Appendix K: Age-related macular degeneration classification

K.1 AMD overview and mapping of classification systems

NICE recommended classification	NICE recommended classification	NICE recommended definitions	Modified International Criteria (NICE favoured classification system)	AREDS 9-step	AREDS 4 step	AREDS Simple Severity	Three continent	CARMS	Sandberg
Normal eyes	NA	Normal- no signs of AMD at all or Small/hard drusen (<63 µm) only [MIC]	Normal- no signs of ARM at all or Small/hard drusen (<63 µm) only [MIC]	Stage 1	Stage 1	Score of 0 (plus fellow eye)	No AMD	Grade 1 (if less than 10 small drusen)	Stage 1-2 (dependent on number of drusen)
Early AMD	NA	1) Low risk of progression: a. Medium drusen (≥63 µm and <125 µm) OR b. Pigmentary abnormalities	1a) Soft distinct drusen (≥63 µm) only [MIC]	Stage 1-2	Stage 2	Score of 0 (plus fellow eye)	No AMD	Grade 2	Stage 1-2 (dependent on number of drusen)
			1b) Pigmentary irregularities (hyper/hypopigmentation) only, no drusen [MIC]			Score of 1 (plus fellow eye)	No AMD	Grade 2	ungradable
		2) Medium risk of progression: a. Large drusen (≥125 µm) OR b. Reticular drusen OR c. Medium drusen with pigmentary abnormalities	2a) Soft indistinct drusen (≥125 µm) or reticular drusen only [MIC]	Stage 2-8	Stage 3	Score of 1 (plus fellow eye)	Mild early AMD	Grade 3	Grade 3
			2b) Soft distinct drusen (≥63 µm) with pigmentary abnormalities [MIC]			Score of 2 (plus fellow eye)	Mild early AMD	Grade 2	Grade 2 (dependent on number)
		3) High risk of progression:	3) Soft indistinct drusen (≥125 µm) or reticular			Score of 2 (plus	Moderate-severe	Grade 3	Grade 3-4

NICE recommended classification	NICE recommended classification	NICE recommended definitions	Modified International Criteria (NICE favoured classification system)	AREDS 9-step	AREDS 4 step	AREDS Simple Severity	Three continent	CARMS	Sandberg
		a. Large drusen (≥125 µm) with pigmentary abnormalities OR b. Reticular drusen with pigmentary abnormalities OR c. pseudovitelliform without significant visual loss (best-corrected acuity better than 6/18)	drusen with pigmentary abnormalities [MIC]			fellow eye)	early AMD		
		4) Atrophy smaller than 175µm and not involving the fovea							
Late AMD	Indeterminate	1) Retinal pigment epithelial (RPE) degeneration and dysfunction (presence of degenerative AMD changes with subretinal or intraretinal fluid in the absence of neovascularisation)	chronic central serous chorioretinopathy [CSCR]						
		2) Serous pigment epithelial detachment [PED] without neovascularisation							
	Wet active	1) Retinal angiomatous proliferation [RAP]							

NICE recommended classification	NICE recommended classification	NICE recommended definitions	Modified International Criteria (NICE favoured classification system)	AREDS 9-step	AREDS 4 step	AREDS Simple Severity	Three continent	CARMS	Sandberg
	(the presence of serous or haemorrhagic retinal PED, a subretinal neovascular membrane, a subretinal haemorrhage, or a combination of the above-modified from [MIC], [AREDS4], [CARMS])	2) Classic choroidal neovascularisation	Grade 4		Stage 4		Late AMD	Grade 5	
		3) Mixed (predominantly and minimally classic with occult)							
		4) Occult (fibrovascular pigment epithelium detachment [PED] and serous PED with neovascularisation)							
		5) Polypoidal choroidal vasculopathy							
	Dry	1) Geographic atrophy (in the absence of neovascular AMD) 2) Significant visual loss (6/18 or worse) associated with: a) Dense or confluent drusen OR b) Advanced pigmentary changes and/or atrophy OR c) Vitelliform lesion		Stage 9	Stage 3 (extra foveal) and stage 4		Late AMD	Grade 4	
	Wet inactive	1) Fibrous scar 2) Retinal pigment epithelial (RPE) tear							

NICE recommended classification	NICE recommended classification	NICE recommended definitions	Modified International Criteria (NICE favoured classification system)	AREDS 9-step	AREDS 4 step	AREDS Simple Severity	Three continent	CARMS	Sandberg
		3) Atrophy (absence or thinning of RPE and/or retina) 4) Cystic degeneration (persistent intraretinal fluid or tubulations unresponsive to treatment)							

*NICE has avoided the term 'dry early' AMD which can easily be confused with 'late dry' AMD especially when the term 'dry' is used alone. NICE has also avoided using the term 'advanced' AMD since this may be confused with having advanced visual loss (which may occur in most if not all of the categories of AMD).

K.2 Neovascular AMD: Subtype descriptions and clinical features in the evidence

		Clinical Features			
		Colour and red free photographs	FA early/late	OCT	FA/ICG and OCT
	Geographic atrophy	Any sharply demarcated area of apparent disappearance of retinal pigment epithelium, larger than 175 µm, with visible choroidal vessels, and in the absence of neovascular AMD [MIC]	Grading based on features observed in the stereoscopic fundus photographs and fluorescein angiograms. According to the revised criteria, GA was defined as an area in which the RPE was absent, as evidenced by hyperfluorescence on late-stage fluorescein angiograms plus one additional feature indicative of RPE atrophy, specifically: visible choroidal vessels, sharp edges, or marked excavation on either CFP or FA. Atrophic drusen (i.e., degenerating drusen associated with RPE atrophy at its margins) were not considered GA unless the drusenoid material was completely encircled by a 360° rim of atrophy. This distinction was made to include regressing drusen located underneath a larger area of atrophy and exclude individual drusen or areas of confluent		

		Clinical Features			
			drusen that are associated with early atrophic changes. [Brader]		
Wet (the presence of serous or haemorrhagic retinal PED, a subretinal neovascular membrane, a subretinal haemorrhage, a periretinal fibrous scar or a combination of the above- [MIC] [AREDS4], [CARMS]))	Classic/type 2	"greyish subretinal lesion occasionally with a surrounding ring of hyperpigmentation" [Jung]	Early intense, well-demarcated hyperfluorescence with a characteristic lacy pattern. [Jung] An area of choroidal hyperfluorescence with well demarcated boundaries that could be discerned in the early phase of the angiogram [Maguire] Late Intense leakage originating from the area of early hyperfluorescence [Jung] Progressive pooling of dye leakage in the overlying subsensory retinal space that usually obscures the boundaries of the CNV [Maguire]	The early lacy hyperfluorescence corresponds to a linear collection of subretinal hyperreflective material directly above the RPE line. The leakage corresponds to intraretinal oedema and or subretinal fluid. [Jung]	
	Occult/type 1	"RPE elevation with irregular height and shape; pigment mottling" [Jung]	Early Stippled hyperfluorescence within 1 or 2 minutes (fibrovascular PED), or lack of early hyperfluorescent signal (late leakage of undetermined source) [Jung] An area of stippled hyperflourescence appeared within 5 minutes [Maguire] Late Mild to moderate staining and/or leakage corresponding to the RPE abnormalities [Jung] Occult lesions were either fibrovascular pigment epithelial detachments or late leakage of an undetermined source. [Olsen] Persistent staining or pooling of dye by 10 minutes {Maguire]	The area of staining corresponds to an elevation of the RPE line with sub-RPE material of mixed reflectivity, often with overlying subretinal fluid. Intraretinal fluid is less common [Jung]	

		Clinical Features			
			Serous pigment epithelial detachment was considered present when there was a uniform, smooth elevation of the retinal pigment epithelium with sharply demarcated, fairly uniform, early Hyperfluorescence that persisted into the late phase of the angiogram. [Maguire]		
	Mixed	Mixed features type 1 and 2 [Jung] Mixed features type 1 and 3 [Jung] Mixed features type 2 and 3 [Jung]	Early Mixed 1 and 2: well-demarcated hyperfluorescent lacy with or without surrounding area of stippled hyperfluorescence. Mixed 1 and 3: Stippled hyperfluorescence with or without hot spot Mixed 2 and 3: Well-demarcated hyperfluorescence. No contrast of the hot spot. Late Mixed 1 and 2: leakage and staining Mixed 1 and 3: staining or leakage, often with cystoid macular oedema Mixed 2 and 3: intense leakage, often with cystoid macular oedema [Jung]	Mixed 1 and 2: Type 1 and type 2 findings. The area of stippled hyperflourescence corresponds to the type 1 findings extending beyond the type 2 findings. Mixed 1 and 3: Type 1 and type 3 findings. The area of angiographic staining corresponds to the type 1 lesion extending beyond the type 3 findings. Mixed 2 and 3: type 3 and type 2 findings. [Jung]	Predominantly classic (equal/greater than 50%) [Cohen] [Holtz] [Olsen] Minimally classic (less than 50%) [Cohen] [Holtz] [Olsen]

		Clinical Features			
	RAP/type 3		Early Early but focal, leakage often seen in close proximity to retinal vessels. May have retinal anastomoses Late focal intense leakage, often with cystoid macular edema [Jung]	There is an intraretinal focal hyperreflective lesion in an area of localised outer retinal disruption. Often, there is a focal defect and variable degree of elevation of the underlying RPE. This intraretinal lesion corresponds to the early focal FA leakage and manifests surrounding intraretinal cystic changes. [Jung]	"Subretinal, intraretinal, or preretinal juxtafoveal haemorrhages; dilated retinal vessels; lipid exudates; and retinal-choroidal anastomosis." [Coscas]
	Polyp/PCV/IPC				"Elevated orange-red lesions, characteristic polypoidal lesions at the edge of a branching vascular network on angiography, and prominent anterior protusion of the retinal pigment epithelium line in OCT images." [Coscas] (FA/ICG and OCT)

K.3 Classification systems: supporting evidence

NICE recommended classification	Definitions	Supporting evidence: agreement scores (kappa and crude agreement)	Prognostic scores (hazard ratios and time adjusted odds ratios) for developing neovascular AMD
Normal eyes	**Normal- no signs of ARM at all** **or** **Small drusen (<63 µm) only [MIC]**		
Early	**1) Medium drusen OR pigmentary abnormalities** **2) Large drusen OR reticular drusen OR medium drusen with pigmentary abnormalities**	Two moderate quality studies found agreement to be 0.73 between graders for the AREDS 9-step severity scale, One moderate quality study found agreement to be 0.88 between graders for the AREDS 4-step severity scale One moderate quality study found agreement to be 0.86 between graders, and 0.78 between grading centres for the Clinical Age-Related Maculopathy Staging system (CARMS). Two moderate quality studies found agreement to be 0.75-0.82 between graders for the Modified International Classification of ARM. One moderate quality study found agreement to be 0.66-0.86 between grading centres for Harmonized Three Continent AMD Consortium Severity Scale.	RQ2) 17 studies showed a positive correlation between neovascular AMD and: • 5 or more drusen (HR: 2.1 (1.3-3.5), • drusen size (HR: 1.5 (1.0-2.2), 2.4 (1.1-5.1)1, 1.96 (1.14-3.36)1 , OR: 60.4 (17.7-206), 40.4 (5.5-297), • soft indistinct drusen (7.4 (2.4-22.6), 18.3 (8.9-37.4)), • reticular drusen OR: 9.89 (2.16, 45.23)), • hyperpigmentation (HR: 2.0 (1.4-2.9), 2.5 (1.3-4.9), 1.84 (1.22-2.76), OR: 5.8 (2.9-11.7)), • depigmentation (OR: 7.8 (3.6-16.6)), • pigmentary changes/ abnormalities (HR: 2.49 (1.51-4.10), OR: 15.2 (7.3-31.6)). RQ 6) • Very low quality evidence from one study showed a higher risk for developing neovascular AMD found with increasing stages of the Sandberg 4-Point Scale. (HR: 1.76 (1.18-2.73)).

NICE recommended classification	Definitions	Supporting evidence: agreement scores (kappa and crude agreement)	Prognostic scores (hazard ratios and time adjusted odds ratios) for developing neovascular AMD
			• Low quality evidence from 1 study showed a higher risk for progression to neovascular AMD found with increasing stages of the Simple Severity Score. (HR: 1) 4.76 (2.43-9.34), 2)12.66 (6.87-23.36), 3) 26.56 (14.53-48.58), 4) 35.89 (19.75-65.21))
	3) **Large drusen with pigmentary abnormalities OR reticular drusen with pigmentary abnormalities**		
Wet active and wet inactive	**The presence of serous or haemorrhagic retinal PED, a subretinal neovascular membrane, a subretinal haemorrhage, a periretinal fibrous scar or a combination of the above- [MIC], [AREDS4], [CARMS]**	Three very low quality studies found agreement to be between 0.37 - 0.64 between graders for the basic MPS/Gass classification. One very low quality study found agreement to be 0.59 between graders for the MPS/GASS classification with pigment epithelial detachment (PED) as a subgroup of occult. One very low quality study found agreement to be 0.65 between two classification systems for multiple graders using the MPS/GASS classification with additional subgroup for retinal angiomatous proliferation (OCT) and the basic MPS/GASS classification (FA). One moderate quality study found agreement to be 0.75-1.00 between graders for the MPS/GASS classification with serous pigment	

NICE recommended classification	Definitions	Supporting evidence: agreement scores (kappa and crude agreement)	Prognostic scores (hazard ratios and time adjusted odds ratios) for developing neovascular AMD
		epithelial detachment (PED) as an additional criteria. One low quality study found agreement with “final diagnosis” to be 79.4- 91.1% (AMD with type 1 CNV), 33.3- 66.6% (AMD with type 1+2 CNV), 60.0- 100% (AMD with type 2 CNV), 83.3% (chorioretinal anastomosis (RAP)) 66.6%, (PCV with type 1 or 2 CNV), 95.6% (PCV without type 1 or 2 CNV), 100% (Other) using fundus photographs, FA, ICG and OCT as investigations. In another cohort, the same low quality study found agreement with “final diagnosis” to be 95.8 - 97.9% (AMD with type 1 CNV), 68.4 - 89.5% (AMD with type 1+2 CNV), 60.0- 100% (AMD with type 2 CNV), 80.0- 100% (chorioretinal anastomosis (RAP)) 66.6-87.5% (PCV without type 1 or 2 CNV), 75-100% (Other) using fundus photographs, FA, ICG and OCT as investigations.	
Dry	**NA**	Two moderate quality studies found agreement to be 0.75-0.82 between graders for the Modified International Classification of ARM. One low quality study found agreement to be 0.536 (0.03-1.04) between graders for a CAPT classification of geographic atrophy alone.	

NICE recommended classification	Definitions	Supporting evidence: agreement scores (kappa and crude agreement)	Prognostic scores (hazard ratios and time adjusted odds ratios) for developing neovascular AMD

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