Visual assessment in children with cerebral palsy: implementation of a functional questionnaire

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ABBREVIATIONS

ADL	Activities of daily living
CVI	Cerebral visual impairment
VCS	Visual classification scale

AIM The aim of this study was to evaluate an interdisciplinary visual assessment for multiply challenged children diagnosed with cerebral palsy (CP).

METHOD A comprehensive ophthalmological assessment together with a visual classification scale (VCS) and a questionnaire evaluating daily visual function were completed regarding 77 children (41 females, 36 males; age range 3–20y; mean age 8y 3mo [SD 4y 3mo]; Gross Motor Function Classification System [GMFCS] level V; Manual Ability Classification System level V) who were diagnosed with CP (79.2% spastic quadriplegia, 6.5% athetoid quadriplegia, 10.4% mixed type, 3.9% hemiplegia). All participants had severe to profound motor and intellectual disability and an inability to communicate consistently through either verbal or assisted communication. The interrater and test–retest reliability of the questionnaire and its validity in comparison with the VCS were examined. In addition, the contribution of ophthalmological testing in predicting daily visual function was assessed.

RESULTS The ophthalmological examination revealed three diagnostic subgroups: a group with cerebral visual impairment (CVI), a group with optic atrophy, and a group without visual impairment. The questionnaire was found to have high values of interrater reliability (interclass correlation coefficient [ICC]=0.873; 95% confidence interval [CI] 0.762–0.935) and test–retest reliability (ICC=0.988; 95% CI 0.964–0.996). Validity was established for the questionnaire factors: task-orientated visual function (r=0.802; 95% CI 0.669–0.885) and basic visual skills (r=0.691; 95% CI 0.504–0.816). The questionnaire provided information about daily visual performance not available from one-time ophthalmological testing, particularly for participants diagnosed with CVI. The visual performance scale significantly predicted daily visual function for all groups.

INTERPRETATION This study highlights the benefits of implementing a diagnostic performance scale as well as a reliable functional questionnaire to achieve a precise visual assessment of children with severe neurological impairment.

Cerebral palsy (CP) is a permanent, non-progressive neurodevelopmental disorder that occurs during pregnancy, delivery, or shortly after birth, and affects approximately 2–3 in every 1000 infants.[1,2] CP manifests itself primarily through sensory and movement disorders, such as muscle spasticity or rigidity, random movements or a lack of balance, or a combination of these factors. In addition, CP is often accompanied by seizures, abnormal speech, intellectual disability, and hearing and visual deficits, including cerebral visual impairment (CVI).[3,4]

CVI is defined as a bilateral loss of central visual function (visual acuity) caused by neurological damage to the visual cortex and/or visual pathway structures. It most commonly results from hypoxic ischaemia causing periventricular leukomalacia in the preterm infant. Clinically, children diagnosed with CVI appear to have poor or absent visual function, despite having a normal or near-normal anterior eye examination.[5–8] A broader diagnosis of CVI, which includes visual-perceptual disorders, has been suggested by some researchers.[9–11] When available, neuroimaging data, including those from magnetic resonance imaging or visual evoked potential testing, are consulted to confirm the diagnosis.[6,12]

Recently, scientific and clinical literature has directed attention to the benefits that can be accrued by integrating functional assessments of CP with standard medical examination tools. Indeed, the latest professional guidelines published in the World Health Organization's International Classification of Functioning, Disability and Health classify motor abilities using a typology that brings together motor disorder classification with a description of functional abilities. As a result, the Gross Motor Classification System (GMFCS) and the Manual

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Ability Classification System (MACS) are being utilized by clinicians to achieve a clearer picture of how children diagnosed with CP use their motor abilities, thus enabling a more precise diagnosis.[13,14] The Executive Committee for the Definition of Cerebral Palsy makes the same recommendation regarding the assessment of impairments associated with CP, including vision.[1,2]

The present study builds upon this assessment approach and attempts to define visual function among children diagnosed with CP who are particularly difficult to assess owing to severe motor, cognitive, and communicative limitations. This is accomplished by considering congruent as well as supplementary information obtained from a functional vision questionnaire when administered alongside ophthalmological testing.

What this paper adds

- This article presents a new reliable, functional questionnaire for the visual assessment of the multiply involved paediatric population.
- It highlights the inherent limitations of interpreting visual function based on diagnosis alone, particularly in children diagnosed with CVI.
- It emphasizes the value of implementing a performance scale to enhance visual diagnoses.

METHOD

Participants

The study participants, recruited from the Aleh Rehabilitation Centre for multiply challenged children in Bnei Brak, Israel, comprised 77 children (36 males, 41 females; age range 3–20y; mean age 8y 3mo; SD 4y 3mo). They were diagnosed as having CP and severe to profound motor and intellectual disabilities. An interdisciplinary committee established this diagnosis using a battery of developmental assessments. Formal IQ testing is not relevant for this population. Demographic information about the participants is presented in Table I.

All participants were classified in level V on the GMFCS, indicating severe motor disability, full dependence on transport, and little voluntary extremity movement. Participants were also classified at level V on the MACS, demonstrating an inability to handle objects and perform simple tasks.[13,14] None of the children was able to communicate verbally or use communication devices in a consistent manner. Participants were totally dependent in activities of daily living (ADL) and self-care.

The majority of the group had no previous documented ophthalmological assessment. The analysis of the ophthalmological data presented here was carried out retrospectively: magnetic resonance imaging data were available for only 26 children, seven of whom were diagnosed with periventricular leukomalacia. Similarly, insufficient visually evoked potential data were available for analysis. No medical justification was found for further electrophysiological testing.

The study was approved by the institutional review board of the Sheba Medical Center, Israel, and all parents gave informed consent.

Visual assessment

Ophthalmological examination

A comprehensive ophthalmological examination was performed by an on-site ophthalmologist (PN) at the educational facility. All eye examinations took place in the same clinical setting with minimal extraneous auditory or visual background stimuli. All participants were seated in their adapted wheelchair to enable optimal positioning and comfort. They were accompanied by a familiar teacher, who was able to monitor associated medical complications such as sudden shortness of breath or complications with a gastrointestinal feeding tube, etc.

Table I: Demographic information and clinical findings of participants (*n*=77)

	CVI (*n*=26)	OA[a] (*n*=25)	No visual impairment (*n*=26)
Demographic information			
Mean age	7y 1mo (SD 2y 9mo)	8y 7mo (SD 4y 6mo)	9y 0mo (SD 4y 9mo)
Sex: M/F	13/13	15/10	8/18
CP type: quadriplegia (spastic/athetoid/mixed), hemiplegia	21/2/2/1	23/–/2/–	17/3/4/2
Preterm (<37wks' gestation)	7	7	4
Seizure disorder	18	14	17
s/p ROP	2	–	2
Pupillary response (slow/normal)	2/24	–/25	–/26
Clinical findings			
Light perception (yes/inconsistent/no)	14/2/10	8/1/16	26/–/–
OKN (yes/occasional/no)	10/2/14	5/2/18	na
Eye movements (limited/normal)	–/26	4/21	3/23
Optic nerve (no damage/pallor/atrophy)	16/10/–	–/–/25	22/4/–
Gaze dysfunction:			
Nystagmus	4	5	4
Roving eye movements	3	2	1
Gaze up	3	2	–
Significant refractive error[b] (myopia/hyperopia/no)	3/4/19	2/4/19	4/3/19
Strabismus (exo/eso/hyper/no)	9/–/1/16	7/2/1/15	4/7/1/14
Focus (yes/inconsistent/no)	4/7/15	3/2/20	25/1/–
Tracking (yes/inconsistent/no)	2/7/17	4/1/20	26/–/–
Visual field (WNL/limited/unable to examine)	6/3/17	4/1/20	24/1/1

s/p ROP, status post retinopathy of prematurity; OKN, optokinetic nystagmus; WNL, within normal limits; na, not applicable. [a]Moderate-severe optic atrophy. [b]Above +2.00 or below –2.00.

The eye examination tested for pupillary responses and for near visual function by examining light perception, optokinetic nystagmus, and visual field (by confrontation), as well as the ability to fixate and track using small brightly coloured toys. The presence of gaze dysfunction was identified, including amblyopia, strabismus, roving eye movements, and the tendency to 'gaze up'. Nystagmus and eye movements were also assessed. Clinical findings are presented in Table I.

Ophthalmoscopy was performed to examine the media, fundus, optic nerve, blood vessels, and macula. After application of cycloplegic drops, retinoscopy was used to estimate refraction. When available, neuroimaging data were considered as part of the diagnostic process. All of these examinations are relatively objective, require minimal active participation, and are appropriate for this population.

Whenever possible, visual grating acuity was tested using the Lea Grating Paddles based on a preferential looking technique. Grating acuity testing was performed on the day of the ophthalmology examination as well as during a follow-up session in order to test the reliability of the results.[15]

A diagnosis of CVI was made if there was poor bilateral visual function despite a normal anterior pathway eye examination or which could not be accounted for based on the clinical examination.[6,7,16]

Children with moderate to severe optic atrophy were grouped together under the primary visual diagnosis of optic atrophy, keeping in mind that this is often accompanied by CVI.[10] The group of children with mild optic nerve damage and lower than expected function were given a primary diagnosis of CVI. Those with functional vision were included in the group of children with no apparent functional visual impairment.[16,17]

After initial diagnosis was established, the results of the ophthalmological examination were collapsed into a five-level Visual Classification Scale (VCS), with each level indicating a higher degree of visual performance than the previous one (Table II).[7,8,15] The VCS characterizes the performance specifically during the ophthalmological examination.

Table II: The Visual Classification Scale

Functional level	Clinical visual performance
1	**Pupillary responses** only
2	**Minimal light perception** or **OKN** positive or negative
3	**Fixation and gaze shift** to a target
4	Fixation, gaze shift, **smooth pursuit,** visual function may be limited in range, GA testing: unreliable
5	Fixation, gaze shift, smooth pursuit, **scanning** and detail discrimination: ability to distinguish detail on GA test
5A	Low GA (<2.0 cpd)[a]
5B	Functional GA (2.0–8.0 cpd)[a]

Bold type indicates additional distinguishing visual abilities, not apparent at the previous level. [a]Distance: 29cm. GA, grating acuity; cpd, cycles per degree.

Functional questionnaire

The primary purpose of the questionnaire was to assess the child's daily visual performance.

The 26-item questionnaire compiled for and implemented in this study resulted from three initial versions and underwent peer review by a professional member of staff who had experience with the participant population. The questions are population specific, designed to include common situations encountered by the participants, and require minimal motor or verbal responses (Appendix S1, published online only). The questionnaire is divided into two sections. Section 1 (questions 1–12) serves as a general assessment of the participant's use of visual motor skills in a classroom setting, in both regular- and low-luminance environments. Section 2 (questions 13–26) assesses the child's visual skills in the following areas of function: communication, ADL, play and leisure, and mobility and orientation.[5]

After a 2-week observation period and before the ophthalmological examination, the participant's primary educator completed the questionnaire. Items were rated on a 5-point ordinal scale reflecting the degree of performance. An additional option of 'not relevant' was available when questions were not applicable to the child's motor or cognitive ability. Such responses were not included in the statistical analysis (Appendix S1). Four items (20–23) applicable only to children with upper extremity movement were removed from the data analysis.

Statistical analysis

The Kaiser–Meyer–Olkin measure of sampling adequacy produced a result of 0.936, which indicates that the questionnaire is appropriate for factor analysis. The 22 questionnaire items were subjected to an exploratory principal component factor analysis with varimax rotation. Rotated factor loadings >0.500 were deemed satisfactory. Therefore, four items (6, 7, 11, and 12) with factor loadings <0.500 were removed from further analysis. Based on results from the Velicer's minimum average partial test, two components were extracted in the subsequent factor analysis of the remaining 18 items.[18]

To establish interrater reliability, a second caregiver implemented the questionnaire on 34 participants. Test–retest reliability of the questionnaire was examined by re-administering the questionnaires (n=14) after 8 months.

To validate the questionnaire, Pearson's correlations (n=47) were performed with two additional sources: the VCS and the visual performance code from the Coding Interactive Behaviour rating system, a global coding scheme for behavioural assessment. The global coding was carried out by independent observers, who reviewed videotapes of the participants' visual performance.[19]

Daily visual function (represented by the resulting questionnaire factors) and the VCS were analysed with a one-way multivariate analysis of variance with visual diagnosis as the between-participant factor. After a main effect for visual diagnosis, univariate analyses of variance with post hoc Scheffé tests were conducted. In order to examine possible

associations between the study variables, Pearson's correlations were conducted.

Finally, in order to assess the contribution of the ophthalmological examination, as summarized by visual diagnosis and the VCS for predicting daily visual performance, two hierarchical multiple regressions were conducted – one for each of the two questionnaire factors. The above-mentioned predictors were entered into the regression in three blocks. In the first block, two dummy variables representing the visual diagnostic groups were entered (dummy 1, CVI; dummy 2, no visual impairment); in the second block, the VCS was entered in order to examine its contribution beyond the visual diagnosis; in the third block, the interactions between the dummy variables and the VCS were entered. These interactions enable analysis of whether the association between the ophthalmologist's evaluation and each of the dependent variables is the same or different in each of the three diagnostic groups.

Statistical analysis was performed using SPSS version 15.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

The ophthalmological examinations revealed three diagnostic subgroups, defined as those with CVI (n=26), those with optic atrophy (n=25), and those with no visual impairment (n=26). Clinical data for all participants are summarized in Table I. These results concur with the findings of other studies performed in children with neurological impairments, although some report an even higher prevalence of CVI.[12,20–22]

Of the participants diagnosed with CVI, 88.46% were classified at VCS levels 1 to 3, as were 84% of those participants diagnosed with optic atrophy. The group without visual impairment were all classified at level 4 and 5. In all, 41 participants had sufficient ocular motor skills (levels 3–5) to perform grating acuity testing, yet only 22 were able to do so reliably, 19 of whom had no visual impairment.

The factor analysis conducted yielded two questionnaire factors accounting for 81.12% of the total variance. Table III presents factor loadings for the 18 items, the percentage of variance accounted for by each factor, and Cronbach's alpha for each factor. The high internal consistency suggests redundancy. However, the questions examine the same behaviours in variant functional situations and are, therefore, distinct. Factor 1 represents task-orientated visual function while factor 2 reflects a more generalized usage of basic visual skills.

Questionnaire reliability

High values of interrater reliability (intraclass correlation coefficient [ICC]=0.873; 95% confidence interval [CI] 0.762–0.935) and test–retest reliability (ICC=0.988; 95% CI 0.964–0.996) were found.

Questionnaire validity

Significant correlations were found between task-orientated visual function and the VCS (r=0.802; 95% CI 0.669–0.885), as well as with the Coding Interactive Behaviour visual performance code (r=0.605; 95% CI 0.385–0.760). Significant correlations were also found between basic visual skills and the VCS (r=0.691; 95% CI 0.504–0.816) and with the Coding Interactive Behaviour (r=0.525; 95% CI 0.280–0.706). These findings confirm the construct validity of the questionnaire.

In addition, the multivariate analysis of covariance revealed a significant main effect for visual diagnosis (Wilks's lambda $F(6,144)$=17.200; p<0.001; Partial eta squared 0.915). Univariate tests presented in Table IV show significant differences in all three assessments of visual performance (factor 1, factor 2,

Table III: Results of exploratory factor analysis[a] (extracted sum of squared loadings; n=77)

		Factor 1 loading	Factor 2 loading
Factor 1: task-orientated visual skills; eigenvalue 8.78%; variance 48.76			
Q26.	Turns head towards someone passing by	0.872	–
Q14.	Identifies/responds to familiar faces	0.858	–
Q25.	Looks around when entering a room	0.854	–
Q19.	Looks at pictures in a book/communication board	0.827	–
Q5.	Identifies an object/toy by sight alone	0.819	–
Q15.	Responds to facial expressions	0.809	–
Q18.	Demonstrates visual preference between two objects	0.786	–
Q13.	Focuses on face when seated opposite individual	0.774	–
Q17.	Focuses on small objects	0.764	–
Q3.	Shifts gaze between two stimuli	0.710	–
Q4.	Searches for an object which has been removed	0.695	–
Q24.	Focuses on a lit TV/computer screen	0.649	–
Factor 2: basic visual skills; eigenvalue 5.83%; variance 32.36; cumulative variance 81.12%			
Q9.	Focuses on light (in adapted low luminance environment)	–	0.899
Q8.	Responds/reacts to light	–	0.846
Q10.	Tracks object (in adapted low luminance environment)	–	0.834
Q1.	Focuses on object	–	0.776
Q16.	Focuses on large objects	–	0.709
Q2.	Tracks an object/toy	–	0.678
Cronbach's alpha		0.975	0.955

Extraction method: principal component analysis. Rotation method: varimax. [a]Only factor loadings >0.500 are indicated. Q, questionnaire item.

Table IV: Differences in visual assessment between diagnostic groups

	CVI (*n*=26)		OA (*n*=25)		No VI (*n*=26)				
	Mean (range)	SD	Mean (range)	SD	Mean (range)	SD	Univariate *F*(2,74)	ES	Scheffé post hoc
VCS	2.080 (1.640–2.520)	1.093	1.920 (1.260–2.580)	1.605	5.190 (4.850–5.540)	0.849	59.284[a]	0.616	No VI >CVI; no VI >OA
Task-orientated visual skills	1.740 (1.378–2.103)	0.900	1.790 (1.330–2.250)	1.110	4.026 (3.640–4.412)	0.956	44.717[a]	0.547	No VI >CVI; no VI >OA
Basic visual skills	2.846 (2.337–3.355)	1.260	2.860 (2.270–3.423)	1.365	4.551 (4.230–4.873)	0.795	18.345[a]	0.331	No VI >CVI; no VI >OA

CVI, cerebral visual impairment; OA, optic atrophy; VI, visual impairment; ES, partial eta squared; VCS, Visual Classification Scale. [a]$p<0.001$.

Table V: Results of hierarchical multiple regression predicting daily visual function from visual diagnosis and the visual classification scale

	Task-orientated visual function[a]				Basic visual skills[b]			
Block	β	95% CI	ΔR^2	ΔF	β	95% CI	ΔR^2	ΔF
1								
CVI	0.016	−0.287 to 0.240	–	–	−0.005	−0.316 to 0.303	–	–
No VI	0.731[c]	0.801 to 1.328	0.547	44.717[c]	0.573[c]	0.496 to 1.114	0.331	18.345[c]
2								
VCS	0.580[c]	0.533 to 1.156	0.129	29.217[c]	0.624[c]	0.496 to 1.257	0.150	21.052[c]
	−0.184				−0.011			
3								
VCS × CVI	–	−0.674 to 0.010	–	–	–	−0.439 to 0.399	–	–
VCS × No VI	−0.098	−0.599 to 0.221	0.017	1.962	−0.247	−0.963 to 0.043	0.024	1.750

CI, confidence interval; CVI, cerebral visual impairment; VI, visual impairment; VCS, Visual Classification Scale. [a]R^2 total=0.694; $F(5,71)=32.140$; $p<0.001$. [b]R^2 total=0.505; $F(5,71)=14.515$; $p<0.001$. [c]$p<0.001$.

and the VCS) with regard to visual diagnosis. These results indicate that the three assessments discriminate according to visual diagnostic categories. Scheffé post hoc tests revealed that children with no visual impairment were classified significantly higher on the VCS and on both aspects of the questionnaire than children in the other two groups. No significant difference was found between the CVI and optic atrophy groups.

Regression analysis results are presented in Table V and reveal that in the first block, 55% of the variance of daily task-orientated visual skills and 33% of daily basic visual skills were explained by visual diagnosis. Specifically, the diagnosis of no visual impairment contributed uniquely to predicting visual function; however, this was not the case for the diagnosis of CVI. In the second block, the VCS variable contributed 13% of the variance of daily task-orientated visual skills and 15% of daily basic visual skills, such that children classified at a higher level on the VCS also used their visual skills regularly and those at a lower level were found to have a weaker daily performance. The interactions between the VCS and diagnostic groups were not found to be significant predictors of daily visual function.

DISCUSSION

This study developed and implemented a functional questionnaire in addition to a one-time medical evaluation in order to assess visual performance among children diagnosed with CP and multiple involvements. The questionnaire was found to be a reliable and valid tool for collecting information about daily visual performance.

As would be anticipated, children with no visual impairment performed significantly better than the other two diagnostic groups on all functional assessments. Nonetheless, by contrast, no significant difference was found between the CVI and optic atrophy groups with regard to their daily visual performance or the ophthalmological scaling of their function during a one-time testing situation, despite diagnostic differences. This finding suggests that many multiply involved children diagnosed with optic atrophy have difficulty utilizing their residual visual abilities, are at risk for CVI, and need to be assessed for CVI.

Overall, the results of this study indicate that visual diagnosis is effective in predicting the daily use of task-orientated visual skills as well as basic visual skills, such as the ability to focus and track large objects, in multiply involved children diagnosed with no apparent visual impairment. However, in the case of children diagnosed with CVI, diagnosis does not predict daily performance; rather, there seems, in this case, to be a discrepancy, with performance either better or worse than that which would be anticipated based on visual diagnosis alone.

In all participants, the use of the VCS was effective in predicting an additional 13–15% of the child's visual function beyond the contribution of the diagnosis. This finding highlights the benefit that can be acquired by elaborating upon the global visual diagnosis through implementation of a

performance spectrum in order to present function more precisely. The performance scale is particularly important for children with CVI, in whom diagnosis alone did not reflect visual abilities.

The discrepancy between visual diagnosis and the primary caregiver's assessment of the participants with CVI reflects environmental influences on visual performance such as positioning, background noise, and colour contrast, as well as factors pertaining to the presented stimulus, such as familiarity, colour, shape, and size, which vary in each setting.[6,23] Endogenous factors such as arousal level and general affect at the time of the assessment may contribute as well. The questionnaire presented here is designed to evaluate the degree and consistency of performance over time in various settings to enable a broad perspective on function and precise assessment of abilities.

A two-pronged integrated visual assessment provides a broader qualitative assessment of visual abilities and enables the subclassification of the visual diagnosis based on several parameters: (1) the VCS; (2) the environment in which these abilities best manifest themselves; and (3) the degree to which the child is able to participate.

The functional questionnaire was developed in parallel with a 'visual inventory' created by McCulloch et al.[24] and was implemented before their article was published. The McCulloch inventory is similar in objective to our questionnaire, addressing the use of visual skills in children with neurological impairment, particularly during ADL tasks such as eating and drinking, during communication with a caregiver, and during play, as well as addressing differences in response to bright and dim environments. The primary lacuna that they acknowledged is the limitation of a 'yes or no' response format of the inventory. The benefit of our performance scale (see Appendix S1) is that it takes into consideration a range of possibilities, facilitating a graded measure of function. This is particularly important when aimed at 'picking up' on nuanced responses of children with multiple disabilities. Ultimately, such a scale will assist in refining the initial ophthalmological diagnosis, integrating within it levels of visual response.

This interdisciplinary approach to visual assessment is also appropriate for other children with minimal communication skills whose physical and cognitive disabilities challenge health professionals in the evaluation of visual function. In addition, several primary caregivers noted anecdotally that implementing the questionnaire led them to develop more accurate observation skills which would enhance their own understanding of the children's responses in future situations.

LIMITATIONS OF THE STUDY

The initial aim of the questionnaire was to address all four areas of visual function: communication, ADL, play and leisure, and mobility and orientation.[5] However, it was difficult to articulate ADL questions relevant to this population, and motor requirements further limited the relevance of other questions. The 26 relevant questions, therefore, assess basic visual skills and reflect function during interactive play and communication situations.

Based on the analysis, we suggest that the questionnaire be divided into a core section focusing on basic visual skills and visual function during communication tasks, with supplementary sections that relate to ADL, play and leisure, and mobility and orientation, which would be utilized only when they appear to be relevant to the specific child. In addition, in order to further develop the questionnaire, we recommend its implementation with a larger participant group as well as with other multiply involved paediatric populations.

Additional issues that still need to be overcome are the subjective nature of the report and the fact that a questionnaire assessment requires retrospective recollection and analysis of behaviour by a single observer.

CONCLUSION

Variability in visual performance along with limited communication abilities among children with profound neurological impairments presents a challenge for accurate and meaningful measurement of visual function. This study highlights the benefits of implementing a two-pronged visual assessment comprising a precise ophthalmological diagnosis that incorporates a performance scale as well as assessment of daily visual function by means of a reliable questionnaire. When the data from both tools are integrated, more precise knowledge of the child's visual function will become available. This will enable treatment staff and families to create adapted classroom and home environments suited to the specific needs of the child, which in turn will facilitate play, learning, and communication.

We suggest continued development of the questionnaire as well as the exploration of additional methods for qualitative assessment of visual performance.

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ONLINE MATERIAL/SUPPORTING INFORMATION

Additional material and supporting information can be found in the online version of this article.

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