Optical coherence tomography of drusenoid pigment epithelial detachments in the Age-Related Eye Disease Study 2

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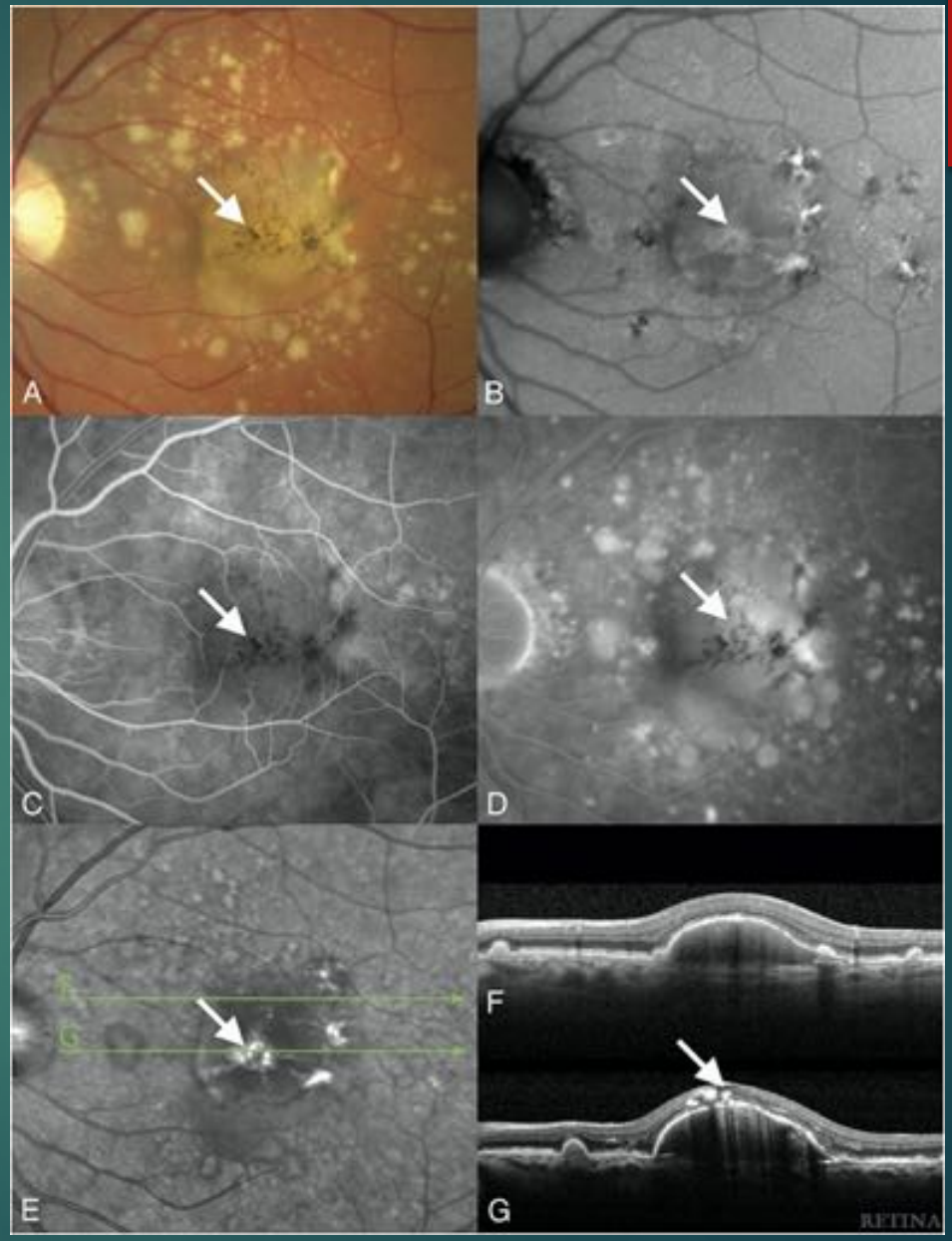
Summary

- Addition of spectral-domain optical coherence tomography (SD-OCT) imaging to color fundus photography (CFP) may allow earlier and more accurate detection of drusenoid pigment epithelial detachments (DPEDs).
- DPEDs change in size at different rates, which may be correlated to the AMD status of the eye.
- Hyperreflective foci were present in all eyes prior to DPED collapse or conversion to neovascularization.

Introduction

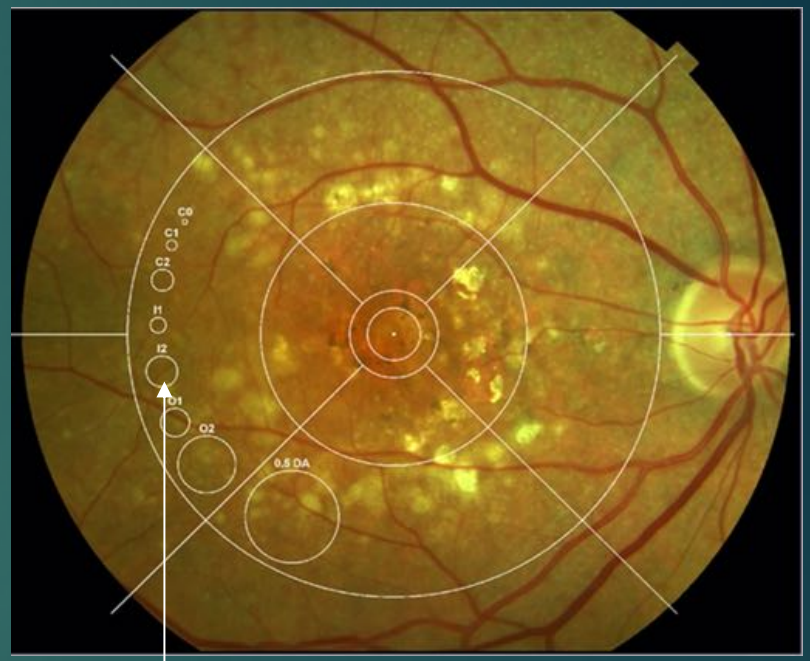
- Drusenoid pigment epithelial detachments (DPEDs) are seen in high-risk age-related macular degeneration (AMD)
- Form from confluence of smaller drusen
- May regress and develop geographic atrophy (GA)



Invest. Ophthalmol. Vis. Sci.. 2013;54(7):4548-4554.
Mrejen S et al. RETINA33(9):1735-1762, October 2013.

Natural History of DPEDs: AREDS2

- 391 eyes of 325 participants had DPED on color fundus photography
- DPED associated with
  - **Increased risk of progression to late AMD** (HR 2.36, 95% CI 1.98-2.82; P<0.001)
  - **Increased risk of ≤3 lines of VA loss** (HR, 3.08; CI, 2.41-3.93; P < 0.001)
- 67% of eyes progressed to late AMD 5 years after DPED detection



Circle I-2 (diameter 433 µm) used to define min DPED size in AREDS2

Yu JJ, Agrón E, Clemons TE, et al. *Ophthalmology*. 2019;126(2):261–273.

Study objectives

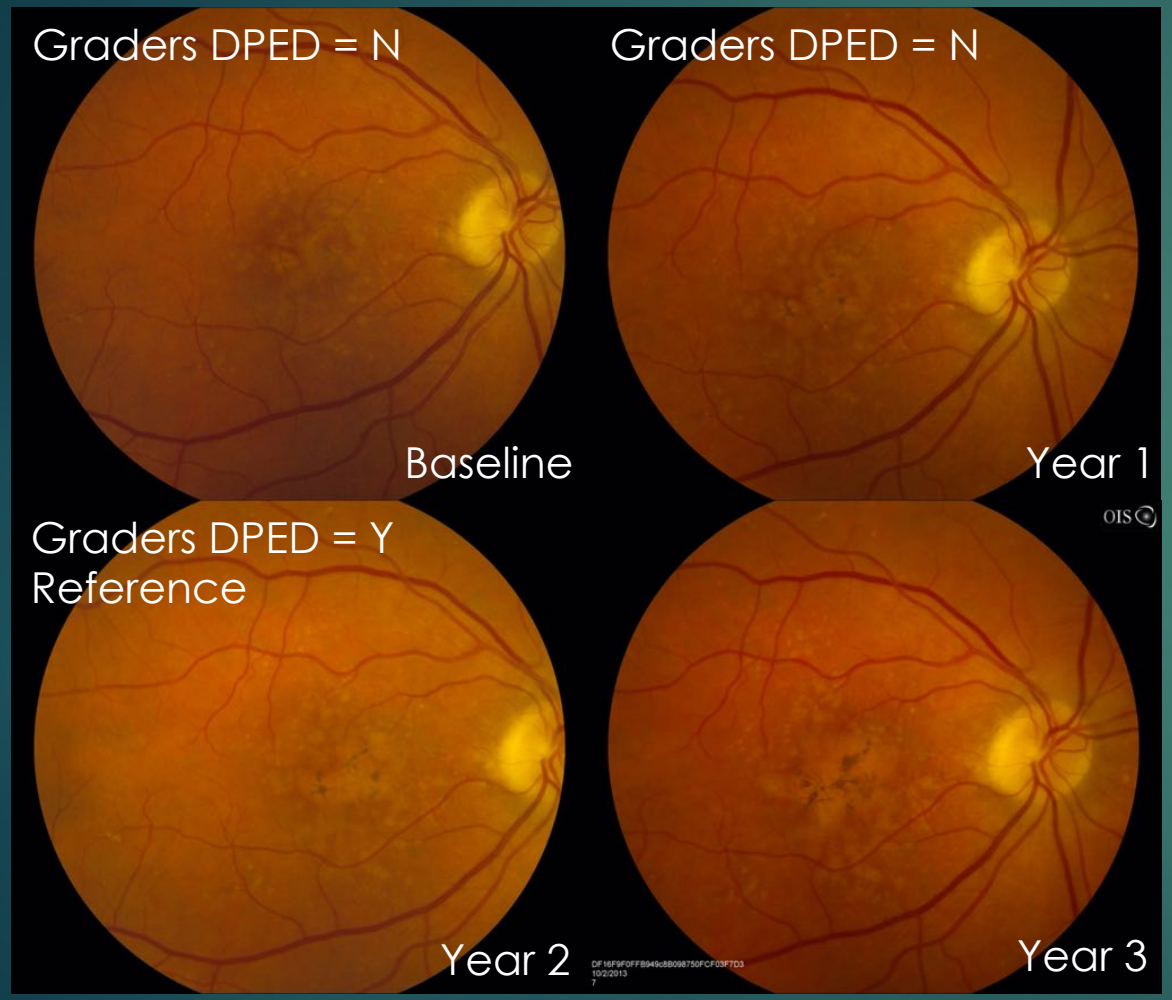
- To use multi-modal imaging to determine the correlation between color fundus photography (CFP) and spectral-domain OCT (SD-OCT) characteristics of DPEDs
- To determine the progression of DPEDs in AREDS2 based on SD-OCT
- To identify risk factors for DPED collapse and GA development

AREDS2 Ancillary SD-OCT (A2A SD-OCT) Study

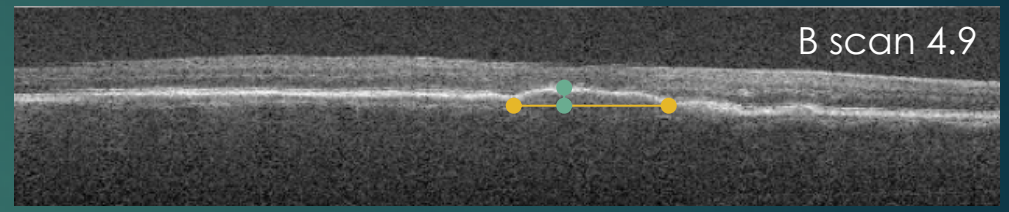
- 4 AREDS2 study sites (Devers Eye Institute, Duke Eye Center, Emory Eye Center, National Eye Institute)
- SD-OCT imaging centered on macula performed using Bioptigen Tabletop SD-OCT system
  - 6.7x6.7 mm volumetric scan
    - 1000 A scans per B scan with 67 µm spacing between the 100 B scans per volume
- Graded by Duke Reading Center for:
  - Subretinal fluid (SRF)
  - Cystoid macular edema (CME)
  - Hyperreflective foci (HRF)
  - Internal drusen characteristics
  - Retinal pigment epithelium (RPE) atrophy
  - Photoreceptor layer thinning

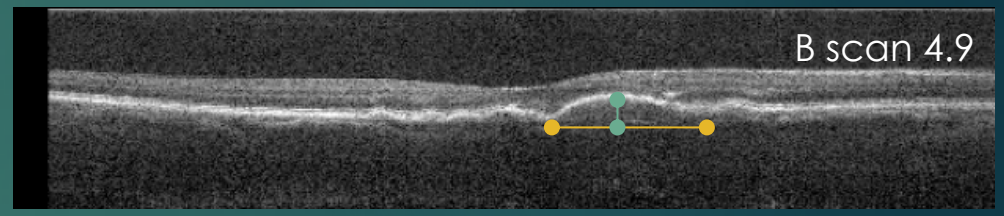
Leuschen JN, Schuman SG, Winter KP, et al. *Ophthalmology*. 2013;120(1):140–150.

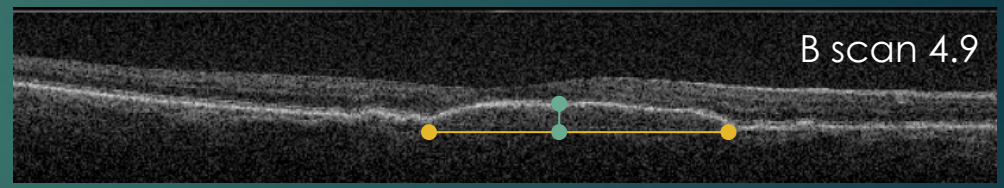
Longitudinal DPED Measurements

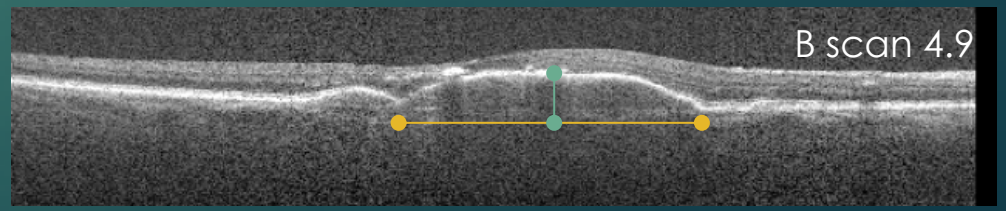


Registered scans



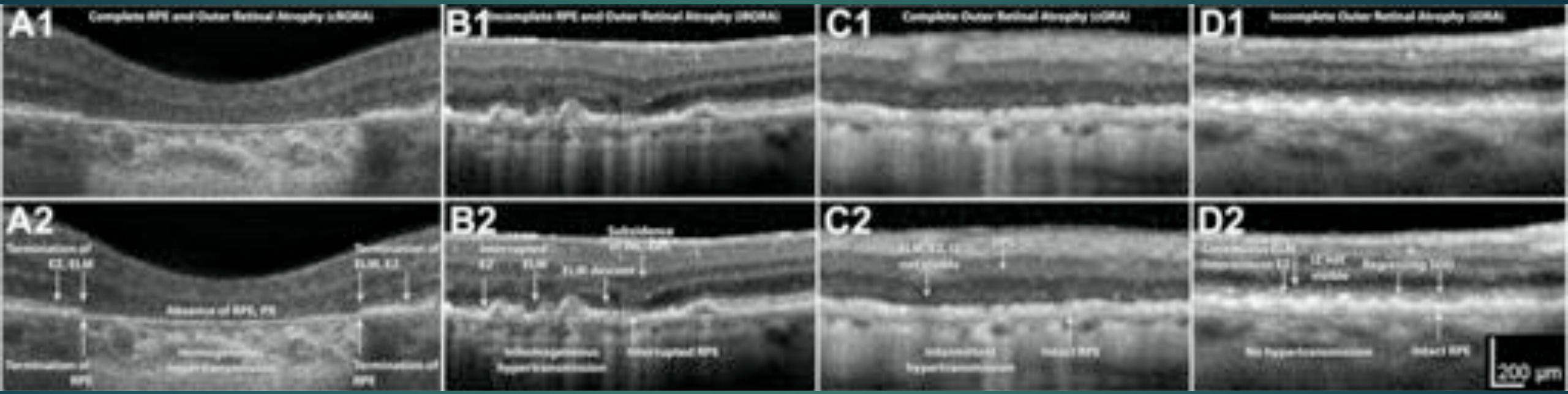






Reference visit = earliest study visit that an eye was graded as having DPED present on CFP; corresponding SD-OCT was the reference scan

Geographic Atrophy

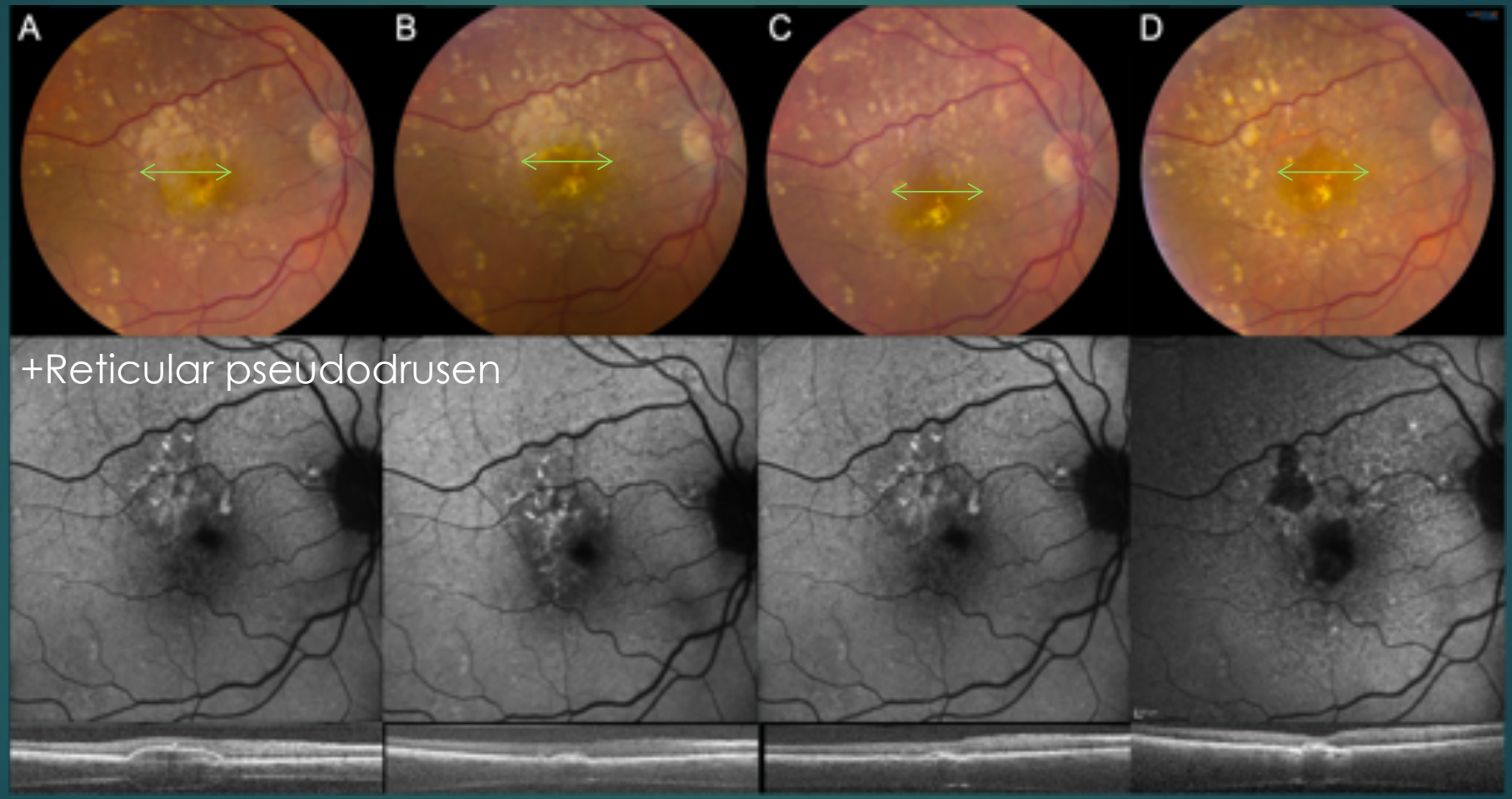


Complete RPE and outer retinal atrophy (cRORA): zone of homogeneous choroidal hypertransmission and absence of the RPE band measuring ≥250 µm with overlying outer retinal thinning and loss of photoreceptors

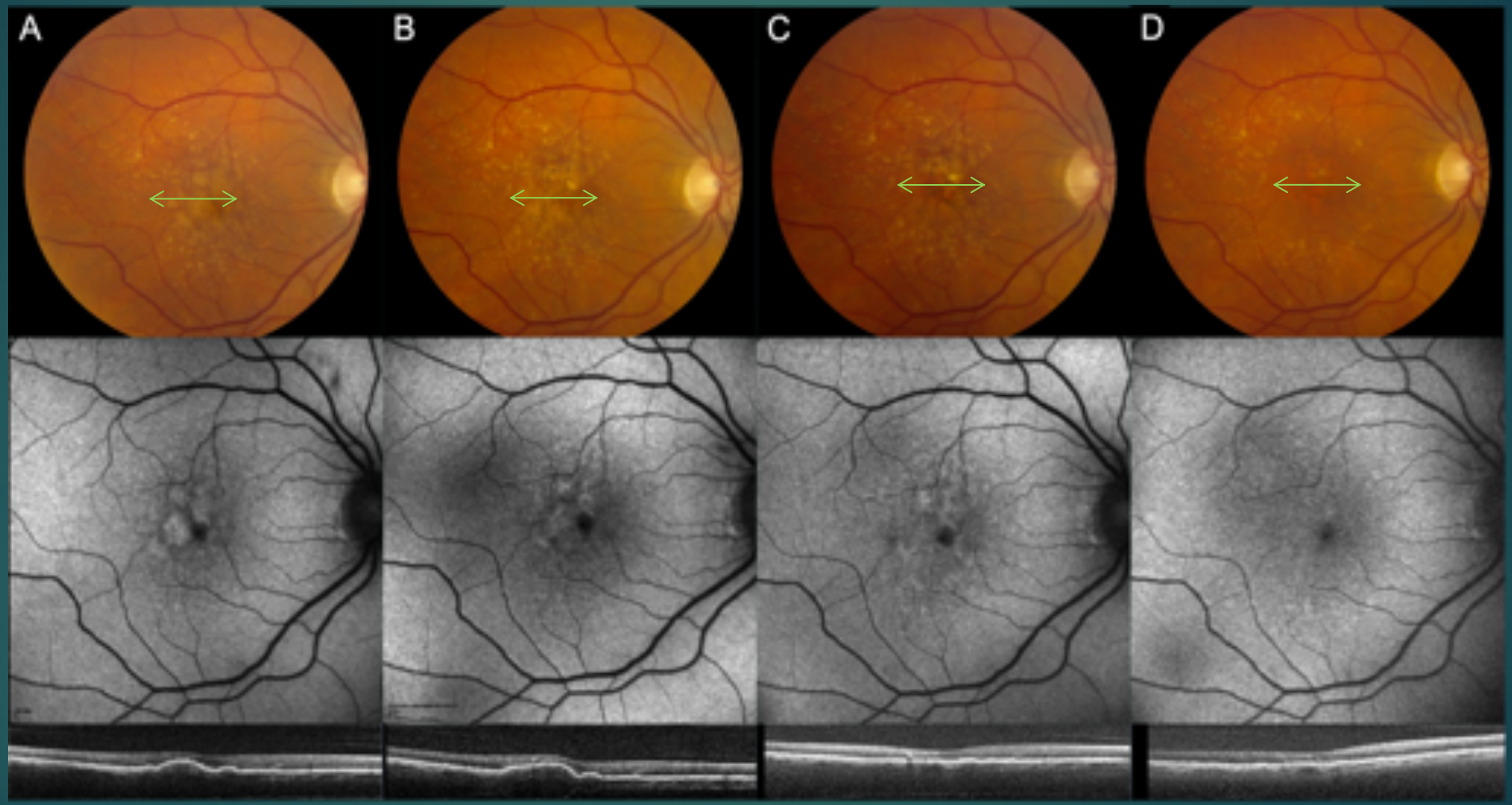
- *Geographic atrophy (GA)* is subset in absence of choroidal neovascularization (CNV)
- *Macular atrophy* encompasses both with and without associated CNV

Sadda SR, Guymer R, Holz FG, et al. *Ophthalmology*. 2018;125(4):537–548.

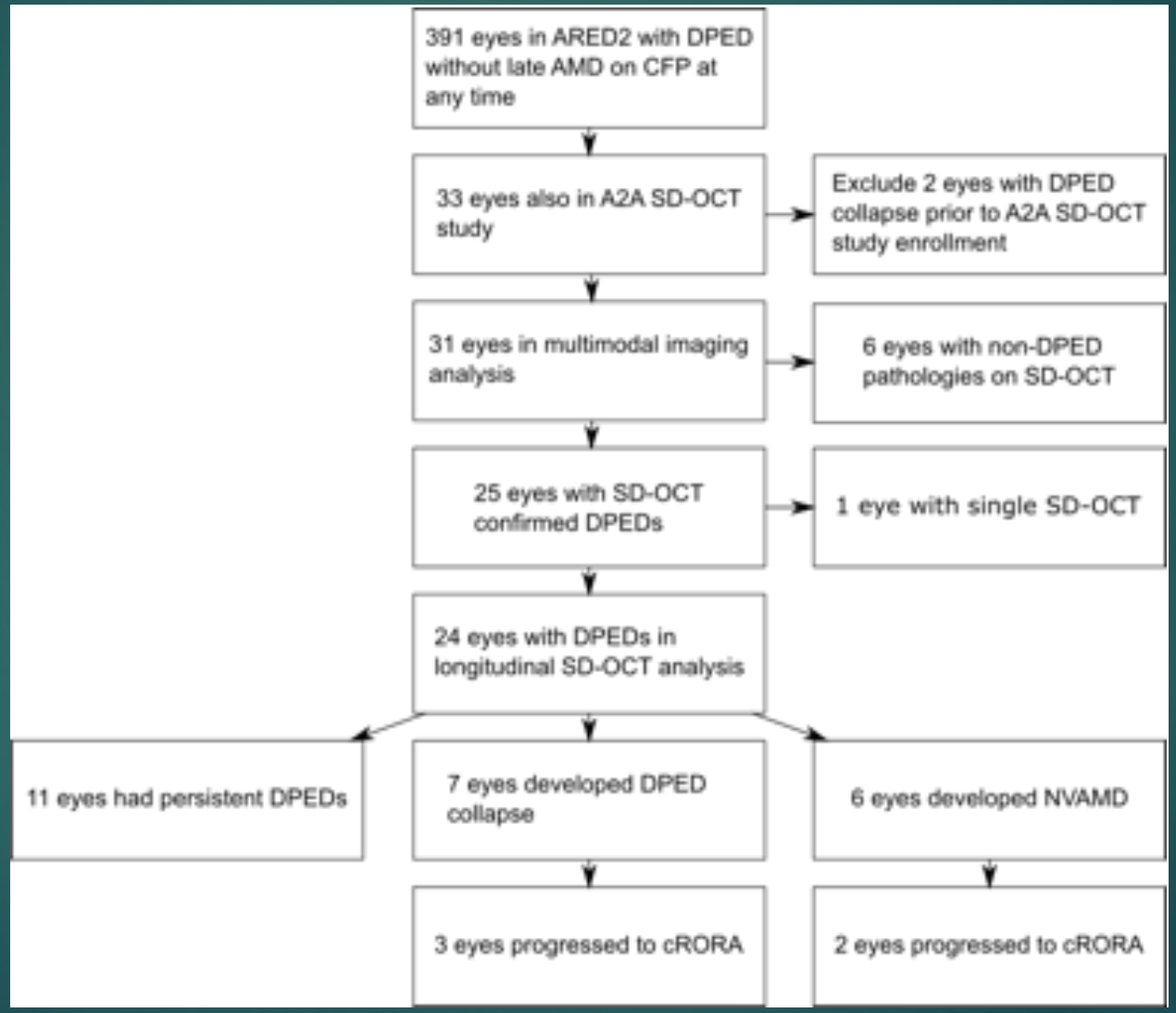
DPED collapse with progression to GA



DPED collapse without GA

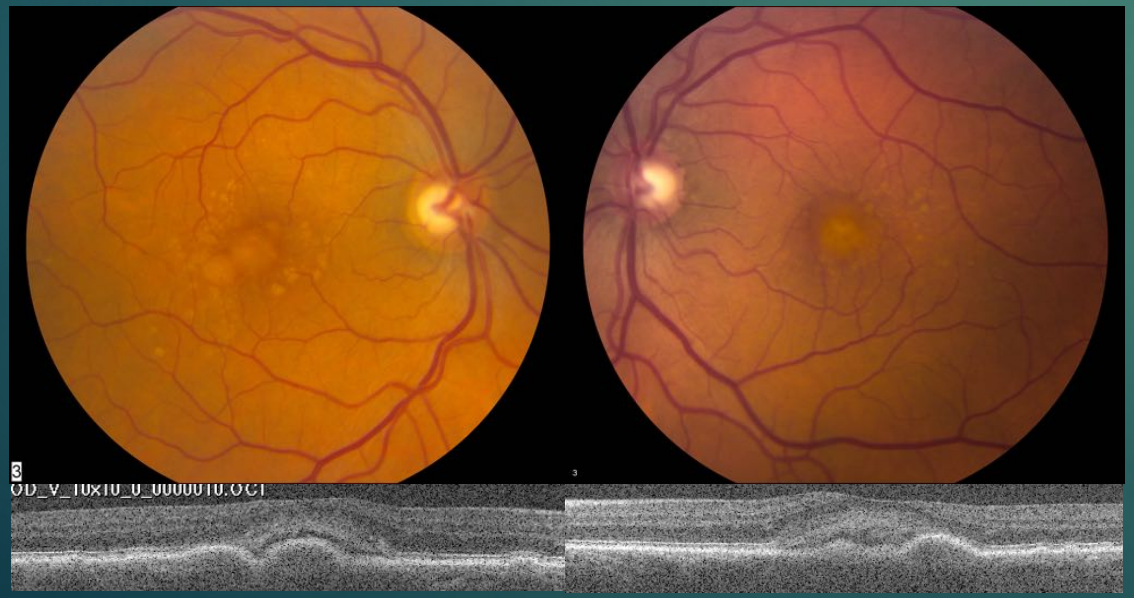


Results


391 eyes in ARED2 with DPED without late AMD on CFP at any time
33 eyes also in A2A SD-OCT study
Exclude 2 eyes with DPED collapse prior to A2A SD-OCT study enrollment
31 eyes in multimodal imaging analysis
6 eyes with non-DPED pathologies on SD-OCT
25 eyes with SD-OCT confirmed DPEDs
1 eye with single SD-OCT
24 eyes with DPEDs in longitudinal SD-OCT analysis
11 eyes had persistent DPEDs
7 eyes developed DPED collapse
6 eyes developed NVAMD
3 eyes progressed to cRORA
2 eyes progressed to cRORA

6 eyes with non-DPED OCT pathology

- Vitelliform lesion (2 eyes of same participant)
- Subretinal fibrosis (2 eyes)
- Epiretinal membrane (1 eye)



CFP and OCT agreement

- Compared to OCT-confirmed DPEDs, CFP alone had:
  - Sensitivity 40.8%
  - Specificity 76.3%
- At the time when DPED was first identified on CFP, DPED
  - Length averaged 1860±691 μm (minimum 433 μm used to define DPED based on AREDS2 size criterion)
  - Height averaged 206±58 μm

Results: Eyes with OCT-confirmed DPEDs

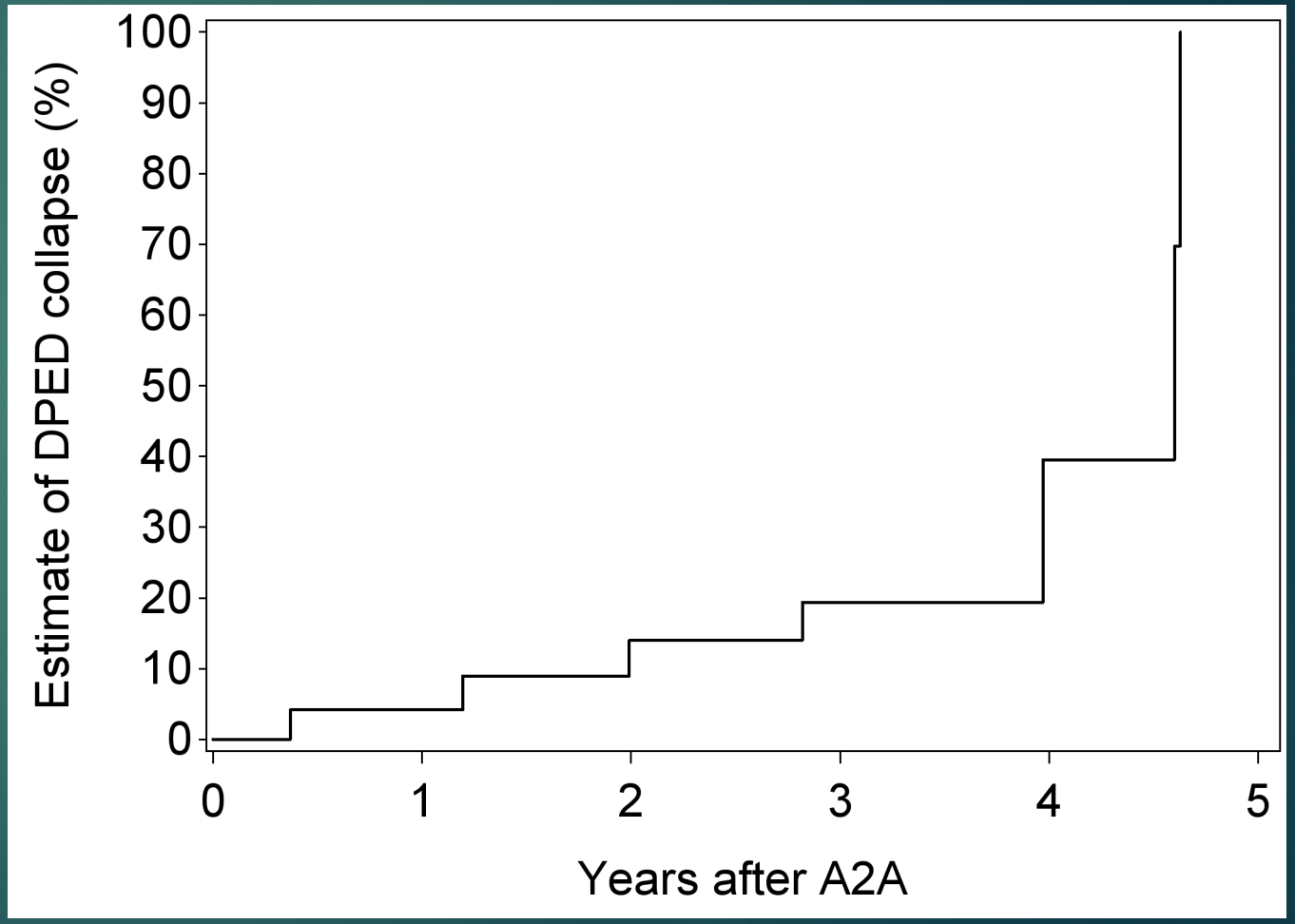
Characteristic	Persistent DPEDs	Collapsed DPEDs	Converted to NVAMD	All eyes with DPEDs
Number of eyes	11 (45.8%)	7 (29.2%)	6 (25%)	25[a]
Number of participants	8 (42.1%)	5 (26.3%)	6 (31.6%)	20
Age (years)	73.0±7.0	73.3±9.0	71.6±6.4	72.6±7.1
Male	5 (45.4%)	1 (14.3%)	1 (16.7%)	7 (28%)
Length of follow-up (years)	3.6±1.0 Median 3.8	4.5±0.4 Median 4.6	4.4±1.1 Median 4.3	3.9±1.2 Median 3.9
Visual acuity at reference visit (letters)	76.5±4.0 Snellen 20/32	78.1±1.9 Snellen 20/25	73.5±6.0 Snellen 20/32	76.1±4.3 Snellen 20/32
Reticular pseudodrusen[b]				
Present	0	3	1	4
Absent	10	4	3	18

[a] Includes 1 eye of 1 participant with single OCT scan not included in longitudinal analysis

[b] Only 21 eyes were graded for reticular pseudodrusen on fundus autofluorescence

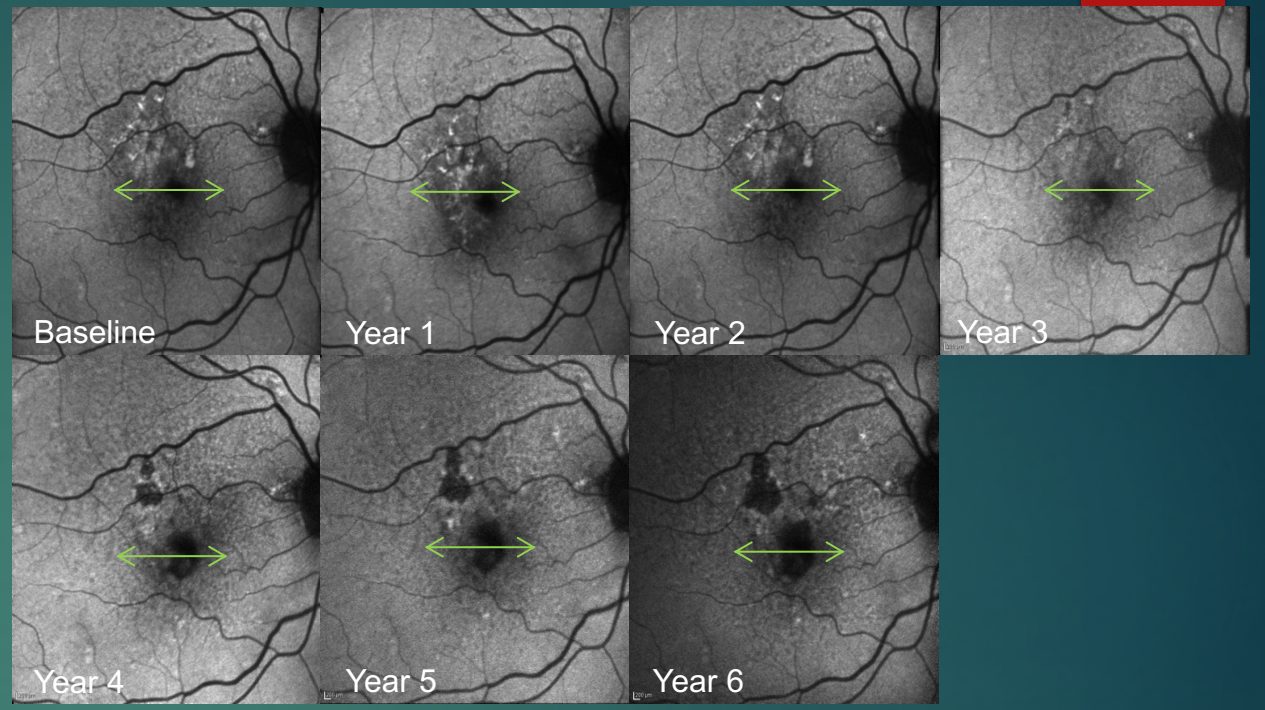
Longitudinal analysis: DPED collapse

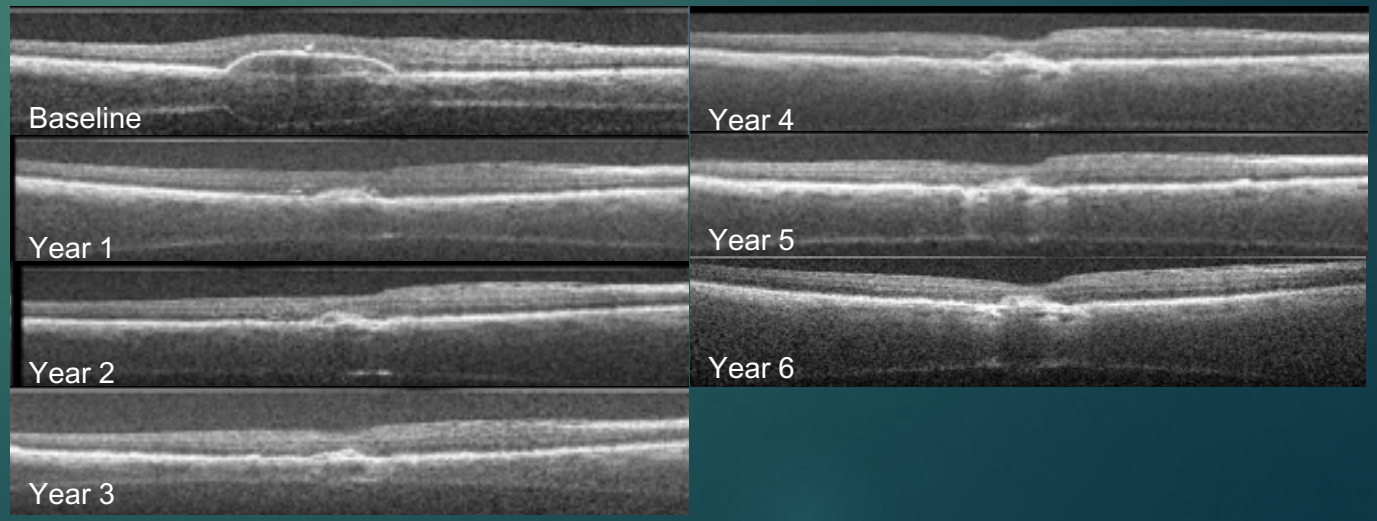
- 7/24 eyes (29.2%) had DPED collapse
- DPED collapse on SD-OCT = when a PED was no longer present (i.e. RPE separated <10 µm from Bruch's membrane) in the reference area
- Average time to collapse 3.9 ± 0.3 years



Progression to cRORA

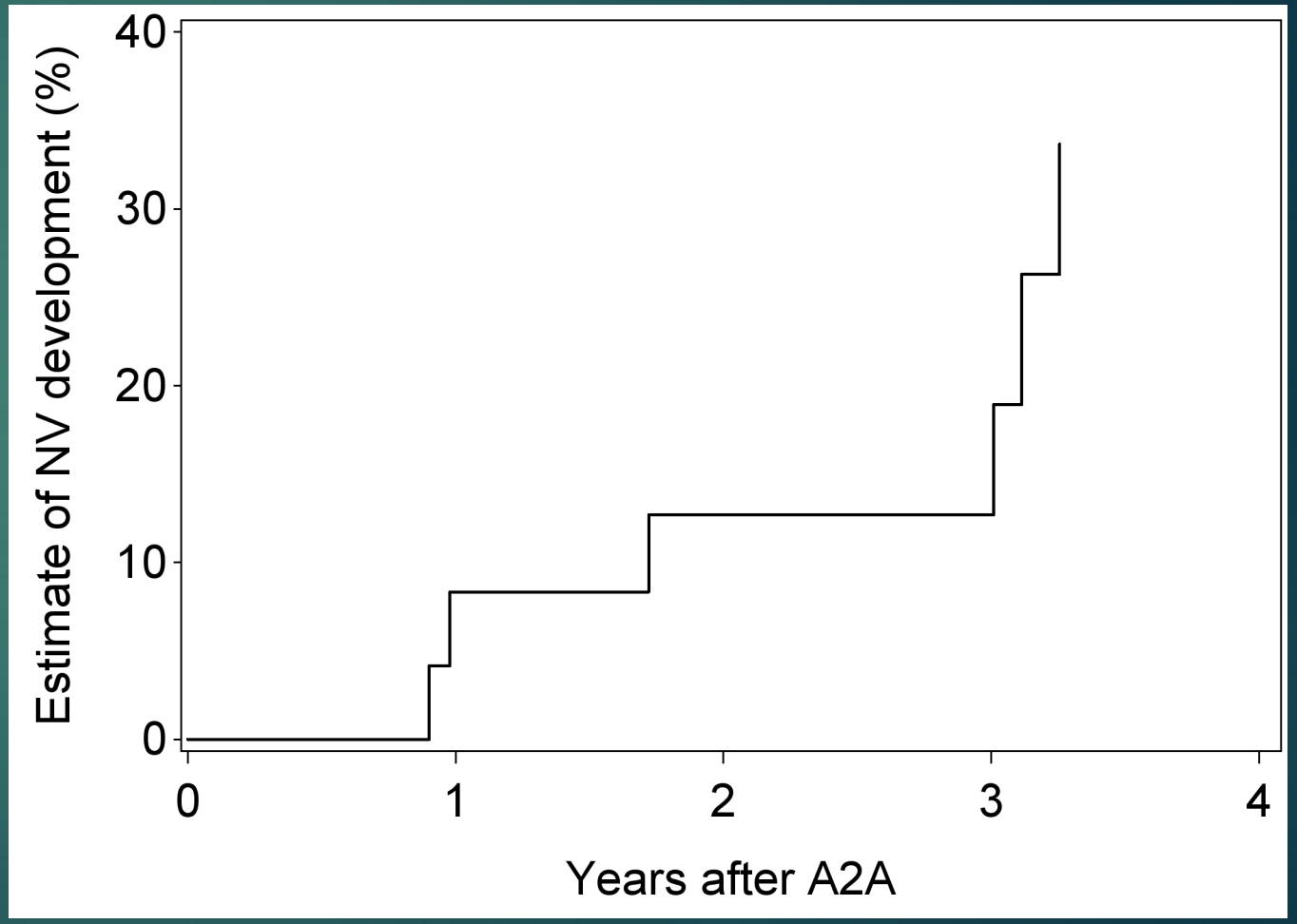
- 3 eyes (42.9%) developed cRORA by last follow-up
- Year 1: DPED collapse
- Years 1-3: iRORA
- Year 5: cRORA based on region of hypertransmission ≥250 µm





Longitudinal analysis: Neovascularization

- 6/24 eyes (25%) developed NVAMD
- NVAMD = definite disciform scar or any treatment for NVAMD or ≥2 of the following features: neurosensory retinal detachment, PED, subretinal/sub-RPE hemorrhage, hard exudates, or fibrous tissue
- Average time to neovascularization 2.9 ± 0.2 years



DPED Measurements

Characteristic	Persistent DPEDs (N=11)	Collapsed DPEDs (N=6)	Converted to NVAMD (N=6)
Max length (µm)	2030 (1233, 2201)	1461 (1204, 2240)	2526 (2293, 2848)
Max height (µm)	192 (167, 211)	232 (210, 255)	274 (266, 312)
Length at reference visit[a] (µm)	1755 (1219, 2184)	1561 (1256, 2238)	2291 (1827, 2585)
Height at reference visit[a] (µm)	172 (159, 206)	208 (166, 233)	259 (239, 269)

Data expressed as median (interquartile range)

[a] Reference visit defined for each eye when color fundus photography first graded DPED as present

- Eyes that later converted to NVAMD had preceding DPEDs that tended to be greater in size than eyes with persistent DPEDs or DPEDs that later collapsed

Fastest DPED size growth in eyes preceding neovascularization

- Mixed-model regression using adjusted repeated measures regression with DPED length, years from baseline, and their interaction term

Characteristic	**Persistent DPEDs (N=11)**	**Collapsed DPEDs (N=6)**	**Converted to NVAMD (N=6)**	***P* value of interaction**
DPED length (µm/yr)	174.3 (95% CI 96.2, 252.5)	48.4 (95% CI -131.0, 227.7)	406.6 (95% CI 194.8, 618.5)	0.04
DPED height (µm/yr)	14.6 (95% CI 5.8, 23.3)	14.5 (95% CI -6.0, 35.0)	28.4 (95% CI 4.2, 52.6)	0.56

SD-OCT Characteristics

- Focal high hyperreflectivity was seen over the RPE elevation in all OCTs at the study visit preceding DPED collapse or conversion to NVAMD

SD-OCT characteristics at last visit with a DPED	Persistent DPEDs (N=11)	Collapsed DPEDs (N=7)	Converted to NVAMD (N=6)
	Last study visit	Last visit prior to DPED collapse	Last visit prior to neovascularization
RPE elevation (Drusen, PED)	11 (100%)	7 (100%)	6 (100%)
RPEE w/ low internal reflectivity (<PRL)	6 (54.5)	4 (57.1%)	6 (100%)
RPEE w/mid internal reflectivity (>PRL to <RPE)	11 (100%)	7 (100%)	5 (83.3%)
RPEE w/high internal reflectivity (>RPE)	10 (90.9%)	4 (57.1%)	3 (50%)
At least 1 definite core	4 (36.4%)	4 (57.1%)	2 (33.3%)
Focal high hyperreflectivity over RPE elevation	9 (81.8%)	7 (100%)	6 (100%)
Photoreceptor thinning above RPE elevation	11 (100%)	7 (100%)	6 (100%)
RPE absence/atrophy	0	0	1 (16.7%)
Cystoid macular edema	0	3 (42.9%)	5 (83.3%)
Subretinal fluid	4 (36.4%)	0	2 (33.3%)

Strengths

- Prospective design
- Integration of multimodal imaging: color fundus photography, fundus autofluorescence, and optical coherence tomography
- Standardized reading center grading of these different imaging modalities

Limitations

- Small number of eyes
- Limited follow-up duration and interval of imaging (annually)

Conclusion

- Addition of SD-OCT imaging to CFP may allow earlier and more accurate detection of DPEDs.
- DPEDs change in size at different rates, which may be correlated to the AMD status of the eye.
- Future work will:
  - Follow eyes after DPED collapse to determine factors influencing progression to cRORA
  - Define DPEDs based on CFP and SD-OCT
  - Detect DPEDs earlier to identify risk factors for DPED growth, collapse, and neovascularization