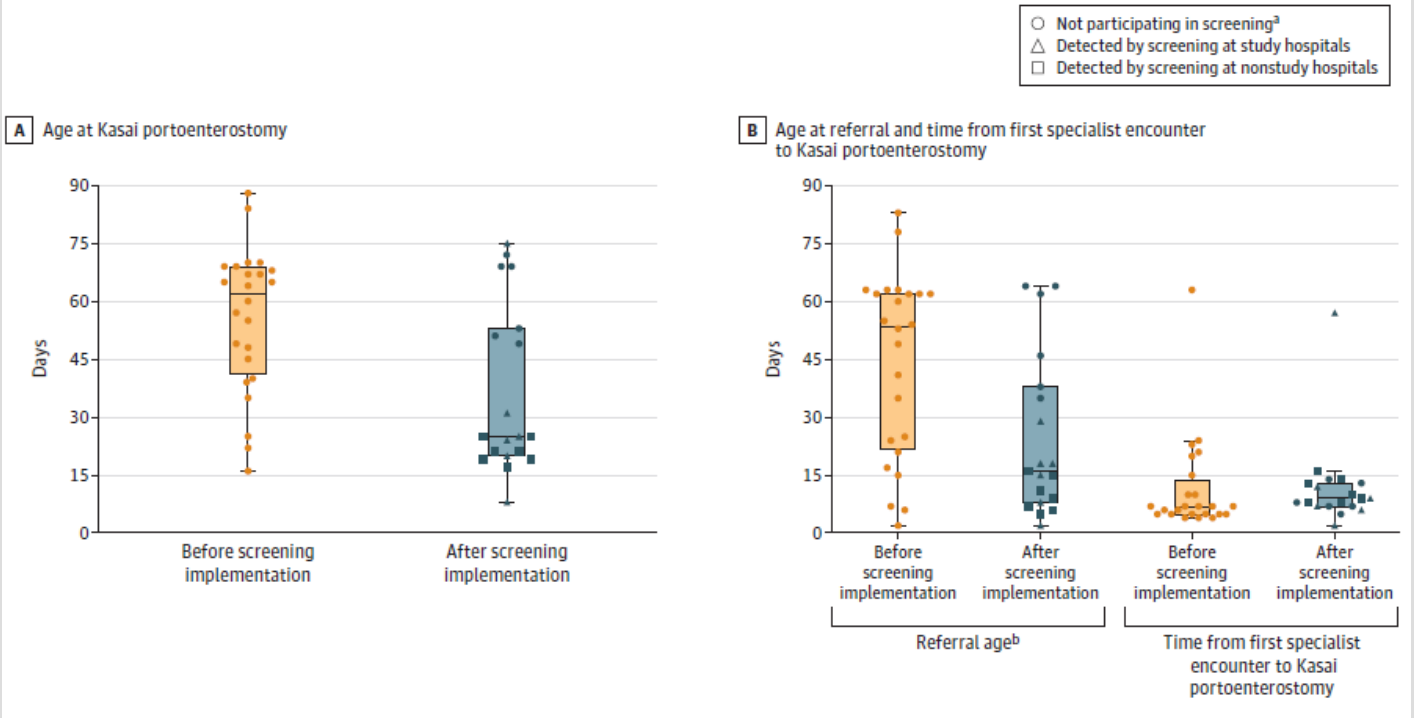
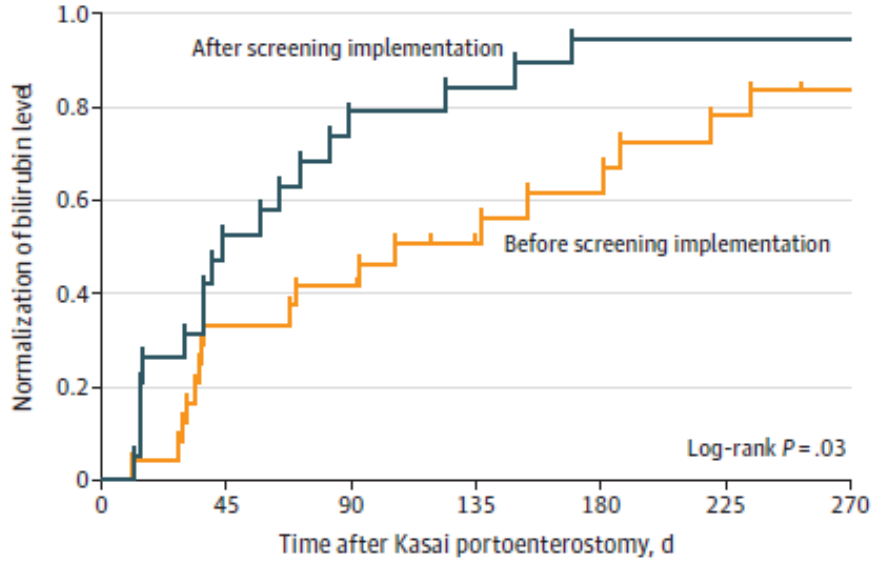
SCREENING LEADS TO TIMELIER KASAI



Harpavat S *et al*, 2020, *JAMA*

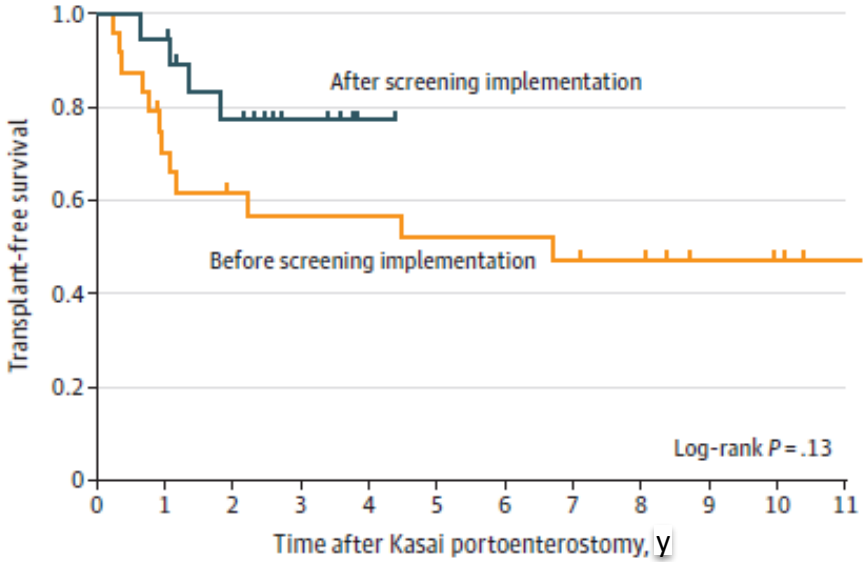
C Time from Kasai portoenterostomy to normalization of bilirubin level



No. at risk

Before	24	16	14	10	7	4	2
After	19	9	4	3	1	1	1

D Time from Kasai portoenterostomy to transplant-free survival



No. at risk

Before	24	16	13	12	12	11	11	10	9	6	4	1
After	19	18	13	6	1	0	0	0	0	0	0	0

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Harpavat S *et al*, 2020, *JAMA*

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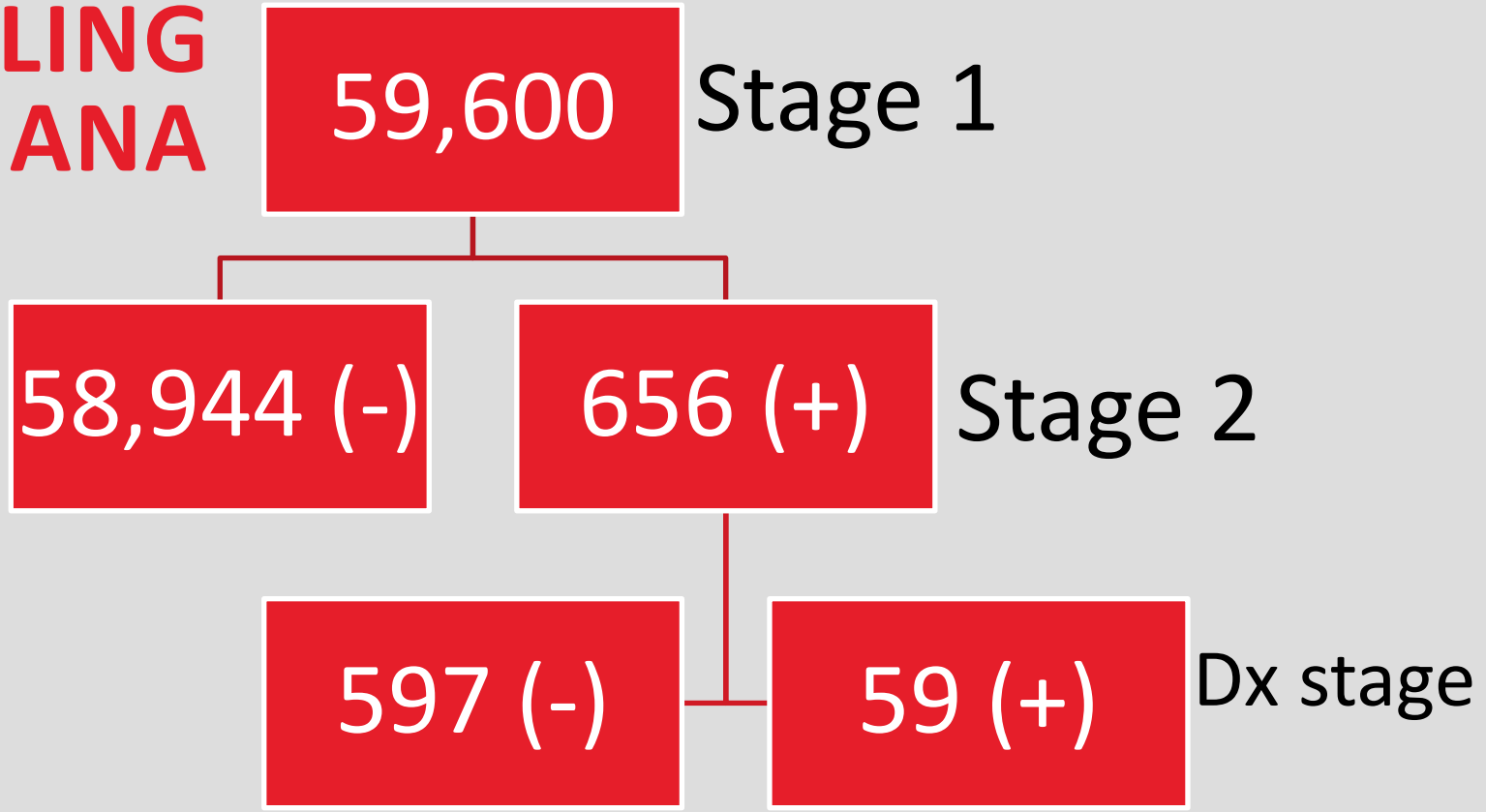
MODELING LOUISIANA



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The Centers for Disease Control and Prevention (CDC), National Vital Statistics Reports (NVSR), Vol. 68, No. 13: Births: Final Data for 2018, November 27, 2019.

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DIAGNOSTIC INVESTIGATIONS

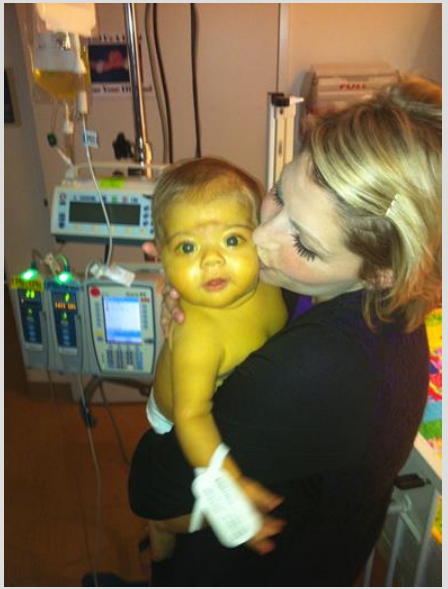
59 patients

- 25% follow-up bilirubin only (15 infants)
- 22% other lab testing (13 infants)
- 34% non-invasive imaging (20 infants)
- 19% liver biopsy±PTC (11 infants)

WHAT ABOUT COST*?

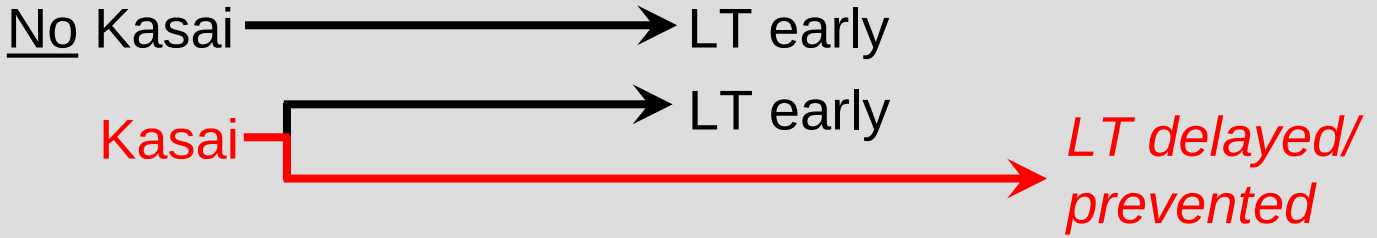
- Stage 1: ~$288,464 (59,600 births x $4.84)
- Stage 2: ~$3,175 (656 patients x $4.84)
- Diagnostics: ~$20,306 (59 patients)

Annual statewide cost ~$311,945



Charges based on Ochsner's charge master-2021

SCREENING = TRANSPLANT SAVINGS



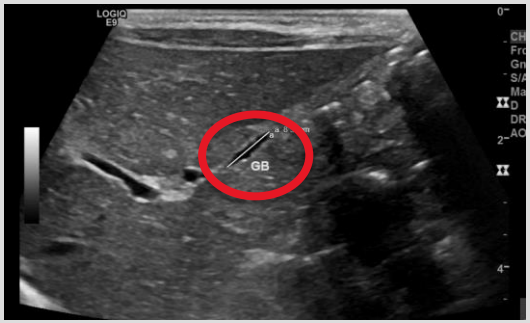
Clinical Course	Early N = 25	Delayed N = 22	*P*
Admission, median days (min, max)	42 (10,199)	9 (5,39)	<0.0001
ICU before Transplant, % (n)	44 (11)	4.5 (1)	0.002
Prolonged Intubation, % (n)	48 (12)	4.5 (1)	0.001
Renal Replacement Therapy, % (n)	28 (7)	0 (0)	0.01

DB SCREENING IN LOUISIANA

- Initiated March 2021 at Ochsner Baptist
- Subsequently expanded to Ochsner Kenner, Ochsner WB & Ochsner Baton Rouge
- 18,733 neonates screened through February 29, 2024 (96.4%)
- Step 1 positivity rate 0.7% (128 babies)
  - 2 babies with biliary atresia (~1:9,400 births)

PATIENT #1; 39-WEEK LGA MALE

- Db 1.5 (Tb 11.1) on DOL 2
- AST 62, ALT 20, GGT 739
- Liver US (DOL 3)



- DOL 7: IR cholangiogram & liver bx
- DOL 12: Intraoperative cholangiogram and Kasai
- Now 2 yrs post-Kasai
  - AST 52, ALT 25, GGT 12, Tb 0.3
  - No post-Kasai hospitalizations

PATIENT #2; 38-WEEK FEMALE

- Induced for known unbalanced AV canal & hypoplastic RV; situs inversus
- Db 0.8 (Tb 5.6) on DOL 2
- AST 36, ALT 11, GGT 366
- Liver US (DOL 2): situs inversus, polysplenia, preduodenal PV, interrupted IVC, hypoplastic GB
- DOL 35: IR cholangiogram & liver bx
- DOL 39: Intraoperative cholangiogram and Kasai
- Now 16-mo post-Kasai
  - AST 34, ALT 19, GGT 25, Tb 0.1
  - No post-Kasai liver-related hospitalizations

COMPARATIVE OUTCOMES OF PATIENTS FROM NON-SCREENING NURSERIES

- 10 infants with BA born at non-screening hospitals but referred to Ochsner during same period
- 5 transplanted
- 1 on the transplant waitlist

SUMMARY: UNIVERSAL NEWBORN SCREENING FOR BILIARY ATRESIA…

- Is feasible using existing technology and systems of care
- Is discrete, objective, and highly sensitive
- Reduces time to diagnosis→ Kasai→ improving TFS
- Associated with modest costs, offset at least in part, by savings from avoiding early transplantation

THANK YOU FOR YOUR COLLABORATION!

ryan.himes@ochsner.org

713-882-0032