New Technologies for Outcome Measures in Glaucoma - Review from the European Vision Institute Special Interest Focus Group

Ghislaine L. Traber[1,2], Maria della Volpe-Waizel[1,2], Peter Maloca[2], Ursula Schmidt-Erfurth[3], Gary Rubin[4], Botond Roska[2], M. Francesca Cordeiro[4,5,6], Tilman Otto[7], Richard Weleber[8], Luis A. Lesmes[9], Angelo Arleo[10], Hendrik P. N. Scholl[1,2*]

1 Department of Ophthalmology, University Hospital Basel, University of Basel, Basel, Switzerland

2 Institute of Molecular and Clinical Ophthalmology Basel (IOB), Basel, Switzerland

3 Medical University of Vienna, Department of Ophthalmology, Vienna, Austria

4 UCL University College London, Institute of Ophthalmology, London, United Kingdom

5 The Western Eye Hospital, Imperial College Healthcare NHS Trust, London, United Kingdom

6 The Imperial College Ophthalmic Research Group (ICORG), Imperial College London, London, United Kingdom

7 Heidelberg Engineering GmbH, Heidelberg, Germany

8 Casey Eye Institute, Departments of Ophthalmology and Molecular and Medical Genetics, University of Oregon Health & Science University, Portland, Oregon, USA

9 Adaptive Sensory Technology, Inc San Diego, California, USA

10 Sorbonne Université, INSERM, CNRS, Institut de la Vision, 17 rue Moreau, F-75012 Paris, France

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*Corresponding Author

Hendrik P.N. Scholl, MD, MA

Institute of Molecular and Clinical Ophthalmology, Basel, Switzerland (IOB)

Mittlere Strasse 91

Basel, CH-4031, Switzerland

Tel: +41 61 265 86 86

E-mail: hendrik.scholl@iob.ch

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1. Abstract (max 200 words)

Glaucoma is the leading cause of irreversible blindness worldwide with increasing prevalence. The complexity of the disease has been a major challenge in moving the field forward both with regard to pathophysiological insight and treatment. In this context, discussion of possible outcome measures in glaucoma trials is of utmost importance and clinical relevance.

A recent meeting of the European Vision Institute (EVI) special interest focus group was held on "New Technologies for Outcome Measures in Retina and Glaucoma" addressing both functional and structural outcomes as well as translational hot topics in glaucoma and retina research. In conjunction with published literature, this review summarizes the meeting focusing on glaucoma.

2. Introduction

Worldwide, glaucoma is the leading cause of irreversible blindness.[1] The hallmark of disease is degeneration of retinal ganglion cells and its axons resulting in a progressive optic neuropathy with typical changes of the optic disc.[2,3] Glaucomatous neurodegeneration is related to the level of intraocular pressure, but also independent thereof, and even seems not confined to the anterior visual pathway.[4] Still, lowering the intraocular pressure is the only proven therapeutic option to date.[2,5]

Given its age-related nature, this global epidemic is still on the rise not only causing significant visual disability but also further adding to our health-economic burden.[6] The complexity of the disease has been a major challenge in moving the field forward both with regard to pathophysiological insight and treatment. In this context, discussion of possible outcome measures in glaucoma trials is of utmost importance and clinical relevance.

A recent meeting of the European Vision Institute (EVI) special interest focus group was held on "New Technologies for Outcome Measures in Retina and Glaucoma" hosted by the Institute of Molecular and Clinical Ophthalmology Basel (IOB), University of Basel, Switzerland, November 8-9, 2018.

The agenda with presentations of international clinicians and scientists was selected by Hendrik Scholl and the EVI steering committee. Backed with published literature, the presentations and discussions are summarized below focusing on glaucoma.

3. Results

Active Learning for Precision Measurement of Visual Function

With the idea of improving the precision of vision testing, **Luis Andres Lesmes** and co-workers from Adaptive Sensory Technology introduced the concept of active learning, which improves the assessment of contrast sensitivity (CS) and visual acuity (VA) through the combination

of digitized displays, novel quantitative Bayesian models of visual function, and intelligent sampling algorithms that personalize testing to each patient. For each patient, the active learning algorithm evaluates an expansive space of potential test outcomes, searches a large library of potential contrast and acuity test items, and converges to a test sequence comprising optimal queries for each patient based on their previous responses.

The contrast sensitivity function (CSF) is fundamental to vision science, a threshold contour that represents the boundary between what one can see in the world and what one cannot see (Figure, left). Rather than estimate contrast sensitivities for individual spatial frequency conditions, the qCSF directly estimates a Bayesian parameterization of the function's global shape. Using the higher pixel and contrast resolution of digital displays, and an intelligent algorithm for sampling stimulus size and contrast, the qCSF algorithm presents the patient with the size-contrast combinations that comprise an optimal assessment of the personalized shape of the patient's CSF (Figure; Right). The CSF shows disease specific patterns of function loss in various ophthalmic conditions including glaucoma [7–13] and might thus serve as a valuable outcome measure by revealing hidden signals of early vision loss and by improving the statistical power for detecting visual changes through better signal-to-noise ratio.[14]

VA testing has typically implemented two complementary but exclusive strategies: (1) static, chart-based testing that presents optotypes of fixed sizes in rows (ETDRS,Pelli-Robson), or (2) computerized testing that applies a staircase to change the size of single optotypes.[15] Lesmes and Dorr (2019)[16] have proposed a quantitative VA (qVA) algorithm, which combines these approaches to changes the size of multiple optotypes, using a row-based psychometric function of expected correct optotypes as a function of logMAR optotype size. With intelligent sampling of optotype size (true .02 logMAR resolution), the algorithm

reduces the noise in VA testing and provides fine-grained information on the threshold and range of the VA psychometric function.

The qCSF and qVA algorithms have exhibited potential to improve the statistical power for reliably detecting subtle but potentially clinically significant signals in visual function. Because the definition of a clinically meaningful change is constrained by what is clinically measurable, there is potential for novel methodology to drive the threshold of what is accepted both by clinicians and by regulatory authorities as clinically relevant.

Microperimetry as Visual Function Endpoint

Gary Rubin's talk focused on microperimetry. There are currently three different commercially available microperimeters. The Nidek MP3 (NIDEK Co. Ltd, Aichi, Japan) and the MAIA (CenterVue, Padova, Italy) combine microperimetry with non-mydriatic color fundus imaging and scanning laser ophthalmoscopy (SLO) imaging, respectively. The OptosOCT SLO (Optos PLC, Dunfermline, United Kingdom) is the first device to superimpose microperimetry data on OCT images. Eye tracking allows projection of stimuli on different retinal locations with imaging of the fundus in real time. Microperimetry is thus providing structure-function correlations and is particularly useful in patients with unstable or eccentric fixation. The technology has mainly been applied in retinal diseases. Gary Rubin comments on its use in the EFFECT trial (Eccentric Fixation From Enhanced Clinical Training) in recent onset macular disease (Rubin G. First results from the EFFECT Trial, an RCT of eccentric viewing training for patients with AMD, ARVO Annual Meeting Abstract, June 2017, Baltimore, MD, May 7-11, 2017, Investigative Ophthalmology & Visual Science June 2017, Vol.58, 4766.)[17] and in gene therapy trials for Leber Congenital Amaurosis.[18,19] However, microperimetry has also been investigated in glaucoma. Published literature highlights aspects of interests including comparison with standard automated perimetry[20–22], structure-function correlations[22–26],

assessment of early glaucoma detection[27], visual field evaluation in advanced glaucoma[28,29], and fixation instability in glaucoma.[30,31]

Modeling and Analysis of the Hill of Vision of Full-Field Static Perimetry (VFMA)

On behalf of **Richard Weleber**, **Hendrik Scholl** explained the concept of Visual Field Modeling and Analysis (VFMA). The hill of vision (HOV) is a functional measure of the total light sensitivity across the retina, which VFMA visualizes by a color coded 3D sensitivity surface. A single volumetric measure in decibel-steradian (dB-sr) units quantitatively estimates the HOV. As opposed to conventional visual field indices (e.g. mean sensitivity MS, mean defect MD, square root of loss variance sLV), VFMA not only captures the whole visual field sensitivity in one single endpoint (dB-sr), but also has a flexible region of interest and is more robust to grid changes. The latter is explained by the fact that HOV computation is achieved by interpolated dense VFMA gridding based on sparse gridding of the measured raw data. As a consequence, the HOV volume is a flexible and robust measure of quantity resulting in a stronger, more focused endpoint. The methodology has been established in 2015[32] and since has been used in several trials including the RPE65 gene therapy trial.[33] VFMA mainly has been adopted in trials on retinal disease, but could without doubt be established in glaucoma as well.

Behavioral Outcome Measures and Naturalistic Testing

Angelo Arleo presented his group's research on visual spatial behavioral performance of young versus elderly subjects. The presented data mainly focused on healthy ageing, and serves as a scientific basis for future assessment of visual spatial behavior in patients with visual or cognitive impairment. Age-related decline of visual spatial function is related to optical, neurosensory and cognitive factors. The experimental setup is designed for cognitive aspects, and analyses how age interferes with spatial perception, spatial action and spatial

learning, which might serve as a functional marker of mobility and autonomy loss in the elderly.

Our internal representation of space is anchored on different types of visual information which is referred to as spatial coding. In order to avoid the possible bias induced by computer screen-based tasks like lack of multisensory integration, coordinate transformation and limited field of view, Arleo and co-workers established an ecological experimental setup (Figure 2) to study spatial learning and to find out what type of visual information different age groups rely on. Assessed in a symmetric Y-shaped maze, vector field analysis of age groups showed that children and healthy elderly adults mainly navigate in an egocentric manner which is referred to a loss of allocentric strategies with age in the literature[34] (Lester et al 2017 Neuron). However, they become able to use allocentric information in an asymmetric Y-shaped maze.[35,36] By contrast, young adults rely on allocentric navigation under both conditions.[35,36] Arleo and co-workers hypothesize that this is more likely related to visual and spatial cue processing rather than strategic choices (egocentric versus allocentric). Exploring a naturalistic maze, children and elderly adults again behave similarly, and mainly depend on the geometry of the environment while young adults mainly focus on landmarks. The latter visual behavior is corroborated by analysis of visual exploration patterns using eye tracking which predicts spatial cue preference (geometry versus landmarks). Extensive visual function and neuropsychological testing did not show any correlation that could possibly explain the age-related preference for geometric cues. However, unpublished data on brain imaging studies revealed impaired high-spatial frequency coding in brain regions responsible for visuo-spatial processing like the visual cortex and retrosplenial cortex, and showed grey matter atrophy in brain regions

at the interface between spatial and visual coding (occipital place area, parahippocampal place area).

The ecological setup mentioned above with both a naturalistic and virtual environment adds a completely new dimension of possible future outcome measures and seems also interesting in the context of glaucoma since glaucoma appears not only restricted to retinal ganglion cell loss with subsequent visual field defects, but might also be associated with more widespread neurodegeneration.[4]

New Developments in Optical Coherence Tomography (OCT)

Peter Maloca, MD, presented his group's hardware and software innovations in optical coherence tomography (OCT) imaging. *Hydra-OCT* is a dual co-axial OCT with a second light source of 1060nm in addition to the existing 870nm light source. The system is based on the Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany) and can be easily integrated into clinical routine. Maloca claims that the Hydra-OCT allows better visualization of deeper retinal structures and provides additional information, since the refractive index can also be calculated due to the two different wavelengths, thus enabling direct tissue measurements. The portable MIMO OCT device implements a very fast so-called *sparse OCT* scanning system and was designed for self-monitoring of patients at home.[37,38] The data is supposed to be analyzed with a cloud-based machine learning platform and data are then displayed to patients or physicians for continuous monitoring of possible disease progression. The latter is applicable both to retinopathies and glaucoma.

With regard to software developments, Maloca presented their *3D-speckle denoiser*[39] that improves the signal to noise ratio not only for OCT imaging but also for 3D-ultrasound, computer tomography and possibly other imaging modalities.[40–44] This might allow more accurate segmentation of retinal and optic nerve structures. Finally, the audience caught a glimpse of the technological potential of original 3D point cloud data being "injected" and instantly rendered into an interactive virtual reality environment (VR).[45] The group has

applied artificial intelligence based segmentation of the data and allows the "VR-pilot" to interact with it. Ultimately, the virtual environment might allow to share standardized mobility mazes between centers as outcome measures.

Advancements in Diagnostic Imaging Modalities

Tilman Otto from Heidelberg Engineering gave a comprehensive overview of advancements in diagnostic imaging modalities, the summary of which is clearly beyond the scope of this review. A more detailed summary is provided by Della Volpe et al (same issue of the journal **REF**). Basically, the imaging technologies either involve single or two photon interactions. Most imaging technologies are based on single photon interactions which include *backscattering* as in conventional fundus photographs, SLO, OCT and OCT angiography imaging, and *detection of fluorescence*, both biofluorescence or fluorescent dyes.

OCT- elastography (OCE) is an imaging development that might be relevant for corneal pathologies or glaucoma. OCE allows OCT based measurements of subtle structural fundus changes due to mechanical stress (e.g. increased IOP) and derives information on tissue elasticity.[46]

Artificial Intelligence in Retinal Imaging

Today, artificial intelligence (AI) is omnipresent and ophthalmology is at its forefront. **Ursula Schmidt-Erfurth,** outlines the tremendous development our field has experienced, starting out from conventional 2D fundus photography, evolving into 3D OCT imaging of even subclinical pathologies over the last 25 years[47], and recently moving into the era of deep learning (DL) since the early 2010s. Rudiments of AI have been available since the 1950ies. However, only the increase of data volume and server capacity have considerably improved its level of operation. Vice versa, the exponential rise of available imaging data necessitates AI to identify and quantify the relevant biomarkers by providing automated segmentation, quantification of lesions, pattern recognition, prediction of recurrence or progression, and

structure-function correlation amongst others. Sequential neuronal networks enable DL to identify clinical features the system had not been trained with before in a so-called “black box” manner[48]. Even though attention maps can highlight the anatomical regions the algorithm took into consideration e.g. for determining the gender[49], the clinician might still not be able to fully retrace how a neural network came to a particular conclusion with obvious implications for data interpretation and reliability assessment.[48] While AI has predominantly been used in the retina, it is also increasingly applied to fundus photographs[50,51], OCT[52] and visual fields[53] in glaucoma with the ultimate goal of early diagnosis, progression analysis and overall risk stratification that would allow appropriate therapeutic interventions.[54]

Detection of Apoptosing Retinal Cells (DARC)

M. Francesca Cordeiro presented the evolution of the DARC (Detection of Apoptosing Retinal Cells) technology from bench to bedside. ATP-dependent ‘flippases’ normally maintain phosphatidylserine (PS) predominantly in the cytosolic leaflet of cell membranes.[55] However, under stress or during early apoptosis PS flips to the cell surface. The DARC technology is based on the high affinity of intravenous fluorescently-labelled annexin A5 to PS, which can be detected *in vivo* using the ICGA settings of the confocal scanning laser ophthalmoscopy (Heidelberg Spectralis, Heidelberg Engineering, Dossenheim, Germany). Individual hyperfluorescent DARC spots (Figure 3) are then quantified as a ‘DARC count’ in real-time. DARC has been investigated and established in multiple rodent studies. A recently published phase I clinical trial[56] allowed proof of concept in humans. DARC proved to be a safe method to monitor RGC apoptosis, and showed a significant difference in DARC count between healthy controls and patients with progressing glaucoma. Late diagnosis and treatment with subsequent visual loss represent a major challenge in the management of glaucoma patients, and research is hampered by lack of clinically meaningful endpoints and by the long duration of clinical trials. In that context, DARC seems a promising early

and objective clinical endpoint, and might provide a new tool for testing clinical efficacy of therapies in glaucoma and other neurodegenerative diseases.[55]

Induced Pluripotent Cell Technology for in-vitro Pre-Clinical Testing

Botond Roska started out from a histological drawing of the retina by Cajal, the 1906 Nobel prize winner for his milestone work on basic principles of the organization of the nervous system. Cajal described different cell morphologies concluding that the retina is a neural network of different cell types. Today we know that these cell types have unique gene expression patterns[57–59] and that most retinal diseases are cell-type specific. While the architecture of the retina is very conserved across vertebrates, the gene expression pattern is different from species to species.[57,58] For this reason, it appears to be difficult to develop gene therapy in mice and translate this to humans. Botond Roska's group instead focusses on human retinal cells. On the one hand, the group uses organ donor retinal explants to study visual processing of the retina with microchips and to build a human gene expression library of the different cell types. On the other hand, Botond Roska's group has managed to grow retinal organoids in a dish from skin biopsies. These retinal organoids are structurally similar to normal retinas and turned out to show an identical rate of development compared to published data on fetal retinal development with a gene expression map convergence around 30 weeks of gestation. Realizing that the retinal ganglion cells would undergo early apoptosis without the connecting neuron in the brain, the group has been successful in growing eye-brain-organoids. GFP (green fluorescent protein) virus vector labelling of ganglion cell axons allows visualization of the organoid optic nerve and its connections to the organoid brain which represents an ideal in vitro model for glaucoma research. The organoid optic nerve can be exposed to pressure, hypoxia, neurotrophic or neurotoxic substances to tackle neurodegeneration mechanisms in glaucoma. In addition, Botond Roska's group has not only produced 230 viral vectors targeting many cell types in the retina[60], but has also developed so-called 'remote controlled viruses'. These are

superinfective viruses packed on the surface of magnetic beads which once injected into the eye can be guided and massaged onto the retinal surface by an external magnetic field for future optimized delivery of gene therapy to the target tissue.[61]

4. Discussion/Conclusion

Reduction of intraocular pressure (IOP) is known to slow glaucoma progression in terms of visual field or functional loss.[62–64] Thus, IOP and standard visual fields are the endpoints accepted by the Food and Drug Administration (FDA) in studies evaluating new therapies for glaucoma.[65] However, given the fact that glaucoma is a complex disease, alternative therapeutic targets are being investigated entailing a need for new surrogate endpoints. Structural parameters in the glaucoma literature typically include retinal nerve fiber layer, ganglion cell layer and optic disc changes. However, structural endpoints are still not established for use in clinical trials for new glaucoma drugs, as long as the structural-functional relationship at different glaucoma stages remains insufficiently characterized.[65] In the meantime, structural endpoints still may have a role in proof-of-concept-studies. And it is conceivable that a combination of functional and structural endpoints will accelerate translational approaches, reduce the duration and cost of clinical trials, and thus improve visual health in the future.

The European Vision Institute (EVI) special interest focus group joined forces to contribute to this long-term ambition by addressing both functional and structural measures as well as translational hot topics in glaucoma and retina research. This meeting impressively illustrated the ongoing scientific and technological progress in our field exploring every magnitude in time and space – from picoseconds to longterm follow-up, from electrons to eye-brain-organoids, from subclinical to augmented reality. With this ever increasing amount of information available from a single subject, it seems natural that more sophisticated, artificial intelligence based analysis and visualization of data becomes indispensable. This in turn is dependent on big data of collaborative projects which is clearly the vision of the European Vision Institute.

5. Appendix

Appendices may contain complementary information that was not integrated into the main text (tables, figures, and/or formulas). They may include references, which should be listed in the general reference list of the manuscript. However, tables and figures should be numbered separately.

6. Supplementary Material

Supplementary Material directly relevant but not essential to the conclusions of the paper may be submitted in separate files. Further information on Supplementary Material can be found in the Guidelines for Authors.

5. Statements

5.1. Acknowledgement

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5.2. Statement of Ethics

The authors have no ethical conflicts to disclose.

5.3. Disclosure Statement

Della Volpe Waizel M received consultation fees from Novartis.

Maloca P is owner of intellectual property on speckle noise analysis and the MIMO-OCT discussed in the manuscript, received lecture fees from Heidelberg Engineering® GmbH and Zeiss.

Schmidt-Erfurth U declares to be a consultant for Novartis, Genentech, Boehringer and Roche.

Rubin G declares that he is a consultant for Pixium Vision SA and MeiraGTxz.

Otto T declares to be Head of Technology Management – Ophthalmic Devices at Heidelberg Engineering® GmbH.

Weleber R declares the following conflicts of interest: Foundation Fighting Blindness: Vice-Chair for Scientific Advisory Board (SAB), Member of Executive Scientific Advisory Board (ESAB) (honorarium received); AGTC: SAB, Co-Investigator for three trials: RPE65 LCA, XLRS1, CNGB3 ACHR; Consultant (Past): Oxford-Biomedica, Pfizer, Novartis; Consultant (Current): NightStaRx, QLT, 4D Molecular Therapeutics; Sanofi: Past P.I. and now Co-Investigator for two clinical treatment trials: USHSTAT,

STARGEN; Holder of U.S. Patent no 8,657,446 Visual Field Modeling and Analysis (VFMA). A subset of his presentation material was given at a NEI/FDA Endpoints Workshop on Age-related Macular Degeneration and Inherited Retinal Disease held at the NEI in November of 2016 (Reference 62: Csaky K, Ferris F III, Chew EY, Nair P, Cheetham JK, Duncan JL. Report from the NEI/FDA Endpoints Workshop on age-related macular degeneration and inherited retinal diseases. Invest Ophthalmol Vis Sci. 2017;58:3456–3463).

Lesmes LA discloses Financial, Intellectual Property, and Employment interests in Adaptive Sensory Technology, which is commercializing novel devices for acuity and contrast sensitivity testing.

Arleo A declares to be the head of the Essilor-ANR SilverSight Chair and to be a consultant for Essilor.

Scholl HPN declares the following conflicts of interest: Data Monitoring Committee: Genentech Inc./F. Hoffmann-La Roche Ltd (CHROMA and SPECTRI trials); Genzyme Corp./Sanofi, and ReNeuron Group Plc/Ora Inc., Steering Committee: Novo Nordisk (FOCUS trial), Scientific Advisory Board: Astellas Institute for Regenerative Medicine; Gensight Biologics; Intellia Therapeutics, Inc.; Ionis Pharmaceuticals, Inc.; ReNeuron Group Plc/Ora Inc.; Pharma Research & Early Development (pRED) of F. Hoffmann-La Roche Ltd; and Vision Medicines, Inc, Consultancy: Boehringer Ingelheim Pharma GmbH & Co. KG; Daiichi Sankyo, Inc.; Gerson Lehrman Group; Guidepoint; and Shire, Co-director of the Institute of Molecular and Clinical Ophthalmology Basel (IOB) which is constituted as a non-profit foundation and receives funding from the University of Basel, the University Hospital Basel, Novartis, and the government of Basel-Stadt.

Except as noted above, all authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; nor with any expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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5.5. Author Contributions

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8. References (Numerical)

1. Tham Y-C, Li X, Wong TY, et al. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. Ophthalmology 2014;121:2081–2090.

2. Weinreb RN, Aung T, Medeiros FA. The pathophysiology and treatment of glaucoma: a review. JAMA 2014;311:1901–1911.

3. Jonas JB, Aung T, Bourne RR, et al. Glaucoma. Lancet 2017;390:2183–2193.

4. Kasi A, Faiq MA, Chan KC. In vivo imaging of structural, metabolic and functional brain changes in glaucoma. Neural Regen Res 2019;14:446–449.

5. Wey S, Amanullah S, Spaeth GL, et al. Is primary open-angle glaucoma an ocular manifestation of systemic disease? Graefes Arch Clin Exp Ophthalmol 2019;257:665–673.

6. Varma R, Lee PP, Goldberg I, Kotak S. An assessment of the health and economic burdens of glaucoma. Am J Ophthalmol 2011;152:515–522.

7. Lesmes LA, Lu Z-L, Baek J, Albright TD. Bayesian adaptive estimation of the contrast sensitivity function: the quick CSF method. J Vis 2010;10:17.1-21.

8. Lin S, Mihailovic A, West SK, et al. Predicting Visual Disability in Glaucoma With Combinations of Vision Measures. Transl Vis Sci Technol 2018;7:22.

9. Hot A, Dul MW, Swanson WH. Development and evaluation of a contrast sensitivity perimetry test for patients with glaucoma. Invest Ophthalmol Vis Sci 2008;49:3049–3057.

10. Ross JE, Bron AJ, Clarke DD. Contrast sensitivity and visual disability in chronic simple glaucoma. Br J Ophthalmol 1984;68:821–827.

11. Stamper RL. The effect of glaucoma on central visual function. Trans Am Ophthalmol Soc 1984;82:792–826.

12. Nguyen AM, Mihailovic A, Friedman DS, Ramulu PY. Comparison of contrast sensitivity, visual acuity, and the contrast sensitivity function as predictors of gait in glaucoma. Invest Ophthalmol Vis Sci 2016;57:1953.

13. Hou F, Lesmes L, Bex P, et al. Using 10AFC to further improve the efficiency of the quick CSF method. J Vis 2015;15:2.

14. Lesmes L, Jackson M, Bex P. Visual Function Endpoints to Enable Dry AMD Clinical Trials. rug Discovery Today: Therapeutic Strategies 2013;10:e43–e50.

15. Bach M. The Freiburg Visual Acuity test--automatic measurement of visual acuity. Optom Vis Sci 1996;73:49–53.

16. Lesmes LA, Dorr M. Active Learning for Visual Acuity Testing. 2nd International Conference on Applications of Intelligent Systems (APPIS 2019) 2019;DOI 10.1145/3309772.3309798.

17. Crossland MD, Culham LE, Kabanarou SA, Rubin GS. Preferred retinal locus development in

patients with macular disease. Ophthalmology 2005;112:1579–1585.

18. Bainbridge JWB, Smith AJ, Barker SS, et al. Effect of gene therapy on visual function in Leber's congenital amaurosis. N Engl J Med 2008;358:2231–2239.

19. Bainbridge JWB, Mehat MS, Sundaram V, et al. Long-term effect of gene therapy on Leber's congenital amaurosis. N Engl J Med 2015;372:1887–1897.

20. Lima VC, Prata TS, De Moraes CGV, et al. A comparison between microperimetry and standard achromatic perimetry of the central visual field in eyes with glaucomatous paracentral visual-field defects. Br J Ophthalmol 2010;94:64–67.

21. Oztürk F, Yavas GF, Küsbeci T, Ermis SS. A comparison among Humphrey field analyzer, Microperimetry, and Heidelberg Retina Tomograph in the evaluation of macula in primary open angle glaucoma. J Glaucoma 2008;17:118–121.

22. Orzalesi N, Miglior S, Lonati C, Rosetti L. Microperimetry of localized retinal nerve fiber layer defects. Vision Res 1998;38:763–771.

23. Matsuura M, Murata H, Fujino Y, et al. Evaluating the Usefulness of MP-3 Microperimetry in Glaucoma Patients. Am J Ophthalmol 2018;187:1–9.

24. Rao HL, Januwada M, Hussain RSM, et al. Comparing the Structure-Function Relationship at the Macula With Standard Automated Perimetry and Microperimetry. Invest Ophthalmol Vis Sci 2015;56:8063–8068.

25. Rao HL, Hussain RSM, Januwada M, et al. Structural and functional assessment of macula to diagnose glaucoma. Eye (Lond) 2017;31:593–600.

26. Sato S, Hirooka K, Baba T, et al. Correlation between the ganglion cell-inner plexiform layer thickness measured with cirrus HD-OCT and macular visual field sensitivity measured with microperimetry. Invest Ophthalmol Vis Sci 2013;54:3046–3051.

27. Klamann MKJ, Grünert A, Maier A-KB, et al. Comparison of functional and morphological diagnostics in glaucoma patients and healthy subjects. Ophthalmic Res 2013;49:192–198.

28. Ratnarajan G, Jolly JK, Yusuf IH, Salmon JF. The effect of trabeculectomy surgery on the central visual field in patients with glaucoma using microperimetry and optical coherence tomography. Eye (Lond) 2018;32:1365–1371.

29. Okada K, Watanabe W, Koike I, et al. Alternative method of evaluating visual field deterioration in very advanced glaucomatous eye by microperimetry. Jpn J Ophthalmol 2003;47:178–181.

30. Longhin E, Convento E, Pilotto E, et al. Static and dynamic retinal fixation stability in microperimetry. Can J Ophthalmol 2013;48:375–380.

31. Shi Y, Liu M, Wang X, et al. Fixation behavior in primary open angle glaucoma at early and moderate stage assessed by the MicroPerimeter MP-1. J Glaucoma 2013;22:169–173.

32. Weleber RG, Smith TB, Peters D, et al. VFMA: Topographic Analysis of Sensitivity Data From Full-Field Static Perimetry. Transl Vis Sci Technol 2015;4:14.

33. Weleber RG, Pennesi ME, Wilson DJ, et al. Results at 2 Years after Gene Therapy for RPE65-Deficient Leber Congenital Amaurosis and Severe Early-Childhood-Onset Retinal Dystrophy. Ophthalmology 2016;123:1606–1620.

34. Lester AW, Moffat SD, Wiener JM, et al. The Aging Navigational System. Neuron 2017;95:1019–1035.

35. Bécu M, Sheynikhovich D, Tatur G, et al. Age-related preference for geometric spatial cues during real-world navigation. Nature Human Behaviour 2019;(in press).

36. Bécu M. Impact of healthy aging on spatial cognition. Spatial navigation and gaze dynamics in ecological conditions. PhD Thesis, Sorbonne University, Paris 2018.

37. Maloca P, Hasler PW, Barthelmes D, et al. Safety and Feasibility of a Novel Sparse Optical Coherence Tomography Device for Patient-Delivered Retina Home Monitoring. Transl Vis Sci Technol 2018;7:8.

38. Quellec G, Kowal J, Hasler PW, et al. Feasibility of support vector machine learning in age-related macular degeneration using small sample yielding sparse optical coherence tomography data. Acta Ophthalmol 2019.

39. Gyger C, Cattin R, Hasler PW, Maloca P. Three-dimensional speckle reduction in optical coherence tomography through structural guided filtering. Optical Engineering 2014;53:073105.

40. Maloca P, Gyger C, Hasler PW. A pilot study to image the vascular network of small melanocytic choroidal tumors with speckle noise-free 1050-nm swept source optical coherence tomography (OCT choroidal angiography). Graefes Arch Clin Exp Ophthalmol 2016;254:1201–1210.

41. Maloca P, Gyger C, Hasler PW. A pilot study to compartmentalize small melanocytic choroidal tumors and choroidal vessels with speckle-noise free 1050 nm swept source optical coherence tomography (OCT choroidal “tumoropsy”). Graefes Arch Clin Exp Ophthalmol 2016;254:1211–1219.

42. Maloca P, Gyger C, Schoetzau A, Hasler PW. Ultra-Short-Term Reproducibility of Speckle-Noise Freed Fluid and Tissue Compartmentalization of the Choroid Analyzed by Standard OCT. Transl Vis Sci Technol 2015;4:3.

43. Maloca PM, Spaide RF, Rothenbuehler S, et al. Enhanced resolution and speckle-free three-dimensional printing of macular optical coherence tomography angiography. Acta Ophthalmol 2019;97:e317–e319.

44. Rothenbuehler SP, Maloca P, Scholl HPN, et al. Three-dimensional Analysis of Submacular Perforating Scleral Vessels by Enhanced Depth Imaging Optical Coherence Tomography. Retina (Philadelphia, Pa) 2018;38:1231–1237.

45. Maloca PM, de Carvalho JER, Heeren T, et al. High-Performance Virtual Reality Volume Rendering of Original Optical Coherence Tomography Point-Cloud Data Enhanced With Real-Time Ray Casting. Transl Vis Sci Technol 2018;7:2.

46. Fazio MA, Clark ME, Bruno L, Girkin CA. In vivo optic nerve head mechanical response to intraocular and cerebrospinal fluid pressure: imaging protocol and quantification method. Scientific Reports 2018;8. Available at: http://www.nature.com/articles/s41598-018-31052-x [Accessed July 2,

2019].

47. Fujimoto J, Swanson E. The Development, Commercialization, and Impact of Optical Coherence Tomography. Invest Ophthalmol Vis Sci 2016;57:OCT1–OCT13.

48. Schmidt-Erfurth U, Sadeghipour A, Gerendas BS, et al. Artificial intelligence in retina. Prog Retin Eye Res 2018;67:1–29.

49. Poplin R, Varadarajan AV, Blumer K, et al. Prediction of cardiovascular risk factors from retinal fundus photographs via deep learning. Nat Biomed Eng 2018;2:158–164.

50. Ting DSW, Tan GSW, Agrawal R, et al. Optical Coherence Tomographic Angiography in Type 2 Diabetes and Diabetic Retinopathy. JAMA Ophthalmol 2017;135:306–312.

51. Li Z, He Y, Keel S, et al. Efficacy of a Deep Learning System for Detecting Glaucomatous Optic Neuropathy Based on Color Fundus Photographs. Ophthalmology 2018;125:1199–1206.

52. Christopher M, Belghith A, Weinreb RN, et al. Retinal Nerve Fiber Layer Features Identified by Unsupervised Machine Learning on Optical Coherence Tomography Scans Predict Glaucoma Progression. Invest Ophthalmol Vis Sci 2018;59:2748–2756.

53. Wang M, Pasquale LR, Shen LQ, et al. Reversal of Glaucoma Hemifield Test Results and Visual Field Features in Glaucoma. Ophthalmology 2018;125:352–360.

54. Ting DSW, Pasquale LR, Peng L, et al. Artificial intelligence and deep learning in ophthalmology. Br J Ophthalmol 2019;103:167–175.

55. Yap TE, Donna P, Almonte MT, Cordeiro MF. Real-Time Imaging of Retinal Ganglion Cell Apoptosis. Cells 2018;7.

56. Cordeiro MF, Normando EM, Cardoso MJ, et al. Real-time imaging of single neuronal cell apoptosis in patients with glaucoma. Brain 2017;140:1757–1767.

57. Macosko EZ, Basu A, Satija R, et al. Highly Parallel Genome-wide Expression Profiling of Individual Cells Using Nanoliter Droplets. Cell 2015;161:1202–1214.

58. Peng Y-R, Shekhar K, Yan W, et al. Molecular Classification and Comparative Taxonomics of Foveal and Peripheral Cells in Primate Retina. Cell 2019;176:1222-1237.e22.

59. Siegert S, Cabuy E, Scherf BG, et al. Transcriptional code and disease map for adult retinal cell types. Nat Neurosci 2012;15:487–495, S1-2.

60. Jüttner J, Szabo A, Gross-Scherf B, et al. Targeting neuronal and glial cell types with synthetic promoter AAVs in mice, non-human primates, and humans. bioRxiv 2018:434720.

61. Schubert R, Trenholm S, Balint K, et al. Virus stamping for targeted single-cell infection in vitro and in vivo. Nat Biotechnol 2018;36:81–88.

62. Wickström K, Moseley J. Biomarkers and Surrogate Endpoints in Drug Development: A European Regulatory View. Invest Ophthalmol Vis Sci 2017;58:BIO27–BIO33.

63. Heijl A, Leske MC, Bengtsson B, et al. Reduction of intraocular pressure and glaucoma

progression: results from the Early Manifest Glaucoma Trial. Arch Ophthalmol 2002;120:1268–1279.

64. Garway-Heath DF, Crabb DP, Bunce C, et al. Latanoprost for open-angle glaucoma (UKGTS): a randomised, multicentre, placebo-controlled trial. Lancet 2015;385:1295–1304.

65. Weinreb RN, Kaufman PL. Glaucoma research community and FDA look to the future, II: NEI/FDA Glaucoma Clinical Trial Design and Endpoints Symposium: measures of structural change and visual function. Invest Ophthalmol Vis Sci 2011;52:7842–7851.

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Examples

Papers published in journals:

Sawant KV, Xu R, Cox R, Hawkins H, Sbrana E, Kolli D, et al. Chemokine CXCL1-mediated neutrophil trafficking in the lung: role of CXCR2 activation. J Innate Immun. 2015 Jul;6(7):647–58.

Journal names should be abbreviated according to the Index Medicus.

Papers published only with DOI number:

Chen C, Hu Z. ApoE polymorphisms and the risk of different subtypes of stroke in the Chinese population: a comprehensive meta-analysis. Cerebrovasc Dis. DOI: 10.1159/000442678.

Monographs:

Matthews DE, Farewell VT. Using and understanding medical statistics. 5th ed, revised. Basel: Karger; 2015.

Edited Books:

Cohen SR, Gardner TW. Diabetic retinopathy and diabetic macular edema. In: Nguyen QD, Rodrigues EB, Farah ME, Mieler WF, Do DV, editors. Retinal pharmacotherapeutics. Dev Ophthalmol. Basel: Karger; 2016. Vol. 55; p. 137–46.

Websites:

Karger Publishers [Internet]. Basel: Transforming Vesalius: The 16th-Century Scientific Revolution Brought to Life for the 21st Century [cited 2013 Feb 4]. Available from: http://www.vesaliusfabrica.com/en/new-fabrica.html.

9. Figure Legends

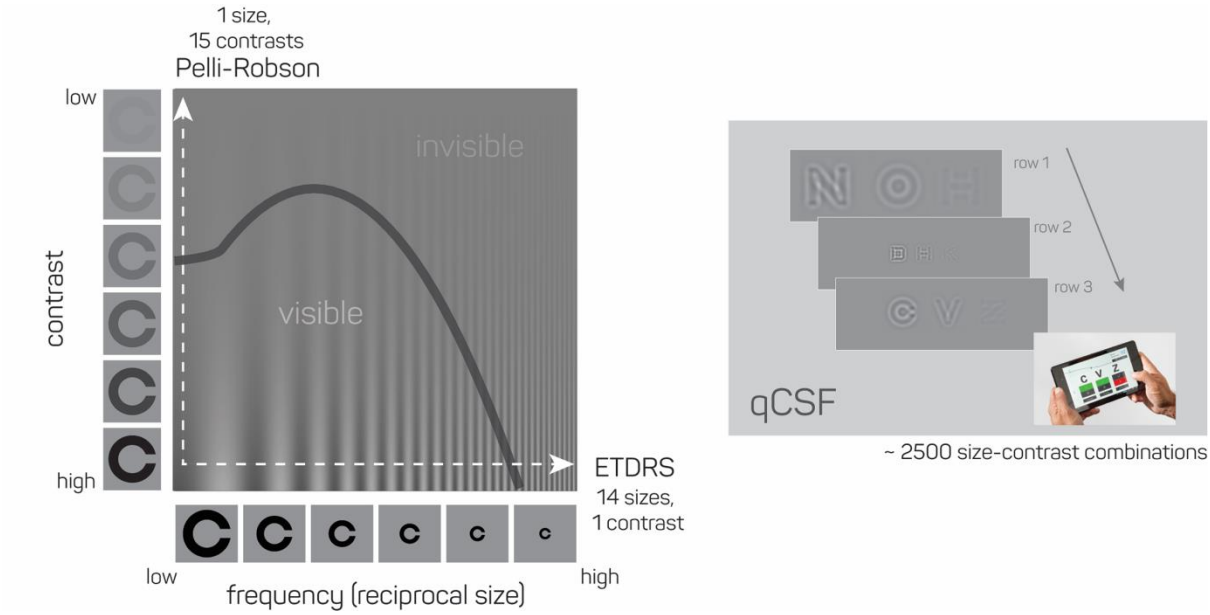

Figure 1.

(Left) It's long been recognized that optotype size and contrast are critical attributes of clinical vision testing, with ETDRS and Pelli-Robson charts for acuity and contrast sensitivity following complementary strategies of fixing one and testing the other. This coarse, piecemeal approach neglects the broader information conveyed by the contrast sensitivity function, a two-dimensional threshold contour that describes how size and contrast affect the visibility of spatial patterns. (Right) The qCSF applies active learning to personalize and directly estimate the global shape of the contrast sensitivity function, by intelligent sampling of size-contrast test patterns that effectively trace out the boundary between visible and invisible for each patient. During testing, a technician enters the responses of patients presented with three special optotypes, with size-contrast combinations selected to provide an optimal, personalized sequence with sampling from above and below the threshold contour.

Figure 2: Ecological, real environment for naturalistic behavioral measures.

The Streetlab platform (Vision Institute, www.streetlab-vision.com) was used to assess the visuo-spatial behaviour of young and older participants. The Streetlab reproduced a 10x5 portion of a street-like environment. It ensured visual immersion through realistic relief elements (imitating doors, windows, and brick walls), and audio immersion through a 3D multi-source sound system. The floor of was covered by a black linoleum surface and there were no obstacles. Light conditions were fully controlled by varying both intensity and temperature parameters. The subject's whole body and eye movements was monitored through a set of biometric sensors: an optoelectronic Vicon motion capture system (10 infrared cameras, at a sampling frequency of 120 Hz), and a wearable eye tracking system (by Mocaplab, at 60 Hz). Data from all sensors were synchronized and recorded in real time, allowing any kinematic recording to be replayed and analyzed offline. Adapted, with permission, from Copyright Streetlab.

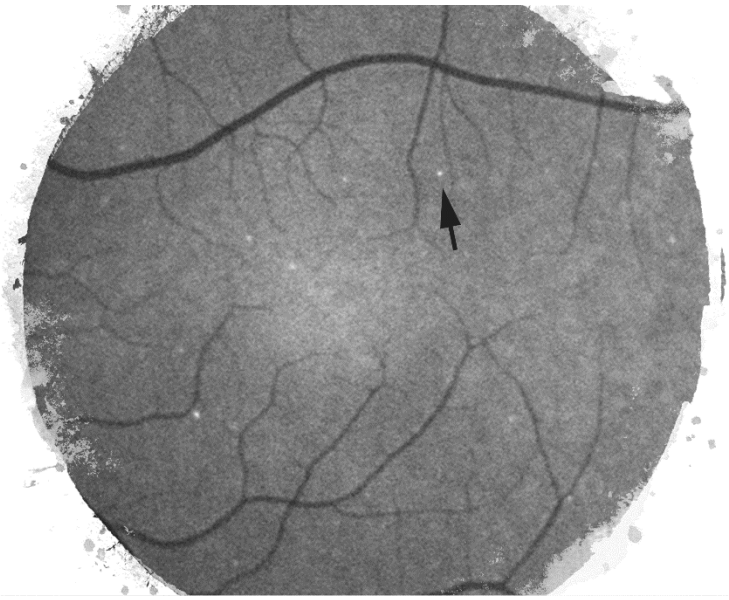

Figure 3. Detection of Apoptosing Retinal Cells (DARC)

Scanning laser ophthalmoscopy (SLO) fundus image showing hyperfluorescent DARC spots (arrow) in a glaucoma patient (**??**). Fluorescently-labelled ANX776 has a high affinity to phosphatidylserine which is exposed to the cell surface under stress. Intravenous injection of ANX776 thus allows imaging of stressed or apoptosing retinal ganglion cells.

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