E.1.1 Classification

RQ6: What effective classification tool should be used to classify different types of AMD?

Bibliographic reference	The age-related eye disease study severity scale for age-related macular degeneration: AREDS report No. 17 (Archives of Ophthamology (2005) 123 (1484-1498)), Archives of Ophthalmology, 124, 289-290, 2006
Country/ies where the study was carried out	USA
Study type	Nested case-control study
Aim of the study	To develop a fundus photographic severity scale for age-related macular degeneration (AMD)
Study dates	Published 2005
Source of funding	National Eye Institute
Sample size	3212 participants (1225 eyes were used to calculate validation outcomes)
Characteristics	Participant demographics not reported
Inclusion Criteria	Participants from the Age-Related Eye Disease Study (AREDS).
Exclusion Criteria	None reported
Tests	Photographs were scheduled at baseline, at the 2-year visit, and annually thereafter. Stereoscopic pairs of fields 1 (disc) and 2 (macula) and a single photograph of field 3 (temporal to the macula) were taken with 30° cameras and mounted in plastic sheets, which were viewed on light boxes with ×5 Donaldson stereo viewers. Graders assessed the photographs for presence, extent, and other features of the abnormalities characteristic of AMD by using a standard grid template adapted from the Early Treatment Diabetic Retinopathy Study and standard circles consisting of opaque black lines printed on transparent stock that could be placed over or under the transparency being evaluated (Figure 1). Photographs from each visit were graded independently of those from all other visits.

Bibliographic reference	**The age-related eye disease study severity scale for age-related macular degeneration: AREDS report No. 17 (Archives of Ophthamology (2005) 123 (1484-1498)), Archives of Ophthalmology, 124, 289-290, 2006**

Grid and standard circles were used in assessing size, area, and location of abnormalities. The radii of the grid circles are one-third, 1, and 2 disc diameters, respectively, and their areas are 4/9, 4, and 16 disc areas (DAs). When the diameter of the optic disc is assumed to be 1500μm, the radius of the central circle of the grid is 500μm, that of the middle (inner) circle is 1500μm, and that of the outer circle is 3000μm. The standard circles have the following diameters and areas:

C-0, 63μm and 0.0017 DA;
C-1, 125μm and 0.0069 DA;
C-2, 250μm and 0.028 DA;
I-2, 354μm and 0.056 DA;
O-2, 650μm and 0.19 DA;
0.5 DA, 1061μm and 0.50 DA.

An additional circle, I-1 (diameter, 175 μm) is used to define the smallest area of depigmentation that can be classified as geographic atrophy.

Reproducibility of the scale was assessed by applying it to duplicate gradings carried out periodically throughout the course of the study as part of ongoing quality control exercises (total number of eyes, 1225).

9-step severity scale		
Step Drusen Area	Increased Pigment	Depigmentation-GA
<C-1	0	0
≥C-1, <C-2	0	0
<C-1	≥Q*	≥, <102
≥C-2, <1-2	0	0
≥1-2, <O-2	0	0

Bibliographic reference	The age-related eye disease study severity scale for age-related macular degeneration: AREDS report No. 17 (Archives of Ophthamology (2005) 123 (1484-1498)), Archives of Ophthalmology, 124, 289-290, 2006

≥C-1, <102	≥Q	≥Q, <1-2
<C-2	≥0	≥1-2, <0.5DA
≥O-2, <0.5DA	0	0
≥1-2, <O-2	≥Q	≥Q, <1-2
≥C-2	≥0	≥1-2, <0.5DF
≥0.5 DA	0	0
≥O-2, <0.5DA	≥Q	≥Q, <1-2
≥1-2, <O-2	≥0	≥1-2, <0.5DA
≥0.5 DA	≥Q	≥Q, <1-2
≥O-2, <0.5DA	≥0	≥1-2, <0.5DA
≥0.5 DA	≥0	≥1-2, <0.5DA
Any	≥0	≥0.5 DA
Any	≥0	Non-central GA

*Q= questionable

Geographic atrophy was defined as an area of partial or complete depigmentation of the RPE in the fundus photographs that had at least 2 of the following 3 characteristics: roughly round or oval shape, sharp margins, and visibility of underlying large choroidal vessels. Depigmentation adjacent to disciform scars was not classified as GA, even if these criteria were met.

Neovascular AMD was defined as the definite presence in the fundus photographs of 1 or more of 4 characteristics: serous sensory retinal detachment, RPE detachment, subretinal hemorrhage, or subretinal fibrous tissue; or of a report from the clinic of the application of photocoagulation for choroidal new vessels at any previous visit.

The presence of central GA was defined as questionable or definite involvement of the center of the macula by definite GA. Advanced AMD was defined as neovascular AMD or CGA.

Bibliographic reference	The age-related eye disease study severity scale for age-related macular degeneration: AREDS report No. 17 (Archives of Ophthamology (2005) 123 (1484-1498)), Archives of Ophthalmology, 124, 289-290, 2006
Methods	Reproducibility Reproducibility of the scale was assessed by applying it to duplicate gradings carried out periodically throughout the course of the study as part of ongoing quality control exercises (total number of eyes, 1225). Development of the scale Baseline and 5-year follow-up gradings were available for the right eyes of 3212 participants without advanced AMD in either eye at baseline (all treatment groups combined). The frequency of development of each of the 2 types of advanced AMD within 5 years in these eyes by the baseline grade for each characteristic were tabulated and cross-tabulations for pairs of characteristics were examined. Associations between the nonadvanced AMD characteristics at baseline and development of advanced AMD at or before the 5-year follow-up visit were explored by means of tree-structured models. Models were run separately for the predictiveness of drusen characteristics alone, pigment abnormalities alone, and the 2 sets of variables together. After the scale was developed, its performance in the left eyes of these same participants was examined, and then in the eye with nonadvanced AMD of other participants who had advanced AMD in one eye at baseline (543 with neovascular AMD and 57 with CGA).
Results	Interobserver Agreement Reproducibility of the scale, expanded to include CGA and neovascular AMD as additional steps, by comparing the original grading with a replicate grading: Complete agreement: 63.4% of eyes, Agreement within 1 step: 86.6%, Agreement within 2 steps in 93.6%. Unweighted κ statistic (SE): 0.58 (0.015), κ weighted to give 75% credit for 1-step disagreement: 0.73(0.013).
Limitations	Since there was no quality assessment tool available for validation studies, the following review of bias tool for diagnostic cross-sectional studies was used and adapted accordingly: QUADAS 2 QUADAS website.

Bibliographic reference	The age-related eye disease study severity scale for age-related macular degeneration: AREDS report No. 17 (Archives of Ophthamology (2005) 123 (1484-1498)), Archives of Ophthalmology, 124, 289-290, 2006
	DOMAIN 1: PATIENT SELECTION A. Risk of Bias Methods of patient selection: Was a consecutive or random sample of patients enrolled? Unclear Was a case-control design avoided? No Did the study avoid inappropriate exclusions? Unclear Could the selection of patients have introduced bias? RISK: UNCLEAR B. Concerns regarding applicability Is there concern that the included patients do not match the review question? CONCERN: LOW- People with a full range of AMD presentations DOMAIN 2: INDEX TEST(S) A. Risk of Bias Describe the index test and how it was conducted and interpreted: Were the index test results interpreted without knowledge of the results of the reference standard? Yes grading was done independently of other visits, unclear if duplicate grading was also done independently of prior grading If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? NA- the purpose of this study is to assess how interpretation may differ between graders B. Concerns regarding applicability Is there concern that the index test, its conduct, or interpretation differ from the review question? CONCERN: LOW DOMAIN 3: REFERENCE STANDARD- NA (same as index test) DOMAIN 4: FLOW AND TIMING A. Risk of Bias Was there an appropriate interval between index test(s) and reference standard? Yes Did all patients receive a reference standard? Yes

Bibliographic reference	**The age-related eye disease study severity scale for age-related macular degeneration: AREDS report No. 17 (Archives of Ophthamology (2005) 123 (1484-1498)), Archives of Ophthalmology, 124, 289-290, 2006**
	Did patients receive the same reference standard? Yes (grader the only difference) Were all patients included in the analysis? No a sample of 1225, unclear how this sample was selected Could the patient flow have introduced bias? RISK: UNCLEAR

Bibliographic reference	**Age-Related Eye Disease Study Research Group, 20011205, The Age-Related Eye Disease Study system for classifying age-related macular degeneration from stereoscopic color fundus photographs: the Age-Related Eye Disease Study Report Number 6, American journal of ophthalmology, 132, 668-681, 2001**
Country/ies where the study was carried out	USA
Study type	Retrospective cohort
Aim of the study	To describe the system for grading age-related macular degeneration from fundus photographs in the Age-Related Eye Disease Study.
Study dates	Published 2001
Source of funding	National Eye Institute, National Institutes of Health
Sample size	Sample of 1230 eyes
Characteristics	No baseline characteristics reported
Inclusion Criteria	Participants of the Age-Related Eye Disease Study
Exclusion Criteria	No exclusion criteria reported
Tests	Sterioscopic slide transparencies mounted in plastic sheets are examined in a lught box fitted with flourescent tubes with a colour rating of approximately 6200 kelvin. The grader uses a Donaldson sterioscopic viewer with 5x magnification, which, combined with the 2.43x magnification results in total magnification of 12x. The grading process uses a standard grid template, before grading the technician centres the grid on the photograph and tapes it in place. A set of graduated circles is used to estimate maximum drusen size and total area involved by pigment abnormalities and drusen. Areas are expressed in disk areas, which for any circle is simply the square of its diameter, for example, a circle with 2 disk areas diameter, contains 4 disk areas.

Bibliographic reference	**Age-Related Eye Disease Study Research Group, 20011205, The Age-Related Eye Disease Study system for classifying age-related macular degeneration from stereoscopic color fundus photographs: the Age-Related Eye Disease Study Report Number 6, American journal of ophthalmology, 132, 668-681, 2001**
	Age-Related Eye Diseases Study Age-related Macular Degeneration Severity Scale Levels Defined: 1- Drusen maximum size < Circle C0 (63µm diameter) and total area < circle C1 (125µm diameter) 2- Presence of one or more of the following: Drusen maximum size ≥circle C0 but < circle C1 Drusen total area ≥circle C1 Retinal pigment epithelial pigment abnormalities consistent with AMD, defined as one of more of the following in the central or inner subfields: depigmentation present, increased pigment ≥circle C1, or increased pigment present and depigmentation at least questionable 3- Presence of one or more of the following: Drusen maximum size ≥ circle C1 Drusen maximum size ≥ circle C0 and total area > circle I2 and type is soft indistinct Drusen maximum size ≥ circle C0 and total area > circle O2 and type is soft distinct Geographic atrophy within grid but none at centre of macula 4- Presence of one or more of the following: Geographic atrophy in central subfield with at least questionable involvement of centre of macula Evidence of neovascular AMD: fibrovascular/serous pigment epithelial detachment; serous (or haemorrhagic) sensory retinal detachment; subretinal pigment epithelial haemorrhage; subretinal fibrous tissue (or fibrin); photocoagulation for AMD.
Methods	During the preliminary grading for photographic quality, a grader also records an estimate of the age-related macular degeneration severity scale level for each eye. During the detailed grading, another grader performs a more extensive evaluation. Then a computorised algorithm extracts the age-related macular degeneration level from the detailed grading and compares it to the estimate from preliminary grading. If the age-related macular degeneration levels differ, a senior grader (who has not been involved in either preliminary or detailed grading) reviews the photographs and discrepant grades, determines the final result and modifies the grading accordingly. All study photographs are graded independently, that is, graders are masked to the photographs and grades from previous visits.

Bibliographic reference	**Age-Related Eye Disease Study Research Group, 20011205, The Age-Related Eye Disease Study system for classifying age-related macular degeneration from stereoscopic color fundus photographs: the Age-Related Eye Disease Study Report Number 6, American journal of ophthalmology, 132, 668-681, 2001**
	Paired contemporaneous gradings were compared by means of cross-tabulations, and the percentages of agreement/disagreement and kappa statistics (K, a measure of inter-observer concordance on categorical scales that adjusts for chance agreement) and their standard errors were calculated. For abnormalities analysed dichotomously (for example, absence/presence of advanced AMD), kappa statistics are unweighted; for abnormalities with extended scales (for example, drusen area), a weighted varient was also computed assigning a weight of 1 for perfect agreement and, 0.75 for one-step disagreements, and 0 for all other disagreements. 0-0.20 was considered slight agreement; 0.21-0.40 fair; 0.41-0.60 moderate; 0.61-0.80 substantial; and more than 0.80, almost perfect agreement.
Results	Interobserver contemporaneous reproducability AMD severity level Agreement- 82.8% Agreement within 1 step: 98.7% Kappa, unweighted (SE)- 0.77 (0.01) Kappa, weighted (SE)- 0.88 (0.01) Intraobserver temporal reproducability AMD severity level Agreement- 88.2% Agreement within 1 step: 98.3% Kappa, unweighted (SE)- 0.83 (0.04) Kappa, weighted (SE)- 0.88 (0.04)
Limitations	Since there was no quality assessment tool available for validation studies, the following review of bias tool for diagnostic cross-sectional studies was used and adapted accordingly: QUADAS 2 QUADAS website. DOMAIN 1: PATIENT SELECTION A. Risk of Bias Methods of patient selection:

Bibliographic reference	Age-Related Eye Disease Study Research Group, 20011205, The Age-Related Eye Disease Study system for classifying age-related macular degeneration from stereoscopic color fundus photographs: the Age-Related Eye Disease Study Report Number 6, American journal of ophthalmology, 132, 668-681, 2001
	Was a consecutive or random sample of patients enrolled? No- the sample was selected to include a wide range of abnormalities and age-related macular degeneration severity. Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Unclear Could the selection of patients have introduced bias? RISK: UNCLEAR B. Concerns regarding applicability Is there concern that the included patients do not match the review question? CONCERN: LOW- People with a full range of AMD presentations DOMAIN 2: INDEX TEST(S) A. Risk of Bias Describe the index test and how it was conducted and interpreted: Were the index test results interpreted without knowledge of the results of the reference standard? Yes grading was masked when assessing contemporaneous and temporal grading variability. If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? NA- the purpose of this study is to assess how interpretation may differ between graders B. Concerns regarding applicability Is there concern that the index test, its conduct, or interpretation differ from the review question? CONCERN: LOW DOMAIN 3: REFERENCE STANDARD- NA (same as index test) DOMAIN 4: FLOW AND TIMING A. Risk of Bias Was there an appropriate interval between index test(s) and reference standard? Yes Did all patients receive a reference standard? Yes Did patients receive the same reference standard? Yes (grader the only difference)

Bibliographic reference	**Age-Related Eye Disease Study Research Group, 20011205, The Age-Related Eye Disease Study system for classifying age-related macular degeneration from stereoscopic color fundus photographs: the Age-Related Eye Disease Study Report Number 6, American journal of ophthalmology, 132, 668-681, 2001**
	Were all patients included in the analysis? No a sample of 1230 eyes chosen to represent the full range of abnormalities and age-related maculopathy severity. Could the patient flow have introduced bias? RISK: LOW

Bibliographic reference	**Danis et al., 2013. Methods and reproducibility of grading optimized digital color fundus photographs in the Age-Related Eye Disease Study 2 (AREDS2 Report Number 2), Investigative Ophthalmology & Visual Science, 54, 4548-4554.**
Country/ies where the study was carried out	USA
Study type	Retrospective cohort
Aim of the study	To establish continuity with the grading procedures and outcomes from the historical data of the Age-Related Eye Disease Study (AREDS).
Study dates	Published 2013
Source of funding	Supported by National Eye Institute Grant
Sample size	1335 eyes were reviewed
Characteristics	Baseline characteristics not reported
Inclusion Criteria	Participants of the AREDS2 study
Exclusion Criteria	None reported
Tests	AREDS2 photographers and clinical site digital camera systems are certified by the reading center. Color stereoscopic fundus photographs were obtained using three photographic fields of the macula and optic nerve with 308 or 358 fundus cameras, as in AREDS. The imaging protocol specifies field position and stereoscopic technique. Seven models of digital fundus cameras were

Bibliographic reference	**Danis et al., 2013. Methods and reproducibility of grading optimized digital color fundus photographs in the Age-Related Eye Disease Study 2 (AREDS2 Report Number 2), Investigative Ophthalmology & Visual Science, 54, 4548-4554.**
	permitted for use in AREDS2. All had a minimum resolution specification of 3 megapixels. For baseline image collection, 20 of 82 clinical sites did not have approved digital fundus cameras and were allowed to use Ektachrome color slide film (Eastman Kodak Co., Rochester, NY) for photography. Subsequently, all clinical sites transitioned to digital color photography. Evaluation was performed using both the original and optimized images. Graders could use limited zoom features in the display software. An electronic Early Treatment Diabetic Retinopathy Study (ETDRS) macular grid, appropriately sized for the magnification of the digital fundus image, was overlaid to specify the location of some macular lesions by grid subfield, similar to the methodology used in AREDS with acetate overlays on color slides. Drusen area circles as employed in AREDS were also scaled to the magnification of the photograph (determined at the time of camera system certification) and overlaid on the digital image as needed. Baseline AREDS2 images were graded by two independent graders. Grading results were assessed by a software processor, and discrepancies on major questions (component questions for the AREDS2 severity scale) were adjudicated by a third, senior grader (JA). If no grading discrepancies were identified, the first grade was submitted as the grade of record. For annual follow-up images, the grading process consists of single-step grading, independent of prior visit and fellow eye images and data. Grid and standard circles were used in assessing size, area, and location of abnormalities. The radii of the grid circles are one-third, 1, and 2 optic disc diameters, respectively, and their areas are 4/9, 4, and 16 optic disc areas (DAs). When the diameter of the optic disc is assumed to be 1500μm, the radius of the central circle of the grid is 500μm, that of the middle (inner) circle is 1500μm, and that of the outer circle is 3000μm. The standard circles have the following diameters and areas: C-0, 63μm and 0.0017 DA; C-1, 125μm and 0.0069 DA; C-2, 250μm and 0.028 DA; I-2, 354μm and 0.056 DA;

Bibliographic reference	**Danis et al., 2013. Methods and reproducibility of grading optimized digital color fundus photographs in the Age-Related Eye Disease Study 2 (AREDS2 Report Number 2), Investigative Ophthalmology & Visual Science, 54, 4548-4554.**

O-2, 650µm and 0.19 DA;
0.5 DA, 1061µm and 0.50 DA.

9-step severity scale		
Step Drusen Area	Increased Pigment	Depigmentation-GA
<C-1	0	0
≥C-1, <C-2	0	0
<C-2	≥Q*	≥, <102
≥C-2, <1-2	0	0
≥1-2, <O-2	0	0
≥C-1, <102	≥Q	≥Q, <1-2
<C-2	≥0	≥1-2, <0.5DA
≥O-2, <0.5DA	0	0
≥1-2, <O-2	≥Q	≥Q, <1-2
≥C-2	≥0	≥1-2, <0.5DF
≥0.5 DA	0	0
≥O-2, <0.5DA	≥Q	≥Q, <1-2
≥1-2, <O-2	≥0	≥1-2, <0.5DA
≥0.5 DA	≥Q	≥Q, <1-2
≥O-2, <0.5DA	≥0	≥1-2, <0.5DA
≥0.5 DA	≥0	≥1-2, <0.5DA
Any	≥0	≥0.5 DA
Any	≥0	Non-central GA

Bibliographic reference	**Danis et al., 2013. Methods and reproducibility of grading optimized digital color fundus photographs in the Age-Related Eye Disease Study 2 (AREDS2 Report Number 2), Investigative Ophthalmology & Visual Science, 54, 4548-4554.**
	*Q= questionable Geographic atrophy was defined as an area of partial or complete depigmentation of the RPE in the fundus photographs that had at least 2 of the following 3 characteristics: roughly round or oval shape, sharp margins, and visibility of underlying large choroidalvessels. Depigmentation adjacent to disciform scars was not classified as GA, even if these criteria were met. Neovascular AMD was defined as the definite presence in the fundus photographs of 1 or more of 4 characteristics: serous sensory retinal detachment, RPE detachment, subretinal hemorrhage, or subretinal fibrous tissue; or of a report from the clinic of the application of photocoagulation for choroidal new vessels at any previous visit. The presence of central GA was defined as questionable or definite involvement of the center of the macula by definite GA. Advanced AMD was defined as neovascularAMD or CGA
Methods	Baseline AREDS2 images were graded by two independent graders. Grading results were assessed by a software processor, and discrepancies on major questions (component questions for the AREDS2 severity scale) were adjudicated by a third, senior grader (JA). If no grading discrepancies were identified, the first grade was submitted as the grade of record. For annual follow-up images, the grading process consists of single-step grading, independent of prior visit and fellow eye images and data. A temporal drift sample of 88 stratified baseline images is regraded annually by the entire grading group; the results were compared to original grades for the same sample. The temporal drift reproducibility exercises allow monitoring the shift due to grader experience, change in grading personnel, and technological advances, particularly in studies with long follow-up such as AREDS2. The contemporaneous quality control included monthly regrade of a random sample of 5% of submissions. These images were duplicated and passed through the grading process with fictitious identifiers for masked replicate grading. The reproducibility of grading is assessed by calculating percentage agreement and weighted Kappa statistics for ordinal variables and correlation coefficients for continuous area measurements for the entire group.

Bibliographic reference	**Danis et al., 2013. Methods and reproducibility of grading optimized digital color fundus photographs in the Age-Related Eye Disease Study 2 (AREDS2 Report Number 2), Investigative Ophthalmology & Visual Science, 54, 4548-4554.**
	Regular training exercises are held for the entire grading group with review of difficult cases and reaffirmation of the grading protocol. Reproducibility statistics were also examined for individual graders, and targeted individual retraining was performed if the grader has reproducibility for specific questions below a set threshold. All graders were encouraged to seek out a reading center ophthalmologist for ‘‘second opinions’’ for assistance with unusual presentations or confounding ocular abnormalities. On an ongoing basis, any eyes meeting the study endpoint were reviewed by a reading center ophthalmologist to confirm the endpoint.
Results	AREDS2 Temporal Drift Regrade Year 4 Compared to BL, (intraobserver agreement) (n=88) Agreement: 92% Weighted Kappa (SE): 0.73 (0.02) Contemporaneous regrades, (interobserver agreement) (n=1335) Agreement: 96% Weighted Kappa (SE): 0.76 (0.01) Historical AREDS Temporal Drift (AREDS Report 6 and 17), (n=119) Agreement: 94% Weighted Kappa (SE): 0.73 (0.01)
Limitations	Since there was no quality assessment tool available for validation studies, the following review of bias tool for diagnostic cross-sectional studies was used and adapted accordingly: QUADAS 2 QUADAS website. DOMAIN 1: PATIENT SELECTION A. Risk of Bias Methods of patient selection:

Bibliographic reference	**Danis et al., 2013. Methods and reproducibility of grading optimized digital color fundus photographs in the Age-Related Eye Disease Study 2 (AREDS2 Report Number 2), Investigative Ophthalmology & Visual Science, 54, 4548-4554.**
	Was a consecutive or random sample of patients enrolled? Random sample of 5% of images were selected for contemporaneous regrading. Unclear selection process when choosing a stratification of images for temporal regrading. Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Unclear Could the selection of patients have introduced bias? RISK: UNCLEAR B. Concerns regarding applicability Is there concern that the included patients do not match the review question? CONCERN: LOW- People with a full range of AMD presentations DOMAIN 2: INDEX TEST(S) A. Risk of Bias Describe the index test and how it was conducted and interpreted: Were the index test results interpreted without knowledge of the results of the reference standard? Yes grading was done independently of past grades or contemporaneous grading. If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? NA- the purpose of this study is to assess how interpretation may differ between graders B. Concerns regarding applicability Is there concern that the index test, its conduct, or interpretation differ from the review question? CONCERN: LOW DOMAIN 3: REFERENCE STANDARD- NA (same as index test) DOMAIN 4: FLOW AND TIMING A. Risk of Bias Was there an appropriate interval between index test(s) and reference standard? Yes Did all patients receive a reference standard? Yes

Bibliographic reference	**Danis et al., 2013. Methods and reproducibility of grading optimized digital color fundus photographs in the Age-Related Eye Disease Study 2 (AREDS2 Report Number 2), Investigative Ophthalmology & Visual Science, 54, 4548-4554.**
	Did patients receive the same reference standard? Yes (grader the only difference, with the exception of optimized digital photographs being used in the AREDS2 study compared to film images in AREDS) Were all patients included in the analysis? No a sample of 1335, this sample was selected randomly for the contemporaneous comparisons. Could the patient flow have introduced bias? RISK: LOW

Bibliographic reference	**Klein et al., 2011. Risk assessment model for development of advanced age-related macular degeneration, Archives of ophthalmology, 129, 1543-1550.**
Country/ies where the study was carried out	USA
Study type	Prospective Cohort Study
Aim of the study	To design a risk assessment model for development of advanced age-related macular degeneration (AMD) incorporating phenotypic, demographic, environmental, and genetic risk factors.
Study dates	Published 2011 Participants in the Age-Related Eye Disease Study
Source of funding	This work was supported by the Casey Eye Institute Macular Degeneration Fund, Research to Prevent Blindness, the Bea Arveson Macular Degeneration Fund, and the Foundation Fighting Blindness.
Number of patients	2846 participants
Inclusion Criteria	• Age 55-80 years • At least one eye had to be free from vision-threatening disease other than AMD and cataract • That eye could not have had surgery, except for cataract surgery

Bibliographic reference	Klein et al., 2011. Risk assessment model for development of advanced age-related macular degeneration, Archives of ophthalmology, 129, 1543-1550.
	• The participants' stages of disease ranged from no evidence of AMD in either eye, to advanced AMD with vision loss in one eye but good vision (at least 20/30) in the other eye
Exclusion Criteria	None described
Diagnostic criteria	Comprehensive ocular and medical histories and examinations were performed at entrance into the study. Recorded information included age, sex, race, body mass index (BMI; calculated as weight in kilograms divided by height in meters squared), education level, cigarette smoking, diet, sunlight exposure, history of skin cancer, arthritis, systemic hypertension, other cardiovascular diseases, diabetes, and history of current and past medications and dietary supplements. For this study, the AREDS simplified severity scale was used to classify participants by their retina phenotype; This scale was designed to define risk categories for development of advanced AMD that could be readily determined by either clinical examination or fundus photography. The system uses 2 retinal abnormalities at baseline to determine a risk score: The end points of this study occurred when participants with no advanced AMD in either eye at baseline progressed to advanced AMD in either eye,and when those with advanced AMD in 1 eye at baseline developed advanced AMD in the fellow eye. Two forms of advanced AMD were recognized: (1) NV and (2) GA, defined as an area of well-demarcated depigmentation of the pigment epithelium, typically round or oval, and within which choroidal vessels are usually visible.
Patient characteristics	Median Age: 69 years 56% female Only white ethnicity included in the analysis
Predictors/risk factors and effect estimates	Risk factors of interest were: Very large drusen, Current smoking, Family history, AAMD in 1 eye, Age, mean (SD), y Hazard ratios were adjusted for age, cigarette smoking, family history, BMI, education, simple scale score, very large drusen (250 µm), unilateral AMD, and variants in the genes CFH, ARMS2, C3, and CFI. The C2/CFB variant. (all significant at univariable level)

Bibliographic reference	Klein et al., 2011. Risk assessment model for development of advanced age-related macular degeneration, Archives of ophthalmology, 129, 1543-1550.
Outcomes	Hazard Ratios for Progression to Advanced Age-Related Macular Degeneration
Analysis used	Cox proportional hazards analysis
Length of follow up	Follow-up averaged 9.3 years
Missing data handling/loss to follow up	Unclear: no description of missing data or how this was managed.
Results	Simple Scale Score: The Simple scale score is determined by the sum of the following risk factors in both eyes: Large drusen (>=125 um diameter) and pigment abnormality. A score of: 0) indicates no risk factors in either eye; 1) 1 risk factor in either eye; 2) total of 2 risk factors in either eye; 3) total of 3 risk factors in both eyes; 4) total of 4 risk factors in both eyes. Multivariate Association of Baseline Independent Variables Included in Final Model With Hazard Ratios for Progression to Advanced Age-Related Macular Degeneration at 2, 5, and 10 Years in 2602 Participants (95% Confidence Interval) 0) referent 1) 6.38 (3.48-11.69) 2) 14.12 (8.06-24.75) 3) 34.53 (19.79-60.26)

Bibliographic reference	Klein et al., 2011. Risk assessment model for development of advanced age-related macular degeneration, Archives of ophthalmology, 129, 1543-1550.
	4) 50.65 (28.86-88.89)
Limitations	Treatment assignment was not considered in this analysis... Quality assessment criteria for prognostic studies as outlined in: Hayden JA, Cote P, Bombardier C (2006) Evaluation of the quality of prognosis studies in systematic reviews. Annals of Internal Medicine 144: 427–37 The study sample represents the population of interest on key characteristics, sufficient to limit potential bias to the results (study participation). PARTLY Loss to follow-up (from sample to study population) is not associated with key characteristics, sufficient to limit potential bias (i.e., the study data adequately represent the sample) (study attrition). UNSURE Prognostic factors of interest are measured appropriately in study participants to sufficiently limit potential bias (outcome measurement). YES Outcome measured appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). YES Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). NO The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results (analysis). YES

Bibliographic reference	Klein et al., 2014. Harmonizing the classification of age-related macular degeneration in the three-continent AMD consortium. Ophthalmic Epidemiol. 2014 Jun;21(3):204-5], Ophthalmic Epidemiology, 21, 14-23.
Country/ies where the study was carried out	USA, Netherlands, Australia
Study type	Retrospective cohort
Aim of the study	To describe methods to harmonize the classification of age-related macular degeneration (AMD) phenotypes across four population-based cohort studies: the Beaver Dam Eye Study (BDES), Blue Mountains Eye Study (BMES), Los Angeles Latino Eye Study (LALES), and Rotterdam Study (RS).
Study dates	Published 2014
Source of funding	The Beaver Dam Eye Study was supported by National Institutes of Health grant EY06594 (BEK Klein and R Klein) and, in part, by an unrestricted grant from Research to Prevent Blindness. The National Eye Institute provided funding for entire study including collection and analyses of data; The Blue Mountains Eye Study was supported by grants from the National Health & Medical Research Council, Canberra, Australia. The Rotterdam Study is supported by Stichting Lijf en Leven, Krimpen aan de Lek; MD Fonds, Utrecht; Rotterdamse Vereniging Blindenbelangen, Rotterdam; Stichting Oogfonds Nederland, Utrecht; Blindenpenning, Amsterdam; Blindenhulp, The Hague; Algemene Nederlandse Vereniging ter Voorkoming van Blindheid (ANVVB), Doorn; Landelijke Stichting voor Blinden en Slechtzienden, Utrecht; Swart van Essen, Rotterdam; Stichting WinckelSweep, Utrecht; Henkes Stichting, Rotterdam; Laméris Ootech BV, Nieuwegein; Medical Workshop, de Meern; Topcon Europe BV, Capelle aan de IJssel, all in the Netherlands, and Heidelberg Engineering, Dossenheim, Germany. The Los Angeles Latino Eye Study was supported by the National Institutes of Health grants, an unrestricted grant from Research to Prevent Blindness, and Pfizer, Inc.
Sample size	60 images were graded by each of the centres
Characteristics	No baseline characteristics were reported in this study.

Bibliographic reference	**Klein et al., 2014. Harmonizing the classification of age-related macular degeneration in the three-continent AMD consortium. Ophthalmic Epidemiol. 2014 Jun;21(3):204-5], Ophthalmic Epidemiology, 21, 14-23.**
Inclusion Criteria	Participants of the Beaver Dam Eye Study with lesions characteristic of the range of severity of AMD.
Exclusion Criteria	None reported
Tests	A Three Continent AMD Consortium severity scale was developed based on harmonized cutpoints defining each early AMD lesion. This scale allowed for the common definitions of prevalence and incidence of AMD to be used. The scale has five categories of AMD severity numbered from 10 to 50, where level 10 represents no AMD and level 50 represents late AMD. Levels 20, 30, and 40 represent mild, moderate, and severe stages of early AMD, respectively. An AMD severity scale score was assigned to each eye based on lesion severity as graded by each study's grading protocol, i.e., each image had four grades, one from each study group. Definitions: Large drusen size: ≥ 125 pm in diameter Large drusen area: ≥ 650 pm in diameter Increased pigment: Any AMD related increased pigment RPE depigmentation: Any AMD related RPE depigmentation Geographic atrophy: Area of atrophy ≥350 µm in diameter and presence of at least 2 of these features: sharp edge, lack of RPE, visible choroidal vessels, and circular shape. Exudative AMD: Presence of any of the following: pigment epithelial detachment and/or retinal detachment, subretinal haemorrhage, subretinal scar, subretinal new vessels, treatment for exudative lesion. <u>Three Continent AMD Consortium age-related macular degeneration severity scale</u> 10- **No AMD:** No, questionable, small, or intermediate sized drusen (<125 µm in diameter) only, regardless of area of involvement, and no pigmentary abnormalities (defined as increased retinal pigment or RPE depigmentation present) OR No definite drusen with any pigmentary abnormality. 20- **Mild early AMD:** Small to intermediate sized drusen (<125 µm in diameter), regardless of area of involvement, with any pigmentary abnormality.

Bibliographic reference	Klein et al., 2014. Harmonizing the classification of age-related macular degeneration in the three-continent AMD consortium. Ophthalmic Epidemiol. 2014 Jun;21(3):204-5], Ophthalmic Epidemiology, 21, 14-23.
	OR Large drusen (≥125 µm in diameter) with drusen area <331,820 µm2 (equivalent to O-2 circle, defined as a circle with diameter of 650 µm) and no pigmentary abnormalities. 30- **Moderate early AMD:** Large drusen (≥125 µm in diameter) with drusen area <331,820 µm2 and any pigmentary abnormality OR Large drusen (≥125 µm in diameter) with drusen area ≥331,820 µm2, with or without increased retinal pigment but no RPE depigmentation. 40- **Severe early AMD:** Large drusen (≥125 µm in diameter) with drusen area ≥331,820 µm2 and RPE depigmentation present, with or without increased retinal pigment. 50- **Late AMD:** Pure geographic atrophy in the absence of exudative macular degeneration OR Exudative macular degeneration with or without geographic atrophy present.
Methods	To assess lesion-specific definitional differences among the three grading centers, there were digitized a set of stereoscopic images of 60 eyes with lesions characteristic of the range of severity of AMD selected from Beaver Dam Eye Study (BDES) participants, then reprinted the images on film and sent identical copies to the 4 grading teams. The image set had a balanced distribution of lesion characteristics considered to be typical of AMD: varying drusen size, type, and area, increased retinal pigment, retinal pigment epithelium (RPE) depigmentation, geographic atrophy, RPE detachment/sensory serous retinal detachment, subretinal hemorrhage, or subretinal fibrous scars. An AMD severity scale score was assigned to each eye based on lesion severity as graded by each study's grading protocol, i.e., each image had four grades, one from each study group. To evaluate grader variability, they then compared the consortium scale score assigned based on each study's grading scheme to the score that was assigned based on each of the other studies' grading schemes. Weighted kappa statistics were calculated using the Fleiss-Cohen weighting method, which was also used by the Age-Related Eye Diseases Study for grading quality control comparisons.

Bibliographic reference	**Klein et al., 2014. Harmonizing the classification of age-related macular degeneration in the three-continent AMD consortium. Ophthalmic Epidemiol. 2014 Jun;21(3):204-5], Ophthalmic Epidemiology, 21, 14-23.**
Results	Using the new harmonized Three Continent AMD Consortium severity scale, the exact grading agreement of the 60 eyes between centers varied from 61.0% to 81.4% between centers, and the within-one-step agreement varied from 84.7% to 98.3% between centers. Weighted kappa scores varied from 0.66 to 0.86, indicating moderate to substantial levels of agreement among the grading centers.
Limitations	Since there was no quality assessment tool available for validation studies, the following review of bias tool for diagnostic cross-sectional studies was used and adapted accordingly: QUADAS 2 QUADAS website. DOMAIN 1: PATIENT SELECTION A. Risk of Bias Methods of patient selection: • Was a consecutive or random sample of patients enrolled? Non-random sample of 60 images were selected for contemporaneous regrading. Images were chosen to represent the full range of AMD presentation. • Was a case-control design avoided? Yes • Did the study avoid inappropriate exclusions? Unclear Could the selection of patients have introduced bias? RISK: UNCLEAR B. Concerns regarding applicability Is there concern that the included patients do not match the review question? CONCERN: LOW- People with a full range of AMD presentations DOMAIN 2: INDEX TEST(S) A. Risk of Bias

Bibliographic reference	Klein et al., 2014. Harmonizing the classification of age-related macular degeneration in the three-continent AMD consortium. Ophthalmic Epidemiol. 2014 Jun;21(3):204-5], Ophthalmic Epidemiology, 21, 14-23.
	Describe the index test and how it was conducted and interpreted: • Were the index test results interpreted without knowledge of the results of the reference standard? Yes grading was done independently of past grades or contemporaneous grading. • If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? NA- the purpose of this study is to assess how interpretation may differ between graders B. Concerns regarding applicability Is there concern that the index test, its conduct, or interpretation differ from the review question? CONCERN: LOW DOMAIN 3: REFERENCE STANDARD- NA (same as index test) DOMAIN 4: FLOW AND TIMING A. Risk of Bias • Was there an appropriate interval between index test(s) and reference standard? Yes • Did all patients receive a reference standard? Yes • Did patients receive the same reference standard? Yes (centre of grading the only difference) • Were all patients included in the analysis? No a sample of 60 eyes, this sample was selected non-randomly from the Beaver Dam Eye Study to represent the full range of AMD severity. Could the patient flow have introduced bias? RISK: LOW

Bibliographic reference	Seddon,J.M., Sharma,S., Adelman,R.A., 20060214, Evaluation of the clinical age-related maculopathy staging system, Ophthalmology, 113, 260-266, 2006
Country/ies where the study was carried out	USA
Study type	Retrospective cohort
Aim of the study	To evaluate a clinical classification system, the Clinical Age-Related Maculopathy Staging system (CARMS) for age-related maculopathy (ARM) using a simple grading scale designed for clinical prctice and clinical research protocols
Study dates	Published 2005
Source of funding	Supported in part by Foundation Fighting Blindness
Sample size	492 eyes
Characteristics	Baseline characteristics of participants not reported
Inclusion Criteria	People recruited for the Progression of Age-Related Macular Degeneration Study
Exclusion Criteria	Exclusion criteria not reported
Tests	Each clinical assessment included a biomicroscopic slit-lamp examination of the macula with a 60 or 90 diopter lens. The area representing about 6000µm in diameter (approximately 4x the diameter of the disc) and centred on the fovea wasevaluated. Small drusen are <63µm; intermediate drusen ≥63µm but <125µm and large drusen ≥125µm. Retinal pigment epithelial hypopigmentation was defined as decreased pigmentation without well defined borders and visible choroidal vessels. Retinal pigment epithelial hyperpigmentation was defined as increased pigment without pigment clumping.

Bibliographic reference	Seddon,J.M., Sharma,S., Adelman,R.A., 20060214, Evaluation of the clinical age-related maculopathy staging system, Ophthalmology, 113, 260-266, 2006
	Geographic atrophy was defined as a well-demarcated area of marked decreased retinal pigment with visualisation of the choroidal vessels involving the fovea, or non central atrophy at least 350µm in diameter (about 3x the width of the retinal vein at the disc margin). The drusenoid or confluent type of retinal pigment epithelial detachment is a well defined cluster of large confluent drusen, often with overlying increased pigment measuring ≥500µm in diameter (about one third of disc diameter) Serous retinal pigment epithelial detachment has ill defined margins with slanting edges. <u>The Clinical Age-Related Maculopathy Staging System</u> 1- No drusen or <10 small drusen without pigment abnormalities 2- Approximately ≥10 small drusen or <15 intermediate drusen or pigment abnormalities associated with ARM • a) Drusen • b) RPE changes (hyperpigmentation and hypopigmentation) • c) Both drusen and RPE changes 3- Approximately ≥15 intermediate drusen or any large drusen • a) No drusenoid RPED • b) drusenoid RPED 4- Geographic atrophy with involvement of the macular center, or noncentral geographic atrophy at least 350µm in size 5- Exudative AMD, including nondrusenoid pigment epithelial detachments, serous or haemorrhagic retinal detachments, choroidal neovascular membrane with subretinal or sub RPE haemorrhages or fibrosis, or scars consistent with treatment of AMD. • a) Serous retinal pigment epithelial detachment without choroidal neovascular membrane • b) Choroidal neovascular membrane or disciform scar

Bibliographic reference	Seddon,J.M., Sharma,S., Adelman,R.A., 20060214, Evaluation of the clinical age-related maculopathy staging system, Ophthalmology, 113, 260-266, 2006
Methods	Fundus photographs of 492 eyes from 246 patients were evaluated by a reader at the Wisconsin Photographic Reading Centre using their grading system. A computorized program converted these gradings to the CARMS 5 point scale. From this database, the photographic files of 50 patients were selected randomly by a co-ordinator not involved in the grading process to yeild between 5 and 15 cases in each of the 5 grades. The photographs of the 50 patients were reviewed and graded according to the CARMS system by the two observers, each of whom was masked to the clinical history and the other graders assessments. The 2 observers were both retinal specialists, one of who had extensive experience with this grading system and one of whom was a senior retinal fellow. The observations from these two observers were compared to determine the amount of interobserver agreement. One observer reviewed and graded the 50 randomly selected photographic files 2 weeks after the initial assessment, without reference to the grades previously assigned, in order to find the intraobserver agreement. Kappa statistics were calculated.
Results	Agreement between Clinical observations and Reading Centre Assessment of Steriophotographs of Eyes with Age-Related Maculopathy Using the Clinical Maculopathy Staging System (CARMS). Agreement: 75% Agreement within 1 step: 89% Kappa, unweighted (95% CI): 0.63 (0.53-0.74) Kappa, weighted (95% CI): 0.78 (0.62-0.93) Agreement between 2 observers assessments of Age-Related Maculopathy based on Steriophotographs using the CARMS. Agreement: 84% Agreement within 1 step: 90% Kappa, unweighted (95% CI): 0.79 (0.47-1.1) Kappa, weighted (95% CI): 0.86 (0.41-1.3) Intraobserver agreement Agreement: 94% Agreement within 1 step: 100% Kappa, unweighted (95% CI): 0.92 (0.58-1.3)

Bibliographic reference	Seddon,J.M., Sharma,S., Adelman,R.A., 20060214, Evaluation of the clinical age-related maculopathy staging system, Ophthalmology, 113, 260-266, 2006
	Kappa, weighted (95% CI): 0.97 (0.49-1.4)
Limitations	Since there was no quality assessment tool available for validation studies, the following review of bias tool for diagnostic cross-sectional studies was used and adapted accordingly: QUADAS 2 QUADAS website. DOMAIN 1: PATIENT SELECTION A. Risk of Bias Methods of patient selection: • Was a consecutive or random sample of patients enrolled? A random sample of 50 images were selected for contemporaneous regrading between centres, to yield between 5-15 cases in each of the 5 CARMS grades. • Was a case-control design avoided? Yes • Did the study avoid inappropriate exclusions? Unclear Could the selection of patients have introduced bias? RISK: UNCLEAR B. Concerns regarding applicability Is there concern that the included patients do not match the review question? CONCERN: LOW- People with a full range of AMD presentations DOMAIN 2: INDEX TEST(S) A. Risk of Bias Describe the index test and how it was conducted and interpreted:

Bibliographic reference	Seddon,J.M., Sharma,S., Adelman,R.A., 20060214, Evaluation of the clinical age-related maculopathy staging system, Ophthalmology, 113, 260-266, 2006
	• Were the index test results interpreted without knowledge of the results of the reference standard? Yes grading was done independently (masked) of past grades or contemporaneous grading. • If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? NA- the purpose of this study is to assess how interpretation may differ between graders B. Concerns regarding applicability Is there concern that the index test, its conduct, or interpretation differ from the review question? CONCERN: LOW DOMAIN 3: REFERENCE STANDARD- NA (same as index test) DOMAIN 4: FLOW AND TIMING A. Risk of Bias • Was there an appropriate interval between index test(s) and reference standard? Yes • Did all patients receive a reference standard? Yes • Did patients receive the same reference standard? Yes (grader the only difference) • Were all patients included in the analysis? No a sample of 50, this sample was selected randomly from The Progression of Age-Related Macular Degeneration Study to yield 5-15 images for each of the CARMS grades. Could the patient flow have introduced bias? RISK: LOW

Bibliographic reference	Hamada,S., Jain,S., Sivagnanavel,V., Patel,N., Chong,N.V., 20060824, Drusen classification in bilateral drusen and fellow eye of exudative age-related macular degeneration, Eye, 20, 199-202, 2006
Country/ies where the study was carried out	UK
Study type	Retrospective cohort
Aim of the study	To assess the value of the modified international classification system in screening high-risk patients with bilateral age-related maculopathy (ARM) from those with lower risk characteristics.
Study dates	Published 2006
Source of funding	Unclear
Sample size	164 images of 106 patients
Characteristics	Group A = bilateral ARM (drusen/drusen) group, which included 133 images. Group B = fellow eye of exudative AMD (drusen/CNV) group which involved 31 images No other baseline characteristics reported
Inclusion Criteria	• Patients with bilateral ARM (drusen in both eyes) • Fellow eye of patients with unilateral exudative AMD. • Images of poor quality
Exclusion Criteria	• no signs of ARM in both eyes • bilateral neovascular disease or advanced atrophy. • Patients with ocular comorbidity from diseases other than AMD such as diabetes.
Tests	Colour fundus images of consecutive patients referred to the Retinal Research Unit at King's College Hospital, London, between December 2002 and December 2003. All images were centred on the macula.

Bibliographic reference	Hamada,S., Jain,S., Sivagnanavel,V., Patel,N., Chong,N.V., 20060824, Drusen classification in bilateral drusen and fellow eye of exudative age-related macular degeneration, Eye, 20, 199-202, 2006
	Images were graded according to the classification below: The Modified International Classification of ARM 0a No signs of ARM at all 0b Hard drusen (<63 µm) only 1a Soft distinct drusen (≥63 µm) only 1b Pigmentary abnormalities only, no soft drusen (≥63 µm) 2a Soft indistinct drusen (≥125 µm) or reticular drusen only 2b Soft distinct drusen (≥63 µm) with pigmentary abnormalities 3 Soft indistinct (≥125 µm) or reticular drusen with pigmentary abnormalities 4 Atrophic or neovascular AMD
Methods	The selected images were randomised by an independent investigator and then graded by two ophthalmologists, independent of each other, using the modified International Classification of ARM. Graders were masked to the patient diagnosis. Discrepancies between the two graders were resolved by a third expert grader. The interobserver variability of the graders was assessed using the Kappa statistical method.
Results	The interobserver consistency between the two graders was high with a Kappa value of 0.82 (SE 0.34).
Limitations	Since there was no quality assessment tool available for validation studies, the following review of bias tool for diagnostic cross-sectional studies was used and adapted accordingly: QUADAS 2 QUADAS website. DOMAIN 1: PATIENT SELECTION A. Risk of Bias

Bibliographic reference	Hamada,S., Jain,S., Sivagnanavel,V., Patel,N., Chong,N.V., 20060824, Drusen classification in bilateral drusen and fellow eye of exudative age-related macular degeneration, Eye, 20, 199-202, 2006
	Methods of patient selection: • Was a consecutive or random sample of patients enrolled? A random sample of 164 images were selected from consecutive patients patients referred to the Retinal Research Unit at King's College Hospital, London. • Was a case-control design avoided? Yes • Did the study avoid inappropriate exclusions? Yes Could the selection of patients have introduced bias? RISK: Unclear, not enough information provided regarding baseline characteristics of included participants B. Concerns regarding applicability Is there concern that the included patients do not match the review question? CONCERN: LOW- People with a range of AMD presentations DOMAIN 2: INDEX TEST(S) A. Risk of Bias Describe the index test and how it was conducted and interpreted: • Were the index test results interpreted without knowledge of the results of the reference standard? Yes grading was done independently (masked) of diagnosis, independent of each other. • If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? NA- the purpose of this study is to assess how interpretation may differ between graders B. Concerns regarding applicability

Bibliographic reference	Hamada,S., Jain,S., Sivagnanavel,V., Patel,N., Chong,N.V., 20060824, Drusen classification in bilateral drusen and fellow eye of exudative age-related macular degeneration, Eye, 20, 199-202, 2006
	Is there concern that the index test, its conduct, or interpretation differ from the review question? CONCERN: LOW DOMAIN 3: REFERENCE STANDARD- NA (same as index test) DOMAIN 4: FLOW AND TIMING A. Risk of Bias • Was there an appropriate interval between index test(s) and reference standard? Yes • Did all patients receive a reference standard? Yes • Did patients receive the same reference standard? Yes (grader the only difference) • Were all patients included in the analysis? Some were excluded due to poor photographic quality. Could the patient flow have introduced bias? RISK: LOW

Bibliographic reference	Sandberg,M.A., Weiner,A., Miller,S., Gaudio,A.R., 19980319, High-risk characteristics of fellow eyes of patients with unilateral neovascular age-related macular degeneration, Ophthalmology, 105, 441-447, 1998
Country/ies where the study was carried out	USA
Study type	Prospective cohort study
Aim of the study	To determine whether clinical tests of ocular function and macular appearence independently can help to predict which patients with unilateral neovascular age-related AMD will have a choroidal neovascular membrane develop in their fellow eye.

Bibliographic reference	Sandberg,M.A., Weiner,A., Miller,S., Gaudio,A.R., 19980319, High-risk characteristics of fellow eyes of patients with unilateral neovascular age-related macular degeneration, Ophthalmology, 105, 441-447, 1998
Study dates	Published 1997 data collected 1990 to 1995
Source of funding	Grants from National Eye Institute, the Foundation for Fighting Blindness and the Massachusetts Lions Eye Research Fund, Inc.
Number of patients	127 patients with unilateral neovascular AMD
Inclusion Criteria	• Snellen visual acuity of 20/60 or better in the fellow eye with sufficiently clear media to allow adequate visualisation of the fundus. • the presence of a choroidal neovascular membrane in the macular of the affected eye • macular drusen in both eyes • no sign of other retinal disease
Exclusion Criteria	• Bilateral dry AMD • Bilateral Neovascular AMD • Choroidal neovascularisation assoicated with high myopia
Diagnostic criteria	On the study eye, best corrected visual acuity was measured using a Snellen chart. Mucular visual field was assessed by letter recognition perimetry. Foveal glare recovery time was assessed by photostress testing. Foveal electroretinograms were recorded with a hand-held stimulator ophthalmoscope. Measurements of ocular function, biomicroscopy and direct and indirect ophthalmoscopy were performed and photographs of each macular were obtained. Fluorescein angiography was performed if a recent one was unavailable. Or if the fundus showed recent changes that could be attributable to choroidal neovascularisation.
Patient characteristics	Age: median 74 years Gender: 57 men, 70 women Ethnicity: not described

Bibliographic reference	Sandberg,M.A., Weiner,A., Miller,S., Gaudio,A.R., 19980319, High-risk characteristics of fellow eyes of patients with unilateral neovascular age-related macular degeneration, Ophthalmology, 105, 441-447, 1998
Predictors/risk factors and effect estimates	Risk factors assessed were: age, spherical equivalent, glare recovary time, focal electroretinal implicit time, No. of large drusen (quartiles 1-4), macular appearance grade. Prognostic factors entered into the analysis were: age, body mass index, blood pressure, spherical equivalent, snellen acuity, STDRS acuity, number of visual field defects, glare recovery time, foveal electroretinogram amplitude, foveal electroretinogram implicit time, and grade of macular appearance.
Outcomes	Relative risk of developing a choroidal neovascular membrane.
Length of follow up	4.5 years follow up follow up visits every 6 months
Missing data handling/loss to follow up	93 people from the initial 127 had been lost to follow up and were censored by the end of 4.5 years.
Results	Hazards ratio for development of choroidal neovascular membrane (95% confidence intervals) Macular appearance scale (4-point scale) Grade 1: rare (<25), predominantly extrafoveal small to intermediate-size distinct soft drusen with slight granularity and minimal-to-slight pigmentary hyperplasia Grade 2: 25 or more small-to intermediate-size distinct soft drusen, rare large distinct soft drusen, and modest RPE disturbance with a few spots of hyperplasia. Grade 3: numerous large distinct soft drusen, rare large confluent drusen, and moderate atrophy and hyperplasia. Grade 4: very large (>300um) soft confluent drusen with atrophy and hyperplasia. Hazard ratio: 1.76 (1.18-2.73)
Limitations	Quality assessment criteria for prognostic studies as outlined in:

Bibliographic reference	**Sandberg,M.A., Weiner,A., Miller,S., Gaudio,A.R., 19980319, High-risk characteristics of fellow eyes of patients with unilateral neovascular age-related macular degeneration, Ophthalmology, 105, 441-447, 1998**
	Hayden JA, Cote P, Bombardier C (2006) Evaluation of the quality of prognosis studies in systematic reviews. Annals of Internal Medicine 144: 427–37 The study sample represents the population of interest on key characteristics, sufficient to limit potential bias to the results (study participation). UNSURE Loss to follow-up (from sample to study population) is not associated with key characteristics, sufficient to limit potential bias (i.e., the study data adequately represent the sample) (study attrition). NO Prognostic factors of interest are measured appropriately in study participants to sufficiently limit potential bias (outcome measurement). YES Outcome measured appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). YES Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). NO The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results (analysis). YES

Bibliographic reference	**Perlee,L.T., Bansal,A.T., Gehrs,K., Heier,J.S., Csaky,K., Allikmets,R., Oeth,P., Paladino,T., Farkas,D.H., Rawlings,P.L., Hageman,G.S., 20131119, Inclusion of genotype with fundus phenotype improves accuracy of predicting choroidal neovascularization and geographic atrophy, Ophthalmology, 120, 1880-1892, 2013**
Country/ies where the study was carried out	USA

Bibliographic reference	**Perlee,L.T., Bansal,A.T., Gehrs,K., Heier,J.S., Csaky,K., Allikmets,R., Oeth,P., Paladino,T., Farkas,D.H., Rawlings,P.L., Hageman,G.S., 20131119, Inclusion of genotype with fundus phenotype improves accuracy of predicting choroidal neovascularization and geographic atrophy, Ophthalmology, 120, 1880-1892, 2013**
Study type	Prospective Cohort Study
Aim of the study	The accuracy of predicting conversion from early-stage age-related macular degeneration (AMD to the advanced stages of choroidal neovascularisation (CNV) or geographic atrophy (GA) was evaluated to determine whether inclusion of clinically relevant genetic markers improved accuracy beyond prediction using phenotypic risk factors alone.
Study dates	Published 2013 Participants in the Age-Related Eye Disease Study
Source of funding	Funding was by the Sequenom Center for Molecular Medicine, San Diego. The sponsor participated in designing and conducting the study; collecting, managing, analysing and interpreting the data; and preparing and reviewing the manuscript.
Number of patients	2415 participants, 940 were disease-free subjects and 1475 were subjects with early or intermediate AMD
Inclusion Criteria	• Subjects participating in AREDS trial • White, non-hispanic • Age 55-81 years
Exclusion Criteria	None described
Diagnostic criteria	Data was derived from subjects participating in the AREDS. The AREDS trial was a multicentre, prospective, longitudinal study evaluating the clinical course of AMD and cataracts, as well as the effect of high-dose vitamin/mineral supplementation on progression of these diseases. Clinical, demographic, and environmental data for each participant were retrieved from the AREDS database of Genotype and Phenotype. The baseline disease assignment used in this study was based on the AREDS 5-step (0-4) simplified severity scale with annual visit data graded according to the AREDS 12-point severity scale. This study applied the same definition of progressors used in the AREDS trial. The term “progressors” was defined as individuals with no, early, or intermediate AMD at baseline who progressed to advanced AMD during follow up and individuals with advanced AMD in 1 eye at baseline who progressed to advanced AMD in both eyes. The definition of a control was

Bibliographic reference	**Perlee,L.T., Bansal,A.T., Gehrs,K., Heier,J.S., Csaky,K., Allikmets,R., Oeth,P., Paladino,T., Farkas,D.H., Rawlings,P.L., Hageman,G.S., 20131119, Inclusion of genotype with fundus phenotype improves accuracy of predicting choroidal neovascularization and geographic atrophy, Ophthalmology, 120, 1880-1892, 2013**
	equivalent to the designation “non-progressor,” which was used to identify subjects with early or intermediate AMD that did not progress to CNV or GA, during the follow up period. Anning the entire range of the baseline simplified severity scale were analysed with an adjustment made for the presence of advanced disease in the non-study eye.
Patient characteristics	Ethnic group: white Age (mean (SE)): 68.57 years (0.10) Gender, n: Female- 1394, Male- 1022 Visual acuity: not reported AMD disease stage (simplified severity scale), n: 0) 940, 1) 417, 2) 397, 3) 287, 4) 368 Comorbidities affecting the eye (e.g. cataracts): not reported Current or previous treatment, n: antioxidants only- 720, antioxidants with zinc- 770, zinc only- 466, placebo- 459
Predictors/risk factors and effect estimates	Risk factors of interest were: Simplified severity scale, previous smoker, current smoker, age
Outcomes	Hazard ratios for progression to choroidal neovascularisation Hazard ratios for progression to geographic atrophy
Analysis used	Cox proportional hazards model
Length of follow up	10 year follow up

Bibliographic reference	Perlee,L.T., Bansal,A.T., Gehrs,K., Heier,J.S., Csaky,K., Allikmets,R., Oeth,P., Paladino,T., Farkas,D.H., Rawlings,P.L., Hageman,G.S., 20131119, Inclusion of genotype with fundus phenotype improves accuracy of predicting choroidal neovascularization and geographic atrophy, Ophthalmology, 120, 1880-1892, 2013
Missing data handling/loss to follow up	Unclear: no description of missing data or how this was managed. Data was taken from existing database.
Results	Simple Severity Score: The Simple Severity score is determined by the sum of the following risk factors in both eyes: Large drusen (>=125 um diameter) and pigment abnormality. A score of: 0) indicates no risk factors in either eye; 1) 1 risk factor in either eye; 2) total of 2 risk factors in either eye; 3) total of 3 risk factors in both eyes; 4) total of 4 risk factors in both eyes. Hazard ratios for progression to choroidal neovascularisation (95% Confidence Interval) 0) referent 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) Hazard ratios for progression to geographic atrophy (95% Confidence Interval)

Bibliographic reference	Perlee,L.T., Bansal,A.T., Gehrs,K., Heier,J.S., Csaky,K., Allikmets,R., Oeth,P., Paladino,T., Farkas,D.H., Rawlings,P.L., Hageman,G.S., 20131119, Inclusion of genotype with fundus phenotype improves accuracy of predicting choroidal neovascularization and geographic atrophy, Ophthalmology, 120, 1880-1892, 2013
	0) referent 1) 6.97 (3.01-16.14) 2) 9.33 (4.13-21.05) 3) 23.29 (10.59-51.22) 4) 34.81 (16.02-75.65)
Limitations	Treatment assignment was not considered in this analysis... Quality assessment criteria for prognostic studies as outlined in: Hayden JA, Cote P, Bombardier C (2006) Evaluation of the quality of prognosis studies in systematic reviews. Annals of Internal Medicine 144: 427–37 The study sample represents the population of interest on key characteristics, sufficient to limit potential bias to the results (study participation). PARTLY Loss to follow-up (from sample to study population) is not associated with key characteristics, sufficient to limit potential bias (i.e., the study data adequately represent the sample) (study attrition). UNSURE Prognostic factors of interest are measured appropriately in study participants to sufficiently limit potential bias (outcome measurement). YES Outcome measured appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). YES Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). UNSURE

Bibliographic reference	**Perlee,L.T., Bansal,A.T., Gehrs,K., Heier,J.S., Csaky,K., Allikmets,R., Oeth,P., Paladino,T., Farkas,D.H., Rawlings,P.L., Hageman,G.S., 20131119, Inclusion of genotype with fundus phenotype improves accuracy of predicting choroidal neovascularization and geographic atrophy, Ophthalmology, 120, 1880-1892, 2013**
	The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results (analysis). YES

Bibliographic reference	**van,Leeuwen R., Chakravarthy,U., Vingerling,J.R., Brussee,C., Hooghart,A.J., Mulder,P.G., de Jong,P.T., 20030902, Grading of age-related maculopathy for epidemiological studies: is digital imaging as good as 35-mm film?, Ophthalmology, 110, 1540-1544, 2003**
Country/ies where the study was carried out	Netherlands, Ireland
Study type	Retrospective cohort
Aim of the study	To compare sterio digital images with sterio 35-mm transparencies as to the quality and reliability of grading AMD in the context of the EUREYE study.
Study dates	Published 2003
Source of funding	European Commission, Macular Disease Society, the society of Prevention of Blindness, Optimex Foundation, Stichting Blindenhulp
Sample size	91 subjects, 131 eyes
Characteristics	Participants in the EUREYE study Random sampling of people aged 65 years and older Fundus photographs were selected on the basis of their AMD status to represent the entire range of AMD severity including eyes with no AMD fundus signs. The quality of slides varied but none of them were ungradable.

Bibliographic reference	van,Leeuwen R., Chakravarthy,U., Vingerling,J.R., Brussee,C., Hooghart,A.J., Mulder,P.G., de Jong,P.T., 20030902, Grading of age-related maculopathy for epidemiological studies: is digital imaging as good as 35-mm film?, Ophthalmology, 110, 1540-1544, 2003
Inclusion Criteria	Participants in the EUREYE study Participants aged 65 years and older
Exclusion Criteria	Lesions that were considered to be the result of generalised vascular disease such as diabetic retinopathy or chorioretinitis, high myopia, trauma, congenital disease, or photocoagulation for reasons other than AMD were excluded from AMD grading.
Tests	35-mm film and 35º sterioscopic colour fundus images were obtained for each eye. framed transparencies were mounted on plastic sheets and were examined with a portable sterio viewer that provided 5X image magnification on a tilted table viewing box with a back light. Digital images were examined on a SONY CRT monitor Two graders both having 8 years of experience in AMD grading were trained for 2 months in digital image grading. After this point graders randomly graded all 35-mm slides and digital images.
Methods	For each eye four scores were obtained by 2 different imaging techniques and 2 different graders.
Results	On all 8 stages: digital images Agreement: 59.0 Weighted kappa: 0.72 On all 8 stages: 35-mm film Agreement: 65.7% Weighted kappa: 0.78 On the 5 main stages: digital images Agreement: 64.9% Weighted kappa: 0.74 On the 5 main stages: 35-mm film Agreement: 72.3% Weighted kappa: 0.79

Bibliographic reference	van,Leeuwen R., Chakravarthy,U., Vingerling,J.R., Brussee,C., Hooghart,A.J., Mulder,P.G., de Jong,P.T., 20030902, Grading of age-related maculopathy for epidemiological studies: is digital imaging as good as 35-mm film?, Ophthalmology, 110, 1540-1544, 2003
Limitations	Since there was no quality assessment tool available for validation studies, the following review of bias tool for diagnostic cross-sectional studies was used and adapted accordingly: QUADAS 2 QUADAS website. DOMAIN 1: PATIENT SELECTION A. Risk of Bias Methods of patient selection: Was a consecutive or random sample of patients enrolled? No images were selected to represent the full range of AMD severity Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes Could the selection of patients have introduced bias? RISK: Unclear, not enough information provided regarding baseline characteristics of included participants B. Concerns regarding applicability Is there concern that the included patients do not match the review question? CONCERN: LOW- People with a range of AMD presentations DOMAIN 2: INDEX TEST(S) A. Risk of Bias Describe the index test and how it was conducted and interpreted: Were the index test results interpreted without knowledge of the results of the reference standard? Yes grading was done independently (masked) of diagnosis, independent of each other. If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? NA- the purpose of this study is to assess how interpretation may differ between graders B. Concerns regarding applicability Is there concern that the index test, its conduct, or interpretation differ from the review question? CONCERN: LOW DOMAIN 3: REFERENCE STANDARD- NA (same as index test)

Bibliographic reference	van,Leeuwen R., Chakravarthy,U., Vingerling,J.R., Brussee,C., Hooghart,A.J., Mulder,P.G., de Jong,P.T., 20030902, Grading of age-related maculopathy for epidemiological studies: is digital imaging as good as 35-mm film?, Ophthalmology, 110, 1540-1544, 2003
	DOMAIN 4: FLOW AND TIMING A. Risk of Bias Was there an appropriate interval between index test(s) and reference standard? Yes Did all patients receive a reference standard? Yes Did patients receive the same reference standard? Yes (grader the only difference) Were all patients included in the analysis? Yes Could the patient flow have introduced bias? RISK: LOW

Bibliographic reference	Cohen, S. Y., Creuzot-Garcher, C., Darmon, J., Desmettre, T., Korobelnik, J. F., Levrat, F., ... & Schluep, H. (2007). Types of choroidal neovascularisation in newly diagnosed exudative age-related macular degeneration. British journal of ophthalmology, 91(9), 1173-1176.
Country/ies where the study was carried out	France
Study type	Prospective cohort
Aim of the study	To describe the types and location of choroidal neovascularisation (CNV) in exudative age-related macular degeneration (AMD), including vascularised pigment epithelial detatchments (PED), and most recently described subtypes, such as retinal choroidal anasmostosis, also termed ‘‘retinal angiomatous proliferation’’ (RAP).
Study dates	Published 2007
Source of funding	Employees of Pfizer

Bibliographic reference	**Cohen, S. Y., Creuzot-Garcher, C., Darmon, J., Desmettre, T., Korobelnik, J. F., Levrat, F., ... & Schluep, H. (2007). Types of choroidal neovascularisation in newly diagnosed exudative age-related macular degeneration. British journal of ophthalmology, 91(9), 1173-1176.**
Sample size	207 patients with newly diagnosed exudative AMD
Characteristics	67.2% of women, Mean age 79.1±7.3 The study did not report characteristics for the following variables: Ethnic group Visual acuity AMD disease stage Comorbidities affecting the eye (e.g. cataracts)
Inclusion Criteria	• Four private and three hospital based referral centres all over France. • Consecutive patients with newly diagnosed exudative AMD • At least one eye undergoing fluorescein angiography in the centre.
Exclusion Criteria	• Patients with myopic CNV or with CNV of origin other than AMD • Patients with idiopathic Polypoidal Choroidal Vasculopathy were not included. • Eyes having already received treatment for CNV.
Tests	Fluorescein and ICG angiography were carried out in accordance with the routine practice at each centre. Fundus camera and/or scanning laser ophthalmoscope were used according to the routine practice of the different centres.

Bibliographic reference	**Cohen, S. Y., Creuzot-Garcher, C., Darmon, J., Desmettre, T., Korobelnik, J. F., Levrat, F., ... & Schluep, H. (2007). Types of choroidal neovascularisation in newly diagnosed exudative age-related macular degeneration. British journal of ophthalmology, 91(9), 1173-1176.**
	For each patient, the centre provided one red-free photograph and at least three images of fluorescein angiography: one early phase (<45s), one mid-phase (between 45 s and 3 min) and one late-phase (>5 min). In cases of suspicion of occult CNV or RAP, ICG angiography was performed in accordance with routine practice in the centres. When performed for ICG angiography, at least two images had to be provided: one early phase (<2 min) and one late-phase (>20 min).
Methods	The centre's ophthalmologist indicated (for each included eye) the size of the lesion as obtained by comparison to the disc diameter of the studied eye, the location of CNV (extrafoveal, juxtafoveal, subfoveal), and the classification of CNV types classic only, predominantly classic, minimally classic, occult without PED (with or without RAP) and vascularised PED (with or without RAP). The prescribed treatment after the visit was also recorded. The selected images and questionnaires were then reviewed by two independent experts who were blinded to the centre and the identity of the subject. All lesions were classified by both experts and the results compared after completion of the evaluation. Any disagreement was resolved by a third, independent expert. At completion of the study, there were two diagnoses for each included subject for the size of the lesion, the location, and the classification of CNV: a local diagnosis delivered by the centre's ophthalmologist and a validated expert diagnosis.
Results	When comparing the local and centralised (final) classification, k was 0.52 for location of the lesions and 0.59 for type of the lesion, showing moderate agreement.
Limitations	Since there was no quality assessment tool available for validation studies, the following review of bias tool for diagnostic cross-sectional studies was used and adapted accordingly: QUADAS 2 QUADAS website. DOMAIN 1: PATIENT SELECTION A. Risk of Bias Methods of patient selection: Was a consecutive or random sample of patients enrolled? Consecutive patients with newly diagnosed exudative neovascular AMD at several different centres Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes

Bibliographic reference	**Cohen, S. Y., Creuzot-Garcher, C., Darmon, J., Desmettre, T., Korobelnik, J. F., Levrat, F., ... & Schluep, H. (2007). Types of choroidal neovascularisation in newly diagnosed exudative age-related macular degeneration. British journal of ophthalmology, 91(9), 1173-1176.**
	Could the selection of patients have introduced bias? RISK: Unclear, not enough information provided regarding baseline characteristics of included participants, many important characteristics were not reported. B. Concerns regarding applicability Is there concern that the included patients do not match the review question? CONCERN: MODERATE- people with polypoidal vascular choroidal neovascularisation were excluded DOMAIN 2: INDEX TEST(S) A. Risk of Bias Describe the index test and how it was conducted and interpreted: Were the index test results interpreted without knowledge of the results of the reference standard? Yes grading was done independently (masked) of diagnosis, independent of each other. If a threshold was used, was it pre-specified? NO PRESPECIFICATION SEEMS TO HAVE BEEN USED. Each centre made the diagnosis based on their own clinical opinion with no shared criteria. Could the conduct or interpretation of the index test have introduced bias? NA- the purpose of this study is to assess how interpretation may differ between graders. However the lack of a clear criteria adds to the uncertainty regarding whether discrepancies were due to interpretation or differing criteria. B. Concerns regarding applicability Is there concern that the index test, its conduct, or interpretation differ from the review question? CONCERN: MODERATE DOMAIN 3: REFERENCE STANDARD- NA (same as index test) DOMAIN 4: FLOW AND TIMING A. Risk of Bias Was there an appropriate interval between index test(s) and reference standard? Yes Did all patients receive a reference standard? Yes Did patients receive the same reference standard? no (some participants also received ICG testing, there was no clear criteria who should receive this and who shouldn't, this seems to vary by centre) Were all patients included in the analysis? Yes

Bibliographic reference	**Cohen, S. Y., Creuzot-Garcher, C., Darmon, J., Desmettre, T., Korobelnik, J. F., Levrat, F., ... & Schluep, H. (2007). Types of choroidal neovascularisation in newly diagnosed exudative age-related macular degeneration. British journal of ophthalmology, 91(9), 1173-1176.**
	Could the patient flow have introduced bias? RISK: MODERATE

Bibliographic reference	**Coscas, G., Yamashiro, K., Coscas, F., De Benedetto, U., Tsujikawa, A., Miyake, M., & Yoshimura, N. (2014). Comparison of exudative age-related macular degeneration subtypes in Japanese and French Patients: multicenter diagnosis with multimodal imaging. American journal of ophthalmology, 158(2), 309-318.**
Country/ies where the study was carried out	France, Japan, Singapore
Study type	Prospective cohort
Aim of the study	To compare and analyze differences and similarities between Japanese and French patients in subtype diagnosis of exudative age-related macular degeneration (AMD) as determined by fundus photography (FP) and fluorescein angiography (FA), and a multimodal imaging involving FP, FA, indocyanine green angiography (ICGA), and optical coherence tomography (OCT).
Study dates	Published 2014
Source of funding	Author conflicts: Allergan, Bayer, Novartis, Pfizer, Roche, GlaxoSmithKline, Topcon Corporation, Nidek, Canon. This research was supported in part by the Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (JSPS).
Sample size	99 consecutive Japanese eyes and 94 consecutive French eyes with exudative AMD
Characteristics	The mean age of the 99 Japanese patients (70 men and 29 women) was 74.0 ± 8.9 years, and all patients were ethnically Japanese.

Bibliographic reference	**Coscas, G., Yamashiro, K., Coscas, F., De Benedetto, U., Tsujikawa, A., Miyake, M., & Yoshimura, N. (2014). Comparison of exudative age-related macular degeneration subtypes in Japanese and French Patients: multicenter diagnosis with multimodal imaging. American journal of ophthalmology, 158(2), 309-318.**
	The mean age of the 85 French patients (45 men and 40 women) was 73.5 ± 7.9 years, and 98% were white. The study did not report characteristics for the following variables: Visual acuity AMD disease stage Comorbidities affecting the eye (e.g. cataracts)
Inclusion Criteria	• Consecutive patients who visited the Department of Ophthalmology, Kyoto University Hospital with a tentative diagnosis of neovascular AMD (Kyoto cases) and patients with presumed neovascular AMD at Centre d'Ophtalmologie de Paris. • Consecutive patients with presumed neovascular AMD
Exclusion Criteria	• Angiographic images of low quality (1 eye excluded)
Tests	All patients underwent comprehensive ophthalmic examinations, including the measurement of best-corrected visual acuity, intraocular pressure testing, indirect ophthalmoscopy, slitlamp biomicroscopy with a contact lens, spectral-domain OCT (Spectralis HRAþOCT; Heidelberg Engineering, Heidelberg, Germany), and FA/ICGA (HRA-2; Heidelberg Engineering). Both Kyoto and Paris cases were subgrouped into: (1) AMD with type 1 CNV; (2) AMD with type 1 + 2 CNV;

Bibliographic reference	Coscas, G., Yamashiro, K., Coscas, F., De Benedetto, U., Tsujikawa, A., Miyake, M., & Yoshimura, N. (2014). Comparison of exudative age-related macular degeneration subtypes in Japanese and French Patients: multicenter diagnosis with multimodal imaging. American journal of ophthalmology, 158(2), 309-318.
	(3) AMD with type 2 CNV only; (4) chorioretinal anastomosis. (5) PCV, either (5a) without CNV or (5b) associated with type 1 or 2 CNV. Eyes with PCV with branching vascular network without CNV were categorized to (5a) PCV without CNV. A diagnosis of PCV was made based on fundus photography, FA/ICGA, and OCT: elevated orange-red lesions, characteristic polypoidal lesions at the edge of a branching vascular network on angiography, and prominent anterior protrusion of the retinal pigment epithelium line in OCT images. A diagnosis of chorioretinal anastomosis was also made based on fundus photography, FA/ICGA, and OCT: subretinal, intraretinal, or preretinal juxtafoveal hemorrhages; dilated retinal vessels; lipid exudates; and retinal–choroidal anastomosis. For the analysis of AMD subtypes, AMD with type 1 CNV, AMD with type 2 CNV, and AMD with type 1þ2 CNV were regarded as typical exudative AMD, and PCV associated with type 1 or 2 CNV and PCV without type 1 or 2 CNV were regarded as PCV.

<table>
<tr><th>Bibliographic reference</th><th>Coscas, G., Yamashiro, K., Coscas, F., De Benedetto, U., Tsujikawa, A., Miyake, M., & Yoshimura, N. (2014). Comparison of exudative age-related macular degeneration subtypes in Japanese and French Patients: multicenter diagnosis with multimodal imaging. American journal of ophthalmology, 158(2), 309-318.</th></tr>
<tr><td>Methods</td><td>At Kyoto University, 2 retina specialists evaluated fundus photography and FA and made the ‘‘firststep diagnosis’’ for both Kyoto cases and Paris cases. If the specialists disagreed regarding the diagnosis, a third retina specialist (N.Y.) was consulted for the final determination. Multimodal images of fundus photography, FA, ICGA, and OCT results were used to make a ‘‘second-step diagnosis.’’

At Centre d’Ophtalmologie de Paris, 2 retina specialists evaluated fundus photography and FA for the ‘‘first-step diagnosis’’ and multimodal images of fundus photography, FA, ICGA, and OCT assessments were used to make a ‘‘second-step diagnosis.’’ In the case of disagreement, a third retina specialist determined the diagnosis. When the ‘‘second-step diagnosis’’ made by the 2 institutes agreed, the diagnosis was regarded as the ‘‘final diagnosis.’’ When the diagnosis by the 2 institutes failed to reach a consensus, retina specialists at Singapore Eye Research Institute were consulted for a diagnosis. In such cases, the diagnosis by Singapore Eye Research Institute was regarded as the ‘‘final diagnosis.’</td></tr>
<tr><td>Results</td><td>Agreement outcomes for Neovascular subtypes of AMD, compared to final diagnosis in Kyoto patients
<table>
<tr><th></th><th>Kyoto investigators first step</th><th>Kyoto Investigators, second step</th><th>Paris investigators first step</th><th>Paris Investigators second step</th></tr>
<tr><td>AMD with type 1 CNV</td><td>79.4%</td><td>91.1%</td><td>82.3%</td><td>79.4%</td></tr>
<tr><td>AMD with type 1+2 CNV</td><td>66.6%</td><td>66.6%</td><td>16.6%</td><td>33.3%</td></tr>
<tr><td>AMD with type 2 CNV</td><td>40.0%</td><td>60.0%</td><td>80%</td><td>100%</td></tr>
<tr><td>Chorioretinal anastomosis</td><td>66.6%</td><td>83.3%</td><td>83.3%</td><td>83.3%</td></tr>
<tr><td>PCV with type 1 or 2 CNV</td><td>33.3%</td><td>66.6%</td><td>33.3%</td><td>66.6%</td></tr>
<tr><td>PCV without type 1 or 2 CNV</td><td>56.5%</td><td>95.6%</td><td>91.3%</td><td>95.6%</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Coscas, G., Yamashiro, K., Coscas, F., De Benedetto, U., Tsujikawa, A., Miyake, M., & Yoshimura, N. (2014). Comparison of exudative age-related macular degeneration subtypes in Japanese and French Patients: multicenter diagnosis with multimodal imaging. American journal of ophthalmology, 158(2), 309-318.**

Other	88.8%	100%	66.6%	100%

For the Kyoto patients 34.3% (34/99) differed from the ‘‘final diagnosis’’ as determined by the 3 facilities together. The number of eyes for which the diagnosis involved disagreement decreased to 10 (10.1%) when considering the ‘‘second step diagnosis,’’ which was based on the additional information provided by ICGA and OCT.

First step: fundus photography and FA

Second step: fundus photography, FA, ICGA, and OCT

*Figures calculated by reviewer from Figure 1 within study, agreement with final diagnosis calculated (that agreed at the third site in Singapore)

<u>Agreement outcomes for Neovascular subtypes of AMD, compared to final diagnosis in Paris patients</u>

For the Paris patients 24.5% (23/94) differed from the ‘‘final diagnosis’’ as determined by the 3 facilities together. The number of eyes with any disagreement related to diagnosis decreased to 9 (9.6%) for the ‘‘second-step diagnosis’’ based on the additional information provided by ICGA and OCT.

First step: fundus photography and FA

Second step: fundus photography, FA, ICGA, and OCT

	Kyoto investigators first step	Kyoto Investigators, second step	Paris investigators first step	Paris Investigators second step
AMD with type 1 CNV	89.5%	97.9%	89.5%	95.8%

Bibliographic reference	**Coscas, G., Yamashiro, K., Coscas, F., De Benedetto, U., Tsujikawa, A., Miyake, M., & Yoshimura, N. (2014). Comparison of exudative age-related macular degeneration subtypes in Japanese and French Patients: multicenter diagnosis with multimodal imaging. American journal of ophthalmology, 158(2), 309-318.**

AMD with type 1+2 CNV	78.9%	89.5%	36.8%	68.4%
AMD with type 2 CNV	60.0%	60.0%	100%	100%
Chorioretinal anastomosis	60.0%	100.0%	80.0%	80.0%
PCV without type 1 or 2 CNV	75.0%	87.5%	33.3%	66.6%
Other	50%	75%	100%	100%

*Figures calculated by reviewer from Figure 2 within study, agreement with final diagnosis calculated (that agreed by the third site in Singapore)

Limitations

Since there was no quality assessment tool available for validation studies, the following review of bias tool for diagnostic cross-sectional studies was used and adapted accordingly:

QUADAS 2 QUADAS website.

DOMAIN 1: PATIENT SELECTION
A. Risk of Bias
Methods of patient selection:
Was a consecutive or random sample of patients enrolled? Consecutive patients with presumed exudative neovascular AMD at two sites
Was a case-control design avoided? Yes
Did the study avoid inappropriate exclusions? Yes
Could the selection of patients have introduced bias? RISK: Unclear, not enough information provided regarding baseline characteristics of included participants,
B. Concerns regarding applicability
Is there concern that the included patients do not match the review question?
CONCERN: LOW

Bibliographic reference	Coscas, G., Yamashiro, K., Coscas, F., De Benedetto, U., Tsujikawa, A., Miyake, M., & Yoshimura, N. (2014). Comparison of exudative age-related macular degeneration subtypes in Japanese and French Patients: multicenter diagnosis with multimodal imaging. American journal of ophthalmology, 158(2), 309-318.
	DOMAIN 2: INDEX TEST(S) A. Risk of Bias Describe the index test and how it was conducted and interpreted: Were the index test results interpreted without knowledge of the results of the reference standard? Yes grading was done independently (masked) of diagnosis, independent of each other. If a threshold was used, was it pre-specified? NO PRESPECIFICATION SEEMS TO HAVE BEEN USED. Each centre made the diagnosis based on their own clinical opinion with no shared criteria. Could the conduct or interpretation of the index test have introduced bias? NA- the purpose of this study is to assess how interpretation may differ between graders. However the lack of a clear criteria adds to the uncertainty regarding whether discrepancies were due to interpretation or differing criteria. B. Concerns regarding applicability Is there concern that the index test, its conduct, or interpretation differ from the review question? CONCERN: MODERATE DOMAIN 3: REFERENCE STANDARD- NA (same as index test) DOMAIN 4: FLOW AND TIMING A. Risk of Bias Was there an appropriate interval between index test(s) and reference standard? Yes Did all patients receive a reference standard? Yes Did patients receive the same reference standard? yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? RISK: LOW

Bibliographic reference	**Jung, J. J., Chen, C. Y., Mrejen, S., Gallego-Pinazo, R., Xu, L., Marsiglia, M. & Freund, K. B. (2014). The incidence of neovascular subtypes in newly diagnosed neovascular age-related macular degeneration. American journal of ophthalmology, 158(4), 769-779.**
Country/ies where the study was carried out	USA
Study type	Prospective cohort
Aim of the study	To determine the frequency of neovascularization subtypes as determined by fluorescein angiography (FA) alone vs FA and optical coherence tomography (OCT) grading in age-related macular degeneration (AMD).
Study dates	Published 2014
Source of funding	Macular foundation inc.
Sample size	374 treatment naïve patients with neovascular AMD in at least 1 eye
Characteristics	Mean age was 86.3 6 8.1 years; 67.7% of eyes (180/266) were from female patients and 95.5% (254/266) from white patients, followed by 2.6% (7/266) Hispanic, 1.5% (4/266) Asian, and 0.4% (1/266) African-American The study did not report characteristics for the following variables: Visual acuity AMD disease stage

Bibliographic reference	**Jung, J. J., Chen, C. Y., Mrejen, S., Gallego-Pinazo, R., Xu, L., Marsiglia, M. & Freund, K. B. (2014). The incidence of neovascular subtypes in newly diagnosed neovascular age-related macular degeneration. American journal of ophthalmology, 158(4), 769-779.**
	Comorbidities affecting the eye (e.g. cataracts)
Inclusion Criteria	• older than 50 years • newly diagnosed treatment-naıve NV as evidenced by clinical examination and FA. • Best-corrected visual acuity was 20/20–20/800 on a Snellen chart • Eyes in the study must have had OCT imaging (time-domain or spectral-domain) performed at the time of diagnosis.
Exclusion Criteria	• Previous treatments for CNV in the study eye, including photodynamic therapy (PDT), intravitreal steroids, intravitreal pegaptanib (Macugen; Valeant, Montreal, Quebec, Canada), or thermal laser • Eyes with CNV lesions presenting with subfoveal fibrosis, central geographic atrophy (GA) at baseline, or retinal pigment epithelial tears, or composed of more than 50% hemorrhage. • Eyes with CNV secondary to other maculopathies, including degenerative myopia, angioid streaks, presumed ocular histoplasmosis syndrome, or inflammatory maculopathies.
Tests	FA images were obtained using a Topcon TRC 501x fundus camera (Topcon Imagenet, Tokyo, Japan). OCT imaging of all patients was performed with time-domain OCT (Stratus; Carl Zeiss Meditec Inc, Dublin, California, USA) or spectral-domain OCT. OCT instrumentation was necessary for additional accurate identification oflesion subtype utilizing the anatomic classification of lesion subtype. Standard methods of image acquisition were employed for all imaging modalities.
Methods	The classification of neovascular lesions was made independently by 2 experienced retina specialists who evaluated the presenting color photographs, FA, and OCT. First, all the color photographs and FA corresponding to the baseline diagnostic visit were analyzed. Neovascular lesions were subtyped according to the MPS criteria and the Digital Angiographic Reading Center (DARC) Reader's Manual as occult or classic CNV. RAP lesions were identified by criteria defined by Yannuzzi and associates and the DARC Reader's Manual. Secondly, OCT images corresponding to the same diagnostic visit were reviewed, and each case was classified according to the guidelines provided by Freund and associates. The anatomic classification, which uses OCT in combination with FA,

Bibliographic reference	**Jung, J. J., Chen, C. Y., Mrejen, S., Gallego-Pinazo, R., Xu, L., Marsiglia, M. & Freund, K. B. (2014). The incidence of neovascular subtypes in newly diagnosed neovascular age-related macular degeneration. American journal of ophthalmology, 158(4), 769-779.**
	categorizes lesions as type 1 (sub–retinal pigment epithelium [RPE]), type 2 (subretinal), type 3 (intraretinal), or mixed NV. Eyes with PCV were considered to be a form of type 1 CNV. Type 1, 2, and 3 NVs corresponded to occult, classic, and RAP angiographic lesions, respectively. Cases with multiple lesion types were identified as mixed NV and each component was also recorded. MORE DETAIL REGARDING CLASSIFICATION SYSTEM WITHIN STUDY
Results	Classification system Agreement Overall, there was good agreement between FA and anatomic classification with a k statistic of 0.65 (standard error 60.37, P < 0.001). In the subgroup on that used spectral domain OCT technology at baseline: Overall, again there was good agreement between FA and anatomic classification, with a k statistic of 0.67 (standard error 60.05, P < .001).
Limitations	Since there was no quality assessment tool available for validation studies, the following review of bias tool for diagnostic cross-sectional studies was used and adapted accordingly: QUADAS 2 QUADAS website. DOMAIN 1: PATIENT SELECTION A. Risk of Bias Methods of patient selection: Was a consecutive or random sample of patients enrolled? Consecutive patients with treatment naïve exudative neovascular AMD were enrolled Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes

Bibliographic reference	**Jung, J. J., Chen, C. Y., Mrejen, S., Gallego-Pinazo, R., Xu, L., Marsiglia, M. & Freund, K. B. (2014). The incidence of neovascular subtypes in newly diagnosed neovascular age-related macular degeneration. American journal of ophthalmology, 158(4), 769-779.**
	Could the selection of patients have introduced bias? RISK: Unclear, not enough information provided regarding baseline characteristics of included participants, B. Concerns regarding applicability Is there concern that the included patients do not match the review question? CONCERN: LOW DOMAIN 2: INDEX TEST(S) A. Risk of Bias Describe the index test and how it was conducted and interpreted: Were the index test results interpreted without knowledge of the results of the reference standard? 2 independent observers were not masked to the original diagnosis of neovascular AMD. If a threshold was used, was it pre-specified? YES. Could the conduct or interpretation of the index test have introduced bias? Unclear NA- the purpose of this study is to assess how interpretation may differ between classification systems using different tests at the same point of diagnosis. B. Concerns regarding applicability Is there concern that the index test, its conduct, or interpretation differ from the review question? CONCERN: MODERATE- we are not so much interested in the agreement between diagnostic tests but graders for a classification system. DOMAIN 3: REFERENCE STANDARD- no reference standard in this study DOMAIN 4: FLOW AND TIMING A. Risk of Bias Was there an appropriate interval between index test(s) and reference standard? Yes Did all patients receive a reference standard? Yes Did patients receive the same reference standard? No, but subgroup analysis was performed for those who received a different type of OCT analysis Were all patients included in the analysis? Yes

Bibliographic reference	**Jung, J. J., Chen, C. Y., Mrejen, S., Gallego-Pinazo, R., Xu, L., Marsiglia, M. & Freund, K. B. (2014). The incidence of neovascular subtypes in newly diagnosed neovascular age-related macular degeneration. American journal of ophthalmology, 158(4), 769-779.**
	Could the patient flow have introduced bias? RISK: LOW

Bibliographic reference	**Friedman, S. M., & Margo, C. E. (2000). Choroidal neovascular membranes: reproducibility of angiographic interpretation. American journal of ophthalmology, 130(6), 839-841.**
Country/ies where the study was carried out	USA
Study type	Retrospective cohort
Aim of the study	To determine interobserver agreement for classifying choroidal neovascular membranes in age-related macular degeneration.
Study dates	Published 2000
Source of funding	Unclear
Sample size	Six fluorescein angiograms of choroidal neovascular membranes
Characteristics	The study did not report characteristics for the following variables: Ethnic group Age Gender Visual acuity AMD disease stage

<table>
<tr><th>Bibliographic reference</th><td>Friedman, S. M., & Margo, C. E. (2000). Choroidal neovascular membranes: reproducibility of angiographic interpretation. American journal of ophthalmology, 130(6), 839-841.</td></tr>
<tr><td></td><td>Comorbidities affecting the eye (e.g. cataracts)
Current or previous treatment</td></tr>
<tr><td>Inclusion Criteria</td><td>• Fluorescein angiograms of choroidal neovascular membranes
• No other clear inclusion criteria</td></tr>
<tr><td>Exclusion Criteria</td><td>• Unclear</td></tr>
<tr><td>Tests</td><td>High-quality fluorescein angiograms (nonstereoscopic films) of choroidal neovascular membranes in age-related macular degeneration were reviewed by 21 ophthalmologists with fellowship training in retinal disease.</td></tr>
<tr><td>Methods</td><td>Participants were told that on clinical examination all patients had findings of exudative macular degeneration and were asked to identify the type of neovascular membrane as classic only, occult only, mixed, or unable to determine;

A total of 122 angiograms were read (96.8%); four angiograms could not be interpreted by two observers.</td></tr>
<tr><td>Results</td><td>
<table>
<tr><th>Case number</th><th>Membrane type % agreement</th><th>Kappa agreement</th></tr>
<tr><td>1</td><td>100</td><td>1</td></tr>
<tr><td>2</td><td>73</td><td>0.65</td></tr>
<tr><td>3</td><td>25</td><td>0.01</td></tr>
<tr><td>4</td><td>82</td><td>0.76</td></tr>
<tr><td>5</td><td>82</td><td>0.76</td></tr>
<tr><td>6</td><td>73</td><td>0.65</td></tr>
<tr><td>Mean (standard deviation)</td><td>72.5 (23.0)</td><td>0.64 (0.30)</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	Olsen, T. W., Feng, X., Kasper, T. J., Rath, P. P., & Steuer, E. R. (2004). Fluorescein angiographic lesion type frequency in neovascular age-related macular degeneration. Ophthalmology, 111(2), 250-255.
Country/ies where the study was carried out	USA
Study type	Retrospective cohort
Aim of the study	To assess the frequency of lesion types using fluorescein angiography (FA) in neovascular age-related macular degeneration (nAMD).
Study dates	Published 2004
Source of funding	Minnesota Lions Macular Degeneration Research and Rehabilitation Center, Research to Prevent Blindness
Sample size	200 cases of nAMD from university-based, tertiary retinal referral practice and one comprehensive, and a community-based eye clinic (100 from each center).
Characteristics	Gender: Female: 135 (68%) Male: 65 (32%) Race: Caucasian: 132 (66%) N/A: 68 (24)

Bibliographic reference	**Olsen, T. W., Feng, X., Kasper, T. J., Rath, P. P., & Steuer, E. R. (2004). Fluorescein angiographic lesion type frequency in neovascular age-related macular degeneration. Ophthalmology, 111(2), 250-255.**
	Age (yrs), Mean: 78 ± 8 years The study did not report characteristics for the following variables: Visual acuity AMD disease stage Comorbidities affecting the eye (e.g. cataracts) Current or previous treatment
Inclusion Criteria	• Angiograms were cataloged on electronic files, these were randomly searched for either “nAMD” or “choroidal neovascularization,” • Fluorescein angiograms (n=100) from the CC were selected by reviewing the film-based files alphabetically (patient last names beginning with the letter A and selecting consecutive cases through M), until 100 cases of nAMD were identified from a total of 430 angiograms reviewed
Exclusion Criteria	• Atrophic AMD alone • Evidence of any other major retinal disorder • Quality of the FA was inadequate to interpret. • Prior PDT or transpupillary hermotherapy.
Tests	Fluorescein Angiograms cataloged on electronic files or film based fluorescein angiograms, depending upon the centre at which the investigations were collected.
Methods	Two graders reviewed the stereoscopic FAs and color fundus photographs and documented the lesion type. Determination of lesion type was based on agreement by 2 graders. When there was disagreement regarding the angiograms, they were

Bibliographic reference	Olsen, T. W., Feng, X., Kasper, T. J., Rath, P. P., & Steuer, E. R. (2004). Fluorescein angiographic lesion type frequency in neovascular age-related macular degeneration. Ophthalmology, 111(2), 250-255.
	rereviewed by both graders simultaneously, and a consensus determination was made. Clinical history was not available during the angiographic evaluation. Lesion location, size, type, subtype, and PDT eligibility were documented for each angiogram. Graders were required to determine whether the nAMD lesion was predominantly classic (area of the entire lesion was 50% classic) or minimally classic (area of the classic component was 50% of the entire lesion). The senior grader subcategorized the lesion subtype of occult subfoveal nAMD. A measurement of intergrader agreement (kappa) was calculated for the graders. The definition of lesion type was based on the definitions of the Macular Photocoagulation Study Group. Occult lesions were either fibrovascular pigment epithelial detachments or late leakage of undetermined source was also defined by the Macular Photocoagulation Study Group.
Results	The kappa score between graders was 0.63.
Limitations	Since there was no quality assessment tool available for validation studies, the following review of bias tool for diagnostic cross-sectional studies was used and adapted accordingly: QUADAS 2 QUADAS website. DOMAIN 1: PATIENT SELECTION A. Risk of Bias Methods of patient selection: Was a consecutive or random sample of patients enrolled? A random sample was taken from one centre and a non-random alphabetical based sample was taken from the community based centre. Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Unclear what was done for participants with PCV

Bibliographic reference	Olsen, T. W., Feng, X., Kasper, T. J., Rath, P. P., & Steuer, E. R. (2004). Fluorescein angiographic lesion type frequency in neovascular age-related macular degeneration. Ophthalmology, 111(2), 250-255.
	Could the selection of patients have introduced bias? RISK: Unclear, not enough information provided regarding baseline characteristics of included participants, many important characteristics were not reported. Also in one of the centres samples were chosen with inadequate randomisation (alphabetical) B. Concerns regarding applicability Is there concern that the included patients do not match the review question? CONCERN: MODERATE- non-random selection, unclear status of PCV. DOMAIN 2: INDEX TEST(S) A. Risk of Bias Describe the index test and how it was conducted and interpreted: Were the index test results interpreted without knowledge of the results of the reference standard? Unclear if grading was done without knowledge of other graders decisions. If a threshold was used, was it pre-specified? Yes and cited (MPS) Could the conduct or interpretation of the index test have introduced bias? NA- the purpose of this study is to assess how interpretation may differ between graders. B. Concerns regarding applicability Is there concern that the index test, its conduct, or interpretation differ from the review question? CONCERN: MODERATE DOMAIN 3: REFERENCE STANDARD- NA (same as index test) DOMAIN 4: FLOW AND TIMING A. Risk of Bias Was there an appropriate interval between index test(s) and reference standard? Yes Did all patients receive a reference standard? Yes Did patients receive the same reference standard? no (some participants were graded based on FA photographs, others on electronic FA photographs) Were all patients included in the analysis? Yes Could the patient flow have introduced bias? RISK: MODERATE

Bibliographic reference	**Holz, F. G., Jorzik, J., Schutt, F., Flach, U., & Unnebrink, K. (2003). Agreement among ophthalmologists in evaluating fluorescein angiograms in patients with neovascular age-related macular degeneration for photodynamic therapy eligibility (FLAP-study). Ophthalmology, 110(2), 400-405.**
Country/ies where the study was carried out	USA
Study type	Prospective cohort
Aim of the study	To determine intraobserver and interobserver variation for classifying types of choroidal neovascularizations (CNV) in exudative age-related macular degeneration (ARMD).
Study dates	Published 2003
Source of funding	The State of Baden-Wurttemberg grant
Sample size	40 patients with neovascular ARMD, graded by 16 retinal specialists.
Characteristics	The study did not report characteristics for the following variables: Ethnic group Age Gender Visual acuity AMD disease stage Comorbidities affecting the eye (e.g. cataracts) Current or previous treatment
Inclusion Criteria	• Neovascular AMD

Bibliographic reference	**Holz, F. G., Jorzik, J., Schutt, F., Flach, U., & Unnebrink, K. (2003). Agreement among ophthalmologists in evaluating fluorescein angiograms in patients with neovascular age-related macular degeneration for photodynamic therapy eligibility (FLAP-study). Ophthalmology, 110(2), 400-405.**
Exclusion Criteria	• No exclusion criteria reported
Tests	Digital high-quality fluorescein angiographies from 40 patients with exudative ARMD were obtained using a confocal scanning laser ophthalmoscope (Heidelberg Retina Angiograph, Heidelberg, Germany). From each angiographic series four to six angiograms were selected with angiograms from early, mid, and late phase. These were printed on one page per patient, and two folders were put together with all 40 angiogram sheets in two different randomized sequences.
Methods	The angiograms of both series were presented to 16 retina specialists who are members of the European Fluorescein Angiography Club (FAN-Club) during a meeting in Lyon, France, in December 2000. After instructions on how to use the evaluation form, readers were not allowed to discuss their interpretation with each other or with the investigators present. All 40 angiogram sheets were organised in two different randomized sequences (series A and B). Each reader had to classify membrane type into classic, occult, or mixed with classic component less or equal/greater than 50%. After completing the classification of series A, the reader was not allowed to return to the evaluation sheet or the angiogram folder when going through series B. As a measure of intraobserver variability, a coefficient for agreement between classification of angiograms in series A and in series B was calculated for each reader. For the assessment of interobserver variability, pair wise coefficients were calculated between all readers, and were given for series A and series B, respectively.
Results	Intraobserver variability (i.e., the agreement between classification of angiograms in series A and in series B by a single reader) Mean kappa: 0.64 (SD 0.11) Interobserver agreement

Bibliographic reference	**Holz, F. G., Jorzik, J., Schutt, F., Flach, U., & Unnebrink, K. (2003). Agreement among ophthalmologists in evaluating fluorescein angiograms in patients with neovascular age-related macular degeneration for photodynamic therapy eligibility (FLAP-study). Ophthalmology, 110(2), 400-405.**
	Mean pairwise kappa coefficient was 0.40 ± 0.05 (series A) and 0.37 ± 0.05 (series B), (indicating less than moderate mean pair wise agreement)
Limitations	Since there was no quality assessment tool available for validation studies, the following review of bias tool for diagnostic cross-sectional studies was used and adapted accordingly: QUADAS 2 QUADAS website. DOMAIN 1: PATIENT SELECTION A. Risk of Bias Methods of patient selection: Was a consecutive or random sample of patients enrolled? Unclear how sample was selected Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Unclear Could the selection of patients have introduced bias? RISK: Unclear B. Concerns regarding applicability Is there concern that the included patients do not match the review question? CONCERN: UNCLEAR DOMAIN 2: INDEX TEST(S) A. Risk of Bias Describe the index test and how it was conducted and interpreted: Were the index test results interpreted without knowledge of the results of the reference standard? Grading was done without knowledge of other graders decisions. If a threshold was used, was it pre-specified? Unclear Could the conduct or interpretation of the index test have introduced bias? NA- the purpose of this study is to assess how interpretation may differ between graders. B. Concerns regarding applicability Is there concern that the index test, its conduct, or interpretation differ from the review question?

Bibliographic reference	**Holz, F. G., Jorzik, J., Schutt, F., Flach, U., & Unnebrink, K. (2003). Agreement among ophthalmologists in evaluating fluorescein angiograms in patients with neovascular age-related macular degeneration for photodynamic therapy eligibility (FLAP-study). Ophthalmology, 110(2), 400-405.**
	CONCERN: UNCLEAR (no criteria defined) DOMAIN 3: REFERENCE STANDARD- NA (same as index test) DOMAIN 4: FLOW AND TIMING A. Risk of Bias Was there an appropriate interval between index test(s) and reference standard? Yes Did all patients receive a reference standard? Yes Did patients receive the same reference standard? Unclear Were all patients included in the analysis? Unclear Could the patient flow have introduced bias? RISK: UNCLEAR

Bibliographic reference	**Brader, H. S., Ying, G. S., Martin, E. R., & Maguire, M. G. (2011). New grading criteria allow for earlier detection of geographic atrophy in clinical trials. Investigative ophthalmology & visual science, 52(12), 9218-9225.**
Country/ies where the study was carried out	USA
Study type	Retrospective cohort
Aim of the study	To evaluate new grading criteria for geographic atrophy (GA), as detected by annual stereoscopic color fundus photographs and fluorescein angiograms, and to assess whether application of the revised criteria provides earlier identification of GA than previous criteria involving only color fundus photography.
Study dates	Published 2011

Bibliographic reference	**Brader, H. S., Ying, G. S., Martin, E. R., & Maguire, M. G. (2011). New grading criteria allow for earlier detection of geographic atrophy in clinical trials. Investigative ophthalmology & visual science, 52(12), 9218-9225.**
Source of funding	National Eye Institute, National Institutes of Health, Department of Health and Human Services; an unrestricted grant from Research to Prevent Blindness, and a grant from the Doris Duke Charitable Foundation
Sample size	A random set of 25 photographs was independently regraded by both the original grader and senior to CAPT reading centre grader to assess intra grader agreement
Characteristics	The study did not report characteristics for the following variables: Ethnic group Age Gender Visual acuity AMD disease stage Comorbidities affecting the eye (e.g. cataracts) Current or previous treatment
Inclusion Criteria	• Geographic atrophy
Exclusion Criteria	• At baseline—if the length of time that a GA lesion had been present could not be accurately assessed • The final visit—if the presence of GA could not be confirmed on later images, which might skew the false-positive rate. • If any annual images were missing or unsuitable for grading due to inadequate photo quality.
Tests	Grading was 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 drusen that are associated with early atrophic changes.)

Bibliographic reference	**Brader, H. S., Ying, G. S., Martin, E. R., & Maguire, M. G. (2011). New grading criteria allow for earlier detection of geographic atrophy in clinical trials. Investigative ophthalmology & visual science, 52(12), 9218-9225.**
Methods	Photographic sets for each patient were graded sequentially. Candidate areas of GA were identified from stereoscopic color films viewed on a light box. For each atrophic area, the presence or absence of five features (visible choroidal vessels, sharp edges, circular shape, excavation, and depigmentation) was noted based on the color photographs. Similarly, film negatives of fluorescein angiograms were reviewed for candidate areas of GA, and the presence or absence of three features (sharp borders, visible choroidal vessels, and excavation) was noted for each candidate area. Final determination of whether a candidate lesion constituted GA was based on the combined features from the color fundus photographs and fluorescein angiograms. Size and shape were not used as criteria in this revised GA definition. Each area of GA was assessed independently from other areas when GA was multifocal in a given fundus image. Year 0 was assigned to the first year in which a specific GA lesion was detected in an eye, and that may or may not have been the first year in which any GA was detected in that eye. Each GA lesion was assigned an identification number, for monitoring changes over time. Monitoring involved classifying each lesion as new (not present at previous visit), previously detected, or merged (formed from two or more previously distinct atrophic areas), as well as tracking the characteristic features present on CFP and FA over time. A sample of 15 photographic sets, some of which included lesions that met the new criteria but not the previously used criteria, was reviewed by the CAPT study chair. In all instances, he confirmed the presence or absence of GA from a clinical perspective. Six months after the initial grading with the revised criteria, a random sample of 25 photographs was independently regraded by both the original grader (HSB) and a senior CAPT reading center grader (ERM), to assess inter- and intragrader agreements.
Results	Interobserver variability kappa: 0.536 Intraobserver agreement kappa: 0.845
Limitations	Since there was no quality assessment tool available for validation studies, the following review of bias tool for diagnostic cross-sectional studies was used and adapted accordingly:

Bibliographic reference	Brader, H. S., Ying, G. S., Martin, E. R., & Maguire, M. G. (2011). New grading criteria allow for earlier detection of geographic atrophy in clinical trials. Investigative ophthalmology & visual science, 52(12), 9218-9225.
	QUADAS 2 QUADAS website. DOMAIN 1: PATIENT SELECTION A. Risk of Bias Methods of patient selection: Was a consecutive or random sample of patients enrolled? Yes (random) Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Unclear Could the selection of patients have introduced bias? RISK: Unclear (status of PCV etc) B. Concerns regarding applicability Is there concern that the included patients do not match the review question? CONCERN: UNCLEAR DOMAIN 2: INDEX TEST(S) A. Risk of Bias Describe the index test and how it was conducted and interpreted: Were the index test results interpreted without knowledge of the results of the reference standard? Yes Grading was done without knowledge of other graders decisions. If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? NA- the purpose of this study is to assess how interpretation may differ between graders. B. Concerns regarding applicability Is there concern that the index test, its conduct, or interpretation differ from the review question? CONCERN: LOW DOMAIN 3: REFERENCE STANDARD- NA (same as index test) DOMAIN 4: FLOW AND TIMING A. Risk of Bias Was there an appropriate interval between index test(s) and reference standard? Yes

Bibliographic reference	Brader, H. S., Ying, G. S., Martin, E. R., & Maguire, M. G. (2011). New grading criteria allow for earlier detection of geographic atrophy in clinical trials. Investigative ophthalmology & visual science, 52(12), 9218-9225.
	Did all patients receive a reference standard? Yes Did patients receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? RISK: LOW

Bibliographic reference	Maguire, M. G., Alexander, J., Fine, S. L., & Complications of Age-related Macular Degeneration Prevention Trial (CAPT) Research Group. (2008). Characteristics of choroidal neovascularization in the complications of age-related macular degeneration prevention trial. Ophthalmology, 115(9), 1468-1473.
Country/ies where the study was carried out	USA
Study type	Retrospective cohort
Aim of the study	To describe the characteristics of incident choroidal neovascularisation in observed and treated eyes in the CAPT trial
Study dates	Published 2008
Source of funding	National Eye Institute, National Institutes of Health, Department of Health and Human Services;
Sample size	282 eyes of 225 patients developed choroidal neovascularisation from a total of 1052 recruited participants. A weighted sample of eyes with and without CNV or SPED was selected for regrading. All photographic images were regraded independently by 2 readers who later openly discussed their discrepancies to arrive at consensus.
Characteristics	Visual acuity (%)

Bibliographic reference	**Maguire, M. G., Alexander, J., Fine, S. L., & Complications of Age-related Macular Degeneration Prevention Trial (CAPT) Research Group. (2008). Characteristics of choroidal neovascularization in the complications of age-related macular degeneration prevention trial. Ophthalmology, 115(9), 1468-1473.**
	20/12- 20/40- 68.7% 20/50- 20/160- 26.8% 20/200- <20/400- 4.5% The study did not report characteristics for the following variables: Ethnic group AMD disease stage Age Gender Comorbidities affecting the eye (e.g. cataracts) Current or previous treatment
Inclusion Criteria	• >= 10 large drusen within 3000 um of the centre of the macula • Visual acuity >= to 20/40
Exclusion Criteria	• Evidence of CNV, serous retinal pigment detachment, geographic atrophy >1MPS disc area in size • Geographic atrophy of any size within 500 um of the foveal centre • Any condition likely to affect visual acuity within the next 5 years
Tests	Grading was based on features observed in the stereoscopic colour fundus photographs and fluorescein angiograms. Choroidal neovascularisation was considered present when there was an expansion or persistant staining of an area of hyperflourescence as the time increased from injection of dye on fluorescein angiography. A SPED was considered present when there was a uniform, smooth elevation of the retinal pigment epithelium with sharply demarcated, fairly uniform, early hyperflourescence that persisted into the late phase of the angiogram.

Bibliographic reference	**Maguire, M. G., Alexander, J., Fine, S. L., & Complications of Age-related Macular Degeneration Prevention Trial (CAPT) Research Group. (2008). Characteristics of choroidal neovascularization in the complications of age-related macular degeneration prevention trial. Ophthalmology, 115(9), 1468-1473.**
	Classic CNV: An area of choroidal hyperfluorescence with well demarcated boundaries that could be discerned in the early phase of the angiogram and Progressive pooling of dye leakage in the overlying subsensory retinal space that usually obscures the boundaries of the CNV in the late phase Occult: An area of stippled hyperflourescence appeared within 5 minutes Persistent staining or pooling of dye by 10 minutes.
Methods	All photographic images described were graded independently by 2 trained readers in the CAPT reading centre. The readers openly discussed their discrepencies to arrive at consensus. Unresolved differences were reviewed by either the reading centre director or principle investigator. A weighted sample of eyes with and without CNV or SPED was selected for regrading. All photographic images were regraded independently by 2 readers who later openly discussed their discrepancies to arrive at consensus.
Results	Interobserver variability Agreement: 80-100% Weighted kappa: 0.75-100
Limitations	Since there was no quality assessment tool available for validation studies, the following review of bias tool for diagnostic cross-sectional studies was used and adapted accordingly: QUADAS 2 QUADAS website. DOMAIN 1: PATIENT SELECTION A. Risk of Bias Methods of patient selection: Was a consecutive or random sample of patients enrolled? Yes (random) Was a case-control design avoided? Yes

Bibliographic reference	**Maguire, M. G., Alexander, J., Fine, S. L., & Complications of Age-related Macular Degeneration Prevention Trial (CAPT) Research Group. (2008). Characteristics of choroidal neovascularization in the complications of age-related macular degeneration prevention trial. Ophthalmology, 115(9), 1468-1473.**
	Did the study avoid inappropriate exclusions? Unclear Could the selection of patients have introduced bias? RISK: Unclear (status of PCV, no baseline characteristic reported for the grading sample) B. Concerns regarding applicability Is there concern that the included patients do not match the review question? CONCERN: UNCLEAR DOMAIN 2: INDEX TEST(S) A. Risk of Bias Describe the index test and how it was conducted and interpreted: Were the index test results interpreted without knowledge of the results of the reference standard? Yes grading was done without knowledge of other graders decisions. If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? NA- the purpose of this study is to assess how interpretation may differ between graders. B. Concerns regarding applicability Is there concern that the index test, its conduct, or interpretation differ from the review question? CONCERN: LOW DOMAIN 3: REFERENCE STANDARD- NA (same as index test) DOMAIN 4: FLOW AND TIMING A. Risk of Bias Was there an appropriate interval between index test(s) and reference standard? Yes Did all patients receive a reference standard? Yes Did patients receive the same reference standard? Yes Were all patients included in the analysis? Unclear Could the patient flow have introduced bias? RISK: Unclear