COMMENTARY

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TO THE EDITOR:

Commentary on the ASH 2020 guidelines on cognitive screening and intervention in sickle cell disease

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Individuals with sickle cell disease (SCD) experience progressive neurocognitive dysfunction resulting from cerebrovascular disease[1,2] and environmental disparities.[1,3,4] In 2020, the American Society of Hematology (ASH) published guidelines outlining the standard care for the prevention, diagnosis, and treatment of cerebrovascular disease in SCD, based on a systematic review of the literature and expert panel consensus.[5] Recommendations 8 and 9 describe guidance pertaining to screening and interventions to address cognitive deficits, respectively. These recommendations established the need to regularly assess for neurodevelopmental and cognitive impairment throughout the lifespan so that interventions can be initiated as early as possible.

The guideline panel necessarily emphasized practices that could be feasibly implemented in most settings while striving to meaningfully raise the bar for care and improve the outcomes. In this commentary, we discuss practical issues with the adoption of the guidelines and highlight the best practices for cognitive screening and intervention. Although we believe the approaches described subsequently offer clinical advantages, we also recognize the very real challenges associated with their implementation in resource-limited settings. Moreover, we acknowledge that our experiences and perspectives are inherently biased as White clinical researchers based in the United States.

ASH guideline recommendations 8.1 and 8.3 suggest that clinicians conduct regular surveillance of neurodevelopment and cognitive functioning using signaling questions and a more thorough assessment, if warranted (8.2 and 8.4). Regular surveillance will likely lead to concerns being identified early for more patients; however, hematology providers should be cognizant of issues that have hindered surveillance in general pediatrics, such as less than half of the infants and toddlers receiving a developmental screening despite it being recommended by the American Academy of Pediatrics.[6] Black caregivers in the United States are less likely to be asked about concerns related to their child's development[7] and are more likely to underreport cognitive and psychological concerns for themselves and their children, potentially because of stigma[8] or distrust toward medical providers.[9] Incorporating signaling questions or other forms of surveillance into electronic surveys completed before the clinic visits may be one way to help ensure universal administration and increase the likelihood that appropriate actions are taken in response to positive screen results.[10]

Signaling questions that ask about milestones (eg, using words) should be used consistently, starting in infancy, to ensure that children with signs of developmental delay are identified at the earliest possible opportunity. Routinely asking questions is important; however, there is an opportunity to rigorously develop and evaluate signaling questions, as described by the guideline panel.[5] For example, some common questions (eg, "How would you describe your child's academic performance?") may not be sensitive to cognitive impairment, resulting in a high rate of false negatives.[11] Using open-ended and domain-specific questions (eg, "What feedback have you heard from your child's teacher about their progress in math?") may elicit more meaningful responses; although, this type of approach relies heavily on clinician interpretation and limits data-driven intervention decisions. Given the heterogeneous nature

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of cognitive deficits, valid and reliable screening questions are needed to better assess for difficulties across a range of domains, including verbal abilities, visual-spatial abilities, executive functioning, and processing speed. Importantly, individuals with SCD and their caregivers should be involved in the development of these questions, potentially through involvement in focus groups in which they could share direct observations of the ways everyday behaviors and tasks are affected by cognitive deficits. Additional research is needed to develop and test cognitive screening tools that address the concerns of individuals with SCD and can be implemented across a range of settings and cultures.

Although signaling questions may represent a feasible strategy for the neurodevelopmental and cognitive screening in SCD, direct measurement using performance-based assessments remains the gold standard toward which we should strive. Challenges exist for universal surveillance using performance-based assessments, but they are not insurmountable. For example, Schlenz and Schatz[12] recently demonstrated that formal developmental screening programs for young children with SCD are feasible, improve the detection of developmental delays, and facilitate referrals to early childhood intervention services. Digital assessments have also ushered in new opportunities for implementation that deemphasize the need for onsite, highly-specialized providers. Furthermore, approaches that rely on less-specialized providers to facilitate digital tests (eg, National Institutes of Health toolbox)[13] could be supplemented with (1) case-conference discussion with experts to aid in the interpretation, or (2) review by a centralized network of specialists.

It is our hope that eventually all children with high-risk genotypes will be considered for a minimum of 1 neurodevelopmental or cognitive assessment before entering school, similar to the recommendation to conduct a 1-time unsedated magnetic resonance imaging screening for silent infarcts (10.1). Neurodevelopmental and cognitive assessments, which provide a direct measurement of cognitive functioning rather than a proxy measurement or indicator of risk, would inform school-based accommodations and instructional modifications as well as guide decisions about the need for future monitoring. Moreover, these assessments confer minimal risks and are relatively inexpensive.

After screening and evaluation, the ASH guidelines recommend cognitive interventions for children (9.1) and adults (9.2), when warranted. To do so, cognitive rehabilitation for SCD should be grounded in efficacy data and should be reimbursable and accessible. Although many domain-specific cognitive interventions have proven to be effective in the general population, there are barriers to implementation for individuals with SCD. Prior attempts to implement cognitive interventions have demonstrated difficulties with adherence, limiting their effectiveness.[14-17] Thus, addressing barriers to adherence and increasing accessibility is critical for intervention success. In the United States, Black caregivers experience greater stigma when seeking help for their children,[18] and Black children are less likely to receive developmental intervention services, compared with their White counterparts.[19] Disease-related stigma is also a significant concern reported by patients and caregivers outside of the UnitedStates, with implications for care-seeking.[20] Therefore, evaluating the acceptability of interventions is particularly critical for individuals with SCD, who identify predominately as minoritized populations.[21]

Intervention recommendations should also be based on known genetic, biological, and psychosocial risks for cognitive decline and treatment responsiveness. School-based accommodations, legally available to students with SCD attending federally funded schools in the United States through a Section 504 plan, exist to minimize the degree to which SCD interferes with one's ability to participate in and benefit from school. However, reports suggest that less than half of the youth with SCD have 504 plans.[22] Similarly, early intervention is a home-based, federally-supported intervention program for children aged from 0 to 3 years with developmental delays, yet outside of comprehensive care centers with established developmental screening programs,[12] children with SCD are not routinely offered preventive services.[23] Because of the progressive nature of SCD, patients typically display increasing neurodevelopmental difficulties as they age. Rather than attempting to remediate these deficits as they appear, early screening and referral to intervention services can alter the patients' trajectory of functioning and limit future deficits.

Investigators should explore ways to reduce barriers to accessing publicly available resources, such as early intervention and 504 plans. Ideally, when pediatricians identify children as having SCD, caregivers will be informed of early intervention programs in their state. Upon school entry, an automatic process should be triggered to establish a 504 plan, for which all children with SCD attending public school in the United States are eligible. At a minimum, students with SCD should be provided with documentation that describes their disease and outlines recommended accommodations before each academic year. Close attention should also be paid to potential eligibility for an individualized education program when students are struggling academically, which would introduce more comprehensive academic support and accountability for implementation. Additionally, pediatricians and other SCD care providers should make efforts to connect families with local and national SCD advocacy groups that can facilitate connections, offer peer support, and empower patients and families to advocate for their needs.

To our knowledge, the ASH 2020 guidelines were the first to provide evidence-based direction on the delivery of comprehensive health care to support optimal cognitive development in SCD. As we have described, the guidelines are an excellent starting point that balance the feasibility of implementation with high-quality care, but there is work to be done to move these recommendations to the clinic and envision higher expectations for care. Policymakers, funders, institutions, and health care teams must embrace science that will accelerate the integration of these guidelines into standard care globally.

The the key barriers to the widespread adoption of the ASH guidelines are unclear, although this could be the focus of qualitative and quantitative inquiries and quality improvement projects. Anecdotally, contributing barriers likely include a lack of awareness about the recommendations, concern about cost and time, low prioritization of cognitive issues amidst myriad other concerns, and an overt or unconscious bias. We posit that the field of implementation science can guide investigators to identify strategies for improving the uptake of the guidelines. Investigators should apply comprehensive frameworks such as the health equity implementation framework to address multilevel factors that may disproportionately affect minoritized populations and can directly

influence clinical encounters.[24] This and other similar models grounded in implementation science align with national priorities focused on addressing social determinants of health that lead to disparities in care. Given the complex set of factors that contribute to cognitive impairment, applying lessons learned through health equity research can support medical teams in implementing best practices to support the cognitive health of people with SCD across their lifespan.[25]

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