Evaluation of coronary artery disease as a risk factor for reticular pseudodrusen

McCarter, R. V., McKay, G. J., Quinn, N. B., Chakravarthy, U., MacGillivray, T. J., Robertson, G., Pellegrini, E., Trucco, E., Williams, M. C., Peto, T., Dhillon, B., van Beek, E. J., Newby, D. E., Kee, F., Young, I. S., & Hogg, R. E. (2017). Evaluation of coronary artery disease as a risk factor for reticular pseudodrusen. *British Journal of Ophthalmology*, 1-7. Advance online publication. https://doi.org/10.1136/bjophthalmol-2017-310526

Published in:
British Journal of Ophthalmology

Document Version:
Peer reviewed version

Evaluation of Coronary Artery Disease as a Risk Factor for Reticular Pseudodrusen.

McCarter RV,[1] McKay GJ,[1] Quinn NB,[1] Chakravarthy U,[1] MacGillivray TJ,[2] Robertson G,[2] Pellegrini E,[2] Trucco E,[3] Williams MC,[4] Peto T,[1] Dhillon B,[2] van Beek EJR,[5] Newby DE,[4] Kee F,[1] Young IS,[1*] Hogg RE.[1a]*

[1]Center for Public Health, Queen's University Belfast. [2]VAMPIRE project, Center for Clinical Brain Sciences, The University of Edinburgh. [3]VAMPIRE project, Computing, School of Science and Engineering, University of Dundee. [4]Center of Cardiovascular Science, University of Edinburgh. [5]Clinical Research Imaging Center, University of Edinburgh.

* NICOLA Study Principal Investigator and Study Originator

[a]Corresponding author: Dr Ruth E. Hogg

Center for Public Health, Queen's University Belfast, Institute of Clinical Science Block A, Royal Hospital, Grosvenor Road, Belfast, Northern Ireland, BT12 6BA.

Email: r.e.hogg@qub.ac.uk

Synopsis: The relationship between reticular pseudodrusen and coronary artery disease was evaluated using ultra-widefield retinal imaging. Validation was performed separately and satisfactorily using other imaging modalities.No association between coronary artery disease and reticular pseudodrusen was found.

ABSTRACT

Purpose: Reticular pseudodrusen (RPD) is a risk factor for late age-related macular degeneration (AMD). Associations between RPD and coronary artery disease (CAD) have been reported from small case-control studies. This study investigated the association of RPD within a predominantly CAD cohort.

Methods: A subgroup of subjects from a multicenter randomized controlled trial of computed tomography coronary angiography (CTCA) underwent ultra-widefield (UWF) retinal imaging CAD determined by CTCA was categorized as normal, non-obstructive or obstructive. Specific AMD features in UWF images were graded. Standardized grids were used to record the spatial location of AMD features, including RPD. Multivariate confounder adjusted regression models assessed the association between RPD and CAD.

Results: The 534 participants were aged from 27-75 years (mean 58 ±9 years; 425 (80%) ≥50 years) with a male preponderance (56%). Within the study sample, 178 (33%) had no CAD, 351 (66%) had CAD. RPD was detected in 30 participants (5.6%) and bilaterally in 23. Most participants with bilateral RPD had intermediate AMD 17 (74%). After adjustment for potential confounders (age, sex, drusen >125 µm, smoking status), multivariate analysis found no significant association between CAD and RPD (odds ratio [OR] 1.31; 95% Confidence

Interval [CI] (0.57-3.01); p=0.52). A significant association was identified between RPD and intermediate AMD (OR 3.18; 95% CI (1.61-6.27); p= 0.001).

Conclusion: We found no evidence to support an association between CAD and RPD. RPD was strongly associated with intermediate AMD features.

INTRODUCTION

Age-related macular degeneration (AMD) is the leading cause of permanent blindness in the developed world with the most sight loss occurring in the late stages, namely geographic atrophy (GA) and choroidal neovascularization (CNV).[1] Risk factors for progression from early to late AMD include advancing age, cardiovascular disease (CVD), obesity, cigarette smoking, ethnicity, hypertension, high cholesterol, genetic variants such as age-related maculopathy susceptibility 2 (*ARMS2*) gene, complement factor H (*CFH*) and apolipoprotein E (*ApoE*) gene and inflammatory markers such as C-reactive protein (*CRP*).[2] Recently, reticular pseudodrusen (RPD) have been shown to be an important independent risk factor for progression to both GA[3,4] and CNV.[3,5] In addition, various risk factors have been reported to be associated with RPD including advancing age, female gender, smoking, *ARMS2*, *C3, VEGFA* and *CFH* genetic variants.[6-8]

RPD is a subtype of AMD associated with subretinal drusenoid deposits (SDD) and is located between the retinal pigment epithelium (RPE) and the inner ellipsoid zone.[6] Associations between RPD, SDD, reticular macular disease (RMD) and coronary artery disease (CAD) have been reported from small case-control studies. The acronyns and associated full titles are mentioned here in order to avoid any confusion. In particular, the term SDD is preferred for the actual physical deposits as first recognized within histopathology by Curcio et al.[9]

In association with the selection of image modality, variations in specific definitions of RPD have also led to substantial differences in reported prevalence rates. Initial reports of the association came from data collected on AMD cohorts recruited in

hospital eye clinics and reported high prevalences ranging from 29 - 52%. [6, 10,11] Data from population based studies are limited and show large variation, such as 0.4% from the Melbourne Collaborative Cohort study to 4.9% in the Rotterdam study and 13% in the Alienor study.[7,8,12] Such varying estimates might be attributed to the different imaging and grading protocols used.

The strong association between RPD and a thin choroid has prompted a spate of small studies that have sought associations between RPD and cardiovascular disease.[13-17] Cymerman et al reported on a small prospective cohort of patients with no known retinal disease recruited from a cardiovascular clinic; 23 participants with coronary artery disease (CAD) had a higher frequency of RPD compared to 15 who did not have CAD.[13] A review by Rastogi and Smith[14] on the association between AMD, RPD and CVD highlighted studies reporting an association between RPD and hypertension and angina.[15-18] Smith and colleagues hypothesized that the increased mortality from systemic-vascular disease that affects males more severely compared to females, may account for the higher proportion of women with RPD that has been observed in various population-based studies.[18] Notably this review highlighted the potential importance of large prospective cohort studies sampling participants >45 years with and without CAD to identify RPD development and potential associations.[14]

A sub-study of the SCOT-HEART (SH) trial that incorporated only ultrawide field (UWF) retinal imaging offered an unique opportunity to explore the relationship between CAD and RPD. The use of widefield technology to evaluate the retinal fundus offered an additional advantage as RPD is commonly located in the retinal arcades and beyond.[15] To date there is one study that has estimated RPD prevalence that has

included central and peripheral retinal locations.[19] In this study, RPD were present in 15% of AMD subjects in zone 2, but none in the controls, a difference that was significant. However the sensitivity of UWF to detect RPD has not been established. We therefore first validated the methodology using images from a population based epidemiological study (the Northern Ireland Cohort for the Longitudinal Study of Ageing [NICOLA]) which captured UWF, color fundus photography (CFP), infra-red (IR) and autofluorescence (AF) images of the retina, and subsequently used the SH trial sub-study UWF images to explore the relationship between RPD and CAD.

MATERIALS AND METHODS

Validation of detection of RPD by UWF imaging

Nine hundred consecutive participants were selected from the NICOLA Study. CFP was performed on the Canon CX-1 Digital Fundus Camera (Canon U.S.A., Inc., Melville, NY, U.S.A.). Stereoscopic pairs centered on the optic disc and macula were captured. CFP images were viewed and graded using the Oculab program (Digital Healthcare Oculab, V3.7.98.0, Emis Health, Leeds, UK). UWF retinal imaging was performed on the Optos Tx200 Scanning Laser Ophthalmoscope (Optos PLC, Dunfermline, UK) using both color and AF acquisition modes. Images were viewed and graded using the Optos V^2 Vantage Pro software (version 2.9.4.2).

UWF images were graded for the presence or absence of RPD by a trained single grader who was not involved in any other grading procedures with quality assurance and review by a retina specialist (UC). All available imaging modalities were used to determine the presence of RPD. This included *en face* images of color, multicolor, AF and IR. In addition high resolution optical coherence tomograms were also scrutinized for the presence of SDD. The image grading was undertaken by trained graders in the network of UK Reading Center's (NetwORC UK) for the presence or absence of RPD.

Detection of RPD on any modality was taken as evidence of presence of this feature. Sensitivity and specificity of the UWF imaging in detecting RPD compared to the RPD detected from the NICOLA cohort's *en face and tomographic* images was computed.

The SCOT-HEART (SH) Study and Sample

The SH trial (ClinicalTrials.gov, number NCT01149590) was a multicenter randomized controlled trial undertaken in Scotland (2010-2014) on 4,146 participants, aged 18-75 years, drawn from 12 cardiology clinics across Scotland.[20] The main aim of the study was to determine the role of multidetector computed tomography in the diagnosis and management of patients attending rapid access chest pain clinics. Participants were randomly assigned to either standard care (control intervention) or standard care and the computed tomography coronary angiography (CTCA) and calcium scores (intervention). CAD was categorized in the SH study as: (i) obstructive CAD, atherosclerotic plaque encompassing a luminal cross-sectional area of ≥70% in at least one major epicardial vessel; (ii) non-obstructive CAD, either atherosclerotic plaque encompassing a luminal cross-sectional area of <70% but >10% in at least one major epicardial vessel, or a calcium score >400 AU (Agatston units) or >90th percentile for age and sex; or (iii) minimal or no CAD. Non-obstructive disease was further sub-divided into mild (10-50% luminal cross-sectional area) or moderate (50-70% luminal cross-sectional area) stenosis. At two sites (Edinburgh and Dundee), consecutive patients were approached to undergo UWF imaging immediately before or after undergoing CTCA. We assessed 534 participants from a sub-study of SH who had UWF imaging captured using two Optos P200C Scanning Laser Ophthalmoscopes (Optos PLC, Dunfermline, UK) in addition to the normal study

procedures at two sites (the Clinical Research Imaging Center in Edinburgh and the Clinical Research Center Dundee).[21]

Image Grading in SH

Specific features of AMD in UWF images were graded for AMD characteristics (increased pigment, decreased pigment, drusen, maximum drusen size, RPD, GA and CNV) and other peripheral abnormalities using the 'Study-specific Grading Procedures for OPERA Study,' guidelines (November 2013).[22] The Optos software utilised a modified Studies of Ocular Complications of AIDS (SOCA) Optos PEripheral RetinA study (OPERA) grid (Figure 1) which was divided into three zones: Zone 1 (posterior pole), Zone 2 (extends from Z1 to a circle through the ampullae of the vortex veins) and Zone 3 (extends from Z2 to the outer periphery). The Manchester grid was superimposed on the SOCA grid to estimate the ungradable areas (Figure 2). In accordance with the OPERA guidelines, at least 50% of the subfield should be visible to grade; if < 50% of the subfield was visible, it was graded as "Cannot Grade." If AMD characteristics and other pathologies were present in a Cannot Grade subfield, and if the grader was ≥ 90% certain the lesion was present, then grading was ascribed. Drusen presence was graded as follows: absent; questionable; 1-5 drusen; 6-20 drusen; >20 drusen or cannot grade. The maximum drusen size was graded as follows: < 125μm; ≥ 125μm, < 250μm distinct; ≥ 125μm, < 250μm indistinct; ≥ 250μm distinct; ≥ 250μm indistinct or cannot grade. RPD was graded as follows: absent; questionable; < 25% of subfield; 25-49% of subfield; 50-74% of subfield; ≥ 75% of subfield or cannot grade. RPD were defined as yellow interlacing networks ranging from 125μm to 250μm in width or lesions that occurred in regular well-defined domains

(Figure 3). Images in which RPD were questionable were arbitrated by a retinal specialist (UC).

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 20 (Portsmouth, UK). Intraobserver agreement was calculated after 1 in 20 of the images were randomly regraded for RPD and drusen using kappa (k) statistics, which express the extent of agreement beyond chance. The interpretation of the k statistic was as follows: 0, no agreement; 0 to 0.2, slight agreement; 0.21 to 0.40, fair agreement; 0.41 to 0.60, moderate agreement; 0.61 to 0.8, substantial agreement; and >0.81, almost perfect agreement.[23]

Univariate analysis (Chi-squared test or Fisher's Exact test for categorical variables and independent t-test for continuous variables) was used to examine differences in the demographic characteristics of participants according to presence or absence of RPD. General estimating equations (GEE) which enabled data from both eyes to be included were used to examine the association between RPD and CAD while accounting for other factors identified as significant from the univariate analysis.

RESULTS

Validation study

The sensitivity and specificity of UWF was compared with enface and tomographic multimoda images in the detection of RPD. Of the images acquired from the 900 consecutive participants included in the validation study, UWF imaging detected 8

participants with reticular drusen (2 unilateral and 6 bilateral; 100% sensitivity). Multimodal imaging (color, multicolor, infra-red and autofluorescence and OCT) detected RPD in 7 of those which were seen on *en face* images The specificity of the UWF imaging was 99.9%. In one case, the UWF imaging detected RPD beyond the field of view captured by the combination of retinal imaging (Figure 4). The positive predictive value (PPV) was calculated at 87.5% and the negative predictive value (NPV) was 100%.

Participant Characteristics in SH study

Table 1 summarizes SH study participant characteristics. In total 534 individuals had UWF retinal images captured. Two participants [4 eyes] proved difficult to scan and images were not obtained. This left 532 pairs of eyes for grading. The mean age was 58 years (range=27-75, SD 9.5) with 425 (80%) aged over 50 years. There were 299 males (56%). 178 (33%) had no CAD, 351 (66%) had CAD present, whilst 182 (34%) had hypertension and 42 (24%) had no CAD or hypertension.

The intragrader agreement illustrated in Table 2 gives the kappa range for the AMD features: for the presence of RPD it ranged from: 0.62-0.76; for drusen: 0.58-0.64, maximum drusen size: 0.55-0.62, increased pigment: 0.54-0.61, decreased pigment: 0.55-0.62; for GA: 0.62-0.76; for neovascular AMD: 0.57-0.66 and for peripheral abnormality: 0.55-0.59 within zones 1-3. For the lesions which were absent in the cohort the discordance in the grading originated from a change of grade of feature absent to ungradeable between the two gradings.

Prevalence of RPD and AMD features in the SH study

RPD was present in one or both eyes of 30 participants (5.6%) and bilateral in 23 participants (4.3%). Intermediate AMD were present in 201 participants (38%). Participants with RPD ranged in age from 33-75 years (mean 59) and there were equal numbers of males and females. The other AMD features graded as present in the participants were as follows: 352 (66%) had hyperpigmentation, 55 (10%) had hypopigmentation, 2 (0.4%) had unilateral GA, none of the participant was classified as having neovascular AMD and 183 (34%) showed other non-AMD peripheral abnormalities.

Association of CAD with RPD

CAD was present in 20 participants and absent in 10 participants with RPD, however, no statistically significant association between RPD and CAD was found on either the unadjusted or adjusted GEE model ($p>0.05$, Table 3). With respect to associations between RPD and other early AMD features a strong association was noted with intermediate AMD in the fully adjusted model (OR 3.18; 95% CI (1.61-6.27); $p= 0.001$). Eighteen participants had both RPD and intermediate AMD, while 11 participants had RPD alone without evidence of soft drusen.

DISCUSSION

We believe that our study is the first to report on the prevalence of RPD using UWF retinal images in patients with confirmed CAD. Contrary to previous reports, our study did not reveal a significant association between RPD and CAD.[13-16,18] Detection of RPD was based on retinal wide field imaging and was graded using standardized protocols. We validated the ability of UWF color images to detect RPD by checking

agreement within a set of images acquired using multimodal technology and demonstrated that UWF was reliable, reproducible and robust. Our findings are in accordance with population based studies and some of the clinical cohorts that did not report significant associations between RPD and CAD or hypertension.[6-8,12,24] In fact, the prevalence of RPD observed in the current SH study (30 out of 534 participants - 5.6%) is similar to that reported by the population based Rotterdam study (4.9%),[7] providing additional support for the view that CAD is not associated with an increased prevalence of RPD. Interestingly, Zarubina et al studied patients from primary care eye clinics with and without AMD, and using multi-modal imaging and strict criteria found that the prevalence of SDD in subjects without AMD was 23%. However, utilizing expanded criteria, Zarubina et al discovered that the prevalence of SDD on any modality, closest to that of the current study, rose to 69% in subjects ~~of~~ with a mean age ~ 68 years. In comparison, the population in the current study had a mean age ~58 years, and a SDD prevalence of only 5.6%. This is a large difference in prevalence, as Zarubina et al. utilized SD-OCT, whereas this study only used UWF, and RPD is better detected on SD-OCT, so it would be expected to have a lower prevalence on UWF.[24]

While 80% of participants were aged over 50, a common age restriction for many AMD studies, interestingly 8 participants with RPD were aged under 50, the youngest aged 33. Of these, 4 (50%) also had evidence of intermediate AMD whereas the rest had no other features of AMD present. If, as has been proposed, the primary lesion is vascular (choroidal insufficiency), then as the disease progresses the development of SDD may follow. It is possible that this may be one explanation for the findings of fewer SDD within a younger population. In the overall sample, 7 participants had RPD

without any other AMD features similar to previous observations,[7] which may reflect a different phenotype given that RPD have been reported in other retinal diseases such as Sorsby fundus dystrophy, pseudoxanthoma elasticum and acquired vitelliform lesions.[25-27] Given the rarity of these participants, it is likely that studies of large sample size or pooled analyses across studies will be required to improve our understanding of the relevance of these isolated RPD.

The RPD phenotype in AMD has been shown to be associated with choroidal thinning[28-33] and thus it has been suggested that RPD arise as a consequence of choroidal vascular pathology such as age-related atherosclerosis. Interestingly Leisy et al. recently found an association between the RPD phenotype and renal dysfunction.[34] However, we were unable to establish a relationship in a large population with a diagnosis of CAD that was established using robust methodology and which constitutes an important marker for systemic vascular disease. Therefore we contend that the pathogenesis of RPD remains unresolved and we suggest that the outer photoreceptor mosaic may be the source of this material which in turn is a consequence of RPE degeneration with withdrawal of trophic/survival factors to the photoreceptors.

This is only the second study, to our knowledge, that used UWF imaging for the evaluation of RPD.[19] Using the NICOLA image repository we confirmed the reliability of this approach to detect reticular drusen which have been observed when using other *en face* modalities such as IR or AF imaging. Nonetheless we are of the view that as with other en face modalities, UWF imaging also underestimates the prevalence because the earliest stages of the SDD phenotype are best appreciated on high

resolution SD OCT.[35] Stage one SDD is defined by the dispersed nature of the deposits of granular hyperreflective material that is present in the outer retina in the region of the photoreceptors' inner and outer segments (the IS/OS boundary) and the retinal pigment epithelium. A characteristic reticulated pattern accompanies stages 2 and 3, which has been attributed to focal deposits that cause marked alterations to the IS/OS boundary and thus become detectable by en face imaging.[35] Currently it is accepted that detection of RPD is best when a multimodal approach, combining IR, AF and SD-OCT is used.[12,36] We were however reassured by the validation study which demonstrated the benefit of the increased field of view provided by UWF imaging. We also noted that RPD was evident in at least one participant in an area of the retinal fundus that is typically not included in color images (35° or 45°) or OCT, raising the possibility of under ascertainment when the field of examination is restricted to the central fundus.

A potential limitation of this study is the choice of controls as all participants (cases and controls) were recruited from cardiology clinics. However comtrol status was only assigned following an extensive and robust clinical examination, computed tomography coronary angiography and calcium scores. This cohort may therefore have characteristics that are dissimilar to that of a random population based sample. Even though we adjusted for age, sex and smoking habit, some of the established AMD risk factors, such as diet, and genetic risk, were not available and therefore residual confounding may have been present. However, concerns over residual confounding are less worrisome, given the absence of the finding of a positive association between CAD and RPD.

In conclusion, our study does not support previously reported associations with CAD. As with other studies we observed the strong association with the hallmark feature of classical drusen which is recognized as early AMD. Our findings highlight the necessity for other studies in this age group with improved phenotyping of the ocular fundus as well as vascular disease in other organ systems. Data from large and well characterized longitudinal population based studies with multimodal imaging will be required. In addition, pooled analyses of multiple studies to improve statistical power may help untangle the complexity of the risk factors and sub-phenotypes involved.

Acknowledgements:

The Chief Scientist Office of the Scottish Government Health and Social Care Directorates funded the SCOT-HEART trial with supplementary awards from Edinburgh and Lothian's Health Foundation Trust and the Heart Diseases Research Fund. We are grateful to the participants of the Northern Ireland Cohort for the Longitudinal study of Ageing (NICOLA), and the NICOLA team, which includes nursing staff, research scientists, clerical staff, computer and laboratory technicians, managers and receptionists. We acknowledge funding support from Atlantic Philanthropies, Economic and Social Research Council, Health and Social Care Research and Development, United Kingdom Clinical Research Collaboration and Queen's University Belfast who provided core financial support for NICOLA. The authors alone are responsible for the interpretation of the data and any views or opinions presented are solely those of the author and do not necessarily represent those of the NICOLA steering committee.

The corresponding author and all of the authors have made the following contributions: (1) Conception and design, or acquisition of data, or analysis and interpretation of data; (2) Drafting the article and/or reviewing, revising it critically for important intellectual content; (3) final approval of the version to be published.

Hogg RE: (1), (2), (3); McCarter RV: (1), (2), (3); McKay GJ: (1), (2), (3); Quinn NB: (1), (2), (3); Chakravarthy U: (2), (3); MacGillivray TJ: (1), (3); Robertson G: (1), (3); Pellegrini E: (1), (3); Trucco E: (1), (3); Williams MC: (1), (3); Peto T: (1), (3); Dhillon B: (1), (3); van Beek EJR: (1), (3); Newby DE: (1), (3); Kee F: (1), (3) and Young IS: (1), (3).

References

1. Klaver CC, Wolfs RC, Vingerling JR, Hofman A, de Jong PT. Age-specific prevalence and causes of blindness and visual impairment in an older population: The Rotterdam study. *Arch Ophthalmol.* 1998;116:653-658.

2. Smith W, Assink J, Klein R, et al. Risk factors for age-related macular degeneration: Pooled findings from three continents. *Ophthalmology.* 2001;108:697-704.

3. Finger RP, Wu Z, Luu CD, et al. Reticular pseudodrusen: A risk factor for geographic atrophy in fellow eyes of individuals with unilateral choroidal neovascularization. *Ophthalmology.* 2014;121:1252-1256.

4. Marsiglia M, Boddu S, Bearelly S, et al. Association between geographic atrophy progression and reticular pseudodrusen in eyes with dry age-related macular degeneration. *Invest Ophthalmol Vis Sci.* 2013;54:7362-7369.

5. Cohen SY, Dubois L, Tadayoni R, Delahaye-Mazza C, Debibie C, Quentel G. Prevalence of reticular pseudodrusen in age-related macular degeneration with newly diagnosed choroidal neovascularisation. *Br J Ophthalmol.* 2007;91:354-359.

6. Wu Z, Ayton LN, Luu CD, Baird PN, Guymer RH. Reticular pseudodrusen in intermediate age-related macular degeneration: Prevalence, detection, clinical, environmental, and genetic associations. *Invest Ophthalmol Vis Sci.* 2016;57:1310-1316.

383 7. Buitendijk GH, Hooghart AJ, Brussee C, et al. Epidemiology of reticular
384 pseudodrusen in age-related macular degeneration: The Rotterdam study. *Invest*
385 *Ophthalmol Vis Sci.* 2016;57:5593-5601.

386 8. Finger RP, Chong E, McGuinness MB, et al. Reticular pseudodrusen and their
387 association with age-related macular degeneration: The Melbourne collaborative
388 cohort study. *Ophthalmology.* 2016;123:599-608.

389 9. Curcio CA, Messinger JD, Sloan KR, McGwin G, Medeiros NE, Spaide RF.
390 Subretinal drusenoid deposits in non-neovascular age-related macular degeneration:
391 morphology, prevalence, tomography and biogenesis model. *Retina*. 2013; 33:265-
392 276.

393 10. Hogg RE, Silva R, Staurenghi G, et al. Clinical characteristics of reticular
394 pseudodrusen in the fellow eye of patients with unilateral neovascular age-related
395 macular degeneration. *Ophthalmology.* 2014;121:1748-1755.

396 11. Huisingh C, McGwin G, Neely D, et al. The association between subretinal
397 drusenoid deposits in older adults in normal macular health and incident age-related
398 macular degeneration. *Invest Ophthalmol Vis Sci.* 2016;57:739-745.

399 12. Chan H, Cougnard-Grégoire A, Delyfer M, et al. Multimodal imaging of reticular
400 pseudodrusen in a population-based setting: The Alienor study. *Invest Ophthalmol*
401 *Vis Sci.* 2016;57:3058-3065.

402 13. Cymerman RM, Skolnick AH, Cole WJ, Nabati C, Curcio CA, Smith RT.
403 Coronary artery disease and reticular macular disease, a subphenotype of early age-
404 related macular degeneration. *Curr Eye Res.* 2016;1:1482-1488.

14. Rastogi N, Smith RT. Association of age-related macular degeneration and reticular macular disease with cardiovascular disease. *Surv Ophthalmol.* 2015; 61:422-433.

15. Klein R, Meuer SM, Knudtson MD, Iyengar SK, Klein BE. The epidemiology of retinal reticular drusen. *Am J Ophthalmol.* 2008;145(2):317-326. e1.

16. Boddu S, Lee MD, Marsiglia M, Marmor M, Freund KB, Smith RT. Risk factors associated with reticular pseudodrusen versus large soft drusen. *Am J Ophthalmol.* 2014;157:985-993. e2.

17. Smith RT, Merriam JE, Sohrab MA, et al. Complement factor H 402H variant and reticular macular disease. *Arch Ophthalmol.* 2011;129:1061-1066.

18. Smith RT, Sohrab MA, Busuioc M, Barile G. Reticular macular disease. *Am J Ophthalmol.* 2009;148:733-743. e2.

19. Domalpally A, Clemons TE, Danis RP, et al. Peripheral retinal changes associated with age-related macular degeneration in the age-related eye disease study 2: Age-related eye disease study 2 report number 12 by the age-related eye disease study 2 optos peripheral retina (OPERA) study research group. *Ophthalmology.* 2017;S0161-6420:31491-31499.

20. Newby DE, Williams MC, Hunter A, et al. CT coronary angiography in patients with suspected angina due to coronary heart disease (SCOT-HEART): an open-label, parallel group, multicentre trial. *Lancet*. 2015;385:2383-2391.

21. Pellegrini E, Robertson G, Trucco E, et al. Blood vessel segmentation and width estimation in ultra-wide field scanning laser ophthalmoscopy. *Biomed Opt Express*. 2014; 5:4329-4337.

22. University of Wisconsin Fundus Photograph Reading Center. Study-specific grading procedures for OPERA study. 2013.

23. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics.* 1977;33(1):159-174.

24. Zarubina AV, Neely DC, Clark ME, et al. Prevalence of subretinal drusenoid deposits in older persons with and without age-related macular degeneration, by multimodal imaging. *Ophthalmology.* 2016;123:1090-1100.

25. Gliem M, Hendig D, Finger RP, Holz FG, Issa PC. Reticular pseudodrusen associated with a diseased bruch membrane in pseudoxanthoma elasticum. *JAMA Ophthalmology.* 2015;133:581-588.

26. Gliem M, Müller PL, Mangold E, et al. Reticular pseudodrusen in sorsby fundus dystrophy. *Ophthalmology.* 2015;122:1555-1562.

27. Freund KB, Laud K, Lima LH, Spaide RF, Zweifel S, Yannuzzi LA. Acquired vitelliform lesions: Correlation of clinical findings and multiple imaging analyses. *Retina.* 2011;31:13-25.

28. Garg A, Oll M, Yzer S, et al. Reticular pseudodrusen in early age-related macular degeneration are associated with choroidal thinning. *Invest Ophthalmol Vis Sci*. 2013; 54:7075-7081.

446 29. Cheng H, Kaszubski PA, Hao H, et al. The relationship between reticular macular
447 disease and choroidal thickness. *Curr Eye Res*. 2016;41:1492-1497.

448 30. Querques G, Querques L, Forte R, Massamba N, Coscas F, Souied EH.
449 Choroidal changes associated with reticular pseudodrusen. *Invest Ophthalmol Vis*
450 *Sci*. 2012;53:1258-1263.

451 31. Haas P, Esmaeelpour M, Ansari-Shahrezaei S, Drexler W, Binder S. Choroidal
452 thickness in patients with reticular pseudodrusen using 3D 1060-nm OCT maps.
453 *Invest Ophthalmol Vis Sci*. 2014;55:2674-2681.

454 32. Alten F, Clemens CR, Heiduschka P, Eter N. Localized reticular pseudodrusen
455 and their topographic relation to choroidal watershed zones and changes in
456 choroidal volumes. *Invest Ophthalmol Vis Sci*. 2013;54:3250-3257.

457 33. Spaide RF. Outer retinal atrophy after regression of subretinal drusenoid
458 deposits as a newly recognized form of late age-related macular degeneration.
459 *Retina*. 2013;33:1800-1808.

460 34. Leisy HB, Ahmad M, Marmor M, Smith RT. Association between decreased renal
461 function and reticular macular disease in age-related macular degeneration.
462 *Ophthalmology Retina*. 2017;1:42-48.

463 35. Zweifel SA, Spaide RF, Curcio CA, Malek G, Imamura Y. Reticular
464 pseudodrusen are subretinal drusenoid deposits. *Ophthalmology.* 2010;117:303-
465 312.e1.

36. Schaal KB, Legarreta AD, Feuer WJ, et al. Comparison between widefield en face swept-source OCT and conventional multimodal imaging for the detection of reticular pseudodrusen. *Ophthalmology.* 2016.

Table 1. Summary statistics for study participants.

	All participants n=534	Reticular Pseudodrusen (one or both eyes)		
		Absent n=504	Present n=30	p
Age				
Mean (SD)	58 (10)	58 (9)	59 (12)	0.76
Sex (%)				
Male	299 (56)	284 (56)	15 (50)	
Female	235 (44)	220 (44)	15 (50)	0.57
Body mass index				
Mean (SD)	30 (7)	30 (7)	28 (6)	0.19
CAD diagnosis (%)				
None	178 (33)	168 (33)	10 (33)	
Non-obstructive to mild	114 (21)	105 (21)	9 (30)	
Non-obstructive to moderate	87 (16)	84 (17)	3 (10)	
Obstructive CAD	150 (28)	142 (28)	8 (27)	
Missing	5 (1)	5(1)	0 (0)	0.71
CAD (%)				
Absent	178 (33)	168 (33)	10 (33)	
Present	351 (66)	331 (66)	20 (67)	
Missing	5 (1)	5 (1)	0 (0)	0.99
Assign Score				
Mean (SD)	18 (12)	18 (12)	17 (11)	0.56
Coronary Artery Calcium Score Mean (SD)	314 (805)	310 (814)	376 (634)	0.67
Hypertension (%)				
No	346 (65)	327 (65)	19 (63)	
Yes	182 (34)	171 (34)	11 (37)	
Missing	6 (1)	6 (1)	0 (0)	0.84
Diabetes (type1 or 2) (%)				
No	483 (90)	455 (90)	28 (93)	
Yes	51 (10)	49 (10)	2 (7)	0.76
Drusen >125μm (%)				
Absent	330 (62)	319 (63)	11 (37)	
Present	201 (38)	183 (36)	18 (60)	
Missing	3 (1)	2 (1)	1 (3)	0.01
Smoking History (%)				
Never	256 (48)	244 (48)	12 (40)	
Ex-smoker	193 (36)	183 (36)	10 (33)	
Current Smoker	85 (16)	77 (15)	8 (27)	0.25

CAD, coronary artery disease.

Table 2. Intragrader agreement for the individual age-related macular degeneration phenotypes.

AMD Characteristic	Kappa Range		
	Zone 1	Zone 2	Zone 3
Neovascular AMD	0.66	0.57	0.61
Increased Pigment	0.59	0.54	0.61
Decreased Pigment	0.66	0.55	0.62
Geographic Atrophy	0.66	0.76	0.62
Drusen	0.59	0.64	0.58
Maximum Drusen Size	0.60	0.62	0.55
Reticular Pseudodrusen	0.67	0.76	0.62
Peripheral Abnormality	NA	0.59	0.55
Presence of other Pathology (All zones)	0.62		

AMD, age-related macular degeneration; NA, not applicable.

Table 3 – Investigation of coronary artery disease as a risk factor for reticular pseudodrusen using generalized estimating equations.

	Unadjusted model			Age and Sex adjusted			Multivariate adjusted*		
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
CAD	1.30	0.58-2.92	0.52	1.33	0.57-3.11	0.52	1.31	0.57-3.01	0.52
Age				1.01	0.95-1.07	0.78	1.00	0.95-1.06	0.92
Sex				1.51	0.67-3.40	0.32	1.40	0.62-3.14	0.42
Drusen >125 μm							3.18	1.61-6.27	**0.001**

*Multivariate model was adjusted for age, sex and smoking status.

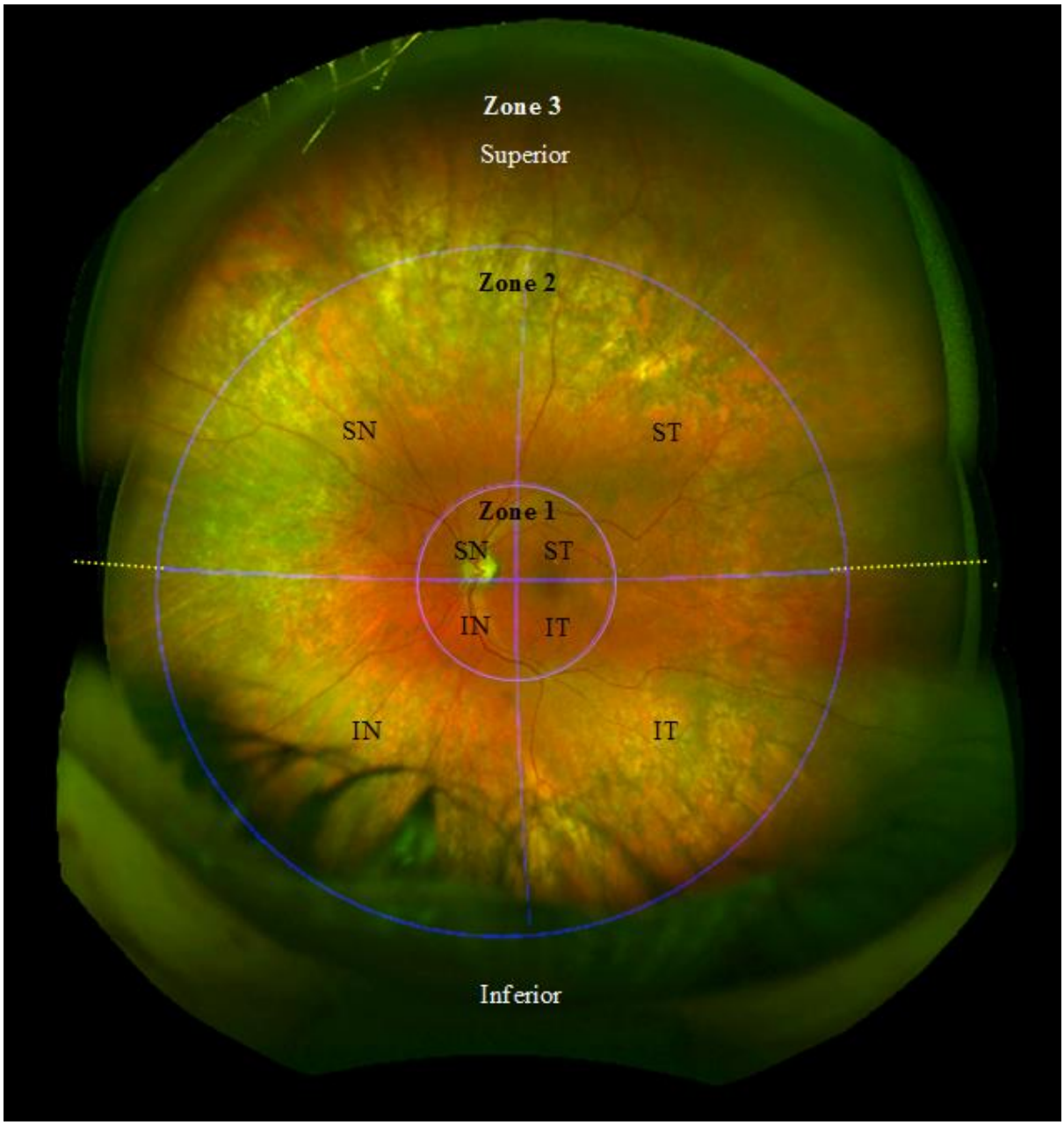

Figure 1: The Modified SOCA Grid utilized on the Optos Software.

Z1 and Z2 are each divided into four quadrants: superonasal (SN), superotemporal (ST), inferotemporal (IT), and inferonasal (IN). Z3 is divided into two hemispheres (superior, inferior) using a visual extension of the horizontal cross line (yellow dashed lines). Taken from the Study-Specific Grading Procedures for OPERA, University of Wisconsin (2013).[33]

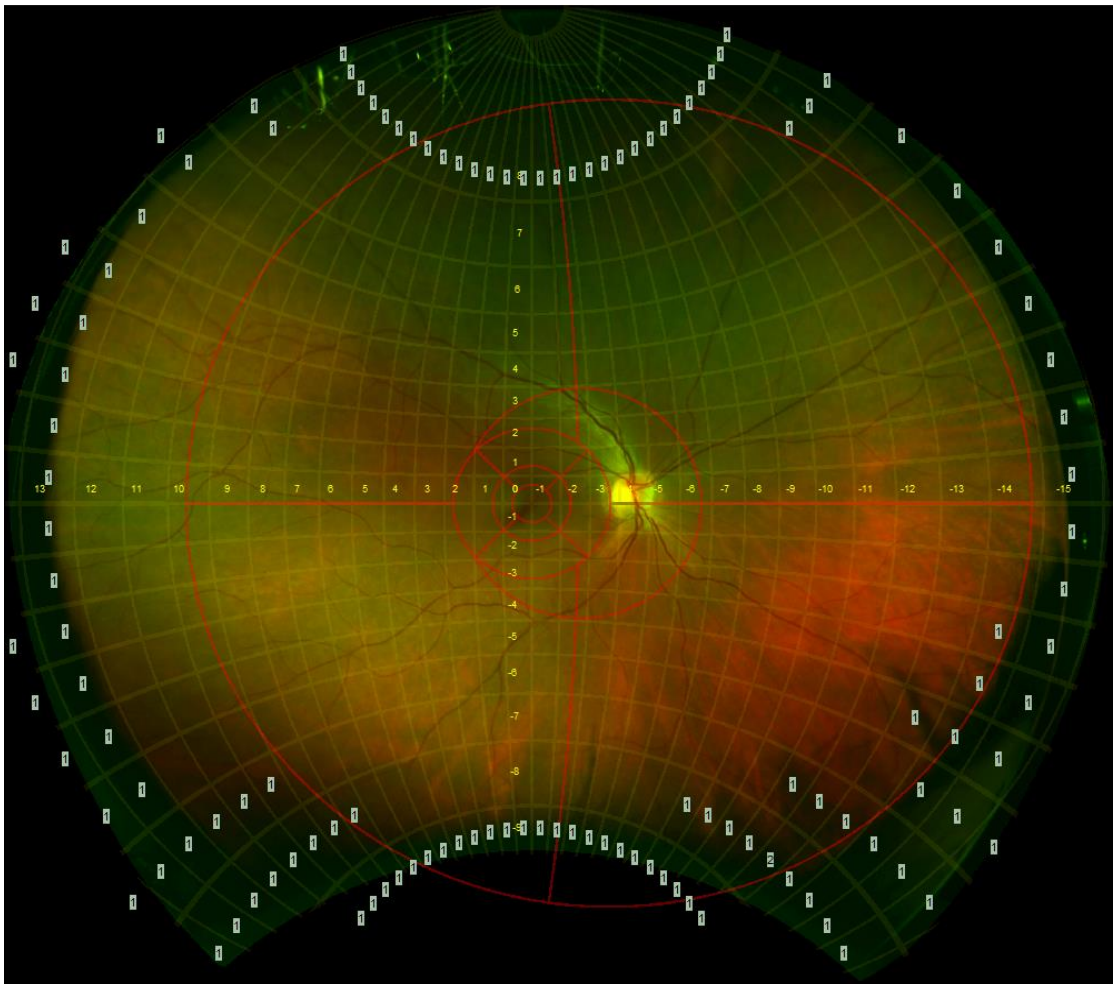

Figure 2: Optos ultra-widefield retinal image grading grids for specific AMD characteristics.

The SOCA grid is divided into three zones: Zone 1 (posterior pole), Zone 2 (extends from Z1 to a circle through the ampullae of the vortex veins) and Zone 3 (extends from Z2 to the outer periphery). The Manchester grid was superimposed onto the SOCA grid to assess the ungradable areas.

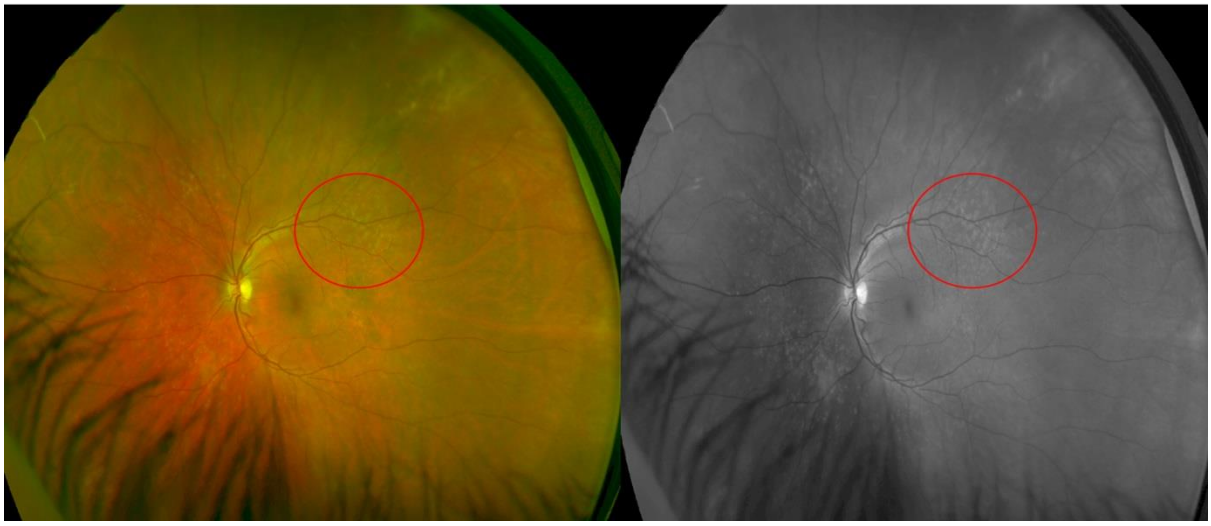

Figure 3: Optos ultra-widefield retinal image illustrating RPD.

The appearance of RPD on UWF is described as an interlacing reticular pattern, which appear superiorally in the outer macula and extend circumferentially and further.

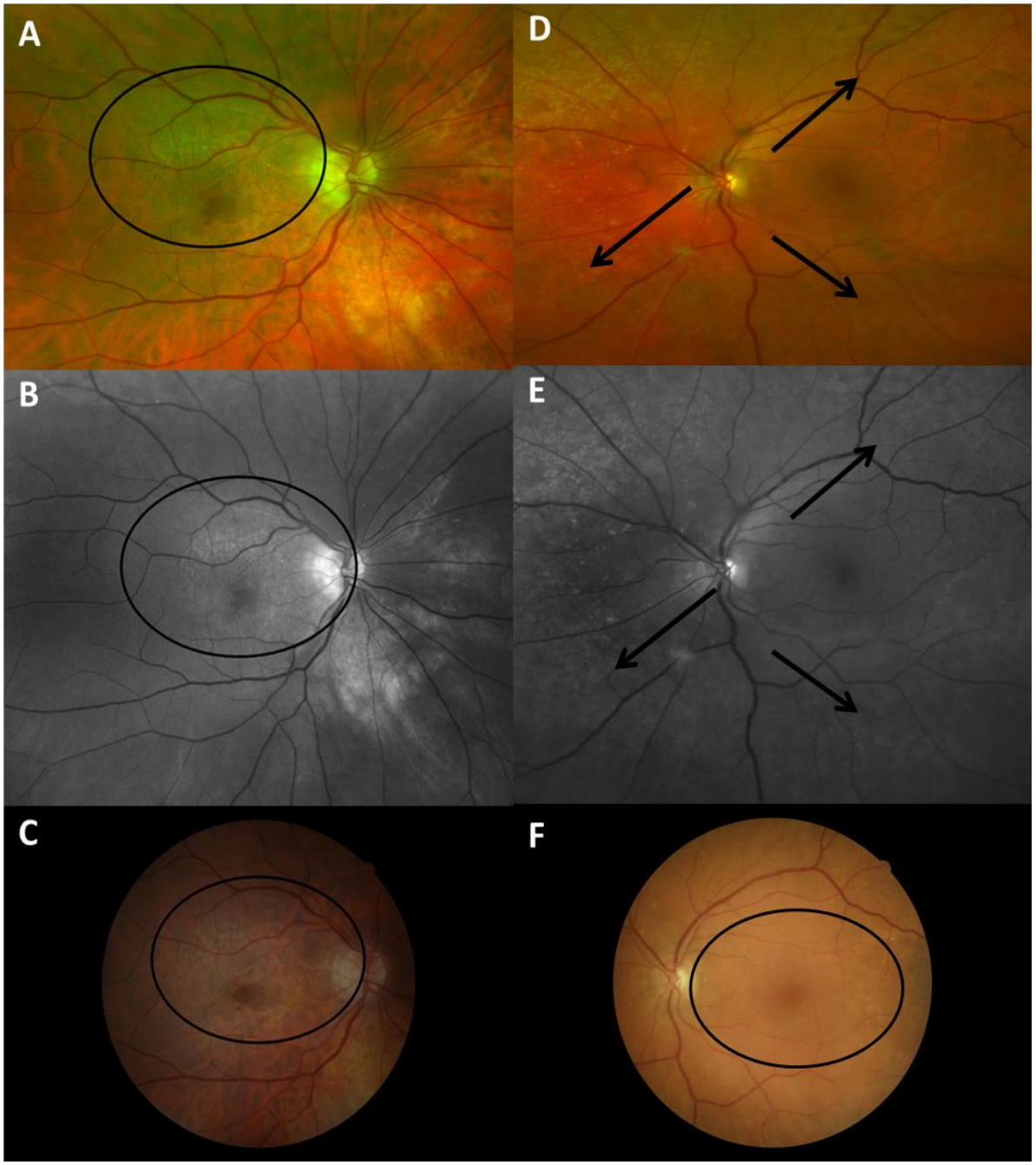

Figure 4 shows the RPD interlacing pattern on both the UWF and fundus camera image. **A.** UWF pseudo color image showing RPD (black circle). **B.** UWF green laser imaging with RPD visible within the black circle. **C.** Fundus camera image with RPD within the black circle. **D.** UWF pseudo color image with arrows pointing to areas of RPD. **E.** UWF green laser imaging with arrows annotating areas of RPD. In this case RPD was detected beyond the field of view of color fundus photography. **F.**

512 Corresponding fundus camera image with no readily visible RPD within the black
513 circle.
514