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Since publication of their article, the authors report no further potential conflict of interest.

1. Meschia JF, Voeks JH, Leimgruber PP, et al. Management of vascular risk factors in the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST). J Am Heart Assoc 2014; 3(6):e001180.
2. Howard VJ, Lutsep HL, Mackey A, et al. Influence of sex on outcomes of stenting versus endarterectomy: a subgroup analysis of the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST). Lancet Neurol 2011;10:530-7.
3. Voeks JH, Howard G, Roubin GS, et al. Age and outcomes after carotid stenting and endarterectomy: the carotid revascularization endarterectomy versus stenting trial. Stroke 2011;42: 3484-90.

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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]

To address this problem, the American Academy of Pediatrics recently requested more studies to evaluate screening strategies for biliary atresia.[3] Potential strategies can capitalize on the well-characterized natural history of the disease. In the preclinical phase, infants appear normal but have an elevated serum concentration of direct or conjugated bilirubin at birth, which rises and plateaus over time.[4,5] Signs such as jaundice and pale stools develop in the first months of life. Without intervention, end-stage liver disease develops in all infants with biliary atresia before 1 year of age.

After receiving institutional review board approval, we prospectively tested a two-stage screening strategy for biliary atresia that was based on serum bilirubin measurements. A total of 11,636 infants born in four Houston hospitals over a 15-month period were included (98.8% of all births) (Table S1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org). These hospitals routinely measure total (and direct or conjugated) bilirubin concentrations in all newborns to assess the need for phototherapy. In stage 1, newborns were considered to be positive if they had a direct or conjugated bilirubin concentration that exceeded the 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

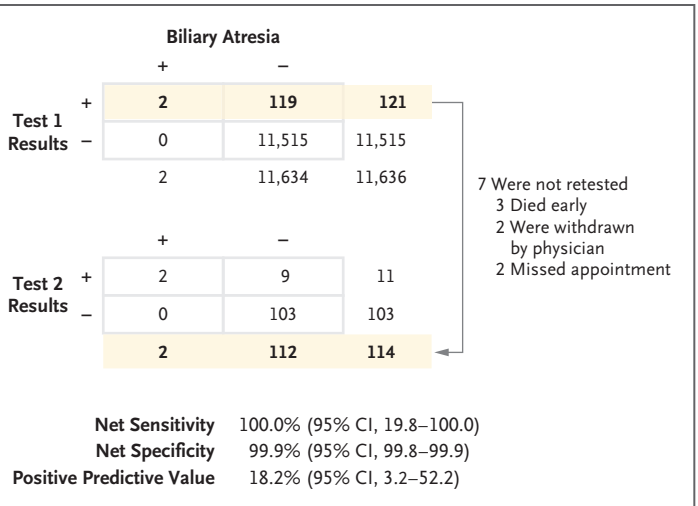

Figure 1. Results of a Two-Stage Screening Strategy for Biliary Atresia, July 2013 through September 2014.

Test 1 was a measurement of the serum concentration of direct or conjugated bilirubin in the newborn period before hospital discharge (≤60 hours of life). Newborns were considered to be positive if they had a direct or conjugated bilirubin concentration that exceeded the 95th percentile reference interval in their laboratory. Test 2 was a measurement of the serum concentration of direct or conjugated bilirubin at or before the first well-child visit (≤2 to 3 weeks of life). Infants were considered to be positive if they had rising concentrations on retesting. Only infants who tested positive in test 1 underwent test 2. CI denotes confidence interval.

evaluation (Table S2 in the Supplementary Appendix). One infant did not have biliary atresia but had alpha$_1$-antitrypsin Z allele heterozygosity. A second infant had a variant of biliary atresia with severe congenital heart disease, which precluded the Kasai procedure. The third infant had isolated biliary atresia. This patient did not have jaundice and had normal-colored stools at detection. The Kasai operation was performed when the infant was 26 days of age. The conjugated bilirubin concentration normalized within 3 months after the procedure, and the patient survived transplant-free past 2 years of age. The net sensitivity of screening was 100.0%, the net specificity 99.9%, and the net positive predictive value 18.2% (Fig. 1).

These preliminary results support the hypothesis that screening of the direct or conjugated bilirubin concentration in newborns can identify infants with biliary atresia early, before symptoms develop. Larger studies are needed to confirm the benefits of screening and to assess the cost-effectiveness.

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Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

1. Jimenez-Rivera C, Jolin-Dahel KS, Fortinsky KJ, Gozdyra P, Benchimol EI. International incidence and outcomes of biliary atresia. J Pediatr Gastroenterol Nutr 2013;56:344-54.
2. Superina R, Magee JC, Brandt ML, et al. The anatomic pattern of biliary atresia identified at time of Kasai hepatoportoenterostomy and early postoperative clearance of jaundice are significant predictors of transplant-free survival. Ann Surg 2011;254:577-85.
3. Wang KS. Newborn screening for biliary atresia. Pediatrics 2015;136(6):e1663-9.
4. Harpavat S, Finegold MJ, Karpen SJ. Patients with biliary atresia have elevated direct/conjugated bilirubin levels shortly after birth. Pediatrics 2011;128(6):e1428-33.
5. Terui K, Higashimoto Y, Saito E, et al. Diagnosis of biliary atresia can not be excluded by declining trend of serum direct bilirubin. Pediatr Rep 2013;5(4):e17.

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The conference will be held in Ponte Vedra Beach, FL, Sept. 7–9. Registration deadline is Aug. 15.

Contact Mayo Medical Laboratories, 3050 Superior Dr. NW, Rochester, MN 55901; or call 507-266-5700; or e-mail mml@mayo.edu; or see http://www.mayomedicallaboratories.com.

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Contact InfoPlus Events, Suite 1406, Lake Central Bldg., Al Abraj St., Burj Khalifa Community, P.O. Box 77108, Dubai, United Arab Emirates; or call (971) 4 4218996; or e-mail DubaiShoulder@InfoPlusEvents.com; or see http://www.dubaishoulder.com.

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The following meetings will be held: "35th Annual Echocardiography Symposium" (Miami, Sept. 23 and 24) and "16th Annual Emergency Radiology Symposium" (Miami Beach, FL, Nov. 13–16).

Contact Julie Zimmett, CME Department, Baptist Health South Florida, 8900 N. Kendall Dr., Miami, FL 33176; or call (786) 596-2398; or e-mail juliez@baptisthealth.net; or see http://MiamiEcho.BaptistHealth.net or http://emradmiami.baptisthealth.net, respectively.

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Harpavat S, Garcia-Prats JA, Shneider BL. Newborn bilirubin screening for biliary atresia. N Engl J Med 2016;375:605-6. DOI: 10.1056/NEJMc1601230

Supplementary Appendix

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Supplement to: Harpavat, S, Garcia-Prats, JA, and Shneider, BL. Newborn Bilirubin Screening for Biliary Atresia.

Contents

Table S1 Subject characteristics (n=11,636)*

Male gender, n (%)	6,004	(51.6)
Race, n (%)		
White	8,785	(75.5)
Black	1,926	(16.6)
Asian	753	(6.5)
Other	172	(1.5)
Hispanic, n (%)	5,547	(47.7)
37-42 weeks gestation, n (%)	10,313	(88.6)
Test 1, median hours of life (IQR)	35	(35)
Test 2, median days of life (IQR)	14	(13)

**Represents 98.8% of newborns at study hospitals; remaining 137 newborns were not tested because of early death (n=55), early transfer (n=22), physician oversight (n=60), or parent refusal (n=1)*

Table S2 Clinical course for subjects screening positive (n=11)

Subject	Test 1			Test 2				Evaluation		
	Type	mg/dL	95%ile RI	Site	Type	mg/dL	95%ile RI	Tier	Diagnosis	Age Normalized
1	D	0.4	0.0-0.3	o	D	0.5	0.0-0.3	1	-	3 weeks
2	D	0.4	0.0-0.3	o	D	0.6	0.0-0.3	1	-	3 weeks
3	D	0.4	0.0-0.3	o	D	0.8	0.0-0.3	1	-	3 weeks
4	D	0.4	0.0-0.3	o	D	1.0	0.0-0.3	1	-	3 weeks
5	D	0.4	0.0-0.3	i	D	1.0	0.0-0.3	3	A1AT heterozygote	15 weeks
6	D	0.4	0.0-0.3	o	D	1.6	0.0-0.3	1	-	3 weeks
7	D	0.5	0.0-0.4	o	D	0.7	0.0-0.5	1	-	3 weeks
8	C	0.3	0.0-0.2	i	C	1.5	0.0-0.2	1	Rhesus incompatibility	7 weeks
9	C	0.4	0.0-0.2	i	C	9.4	0.0-0.2	3	Heart disease/biliary atresia	*
10	C	0.5	0.0-0.2	o	D	2.3	0.0-0.6	4	Biliary atresia	post-Kasai
11	C	1.6	0.0-0.2	i	C	6.2	0.0-0.2	2	Infection, prematurity	5 weeks

**Died at 15 weeks from heart complications (patient was too ill for the Kasai operation)*
Abbreviations: D = direct bilirubin, C = conjugated bilirubin, o = outpatient laboratory, i = inpatient (nursery) laboratory, RI = reference interval
Legend: Tier 1 = serum bilirubin measurement only; Tier 2= other laboratory tests ± imaging, Tier 3 (invasive) = liver biopsy ± percutaneous transhepatic cholangiogram, Tier 4 (gold standard) = intraoperative cholangiogram ± histopathological examination of bile duct remnants