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Confocal Infrared imaging with Optical Coherence Tomography provides superior detection of a number of common macular lesions compared to colour fundus photography

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Color fundus photography, confocal infrared reflectance imaging, Optical Coherence Tomography, age-related pathology

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Comparison of retinal imaging modalities

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Abstract

Purpose

To compare diagnostic accuracy of confocal infrared reflectance (IR), with and without optical coherence tomography (OCT), to color fundus photography (CFP) in the Northern Ireland Cohort for the Longitudinal Study of Ageing (NICOLA) Study.

Methods

Cross sectional observational study of participants in NICOLA. CFP, IR and IR/OCT of 640 eyes were graded for: hard, soft and reticular pseudodrusen (RPD), geographic atrophy (GA), choroidal neovascularisation (CNV), naevus, epiretinal membrane (ERM) and haemorrhages. Test characteristics (sensitivity and specificity) for each imaging modality with respect to each retinal feature were calculated.

Results

With CFP as the reference standard, sensitivity of IR by itself ranged from 75% for RPD to 93.5% for hard drusen and specificity was above 90% for all features except hard drusen (71.7%). For IR combined with OCT, sensitivity ranged from 80% for CNV to 96.5% for hard drusen. When IR alone was the reference standard, CFP sensitivity was high for naevi (97.5%) but reduced markedly for ERM (48.5%). When the combination of IR and OCT was the reference standard, sensitivity for CFP was least for ERM (31.5%), low for GA and RPD (77.8 and 76.2% respectively) and high for all other lesion types.

Conclusion

Our findings support the use of confocal IR with OCT as a screening tool for a variety of features of macular disease in community optometric practice.

Introduction

Color Fundus Photography (CFP) has been the predominant technology used in the evaluation of retinal health and disease, in optometric practices, clinics and in population screening. This is because it is widely available, easy to capture and comparable to ophthalmoscopy. The practice of using CFP continues to this day with the recent publications reflecting international consensus describing both aging changes and pathology in terms of CFP findings.(1) Although CFP screening remains a cornerstone for the detection of diabetic retinopathy, glaucoma and age-related macular degeneration (AMD), many morphological biomarkers such as specific drusen types, macular oedema, and retinal neovascularisation are not consistently detected by this technology. Other limitations of CFP include reduced image clarity in the presence of ocular medial opacities and the presence of artefacts which can have a substantial effect on the quality of images and thus affect the detection rates of ocular pathology. New non-invasive methods to obtain high quality images of the retina have become available and these include the use of monochromatic laser wavelengths of the electromagnetic spectrum along with confocal technology, to improve delineation of pathology in the fundus. Confocal scanning laser ophthalmoscopy Infrared (IR) imaging is one such application of this technology and along with Optical Coherence Tomography (OCT) has been shown to have superior sensitivity and specificity in the detection of several retinal phenotypes including reticular pseudodrusen (RPD)(2)(3) and epiretinal membranes (ERM)(4) respectively. Walsh *et al* compared the sensitivity of OCT to nonmydriatric CFP for the detection of irregularities on the retina in asymptomatic individuals and concluded that OCT was more sensitive in the detection of retinal pathology and had a lower ungradable image rate.(5)

CFP has been commonly used in community optometry practices for many years, in many instances the images are used as a form of disease screening in combination with information from the eye test and direct clinical examination. More recently Optometrists have added OCT technology to their practice.(6)(7) Some machines incorporate CFP which is captured at the same time as the OCT while others include infrared with OCT.

To date there has been no systematic comparison of the agreement between CFP, with IR and OCT in detecting multiple forms of retinal pathology that may be

encountered in a community setting, to know whether IR and OCT could be used without CFP. We exploited the availability of both CFP and IR/OCT image sets from the same participants in an ongoing epidemiological study of aging in order to examine the sensitivity and specificity of the latter in the detection of common retinal pathologies.

Methods

Participants and image acquisition

Ethical approval for the study was obtained from the School of Medicine, Dentistry and Biomedical Sciences Ethics Committee, Queen's University Belfast (Ethics number: 12/23).

Images for this study were taken from the Northern Ireland Cohort for the Longitudinal Study of Ageing (NICOLA) Study repository. The NICOLA Study is an ongoing epidemiological study on the ageing population of Northern Ireland, United Kingdom, which includes multi-modal retinal imaging. A random sample of men and women aged 50 years and over were invited to participate in both a home interview and health assessment at which retinal imaging was undertaken. Participants were given the option of having the pupils of one or both eyes dilated or refusing pupillary dilation. CFP, IR and IR/OCT images were captured irrespective of pupillary dilation. CFP was performed on the Canon CX-1 Digital Fundus Camera (https://www.canon-europe.com/medical/eye_care/cx-1/) to capture images with 50° field of view. IR images were obtained on the Heidelberg Engineering Spectralis spectral domain optical coherence tomography/confocal scanning laser ophthalmoscope (SD-OCT/cSLO) (https://www.heidelbergengineering.com/int/company/), with a 30° field of view, and a single macula-centred image was obtained. High-resolution OCT images were obtained on the Heidelberg Engineering Spectralis SD-OCT/cSLO. Each fundus image (768 x 768 pixels) at a resolution of approximately 11µm per pixel was captured using the high speed mode. OCT volume scans were composed of 61 horizontal B-scan lines with a spacing between each scan of approximately 125µm on a 30° x 25° (horizontal x vertical) scan angle. Images were acquired using active eye tracking and

automatic real-time mean image averaging of 8 scans per B-scan. In each image, the macula was well positioned at the centre of the photograph.

Image selection

Over 3800 participant images were available from the repository which had been uploaded into a secure server at the Central Angiographic Resource Facility based at Queen's University, Belfast. As part of the main NICOLA Study the image sets had undergone grading previously for age related retinal changes and features of clinical importance or disease according to protocol by trained graders from the Network of Ophthalmic Reading Centres UK. Graders are trained in the recognition of features of ophthalmic eye diseases and are certified for study specific grading. Certification involves grading set numbers of images to a defined protocol, with the results compared to the standard set by an expert grader. Graders are required to achieve 90% concordance with the grading outcomes in the standard set and this process may be repeated over time to check for drift.

For the purposes of the present study, a test dataset was constructed using a subset of the overall dataset consisting of pairs of CFP and IR/OCT images which were selected, depending on the presence or absence of specific macular lesions, that we decided were most relevant for referral decisions within a primary care setting. We focused our analysis on those features that occurred at a frequency of around 5% within the overall dataset and therefore did not include macular holes, vitreomacular traction, macular dystrophies, pachychoroid spectrum disease as these were present at too low a frequency in our cohort. We also included a random selection of 100 eyes that had been graded as exhibiting no retinal abnormality. We did not perform a formal sample size calculation but we estimated that a sample of 640 right or left eyes would give us sufficient numbers of eyes with the features of interest at a prevalence of close to 5% or greater.

The test data set were allocated to a panel of selected graders (n = 6) who were previously certified for grading images from the NICOLA study. Graders used a

standardised protocol to determine whether the lesions of interest were present, absent or if the image was ungradable. The images from the different imaging modalities were presented to the graders in sequential fashion. At the first point in time only CFP were released for grading. On completion of grading of all CFP images, the next test technology was released for grading after an interval of one week. The same pattern was followed for the release of IR plus OCT. The graders were blinded to the results from the previously tested image modalities. At each grading wave the images were assigned randomly to each of the 6 graders thus minimising any risk of bias. CFP were viewed on Oculab (V3.7.98.0) and the IR and IR plus OCT Images were viewed using the Heidelberg Eye Explorer (version 1.7.1.0). All grading was conducted with screen settings standardised to the highest available resolution (1920 x 1080).

Retinal grading

Grading for AMD related lesions found on CFP and IR was performed using standard definitions based on the Wisconsin Age-Related Maculopathy Grading Scheme (WARMGS)(8) and Ly *et al*(9) respectively. CFP, IR and IR/OCT grading definitions are shown in Table 1.

All images were graded independently for each lesion type. Color and IR images were deemed ungradable if the retinal vessels could not be seen and less than 25% of the image was of sufficient quality to grade any lesion confidently. OCT images were deemed ungradable if the discrimination of retinal layers were not of suitable quality throughout the majority of the scans. Those discrepancies that arose due to the features of interest lying outside the field of view covered by IR and IR/OCT were excluded. All remaining discrepancies between CFP and the test technologies were then reviewed by a group consisting of an expert clinician (UC), senior grader (BH) and the research fellow involved in the study (NQ).

Sensitivity and specificity between the test technologies were calculated for hard, soft, RPD, GA, CNV, retinal haemorrhages, naevi and ERMs.

Statistical Analysis

Data were analysed using SPSS version 20.0 statistical software (SPSS; IBM, Armonk, NY, USA). The frequency of features that appeared outside the field of view on IR and IR/OCT imaging but within that seen on CFP was determined. Cross tabulation was used to compare the presence or absence of each feature only when present within the overlapping fields of view.

With CFP as the reference and IR and IR/OCT as the test, we computed sensitivity and specificity values. Similarly, sensitivity and specificity values were computed using IR/OCT as the reference standard and IR and CFP as the test. Lastly, sensitivity and specificity values were computed using IR as the reference standard and CFP and IR/OCT as the test. Sensitivity and specificity analysis was carried out on gradable image pairs.

Results

A total of 640 images sets were available for analysis. Of the image sets available 1.3% (20) CFP and 0.3% (2) IR and IR/OCT images were deemed ungradable for at least one feature.

Table 2 shows the frequency of the features of interest which were detected on CFP but which lay outside the field of view on IR and IR/OCT images. It also shows the frequencies of features that where seen on both IR and IR/OCT which lay within the field of view. A small proportion of eyes with early AMD features of hard soft and RPD were found on CFP but lay outside the field of view of IR and IR/OCT. Around one third of naevi that were seen on CFP were located outside the field covered by IR and IR/OCT.

Table 3 shows the frequency of the different features by test technology after exclusion of those that lay outside the field of view. Hard drusen were more frequently observed in IR/OCT (62.7%) and IR (61.4%) when compared to CFP where the detection rate was 52.6%. Soft drusen were detected with similar frequency in CFP (12.2%), IR (10.7%) and IR/OCT (11.0%). RPD were present at low frequency in the sample (4.0% of CFP, 3.6% of IR and 3.9% of IR/OCT images). GA was observed in 3.5% of CFP,

3.3% of IR and 4.5% on IR/OCT. CNV was detected in 0.8% of CFP and IR and 0.9%on IR/OCT.

Naevi were present at a higher frequency in CFP (10.7%), than that of IR (6.3%) and IR/OCT (6.1%). ERMs were most frequently graded as present in IR/OCT (17.7%). By contrast they were found in 6.1% in CFP and 10.8% of IR images. The detection rate of haemorrhages was 14.9% on CFP, 14.2% and 14.1% on IR and IR/OCT respectively.

With CFP as the reference standard (Table 4), sensitivity of IR alone was highest for naevi (95.1%) and least for RPD (75.0%). Specificity exceeded 90% for all other features except hard drusen (71.7%). On testing the combination of IR/OCT against CFP, sensitivity was high for hard drusen (96.5%), GA (95.5%) and naevi (92.7%) and least for CNV (80.0%). Specificity values exceeded 90% for most features except for hard drusen (71.1%) and ERM (87.0%). Figure 1 shows cases where soft drusen and RPD were detected on CFP but not present on IR/OCT.

With IR/OCT as the reference standard (Table 5) sensitivity of IR alone was highest for naevi (100.0%) and least for GA (72.4%). Similarly specificity was high >90% for all features except hard drusen (77.6%). For CFP, sensitivity was high for naevi (97.4%) but dropped markedly for ERM (31.5%). Specificity values exceeded 90% for all features. Figure 2 shows cases where IR/OCT detected RPD, ERM and GA when CFP failed to do so.

Using IR alone as the reference standard (Table 6) findings were similar to that observed when the combined IR and OCT images were used as the comparator. Figure 3 shows a case where hard and soft drusen were seen on IR but not detected on OCT.

Discussion

Despite the many advances in imaging of the retina, acquisition of CFP remains a key determinant in the diagnosis of AMD and its classification into the different stages of disease.(1) CFP also continues to be used widely in screening for diabetic retinopathy in community settings.(24) Nonetheless there is increasing recognition that newer imaging technologies can provide better definition and improved detection of pathology in the fundus, therefore in this study we investigated the ability of IR alone and IR combined with OCT to detect a variety of fundus pathology and compared the diagnostic accuracy against the accepted gold standard of CFP. Our sample for this study came from a repository acquired as part of a large epidemiological study of aging in an older population.

The present analysis has demonstrated the value of IR and OCT for the detection of early and late AMD features and other pathology such as ERMs, naevi and retinal haemorrhages, which are commonly encountered in older adults. We therefore postulate that the use of combined IR and OCT in the absence of CFP is effective as a rapid, low cost screening tool, particularly since these images can be captured with high fidelity even through an undilated pupil.(25) However, it must be remembered that the retinal grading needed to analyse such images requires a substantial amount of time and expertise as IR and OCT grading is different from the standard CFP grading. In terms of optometric practices opticians may require specialised training in order to confidently grade these images.

When compared against CFP, both IR and IR combined with OCT showed low specificity for hard drusen with values around 70% suggesting a high rate of false positives. However, on switching to IR/OCT as the reference technology, sensitivity values for CFP fell for hard drusen suggesting that the latter yields a higher rate of false negatives. OCT permits detailed scrutiny of the cross sectional profiles of the outer retina and the presence of an intact smooth retinal pigment epithelium layer without imperfections can be declared free of even small drusen. Thus it is possible that the higher frequency of false negatives for small drusen that were observed on CFP when IR/OCT was the reference standard may have arisen due to over interpretation of minor imperfections seen on the en face imaging modalities.

Among other features of the aging fundus are RPD and their role in the pathogenesis of AMD and their association with systemic disease is of major interest and the subject of ongoing studies.(26)(27)(28) Thus, identification of their presence and extent of involvement with fidelity is of high importance. When using CFP as the reference technology, both IR and IR/OCT showed reduced sensitivity for RPD. Our findings are in accord with those of Schmitz-Valckenberg et al (2011)(29) and Ueda-Arakawa et al (2013)(3) and support the view that CFP is less sensitive in the detection of RPD (Figure 2).

The confocal optical setup used in an IR scanning laser ophthalmoscope enables depth selective detection of RPD and supports a high sensitivity of identifying outer retinal pathology. Moreover, the confocality reduces the negative impact of cataract and scatter on the image quality when compared to CFP. With respect to naevi all three technologies, CFP, IR and IR combined with OCT performed with high sensitivity and specificity. Unsurprisingly IR/OCT was best for the detection of ERM. ERMs are seen on OCT as hyperreflective bands adjacent to the inner retina. CFP and IR alone can detect ERM when the area of involvement is large and the inner retina is deformed by this structure. However, OCT can detect ERM at the earliest stages where focal regions of dense hyperreflective bands are observed at the vitreoretinal interface.

We also noted that the quality of the acquired images was higher with IR/OCT and IR compared to CFP (Table 3). Notably the percentages of ungradable images were least with IR/OCT and IR (0.3%) compared to CFP (3.1%). An explanation for this may be due to the confocality reducing the negative impact of cataract and scatter on the image quality when compared to CFP. A number of IR and IR/OCT images failed to detect some of the retinal features of interest owing to the smaller field of view compared to that of CFP. Pathology that lay outside the region that was visualised on IR alone and IR/OCT was missed in 56 of 640 (8.8%) of eyes. Nevertheless, with technological improvements that yield larger fields of view with the current generation of tomographic acquisition systems this limitation should be overcome.

A potential limitation of our study is that the images were pre-selected to contain a sufficient number of retinal features for analysis contrary to STARD recommendations for reporting diagnostic accuracy of tests(30) increasing the risk that the test performance statistics may vary when employed in different population subgroups.

However, as this study drew its sample from the NICOLA population which enrolled participants older than 50 years of age, we believe that the features of interest are unlikely to differ markedly from any other older population group. We analysed the most popular features found in the NICOLA population thus features that occurred infrequently were not included e.g. macular hole and vitreomacular traction. A systematic comparison using images from a clinical population such as an eye casualty cohort would be useful in future for such lesions. Another potential limitation is that the numbers of eyes with CNV present was very low (n=6), thus yielding low sensitivity values. A larger sample is needed to investigate the value of IR and OCT in its detection.

In conclusion, the lower rate of ungradable images, the rapidity of image acquisition, the ability to identify outer retinal aging and pathological features with high precision support a transition to newer technologies as screening tools for macular disease.

References

1. Ferris FL, Wilkinson CP, Bird A, Chakravarthy U, Chew E, Csaky K, et al. Clinical classification of age-related macular degeneration. Ophthalmology. Elsevier; 2013;120(4):844–51.

2. Smith RT, Sohrab MA, Busuioc M, Barile G. Reticular macular disease. Am J Ophthalmol. Elsevier; 2009;148(5):733–743. e2.

3. Ueda-Arakawa N, Ooto S, Tsujikawa A, Yamashiro K, Oishi A, Yoshimura N. Sensitivity and specificity of detecting reticular pseudodrusen in multimodal imaging in Japanese patients. Retina. Department of Ophthalmology and Visual Sciences, Kyoto University Graduate School of Medicine, Kyoto, Japan.; 2013 Mar;33(3):490–7.

4. Do D V, Cho M, Nguyen QD, Shah SM, Handa JT, Campochiaro PA, et al. The impact of optical coherence tomography on surgical decision making in epiretinal membrane and vitreomacular traction. Trans Am Ophthalmol Soc [Internet]. The American Ophthalmological Society; 2006 Dec;104:161–6. Available from: https://www.ncbi.nlm.nih.gov/pubmed/17471336

5. Walsh AC, Heussen FM, Sadda SR, Ouyang Y. Prospective Comparison of Nonmydriatic Imaging and 3D Optical Coherence Tomography (3D-OCT) for Detecting Retinal Abnormalities. Invest Ophthalmol Vis Sci. The Association for Research in Vision and Ophthalmology; 2011;52(14):2176.

6. Dabasia PL, Edgar DF, Garway□Heath DF, Lawrenson JG. A survey of current and anticipated use of standard and specialist equipment by UK optometrists. Ophthalmic Physiol Opt. Wiley Online Library; 2014;34(5):592–613.

7. Ly A, Nivison□Smith L, Zangerl B, Assaad N, Kalloniatis M. Self□reported optometric practise patterns in age□related macular degeneration. Clin Exp Optom. Wiley Online Library; 2017;100(6):718–28.

8. Klein R, Davis MD, Magli YL, Segal P, Klein BEK, Hubbard L. The Wisconsin age-related maculopathy grading system. Ophthalmology. Elsevier;

1991;98(7):1128–34.

9. Ly A, Nivison□Smith L, Assaad N, Kalloniatis M. Infrared reflectance imaging in age□related macular degeneration. Ophthalmic Physiol Opt. Wiley Online Library; 2016;36(3):303–16.

10. Spaide RF, Curcio CA. Drusen characterization with multimodal imaging. Retina. Vitreous-Retina-Macula Consultants of New York, New York, USA. rickspaide@yahoo.com; 2010 Oct;30(9):1441–54.

11. Smith RT, Merriam JE, Sohrab MA, Pumariega NM, Barile G, Blonska AM, et al. Complement factor H 402H variant and reticular macular disease. Arch Ophthalmol. American Medical Association; 2011;129(8):1061–6.

12. Fleckenstein M, Issa PC, Helb H-M, Schmitz-Valckenberg S, Finger RP, Scholl HPN, et al. High-resolution spectral domain-OCT imaging in geographic atrophy associated with age-related macular degeneration. Invest Ophthalmol Vis Sci. The Association for Research in Vision and Ophthalmology; 2008;49(9):4137–44.

13. Bearelly S, Chau FY, Koreishi A, Stinnett SS, Izatt JA, Toth CA. Spectral domain optical coherence tomography imaging of geographic atrophy margins. Ophthalmology. Elsevier; 2009;116(9):1762–9.

14. Keane PA, Patel PJ, Liakopoulos S, Heussen FM, Sadda SR, Tufail A. Evaluation of age-related macular degeneration with optical coherence tomography. Surv Ophthalmol. Elsevier; 2012;57(5):389–414.

15. Krohn J, Frøystein T, Dahl O. Topographical distribution of choroidal naevi in the ocular fundus. Eye. Nature Publishing Group; 2009;23(8):1685–90.

16. Vallabh NA, Sahni JN, Parkes CK, Czanner G, Heimann H, Damato B. Near-infrared reflectance and autofluorescence imaging characteristics of choroidal nevi. Eye. Nature Publishing Group; 2016;30(12):1593–7.

17. Shields CL, Manalac J, Das C, Saktanasate J, Shields JA. Review of spectral domain enhanced depth imaging optical coherence tomography of tumors of the choroid. Indian J Ophthalmol. Department of Oncology Service, Wills Eye

Hospital, Thomas Jefferson University, Philadelphia, PA, USA.; 2015 Feb;63(2):117–21.

18. Wickham L, Gregor Z. Epiretinal membranes. In: Retina (Fifth Edition). Elsevier; 2013. p. 1954–61.

19. Kilic Muftuoglu I, Bartsch DU, Barteselli G, Gaber R, Nezgoda J, Freeman WR. Visualization of Macular Pucker by Multicolor Scanning Laser Imaging. Retina. *Department of Ophthalmology, Jacobs Retina Center, Shiley Eye Institute, University of California San Diego, La Jolla, California; and daggerGenentech Inc, South San Francisco, California.; 2017 Feb 1;

20. Stevenson W, Prospero Ponce CM, Agarwal DR, Gelman R, Christoforidis JB. Epiretinal membrane: optical coherence tomography-based diagnosis and classification. Clin Ophthalmol. Department of Ophthalmology, University of Arizona Medical Center, Tucson, AZ, USA.; Department of Ophthalmology, University of Arizona Medical Center, Tucson, AZ, USA.; Department of Ophthalmology, University of Arizona Medical Center, Tucson, (TRUNCATED; 2016 Mar 29;10:527–34.

21. Kanski JJ, Bowling B. Clinical ophthalmology: a systematic approach. Elsevier Health Sciences; 2011.

22. Theelen T, Hoyng CB, Klevering BJ. Near-infrared subretinal imaging in choroidal neovascularization. In: Medical Retina. Springer; 2010. p. 77–93.

23. Gella L, Raman R, Rani PK, Sharma T. Spectral domain optical coherence tomography characteristics in diabetic retinopathy. Oman J Ophthalmol. Department of Optometry, Elite School of Optometry, No. 8, G. S. T. Road, St. Thomas Mount, India.; Shri Bhagwan Mahavir Vitreoretinal Department, 18, College Road, Sankara Nethralaya, Chennai, Tamil Nadu, India.; Shri Bhagwan Mahavir Vitreoreti(TRUNCATED; 2014 Sep;7(3):126–9.

24. Salz DA, Witkin AJ. Imaging in diabetic retinopathy. Middle East Afr J Ophthalmol. New England Eye Center, Tufts Medical Center, Boston, MA 02108, USA.; New England Eye Center, Tufts Medical Center, Boston, MA 02108, USA.; 2015;22(2):145–50.

25. Tanga L, Roberti G, Oddone F, Quaranta L, Ferrazza M, Berardo F, et al. Evaluating the effect of pupil dilation on spectral-domain optical coherence tomography measurements and their quality score. BMC Ophthalmol. BioMed Central; 2015;15(1):175.

26. Hogg RE. Reticular pseudodrusen in age-related macular degeneration. Optom Vis Sci. *BSc(Hons)Optom, PhD Centre for Experimental Medicine, Institute of Clinical Sciences A, Grosvenor Rd, Royal Victoria Hospital, Belfast, Northern Ireland, United Kingdom.; 2014 Aug;91(8):854–9.

27. Steinberg JS, Gobel AP, Fleckenstein M, Holz FG, Schmitz-Valckenberg S. Reticular drusen in eyes with high-risk characteristics for progression to late-stage age-related macular degeneration. Br J Ophthalmol. Department of Ophthalmology, University of Bonn, Bonn, Germany.; Department of Ophthalmology, University of Bonn, Bonn, Germany.; Department of Ophthalmology, University of Bonn, Bonn, Germany.; Department of Ophthalmology, University of Bonn, B(TRUNCATED; 2015 Sep;99(9):1289–94.

28. McCarter R V, McKay GJ, Quinn NB, Chakravarthy U, MacGillivray TJ, Robertson G, et al. Evaluation of coronary artery disease as a risk factor for reticular pseudodrusen. Br J Ophthalmol. Centre for Public Health, Queen's University Belfast, Belfast, UK.; Centre for Public Health, Queen's University Belfast, Belfast, UK.; Centre for Public Health, Queen's University Belfast, Belfast, UK.; Centre for Public Health, Queen's Univers(TRUNCATED; 2017 Aug 19;

29. Schmitz-Valckenberg S, Alten F, Steinberg JS, Jaffe GJ, Fleckenstein M, Mukesh BN, et al. Reticular drusen associated with geographic atrophy in age-related macular degeneration. Invest Ophthalmol Vis Sci. The Association for Research in Vision and Ophthalmology; 2011;52(9):5009–15.

30. Cohen JF, Korevaar DA, Altman DG, Bruns DE, Gatsonis CA, Hooft L, et al. STARD 2015 guidelines for reporting diagnostic accuracy studies: explanation and elaboration. BMJ Open. Department of Clinical Epidemiology, Biostatistics and Bioinformatics, Academic Medical Centre, University of Amsterdam,

Amsterdam, The Netherlands.; Department of Pediatrics, INSERM UMR 1153, Necker Hospital, AP-HP, Paris Descartes University, (TRUNCATED; 2016 Nov 14;6(11):e012799-2016-012799.

Figure 1A. The CFP from the right eye of this participant was graded as showing yellow interlacing networks in the superior and inferior arcades which corresponds to RPD (white arrows). The corresponding IR/OCT does not exhibit subretinal drusenoid deposits If seen subretinal drusenoid deposits appear as increased bands of hyperreflectivity distributed as peaks or undulating waves in the outer retina at the level of the photoreceptor matrix causing deviations of the external limiting membrane. **Figure 1B.** The CFP from the left eye of this participants was graded as showing a small drusen (white arrow). The corresponding OCT image shows a smooth RPE band with no visible drusen.

Figure 2A. The CFP from the right eye of this participant was graded as showing pallor in the central macula, with a cresentic patch of atrophy on the temporal aspect of the optic disk and hard drusen. The IR/OCT shows an increased undulating band of reflectivity in the outer retina causing deviations of the external limiting membrane on OCT signifying the presence of subretinal drusenoid deposits (white arrows) which corresponds to clusters of ill-defined hyperreflective areas on IR. A discontinuous band of hyperreflectivity is also visible on the inner aspect of the retina indicating the presence of an ERM (red arrow). **Figure 2B** The CFP from the right eye of this participant was graded as showing distinct and indistinct soft drusen (white arrow) and diffuse pallor. In the IR/OCT image there is narrowing of the outer nuclear layer with subsidence of the inner retinal layers towards Bruch's membrane (white arrow). There is a region of complete loss of the outer retina including RPE through which there is a well-defined band of hyper transmission (red arrows) which corresponds to the well delineated hyperreflective area on IR. As in the case shown in panel A there is an epiretinal membrane on the inner surface of the retina and subretinal drusenoid deposits corresponding to the presence of reticular pseudo drusen both of which were not detected on CFP.

Figure 3A. The IR from the right eye of this participant was graded as showing soft drusen in the macular area of the retina. On IR soft drusen appears as focal interspersed areas of increased reflectivity (white arrow). The corresponding OCT image shows a smooth undeviated RPE band without drusen. **Figure 3B.** The IR from

the right eye of this participant was graded as exhbiting small drusen. On IR hard drusen appears as focal, well-defined spots of increased reflectivity (white arrow). The corresponding IR/OCT image shows no focal deformation or thickening between the basal lamina of the RPE and Bruch's membrane indicating the absence of drusen.