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

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16 **Key words**

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20 Comparison of retinal imaging modalities

21

22

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# 1 **Abstract**

## 2 **Purpose**

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

## 6 **Methods**

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

## 12 **Results**

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

## 21 **Conclusion**

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

24

# 1 Introduction

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

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

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

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

6

## 7 **Methods**

### 8 **Participants and image acquisition**

9 Ethical approval for the study was obtained from the School of Medicine, Dentistry and  
10 Biomedical Sciences Ethics Committee, Queen's University Belfast (Ethics number:  
11 12/23).

12 Images for this study were taken from the Northern Ireland Cohort for the Longitudinal  
13 Study of Ageing (NICOLA) Study repository. The NICOLA Study is an ongoing  
14 epidemiological study on the ageing population of Northern Ireland, United Kingdom,  
15 which includes multi-modal retinal imaging. A random sample of men and women aged  
16 50 years and over were invited to participate in both a home interview and health  
17 assessment at which retinal imaging was undertaken. Participants were given the  
18 option of having the pupils of one or both eyes dilated or refusing pupillary dilation.  
19 CFP, IR and IR/OCT images were captured irrespective of pupillary dilation. CFP was  
20 performed on the Canon CX-1 Digital Fundus Camera ([https://www.canon-](https://www.canon-europe.com/medical/eye_care/cx-1/)  
21 [europe.com/medical/eye\\_care/cx-1/](https://www.canon-europe.com/medical/eye_care/cx-1/)) to capture images with 50° field of view. IR  
22 images were obtained on the Heidelberg Engineering Spectralis spectral domain  
23 optical coherence tomography/confocal scanning laser ophthalmoscope (SD-  
24 OCT/cSLO) (<https://www.heidelbergengineering.com/int/company/>), with a 30° field of  
25 view, and a single macula-centred image was obtained. High-resolution OCT images  
26 were obtained on the Heidelberg Engineering Spectralis SD-OCT/cSLO. Each fundus  
27 image (768 x 768 pixels) at a resolution of approximately 11µm per pixel was captured  
28 using the high speed mode. OCT volume scans were composed of 61 horizontal B-  
29 scan lines with a spacing between each scan of approximately 125µm on a 30° x 25°  
30 (horizontal x vertical) scan angle. Images were acquired using active eye tracking and

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

3

#### 4 **Image selection**

5 Over 3800 participant images were available from the repository which had been  
6 uploaded into a secure server at the Central Angiographic Resource Facility based at  
7 Queen's University, Belfast. As part of the main NICOLA Study the image sets had  
8 undergone grading previously for age related retinal changes and features of clinical  
9 importance or disease according to protocol by trained graders from the Network of  
10 Ophthalmic Reading Centres UK. Graders are trained in the recognition of features of  
11 ophthalmic eye diseases and are certified for study specific grading. Certification  
12 involves grading set numbers of images to a defined protocol, with the results  
13 compared to the standard set by an expert grader. Graders are required to achieve  
14 90% concordance with the grading outcomes in the standard set and this process may  
15 be repeated over time to check for drift.

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

28

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

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

12

### 13 **Retinal grading**

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

18

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

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

30



## 1 **Statistical Analysis**

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

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

## 13 **Results**

14 A total of 640 images sets were available for analysis. Of the image sets available  
15 1.3% (20) CFP and 0.3% (2) IR and IR/OCT images were deemed ungradable for at  
16 least one feature.

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

24 Table 3 shows the frequency of the different features by test technology after exclusion  
25 of those that lay outside the field of view. Hard drusen were more frequently observed  
26 in IR/OCT (62.7%) and IR (61.4%) when compared to CFP where the detection rate  
27 was 52.6%. Soft drusen were detected with similar frequency in CFP (12.2%), IR  
28 (10.7%) and IR/OCT (11.0%). RPD were present at low frequency in the sample (4.0%  
29 of CFP, 3.6% of IR and 3.9% of IR/OCT images). GA was observed in 3.5% of CFP,

1 3.3% of IR and 4.5% on IR/OCT. CNV was detected in 0.8% of CFP and IR and  
2 0.9%on IR/OCT.

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

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

15 With IR/OCT as the reference standard (Table 5) sensitivity of IR alone was highest  
16 for naevi (100.0%) and least for GA (72.4%). Similarly specificity was high >90% for  
17 all features except hard drusen (77.6%). For CFP, sensitivity was high for naevi  
18 (97.4%) but dropped markedly for ERM (31.5%). Specificity values exceeded 90% for  
19 all features. Figure 2 shows cases where IR/OCT detected RPD, ERM and GA when  
20 CFP failed to do so.

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

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# 1 Discussion

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

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

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

1 Among other features of the aging fundus are RPD and their role in the pathogenesis  
2 of AMD and their association with systemic disease is of major interest and the subject  
3 of ongoing studies.(26)(27)(28) Thus, identification of their presence and extent of  
4 involvement with fidelity is of high importance. When using CFP as the reference  
5 technology, both IR and IR/OCT showed reduced sensitivity for RPD. Our findings are  
6 in accord with those of Schmitz-Valckenberg et al (2011)(29) and Ueda-Arakawa et al  
7 (2013)(3) and support the view that CFP is less sensitive in the detection of RPD  
8 (Figure 2).

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

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

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

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

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

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

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

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

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

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