

## FEATURED ARTICLE

### Validation Of an Automated Fluid Algorithm on Real-World Data of Neovascular Age-Related Macular Degeneration Over Five Years.

Retina. 2022 Sep 1

Gerendas BS, Sadeghipour A, Michl M, Goldbach F, Mylonas G, Gruber A, Alten T, Leingang O, Sacu S, Bogunovic H, Schmidt-Erfurth U.

**Background/Purpose:** To apply an automated deep learning automated fluid algorithm on data from real-world management of patients with neovascular age-related macular degeneration for quantification of intraretinal/subretinal fluid volumes in optical coherence tomography images.

**Methods:** Data from the Vienna Imaging Biomarker Eye Study (VIBES, 2007-2018) were analyzed. Databases were filtered for treatment-naive neovascular age-related macular degeneration with a baseline optical coherence tomography and at least one follow-up and 1,127 eyes included. Visual acuity and optical coherence tomography at baseline, Months 1 to 3/Years 1 to 5, age, sex, and treatment number were included. Artificial intelligence and certified manual grading were compared in a subanalysis of 20%. Main outcome measures were fluid volumes.

**Results:** Intraretinal/subretinal fluid volumes were maximum at baseline (intraretinal fluid: 21.5/76.6/107.1 nL; subretinal fluid 13.7/86/262.5 nL in the 1/3/6-mm area). Intraretinal fluid decreased to 5 nL at M1-M3 (1-mm) and increased to 11 nL (Y1) and 16 nL (Y5). Subretinal fluid decreased to a mean of 4 nL at M1-M3 (1-mm) and remained stable below 7 nL until Y5. Intraretinal fluid was the only variable that reflected VA change over time. Comparison with human expert readings confirmed an area under the curve of >0.9.

**Conclusion:** The Vienna Fluid Monitor can precisely quantify fluid volumes in optical coherence tomography images from clinical routine over 5 years. Automated tools will introduce precision medicine based on fluid guidance into real-world management of exudative disease, improving clinical outcomes while saving resources.

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## DIAGNOSIS AND IMAGING

### Changes in drusen-associated autofluorescence over time observed by fluorescence lifetime imaging ophthalmoscopy in age-related macular degeneration.

Acta Ophthalmology. 2022 Aug 26

Schwanengel LS, Weber S, Simon R, Lehmann T, Augsten R, Meller D, Hammer M.

**Purpose:** To observe fundus autofluorescence (FAF) lifetimes and peak emission wavelength (PEW) of drusen with respect to the pathology of the overlying RPE in the follow-up of AMD-patients.

**Methods:** Forty eyes of 38 patients (age:  $75.1 \pm 7.1$  years) with intermediate AMD were included. FAF lifetimes and PEW were recorded by fluorescence lifetime imaging ophthalmoscopy (FLIO). Twenty-six eyes had a follow-up investigation between months 12 and 36, and 10 at months 37-72. AMD progression was retrieved from color fundus photography (CFP) and OCT. Drusen were

classified with respect to changes in the overlying RPE into groups no, questionable or faint, and apparent hyperpigmentation based on CFP.

**Results:** Among the 210 hyperautofluorescent drusen found at baseline, those with hyperpigmentation had longer lifetimes and shorter PEW than those without. Drusen without hyperpigmentation had shorter lifetimes and PEW than neighboring RPE (all  $p < 0.001$ ) at baseline, but drusen lifetimes increased, and PEW shortened further over follow-up. Eyes, showing AMD progression, had significantly longer FAF lifetimes at baseline than non-progressing eyes:  $282 \pm 102$  ps versus  $245 \pm 98$  ps,  $p < 0.001$  and  $365 \pm 44$  ps vs.  $336 \pm 48$  ps,  $p = 0.025$  for short and long wavelength FLIO channel, respectively.

**Conclusions:** Depending on hyperpigmentation properties, drusen show lifetimes and PEW different from that of adjacent RPE which change over the natural history of AMD. This difference and change, however, might reflect progressive dysmorphism of the RPE rather than representing fluorescence of drusen material itself. Nevertheless, the observed FAF changes could make FLIO a useful tool for the early detection of AMD progression risk.

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## Multimodal Imaging Characteristics and Functional Correlates in Rip Healing.

Retina. 2022 Aug 17

Romano F, Zicarelli F, Cozzi M, Bertoni AI, Cereda MG, Bottoni F, Staurenghi G, Invernizzi A.

**Purpose:** To report the imaging and functional features of the repair tissue following retinal pigment epithelium (RPE) tears.

**Methods:** This cross-sectional, observational study included patients with RPE tears secondary to neovascular age-related macular degeneration and at least 12 months of follow-up. The following variables were analyzed: best-corrected visual acuity (BCVA); retinal sensitivity (RS) using microperimetry; outer retinal layers status and RPE resurfacing on optical coherence tomography; fibrosis; autofluorescence signal recovery using blue-light (BAF) and near-infrared autofluorescence (NIR-AF).

**Results:** Overall, forty-eight eyes were included (age:  $82 \pm 5$  years) and 34 of them showed signs of healing. RPE resurfacing was noticed in 22 cases, whereas fibrosis appeared in 21 eyes. Autofluorescence improved in 17 cases using BAF and 7 eyes on NIR-AF. Outer retinal layers were more frequently preserved when RPE resurfacing and autofluorescence improvement occurred ( $p < 0.05$ ). While BCVA was higher for smaller RPE tears ( $p = 0.01$ ), RS of the healing tissue was positively affected by autofluorescence improvement ( $p < 0.001$ ) and by absence of fibrosis ( $p = 0.03$ ).

**Conclusions:** Autofluorescence signal recovery after rip occurrence possibly reflects the underlying status of the RPE and is associated with better functional outcomes. Our findings highlight the importance of BAF and especially NIR-AF assessment in the setting of rip healing.

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## PATIENT OUTCOMES

## Glycemic Control after Initiation of Anti-VEGF Treatment for Diabetic Macular Edema.

Journal of Clinical Medicine. 2022 Aug 9

Oshima H, Takamura Y, Hirano T, Shimura M, Sugimoto M, Kida T, Matsumura T, Gozawa M, Yamada Y, Morioka M, Inatani M.

Diabetic macular edema (DME) induces visual disturbance, and intravitreal injections of anti-vascular endothelial growth factor (VEGF) drugs are the accepted first-line treatment. We investigate its impact on glycemic control after starting VEGF treatment for DME on the basis of a questionnaire and changes in hemoglobin A1c (HbA1c). We conducted a retrospective multicenter study analyzing 112 patients with DME who underwent anti-VEGF therapy and their changes in HbA1c over two years. Central retinal thickness and visual acuity significantly improved at three months and throughout the period after initiating therapy ( $p < 0.0001$ ); a significant change in HbA1c was not found. A total of 59.8% of patients became more active in glycemic control through exercise and diet therapy after initiating therapy, resulting in a significantly lower HbA1c at 6 ( $p = 0.0047$ ), 12 ( $p = 0.0003$ ), and 18 ( $p = 0.0117$ ) months compared to patients who did not. HbA1c was significantly lower after 18 months in patients who stated that anti-VEGF drugs were expensive ( $p = 0.0354$ ). The initiation of anti-VEGF therapy for DME affects HbA1c levels in relation to more aggressive glycemic control.

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## REVIEW

### Ambient Air Pollution and Age-Related Eye Disease: A Systematic Review and Meta-Analysis.

Investigative Ophthalmology & Vision Science. 2022 Aug 2

Grant A, Leung G, Freeman EE.

**Purpose:** To compare the burden of age-related eye diseases among adults exposed to higher versus lower levels of ambient air pollutants.

**Methods:** MEDLINE, EMBASE, and Scopus were searched for relevant articles until September 30, 2021. Inclusion criteria included studies of adults, aged 40+ years, that provided measures of association between the air pollutants (nitrogen dioxide, carbon monoxide [CO], sulfur dioxide, ozone [O<sub>3</sub>], particulate matter [PM] less than 2.5  $\mu\text{m}$  in diameter [PM2.5], and PM less than 10  $\mu\text{m}$  in diameter [PM10]) and the age-related eye disease outcomes of glaucoma, age-related macular degeneration (AMD), or cataract. Pooled odds ratio (OR) estimates and 95% confidence intervals (CIs) were calculated using a random-effects meta-analysis model. PROSPERO registration ID: CRD42021250078.

**Results:** A total of eight studies were included in the review. Consistent evidence for an association was found between PM2.5 and glaucoma, with four of four studies reporting a positive association. The pooled OR for each 10- $\mu\text{g}/\text{m}^3$  increase of PM2.5 on glaucoma was 1.18 (95% CI, 0.95-1.47). Consistent evidence was also found for O<sub>3</sub> and cataract, with three of three studies reporting an inverse association. Two of two studies reported a null association between PM2.5 and cataract, while one of one studies reported a positive association between PM10 and cataract. One of one

studies reported a positive relationship between CO and AMD. Other relationships were less consistent between studies.

**Conclusions:** Current evidence suggests there may be an association between some air pollutants and cataract, AMD, and glaucoma.

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## GENETICS

### Phenotypic and Genetic Characteristics in a Cohort of Patients with Usher Genes.

Genes (Basel). 2022 Aug 10

Feenstra HM, Al-Khuzaei S, Shah M, Broadgate S, Shanks M, Kamath A, Yu J, Jolly JK, McLaren RE, Clouston P, Halford S, Downes SM.

**Background:** This study aimed to compare phenotype-genotype correlation in patients with Usher syndrome (USH) to those with autosomal recessive retinitis pigmentosa (NS-ARRP) caused by genes associated with Usher syndrome.

**Methods:** Case notes of patients with USH or NS-ARRP and a molecularly confirmed diagnosis in genes associated with Usher syndrome were reviewed. Phenotypic information, including the age of ocular symptoms, hearing impairment, visual acuity, Goldmann visual fields, fundus autofluorescence (FAF) imaging and spectral domain optical coherence tomography (OCT) imaging, was reviewed. The patients were divided into three genotype groups based on variant severity for genotype-phenotype correlations.

**Results:** 39 patients with Usher syndrome and 33 patients with NS-ARRP and a molecular diagnosis in an Usher syndrome-related gene were identified. In the 39 patients diagnosed with Usher syndrome, a molecular diagnosis was confirmed as follows: USH2A (28), MYO7A (4), CDH23 (2), USH1C (2), GPR98/VLGR1 (2) and PCDH15 (1). All 33 patients with NS-ARRP had variants in USH2A. Further analysis was performed on the patients with USH2A variants. USH2A patients with syndromic features had an earlier mean age of symptom onset (17.9 vs. 31.7 years,  $p < 0.001$ ), had more advanced changes on FAF imaging ( $p = 0.040$ ) and were more likely to have cystoid macular oedema ( $p = 0.021$ ) when compared to USH2A patients presenting with non-syndromic NS-ARRP. Self-reported late-onset hearing loss was identified in 33.3% of patients with NS-ARRP. Having a syndromic phenotype was associated with more severe USH2A variants ( $p < 0.001$ ). Eighteen novel variants in genes associated with Usher syndrome were identified in this cohort.

**Conclusions:** Patients with Usher syndrome, whatever the associated gene in this cohort, tended to have an earlier onset of retinal disease (other than GPR98/VLGR1) when compared to patients presenting with NS-ARRP. Analysis of genetic variants in USH2A, the commonest gene in our cohort, showed that patients with a more severe genotype were more likely to be diagnosed with USH compared to NS-ARRP. USH2A patients with syndromic features have an earlier onset of symptoms and more severe features on FAF and OCT imaging. However, a third of patients diagnosed with NS-ARRP developed later onset hearing loss. Eighteen novel variants in genes associated with Usher syndrome were identified in this cohort, thus expanding the genetic spectrum of known pathogenic variants. An accurate molecular diagnosis is important for diagnosis and prognosis and has become particularly relevant with the advent of potential therapies for Usher-related gene.

DOI: [10.3390/genes13081423](https://doi.org/10.3390/genes13081423)

## **Retinal Transcriptome and Cellular Landscape in Relation to the Progression of Diabetic Retinopathy.**

Investigative Ophthalmology & Vision Science. 2022 Aug 2

Wang JH, Wong RCB, Liu GS.

**Purpose:** Previous studies that identify putative genes associated with diabetic retinopathy are only focusing on specific clinical stages, thus resulting genes are not necessarily reflective of disease progression. This study identified genes associated with the severity level of diabetic retinopathy using the likelihood-ratio test (LRT) and ordinal logistic regression (OLR) model, as well as to profile immune and retinal cell landscape in progressive diabetic retinopathy using a machine learning deconvolution approach.

**Methods:** This study used a published transcriptomic dataset (GSE160306) from macular regions of donors with different degrees of diabetic retinopathy (10 healthy controls, 10 cases of diabetes, 9 cases of nonproliferative diabetic retinopathy, and 10 cases of proliferative diabetic retinopathy or combined with diabetic macular edema). LRT and OLR models were applied to identify severity-associated genes. In addition, CIBERSORTx was used to estimate proportional changes of immune and retinal cells in progressive diabetic retinopathy.

**Results:** By controlling for gender and age using LRT and OLR, 50 genes were identified to be significantly increased in expression with the severity of diabetic retinopathy. Functional enrichment analyses suggested these severity-associated genes are related to inflammation and immune responses. CCND1 and FCGR2B are further identified as key regulators to interact with many other severity-associated genes and are crucial to inflammation. Deconvolution analyses demonstrated that the proportions of memory B cells, M2 macrophages, and Müller glia were significantly increased with the progression of diabetic retinopathy.

**Conclusions:** These findings demonstrate that deep analyses of transcriptomic data can advance our understanding of progressive ocular diseases, such as diabetic retinopathy, by applying LRT and OLR models as well as bulk gene expression deconvolution.

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## **CASE REPORT**

### **Paracentral Acute Middle Maculopathy in a Patient with Frequent Migraine with Aura: A Case Report.**

Retina Cases & Brief Report. 2022 Sep 1

Dasari VR, Selliyam A, Gratton SM.

**Background/Purpose:** To explore the possible relationship between Paracentral Acute Middle Maculopathy (PAMM) and migraine. Paracentral acute middle maculopathy is a recently described clinical and optical coherence tomography entity involving infarction of the inner nuclear layer secondary to deep retinal capillary ischemia. It presents as a painless paracentral scotoma and often results in permanent visual deficits. Migraine, especially migraine with aura, has been shown to cause structural changes in the retinal microvasculature and to be a risk factor for retinal ischemia.

**Methods:** A case report and review of the literature.

**Results:** A 39-year-old woman with migraine with visual aura presented with a discrete, monocular, painless "buffalo-shaped" paracentral scotoma, which started during a period of frequent typical visual auras. Her exam and optical coherence tomography were consistent with PAMM.

**Conclusion:** We propose that migraine is a risk factor for the development of PAMM. The changes in retinal microvasculature in migraine may increase a patient's susceptibility to retinal ischemia. Other risk factors for retinal ischemia, including diabetes, hypertension, hyperlipidemia, sickle cell disease, and orbital trauma, have been shown to be associated with PAMM. Further research should be conducted to determine whether there is a definite relationship between migraine and PAMM.

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## PATHOPHYSIOLOGY

### Clinical Observation of Macular Vessel Density in Type 2 Diabetics with High Myopia.

Ophthalmic Research. 2022 Aug 22

Su R, Jia Z, Fan F, Li J, Li K.

**Introduction:** To compare the macular retinal vessel density(VD) of diabetics with high myopia, diabetics without high myopia and healthy controls.

**Methods:** This cross-sectional study recruited type 2 diabetic (T2D) people with no history of ocular treatment in our hospital. Thirty T2D people with high myopia (30 eyes) were included in group A, while 30 T2D people (30 eyes) without myopia were included in group B. Another healthy volunteers (30 eyes) were included in group C. The superficial and deep capillary plexuses VD of macular were measured in all subjects by optical coherence tomography angiography (OCTA). In T2D people with high myopia, the correlation between VD in macular regions and baseline data was investigated.

**Results:** ① Overall comparison of the 3 groups: No statistically significant differences in macular central superficial vessel density (SVD) were found in the three groups ( $P > 0.05$ ). There were significant differences in the temporal, superior, nasal, inferior SVD between the 3 groups ( $P < 0.05$ ). There were significant differences in macular central, temporal, superior, nasal, and inferior deep vessel density (DVD) between the three groups ( $P < 0.05$ ). ② Comparison of B (no myopia, T2D group) and C (healthy control group): Inferior SVD in group B was lower than that in group C ( $P < 0.05$ ). Temporal, superior, nasal, and inferior DVD in group B were lower than those in group C ( $P < 0.05$ ). ③ A (high myopia group, T2D) compared with B (no myopia, T2D group), A group compared with C (healthy control group): Temporal, superior, nasal, inferior SVD and DVD in group A were all lower than those in group B and C ( $P < 0.05$ ), DVD in group B were lower than those in group C ( $P < 0.05$ ). ④ The mean SVD and DVD were not correlated with age, IOP , anterior chamber depth, corneal curvature but they were negatively correlated with axial length and duration of diabetes in the T2D people with high myopia.

**Conclusion:** Myopia and diabetes are two important factors affecting macular retinal vessel density. Comparing with the eyes of T2D people without high myopia, the VD in macular regions shows a higher decline in the eyes of T2D people with high myopia.

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## VISUAL FUNCTION

### **Binocular Principles of PRL Development in Patients With Macular Disease.**

Investigative Ophthalmology & Visual Science. 2022 Aug 2

Tarita-Nistor L, Mandelcorn MS.

**Purpose:** We tested the hypothesis that binocular requirements for correspondence play a role in establishing the preferred retinal locus (PRL) in macular degeneration.

**Methods:** Monocular PRL locations in 202 eyes of 101 patients with macular degeneration ( $79 \pm 10$  years) were recorded with the MP1 microperimeter. Corresponding PRLs were those with similar polar angle and distance from former fovea in the better eye (BE) and the worse eye (WE).

**Results:** On average, the PRL in the BE was in the foveal proximity at  $1.1 \pm 0.99$  degrees for 55 patients (foveal-driven PRL) and eccentrically at  $6.9 \pm 3.4$  degrees for 46 patients with central lesions involving the fovea (peripheral-driven PRL). For the foveal-driven PRL group, the PRL in the BE was not affected by the status of the WE. In 100% of cases, the monocular PRL in the WE was in a corresponding location either on functioning retina or onto the lesion, or would fall onto the lesion during binocular viewing. For the peripheral-driven PRL group, the PRL location depended on the lesion size in both eyes to maximize correspondence and/or the function of peripheral vision during binocular viewing. In this group, PRL correspondence status was different for those with equal, unequal, or extensive lesions in both eyes.

**Conclusions:** Binocular requirements for correspondence play an important role in determining the PRL location. We formulated two principles based on whether the BE has foveal sparing (foveal-driven PRL) or central lesions affecting the fovea (peripheral-driven PRL). The PRL should be evaluated in the framework of binocular viewing.

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