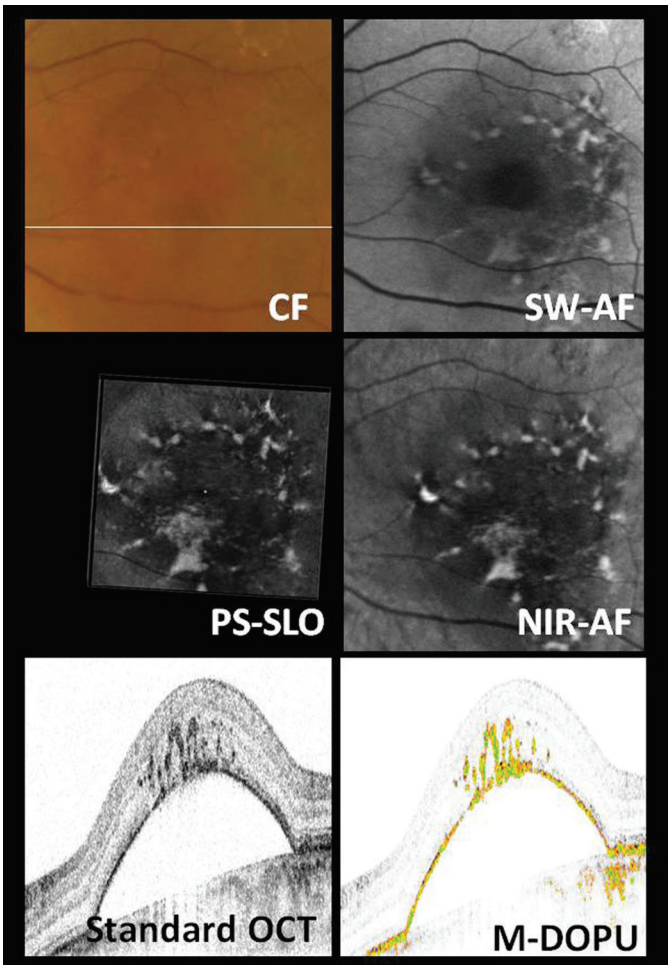
362 AMD Imaging
Tuesday, May 03, 2016 3:45 PM–5:30 PM
6C Paper Session
Program #/Board # Range: 3771–3777
Organizing Section: Retina

Program Number: 3771
Presentation Time: 3:45 PM–4:00 PM
Peripheral Retinal Abnormalities Associated with Age-Related Macular Degeneration in the Age-Related Eye Diseases Study 2 (AREDS2)
Thomas R. Friberg[1], Amitha Domalpally[2], Ron Danis[2], Traci E. Clemons[3], Srinivas R. Sadda[4], Cynthia A. Toth[5], Emily Y. Chew[6]. [1]Ophthalmology and BioEngineering, Univ of Pittsburgh, Pittsburgh, PA; [2]Reading Center, Univ of Wisconsin, Madison, WI; [3]Emmes Corporation, Bethesda, MD; [4]Doheny, Los Angeles, CA; [5]Duke Eye Center, Durham, NC; [6]National Eye Institute, Bethesda, MD.
Purpose: Purpose: Although age-related macular degeneration (AMD) is considered a macular disease, researchers have detected peripheral retinal abnormalities in autopsy eyes. Others have suggested that this is a disease of the retinal pigment epithelium (RPE) throughout the entire retina. The purpose of this study is to assess the association of peripheral retinal abnormalities in AMD.
Methods: A subset of AREDS2 participants, who had late AMD or intermediate AMD (bilateral large drusen), were enrolled in a study of ultra-widefield (up to 200 degrees) color and fundus autofluorescence imaging using the Optos 200Tx laser scanning ophthalmoscope (Optos plc) at study close-out. An age-matched comparator group enriched with participants without AMD were also imaged. Images were graded at a reading center with a standard grid of 3 zones on the entire retina. Peripheral lesions were compared among the two groups.
Results: Of the 575 enrolled, 484 (951 eyes) of the AREDS2 participants and 183 (347 eyes) of controls had gradable images at least in zone 1 (or the posterior pole) images. Among the AREDS2 participants, all had large drusen, 30% had neovascular (NV) AMD and 26% had geographic atrophy (GA) in the posterior pole (zone 1). In the comparator group, 47% had large drusen, 31 eyes had advanced AMD. Additional NV and GA could be detected peripherally: in zone 2 (covering the midperipheral retina) 5% and 6%, in AREDS2 and comparator groups respectively, and in zone 3 (midperiphery to the ora serrata) 0.8% and 6%, respectively. The following peripheral abnormalities were found in AREDS2 versus comparator group for zone 2: large drusen 97% vs. 62%, pseudoreticular drusen 15% vs. 3%, hyperpigmentation 46% vs.18%, and hypopigmentation 27% vs. 1%, respectively. Other common peripheral abnormalities the superior zone 3: cobblestone 18% vs. 19%, and reticular pigmentary changes: 62% vs. 43% respectively.
Conclusions: Preliminary analysis of these groups suggests persons with AMD have a markedly higher risk of having peripheral large drusen, hypo/hyperpigmentation, and reticular pseudodrusen. Peripheral abnormalities in aggregate also occurred more commonly in AREDS eyes. These data demonstrate that AMD is indeed a pan-retinal disease, accounting for some of the functional changes that occur early in AMD. Examination of the retinal periphery may be important in persons with AMD.
Commercial Relationships: Thomas R. Friberg, Optos (C); **Amitha Domalpally**; **Ron Danis**, None; **Traci E. Clemons**, None; **Srinivas R. Sadda**, None; **Cynthia A. Toth**, None; **Emily Y. Chew**, None
Support: Optos, NEI
Clinical Trial: NCT00345176

Program Number: 3772
Presentation Time: 4:00 PM–4:15 PM
Evaluation of intraretinal migration of retinal pigment epithelium in age-related macular degeneration by polarization sensitive SLO and OCT
Masahiro Miura[1, 2], Satoshi Sugiyama[3, 5], Ann E. Elsner[4], Shuichi Makita[5], Young-Joo Hong[5], Yoshiaki Yasuno[5], Takuya Iwasaki[1, 2], Hiroshi Goto[2]. [1]Tokyo Medical University, Ibaraki Medical Center, Ophthalmology, Ami, Japan; [2]Tokyo Medical University, Ophthalmology, Tokyo, Japan; [3]Tomey Corp, Nagoya, Japan; [4]School of Optometry, Indiana University, Bloomingtom, IN; [5]Computational Optics Group, Univ of Tsukuba, Tsukuba, Japan.
Purpose: We hypothesized that depolarization in polarimetry imaging is useful to evaluate the retinal pigment epithelium (RPE). In this study, we evaluated the intraretinal migration of RPE in age-related macular degeneration (AMD) using polarimetry methods
Methods: We prospectively examined 110 eyes of 84 patients with AMD, including 14 eyes of early AMD, 22 eyes of serous retinal pigment epithelial detachment (PED), 17 eyes of remission stage of exudative AMD, 49 eyes of end stage of exudative AMD with fibrotic scar, and 8 eyes of dry AMD with geographic atrophy. Depolarized light images were computed using a polarization-sensitive scanning laser ophthalmoscope (PS-SLO) at 780 nm. To obtain polarimetry information with improved axial resolution, we calculated the Makita's degree of polarization uniformity (M-DOPU) from the data set obtained by a Jones-matrix polarization-sensitive swept-source optical coherence tomography (OCT) with 1-μm probing wavelength. Melanin-containing structures like RPE are source of depolarization, and induce low M-DOPU in PS-OCT and depolarization in PS-SLO. Each polarimetry image was compared with auto-fluorescence image at 500 nm (SW-AF) and 800 nm (NIR-AF). Intraretinal RPE migration was defined by the presence of low M-DOPU in PS-OCT at intraretinal hyper-reflective foci in standard OCT, and hyper-AF in both NIR-AF and SW-AF images at corresponding location.
Results: Intraretinal RPE migrations were detected in 45 of 110 eyes (41%) [5 of 14 eyes with early AMD (36 %), 18 of 22 eyes with PED (82 %), 8 of 17 eyes with remission stage (47 %), 11 of 49 eyes with end stage (22 %), and 3 of 8 eyes with dry AMD (38 %)]. Intraretinal RPE migrations were observed in PED with significantly higher frequency than other groups ($P = 0.04$). Numerous RPE migrations were observed in 10 eyes with PED. PS-SLO showed depolarization at corresponding location to intraretrinal RPE migration, and showed similar feature to NIR-AF images. Findings at intraretrinal RPE migration in NIR-AF and PS-SLO were clearer than SW-AF.
Conclusions: Intraretinal RPE migration occur in the various stage of AMD, and occur more commonly in the eyes with PED. Polarimetric imaging is useful to evaluate intraretinal RPE migration in AMD.



Multiple intraretinal RPE migration in an eye with PED

Commercial Relationships: Masahiro Miura, Santen (F), Santen (R), Novartis (R), Alcom (F), Bayer (F), Novartis (F); **Satoshi Sugiyama**, Tomey; **Ann E. Elsner**, Aeon imaging (F), Aeon imaging (P); **Shuichi Makita**, Tomey (F), Topcon (F), Tomey (P), Canon (F), Nidek (F); **Young-Joo Hong**, Tomey (F), Topcon (F), Canon (F), Nidek (F); **Yoshiaki Yasuno**, Tomey (F), Topcon (F), Tomey (P), Canon (F), Nidek (F); **Takuya Iwasaki**; **Hiroshi Goto**, None
Support: KAKENHI 15K10905

Program Number: 3773
Presentation Time: 4:15 PM–4:30 PM

Evaluating choroidal pigmentation in the setting of polypoidal choroidal vasculopathy in a Caucasian population

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Purpose: To evaluate the inter- and intra-observer reproducibility of a clinical choroidal pigmentation grading scale for the assessment of choroidal pigmentation in Caucasian patients with polypoidal choroidal vasculopathy (PCV).
Methods: To establish the scale reproducibility, a single master grader assessed 15 patients (5 in each group) to have a either a "light", "medium" or "dark" choroid (Figure 1). Two cropped images from the inferior and superior mid-peripheral retina of each eye were graded twice, 3 weeks apart, by 3 independent, blinded graders. Similarly, the choroidal pigmentation of a separate cohort of 16 Caucasian patients (31 eyes) with PCV was compared with a control group of 16 Caucasian patients (32 eyes). The controls were identified by reviewing 145 consecutive patients seen by LY at VRM. Exclusion criteria included age < 50, non-Caucasian by self-identification, known choroidal pathology or subfoveal choroidal thickness < 200 or > 350 microns. Because significant media opacity and variation in choroidal thickness can affect the contrast of the choroidal vasculature against the surrounding choroid, patients with either were excluded.
Results: The clinical grading of choroidal pigmentation was shown to be reproducible, with an average intra-observer agreement of 93.33% (SD 1.67). We demonstrated high inter-observer agreement as well, with Kappa values of 0.9333 and 0.8997 on the 1st and 2nd randomization, respectively. The mean choroidal thickness for eyes with PCV compared to the control eyes was comparable (232 versus 263 microns). The PCV cohort was 56% female versus 50% in the controls and was older than the patients with no disease (mean age: 78.9 years versus 70.4 years). Preliminary grading results showed that PCV patients had darker choroidal pigmentation versus patients with no choroidal disease (71% of PCV patients had a "dark" choroid, compared with 47% of the controls, p = 0.0103).
Conclusions: This study demonstrates that our method of clinical grading of choroidal pigmentation has good inter- and intra-observer reproducibility. Preliminary results suggest that Caucasian patients with PCV may have darker choroidal pigmentation compared to patients with no choroidal disease.

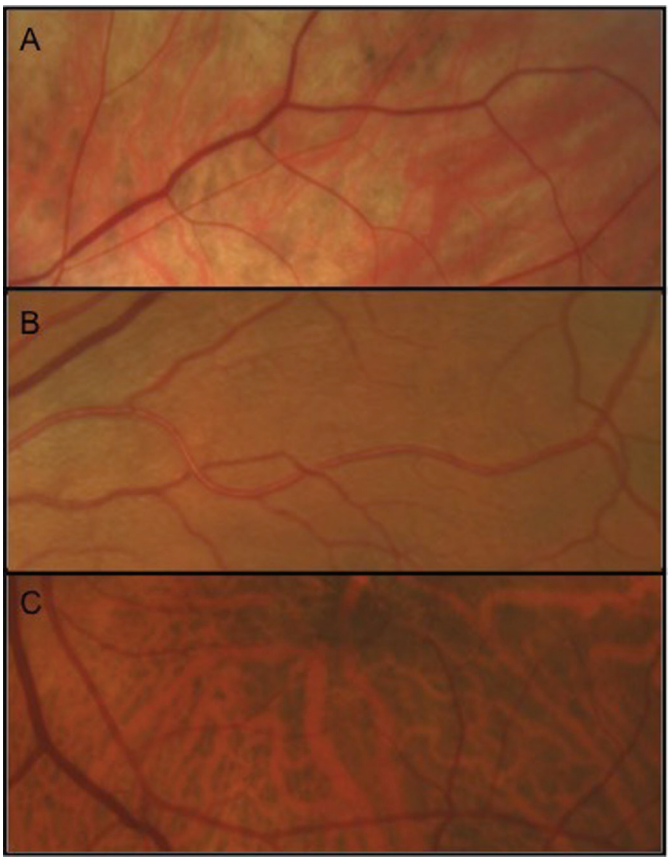
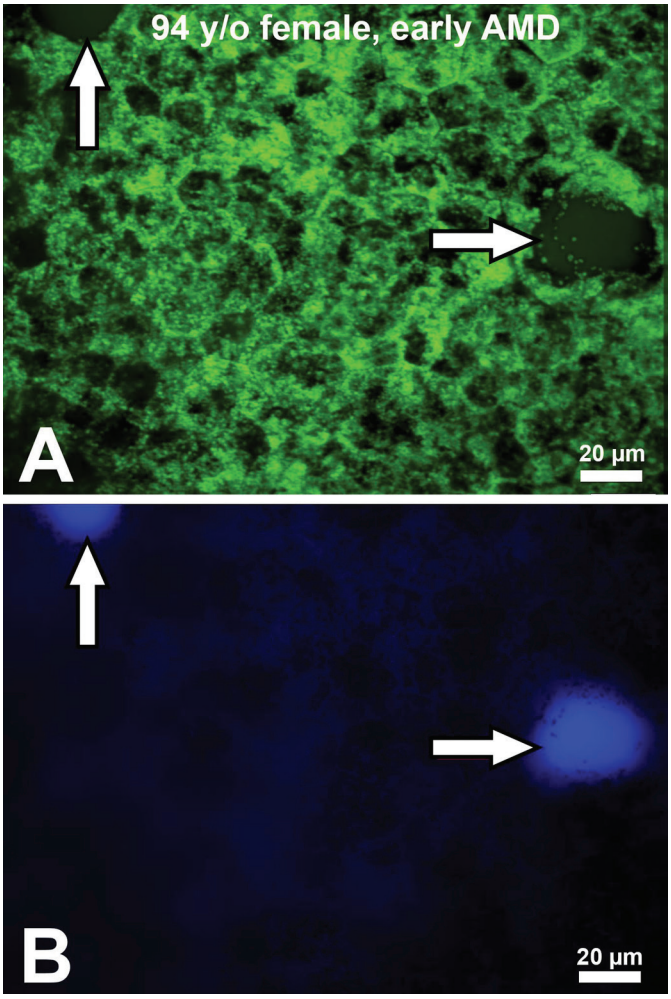


Figure 1: An example of light (A), medium (B) and dark (C) choroidal pigmentation, defined by comparing the color of the choroidal vasculature to the surrounding choroidal pigmentation

Commercial Relationships: Talia R. Kaden; **Anna C. Tan**, None; **Fatimah Gilani**, None; **Sarwar Zahid**, None; **Lawrence A. Yannuzzi**, None

Program Number: 3774
Presentation Time: 4:30 PM–4:45 PM
Autofluorescent (AF) sub-retinal pigment epithelium (sub-RPE) deposits in age-related macular degeneration (AMD) accumulate preferentially at the fovea
Thomas Ach[1, 3], Joshua S. Koplon[3], Carrie E. Huisingh[3], Jeffrey D. Messinger[3], Anna V. Zarubina[3], Kenneth R. Sloan[2], Christine A. Curcio[3]. [1]Department of Ophthalmology, University Hospital Wuerzburg, Wuerzburg, Germany; [2]Computer and Information Sciences, University of Alabama at Birmingham, Birmingham, AL; [3]Department of Ophthalmology, University of Alabama at Birmingham, Birmingham, AL.
Purpose: Sub-RPE deposits (drusen/basal linear deposits, basal laminar deposits) are common in aging and in AMD. They exhibit AF after blue light excitation (PMID 12091448). Here, we describe spatial distribution and frequencies of AF-sub-RPE deposits in normal aged and AMD.
Methods: RPE-Bruch's membrane flatmounts (human donor eyes; 10 Controls (median age 84 yrs), 10 early AMD (median age 87 yrs) were previously imaged (PMID 25034602) at 3 eccentricities (fovea, perifovea, near-periphery) and 4 quadrants (superior, inferior, nasal, temporal) using confocal AF-imaging (exc. 390 nm (UV) and 488 nm (blue)). AF areas in the UV images were counted (areas/location), and the size of the area occupied was estimated. Lesion prevalence was adjusted for RPE spatial density (#/sq mm).
Results: Sub-RPE deposits exhibit strong UV-AF signal (Fig.1). A total of 116 locations in AMD and 115 in Controls were analyzed. In AMD eyes, 64.7% of the locations showed deposits, and 57.4% in Controls. The number of deposits/location (mean±SD) was 1.4±1.5 in AMD and 0.7±0.8 in Controls (no significant difference). When accounting for the RPE cell density of the location, the mean number of deposits/location was significantly higher among AMD eyes than Controls (p=0.0019), and significantly different at fovea (p<0.0001), but not at perifovea or periphery. Deposits occupied larger areas in AMD eyes (7.4±13.7 %) than Controls (1.4±2.4 %), but after adjusting for cell density, these proportions were not statistically different (p=0.58).
Conclusions: This is the first study to report number, proportion of locations with any sub-RPE deposits, and occupied area of sub-RPE deposits in aging and AMD from a systematic survey of flatmounts viewed *en face*. AMD and Control eyes have a similar proportion of affected locations; however, the number of sub-RPE deposits was higher among AMD eyes than normal eyes, particularly in the fovea. The extensive deposition, though not clinically visible, might disturb nutrition supply and lead to early functional RPE and photoreceptor impairments.



Small drusen (arrows) show minimal AF at blue light excitation in contrast to RPE's lipofuscin granules (A). Deposits displace overlying RPE cells towards the edge. A few scattered lipofuscin granules atop the deposits block emission from below. By UV light excitation, sub-RPE deposits are highly AF (B).
Commercial Relationships: Thomas Ach, None; **Joshua S. Koplon**, None; **Carrie E. Huisingh**, None; **Jeffrey D. Messinger**, None; **Anna V. Zarubina**, None; **Kenneth R. Sloan**, None; **Christine A. Curcio**, Novartis (C), Genentech (C), Janssen Cell Therapy (C), Merck (C)
Support: German Research Foundation (DFG) Ac265/1-1, Ac265/2-1 (TA); NIH grant EY06109, EyeSight Foundation of Alabama, Research to Prevent Blindnes (CAC)

Program Number: 3775
Presentation Time: 4:45 PM–5:00 PM
Histological stages of subretinal drusenoid deposits (SDD) in eyes with age-related macular degeneration (AMD)
Christine A. Curcio[1], Jeffrey D. Messinger[1], Yuhua Zhang[1], David Neely[1], K Bailey Freund[2, 3], Richard F. Spaide[2, 3].
[1]Ophthalmology, Univ of Alabama at Birmingham, Birmingham, AL; [2]Vitreous Retina Macula Consultants of New York, New York, NY; [3]LuEsther T. Mertz Retinal Research Center, Manhattan Eye, Ear, and Throat Hospital Manhattan Eye, Ear, and Throat Hospital, New York, NY.

Purpose: To guide clinical and laboratory studies of SDD lifecycle we seek correlates for the 3- and 4-stage SDD scales [*1*] [*2*] and for imaging-revealed features of dynamism [*3,4*], dots-ribbons [*5*], outer retinal atrophy [*3*], peripapillary SDD [*6,7*], hyperreflective spots [*2*]).
Methods: Eyes from 82 white donors with AMD and one eye of a clinically imaged 98-year-old donor with neovascular AMD and abundant SDD [*8*] were processed for macula-wide high-resolution sections (http://projectmacula). In fovea and superior perifovea of 32 eyes, 79 examples of SDD attached to photoreceptors were photodocumented and assessed (early AMD, n=15; geographic atrophy; n=10, neovascular AMD, n=8).
Results: The smallest SDD observed were solitary 4 μm-diameter dollops. Bundled retinal pigment epithelium (RPE) apical processes with melanosomes embraced lesions and maintained contact with outer segments. Bundles punctuated confluent lesions and were less visible in extensive lesions. Disintegrated SDD material infiltrated among photoreceptor inner and outer segments, rarely occupying gaps in the outer nuclear layer (ONL). Outer retinal atrophy corresponded to shortened photoreceptors and thinned ONL over RPE with continuous basal laminar deposit. In the previously imaged patient, reflective transdifferentiated RPE in the subretinal space and within the retina associated with SDD. As described [*9*], macular SDD were finely granular and distinct from outer segments, RPE lipofuscin, and basal laminar/ linear deposit. SDD with vesicular contents were seen in the peripapillary area only.
Conclusions: Histological observations of SDD reveal an intimate proximity to photoreceptors, particularly as lesions progress. Our current data do not support stage 4 as originally described, because SDD material internal to the ELM was infrequent. Cells participating in SDD clearance could be photoreceptors, RPE, or Müller cells. Importantly other cells with potential clearance capacity like macrophages or microglia were not seen. Association of sloughed RPE with SDD warrants investigation.
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7. Zarubina. *Ophthalmology.* in revision.
8. Curcio. *Am J Ophthalmol.* 2015; online.
9. Curcio. *Retina.* 2013;33:265.
Commercial Relationships: Christine A. Curcio, Genentech (C), Janssen Cell Therapy (C), Merck (C); **Jeffrey D. Messinger**, None; **Yuhua Zhang**, None; **David Neely**, None; **K Bailey Freund**, Genentech (C), Ohr Pharmaceutical (C), Optos (C), Heidelberg Engineering (C), ThromboGenics (C), REGENXBIO (C), Optovue (C); **Richard F. Spaide**, Genentech (C), Bausch and Lomb (C), Topcon (C)
Support: 2014 von Sallmann Prize; EyeSight Foundation of Alabama; Research to Prevent Blindness; NEI EY06109; NEI P30 EY003039, Edward N. and Della L. Thome Foundation, Beckman Initiative for Macular Research, Macula Foundation

Program Number: 3776
Presentation Time: 5:00 PM–5:15 PM
Fully Automated Identification of Lesion Activity in Neovascular AMD
Anat Loewenstein[1], Dafna Goldenberg[1], Usha Chakravarthy[2], Graham Young[3], Moshe Havilio[3], Omer Rafaeli[3], Gidi Benyamini[3]. [1]Ophthalmology, Tel Aviv Medical Center, Tel Aviv, Israel; [2]Queen's University, Center for Experimental Medicine, Belfast, Ireland; [3]Notal Vision, Tel Aviv, Israel.

Purpose: Objective: The objective of the study was to evaluate the accuracy of the Notal OCT Analyzer (NOA) versus retina specialists (RS) in the automatic detection of fluid on optical coherence tomography (OCT).
Methods: Design: A prospective study of the performance of the NOA, which is compared to three retina specialists. The data source was OCT volume scans acquired in a retina clinic.
Participants: A random selection of anonymization OCT scans (Zeiss Cirrus, Carl Zeiss Meditec, Dublin CA) of 165 AMD patients attending a single tertiary referral center (Belfast HSC, UK).
Methods: OCT scans of AMD patients were exported. Each scan set was analyzed by the NOA, and by three independent RS for the presence of intra-retinal or sub-retinal fluid. NOA also ranked cross-sections of scans for likelihood of CNV activity allowing a second grading session by the three RS.
Outcome measures: NOA's sensitivity and specificity versus the RS grading and NOA's performance in ranking cross-section for activity.
Results: Results: 142 scan sets met the criteria for the primary analysis. On testing the RS grading versus the NOA, the accuracy was 91% (95% CI ±7%), sensitivity was 92% (±6%) and specificity was 91% (±6%). The graders' accuracy when compared to majority of the other readers (including a 4th reader) was 93%. On average, the three readers could identify fluid in 95% of scans by just reviewing a single cross section with the highest NOA score, 99.5% of scans by viewing the top three cross sections.
the RS grading and NOA's performance in ranking cross-section for activity.
Conclusions: Conclusions: Concordance between the NOA and the RS determination of lesion activity was extremely high. The level of discrepancy between RS and the NOA was similar to the NOA's mismatches. Our results show that automated delineation of the retinal contours combined with interpretation of disease activity is feasible and has the potential to become a powerful tool in terms of its clinical applications.
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the RS grading and NOA's performance in ranking cross-section for activity.
Commercial Relationships: Anat Loewenstein, Notal (C); **Dafna Goldenberg**; **Usha Chakravarthy**, Notal (C); **Graham Young**, None; **Moshe Havilio**, None; **Omer Rafaeli**, None; **Gidi Benyamini**, None
Support: Notal

Program Number: 3777
Presentation Time: 5:15 PM–5:30 PM
Automated identification and quantification of subretinal fibrosis in neovascular age-related macular degeneration using polarization-sensitive optical coherence tomography
Philipp K. Roberts[2], Mitsuro Sugita[1], Gabor Dèak[2], Bernhard Baumann[1], Stefan Zotter[1], Michael Pircher[1], Stefan Sacu[2], Christoph K. Hitzenberger[1], Ursula Schmidt-Erfurth[2]. [1]Center for Medical Physics and Biomedical Engineering, Medical University of Vienna, Vienna, Austria; [2]Department of Ophthalmology, Medical University of Vienna, Vienna, Austria.
Purpose: To identify and quantify subretinal fibrosis in eyes with advanced neovascular age-related macular degeneration (AMD) using polarization-sensitive optical coherence tomography (PS-OCT).
Methods: Eyes of patients with subretinal or sub-retinal pigment epithelium (RPE) fibrosis secondary to neovascular AMD were included in this case series. All patients underwent a complete standardized ophthalmic examination to clearly identify advanced neovascular AMD lesions with scarring. PS-OCT examinations were performed using a novel PS-OCT system with an integrated

eye-tracker allowing to selectively detect the intrinsic birefringence of collagenous fibres. Areas of fibrosis in PS-OCT, automatically segmented using a proprietary algorithm, were compared to conventional imaging modalities including spectral-domain OCT, fluorescein angiography (FA) and color fundus photography (CF) in their potential to visualize fibrotic scarring in AMD.
Results: Fifteen eyes of 15 consecutive patients with subretinal scarring secondary to advanced neovascular AMD were included. In PS-OCT B-scans, a distinct "column-like" pattern was observed in averaged axis orientation images, indicative of the specific orientation of collagenous fibers within the surrounding tissue. En face analysis provides a precise 3D mapping of the fibrotic scar component. Fibrous tissue was selectively identified by PS-OCT based on birefringence in all lesions, whereas in SD-OCT subretinal hyperreflective material (SHRM) could not be further classified into scar tissue, fibrovascular material or other AMD-specific material. Based on simultaneous polarization analyses in PS-OCT, the level of RPE alteration could be evaluated as well, showing thinning and loss of RPE associated with subretinal fibrosis.
Conclusions: Using PS-OCT, subretinal fibrosis can be identified as an intrinsically birefringent structure and can be quantified based solely on its tissue-specific contrast. PS-OCT offers a unique method to identify clinically relevant components of SHRM (i.e. neovascular tissue vs. fibrous tissue) and therefore allow for an optimized disease management as well as evaluation of therapeutic strategies.
Commercial Relationships: Philipp K. Roberts, Canon Inc. (F); **Mitsuro Sugita**, Canon Inc. (F); **Gabor Dèak**, None; **Bernhard Baumann**, Canon Inc. (F); **Stefan Zotter**, Canon Inc. (F); **Michael Pircher**, Canon Inc. (F); **Stefan Sacu**, None; **Christoph K. Hitzenberger**, Canon Inc. (C); **Ursula Schmidt-Erfurth**, None