The European Eye Epidemiology spectral-domain optical coherence tomography classification of macular diseases for epidemiological studies

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The European Eye Epidemiology spectral-domain optical coherence tomography classification of macular diseases for epidemiological studies

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ABSTRACT.

Purpose: **The aim of the European Eye Epidemiology (E3) consortium was to develop a spectral-domain optical coherence tomography (SD-OCT)-based classification for macular diseases to standardize epidemiological studies.**

Methods: **A European panel of vitreoretinal disease experts and epidemiologists belonging to the E3 consortium was assembled to define a classification for SD-OCT imaging of the macula. A series of meeting was organized, to develop, test and finalize the classification. First, grading methods used by the different research groups were presented and discussed, and a first version of classification was proposed. This first version was then tested on a set of 50 SD-OCT images in the Bordeaux and Rotterdam centres. Agreements were analysed and discussed with the panel of experts and a final version of the classification was produced.**

Results: **Definitions and classifications are proposed for the structure assessment of the vitreomacular interface (visibility of vitreous interface, vitreomacular adhesion, vitreomacular traction, epiretinal membrane, full-thickness macular hole, lamellar macular hole, macular pseudo-hole) and of the retina (retinoschisis, drusen, pigment epithelium detachment, hyper-reflective clumps, retinal pigment epithelium atrophy, intraretinal cystoid spaces, intraretinal tubular changes, subretinal fluid, subretinal material). Classifications according to size and location are defined. Illustrations of each item are provided, as well as the grading form.**

Conclusion: **The E3 SD-OCT classification has been developed to harmonize epidemiological studies. This homogenization will allow comparing and sharing data collection between European and international studies.**

Key words: epidemiology – macular degeneration – optical coherence tomography – retina – vitreous

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§List are present in Appendix.

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Introduction

Optical coherence tomography (OCT) is a noninvasive imaging technique that was introduced in ophthalmology in 1991 to obtain cross-sections of the ocular fundus *in vivo*. Today, spectral-domain OCT (SD-OCT) represents the standard for *in vivo* imaging in both clinical and research applications (Huang et al. 1991).

The emergence of SD-OCT has dramatically improved the diagnosis of macular diseases compared to the previous generation, time domain OCT (TD-OCT). The axial resolution increased, providing an excellent visualization of the vitreomacular interface and a better understanding of macular diseases such as macular holes or epiretinal membranes (ERM) (Koizumi et al. 2008). In age-related macular degeneration (AMD), SD-OCT allowed to better evaluate drusen (Yi et al. 2009), describe morphologic variations in outer retinal layers in geographic atrophy and evaluate the disease activity in neovascular forms (Forooghian et al. 2008). Spectral-domain (SD)-OCT has also improved

the measurement of macular oedema in diabetic retinopathy (Forooghian et al. 2008).

The development of SD-OCT was revolutionary in the clinical practice. However, current epidemiological studies of retinal diseases are still mainly based on fundus photography. Some epidemiological studies have graded SD-OCT images (Gupta et al. 2013; Meuer et al. 2015; Patel et al. 2016), and many others have collected such examinations, but there is no consensus on the classification of retinal diseases based on SD-OCT examination, limiting analysis and comparison of studies. Only classifications focusing on normal SD-OCT or on the vitreomacular interface have been published (Duker et al. 2013; Staurenghi et al. 2014). The aim of this consorted study was to develop a SD-OCT-based classification for macular diseases to standardize the analysis of imaging data obtained in epidemiological studies.

Materials and Methods

Participants

The European Eye Epidemiology (E3) consortium is a consortium of 29 groups from 12 European countries (Williams et al. 2015a,b; Delcourt et al. 2016; Colijn et al. 2017). It currently comprises 21 population-based studies and 20 other studies (case–control, cases only, randomized trials), providing ophthalmological data of more than 170 000 European participants. The aim of the consortium is to promote and sustain collaboration and sharing of data and knowledge in the field of ophthalmic epidemiology in Europe, with particular focus on the harmonization of methods (classification of ocular outcomes, measures of risk factors), the estimation of frequency and impact of visual outcomes in European populations, the identification of risk factors and pathways for eye diseases (lifestyle, vascular and metabolic factors, genetics, epigenetics and biomarkers) and development and validation of prediction models for eye diseases.

Development of the classification

The grading form is the result of a series of meetings. At the second meeting of the E3 consortium (Bordeaux, June 2012), grading methods used by the different research groups were presented and discussed, and the items to be included in the classification were chosen. A first version of the classification was proposed to the group at the third E3 meeting (Bordeaux, June 2013). This version was subsequently tested on a set of 50 SD-OCT images in the Bordeaux and Rotterdam centres. The results of the agreements were presented and discussed at the fourth E3 meeting (Rome, June 2014). After this roundtable, modifications were made in the grading form and the final version of the classification was approved by the E3 consortium during the fifth E3 meeting in June 2015 (London, UK).

Grading

Grading is based on the SD-OCT images only. It does not include other images such as colour fundus photography, infrared reflectance, or fundus autofluorescence. In the development of the grading form, we used the definition of the fovea as the area with a diameter of 1000 μm centred on the foveola. A foveal scan was defined as a scan through the centre of the fovea, indicated by the maximum dip in a normal retina.

For each items, there are several options:
1: No (or absent)
2: Yes (or present)
7: Questionable when the lesion to grade is at least partly visible but is not clear
8: Not applicable when the question is not applicable for that particular image
9: Not gradable due to image quality.

Items of the classification are gathered in a standardized grading form (online supplementary material) and described below.

Quality of images

The quality of the images is evaluated by human grading:

- Good: all layers of the retina are clearly visible and distinguishable one from each other.
- Fair: layers of the retina are visible with adequate clarity to grade the image, in the absence of optical quality.
- Not gradable: layers of the retina are not visible and cannot be distinguished one from each another. No features can be graded based on this OCT scan.

Reflectivity

In greyscale scans, a complete absence of reflectivity appears as black areas. On the other hand, an increase in reflectivity appears as white areas.

In black on white images, a complete absence of reflectivity appears as white areas. An increase in reflectivity appears as black areas.

Results

The final version of the definition and classification was approved by the panel. The standardized grading form is provided as online supplementary material.

Status of outer retina layers

Ellipsoid zone

Current-generation of SD-OCT instruments detects four hyper-reflective bands in the outer retina. The ellipsoid zone is the second innermost hyper-reflective band (Staurenghi et al. 2014). The clinicopathologic correlation of this layer remains debated. Spaide & Curcio (2011) attributed the hyper-reflectivity of the second band to the ellipsoid portion of the inner segments. In the grading form, the integrity of the ellipsoid zone is graded. If the ellipsoid zone is not intact in the entire scan, it is asked whether this layer is intact at least in the centre subfield.

SD-OCT structure assessment of the vitreous interface

Vitreous interface

The vitreous body lies in the posterior vitreous cortex. This posterior cortex is bound with the internal limiting membrane of the retina at birth. With ageing, there is a progressive separation between the vitreous and the retina which usually begins in the perifoveal area, progresses through the fovea and finally ends with the separation of the vitreous from the optic nerve head. The posterior vitreous cortex or posterior hyaloid may not be visible when it is completely attached to the macula; however, when the posterior vitreous detachment process begins, it appears as a hyper-reflective line anterior to the inner boundary of the retina with variable thickness. In the SD-OCT grading form, the visibility of the vitreous interface is graded.

Vitreomacular adhesion

Vitreomacular adhesion (VMA) was defined by the International Vitreomacular Traction Study Group (IVTS) and is characterized by an 'elevation of

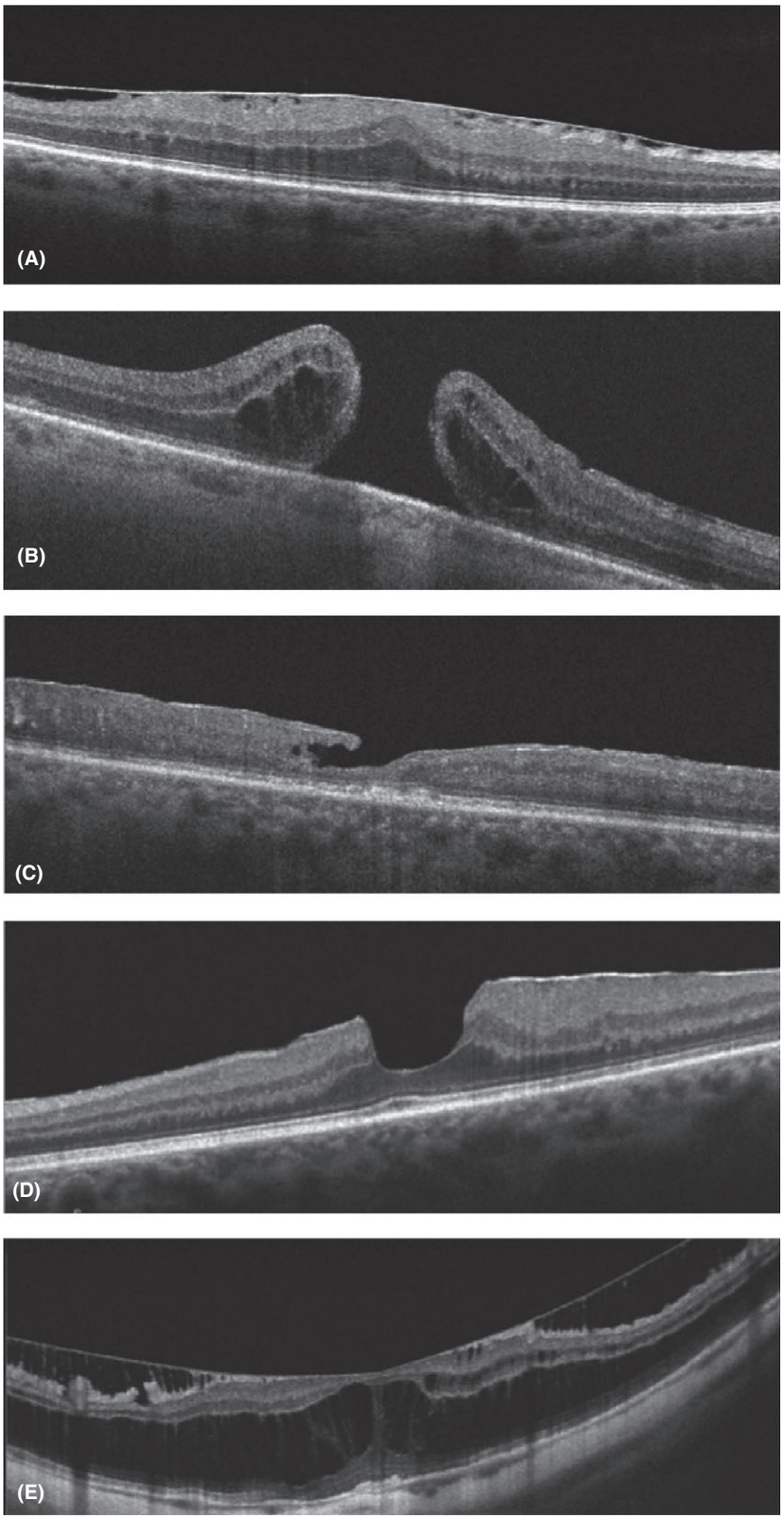

Fig. 1. Spectral-domain-optical coherence tomography scans show pathophysiologic lesions for retina. (A) Epiretinal membrane, (B) full-thickness macular hole, (C) Lamellar defects, (D) Macular pseudohole, (E) Retinoschisis.

the cortical vitreous above the retinal surface, with the vitreous remaining attached within a 3-mm radius of the fovea without retinal abnormalities' (Duker et al. 2013). Vitreomacular adhesion (VMA) can be sub-classified by the size of the adhesion as focal (<1500 μm) or broad (>1500 μm).

Vitreomacular traction

Vitreomacular traction (VMT) was defined by the IVTS and all of the following anatomic criteria must appear on at least 1 B-mode OCT scan to classify an eye as having VMT: (i) evidence of perifoveal vitreous cortex detachment from the retinal surface; (ii) macular attachment of the vitreous cortex within a 3-mm radius of the fovea; and (iii) association of attachment with distortion of the foveal surface, intraretinal structural changes, elevation of the fovea above the retinal pigment epithelium (RPE), or a combination thereof, but no full-thickness interruption of all retinal layers. Like VMA, VMT can be subclassified into either focal or broad, depending on the width of vitreous attachment (Duker et al. 2013).

Epiretinal membrane

Epiretinal membrane (ERM) is a fibrocellular proliferation on the surface of the internal limiting membrane (Snead et al. 2008). On SD-OCT, ERM is visualized as a 'highly reflective membranous structure at the vitreomacular interface' (Fig. 1A) (Stevenson et al. 2016). Epiretinal membrane (ERM) contracture can involve the centre of the macula, with flattening of foveal pit and other changes in the outer retinal layers.

Full-thickness macular hole

Full-thickness macular hole is a defect of all retinal layers from the internal limiting membrane to the RPE. Aperture size can be measured on SD-OCT and the macular hole can be subclassified as: small (<250 μm), medium (>250 to ≤400 μm) and large macular hole (>400 μm; Fig. 1B).

Lamellar hole

Lamellar hole (or lamellar defects) is a partial-thickness defect in retinal layers.

International Vitreomacular Traction Study Group (IVTS) proposed an anatomic OCT-based definition including the following features: '(i) an irregular foveal contour; (ii) a defect in the inner fovea (may not have actual loss of tissue); (iii) intraretinal splitting (schisis), typically between the outer plexiform and outer nuclear layers; and (iv) maintenance of an intact photoreceptor layer' (Fig. 1C).

Macular pseudohole

International Vitreomacular Traction Study Group (IVTS) proposed an SD-OCT-based definition of macular

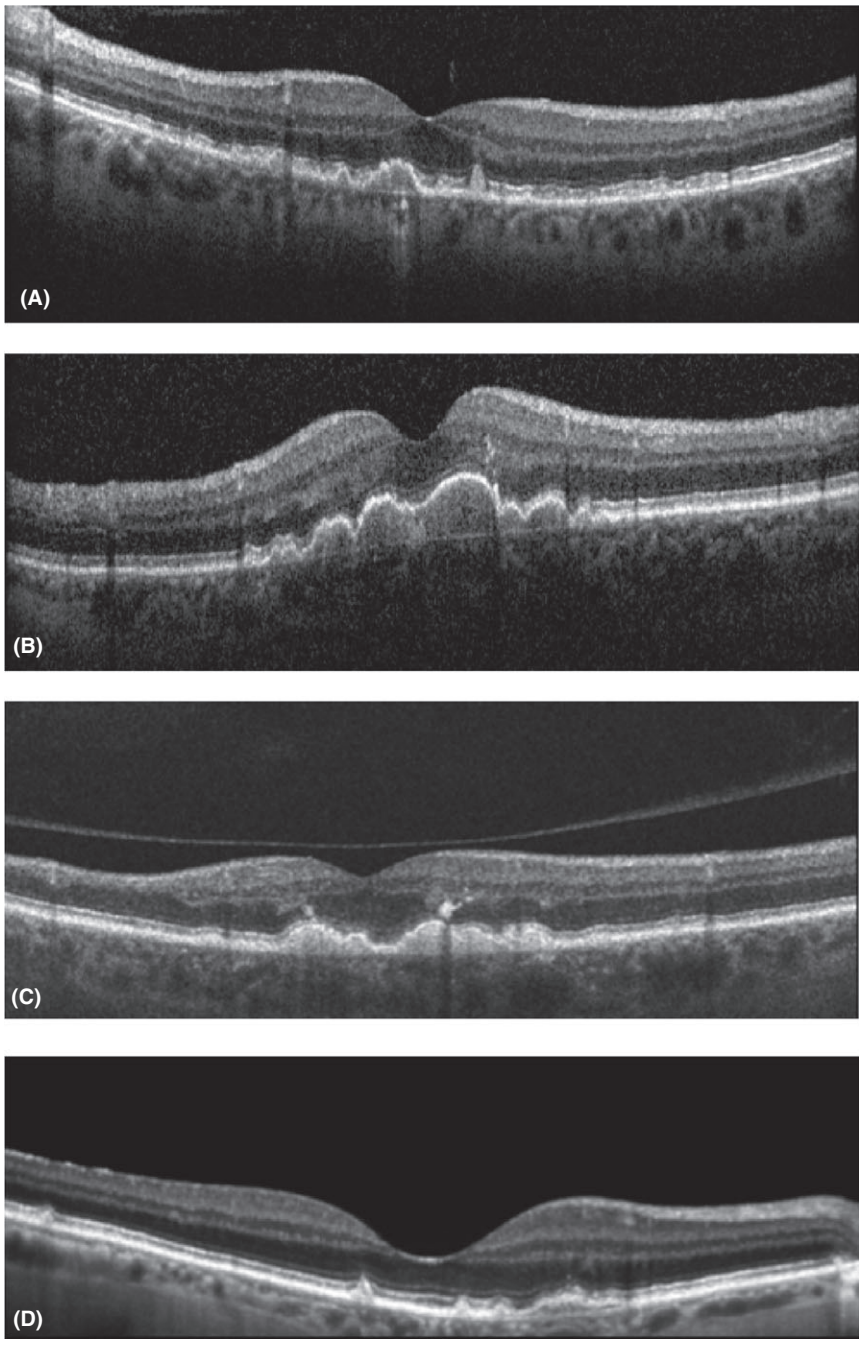

Fig. 2. Spectral-domain-optical coherence tomography scans show pathophysiologic lesions for retina. (A) Drusen, (B) Confluent Drusen, (C) Hyper-reflectivity above drusen, (D) Reticular drusen.

pseudoholes with four characteristics: '(i) invaginated or heaped foveal edges, (ii) concomitant ERM with central opening, (iii) steep macular contour to the central fovea with near-normal central foveal thickness, and (iv) no loss of photoreceptors' (Fig. 1D) (Duker et al. 2013).

SD-OCT structure assessment of the retina

Retinoschisis

Retinoschisis is a lamellar splitting of neurosensory retina, involving outer or inner nuclear layer (Fig. 1E).

Drusen

Drusen are accumulations of extracellular material between the Bruch's membrane and the RPE (Fig. 2A–E). The material within the lesions is mild to highly hyper-reflective, and the distribution can be homogenous or heterogeneous. The location and the size of drusen are specified in the SD-OCT grading form. The size of the largest subfoveal drusen and the location of the nearest drusen from the centre are measured. Drusen can appear as single or confluent lesions. Some drusen may have overlying hyper-reflective lesions.

Reticular drusen or subretinal drusenoid deposits are granular, irregular and hyper-reflective lesions located above the RPE.

Pigment epithelial detachment

A pigment epithelial detachment (PED) is an elevation of the RPE away from Bruch's membrane with a size >400 μm wide and >75 μm high or >200 μm high. The reflectivity can be sub-classified in: homogenous hypo-reflectivity, homo genous hyper-reflectivity, heterogeneous reflectivity (Fig. 3A).

Hyper-reflective clumps

Hyper-reflective clumps are clusters of intraretinal material in the absence of underlying drusen (Fig. 3B).

RPE atrophy

Macular atrophy diagnosis is based, in accordance with Doheny Image Reading centre protocols for OCT, on the presence of two or three criteria of the following criteria in an area $\geq$125 μm: increased signal transmission through the choroid (choroidal hypertransmission), attenuation of the RPE band, and collapse or loss of the outer retinal layers (Fig. 3C) (Abdelfattah et al. 2017). The location relative to the fovea (involvement or preservation of the foveal area) is graded.

Intraretinal cystic spaces

Intraretinal cystic spaces are shown as circular or ovoid areas of low reflectivity in the outer or inner nuclear retinal layers (Fig. 4A). They must be differentiated from retinal schisis, with which they can be associated.

Intraretinal tubular changes

Outer retinal tubulation (ORT) is an end-stage degenerative of outer retina reorganization. ORT is characterized a circular or ovoid hyper-reflective band around a hyporeflective core, located within the outer nuclear layer overlying degenerated or absent RPE (Fig. 4B) (Zweifel et al. 2009).

Subretinal fluid

The presence of a hyporeflective space between the sensory retina and the RPE was defined as subretinal fluid. The location relative to the fovea is graded (Fig. 4C).

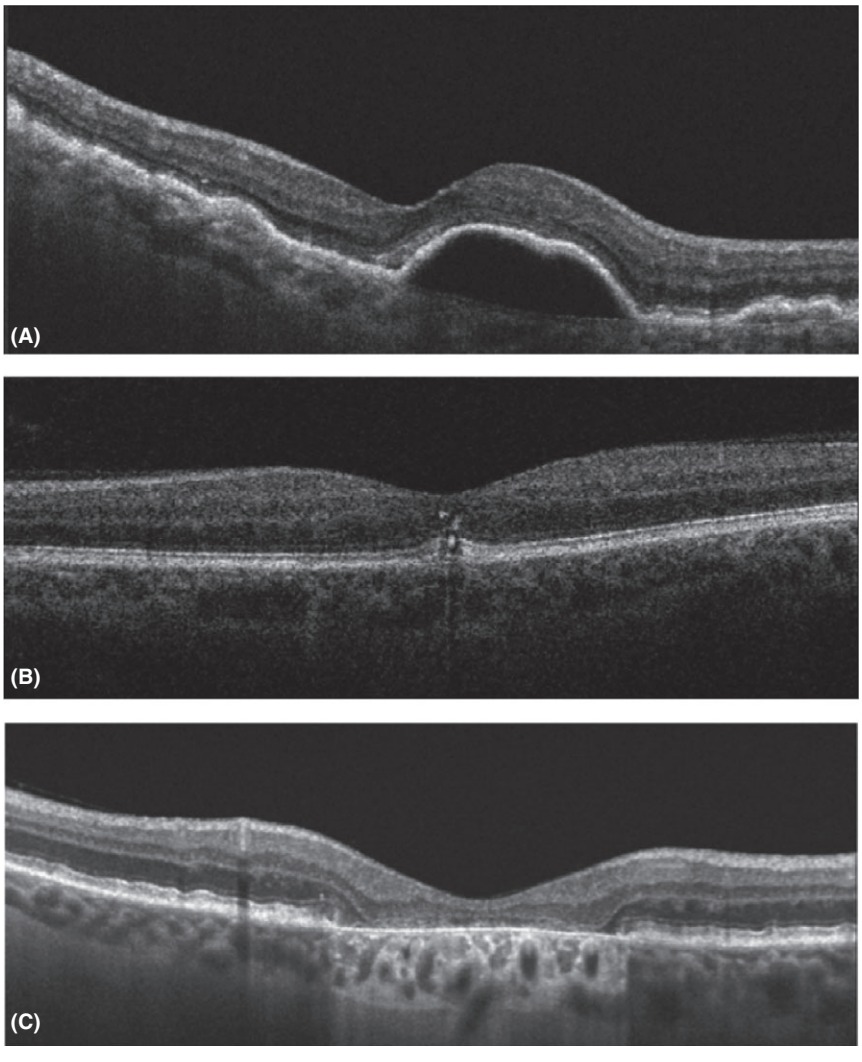

Fig. 3. Spectral-domain-optical coherence tomography scans show pathophysiologic lesions for retina. (A) Pigment epithelial detachment, (B) Hyper-reflective Clumps, and (C) Retinal pigment epithelium atrophy.

Subretinal material

Subretinal material is defined as hyper-reflective material, of any shape, but most often spindle- or squared- shaped between the sensory retina and the RPE or/and between the RPE and the choroid other than drusen, PED or fluid. The contents are generally heterogeneous. The location relative to the fovea is graded (Fig. 4D).

Discussion

The aim of this study was to develop a classification resulting from a consensus of retinal imaging experts. This is an anatomic classification based on SD-OCT, without regards to symptoms.

While SD-OCT examinations are currently being performed in many epidemiological studies, there is no consensus on the methods to interpret these examinations. Several quantitative parameters, such as retinal thickness, retinal nerve fibre layer thickness or, more recently, choroidal thickness, are measured using automatic segmentation of SD-OCT scans. These measurements are highly reproducible and have many clinical uses for the diagnosis and follow-up of several eye diseases (in particular glaucoma or macular oedema) (Michelessi et al. 2015; Virgili et al. 2015). Such parameters have been described in several epidemiological studies, in various settings (age range, geographical area, ethnical background) (Khawaja et al. 2013; Zhu et al. 2013; Springelkamp et al. 2014; Gupta et al. 2015; Rougier et al. 2015; Patel et al. 2016; Schweitzer et al. 2016).

By contrast, a consensus is still lacking on the classification of qualitative features, such as described in the present article. Such features are of major importance in the diagnosis and follow-up of many retinal diseases (for the instance presence of subretinal fluid or subretinal material for the diagnosis and treatment of neovascular AMD, or the presence of intraretinal cystoid spaces for the diagnosis of macular oedema). Thus, a significant part of the information available in SD-OCT examinations is currently not used in epidemiological studies, because of the lack of consensus on the method for interpretation.

In the past, such standardized classifications have had great influence in the field of ophthalmological epidemiology. The classifications proposed in the 1990s were the basis for the interpretation of retinal colour photographs in all subsequent epidemiological studies, resulting in sufficient homogeneity to allow for comparison of results among studies performed anywhere in the world, as well as for the conduct of meta-analysis (Klein et al. 1991; Bird et al. 1995; Vingerling et al. 1995; Wong et al. 2014).

The present grading scheme will be used by epidemiological studies participating in the E3 consortium which have collected SD-OCT examinations. It is likely that the greater use of this classification system will lead to the detection of limitations, and modifications may be proposed after initial experience. We encourage other epidemiologic eye studies to implement this classification as well. The protocol is freely available upon request.

The use of the E3 classification of SD-OCT examinations will allow a more precise diagnosis of retinal diseases, which will also be closer to current clinical practice. Studies using such methodology (rather than relying only on retinal photographs, as it is still the case in most of the studies), will give better estimates of the prevalence of retinal diseases, as well as better estimates of needs regarding ophthalmological care. In addition, SD-OCT examinations allow for the diagnosis of conditions that were difficult to diagnose previously, in particular in the framework of epidemiological studies, such as abnormalities of the vitreomacular interface (VMA and traction, ERMs).

Recently, many papers on automated image analysis in several retinal

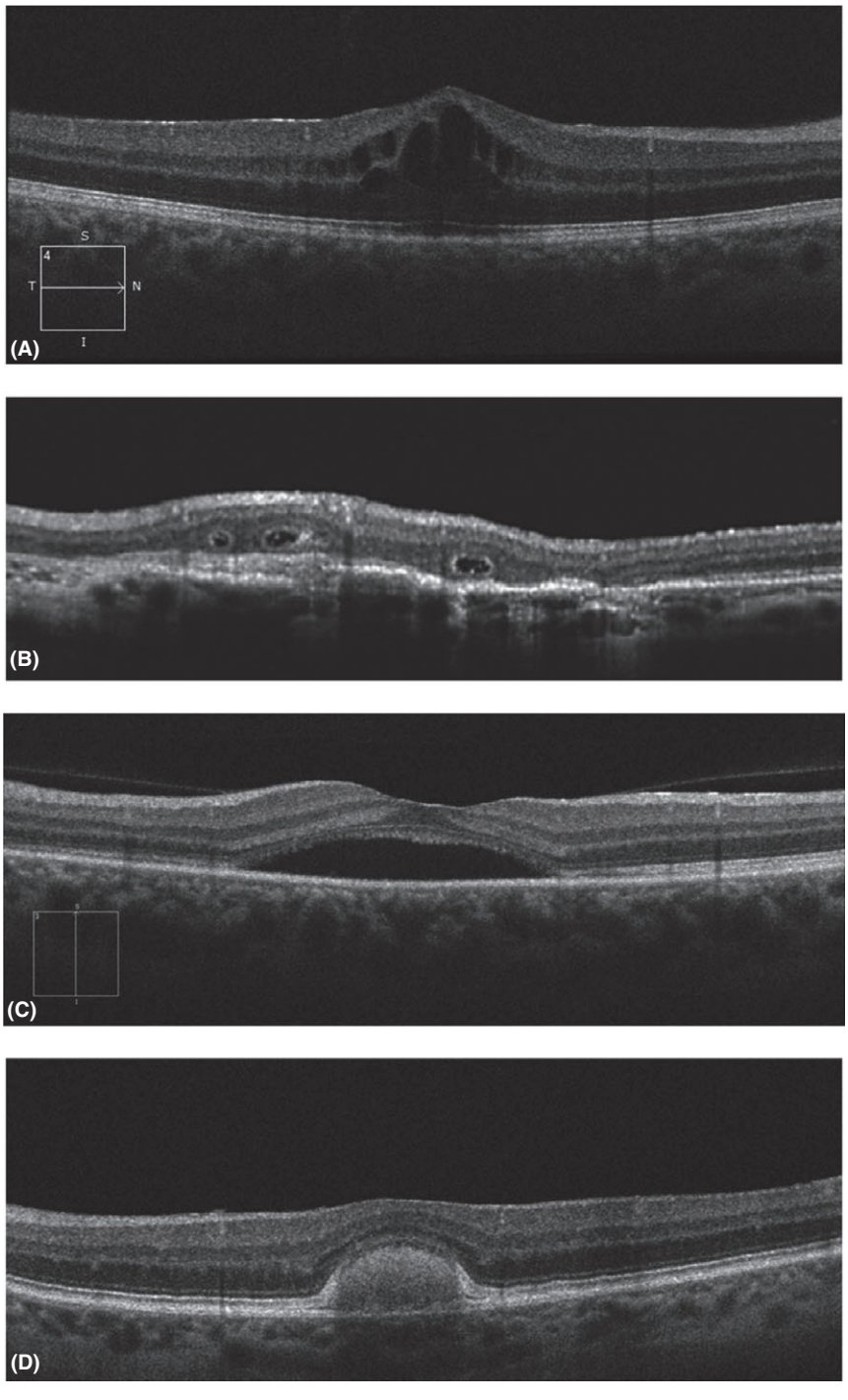

Fig. 4. Spectral-domain-optical coherence tomography scans show pathophysiologic lesions for retina. (A) Intraretinal cysts, (B) Intraretinal tubular changes, (C) Subretinal fluid, (D) Subretinal material.

diseases have been published (Bogunovic et al. 2017; Karri et al. 2017; Khalid et al. 2017). For instance, in AMD automated detection of drusen, geographic atrophy or subretinal fluid has been developed (Wintergerst et al. 2017). The potential benefits are to facilitate access and allow an early detection. Machine-learning uses features chosen by experts to create algorithms to detect patterns on imaging. Therefore, there is still the need for a standardized definition of the main features of macular diseases.

Furthermore, even if the quality of automated grading seems to be good, most studies were performed in preselected pool of patients with pathology and good quality of imaging. Few algorithms had the capacity to analyse different pathologies at the same time (Chen et al. 2012; Chiu et al. 2012). Moreover, there is no automated analysis for OCT images available for some of the pathologies like subretinal deposits.

The algorithm can be trained directly by the machine using images from very large data sets without specifying lesion-based features: this is deep learning which is the future of artificial intelligence (LeCun et al. 2015).

In conclusion, the proposed classification results from a consensus of European retina specialists for use in epidemiological studies. A standardized grading scheme will improve diagnostic skills, risk assessments and prognostic analysis of retinal diseases in epidemiologic research.

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Appendix 1: List of E3 consortium members

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