Clinical Trial Endpoints for Macular Diseases

Developed in collaboration

Med-IQ DukeHealth

Learning Objective

Upon completion, participants should be able to:

- Summarize types of biomarkers of progression and treatment response in macular diseases, with an emphasis on functional endpoints in dry age-related macular degeneration

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Biomarkers of Progression and Treatment Response in Dry AMD

- Functional
- Structural (imaging)
- Blood (genetics, flow cytometry)

Lambert NG, et al. *Prog Retin Eye Res*. 2016;54:64-102; Gemenetzi M, et al. *Eye (Lond)*. 2016;30:1-14.

Visual Function Biomarkers in Early-Intermediate Dry AMD for Use as Clinical Trial Endpoints

Vision Impairment in Dry AMD—More Than BCVA

Normal

Late AMD

- Patients with late AMD (NVAMD or foveal-involving GA) often lose central BCVA
- Patients with intermediate AMD with HRD also experience visual function deficits
- In HRD, BCVA may be normal, but other measures of visual function (low luminance visual acuity, dark adaptation, MP, and color vision) are often significantly impaired

Images courtesy of Dr. Lad.
Personal communication, Dr. Lad; Scilley K, et al. *Ophthalmology*. 2002;109:1235-42.

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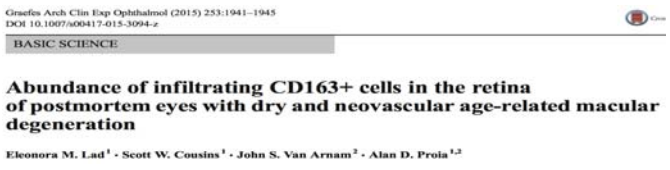
Retina Overlying HRD or GA Expresses Many CD163+ Cells in the Outer Retina

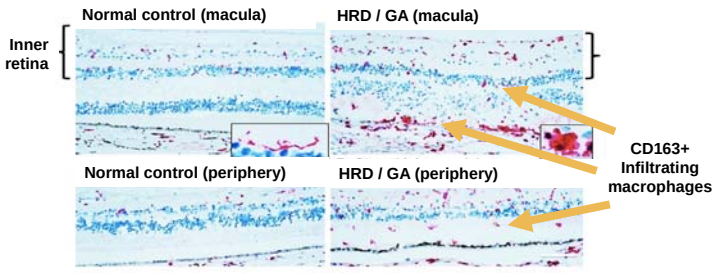


Graefes Arch Clin Exp Ophthalmol (2015) 253:1941–1945
DOI 10.1007/s00417-015-3094-z

BASIC SCIENCE

Abundance of infiltrating CD163+ cells in the retina of postmortem eyes with dry and neovascular age-related macular degeneration

Eleonora M. Lad[1] · Scott W. Cousins[1] · John S. Van Arnam[2] · Alan D. Proia[1,2]



Images courtesy of Dr. Lad (unpublished data).
Lad EM, et al. *Graefes Arch Clin Exp Ophthalmol.* 2015;253:1941-5.

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Duke Natural History Study of Early AMD

- Arm 1: a pilot exploratory study
  - Evaluated 20 patients with dry AMD (AREDS stages 2 = early and 3 = intermediate/HRD) and 10 normal age-matched controls
  - Objective: to examine 1) the feasibility of performing the visual function tests in this population and 2) test/retest reliability at 1 month (+/- 30 days)
- Arm 2: longitudinal observational natural history study
  - Evaluated 101 patients
  - Objective: to evaluate changes in visual function in dry AMD over time
  - With 6-, 12-, 18-, and 24-month follow-up
  - Additional testing (dark adaptometry, MPOD, questionnaires, mobile tech, genetics)

Image courtesy of Dr. Lad.
Chandramohan A, et al. *Retina*. 2016;36:1021-31; Cocce K, et al. *Invest Ophthalmol Vis Sci*. 2017;58:3765.

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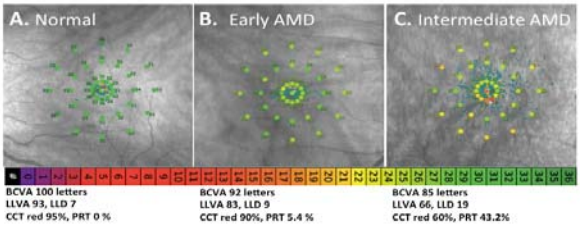
Arm 1: Conclusion of Pilot Natural History Study



- This study supports the feasibility of using LLVA, MAIA, MP, and CCT in subjects with early and intermediate dry AMD
- The intermediate AMD group exhibited visual dysfunction on LLVA, MP, and red CCT but not on computerized contrast sensitivity testing
- LLVA, MP, and CCT can be used as alternative clinical trial endpoints for future proof-of-concept studies in dry AMD

Images courtesy of Dr. Lad.
Chandramohan A, et al. *Retina*. 2016;36:1021-31.

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Arm 2: Data Collected

Baseline Visit

- Demographics
- Ocular, medical, and social history
- BCVA
- MAIA mesopic MP
- Dark adaptation (AdaptDx, MacuLogix)
- LLVA (standard and computerized)
- Cone Contrast Test
- Stereo color fundus photographs
- SD-OCT
- FAF and MPOD
- IR reflectance
- Quality of life questionnaire (NEI VFQ)
- LLQ
- Mobile Technology Arm (mVT)
- DNA blood sample for genetic testing

Follow-Up Visits

- Collected all listed data except blood sample

Cocce K, et al. *Invest Ophthalmol Vis Sci*. 2017;58:3765.

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Results: Demographics

- All groups were balanced for:
  - Age
  - Sex
  - Race/ethnicity
  - Smoking history
  - Past medical and past ocular history

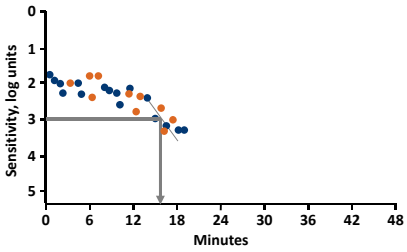
Hypertension
Diabetes
Myocardial infarction
Coronary artery disease
Dyslipidemia
Dementia

Glaucoma suspect
Fuchs' dystrophy
Dry eye

Cocce K, et al. *Invest Ophthalmol Vis Sci*. 2017;58:3765.

Summary of Key Findings of Arm 2 at Baseline

- Measures that differentiate AREDS3 from normal controls:
  - Standard LLVA
  - Computerized BCVA and LLVA2 (0.5 cd/m^2)
  - CCT red, green, and blue
  - MP average threshold and percent reduced threshold
  - Dark adaptation rod intercept
- Measures that differentiate AREDS3 from AREDS2:
  - Computerized LLD2
  - MP percent reduced threshold
  - Dark adaptation rod intercept

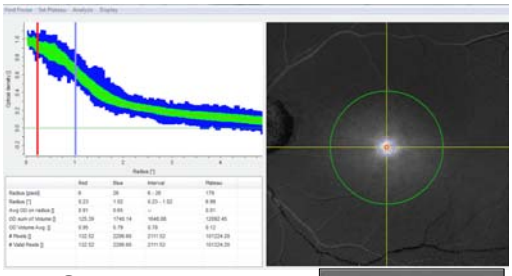


Cocce K, et al. *Invest Ophthalmol Vis Sci*. 2017;58:3765.

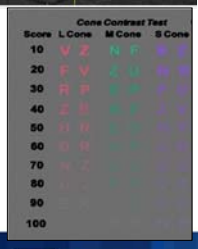
Summary of Key Findings of Arm 2

- Measures that differentiate AREDS2 from normal controls:
  - Computerized BCVA

    (MPOD: Observed no differences between groups with radii: 0.25°, 0.5°, 1°, 1.75°)
- Correlations:
  - Across CCT measures: red, blue, and green
  - Between CCT measures + LLVA2



MPOD



Courtesy of Dr. Lad (unpublished data); Cocce K, et al. *Invest Ophthalmol Vis Sci.* 2017;58:3765.

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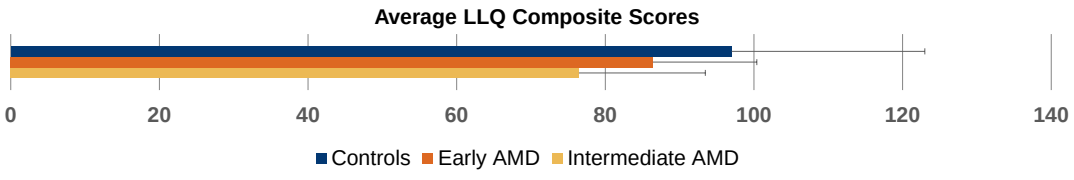
Association of LLQ With Functional Measures

- Participants with intermediate AMD had significantly lower LLQ composite scores than those with early AMD or controls ($P < .05$)



- LLQ composite scores were associated with computerized BCVA, standard LLVA, computerized LLVA1 and LLVA2, LLD2, rod intercept, and CCT green
- Only computerized LLVA1 and LLVA2 and LLD1 were statistically significant after adjusting for AMD versus control status
- Among participants with dry AMD, **LLQ composite scores were significantly associated with computerized LLVA1 and LLVA2, LLD1, and LLD2, but only computerized LLVA1 was independent of AMD severity**

Courtesy of Dr. Lad (unpublished data); Thompson AC, et al. *Invest Ophthalmol Vis Sci.* 2017;58:2334.

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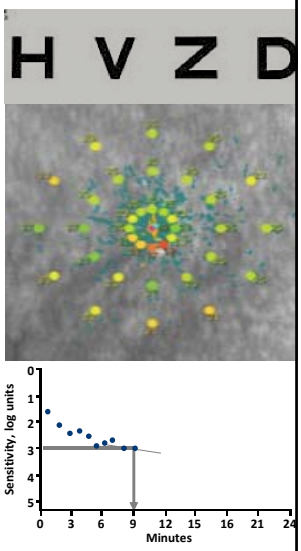
Conclusions of Duke Natural History Study of Early AMD

- Development of treatments for early-intermediate dry AMD before severe disease occurs is hampered by lack of clinical trial endpoints
- LLVA, MAIA MP, CCT, and dark adaptation may be used as reliable functional measures of disease progression for eyes with early and intermediate AMD
- Once fully characterized longitudinally, these visual function measures can serve as endpoints for future clinical trials on dry AMD
- LLQ is a robust, patient-centered functional measure of early visual impairment in dry AMD
- Future directions: In flow cytometry studies, high ratio of CD163+ to CD68+ monocytes in the blood will correlate with key clinical metrics of visual dysfunction (eg, dark adaptation, MP, LLVA) and structural markers of progression (RPD, hyperreflective foci)



Courtesy of Dr. Lad (unpublished data); Cocce K, et al. *Invest Ophthalmol Vis Sci*. 2017;58:3765.

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Correlation Between Structure and Function in Early-Intermediate AMD

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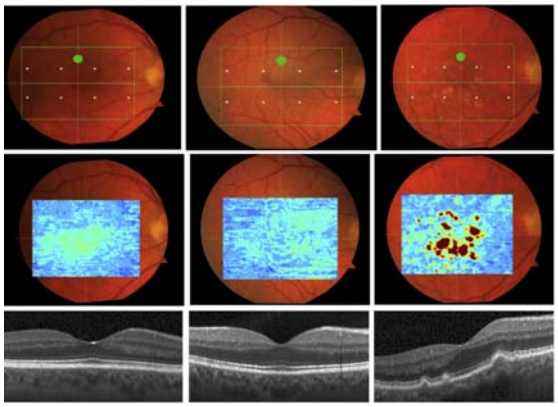
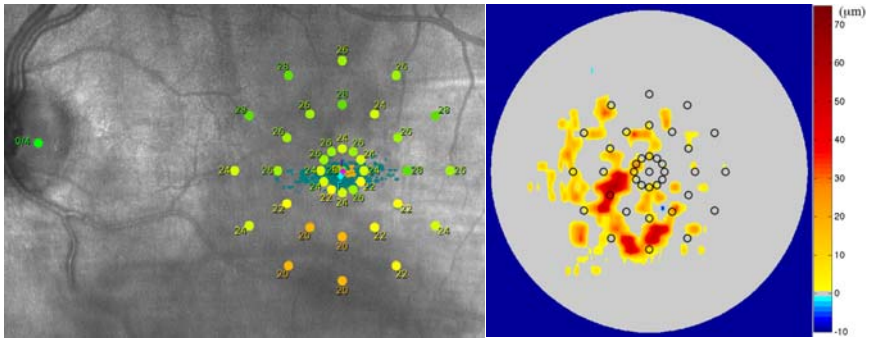
Correlation Between Structure (SD-OCT) and Function (Dark Adaptation and HVF)



- Worse cone-mediated sensitivity and slower dark adaptation were related to structural markers on SD-OCT (greater RPE abnormal thinning)

Courtesy of Dr. Lad (unpublished data); Sevilla MB, et al. *Am J Ophthalmol*. 2016;165:65-77.

AMD Genotype and Phenotype Study (NEI, Beckman Foundation): SD-OCT Volume vs MP



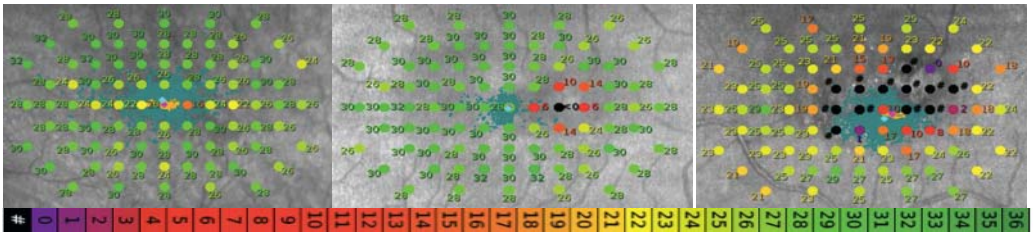
- Retinal sensitivities at individual MP loci inversely correlate with underlying SD-OCT drusen volume

Courtesy of Dr. Lad (unpublished data); Tai V, et al. *Invest Ophthalmol Vis Sci.* 2015;58:5154.

Correlation Between Structure and Function in Type 2 Idiopathic MacTel

Methods: Study Participants and Imaging

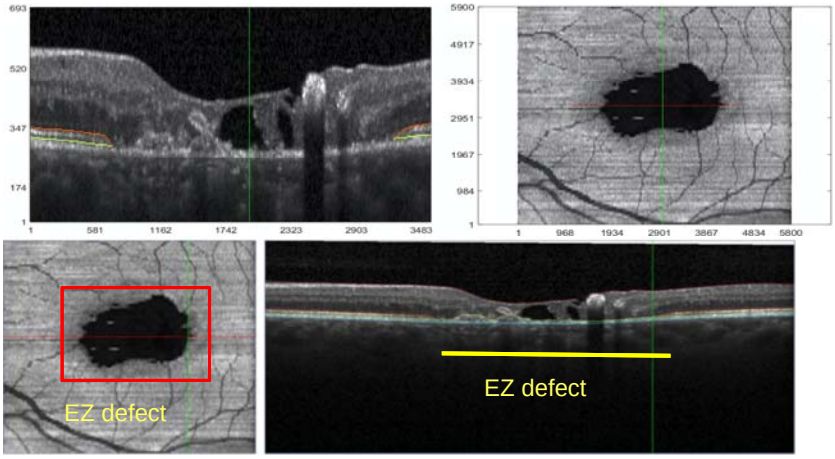
- MAIA-1 MP sensitivity maps were obtained during both **screening** and **baseline** visits in the international, multicenter, randomized, phase 2 trial of CNTF for type 2 MacTel (NTMT02)



- High-resolution SD-OCT volume scans (97 B-scans, 20 degree × 20 degree, resolution 1024 A-scans per B-scan, ART 9) were acquired at the **screening** visit using a Spectralis unit

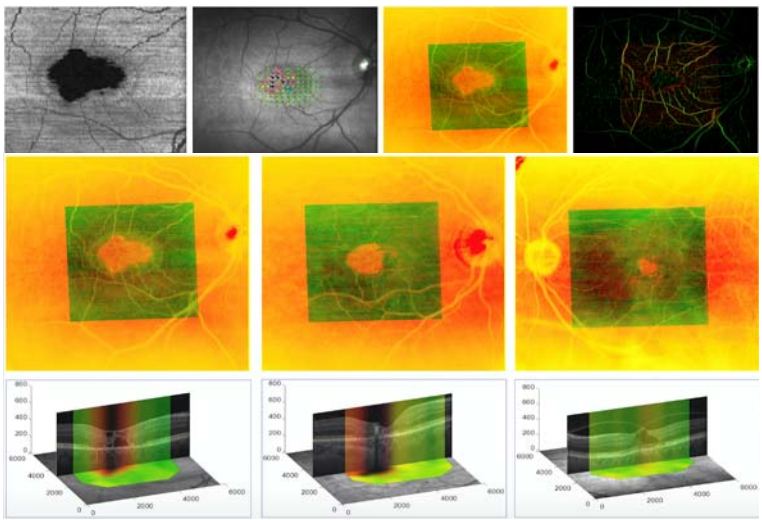
Courtesy of Dr. Lad (unpublished data); Mukherjee D, et al. *Invest Ophthalmol Vis Sci.* 2017;58:BIO291-9.

“En Face” OCT Image and Corresponding B-Scans



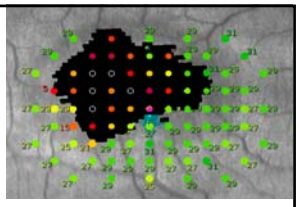
Courtesy of Dr. Lad (unpublished data); Mukherjee D, et al. *Invest Ophthalmol Vis Sci.* 2017;58:BIO291-9.

Examples of SD-OCT-MP Overlays

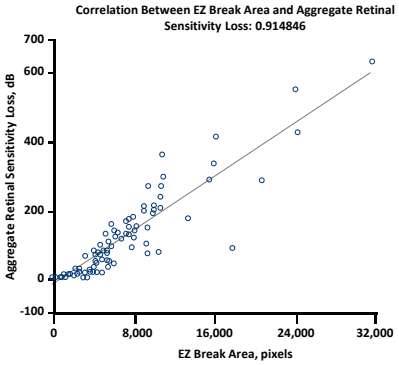


Courtesy of Dr. Lad (unpublished data); Mukherjee D, et al. *Invest Ophthalmol Vis Sci.* 2017;58:BIO291-9.

Conclusions



- A high positive correlation (Pearson correlation coefficient = 0.914 and 0.912 for screening and baseline, respectively) was found between aggregate sensitivity loss and EZ defect area
- Differences in retinal sensitivity loss between affected and unaffected areas were statistically significant
- This software allowed determination of functional and structural changes and demonstrates that functional loss on the MP may be a surrogate marker and early predictor of EZ loss on SD-OCT in type 2 MacTel



Courtesy of Dr. Lad (unpublished data); Mukherjee D, et al. *Invest Ophthalmol Vis Sci.* 2017;58:BIO291-9.

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Abbreviations and Acronyms: Clinical Trial Endpoints for Macular Diseases

AMD = age-related macular degeneration
AREDS = Age-Related Eye Disease Study
ART = automatic real tracking
BCVA = best-corrected visual acuity
CCT = cone-specific contrast
CNTF = ciliary neurotrophic factor
EZ = ellipsoid zone
FAF = fundus autofluorescence
GA = geographic atrophy
HRD = high-risk drusen
HVF = Humphrey visual field
IR = infrared
LLD = low-luminance deficit
LLQ = Low Luminance Questionnaire
LLVA = low-luminance visual acuity
MacTel = macular telangiectasia
MAIA = macular analyzer integrity assessment
MP = microperimetry
MPOD = macular pigment optical density
NEI VFQ = National Eye Institute Visual Function Questionnaire
NVAMD = neovascular age-related macular degeneration
RPD = reticular pseudodrusen
RPE = retinal pigment epithelium
SD-OCT = spectral-domain optical coherence tomography