# ProAMD

## Patient reported outcome documented by A Metamorphopsia Detector

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## Purpose

*AMD – A Metamorphopsia Detector* (patent pending)[1] is the first computer–based interactive tool to detect, quantitatively measure, document, compare and control the degree, localization and area of metamorphopsias[2]. Quantification of metamorphopsias[2,13] using the Metamorphopsia Detector provides documentation of a patient reported outcome[3] and is a tool to evaluate burden of disease[11], quality of life[1,10] and monitor patients with the aim to improve diagnostic compliance[12], enhance therapy adherence[9], reduce therapy drop-outs[14] and support disease management programs.

This study investigates the correlation of *AMD – A Metamorphopsia Detector's* Metamorphopsia index with central retinal thickness and examines the test's sensitivity and specificity for anatomical or for clinically relevant findings respectively in eyes with and without macular diseases.

## Material and Methods

*AMD – A Metamorphopsia Detector*, central retinal thickness (CRT; SD-OCT)[4], best-corrected visual acuity (BCVA) and dilated fundus examination were recorded in 375 eyes of 375 patients (169 male, 206 female, age 36-94 years). Metamorphopsia index is calculated by the program: monocularly perceived distorted lines are straightened on a screen by using a mouse (adequate near correction). Metamorphopsia sum index consists of 3 indices representing degree (v), localization (ex) and area (a). In monocular disease the pathological eye was included. In binocular normal or pathological cases the included eye was randomly chosen[5]. Diagnoses were classified based on a diversified Beckman classification[6] (Fig.1). Prior to the study all patients signed informed consent (declaration of Helsinki/Edinburgh resp.)[7].

Correlation[8] of Metamorphopsia sum index and central retinal thickness were explored, sensitivity and specificity of *AMD – A Metamorphopsia Detector* was examined regarding two perspectives: clinical relevance, i.e. therapeutic consequences (recommendation for further diagnostic, intensified control or for therapy (laser or operation)) and morphology, i.e. SD-OCT- confirmed anatomical findings respectively.

| No.# | Diagnosis | N | Beckman class. [6] |
|---|---|---|---|
| 1 | AMD with pre(existing) edema = advanced AMD | 29 | 1 |
| 2 | No AMD, AREDS 1 or 2, small or intermediate drusen, mild RPE abnormalities | 21 | 2 |
| 3 | Numerous drusen, intermediate AMD, geographic atrophy | 40 | 3 |
| 4 | Advanced AMD: Geographic atrophy of the RPE involving the foveal center | 16 | 4 |
| 5 | Epiretinale membrane | 48 | 5 |
| 6 | Macular hole | 2 | 6 |
| 7 | DME = (former) diabetic macular edema | 9 | 7 |
| 8 | Myopic macula edema (former) | 4 | 8 |
| 9 | Uveitic macular edema (former) | 3 | 9 |
| 10 | Normal macula | 143 | 10 |
| 11 | Disciform scar (subretinal fibrosis) = advanced AMD | 11 | 11 |
| 12 | Isolated serous and/or hemorrhagic RPE-/retinal detachment = advanced AMD | 7 | 12 |
| 13 | Scar + active choroidal neovascularization | 0 | 13 |
| 14 | Central serous retinopathy (former) | 4 | 14 |
| 15 | Macular edema due to (central) venous thrombosis (former) | 6 | 15 |
| 16 | VMT = vitreomacular traction | 13 | 16 |
| 17 | RPE – detachment + subretinal foveal scar | 2 | 17 |
| 18 | Non proliferative diabetic retinopathy NPDRP without DME | 4 | 18 |
| 19 | Macular edema due to Irvine Gass Syndrome | 1 | 19 |
| 20 | AMD without edema (= after therapy) | 6 | 20 |
| 21 | AMD with atrophy/scar, no intraretinal fluid (after therapy) | 6 | 21 |

Fig. 1: Diagnoses

## Results

### I. Correlation AMD-Index and CRT

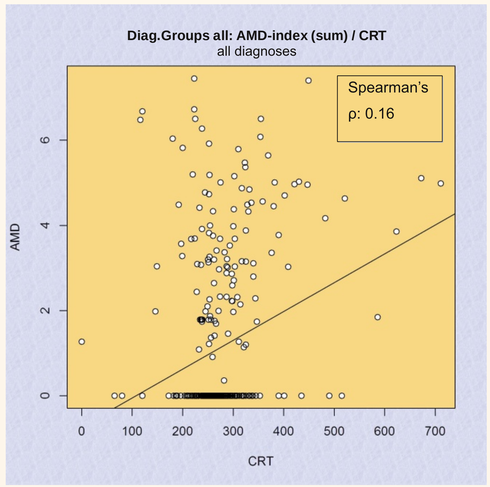
Metamorphopsia sum index and CRT showed

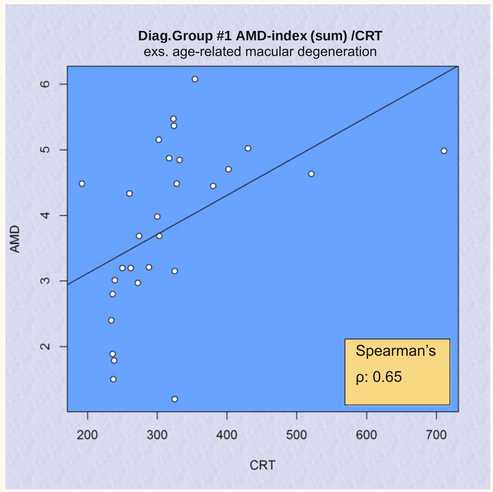
strong correlation:
- age-related macular degeneration with edema:
  #1: Spearman's ρ: 0.65, p: 0.0002
- diabetic macular edema:
  #7: Spearman's ρ: 0.85, p: 0.004
- edema due to myopia, uveitis, venous thrombosis, Irvine Gass:
  #8, 9, 15, 19: Spearman's ρ: 0.73, p: 0.003

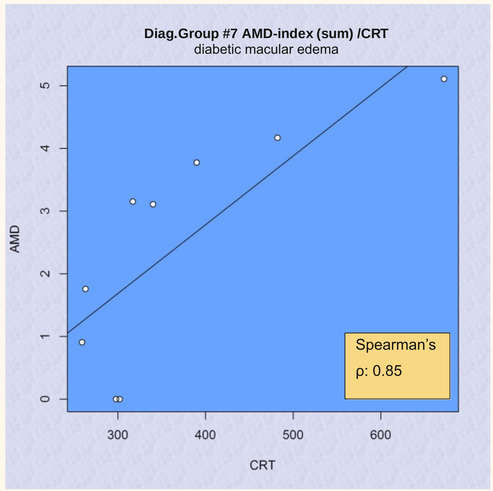
weak correlation:
- numerous drusen, intermediate, geographic:
  #3, Spearman's ρ: 0.35, p: 0.03
- RPE-detachment and RCS:
  #12,14, Spearman's ρ: 0.11, p: 0.75

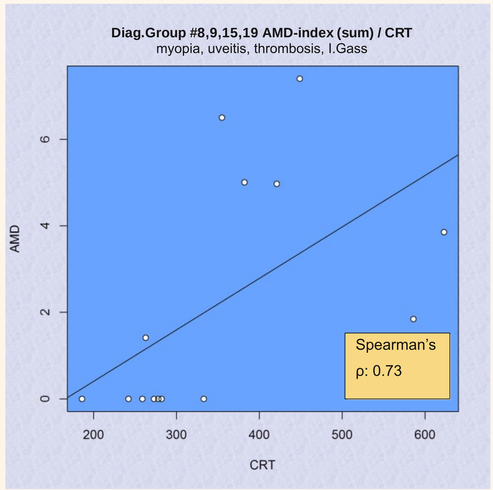
no correlation:
#10, Spearman's ρ: -0.054, p: 0.51
#2, 18, 20: Spearman's ρ: 0.0
#5, 16: Spearman's ρ: -0.013, p: 0.92

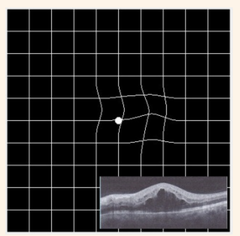
negative correlation:
#4, 6, 11, 17, 21: av. scotoma index: 21.33
Spearman's ρ: -0.1, p: 0.54

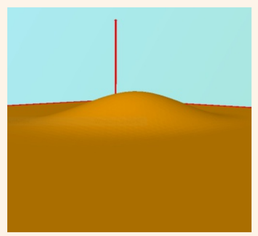




### Literature

1. Claessens, D., Krüger, R., AMD-A Metamorphopsia Detector. ARVO Association for Research and Vision in Ophthalmology, 2015.
2. Simunovic, M.P., Metamorphopsia and Its Quantification. Retina, 2015. 35(7): p. 1285-91.
3. AAO Retina/Vitreous PPP Panel, H.C.f.Q.E.C., Age-Related Macular Degeneration PPP - Updated 2015. 2015.
4. Jacobsen, A.G., et al., Normal Value Ranges for Central Retinal Thickness Asymmetry in Healthy Caucasian Adults Measured by SPECTRALIS SD-OCT. Invest Ophthalmol Vis Sci, 2015. 56(6): p. 3875-82.
5. Lee, C.F., A.C. Cheng, and D.Y. Fong, Eyes or subjects: are ophthalmic randomized controlled trials properly designed and analyzed ? Ophthalmology, 2012. 119(4): p. 869-72.
6. Ferris FL 3rd1, W.C., Bird A. et.al., Clinical classification of age-related macular degeneration. Ophthalmology, 2013: p. 844-51.
7. WMA, WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. 2013.
8. Held, U., Tücken von Korrelationen: die Korrelationskoeffizienten von Pearson und Spearman. Biostatistik, 2010. 10(38): p. 652-53.
9. Crossland, M. and G. Rubin, The Amsler chart: absence of evidence is not evidence of absence. Br J Ophthalmol, 2007. 91(3): p. 391-3.
10. Claessens, D., Gegenüberstellung von sehkraftbezogener Lebensqualität und Visusverlauf nach intravitrealer Anti-VEGF Therapie bei altersbedingter feuchter Makuladegeneration 2010.
11. Claessens, D., Comparison Of Self-reported Distance- And Near-vision Related Quality Of Life With Best Corrected Visual Acuity Outcome After Intravitreal Anti-VEGF Therapy For Age Related Macular Degeneration. IOVS Investigative Ophthalmology & Visual Science March 2012.
12. Sandhu, S.S. and S.J. Talks, Correlation of optical coherence tomography, with or without additional colour fundus photography, with stereo fundus fluorescein angiography in diagnosing choroidal neovascular membranes. Br J Ophthalmol, 2005. 89(8): p. 967-70.
13. Midena, E. and S. Vujosevic, Metamorphopsia: An Overlooked Visual Symptom. Ophthalmic Res, 2015. 55(1): p. 26-36.
14. Holz, F.G., et al., Multi-country real-life experience of anti-vascular endothelial growth factor therapy for wet age-related macular degeneration. Br J Ophthalmol, 2014.
15. Amsler, M., Die Untersuchung des qualitativen Sehens mit dem quadratischen Netz. Anweisung zum Gebrauch der Testtafeln. Theodore Hamblin LTD, 1958.
16. Hernandez-Martinez, C., et al., Detection of diabetic macular oedema: validation of optical coherence tomography using both foveal thickness and intraretinal fluid. PeerJ, 2015. 3: p. e1394.

### II. Sensitivity and Specificity

#### Perspective of clinical relevance

Regarding therapeutic recommendation for further diagnostic or for therapy *AMD – A Metamorphopsia Detector* had a
sensitivity of 94.12% and a
specificity of 97.27%.
Of all 375 eyes, 96.26% were correctly classified by *AMD – A Metamorphopsia Detector* (112 correct positive, 249 correct negative, Cohen's Kappa 0.92).
False negative test rate of AMD-index was 2.73%. All of these 7 eyes had diagnosis #3 (AREDS 3).

#### Perspective of morphology

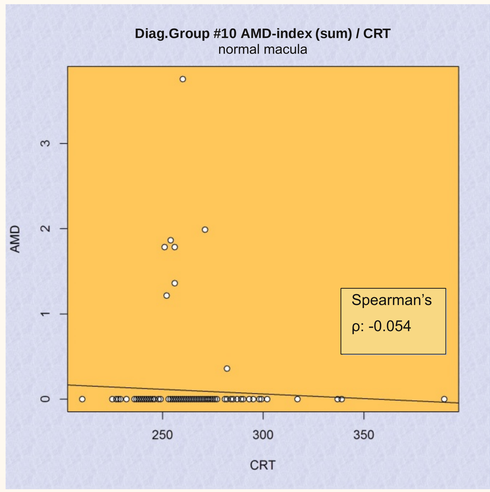
Sensitivity of *AMD – A Metamorphopsia Detector* for OCT-confirmed anatomical findings regardless of clinical relevance was 54.59 %, specificity was 95.83%.
Of all 375 eyes, 274 (73.07%) were correctly classified by *AMD – A Metamorphopsia Detector* (Cohen's Kappa 0.5).

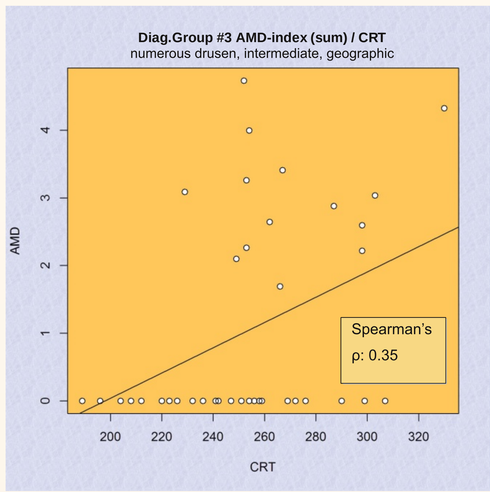
## Discussion

The gap between clinical (sensitivity 94.12%) and anatomical detection rate (54.59 %) illustrates that a not-ideal OCT does not necessarily lead to clinical consequences: #2 (AREDS I): 22%, #3 (intermediate): 29%, #5 (vitreomacular adhesion): 27%. False negative AMD-index with clinical perspective can partially be explained by perceptual completion ("filling in")[9]: 7 of 259 cases (2.73%), all #3 (AREDS 3) pointing out the importance of close-meshed controls in intermediate AMD. In groups #8, 9, 15, 19 and #4, 6, 11, 17, 21 metamorphopsias were no longer observable in case of central scotoma. This lead to a negative correlation index.
Contrary to qualitative tests with attribute data *AMD – A Metamorphopsia Detector* provides variable, operationalizable data, reflects visual impression precisely and can be implemented in multimodal diagnostic and case management systems of chronic diseases like diabetes or age related macular degeneration. In scenarios without fix treatment schedules (pro re nata) and after treatment cycles are terminated *AMD - A Metamorphopsia Detector* may play a role as an easy to use, cost-effective, interactive device with high sensitivity and specificity for clinically relevant findings that can be used as a clinical or home based test.

### Limitations, Confounding, Bias

Randomized selection of the eye reduced confounding. Patient's experience with a computer mouse may lead to performance and selection bias. Therapeutical recommendation by different clinics reduced classification bias. Not-blinded or false OCT evaluation might imply observer bias, lacking information from FAG detection and information bias[16].




## Conclusion

*AMD – A Metamorphopsia Detector* as an easy to use, cost-effective clinical or home based interactive device delivers variable data reflecting a patient reported outcome with high clinical sensitivity and specificity and good correlation of AMD-Index and CRT in exsudative AMD, DME and edema due to myopia, uveitis and thrombosis. *AMD – A Metamorphopsia Detector* has the potential – especially when implemented in screening programs, multimodal diagnostic and case management systems - to improve self efficiency, diagnostic and therapeutic compliance, adherence, effectiveness and quality in the monitoring and treatment of macular diseases.

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