Reference and design	Diagnostic tests	Participants	Outcome
_		_	measures
Condition being	Index test:	Number of	Primary outcome
diagnosed / detected:	Fundus autofluorescence	participants:	of study:
Choroidal neovascular-	(FAF): acquired with	62 (52 included in	Presence of
isation (CNV) in exudative	confocal scanning	analysis)	conversion from
AMD	laser ophthalmoscopy		early AMD to wet
	(cSLO) HRA II	Number of eyes:	AMD: sensitivity
First author:	(Heidelberg Retina	52	and specificity
Cachulo <sup>99</sup>	Angiograph)		
	Excitation 488nm; barrier	Sample	(repeated imaging
Publication year: 2011	filter beginning at	attrition/dropout:	assessments at 6-
	500nm.	52 participants	monthly intervals
Country: Portugal		completed the 2 year	for 2 years or until
	Each FAF image was	follow-up, dropout	CNV presence was
Study design:	compiled from at least 17	was due to death (4	confirmed in the
Prospective observational	single scans in movie	patients), withdrawal	study eye)
longitudinal 2 year study	mode and automatically	of informed consent	
	aligned and averaged.	(4 patients),	
Number of centres:		hospitalisation (1	Other relevant
One	<b>Reference standard:</b>	patient), loss to	outcomes:
	Fluorescein angiography	follow-up (1 patient	None
Funding:	(FA): acquired using the	treated in another	
Not reported	HRA II (Heidelberg	country)	Diagnostic
	Retina Angiograph)		threshold:
<b>Competing interests:</b>	scanning laser	Selection of	
Not reported	ophthalmoscope	participants:	FAF (observed
1 author appears to be		Patients with	from results, but
employed by Pfizer Inc.	Comparator:	neovascular AMD in	not stated in
	1) Colour fundus	one eye and early	methods): patchy
	photography	AMD in the fellow	pattern; reticular
	2) Fluorescein	eye (study eye) at	pattern; speckled
	angiography	risk for development	pattern; focal
	3) Indocyanine green	of CNV. Not	increased pattern;
	angiography	reported whether	lacelike pattern
	4) Optical coherence	patients selected	
	tomography	consecutively	FA: not reported
	5) Retinal angiography		
	(retinal leakage	Inclusion criteria	
	analysis – RLA –	for study entry:	Recruitment
	measuring retinal	1) Older than 50	dates:
	fluorescein leakage	years	Not reported
	from the blood	2) Any race and	
	stream into the	either sex	
	vitreous using cSLO)	3) Clinical diagnosis	
		of wet AMD in one	
		eye (non-study eye)	
		4) Presence of the	
		following	
		characteristics in the	

Study 1 of 8 – Cachulo and colleagues

	study eve:	
	a) 5 or more	
	intermediate soft	
	drusen >63µm or 1	
	large soft	
	$druse > 125 \mu m$	
	$druse > 12.5 \mu m$ ,	
	and/or confluent	
	drusen within 3,000	
	um of the foveal	
	centre	
	b) With or without	
	b) with of without	
	pigmentary changes	
	Exclusion criteria	
	for study entry.	
	1) Compare	
	1) Current or past	
	medical condition	
	that would preclude	
	scheduled visits or	
	completion of the	
	study	
	2) Current or past	
	history of ophthalmic	
	disease in the study	
	ansease in the study	
	eye (other than	
	AMD), that would	
	likely compromise	
	the visual acuity of	
	the study eye	
	2) Clinical signs of	
	5) Chinear signs of	
	myopic retinopathy	
	or refractive power	
	of >8 diopters or	
	fundusconic	
	avidance of	
	degenerative myopia	
	4) Past history of	
	intraocular surgery	
	within 60 days prior	
	to amolling in the	
	to enrolling in the	
	study	
	5) Evidence of past	
	or present CNV in	
	the study eve	
	the study cyc	

Participant characteristics		
Sex, m:f (%male)	26:26 (50)	
Age, years, mean (SD)	76 (6), range 56-92	

#### **Results – FAF versus FA**

Kesuits – FAF versus FA	Results – PAP versus PA				
Calculations are based on	Population with disease	<b>Population</b> without	Total		
number of eyes (single eyes	on FA reference	disease on FA			
of 52 subjects)	standard	reference standard			
FAF imaging positive	15 a	23 c	38		
FAF imaging negative	2 b	12 d	14		
Total	17	35	52		
Diagnosis 95% CI					
Clinical sensitivity a / (a + b)		88.24 %	63.52 to 98.20		
Clinical specificity d / (c + d)		34.29 %	19.15 to 52.21		
PPV a / (a + c)		39.47 %	24.05 to 56.61		
NPV $d/(b+d)$		85.71 %	57.16 to 97.80		
Positive likelihood ratio [sensitivity/(100-specificity)]		1.34	1.00 to 1.80		
Negative likelihood ratio [(100-sensitivity)/specificity]		0.34	0.09 to 1.36		
Diagnostic odds ratio (a x d)/(b x c)		3.91	0.77 to 20.02		

Comments: Calculations do not agree with values reported in paper. Reported values for FAF are: sensitivity 93%, specificity 37%, positive predictive value 57% and negative predictive value 93%. This may be because of different ways that the reviewer and authors categorised the 2 eyes in FAF in which the pattern of autofluorecence could not be determined because of poor quality images.

Interpretability and acceptability of test	
Numbers excluded from analysis due to poor image quality	2/52 (3.85%)
Inter-observer agreement	Not reported
Intra-observer agreement	Not reported
Test acceptability (patients / clinicians)	Not reported
Adverse events	Not reported

AMD: age-related macular degeneration; CNV: choroidal neovascularisation; cSLO: confocal scanning laser ophthalmoscopy; FA: fluorescein angiography; FAF: fundus autofluorescence; NPV: negative predictive value; PPV: positive predictive value.

**Cachulo and colleagues<sup>99</sup> critical appraisal criteria** (based on Reitsma et al.<sup>81</sup> adaptation of the QUADAS Tool<sup>93</sup>)

	Item	Description	Judgement
1	Was the spectrum of patients representative of the patients who will receive the test in practice?	Study is prospective but unclear if it involved consecutive patients. Participants had confirmed CNV in one eye, so may be an atypical case-mix	No
2	Is the reference standard likely to classify the target condition correctly?	FA is described as the gold standard for assuming conversion from early AMD to wet AMD	Yes
3	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	It is reported that each patient underwent study assessments at baseline and every six months for two years. However, no detail is given about the time between tests	Unclear
4	Did the whole sample or a random selection of the sample receive verification using the intended reference standard?	Of 62 patients enrolled in the study, 10 dropped out, due to death (n=4), withdrawal of consent (n=4), hospitalisation (n=1) and loss to follow up (n=1). It is confirmed in the results section that 52/52 of the remaining patients underwent the fluorescein angiography test	Yes
5	Did patients receive the same reference standard irrespective of the index test result?	The results confirm that 52/52 patients underwent the fluorescein angiography test	Yes
6	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	Yes	Yes
7	Were the reference standard results interpreted without knowledge of the results of the index test?	Not reported	Unclear
8	Were the index test results interpreted without knowledge of the results of the reference standard?	Not reported	Unclear
9	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Not reported	Unclear
10	Were uninterpretable or intermediate test results reported?	It is stated that in 2 eyes the pattern of autofluorescence could not be determined because of poor quality images	Yes
11	Were withdrawals from the study explained?	Yes	Yes

# Study 2 of 8 – Dinc and colleagues

Reference and design	Diagnostic tests	Participants	Outcome
	2	- ur ur ur punto	measures
Condition being	Index test:	Number of	Primary outcome
diagnosed / detected:	Fundus autofluorescence	participants: 55	of study:
Cystoid macular oedema	(FAF) acquired with	r	Detection of CMO
(CMO) (secondary to	confocal scanning	Number of eves: 67	by FAF and FA
diabetic retinonathy	laser ophthalmoscopy	rumber of eyest of	
retinal vein occlusions	(cSLO) (Heidelberg	Sample	Other relevant
uveitis cataract surgery	Retinal Angiograph	attrition/dronout	outcomes.
eniretinal membrane or	2 Heidelberg	None (results	Central macular
age_related macular	Engineering Germany)	reported for all eves)	thickness assessed
degeneration)	View mode 30°: pupil	reported for all cycs)	by OCT (data not
degeneration)	dilated to a diameter $> 6$	Solaction of	extracted here)
First author: Dina <sup>83</sup>	mm Excitation $482$ nm:	nertiginants. Stated	extracted here)
First author. Diffe	harrian filtar 500nm	only that the nationts	Diagnostia
Publication years 2010	Stated that a mean of 0	diagnosed with	threshold
rublication year. 2010	frames was obtained	CMO ware calcoted	Mot ovnligitly
Country Turkey (not	frames was obtained.	from a EAE database	stated but implied
country: Turkey (not	Defenence standard	from a FAF database	to he increased
stated explicitly)	Reference standard:	(no criteria	to be increased
Standar destante Dationate	Electronic en dis angular	specified)	automuorescence in
Study design: Patients	Fluorescein angiography	T 1	a round or oval
were selected from a FAF	(FA). Method not	Inclusion criteria	fashion at the
database (no further details	reported except that in the	for study entry:	iovea (example
given); informed consent	late phase of FA, path-	Patients with CMO	image given for
was obtained from all	ognomonic leakage	secondary to	reference)
patients, suggesting the	of fluorescein at the fovea	diabetic retinopatny,	
study was prospective	in a petaloid configur-	retinal vein occiu-	Recruitment
	ation with feathery	sions, uveitis,	dates: Unclear.
Number of centres: Not	margins was considered	cataract surgery,	Stated that patients
explicitly reported but	as CMO.	epiretinal membrane	were selected from
appears to be single centre		or age-related mac-	the FAF database
	Comparator:	ular degeneration	between January
Funding: No information	Optical coherence		2008 and June
provided	tomography (OCT) (type	Exclusion criteria	2009
~	not reported)	for study entry:	
Competing interests: No		Eyes with significant	
information provided		media opacity,	
		cataract, poor FAF	
		images, or having	
		subfoveal serous	
		retinal detachment	
		on OCT	

Participant characteristics	
Sex, m:f (%male)	28:27 (51)
Age, years, mean (SD)	62.1 (14.4)
Origin of CMO (n= no. of	Diabetic retinopathy, n=36
eyes)	Branch retinal vein occlusion, n=13
	Macular epiretinal membrane, n=5
	Age-related macular degeneration, n=5
	Uveitis, n=4
	Cataract extraction, n=3
	Central retinal vein occlusion, n=1

### **Results – FAF compared against FA**

Calculations are based on the numbers of eyes (both eyes of 12 subjects and single eyes of 43 subjects)	Population with CM on FA	10	Population withou CMO on FA	t Total
FAF imaging positive	64	а	2	c 66
FAF imaging negative	1	b	0 0	l 1
Total	65		2	67
	·		·	•
Diagnosis				95% CI
Clinical sensitivity a / (a + l	b)	98.4	6%	91.69 to 99.74
Clinical specificity d / (c + c	d)	0.00	%	0.00 to 80.71
PPV a / (a + c)		96.9	7%	89.46 to 99.54
NPV d / (b + d)		0.00	%	0.00 to 83.45
Positive likelihood ratio [se	nsitivity/(100-	0.98		0.96 to 1.01
specificity)]				
Negative likelihood ratio [(	100-	Not	calculable	
sensitivity)/specificity]				
Diagnostic odds ratio (a x d	l)/(b x c)	8.60		0.28 to 268.48
Commente: Diagnostia outer	mas are not reported in	n nono	r calculated by ravi	Nuor .
Comments. Diagnostic outco	ines are not reported in	n pape	I – calculated by levi	ewer
Interpretability and accept	ability of test			
Numbers excluded from anal	lysis due to poor	None – results are reported for all 67 study eyes		
image quality			-	
Inter-observer agreement		Not	Not reported	
Intra-observer agreement		Not	Not reported	
Test acceptability (patients /	clinicians)	Not	reported	
Adverse events		Not	reported	

CMO: cystoid macular oedema; cSLO: confocal scanning laser ophthalmoscopy; FA: fluorescein angiography; FAF: fundus autofluorescence; NPV: negative predictive value; OCT: optical coherence tomography; PPV: positive predictive value

# **Dinc and colleagues<sup>83</sup> critical appraisal criteria** (based on Reitsma et al.<sup>81</sup> adaptation of the QUADAS Tool<sup>93</sup>)

	Item	Description	Judgement
1	Was the spectrum of patients representative of the patients who will receive the test in practice?	Unclear if study is prospective, but it involved consecutive patients. CMO was secondary to a range of conditions, and patients with CMO and serous retinal detachment were excluded, so is an atypical case- mix	No
2	Is the reference standard likely to classify the target condition correctly?	FA is described as the gold standard for detecting CMO	Yes
3	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	Order, but not timing, of tests specified	Unclear
4	Did the whole sample or a random selection of the sample receive verification using the intended reference standard?	Whole sample	Yes
5	Did patients receive the same reference standard irrespective of the index test result?	Yes	Yes
6	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	Separate tests applied at different times	Yes
7	Were the reference standard results interpreted without knowledge of the results of the index test?	Stated that the data on FA and FAF images were evaluated by as single clinician; masking not reported	Unclear
8	Were the index test results interpreted without knowledge of the results of the reference standard?	FAF images were obtained prior to FA images	Yes
9	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Not reported	Unclear
10	Were uninterpretable or intermediate test results reported?	All eyes included in analysis but not stated whether image quality was an inclusion or exclusion criterion	No
11	Were withdrawals from the study explained?	Results data reported for all eyes – implies no withdrawals	Not applicable

# Study 3 of 8 – Hogg and colleagues

Reference and design	Diagnostic tests	Participants	Outcome
itererenee and design		i ui ticipunto	measures
Condition being diagnosed	Index test: fundus	Number of	Primary outcome
/ detected:	autofluorescence (FAF)	narticinants: 105	of study:
Reticular pseudodrusen	acquired using scanning	pur ticipuntor 100	Presence of RPD
(RPD) in age-related	laser on thalmoscony	Number of eves:	
macular degeneration	(SLO): Spectralis	105	Other relevant
(AMD)	HPA + OCT (Heidelberg	105	outcomes.
(mind)	Engineering Heidelberg	Sample	Between_grader
First author. Hogg <sup>96</sup>	Germany) Excitation	attrition/dronout	repeatability (K
<b>1 II St authol :</b> 11055	not stated: harriar filter	Not reported but	statistics) for each
Publication Vear. 2014	not stated	appears to have	imaging method
Tublication Teat. 2014	not stated.	excluded 12 eves	inaging method
Country. Italy Portugal	Sattings: Field of view	with poor image	Diagnostic
UK (Northern Ireland)	$30^{\circ}$ centred on the	$\alpha_{\text{mality}} (n=93 \text{ after})$	threshold
	macula: automatic image	exclusion)	Definitions of
Study design:	brightness (also called	exercision	RPD.
Prospective cohort study	gain): high_speed mode:	Selection of	IC D.
	movie duration 30	narticinants:	FAF <sup>•</sup> "clusters of
Number of centres: 3	seconds: average of 15	Patients attending	ill-defined hypo-
	frames (Spectralis mean	retina clinics at each	autofluorescent
Funding: Educational grant	function): and	study site who had a	lesions interspersed
from Pfizer Inc	tomography settings	diagnosis of	against a
	7mm for 7-scan images	neovascular AMD in	background of
Competing interests:	/ min for Z-sean images	1 eve were	mildly increased
Authors declared financial	Reference standard:	approached and	AF occurring in a
support or consultancies	Reference standard.	invited to take part.	regular and well-
from Pfizer. Heidelberg	(1) Reference standard	Neovascular AMD	defined array."
Engineering, Zeiss Meditec.	relevant to the current	not defined in the	
Novartis, Allergan, Zeiss,	review: Colour fundus	publication	CFP: vellow
Alcon, Bayer, and THEA	photography (CFP):	L	interlacing
	Stereopair colour images	Inclusion criteria	networks ranging
	acquired using a Topcon	for study entry:	from 125 to 250
	50X fundus camera. No	Men and women	um in width or
	further details given.	older than 50 years	lesions that
		with a confirmed	occurred in regular.
	(2) Reference standard	diagnosis of	well-defined
	according to the primary	neovascular AMD in	domains.
	study: Presence or	1 eye; study eye	
	absence of RPD on $>1$ of	(fellow eye) free of	IR and RF:
	5 modalities: CFP, red-	any features of late	"clusters of ill-
	free photography (RF).	AMD (i.e., no	defined hypo-
	Infrared photography	neovascularization	reflective lesions
	(IR), fundus auto-	or geographic	interspersed
	fluorescence (FAF), and	atrophy) with a	against a
	optical coherence	visual acuity of	background of
	tomography (OCT)	20/40 or better;	mild hyper-
		sufficiently clear	reflectance."
	CFP: details as above	ocular media and	
		adequate pupillary	OCT: discrete
	IR: acquired using same	dilatation to permit	accumulations of
	equipment as index test	good-quality	material anterior to
	and same settings	fundus imaging of	the RPE often
		the study eye; and	occurring as sharp

	willing and able to	peaks visible
RF: acquired using	comply with	within the layers
same equipment as index	scheduled visits,	corresponding to
test and same settings	laboratory tests, and	the outer regions of
	other trial	the photoreceptors
OCT acquired using	procedures.	
same equipment as index		Recruitment
test. Centred on the	Exclusion criteria	dates:
macula, using evenly	for study entry:	Not reported
spaced lines in the scan	Evidence of a	
$15^{\circ}$ (vortical) area:	on EA in the study	
number of sections set to	on FA in the study	
37: mean function used	feature of	
with 5 scans per line.	neovascular AMD	
high-speed acquisition	(eg subretinal or	
mode	intraretinal fibrosis	
mode	within the macular	
Note: SD-OCT implied	region, RPE tear);	
but not stated	significant media	
	opacities, cataracts,	
	lens opacification	
	requiring cataract	
	surgery within 2	
	year follow-up;	
	other retinal	
	disease eg.	
	pathologic myopia	
	(spherical equivalent	
	of -8 diopters or	
	more or axial length	
	of 25 mm or more),	
	ocular istoplasmosis	
	syndrome, angioid	
	streaks, choroidai	
	choroiditis: ocular	
	progressive disease	
	eg glaucoma or	
	diabetic retinonathy	
	in the study eve:	
	medical condition	
	that would interfere	
	with the patient's	
	ability to complete	
	the trial; concurrent	
	enrolment in any	
	other observational	
	or interventional	
	clinical study;	
	treatment with an	
	ocular or systemic	
	investigational agent	
	in the past 60 days	
	tor medical	

	condition; or known serious allergies to the dye used in FA or ICGA.	
	of ICOA.	

Participant characteristics	
Sex, m:f (%male)	53:52 (50)
Age, years, mean (SD)	75.6 (7.5), range 52-93
Visual acuity in patients with vs. without drusen	
1) Distance visual acuity (letters), mean (SD)	1) 83 (6) vs. 81 (6)
2) Near visual acuity (logarithm of the minimum angle of	2) 0.3 (0.1) vs. 0.2 (0.1)
resolution), mean (SD)	
3) Low luminescence visual acuity (SKILL score), mean (SD)	3) 38 (12) vs. 33 (9)

## Results – (1) FAF versus Spectralis OCT

Calculations are based on numbers of eyes (single	Population with disease on Spectra	1	Population without disease on Spectral		Total
eyes of 93 subjects)	OCT	-	OCT	~p••••	
FAF imaging positive	29	а	9	с	38
FAF imaging negative	4	b	48	d	52
Total	33		57		90
Diagnosis					95% CI
Clinical sensitivity a / (a + b)	)	87.88 %			71.78 to 96.52
Clinical specificity d / (c + d	)	84.21 %			72.13 to 92.30
<b>PPV a / (a + c)</b>		76.32 %			59.75 to 88.53
NPV d / (b + d)		92.31 %			81.44 to 97.82
Positive likelihood ratio [sen	sitivity/(100-	5.57			3.02 to 10.27
specificity)]					
Negative likelihood ratio [(1	00-	0.14			0.06 to 0.36
sensitivity)/specificity]					
Diagnostic odds ratio (a x d)/(b x c)*		38.67			10.92 to 136.97
*0.5 added to each number to avoid division by					
zero					
Interpretability and accepta	bility of test – see ta	ble	below		

## Results – (2) FAF versus CFP

(-)	-				
Calculations are based on numbers of eyes (single eyes of 93 subjects)	Population with disease on CFP		Population disease on	n without CFP	Total
FAF imaging positive	15	а	26	с	41
FAF imaging negative	0	b	52	d	52
Total	15		78		93

Diagnosis		95% CI
Clinical sensitivity a / (a + b)	100.00 %	78.03 to 100.00
Clinical specificity d / (c + d)	66.67 %	55.08 to 76.94
PPV $a / (a + c)$	36.59 %	22.13 to 53.06
NPV d / (b + d)	100.00 %	93.08 to 100.00
Positive likelihood ratio [sensitivity/(100-	3.00	2.19 to 4.11
specificity)]		
Negative likelihood ratio [(100-	0.00	Not calculable
sensitivity)/specificity]		
Diagnostic odds ratio (a x d)/(b x c)*	61.42	3.54 to 1066.71
*0.5 added to each number to avoid division by		
zero		

Comments: CFP is the usual method for diagnosing RPD but was not the reference standard in the primary study. Diagnostic outcomes for this comparison were not reported in the paper but have been calculated by reviewers from data in Table 4 in the paper.

**Interpretability and acceptability of test** – see table below

### **Results – (3) FAF versus >1 imaging modality**

Calculations are based on	Population with		Populatio	n without	Total		
numbers of eyes (single	disease on >1		disease on	1 >1 imaging			
eyes of 93 subjects)	imaging modality		modality				
FAF imaging positive	41	a	0	с	41		
FAF imaging negative	2	b	50	d	52		
Total	43		50		93		
Diagnosis					95% CI		
Clinical sensitivity a / (a + b)		95.35 %			84.16 to 99.30		
Clinical specificity d / (c + d)	)	100.00 %			92.82 to 100.00		
PPV a / (a + c)		100.00 %			91.31 to 100.00		
NPV d / (b + d)		96.15 %			86.76 to 99.42		
Positive likelihood ratio [sen	sitivity/(100-	Not calculable					
specificity)]							
Negative likelihood ratio [(1	00-	0	0.05		0.01 to 0.18		
sensitivity)/specificity]							
Diagnostic odds ratio (a x d)/(b x c)		1	1676.60		78.30 to 35903.35		
Comments: The diagnostic of	Comments: The diagnostic odds ratio was not reported in the paper. The calculation of specificity						

Comments: The diagnostic odds ratio was not reported in the paper. The calculation of specificity differs as the paper reported specificity to be 98%.

Interpretability and acceptability of test	
Numbers excluded from analysis due to poor	Not reported.
image quality	Appears to have excluded 12 eyes that were ungradable for RPD: Instead of 105 eyes, results are presented for 93 eyes comparing FAF with >1 imaging modality; 93 eyes comparing FAF with fundus photography; and 90 eyes comparing FAF with OCT. However, the numbers that were ungradable on each imaging modality are not specified
Inter-observer agreement (only for the UK [Belfast] site, n=35), kappa statistics	Colour photography, 0.72 (P<0.001); IR, 0.87 (P<0.001); RF, 0.53 (P = 0.002); FAF, 0.94 (P<0.001); OCT, 0.86 (P<0.001); ICGA, 0.93 (P<0.001); RPD on 1 or more imaging method, 1.0.
Intra-observer agreement	Not reported
Test acceptability (patients / clinicians)	Not reported
Adverse events	Not reported

AF: autofluorescence; AMD: age-related macular degeneration; CFP: colour fundus photography; cSLO: confocal scanning laser ophthalmoscopy; FA: fluorescein angiography; FAF: fundus autofluorescence; ICGA: indocyanine green angiography; IR: infrared photography; NPV: negative predictive value; OCT: optical coherence tomography; PPV: positive predictive value; RF: red-free photography; RPD: reticular pseudodrusen; RPE: retinal pigment epithelium; SD-OCT: spectral-domain optical coherence tomography

E	logg and	colleague	es <sup>96</sup> critical	appraisal	criteria	(based of	on Re	eitsma	et al. <sup>81</sup>	adaptation	of the
Ç	UADAS	$Tool^{93}$ )									

	Item	Description	Judgement
1	Was the spectrum of patients representative of the patients who will receive the test in practice?	Study is prospective, and involved consecutive patients. Patients had neovascular AMD in only one eye, and no signs of AMD or other eye conditions in the other eye, so this is an atypical case-mix	No
2	Is the reference standard likely to classify the target condition correctly?	Study reference standard is positive result on ≥1 of 5 modalities (CFP, RFP, IRP, FAF, OCT), but CFP is the standard approach in clinical practice, with SD-OCT and FA also useful for detecting RPD	Unclear
3	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	Not reported	Unclear
4	Did the whole sample or a random selection of the sample receive verification using the intended reference standard?	Multiple imaging methods were used, but it is unclear whether all participants received all tests but data was excluded, or whether some participants did not receive all tests. Attrition is not reported	Unclear
5	Did patients receive the same reference standard irrespective of the index test result?	No, the combination of the ≥1 test modalities making up the reference standard varied between patients.	No
6	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	The index test was one of the tests contributing to a diagnosis	No
7	Were the reference standard results interpreted without knowledge of the results of the index test?	Not reported	Unclear
8	Were the index test results interpreted without knowledge of the results of the reference standard?	Not reported	Unclear
9	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Not reported	Unclear
10	Were uninterpretable or intermediate test results reported? Were withdrawals from the study explained?	12 subjects were ungradable for RPD and these appear to have been excluded from analysis – but the number of ungradable images on the index test is not reported No	No

### Study 4 of 8 – McBain and colleagues

Reference and design	Diagnostic tests	Participants	Outcome
			measures
Condition being	Index test:	Number of	Primary outcome
diagnosed/detected:	FAF imaging using	participants: 34	of study:
Cystoid macular oedema	cSLO. This was		Diagnostic
(CMO)	obtained using	Number of eyes: 34	accuracy
<b>D</b>	Heidelberg retina	~ .	(sensitivity and
First author: McBain <sup>100</sup>	anglograph which	Sample	specificity)
	consisted of a solid-state	attrition/dropout:	
Publication Year: 2008	argon blue excitation	106 consecutive	Other relevant
	laser (488nm) and	patients with	outcomes:
Country: UK	barrier filter (500nm).	clinically suspected	Interpretability and
	30 degree field-of-view	CMO had FAF	acceptability of
Study design:	mode was used for the	imaging, of which	test; adverse events
Retrospective, consecutive,	images. Sequential	34 patients were	Diamantia
observational case series	and 20 frames were	engible for inclusion	threshold
Number of contrast 1	and 20 frames were	and 62 were	threshold:
Number of centres: 1	selected and averaged to	excluded.*	EAE, CMO
Funding: Not stated		Solation of	rAr. CNIO
runung: Not stated	FAF.	Selection of	whenever there
Compating interests: Stated	Deference standard	Consecutive patients	whenever there
none	Fluorescein angiography	with clinically	areas of fundus
none	(FA) Digital stereo	suspected CMO	autofluorescence at
	images obtained using	were selected from	the fovea with a
	Toncon-Imagenet	FAF imaging	fundus auto-
	system	database of the	fluorescence signal
	System -	Ophthalmology	similar to back-
		Department	ground levels FAF
	<b>Comparator:</b> None	D'opartitiont.	signal is usually
		Inclusion criteria	reduced at the
		for study entry:	fovea compared
	Time period between	CMO secondary to	with background.
	tests: within 2 weeks of	cataract extraction,	due to blockage of
	each other; there was a	inherited	the signal by the
	minimum gap of 4 days	retinopathies,	luteal pigment.
	washout if FAF was	inflammatory eye	1.6
	obtained following FA	disease or idiopathic	FA: CMO was
		cases, where both	considered present
		FAF and FA were	whenever leakage
		obtained to confirm	of fluorescein dye
		diagnosis. One eye	was observed in a
		per person included,	petaloid pattern
		left eye chosen in	around the fovea in
		bilateral cases.	the late phase of
		Patients were	the angiogram
		eligible if FAF was	(recirculation phase
		performed within 2	or later)
		weeks of FA	
		Exclusion criteria	Recruitment
		tor study entry: No	dates: February
		additional criteria	2004 - May 2007*
		cited.	

\*The numbers do not add up to 106 but 96. There is a discrepancy in reporting the total numbers in the abstract (which reports 96) vs the text (reporting 106). There is also a discrepancy in recruitment dates in the abstract (reported as between Aug 2004 and June 2006) vs the text (Feb 2004 and May 2007). It appears that the main text has been updated but the abstract has not, and that 10 exclusions have not been accounted for.

Participant characteristics					
Sex, m:f (%male:female)	20:14 (59)				
Age, years, mean (SD)	59 (range 17-89)				
CMO secondary to inflammatory disease, n (%)	17/34 (50)				
CMO following cataract surgery, n (%)	11/34 (32)				
CMO associated with inherited retinal dystrophies, n	3/34 (9)				
(%)					
CMO idiopathic, n (%)	4/34 (12)				

### **Results – FAF versus FA**

Calculations are based on numbers of eyes (= number of patients as only one eye per patient was included)	Population with disease on FA		Populati disease o	ion without on FA	Total
FAF imaging positive	17 a		4	с	21
FAF imaging negative	4 b		9	d	13
Total	21		13		34
Diagnosis					95% CI
Clinical sensitivity a / (a + b)		80.95			58.08 to 94.44
Clinical specificity d / (c + d)		69.23			38.61 to 90.72
PPV a / (a + c)		80.95			58.08 to 94.44
NPV d / (b + d)		69.23			38.61 to 90.72
Positive likelihood ratio [sensitivity/(100- specicifcity)]		2.63			1.13 to 6.10
Negative likelihood ratio [(1	00-	0.28			0.11 to 0.71
sensitivity)/specificity]					
Diagnostic odds ratio (a x d)	/(b x c)	9.56			1.92 to 47.57
Comments: Calculations agree with values reported in paper except for values for PPV and NPV,					

which are switched in the paper.

Interpretability and acceptability of test	
Poor FAF images related to media opacities	9/96 (9.4%)
(cataract), n (%)	
Inter-observer agreement	Not reported
Intra-observer agreement	Not reported
Test acceptability (patients / clinicians)	Not reported
Adverse events	No side effects were observed related to FAF or
	AF images during the study period.
The percentage has been calculated by reviewers us	ing the denominator 96 rather than 106, as the

The percentage has been calculated by reviewers using the denominator 96 rather than 106, as the reasons for 10 exclusions appear to have been omitted from the paper (see above). CMO: cystoid macular oedema; FA: fluorescein angiography; FAF: fundus autofluorescence; NPV:

negative predictive value; PPV: positive predictive value

# **McBain and colleagues<sup>100</sup> critical appraisal criteria** (based on Reitsma et al.<sup>81</sup> adaptation of the QUADAS Tool<sup>93</sup>)

	Item	Description	Judgement
1	Was the spectrum of patients representative of the patients who will receive the test in practice?	Study is retrospective, but involved consecutive patients. Patients had CMO secondary to specific conditions, so this may be an atypical case-mix	No
2	Is the reference standard likely to classify the target condition correctly?	FA is described as used routinely for diagnosis of CMO	Yes
3	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	Within two weeks of each other, with a minimum gap of 4 days if FAF followed AF.	Yes
4	Did the whole sample or a random selection of the sample receive verification using the intended reference standard?	All included patients received both tests.	Yes
5	Did patients receive the same reference standard irrespective of the index test result?	FA was used in all analysed patients	Yes
6	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	FAF was not part of reference standard	Yes
7	Were the reference standard results interpreted without knowledge of the results of the index test?	Evaluation of results was done in a masked fashion by a single observer; images evaluated independently from one another.	Unclear
8	Were the index test results interpreted without knowledge of the results of the reference standard?	As above	Unclear
9	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	States no information was provided to the observer with regards to the patient.	Unclear
10	Were uninterpretable or intermediate test results reported?	Reports number of patients excluded due to poor FAF images (9/96)	Yes
11	Were withdrawals from the study explained?	62/96 patients excluded: 23 no AF, 14 had more than two weeks	Yes

between tests. 2 had FAF less	
than four days after EA . 9 had	
than four days after FA, 9 had	
poor AF images related to media	
opacities (cataract), 14 had CMO	
related to other diseases, e.g.	
precious branch vein occlusion,	
diabetic retinopathy or AMD.	
However, there is a discrepancy	
between the recruitment dates	
and numbers recruited between	
the abstract and main text,	
which suggests that there are	
10/106 exclusions which are not	
accounted for.	

# Study 5 of 8 – Smith and colleagues

Reference and design	Diagnostic tests	Participants	Outcome
	_	-	measures
Condition being diagnosed	Index test:	Number of	Primary outcome
/ detected: Reticular	Fundus autofluorescence	participants: 138	of study: The
pseudodrusen (RPD) in age-	(FAF) imaging. No		fraction and
related macular degener-	details of method	Number of eyes:	relative prob-
ation (AMD)	reported; introduction	221 (166 eyes of 83	ability of focally
	suggests probably	patients with early	increased auto-
First author: Smith <sup>101</sup>	confocal scanning laser	AMD or GA,	fluorescence
	ophthalmoscopy (cSLO)	without evidence of	corresponding
<b>Publication year: 2006</b>		choroidal neo-	spatially with
	<b>Reference standard:</b>	vascularisation	drusen and
<b>Country:</b> UK and USA	Colour fundus	(CNV)) and 55	pigment as
	photography (CFP).	unaffected eyes of 55	identified by
Study design:	Colour photographs	patients with	fundus colour
Retrospective case series (2	were studied both in	unilateral CNV)	photography; and
distinct case series	their original state and as		the presence or
combined)	highly contrast-enhanced	Sample	absence of
	versions, to facilitate	attrition/dropout:	reticular FAF and
Number of centres:	RPD identification. No	None (retrospective	RPD
Not reported	further details of method	database selection)	
	reported.		Other relevant
Funding: New York		Selection of	outcomes:
Community Trust (lead	Comparator:	participants: From	None reported
author) and unrestricted	None reported	two databases: an	
funds from Research to	-	AMD study database	Diagnostic
Prevent Blindness		at the UK Institute of	threshold:
		Ophthalmology; and	FAF: Reticular
<b>Competing interests:</b>		a database of patients	pattern of auto-
Stated none		imaged at Columbia	fluorescence
		Eye University,	(hypofluorescent
		USA. Not reported	lesions)
		whether patients	,
		were selected	CFP: Image
		consecutively.	segmentation
			method reported,
		Inclusion criteria	but morphological
		for study entry: Not	criteria for
		explicitly reported.	diagnosing RPD
		Stated only that the	on CFP not
		eves had either:	reported
		bilateral soft drusen	1
		± pigment abnor-	Recruitment
		malities, but no	dates: Not
		evidence of CNV: or	reported
		they had unilateral	1 Police
		CNV.	
		Exclusion criteria	
		for study entry:	
		Eves that did not	
		receive both FAF	
		imaging and colour	
		fundus photography.	

Participant characteristics					
Say m.f (%mala)	Not reported				
Ago yours moon (SD)	Not reported				
Age, years, mean (SD)	None reported				
Other Rey characteristics	None reported				
<b>Results</b> – <b>FAF</b> imaging					
Calculations are based on	Population with RF	מי	Population with	t	Total
numbers of eyes (both eyes	an colour fundus	ν	RPD on colour	uı	IUtai
of 83 subjects and single	nhotogranhy		fundus		
eves of 55 subjects)	photography		nhotogranhy		
<b>FAF</b> imaging positive	28	9		C	32
FAF imaging positive	20	a b	187		180
Total	2	0	101	u	221
10(a)	30		191		221
Diagnosia		1			059/ CI
Clinical consistivity of ( o + b	)	02.2	20/		<b>93% CI</b>
Clinical sensitivity $a / (a + b)$	)	93.3	370 10/		77.89 to 98.99
Clinical specificity $d / (c + d)$	)	97.9	1%		94.72 to 99.41
$\frac{PPV a / (a + c)}{NPV a / (a + c)}$		8/.5	<u>0%</u>		70.99 to 96.41
$\frac{NPV d}{(b+d)}$	11 11 1/100	98.9	4% <sub>0</sub>		96.22 to 99.84
Positive likelihood ratio [ser	tive likelihood ratio [sensitivity/(100-				16.82 to 118.08
specificity)]	0.0	0.07			
Negative likelihood ratio [(1	00-	0.07			0.02 to 0.26
sensitivity)/specificity]		6.8.4	<b>5</b> 0		
Diagnostic odds ratio (a x d	)/(b x c)	654.	50	<b>.</b>	114.50 to 3/41.07
Comments: Sensitivity calculation agrees with statement in the paper that "AF imaging was over 90% sensitive" (no other diagnostic results were reported in the paper)					
sensitive" (no other diagnostic	c results were reported	in the	e paper).		CC 1 C 11
Sensitivity and specificity are	also calculable for a s	ub-gr	oup of patients base	ed on	unaffected fellow
eyes of those with unilateral (	CNV ("CNV-R" group	). Hov	wever, subgroup is	defir	ied by auto-
fluorescence pattern (reticular	AF and / or RPD) and	d does	not include all pati	ents	with unilateral
CNV. Therefore data have no	t been extracted here.				
	1 110				
Interpretability and accepta	bility of test	<b>.</b>	<b>TT</b>	1.1	
Numbers excluded from analysis due to poor		None. However, reported that for one patient			
image quality w		with RPD only this was "perhaps due to			
		marg	marginal scan quality" and another patient had		
		bila	iteral RPD and an A	AF 111	nage in the left eye
		that	could not be graded	1 for	reticular AF".
	Unclear w		clear whether these were the only poor-		
		qual	ity images present.		
Inter-observer agreement N		Not	Not reported		

Test acceptability (patients / clinicians) Adverse events

Intra-observer agreement

AF: autofluorescence; AMD: age-related macular degeneration; CFP: colour fundus photography; CNV: choroidal neovascularisation; cSLO: scanning laser ophthalmoscopy; FAF: fundus autofluorescence; GA: geographic atrophy; NPV: negative predictive value; PPV: positive predictive value; RPD: reticular pseudodrusen

Not reported

Not reported

Not reported

# **Smith and colleagues<sup>101</sup> critical appraisal criteria** (based on Reitsma et al.<sup>81</sup> adaptation of the QUADAS Tool<sup>93</sup>)

	Item	Description	Judgement
1	Was the spectrum of patients representative of the patients who will receive the test in practice?	Study is retrospective but unclear if it involved consecutive patients. Two separate cohorts of eyes were combined: patients from the UK without evidence of CNV and unaffected eyes of patients from the USA who had unilateral CNV, so is an atypical case mix	No
2	Is the reference standard likely to classify the target condition correctly?	Although not stated explicitly, CFP is a standard approach for detecting RPD	Yes
3	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	Not reported	Unclear
4	Did the whole sample or a random selection of the sample receive verification using the intended reference standard?	Whole sample – appears to have been purposively selected to ensure patients had received both tests	Yes
5	Did patients receive the same reference standard irrespective of the index test result?	Yes	Yes
6	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	Yes	Yes
7	Were the reference standard results interpreted without knowledge of the results of the index test?	Not reported	Unclear
8	Were the index test results interpreted without knowledge of the results of the reference standard?	Not reported	Unclear
9	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Not reported	Unclear
10	Were uninterpretable or intermediate test results reported? Were withdrawals from the study explained?	No. Unclear whether patient selection purposively excluded those with uninterpretable or indeterminate test results. Some poor-quality images may have influenced results classification (see 'Interpretability and acceptability of test' above) No withdrawals	No
11	were withdrawais norm the study explained:		applicable

# Study 6 of 8 – Ueda-Arakawa and colleagues

Reference and design	Diagnostic tests	Particinants	Outcome
iterer enee und design		i ui ticipunto	measures
Condition being	Index test:	Number of	Primary outcome
diagnosed / detected:	(1) Fundus auto-	narticinants: 114	of study: Not
Reticular pseudodrusen	fluorescence (FAF):	Purturpunter	stated. Paper
(RPD) in age-related	acquired using confocal	Number of eves:	focuses on
macular degeneration	scanning laser ophthal-	220	sensitivity and
(AMD)	moscope (cSLO)		specificity of each
	(Spectralis HRA+OCT;	Sample	imaging modality
First author: Ueda-	Heidelberg Engineering,	attrition/dropout:	at detecting RPD.
Arakawa <sup>97</sup>	Heidelberg, Germany).	8/228 eyes excluded,	
	Excitation 488nm; barrier	due to phthisis bulbi	Other relevant
Publication year: 2013	filter beginning at	(n=2) or poor image	outcomes:
	500nm.	quality in $\geq 3$	Inter-grader
Country: Japan		imaging modalities	agreement rates for
	(2) Near-infrared fundus	(n=6). Further	detecting RPD in
Study design:	autofluorescence (NIR-	excluded due to poor	each imaging
Retrospective case series	FAF): acquired with	image quality: FAF	modality.
	cSLO (same equipment	imaging: 3/220;	
Number of centres: One	as FAF), in the	NIR-FAF imaging:	Diagnostic
	indocyanine green	84/220.	threshold:
Funding: Not stated	angiography mode		RPD diagnosed
~	(excitation: 790nm;	Selection of	if reticular patterns
Competing interests:	detection 800nm).	participants:	showed on at least
Stated none		Consecutive patients	two of the follow-
	Each FAF or NIR-FAF	with AMD who first	Ing: Diue-channel
	image was compiled from	visited ophthal-	EAE CRD IA or
	an average of 15 to 20	mology department	SD-OCT
	scans by the cSLO	during recruitment	50-001.
	sonware.	dates	Characterisation of
	Deference standard	Inclusion aritaria	reticular lesions:
	At least 2 of 7 imaging	for study entry	
	modalities (in any	Farly $\Delta MD$	FAF and NIR-FAF:
	combination) positive for	$\frac{1}{1}$	A group of ill-
	RPD.	geographic atrophy	defined, hypo-
		in at least one eve	fluorescent lesions
	(1) Contrast-enhanced	Early AMD defined	against a back-
	colour fundus photo-	as presence of soft	ground of mildly
	graphy (CFP): 30°–40°	drusen (> 63 $\mu$ m) or	elevated AF.
	field acquired digitally	areas of hyper- or	
	using Topcon TRC	hypopigmentation in	blue-channel UFP
	NW6S non-mydriatic	the RPE. Geographic	interlacing
	retinal camera (Topcon,	atropy defined on	networks 125-
	Tokyo, Japan). Blue	colour fundus	250um wide
	channel examined using	photography as a	
	Image J software (Nat-	sharply delineated	IR: groups of hypo-
	ional Institutes of Health,	area (≥ 175 µm) ie	reflectant lesions
	Bethesda, MD, USA).	hypopigmentation,	against a back-
	(NB: paper notes that this	depigmentation or	ground of mild
	has been the traditional	apparent absence of	hyper-reflectance
	method for detecting	RPE in which	with anomalous
	RPD).	choroidal vessels	characteristics.
		were clearly visible.	

(2) Infrared reflectance	Neovascular AMD	
(IR): acquired using	defined as	ICGA: A distinctive
cSLO (same equipment	neovascularisation	grouping of hypo-
as the index test). Light	detected using FA or	fluorescent dots
stimulus 820nm	indocvanine	present in the late
Sumarab OZomin.	angiography Only	angiogram phases.
(3) FAF imaging (i.e. an	images of eligible	001
index test – see above)	quality were	SD-OCT: ≥5 hyper-
index test see above).	analysed and only	reflective mounds
(4) NIP EAE imaging	eves with eligible	or triangular
(i.e. an index test see	image quality in at	lesions above the
(i.e., all index test – see	least five imaging	RPE in ≥1 B-scan.
above).	modalities were	
(5) C C 111	included	
(5) Contocal blue	menuueu.	Recruitment
reflectance (CBR):	Exclusion critaria	dates: January
acquired with cSLO	for study ontry:	2010 – November
(same equipment as the	People aged $< 50$	2010
index test). Light	voors avos with high	2010
stimulus 488nm; field of	myonia eves with	
view 30° x 30°, centred	ather magular	
on the macula.	abnormalitios	
	autormanties.	
(6) Late-phase		
indocyanine green		
angiography (ICGA):		
acquired with cSLO		
(same equipment as the		
index test). Excitation:		
790nm; detection 800nm.		
(/) Spectral domain		
optical coherence		
tomography (SD-OCT):		
conducted using		
Spectralis HRA+OCT		
(Heidelberg		
Engineering). Horizontal		
and vertical line scans		
through the fovea centre		
obtained at a 30° angle,		
followed by serial		
horizontal scans with an		
examination field size		
ranging from 30° x 10° to		
30° x 25. At each		
location of interest on the		
retina, 50 images were		
averaged to reduce		
speckle noise.		

Participant characteristics	
Sex, m:f (%male)	79:35 (69)
Age, years, mean (SD)	73.8 (9.4), range 52-92
Visual acuity (logarithm of the minimum	0.396 (0.512), range 0.01-1.5
angle of resolution), mean (SD)	

# Results

#### FAF versus $\geq 2$ (of 7) imaging modalities

Calculations are based on numbers	Population with	l	Population		Total
of eyes, including both eyes of	disease on ≥2		without disease of	n	
each subject	imaging		≥2 imaging		
	modalities		modalities		
FAF imaging positive	32	а	9	с	41
FAF imaging negative	5	b	171	d	176
Total	37		180		217

Diagnosis		95% CI
Clinical sensitivity a / (a + b)	86.49%	71.21 to 95.41
Clinical specificity d / (c + d)	95.00%	90.72 to 97.68
PPV $a / (a + c)$	78.05%	62.38 to 89.42
NPV $d / (b + d)$	97.16%	93.49 to 99.06
Positive likelihood ratio [sensitivity/(100-specificity)]	17.30	9.04 to 33.11
Negative likelihood ratio [(100-sensitivity)/specificity]	0.14	0.06 to 0.32
Diagnostic odds ratio (a x d)/(b x c)	121.60	38.25 to 386.57

Comments: Calculations agree with values reported in paper (except diagnostic odds ratio not reported). Paper also reports (in Supplementary Table 2) that the sensitivity of FAF imaging is 86.5% when the field size is limited to the same imaging area as SD-OCT, i.e.  $30^{\circ} \times 10^{\circ}$  – but sample sizes (n/N) for this calculation (32/37) are not explained.

Note that CFP is the test usually considered as a reference standard for diagnosing RPD. Although diagnostic outcomes for a comparison of FAF versus CFP are given in supplementary Table 1 of the paper, these relate only to a subset of 37 eyes that had a reticular pattern on  $\geq 2$  imaging modalities, therefore these data have not been extracted.

Interpretability and acceptability of test	
Number of eyes excluded from analysis due to poor	3/220 (1.4%)
image quality	
Inter-observer agreement (grading reticular pattern)	89.3%; kappa = 0.700
Intra-observer agreement	Not reported
Test acceptability (patients / clinicians)	Not reported
Adverse events	Not reported

# NIR-FAF versus ≥2 (of 7) imaging modalities

NIR-FAF versus $\geq 2$ (01 /) imaging modalities					
Calculations are based on numbers	Population with		Population	Total	
of eyes, including both eyes of each	disease on $\geq 2$		without disease on		
subject	imaging		≥2 imaging		
	modalities		modalities		
NIR-FAF imaging positive	9	а	5	c 14	
NIR-FAF imaging negative	19	b	103	d 122	
Total	28		108	136	
Diagnosis				95% CI	
Clinical sensitivity a / (a + b)		32.1	4%	15.91% to 52.35%	
Clinical specificity d / (c + d)		95.3	7%	89.52% to 98.46%	
<b>PPV</b> $\mathbf{a} / (\mathbf{a} + \mathbf{c})$		64.2	9%	35.18% to 87.11%	
NPV d / (b + d)		84.43%		76.75% to 90.35%	
Positive likelihood ratio [sensitivity/(100-		6.94		2.53 to 19.08	
specificity)]					
Negative likelihood ratio [(100-		0.71		0.55 to 0.92	
sensitivity)/specificity]					
Diagnostic odds ratio (a x d)/(b x c)		9.76		2.95 to 32.33	
Comments: Calculations agree with values reported in		n pap	er (except diagnostic	odds ratio not	
reported). Paper also reports (in Supplementary Table		e 2) th	hat the sensitivity of	NIR-FAF imaging is	
28.6% when the field size is limited to the same imag		ging a	rea as SD-OCT, i.e. 1	$30^{\circ} \ge 10^{\circ} - but \text{ sample}$	
sizes (n/N) for this calculation (8/28) are not explaine		ed.			
Interpretability and acceptability of test					
Number of eyes excluded from analysis due to poor		64/2	64/220 (29%)		
image quality					
Inter-observer agreement (grading reticular pattern)		84.2%; kappa = 0.563			
Intra-observer agreement		Not	Not reported		
Test acceptability (patients / clinician	s)	Not	reported		
Adverse events		Not	Not reported		

Number of eyes with good image quality – results for all imaging tests			
FAF	217/220 (99%)		
NIR-FAF	136/220 (62%)		
Blue-channel CFP	220/220 (100%)		
IRR	220/220 (100%)		
ICGA	220/220 (100%)		
SD-OCT	220/220 (100%)		
CBR	204/220 (93%)		

AMD: age-related macular degeneration; CBR: confocal blue reflectance; CFP: colour fundus photography; CNV: choroidal neovascularisation; cSLO: confocal scanning laser ophthalmoscopy; FAF: fundus autofluorescence; GA: geographic atrophy; ICGA: indocyanine green angiography; IRR: infrared reflectance; NIR-FAF: near-infrared fundus autofluorescence; NPV: negative predictive value; PPV: positive predictive value; RPD: reticular pseudodrusen; RPE: retinal pigment epithelium; SD-OCT: spectral-domain optical coherence tomography

**Ueda-Arakawa and colleagues**<sup>97</sup> **critical appraisal criteria** (based on Reitsma et al.<sup>81</sup> adaptation of the QUADAS Tool<sup>93</sup>)

	Item	Description	Judgement
1	Was the spectrum of patients representative of the patients who will receive the test in practice?	Study is retrospective but involved consecutive patients. Patients are Japanese, with newly diagnosed AMD, and patients with comorbidities excluded (including, among others, certain types of CNV and central serous chorioretinopathy), so is an atypical case-mix	No
2	Is the reference standard likely to classify the target condition correctly?	Paper describes CFP as traditional test for detecting RPD. Study reference standard is positive result on ≥2 of 7 modalities, but individual eyes were diagnosed using different combinations of modalities	Unclear
3	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	Not reported	Unclear
4	Did the whole sample or a random selection of the sample receive verification using the intended reference standard?	Multiple imaging methods used in all patients but the diagnostic tests differed between patients	Yes
5	Did patients receive the same reference standard irrespective of the index test result?	No, the combination of the ≥2 test modalities making up the reference standard varied between patients	No
6	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	The index test(s) could have been one (or both) of the two tests contributing to a diagnosis	No
7	Were the reference standard results interpreted without knowledge of the results of the index test?	Not reported	Unclear
8	Were the index test results interpreted without knowledge of the results of the reference standard?	Not reported	Unclear
9	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Not reported	Unclear
10	Were uninterpretable or intermediate test results reported?	Stated that 3/220 eyes for FAF (1%), 84/220 eyes for NIR-FAF (38%) and 16 eyes for CBR (7%) did not have good quality images and were excluded	Yes
11	Were withdrawals from the study explained?	Yes – phthisis bulbi or poor image quality	Yes

# Study 7 of 8 – Vujosevic and colleagues

Acterience and design Condition being diagnosed / detected: diabetic macular oedema (DMO)Index test: Fundus autofluorescence (FAF) acquired with confocal scanning laser ophthalmoscopy (SLO) (Heidelberg Regineering, Heidelberg, Germany). Solid-pumped laser; excitation 488m; excitation 488m; excitation 488m; excitation 488m; emission detected above 500nm using barrier fifter. FAF signal amplified by calculating in age analysis software.Number of eyes: participants: 137 Sample attrition/dropout: Not reportedDiter relevant outcomes: Sensitivity and specificity for detection of participants: laser ophthalmoscopy (RM-SLO): images taken with F-10 SLO (Nidek Co, Gamagori, Japan), which uses 4 wavelengths: blue, green, red and unareated or treated primes attra top) and five stop and a laterally oriented oval-shaped opacitiesDiagnostic three detection primery outcome of study infarced. Selection of participants: Inclusion criteria for study entry: Sinificant media or different foxeal patters for study entry: Sinificant media opacitiesDiagnostic three detection section of participants: Inclusion criteria for study entry: Sinificant media opacitiesDiagnostic three detection section of participants: Inclusion criteria for study entry: Sinificant media opacitiesPrimary outcome of study: Inter-method agreement in identifying different patters for barbolic three detection of participants: Inter for study entry: Sinificant media opacitiesFunding: None received (RM-SLO): images taken with F-10 SLO (Nidek Co, Gamagori, Japan), which uses 4 stop and a laterally oriented oval-shaped opacities stated only that l
Control being unglosed ocdema (DMO)Index test:Fundage statofluorescence (FAF) acquired with confocal scanning laser ophthalmoscopy (SLO) (Heidelberg Regineering, Heidelberg, Germany).Number of eyes: 263Fundage statofluorescence (Heidelberg Regineering, Heidelberg, Germany). Solid-pumped laser; excitation 488nm; excitation 4880m; for study entry: Significat media opacitiesOther relevant outcomes: Sentification of DMO:Number of exert. Signification for infared (15 ligned) infared (25 ligned) <br< th=""></br<>
PublicationPublication distributionPublication vericePublication vericePublic
Occentia (DMO)(FAF) acquired win confocal scanning laser ophthalmoscopy (cSLO) (Heidelberg Retinal Angioraph, HRA 2; Heidelberg, Germany). Solid-pumped laser; excitation 488nm; erission detected above prospective (not explicitly stated but all patients provided consent)Number of eyes: 263agreement in identifying different patterns of DMONumber of eyes: 263Sample attrition/dropout: Not reported evidentOther relevant outcomes: Sensitivity and specificity for detecting DMOCountry: Italy prospective (not explicitly stated but all patients provided consent)Solid-pumped laser; evidentNot reported evidentSelection of participants: Recruited images after correction of eye movements using image analysis software.Diagnostic threshold: Inclusion criteria for study entry: Type 1 or 2 diabetes mellitus; any stage of untreated or treated on the same dayDiagnostic threshold: Increased] and muspecified diabetic retinopathy (DR) clinicsFAF: Not reported (stade only that images were graded for study entry: Type 1 or 2 diabetes mellitus; any stage of untreated or treated on the same dayFAF: Not reported increased and presence/absence of decreased/ in the macula)Funding: None received information providedReference standard: Reference standard: Reference standard: Reference standard: Reference standard: New Stops. To obtain a RM- SLO image, a central stop and a laterally oriented oval-shaped opening was used, from both right and left sides.Number of eyes: 263Diagreement in adentifying different both right and left sides.Comparators: Time
First author: Vujosevic%Contocal scanning laser ophthalmoscopy (CSLO) (Heidelberg Reinal Angiograph, HRA 2; Heidelberg Reinering, Heidelberg Reiner, Heidelberg Reiner, Excitant 488 million 488 million, Solid-pumped laser; excitation 488 million, solid-pumped laser, excitation 488 million, solid-pumped laser, excitation, solid-pumped laser, excitation, solid-pumped laser, excitation, solid-pumped laser, excitation, solid-pumped laser, excitation, solid-pumped laser, exc
First aution: Vujosevicopintalmoscopy (CSLD)265patterns of DMOPublication year: 2012Angiograph, HRA 2; Heidelberg, Engineering, Solid-pumped laser; excitation 488nm; sectional study. Probably prospective (not explicitly stated but all patients provided consent)Sample attrition/dropout: Not reported excitation 488nm; emission detected above 500mu using barrier filter. FAF signal a mean of 15 aligned images after correction of eye movements using laser ophthalmoscopy (RM-SLO): images taken with F-10 SLO (Nidek Co, Gamagori, Japan), which uses 4 wavelengths: blue, oreintal stop) and five stops. To obtain a RM- SLO image, a central stop and a laterally oriented oval-shaped opening was used, from both right and left sides.265Other relevant outcomes: Sample attrition/dropout: Not reported centrest. Competing interests: No information providedOther relevant outcomes: Selection of participants: Reference standard: Reference standa
Publication year: 2012(Heidelberg Refman Angiograph, HRA 2; Heidelberg, Germany). Solid-pumped laser; excitation 488mn; ectional study. Probably prospective (not explicitly stated but all patients provided consent)Sample attrition/dropout: Not reported explicitly but none excitation 488mn; emission detected above 500m using barrierCountry: ItalyOther relevant outcomes: Sensitivity and specificity for detecting DMONumber of centres: Not reported (>1 clinic implied) information providedFafference standard: Reference standard: Reference standard: Retromode scanning laser ophthalmoscopy (RM-SLQ): mages taken with F-10 SLO (Nidek Co, Gamagori, Japan), which uses 4 wavelengths: blue, green, red and infrared. Infrared laser was set at 790mn F-10 contains 8 apertures (five confocal and 3 with a central stop) and five stop. To obtain a RM- SLO image, a central stop and a laterally oriented oval-shaped opening was used, from both right and left sides.Sample state/but allottion resonce/absence of decreased/ increased auto- fluorescence intereased auto- fluorescence intereased auto- fluorescence intereased auto- fluorescence intereased auto- fluorescence intereased/ intereased/ intereased/ intereased auto- fluorescence intereased auto- fluorescence intereased/ intereased/ intereased auto- fluorescence intereased/ intereased auto- fluorescence of intereased or the pase FA images of the macula were graded for the presence of the mac
Publication year: 2012Angiograph, HKA 2; Heidelberg, Germany). Solid-pumped laser; excitation 488nm; emission detected above 500mm using barrier filter. FAF signal amen of 15 aligned image analysis software.Sample attrition/dropout: Not reported explicitly but none evidentOther relevant outcomes: Sensitivity and specificity for detecting DMONumber of centres: Not reported (>1 clinic implied)50 mu using barrier filter. FAF signal a mean of 15 aligned image analysis software.Selection of participants: Recruited consecutively from unspecified diabetic for study entry: Type 1 or 2 diabetes mellitus; any stage of infrared. Infrared laser was set at 790nm, F-10 contains 8 apertures (five confocal and 3 with a central stop) and five stop and a laterally oriented oval-shaped opening was used, from both right and left sides.Comparators: Time domain OCT (TD- OCT)Differ relevant outcomes: Sample attrition/dropout: Not reported contextent pase fA images of the entral stop
Country: ItalyHeidelberg Engineering, Solid-pumped laser; excitation 488mm; emission detected above prospective (not explicitly stated but all patients provided consent)attrition/dropout: excitation 488mm; emission detected above solid-pumped laser; excitation 488mm; emission detected above filter. FAF signal a mean of 15 aligned image analysis software.Selection of participants: narticipants: retrinopathy (DR) clinicsDiagnostic threshold: Identification of DMO:Number of centres: Not reported (>1 clinic implied)mean of 15 aligned image analysis software.Selection of participants: retrinopathy (DR) clinicsDiagnostic threshold: Identification of DMO:Funding: None receivedReference standard: Retromode scanning laser ophthalmoscopy (RM-SLO): images taken with F-10 SLO unfrared. Infrared laser; was set at 790m. F-10 contains 8 apertures (five confocal and 3 with set 4 wavelengths: blue, green, red and infrared. Infrared laser was set at 790m. F-10 contains 8 apertures (five confocal and 3 with a central stop) and five stops. To obtain a RM- SLO image, a central stop and a laterally oriented oval-shaped opening was used, from both right and left sides.attrition/dropout: solid-participants: retrinopathy (DR) clinees compound five stops. To obtain a RM- SLO image, a central stop and a laterally oriented oval-shaped opening was used, from both right and left sides.attrition/dropout: solid-participants compound CT (TD- OCT)attrition/dropout: prosecein laek/ragComparators: Time domain OCT (TD- OCT)meacula were graded for the presence of laek/rag
Country: ItalyHeidelberg, Germany). Solid-pumped laser; excitation 488m; emission detected above 500nm using barrier a mean of 15 aligned image analysis software.Not reported explicitly but none evidentSenstruty and specificity for detecting DMONumber of centres: Not reported (>1 clinic implied)of eye movements using image analysis software.Selection of participants: nereceively from unspecified diabetic retinopathy (DR) clinicsDiagnostic threshold: Identification of DMO:Funding: None received Competing interests: No information providedReference standard: Reference standard: Retromode scanning laser ophthalmoscopy (RM-SLO): images taken with F-10 SLO untreated or treated green, red and infrared. Infrared laser was set at 790nm. F-10 contains 8 apertures (five stops. To obtain a RM- SLO image, a central stop. To obtain a RM- SLO image, a central stop and a laterally oriented oval-shaped opening
Study design: Cross- sectional study. Probably prospective (not explicitly stated but all patients provided consent)Solid-pumped laser; excitation 488nm; emission detected above 500nm using barrier filter. FAF signal a mean of 15 aligned i mages anleys software.selection of participants: consecutively from unspecified diabetic retinopathy (DR)specificitly for detecting DMONumber of centres: Not reported (>1 clinic implied)a mean of 15 aligned images anley software.selection of participants: retinopathy (DR)Diagnostic threshold: Inclusion criteria for study entry: Type 1 or 2 diabetes mellitus; any stage of untreated or treated OCT, FAF, FA and retinopathy (DR)FAF: Not reported for different foveal patterns [normal, single spot increased] and multiple spots increased] and presence/absence of decreased/ increased auto- fluerscence increased auto- fluerscence infared lafared laser was set at 790nm. F-10 contains 8 apertures (five stops. To obtain a RM- SLO image, a central stop and a laterally oriented val-shaped opening was used, from both right and left sides.Exclusion criteria for study entry: Significant media opacitiesTD-OCT: central retinal thickness > 230 µm (measured in the central for study entry: Significant media opacitiesTD-OCT: central retinal thickness > 230 µm (measured in the central for study entry: signes of the macula were graded for the presence of the macula
Study design: Cross- sectional study. Probably prospective (not explicitly stated but all patients provided consent)excitation 488m; emission detected above 500nm using barrier filter. FAF signal amplified by calculating a mean of 15 aligned images after correction of eye movements using image analysis software.evidentdetecting DMONumber of centres: Not reported (>1 clinic implied)amean of 15 aligned images after correction of eye movements using image analysis software.Selection of participants: Recruited consecutively from unspecified diabetic for study entry: Type 1 or 2 diabets untreated or treated OCT, FAF, FA and wavelengths: blue, green, red and infrared. Infrared laser was set at 790nm. F-10 contains 8 apertures (five confocal and 3 with a central stop) and five stops. To obtain a RM- SLO image, a central stop and a laterally oriented oval-shaped opening was used, from both right and left sides.mexical and presence of the macula were graded for the presence of for study entry:TD-OCT: central retinal thickness > 230 µm (measured in the central foveal zone)
sectional study. Probably prospective (not explicitly stated but all patients provided consent) Number of centres: Not reported (>1 clinic implied) of eye movements using information provided Methods in the state standard: Competing interests: No information provided Market states with F-10 SLO (Nidek Co, Gamagori, Japan), which uses 4 wavelengths: blue, green, red and infrared laser was set at 790nm. F-10 SLO contains 8 apertures (frue stops. To obtain a RM- SLO period a laterally oriented oval-shaped opening was used, from both right and left sides. Selection of participants: Recruited consecutively from unspecified diabetic retinopathy (DR) clinics Herewited consecutively from unspecified diabetic retinopathy (DR) clinics Selection of participants: Recruited consecutively from unspecified diabetic retinopathy (DR) clinics
prospective (not explicitly stated but all patients provided consent)500nm using barrier filter. FAF signal amplified by calculating a mean of 15 aligned images after correction of eye movements using image analysis software.Selection of participants: Recruited consecutively from unspecified diabetic retinopathy (DR) clinicsDiagnostic threshold: Identification of DMO:Funding: None receivedReference standard: Reference standard: Retromode scanning laser ophthalmoscopy (RM-SLO): images taken with F-10 SLO (Nidek Co, Gamagori, Japan), which uses 4 wavelengths: blue, green, red and infrared. Infrared laser was set at 790nm. F-10 contions 8 apertures (five confocal and 3 with a central stop) and five stops. To obtain a RM- SLO image, a central stop and a laterally oriented oval-shaped opening was used, from both right and left sides.Diagnostic threshold: Identification of DMO:Diagnostic threshold: Identification of DMO:FA: Not reported (stated only that increased auto- fluorescence in the macula)FAF: Not reported (stated only that late- phase FA images of the central stop) and five stops. To obtain a RM- SLO image, a central stop and a laterally oriented oval-shaped opening was used, from both right and left sides.Diagnostic threshold: Identification of DMO:Diagnostic threshold: Identification of DMO:FA: Not reported (stated only that late- phase FA images of the macula were graded for the presence of the macula were graded for the presence of threshold:Diagnostic threshold: Identification of DMO:FA: Not reported (stated only that late- phase
stated but all patients provided consent) Number of centres: Not reported (>1 clinic implied) armages after correction funding: None received Competing interests: No information provided Reference standard: Competing interests: No information provided Reference standard: Competing interests: No information provided Reference standard: Competing interests: No information provided Reference standard: Retromode scanning laser ophthalmoscopy (RM-SLO): images taken with F-10 SLO (Nidek Co, Gamagori, Japan), which uses 4 wavelengths: blue, green, red and infrared. Infrared laser was set at 790nm. F-10 contains 8 apertures (five stops. To obtain a RM- SLO image, a central stop and a laterally oriented oval-shaped opening was used, from both right and left sides. Comparators: Time domain OCT (TD- OCT)
provided consent)amplified by calculating a mean of 15 aligned images after correction of eye movements using image analysis software.Recruited consecutively from unspecified diabetic retinopathy (DR)Identification of DMO:Funding: None receivedReference standard: Reference standard: Reformation providedReference standard: Reference standard: Retromode scanning laser ophthalmoscopy (RM-SLO): images taken with F-10 SLO (Nidek Co, Gamagori, Japan), which uses 4 wavelengths: blue, green, red and infrared. Infrared laser was set at 790nm. F-10 contains 8 apertures (five confocal and 3 with a central stop) and five stops. To obtain a RM- SLO image, a central stop and a laterally oriented oval-shaped opening was used, from both right and left sides.Recuited contented comparators: Time domain OCT (TD- OCT)Recuited contains application of contains and a laterally oriented oval-shaped opening was used, from both right and left sides.Recuited contains application of contains application of Data and and the sides.Comparators: Time domain OCT (TD- OCT)Comparators: Time domain OCT (TD-FA: Not reported (stated only that late- phase FA images of the macula were graded for the presence of the macula were grade
Number of centres: Not reported (>1 clinic implied)a mean of 15 aligned images after correction of eye movements using image analysis software.consecutively from unspecified diabetic retinopathy (DR) clinicsDMO:Funding: None receivedReference standard: Retromode scanning laser ophthalmoscopy (RM-SLO): images taken with F-10 SLO (Nidek Co, Gamagori, Japan), which uses 4 wavelengths: blue, green, red and infrared. Infrared laser was set at 790nm. F-10 contains 8 apertures (five stops. To obtain a RM- SLO image, a central stop and a laterally oriented oval-shaped opening was used, from both right and left sides.Inclusion criteria for study entry: DCT, FAF, FA and RM-SLO performed on the same dayDMO:TD-OCT: central retinal thickness > 230 µm (measured in the central stop and a laterally oriented oval-shaped opening was used, from both right and left sides.DMO:Comparators: Time domain OCT (TD- OCT)Comparators: Time domain OCT (TD- OCT)FAF: Not reported (stated only that late- phase FA images of the macula were graded for the presence of fluorescenin lawlarge
Number of centres: Not reported (>1 clinic implied)images after correction of eye movements using image analysis software.unspecified diabetic retinopathy (DR) clinicsFAF: Not reported (stated only that images were graded for different foveal patterns [normal, single spot increased and multiple spots increased] and presence/absence of decreased/ increased auto- fluorescein tertial for study entry:FAF: Not reported (stated only that images were graded for different foveal patterns [normal, single spot increased and multiple spots increased] and presence/absence of decreased/ increased auto- fluorescence in the macula)Number of centres: Funding: None receivedReference standard: Reference standard: Reference standard: Retromode scanning laser ophthalmoscopy (RM-SLO): images taken with F-10 SLO (Nidek Co, Gamagori, Japan), which uses 4 wavelengths: blue, green, red and infrared. Infrared laser was set at 790nm. F-10 confocal and 3 with a central stop) and five stops. To obtain a RM- SLO image, a central stop and a laterally oriented oval-shaped opening was used, from both right and left sides.Exclusion criteria for study entry: Significant media opacitiesTD-OCT: central retinal thickness > 230 µm (measured in the central foveal zone)FA: Not reported (stated only that late- phase FA images of the macula were graded for the presence of fluorescein lashapeFA: Not reported (stated only that late- phase FA images of the macula were graded for the presence of fluorescein lashape
reported (>1 clinic implied) Funding: None received Competing interests: No information provided Reference standard: Reference standard: Reference standard: Reference standard: Reference standard: Retromode scanning laser ophthalmoscopy (RM-SLO): images taken with F-10 SLO (Nidek Co, Gamagori, Japan), which uses 4 wavelengths: blue, green, red and infrared. Infrared laser was set at 790nm. F-10 contains 8 apertures (five confocal and 3 with a central stop) and five stops. To obtain a RM- SLO image, a central stop and a laterally oriented oval-shaped opening was used, from both right and left sides. Comparators: Time domain OCT (TD- OCT)
Funding: None receivedimage analysis software.clinics(stated only that images were graded for different foveal patterns [normal, single spot increased and multiple spots increased] and presence/absenceCompeting interests: No information providedReference standard: Retromode scanning laser ophthalmoscopy (RM-SLO): images taken with F-10 SLO Japan), which uses 4 wavelengths: blue, green, red and infrared. Infrared laser was set at 790nm. F-10 contains 8 apertures (five confocal and 3 with a central stop) and five stop and a laterally oriented oval-shaped opening was used, from both right and left sides.clinics(stated only that images were graded for different foveal patterns [normal, and multiple spots increased] and presence/absence of decreased/ increased auto- fluorescence in the macula)FA: Not reported (stated only that indeced presence/absenceFA: Not reported (stated only that indeced increased auto- fluorescence in the central foveal zone)FA: Not reported (stated only that late- phase FA images of the macula were graded for the presence oiFA: Not reported (stated only that late- phase FA images of the macula were graded for the presence oi
Funding: None receivedReference standard: Retromode scanning laser ophthalmoscopy (RM-SLO): images taken with F-10 SLO (Nidek Co, Gamagori, Japan), which uses 4 wavelengths: blue, green, red and infrared. Infrared laser was set at 790nm. F-10 contains 8 apertures (five confocal and 3 with a central stop) and five stops. To obtain a RM- SLO image, a central stop and a laterally oriented oval-shaped opening was used, from both right and left sides.Inclusion criteria for study entry: Type 1 or 2 diabetes mellitus; any stage of untreated or treated oCT, FAF, FA and OCT, FAF, FA and RM-SLO performed on the same dayimages were graded for different foveal patterns [normal, single spot increased] and multiple spots increased] and presence/absence of decreased/ increased auto- fluorescence in the macula)FA: Not reported (stated only that late- phase FA images of the macula were graded for the presence of and opersence of the macula were graded for the presence of the macula were
Competing interests: No information providedReference standard: Retromode scanning laser ophthalmoscopy (RM-SLO): images taken with F-10 SLO Japan), which uses 4 wavelengths: blue, green, red and infrared. Infrared laser was set at 790nm. F-10 contains 8 apertures (five confocal and 3 with a central stop) and five stop. To obtain a RM- SLO image, a central stop and a laterally oriented oval-shaped opening was used, from both right and left sides.Inclusion criteria for study entry: Type 1 or 2 diabetes mellitus; any stage of untreated or treated DR; and having TD- OCT, FAF, FA and RM-SLO performed on the same dayfor different foveal patterns [normal, single spot increased] and multiple spots increased] and presence/absence of decreased/ increased auto- fluorescence in the macula)FAI: Not reported (stated only that late- phase FA images of the macula were graded for the presence of OCT.FA: Not reported (stated only that late- phase FA images of the macula were graded for the presence of fluorescence of the macula were graded for the presence of the macula were graded for the presence of fluorescence of the macula were graded for the presence of fluorescence presence of fluorescence of the macula were graded for the presence of fluorescence presence of fluorescenc
Competing interests: No information providedRetromode scanning laser ophthalmoscopy (RM-SLO): images taken with F-10 SLO (Nidek Co, Gamagori, Japan), which uses 4 wavelengths: blue, green, red and infrared. Infrared laser was set at 790nm. F-10 contains 8 apertures (five confocal and 3 with a central stop) and five stops. To obtain a RM- SLO image, a central stop and a laterally oriented oval-shaped opening was used, from both right and left sides.for study entry: Type 1 or 2 diabetes mellitus; any stage of untreated or treated DR; and having TD- OCT, FAF, FA and RM-SLO performed on the same daypatterns [normal, single spot increased and multiple spots increased] and presence/absence of decreased/ increased auto- fluorescence in the macula)Exclusion criteria for study entry: Significant media opacitiesTD-OCT: central retinal thickness > 230 µm (measured in the central foveal zone)FA: Not reported (stated only that late- phase FA images of the macula were graded for the presence of fluorescein leakage
information providedlaser ophthalmoscopy (RM-SLO): images taken with F-10 SLO (Nidek Co, Gamagori, Japan), which uses 4 wavelengths: blue, green, red and infrared. Infrared laser was set at 790nm. F-10 contains 8 apertures (five confocal and 3 with a central stop) and five stops. To obtain a RM- SLO image, a central stop and a laterally oriented oval-shaped opening was used, from both right and left sides.Type 1 or 2 diabetes mellitus; any stage of untreated or treated DR; and having TD- OCT, FAF, FA and RM-SLO performed on the same daysingle spot increased and multiple spots increased] and presence/absence of decreased/ increased auto- fluorescence in the macula)Exclusion criteria for study entry: Significant media opacitiesTD-OCT: central retinal thickness > 230 µm (measured in the central foveal zone)FA: Not reported (stated only that late- phase FA images of the macula were graded for the presence of fluorescein leakage
Image: The systemThe systemThe systemThe systemThe system(RM-SLO): image: taken with F-10 SLO (Nidek Co, Gamagori, Japan), which uses 4 wavelengths: blue, green, red and infrared. Infrared laser was set at 790nm. F-10 contains 8 apertures (five confocal and 3 with a central stop) and five stops. To obtain a RM- SLO image, a central stop and a laterally oriented oval-shaped opening was used, from both right and left sides.mellitus; any stage of untreated or treated DR; and having TD- OCT, FAF, FA and RM-SLO performed on the same dayand multiple spots increased] and presence/absence of decreased/ increased auto-fluorescence in the macula) <b>Exclusion criteria</b> for study entry: Significant media opacitiesTD-OCT: central retinal thickness > 230 μm (measured in the central foveal zone)FA: Not reported (stated only that late- phase FA images of the macula were graded for the presence of fluorescenip laphage
taken with F-10 SLO (Nidek Co, Gamagori, Japan), which uses 4 wavelengths: blue, green, red and infrared. Infrared laser was set at 790nm. F-10 contains 8 apertures (five confocal and 3 with a central stop) and five stops. To obtain a RM- SLO image, a central stop and a laterally oriented oval-shaped opening was used, from both right and left sides.untreated or treated DR; and having TD- OCT, FAF, FA and RM-SLO performed on the same dayincreased] and presence/absence of decreased/ increased auto- fluorescence in the macula)TD-OCT: central retinal thickness > 230 μm (measured in the central foveal zone)TD-OCT: central retinal thickness > 230 μm (measured in the central foveal zone)FA: Not reported (stated only that late- phase FA images of the macula were graded for the presence of fluoresceni lagbage
<ul> <li>(Nidek Co, Gamagori, Japan), which uses 4 wavelengths: blue, green, red and infrared. Infrared laser was set at 790nm. F-10 contains 8 apertures (five confocal and 3 with a central stop) and five stops. To obtain a RM-SLO image, a central stop and a laterally oriented oval-shaped opening was used, from both right and left sides.</li> <li>Comparators: Time domain OCT (TD-OCT)</li> </ul>
Japan), which uses 4 wavelengths: blue, green, red and infrared. Infrared laser was set at 790nm. F-10 contains 8 apertures (five confocal and 3 with a central stop) and five stops. To obtain a RM- SLO image, a central stop and a laterally oriented oval-shaped opening was used, from both right and left sides.OCT, FAF, FA and RM-SLO performed on the same dayof decreased/ increased auto- fluorescence in the macula)Value was set at 790nm. F-10 contains 8 apertures (five confocal and 3 with a central stop) and five stops. To obtain a RM- SLO image, a central stop and a laterally oriented oval-shaped opening was used, from both right and left sides.OCT, FAF, FA and RM-SLO performed on the same dayof decreased/ increased auto- fluorescence in the macula)FA: Not reported (stated only that late- phase FA images of the macula were graded for the presence of fluorescein lashage
wavelengths: blue, green, red and infrared. Infrared laser was set at 790nm. F-10 contains 8 apertures (five confocal and 3 with a central stop) and five stops. To obtain a RM- SLO image, a central stop and a laterally oriented oval-shaped opening was used, from both right and left sides.RM-SLO performed on the same dayincreased auto- fluorescence in the macula)FA: Not reported (stated only that late- phase FA images of the macula were graded for the presence of fluorescenceFA: Not reported (stated only that late- phase FA images of the macula were graded for the presence of fluorescence
green, red and infrared. Infrared laser was set at 790nm. F-10 contains 8 apertures (five confocal and 3 with a central stop) and five stops. To obtain a RM- SLO image, a central stop and a laterally oriented oval-shaped opening was used, from both right and left sides.on the same dayfluorescence in the macula)FA: Not reported (stated only that late- phase FA images of the macula were graded for the presence of fluorescenceTD-OCT: central retinal thickness > 230 μm (measured in the central foveal zone)
infrared. Infrared laser was set at 790nm. F-10 contains 8 apertures (five confocal and 3 with a central stop) and five stops. To obtain a RM- SLO image, a central stop and a laterally oriented oval-shaped opening was used, from both right and left sides.Exclusion criteria for study entry: Significant media opacitiesTD-OCT: central retinal thickness > 230 µm (measured in the central foveal zone)FA: Not reported (stated only that late- phase FA images of the macula were graded for the presence of fluorescein laskage
was set at 790nm. F-10 contains 8 apertures (five confocal and 3 with a central stop) and five stops. To obtain a RM- SLO image, a central stop and a laterally oriented oval-shaped opening was used, from both right and left sides.Exclusion criteria for study entry: Significant media opacitiesTD-OCT: central retinal thickness > 230 µm (measured in the central foveal zone)FA: Not reported (stated only that late- phase FA images of the macula were graded for the presence of fluorescein lashage
contains 8 apertures (five confocal and 3 with a central stop) and five stops. To obtain a RM- SLO image, a central stop and a laterally oriented oval-shaped opening was used, from both right and left sides.for study entry: Significant media opacitiesTD-OCT: central retinal thickness > 230 µm (measured in the central foveal zone)FA: Not reported (stated only that late- phase FA images of the macula were graded for the presence of fluorescein lashare
confocal and 3 with a central stop) and five stops. To obtain a RM- SLO image, a central stop and a laterally oriented oval-shaped opening was used, from both right and left sides.Significant media opacitiesretinal thickness > 230 µm (measured in the central foveal zone)FA: Not reported (stated only that late- phase FA images of the macula were graded for the presence of fluorescein lashage
central stop) and five stops. To obtain a RM- SLO image, a central stop and a laterally oriented oval-shaped opening was used, from both right and left sides. Comparators: Time domain OCT (TD- OCT)
stops. To obtain a RM- SLO image, a central stop and a laterally oriented oval-shaped opening was used, from both right and left sides.ESO µm (incustred m the central foveal zone)FA: Not reported (stated only that late- phase FA images of the macula were graded for the presence of fluorescein leakage
SLO image, a central stop and a laterally oriented oval-shaped opening was used, from both right and left sides.FA: Not reported (stated only that late- phase FA images of the macula were graded for the presence of fluorescein leakage
stop and a laterally oriented oval-shaped opening was used, from both right and left sides.FA: Not reported (stated only that late- phase FA images of the macula were graded for the presence of fluorescein leakage
stop and a naterally oriented oval-shaped opening was used, from both right and left sides.FA: Not reported (stated only that late- phase FA images of the macula were graded for the presence of fluorescein leakageComparators: Time domain OCT (TD- OCT)graded for the presence of fluorescein leakage
Oriented oval-shapedFA. Not reportedopening was used, from both right and left sides.(stated only that late- phase FA images of the macula were graded for the presence of fluorescein leakage
opening was used, nom(stated only that late-both right and left sides.phase FA images ofComparators:graded for theTime domain OCT (TD-presence ofOCT)fluorescein leakage
Ooth right and left sides.phase FA images of the macula were graded for the presence of fluorescein leakage
Comparators:the macula wereTime domain OCT (TD-graded for theOCT)fluorescein leakage
Comparators:graded for theTime domain OCT (TD-presence ofOCT)fluorescein leakage
DCT) presence of fluorescein leakage
The second secon
Fluorescein angiography and pattern of
(FA) leakage [cystoid and
non-cystoid]).
RM-SLO: Not
RM-SLO: Not reported (stated only
RM-SLO: Not reported (stated only that images were
RM-SLO: Not reported (stated only that images were graded for

	DMO)
	2010)
	For all methods 2
	masked refinal
	specialists trained in
	· · · ·
	imaging grading
	independently graded
	all images on a 17
	all illiages off a 17-
	inch monitor
	dedicated to DR
	according In ange of
	screening. In case of
	disagreement, a 3 <sup>rd</sup>
	specialist
	specialist
	adjudicated.
	Dearwitment dates
	Recruitment dates:
	March to August
	2009

Participant characteristics	
Sex, m:f (%male)	87:50 (64)
Age, years, mean (SD)	Type I diabetes: 48.8 (11.5), range 28-64
	Type II diabetes: 66.6 (8.1), range 41-85
	Overall : Not reported (numbers with diabetes do not account for all
	patients – see below)
With Type I or II diabetes,	Type I: 12 (8.8) [reported as 10.1% in the paper]
N(%)	Type II: 107 (78.1) [reported as 89.9% in the paper]
	Not reported: 18 (13.1)
Duration of diabetes,	Type I: 28.8 (11.9), range 5-51
years, mean (SD)	Type II: 15.4 (8.8), range 1-39
Central macular thickness,	323.4 (125.2), range 154.0-884.0
mean (SD), μm	

### **Results - FAF versus RM-SLO**

Diagnostic odds ratio (a x d)/(b x c)

Results - I'AF versus RM-SLO					
Calculations based on numbers of eyes (both eyes	Population with on RM-SLO	h DMO	Populati DMO or	ion without n RM-SLO	Total
of 126 subjects and single					
eyes of 11 subjects)					
FAF imaging positive	195	а	8	с	203
FAF imaging negative	16	b	44	d	60
Total	211		52		263
Diagnosis					95% CI
Clinical sensitivity a / (a + b) 92.42%				87.98 to 95.60	
Clinical specificity d / (c + d) 84.62%				71.91 to 93.10	
<b>PPV a / (a + c)</b> 96.06%				92.38 to 98.28	
<b>NPV d / (b + d)</b> 73.33%				60.34 to 83.92	
Positive likelihood ratio [sensitivity/(100- 6.01				3.17 to 11.38	
specificity)]					
Negative likelihood ratio [(100-		0.09			0.06 to 0.15
sensitivity)/specificity]					

Comments: Data reported in the paper are for RM-SLO compared against a FAF reference; recalculated by reviewers to give sensitivity and specificity of FAF compared against a RM-SLO reference.

67.03

26.99 to 166.45

Paper states (in the Discussion) that OCT is the 'new gold standard' for diagnosing DMO. However, a diagnostic accuracy comparison of FAF versus TD-OCT is not possible from the reported data (only the diagnostic accuracy of RM-SLO versus TD-OCT, FA and FAF are reported and calculable – not extracted here).

Interpretability and acceptability of test	
Numbers excluded from analysis due to poor image quality	Not reported
Inter-observer agreement	Not reported
Intra-observer agreement	Not reported
Test acceptability (patients / clinicians)	Not reported
Adverse events	Not reported

cSLO: confocal scanning ophthalmoscopy; DMO: diabetic macular oedema; DR: diabetic retinopathy; FA: fluorescein angiography; FAF: fundus autofluorescence; NPV: negative predictive value; OCT: optical coherence tomography; PPV: positive predictive value; RM-SLO: retromode scanning laser ophthalmoscopy; TD-OCT: time domain optical coherence tomography

**Vujosevic and colleagues<sup>98</sup> critical appraisal criteria** (based on Reitsma et al.<sup>81</sup> adaptation of the QUADAS Tool<sup>93</sup>)

	Item	Description	Judgement
1	Was the spectrum of patients representative of the patients who will receive the test in practice?	Unclear if study is prospective, but it involved consecutive patients. Patients had any stage of untreated or treated diabetic retinopathy so this may be a typical case-mix	Unclear
2	Is the reference standard likely to classify the target condition correctly?	Paper describes OCT (i.e. not RM-SLO) as the 'new gold standard' for classifying DMO	Unclear
3	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	Same day	Yes
4	Did the whole sample or a random selection of the sample receive verification using the intended reference standard?	Whole sample	Yes
5	Did patients receive the same reference standard irrespective of the index test result?	Yes	Yes
6	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	Yes	Yes
7	Were the reference standard results interpreted without knowledge of the results of the index test?	Order of tests not reported but stated that images were independently graded in a masked fashion	Yes
8	Were the index test results interpreted without knowledge of the results of the reference standard?	Order of tests not reported but stated that images were independently graded in a masked fashion	Yes
9	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Not reported	Unclear
10	Were uninterpretable or intermediate test results reported?	Not reported	No
11	Were withdrawals from the study explained?	No withdrawals evident	Not applicable

Study o of o – waldstelli allo	u concagues		
Reference and design	Diagnostic tests	Participants	Outcome
			measures
Condition being diagnosed	Index tests:	Number of	Primary outcome
/ detected: Diabetic macular	FAF imaging using	participants:71	of study:
oedema (DMO)	cSLO (modified HRA		Comparison of
84	classic, Heidelberg	Number of eyes:	sensitivity and
<b>First author:</b> Waldstein <sup>64</sup>	Engineering, Heidelberg,	125	specificity of FAF
	Germany) with an		and MPOD for
Publication year: 2012	external source of a	Sample	detection of DMO
	solid-state laser emitting	attrition/dropout:	
<b>Country:</b> Not stated,	at 488nm at a 30° field	Not reported	Other relevant
appears to be UK	of view; and FAF	explicitly; but all	outcomes:
	imaging using cSLO	included eyes were	Inter-grader
Study design:	with an argon-ion laser	analysed.	variability.
Retrospective cross-	emitting at 514nm at a		(Cohen's kappa
sectional.	30° field of view; mean	Selection of	was used to
	of 16 images.	participants:	estimate inter-
Number of centres: One		Patients who	grader agreement)
	<b>Reference standard:</b>	underwent OCT and	
Funding: 2 authors received	SD-OCT (Heidelberg	two-wavelength FAF	
Marie Curie Intra European	Engineering, software	imaging in the	Diagnostic
Fellowship; Worshipful	version 1.6.4.0). Each B-	diabetic retinopathy	threshold:
Company of Barbers-	scan consisted of 512 A-	clinic of a university	Diagnosis of DMO
Waitangi Foundation	scans and was averaged	hospital were	was based on
Fellowship; and funding	nine times using the	selected	DMO visibility
from the University of	ART mode. A 20° x 20°	consecutively.	which was
Auckland.	scan pattern using 25		compared across
	sections with an inter-		the technologies
<b>Competing interests:</b>	scan distance of 240µm	Inclusion criteria	using the following
Stated none	was recorded.	for study entry:	scoring system:
		The presence of	-no DMO visible
	Comparator:	diabetic retinopathy	-DMO suspected
	Macular Pigment Optical	with or without	-DMO clearly
	Density (MPOD)	DMO; clear ocular	visible
	imaging (sequential use	media that allow	
	of both 488nm and	recording of high-	FAF:
	514nm FAF allowed	quality FAF images;	Relatively
	calculation of macular	availability of both	bright, single or
	pigment optical	two-wavelength FAF	multiple, round or
	density (MPOD) maps	and OCT imaging	oval areas that are
	that topographically	within a 2-week	mostly bordered by
	illustrate the relative	period.	darker rims.
	distribution of macular		
	pigment)	Exclusion criteria	OCT:
		for study entry:	Intraretinal cysts
		Presence of any	(no details given)
		ocular comorbidity	
		affecting the macula,	
		such as retinal vein	Recruitment
		occlusion or age-	dates: Between
		related macular	May 2009 and
		degeneration.	November 2010

### Study 8 of 8 – Waldstein and colleagues

Participant characteristics	
Sex, m:f (%male)	46:25 (65%)
Age, years, mean (SD)	63 (15)

### Results: FAF (488nm) versus OCT

Calculations are based on	Eyes with signs of	Eyes without signs of	Total
no. of eyes (single eyes	DMO on SD-OCT	DMO on SD-OCT	
from 17 subjects and both			
eyes from 54 subjects)			
FAF imaging positive	54 a	6 c	60
FAF imaging negative	13 b	52 d	65
Total	67	58	125

Diagnosis		95% CI
Clinical sensitivity a / (a + b)	80.60	69.11 to 89.24
Clinical specificity d / (c + d)	89.66	78.82 to 96.08
PPV a / (a + c)	90.00	79.48 to 96.22
NPV d / (b + d)	80.00	68.23 to 88.89
Positive likelihood ratio [sensitivity/(100-	7.79	3.62 to 16.77
specicifcity)]		
Negative likelihood ratio [(100-	0.22	0.13 to 0.36
sensitivity)/specificity]		
Diagnostic odds ratio (a x d)/(b x c)	36.00	12.73 to 101.81

Comments: Diagnostic values are calculated by the reviewer from the reported sensitivity and specificity. The calculations agree with the results reported in the paper.

Sensitivity and specificity are reported also for MPOD based on combining FAF488 nm and 514nm images. MPOD sensitivity and specificity were very similar to those of FAF 488nm alone (data not extracted here).

# Results: FAF (514nm) versus OCT

Kesuits: FAF (514nm) versus OC1							
Calculations are based	Eyes with signs of	Eyes without signs of	Total				
on numbers of eyes	DMO on SD-OCT	DMO on SD-OCT					
(single eyes from 17							
subjects and both eyes							
from 54 subjects)							
FAF imaging positive	37 a	3	40				
FAF imaging negative	30 b	55	1 85				
Total	67	58	125				
Diagnosis			95% CI				
Clinical sensitivity a / (a + b)		55.22	42.58 to 67.39				
Clinical specificity d / (c + d)		94.83 85.60 to 98.86					
PPV a / (a + c)		92.50	79.59 to 98.34				
NPV d / (b + d)		64.71	53.59 to 74.77				
Positive likelihood ratio [sensitivity/(100-		10.68	3.47 to 32.82				
specificity)]							
Negative likelihood ratio [(100-		0.47	0.36 to 0.62				
sensitivity)/specificity]							
Diagnostic odds ratio (a x d)/(b x c)		22.61	6.43 to 79.54				
Comments: Diagnostic values are calculated by the reviewer from the reported sensitivity and							
specificity. The calculations agree with the results reported in the paper.							

Distinct patterns of DMO on OCT (no. of eyes, %):		
Predominantly foveal intraretinal cysts	51 (76)	
Predominantly extrafoveal intraretinal cysts	5 (7)	
Diffuse, small intraretinal cysts	11 (16)	
Sensitivity for detecting Foveal cysts compared to OCT imaging		
FAF (488nm)	90.0%	
FAF (514nm)	20.0%	
MPOD	96.0%	
Sensitivity for detecting Extrafoveal or diffuse cysts compared to OCT imaging		
FAF (488nm)	60.8%	
FAF (514nm)	70.0%	
MPOD	45.5%	
MPOD vs OCT		
Clinical sensitivity	80.6%	
Clinical specificity	91.4%	

FAF: Fundus Autofluorescence; NPV: negative predictive value; PPV: positive predictive value; MPOD: Macular Pigment Optical Density; SD-OCT: Spectral Domain Optical Coherence Tomography; cSLO: Confocal Scanning Laser Ophthalmoscope; DMO: Diabetic Macular Oedema

Interpretability and acceptability of test			
Numbers excluded from analysis due to poor image quality	Not reported		
Intra-observer agreement	Not reported		
Test acceptability (patients/clinicians)	Not reported		
Adverse events	Not reported		
Inter-observer agreement (Cohen's kappa)			
FAF (488nm)	0.84		
FAF (514nm)	0.63		
MPOD	0.79		

**Waldstein and colleagues<sup>84</sup> critical appraisal criteria** (based on Reitsma et al.<sup>81</sup> adaptation of the QUADAS Tool<sup>93</sup>)

	Item	Description	Judgement
1	Was the spectrum of patients representative of the patients who will receive the test in practice?	Study is retrospective, but involved consecutive patients. Patients had diabetic retinopathy with or without DMO, with no macular comorbidities, so this may be an atypical case-mix	No
2	Is the reference standard likely to classify the target condition correctly?	Paper describes OCT as clinical standard for the non-invasive diagnosis of DMO	Yes
3	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	Both two-wavelength FAF and OCT imaging were available within a 2 week period.	Yes
4	Did the whole sample or a random selection of the sample receive verification using the intended reference standard?	Patients were required to have both tests for inclusion	Yes
5	Did patients receive the same reference standard irrespective of the index test result?	Yes	Yes
6	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	Yes	Yes
7	Were the reference standard results interpreted without knowledge of the results of the index test?	Same grader who assessed OCT scans was one of the FAF graders. No masking reported.	Unclear
8	Were the index test results interpreted without knowledge of the results of the reference standard?	All FAF and MPOD were evaluated by two independent graders who were blinded to the patient but not to the mode of imaging. No further details provided.	Unclear
9	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Not reported	Unclear
10	Were uninterpretable or intermediate test results reported?	No	No
11	Were withdrawals from the study explained?	All included eyes were analysed	Not applicable