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OPTICAL COHERENCE TOMOGRAPHY, FLUORESCEIN ANGIOGRAPHY, AND DIAGNOSIS OF CHOROIDAL NEOVASCULARIZATION IN AGE-RELATED MACULAR DEGENERATION

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Purpose: To determine the sensitivity and specificity of different retinal imaging combinations for the diagnosis of choroidal neovascularization (CNV) in age-related macular degeneration.

Methods: Patients aged 50 years or older referred for suspicious recent-onset CNV related to age-related macular degeneration were prospectively included for 6 months. Data recorded included color fundus photographs (CFPs), spectral domain optical coherence tomography (SD-OCT), and fluorescein angiography (FA) images. Five retina specialists randomly interpreted SD-OCT combined with CFP, and then FA combined with CFP. The reference diagnosis of CNV was based on the agreement of two readers in the interpretation of the SD-OCT + FA + CFP combination.

Results: One hundred and forty-eight patients (148 eyes) were included. For the diagnosis of CNV, the sensitivity of both SD-OCT + CFP and FA + CFP was of 90.9%. Type 2 CNV was diagnosed in 98% to 100% of cases with SD-OCT + CFP or FA + CFP, whereas Type 1 CNV was diagnosed in 82.9% of cases with SD-OCT + CFP and 81.6% with FA + CFP.

Conclusion: When used as a first diagnostic test, SD-OCT combined with CFP had sensitivity and specificity similar to those of FA combined with CFP, for the diagnosis of CNV in age-related macular degeneration. This shows the increasingly important role of SD-OCT as a first-line test in the diagnosis of CNV.

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The use of optical coherence tomography (OCT) has progressively emerged as the first-line diagnostic test for detecting exudative age-related macular degeneration (AMD). Although fluorescein angiography (FA) was and may still be considered by some as the gold standard to establish the diagnosis of macular choroidal neovascularization (CNVs),[1–3] its concomitant use with OCT has, in fact, become the standard in current practice.[4,5] Optical coherence tomography has even progressively emerged as the first-line diagnostic tool for detecting exudative AMD. Thus, combining FA and OCT may be considered the new gold standard for diagnosis of exudative AMD.[6,7] Even more, the follow-up of treated eyes, including decisions for re-treatment, is most often only based on OCT findings.[8,9] The recent advent of OCT angiography (OCTA) in combination with structural OCT emerges as a possible alternative to FA.[7,10] However, OCTA is still an improving technology and is not yet available everywhere. Few studies have compared the diagnostic power of FA and structural OCT to diagnose CNV in AMD and most of them used time domaine OCT (TD-OCT),[11–13] although spectral domain OCT (SD-OCT), now used in routine, has the advantage to provide a high-density raster of B-scans allowing for mapping more precisely the macular area.[14–16] Based on the observation that in current clinical practice, the diagnosis of CNV is often anticipated before obtaining

the results of FA, we aimed to compare the relative performances of SD-OCT combined with color fundus photograph (CFP) and FA combined with CFP for establishing the diagnosis of CNV in patients referred for suspicious exudative AMD. A prospective observational study was then conducted in which several retina specialists read SD-OCT + CFP and FA + CFP images separately without interfering with patient management. Each reader had access to CFP as a surrogate to biomicroscopic fundus examination to be close to the current clinical practice. For each case, the reference diagnosis was made based on the whole data set (SD-OCT + FA + CFP).

Methods

This prospective, multicentric, observational study was conducted in two tertiary care retina practices. The Institutional Review Board (IRB)/Ethics Committee of Saint Louis Hospital (Paris) approval was obtained, and digital data management was declared and approved by a French national committee (Commission Nationale de l'Informatique et des Libertés), as required by the French law. The study was also registered in the database of the National Institutes of Health (NIH) on clinicaltrials.gov (identifier no. NCT01080898). All patients signed a consent form for the use of their data.

Patients

A total of 148 consecutive patients aged 50 years or older referred for suspicious recent-onset CNV secondary to AMD were included for 6 months (62 patients in Center 1 and 86 in Center 2). Eligibility criteria are summarized in Table 1. Patients were included in the study by the ophthalmologists of the two study centers, referred to as investigators, who did not participate thereafter in the double-masked reading of fundus imaging. Only one eye per patient was included in the study.

Table 1. Eligibility Criteria for Including Patients in the Study

Inclusion Criteria	Exclusion Criteria
Minimum age: 50 years	Allergy to fluorescein dye
Suspicious recent-onset CNV secondary to AMD	Diabetes mellitus
First visit to a retina specialist	Previous laser treatment, photodynamic treatment, or intravitreal injection
SD-OCT and FA prescribed by the investigator as part of his routine practice	Clear evidence on fundus examination of
	Central retinal vein occlusion
	Epiretinal membrane
	Retinal detachment
	Macular hemorrhage >1/3 of the macula

Data Collection

Only data obtained at the first examination were used, including CFP, SD-OCT, and FA. The study did not interfere with patient management, which was at the investigator's discretion, regardless of the subsequent interpretation of imaging data by the readers. In practice, imaging data of each patient were duplicated, anonymized, and recorded in a secured computer for further analysis.

Color fundus photography. The Topcon TRC 50 DX was used in the two inclusion centers to obtain CFP centered on the macula after pupil dilation.

Spectral domain optical coherence tomography. The Cirrus 4000 OCT (Carl Zeiss Meditec, Dublin, CA) was used to acquire a macular cube (128 lines × 512 pixels) and horizontal and vertical 5-line raster scans spaced 75 μm apart centered on the fovea, corresponding to our routine practice.

Fluorescein angiography. The Topcon TRC 50 DX digital camera was used in the two inclusion centers. Fifty-degree images centered on the macula were acquired. Four images of the total angiographic sequence were selected for subsequent reading, including early-phase (<30 seconds), mid-phase (<1 minute and <3 minutes), and late-phase (>5 minutes) images.

Image Interpretation

Five retina specialists randomly and individually interpreted SD-OCT combined with CFP, and then FA combined with CFP. All data were analyzed in the same center on two dedicated computers. One computer used the Cirrus viewer (Carl Zeiss Meditec),

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which allowed for interpreting images as in clinical practice with access to all SD-OCT acquired lines. The second computer was used to visualize CFP and FA. Liquid crystal display monitors used had a 1,900 × 1,200-pixel resolution. During each session, each reader interpreted a portion (2/5) of all cases so that each case was interpreted by two different readers. Each reader did not read the same cases on SD-OCT + CFP and FA + CFP to avoid a recall bias. Sessions were spaced by at least 1 month.

The readers were not aware of the ongoing patient management.

During image interpretation, the main objective was to determine whether any type of CNV could be identified or not. When CNV was diagnosed, it was then classified as Type 1 CNV, Type 2 CNV, or "other CNV," which included retinal angiomatous proliferation and polypoidal choroidal vasculopathy.

Imaging analysis criteria for Sets 1 and 2 are summarized in Tables 2 and 3, respectively. Because the diagnosis was only established based on imaging findings, the readers received no information on the history of symptoms or visual acuity.

Reference Diagnosis

A third session was organized during which each reader randomly and individually interpreted the cases with the combination of SD-OCT, FA, and CFP. Each reader interpreted a portion (2/5) of the total cases so that each case was interpreted by two different readers. The reference diagnosis of CNV was based on the combination of SD-OCT, FA, and CFP when two readers agreed for the diagnosis. In the few cases for which the readers disagreed, a reconciliation session was organized with the five readers to establish the reference diagnosis.

The diagnoses made based on SD-OCT + CFP or FA + CFP were then compared with the reference diagnosis.

Data Analysis

All descriptive analyzes included the mean, SD, median (quartiles), and bilateral 95% confidence intervals (CIs). Each response of a single reader was interpreted as an independent result. The intervariability calculation was based on kappa coefficients.

Statistical calculations were performed using SAS software version 9.2.

Results

Patient median age was 81 years (range: 51–94). One hundred and ten eyes (74.3%, 95% CI [67.3–81.4]) had CNV: 22.7% (95% CI [14.9–30.6]) were Type 2 CNV, 34.6% (95% CI [25.7–43.4]) were Type 1 CNV, and 42.7% (95% CI [33.5–52.0]) were classified as "other CNV."

A reconciliation session was organized with the 5 readers to establish the reference diagnosis for 12 cases. The sensitivity of SD-OCT combined with CFP to diagnose new-onset CNV was of 90.9% (95% CI [87.1–94.7]) and its specificity was of 88.2% (95% CI [80.9–95.4]). The sensitivity of FA combined with CFP was of 90.9% (95% CI [87.1–94.7]) and its specificity was of 87.7% (95% CI [80.1–95.2]). Type 2 CNV was identified as CNV in 98% and 100% of cases with SD-OCT + CFP and FA + CFP, respectively. Type 1 CNV was identified as CNV in 82.9% and 81.6% of cases with SD-OCT + CFP and FA + CFP, respectively. "Other CNV" was identified as CNV in 93.6% of cases with SD-OCT + CFP or FA + CFP. Results are summarized in Tables 4 and 5. The

Table 2. Diagnostic Criteria for Set 1*: SD-OCT + CFP

For the Diagnosis of Macular CNV in General	For the Diagnosis of Type 1 CNV	For the Diagnosis of Type 2 CNV
Presence on SD-OCT of at least one component from each group	Presence on SD-OCT of at least one component from each group	Presence on SD-OCT of at least one component from each group
Irregular elevation of the RPE in the macular area	Irregular elevation of the RPE in the macular area	Hyperreflective fusiform lesion above the RPE
Serous pigment epithelial detachment	Ruling out a hyperreflective fusiform lesion above the RPE	Ruling out an irregular elevation of the RPE in the macular area
Hyperreflective fusiform lesion above the RPE		
Subretinal fluid, even limited	Subretinal fluid, even limited	Subretinal fluid, even limited
Macular retinal thickening	Macular retinal thickening	Macular retinal thickening

*Color fundus photograph should not preclude the diagnosis. Cases that could not clearly be identified as Type 1 or Type 2 CNV were classified as "other CNV." However, if the diagnostic criteria were not fully met, the reader could diagnose CNV based on his own conviction and experience, as he would do in his current practice.

Table 3. Diagnostic Criteria for Set 2: FA + CFP

For the Diagnosis of Macular CNV in General	For the Diagnosis of Type 1 CNV	For the Diagnosis of Type 2 CNV
At least progressive subretinal dye leakage associated with one of the typical features of CNV subgroups	Vascularized pigment epithelial detachment	Bright area of well-delineated choroidal fluorescence in the early phase of the angiogram
	Late leakage of undetermined source	

Color fundus photograph should not preclude the diagnosis. Cases that could not clearly be identified as Type 1 or Type 2 CNV were classified as "other CNV." However, if the diagnostic criteria were not fully met, the reader could diagnose CNV based on his own conviction and experience, as he would do in his current practice.

interrater reproducibility of SD-OCT + CFP and FA + CFP for the diagnosis of CNV was kappa = 0.82 and 0.74, respectively. The number of different diagnoses made per reader based on SD-OCT + CFP and FA + CFP compared with the reference diagnosis of the study is shown in Table 6.

Discussion

Optical coherence tomography is commonly used as a reference imaging tool to assess the response of exudative AMD to anti–vascular endothelial growth factor therapy.[8,9,17–19] In current practice, when CNV is suspected for the first time, SD-OCT is often the first test performed to guide the diagnosis. However, although FA still remains the reference to establish the diagnosis of CNV,[1–3] many studies have shown the increasingly important role of SD-OCT.[11,20–22] In this prospective study, we showed that SD-OCT or FA combined with CFP had similar sensitivity (90.9%) and specificity (88.2% for SD-OCT; 87.7% for FA) for the primary diagnosis of CNV due to AMD, in settings close to that of the current practice in patients referred for recent visual impairment due to macular symptoms.

The novelty of our study was to use a combination of SD-OCT, FA, and CFP for the reference diagnosis and not just FA alone, as performed in previous comparable studies, which would have resulted in an unproved 100% accuracy.[23] These results thus differ from those of previous studies aiming at comparing the power of OCT and FA to detect a conversion from non–neovascular AMD to neovascular AMD.[11,12] The place of FA as a gold standard in CNV diagnosis has also been recently questioned by the results of a retrospective study comparing OCTA combined with structural OCT versus OCTA alone or FA alone, in which FA alone was able to detect Type 1 CNV in only 66.7% of cases, that is, not more than what was detected with OCTA alone.[10] In the past, the use of TD-OCT has shown sensitivity and specificity less than those of FA.[11,12,24]

Our study, which was designed and performed before the availability of OCTA, anticipated the obsolescence of FA alone as a gold standard and we therefore used the combination of multimodal tests, SD-OCT, FA, and CFP for the reference diagnosis.

Other studies have shown a good sensitivity with SD-OCT for detecting CNV. In a study only assessing 21 eyes, Park et al[25] have found a sensitivity of 100%. Wilde et al[23] have reported sensitivity and specificity of SD-OCT for detecting CNV of 100% and 80.8%, respectively. However, they concluded that SD-OCT cannot replace FA in the diagnosis of neovascular AMD in current clinical practice because of a lower specificity and higher false-positive rates compared with FA. Other studies have found a very high sensitivity of SD-OCT, close to 100%, for detecting CNV activity.[23,25,26] But all these studies used FA as the gold standard and when SD-OCT showed some CNV activity, whereas FA did not, it was

Table 4. Sensitivity for the Diagnosis of CNV: Overall Sensitivity and Sensitivity for the Different CNV Types

Tests	Overall Sensitivity (%)	Sensitivity for Type 1 CNV (%)	Sensitivity for Type 2 CNV (%)	Sensitivity for Other CNV (%)
FA + CFP	90.9	100	81.6	93.6
SD-OCT + CFP	90.9	98	82.9	93.6

Table 5. Specificity for the Diagnosis of CNV and Interrater Reproducibility

Tests	Specificity (%)	Interrater Reproducibility
FA + CFP	87.7	Kappa = 0.74
SD-OCT + CFP	88.2	Kappa = 0.82

considered as a false-positive and decreased SD-OCT specificity. In fact, it is likely that SD-OCT in some cases is more sensitive than the presumed gold standard, FA, and that minimal SD-OCT signs may represent very early structural changes that occur before a leak detectable with FA in some eyes.[27,28]

All study readers were retina specialists experienced with all imaging techniques used. None of the readers seemed to have obviously overdiagnosed or underdiagnosed based on a specific imaging modality with an obvious difference compared with the reference diagnosis.

However, it should be noted that the interobserver agreement for SD-OCT + CFP was greater than that for FA + CFP, which corresponds to a greater degree of reproducibility in the interpretation of SD-OCT + CFP examination. Similar findings have been reported by Inoue et al[10] by comparing OCTA alone and OCTA combined with structural OCT and FA.

Overall, SD-OCT + CFP or FA + CFP had the same power and limitation for the diagnosis of CNV because both techniques had an excellent sensitivity of 90.9%. In case of Type 2 CNV, the performance of SD-OCT + CFP and FA + CFP was very high (98 and 100%, respectively) for the suspected diagnosis of CNV, whereas both techniques were less powerful in case of Type 1 CNV (sensitivity of 82.9 and 81.6%, respectively).

In less than 10% of cases, in our study, SD-OCT + CFP (9.8%) or FA + CFP (9.9%) resulted in different diagnoses compared with the reference diagnosis (SD-OCT + FA + CFP) because of various causes. Most often for the SD-OCT + CFP set, confluent soft drusen were present and SD-OCT + CFP did not show CNV, despite an irregular elevation of the retinal pigment epithelium (RPE) on SD-OCT because of the absence of subretinal fluid or retinal thickening. However, after FA + CFP reading, the readers diagnosed CNV because they observed a late fuzzy hyperfluorescence with some pin points on FA. In other cases, a small shallow extrafoveal subretinal fluid area was missed on SD-OCT, whereas FA easily showed a suggestive aspect of Type 1 CNV (Figure 1). By contrast, in other cases, FA + CFP did not allow for detecting CNV in patients with multiple drusen and atrophy, whereas SD-OCT + CFP revealed a small area of subretinal fluid (Figure 2). In one case, an epiretinal membrane was clearly visible on SD-OCT + CFP, whereas the reader of FA + CFP identified CNV. Adding two different imaging sources changes the way to detect suspected CNV, especially Type 1 CNV. In particular, in recent-onset cases with incomplete features or cases with atypical presentation, it seemed that combining SD-OCT, FA, and CFP findings was beneficial.

This study has some limitations. Each reader had access to CFP as a surrogate to biomicroscopic fundus examination to be close to the current clinical practice. However, it was not stereophotography, which would have allowed clinicians to view retinal thickness and macular edema. The diagnosis was simply based on a consensus opinion because no follow-up data were included in this study. The reference was purely qualitative because we did not try to quantify any CNV feature. We did not follow the procedures of a reading center,[29] but rather remained as close as possible to the current practice: the reading was made by retina specialists involved in the management of exudative AMD and relied on their clinical expertise. The study was performed using the Cirrus 4000 spectral domain OCT. Results could have been different with a device including eye

Table 6. Number of Different Diagnoses Made Per Reader Based on SD-OCT + CFP and FA + CFP Compared With the Reference Diagnosis of the Study (SD-OCT + FA + CFP)

	No. of Different Diagnoses Made Using OCT + CFP Reading Compared With the Reference Diagnoses of the Study (P = 0.43)	No. of Different Diagnoses Made Using FA + CFP Reading Compared With the Reference Diagnoses of the Study (P = 0.7)	Total No. of Different Diagnoses During Reading Sessions Compared With the Reference Diagnoses of the Study (P = 0.39)
Reader 1	6	4	10
Reader 2	3	4	7
Reader 3	4	8	12
Reader 4	9	7	16
Reader 5	6	6	12

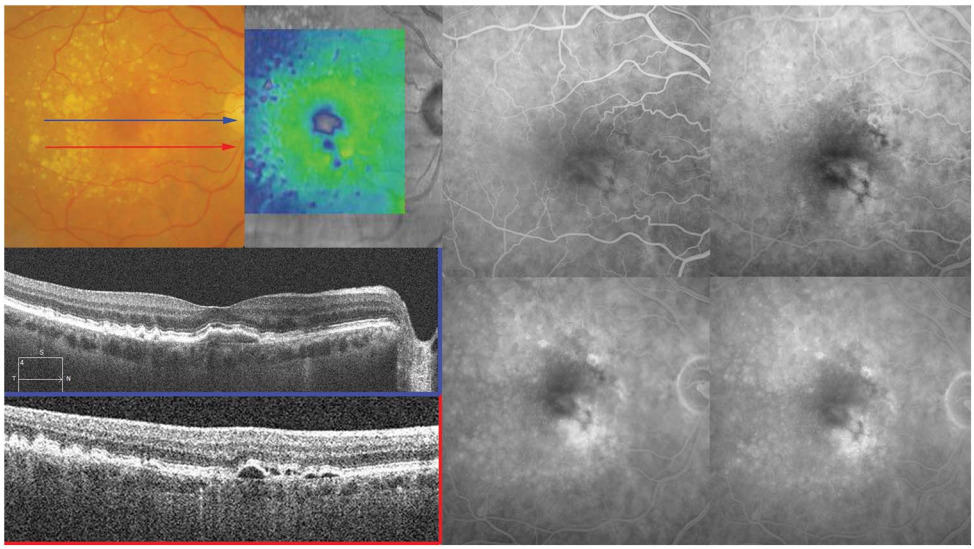

Fig. 1. Type 1 CNVs diagnosed with FA + CFP and not with SD-OCT + CFP. (Top left) Color fundus photograph shows confluent soft drusen in the macular area. Red and blue arrows represent the location of SD-OCT B-scans. The macular thickness mapping does not show evidence of retinal thickening. (Bottom left) Spectral domain OCT should have suspected CNV: SD-OCT B-scan passing through the foveal center (blue arrow) showing an irregular elevation of the RPE, without subretinal fluid or macular edema; SD-OCT B-scan passing under the foveal center (red arrow) showing shallow subretinal fluid. However, the diagnosis of CNV was not made by one reader of SD-OCT + CFP probably because of the presence of a minute shallow subretinal fluid only present on one B-scan. (Top and bottom right) Fluorescein angiography shows subretinal pigmentation followed by a progressive irregular staining and discrete fuzzy dye leakage in the lower part of the macula, which allowed the readers of FA + CFP to suspect Type 1 CNV.

tracking and averaging. However, the advantage of this device was to simply provide a high-density mapping with acquisition of a dense macular cube (128 lines × 512 pixels) in 2.4 seconds. In this study, we did not use indocyanine green angiography because this test is not routinely used in current practice. Indocyanine green angiography could help making a diagnosis, especially in some cases with Type 1 CNV or polypoidal choroidal vasculopathy. The investigators could ask to perform indocyanine green angiography and it was performed for some patients, but this examination was not used to make the reference diagnosis. As indocyanine green angiography is not routinely used as a first diagnostic tool, we preferred to mimic the situation upstream of its prescription.

Our study was conducted before OCTA was available. This new technique will certainly change completely the paradigm of CNV detection in association with structural OCT and we have previously shown its value.[7] Our results may thus also be useful for designing prospective studies assessing the value of SD-OCT combined with OCTA capacities for the diagnosis of CNV. For example, the benefit of OCTA in terms of sensitivity for the diagnosis of CNV should be more easily confirmed in Type 1 CNV than in Type 2 CNV

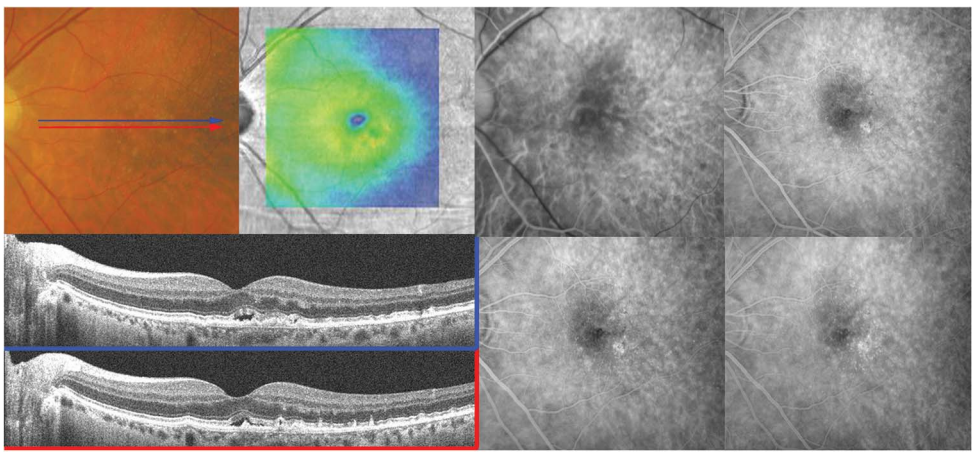

Fig. 2. Type 1 CNVs diagnosed with SD-OCT + CFP and not with FA + CFP. (Top left) Color fundus photograph shows drusen in the macular area. Red and blue arrows represent the location of SD-OCT B-scans. The macular thickness mapping shows a small inferomacular retinal thickening. (Bottom left) Spectral domain OCT suspected CNV: SD-OCT B-scan passing through the foveal center (blue arrow) showing an irregular elevation of the RPE, with a shallow subretinal fluid; SD-OCT B-scan passing under the blue arrow (red arrow) showing shallow subretinal fluid which allowed the readers of SD-OCT + CFP to suspect Type 1 CNV. (Top and bottom right) Fluorescein angiography shows pigment epithelium impairments and no evidence of progressive staining in the area of drusen interpreted as no CNV by one reader of FA + CFP. The patient was monitored for 6 months after the study without treatment and the SRF slowly increased, confirming the suspicion of the presence of CNV during the study.

where structural OCT + CFP has already a nearly 100% sensitivity. This work could also have an interest in the development of telemedicine. The combination of SD-OCT and CFP has the advantage of not requiring the presence of a physician and could be a valid telemedicine or computer artificial intelligence screening method for AMD where the access to retina specialists is limited.

In conclusion, our results showed no statistical difference between SD-OCT + CFP and FA + CFP in terms of sensitivity and specificity to detect the presence of recent-onset CNV secondary to AMD when the reference diagnosis is based on SD-OCT combined with FA and CFP. The sensitivity of SD-OCT + CFP, such as FA + CFP, in Type 2 CNV is very high. If Type 1 CNV is suspected, combining both imaging techniques could be needed until determining whether OCTA is sensitive enough.

Key words: age-related macular degeneration, color fundus photograph, choroidal neovascularization, optical coherence tomography, fluorescein angiography, sensitivity, specificity.

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