Non-invasive testing for early detection of neovascular macular degeneration in unaffected second eyes of older adults: EDNA diagnostic accuracy study

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Scientific summary

EDNA diagnostic accuracy study

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Scientific summary

Background

Wet or neovascular age-related macular degeneration (nAMD) is a leading cause of sight loss in older people. In nAMD, abnormal vessels arising from the choroidal vasculature/retinal circulation can leak fluid and whole blood, distorting the architecture of the neurosensory retina and adjacent tissue layers. This results in severe visual disturbances and, if left untreated, permanent vision loss. At onset, symptoms may be absent or subtle depending on the location of the nAMD lesion. Managing nAMD presents an enormous burden to the NHS. Ophthalmology accounts for 10% (5 million per year) of all NHS outpatient attendances, and age-related macular degeneration (AMD) accounts for 15% of all ophthalmology attendances.

Biological therapies targeting vascular endothelial growth factor (VEGF) are available to stop leakage into the macula in nAMD. The drugs are given as injections into the eye and require multiple visits, usually every 8 weeks, alongside an assessment to check if more treatment is required. It is usual practice to monitor the second eye, which is at very high risk of developing nAMD. The test that can confirm the diagnosis of nAMD is fundus fluorescein angiography (FFA). FFA is an invasive test, albeit with a low risk of severe anaphylaxis and death. Advances in imaging have resulted in newer technologies that are non-invasive and can provide information to make a diagnosis of nAMD. Therefore, we included a portfolio of pragmatic and simple tests of function and morphology to test against the gold standard of FFA in the second eye of persons with nAMD in one eye.

Objectives

The primary objective was to determine the diagnostic monitoring performance (sensitivity and specificity) of five index tests for diagnosing nAMD against a primary reference standard of FFA determination of conversion to nAMD in the second eye [Early Detection of Neovascular Age-related macular degeneration (EDNA) study eye] of patients with confirmed nAMD in the first eye. The index tests were:

- Amsler test – participants self-check onset of distortion using the Amsler chart
- fundus clinical examination – clinical evaluation of the fundus for signs of nAMD
- optical coherence tomography (OCT) – clinical assessment of images captured on an OCT scan
- self-reported vision – participants subjective assessment of their vision
- visual acuity – Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity.

The secondary objectives were to (1) develop an economic model to identify an optimal monitoring regime, (2) develop a risk prediction model using baseline characteristics to predict the development of nAMD in the EDNA study eye and (3) create a cohort (including Biobank) for future studies.

Methods

Diagnostic study

The EDNA study was a multicentre, prospective, cohort diagnostic accuracy study testing five index tests in a monitoring setting. At recruitment (baseline), participants had a diagnosis of nAMD in the first-presenting eye and no active nAMD the second eye (designated the EDNA study eye).

After enrolment, both eyes of participants were monitored in each clinical site for up to 3 years or until onset of nAMD in the study eye.

Clinical sites monitored and reviewed patient attendance records and collected data on index tests that were carried out in the EDNA study eye. Clinical care teams were instructed to request FFA if any of the index tests were positive (a trigger) for nAMD. In the absence of a trigger, planned study visits were undertaken at 18 months or at study exit, which occurred after a minimum of 30 months of follow-up, at which a detailed clinical assessment and retinal imaging that included FFA were performed.

Participants

The participants were patients with nAMD in the first-presenting eye and a second eye unaffected by nAMD at baseline (EDNA study eye).

Inclusion criteria

Patients who were aged $\geq$ 50 years with newly diagnosed nAMD (with diagnostic FFA performed within 6 weeks prior to consent) in one eye and the second eye free of nAMD, and who were about to commence or had recently commenced anti-VEGF therapy in the first eye, were included in the study.

Exclusion criteria

Exclusion criteria for the study eye were nAMD detected at baseline, presenting visual acuity worse than 68 letters and retinal pathology that can confound subsequent assessments. Other criteria were not undergoing regular monitoring, an inability to give informed consent, an inability to undergo FFA and patients in whom diagnostic FFA was carried out more than 6 weeks prior to enrolment.

Reference standard

The primary reference standard was FFA determination of conversion to nAMD in the study eye at the clinical site by an experienced clinician. Secondary reference standards were ophthalmic reading centre confirmation of diagnosis of nAMD and a clinical determination of conversion to nAMD (with or without FFA).

Definition of positive index test

- Amsler test: as assessed by the clinician, appearance of a new area of distortion in the Amsler chart or regions in which the grid pattern disappears when previously no distortion was present (this test was included for a participant only if the test result was negative at baseline).
- Fundus clinical examination: slit-lamp biomicroscopy or fundus photography showing clinical signs of nAMD on the fundus, as determined by an expert.
- OCT: abnormal findings that are indicative of nAMD.
- Self-reported vision: patients' subjective assessment of their vision being 'much worse' than the previous visit on a patient questionnaire.
- Visual acuity: drop of $\leq$ 10 letters in best corrected visual acuity from baseline.

Outcomes

The outcomes were sensitivity and specificity, performance of risk predictor algorithm, costs and quality-adjusted life-years (QALYs).

Sample size

The sample size calculation was based on McNemar's test. At a two-sided 5% significance level and 90% power, a paired difference in sensitivity of 15% (80% to 65%) required 491 participants (560 participants allowing for indeterminate/missing data results), giving a cumulative incidence of 28% at 3 years, assuming a disagreement rate of 0.30.

Statistical analysis

Participants were classified as having progressed to nAMD, or not, with the diagnosis determined by the site clinician during the follow-up on FFA. In the main analysis, all repeated test assessments are combined to give a single index test result (e.g. any positive index test result prior to the last FFA conducted is treated as a positive). The secondary analyses considered the diagnostic performance of varying the definition of the reference standard, combining OCT with each of the other index tests and varying the definition of the time period in which a positive index test was recorded. Sensitivity and specificity were calculated for all analyses.

Prognostic model

A risk prediction model using Cox regression was developed to predict the development of nAMD in the EDNA study eye using baseline candidate predictors. The baseline variables were selected through discussion between the study clinicians and the statisticians. They included person-specific risk factors collected via a baseline clinical form (age, raised blood pressure, smoking history, cardiovascular disease, diabetes, sex, nutritional supplements, family history of age-related macular degeneration and body mass index), ocular variables in the EDNA study eye and ocular variables in the first-presenting eye (type of wet AMD, lesion size and severity of AMD). Predictive performance was assessed using Harrell's *c*-index.

Economic evaluation

A Markov microsimulation model was developed to assess the cost-effectiveness of using the alternative index tests in hospital outpatient eye services to monitor the second eye of people attending for the treatment of their first-presenting eye. The model focused on the second eye and was structured around disease status (no nAMD or nAMD), diagnosis status (undetected or detected), treatment status (untreated or treated) and visual acuity. The model incorporated data from the EDNA study, supplemented by external evidence to inform long-term treatment pathways and visual acuity outcomes. Visual acuity was linked to a health state utility score using a published equation. The costs of preconversion monitoring, subsequent treatment and monitoring, and severe visual impairment were incorporated in the model. The alternative tests were compared in terms of mean costs and QALYs in a full incremental analysis over a 25-year time horizon. Uncertainties surrounding key structural assumptions and parameter input sources were addressed using deterministic scenario analysis. Probabilistic sensitivity analysis was conducted for the model base case.

Results

Diagnostic study

Between June 2015 and March 2017, 578 participants from 24 NHS hospital eye services consented to take part in the EDNA study. Following consent, 16 participants were subsequently excluded because they had been consented in error (ineligible) and 10 participants withdrew consent to the use of their data during the EDNA study follow-up. The remaining 552 participants formed the EDNA monitoring cohort.

Never smokers accounted for around 40% of the cohort, half of the participants were former smokers (47%) and only a small proportion were current smokers (12%). Over half of the participants had a history of treated hypertension (53%) and just under one-quarter reported cardiovascular disease (22%). Approximately one-sixth of participants had diabetes (16%) and around one-third were taking nutritional supplements (30%). A family history of AMD was recorded in the majority of participants (85%).

Participants were, on average, 77 years old, and there was a higher proportion of women (57%). The average body mass index was 28 kg/m^2.

With respect to lens status in the study eye at baseline, 30% of participants had a clear lens, 20% were psuedophakic and half were phakic with cataract. Of study eyes with cataract, nuclear sclerosis was

seen in 89% and one-third had cortical and just under 10% had posterior subcapsular opacities. The mean visual acuity in the first-presenting eye (non-study eye) was 57 ± 5.4 ETDRS letters. The most common anti-VEGF agent initiated in the non-study eye was aflibercept (Eylea; Bayer AG, Leverkusen, Germany) (69%), with around 30% treated with ranibizumab (Lucentis; Genentech, Inc., South San Francisco, CA, USA). Less than 1% of eyes were treated with bevacizumab (Avastin; F. Hoffmann-La Roche AG, Basel, Switzerland).

The average number of clinic visits during follow-up was 15.6 (range 1 to 35). Among the participants who had were followed up, a positive Amsler test at baseline was recorded in 92 (17%).

During the study, 145 conversions to nAMD were detected, of which 120 were confirmed by FFA, yielding a crude conversion rate of 26% [95% confidence interval (CI) 22.3% to 30.6%], with a median follow-up time of 33 months (range 0.8–38.5 months).

Based on this cohort of 120 participants with a FFA-determined diagnosis of nAMD as the primary reference standard, the sensitivity of OCT was markedly better than that of all other tests (*Table a*).

Using the secondary reference standards, which included a clinician determination of conversion to nAMD with or without FFA ($n = 145$), or the reading centre-confirmed diagnosis of nAMD ($n = 460$), the highest sensitivity and specificity were observed consistently for OCT and OCT remained significantly superior to all other index tests.

Despite the fact that the specificity of fundus clinical examination and self-reported vision (which ranged from 97% to 99%) exceeded that of OCT, sensitivity was significantly lower and at an unacceptable level (consistently lower than 60% and 10% for each test, respectively).

The sensitivity and specificity of pair-wise combinations of OCT with each of the other index tests showed that, when either test was positive, sensitivity increased for most combinations, achieving 96% for OCT and visual acuity. However, specificity decreased for all combinations, except for OCT combined with fundus clinical examination. When the pair-wise combinations of tests were both required to be positive, sensitivity was markedly reduced for all combinations compared with that of OCT by itself.

In a prespecified subgroup analysis comparing choroidal neo-vascularisation (CNV) with the retinal angiomatous proliferation (RAP) subtype, OCT achieved 100% sensitivity in the detection of participants who developed the latter subtype of nAMD.

Prognostic modelling

Our final prediction model for onset of nAMD in the EDNA study eye included smoking status, family history of nAMD, presence of nodular drusen with or without RPD, and presence of pigmentary abnormalities. The *c*-statistic (discriminative ability) was only 0.66 (95% CI 0.62 to 0.71). This level of discriminative ability is lower than that observed in other cohorts that developed nAMD in the second eye.

TABLE a Index test sensitivity and specificity in the main analysis (with 95% confidence intervals)

Index test	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
Amsler	33.7 (25.1 to 43.5)	81.4 (76.4 to 85.5)
Fundus examination	53.8 (44.8 to 62.5)	97.6 (95.3 to 98.9)
OCT	91.7 (85.2 to 95.6)	87.8 (83.8 to 90.9)
Self-reported vision	4.2 (1.6 to 9.8)	97.0 (94.6 to 98.5)
Visual acuity	30.0 (22.5 to 38.7)	66.3 (61.0 to 71.1)

Economic evaluation

The results of the base-case economic analysis show that OCT is expected to generate the greatest number of QALYs per patient (OCT, 5.830; fundus, 5.787; Amsler chart, 5.736, self-reported vision, 5.630; and visual acuity, 5.600) for the lowest health-care and social care costs (OCT, £19,406; fundus, £19,649; Amsler chart, £19,751; self-reported vision, £20,198; and visual acuity, £20,444) over the lifetime of the simulated cohort. The increased treatment costs associated with the earlier detection with OCT were more than offset by reductions in costs associated with severe visual impairment. This was not true of less sensitive tests that resulted in greater visual acuity loss prior to detection and treatment. OCT was found to dominate the other tests or to have an incremental cost-effectiveness ratio (ICER) below accepted cost-effectiveness thresholds across the range of scenarios explored. The probabilistic sensitivity analysis indicated a high probability of OCT being cost-effective across a range of cost-effectiveness thresholds typically applied by NHS decision-making bodies.

Conclusions

Implications for health care

The EDNA study confirms that, among the test technologies investigated, OCT was the most accurate test for the diagnosis of the conversion to nAMD in the second eye of people with unilateral nAMD. Visual function measures (including a drop in visual acuity of 10 letters) have low accuracy in detecting onset of nAMD. Furthermore, patients' own perception of visual deterioration and the Amsler test had similarly poor sensitivity and specificity. These data have serious implications for guiding the way in which we observe patients during follow-up for treatment of nAMD in the first-presenting eye because it is routine clinical practice to instruct patients to be aware of and report the onset of symptoms in the second eye. In addition, self-completion of the Amsler test and visual acuity checks at clinic visits are established practices for monitoring the state of the second eye. The demonstration in the EDNA study that these cannot be relied on to consistently detect the onset of nAMD is a matter of concern and should be communicated to stakeholders, such as the relevant professional bodies and health commissioners and providers.

The economic modelling suggests that the use of OCT, compared with other available diagnostic tests, leads to a substantial reduction in the time from conversion to diagnosis of and treatment for nAMD in the second eye of patients being treated for nAMD in their first-presenting eye. Early initiation of treatment in the second eye, based on FFA-confirmed OCT-positive findings, can be expected to maintain better visual acuity and health-related quality of life over time than that of less sensitive monitoring strategies. Moreover, this strategy may be cost-saving in the long run compared with less sensitive monitoring strategies that result in greater visual acuity loss occurring before treatment is initiated.

Recommendations for research

1. The feasibility of using OCT for diagnosis and management of nAMD in a primary care or home monitoring setting should be investigated.
2. Further development of the risk prediction model including exploration of biomarkers and additional imaging characteristics should be undertaken.
3. Longer-term visual outcomes and subsequent treatment strategies for patients with nAMD need to be assessed.
4. Explore the role of artificial intelligence algorithms for improving the diagnosis and monitoring of nAMD.
5. Assess the performance of diagnostic tests for AMD in people aged > 70 years without AMD who are, therefore, at high risk of developing it.

Study registration

This study was registered as ISRCTN48855678.

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This report

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