Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix. Methods

Grading of FAF images

De-identified and anonymized FAF images of eligible patients and visits were sent by the participating sites to the reading center (RC, Doheny Imaging Reading Center, Doheny Eye Institute, David Geffen School of Medicine at UCLA, Los Angeles, CA). The quality of the images submitted for grading was assessed and poor images were excluded from analysis. Patients with at least 2 visits with gradable photographs and lesion present were included in this analysis. Data from up to 4 visits could be includedDe-identified and anonymized FAF images of eligible patients and visits were sent by the participating sites to the reading center (RC, Doheny Imaging Reading Center, Doheny Eye Institute, David Geffen School of Medicine at UCLA, Los Angeles, CA). The quality of the images submitted for grading was assessed and poor images were excluded from analysis. Patients with at least 2 visits with gradable photographs and lesion present were included in this analysis. Data from up to 4 visits could be included.

Quantitative grading

The area of the respective lesions was semi-automatically evaluated using the RegionFinder module of the Heidelberg Eye Explorer™ (Heidelberg Engineering©, Heidelberg, Germany) with grading conventions: shadow correction was applied when the FAF images were unevenly or inadequately illuminated; algorithm growth power was adjusted and refined manually until the region fully captured the area of decreased FAF; manual line, circles, contours or free-hand constraints were used as needed to distinguish lesion boundaries and exclude vascular structures; in case of confluence of central and peripapillary atrophy, an approximately vertical line constraint had to be set at the narrowest part ("bridge"), with atrophy quantification including only atrophy temporal to the constraint, and disregarding atrophy nasal to the constraint. For multifocal lesions, the sum of all areas of DAF (within each subtype) was calculated. Number of foci of DDAF was recorded and graded as either unifocal (n=1) or multifocal (n>1).

As the distinction between normal foveal DAF and abnormal DAF can be challenging when using FAF images alone, additional infrared reflectance (IR) fundus images if provided could be used to add supplementary information, particularly when confirming the presence of foveal atrophy. FAF images were independently reviewed by 2 certified graders. At least 1 of the graders was a senior-level grader. Any assessments where initial answers were not concordant underwent adjudication. If consensus could not be reached between 2 adjudicating graders, the final answer was determined by a reading center investigator.

In 8 single visits of 7 patients (16 eye visits of 14 eyes), images could not be opened and analyzed using the RegionFinder tool, due to image size constraints. In these patients, grading was performed using a planimetric grading software program (GRADOR), developed by the RC which demonstrates good agreement and equivalence.

eTable 1. Demographic Characteristics at First Included Visit (= Baseline) of Patients With FAF Images of Sufficient Quality and DDAF and/or Any Lesion in at Least 2 Study Visits

Demographic Characteristics	Participants/eyes with at least 2 visits with DDAF lesions	Participants/eyes with at least 2 visits with DDAF and/or QDAF lesions
Number of participants	133	215
Mean age [years] at first visit (mean (SD))	33.2 (±15.1)	29 (±14.7)
Age at first visit (categories)		
Younger than 18 years	24 (18.8%)	52 (24.2%)
18 to 29 years	39 (29.3%)	69 (32.1%)
30 years or older	70 (52.6%)	94 (43.7%)
Age [years] of onset of symptoms(mean(SD))	22.9(±14.6)*	21.9 (±13.3)**
Age of onset of symptoms (categories)		
Younger than 18 years	54 (48.2%)	93 (50.8%)
18 to 29 years	30 (26.8%)	47 (25.7%)
30 years or older	28 (25.0%)	43 (23.5%)
Female	74 (55.6%)	126 (58.6%)
Race		
White/Middle Eastern	90 (66.7%)	146 (67.9%)
Black	4 (3.0%)	9 (4.2%)
Asian/Indian	6 (4.5%)	8 (3.7%)
Other	3 (2.3%)	4 (1.9%)
Several	1 (0.8%)	2 (0.9%)
Unknown	29 (21.8%)	46 (21.4%)
Eyes per participant		
One	42 (31.6%)	44 (20.5%)

Two	91 (68.4%)	171 (79.5%)
Number of visits (eye level)		
Two	110 (49.1%)	156 (40.4%)
Three	90 (40.2%)	173 (44.8%)
Four	24 (10.7%)	57 (14.8%)
Mean follow-up time (mean (SD))	3.6 (1.7)	3.9 (1.6)

*missing for 21 subjects, ** missing for 32 subjects

eTable 2. Estimates of Yearly Growth Rates DDAF and the Total Area (DDAF+QDAF) by Baseline Lesion Size

Lesion Type	First visit lesion size	Estimated progression rate (slope of time) & 95% Confidence Limits [mm^2 per year]
DDAF N=224 eyes	≤1.92 mm^2	**0.32 (0.24 – 0.39) §**
	>1.92 mm^2	**0.86 (0.67 – 1.06) §**
	Overall	0.51 (0.42 – 0.61)
TOTAL AREA N=386 eyes	≤2.50 mm^2	**0.26 (0.21 – 0.32) €**
	>2.50 mm^2	**0.74 (0.57 – 0.91) €**
	Overall	0.35 (0.28 -0.43)

In bold significant interaction; § p=0.005; € p =0.0001

eTable 3. Estimated Progression Rate (Slope of Time) Using the Square Root Transformation for Areas of Definitely Decreased Autofluorescence (DDAF) and Total Area of Decreased Autofluorescence

Lesion Type	First visit lesion size	**Scale square root of the area** Estimated progression rate (slope of time) & 95% Confidence Limits [mm per year]
DDAF N=224 eyes	≤1.92 mm^2	0.136 (0.110 – 0.161) #
	>1.92 mm^2	0.160 (0.130 – 0.190) #
	Overall	0.145 (0.125 – 0.166)
TOTAL AREA N=386 eyes	≤2.50 mm^2	**0.095 (0.080 – 0.111) $**
	>2.50 mm^2	**0.133 (0.106 – 0.160) $**
	Overall	0.107 (0.093 – 0.122)

p=0.25; $ p=<0.001

Interpretation when back translating to area:

At time t: $area = (a + \beta t)^2$ -> $area = a^2 + 2a\beta t + \beta^2 t^2$

At time $(t+1)$: $area = (a + \beta(t + 1))^2$ → $area = a^2 + 2a\beta(t + 1) + \beta^2(t + 1)^2$

→:$area = a^2 + 2a\beta t + 2a\beta + \beta^2 t^2 + 2\beta^2 t + \beta^2$

Increase in area from time t to time $t+1$ →$\Delta area = 2a\beta + 2\beta^2 t + \beta^2$

Where a is the intercept t is time and β the estimated slope

When modeling the square root of the area, the yearly increase in area depends on the intercept 'a' (mean value of the square root of the area at time 0), the estimated yearly increase in the square root of the area 'β', and the time when the increase is being evaluated.