Supplementary Material

Manuscript Title: Multispectral pattern recognition reveals a diversity of clinical signs in intermediate age-related macular degeneration (AMD)

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This work describes a novel, proof of concept approach using fundus images derived through different spectral sources to map out clinically relevant features in 36 eyes of patients with intermediate AMD (Supplementary Figure 1). The usefulness of several unsupervised clustering algorithms and parameters was explored, including: K means, Fuzzy K means, and ISODATA (Supplementary Figure 2).¹ Down merging describes the approach in which the number of classes was initially stipulated at 16; separate classes with the lowest separability in the first classification result are then aggregated into one class and the process repeated until a certain pre-specified criterion was reached. The example demonstrates that the approach using ‘K means, down-merging’ provides the best concordance with drusen in the reference fundus photograph. These areas of interest were then compared against expert annotation. In addition to the core analysis, we also explored if this approach could identify evidence of disease progression, including drusen regression.²-⁴ Two eyes with intermediate AMD followed up over a 15 and 6 month period, respectively were analysed. The former showed evidence of drusen enlargement (Supplementary Figure 3A), while the latter showed drusen regression (Supplementary Figure 3B), confirmed by structural optical coherence tomography (data not shown). Validation via a larger replication sample is currently underway.

References

Supplementary Figure 1. Collage of all 36 eyes with intermediate AMD analysed in the study. Note the diversity in fundus pigmentation and visibility of choroidal vasculature.
**Supplementary Figure 2.** Collage juxtaposing the results of the described method against other clustering algorithms. The black outline delineates the drusen associated signatures in each classified image, derived using down-merging and A) K means cluster analysis as described in the manuscript, B) Fuzzy K means with down-merging, C) ISODATA with down-merging, or D) K means clustering with a fixed maximum number of eight classes, E) Fuzzy K means with a fixed maximum number of eight classes, and F) ISODATA with a specified minimum number of 8 clusters. The OCT scans reveal that the preponderance of drusen indicated in the top of Figure A are likely to be truly present.
Supplementary Figure 3. Case figures illustrating a potential application of multispectral pattern recognition for change analysis in intermediate AMD. Reference fundus photographs of the macula taken at baseline and at one follow up visit appear in the left column, and may be overlaid with an outline of the pattern recognition identified signatures for drusen (second column). Magnified inserts and a composite change map are shown adjacent. **A)** Case images taken 15 months apart from an eye showing drusen enlargement. Using unsupervised pattern recognition, the drusen related signatures increased from occupying 3.1% of the total image area at baseline to 5.6% at follow up. The change map depicts the baseline photograph with drusen signatures outlined in black, and areas of enlargement shown in grey. **B)** Using the same approach applied to a different eye followed up over a 6 month period, sites of drusen regression may be shaded white in the change map.