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Additional measures of macular function beyond visual acuity

The Vision Academy is a group of over 100 international experts who, through their collective expertise, provide consensus guidance for managing clinically challenging situations, especially in areas of controversy or with insufficient conclusive evidence.

The Vision Academy is funded and facilitated by Bayer.

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Objectives

To review current measures of visual function beyond acuity

To provide recommendations on the application of additional measures in the management of retinal diseases

- The Vision Academy provides ophthalmic specialists with a forum to share existing skills and knowledge, provide consensus guidance for managing clinically challenging situations, and lead the wider community in the drive toward optimized, compassionate patient care
- Through their collective expertise, the Vision Academy seeks to provide consensus guidance for managing clinically challenging situations, especially in areas of controversy or with insufficient conclusive evidence

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QUESTION

How can further measurements beyond visual acuity help us achieve a more precise assessment of visual function?

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Background

Visual function

Visual function is a complex process involving multiple interactions between the eye and the brain, and is influenced by both external environmental and internal factors[1-3]

- As vision in daily life depends on varying dimensions,[4] measuring visual function is not straightforward
- **Limitations** of well-established methods of measuring visual function include:[5]
  - Insufficient sensitivity to allow detection of the slow deterioration of visual function components
  - Lack of reliable reproducibility (e.g., the Amsler grid)[6]
  - Inability to differentiate the long-term effects of intravitreal drugs, particularly in cases where best-corrected visual acuity seems unchanged

Additional measures may help to further characterize the impact of retinal diseases on patients' visual function and quality of life, and identify those patients who could benefit from:[7]

- Earlier diagnosis
- Detection of disease progression
- Prompt therapeutic intervention

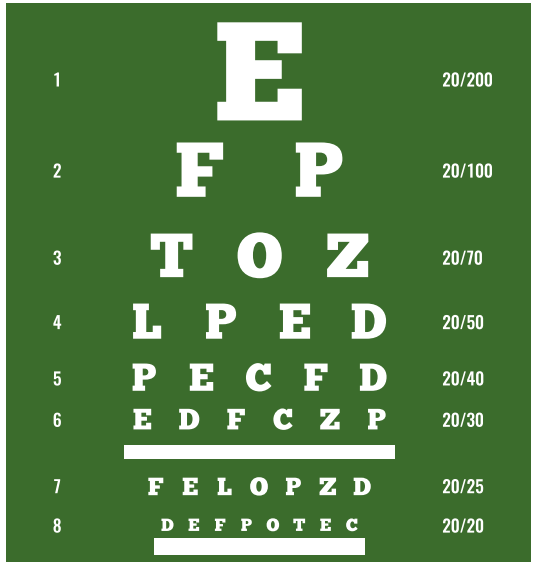
1. Trick GL. *Neurol Clin* 2003; 21 (2): 363–386; 2. Kniestedt C, Stamper RL. *Ophthalmol Clin North Am* 2003; 16 (2): 155–170; 3. Wall M, Johnson CA. Principles and techniques of the examination of the visual sensory system. In: Miller NR, Newman NJ, Biousse V, Kerrison JB, eds. *Walsh and Hoyt's Clinical Neuro-Ophthalmology*. 6th ed. Lippincott Williams & Wilkins; 2005: 89–93; 4. Haegerstrom-Portnoy G *et al. Optom Vis Sci* 1999; 76 (3): 141–158; 5. Ríos HA *et al. Graefes Arch Clin Exp Ophthalmol* 2024; 262 (6): 1723–1736; 6. Schuchard RA. *Arch Ophthalmol* 1993; 111 (6): 776–780; 7. Nasralah Z *et al. J Clin Exp Ophthalmol* 2013; 4 (6): 1–8.

Visual acuity

Visual acuity, the most frequently used measure of visual function,[1] is the ability to discern subtle differences in the environment[2]

Excellent VA indicates that:[3]

- The image is clearly focused on the retina
- The visual pathway is functioning correctly
- Appropriate interpretation of the visual stimuli has occurred



VA is often evaluated using a Snellen chart,[2] as shown above

Aspects of visual function not assessed during VA tests include:[2]

- Distortion
- Color
- Contrast
- Fixation
- Dark adaptation

These are also important for a **comprehensive assessment of visual function**[4-10]

Complementary methods to VA measurement may provide a more comprehensive assessment of a patient's vision and its impact on day-to-day functioning and quality of life[2]

VA, visual acuity.

1. Sheedy JE *et al. Am J Optom Physiol Opt* 1984; 61 (9): 595–600; 2. Ríos HA *et al. Graefes Arch Clin Exp Ophthalmol* 2024; 262 (6): 1723–1736; 3. Levenson JH, Kozarsky A. Visual acuity. In: Walker HK, Hall WD, Hurst JW, eds. *Clinical Methods: The History, Physical, and Laboratory Examinations*. 3rd ed. Butterworths; 1990; 4. Haegerstrom-Portnoy G *et al. Optom Vis Sci* 1999; 76 (3): 141–158; 5. Schuchard RA. *Arch Ophthalmol* 1993; 111 (6): 776–780; 6. Jakobsen NS *et al. Ophthalmic Res* 2017; 58 (3): 142–149; 7. Labrique AB *et al. BMC Ophthalmol* 2015; 15 (1): 1–9; 8. Midena E *et al. Invest Ophthalmol Vis Sci* 1997; 38 (2): 469–477; 9. Sunness JS *et al. Ophthalmology* 2008; 115 (9): 1480–1488; 10. Longhin E *et al. Eur J Ophthalmol* 2016; 26 (5): 418–424.

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Clinical challenges

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Clinical challenges requiring guidance

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More comprehensive assessment of visual function

- What measures can help better characterize the impact of visual function on patients' quality of life?

Visual function measures requiring further research

- Are there additional measures that require further optimization and should only be used with caution?

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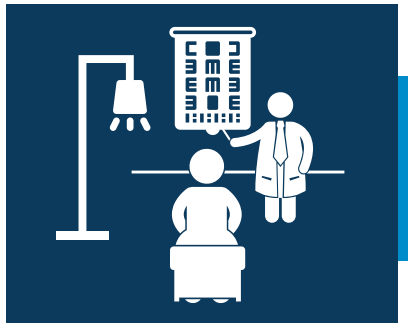
Vision Academy recommendations

Low-luminance visual acuity



LLVA is a simple, inexpensive, and rapid measure of visual function[1] that is a more accurate surrogate for VA[2,3]

- Chart luminance plays a vital role when evaluating VA[4]
- **LLVA** is assessed by decreasing luminance during VA testing, either by placing a filter between the chart and the eye or using a digital screen with luminance control[1]
- VA tests carried out under low-luminance conditions have been found to be useful in:
  - Detecting and monitoring different stages of AMD progression, particularly GA[5]
  - Predicting the risk of future VA loss in patients with GA due to non-neovascular AMD[6,7]
- The **low-luminance deficit**[a] is also potentially predictive of subsequent VA loss and GA progression in patients with AMD[6,8]
- Despite extensive use, there is a lack of standardization in LLVA testing and currently no guidelines are available for its application in clinical practice[1]

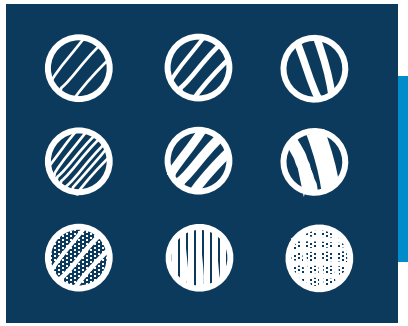
Recommended measure of visual function.

[a]Low-luminance deficit is defined as the difference between LLVA and best-corrected VA measurements.[6]

AMD, age-related macular degeneration; GA, geographic atrophy; LLVA, low-luminance visual acuity; VA, visual acuity.

1. Ríos HA *et al. Graefes Arch Clin Exp Ophthalmol* 2024; 262 (6): 1723–1736; 2. Sheedy JE *et al. Am J Optom Physiol Opt* 1984; 61 (9): 595–600; 3. Johnson CA *et al. Optom Vis Sci* 1995; 72 (2): 864–869; 4. Durst W *et al. Br J Ophthalmol* 2011; 95 (11): 1506–1508; 5. Sunness JS *et al. Ophthalmology* 1997; 104 (10): 1677–1691; 6. Sunness JS *et al. Ophthalmology* 2008; 115 (9): 1480–1488; 7. Chandramohan A *et al. Retina* 2016; 36 (5): 1021–1031; 8. Yehoshua Z *et al. Ophthalmology* 2014; 121 (3): 693–701.

Contrast sensitivity



CS testing assesses the eye's ability to distinguish between similar shades,[1] making it an important adjunct to, or even a replacement for, VA testing[2]

- Studies suggest that:
  - CS may be a more sensitive measure of early retinal changes than VA in patients with diabetes[3]
  - CS is useful in the diagnosis, follow-up, and treatment of DME and DR, and after panretinal photocoagulation treatment[4]
  - There may be an association between CS findings and the initial stages of AMD,[5-7] although one prospective study failed to show that CS deficit is a predictable risk factor for AMD development[8]
- Some of the most common tools for measuring CS are:[2]
  - **Sine-wave grating stimuli**
  - **Pelli-Robson CS chart**[9]
  - **Mars Letter Contrast Sensitivity Test**[10,11]

Recommended measure of visual function.

AMD, age-related macular degeneration; CS, contrast sensitivity; DME, diabetic macular edema; DR, diabetic retinopathy; VA, visual acuity.

1. Sunness JS *et al. Ophthalmology* 2008; 115 (9): 1480–1488; 2. Ríos HA *et al. Graefes Arch Clin Exp Ophthalmol* 2024; 262 (6): 1723–1736; 3. Nasralah Z *et al. J Clin Exp Ophthalmol* 2013; 4 (6): 1–8; 4. Lövestam-Adrian M *et al. Acta Ophthalmol Scand* 2000; 78 (6): 672–676; 5. Midena E *et al. Invest Ophthalmol Vis Sci* 1997; 38 (2): 469–477; 6. Maynard ML *et al. Acta Ophthalmol* 2016; 94 (8): e772–e778; 7. Puell MC *et al. Invest Ophthalmol Vis Sci* 2012; 53 (11): 7310–7314; 8. Owsley C *et al. Invest Ophthalmol Vis Sci* 2016; 57 (4): 1782–1789; 9. Pelli DG *et al. Clin Vis Sci* 1998; 2: 187–199; 10. Dougherty BE *et al. Optom Vis Sci* 2005; 82 (11): 970–975; 11. Arditi A. *Invest Ophthalmol Vis Sci* 2005; 46 (6): 2225–2229.

Retinal fixation and microperimetry

Retinal fixation and microperimetry are valuable tools for monitoring and assessing macular function in patients with retinal diseases, and are potential indirect indicators of visual function[1]

- As a result of damage to the fovea, patients with retinal diseases can experience alterations in retinal fixation, limiting their ability to focus on a single object.[1] This affects the patient's reading performance and ability to perform everyday tasks[2-4]
- **Microperimetry** can be used to quantify unstable fixation,[5,6] automatically analyzing fixation stability through the **clinical classification** method or the **bivariate contour ellipse area analysis** method[6,7]
- Microperimetry may be useful to:
  - Detect decreased retinal sensitivity in patients with early AMD[8] and individuals with prediabetes[9]
  - Investigate correlations between anatomical features of the macula and functional parameters, such as the location and stability of fixation, in patients with AMD[10,11]
  - Objectivize macular function in patients with subtle vision loss due to AMD, who report difficulty with everyday vision despite good VA[12]

Recommended measure of visual function.
AMD, age-related macular degeneration; VA, visual acuity.

1. Ríos HA *et al. Graefes Arch Clin Exp Ophthalmol* 2024; 262 (6): 1723–1736; 2. Møller F *et al. Acta Ophthalmol Scand* 1996; 74 (6): 578–583; 3. Møller F *et al. Graefes Arch Clin Exp Ophthalmol* 2006; 244 (4): 465–471; 4. Pedersen KB *et al. Graefes Arch Clin Exp Ophthalmol* 2016; 254 (10): 1897–1908; 5. Crossland MD *et al. Ophthalmology* 2005; 112 (9): 1579–1585; 6. Timberlake GT *et al. Optom Vis Sci* 2005; 82 (3): 177–185; 7. Longhin E *et al. Can J Ophthalmol* 2013; 48 (5): 375–380; 8. Midena E *et al. Br J Ophthalmol* 2007; 91 (11): 1499–1503; 9. Al Shafaee M *et al. Eur J Ophthalmol* 2011; 21 (6): 771–776; 10. Mathew R *et al. Am J Ophthalmol* 2012; 153 (3): 490–496.e1; 11. Cassels NK *et al. Surv Ophthalmol* 2018; 63 (1): 40–55; 12. Tran B-K, Herbort CP Jr. *Klin Monbl Augenheilkd* 2015; 232 (4): 529–532.

Reading performance

Reading performance is a strong predictor of vision-related quality of life,[1] and its improvement is a high priority for patients threatened with vision loss[2]

- Given that many everyday tasks rely on reading, patients with low vision often report reading difficulties as their primary concern in quality-of-life studies[3,4]
- Fixation instability and CS loss are key factors in the impaired reading performance of patients with low vision due to AMD or DR[5]
- Reading performance may be a valuable indicator of response to anti-VEGF therapy in patients with AMD[6]
  - Average reading speed improved after three anti-VEGF injections in a prospective case series assessing 30 eyes. However, other factors such as literacy level and cognitive level also influence reading speed, so these results must be interpreted with caution
- Reading performance can be assessed using:
  - **Sentence-level reading acuity tests:** Colenbrander, MNread, and Radner cards[7,8]
  - The **IReST** tool, which employs standardized passages of text instead of single sentences[8]

Recommended measure of visual function.

AMD, age-related macular degeneration; CS, contrast sensitivity; DR, diabetic retinopathy; IReST, International Reading Speed Texts; VA, visual acuity; VEGF, vascular endothelial growth factor.

1. Mangione CM *et al. Arch Ophthalmol* 1998; 116 (11): 1496–1504; 2. Ríos HA *et al. Graefes Arch Clin Exp Ophthalmol* 2024; 262 (6): 1723–1736; 3. Crossland MD *et al. Vis Impair Res* 2007; 9 (2-3): 59–66; 4. Elliott DB *et al. Invest Ophthalmol Vis Sci* 1997; 38 (12): 2566–2575; 5. Giacomelli G *et al. Invest Ophthalmol Vis Sci* 2013; 54 (6): 4403–4408; 6. Frennesson C *et al. Acta Ophthalmol* 2010; 88 (4): 420–425; 7. Rubin GS. *Vision Res* 2013, 90: 43–51; 8. Trauzettel-Klosinski S *et al. Invest Ophthalmol Vis Sci* 2012; 53 (9): 5452–5461.

Dark adaptation

- Dark adaptometry measures the absolute thresholds of cone and rod sensitivity in complete darkness[1-3]
- In patients with AMD, rod[4,5] and cone[1-3] adaptation are impaired, and dark adaptation has been shown to be a highly reliable measure of early disease[1,6,7]
- Dark adaptation is a potential biomarker for AMD diagnosis and progression,[8] and is also useful in the early detection and prevention of retinal damage caused by diabetes mellitus[9]
  - Nevertheless, the clinical and diagnostic value of dark adaptation is limited by shortcomings such as a long test duration and lack of reproducibility[8]

Binocular vision testing

- In patients with AMD that affects one eye more than the other, or with monocularly preferred retinal fixation points that are not in corresponding positions, VA in the better-seeing eye can be affected by the performance of the worse-seeing eye, and vice versa, when vision is assessed under binocular viewing conditions[10-13]
- Binocularity provides a more realistic measure of functional visual performance than VA, and after further research, could be tested daily to evaluate visual function in real-life situations[8]

Further research and standardization are needed before these measures can be routinely used in clinical practice[8]

AMD, age-related macular degeneration; VA, visual acuity.

1. Gaffney AJ *et al. Doc Ophthalmol* 2013; 127 (3): 191–199; 2. Gaffney AJ *et al. Optom Vis Sci* 2012; 89 (8): 1219–1224; 3. Tahir HJ *et al. Invest Ophthalmol Vis Sci* 2018; 59 (4): AMD202–210; 4. Jackson GR, Edwards JG. *J Ocul Biol Dis Infor* 2008; 1 (1): 7–11; 5. Owsley C *et al. Invest Ophthalmol Vis Sci* 2000; 41 (1): 267–273; 6. Flamendorf J *et al. Ophthalmology* 2015; 122 (10): 2053–2062; 7. Chen KG *et al. Ophthalmology* 2019; 126 (6): 856–865; 8. Ríos HA *et al. Graefes Arch Clin Exp Ophthalmol* 2024; 262 (6): 1723–1736; 9. Ramsey DJ, Arden GB. *Curr Diab Rep* 2015; 15 (12): 118; 10. Faubert J, Overbury O. *J Am Geriatr Soc* 2000; 48 (4): 375–380; 11. Quillen DA. *Arch Ophthalmol* 2001; 119 (11): 1725–1726; 12. Jakobsen NS *et al. Ophthalmic Res* 2017; 58 (3): 142–149; 13. Tarita-Nistor L *et al. Invest Ophthalmol Vis Sci* 2011; 52 (3): 1887–1893.

Color vision testing

- An association has been found between color vision defects and retinal diseases[1]
- Color discrimination tests can be useful in:
  - Assessing disease severity and treatment effects in patients with DR and DME[1-3]
  - Monitoring patients with late AMD[4]
- Improved studies with greater statistical weight are needed to determine whether there is a role for color discrimination tests in routine clinical practice[5]

Visual recognition tests

- Advanced AMD is often associated with central scotoma, which can significantly impair higher-level visual functions such as reading and face recognition[6,7]
- Tests that evaluate visual recognition of objects provide a simple and reliable means of determining AMD severity and its impact on daily activities[8]
- The use of visual recognition tests is currently limited by a lack of standardization and the patient's cognition level[5]

Shape discrimination

- Metamorphopsia, aniseikonia, and other shape alterations are common symptoms in various macular disorders; however, clinically validated tests for these symptoms are currently lacking[5,9-12]
- A number of shape discrimination tests are now under development (e.g., preferential hyperacuity perimetry[13], MonCV3[a]), but further research is needed to determine their role in clinical practice[5]

Further research and standardization are needed before these measures can be routinely used in clinical practice[8]

[a]MonCV3 (Metrovision, Pérenchies, France) is a multifunction perimeter.
AMD, age-related macular degeneration; DME, diabetic macular edema; DR, diabetic retinopathy.

1. Bresnick GH *et al. Arch Ophthalmol* 1985; 103 (9): 1317–1324; 2. Fong DS *et al. Am J Ophthalmol* 1999; 128 (5): 612–617; 3. Abdel-Hay A *et al. PLoS One* 2018; 13 (6): e0199693; 4. Dorrepaal SJ, Markowitz SN. *Can J Ophthalmol* 2013; 48 (3): 199–203; 5. Ríos HA *et al. Graefes Arch Clin Exp Ophthalmol* 2024; 262 (6): 1723–1736; 6. Legge GE *et al. Optom Vis Sci* 1989; 66 (12): 843–853; 7. Tejeria L *et al. Br J Ophthalmol* 2002; 86 (9): 1019–1026; 8. Thibaut M *et al. J Fr Ophtalmol* 2016; 39 (1): 82–89; 9. Midena E, Vujosevic S. *Ophthalmic Res* 2015; 55 (1): 26–36; 10. de Wit GC, Muraki CS. *Ophthalmology* 2006; 113 (1): 58–62; 11. Loffler G. *J Vis* 2015; 15 (7): 1–19; 12. Wada I *et al. Clin Ophthalmol* 2017; 11: 1719–1726; 13. Loewenstein A *et al. Retina* 2010; 30 (7): 1058–1064.

Recommended measures of visual function beyond visual acuity[1]

Measure	When, where, and why to use it	Advantages	Limitations	Specific recommendations for application
Low-luminance visual acuity	• AMD, DME, central serous chorioretinopathy, PDR (PRP), and IRD • Follow-up for patients with dry AMD	• Simple, inexpensive, and rapid measure	• Should be explained to the patient that the result will naturally be lower than best-corrected visual acuity	• Use a 2.0-log unit neutral-density filter • Larger benefit in non-neovascular AMD • A self-administered test could be considered
Contrast sensitivity	• AMD, DME, refractive surgery, central serous chorioretinopathy, PDR (PRP), and IRD • After PRP in patients with diabetes • When visual acuity does not match reported visual problems	• Rapid measure • Linked to vision-related quality of life	• Variability of results • Influenced by cataracts	• Use of a computer-controlled screen is preferable
Retinal fixation and microperimetry	• AMD, DME, vitreoretinal disorders, retinotoxicity disorders, macular dystrophies, and IRD • Better correlation and understanding of morphology (i.e., imaging) and function, especially retinal sensitivity	• Good correlation between retinal fixation and reading performance	• Equipment not available at all retinal clinics • Long testing duration traditionally but duration has improved with recent developments	• Use short-duration testing strategies • Print out results with probability maps of disease progression • Use to determine fixation in advanced AMD
Reading performance	• AMD, DME, vitreoretinal disorders, refractive surgery • During follow-up visits, evaluate response after anti-VEGF treatment for AMD or DME • Better assessment of the impact of visual impairment on quality of life than ETDRS charts	• Strongly linked to vision-related quality of life	• Lack of standardization • Lack of agreement on methodology • Depends on a patient's literacy	• Example: Radner reading charts • Comparability needs to be ensured • May be performed uni- or binocularly

AMD, age-related macular degeneration; DME, diabetic macular edema; ETDRS, Early Treatment Diabetic Retinopathy Study; IRD, inherited retinal disease; PDR, proliferative diabetic retinopathy; PRP, panretinal photocoagulation; VEGF, vascular endothelial growth factor.

1. Ríos HA *et al. Graefes Arch Clin Exp Ophthalmol* 2024; 262 (6): 1723–1736.

Measures of visual function requiring further optimization[1]

Measure	When, where, and why to use it	Advantages	Limitations	Specific recommendations for application
Dark adaptation	• AMD, DME, PDR (PRP) • To differentiate AMD from variants of genetic disease • Early diagnosis of AMD progression if short-duration testing strategies prove effective	• Assesses photoreceptor dynamic response	• Lack of standardization • Time-consuming • Requires special examination equipment and a dedicated dark room, which are not always available	• Use short-duration testing strategies
Binocular vision testing	• Neurological disorders, squinting, IRD, and nystagmus • Driver's license testing in some countries • Evaluation of real-life visual performance for medical or legal purposes	• Meaningful for real-life activities • Strongly linked to vision-related quality of life	• Underestimation of monocular visual changes • Lack of standardization	Not applicable
Color vision testing	• Diabetic retinopathy, DME • Driver's license testing in some countries • Neurological disorders • IRD	• Easily performed • Standardized (printed charts)	• Influenced by media opacities, namely cataracts • Tests a different function from visual discrimination, therefore correspondence with other tests is limited	• Use of Cambridge Colour Test or other computerized tests is faster than the classic print-based tests (e.g., Ishihara, Farnsworth)
Visual recognition tests	• AMD • To differentiate from neurological or cognitive disorders such as Charles Bonnet syndrome	• Linked to vision-related quality of life	• Lack of standardization • Limited relevance for monitoring AMD progression	Not applicable
Shape discrimination	• AMD, DME • To differentiate from neurological or cognitive disorders such as Charles Bonnet syndrome	• Linked to vision-related quality of life	• Lack of standardization	• Can be used for self-monitoring of AMD

AMD, age-related macular degeneration; DME, diabetic macular edema; IRD, inherited retinal disease; PDR, proliferative diabetic retinopathy; PRP, panretinal photocoagulation.

1. Ríos HA *et al. Graefes Arch Clin Exp Ophthalmol* 2024; 262 (6): 1723–1736

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Further considerations

While the techniques reviewed in this deck are largely focused on AMD and DME, they are also applicable to other retinal diseases, including inherited retinal diseases and nystagmus[1-4]

Methods such as multifocal electroretinograms and multifocal visual evoked potentials can be valuable in the differential diagnosis of retinal and optic nerve diseases,[5-8] and have the potential to assess visual field effects not yet detected by automated perimetry.[9] However, the multifocal visual evoked potential method requires specialized software and is not widely applied in clinical practice[6]

Methods that employ frequency-doubling technology are mainly used to identify visual field defects in optic nerve-related diseases, rather than for macular assessment[10]

AMD, age-related macular degeneration; DME, diabetic macular edema.

1. Wood LJ *et al. Transl Vis Sci Technol* 2021; 10 (2): 28; 2. McAnany JJ *et al. Transl Vis Sci Technol* 2022; 11 (3): 7; 3. Michalakis S *et al. Mol Diagn Ther* 2022; 26 (1): 51–59; 4. Schneider RM *et al. PLoS One* 2013; 8 (2): e56556; 5. Hood DC *et al. J Neuroophthalmol* 2003; 23 (3): 225–235; 6. Hood DC *et al. J Neuroophthalmol* 2003; 23 (4): 279–289; 7. Creel DJ. *Handb Clin Neurol* 2019; 160: 481–493; 8. Creel DJ. *Handb Clin Neurol* 2019; 160: 501–522; 9. Young B *et al. Curr Opin Ophthalmol* 2012; 23 (6): 497–505; 10. Kim SA *et al. Sci Rep* 2022; 12 (1): 10173.