



City Research Online

## City, University of London Institutional Repository

---

**Citation:** Terheyden, J. H., Holz, F. G., Behning, C., Dunbar, H. M. P., Schmitz-Valckenberg, S., Tufail, A., Schmid, M., Crabb, D. P., Saßmannshausen, M., Binns, A., et al (2025). The Spectrum of Functional, Structural and Patient-Reported Outcomes in Intermediate Age-Related Macular Degeneration – A MACUSTAR Study Report. *Ophthalmologica*, pp. 1-19. doi: 10.1159/000543231

This is the published version of the paper.

This version of the publication may differ from the final published version.

---

**Permanent repository link:** <https://openaccess.city.ac.uk/id/eprint/34947/>

**Link to published version:** <https://doi.org/10.1159/000543231>

**Copyright:** City Research Online aims to make research outputs of City, University of London available to a wider audience. Copyright and Moral Rights remain with the author(s) and/or copyright holders. URLs from City Research Online may be freely distributed and linked to.

**Reuse:** Copies of full items can be used for personal research or study, educational, or not-for-profit purposes without prior permission or charge. Provided that the authors, title and full bibliographic details are credited, a hyperlink and/or URL is given for the original metadata page and the content is not changed in any way.

---

City Research Online:

<http://openaccess.city.ac.uk/>

[publications@city.ac.uk](mailto:publications@city.ac.uk)

---

# The Spectrum of Functional, Structural, and Patient-Reported Outcomes in Intermediate Age-Related Macular Degeneration: A MACUSTAR Study Report

Jan Henrik Terheyden<sup>a</sup> Frank G. Holz<sup>a,b</sup> Charlotte Behning<sup>c</sup>  
Hannah M.P. Dunbar<sup>d</sup> Steffen Schmitz-Valckenberg<sup>a,b,e</sup> Adnan Tufail<sup>f</sup>  
Matthias Schmid<sup>c</sup> David P. Crabb<sup>g</sup> Marlene Saßmannshausen<sup>a,b</sup>  
Alison Binns<sup>g</sup> Carel B. Hoyng<sup>h</sup> Nadia Zakaria<sup>i</sup> Stephen Poor<sup>i</sup>  
Klaus-Peter Moll<sup>i</sup> Deborah Cosette<sup>j</sup> Cecilia Martinho<sup>k</sup> Joana Batuca<sup>l</sup>  
José Cunha-Vaz<sup>k</sup> Ulrich F.O. Luhmann<sup>m</sup> Sergio Leal<sup>n</sup> Robert P. Finger<sup>a,o</sup>  
on behalf of the MACUSTAR consortium

<sup>a</sup>Department of Ophthalmology, University Hospital Bonn, Bonn, Germany; <sup>b</sup>GRADE Reading Center, Bonn, Germany; <sup>c</sup>Informatics and Epidemiology, Medical Faculty, Institute for Medical Biometry, University of Bonn, Bonn, Germany; <sup>d</sup>UCL Institute of Ophthalmology, University College London, London, UK; <sup>e</sup>Department of Ophthalmology and Visual Sciences, John A. Moran Eye Center, University of Utah, Salt Lake City, UT, USA; <sup>f</sup>Moorfields Eye Hospital NHS Foundation Trust, London, UK; <sup>g</sup>Department of Optometry and Visual Science, City, University of London, London, UK; <sup>h</sup>Radboud University Medical Center, Nijmegen, The Netherlands; <sup>i</sup>Novartis Institutes for Biomedical Research, Cambridge, MA, USA; <sup>j</sup>Carl Zeiss Meditec AG, Dublin, CA, USA; <sup>k</sup>Association for Innovation and Biomedical Research on Light and Image, Coimbra, Portugal; <sup>l</sup>European Clinical Research Infrastructure Network, Paris, France; <sup>m</sup>Roche Pharmaceutical Research and Early Development, Translational Medicine Ophthalmology, Roche Innovation Center Basel, Basel, Switzerland; <sup>n</sup>Bayer Consumer Care AG, Basel, Switzerland; <sup>o</sup>Department of Ophthalmology, University Hospital Mannheim & Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany

## Keywords

Age-related macular degeneration · Baseline characteristics · Clinical endpoint · Imaging · Visual function · Patient-reported outcome

## Abstract

**Introduction:** There is an unmet medical need for therapies in intermediate age-related macular degeneration (iAMD). The prospective European multicenter cohort study MAC-

USTAR validates structural, functional, and patient-reported iAMD endpoints for use in future trials. The multiplicity of assessments allows characterizing iAMD in more dimensions than previously available. We describe the heterogeneity of assessments in the iAMD baseline cohort of the MACUSTAR study. **Methods:** A wide range of assessments was

Trial registration: ClinicalTrials.gov, NCT03349801. Registered on November 22, 2017.

administered across 20 European study sites in accordance with established guidelines. These assessments encompassed multiple structural evaluations, such as color fundus photography, fundus autofluorescence, and optical coherence tomography. Additionally, functional tests were conducted, including assessments of best-corrected and low-luminance visual acuity (VA), Moorfields acuity, contrast sensitivity, reading speed, mesopic and scotopic microperimetry, and dark adaptometry. Moreover, patient-reported outcome assessments, specifically the Vision Impairment in Low Luminance questionnaire, were also incorporated into the evaluation process. Associations between variables were investigated using Phi coefficients, Pearson correlation coefficients and age-corrected regression models. **Results:** Five-hundred eighty-five individuals with iAMD (66% women; mean (standard deviation) age: 72 ± 7 years) were included in the MACUSTAR study. Forty-nine percent had pigmentary abnormalities, 27% had reticular pseudodrusen; 10% and 9% had incomplete and complete retinal pigment epithelium and outer retinal atrophy at baseline, respectively. Mean best-corrected VA, low-luminance VA and mesopic average threshold on microperimetry at baseline were 0.03 ± 0.11 logMAR, 0.24 ± 0.16 logMAR, and 23.3 ± 3.7 dB. Mean Vision Impairment in Low Luminance (VILL) subscale scores at baseline were 2 ± 2 to 2 ± 3 logits. Phi coefficients between structural assessments ranged between 0.17 and 0.22 (median 0.21); correlation coefficients between function tests ranged between 0.07 and 0.69 (median 0.34) and between VILL scores ranged between 0.21 and 0.68 (median 0.23). **Conclusion:** The findings from this broad and comprehensive spectrum of assessments of structure, function, and patient-reported outcomes in iAMD suggest that the disease spectrum is diverse and heterogeneous and that further efforts are necessary to fully understand and characterize iAMD in all its complexities. A further in-depth characterization will enable novel enrichment strategies for clinical trials in iAMD.

© 2025 The Author(s).

Published by S. Karger AG, Basel

## Introduction

Age-related macular degeneration (AMD) is the leading cause of visual impairment in industrialized countries and affects an increasing number of older individuals worldwide [1–3]. Research activities have fundamentally improved the understanding of the disease pathway over the last decades. Since the introduction of vascular endothelial growth factor inhibitors, the prognosis of patients affected by the late, neovascular stage has

been much improved [4–7] and recently, complement inhibitors were the first drugs approved in the USA for the indication of geographic atrophy [8]. However, the majority of individuals affected by AMD globally have earlier AMD stages, which puts people at risk of future disease progression and functional loss [2, 9]. Intermediate AMD (iAMD) is the most high-risk AMD stage for progressing to late AMD [10]. Currently, no approved treatment exists for iAMD that may reverse it or stop or slow down progression to late AMD, but there is a large unmet need with the global rise in AMD prevalence [11, 12]. To effectively evaluate potential interventions, there is a need for improved clinical trial endpoints for iAMD trials. Achieving this requires a deeper understanding of the relationships between the structural, functional, and patient-reported aspects of iAMD [13].

The MACUSTAR study is a prospective European multicenter study that develops and validates clinical trial endpoints for the progression from iAMD to late AMD in accordance with recommendations by regulators and health authorities [13, 14]. Previous studies [15–19] suggest iAMD as defined by the Beckman AMD classification [10] is highly heterogeneous by means of structural and functional changes. In particular, the current knowledge of heterogeneity of visual function is limited and only a few larger AMD studies have included not only multimodal imaging but also multiple visual function assessments. The MACUSTAR study assesses both of these aspects and in addition integrates patient-reports as a third pillar of the study design [13, 14].

By studying these associations in the MACUSTAR study, we can gain a deeper understanding of how visual function, structural changes, and patient-reported outcomes (PROs) are interconnected in iAMD. This knowledge is important for improving our understanding of the disease and may aid in the development of iAMD clinical trials and more targeted interventions in the future.

## Materials and Methods

The MACUSTAR study (ClinicalTrials.gov Identifier: NCT03349801) is a prospective, multi-center cohort study conducted at 20 sites in 7 European countries. It is run by an international consortium forming a public-private partnership and is funded by the European Union's Horizon 2020 program and the European Federation of Pharmaceutical Industries and Associations (EFPIA). During the study, participants undergo a battery

of visual function tests, imaging modalities, and PRO assessments, as previously reported [14]. The assessments include:

- Functional assessments: best-corrected visual acuity (BCVA), low-luminance visual acuity (LLVA), Moorfields acuity test (MAT), Pelli-Robson contrast sensitivity, reading speed assessment (international reading speed texts), fundus-controlled perimetry (Macular Integrity Assessment, iCare, Finland), dark adaptometry (AdaptDx, Lumithera, USA)
- Structural assessments: spectral domain and swept-source optical coherence tomography (OCT), fundus autofluorescence imaging, confocal laser ophthalmoscopy, color fundus photography, OCT angiography, quantitative fundus autofluorescence, adaptive optics, fluorescein angiography if choroidal neovascularization is suspected

#### *PRO Assessments: Vision Impairment in Low Luminance Questionnaire, EQ-5D-5L Questionnaire*

All participants gave written informed consent before any study procedures were performed, as approved by Institutional Ethics Committees at all sites. The MACUSTAR study consists of a cross-sectional and a longitudinal part, for which individuals at all AMD stages and without AMD have been recruited. The longitudinal part of MACUSTAR includes semi-annual study visits for participants with iAMD and annual visits for participants with early AMD, while individuals with no AMD and late AMD were not followed longitudinally [14]. The inclusion and exclusion criteria have previously been published [14]. In brief, participants had to be aged between 55 and 85 years and the diagnosis of AMD confirmed by a central reading center (GRADE Reading Centre, Bonn, Germany), which also evaluated all structural outcomes reported here [20]. Any concurrent diseases impairing the interpretation of data were excluded. Disease stage [10] was required to be symmetrical except in iAMD, where an asymmetrical disease stage was allowed after an update of the original study protocol [14]. All study procedures were conducted following procedure manuals specifically designed for the MACUSTAR study and all study staff were certified centrally to maximize data quality and comparability across study sites [14, 21, 22]. More details on the imaging, visual function testing and PRO assessment and grading protocols have been described previously [13, 14, 20–23].

#### *Statistical Analyses*

In our study, we present the baseline data from the entire MACUSTAR iAMD cohort, which is currently being followed longitudinally. For this analysis, we report

summary statistics of the measured features. We also compared these features between participants who had and did not have late AMD in their non-study eye. Where noticeable differences between the groups were observed, multivariable regression, controlling for age and sex, was used to test associations. Relationships between functional, structural, and PROs were investigated using Phi coefficients for associations between two dichotomous variables, point-biserial correlation coefficients for associations between a dichotomous and a continuous variable and Pearson correlation coefficients for continuous variables. Phi coefficients were interpreted as weak for  $0.05 < \Phi \leq 0.1$ , as moderate for  $0.10 < \Phi \leq 0.15$ , as strong for  $0.15 < \Phi \leq 0.25$ , and as very strong for  $\Phi > 0.25$  [24]. Correlation coefficients were interpreted as weak for  $0.1 < |r| \leq 0.4$ , as moderate for  $0.4 < |r| \leq 0.7$ , as strong for  $0.7 < |r| \leq 0.9$ , and as very strong for  $r > 0.9$  [25]. No imputation of missing data was performed during our analysis. To control the analyses for age and sex of participants, linear and logistic regression analyses were additionally performed. *p* values  $< 0.05$  were considered statistically significant. All analyses were performed with R, version 4.0.2 (R Core Team, Vienna, Austria).

## **Results**

A total of 718 individuals were included in the MACUSTAR study, of which 585 had iAMD and 133 were included in the control ( $n = 56$ ) and neighboring disease stage groups (early and late AMD,  $n = 34$  and  $43$ , respectively). Only study participants with iAMD were included in this report. The rate of missing data was  $\leq 6.3\%$  in the structural biomarkers assessed,  $\leq 0.3\%$  in chart-based visual function tests,  $\leq 0.3\%$  in PROs and higher in device-based visual function assessment (mesopic and scotopic microperimetry:  $9.9\%$  and  $15.2\%$ , respectively; dark adaptometry:  $30.3\%$ ).

Participants were on average  $72 \pm 7$  years old and more than two-thirds were female (Table 1). Pigmentary abnormalities can be present in iAMD according to the Beckman classification [10] and were found in about half of the cohort. Reticular pseudodrusen (or subretinal drusenoid deposits) were present in less than 30% of participants according to the grading results of multimodal imaging and about ten percent had incomplete (i) or complete retinal pigment epithelium (RPE) and outer retinal atrophy (cRORA), respectively. Hyperreflective foci were present in 278 (47.5%) eyes and absent in 304 (52.0%) eyes. The majority ( $n = 539$ , 92.1%) of

**Table 1.** Baseline characteristics of the MACUSTAR longitudinal iAMD cohort

| Assessment                                  | iAMD<br>(n = 585) | Bilateral iAMD <sup>a</sup><br>(n = 539) | Unilateral iAMD, late<br>AMD in FE <sup>a</sup> (n = 46) |
|---|-------------------|--|--|
| <i>General study data</i>                   |                   |  |  |
| Age, mean (SD), years                       | 72.1 (7.0)        | 71.9 (7.1)                               | 74.3 (6.29)  |
| Sex, n (%)                                  |                   |  |  |
| Female                                      | 389 (66.5)        | 357 (66.2)                               | 32 (69.6)  |
| Male  | 196 (33.5)        | 182 (33.8)                               | 14 (30.4)  |
| Phakic state, n (%)                         |                   |  |  |
| Phakic                                      | 465 (79.5)        | 428 (79.4)                               | 37 (80.4)  |
| Pseudophakic                                | 120 (20.5)        | 111 (20.6)                               | 9 (19.6)   |
| <i>Structural biomarkers</i>                |                   |  |  |
| Reticular pseudodrusen, n (%)               |                   |  |  |
| Yes   | 158 (27.0)        | 134 (24.9)                               | 24 (52.2)  |
| No  | 425 (72.6)        | 403 (74.8)                               | 22 (47.8)  |
| Missing <sup>b</sup>                        | 2 (0.3)           | 2 (0.4)                                  | 0 (0)  |
| Pigmentary abnormalities, n (%)             |                   |  |  |
| Yes   | 287 (49.1)        | 256 (47.5)                               | 31 (67.4)  |
| No  | 281 (48.0)        | 269 (49.9)                               | 12 (26.1)  |
| Missing <sup>b</sup>                        | 17 (2.9)          | 14 (2.6)                                 | 3 (6.5)  |
| RPEDC volume, mean (SD)                     | 0.057 (0.090)     | 0.057 (0.091)                            | 0.066 (0.080)  |
| Missing <sup>b</sup> , n (%)                | 37 (6.3)          | 32 (5.9)                                 | 5 (10.9)   |
| iRORA, n (%)                                |                   |  |  |
| Yes   | 56 (9.6)          | 44 (8.2)                                 | 12 (26.1)  |
| No  | 524 (89.6)        | 492 (91.3)                               | 32 (69.6)  |
| Missing <sup>b</sup>                        | 5 (0.9)           | 3 (0.6)                                  | 2 (4.3)  |
| cRORA, n (%)                                |                   |  |  |
| Yes   | 52 (8.9)          | 42 (7.8)                                 | 10 (21.7)  |
| No  | 530 (90.6)        | 494 (91.7)                               | 36 (78.3)  |
| Missing <sup>b</sup>                        | 3 (0.5)           | 3 (0.6)                                  | 0 (0)  |
| <i>Visual function</i>                      |                   |  |  |
| BCVA [logMAR], mean (SD)                    | 0.03 (0.11)       | 0.03 (0.10)                              | 0.06 (0.10)  |
| Missing, n (%)                              | 1 (0.2)           | 1 (0.2)                                  | 0 (0)  |
| LLVA [logMAR], mean (SD)                    | 0.24 (0.16)       | 0.24 (0.15)                              | 0.28 (0.19)  |
| Missing, n (%)                              | 2 (0.3)           | 2 (0.4)                                  | 0 (0)  |
| MAT [logMAR], mean (SD)                     | 0.44 (0.16)       | 0.44 (0.16)                              | 0.47 (0.15)  |
| Missing, n (%)                              | 1 (0.2)           | 1 (0.2)                                  | 0 (0)  |
| PR-CS [logCS], mean (SD)                    | 1.55 (0.18)       | 1.55 (0.18)                              | 1.54 (0.18)  |
| Missing, n (%)                              | 2 (0.3)           | 2 (0.4)                                  | 0 (0)  |
| Reading speed [words per minute], mean (SD) | 144 (40)          | 144 (40)                                 | 141 (42)   |
| Missing, n (%)                              | 37 (6.3)          | 35 (6.5)                                 | 2 (4.3)  |
| Mesopic AT [dB], mean (SD)                  | 23.4 (3.7)        | 23.4 (3.6)                               | 22.0 (3.8)   |
| Missing, n (%)                              | 58 (9.9)          | 48 (8.9)                                 | 10 (21.7)  |
| Scotopic AT [dB], mean (SD)                 | 18.7 (3.8)        | 18.9 (3.6)                               | 16.4 (4.8)   |
| Missing, n (%)                              | 89 (15.2)         | 76 (14.1)                                | 13 (28.3)  |
| RIT [min], mean (SD) <sup>c</sup>           | 7.2 (5.1)         | 7.1 (5.0)                                | 8.7 (6.1)  |
| Missing, n (%)                              | 177 (30.3)        | 162 (30.1)                               | 15 (32.6)  |

**Table 1** (continued)

| Assessment                         | iAMD<br>( <i>n</i> = 585) | Bilateral iAMD <sup>a</sup><br>( <i>n</i> = 539) | Unilateral iAMD, late<br>AMD in FE <sup>a</sup> ( <i>n</i> = 46) |
|------------------------------------|---------------------------|--|--|
| <i>PROs</i>                        |                           |  |  |
| VILL-reading subscale, mean (SD)   | 2.4 (1.8)                 | 2.4 (1.8)  | 2.3 (1.8)  |
| Missing, <i>n</i> (%)              | 1 (0.2)                   | 0 (0)  | 1 (2.2)  |
| VILL-mobility subscale, mean (SD)  | 2.4 (2.0)                 | 2.4 (2.00)                                       | 2.3 (2.2)  |
| Missing, <i>n</i> (%)              | 1 (0.2)                   | 0 (0)  | 1 (2.2)  |
| VILL-emotional subscale, mean (SD) | 2.1 (3.2)                 | 2.1 (3.3)  | 1.8 (3.1)  |
| Missing, <i>n</i> (%)              | 2 (0.3)                   | 1 (0.2)  | 1 (2.2)  |

AT, average threshold on microperimetry; BCVA, best-corrected visual acuity; cRORA, complete retinal pigment epithelium and outer retinal atrophy; iRORA, incomplete retinal pigment epithelium and outer retinal atrophy; LLVA, low-luminance visual acuity; MAT, Moorfields acuity; PR-CS, Pelli-Robson contrast sensitivity; RIT, rod intercept time on dark adaptometry; RPEDC, retinal pigment epithelium drusen complex; VILL, Vision Impairment in Low Luminance questionnaire. <sup>a</sup>25 participants had geographic atrophy in the fellow eye and 18 participants had active neovascular AMD in the fellow eye. <sup>b</sup>Not gradable. <sup>c</sup>Rod intercept time capped after 30 min.

participants had bilateral iAMD, with a minor proportion (*n* = 46, 7.9%) exhibiting unilateral disease with late AMD in the non-study eye. The structural risk features reticular pseudodrusen, pigmentary abnormalities, RPE-drusen complex volume, iRORA and cRORA were all noticeably more prevalent in individuals with late AMD in the fellow eye (Table 1). This effect reached statistical significance for reticular pseudodrusen, pigmentary abnormalities, iRORA and cRORA (online suppl. Table 1; for all online suppl. material, see <https://doi.org/10.1159/000543231>). Differences between participants with bilateral iAMD and individuals with late AMD in the fellow eye, however, were small in most visual function tests, with rod intercept time being a noticeable exception (Table 1).

Associations between common structural biomarkers were generally strong, with combinations between pigmentary abnormalities, iRORA and cRORA yielding Phi coefficients between 0.17 and 0.22 (Table 2). Strongest correlations existed between RPE-drusen complex volume and PA (0.26), whilst correlations between RPEDC volume and all other structural measures were weak to moderate. Absolute Pearson correlation coefficients between visual function assessments ranged between 0.07 and 0.70 (Table 3, online suppl. Table 2), with the highest associations observed between mesopic and scotopic microperimetry average thresholds, and between BCVA and LLVA (Fig. 1). Associations between RIT and all other variables were the weakest. The associations between Vision Impairment in Low Luminance (VILL) ques-

tionnaire subscales were moderate for the reading and mobility subscales but weak for emotional well-being and the other subscales (Table 4).

## Discussion

The presented baseline data from the longitudinal iAMD cohort of the MACUSTAR study show the need for adequate biomarkers that allow stratification of the intermediate disease stage further and identification of patients that could benefit from novel therapies. In line with the objectives of the MACUSTAR consortium, further work to understand the heterogeneity in the functional performance within iAMD in the context of structural biomarkers and patient-reported data is necessary to identify those patients at highest risk for progression. The ongoing review of MACUSTAR participants aims to identify such baseline biomarkers for disease progression among the structural, functional, and PRO measures to facilitate the selection of patients and endpoints for future interventional trials.

The presence of intermediate or large drusen and/or pigmentary abnormalities is long established structural risk factors for progression to late AMD [26]. Consensus about their contribution to the risk of developing late AMD was reached more than 25 years ago by integrating both factors into AMD classifications [10, 27–31]. Other structural risk factors for progression to late AMD, such as reticular pseudodrusen, is challenging since they can develop independently from the other structural features

**Table 2.** Pairwise associations (Phi coefficients or point-biserial correlation coefficients) of structural variables in intermediate AMD study eyes

|              | Metric        | RPD               | PA               | iRORA             | cRORA            |
|--------------|---------------|-------------------|------------------|-------------------|------------------|
| PA           | Phi [95% CI]  | 0.22 [0.14–0.30]  |                  |                   |                  |
| iRORA        | Phi [95% CI]  | 0.17 [0.07–0.28]  | 0.17 [0.08–0.25] |                   |                  |
| cRORA        | Phi [95% CI]  | 0.22 [0.10–0.33]  | 0.21 [0.12–0.30] |                   |                  |
| RPEDC volume | PBCC [95% CI] | 0.01 [–0.07–0.10] | 0.26 [0.17–0.33] | 0.08 [–0.01–0.16] | 0.12 [0.03–0.20] |

CI, confidence interval; cRORA, complete retinal pigment epithelium and outer retinal atrophy; iRORA, incomplete retinal pigment epithelium and outer retinal atrophy; PA, pigmentary abnormalities; PBCC, point-biserial correlation coefficient; RPD, reticular pseudodrusen; RPEDC, retinal pigment epithelium drusen complex.

**Table 3.** Pairwise correlation coefficients with 95% confidence intervals (Pearson) of functional variables in intermediate AMD study eyes

|       | BCVA             | LLVA             | PR-CS            | MAT              | RS                | mesAT            | scoAT            |
|-------|------------------|------------------|------------------|------------------|-------------------|------------------|------------------|
| LLVA  | 0.69 [0.65–0.73] |                  |                  |                  |                   |                  |                  |
| PR-CS | 0.44 [0.38–0.51] | 0.40 [0.33–0.47] |                  |                  |                   |                  |                  |
| MAT   | 0.61 [0.55–0.65] | 0.61 [0.55–0.66] | 0.40 [0.33–0.46] |                  |                   |                  |                  |
| RS    | 0.26 [0.18–0.34] | 0.24 [0.16–0.32] | 0.22 [0.14–0.30] | 0.23 [0.15–0.31] |                   |                  |                  |
| mesAT | 0.34 [0.26–0.41] | 0.36 [0.29–0.43] | 0.39 [0.32–0.46] | 0.34 [0.26–0.41] | 0.38 [0.30–0.45]  |                  |                  |
| scoAT | 0.39 [0.31–0.46] | 0.40 [0.32–0.47] | 0.40 [0.32–0.47] | 0.35 [0.27–0.42] | 0.26 [0.17–0.34]  | 0.70 [0.66–0.75] |                  |
| RIT   | 0.12 [0.02–0.21] | 0.10 [0.01–0.20] | 0.14 [0.05–0.24] | 0.14 [0.05–0.24] | 0.07 [–0.03–0.17] | 0.16 [0.06–0.26] | 0.12 [0.01–0.22] |

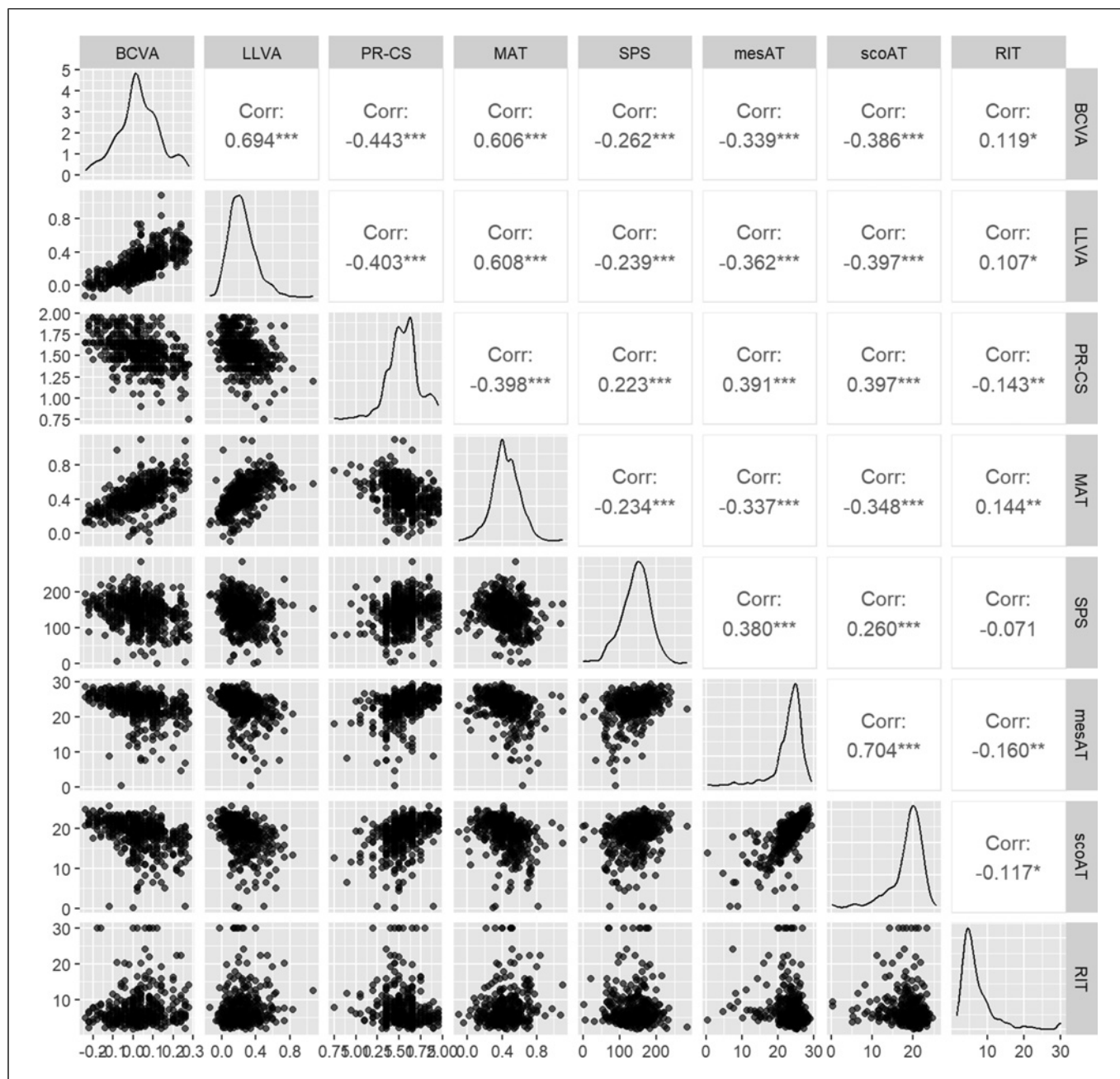
BCVA, best-corrected visual acuity; LLVA, low-luminance visual acuity; MAT, Moorfields acuity test; mesAT, mesopic average threshold on microperimetry; PR-CS, Pelli-Robson contrast sensitivity; RIT, rod intercept time on dark adaptometry; RS, reading speed (short paragraph standardized, using the International Reading Speed Texts); scoAT, scotopic average threshold on microperimetry.

in the current classifications [32, 33]. Data from the MACUSTAR study suggest a strong association between pigmentary changes and reticular pseudodrusen. This contributes to the existing evidence of an increasing risk of reticular pseudodrusen in the presence of pigmentary abnormalities in iAMD [34]. However, the associations with other structural risk factors were weaker, suggesting a need for an intermediate AMD subclassification given these heterogeneous morphological manifestations. Consensus on an OCT-based classification of early geographic atrophy stages has recently been reached by the Classification of Atrophy Meeting (CAM)-group [35] but at the current point the categories iRORA and cRORA are not yet fully integrated into the clinical classification of AMD. Based on the wide availability of advanced OCT devices, the level of standardization, high-

resolution datasets, and the numerous biomarkers that can be assessed through OCT imaging, we propose that a revised classification of AMD should integrate OCT-based features [36–39].

In addition to this, the spectrum of visual function changes in iAMD was broad across tests (Fig. 1) [40]. Despite the reliance of existing AMD classification systems on structural parameters [10, 27–31], visual function (specifically dark adaptometry) has been found to be reduced before the structural onset of AMD [41]. Anatomical changes at different test locations for dark adaptation might partially explain why the intra-test correlation in visual function assessments remains imperfect [42]. It is accepted that BCVA at high luminance is an insensitive marker of disease progression in early AMD stages, as it is often not significantly





**Fig. 1.** Pairwise associations of functional variables in participants with intermediate AMD. The lower part of the plots contains scatter plots of the variables and the upper part displays the Pearson correlation coefficient. Stars indicate if the Pearson correlation is different from zero (\*\*\*:  $p < 0.001$ , \*\*:  $p < 0.01$ , \*:  $p < 0.05$ ). The density of the visual function metric using a Gaussian kernel is shown on the diagonal.

different from patients without AMD and relatively stable over time in iAMD [43–45]. Mesopic, scotopic, and contrast vision and dark adaptation in iAMD, however, may undergo a slow and progressive decline that precedes the progression to late AMD [18, 43–47].

While most of the mentioned studies have investigated differences in visual function between iAMD and healthy control eyes and the prognostic value of visual function assessment in iAMD, the variety of visual function assessments in MACUSTAR allows for a more

**Table 4.** Pairwise correlation coefficients (Pearson) and 95% confidence intervals of VILL questionnaire scores in participants with intermediate AMD

|                | VILL-reading     | VILL-mobility    |
|----------------|------------------|------------------|
| VILL-mobility  | 0.68 [0.63–0.72] |                  |
| VILL-emotional | 0.21 [0.13–0.29] | 0.23 [0.15–0.31] |

VILL, Vision Impairment in Low Luminance.

in-depth characterization of the spectrum of visual function changes in iAMD.

Positive associations between visual function assessments of varying degrees were also described in the Duke study of Functional Endpoints for AMD and discussed in the context of changes in rod/cone function. The distribution of visual function outcomes across different tests in the Duke study further supports the broad spectrum of iAMD observed in MACUSTAR [18, 44, 45]. Wu and colleagues described a positive relationship between retinal sensitivity on microperimetry and low-luminance deficit (calculated as the difference between LLVA and BCVA) [48], and results from the PINNACLE study suggest that retinal sensitivity is more strongly associated with LLVA than other AMD risk factors [49]. In line with our results, these studies suggest identifying further substrata in the disease category iAMD.

The moderate associations across the VILL questionnaire’s patient-reported subscales “reading and accessing information,” “mobility and safety,” and “emotional well-being” suggest that patient-reports in iAMD cover different dimensions of vision-related quality of life. Like our work on the VILL questionnaire, Owsley and colleagues developed the Low Luminance Questionnaire (LLQ) to capture the impact of low luminance and low contrast conditions on patients’ daily lives. They reported positive associations between its subscales (driving, extreme lighting, mobility, emotional distress, general dim lighting, and peripheral vision) and the National Eye Institute Visual Function Questionnaire (NEI VFQ) [50]. The data by Owsley et al. are comparable to the data from the MACUSTAR dataset to a limited extent because of the NEI VFQ being a general (not low luminance-specific) PRO instrument [50]. Further analyses of the VILL questionnaire’s convergent and discriminant validity are currently pending. Of note, inter-eye difference in visual function can have a noticeable impact on vision-related quality of life, which needs to be reflected in the use of patient-reports in AMD studies [51, 52].

While AMD stage is defined bilaterally [10], a minority of 46 (7.9%) MACUSTAR study participants met the structural definition of intermediate AMD in the study eye but of late AMD in the fellow eye. This approach enriched the MACUSTAR study population for individuals at a higher risk of structural AMD progression but may raise question about the comparability of the sub-cohorts with symmetrical and asymmetrical AMD stages. Our results support that most functional and patient-reported variables were comparable between the sub-cohorts and therefore suggest that fellow eye AMD stage could be a promising enrichment criterion for future iAMD controlled trials. In this context, it could be valid to extrapolate findings to eyes with iAMD in both eyes.

Our full baseline results further support that the MACUSTAR data are in principle comparable to results of the AREDS2 and LEAD studies, as previously suggested based on data from the cross-sectional part of MACUSTAR [20]. The prevalence of reticular pseudodrusen in AREDS2 was 26% [53] and in 24% in LEAD [54], which is only slightly lower to the prevalence in MACUSTAR (28%). Among the three studies, pigmentary abnormalities were most prevalent in the AREDS2 cohort (76%) [55] and least prevalent in LEAD (31–35%) [54]. As the MACUSTAR prevalence falls in between (49%), the disease severity in the MACUSTAR population may be between AREDS2 and LEAD. This is further supported by the prevalence of late AMD in the fellow eye within these studies. LEAD excluded any late AMD in the fellow eye [54] whilst late AMD was present in 35% of AREDS2 fellow eyes [56]. This compared to 46 eyes (7%) in the baseline MACUSTAR cohort.

Strengths of this study include the large, well-phenotyped cohort from the European multi-center study MACUSTAR, image grading performed by a central reading center (GRADE Reading Centre, Bonn, Germany), continuous data quality checks and independent monitoring ensuring a high-quality dataset was available for analyses. Additionally trained and certified clinical staff used standardized SOPs for data acquisition, and the included tests were previously proven to be reliable and valid in independent studies, with the VILL questionnaire being rigorously evaluated prior to MACUSTAR [21–23, 57–59]. Furthermore, the full baseline cohort characteristics were generally comparable to the cross-sectional MACUSTAR dataset [20–22]. Limitations include the limited number of analyses of different structural biomarkers available so far, as the initial focus was on the analysis of the functional assessments, and the lack of a further sub-stratification of AMD, for which further work is required.

## Conclusions

In conclusion, iAMD includes a broad spectrum of disease with a variable extent of structural, functional and patient-reported changes. Further efforts from the MACUSTAR consortium and other international collaborations are required to better understand this spectrum, inform a more granular iAMD subclassification or AMD reclassification efforts and develop enrichment criteria and endpoints for future iAMD trials. The importance of such work is underlined by the considerable unmet medical need in preventing the vision loss of late stages of AMD.

## Acknowledgments

MACUSTAR consortium members: H. Agostini, I.D. Aires, L. Altay, R. Atia, F. Bandello, P.G. Basile, J. Batuca, C. Behning, M. Belmouhand, M. Berger, A. Binns, C.J.F. Boon, M. Böttger, J.E. Brazier, C. Carapezzi, J. Carlton, A. Carneiro, A. Charil, R. Coimbra, D. Cosette, M. Cozzi, D.P. Crabb, J. Cunha-Vaz, C. Dahlke, H. Dunbar, R.P. Finger, E. Fletcher, M. Gutfleisch, F. Hartgers, B. Higgins, J. Hildebrandt, E. Höck, R. Hogg, F.G. Holz, C.B. Hoyng, A. Kilani, J. Krätzschar, L. Kühlewein, M. Larsen, S. Leal, Y.T.E. Lechanteur, D. Lu, U.F.O. Luhmann, A. Lüning, N. Manivannan, I. Marques, C. Martinho, A. Miliu, K.P. Moll, Z. Mulyukov, M. Paques, B. Parodi, M. Parravano, S. Penas, T. Peters, T. Peto, S. Priglinger, R. Ramamirtham, R. Ribeiro, D. Rowen, G.S. Rubin, J. Sahel, C. Sánchez, O. Sander, M. Saßmannshausen, M. Schmid, S. Schmitz-Valckenberg, J. Siedlecki, R. Silva, E. Souied, G. Staurengi, J. Tavares, D.J. Taylor, J.H. Terheyden, A. Tufail, P. Valmaggia, M. Varano, A. Wolf, and N. Zakaria.

## Statement of Ethics

The study is conducted according to Good Clinical Practice guidelines and it follows the tenets of the Declaration of Helsinki. Ethics approval has been obtained at all clinical sites and informed consent needs to be signed before inclusion. All participants gave written informed consent before any study procedures were performed, as approved by Institutional Ethics Committees at all sites.

## Conflict of Interest Statement

Jan Henrik Terheyden: Heidelberg Engineering, Optos, Carl Zeiss Meditec, CenterVue, Novartis, Okko Frank G. Holz: Allergan, Annexon, Alzheon, Apellis, Astellas, Bayer, Boehringer-Ingelheim, Bioeq/Formycon, CenterVue, Roche/Genentech, 4D Molecular Therapeutics, Geuder, Grayburg, Heidelberg Engineering, IvericBio/Astellas, Janssen, LinBiosciences, NightStarX, Novartis, Optos, Oxurion, Pixium Vision, Stealth BioTherapeutics,

Carl Zeiss Meditec, Grade Reading Centre. Charlotte Behning: None. Hannah M.P. Dunbar: Boehringer-Ingelheim, Apellis. Steffen Schmitz-Valckenberg: AlphaRET, Apellis, Bayer, Carl Zeiss Meditec, Formycon, Galimedix, Heidelberg Engineering, Katairo, Kubota Vision, Novartis, Perceivve Therapeutics, Pixium, Roche, Sparing Vision; Adnan Tufail: Allergan, Bayer, Kanghong, Heidelberg Engineering, Novartis, Roche/Genentech, IvericBio, Apellis, Thea Matthias Schmid: Pixium Vision David P. Crabb: Apellis, Santen, Allergan/Abbvie, Janssen; Thea Marlene Saßmannshausen: Heidelberg Engineering, Optos, Carl Zeiss Meditec, CenterVue Alison Binns: Apparatus and method for retinal measurement; Patent number 9492081 Carel B. Hoyng: Optos, Bayer Nadia Zakaria: Employee of Novartis Stephen Poor: Employee of Novartis Klaus-Peter Moll: Employee of Novartis Deborah Cosette: Employee of Carl Zeiss Meditec Cecilia Martinho: None. Joana Batuca: None. José Cunha-Vaz: Alimera Sciences, Allergan, Bayer, Gene Signal, Novartis, Pfizer, Precision Ocular Ltd., Roche, Sanofi-Aventis, Vifor Pharma and Carl Zeiss Meditec. Ulrich F.O. Luhmann: Employee of and financial interest in F. Hoffmann-La Roche Ltd. Sergio Leal: Employee of Bayer Pharma AG. Robert P. Finger: Alimera, Apellis, Bayer, Boehringer-Ingelheim, Novartis, ODOS, Oxford Innovation, ProGenerika, Roche/Genentech, Biogen, Icare, Heidelberg Engineering, Carl Zeiss Meditec.

## Funding Sources

This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under Grant agreement No 116076. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA.

## Author Contributions

The recommendations of the International Committee of Medical Journal Editors (ICMJE) were followed for all authors of this article. J.H.T., F.G.H., R.P.F., C.B., H.M.P.D., S.S.-V., A.T., M.Sa., U.F.O.L., and S.L.: designed the study. C.B., M.Sa., H.M.P.D., A.B., J.H.T., U.F.O.L., S.S.-V., R.P.F., M.Sc., C.M., J.C.-V., D.P.C., and F.G.H.: curated the data. C.B., J.H.T., R.P.F., M.Sc., A.T., D.P.C., H.M.P.D., S.L., U.F.O.L., and F.G.H.: analyzed and interpreted the data. S.S.-V., M.Sa., A.B., C.B.H., N.Z., S.P., K.-P.M., D.C., C.M., J.B., and J.C.-V.: interpreted the data. J.H.T., C.B., F.G.H., and R.P.F.: drafted the manuscript. H.M.P.D., S.S.-V., A.D., M.Sc., D.P.C., M.Sa., A.B., C.B.H., N.Z., S.P., K.-P.M., D.C., C.M., J.B., J.C.-V., U.F.O.L., and S.L.: critically revised it. All authors read and approved the final manuscript and agreed to be accountable for all aspects of the work.

## Data Availability Statement

The data that support the findings are not publicly available since information contained could compromise the privacy of research participants but are available from the MACUSTAR consortium on individual request via [dataaccess@macustar.eu](mailto:dataaccess@macustar.eu).

## References

- 1 Wong WL, Su X, Li X, Cheung CMG, Klein R, Cheng C-Y, et al. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. *Lancet Glob Health*. 2014;2(2):e106–16. [https://doi.org/10.1016/S2214-109X\(13\)70145-1](https://doi.org/10.1016/S2214-109X(13)70145-1)
- 2 Li JQ, Welchowski T, Schmid M, Mauschitz MM, Holz FG, Finger RP. Prevalence and incidence of age-related macular degeneration in Europe: a systematic review and meta-analysis. *Br J Ophthalmol*. 2020;104(8):1077–84. <https://doi.org/10.1136/bjophthalmol-2019-314422>
- 3 Colijn JM, Buitendijk GHS, Prokofyeva E, Alves D, Cacho ML, Khawaja AP, et al. Prevalence of age-related macular degeneration in Europe: the past and the future. *Ophthalmology*. 2017;124(12):1753–63. <https://doi.org/10.1016/j.ophtha.2017.05.035>
- 4 Wong TY, Chakravarthy U, Klein R, Mitchell P, Zlateva G, Buggage R, et al. The natural history and prognosis of neovascular age-related macular degeneration: a systematic review of the literature and meta-analysis. *Ophthalmology*. 2008;115(1):116–26. <https://doi.org/10.1016/j.ophtha.2007.03.008>
- 5 Skaat A, Chetrit A, Belkin M, Kinori M, Kalter-Leibovici O. Time trends in the incidence and causes of blindness in Israel. *Am J Ophthalmol*. 2012;153(2):214–21.e1. <https://doi.org/10.1016/j.ajo.2011.08.035>
- 6 Bloch SB, Larsen M, Munch IC. Incidence of legal blindness from age-related macular degeneration in Denmark: year 2000 to 2010. *Am J Ophthalmol*. 2012;153(2):209–13.e2. <https://doi.org/10.1016/j.ajo.2011.10.016>
- 7 Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, Chung CY, et al. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med*. 2006;355(14):1419–31. <https://doi.org/10.1056/NEJMoa054481>
- 8 Heier JS, Lad EM, Holz FG, Rosenfeld PJ, Guymer RH, Boyer D, et al. Pegcetacoplan for the treatment of geographic atrophy secondary to age-related macular degeneration (OAKS and DERBY): two multicentre, randomised, double-masked, sham-controlled, phase 3 trials. *Lancet*. 2023;402(10411):1434–48. [https://doi.org/10.1016/S0140-6736\(23\)01520-9](https://doi.org/10.1016/S0140-6736(23)01520-9)
- 9 Klein R, Cruickshanks KJ, Nash SD, Krantz EM, Nieto FJ, Huang GH, et al. The prevalence of age-related macular degeneration and associated risk factors. *Arch Ophthalmol*. 2010;128(6):750–8. <https://doi.org/10.1001/archophthalmol.2010.92>
- 10 Ferris FL, Wilkinson CP, Bird A, Chakravarthy U, Chew E, Csaky K, et al. Clinical classification of age-related macular degeneration. *Ophthalmology*. 2013;120(4):844–51. <https://doi.org/10.1016/j.ophtha.2012.10.036>
- 11 Holz FG, Strauss EC, Schmitz-Valckenberg S, van Lookeren Campagne M. Geographic atrophy: clinical features and potential therapeutic approaches. *Ophthalmology*. 2014;121(5):1079–91. <https://doi.org/10.1016/j.ophtha.2013.11.023>
- 12 Rosenfeld PJ, Feuer WJ. Warning: do not treat intermediate AMD with laser therapy. *Ophthalmology*. 2019;126(6):839–40. <https://doi.org/10.1016/j.ophtha.2018.12.016>
- 13 Finger RP, Schmitz-Valckenberg S, Schmid M, Rubin GS, Dunbar H, Tufail A, et al. MAC-USTAR: development and clinical validation of functional, structural, and patient-reported endpoints in intermediate age-related macular degeneration. *Ophthalmologica*. 2019;241(2):61–72. <https://doi.org/10.1159/000491402>
- 14 Terheyden JH, Holz FG, Schmitz-Valckenberg S, Lüning A, Schmid M, Rubin GS, et al. Clinical study protocol for a low-interventional study in intermediate age-related macular degeneration developing novel clinical endpoints for interventional clinical trials with a regulatory and patient access intention-MACUSTAR. *Trials*. 2020;21(1):659. <https://doi.org/10.1186/s13063-020-04595-6>
- 15 De La Paz MA, Pericak-Vance MA, Haines JL, Seddon JM. Phenotypic heterogeneity in families with age-related macular degeneration. *Am J Ophthalmol*. 1997;124(3):331–43. [https://doi.org/10.1016/s0002-9394\(14\)70825-6](https://doi.org/10.1016/s0002-9394(14)70825-6)
- 16 Yehoshua Z, Wang F, Rosenfeld PJ, Penha FM, Feuer WJ, Gregori G. Natural history of drusen morphology in age-related macular degeneration using spectral domain optical coherence tomography. *Ophthalmology*. 2011;118(12):2434–41. <https://doi.org/10.1016/j.ophtha.2011.05.008>
- 17 Chandramohan A, Stinnett SS, Petrowski JT, Schuman SG, Toth CA, Cousins SW, et al. Visual function measures in early and intermediate age-related macular degeneration. *Retina*. 2016;36(5):1021–31. <https://doi.org/10.1097/IAE.0000000000001002>
- 18 Cocce KJ, Stinnett SS, Luhmann UFO, Vajzovic L, Horne A, Schuman SG, et al. Visual function metrics in early and intermediate dry age-related macular degeneration for use as clinical trial endpoints. *Am J Ophthalmol*. 2018;189:127–38. <https://doi.org/10.1016/j.ajo.2018.02.012>
- 19 Taylor DJ, Edwards LA, Binns AM, Crabb DP. Seeing it differently: self-reported description of vision loss in dry age-related macular degeneration. *Ophthalmic Physiol Opt*. 2018;38(1):98–105. <https://doi.org/10.1111/opo.12419>
- 20 Saßmannshausen M, Behning C, Weinz J, Goerdit L, Terheyden JH, Chang P, et al. Characteristics and spatial distribution of structural features in age-related macular degeneration: a macustar study report. *Ophthalmol Retina*. 2023;7(5):420–30. <https://doi.org/10.1016/j.oret.2022.12.007>
- 21 Dunbar HMP, Behning C, Abdirahman A, Higgins BE, Binns AM, Terheyden JH, et al. Repeatability and discriminatory power of chart-based visual function tests in individuals with age-related macular degeneration: a macustar study report. *JAMA Ophthalmol*. 2022;140(8):780–9. <https://doi.org/10.1001/jamaophthalmol.2022.2113>
- 22 Higgins BE, Montesano G, Dunbar HMP, Binns AM, Taylor DJ, Behning C, et al. Test-retest variability and discriminatory power of measurements from microperimetry and dark adaptation assessment in people with intermediate age-related macular degeneration - a macustar study report. *Transl Vis Sci Technol*. 2023;12(7):19. <https://doi.org/10.1167/tvst.12.7.19>
- 23 Terheyden JH, Pondorfer SG, Behning C, Berger M, Carlton J, Rowen D, et al. Disease-specific assessment of Vision Impairment in Low Luminance in age-related macular degeneration - a MACUSTAR study report. *Br J Ophthalmol*. 2023;107(8):1144–50. <https://doi.org/10.1136/bjophthalmol-2021-320848>
- 24 Akoglu H. User's guide to correlation coefficients. *Turk J Emerg Med*. 2018;18(3):91–3. <https://doi.org/10.1016/j.tjem.2018.08.001>
- 25 Schober P, Boer C, Schwarte LA. Correlation coefficients: appropriate use and interpretation. *Anesth Analg*. 2018;126(5):1763–8. <https://doi.org/10.1213/ANE.0000000000002864>
- 26 Heesterbeek TJ, Lorés-Motta L, Hoyng CB, Lechanteur YTE, den Hollander AI. Risk factors for progression of age-related macular degeneration. *Ophthalmic Physiol Opt*. 2020;40(2):140–70. <https://doi.org/10.1111/opo.12675>
- 27 Bird AC, Bressler NM, Bressler SB, Chisholm IH, Coscas G, Davis MD, et al. An international classification and grading system for age-related maculopathy and age-related macular degeneration. The International ARM Epidemiological Study Group. *Surv Ophthalmol*. 1995;39(5):367–74. [https://doi.org/10.1016/s0039-6257\(05\)80092-x](https://doi.org/10.1016/s0039-6257(05)80092-x)
- 28 Age-Related Eye Disease Study Research Group. The age-related eye disease study system for classifying age-related macular degeneration from stereoscopic color fundus photographs: the age-related eye disease study report number 6. *Am J Ophthalmol*. 2001;132(5):668–81. [https://doi.org/10.1016/s0002-9394\(01\)01218-1](https://doi.org/10.1016/s0002-9394(01)01218-1)
- 29 Klaver CC, Assink JJ, van Leeuwen R, Wolfs RC, Vingerling JR, Stijnen T, et al. Incidence and progression rates of age-related maculopathy: the Rotterdam Study. *Investig Ophthalmol Vis Sci*. 2001;42(10):2237–41.
- 30 Ferris FL, Davis MD, Clemons TE, Lee L-Y, Chew EY, Lindblad AS, et al. A simplified severity scale for age-related macular degeneration: AREDS Report No. 18. *Arch Ophthalmol*. 2005;123(11):1570–4. <https://doi.org/10.1001/archophth.123.11.1570>

- 31 Davis MD, Gangnon RE, Lee L-Y, Hubbard LD, Klein BEK, Klein R, et al. The Age-Related Eye Disease Study severity scale for age-related macular degeneration: AREDS Report No. 17. *Arch Ophthalmol*. 2005; 123(11):1484–98. <https://doi.org/10.1001/archophth.123.11.1484>
- 32 Klein R, Meuer SM, Knudtson MD, Iyengar SK, Klein BEK. The epidemiology of retinal reticular drusen. *Am J Ophthalmol*. 2008; 145(2):317–26. <https://doi.org/10.1016/j.ajo.2007.09.008>
- 33 Joachim N, Mitchell P, Rochtchina E, Tan AG, Wang JJ. Incidence and progression of reticular drusen in age-related macular degeneration: findings from an older Australian cohort. *Ophthalmology*. 2014;121(4):917–25. <https://doi.org/10.1016/j.ophtha.2013.10.043>
- 34 Wu Z, Fletcher EL, Kumar H, Greferath U, Guymer RH. Reticular pseudodrusen: a critical phenotype in age-related macular degeneration. *Prog Retin Eye Res*. 2022;88: 101017. <https://doi.org/10.1016/j.preteyeres.2021.101017>
- 35 Guymer RH, Rosenfeld PJ, Curcio CA, Holz FG, Staurengi G, Freund KB, et al. Incomplete retinal pigment epithelial and outer retinal atrophy in age-related macular degeneration: classification of atrophy meeting report 4. *Ophthalmology*. 2020;127(3): 394–409. <https://doi.org/10.1016/j.ophtha.2019.09.035>
- 36 Abidi M, Karrer E, Csaky K, Handa JT. A clinical and preclinical assessment of clinical trials for dry age-related macular degeneration. *Ophthalmol Sci*. 2022;2(4):100213. <https://doi.org/10.1016/j.xops.2022.100213>
- 37 Lad EM, Finger RP, Guymer R. Biomarkers for the progression of intermediate age-related macular degeneration. *Ophthalmol Ther*. 2023;12(6):2917–41. <https://doi.org/10.1007/s40123-023-00807-9>
- 38 Schaal KB, Rosenfeld PJ, Gregori G, Yehoshua Z, Feuer WJ. Anatomic clinical trial endpoints for nonexudative age-related macular degeneration. *Ophthalmology*. 2016;123(5):1060–79. <https://doi.org/10.1016/j.ophtha.2016.01.034>
- 39 Aytulun A, Cruz-Herranz A, Aktas O, Balcer LJ, Balk L, Barboni P, et al. APOSTEL 2.0 recommendations for reporting quantitative optical coherence tomography studies. *Neurology*. 2021;97(2):68–79. <https://doi.org/10.1212/WNL.00000000000012125>
- 40 Dunbar HMP, Crabb DP, Behning C, Binns A, Abdurahman A, Terheyden JH, et al. Heterogeneous visual function deficits in intermediate age-related macular degeneration – a MACU-STAR report. *Ophthalmol Sci*. 2025;100708. <https://doi.org/10.1016/j.xops.2025.100708>
- 41 Owsley C, McGwin G, Clark ME, Jackson GR, Callahan MA, Kline LB, et al. Delayed rod-mediated dark adaptation is a functional biomarker for incident early age-related macular degeneration. *Ophthalmology*. 2016;123(2):344–51. <https://doi.org/10.1016/j.ophtha.2015.09.041>
- 42 Swain TA, McGwin G Jr, Owsley C, Clark ME, Kar D, Curcio CA. Re: Higgins et al.: Assessment of the classification of age-related macular degeneration severity from the Northern Ireland Sensory Ageing Study using a measure of dark adaptation (*Ophthalmol Sci*. 2023;3(2):100204). *Ophthalmol Sci*. 2023; 3(3):100376. <https://doi.org/10.1016/j.xops.2023.100376>
- 43 Wu Z, Ayton LN, Luu CD, Guymer RH. Longitudinal changes in microperimetry and low luminance visual acuity in age-related macular degeneration. *JAMA Ophthalmol*. 2015;133(4):442–8. <https://doi.org/10.1001/jamaophthalmol.2014.5963>
- 44 Hsu ST, Thompson AC, Stinnett SS, Luhmann UFO, Vajzovic L, Horne A, et al. Longitudinal study of visual function in dry age-related macular degeneration at 12 months. *Ophthalmol Retina*. 2019;3(8): 637–48. <https://doi.org/10.1016/j.oret.2019.03.010>
- 45 Lad EM, Fang V, Tessier M, Rautanen A, Gayan J, Stinnett SS, et al. Longitudinal evaluation of visual function impairments in early and intermediate age-related macular degeneration patients. *Ophthalmol Sci*. 2022; 2(3):100173. <https://doi.org/10.1016/j.xops.2022.100173>
- 46 Ou WC, Denlar RA, Csaky KG. The relationship between central drusen volume and low-luminance deficit in age-related macular degeneration. *Transl Vis Sci Technol*. 2020; 9(4):10. <https://doi.org/10.1167/tvst.9.4.10>
- 47 Owsley C, Clark ME, McGwin G. Natural history of rod-mediated dark adaptation over 2 Years in intermediate age-related macular degeneration. *Transl Vis Sci Technol*. 2017; 6(3):15. <https://doi.org/10.1167/tvst.6.3.15>
- 48 Wu Z, Ayton LN, Guymer RH, Luu CD. Low-luminance visual acuity and microperimetry in age-related macular degeneration. *Ophthalmology*. 2014;121(8):1612–9. <https://doi.org/10.1016/j.ophtha.2014.02.005>
- 49 Anders P, Traber GL, Pfau M, Riedl S, Hagag AM, Camenzind H, et al. Comparison of novel volumetric microperimetry metrics in intermediate age-related macular degeneration: PINNACLE study report 3. *Transl Vis Sci Technol*. 2023;12(8):21. <https://doi.org/10.1167/tvst.12.8.21>
- 50 Owsley C, McGwin G, Scilley K, Kallies K. Development of a questionnaire to assess vision problems under low luminance in age-related maculopathy. *Investig Ophthalmol Vis Sci*. 2006;47(2):528–35. <https://doi.org/10.1167/iovs.05-1222>
- 51 Finger RP, Fenwick E, Hirneiss CW, Hsueh A, Guymer RH, Lamoureux EL, et al. Visual impairment as a function of visual acuity in both eyes and its impact on patient reported preferences. *PLoS One*. 2013;8(12):e81042. <https://doi.org/10.1371/journal.pone.0081042>
- 52 Nickels S, Schuster AK, Elflein H, Wolfram C, Schulz A, Münzel T, et al. Vision-related quality of life considering both eyes: results from the German population-based Gutenberg Health Study (GHS). *Health Qual Life Outcomes*. 2019;17(1):98. <https://doi.org/10.1186/s12955-019-1158-1>
- 53 Domalpally A, Agrón E, Pak JW, Keenan TD, Ferris FL, Clemons TE, et al. Prevalence, risk, and genetic association of reticular pseudodrusen in age-related macular degeneration: age-related eye disease study 2 report 21. *Ophthalmology*. 2019;126(12):1659–66. <https://doi.org/10.1016/j.ophtha.2019.07.022>
- 54 Guymer RH, Wu Z, Hodgson LAB, Caruso E, Brassington KH, Tindill N, et al. Sub-threshold nanosecond laser intervention in age-related macular degeneration: the LEAD randomized controlled clinical trial. *Ophthalmology*. 2019;126(6):829–38. <https://doi.org/10.1016/j.ophtha.2018.09.015>
- 55 Folgar FA, Chow JH, Farsiu S, Wong WT, Schuman SG, O'Connell RV, et al. Spatial correlation between hyperpigmentary changes on color fundus photography and hyperreflective foci on SDOCT in intermediate AMD. *Investig Ophthalmol Vis Sci*. 2012;53(8):4626–33. <https://doi.org/10.1167/iovs.12-9813>
- 56 AREDS2 Research Group, Chew EY, Clemons T, SanGiovanni JP, Danis R, Domalpally A, et al. The Age-Related Eye Disease Study 2 (AREDS2): study design and baseline characteristics (AREDS2 report number 1). *Ophthalmology*. 2012;119(11):2282–9. <https://doi.org/10.1016/j.ophtha.2012.05.027>
- 57 Pondorfer SG, Terheyden JH, Overhoff H, Stasch-Bouws J, Holz FG, Finger RP. Development of the vision impairment in low luminance questionnaire. *Transl Vis Sci Technol*. 2021;10(1):5. <https://doi.org/10.1167/tvst.10.1.5>
- 58 Terheyden JH, Gerhards J, Ost RAD, Wintergerst MWM, Holz FG, Finger RP. Patient-reported vision impairment in low luminance predicts multiple falls. *BMC Geriatr*. 2023; 23(1):583. <https://doi.org/10.1186/s12877-023-04317-y>
- 59 Terheyden JH, Mekschat L, Ost RAD, Bildik G, Berger M, Wintergerst MWM, et al. Interviewer administration corresponds to self-administration of the vision impairment in low luminance (VILL) questionnaire. *Transl Vis Sci Technol*. 2022;11(4):21. <https://doi.org/10.1167/tvst.11.4.21>