E.3 Diagnosis

E.3.1 Signs and symptoms of AMD

RQ1: What signs and symptoms should prompt a healthcare professional to suspect AMD in people presenting to healthcare services?

Bibliographic reference	Hessellund,A., Larsen,D.A., Bek,T., The predictive value of subjective symptoms and clinical signs for the presence of treatment-requiring exudative age-related macular degeneration, Acta ophthalmologica, 90, 471-475, 2012
Country/ies where the study carried out	Denmark
Aim of the study	The introduction of vascular endothelial growth factor inhibitors for the treatment of exudative age-related macular degeneration (AMD) has increased the referral rates of AMD patients with visual symptoms to treating centres considerably. However, a large proportion of the referred patients do not qualify for treatment implying that considerable resources could be saved if these patients could be identified on the basis of the clinical data available in the referring nonspecialized setting. This study sought to find the association between said clinical data and treatable choroidal neovascularisation.
Study type	Prospective cohort study
Study dates	Published 2012
Source of funding	VELUX foundation
Sample size	1,683 consecutive patients
Inclusion Criteria	All patients referred to the AMD clinic at the Department of Ophthalmology, Arhus University Hospital between 1 January 2007 and 31 October 2009.
Exclusion Criteria	None described
Diagnostic criteria	The patients underwent structured interviewing to record the time of occurrence and the duration of the following symptoms: blurred vision, central dark spot, metamorphopsia, micropsia, and dyschromatopsia.
Patient characteristics	Study did not report baseline characteristics for ethnic group, age, gender, visual acuity, refractive myopia, AMD disease stage, Comorbidities affecting the eye (e.g. cataracts) or other co-morbidities. Visual acuity (ETDRS steps ± SD) was 57.4 ± 16.7 in the treatment group and 63.1 ± 20.8 in the non-treatment group
Methods	The clinical examination consisted of a measurement of the visual acuity using ETDRS charts and fundoscopy of the retina using a 90-D lens to identify central macular oedema, retinal haemorrhages, and exudates. In all patients, an OCT scanning

<table>
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<tr><td></td><td>(Top-con 3D OCT-1000; Topcon Inc, Paramus, NJ, USA) was carried out. When macular oedema was present, a fluorescein angiography was performed using a Canon CF-1 angiography system. The angiography was analysed by a senior consultant to classify the patients as having classic, predominantly classic, minimally classic, or occult subretinal neovascularization, or none of these alternatives. In case of discrepant opinions about the interpretation of the angiography, the opinion of the most experienced consultant in the clinic was followed.
Treatable Neovascularisation:
In cases with overt or suspected subretinal neovascularization, intravitreal injection of VEGF inhibitor was commenced. Patients with visual acuity below 0.05 and with significant preretinal fibrosis are excluded from treatment. In the remaining patients, OCT is performed to exclude patients with no signs of retinal oedema. The remaining patients are subjected to fluorescein angiography, and cases with early leakage because of overt or suspected subretinal neovascularization are included for treatment.</td></tr>
<tr><td>Results</td><td>Blurred Vision
<table>
<tr><td></td><td>REFERENCE test result</td><td></td></tr>
<tr><td>INDEX test result</td><td>+ve for target condition</td><td>-ve for target condition</td></tr>
<tr><td>+ve for target condition</td><td>462</td><td>834</td></tr>
<tr><td>-ve for target condition</td><td>94</td><td>293</td></tr>
</table>
Sensitivity = 0.831
Specificity = 0.260
PPV = 0.356
NPV = 0.757
Diagnostic accuracy = 0.449

Central Dark Spot
<table>
<tr><td></td><td>REFERENCE test result</td><td></td></tr>
<tr><td>INDEX test result</td><td>+ve for target condition</td><td>-ve for target condition</td></tr>
</table></td></tr>
</table>

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+ve for target condition	257	360
-ve for target condition	299	767

Sensitivity = 0.462
Specificity = 0.681
PPV = 0.417
NPV = 0.720
Diagnostic accuracy =0.608

Metamorphosia

	REFERENCE test result	
INDEX test result	+ve for target condition	-ve for target condition
+ve for target condition	282	452
-ve for target condition	274	675

Sensitivity = 0.507
Specificity = 0.599
PPV = 0.384
NPV = 0.711
Diagnostic accuracy = 0.569

Micropsia

	REFERENCE test result	
INDEX test result	+ve for target condition	-ve for target condition
+ve for target condition	54	124

Bibliographic reference	Hessellund,A., Larsen,D.A., Bek,T., The predictive value of subjective symptoms and clinical signs for the presence of treatment-requiring exudative age-related macular degeneration, Acta ophthalmologica, 90, 471-475, 2012

-ve for target condition	502	1003

Sensitivity = 0.097
Specificity = 0.890
PPV = 0.303
NPV = 0.666
Diagnostic accuracy = 0.628

Dyschromatopsia

	REFERENCE test result	
INDEX test result	+ve for target condition	-ve for target condition
+ve for target condition	102	128
-ve for target condition	454	999

Sensitivity = 0.183
Specificity = 0.886
PPV = 0.443
NPV = 0.688
Diagnostic accuracy = 0.654

Sudden Onset

	REFERENCE test result	
INDEX test result	+ve for target condition	-ve for target condition
+ve for target condition	200	310
-ve for target condition	356	817

<table>
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<tr><td></td><td>Sensitivity = 0.360
Specificity = 0.725
PPV = 0.392
NPV = 0.697
Diagnostic accuracy = 0.604

Worsening of symptoms
<table><tr><td></td><td>REFERENCE test result</td><td></td></tr><tr><td>INDEX test result</td><td>+ve for target condition</td><td>-ve for target condition</td></tr><tr><td>+ve for target condition</td><td>343</td><td>606</td></tr><tr><td>-ve for target condition</td><td>213</td><td>521</td></tr></table>Sensitivity = 0.617
Specificity = 0.462
PPV = 0.361
NPV = 0.710
Diagnostic accuracy = 0.513</td></tr>
<tr><td>Limitations</td><td>QUADAS 2 diagnostic study checklist

DOMAIN 1: PATIENT SELECTION
A. Risk of Bias Methods of patient selection:
Was a consecutive or random sample of patients enrolled? Consecutive
Was a case-control design avoided? Yes
Did the study avoid inappropriate exclusions? Yes
Could the selection of patients have introduced bias? RISK: LOW</td></tr>
</table>

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	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 Were the index test results interpreted without knowledge of the results of the reference standard? Unclear If a threshold was used, was it pre-specified? Unclear Could the conduct or interpretation of the index test have introduced bias? Unclear B. Concerns regarding applicability Is there concern that the index test, its conduct, or interpretation differ from the review question? CONCERN: HIGH: Unclear definitions DOMAIN 3: REFERENCE STANDARD Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unclear (unlikely) Could the reference standard, its conduct, or its interpretation have introduced bias? RISK: LOW B. Concerns regarding applicability Is there concern that the target condition as defined by the reference standard does not match the review question? CONCERN: HIGH - People defined as not being treatable for neovascular AMD included those with visual acuity below 0.05 and with significant pre-retinal fibrosis, also the patients excluded from treatment in this study represented a heterogeneous group of fundus morphologies, including both atrophic AMD, pigment epithelial detachment alone, and exudative AMD with severe visual loss and/or signs of irreversible retinal damage. DOMAIN 4: FLOW AND TIMING A. Risk of Bias Was there an appropriate interval between index test(s) and reference standard? Unclear Did all patients receive a reference standard? Yes (same flow of tests) Did patients receive the same reference standard? Yes (same flow of tests) Were all patients included in the analysis? Yes