Accuracy of fundus autofluorescence imaging for the diagnosis and monitoring of retinal conditions: a systematic review

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Scientific summary

FAF imaging for the diagnosis and monitoring of retinal conditions

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Background

Retinal conditions are diseases associated with the retina, that is, the part of the eye that collects light and converts it into electrical signals. They include, among others, age-related macular degeneration (AMD), central serous chorioretinopathy (CSC), inherited retinal dystrophies, diabetic retinopathy and cystoid macular oedema. Early identification of retinal conditions and disease stage is essential to allow prompt diagnosis, enabling timely treatment to prevent visual loss for treatable conditions such as neovascular AMD. However, for many retinal conditions it may be possible to reduce only the symptoms or slow disease progression, which can prolong the time during which affected people can continue their normal activities. Information about diagnosis is also important for patients, particularly regarding the prognosis and genetic risks of inherited eye disease. Developments in imaging techniques, particularly with the evolution of scanning laser ophthalmoscopes, have enabled more detailed inspection of the retina and provided less invasive tools to guide treatment and monitor the efficacy and safety of treatments. At the same time, advances in treatments for retinal conditions have increased the need for more accurate information on differential diagnosis and prognosis, so that treatment can be appropriately targeted. Fundus autofluorescence (FAF) imaging, based on scanning laser ophthalmoscopy, is a relatively new method that assesses retinal health by detecting changes in the natural fluorescence of the retina. The presence, absence and intensity of FAF can be affected by diseases of the retina, meaning that FAF imaging could aid in the diagnosis and/or monitoring of retinal conditions. However, the accuracy of the method for diagnosing and monitoring different retinal conditions is unclear.

Objectives

The aim of this project was to assess the accuracy of FAF imaging using confocal scanning laser ophthalmoscopy (cSLO) for the diagnosis and monitoring of retinal conditions. Specific research objectives were:

- for each retinal condition, to determine the diagnostic and monitoring accuracy of FAF imaging using cSLO, including monitoring of disease management
- to identify future research needs and develop research recommendations.

Methods

A review of evidence for the diagnostic and monitoring accuracy of FAF imaging for retinal conditions was undertaken systematically based on pre-specified inclusion criteria. Patients with any retinal condition were eligible, except malignancy, other ocular disease (e.g. glaucoma), or retinal trauma. Electronic databases searched included MEDLINE (via Ovid); MEDLINE In-Process & Other Non-Indexed Citations; EMBASE; The Cochrane Library; Web of Science; Database of Abstracts of Reviews of Effects; Health Technology Assessment database; and the Medion database of diagnostic accuracy studies. Internet pages of relevant organisations and meeting and trial registries were also searched, and reference lists of included studies and relevant systematic reviews were checked. All databases were searched from 1990 (approximately 10 years prior to the likely publication of the earliest relevant evidence) to November 2014 and searches were limited to the English language. The evidence synthesis and analysis followed good practice approaches, as recommended by the Centre for Reviews and Dissemination and the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy. Two reviewers independently screened the titles and abstracts of all bibliographic records identified against prespecified inclusion criteria. Full-text records were

obtained for those titles and abstracts that either appeared to meet the inclusion criteria or for which relevance was unclear, and these were screened against the prespecified eligibility criteria by one reviewer and checked by a second reviewer. Extraction of data from included studies was undertaken by one reviewer and checked by a second. Two reviewers independently assessed the risk of bias of the diagnostic studies using a modified version of the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) instrument. At all stages of the review, any disagreement between the two reviewers was resolved through discussion or, if necessary, arbitration by a third reviewer. Synthesis of included studies consisted of a structured narrative with tabulation of results. An advisory group comprising two independent clinical experts and a representative of a national charity supporting people with sight problems informed the review.

Results

Number and quality of studies

Searches identified 2240 bibliographic records, from which 206 full-text papers were obtained for further inspection; eight full-text papers reporting eight primary research studies were included in the systematic review. These eight studies all reported diagnostic accuracy of FAF imaging. No studies on the accuracy of FAF imaging for monitoring retinal conditions (i.e. monitoring progression or response to therapy) met the inclusion criteria. The diagnostic accuracy of FAF imaging was reported for choroidal neovascularisation in neovascular AMD in one study; for reticular pseudodrusen in three studies [in early AMD, geographic atrophy (GA) or neovascular AMD]; for cystoid macular oedema secondary to various conditions in two studies; and for diabetic macular oedema in two studies. The included studies have a number of limitations when assessed against the QUADAS criteria. Notably, the studies were considered to be at high (or in one case unclear) risk of spectrum bias (i.e. the patient population would not be representative of people presenting for retinal imaging in current NHS practice) and there are uncertainties around the relevance of the reference standards in most of the studies. Although the reference standards were not necessarily inappropriate, they were all single imaging tests, whereas in clinical practice diagnosis would more likely be based on combined information from several tests. In all studies the risk of clinical review bias was deemed unclear, as the information required to interpret FAF images was not reported.

Diagnostic outcomes

Meta-analysis of sensitivity and specificity of FAF imaging was considered inappropriate owing to the heterogeneity of the study populations, as well as the limited number of studies available for each retinal condition. Most included studies used an excitation wavelength of 488 nm and reported high sensitivity of FAF imaging (range 81–100%). However, sensitivity was lower in two studies that used longer excitation wavelengths: 32% in a study of reticular pseudodrusen in AMD using 790 nm; and 55% in a study of diabetic macular oedema using 514 nm. The specificity of FAF imaging across all studies ranged from 34% to 100% and was not clearly related to the excitation wavelength. However, owing to the relative paucity of reliable data, and limitations in experimental rigour, these diagnostic outcomes are subject to considerable uncertainty and may not accurately reflect the diagnostic accuracy of FAF imaging when applied in clinical practice. As such, none of the eight primary studies provides conclusive quantitative evidence for the diagnostic accuracy of FAF imaging in any of the four retinal conditions they examined. More robust studies would be helpful to quantify test accuracy and these should ideally be conducted to address clinical scenarios relevant to current NHS practice. There is currently no information available on the diagnostic or monitoring accuracy of FAF imaging for inherited retinal dystrophies (such as retinitis pigmentosa, Stargardt disease and rod–cone dystrophies), early AMD, AMD-related GA or CSC. These conditions were identified by the review advisory group as being where FAF imaging might potentially be most useful for assisting diagnosis or monitoring disease progression in NHS practice.

Discussion

Strengths of the evidence synthesis

The current review is based on a prespecified, peer-reviewed protocol. It included comprehensive literature searches in a wide variety of data sources undertaken by an experienced information specialist. The study selection and data extraction steps were pilot-tested and are based on prespecified worksheets, which are provided as appendices to this report. The primary evidence was assessed using prespecified and internationally accepted critical appraisal criteria for test accuracy studies. All studies excluded at the full-text screening step are listed in an appendix, stating the reasons for exclusion. All steps of the systematic review were carried out by at least two reviewers, to minimise the risks of errors and bias. An independent advisory group informed the review.

Limitations of the evidence synthesis

Interpretation of the primary research is hampered by clinical heterogeneity among the included studies and limitations in their methodological rigour. In some cases where studies included both eyes of patients in the analysis, intrasubject correlations may have led to underestimation of standard errors for diagnostic outcomes. This was not assessed quantitatively; however, it would not have markedly affected the overall conclusions. As prespecified in the protocol, searches were limited to evidence published in the English language.

Uncertainties

The extent of use of FAF imaging for diagnosing and/or monitoring retinal conditions in the NHS is not generally known, although the project's advisory group suggested specialists in the field of inherited retinal degeneration might already use FAF imaging routinely. The diagnostic accuracy of FAF imaging has been assessed only in primary research studies on four retinal conditions, and it remains unclear whether or not the technique would accurately diagnose other conditions, including the inherited retinal dystrophies, early AMD, GA and CSC. Numerous studies have monitored qualitatively the progression of retinal conditions or their response to therapy using FAF imaging, but it is unclear whether or not FAF imaging is accurate as a monitoring tool since no studies have formally assessed this quantitatively. A key limitation of the included studies is that none reported the clinical information necessary to interpret the FAF images, so it is unclear whether or not the interpretation in the studies would be consistent with how FAF images are interpreted in clinical practice.

Conclusions

It is not possible to give a clear indication of the diagnostic or monitoring accuracy of FAF imaging for retinal conditions based on existing research, even though FAF imaging appears to be already used in the NHS for diagnosing certain retinal conditions. Although some studies reported relatively high diagnostic sensitivity, these had various methodological limitations that hinder the interpretation of test accuracy. There is an indication that standard wavelength FAF imaging (488 nm) may be more sensitive than longer-wavelength approaches, but this is based on only two studies, involving 790-nm imaging for detecting reticular pseudodrusen and 514-nm imaging for detecting diabetic macular oedema. Owing to the relative paucity of reliable data, further studies are required. In particular, prospective studies are required in inherited retinal dystrophies, dry AMD, GA and CSC, and the studies should be designed according to the paradigm for the quantitative assessment of test accuracy.

Implications for service provision

Owing to a lack of studies addressing the appropriate populations and employing appropriate imaging methods it is unclear whether or not FAF imaging is accurate for the diagnosis and monitoring of retinal conditions in clinical practice.

Any future research into the accuracy of FAF imaging should consider whether FAF imaging is intended to supplement or replace existing imaging modalities. Given that FAF imaging is non-invasive, there might be benefits to patients and the NHS if FAF imaging could replace fluorescein angiography, which is the most frequently used invasive retinal imaging test, although fluorescein angiography would still be needed to assess some aspects of eye disease, for example perfusion. None of the studies included in the current review assessed patients' perceptions of the test procedures or reported whether or not the angiography reference standard was associated with any adverse events. Further evidence would therefore be required to clarify the magnitude of benefits or disadvantages to patients and the NHS of any switch from fluorescein angiography to FAF imaging.

Quality assessment of FAF imaging would be necessary to ensure consistency of diagnostic interpretation. The primary studies included in the systematic review provided no clear information on how this might be achieved. Although intergrader agreement for interpreting FAF images was good in three studies, this is difficult to extrapolate because of methodological limitations of the studies.

Suggested research priorities

- Prospective studies that conform to the paradigm for test accuracy assessments (i.e. which include a clearly specified population, index test, reference standard and diagnostic outcomes) would be helpful to evaluate the diagnostic accuracy of FAF imaging in the inherited retinal dystrophies, early AMD, GA and CSC.
- Prospective studies that conform to the paradigm for test accuracy assessments would be helpful to evaluate the accuracy of FAF imaging in monitoring the progression of retinal conditions and their response to therapy, alongside current best practice, for the inherited retinal dystrophies, early AMD, GA and CSC.
- Future test accuracy studies for FAF imaging should:
    - recruit participants who are representative of those likely to present for retinal screening in the NHS
    - consider carefully whether FAF imaging is appropriate as an ancillary test or as a replacement for an existing test
    - employ all relevant components of currently used reference standards
    - clearly report the clinical information required to interpret FAF images in order to reach diagnostic and/or therapeutic decisions
    - report intergrader and intragrader agreement and other aspects of test acceptability (e.g. patient acceptability, adverse events)
    - and report clearly the duration of imaging and any resources associated with the acquisition, processing, quality assurance and interpretation of FAF images.
- A survey or audit of the current use of FAF imaging in NHS practice would be helpful to clarify current practice and any limitations and research requirements associated with it.

Study registration

This study is registered as PROSPERO CRD42014014997.

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