Evaluating a Novel, Portable, Self-Administrable Device ("Beacon") That Measures Critical Flicker Frequency as a Test for Hepatic Encephalopathy

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INTRODUCTION: **We compared critical flicker frequency (CFF) thresholds obtained using a novel portable device "Beacon" with thresholds from the commercially available Lafayette Flicker Fusion System (Lafayette-FFS) in patients with cirrhosis.**

METHODS: **One hundred fifty-three participants with chronic liver disease underwent CFF testing using Beacon and Lafayette-FFS with a method-of-limits and/or forced-choice protocol.**

RESULTS: **Beacon demonstrated excellent test-retest reliability (intraclass correlation 0.91–0.97) and good correlation with the Lafayette-FFS values (intraclass correlation 0.77–0.84). Forced-choice CFF were on average 4.1 Hz higher than method-of-limits descending CFFs.**

DISCUSSION: **Beacon can be self-administered by patients with chronic liver disease and cirrhosis to measure CFF, a validated screening test for minimal hepatic encephalopathy.**

KEYWORDS: Flicker fusion; covert encephalopathy; Beacon-App; Beacon; home testing

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/C885

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INTRODUCTION

The critical flicker frequency (CFF) is a well-studied neurophysiologic screening test for minimal hepatic encephalopathy (MHE) (1–4). Currently available devices that measure CFF, such as the Flicker Fusion System (Lafayette-FFS; Lafayette Instrument Company, Lafayette, IN), are large, expensive, and not designed for at-home use (5). To address this limitation, we developed Beacon, a novel portable device that measures CFF and is administered by a smartphone app (6). Beacon has not yet been evaluated in patients with chronic liver disease or cirrhosis. In addition, CFF is typically measured using a method-of-limits descending (MOL-D) protocol, which is prone to a response bias due to observer familiarity with testing. The aims of this study were to

1. Determine whether patients with chronic liver disease can self-measure CFF using Beacon.
2. Evaluate the level of agreement for measures obtained by Beacon and the Lafayette-FFS.
3. Compare the frequencies obtained from a forced-choice protocol with those obtained from an MOL-D protocol.

METHODS

Study participants and testing

We recruited participants from the hepatology clinics of the University of Washington between January 2019 and December 2021. Study participants completed CFF testing with Beacon (Figure 1a–b) and/or the Lafayette-FFS (Figure 1c) using an MOL-D and/or a forced-choice protocol (see Supplementary Methods and Supplementary Figure 1, http://links.lww.com/AJG/C885).

Statistical analysis

We calculated the intraclass correlation to assess the degree of correlation between Beacon and the Lafayette-FFS. The intraclass correlation assesses the degree of correlation between 2 scores but allows for a systematic difference between the 2 scores (e.g., *score1 = score2 + c, where c is a constant*). Difference plots

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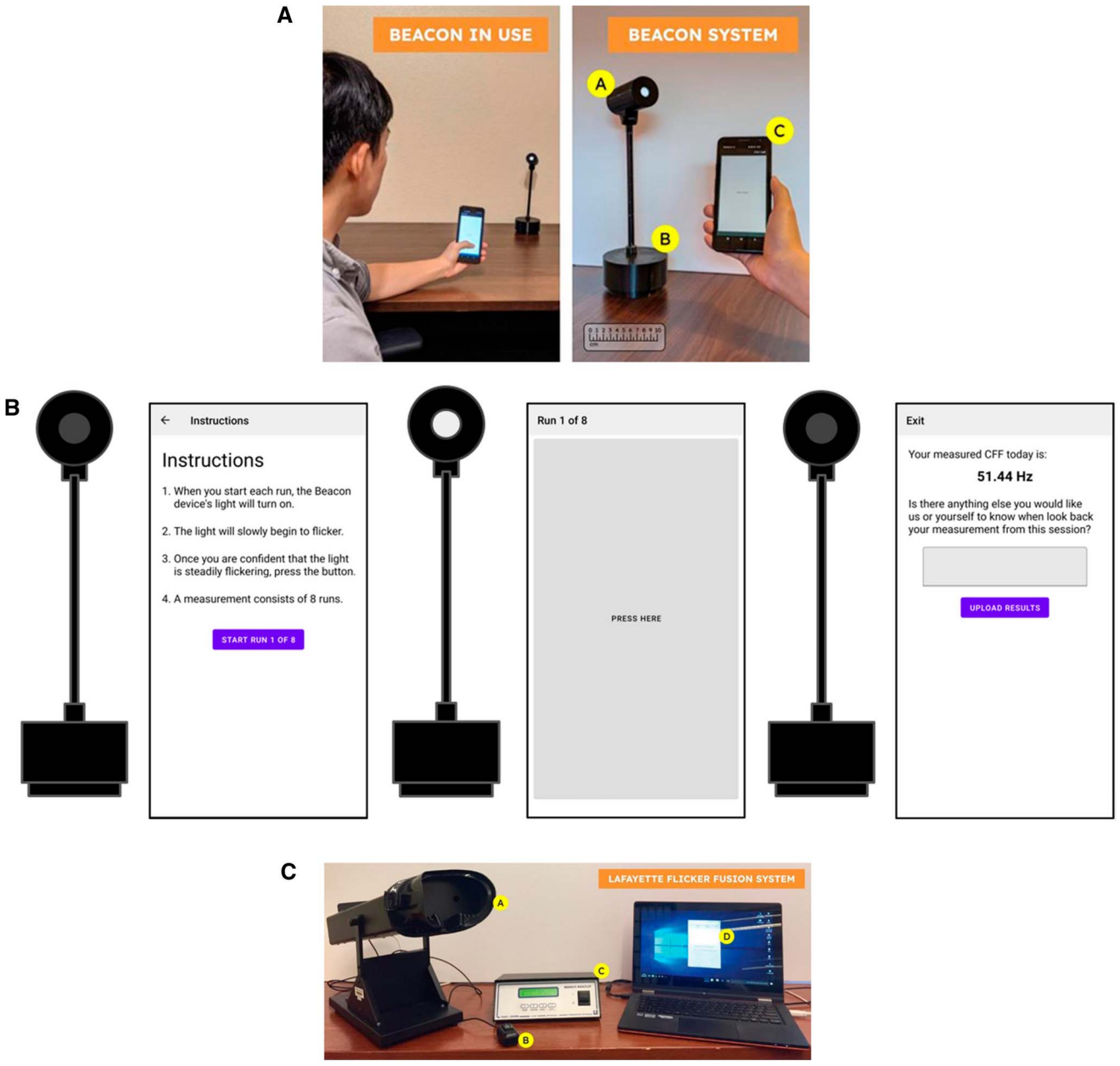

Figure 1. Devices used in this study to measure critical flicker frequency. (**a**) Beacon light source. The Beacon system consists of 2 components: The light stimulus source (A) with wireless controller and battery base (B) (overall dimensions: 8.9 × 30 cm) and an application running on a smartphone for user input and to record results (C). (**b**) Smartphone application. The light stimulus source is controlled by a companion application running on a smartphone connected through Bluetooth. Users are presented with instructions (left); an interface for inputting when they see the light flicker, by pressing anywhere on the full screen "Press Here" button (middle); and their CFF measurement in Hz (right). (**c**) The Lafayette flicker fusion system. There are 4 components: a viewing chamber with the light stimulus (A), a clicker (B), a controller (C), and a software program to record results (D). CFF, critical flicker frequency.

were also generated to display differences between devices and protocols. All statistical analyses were run in R software, version 1.4.1717.

RESULTS

Among the 153 study participants, 108 had cirrhosis and 45 had chronic liver disease without cirrhosis (Table 1). The test-retest intraclass correlation of Beacon was 0.95 (95% confidence interval [CI] 0.91–0.97) for the MOL-D protocol and 0.92 (95% CI 0.88–0.95) for the forced-choice protocol (Figure 2a–b).

CORRELATION BETWEEN CFF THRESHOLDS DETERMINED BY BEACON AND LAFAYETTE-FFS

The mean values were similar (39.2 Hz for Beacon vs 39.3 Hz for Lafayette-FFS) for MOL-D derived CFF thresholds, and the intraclass correlation between the 2 devices was 0.77 (95% 0.67–0.85) (see Supplementary Table 1, http://links.lww.com/AJG/C885). Among those with cirrhosis (n = 60), the mean CFF thresholds for the 2 devices were similar (38.1 Hz for Beacon vs 37.9 Hz for Lafayette-FFS, mean difference 0.4 Hz), and the intraclass correlation was 0.76 (95% CI 0.63–0.85).

Table 1. Baseline characteristics of the study participants who underwent in-clinic testing with the Lafayette-FFS and Beacon devices

Baseline characteristics	All participants (N = 153)	Participants with cirrhosis (n = 108)	Participants without cirrhosis (n = 45)
Age, yr (mean ± SD)	53.4 ± 13.8	56.9 ± 12.5	44.9 ± 13.1
Male	89 (58.2%)	66 (61.1%)	22 (48.9%)
Race/ethnicity			
White, non-Hispanic	128 (83.7%)	92 (85.2%)	36 (80%)
Black, non-Hispanic	5 (3.3%)	3 (2.8%)	2 (4.4%)
Asian	8 (5.2%)	2 (1.9%)	6 (13.3%)
Hispanic or Latino	6 (3.9%)	5 (4.6%)	1 (2.2%)
Other	6 (3.9%)	6 (5.6%)	0 (0%)
Underlying liver disease			
Hepatitis C	29 (19.0%)	26 (24.1%)	3 (6.7%)
Hepatitis B	11 (7.2%)	1 (0.9%)	10 (22.2%)
Nonalcoholic fatty liver disease or cryptogenic	33 (21.6%)	33 (30.6%)	7 (15.6%)
Alcohol-related disease	27 (17.6%)	25 (23.1%)	2 (4.4%)
Autoimmune, PBC, PSC	32 (20.9%)	19 (17.6%)	13 (28.9%)
Other liver disease	14 (9.2%)	4 (3.7%)	10 (22.2%)
MELD score (mean ± SD)	—	14.5 ± 6.3	—
CTP class			
A	—	47 (43.5%)	—
B	—	44 (40.7%)	—
C	—	17 (15.7%)	—
Nonbleeding esophageal varices	—	68 (63.0%)	—
Bleeding esophageal varices	—	28 (25.9%)	—
History of TIPS	—	17 (15.7%)	—
History of hepatic encephalopathy		49 (45.4%)	
Medication use*			
Diuretic use	—	53 (49.1%)	—
Beta blocker	—	27 (25%)	—
Lactulose	—	42 (38.9%)	—
Rifaximin	—	28 (25.9%)	—
Critical flicker frequency (Hz, mean ± SD)			
Lafayette-FFS: MOL-D	39.3 ± 6.1	37.9 ± 5.9	43.1 ± 5.0
Beacon: MOL-D	39.2 ± 4.4	38.1 ± 4.2	42.0 ± 3.7
Beacon: forced-choice	44.7 ± 5.4	43.0 ± 6.8	46.9 ± 4.8

CTP, Child-Turcotte-Pugh; MELD, model for end-stage liver disease; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; TIPS, transjugular intrahepatic portosystemic shunt.

CFF thresholds obtained using the forced-choice protocol were higher than those obtained using the MOL-D protocol

The mean threshold obtained using the forced-choice protocol was higher (44.9 Hz for the forced-choice protocol vs 40.8 Hz for the MOL-D protocol, mean difference 4.1 Hz) (see Supplementary Table 2, http://links.lww.com/AJG/C885), and the intraclass correlation for the 2 protocols was 0.73 (95% CI 0.61–0.82).

Beacon-derived CFF thresholds are lower for those with cirrhosis

Compared with participants without cirrhosis, those with cirrhosis had lower MOL-D–derived thresholds (Beacon: 38.1 vs 42 Hz, $P < 0.001$) (Table 1, Figure 2). In a subgroup analysis of participants with cirrhosis, there was no significant difference in thresholds between those without prior overt encephalopathy (mean 39.0 Hz for MOL-D, mean 43.1 Hz for forced-choice) and those with prior overt encephalopathy (mean 37.4 Hz for MOL-D, mean 43.3 Hz for forced-choice) (Figure 2).

Beacon-derived CFF thresholds are lower with increasing age

Among those with cirrhosis, for each decade increase in age, CFF thresholds decreased an average of 1.3 Hz (95% CI 0.7–1.9 Hz) for the MOL-D protocol and 2.3 Hz (95% CI 1.3–3.3 Hz) for the

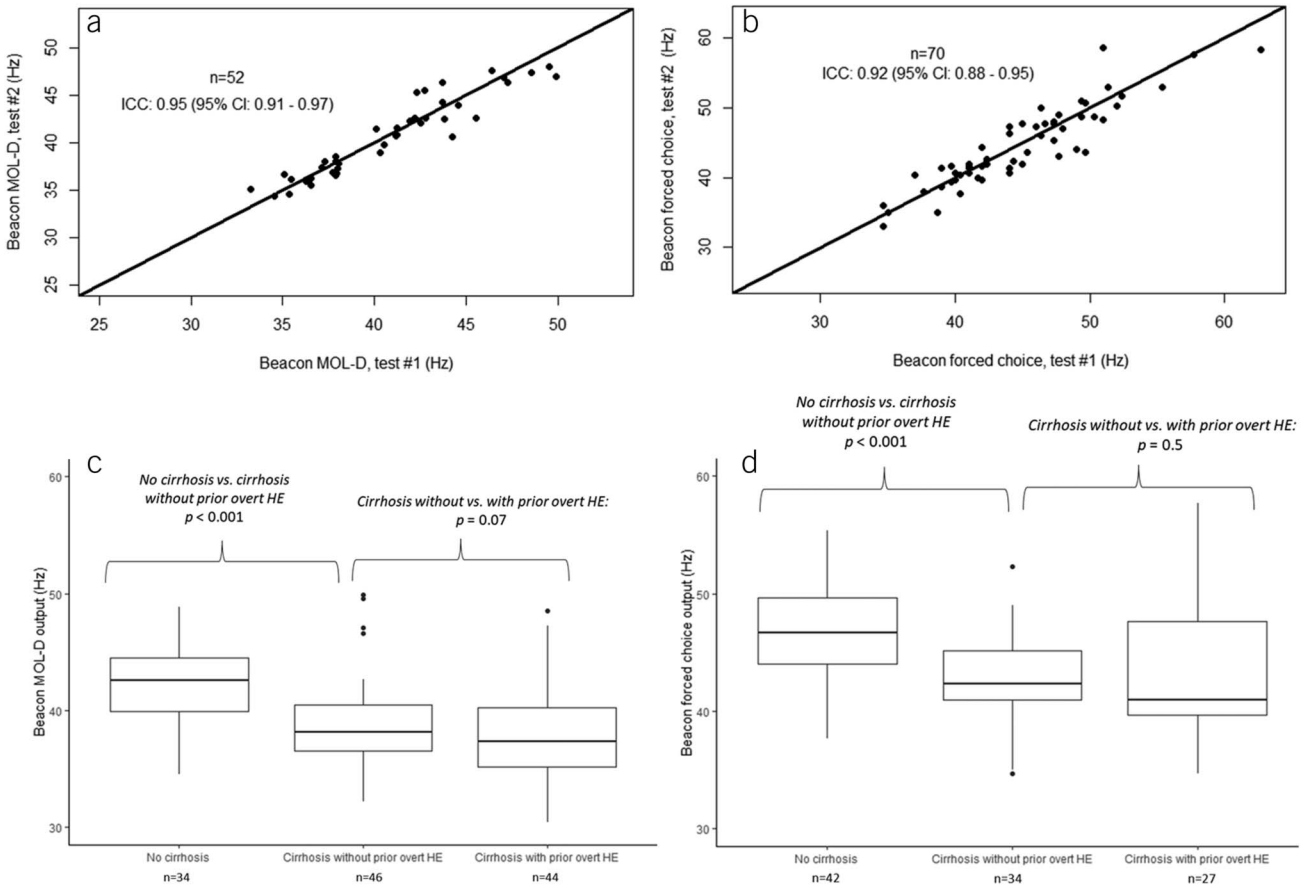

Figure 2. (**a** and **b**) Beacon test-retest characteristics (**a** and **b**) and output by cirrhosis and prior overt hepatic encephalopathy (**c** and **d**). (**a**) Beacon demonstrated excellent test-retest reliability using the MOL-D protocol (intraclass correlation 0.95, 95% confidence interval [CI] 0.91–0.97). (**b**) Beacon demonstrated excellent test-retest reliability using the forced-choice protocol (intraclass correlation 0.92, 95% CI 0.88–0.95). (**c** and **d**) compared with participants without cirrhosis, those with cirrhosis had lower MOL-D (**c**)–derived and forced-choice (**d**)–derived thresholds. Among patients with cirrhosis, there was no significant difference in thresholds between those without a history of overt encephalopathy (mean 39.0 Hz for MOL-D, mean 43.1 Hz for forced-choice) and those without prior overt encephalopathy (mean 37.4 Hz for MOL-D, 43.3 Hz for forced-choice). CI, confidence interval; HE, hepatic encephalopathy; MOL-D, method-of-limits descending.

forced-choice protocol (see Supplementary Figures 2 and 3, http://links.lww.com/AJG/C885).

DISCUSSION

Patients with chronic liver disease and cirrhosis were able to self-administer Beacon to measure CFF, a validated screening test for MHE (1,2,4,7). Beacon-derived CFF thresholds were reliable and demonstrated good correlation with those obtained using the commercially available Lafayette-FFS device.

Beacon offers a portable option for CFF testing that can complement available MHE screening tests, such as the Stroop test, inhibitory control test, and electroencephalogram. One widely used test is the smartphone application EncephalApp, which administers the Stroop test, a psychometric test of cognitive flexibility and response inhibition (8–10). However, as a psychometric test, performance can be confounded by effort, education, and other social determinants of health. Beacon, as a *neurophysiologic test* that measures CFF, is unlikely to be affected by these factors, although it is clearly affected by age (indicating that age-adjusted thresholds for MHE are likely required) and the intensity of light source. As such, CFF testing with Beacon can serve as an alternative or complementary at-home screening test that can improve HE screening rates, which are currently low (11,12). We hope to make Beacon available to patients, clinical providers, and other investigators.

Prior studies evaluating CFF as a screening test for MHE have generally used a method-of-limits protocol, which is prone to a response bias from test familiarity (13). We piloted an alternative forced-choice protocol (13). We found that the forced-choice protocol was reliable; however, the average completion time (>5 minutes) may be inconvenient for routine at-home screening of MHE.

We note potential study limitations. First, prior studies in patients with liver disease have used the Hepatonorm Analyzer (NevoLAB, Maierhofen, Germany) to measure CFF. However, this device was not available for purchase in the United States. We instead used the commercially available Lafayette-FFS, which has been used for CFF measurement for other disease processes (14,15). Second, we did not evaluate for the presence of MHE using other measures such as psychometric testing. Finally, this study was also not designed to assess the risk of clinical outcomes associated with baseline CFF values. Additional studies are planned to evaluate whether at-home CFF measurements using Beacon are associated with the development of clinical outcomes including overt hepatic encephalopathy.

Beacon is a reliable, portable, and self-administrable device that measures CFF as a screening test for MHE. Further studies

with a long-term follow-up are needed to study the impact of home-based self-monitoring of CFF using Beacon on clinical outcomes, including overt hepatic encephalopathy, hospitalizations, and mortality.

CONFLICTS OF INTEREST

Guarantors of the article: George N. Ioannou, BMBCh, MS, Philip Vutien, MD, MS.

Specific author contributions: P.V. and R.L.: study concept and design, analysis and interpretation of data, drafting and critical review of the manuscript. R.K., S.A.M., and J.F.: study concept and design, analysis and interpretation of data, critical review of the manuscript. K.W.: study concept and design, acquisition of data, critical review of the manuscript. M.Y.: acquisition of data, critical review of the manuscript. G.N.I.: study concept and design, analysis and interpretation of data, and drafting and critical review of the manuscript.

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Potential competing interests: None to report.

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