

# Animal Naming Test Is Associated With Poor Patient-Reported Outcomes and Frailty in People With and Without Cirrhosis: A Prospective Cohort Study

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**INTRODUCTION:** Cognitive dysfunction is a major driver of care complexity, poor patient-reported outcomes, and frailty for people with cirrhosis. The performance and clinical associations of the animal naming test (ANT) in the general population are unknown. We evaluated ANT performance in a representative sample of older Americans with and without chronic liver disease (CLD).

**METHODS:** We analyzed 6,661 subjects enrolled in the 2010–2016 Health and Retirement Survey, a representative cohort of >30,000 US adults. Average age of participants was 75 years. We evaluated 3 subject subgroups: (i) without CLD, (ii) noncirrhosis CLD, and (iii) cirrhosis. We determined the association between the ANT (overall) and S-ANT1 <10 (adjusted for age and education) and health status, basic and instrumental activities of daily living, healthcare utilization (care hours received and hospitalizations), and frailty measures (hand grip and walk speed).

**RESULTS:** Overall, 8.2% of the sample had noncirrhotic CLD and 1.3% had cirrhosis. CLD or cirrhosis was not independently associated with ANT. Poor ANT performance was associated with poor health status and frailty overall. An S-ANT <10 was associated with fair-poor self-reported health (odds ratio [OR] 1.37; 95% confidence interval [CI]: 1.20–1.56), care hours received (incidence rate ratio [IRR] 2.39; 95% CI: 1.79–3.19), and hospitalizations (IRR 1.14; 95% CI: 1.03–1.26). S-ANT <10 was also associated with activities of daily living disability (OR 1.31; 95% CI: 1.13–1.51), instrumental activities of daily living disability (OR 1.85; 95% CI: 1.59–2.14), weaker hand grip (IRR 0.94; 95% CI: 0.92–0.96), and time to walk 2.5 m (IRR 1.23; 95% CI: 1.17–1.29).

**DISCUSSION:** ANT performance is not specific to CLD/cirrhosis but is associated with patient-reported outcomes and frailty in a nationally representative sample of elderly subjects with and without CLD.

**SUPPLEMENTARY MATERIAL** accompanies this paper at <http://links.lww.com/CTG/A740>

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## INTRODUCTION

Cognitive dysfunction is a major driver of morbidity and care complexity in chronic liver disease (CLD) (1–3). Cognitive dysfunction due to hepatic encephalopathy (HE), whether overt or covert, is associated with morbidity, mortality, frailty, and poor health status (2,4–6). There are many, possibly additive, sources of cognitive dysfunction among contemporary patients with CLD. For those with cirrhosis, these include hyperammonemia and inflammation (7). However, the prevailing underlying CLD carries important implications for cognitive function related to other brain disease pathways that can present before the onset of

cirrhosis. These are metabolic, age-related, vascular, and/or alcohol-related (8,9). Psychometric testing, for this reason, cannot specify the underlying physiology of cognitive dysfunction (10). Data regarding the performance of cognitive testing among older multimorbid patients with CLD are limited.

The animal naming test (ANT) is a widely used tool for assessing cognitive function. It is promising for its ease. It takes 1 minute and can even be performed remotely. Adequate performance requires efficient organization of verbal retrieval and recall, as well as self-monitoring, effortful self-initiation, and inhibition of incorrect responses (11). The ANT was recently

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validated as a test of covert HE and predictor of clinical outcomes among 327 Italian patients with cirrhosis (12). Data are limited regarding both the clinical utility of the ANT among older Americans and its association with patient-reported outcomes (PROs).

In this article, we linked prospective cross-sectional survey responses from the Health and Retirement Survey to Medicare data to (i) describe the determinants of ANT performance in a cohort with and without CLD and/or cirrhosis and (ii) determine the association between the ANT and both PROs and frailty.

## METHODS

This study was conducted using prospectively collected data from the Health and Retirement Study (HRS) linked to the Center for Medicare and Medicaid Services standard analytic files. The HRS is a biennial survey of a nationally representative cohort of >30,000 US adults older than 50 years. Surveys provide detailed information on participants' functional condition, health status, and caregiver assistance. The HRS has been used previously to characterize the functioning and caregiver support for individuals with cirrhosis (13). HRS respondents that met the following criteria were included in the study population: completed an interview between 2010 and 2016 and aged more than 67 years at the time of the interview. All patients were required to have  $\geq 2$  years of continuous enrollment in Medicare before their interview date. We evaluated 3 subgroups: subjects without CLD, subjects with CLD but without cirrhosis, and subjects with cirrhosis. We included the earliest HRS interview after a CLD/cirrhosis diagnosis. We linked HRS surveys to Medicare claims using the *International Classification of Diseases* codes (see Supplementary Table 1, Supplementary Digital Content 1, <http://links.lww.com/CTG/A740>). In brief, we used an algorithm previously validated for the identification of cirrhosis in Medicare-linked HRS survey data (13). Cirrhosis was defined as 2 outpatient diagnosis codes, 1 inpatient diagnosis code for cirrhosis, or a cirrhosis complication. CLD was defined as all diseases which mapped to the Charlson-Deyo definition of mild CLD (13,14). We excluded all patients with survey-reported dementia and/or any prescription for memory problems. We excluded all proxy respondents because they do not have cognitive testing data.

### Animal naming test

Subjects were asked to list as many animals as they could over 60 seconds, yielding a final sum excluding repetitions and errors. Potential ANT thresholds for cognitive dysfunction were previously determined about Italian matched controls noting that ANT is influenced by age and education, namely, for subjects older than 80 years and education <8 years (12). We therefore used raw ANT values and the S-ANT1 (which provides corrections for age older than 80 years and education <8 years). An S-ANT1 of <10 animals is considered abnormal and associated with the future development of overt HE among persons with cirrhosis.

### Outcomes

We categorized outcomes as those relating to health status and frailty. We assessed health status using PROs, including a global rating of health (asking participants to rate their health as excellent, very good, good, fair, or poor) dichotomized as fair-poor or not, care hours required, and hospitalizations. Physical frailty was assessed using 2 PROs—activities of daily living (ADL) and

instrumental ADLs (measured as full ability vs any disability)—and 2 performance measures—walk speed (best of 2 timed walks of 2.5 m) and hand-grip strength (best of 2 measures from the dominant hand).

### Covariates

A complete list of the covariates assessed is given in Table 1. Survey responses were supplemented with diagnoses obtained from the Medicare linkage. Comorbidities were defined by the Charlson Comorbidity Index (15). Alcohol use disorder and important cardiovascular comorbidities (e.g., myocardial infarction and heart failure) were specifically enumerated.

### Analysis

Raw ANT performance was evaluated using negative binomial regression and adjusted for sociodemographic and clinical covariates listed in Table 2. We used negative binomial regression because of the overdispersion of the count data, in which the conditional variance exceeded the conditional mean. Negative binomial regression shares the same mean structure as Poisson regression but includes an extra parameter, which adjusts the variance independently from the mean. We also used negative binomial regression to assess the outcomes: care hours received, hospital stays, hand-grip strength, and timed walk test. The results are presented as incidence rate ratios with 95% confidence intervals (CIs). The remaining dichotomous outcomes (self-reported poor health, ADL difficulty, and iADL difficulty) were evaluated using logistic regression and presented as odds ratios with 95% CI. Each outcome was assessed in 2 ways. The first method adjusted for the raw ANT score, age, education, along with covariates that were found to have significant associations from Table 2. The second method adjusted for the dichotomous S-ANT <10 variable and significant covariates from Table 2. In this case, age and education were not included in the model because S-ANT takes these factors into account. We also analyzed each outcome using alternative models adjusting for the interaction terms CLD\*ANT and cirrhosis\*ANT. In all cases, the *P* values presented were 2-tailed with a <0.05 threshold for significance. Bonferroni correction was applied (0.0071) to avoid type I error. All analyses were performed using Stata (StataCorp LLC, College Station, TX) and SAS 9.4 (SAS Institute, Cary, NC).

## RESULTS

### Demographics and clinical factors

Cohort characteristics are delineated in Table 1. The 6,661-person sample was aged an average of 75 years, with >50% female and 85% White. Overall, 8.2% of the sample had liver disease without cirrhosis and 1.3% had cirrhosis. Among those with cirrhosis, few had ascites, 20 (23%) had varices, and 11 (12.5%) had a history of HE. Subjects with cirrhosis reported more alcohol abuse (17.1%) and were most likely to have diagnosed alcohol use disorder (26.1%) and viral hepatitis (12.5%). Subjects with cirrhosis were also more likely to report fair-poor health, difficulties with ADLs, and had weaker hand grip as well as slower walk speeds. They were also more likely to have been hospitalized and had more physician visits.

### Associations With ANT performance

In Table 2, we detail the unadjusted associations between sociodemographic and clinical covariates and raw ANT performance. Overall, the factors most associated with ANT performance were

**Table 1. Cohort characteristics**

| Variable  | No liver disease    | Noncirrhotic chronic liver disease | Cirrhosis           |
|---|---------------------|------------------------------------|---------------------|
| Number  | 6,027 (90.5)        | 546 (8.2)                          | 88 (1.3)            |
| Age, mean (SD)                                      | 75.9 (7.0)          | 75.3 (6.9)                         | 75.6 (6.2)          |
| Male (%)  | 2,451 (40.7)        | 230 (42.1)                         | 39 (44.3)           |
| Non-White race                                      | 922 (15.3)          | 98 (17.9)                          | 13 (14.8)           |
| Ethnicity, Hispanic                                 | 343 (5.7)           | 54 (9.9)                           | 8 (9.1)             |
| Smoker  | 2,652 (44.0)        | 237 (43.4)                         | 36 (40.9)           |
| Alcohol abuse <sup>a</sup>                          | 541 (9.0)           | 53 (9.7)                           | 15 (17.1)           |
| Unmarried   | 2,594 (43.0)        | 262 (48.0)                         | 44 (50.0)           |
| Education   |                     |                                    |                     |
| No degree   | 1,150 (19.1)        | 118 (21.6)                         | 17 (19.3)           |
| High school diploma                                 | 3,353 (55.6)        | 279 (51.1)                         | 47 (53.4)           |
| Some college or more                                | 1,524 (25.3)        | 149 (27.3)                         | 24 (27.3)           |
| Net worth (\$), mean (SD)                           | 450,218 (1,167,311) | 339,523 (807,796)                  | 343,977 (1,185,526) |
| Congestive heart failure                            | 988 (16.4)          | 144 (26.4)                         | 33 (37.5)           |
| Diabetes  | 2,012 (33.4)        | 250 (45.8)                         | 48 (54.6)           |
| Acute myocardial infarctions                        | 477 (7.9)           | 65 (11.9)                          | 16 (18.2)           |
| Chronic obstructive pulmonary disease               | 1,713 (28.4)        | 234 (42.9)                         | 37 (42.1)           |
| Cerebrovascular disease                             | 1,315 (21.8)        | 168 (30.8)                         | 26 (29.6)           |
| Viral hepatitis                                     | 0 (0.0)             | 19 (3.5)                           | 11 (12.5)           |
| Alcohol use disorder                                | 20 (0.3)            | 82 (15.0)                          | 23 (26.1)           |
| ANT, raw <sup>b</sup>                               | 14.4 (6.5)          | 13.8 (6.3)                         | 14.3 (6.0)          |
| S-ANT <10 <sup>b</sup>                              | 1,277 (21.2)        | 123 (22.5)                         | 20 (22.7)           |
| ADL (number with difficulties)                      | 1,221 (20.3)        | 148 (27.1)                         | 32 (36.4)           |
| iADL (number difficult)                             | 964 (16.0)          | 124 (22.7)                         | 19 (21.6)           |
| Hand strength (kg) <sup>c</sup>                     | 28.5 (10.2)         | 28.7 (9.6)                         | 25.4 (9.9)          |
| Walk speed (s) <sup>c</sup>                         | 3.6 (1.8)           | 3.8 (1.7)                          | 4.1 (2.0)           |
| Rate-health (fair or poor)                          | 1,625 (27.0)        | 213 (39.0)                         | 47 (53.4)           |
| Hospital stays, past 2 yr                           | 0.6 (1.6)           | 1.2 (2.1)                          | 1.9 (3.1)           |
| Physician visits, past 2 yr                         | 11.5 (17.2)         | 20 (45.6)                          | 21 (69.1)           |
| Skilled nursing facility admission (over past 2 yr) | 0.1 (0.3)           | 0.1 (0.5)                          | 0.3 (0.7)           |

ADL, activities of daily living; ANT, animal naming test; iADL, instrumental activities of daily living.

<sup>a</sup>Alcohol abuse is considered present if respondent has  $\geq 1$  episode of binge drinking in the past 3 months or  $>14$  drinks per week if male or  $>7$  drinks per week if female.

<sup>b</sup>ANT scores are truncated at zero (if mistakes outnumber correct responses).

<sup>c</sup>Questions are conducted in face-to-face interviews only. These data represent a subset of the entire cohort.

age, education, marriage, alcohol use disorder, smoking, diabetes, and cerebrovascular disease. In general, there were no major quantitative or qualitative differences of association for persons with liver disease compared with the whole cohort. Liver disease and cirrhosis specifically had no significant independent association with ANT performance.

### Measures of health status

After adjusting for age, education, and the factors associated with ANT performance in Table 3, higher (better) raw ANT performance was associated with lower odds of fair-poor self-reported health status (odds ratio [OR] 0.98; 95% CI: 0.97–99) per animal,

fewer care hours received (incidence rate ratio [IRR] 0.94; 95% CI: 0.93–0.96), and fewer hospitalizations (IRR 0.99; 95% CI: 0.99–1.00). When the dichotomized S-ANT was applied, poor (lower) performance was also strongly associated with each outcome. A poor S-ANT score ( $<10$ ) is associated with greater odds of fair-poor self-reported health status (OR 1.37; 95% CI: 1.20–1.56), higher care hours received (IRR 2.39; 95% CI: 1.79–3.19), and more hospitalizations (IRR 1.14; 95% CI: 1.03–1.26). It is important to note, however, that hospitalizations are not considered significant when the Bonferroni correction is applied. By contrast, although the direction and significance of the effects were unchanged after including interaction terms for

**Table 2. Unadjusted associations with animal naming test (number of animals named)**

| Variable                           | Whole cohort |                  | People with liver disease |                  |
|------------------------------------|--------------|------------------|---------------------------|------------------|
|                                    | Univariate   | aIRR (95% CI)    | Univariate                | aIRR (95% CI)    |
| Age, correlation coefficient       | -0.25        | 0.99 (0.98–0.99) | -0.31                     | 0.98 (0.98–0.99) |
| Sex                                |              |                  |                           |                  |
| Male                               | 14.8 (6.5)   | 1.02 (1.00–1.04) | 14.0 (6.6)                | 1.00 (0.93–1.08) |
| Female                             | 14.1 (6.6)   | 1.00 (ref)       | 13.7 (5.6)                | 1.00 (ref)       |
| Smoker (self-report)               |              |                  |                           |                  |
| No                                 | 14.5 (6.4)   | 1.00 (ref)       | 13.7 (5.7)                | 1.00 (ref)       |
| Yes                                | 13.6 (6.3)   | 0.95 (0.91–0.99) | 12.8 (6.2)                | 0.88 (0.78–1.01) |
| Unknown                            | 14.2 (6.5)   | 1.03 (1.00–1.05) | 14.3 (6.8)                | 1.07 (1.00–1.15) |
| Alcohol abuse                      | 16.1 (6.8)   | 1.01 (0.97–1.05) | 16.5 (6.7)                | 1.16 (1.03–1.30) |
| Marital status                     |              |                  |                           |                  |
| Married                            | 15.2 (6.5)   | 1.00 (ref)       | 14.8 (6.7)                | 1.00 (ref)       |
| Not married                        | 13.4 (6.3)   | 0.97 (0.95–0.99) | 12.9 (5.6)                | 0.94 (0.88–1.01) |
| Education                          |              |                  |                           |                  |
| No degree                          | 11.2 (5.4)   | 1.00 (ref)       | 11.1 (5.2)                | 1.00 (ref)       |
| High school                        | 14.1 (6.0)   | 1.20 (1.16–1.23) | 13.5 (5.6)                | 1.15 (1.05–1.26) |
| Some college or more               | 17.3 (6.9)   | 1.40 (1.36–1.45) | 16.6 (7.0)                | 1.39 (1.26–1.54) |
| Net worth, correlation coefficient | 0.11         | 1.00 (1.00–1.00) | 0.08                      |                  |
| CHF                                | 12.7 (6.0)   | 0.97 (0.94–1.00) | 12.3 (5.7)                | 0.93 (0.86–1.01) |
| Diabetes                           | 13.5 (6.3)   | 0.96 (0.93–0.98) | 13.1 (6.2)                | 0.97 (0.90–1.03) |
| AMI                                | 13.0 (5.8)   | 0.98 (0.95–1.02) | 12.7 (5.8)                | 0.99 (0.89–1.10) |
| COPD                               | 13.7 (6.2)   | 1.00 (0.98–1.03) | 14.0 (6.1)                | 1.09 (1.02–1.17) |
| Cerebrovascular disease            | 13.1 (6.3)   | 0.95 (0.92–0.97) | 13.2 (5.9)                | 0.98 (0.91–1.06) |
| Alcohol use disorder               | 12.9 (6.1)   | 0.92 (0.85–1.00) | 13.3 (6.3)                | 0.93 (0.84–1.02) |
| Liver disease                      |              |                  |                           |                  |
| None                               | 14.4 (6.5)   | 1.00 (ref)       |                           |                  |
| Noncirrhosis CLD                   | 13.8 (6.3)   | 0.98 (0.94–1.02) |                           |                  |
| Cirrhosis                          | 14.3 (6.0)   | 1.06 (0.96–1.16) |                           |                  |
| Liver disease                      |              |                  |                           |                  |
| Noncirrhosis CLD                   |              |                  | 13.8 (6.3)                | 1.00 (ref)       |
| Cirrhosis                          |              |                  | 14.3 (6.0)                | 1.08 (0.98–1.19) |

Adjusted estimates account for all other factors in the table. The variables which are significantly associated with ANT are marital status, income, smoking, alcohol use disorder, cerebrovascular disease, congestive heart failure, and diabetes.

aIRR, adjusted incidence rate ratio; AMI, acute myocardial infarction; CHF, congestive heart failure; CLD, chronic liver disease; COPD, chronic obstructive pulmonary disease.

CLD and cirrhosis with ANT in a sensitivity analysis, the effect on hospitalizations was strengthened (IRR for S-ANT <10 of 2.18; 95% CI: 2.14–2.22).

### Frailty measures

ANT performance was associated with ADL and iADL disabilities, hand grip, and walk speed (Table 4). This was the case for both the raw ANT and S-ANT. When the dichotomized S-ANT was applied, poor performance was also strongly associated with each outcome. A poor S-ANT score (<10) is associated with greater odds of ADL disability (OR 1.31; 95% CI: 1.13–1.51),

greater odds of iADL disability (OR 1.85; 95% CI: 1.59–2.14), weaker hand grip (IRR 0.94; 95% CI: 0.92–0.96), and longer time to walk 2.5 m (IRR 1.23; 95% CI: 1.17–1.29). In all cases, the effects of ANT on the frailty measures maintained their direction and significance after adding interaction terms.

### DISCUSSION

Cognitive dysfunction has a meaningful, deleterious impact on clinical outcomes and well being. As bedside tools to assess and quantify cognitive dysfunction proliferate, it is important to optimize their interpretation (16). In their 2017 landmark article,

**Table 3. Adjusted association between ANT and patient-reported health measures**

|                            | Self-reported poor health<br>Odds ratio (95% confidence interval) | Care hours received<br>Incidence rate ratio (95% confidence interval) | Hospital stays   |
|----------------------------|---|---|------------------|
| Raw ANT (per animal)       | 0.98 (0.97–0.99)  | 0.94 (0.93–0.96)  | 0.99 (0.99–1.00) |
| Control                    | 1.00  | 1.00  | 1.00             |
| Noncirrhotic liver disease | 1.49 (1.21–1.83)  | 1.24 (0.80–1.92)  | 1.66 (1.44–1.92) |
| Cirrhosis                  | 2.63 (1.64–4.20)  | 1.68 (0.61–4.63)  | 2.08 (1.54–2.81) |
| S-ANT <10                  | 1.37 (1.20–1.56)  | 2.39 (1.79–3.19)  | 1.14 (1.03–1.26) |
| Control                    | 1.00  | 1.00  | 1.00             |
| Noncirrhotic liver disease | 1.45 (1.19–1.78)  | 1.22 (0.78–1.91)  | 1.64 (1.43–1.89) |
| Cirrhosis                  | 2.35 (1.49–3.72)  | 1.30 (0.46–3.64)  | 2.08 (1.54–2.80) |

S-ANT is adjusted for age and education and dichotomized at 10 according to published associations with clinical outcomes in cirrhosis. All measures are adjusted for marital status, smoking status, alcohol use disorder, cerebrovascular disease, congestive heart failure, and diabetes, and raw ANT associations are also adjusted for age and education. The only outcome which is not significantly associated with ANT or S-ANT when using Bonferroni-corrected *P* values is hospital stays.  
ANT, animal naming test.

Campagna et al. validated the use of the ANT for the determination of cognitive dysfunction in patients with cirrhosis (12). However, it is neither clear whether associations with ANT performance from a study of carefully enrolled study subjects will generalize to unselected populations at risk for other forms of brain disease nor what physiology explains poor ANT performance. In this study of a representative population-based sample of older Americans, we show that although poor ANT performance was not specific to CLD or cirrhosis, ANT was associated with poor PROs, physical frailty, and disability for all patients, especially those with CLD and cirrhosis. The goal of cognitive testing is to identify at risk patients, and the ANT identifies a high-risk subset of the population. The ANT identifies patients who could benefit from additional evaluation and potentially changes in their clinical management.

#### Health status is associated with cognitive function

We confirm and extend the literature associating cognitive dysfunction with PROs in cirrhosis. It is well known that cognitive

dysfunction defined by psychometric testing is associated with poor PROs (2,10,17,18). Now, our study shows that patients with poor health status can be identified with the ANT/S-ANT1, a simple tool that can be ascertained in-person or even remotely (19). We also show that the ANT/S-ANT identifies patients with increased caregiving requirements and healthcare utilization. In this regard, the ANT/S-ANT may be able to efficiently identify patients at high risk for hospitalization and those with caregivers at high risk of burnout.

#### Frailty measures are associated with cognitive function

Our data demonstrate that the ANT/S-ANT identifies patients who are more likely to have disability (in iADLs and ADLs) and physical frailty (slow walk speed or weak hand grip). Importantly, the association was significant after controlling for age, education, marital status, and comorbidities. Although we previously illustrated the impact of HE on frailty (6), it was unclear whether its impact was a product of advanced disease or whether it identified

**Table 4. Adjusted association between ANT and frailty measures**

|                            | ADL difficulty<br>Odds ratio (95% confidence interval) | iADL difficulty<br>Odds ratio (95% confidence interval) | Hand strength (kg)<br>Incidence rate ratio (95% confidence interval) | Timed walk (s/2.5 m)<br>Incidence rate ratio (95% confidence interval) |
|----------------------------|--|---|--|--|
| Raw ANT (per animal)       | 0.98 (0.97–0.99)                                       | 0.96 (0.94–0.97)  | 1.00 (1.00–1.00)   | 0.99 (0.98–0.99)   |
| Control                    | 1.00   | 1.00  | 1.00   | 1.00   |
| Noncirrhotic liver disease | 1.16 (0.93–1.46)                                       | 1.32 (1.03–1.68)  | 1.01 (0.98–1.05)   | 0.99 (0.91–1.07)   |
| Cirrhosis                  | 1.60 (0.98–2.59)                                       | 1.13 (0.64–1.97)  | 0.90 (0.83–0.97)   | 1.09 (0.91–1.30)   |
| S-ANT <10                  | 1.31 (1.13–1.51)                                       | 1.85 (1.59–2.14)  | 0.94 (0.92–0.96)   | 1.23 (1.17–1.29)   |
| Control                    | 1.00   | 1.00  | 1.00   | 1.00   |
| Noncirrhotic liver disease | 1.11 (0.89–1.39)                                       | 1.24 (0.98–1.57)  | 1.03 (0.99–1.07)   | 0.98 (0.91–1.07)   |
| Cirrhosis                  | 1.46 (0.91–2.36)                                       | 1.00 (0.58–1.74)  | 0.94 (0.86–1.02)   | 1.05 (0.88–1.25)   |

S-ANT is adjusted for age and education and dichotomized at 10 according to published associations with clinical outcomes in cirrhosis. All measures are adjusted for marital status, smoking status, alcohol use disorder, cerebrovascular disease, congestive heart failure, and diabetes, and raw ANT associations are also adjusted for age and education. Hand grip is also adjusted for sex and body mass index. All outcomes are significant when using Bonferroni-corrected *P* values.  
ADL, activities of daily living; ANT, animal naming test; iADL, instrumental activities of daily living.

an independent role of cognitive dysfunction in the pathogenesis of the frailty phenotype. In a recent study evaluating the association between the ANT and the Liver Frailty Index among participants of the Framingham Heart Study who lacked cirrhosis, we found that ANT performance, in addition to systemic inflammation and sarcopenia, was associated with frailty (20). Taken together, these data show that cognitive dysfunction is robustly associated with frailty across representative population samples in patients with and without cirrhosis.

### Using the ANT

The ANT requires 1 minute to perform and can be accomplished in clinic, over the phone, or video visit. We present 2 ways of evaluating the ANT: either as a raw, continuous variable or as the S-ANT, which is adjusted for age (older than 80 years or not) and education (<8 years or not). Most patients will not require any adjustments for age or education, and therefore, the raw ANT and S-ANT1 will be equivalent. Because dichotomization is often useful for clinical decision-making at the point of care, we evaluated associations with both the continuous ANT and S-ANT <10. Because conventional psychometric testing is burdensome and therefore rarely performed (21), the ANT is a promising alternative. It is clear from our data, however, that the ANT cannot identify HE without a careful consideration of competing etiologies.

### Acting on the ANT

The utility of the ANT is context dependent. ANT can be helpful if frailty is identified clinically. Guidance from the American Association for the Study of Liver Disease recommends that effort should be taken to determine the reasons underlying frailty (22). Patients with cognitive dimensions to their frailty phenotype or health status may benefit from medical or supportive therapy commensurate with their stage of disease and aimed at the source of their cognitive dysfunction. Cognitive dysfunction can be caused by polypharmacy or sleep apnea (23,24). Patients with cirrhosis and a sufficiently high index of suspicion for HE could consider trials of HE therapy, intensified nutritional support, and closer monitoring (25). For patients with a low suspicion of HE or those without cirrhosis, further evaluation by geriatricians or neuropsychologists may be warranted. Adjunctive therapies, such as intensive cognitive exercises, have been associated with a significant improvement in the Fried Frailty Index (26).

### ANT is not specific to cirrhosis

We show that the association between the ANT/S-ANT and health status or frailty is present across the entire cohort. Further, we find that CLD/cirrhosis itself is not independently associated with unadjusted ANT performance. This finding underscores 2 facts about the ANT/S-ANT. First, the ANT links cognitive functioning to well-being and physical functioning in a generalizable, disease-agnostic fashion. ANT performance elsewhere is associated with other forms of cognitive impairment or social vulnerability (27,28). The ANT is associated with walk speed in community dwelling subjects older than 65 years (29) and predicts the development of postoperative delirium among septuagenarians undergoing elective operations (30). Given this general association, when using ANT to identify cognitive dysfunction in patients with CLD, one must have a high pretest probability of cirrhosis and HE, or additional testing may be required before initiating HE-specific therapy.

### Contextual factors

These data must be interpreted in the context of the study design. First, we determined the presence of liver disease and cirrhosis using administrative codes. Although the coding algorithms are validated and specific for cirrhosis, it is possible that some people with liver disease were misclassified as not having cirrhosis. Second, although a 1.3% prevalence of cirrhosis reflects the expected rates of cirrhosis nationally (17), this sample size is too small to allow for extensive subgroup analyses (alcohol use disorder or not and HE or not). Third, we could not evaluate any blood-based markers of liver disease severity. Fourth, we did not have access to medication linkage to assess the impact of specific therapies. Fifth, future data with later HRS waves will be needed to evaluate the impact of changes in the ANT/S-ANT on clinical outcomes and PROs. Finally, we lack the sample size to evaluate associations with specific complications such as ascites or HE.

The ANT/S-ANT is a powerful, simple, and widely applicable tool for the determination of cognitive dysfunction. Although these data do not explicitly link the ANT/S-ANT to HE, they show that the ANT identifies a population with poor health status and increased rates of frailty and disability who merit further evaluation for underlying mechanisms. Future studies to determine the optimal clinical response to therapies initiated after poor ANT performance among patients with cirrhosis are needed.

### CONFLICTS OF INTEREST

**Guarantor of the article:** Elliot B. Tapper, MD.

**Specific author contributions:** E.B.T.: concept, analysis, data acquisition, and writing. B.K. and S.N.: analysis, data acquisition, and critical revision of the manuscript. A.K.W.: analysis and critical revision of the manuscript. D.A.L.: data acquisition and critical revision of the manuscript.

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## Study Highlights

### WHAT IS KNOWN

- ✓ The Animal Naming Test (ANT) is a validated 1-minute tool to detect cognitive dysfunction.
- ✓ The ANT can be used to predict hepatic encephalopathy in people with cirrhosis.
- ✓ Associations between the ANT and patient reported outcomes or frailty are unknown.

### WHAT IS NEW HERE

- ✓ In this study of a representative population-based sample of older Americans, we show that the ANT was associated with poor PROs, physical frailty, and disability.
- ✓ The ANT is not independently associated with cirrhosis and but is especially associated with poor outcomes for those with CLD and cirrhosis.

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