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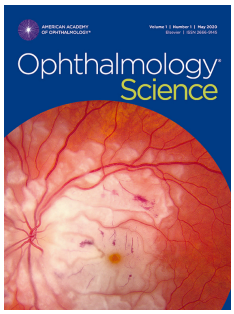

Heterogenous visual function deficits in intermediate age-related macular degeneration – A MACUSTAR report

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PII: S2666-9145(25)00006-5

DOI: https://doi.org/10.1016/j.xops.2025.100708

Reference: XOPS 100708

To appear in: *Ophthalmology Science*

Received Date: 13 May 2024

Revised Date: 3 December 2024

Accepted Date: 7 January 2025

Please cite this article as: Dunbar H.M.P., Crabb D.P., Behning C., Binns A.M., Abdirahman A., Terheyden J.H., Poor MRCOphth S., Finger R.P., Leal S., Tufail A., Holz F.G., Schmid M., Luhmann U.F.O. & On behalf of the MACUSTAR Consortium, Heterogenous visual function deficits in intermediate age-related macular degeneration – A MACUSTAR report, *Ophthalmology Science* (2025), doi: https://doi.org/10.1016/j.xops.2025.100708.

Heterogenous visual function deficits in intermediate age-related macular degeneration – A MACUSTAR report

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Key Words: age-related macular degeneration, visual function, visual dysfunction

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Meeting Presentation
A poster of this work was presented at ARVO 2023 in New Orleans in May 2023.

Financial Support
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. The sponsors or funding organizations had no role in the design or conduct of the MACUSTAR study (project number: 116076) research, including collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Conflicts of Interest:
Hannah M.P. Dunbar: Boehringer Ingelheim, Apellis
David P. Crabb: Allergan/Abbvie, Apellis, Janssen, Santen, THEA, Glaukos
Charlotte Behning: None
Alison Binns: Boehringer Ingelheim, **Apparatus and method for retinal measurement:** Patent number: 9492081; 2016.
Amina Abdirahman: None
Jan H. Terheyden: Carl Zeiss MedicTec, CenterVue (now Icare), Heidelberg Engineering, Optos, Novartis, Okko
Stephen Poor: Employee of Novartis Institutes for Biomedical Research
Robert P. Finger: Alimera, Apellis, Bayer, Böhringer-Ingelheim, Caterna, Novartis, ODOS, Oxford Innovation, ProGenerika, Roche/Genentech, Biogen, CenterVue (now Icare), Heidelberg Engineering, Zeiss Meditec
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Frank G. Holz: Acucela, Alexion, Alzheon, Allergan, Apellis, Astellas, Bayer, Boehringer-Ingelheim, Bioeq/Formycon, CenterVue, Roche/Genentech, Geuder, Graybug, Gyroscope, Heidelberg Engineering, IvericBio, Janssen, Kanghong, LinBioscience, NightStarX, Novartis, Optos, Oxurion, Pixium Vision, Oxurion, Stealth BioTherapeutics, Zeiss, GRADE Reading Center
Matthias Schmid: None
Ulrich F.O. Luhmann: Employee of and financial interest in F. Hoffmann-La Roche Ltd

Running head
Visual function deficits in iAMD

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This article contains additional online-only material. The following should appear online-only: Tables 4, 5 and 6

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Appendix:

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Abstract

Objective: To examine the extent to which visual function in Beckman age-related macular degeneration (AMD) disease stages differ from age similar peers with no AMD and using reference limits derived from those with no AMD, test the hypothesis that people with intermediate AMD (iAMD) have heterogenous visual function deficits.

Design: Cross-sectional analyses of a range of baseline visual function measures from the MACUSTAR study; an international, multi-center (n=20), non-interventional clinical trial.

Participants: 585 participants with iAMD (67% female, mean [standard deviation] age 72 [7] years) were recruited alongside 56 with no AMD (59% female, 68 [6]), 34 with early AMD (79% female, 72 [6]) and 43 with late AMD (49% female, 75 [6]).

Methods: Participants performed best-corrected visual acuity (BCVA), low luminance visual acuity (LLVA), Moorfields acuity test (MAT), Pelli-Robson contrast sensitivity (PR-CS), Small Print Standardized International Reading Speed Test (SPS), mesopic and scotopic Average Threshold (MesAT and ScoAT; Macular Integrity Assessment, iCare,) and Rod Intercept Time (RIT; AdaptDx, Lumithera).

Main Outcome Measures: Relationship between each visual function measure and disease classification was examined by linear regression adjusted for age, sex and phakic status. No AMD data were used to estimate normal reference limits for each

visual function test. iAMD scores were dichotomised against reference limits and proportion worse than each limit calculated.

Results: Relative to no AMD, SPS was significantly worse in early AMD ($p = 0.001$), all measures except SPS were significantly reduced in iAMD ($p<0.02$) and all measures were markedly reduced in late AMD ($p<0.0001$). 31% of iAMD participants breached reference limits for PR-CS, 29% for RIT, 24% for LLVA, 23% for MAT, 21% for BCVA, 20% for MesAT, 18% for ScoAT and 13% for SPS. 69.6% and 42.7% of iAMD participants breached ≥1 and ≥2 reference limits respectively, whereas 33.6% and 5.7% would be expected by chance.

Conclusions: A large proportion of people with structurally defined iAMD exhibit heterogenous visual function deficits outside normal reference limits. This observation may be relevant for the design and inclusion criteria of future interventional trials.

Trial registration:

Clinicaltrials.gov Reference: NCT03349801

https://clinicaltrials.gov/ct2/show/NCT03349801

Age-related macular degeneration (AMD) is a major cause of severe sight impairment globally affecting 196 million people, projected to rise to 288 million by 2040[1]. The progressive stages of AMD, referred to as early, intermediate and late disease are identified based on structural features present in colour fundus photography[2]. The value of incorporating optical coherence tomography (OCT) features within future classification paradigms is being explored[3-5]. Despite relevance to patients, visual function measures are not currently considered within AMD classification systems and could potentially distinguish structurally similar disease with differing functional impacts, underlying pathology, or responsiveness to therapeutics.

Patient reported outcome studies suggest people with intermediate age-related macular degeneration (iAMD) experience difficulty under low luminance conditions[6, 7]. Multiple measures of visual function under photopic, mesopic and scotopic conditions are also significantly worse in iAMD compared to healthy controls [8-15], however as absolute differences are small, clinical significance is unclear. Substantial functional heterogeneity within measures of low-luminance vision, contrast sensitivity, retinal sensitivity, and rod adaptation have been observed in iAMD [10, 12, 16] suggesting that comparing mean visual function measures between disease classifications may miss the presence of subgroups of people with iAMD experiencing meaningful functional impairment. Establishing evidence of visual function heterogeneity in people with iAMD, its prevalence and the extent to which different dimensions of visual function are affected could be useful for future trial design, regulatory purposes, and studies of new therapies.

Here we interrogate data from a large multi-center study on a range of clinical visual function assessments, to examine the extent to which visual function in AMD stages differs from age similar peers with no AMD and using reference limits derived from those with no AMD, test the hypothesis that people with iAMD have heterogenous visual deficits.

Methods:

MACUSTAR (Registration NCT03349801; www.clinicaltrials.gov) is a non-interventional 20 center clinical trial, the protocol of which has been published previously[17]. Briefly, MACUSTAR has two parts; a cross-sectional study where structural and functional candidate endpoints have been evaluated with respect to their repeatability and ability to distinguish normal aging changes from Beckman[2] classified AMD stages (No AMD, early AMD, iAMD and late AMD [includes both geographic atrophy and neovascular AMD])[18, 19] and a longitudinal study where the ability of candidate endpoints to detect change over time and predict progression of iAMD to late AMD is being evaluated over a 3-year time course in a larger cohort with iAMD, with an extension to 6 year follow up recently announced. The present work uses the full baseline dataset across both components of the MACUSTAR study.

Written informed consent was obtained from all participants. The research was approved by individual local ethics committees (summarised in [20]) and conformed to the Declaration of Helsinki. Inclusion and exclusion criteria have previously been published[17, 21]. Disease classification was confirmed by a central reading center based on multi-modal imaging (colour fundus photography, near-infrared reflectance

scanning laser ophthalmoscopy, fundus autofluorescence and spectral-domain optical coherence tomography) graded according to a standardized, predefined grading protocol based on Beckman AMD classification[2, 22].

All participants performed a battery of visual function assessments including best-corrected visual acuity (BCVA), low luminance visual acuity (LLVA)[23], Moorfields acuity test (MAT)[24], Pelli-Robson contrast sensitivity (PR-CS) [25], Small Print Standardized International Reading Speed Test (SPS)[26, 27], average threshold from mesopic and scotopic fundus-controlled perimetry (MesAT and ScoAT; Macular Integrity Assessment, iCare, Finland) and rod intercept time (RIT) from dark adaptometry (AdaptDx, Lumithera, USA). A full description of all examination procedures including their standardized operating procedures (SOPs) have been published elsewhere[18, 19]. As MACUSTAR was conceived to examine the potential of candidate endpoints within iAMD, test were selected with respect to relevance in iAMD, adequate measurement quality, compatibility with repeated standardized administration under multi center clinical trial conditions and being accepted by patients and examiners[17]. All tests were performed monocularly with the study eye (defined as that with better BCVA or selected by the investigator if BCVA was equal in both eyes). Visual function data were subject to 6 monthly quality control procedures. MesAT, ScoAT and RIT data were assessed for quality and reliability as per their SOPs so that only high-quality data were retained for analysis. RIT values were capped at the maximum test duration (30 minutes). The relationship between each visual function measure and Beckman disease classification was plotted and examined by linear regression adjusted for age, sex and phakic status with Benjamini-Hochberg adjustment for multiple comparisons.

Cross-sectional data from those with no AMD were used to define a reference limit for normal function on each visual function test against which iAMD results were dichotomised. For visual function measures where higher values equate to better function, the reference limit was defined as the 5th percentile of baseline no AMD data. For measures where lower values equate to better function, the 95th percentile was used. Percentiles were computed using the default quantile type of the *quantile* function, which corresponds to continuous sample quantile type 7 described here[28]. The proportion of participants with iAMD exhibiting function worse than each reference limit was calculated, together with the proportion falling outside, or breaching 0, 1, 2, 3, 4, 5, 6, 7 or 8 reference limits. Missing data points were classified as not exceeding the threshold. An UpSet plot[29, 30] was used to graphically display the number and variety of reference limits breached. A negative binomial regression model was fitted to investigate the association between the number of breached visual function limits and phakic status. All analyses were performed in R, version 4.3.0[31]. STROBE reporting guidelines were followed[32].

Results:

Five hundred and eighty five participants with iAMD (67% female, mean [± standard deviation] age 72 ± 7 years) were recruited alongside 56 with no AMD (59% female, 68 ± 6 years), 34 with early AMD (79% female, 72 ± 6 years) and 43 with late AMD (49% female, 75 ± 6 years). More than 99% of participants completed BCVA, LLVA, MAT and PR-CS measures, with 93.7% performing the SPS. SPS was not performed at one site (n=30) where a native language (Danish) test was not available. The proportion of participants able to return a valid MesAT, ScoAT and

RIT measurement was 90.8%, 85.2% and 69.1% respectively. Table 1 provides the distribution of demographic and visual function measures by disease classification, presented graphically in figure 1.

A linear regression model adjusted for age, sex and phakic status examined the relationship between each visual function measure and disease classification, where no AMD was the reference level. Model results are summarised in Table 2. Relative to no AMD, only SPS was significantly worse on average in early AMD ($p=0.001$), whereas all measures apart from SPS were significantly worse in iAMD ($p<0.02$). Though statistically significant, in each case model estimates were smaller than the limits of agreement defined during the cross-sectional part of MACUSTAR.[18, 19] All visual function measures were significantly and markedly poorer in late AMD relative to no AMD ($p<0.0001$), with all estimates being between 1.6x to 5x larger than the limits of agreement defined on the MACUSTAR late AMD cohort.[18, 19] Additionally age was associated with all visual function measures except for RIT ($p<0.0003$).

Calculated reference limits and the proportion of iAMD participants breaching said limits for each visual function test is provided in Table 3 and shown in Figure 1 as a red dashed line. The proportion of those with iAMD breaching individual reference limits was largest for PR-CS (31.3%), followed by RIT (29.4%), LLVA, (24.1%) and MAT (23.2%). Roughly one fifth breached BCVA (20.5%), MesAT (19.8%) and ScoAT (17.9%) reference limits, dropping to an eighth for SPS (12.6%). Average differences between each impaired subgroup and the no AMD group were calculated and are shown in Table 3. The impaired subgroup for BCVA, LLVA and MAT were between 0.22 LogMAR (11 letters) - 0.32 LogMAR (16 letters) poorer than the no

AMD group. PR-CS was 0.35 LogCS (7 letters) poorer, SPS reading speed was 82 wpm slower, MesAT and ScoAT were 7.2dB and 8.4dB lower respectively and RIT was 7.89 minutes slower.

407 (69.6%) iAMD participants breached the no AMD reference limits on at least one visual function test, with 250 (42.7%) breaching at least 2. Binomial probability calculations were used to determine how many participants would be expected to exceed at least one ([1 – 1*(1-0.05)^8] = 33.6%) and at least 2 ([1 – 1*(1-0.05)^8 – 8! / 7!*0.05*(1-0.05)^7] = 5.7%) limit by chance under the null hypothesis that people exhibiting function worse than the reference limit have equivalent visual function to peers with no AMD. The number and proportion of those with iAMD who breached 0 – 8 reference limits are provided in Table 4 (available at https://www.aaojournal.org).

The Upset plot in Figure 2 graphically displays the quantity of iAMD participants who breached the reference limit for each visual function test and the extent to which iAMD participants breached reference limits on single and / or multiple visual function tests. Though the PR-CS reference limit was breached most commonly overall, RIT was the most common reference limit breached in isolation, whereas individuals who breached the PR-CS limits, more often breached one or more additional limit in combination. The most common combination of 2 reference limits breached was PR-CS and MAT (n = 134, [22.9%]), with RIT and SPS being the least common (n = 47, [8.0%]). Four individuals exceeded all 8 limits. No association was found between the number of breached visual function limits and phakic status (p>0.16).

Since reference limits calculated for these analyses account for measurement variability between those with no AMD but not within individuals, a sensitivity analysis was performed exploiting no AMD data obtained at both baseline (Day 0) and validation (Day 14 ± 7) study visits. Results are provided in Table 5 and 6 (available at https://www.aaojournal.org). Applying secondary reference limits revealed 360 (61.5%) iAMD participants breached at least one limit and 209 (35.7%) breached at least 2.

Discussion

In this large, multi-center dataset, a range of visual function tests did not show clinically meaningful average differences in functional performance between normal aging and both early AMD and iAMD. Conversely visual function in those with late AMD was markedly and significantly reduced, exceeding limits of agreement defined for the MACUSTAR visual function test battery by between 1.6 and 5 times. Despite average visual function in iAMD being clinically comparable to no AMD on a population level, 69.6% of iAMD participants had deficits in at least 1 visual function test falling outside reference limits established in visually healthy peers; more than two-fold greater than that expected by chance. Additionally, 42.7% of participants with iAMD had deficits in two or more visual function tests; seven times more than that expected by chance. Estimates of the proportion affected by chance assume tests are unrelated. Correlation coefficients between the visual function measures in this cohort are in the weak to moderate range (Under review with Ophthalmologica: Terheyden, 2024: The Heterogeneous Spectrum of Functional, Structural and Patient-Reported Outcomes in Intermediate Age-Related Macular Degeneration – A MACUSTAR Study Report). Taken together, this supports the notion that functional

heterogeneity in the baseline iAMD population of MACUSTAR cannot be explained as a chance finding. That said, the observed proportions depend on the veracity of the reference limits used.

There are no universally accepted thresholds for normal function in older eyes. Therefore, we defined reference limits on data from 56 visually healthy peers in the same study. This dataset has the unique advantage of being obtained under the same multi-center, multi-technician conditions, using the same publicly available SOPs[18, 19]. We additionally exploited the availability of repeat no AMD visual function data to assess the impact of intra-observer variability on our calculated reference limits. This sensitivity analysis adopted the cautious approach of basing a set of secondary reference limits on the worst of 2 visual function measurements. Comparing these to our initial limits showed that for letter scored tests (BCVA, LLVA, MAT and PR-CS) reference limits differed by between 0 and 1.5 letters. SPS limits differed by 3 wpm, microperimetry average threshold measures by between 0.8 – 1dB and RIT by 0.27 minutes. Logically, applying these adjusted thresholds resulted in a smaller proportion of iAMD participants outside reference limits, however the proportion outside at least one (61.5%) and 2 (35.7%) limits were roughly 1.8x and 6x that expected by chance respectively, corroborating our primary finding that a large proportion of participants with iAMD have deficits in visual function falling outside reference limits established in visually healthy peers.

A comparative study of visual function in normal controls and iAMD assessed BCVA, LLVA, MAT, PR-CS, SPS, MesAT and ScoAT in 24 control eyes in a single center (61.7 ± 6.1 years) using equivalent equipment and testing protocols.[9] Using their published no AMD data to calculate the mean ± 2 x standard deviation for each

visual function measure as a proxy for the 5th/95th percentile revealed roughly equivalent values to our reference limits (BCVA: 0.12 LogMAR; LLVA: 0.38 LogMAR; MAT: 0.50 LogMAR; PR-CS: 1.50 LogCS; SPS: 116wpm; MesAT: 22.7dB; ScoAT: 19.5dB). The single center ALSTAR2 study has also assessed a range of visual function parameters in 239 people (70.8 ± 5.6 years) in normal macular health (Age-Related Eye Disease Study[33] [AREDS] grade 1).[13, 34] Though defining reference limits was not the primary aim of ALSTAR2, as one of the largest published studies of normal macular health it serves as a very useful comparator. Further there is some overlap between the visual function test batteries of ALSTAR2 and MACUSTAR (both assess BCVA, LLVA, contrast sensitivity, MesAT, ScoAT and RIT), though testing equipment and protocols differ. These factors limit a true, direct comparison. Nevertheless, proxy reference limits calculated using baseline ALSTAR2 control data (using the method described above) reveal slightly more conservative values than our reference limits for all tests except RIT (BCVA: 0.15 LogMAR; LLVA: 0.42 LogMAR; MARS contrast sensitivity[35]: 1.39 LogCS; MesAT: 19.1dB; ScoAT: 16.0dB). A direct comparison for RIT is more challenging as test parameters differ. Based on data from the same 12° retinal location used in MACUSTAR, though using a higher bleach and longer maximum test duration[34], the proxy RIT limit is 16.2mins. Recent evidence suggests dark adaptation deficits in early AMD are likely greatest when assessed at 5° eccentricity)[34]. In MACUSTAR, the 12° test location was chosen based on pilot data showing that a deficit is present in people with iAMD at 12°, and that a smaller proportion of participants would demonstrate a ceiling effect within a clinically practical test duration.[36-38] In line with this pilot data, our results support the existence of an RIT deficit at 12°, as a higher proportion of participants fell outside the RIT reference limit than any other functional

parameter except for PR-CS. However, we note that a more centrally located target may have identified an even higher proportion of individuals with abnormal RIT, had the test duration been extended to 45 or 60 minutes. In addition to test parameter differences and the different method of reference limit calculation, the slightly older age of the ALSTAR2 cohort ([70.8 ± 5.6] versus [68 ± 6] years) may also contribute to the difference in reference limits between studies.

MACUSTAR reference limits presented here cannot be considered true normative cut off values given the small dataset on which they are based; this is a limitation. Nevertheless, we suggest this method of defining reference limits for exposing functional heterogeneity is justified by its statistical underpinning, consensus with previous work and cautious nature. However, future work characterizing normative visual function on the MACUSTAR test battery in a larger cohort with a wider and balanced age-range is warranted to fully explore the concept of functional heterogeneity in iAMD and other ocular disease cohorts.

Functional heterogeneity in AREDS defined iAMD has been previously observed based on mesopic microperimetry, low luminance deficit and dark adaptation measures in single center studies.[36, 38, 39] Here we add further evidence that this heterogeneity extends to a wider range of clinical visual function tests and is observable in a large, multi-center population of people with Beckman classified iAMD examined under clinical trial conditions. Recent work using qualitative autofluorescence to assess early changes in AMD suggests some eyes classified as Beckman iAMD may be at an earlier stage disease stage[40]. This suggests functional heterogeneity may not only be the preserve of iAMD but may extent to those with earlier disease.

Though a certain degree of heterogeneity could be introduced by technical variability or execution, especially in a multi center setting, efforts were employed to minimise this. Technician were certified, 6 monthly quality control assessments were performed to recognise any additional training needs and to identify and exclude invalid data, test-retest variability was determined for all tests[18, 19] and pilot testing performed to optimise test parameters[37, 41]. Thus, we consider our data to have high quality and conclusions valid.

The average differences between the iAMD subgroup with impaired function and normal peers exceed the test-retest limits for each visual function test[18, 19], supporting the clinical relevance of functional heterogeneity in iAMD. Furthermore, differences approximate changes proposed to represent clinical relevance (15-letters on acuity tests [42], 6-letters on PR-CS[43, 44], 80 wpm on SPS[45, 46], 7dB in retinal sensitivity[47], and 6.5 minutes on RIT albeit at a different retinal location[48]) based on methods including expert consensus, association of functional measures with task performance or self-report and diagnostic sensitivity and specificity.

Deficits were most commonly found in PR-CS and RIT, however PR-CS deficits occurred more often in combination with other deficits whilst RIT deficits were more frequently seen in isolation suggesting the possibility of distinct functional profiles within the structural classification of iAMD. For example, given delayed RIT in normal macular health is associated with development of incident AMD after 3 years,[49] those with RIT deficits may be at an earlier stage of progression than those who have accumulated multiple visual function deficits. It is also accepted that functional performance in iAMD varies with and without reticular pseudodrusen

448 (RPD)[34, 50-54]. As such, differing functional outcomes may be associated with distinct
449 structural phenotypes.
450
451 Given the functional impact of cataract, we were reassured phakic status was not
452 related to the number breached visual function limits. Age however was associated
453 with all visual function measures apart from RIT. If age deputises for disease
454 duration, functional heterogeneity may in part be explained by various stages of
455 progression within the baseline iAMD cohort, rather than visual deficits indicating
456 faster progression toward late disease. That said, 549/585 (94%) of the iAMD cohort
457 had bilateral iAMD, with the remainder having iAMD in the study eye and late AMD in
458 the fellow eye 46/585 (8%). With late AMD in the fellow eye associated with higher
459 rates of progression to late disease[55], symmetrical disease in the vast majority of
460 the iAMD population may reduce the likelihood that the heterogeneity observed is
461 the result of differing stages of progression. We acknowledge that chronological, not
462 biological age was adjusted for. It has been shown that those with a higher biological
463 than chronological age are at higher risk of poorer health outcomes, which may be
464 influencing the heterogeneity observed[56]. We will shortly investigate whether iAMD
465 associated with functional deficits increases the risk of progression to late AMD with
466 longitudinal MACUSTAR data. If so, this may go toward supporting the clinical
467 relevance of functional impairment in iAMD and its potential to be a treatment
468 indication in itself.
469
470 Functional heterogeneity may also have a substantial bearing on inclusion criteria for
471 future interventional trials. If criteria are based solely on structural classification, this
472 risks recruiting a cohort with an assorted or variable profile of visual function deficits.

If, as regulators prefer, visual function endpoints are employed, baseline variation within the assessed visual domain may obscure any potential intervention related signal.

There are further limitations in this work that should be considered. As described above, the calculation of references limits is based on a limited sample of 56 no AMD participants. Furthermore, the small size of the early (n = 34) and late AMD (n = 43) groups are also a limitation. The rationale for our sample sizes has been explained previously[18]. That visual function tests were not chosen based on AMD pathogenesis could be considered a limitation, however this was not customary at the time of study design. Rather as described in the methods section, clinical data informed test selection with an emphasis on tests that could potentially be adopted in multi center clinical trial settings.

We conclude that when multiple domains of visual function in normal aging are compared to early AMD and iAMD on population level, average differences across groups are not clinically meaningful, being considerably less than limits of agreement. However, population level change may obscure person level functional decline in iAMD. Using reference limits established in visually healthy peers, 69.6% of those with structurally defined iAMD have at least one functional deficit, more than two fold that expected by chance. 42.7% have at least two deficits, seven times greater than chance. Average differences between those with iAMD who display functional impairment and those with no AMD approximate clinically meaningful change across visual function assessments. This evidence of visual function heterogeneity in iAMD in our large, multi-center cohort may be relevant to the design and participant inclusion criteria of future intervention iAMD trials, especially those

aiming to halt or slow photoreceptor degeneration and loss. It remains to be seen whether people with iAMD who have specific visual function deficits are more likely to progress to late AMD, or whether these findings are a reflection of various stages of progression within the MACUSTAR iAMD cohort.

Tables titles, descriptions and footnotes

Table 1: Summary of demographic and visual function measures.

Summary of demographic and visual function measures segregated by Beckman disease classification.

*AMD: age-related macular degeneration; SD: standard deviation; Min: minimum; Max: maximum; LogMAR: logarithm of the minimum angle of resolution; LogCS: logarithm of contrast sensitivity; ~20/XX approximate Snellen equivalent; wpm: words per minute; IReST: International Reading Speed Test; dB: decibels. *30 participants without access to Danish language IReST included in missing data rate.*

Table 2: Relationship between visual function measures and disease classification

Linear regression model examining the relationship between each visual function measure (as dependent variable) and disease classification, adjusted for age, sex and phakic status.

AMD: age-related macular degeneration; i: intermediate; BCVA: best corrected visual acuity; LLVA: low luminance visual acuity; MAT: Moorfields acuity test; PR-CS: Pelli-Robson contrast sensitivity; SPS: Small print standardised International Reading Speed Test; MesAT: Mesopic average threshold; ScoAT: Scotopic average threshold; RIT: Rod Intercept Time; LogMAR: logarithm of the minimum angle of resolution; LogCS: logarithm of contrast sensitivity; wpm: words per minute; dB: decibel, mins: minutes. Bold indicates significant result.

Table 3: Summary of iAMD participants breaching visual function reference limits

Number and proportion iAMD participants breaching the reference limit for each visual function test calculated as a proportion of the complete iAMD cohort (585). Mean ± standard deviation of those breaching the reference limited (functionally impaired) and not breaching the reference limit (function not impaired) for each variable. No AMD data provided for comparison between iAMD function impaired and no AMD.

BCVA: best corrected visual acuity; LLVA: low luminance visual acuity; MAT: Moorfields acuity test; PR-CS: Pelli-Robson contrast sensitivity; SPS: Small Print Standardised International Reading Speed Test; MesAT: Mesopic average threshold; ScoAT: Scotopic average threshold; RIT: Rod Intercept Time; LogMAR: logarithm of the minimum angle of resolution; LogCS: logarithm of contrast sensitivity; wpm: words per minute; dB: decibel, mins: minutes.

Table 4: Summary of iAMD participants breaching 0 – 8 reference limits

Number and proportion of iAMD participants breaching 0 through 8 worse than reference limits.

AMD: age-related macular degeneration; i: intermediate.

Table 5: Summary of secondary reference limits and proportion of iAMD participants breaching secondary reference limits.

Number and proportion iAMD participants breaching secondary worse than reference limits for each visual function test calculated as a proportion of the complete iAMD cohort (585).

BCVA: best corrected visual acuity; LLVA: low luminance visual acuity; MAT: Moorfields acuity test; PR-CS: Pelli-Robson contrast sensitivity; SPS: Small Print Standardised International Reading Speed Test; MesAT: Mesopic average threshold; ScoAT: Scotopic average threshold; RIT: Rod Intercept Time; LogMAR: logarithm of the minimum angle of resolution; LogCS: logarithm of contrast sensitivity; wpm: words per minute; dB: decibel, mins: minutes.

Table 6: Summary of iAMD participants breaching 0 – 8 secondary reference limits

Number and proportion iAMD participants breaching 0 through 8 secondary worse than reference limits.

AMD: age-related macular degeneration; i: intermediate.

Figures Legends

Figure 1: Distribution of the visual function measures by disease classification.

Red dashed line indicates reference limit for each test based on no AMD data. AMD: age-related macular degeneration; i: intermediate; BCVA: best corrected visual acuity; LLVA: low luminance visual acuity; MAT: Moorfields acuity test; PR-CS: Pelli-Robson contrast sensitivity; SPS: Small print standardised International Reading Speed Test; MesAT: Mesopic average threshold; ScoAT: Scotopic average threshold; RIT: Rod Intercept Time; LogMAR: logarithm of the minimum angle of resolution; LogCS: logarithm of contrast sensitivity; wpm: words per minute; dB: decibel, mins: minutes.

Figure 2: **Upset plot describing number and extent of reference limits breached in participants with iAMD.**

Horizontal black bars indicate the set size or number of iAMD participants who breached the reference limit for each visual function (VF) test shown by the adjacent

label. Vertical black bars indicate the intersection size or number of iAMD participants who breached the reference limit of the visual function test(s) indicated by the filled black circles beneath. For example, the left most vertical black bar indicates that 59 iAMD participants breached the RIT reference limit only, whilst the right most vertical black bar indicates that 4 iAMD participants breached the reference limit on all 8 visual function tests. BCVA: best corrected visual acuity; LLVA: low luminance visual acuity; MAT: Moorfields acuity test; PR-CS: Pelli-Robson contrast sensitivity; SPS: Small Print Standardised International Reading Speed Test; MesAT: Mesopic average threshold; ScoAT: Scotopic average threshold; RIT: Rod Intercept Time.

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		No AMD (n = 56)	Early AMD (n = 34)	Intermediate AMD (n = 585)	Late AMD (n = 43)
Age, years	Mean (SD)	68 (6)	72 (6)	72 (7)	75 (6)
	Median [Min, Max]	68 [55, 88]	72 [57, 82]	72 [55, 88]	75 [64, 84]
Sex	Female	33 (58.9%)	27 (79.4%)	389 (67%)	21 (48.8%)
	Male	23 (41.1%)	7 (20.6%)	196 (33%)	22 (51.2%)
Best Corrected Visual Acuity (BCVA), LogMAR	Mean (SD)	-0.04 (~20/20) (0.08)	0.01 (~20/20) (0.08)	0.03 (~20/20) (0.10)	0.77 (~20/125) (0.25)
	Median [Min, Max]	-0.06 (~20/16) [-0.24,0.14]	0.02 (~20/20) [-0.18, 0.20]	0.02 (~20/20) [-0.24, 0.28]	0.84 (~20/125) [0.20,1.24]
	Missing	0	0	1 (0.2%)	0
Low Luminance Visual Acuity (LLVA), LogMAR	Mean (SD)	0.14 (~20/25) (0.09)	0.19 (~20/32) (0.14)	0.24 (~20/32) (0.16)	0.95 (~20/200) (0.24)
	Median [Min, Max]	0.13 (~20/25) [-0.02, 0.38]	0.17 (~20/32) [-0.04, 0.50]	0.22 (~20/32) [-0.14, 1.08]	0.96 (~20/200) [0.52, 1.52]
	Missing	0	0	2 (0.3%)	0
Moorfields Acuity Test (MAT), LogMAR	Mean (SD)	0.36 (~20/50) (0.11)	0.42 (~20/50) (0.12)	0.44 (~20/50) (0.16)	1.03 (~20/200) (0.20)
	Median [Min, Max]	0.35 (~20/50) [0.16, 0.62]	0.41 (~20/50) [0.20, 0.72]	0.42 (~20/50) [-0.10, 1.10]	1.00 (~20/200) [0.66, 1.48]
	Missing	0	0	1 (0.2%)	0
Pelli Robson Contrast Sensitivity (PR-CS), LogCS	Mean (SD)	1.71 (0.16)	1.63 (0.16)	1.55 (0.18)	1.07 (0.34)
	Median [Min, Max]	1.75 [1.05, 1.95]	1.65 [1.25, 1.90]	1.55 [0.75, 1.95]	1.15 [0.20, 1.55]
	Missing	0	0	2 (0.3%)	0
Small Print Standardsed (SPS) IReST, wpm	Mean (SD)	156 (38)	123 (44)	144 (40)	25(36)
	Median [Min, Max]	154 [77, 293]	129 [51, 215]	147 [0, 285]	1 [0, 132]
	Missing*	1 (1.8%)	0 (0%)	37 (6.3%)	4 (9.3%)
Mesopic Average Threshold (MesAT), dB	Mean (SD)	25.4 (2.06)	23.9 (2.61)	23.3 (3.65)	7.92 (6.85)
	Median [Min, Max]	25.6 [19.4, 29.2]	24.6 [17.1, 27.6]	24.2 [0.50, 29.4]	7.20 [0, 21.1]
	Missing	2 (3.6%)	0 (0%)	58 (9.9%)	6 (14.0%)
Scotopic Average Threshold (ScoAT), dB	Mean (SD)	21.30 (2.44)	19.60 (3.27)	18.70 (3.78)	6.0 (6.0)
	Median [Min, Max]	21.5 [16.1, 29.2]	20.3 [12.4, 24.2]	19.6 [0.20, 25.6]	3.20 [0, 20.6]
	Missing	3 (5.4%)	0 (0%)	89 (15.2%)	14 (32.6%)
Rod Intercept Time, (RIT) at 12° inferiorly, minutes	Mean (SD)	4.24 (1.36)	6.15 (4.81)	7.21 (5.07)	13.4 (11.8)
	Median [Min, Max]	4.20 [1.58, 9.02]	5.21 [2.68, 30.0]	5.62 [1.59, 30.0]	7.25 [1.87, 30.0]
	Missing	13 [23.2%]	5 (14.7%)	177 (30.3%)	27 (62.8%)

Table 1: Summary of demographic and visual function measures.

Summary of demographic and visual function measures segregated by Beckman disease classification.

*AMD: age-related macular degeneration; SD: standard deviation; Min: minimum; Max: maximum; LogMAR: logarithm of the minimum angle of resolution; LogCS: logarithm of contrast sensitivity; ~20/XX approximate Snellen equivalent; wpm: words per minute; IReST: International Reading Speed Test; dB: decibels. *30 participants without access to Danish language IReST included in missing data rate.*

Visual function measure	No AMD versus Early AMD		No AMD versus iAMD		No AMD versus Late AMD	
	Estimate (CI)	*Adjusted p value*	*Estimate (CI)*	*Adjusted p value*	*Estimate (CI)*	*Adjusted p value*
BCVA (LogMAR)	0.04 (-0.10, 0.08)	0.22	**0.05 (0.02, 0.09)**	**0.0017**	**0.79 (0.74, 0.83)**	**<0.0001**
	No AMD n = 56 Early AMD n = 34		No AMD n = 56 i AMD n = 584		No AMD n = 56 Late AMD n = 43	
LLVA (LogMAR)	0.03 (-0.03, 0.09)	0.47	**0.08 (0.04, 0.12)**	**0.0004**	**0.77 (0.71, 0.83)**	**<0.0001**
	No AMD n = 56 Early AMD n = 34		No AMD n = 56 i AMD n = 583		No AMD n = 56 Late AMD n = 43	
MAT (LogMAR)	0.03 (-0.03, 0.09)	0.47	**0.06 (0.01, 0.10)**	**0.02**	**0.63 (0.57, 0.69)**	**<0.0001**
	No AMD n = 56 Early AMD n = 34		No AMD n = 56 i AMD n = 584		No AMD n = 56 Late AMD n = 43	
PR-CS (LogCS)	-0.06 (-0.14, 0.02)	0.21	**-0.14 (-0.19, -0.08)**	**<0.0001**	**-0.59 (-0.67, -0.52)**	**<0.0001**
	No AMD n = 56 Early AMD n = 34		No AMD n = 56 i AMD n = 583		No AMD n = 56 Late AMD n = 43	
SPS (wpm)	**-31 (-48, -14)**	**0.001**	-10 (-21, 2)	0.17	**-125 (-141, -109)**	**<0.0001**
	No AMD n = 55 Early AMD n = 34		No AMD n = 55 i AMD n = 548		No AMD n = 55 Late AMD n = 39	
MesAT (dB)	-1.13 (-2.72, 0.46)	0.27	**-1.69 (-2.73, -0.65)**	**0.004**	**-16.61 (-18.17, -15.05)**	**<0.0001**
	No AMD n = 54 Early AMD n = 34		No AMD n = 54 i AMD n = 527		No AMD n = 54 Late AMD n = 37	
ScoAT (dB)	-1.41 (-3.04, 0.22)	0.17	**-2.29 (-3.37, -1.21)**	**0.0001**	**-14.56 (-16.27, -12.84)**	**<0.0001**
	No AMD n = 53 Early AMD n = 34		No AMD n = 53 i AMD n = 496		No AMD n = 53 Late AMD n = 29	
RIT (mins)	1.41 (-1.00, 3.82)	0.37	**2.35 (0.72, 3.98)**	**0.01**	**8.32 (5.36, 11.28)**	**<0.0001**
	No AMD n = 43 Early AMD n = 29		No AMD n = 43 i AMD n = 408		No AMD n = 43 Late AMD n = 16	

Table 2: Relationship between visual function measures and disease classification

Linear regression model examining the relationship between each visual function measure (as dependent variable) and disease classification, adjusted for age, sex and phakic status.

AMD: age-related macular degeneration; i: intermediate; BCVA: best corrected visual acuity; LLVA: low luminance visual acuity; MAT: Moorfields acuity test; PR-CS: Pelli-Robson contrast sensitivity; SPS: Small print standardised International Reading Speed Test; MesAT: Mesopic average threshold; ScoAT: Scotopic average threshold; RIT: Rod Intercept Time; LogMAR: logarithm of the minimum angle of resolution; LogCS: logarithm of contrast sensitivity; wpm: words per minute; dB: decibel, mins: minutes. Bold indicates significant result.

Visual function measure	Reference limit	n (%) of iAMD participants breaching reference limit	iAMD (mean ± SD)		No AMD (mean ± SD)	Δ |iAMD (function impaired – no AMD)
			Function impaired	Function not impaired		
BCVA (LogMAR)	> 0.10	120 (20.5%)	0.18 (0.05)	-0.01 (0.08)	-0.04 (0.08)	0.22 (11 letters)
LLVA (LogMAR)	> 0.32	141 (24.1%)	0.46 (0.12)	0.18 (0.09)	0.14 (0.09)	0.32 (16 letters)
MAT (LogMAR)	> 0.55	136 (23.2%)	0.65 (0.09)	0.38 (0.12)	0.36 (0.11)	0.29 (14.5 letters)
PR-CS (LogCS)	< 1.49	183 (31.3%)	1.36 (0.12)	1.64 (0.12)	1.71 (0.16)	-0.35 (7 letters)
SPS (wpm)	< 100	74 (12.6%)	74 (23)	155 (29)	156 (38)	-82
MesAT (dB)	< 21.7	116 (19.8%)	18.2 (4.2)	24.8 (1.6)	25.4 (2.1)	-7.2
ScoAT (dB)	< 17.0	105 (17.9%)	12.9 (3.7)	20.3 (1.7)	21.3 (2.4)	-8.4
RIT (mins)	> 6.21	172 (29.4%)	12.10 (11.6)	4.39 (1.07)	4.24 (1.36)	-7.86

Table 3: Summary of iAMD participants breaching visual function reference limits

Number and proportion iAMD participants breaching the reference limit for each visual function test calculated as a proportion of the complete iAMD cohort (585). Mean ± standard deviation of those breaching the reference limited (functionally impaired) and not breaching the reference limit (function not impaired) for each variable. No AMD data provided for comparison between iAMD function impaired and no AMD.

BCVA: best corrected visual acuity; LLVA: low luminance visual acuity; MAT: Moorfields acuity test; PR-CS: Pelli-Robson contrast sensitivity; SPS: Small Print Standardised International Reading Speed Test; MesAT: Mesopic average threshold; ScoAT: Scotopic average threshold; RIT: Rod Intercept Time; LogMAR: logarithm of the minimum angle of resolution; LogCS: logarithm of contrast sensitivity; wpm: words per minute; dB: decibel, mins: minutes.

Number of reference limits breached	iAMD n (%)
0	178 (30.4%)
1	157 (26.8%)
2	92 (15.7%)
3	51 (8.7%)
4	37 (6.3%)
5	35 (6.0.%)
6	19 (3.2%)
7	12 (2.1%)
8	4 (0.7%)

Table 4: Summary of iAMD participants breaching 0 – 8 reference limits

Number and proportion of iAMD participants breaching 0 through 8 worse than reference limits.

AMD: age-related macular degeneration; i: intermediate.

Visual function measure	n (%) with valid data	Reference Limit based on worse of V2 and V3	n (%) of iAMD participants breaching worse reference limit
BCVA	584 (99.8%)	> 0.11 LogMAR	120 (20.5%)
LLVA	583 (99.6%)	> 0.32 LogMAR	141 (24.1%)
MAT	584 (99.8%)	> 0.58 LogMAR	136 (23.2%)
PR-CS	583 (99.6%)	< 1.45 LogCS	183 (31.3%)
SPS	548 (93.7%)	< 97 wpm	74 (12.6%)
MesAT	527 (90.1%)	< 20.7 dB	116 (19.8%)
ScoAT	496 (84.8%)	< 16.2 dB	105 (17.9%)
RIT	408 (69.7%)	> 6.48 mins	172 (29.4%)

Table 5: Summary of secondary reference limits and proportion of iAMD participants breaching.

Number and proportion iAMD participants breaching secondary worse than reference limits for each visual function test calculated as a proportion of the complete iAMD cohort (585).

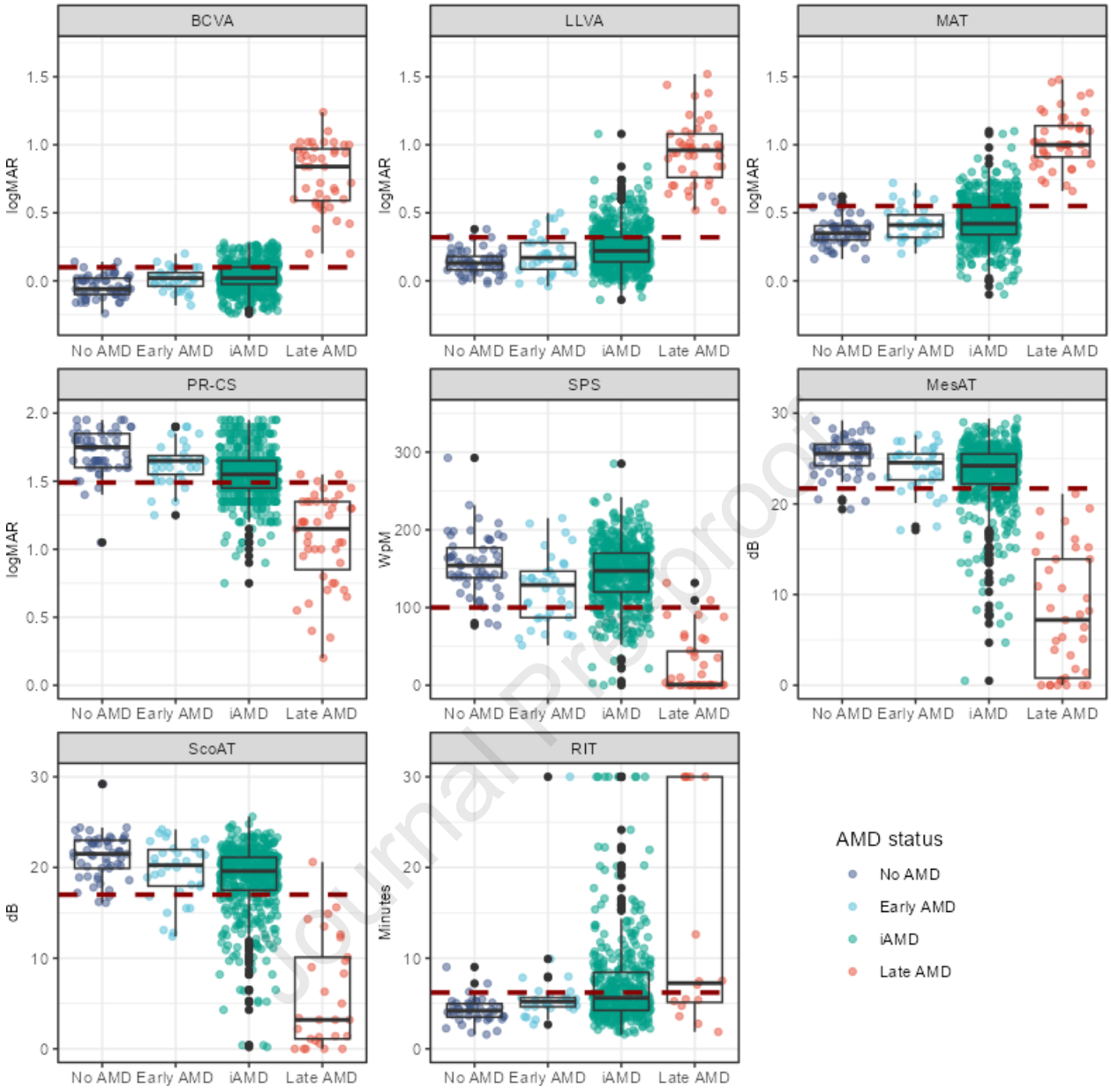
BCVA: best corrected visual acuity; LLVA: low luminance visual acuity; MAT: Moorfields acuity test; PR-CS: Pelli-Robson contrast sensitivity; SPS: Small Print Standardised International Reading Speed Test; MesAT: Mesopic average threshold; ScoAT: Scotopic average threshold; RIT: Rod Intercept Time; LogMAR: logarithm of the minimum angle of resolution; LogCS: logarithm of contrast sensitivity; wpm: words per minute; dB: decibel, mins: minutes.

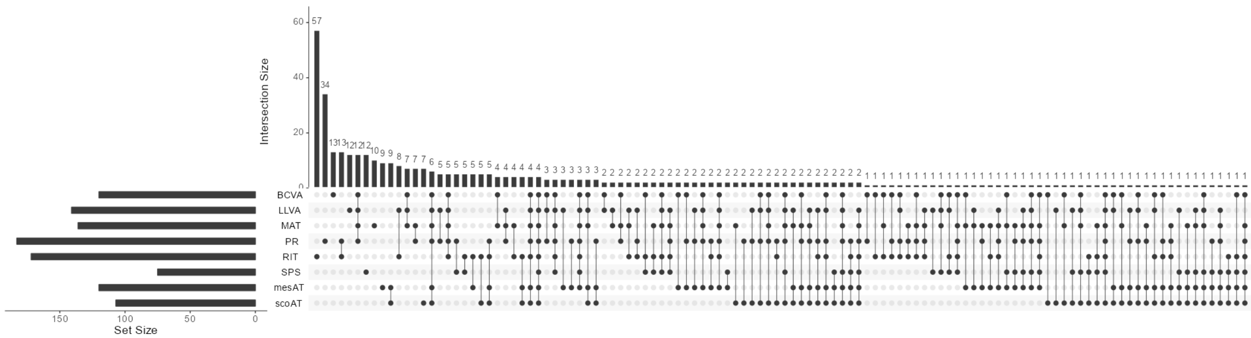
Number of reference limits breached	iAMD n (%)
0	225 (38.5%)
1	151 (25.8%)
2	84 (14.4%)
3	44 (7.5%)
4	31 (5.3%)
5	27 (4.6%)
6	11 (1.8%)
7	10 (1.7%)
8	2 (0.3%)

Table 6: Summary of iAMD participants breaching 0 – 8 secondary reference limits

Number and proportion iAMD participants breaching 0 through 8 secondary worse than reference limits.

AMD: age-related macular degeneration; i: intermediate.





Précis

In the MACUSTAR study, multiple tests of clinical visual function reveal functional heterogeneity in intermediate age-related macular degeneration which is relevant to future trial design.

Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Hannah Dunbar reports financial support was provided by Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 116076. Hannah Dunbar reports a relationship with Boehringer Ingelheim GmbH that includes: consulting or advisory. Hannah Dunbar reports a relationship with Apellis Pharmaceuticals, Inc that includes: travel reimbursement. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.