The Montreal cognitive assessment as a cognitive screening tool in sickle cell disease: Associations with clinically significant cognitive domains

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Summary
Adults with sickle cell disease (SCD) are at risk for cognitive impairment, which causes significant morbidity. Guidelines support routine cognitive screening, but no screening test is validated in this population. We explored the Montreal Cognitive Assessment (MoCA) as a possible screening test in SCD. We administered the MoCA; a literacy test, the Wide Range Achievement Test, fourth edition (WRAT-4); and a health literacy test, the Shortened Test of Functional Health Literacy in Adults (S-TOFHLA) to adults with SCD and gathered clinical variables through chart review. Spearman’s rho, Mann–Whitney, and Kruskal–Wallis tests and quantile regression models were used. Among our sample of 49 adults with SCD, the median MoCA score was 25.0 [interquartile range (IQR) 22.0–28.0]. Higher educational attainment was associated with MoCA scores (p = 0.001). In multivariable models, MoCA scores were associated with S-TOFHLA (p = 0.001) and WRAT-4 Reading (p = 0.002) scores, and overt stroke (p = 0.03) at the median. This pilot study adds to the limited literature of cognitive screening tests in adults with SCD and demonstrates a relationship between MoCA scores and measures of literacy and health literacy. The MoCA is a promising option for briefly screening for cognitive impairment in adults with SCD, though further study is needed to confirm its validity.

KEYWORDS
cognitive performance, cognitive screening, health literacy, Montreal Cognitive Assessment, sickle cell disease
INTRODUCTION

Adults with sickle cell disease (SCD) experience haemolysis, inflammation, and vascular occlusion, which cause end-organ damage. The brain in people with SCD is vulnerable to the effects of anaemia, cerebrovascular accident, vaso-occlusive events, decreased cerebrovascular reserve, and arteriopathies. Affected individuals may have clinical or subclinical cognitive impairment, which negatively affects educational attainment, employment status, quality of life, and health behaviours. Rehabilitation and prevention of further damage relies on early identification of cognitive impairment. To this end, the American Society of Haematology recommends routine cognitive assessment for adults with SCD. No cognitive screening test has been validated in this population, and more work is needed.

Cognitive screening tests must be feasible to implement routinely and must assess clinically meaningful cognitive domains affected by SCD. SCD has been shown to affect memory, attention, executive function, and visual–spatial function. Literacy, the ability to read and write, and health literacy, the degree to which individuals have the capacity to obtain, process and understand basic health information, are also decreased in SCD. In the general population, low literacy and health literacy are linked to poor adherence to health-promoting behaviours, such as attending clinic visits, or taking medications as prescribed. While studies are limited in SCD, there are interventions that have been shown to improve health literacy in other chronically ill patients. In SCD, improved literacy predicts successful transition to adult care. A cognitive screening test that is sensitive to deficits in these domains would aid identification and intervention to improve outcomes.

The Montreal Cognitive Assessment (MoCA) was originally developed to screen for mild cognitive impairment in ageing populations, and is commonly used among chronic disease populations. It is not yet known if MoCA scores are associated with measures of literacy or health literacy. The tool requires minimal training to administer, has in-person and virtual validated administration options, and takes approximately 15 min to complete. Previous groups have established the feasibility of using the MoCA in adults with SCD. Further work is needed to evaluate this candidate screening tool.

The purpose of this study was to: (1) investigate whether MoCA scores correlate with literacy and health literacy scales in adults with SCD; (2) identify clinical factors associated with poor performance on the MoCA, literacy and health literacy assessments; and (3) characterize the patients with high educational attainment who obtain abnormal cognitive testing scores. We hypothesized that MoCA scores would correlate with scores on literacy and health literacy assessments. We further hypothesized that lower baseline haemoglobin, higher average daily pain, and clinical history of a neurologic event like cerebrovascular accident (CVA) would predict lower scores on MoCA and on literacy and health literacy assessments.

MATERIALS AND METHODS

The Johns Hopkins Medicine Institutional Review Board approved this study.

Participants and recruitment

Between April 2015 and December 2016, we enrolled adults with SCD who received care at the Johns Hopkins Sickle Cell Center for Adults. A sample size of 50 was selected by convenience, since this was a pilot study and among the first to administer the MoCA in the adult SCD population. Inclusion criteria were: age over 18 years, SCD diagnosis, English proficiency, and capacity to consent. Eligible patients were recruited at scheduled outpatient appointments. During their study visits, all participants were at clinical baseline. Participants completed a brief demographic survey including gender, age and educational attainment. Educational attainment was grouped into ‘high school or less’, ‘some college’ and ‘college graduate’ for analysis. Participants provided written informed consent.

Cognitive testing protocol

A trained research team member administered a brief cognitive testing battery before or after a routine in-person clinic visit.

1. Montreal Cognitive Assessment (MoCA), introduced above, was conducted using printed materials with the trained research team member providing standardized directions and administering all interactive tasks. The MoCA has a maximum score of 30. Many research groups classify scores of 26 and above as normal, though there is considerable variation. When originally validated in an elderly dementia cohort, an educational adjustment was applied by adding one point to the final scores of individuals with no post-secondary education. Since no normative data exist in the SCD population, we opted to control for educational attainment in regression analyses in lieu of using the educational adjustment.

2. Shortened Test of Functional Health Literacy in Adults (S-TOFHLA) measures an adult’s ability to read and understand health-related materials. A printed version of the 36-item prose portion of the assessment was used. Scores were classified as follows: 23–36, adequate health literacy; 17–22, marginal health literacy; and less than 17, inadequate health literacy.

3. Wide Range Achievement Test, fourth edition (WRAT-4) measures literacy. We included the WRAT-4 Reading subtest, which measures an individual’s ability to recognize letters and words, and the WRAT-4 Sentence Comprehension subtest, which measures an individual’s ability to comprehend the meaning of words and
sentences. We followed adult administration guidelines using paper testing forms. WRAT-4 scores for each subtest are normalized for age, with a population mean of 10 and a standard deviation of 15. Scores less than 90 on any subtest are considered 'below average'.

Chart review protocol

The study team performed a retrospective review of participants’ electronic medical records. Labs, notes and admissions contemporary to the cognitive testing were recorded. We referred to haematology clinic and inpatient notes to identify use of disease-modifying therapy including hydroxyurea (hydroxyurea) or chronic transfusions at the time of testing, history of acute chest syndrome (ACS), patient-reported pain level (0–10) on an average day, and history of neurologic events including CVA or transient ischaemic event. Since availability and timing of neuroimaging differed widely across the participant pool, we did not include information from neuroimaging in our analyses.

Data analysis

Of the 50 participants, one had significant missing data and was excluded, so analyses include 49 participants. We calculated summary statistics of key variables. Our primary objective was to assess the relationship between MoCA scores and scores on literacy and health literacy tests. Secondarily, we were interested in the relationships between test scores and clinical characteristics. Because reliable cut-off scores have not been established in adults with SCD, we treated test scores as continuous variables.

Our data were not normally distributed, so we used non-parametric tests. First, we applied statistical tests (Mann–Whitney U test, Kruskal–Wallis tests, and Spearman’s rho) to understand whether pairs of variables were related in our dataset. If a relationship approached significance (p<0.15), we performed quantile linear regression at the 25th and 50th percentile of the outcome variables to better model the size and direction of the association. The 25th percentile of test scores represents patients with low performance on cognitive tests, who are important to identify for possible intervention, and the 50th percentile offers a measure of central tendency of our participants’ performance. We controlled for educational attainment and age, since these demographic variables are biologically plausible confounders of the relationship between cognitive test performance and health literacy. We report quantile regression coefficients, 95% confidence intervals (CIs), and probability values. We used Stata, Version 17.0 for all statistical testing, with a p<0.05 (two-sided) standard for significance in regression models. We considered the impact of multiple comparisons, and ultimately decided against multiple comparison adjustment would further underpower our analyses. Thus, our interpretation focuses less on statistical inference and more on identifying possible relationships between the MoCA, clinical variables, and cognitive domains of interest, in accordance with recommended methods for pilot studies.

RESULTS

Descriptive

Participants’ socio-demographic characteristics, clinical characteristics and cognitive test scores are described in Table 1. All participants self-reported Black race and non-Hispanic ethnicity. Participants were mostly female (n = 31, 63%), median age was 40 years [interquartile range (IQR) 30–51], and most participants had HbSS and HbS0 disease (n = 30, 61%). Most had at least some college education (n = 35, 71%), and almost half were privately insured (n = 23, 47%). Six patients had a history of at least one clinically significant neurologic event. Four patients had a clinical history of CVA: three patients had previous arterial ischaemic stroke, and one patient had a previous haemorrhagic stroke. One patient experienced hypoxic ischaemic encephalopathy in the context of multiorgan failure, and a second patient had posterior reversible encephalopathy syndrome attributed to sirolimus. Approximately half of patients (n = 22, 45%) were prescribed disease-modifying therapy at the time of testing, including hydroxyurea (n = 12), chronic exchange transfusions (n = 8), and chronic simple transfusions (n = 3). One patient both took hydroxyurea and received monthly exchange transfusions. The median baseline haemoglobin was 97.0 g/l (IQR 81.0–107.0), and 61% (n = 30) of participants had a history of ACS.

Forty-nine participants completed the cognitive testing protocol. The median MoCA score was 25.0 (IQR 22.0–28.0). Using a cut-off of 26, 47% (n = 23) of participants had normal MoCA scores. In our cohort, the median S-TOFHLA score was 35.0 (IQR 30.0–36.0). There was a strong ceiling effect in S-TOFHLA performance: 96% (n = 47) had ‘adequate’ health literacy. In this cohort, the median score on WRAT-4 Reading was 96.5 (IQR 87.0–104.5), and 67% (n = 32) scored average or better. The median score on WRAT-4 Sentence Comprehension was 91.5 (IQR 84.5–98.0), and 63% (n = 30) scored average or better.

Relationships between cognitive assessments and demographic and clinical variables

Table 2 lists the probability values derived from tests of association between cognitive test scores and demographic and clinical characteristics. Guided by the results of these hypothesis tests along with our understanding of plausible mechanisms, we
TABLE 1  Descriptive demographic characteristics, clinical characteristics, and cognitive test scores among sickle cell disease (SCD) health literacy pilot study participants (n = 49)

| Demographic characteristics                  | n (%)   |
|----------------------------------------------|---------|
| Female                                       | 31 (63.3) |
| Age, years (median, IQR)                     | 40 (30–51) |
| Highest level of education attained (n, %)†  |         |
| High-school diploma or less                  | 13 (26.5) |
| Some college/higher education                | 17 (34.7) |
| College graduate                             | 18 (36.7) |
| Insurance provider (n, %)                    |         |
| Public                                       | 18 (36.7) |
| Private                                      | 23 (46.9) |
| Mixed                                        | 8 (16.3)  |

| Clinical characteristics                     |         |
| Genotype (n, %)                              |         |
| Sickle cell anaemia (HbSS, HbSB⁺)            | 30 (61.2) |
| Heterozygote (HbSC, HbSB⁺, and others)       | 19 (38.8) |
| Baseline haemoglobin, g/l (mean, SD)         | 94 (19)  |
| History of acute chest syndrome (n, %)       | 30 (61.2) |
| History of clinically symptomatic ischaemic neurologic event (n, %) | 6 (12.2) |
| Overt stroke                                 | 4 (8.2)  |
| Hypoxic ischaemic encephalopathy             | 1 (2.0)  |
| Posterior reversible encephalopathy syndrome | 1 (2.0)  |
| Self-reported pain level on an average day (n, %) |         |
| 0: No pain                                   | 23 (46.9) |
| 1–3: Mild pain                               | 8 (16.3)  |
| 4–6: Moderate pain                           | 12 (24.5) |
| 7–10: Severe pain                            | 1 (2.0)   |
| Use of disease-modifying therapy at time of testing (n, %) | 22 (44.9) |
| Hydroxyurea⁺                                 | 12 (24.5) |
| Chronic exchange transfusions⁺               | 8 (16.3)  |
| Chronic simple transfusions                  | 3 (6.1)   |

| Scores on cognitive tests                    |         |
| MoCA score (median, IQR)                     | 25.0 (22.0–28.0) |
| S-TOFHLA score (median, IQR)                 | 35.0 (34.0–36.0) |
| WRAT-4 Reading Standardized Score (median, IQR) | 96.5 (87.0–104.5) |
| WRAT-4 Sentence Comprehension Standardized Score (median, IQR) | 91.5 (84.5–98.0) |

Abbreviations: IQR, interquartile range; MoCA, Montreal Cognitive Assessment; SD, standard deviation; S-TOFHLA, Shortened Test of Functional Health Literacy in Adults; WRAT-4, Wide Range Achievement Test, 4th edition.
†Some college includes those who attended trade-school and those who began taking college courses but did not complete the degree. College graduate includes those who completed an Associates, Bachelors, Masters or Doctorate degree.
⁺Includes HbSS with hereditary persistence of fetal haemoglobin and HbSOther.
*One patient was receiving both hydroxyurea (hydroxycarbamide) and chronic exchange transfusions at the time of cognitive testing.

used univariable quantile regression to quantify the effect size of the relationship between test scores and educational attainment at the median and 25th percentile. The effect of higher educational attainment on MoCA scores was similar at the median (β = 2.50; 95% CI: 1.00–4.00; p = 0.002) and at the 25th percentile (β = 2.50; 95% CI: 0.43–4.57, p = 0.02). Higher educational attainment was significantly associated with the WRAT-4 Reading subtest at the median (β = 6.50; 95% CI: 0.35–12.65; p = 0.04), but not at the 25th percentile (β = 5.00; 95% CI: −6.37 to 16.37; p = 0.38). The effect of higher educational attainment on median WRAT-4 Sentence Comprehension subtest scores approached significance (β = 5.00; 95% CI: −0.55 to 10.55; p = 0.08). Higher educational attainment was not significantly associated with WRAT-4 Sentence Comprehension at the 25th percentile (p = 0.22), nor with S-TOFHLA at the median (p = 1.00) or 25th percentile (p = 0.84).

Figure 1 uses regression coefficients with 95% CIs from multivariable quantile regression models to depict the relationship between test scores and any clinical variable with a p value of less than 0.15 in hypothesis testing. Multivariable models controlled for educational attainment and age. Median MoCA scores were associated with overt stroke (p = 0.03), but were not significantly associated with baseline haemoglobin (p = 0.20), ACS (p = 0.21), or clinical ischaemia (p = 0.54). MoCA scores at the 25th percentile were significantly associated with haemoglobin (p = 0.03) but not with overt stroke (p = 0.35), clinical ischaemia (p = 0.30), or ACS (p = 0.12) in our small, pilot sample. S-TOFHLA scores at the 25th percentile were associated with overt stroke (p < 0.001) and at the median with clinical ischaemia (p = 0.03). Median WRAT-4 Reading subtest scores were associated with clinical ischaemia (p = 0.001). The relationship between median WRAT-4 Sentence Comprehension subtest scores and clinical ischaemia approached significance (p = 0.06).

Associations between MoCA and S-TOFHLA, and WRAT-4 subtest scores

We measured associations between MoCA scores and scores on the S-TOFHLA and WRAT-4 subtests, as depicted in scatterplots (Figure 2). We fit a quantile regression model to describe the associations between literacy and health literacy and MoCA performance, controlling for educational attainment and age. Median MoCA scores were associated with S-TOFHLA scores (β = 0.44; 95% CI: 0.20–0.68, p = 0.001) and WRAT-4 Reading scores (β = 0.13; 95% CI: 0.06–0.21, p = 0.002). The relationship between median MoCA scores and the WRAT-4 Sentence Comprehension subtest approached significance (β = 0.09; 95% CI: −0.01 to 0.19, p = 0.07). The relationship between MoCA scores at the 25th percentile and scores on the WRAT-4 Reading subtest (β = 0.12; 95% CI: −0.01 to 0.24, p = 0.08) and WRAT-4 Sentence Comprehension subtest (β = 0.12; 95% CI: −0.03 to 0.27, p = 0.12) approached significance. In our sample, MoCA scores at the 25th percentile...
after adjusting for educational attainment and age. Median scores are associated with the cognitive domains of literacy and health literacy in a United States-based sample, even after adjusting for educational attainment and age. Median MoCA scores were associated with the WRAT-4 Reading subtest and the S-TOFHLA; associations with WRAT-4 Sentence Comprehension subtest approached significance. The S-TOFHLA and WRAT-4 subtests are validated tests of health literacy and literacy, which are clinically meaningful cognitive domains that can be modified by rehabilitation and mitigated by changes in clinical practice. It is not feasible to routinely administer a lengthy battery of cognitive tests to patients with SCD, so it is important that a screening test used in SCD correlates with intervenable domains of interest.

We hypothesized that baseline haemoglobin and history of ACS would be associated with cognitive test scores. All negative results should be interpreted in the context of the limited sample size of our pilot study; it is possible that a large sample with a more representative population would yield more or stronger associations. In our sample, baseline haemoglobin was only associated with MoCA scores at the 25th percentile, which is inconsistent with previous literature. History of ACS has not been previously explored in relation to cognitive performance, but might indicate increased disease severity. In our sample, there was no significant association between history of ACS and cognitive performance. However, more than 60% of participants had a history of ACS; operationalizing ACS differently, such as identifying those with ACS in the past two years, might have more predictive power. Previous literature suggests that disease-modifying therapies improve cognitive outcomes, but our data showed no significant association between disease-modifying therapy and scores on cognitive tests. Since those with more severe disease are more likely to receive disease-modifying therapy, disease severity might offset any positive impact of these therapies on cognitive performance.

We further hypothesized that overt stroke and any neurologic event, had at least one abnormal test score, compared to participants with some college experience and at least some college experience had abnormal test scores. Thirty-two (65%) participants had an abnormal score on at least one test, using a MoCA cut-off of 26. Table 3 lists the number of abnormal scores for each participant by education level. Nine college graduates and 18 total participants with at least some college experience who had a clinical history of a neurologic event, had at least one abnormal test score. Compared to participants with some college experience and normal test scores, those with abnormal test scores did not differ by genotype \((p = 0.19)\), baseline haemoglobin level \((p = 0.88)\), or use of disease-modifying therapy \((p = 0.43)\). Though the difference did not reach significance, all participants with at least some college experience who had a clinical history of a neurologic event, had at least one abnormal test score \((n = 3, p = 0.11)\). Two participants with at least some college and abnormal scores had presented for neuropsychological testing in the years preceding this study due to observed changes in cognition, and a third participant had newly screened positive for moderately severe depression around the time of testing.

**DISCUSSION**

To our knowledge, this is the first study to show that MoCA scores are associated with the cognitive domains of literacy and health literacy in a United States-based sample, even after adjusting for educational attainment and age. Median

| Demographic characteristics | MoCA scores | S-TOFHLA scores | WRAT-4 Reading | WRAT-4 Sentence Comprehension |
|----------------------------|-------------|-----------------|----------------|-----------------------------|
| Sex                        | \(p = 0.39\) | \(p = 0.67\)    | \(p = 0.08\)   | \(p = 0.23\)               |
| Age, years                 | \(p = 0.56\) | \(p = 0.71\)    | \(p = 0.89\)   | \(p = 0.53\)               |
| Educational attainment     | \(p = 0.001\)| \(p = 0.08\)    | \(p = 0.08\)   | \(p = 0.02\)               |
| Insurance provider         | \(p = 0.61\) | \(p = 0.67\)    | \(p = 0.23\)   | \(p = 0.36\)               |

**Clinical characteristics**

| Genotype (n, %) | MoCA scores | S-TOFHLA scores | WRAT-4 Reading | WRAT-4 Sentence Comprehension |
|-----------------|-------------|-----------------|----------------|-----------------------------|
| Baseline haemoglobin, g/l (mean, SD) | \(p = 0.90\) | \(p = 0.30\)    | \(p = 0.25\)   | \(p = 0.38\)               |
| History of acute chest syndrome (n, %) | \(p = 0.12\) | \(p = 0.40\)    | \(p = 0.40\)   | \(p = 0.42\)               |
| History of clinical ischaemia | \(p = 0.09\) | \(p = 0.70\)    | \(p = 0.95\)   | \(p = 0.81\)               |
| History of overt stroke | \(p = 0.21\) | \(p = 0.02\)    | \(p = 0.004\)  | \(p = 0.002\)              |
| Self-reported pain level on an average day (n, %) | \(p = 0.12\) | \(p = 0.02\)    | \(p = 0.01\)   | \(p = 0.04\)               |
| Use of disease-modifying therapy at time of testing (n, %) | \(p = 0.83\) | \(p = 0.32\)    | \(p = 0.57\)   | \(p = 0.48\)               |

Abbreviations: MoCA, Montreal Cognitive Assessment; SD, standard deviation; S-TOFHLA, Shortened Test of Functional Health Literacy in Adults; WRAT-4, Wide Range Achievement Test, 4th edition.
cognitive testing. Data in our sample provided a mixed picture. Overt stroke was associated with median MoCA and WRAT-4 Reading scores and S-TOFHLA at the 25th percentile, and clinical ischaemia was associated with S-TOFHLA and WRAT-4 Reading at the median; median WRAT-4 Sentence Comprehension scores approached significance. The rate in our sample of overt stroke was 8% and of any neurologic event was 12%, which is lower than expected among adults with SCD.4 Our retrospective data were limited by lack of universal neurologic imaging, so we relied only on clinical diagnoses of events, which might result in underdiagnosis.

Scores on most cognitive tests, including the MoCA, are correlated with educational attainment,19,31 and our data were consistent with these previous findings. Since education improves cognitive performance,41 any sensitive cognitive test is likely to be associated with educational attainment. However, SCD patients with high educational attainment are still vulnerable to cognitively deleterious disease processes. In our sample, 18 participants with post-secondary education, including nine college graduates, had abnormal scores on at least one cognitive test. Individuals with high baseline cognitive capacity might mask symptoms of cognitive impairment in activities of daily life, leading to delays in diagnosis,42 which makes routine screening with a sensitive instrument essential.

This study has several limitations. Our sample was more highly educated43 and had a lower rate of public insurance44 than the general population of adults with SCD. These data might not be generalisable to the wider sickle cell population. Because of our small sample size, tests of relationships between cognitive test scores and clinical and demographic variables are underpowered. We did not include neuroimaging in our retrospective study because many participants had no or outdated neuroimaging. Without neuroimaging, we could not include among our clinical variables the presence of silent cerebral infarcts, which are prevalent among people with SCD. We ran numerous statistical tests, which exposes our results to increased risk for type I error. We did not adjust for multiple comparison to avoid further underpowering our analyses in this pilot study. Future studies should confirm all results in larger, more representative samples.
samples and consider targeted sampling by educational attainment. Finally, trends in MoCA scores over time might be more useful than cross-sectional scores in identifying cognitive impairment in individuals, and multi-centre work is currently underway to collect longitudinal MoCA scores in adult SCD patients.45

The MoCA is a promising option for briefly assessing cognitive impairment in adults with SCD, though further research is needed to validate the tool in a representative sample. Future studies should also assess the relationship between MoCA scores, other cognitive domains, and advanced activities of daily living in adults with SCD. There are no norms guiding interpretation of MoCA scores among adults with SCD. Future studies should compare MoCA scores to the gold standard of neuropsychological testing and examine the utility of adjusting for educational attainment. In the interim, our work adds to the limited literature describing the performance of adults with SCD on the MoCA, which helps clinicians and researchers interpret results.

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**FIGURE 2** Scores on the Montreal Cognitive Assessment (MoCA), which measures general cognitive performance, is related to scores on the (A) Shortened Test of Functional Health Literacy in Adults (S-TOFHLA), which measures health literacy, and (B/C) Wide Range Achievement Test, fourth edition (WRAT-4): Reading and Sentence Comprehension subtests, which measure literacy. CI, confidence interval

**TABLE 3** Participants with lower educational attainment are more likely to have abnormal test scores

| Number of abnormal scores | None | One | Two | Three | Four |
|---------------------------|------|-----|-----|-------|------|
| **n ( % of educ group)**  |      |     |     |       |      |
| High school or less       | 0    | 2 (14) | 9 (64) | 2 (14) | 1 (7) |
| Some college              | 8 (47) | 3 (18) | 2 (12) | 3 (18) | 1 (6) |
| College graduate          | 10 (53) | 4 (21) | 4 (21) | 1 (5) | 0 |

Abnormal test score defined as ≤25 for the Montreal Cognitive Assessment (MoCA), ≤16 for the Shortened Test of Functional Health Literacy in Adults (S-TOFHLA), ≤89 for the standardized Wide Range Achievement Test, fourth edition (WRAT-4) Reading, and ≤89 for the WRAT-4 Sentence Comprehension.
analysis. Macy L. Early collected data and wrote the manuscript. Allison Bosch, Timothy Campbell and Felicia Hill-Brigg recruited patients, performed cognitive testing and collected demographic information on participants. All authors provided feedback on the manuscript, and Lydia H. Pecker, Eboni I. Lance and Sophie Lanzkron provided extensive comments and revision, in addition to continuous mentorship.

CONFLICT OF INTERESTS
Sophie Lanzkron receives funding from Global Blood Therapeutics, Imara, Shire, Novartis, and the NIH; is a consultant for Bluebird Bio and Novo Nordisk; and holds stock in Pfizer and Teva. The other authors have nothing to disclose.

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