4/20/21

Dear Editors and Reviewer,

Thank you for your helpful feedback. I have incorporated the changes you have requested. The changes are on pages 5, 6, 7, and 10. In addition numerous references were added. Below I have highlighted the changes that correspond with the reviewers comments. I hope these revisions will meet your expectations and requirements.

Sincerely,

Amanda Rose, PsyD

Specific Comments to Authors: …

1. Possible conflicts of interest - One of the authors has acted as a consultant and speaker for Cognivue Inc. while the other two are employees of Cognivue Inc. Though this is not clearly stated the study appeared to be funded by the same company. Therefore, validation by an independent set of authors was clearly required. This has been carried out by the authors of this editorial and the results of the comparisons with the MOCA suggest some limitations in the Cognivue® screening.

3. Costs of screening with the Cognivue® - It is not clear whether screening with the Cognivue® will be cost-effective compared to simpler paper and pencil tests like the MOCA.

Changes for reviewers points 1 & 3:

Pg 6. “Importantly, there are potential conflicts of interest with the aforementioned article. The research was funded by the makers of Cognivue® and the authors were employees or consultants for the company. Therefore it is important that studies with larger sample sizes are completed by unaffiliated researchers for validation of the Cognivue®. Additionally the company did not use trained psychologists or clinicians to administer the neuropsychological assessments in their research, calling the validity of the results into question. These authors

concluded that the Cognivue® is either the equivalent or superior to the SLUMS when screening for cognitive impairment and "superior" for test-retest reliability [6 -9]. They do admit more comparison studies are warranted; however they go on to infer that the Cognivue® will be equivalent in terms of its sensitivity, specificity, and psychometric validity to commonly used screeners like the MoCA and MMSE[6]. Without more research, with larger sample sizes, it is not appropriate to suggest the Cognivue® is more useful or accurate than other screening instruments. Furthermore the researchers claim the Cognivue® reduces "costs" associated with screening for cognitive impairments; however the cost saving advantage of this device versus other tools has not been established.

2. Lack of data – There appears to be a lack of validation studies with the Cognivue® screening apart from the ones cited by the Cahn-Hidalgo et al. The only other study cited is among patients with multiple sclerosis (reference 30 of the manuscript). Without further testing on larger samples it is not possible to comment on the usefulness of the Cognivue® versus other screening instruments.

Pg 6. "Unfortunately there are limited validation studies of the Cognivue®, especially ones that are not associated with or funded by the company. There has been research examining the use of the Cognivue® with a small sample of MS patients, which was coauthored by the founder and CEO of Cerebral Assessment Systems and inventor of Cognivue®. This study compared Cognivue® total scores to The Paced Auditory Serial Addition Test (PASAT) (which assesses auditory information processing speed, attention, and flexibility) and Symbol Digit Modalities Test (SDMT) (which assesses visual processing speed and attention) [10]. The PASAT and SDMT are commonly used cognitive screeners and research tools when working with MS patients [11]. Smith *et al* found strong correlation between the Cognivue® Total Score and SDMT (.79) and the PASAT (.61) [10]. In 2020 Bomprezzi expanded this research and found moderate correlations (0.67) between the Cognivue® Total Score and SDMT results in a small sample of MS patients [12]. The finding of these studies suggests the Total Cognivue® score correlates with tests that are measuring elements of attention and processing speed."

4. The nature of domains and tests for these - The authors of this editorial have already pointed out the limitations of the Cognivue® in this regard. Thus, the nature of subtests included in the Cognivue® will probably be crucial in determining the usefulness of this screening measure.

Pg 5: “There was no good indication in this research that the Cognivue® tapped into the domains of attention, immediate memory, delayed recall, or abstraction, which are important areas to consider when screening for neurocognitive disorders. For example Cognivue® presentation of stimuli is all visual, which is a limitation. After initial exposure a few seconds pass before the participant is given a multiple choice paradigm to recognize and respond. This brief delay can be categorized as a short-term memory process, but not a long-term memory one. Additionally when considering models of memory, recognition of stimuli in a multiple choice format is easier than free recall of information or encoding the stimuli to long-term memory [2]. Since recognition can be intact in some individuals with neurocognitive disorders, such as with vascular dementia or mild cognitive impairment, presentation of information in this way could lead to false-negatives. Additionally it is unclear how the Cognivue® subtests measure executive functioning skills even though Cahn-Hidalgo *et al* research suggests correlations with Trails B, an executive function test.”

Pg. 10 “Additionally the subtests do not appear to assess long-term memory, executive functioning, language, or abstraction. Clearly defining the subtests of the Cognivue® is crucial in determining its efficacy as a screening tool. More research by unaffiliated researchers, on large samples of participants, is needed to determine what specifically the Cognivue® subtests are measuring and what modifications can be made to improve its screening capabilities. “

5. Diagnostic accuracy of automated tests for cognitive impairment – A systematic review by Aslam et al. (Int J Geriatr Psychiatry. 2018;33:561–575) had pointed out that: "Some tests have shown promising results for identifying MCI and early dementia. However, concerns over small sample sizes, lack of replicability of studies, and lack of evidence available make it difficult to make recommendations on the clinical use of the computerised tests for diagnosing, monitoring progression, and treatment response for MCI and early dementia. Research is required to establish stable cut-off points for automated computerised tests used to diagnose patients with MCI or early dementia." All these issues are relevant while determining the utility and validity of the Cognivue®

screen. I think the authors of the editorial can consider and comment on some of the issues listed above.

Pg 7. Digital and computer based screeners and tests show promise for detecting cognitive impairments [13]. In addition to the Cognivue® there has been development of different computerized cognitive screeners. For example the historical Clock Drawing Test has been transformed into a digital version. The five minute Digital Clock Drawing Test is registered as a FDA Class II medical device for cognitive screening [14]. The tablet uses a digitizing pen that captures and analyzes the drawing. One Harvard research study concluded the DCT clock showed "excellent discrimination" between individuals with cognitive impairment and controls [14]. Unfortunately much of the technology and test adaptations for these devices are new, with few studies, small sample sizes, and lack of evidence, making it risky to suggest that computerized testing should be used clinically for the detection, diagnosis, and monitoring of neurocognitive disorders without complete and validated research [13]. ”

Tables: Moved to requested location

Additional References added:

7 **Andrefsky, J**, Cahn-Hidalgo, D, Benabou, R. Superior test-retest reliability of a computerized cognitive assessment vs SLUMS during an 18-month longitudinal study. *Sleep* 2020*;* **43**: A426. Available from: https://doi.org/10.1093/sleep/zsaa056.1114

8 **Andrefsky, J.** & Cahn-Hidalgo, D, Benabou, R Superior test-retest reliability of cognitive assessment with COGNIVUE® vs SLUMS during an 18-month longitudinal study. *American J of Geriatric Psychiatry* 2020*;* **28**: S106-S107. [DOI: 10.1016/j.jagp.2020.01.133]

9 **Andrefsky J,** Cahn-Hidalgo D, Benabou R. Superior test-retest reliability of cognitive assessment with Cognivue® vs Slums during an 18-month longitudinal study. *Neurol Sci Neurosurg* 2021 Jan 25; **2**(1): 114. Available from: https://doi.org/10.47275/2692-093X-114

10 **Smith AD**, Duffy C, Goodman AD. Novel computer-based testing shows multi-domain cognitive dysfunction in patients with multiple sclerosis. *Mult Scler J Exp Transl Clin* 2018 Apr 27; **4**(2): 1-9. [PMID: 29900003; PMCID: PMC5993067; DOI: 10.1177/2055217318767458].

11 **Benedict, R H,** DeLuca, J, Phillips, G, LaRocca, N, Hudson, LD, Rudick, R, Multiple Sclerosis Outcome Assessments Consortium. Validity of the Symbol Digit Modalities Test as a cognition performance outcome measure for multiple sclerosis. *Multiple Sclerosis Journal* 2017; **23**(5): 721–733. [DOI: 10.1177/1352458517690821]

12 **Bomprezzi, R.** Cognitive impairment in patients with multiple sclerosis as assessed by objective computerized testing. *Scholars Literature* 2020; Available from: https://www.scholarsliterature.com/journals/neurological-sciences-and-neurosurgery/fulltext/cognitive-impairment-in-patients-with-multiple-sclerosis-as-assessed-by-objective-computerized-testing

13 **Aslam, RW,** Bates, V, Dundar, Y, & Hockenhull, JC. A systematic review of the diagnostic accuracy of automated tests for cognitive impairment. *Int J Geriatr Psychiatry* 2018; **33**(1): 561–575. [DOI:10.1002/gps.4852].

14 **Brooks, M.** Five-minute digital clock test may speed early alzheimer's diagnosis. *Medscape* 2021 Apr 16*;* Available from: https://www.medscape.com/viewarticle/949410?src=WNL_mdpls_210416_mscpedit_psych&uac=308767AR&spon=12&impID=3315767&faf=1#vp_1

15 **Nasreddine ZS.** MoCA test mandatory training and certification: What is the purpose*? J Am Geriatr Soc* 2020; **68**(2): 444-445. [DOI: 10.1111/jgs.16267]