Imagerie Multimodale de la DMLA
DRUSEN

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DU DMLA
14 juin 2023

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Vitreous-Retina-Macula Consultants of New York, P.C.

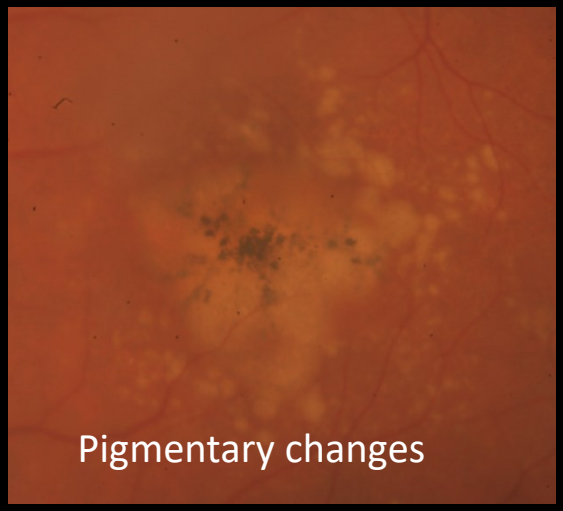
Age-Related Macular Degeneration
General Facts

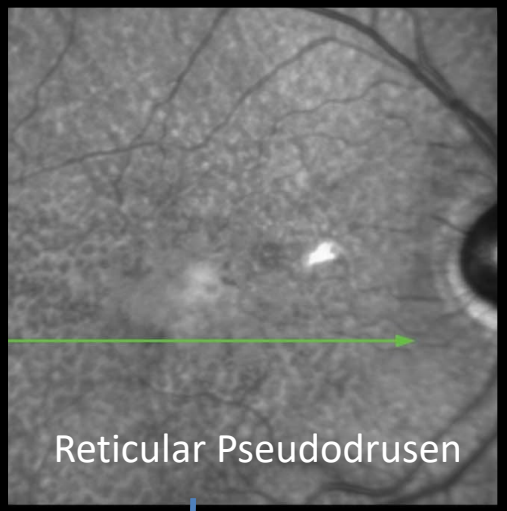
- Heterogeneous chronic progressive degenerative disease of the central retina, in older adults
- First cause of blindness in industrialized countries
- Paramount observations by Gass
  - 1967: CNV
  - 1973: drusen evolve to CNV
- Classifications evolve to become more predictive of evolutive risks towards late stages

Gass JD. Pathogenesis of disciform detachment of the neuroepithelium. Am J Ophthalmol 1967.
Gass JD. Drusen and disciform macular detachment and degeneration. Arch Ophthalmol 1973.

Advanced Age-Related Macular Degeneration

Common genetic and environmental risk factors for wet and atrophic AMD
Common imaging biomarkers predictive of atrophy and CNV
- Large soft drusen
- Pigmentary changes
- Reticular Pseudodrusen





Neovascular AMD

Atrophic AMD

Age-Related Macular Degeneration

Phenotypes through Multimodal Imaging

- Towards a new anatomic classification of drusen
  - Sub-RPE Drusen
    - Conventional drusen
    - Cuticular drusen
  - Subretinal Drusen
    - Reticular pseudodrusen

- Towards a new anatomic classification of neovascular AMD (1)
  - Type 1 neovascularisation (NV): sub-RPE NV, occult
  - Type 2 NV: subretinal, classic
  - Type 3 NV: intraretinal, Retinal Angiomatous Proliferation (RAP)

- Towards a new anatomical classification of atrophy?
  - RPE atrophy or Geographic atrophy
  - Outer retinal atrophy without RPE loss (2)

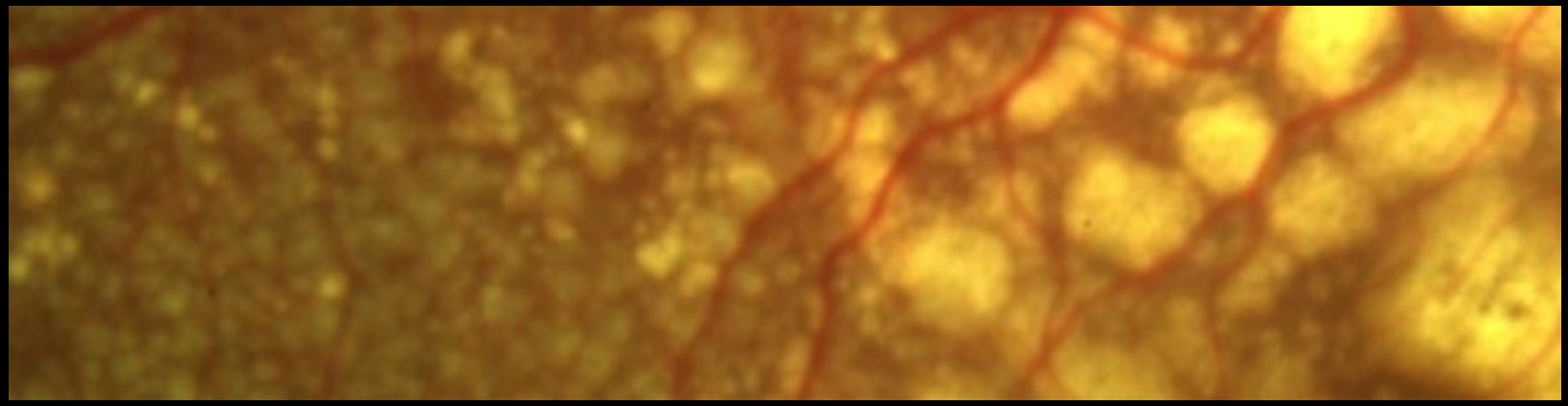
1. *Freund KB, Zweifel SA, Engelbert M. Do we need a new classification for choroidal neovascularization in age-related macular degeneration? Retina 2010.*
2. *Spaide RF. Outer retinal atrophy after regression of subretinal drusenoid deposits as a newly recognized form of late AMD. Retina 2013.*

Drusen
Classification

Small drusen
< 63 microns

Intermediate drusen
63 to 124 microns

Large drusen
>125 microns



1991

Klein R, Davis MD, Magli YL, et al. The Wisconsin age-related maculopathy grading system. Ophthalmology 1991.

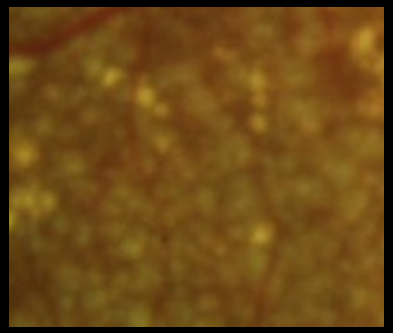
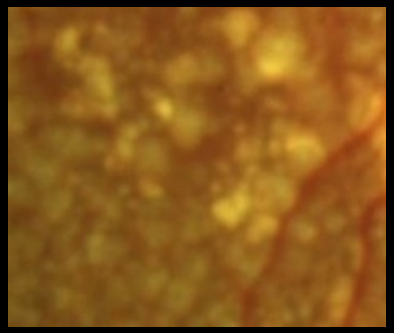
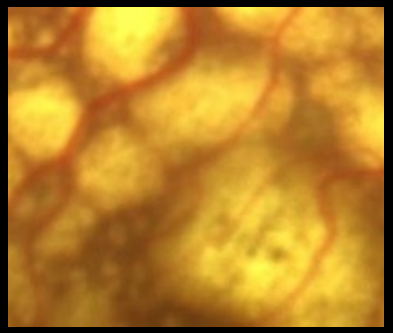
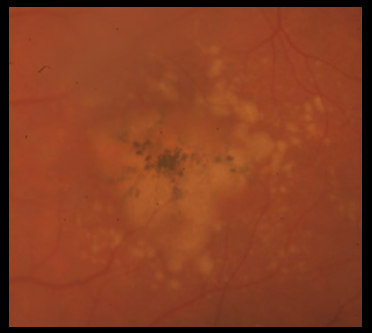
Ferris et al, 2013

Drusen
Classification

Clinical Classification of Age-related Macular Degeneration

Frederick L. Ferris III, MD,[1] C. P. Wilkinson, MD,[2] Alan Bird, MD,[3] Usha Chakravarthy, MD,[4] Emily Chew, MD,[1] Karl Csaky, MD,[5] SriniVas R. Sadda, MD,[6] on behalf of the Beckman Initiative for Macular Research Classification Committee*

Small drusen	**Medium drusen**	**Large drusen**	**Pigmentary Changes**
< 63 microns	*63 to 124 microns*	*>125 microns*	
NORMAL AGEING	EARLY AMD	INTERMEDIATE AMD	INTERMEDIATE AMD

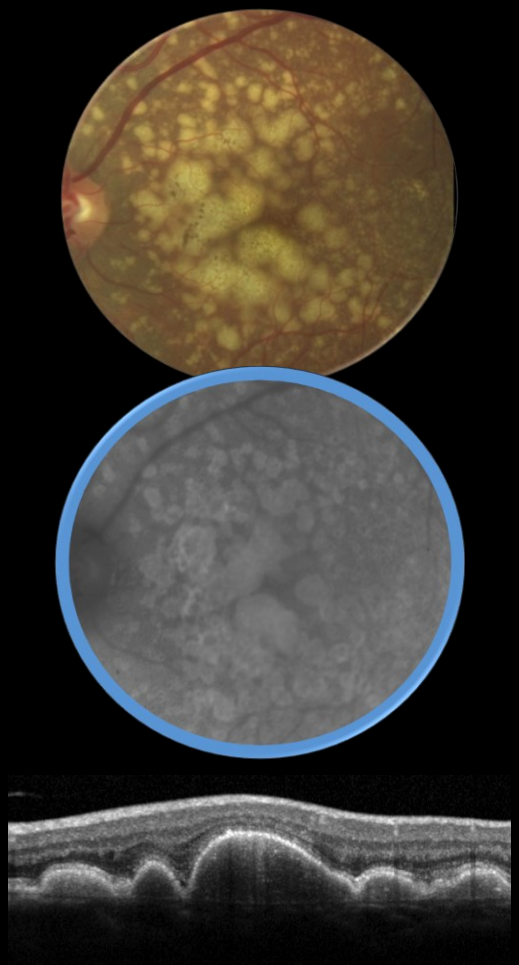
1 eye	0.4%	0.5%	3.9%	medium drusen 20%
2 eyes	0.4%	2.1%	13%	large drusen 47.3%

5-year rate of developing advanced AMD for conventional drusen

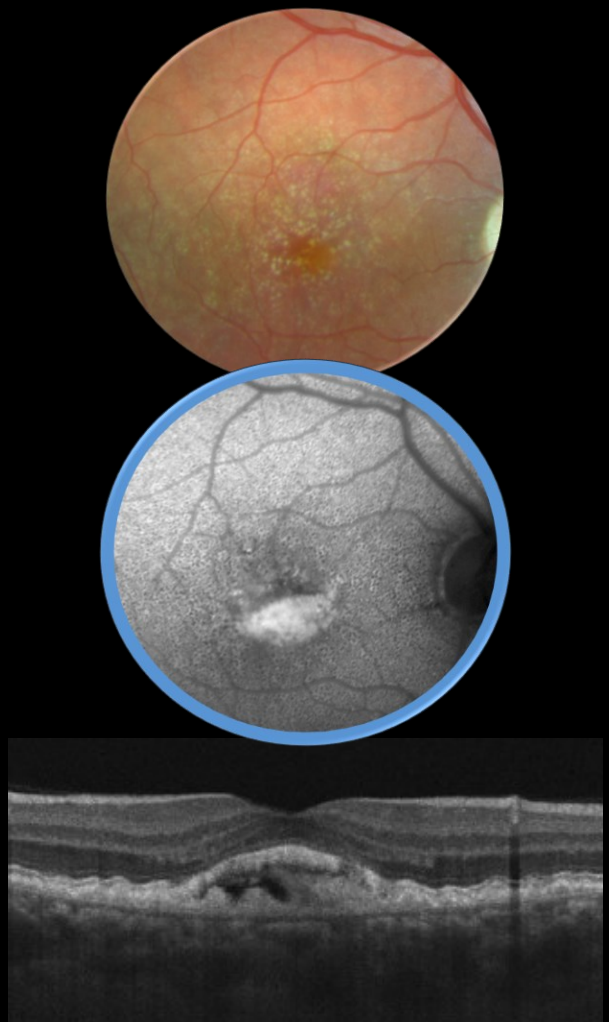
Drusen

Classification using Multimodal Imaging

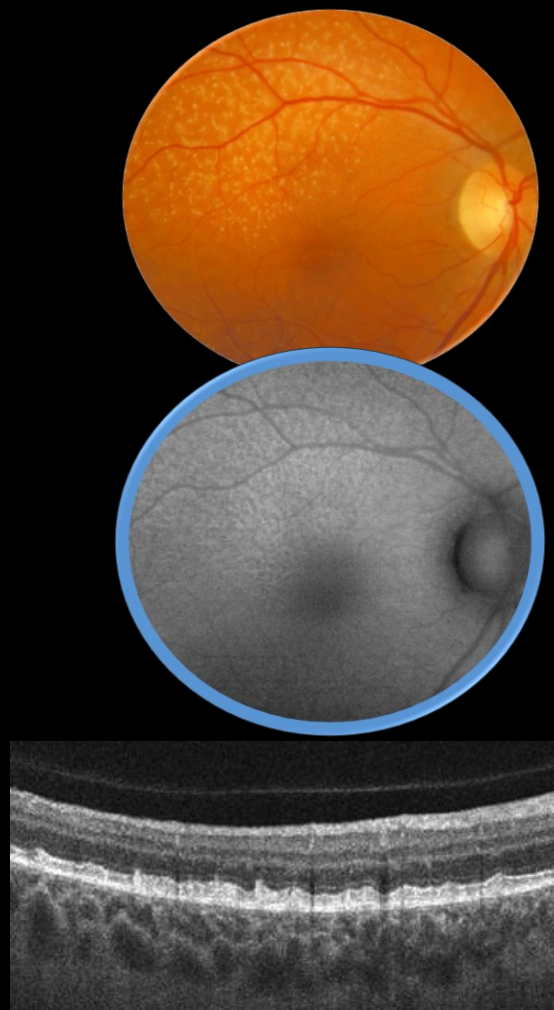
Conventional Drusen



Cuticular Drusen



Reticular Pseudodrusen



Multimodal Imaging

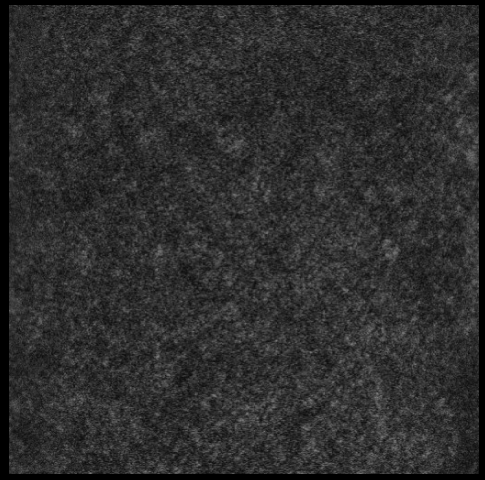
Tools to investigate the pathogenesis

- SD OCT and eye-tracking → Dynamic evaluation
  - sequence of events leading to late AMD
  - predictive biomarkers
- SD OCT biomarkers correlation with histology
- Cellular level imaging *in vivo* → Adaptive Optics
- Evaluating perilesional areas
  - Space is a surrogate for time

Multimodal Imaging
Adaptive Optics

Correcting element
electromagnetic deformable mirror

Rtx-1 Adaptive Optics (AO)
Flood-Illuminated Retinal Camera



Wavefront sensor
1024-lenslet Shack-Hartmann sensor

Charge-Coupled Device Camera

2 light sources: SLD 750nm (optical aberrations)
LED 830nm (retinal imaging)

Our protocol
multiple AO images
1 to 8˚ of retinal eccentricity
consent form / IRB approval

transverse resolution: 3 µm

Image size : 4x4 degrees

Acquisition time: 4 seconds, 40 images

Multimodal Imaging
Adaptive Optics

Imaging cells in the living retina with adaptive optics

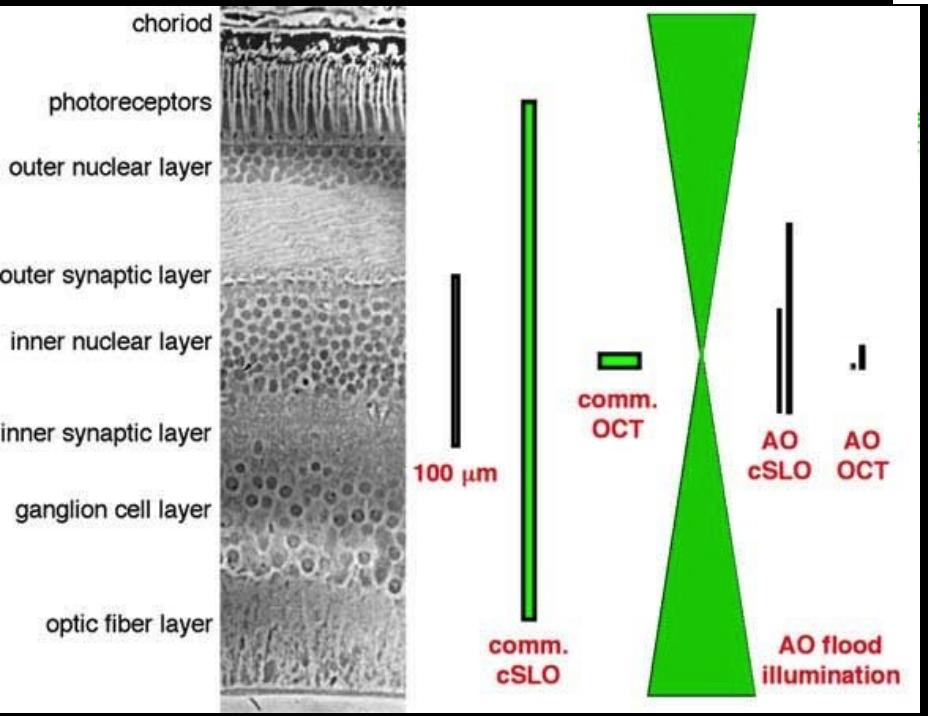
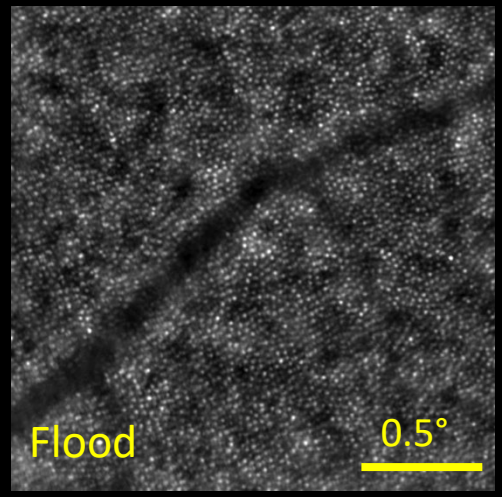
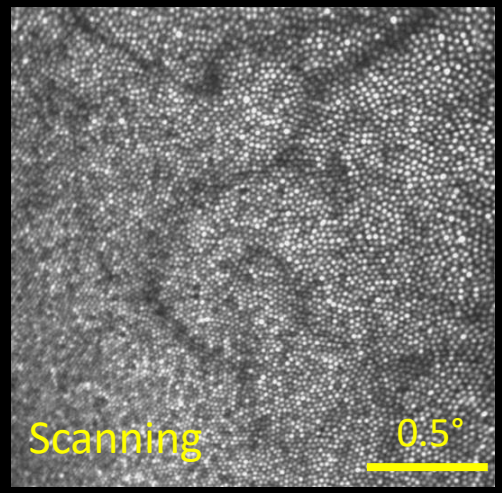


Figure: D. Miller, University of Indiana



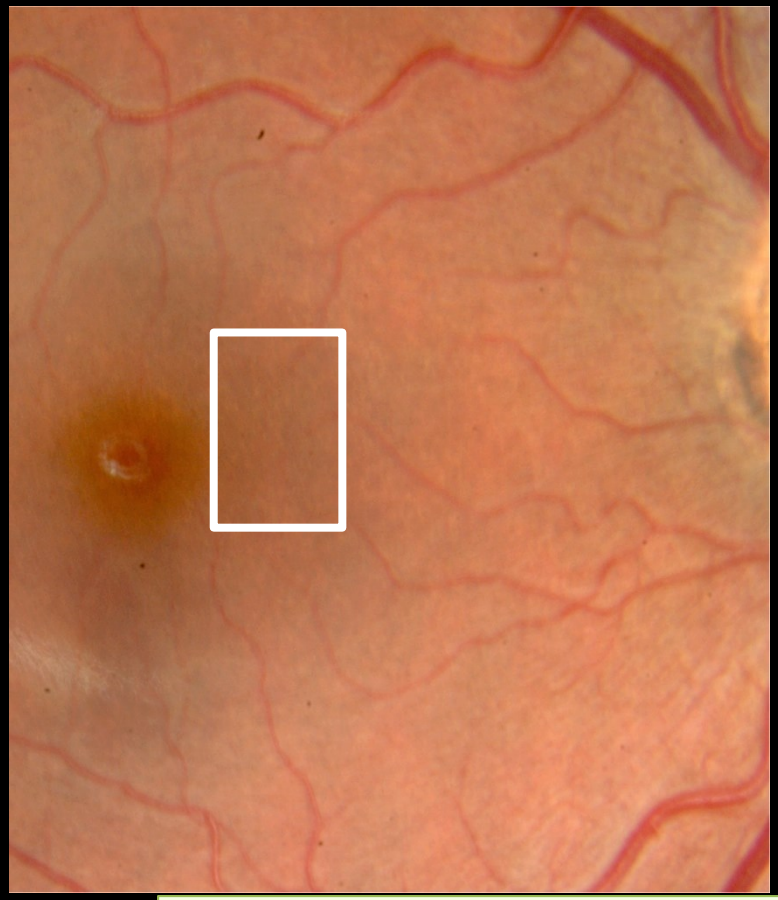
Imagine Eyes RTX1 AO retinal camera

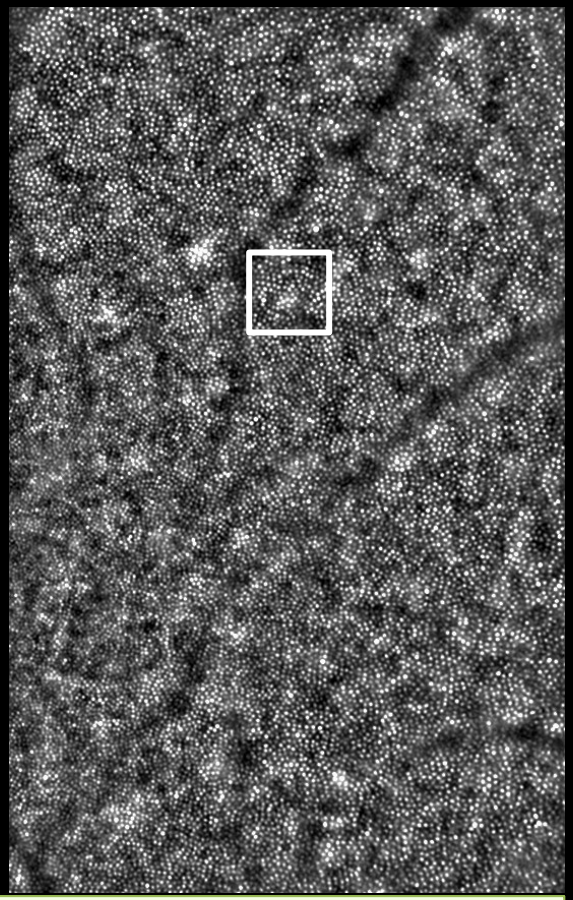


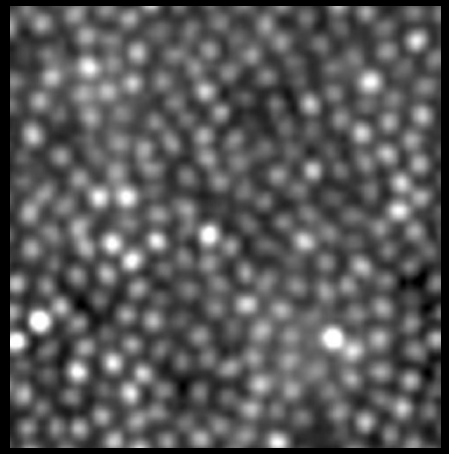
PSI MAORI scanning AO-SLO-OCT

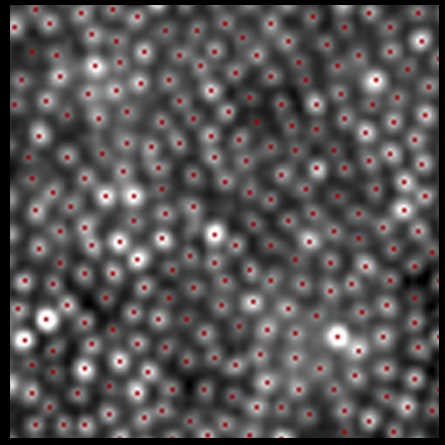
Kate Grieve

Multimodal Imaging
Adaptive Optics









17580 cones / mm²

cone detection and packing density measurement

Software programs provided by the manufacturer
CK v0.1 and AO detect v0.1 (Imagine Eyes, France)

Drusen: différents phénotypes

Dépôts focaux de matériel extra-cellulaire

Tous les drusen composition biochimique similaire

- Dérivés des glucides, zinc, cellules inflammatoires
- Protéines
  - Vitronectine, Apolipoprotéines E, B, béta-amyloïde, complément
- Lipides
  - Cholestérol estérifié et non estérifié

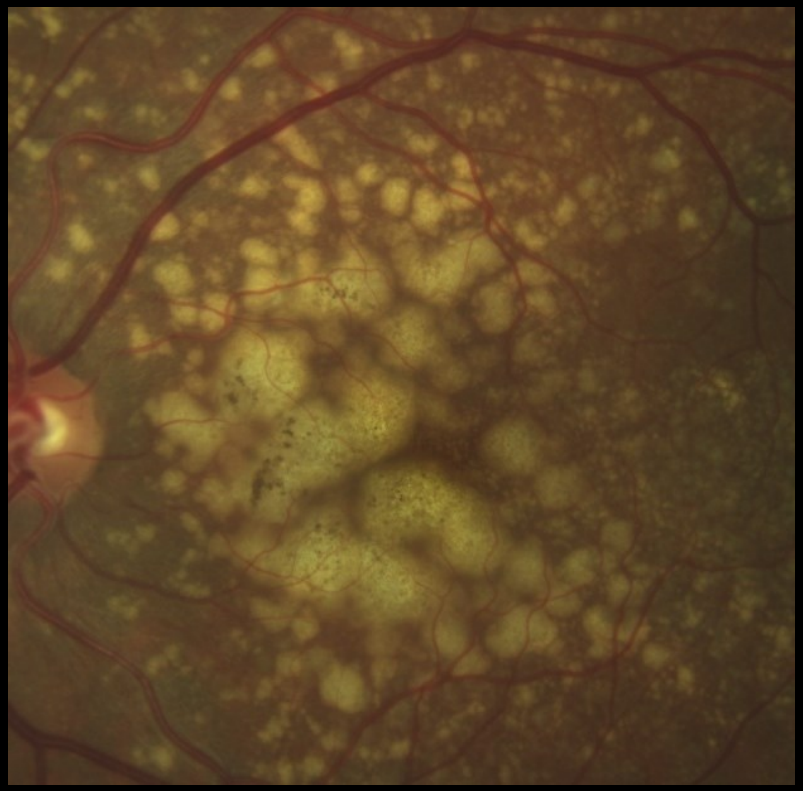
Vers une nouvelle classification anatomique des drusen

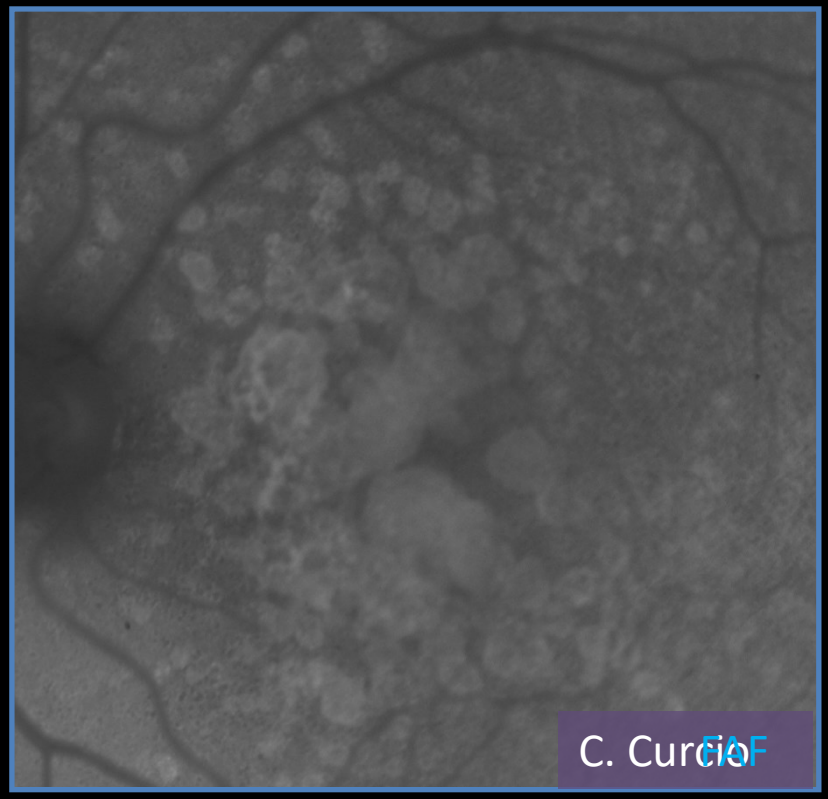
- Drusen sous-épithéliaux
  - Drusen séreux conventionnels
  - Drusen cuticulaires
- Drusen pré-épithéliaux
  - Pseudodrusen réticulés

Pertinence d'une classification des drusen basée sur l'imagerie multimodale?

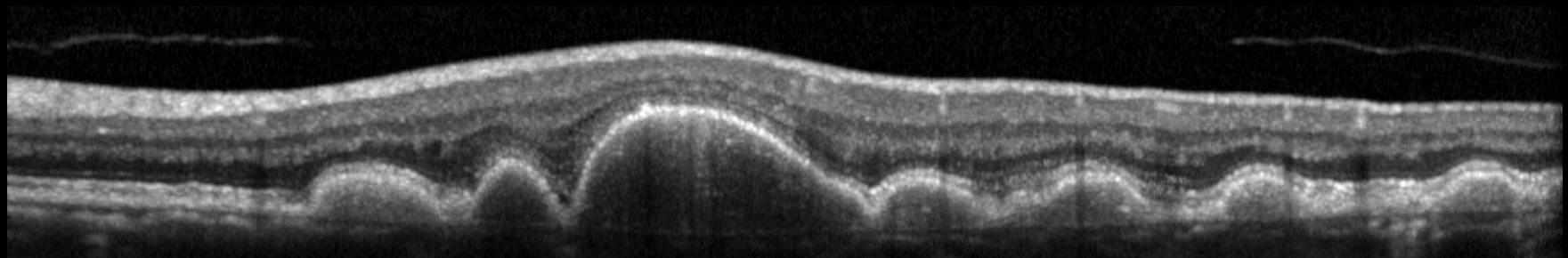
- Retentissement différent sur les photorécepteurs → sensibilité rétinienne
- Evolution différente? Complications spécifiques
- Risque différentiel d'évolution vers les stades de DMLA tardive

Large Soft Drusen





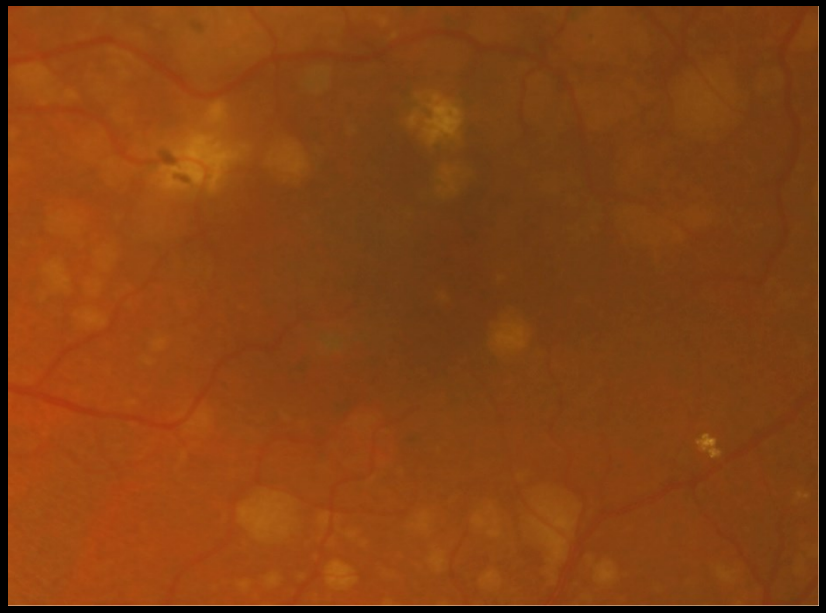
Basal lamina of RPE
Inner collagenous layer of Bruch's

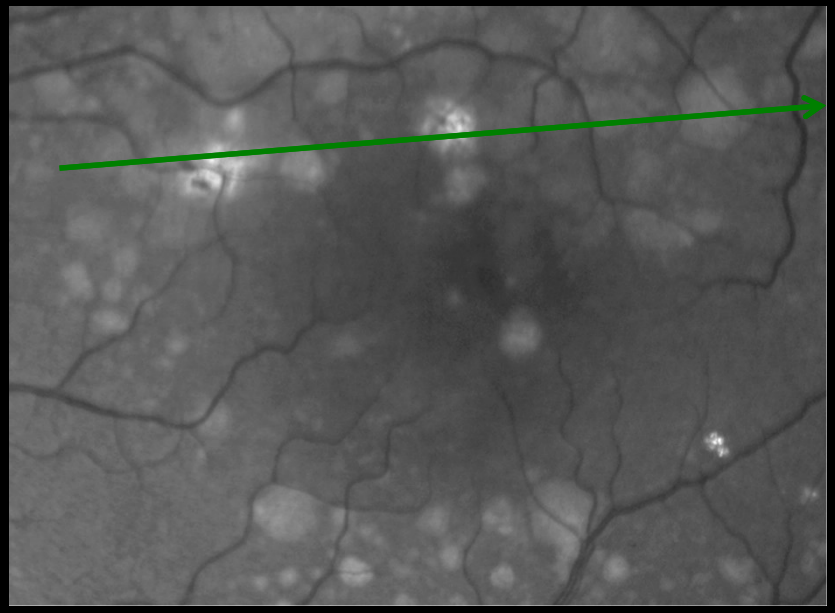


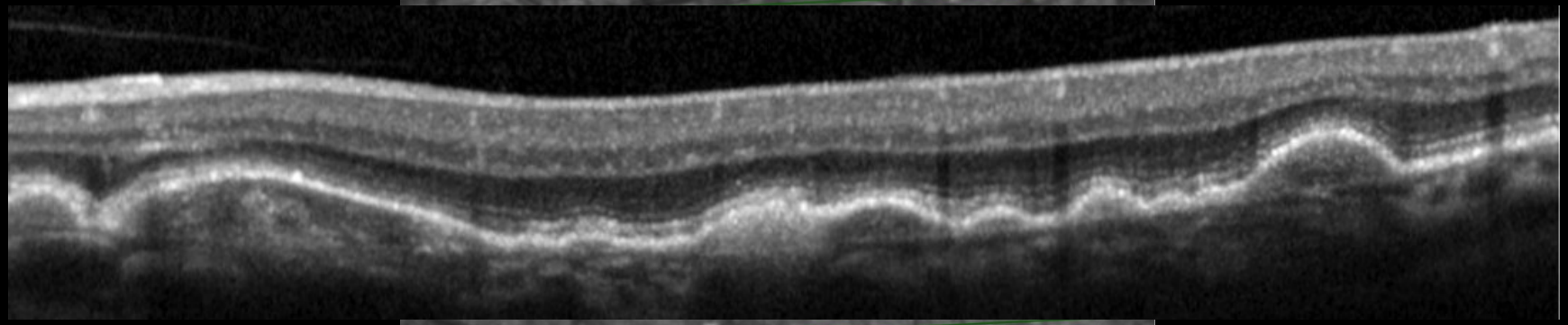
Curcio: "lipoprotein-derived debris: esterified and unesterified cholesterol"
More frequent in the central macula

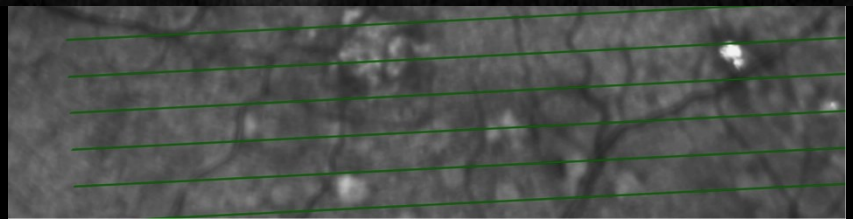
Soft Drusen

Multimodal Imaging









Soft Drusen

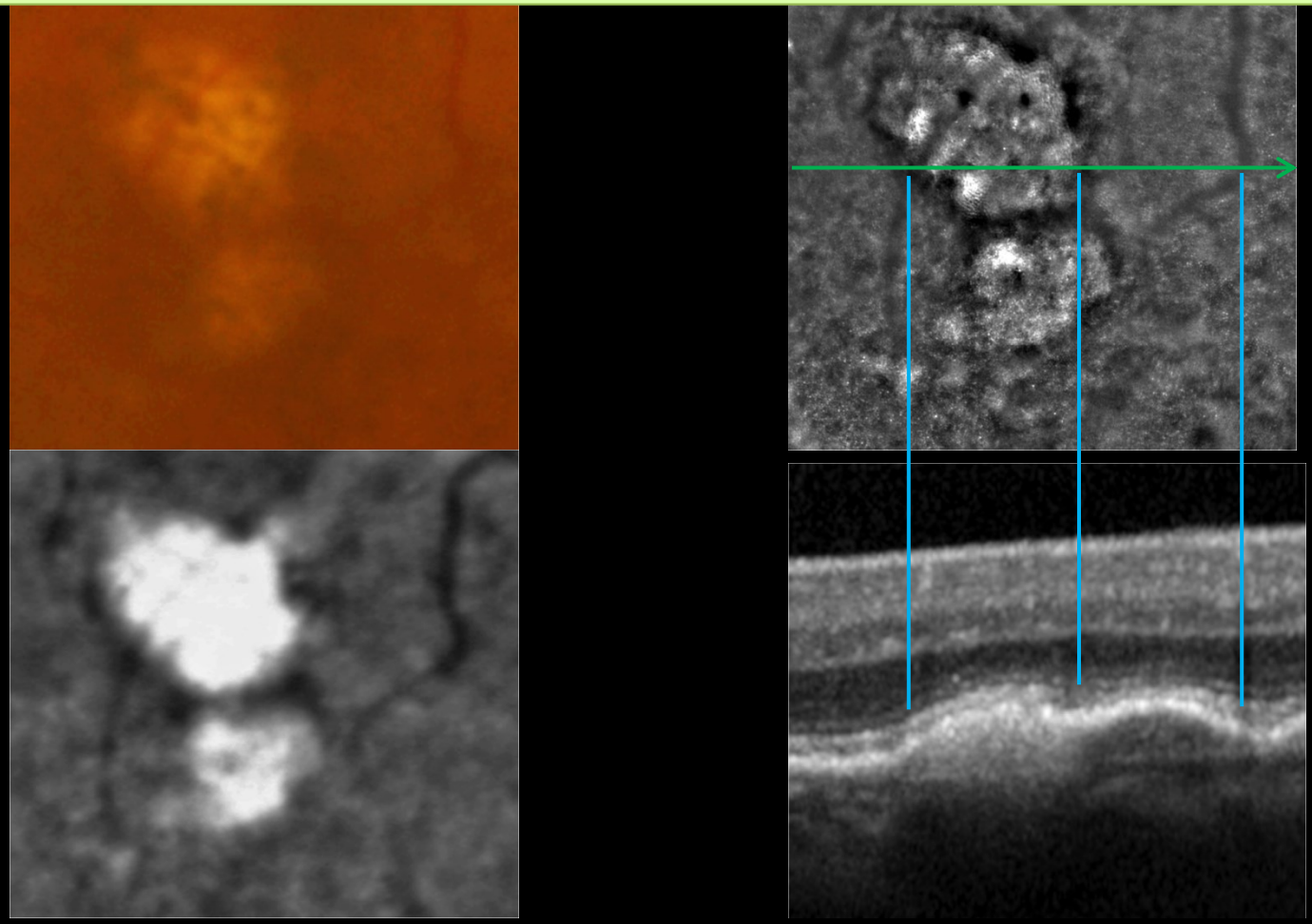
Adaptive Optics

Rtx-1 Adaptive Optics (AO)
Flood-Illuminated Retinal Camera

Soft Drusen

Adaptive Optics

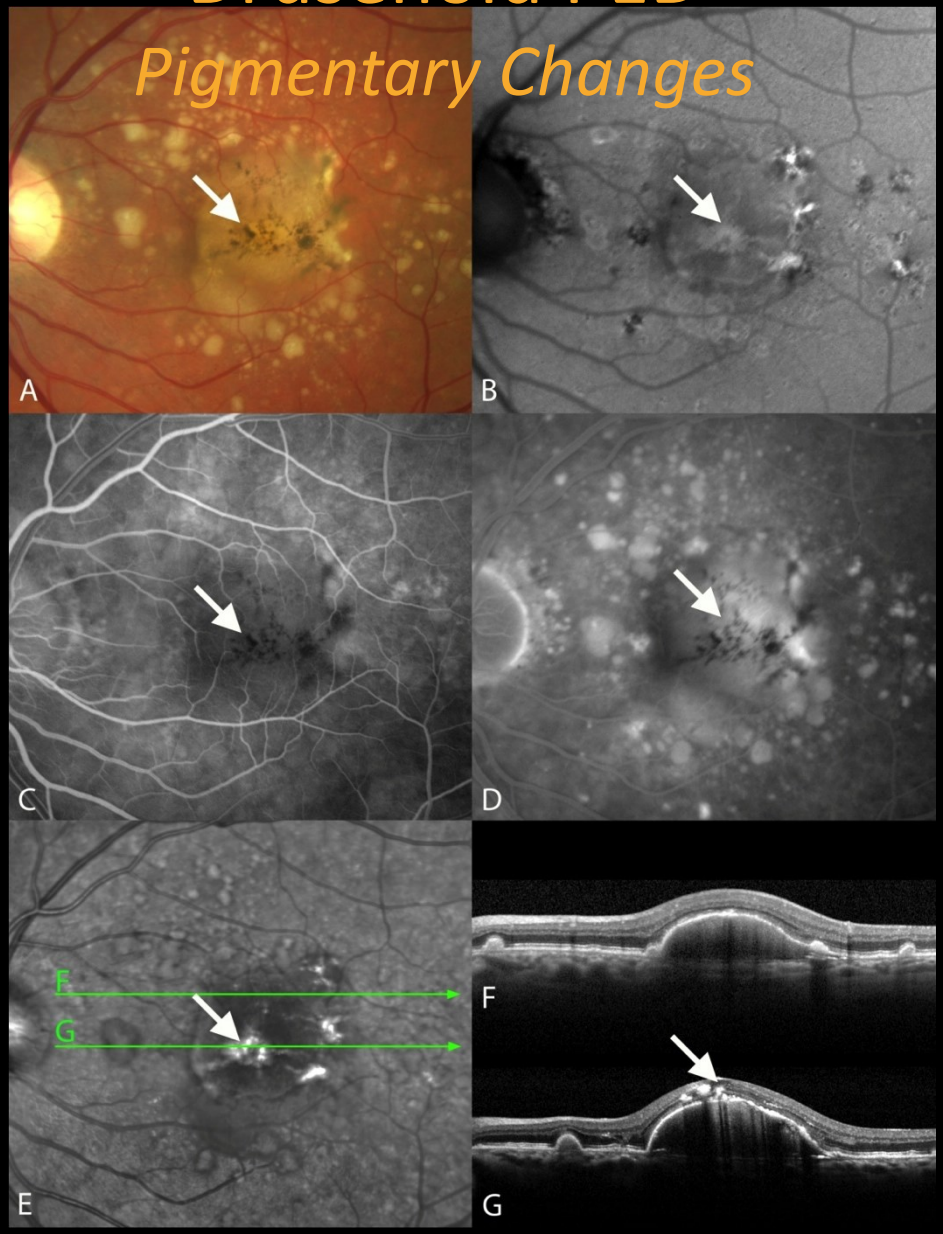
Co-localization of soft drusen with IR-SLO, SD-OCT and AO



Mrejen S, Sato T, Curcio CA, Spaide RF. Assessing the cone photoreceptor mosaic in eyes with pseudodrusen and soft drusen in vivo using adaptive optics imaging. Ophthalmology 2013.

Drusenoid PED

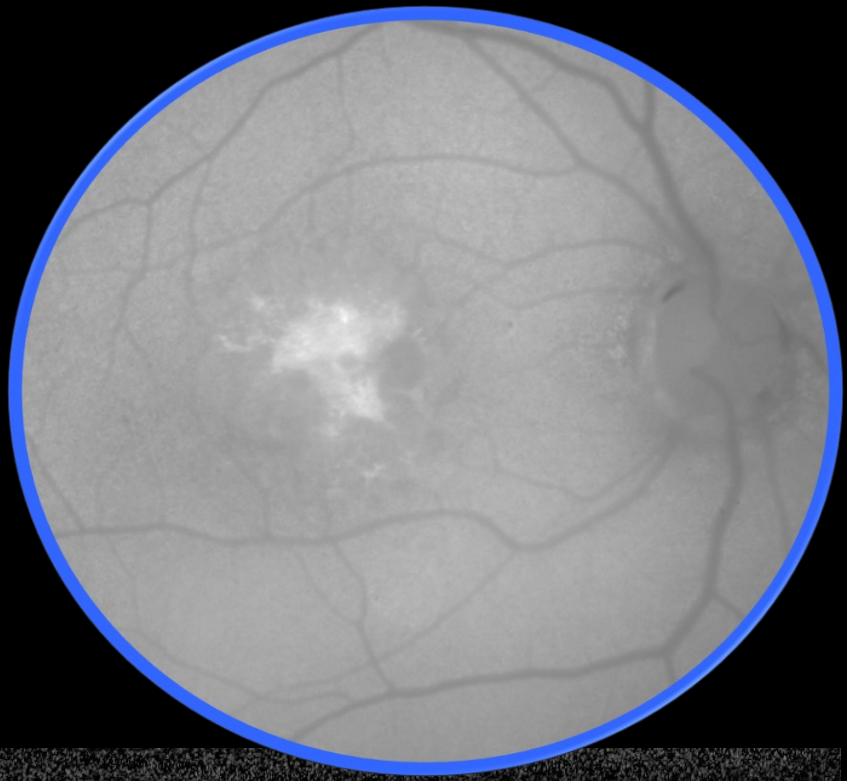
Pigmentary Changes

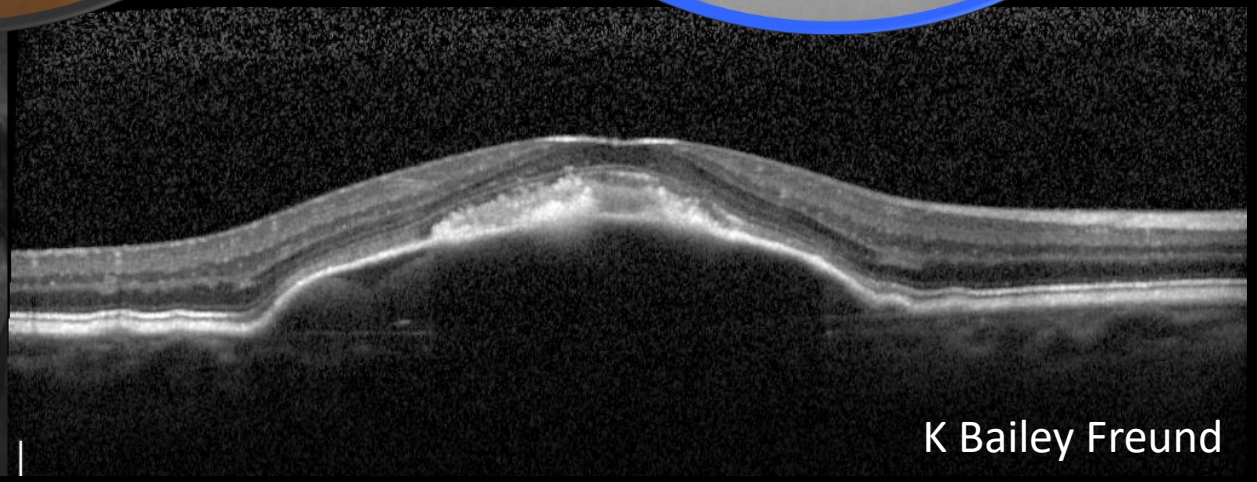


Mrejen S, Sarraf D, Mukkamala SK, Freund KB. Multimodal imaging of pigment epithelial detachment: a guide to evaluation. Retina. 2013.

Drusenoid PED

Acquired Vitelliform Lesions





Drusenoid PED

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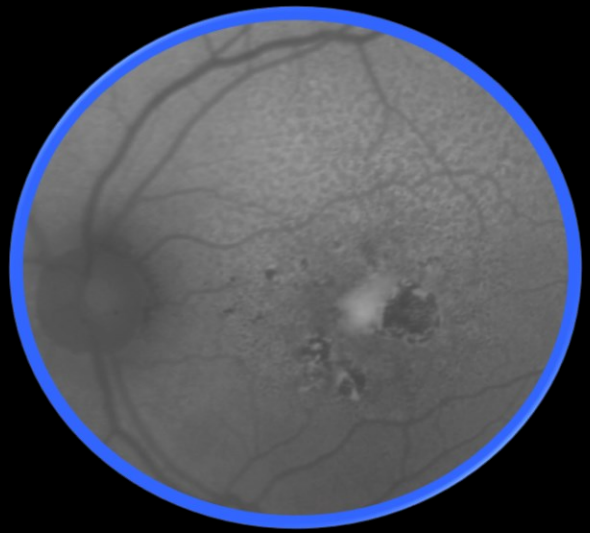
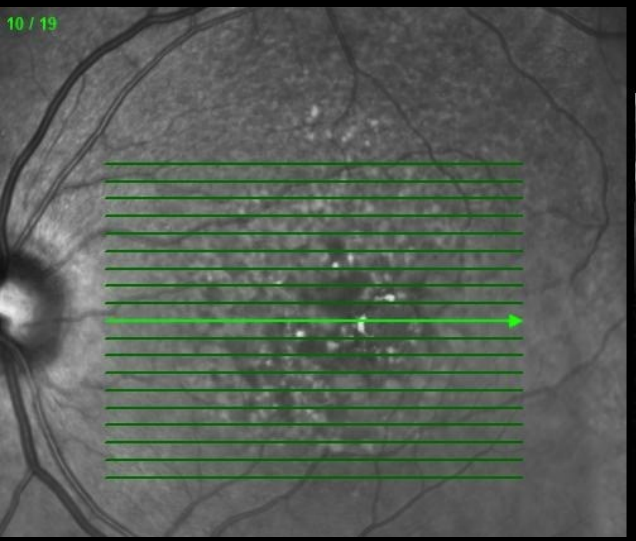


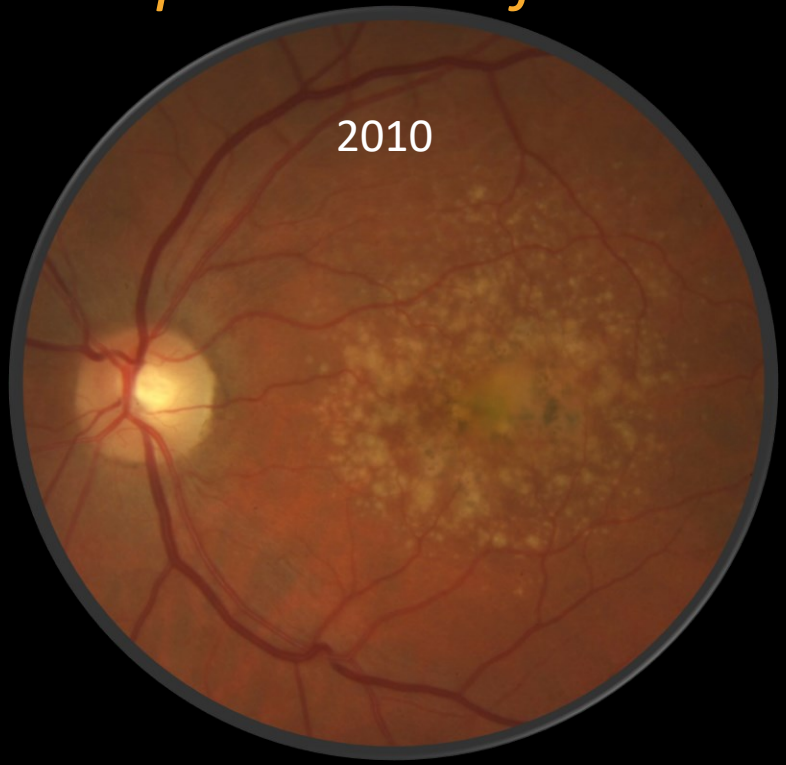


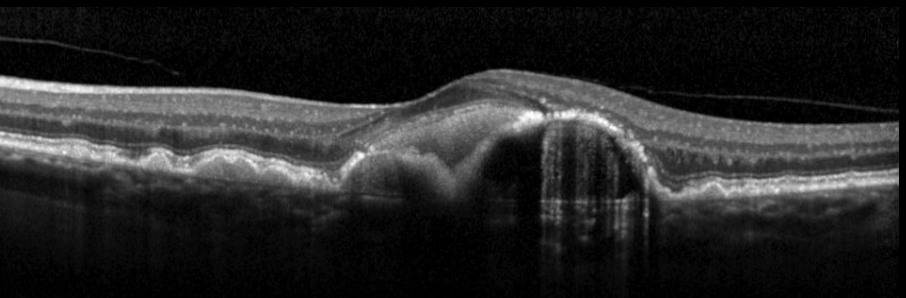
RPE atrophy predates the collapse of the PED

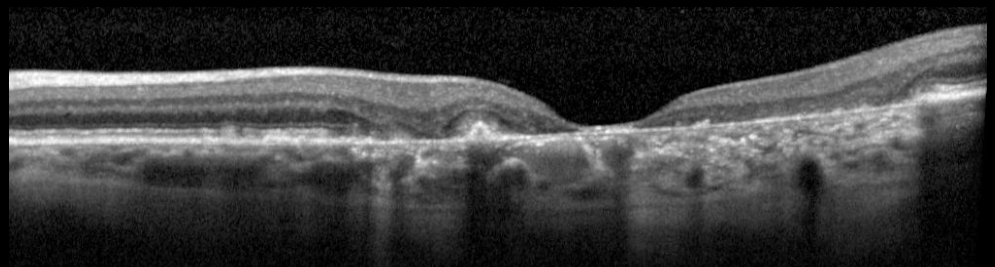
Mrejen S, Sarraf D, Mukkamala SK, Freund KB. Multimodal imaging of pigment epithelial detachment: a guide to evaluation. Retina. 2013.

Drusenoid PED

Acquired Vitelliform Lesion and Evolution to RPE Atrophy







RPE atrophy predates the collapse of the PED

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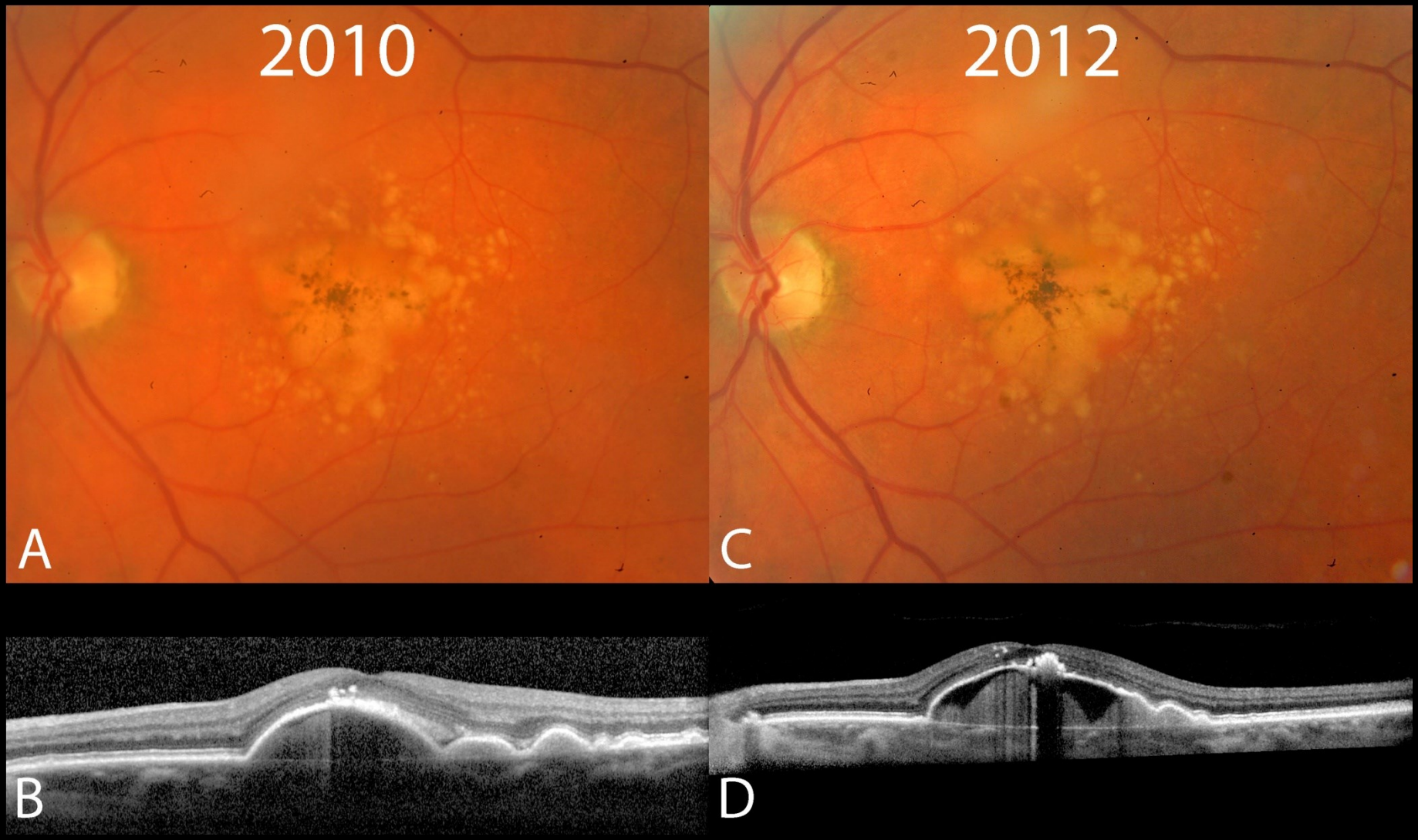
Drusenoid PED

Pigmentary changes and Mixed content serous and drusenoid



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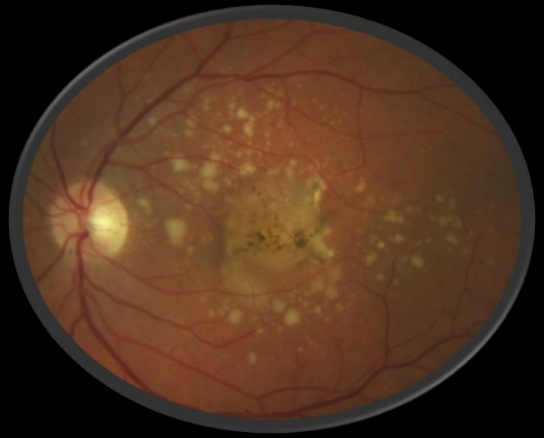
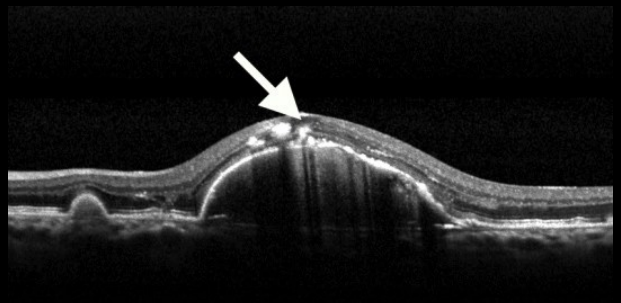
Drusenoid PED

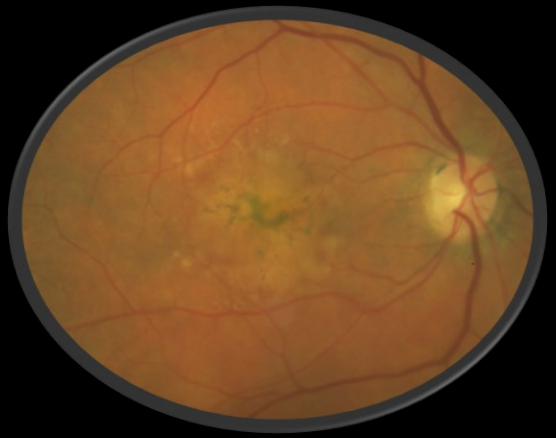
Associated features

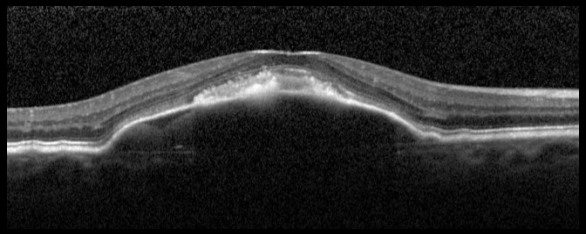
Pigmentary Changes
Hyperreflective Foci



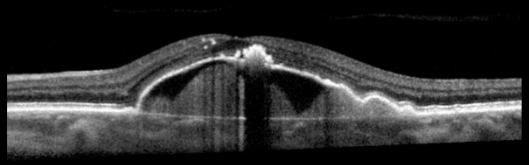


Acquired Vitelliform Lesion





Mixed content



Pigmentary changes, acquired vitelliform lesions and mixed content often associated
Rule out neovascularization through multimodal imaging
Signs of RPE decompensation that predates RPE atrophy and PED collapse

Drusen séreux

Biomarqueurs de l'atrophie en OCT SD

Optical Coherence Tomography–Defined Changes Preceding the Development of Drusen-Associated Atrophy in Age-Related Macular Degeneration

Zhichao Wu, BAppSc(Optom),[1] Chi D. Luu, PhD,[1] Lauren N. Ayton, PhD,[1] Jonathan K. Goh, MBBS, BMedSci,[1] Lucia M. Lucci, MD,[2] William C. Hubbard, BS,[2] Jill L. Hageman, RN,[2] Gregory S. Hageman, PhD,[2] Robyn H. Guymer, MBBS, PhD[1]

Ophthalmology *Volume 121, Number 12, December 2014*

Analyse longitudinale de cas de DMLA intermédiaire sur 20 mois

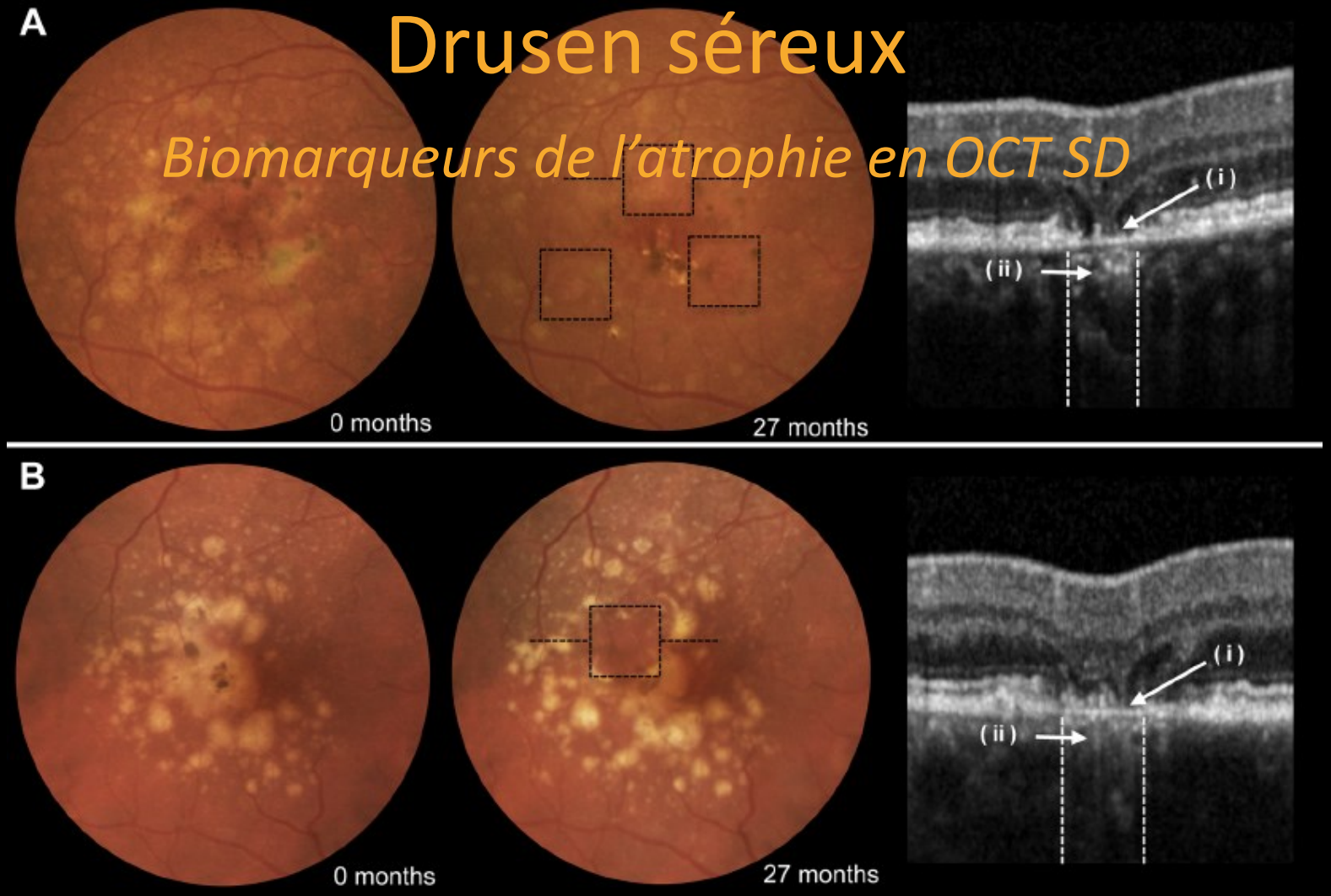
221 yeux de 181 patients DMLA intermédiaire sans aucun signe d'atrophie

16 /221 yeux ont développé de l'atrophie au niveau des drusen en 20 mois

Définition de signes prédictifs d'évolution vers l'atrophie en SD OCT

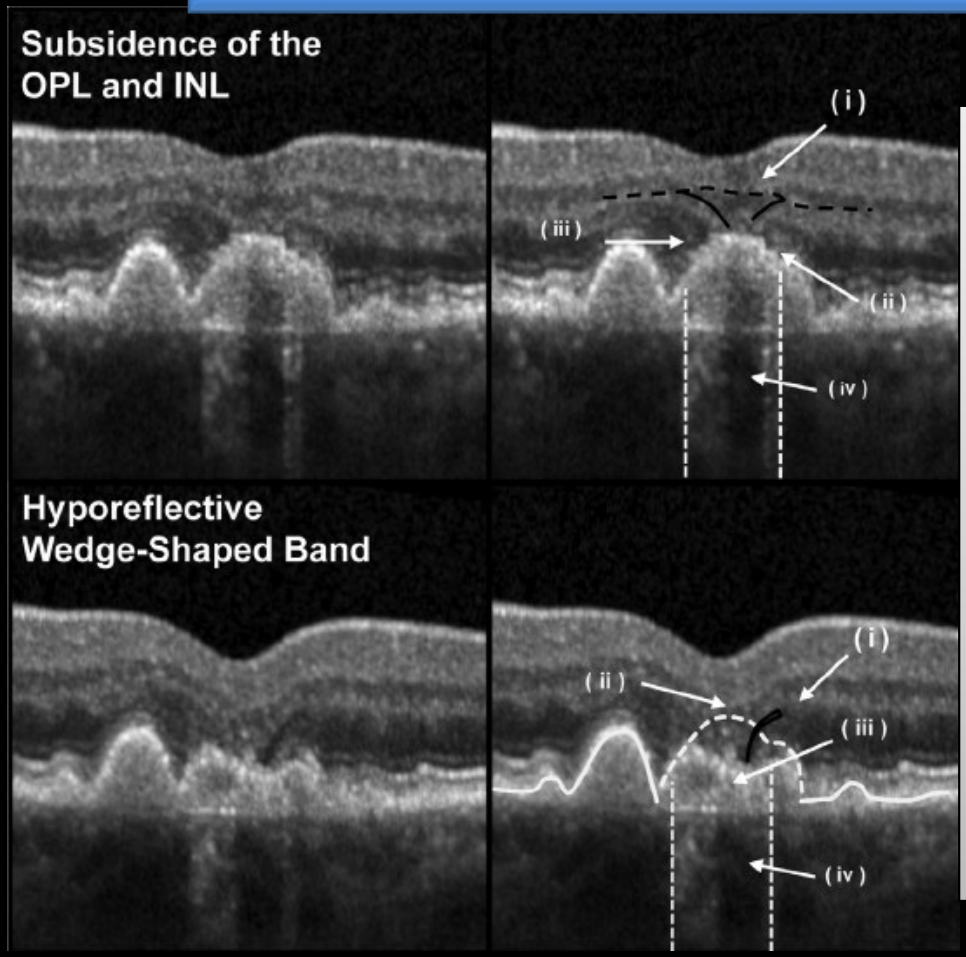
Drusen séreux

Biomarqueurs de l'atrophie en OCT SD



16/221 yeux ont développé de l'atrophie sur des zones de drusen
après régression des drusen
après un délai moyen de 20 mois

Atrophie géographique naissante - « Nascent GA »



Atrophie géographique naissante
« nascent GA »

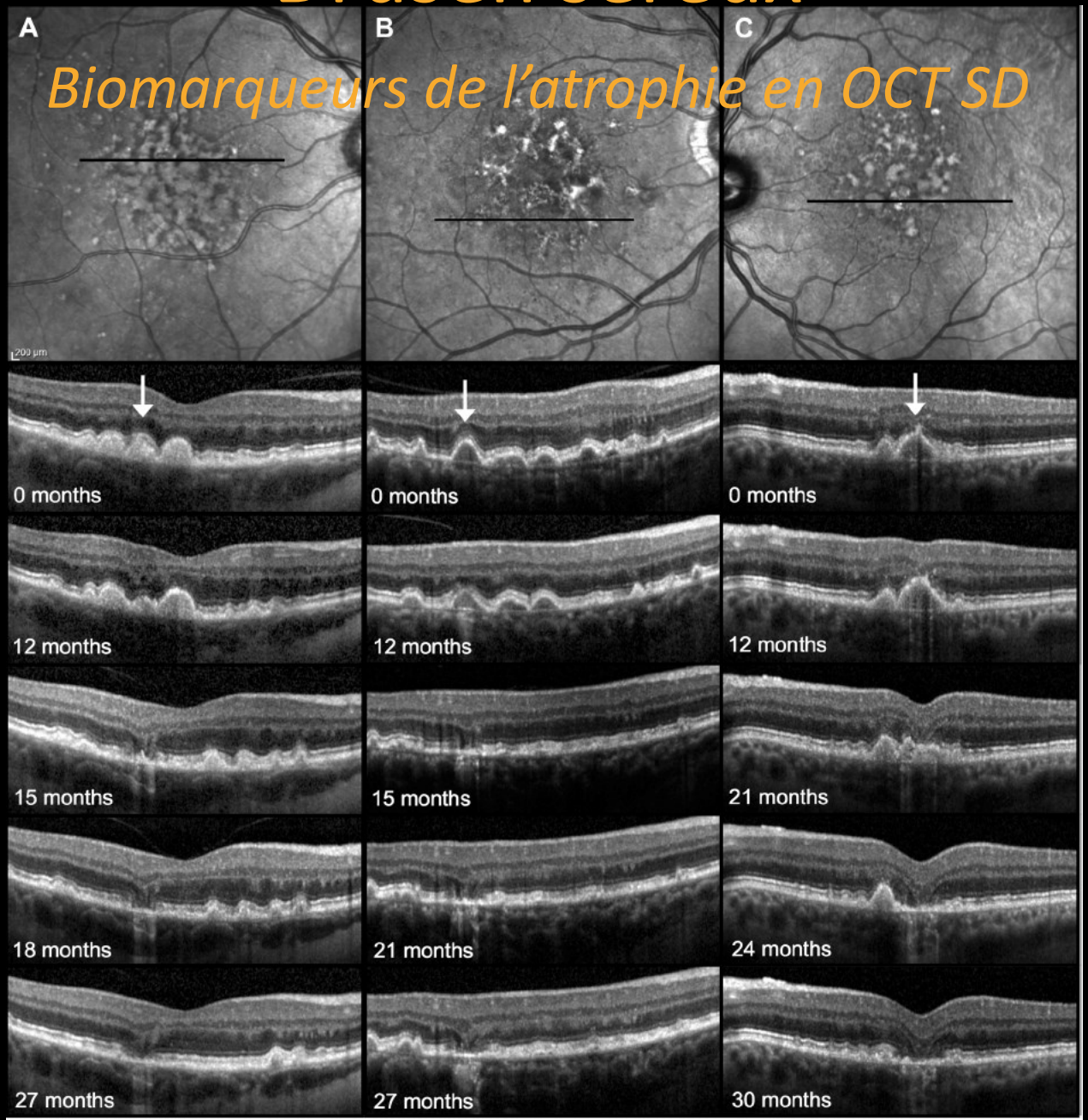
Définition de signes prédictifs d'évolution vers l'atrophie en SD OCT

- Affaissement de l'OPL et INL
- Discontinuité de l'ellipsoïde
- Image de bande hyporéfléctive en V aux bords de l'atrophie naissante
- Régression du drusen
- Augmentation inhomogène du signal choroïdien

Signes d'atrophie naissante dans 16/221 yeux (7%)
Dans 20% des yeux avec drusen grande taille > 125 microns et migrations de pigment
Signes d'atrophie naissante dans 90% des cas dans les 1500 microns centraux
En moyenne 12 mois pour évoluer vers l'atrophie géographique (5 à 21 mois)

Drusen séreux

Biomarqueurs de l'atrophie en OCT SD



Drusen séreux

Biomarqueurs de l'atrophie en OCT SD

Optical Coherence Tomography—Defined Changes Preceding the Development of Drusen-Associated Atrophy in Age-Related Macular Degeneration

Zhichao Wu, BAppSc(Optom),[1] Chi D. Luu, PhD,[1] Lauren N. Ayton, PhD,[1] Jonathan K. Goh, MBBS, BMedSci,[1] Lucia M. Lucci, MD,[2] William C. Hubbard, BS,[2] Jill L. Hageman, RN,[2] Gregory S. Hageman, PhD,[2] Robyn H. Guymer, MBBS, PhD[1]

Ophthalmology *Volume 121, Number 12, December 2014*

Analyse longitudinale de cas de DMLA intermédiaire sur 20 mois
221 yeux de 181 patients DMLA intermédiaire sans aucun signe d'atrophie
16 /221 yeux ont développé de l'atrophie au niveau des drusen en 20 mois
Définition de signes prédictifs d'évolution vers l'atrophie en SD OCT

Facteurs de risque de dvpt d'atrophie naissante

- **Migrations pigmentaires**
- **Atrophie géographique naissante œil adelphe**

Apparition de biomarqueurs d'imagerie pédictifs d'atrophie

Signes OCT d'atrophie naissante plus précoces → ttts plus précoces

Intraretinal Hyperreflective Foci

SD-OCT biomarker to atrophy atop drusenoid lesions

Optical Coherence Tomography–Based Observation of the Natural History of Drusenoid Lesion in Eyes with Dry Age-related Macular Degeneration

Yanling Ouyang, MD,[1,2,] Florian M. Heussen, MD,[1,2,*] Amirhossein Hariri, MD,[1] Pearse A. Keane, MD, MRCOphth,[3] SriniVas R. Sadda, MD[1]*

Ophthalmology 2013

29 patients, 41 eyes, 571 individual drusenoid lesions
Follow-up 21 months
18/571 (3,2%) lesions evolved to RPE atrophy
Independent predictors of atrophy: HRF and heterogeneous lesion reflectivity

Progression of Intermediate Age-related Macular Degeneration with Proliferation and Inner Retinal Migration of Hyperreflective Foci

*Joseph G. Christenbury, BS,[1] Francisco A. Folgar, MD,[1] Rachelle V. O'Connell, BSE,[1] Stephanie J. Chiu, BSE,[2] Sina Farsiu, PhD,[1,2] Cynthia A. Toth, MD,[1,2] for the Age-related Eye Disease Study 2 Ancillary Spectral Domain Optical Coherence Tomography Study Group**

Ophthalmology 2013

299 patients (299 eyes), follow-up 2 years
Proliferation and inner retinal migration of HRF are predictors of atrophy

Intraretinal Hyperreflective Foci

SD-OCT biomarker to atrophy

Proposal of a simple optical coherence tomography-based scoring system for progression of age-related macular degeneration

Jianqin Lei[1,2,3] · Siva Balasubramanian[1,2] · Nizar Saleh Abdelfattah[1,2] · Muneeswar G. Nittala[1,2] · SriniVas R. Sadda[1,2]

Graefes, 2017

138 patients

Simplified OCT-based system to predict both neovascular and atrophic AMD

HRF, internal hyporeflectivity within drusen, total drusen volume, SDD

Retina

Associations Between Retinal Pigment Epithelium and Drusen Volume Changes During the Lifecycle of Large Drusenoid Pigment Epithelial Detachments

Chandrakumar Balaratnasingam,[1–4] Lawrence A. Yannuzzi,[1,2] Christine A. Curcio,[5] William H. Morgan,[3] Giuseppe Querques,[6,7] Vittorio Capuano,[6] Eric Souied,[6,7] Jesse Jung,[1,2,8] and K. Bailey Freund[1–3]

IOVS, 2016

21 cases of drusenoid PEDs, follow-up 4 years

Life cycle: slow growth and fast collapse

AVLs and HRF precede the breakpoint, concomitant to the RPE disruption, before PED collapse

Drusenoid PEDs

Imaging biomarkers to atrophy

21 cases of drusenoid PEDs
follow-up 4 years

Acquired vitelliform lesions
Hyperreflective foci
- precede the breakpoint of PED
- concomitant to the RPE disruption
- before PED collapse

Balaratnasingam C, Yannuzzi LA, Curcio CA, et al. Associations between retinal pigment epithelium and drusen volume changes during the lifecycle of large drusenoid pigment epithelial detachments. Invest Ophthalmol Vis Sci. 2016.

Intraretinal Hyperreflective Foci

SD-OCT biomarker to atrophy and histopathologic correlate

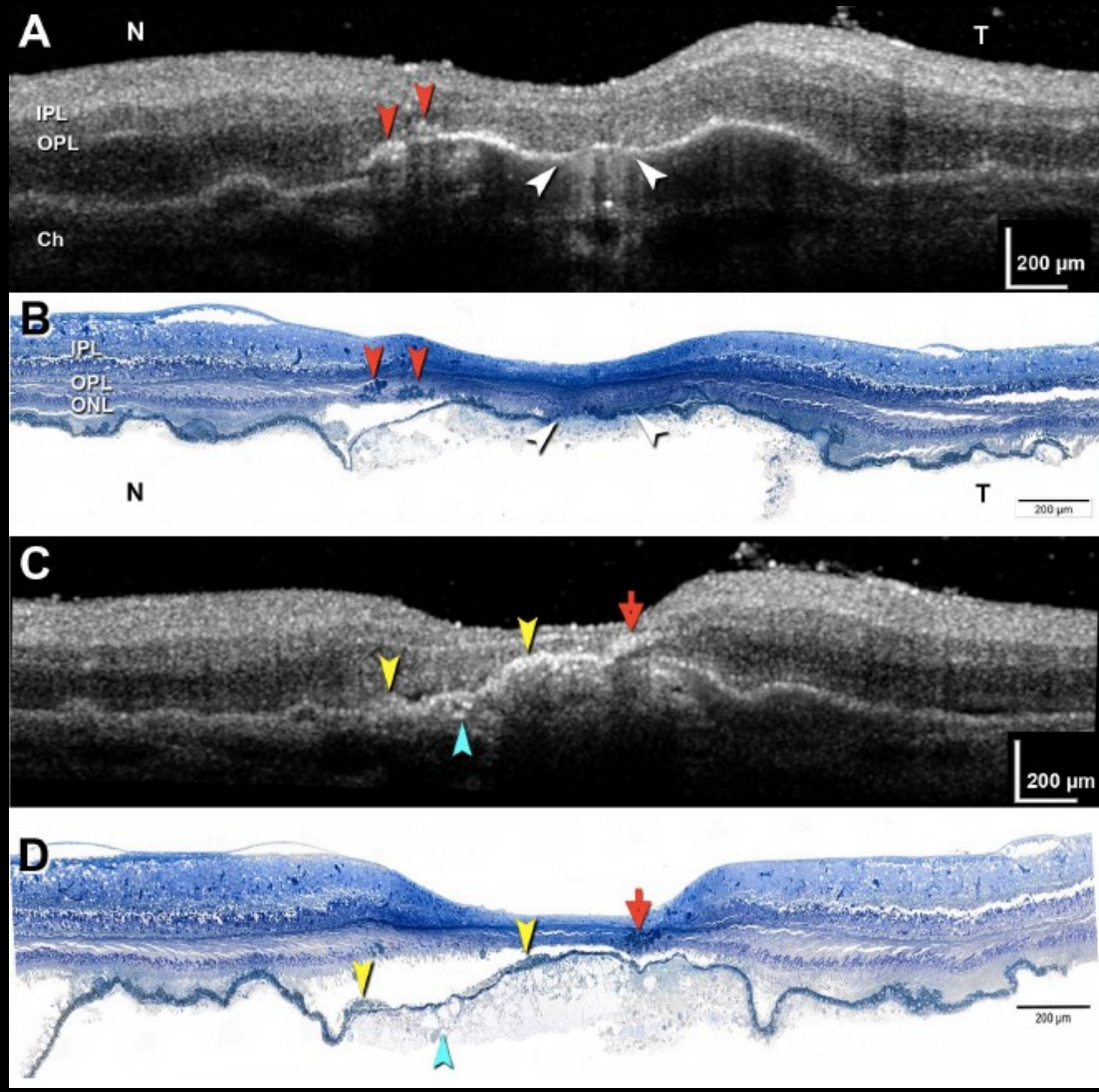
Special Issue

Activated Retinal Pigment Epithelium, an Optical Coherence Tomography Biomarker for Progression in Age-Related Macular Degeneration

Christine A. Curcio,[1] Emma C. Zanzottera,[2] Thomas Ach,[3] Chandrakumar Balaratnasingam,[4,5] and K. Bailey Freund[6–8]

IOVS, 2017

Christine Curcio



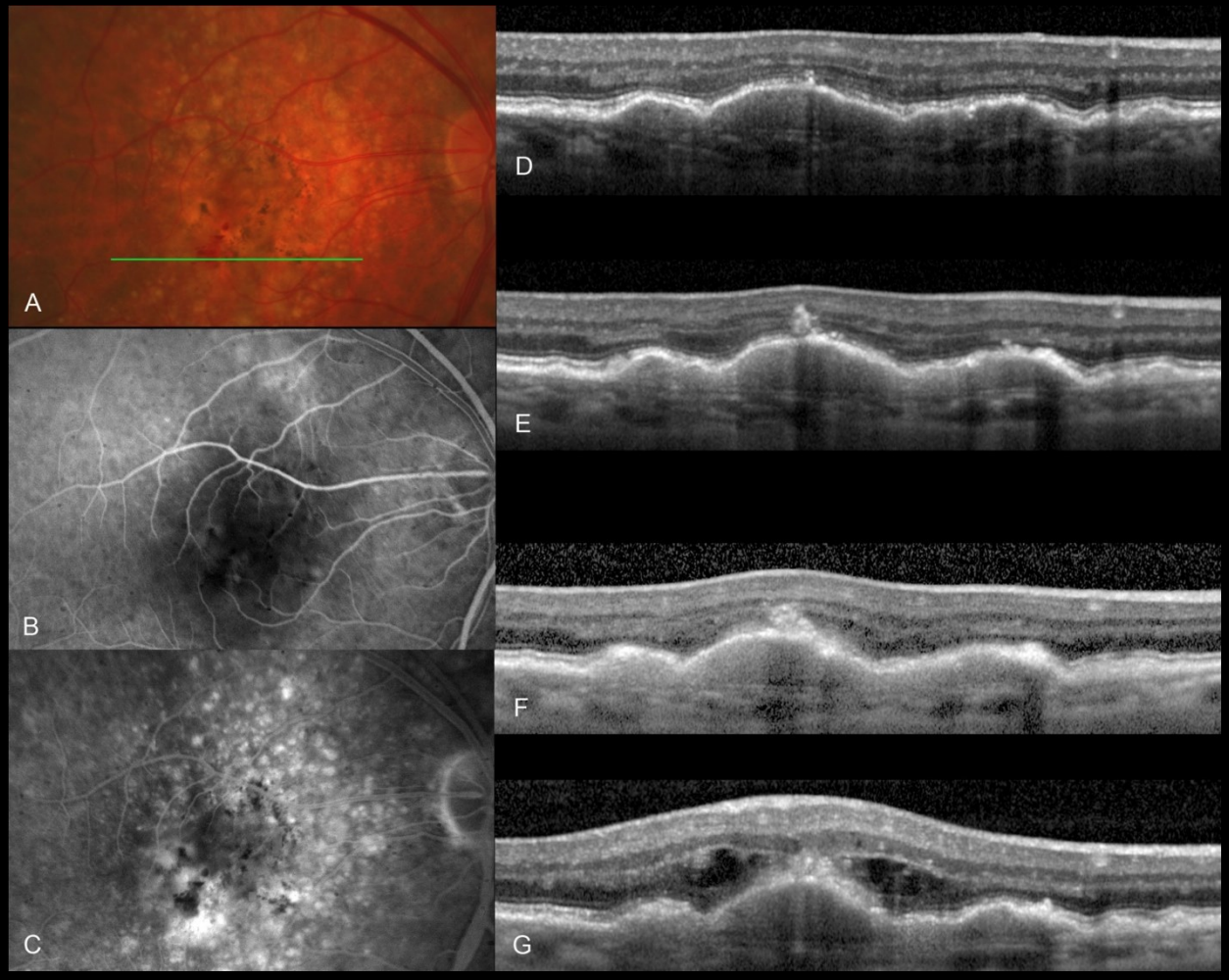
Hyperreflective foci over PEDs

Activated RPE cells migrating anteriorly

RPE death prevents production of druse components and precede PED collapse

Intraretinal Hyperreflective Foci

SD-OCT biomarker to neovascularization



45 weeks

K Bailey Freund

Freund KB, Zweifel SA, Engelbert M. Do we need a new classification for CNV in AMD? Retina 2010.

Coscas G, Benedetto U, Coscas F, Li Calzi CI, Vismara S, Roudot-Thoraval F, Bandello F, Souied E. Hyperreflective dots: a new SD-OCT entity for follow-up and prognosis in exudative AMD. Ophthalmologica 2013

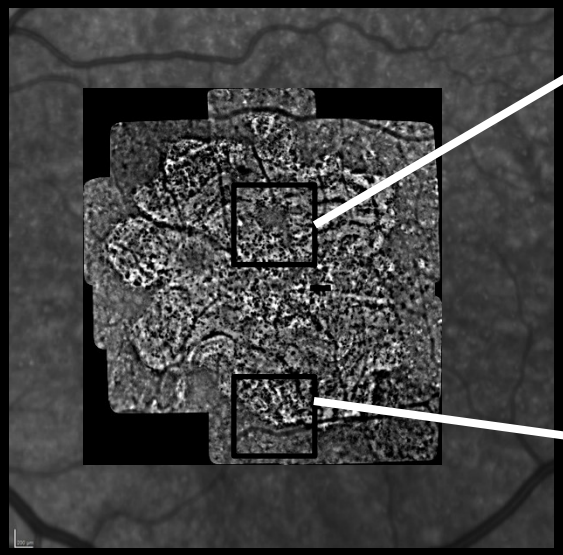
Intraretinal Hyperreflective Foci

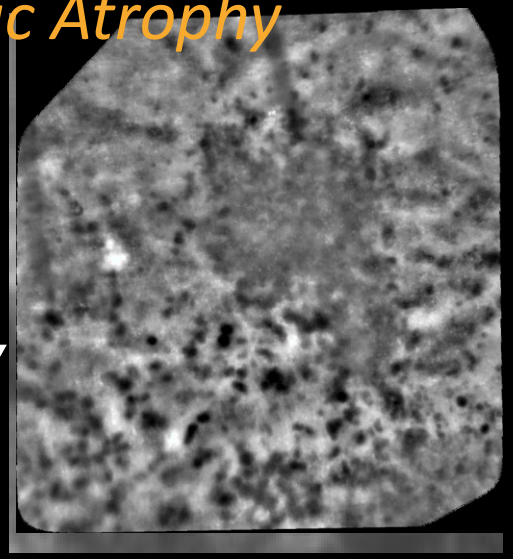
AO imaging in Geographic Atrophy

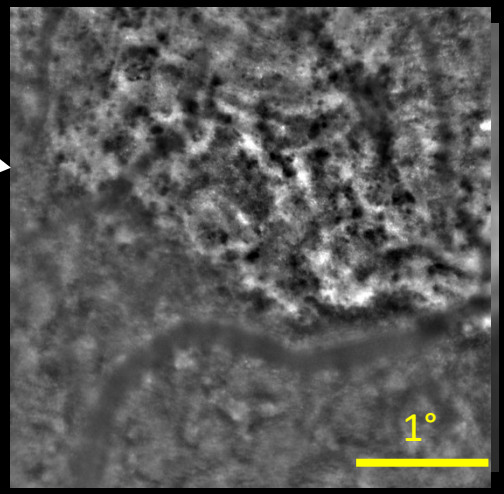
Kiyoko Gocho

Flood illumination; 840nm

imagine eyes



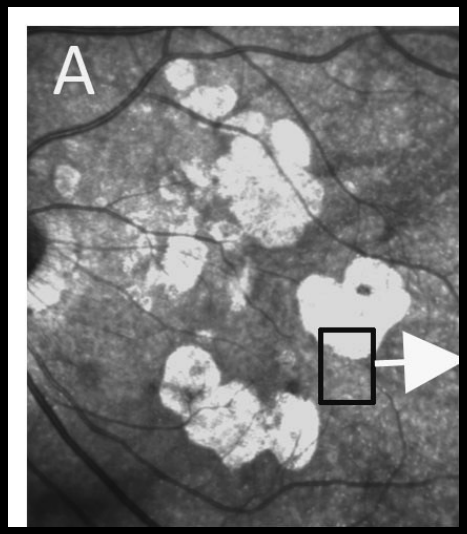


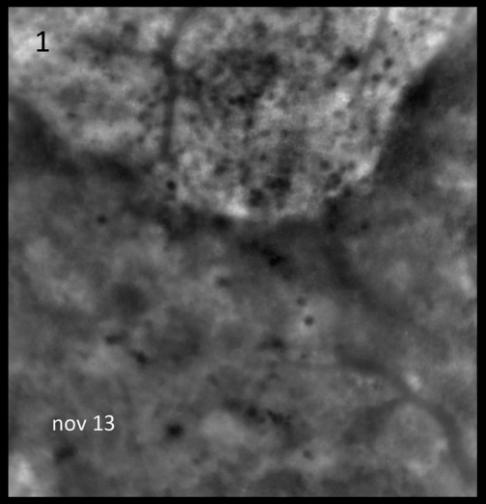


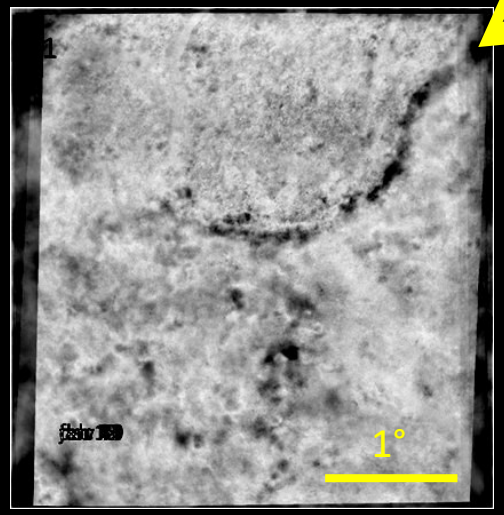
Flood AO shows RPE disruption and melanin redistribution (Gocho et al. IOVS 2013)

AO imaging in Geographic Atrophy

Time lapse over 3 months



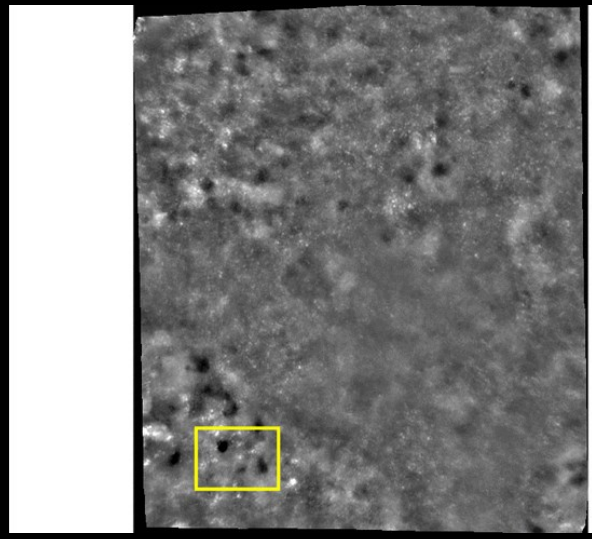


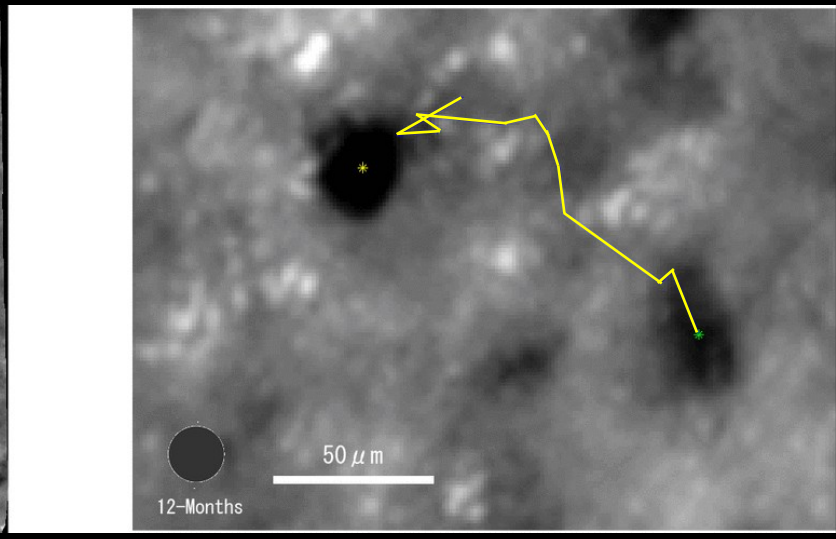


Melanin deposits at margins may accompany progression

Standard deviation: Changes over time

The various locations of pigmented cells (retinal/ subretinal/ in tubulations/ under basal laminar drusens) may determine their migration pathways



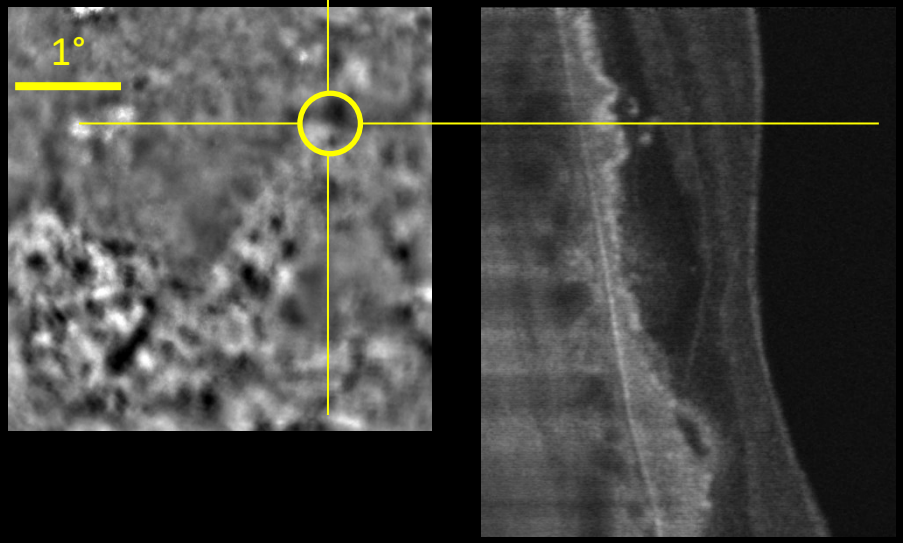


Current work: Automated cell tracking to look at scale and rate of migration in atrophy versus preserved zones

Michel Paques

Intraretinal Hyperreflective Foci

AO imaging at Geographic Atrophy Borders



At which retinal depth are these dark spots located? Look at OCT

Challenging to locate single melanin clumps on the OCT slice…

If these dark spots contain melanin, we should see them in near infrared autofluoresence (NIRAF) AO imaging

⇒We plan to perform NIRAF AO imaging in 2017
(collaboration Dr Ethan Rossi, University of Pittsburgh Medical Center)

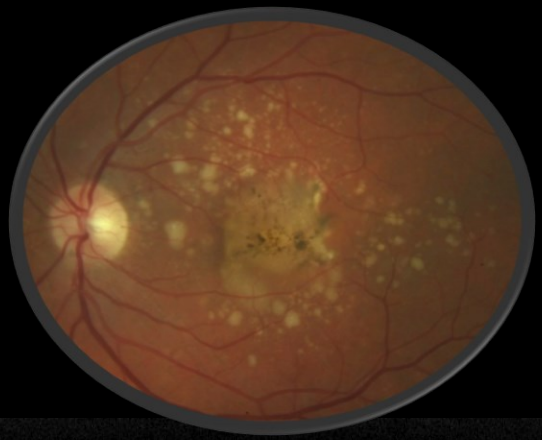
Drusenoid Lesions

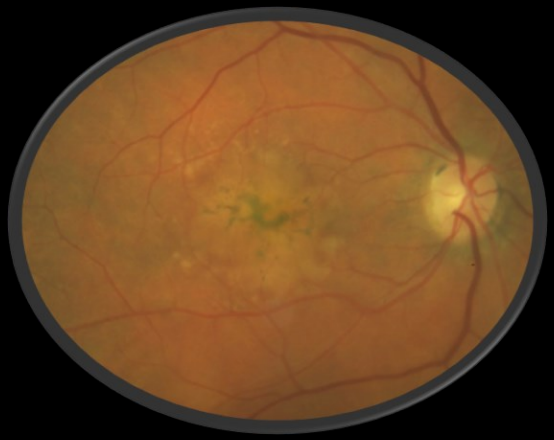
Conclusions

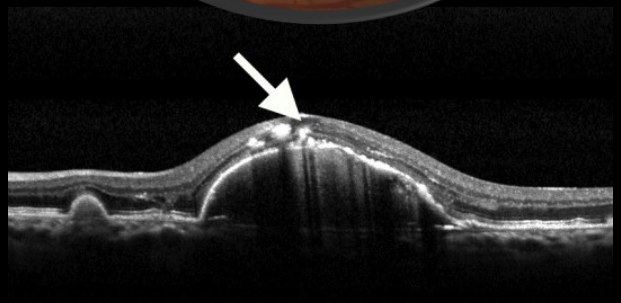
Hyperreflective Foci (HRF)

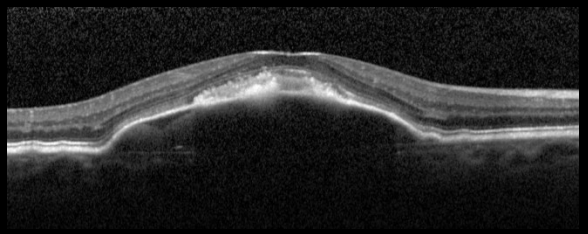
Acquired Vitelliform Lesion (AVL)

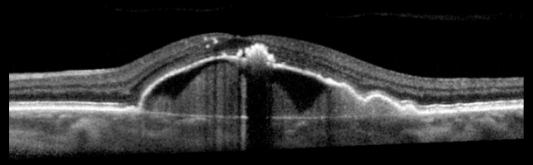
Mixed content











Total drusen volume, HRF and AVL are imaging biomarkers of RPE loss

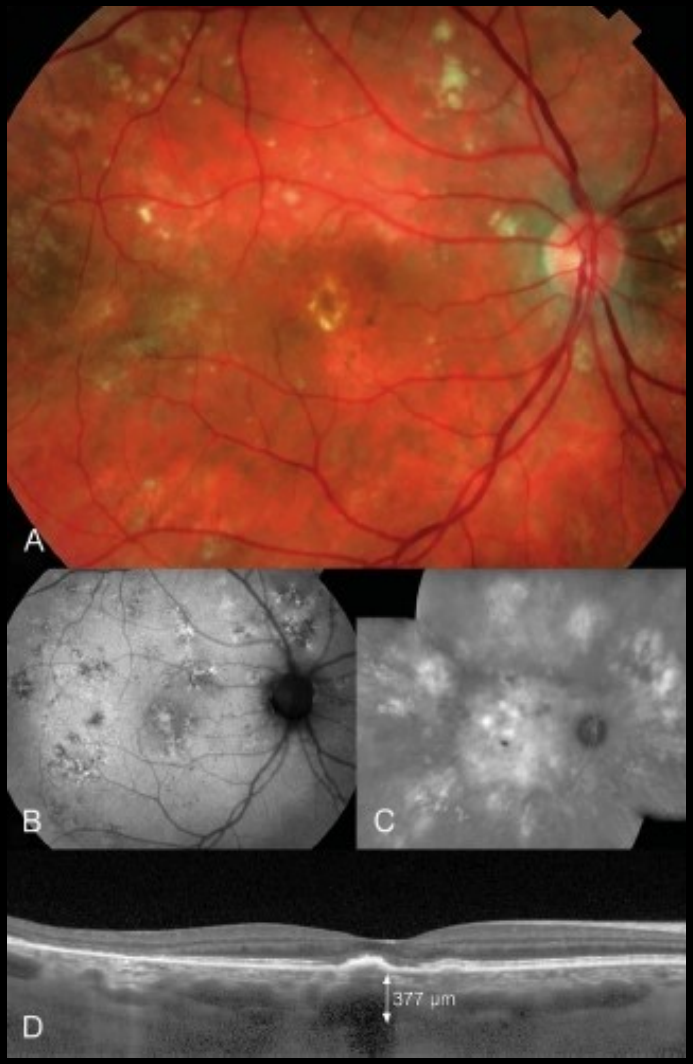
Total drusen volume and HRF are imaging biomarkers of neovascularization

Histologic correlate of HRF may be

- migrating RPE cells
- macrophages/microglial cells
- both

La choroïde module l'expression de la DMLA

Pachydrusen = Drusen associés à la pachychoroïde



Dépôts ovoïdes, formes complexes
Larges > 125 microns
Pas de distribution radiaire
Pas de confluence au centre macula
Pas de pigment

71 patients (94 yeux) de DMLA précoce
pachydrusen = 12%

Spaide RF. Disease expression in nonexudative AMD varies with choroidal thickness. Retina 2017

La choroïde module l'expression de la DMLA

Pachydrusen = Drusen associés à la pachychoroïde

DISEASE EXPRESSION IN NONEXUDATIVE AGE-RELATED MACULAR DEGENERATION VARIES WITH CHOROIDAL THICKNESS

RICHARD F. SPAIDE, MD

Drusen séreux

Pachydrusen

Cuticular Drusen

Bilateral, symmetrical, earlier age at onset than AMD

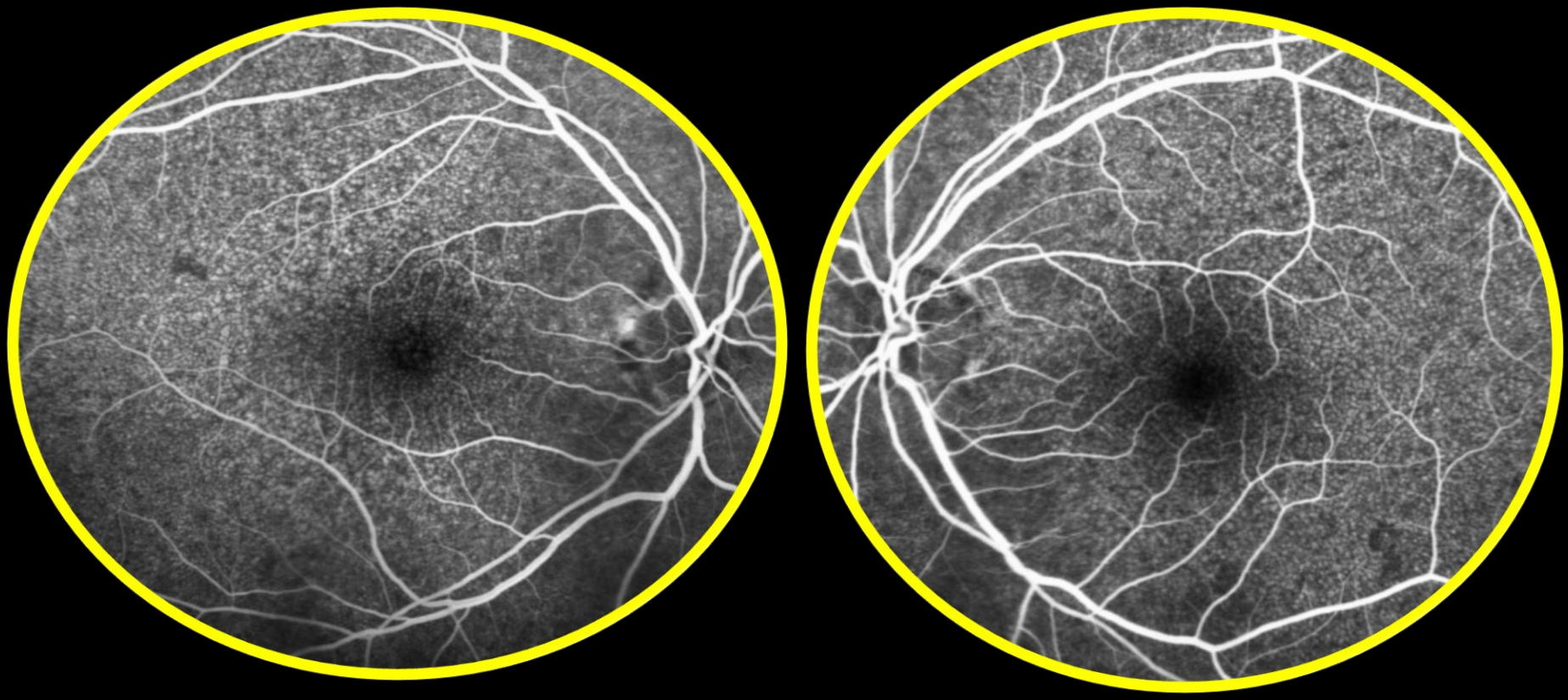
« Innumerable, small, uniformly sized, discretely round, slightly raised, yellow »

Gass JD. Stereoscopic Atlas of Macular Disease Diagnosis and Treatment. St. Louis: Mosby; 1977. p. 170-5

Cuticular Drusen

Fluorescein Angiography: Stars- in-the-sky pattern

Bilateral, symmetrical, earlier age at onset than AMD, stronger familial component



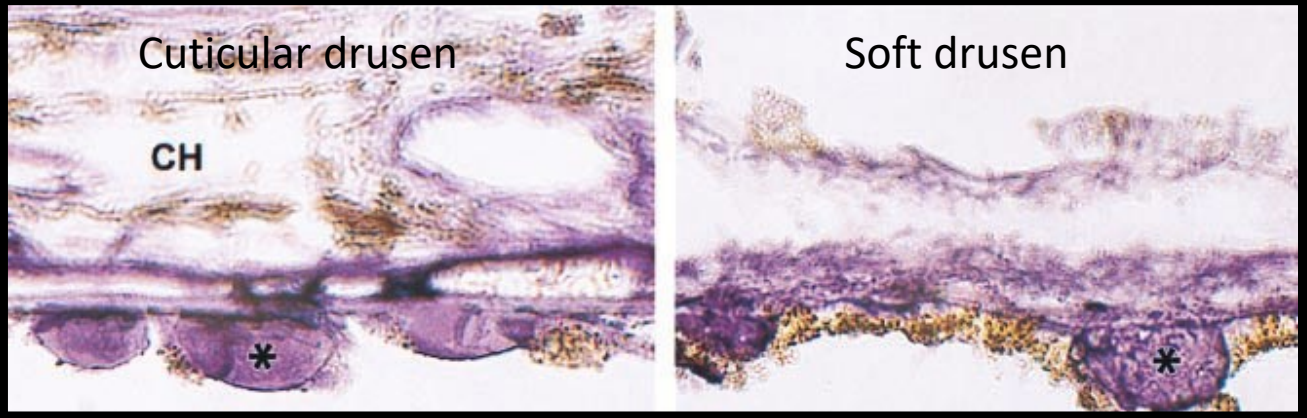
Gass JD. Stereoscopic Atlas of Macular Disease Diagnosis and Treatment. St. Louis: Mosby; 1977. p. 170-5
Boon CJF, van de Ven JPH, Hoyng CB, den Hollander AI, Klevering BJ (2013) Cuticular drusen: stars in the Sky. Prog Retin Eye Res. 2013

Cuticular Drusen

Is it AMD?

- Younger patients, different risk alleles profiles than what is found in AMD

- Histopathology:
  - 1985: Gass et al « basal laminar drusen »: nodular thickening of Bruch's membrane
  - 2000: Russell et al. location and composition similar to drusen from AMD



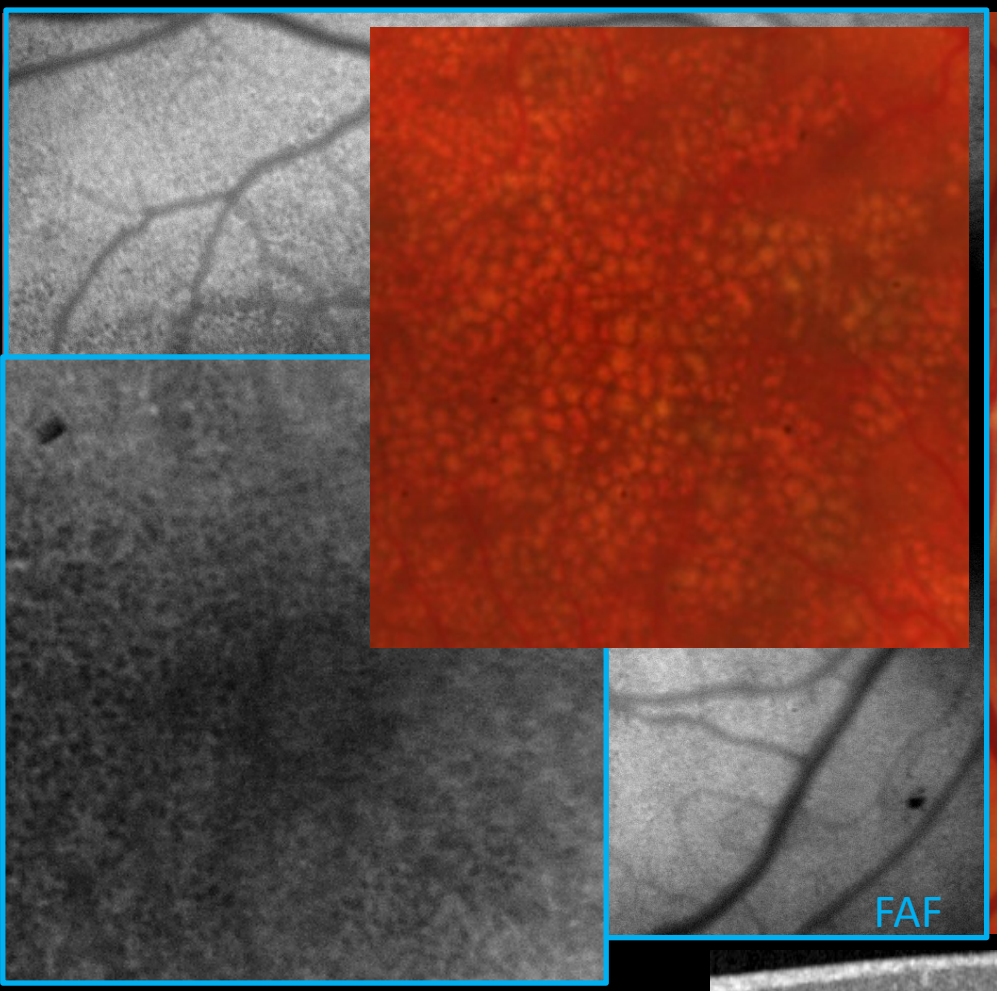
« similar to and perhaps indistinguishable from typical drusen from AMD.»

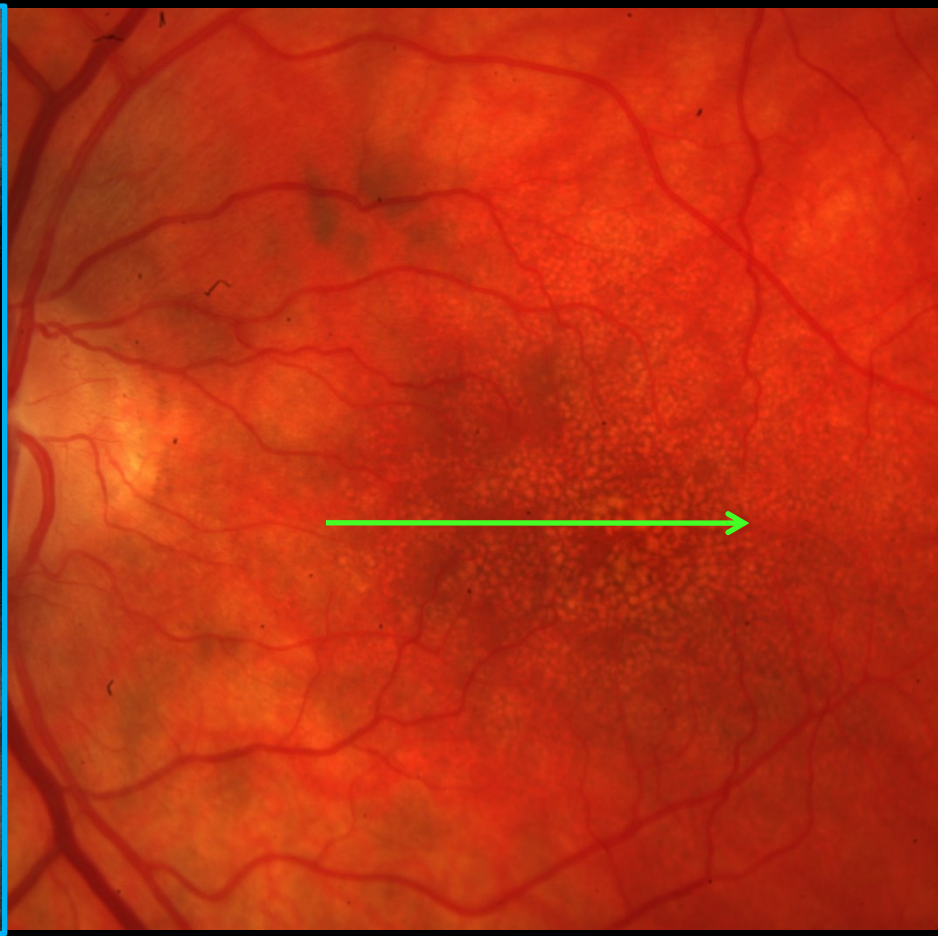
- However, lack of evidence of progression to atrophy or neovascular disease

Gass JD, Jallow S, Davis B. Adult vitelliform macular detachment occurring in patients with basal laminar drusen. Am J Ophthalmol. 1985
Russell SR, Mullins RF, Schneider BL, Hageman GS. Location, substructure, and composition of basal laminar drusen compared with drusen associated with aging and age-related macular degeneration. Am J Ophthalmol. 2000
Boon CJF, van de Ven JPH, Hoyng CB, den Hollander AI, Klevering BJ (2013) Cuticular drusen: stars in the Sky. Prog Retin Eye Res. 2013

Cuticular Drusen

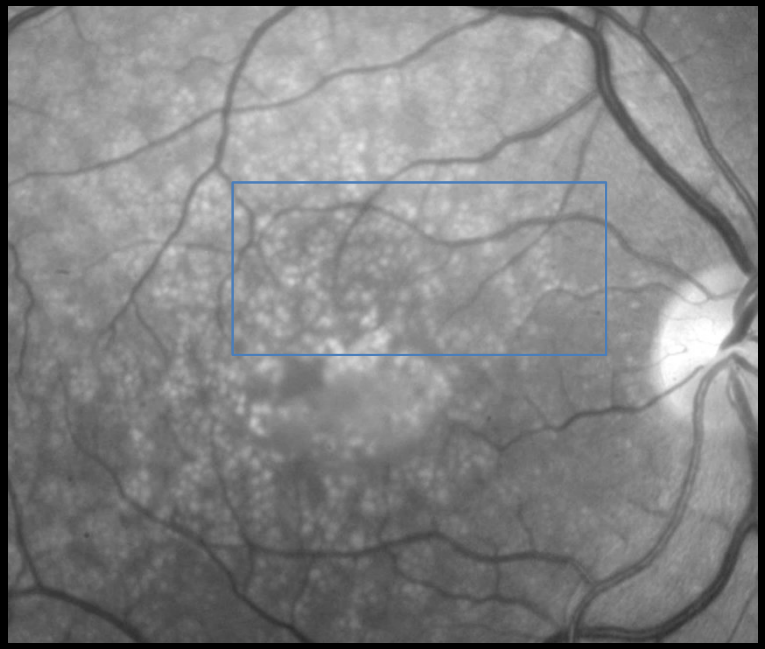
Is it AMD?

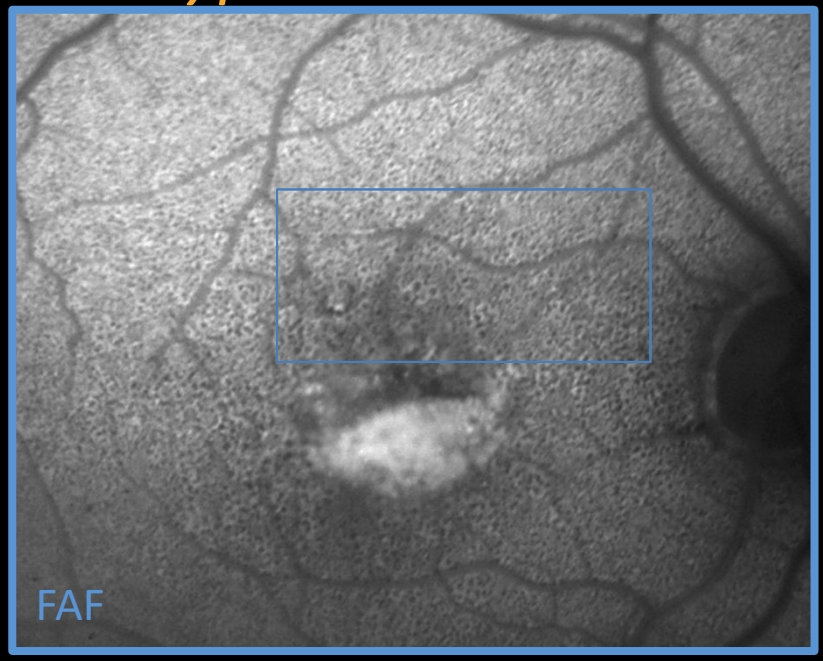


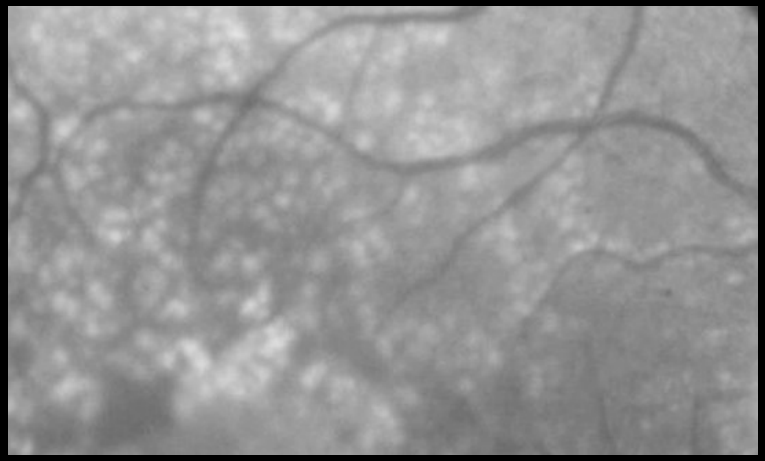


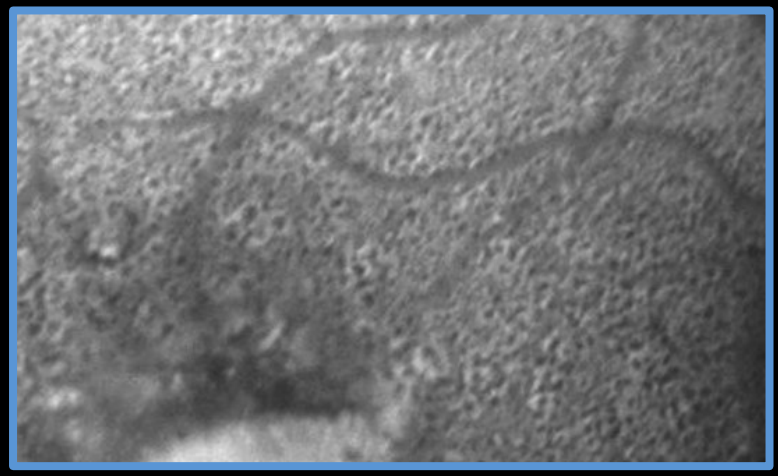
Cuticular Drusen

Fundus Autofluorescence Typical Pattern

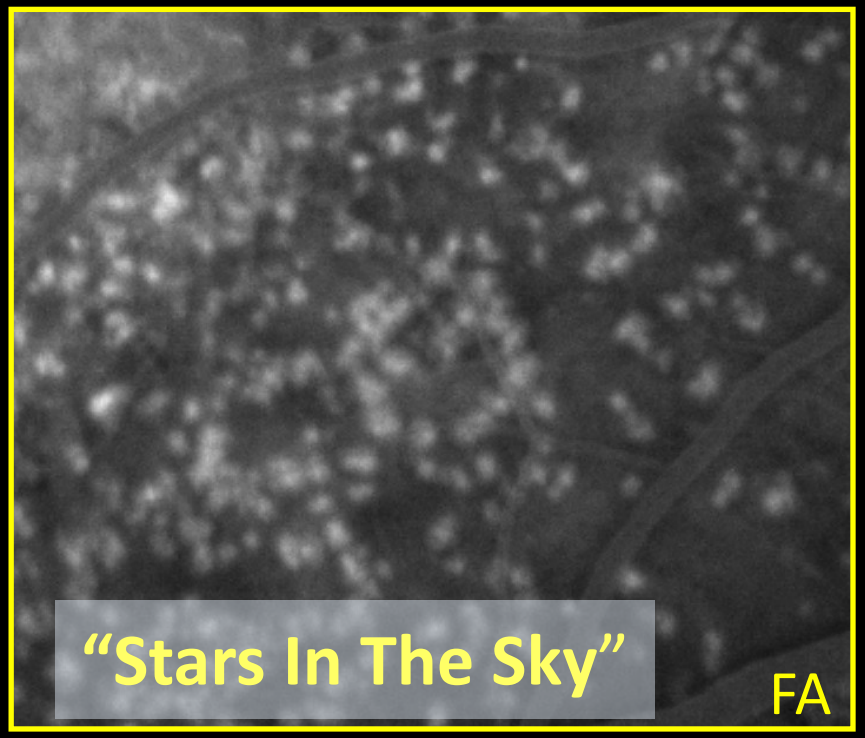


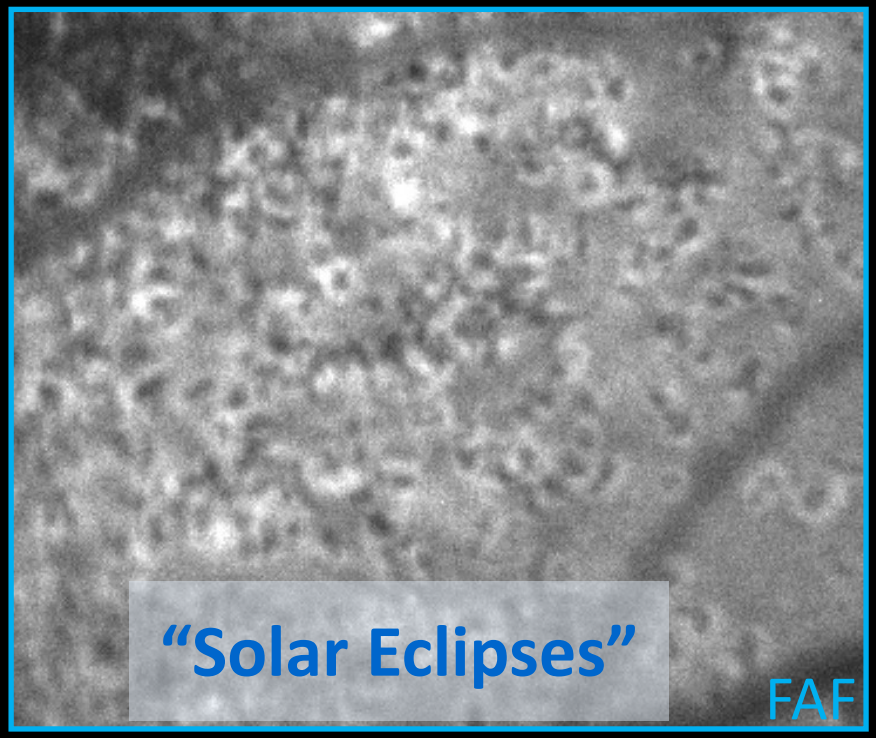






Cuticular Drusen

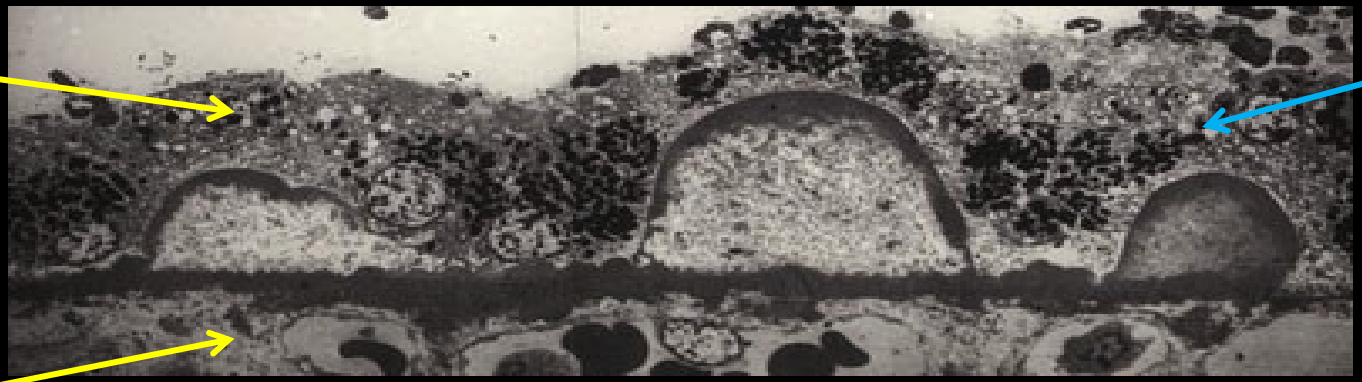




RPE thinning

HYPER-FA

Intact chorio-capillaris



Decreased Lipofuscin

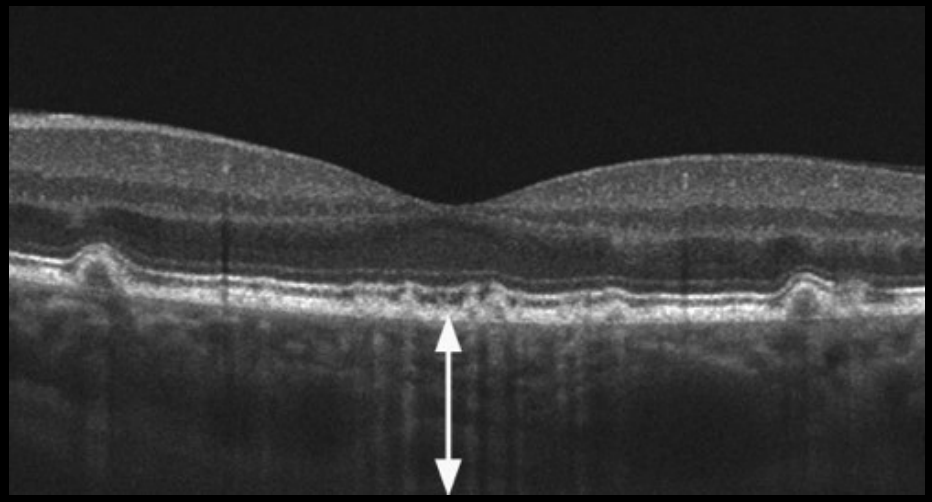
HYPO-FAF

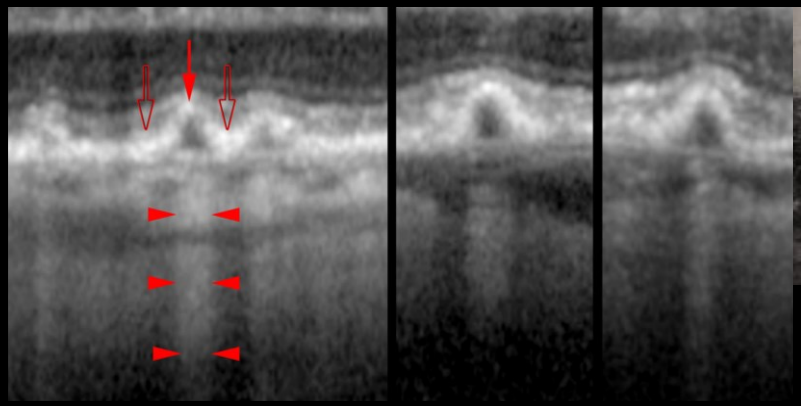
J Sarks

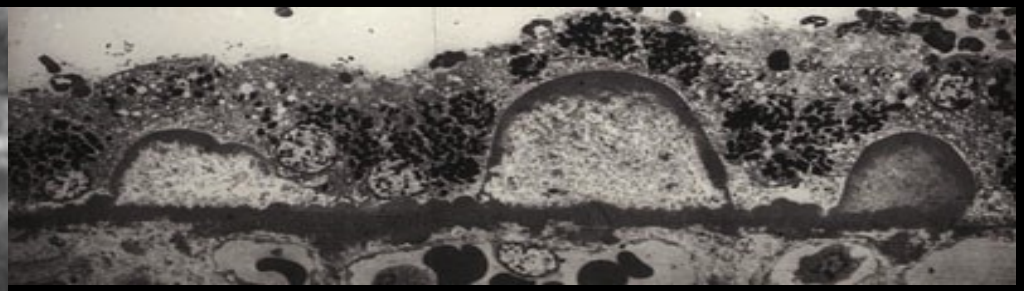
Lawrence Yannuzzi

Cuticular Drusen

SD-OCT Saw-Tooth Pattern







J Sarks

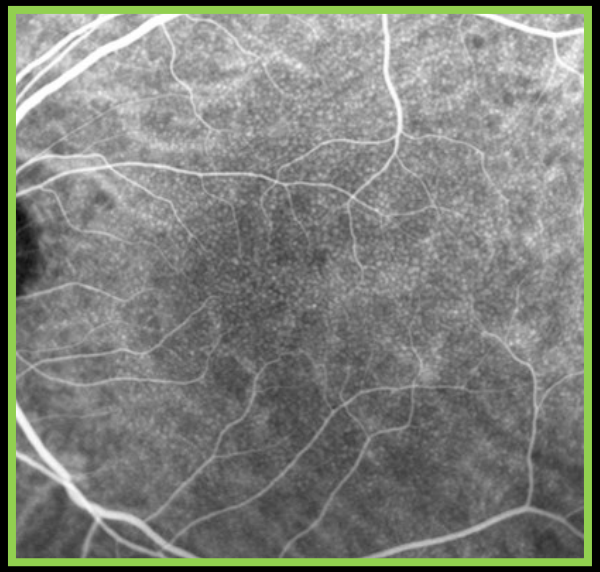
Spaide RF, Curcio CA. Drusen characterization with multimodal imaging. Retina. 2010 Oct;30(9):1441-54

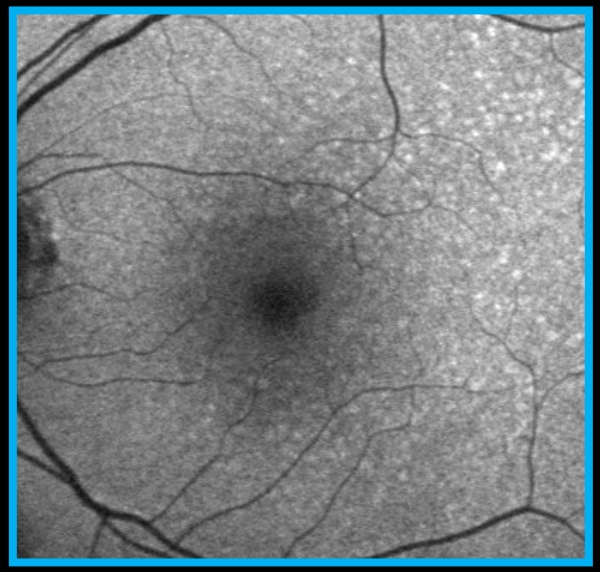
Leng T, Rosenfeld PJ, Gregori G, Puliafito CA, Punjabi OS. Spectral domain optical coherence tomography characteristics of cuticular drusen. Retina. 2009

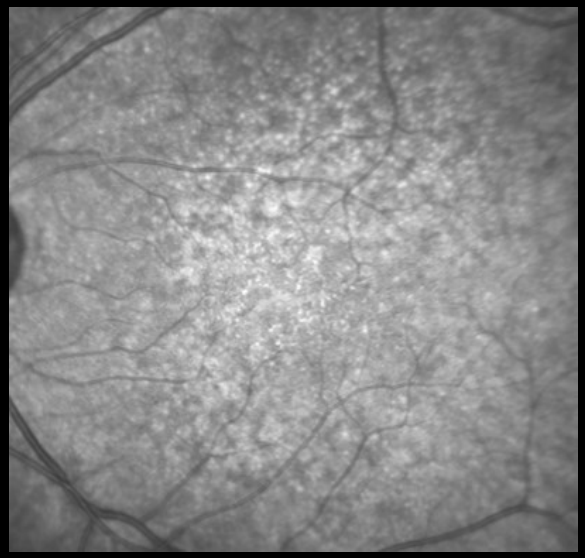
Querques G, Guigui B, Leveziel N, et al. Insights into pathology of cuticular drusen from integrated confocal scanning laser ophthalmoscopy imaging and corresponding spectral domain optical coherence tomography. Graefes Arch Clin Exp Ophthalmol. 2011 Nov;249(11):1617-25.

Cuticular Drusen

Multimodal Imaging Various Patterns



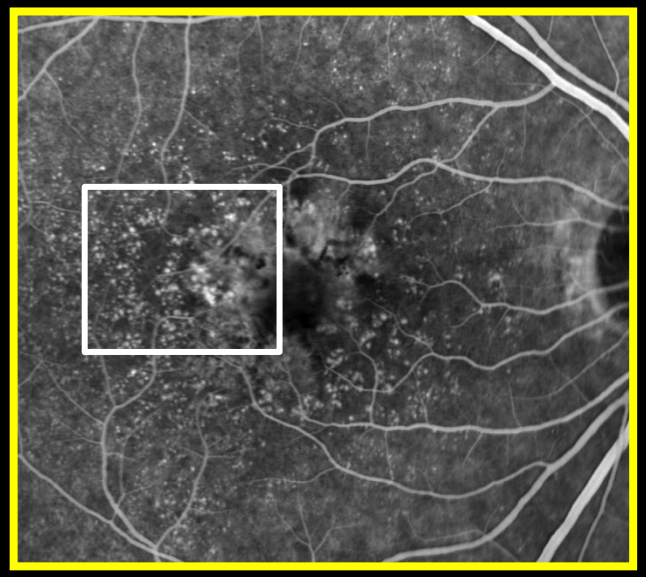


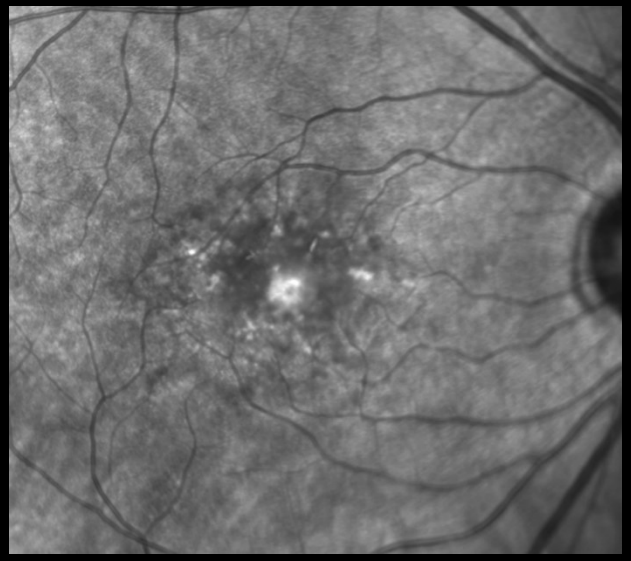


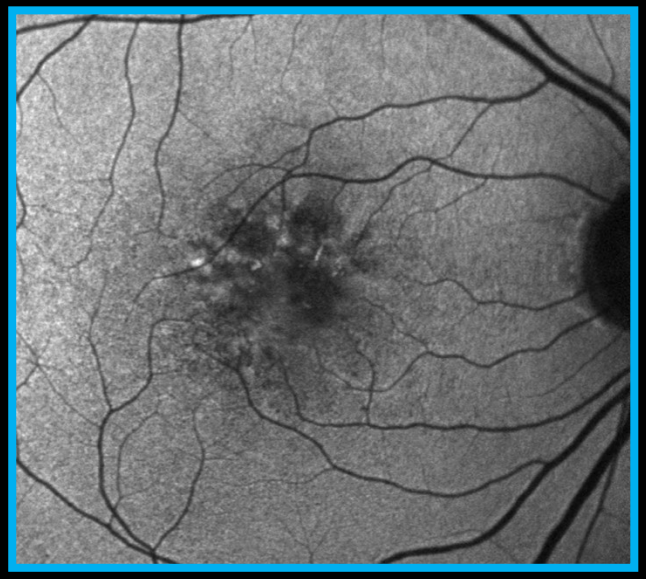
59-year-old
female

Cuticular Drusen

Multimodal Imaging Various Patterns



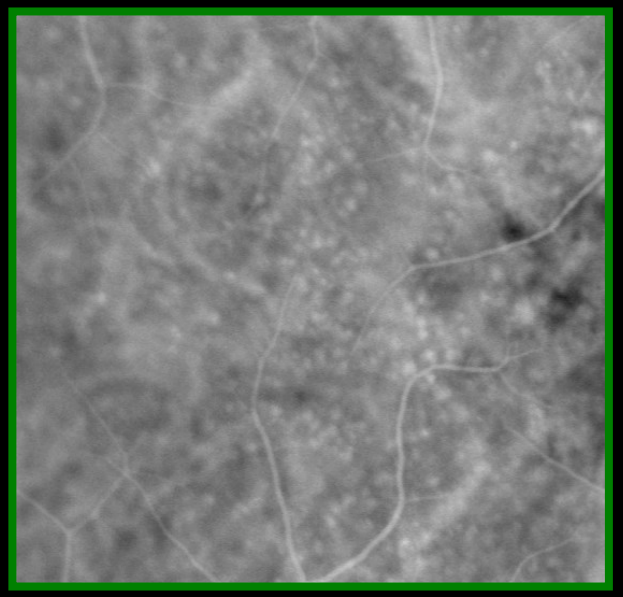


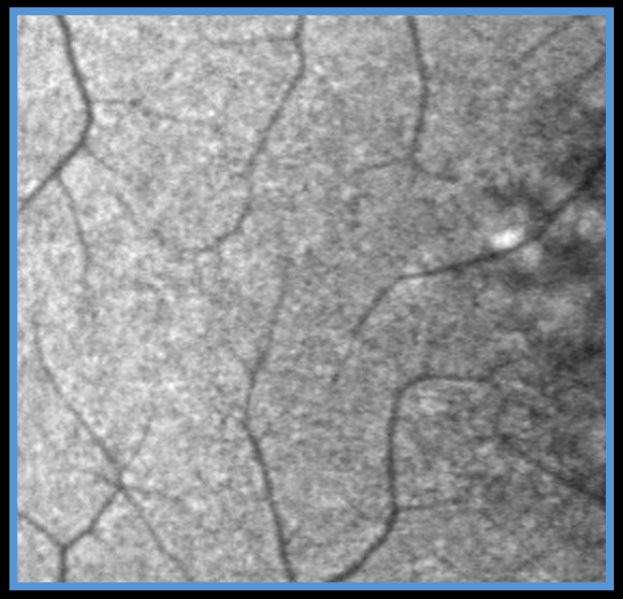


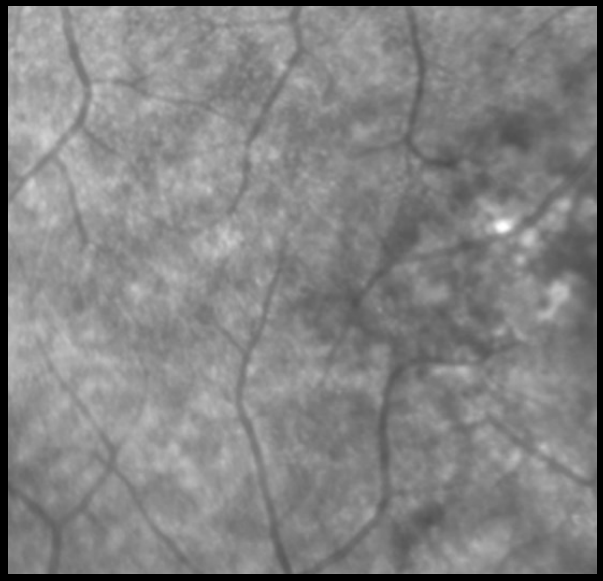
62-year-old
female

Cuticular Drusen

Multimodal Imaging

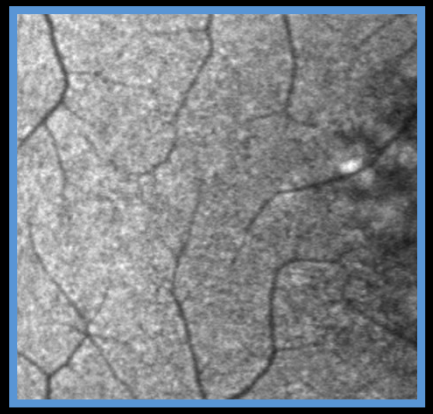




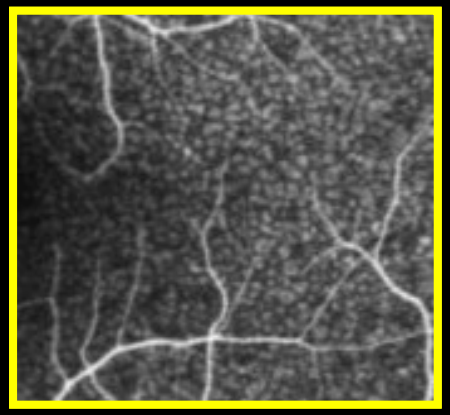


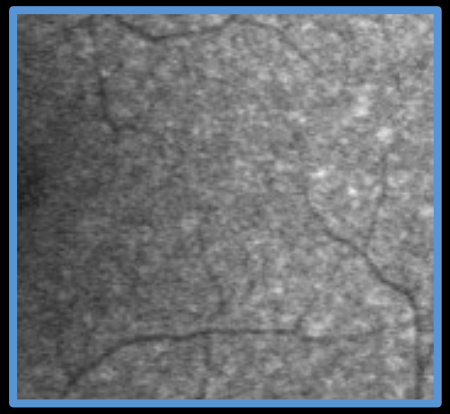
Cuticular Drusen

Fundus Autofluorescence Various Patterns

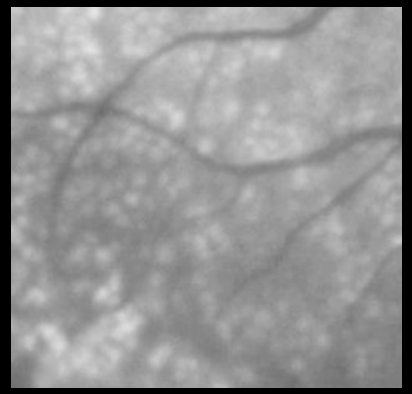


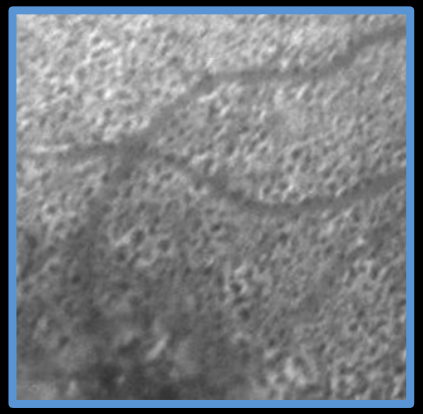
FAF: silent





FAF: hyperAF





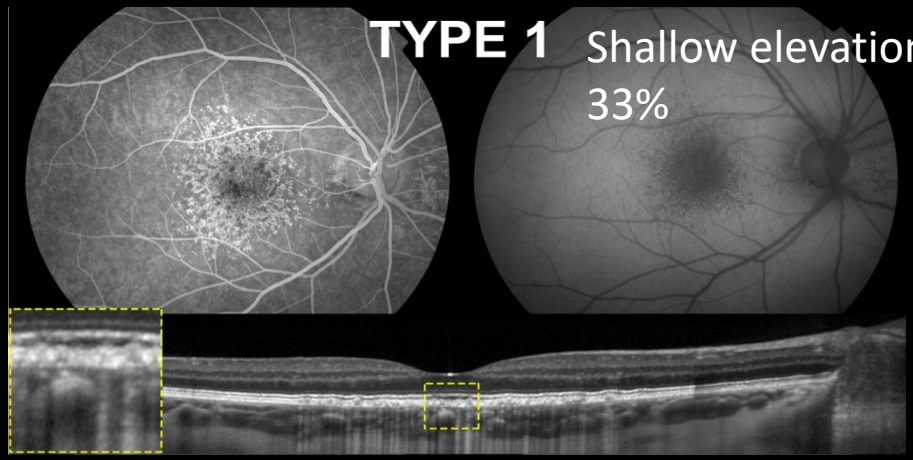
FAF: hypoAF with hyperAF rim

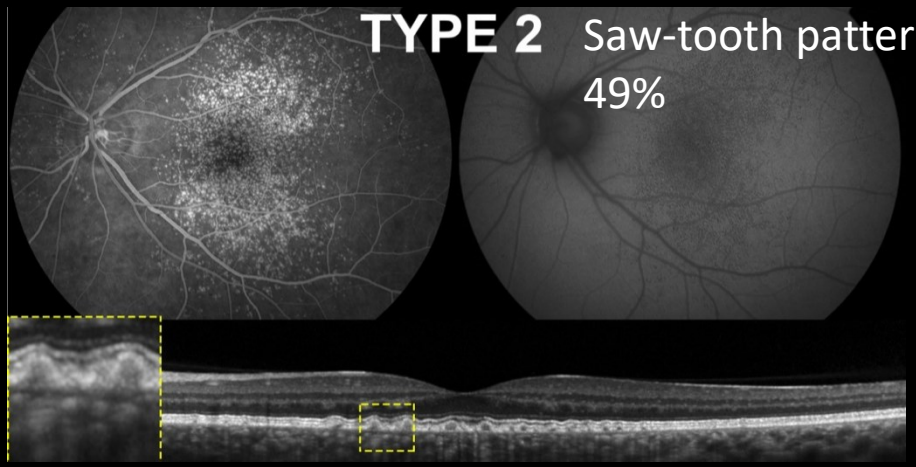
Various imaging patterns may correspond to evolutive stages or different phenotypes

120 patients (240 eyes)
58 years

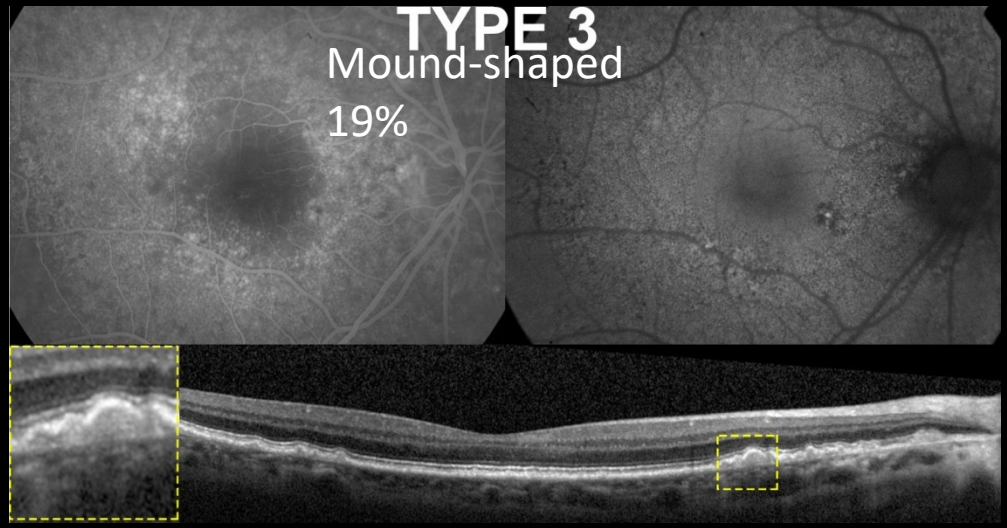
Cuticular Drusen

SD-OCT Various Patterns



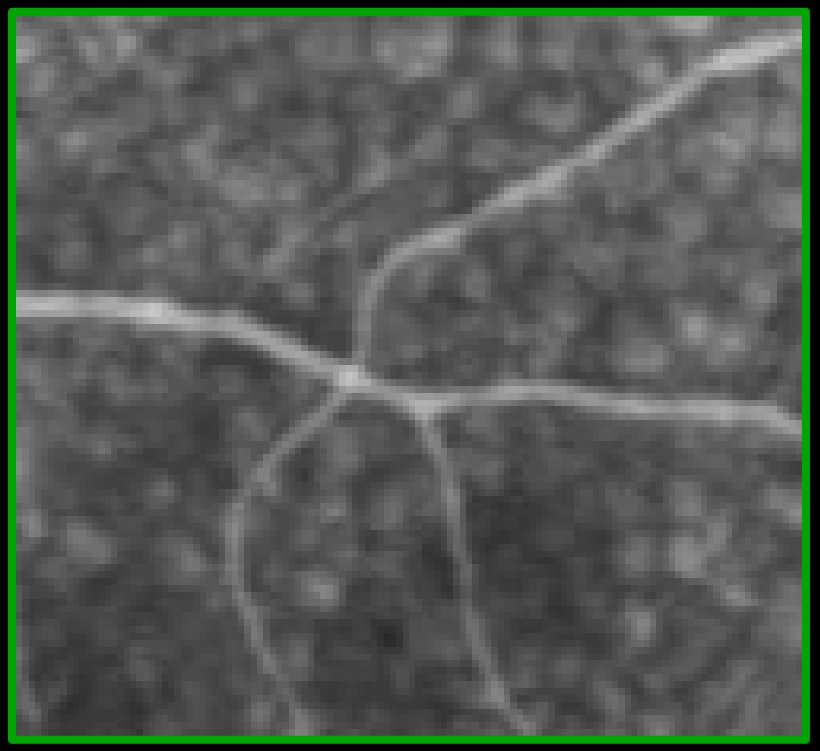


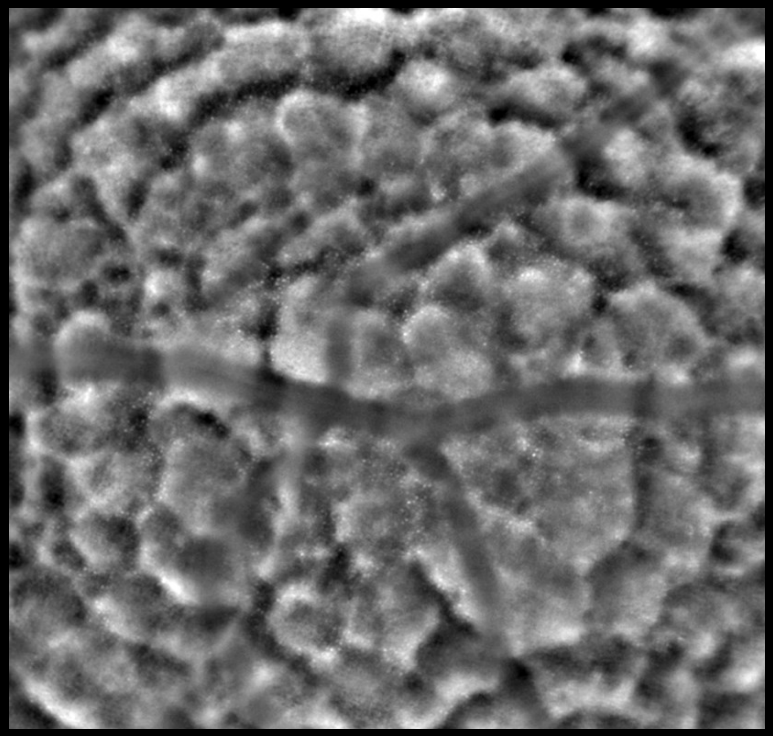
Chandrakumar Balaratnasingam



Balaratnasingam, Cherepanoff, Dolz-Marco, Killingsworth, Chen, Mendis, Mrejen, Curcio, Freund, Yannuzzi. Cuticular drursen: clinical phenotypes and natural history defined using multimodal imaging. Ophthalmology. Accepted. 2017

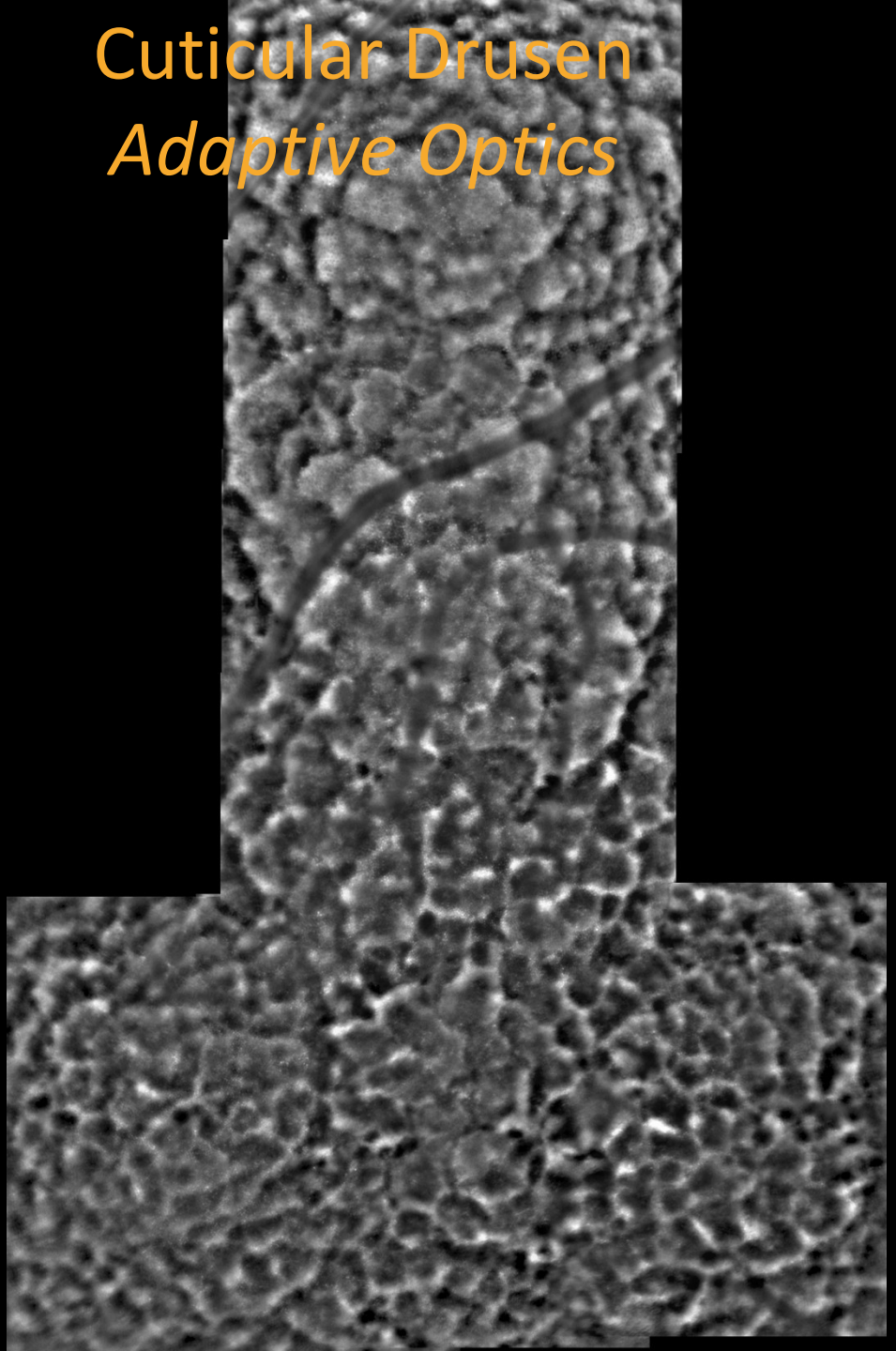
Cuticular Drusen
Adaptive Optics



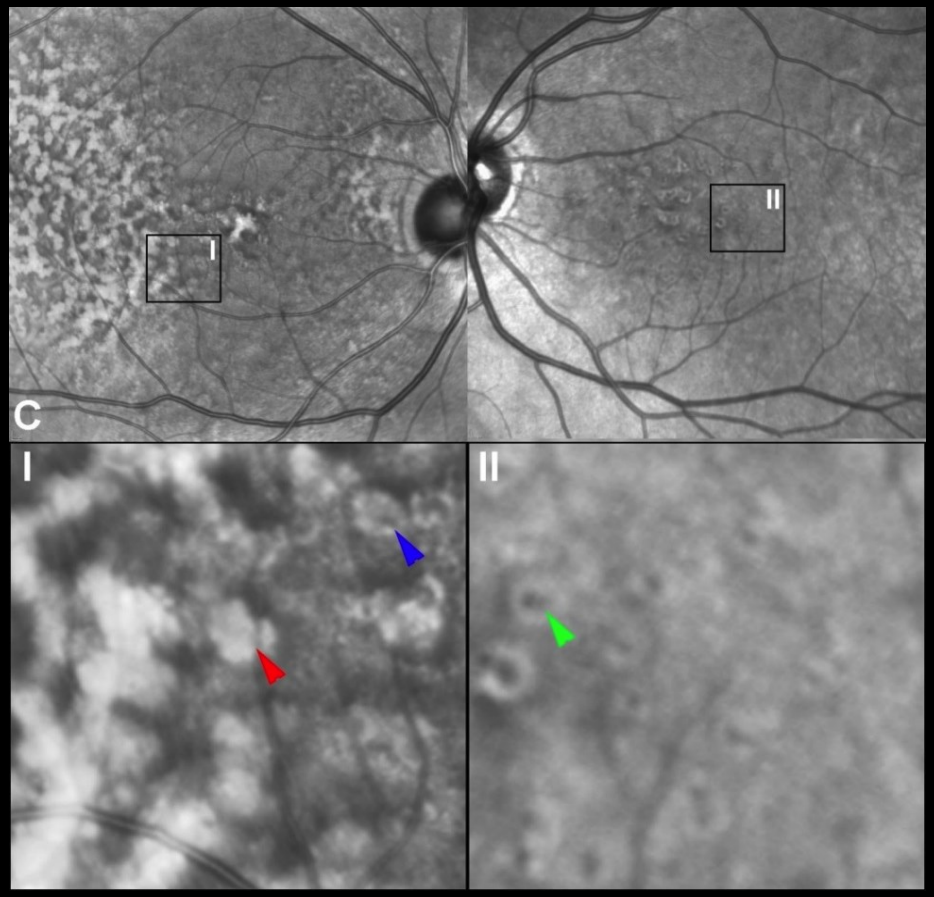


Cuticular Drusen

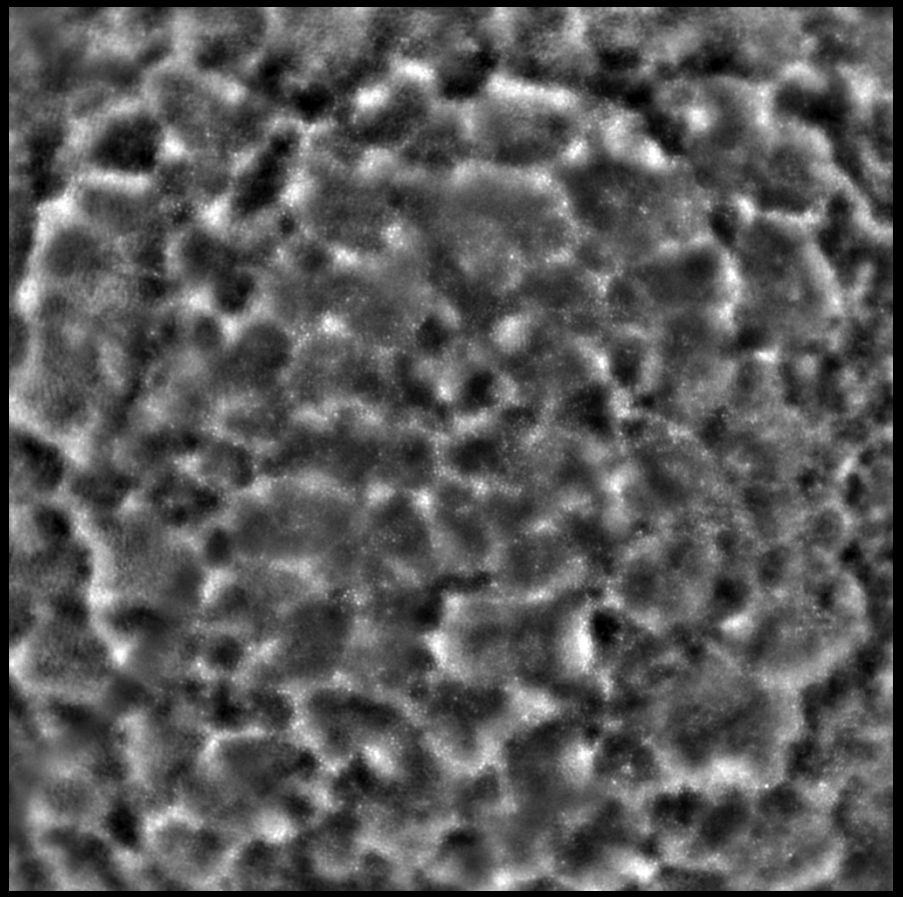
Adaptive Optics



Cuticular Drusen
Adaptive Optics



IR SLO

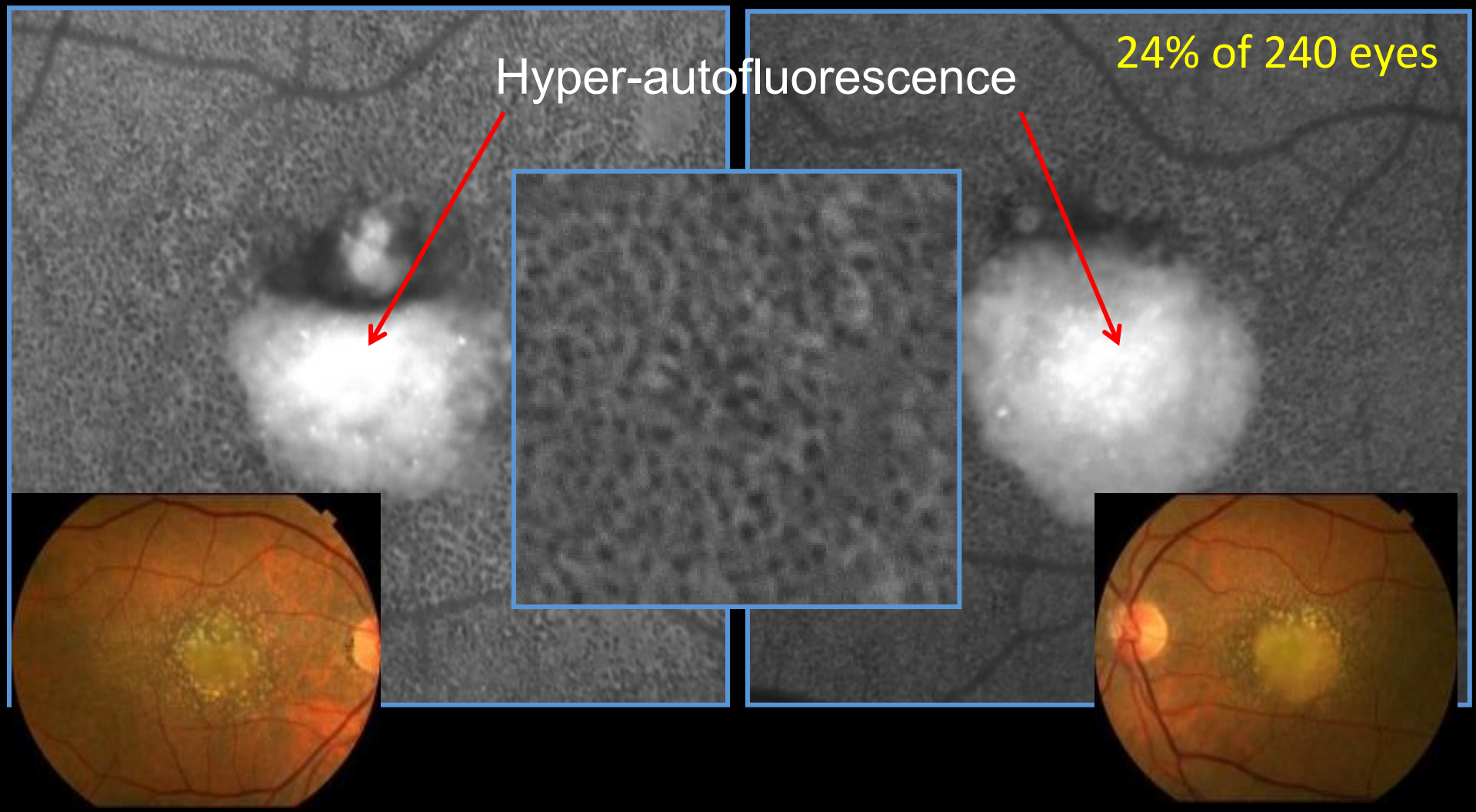


flood-illuminated IR AO

Balaratnasingam, Cherepanoff, Dolz-Marco, Killingsworth, Chen, Mendis, Mrejen, Curcio, Freund, Yannuzzi. Cuticular drursen: clinical phenotypes and natural history defined using multimodal imaging. Ophthalmology. Accepted. 2017

Cuticular Drusen

Acquired Vitelliform Lesions



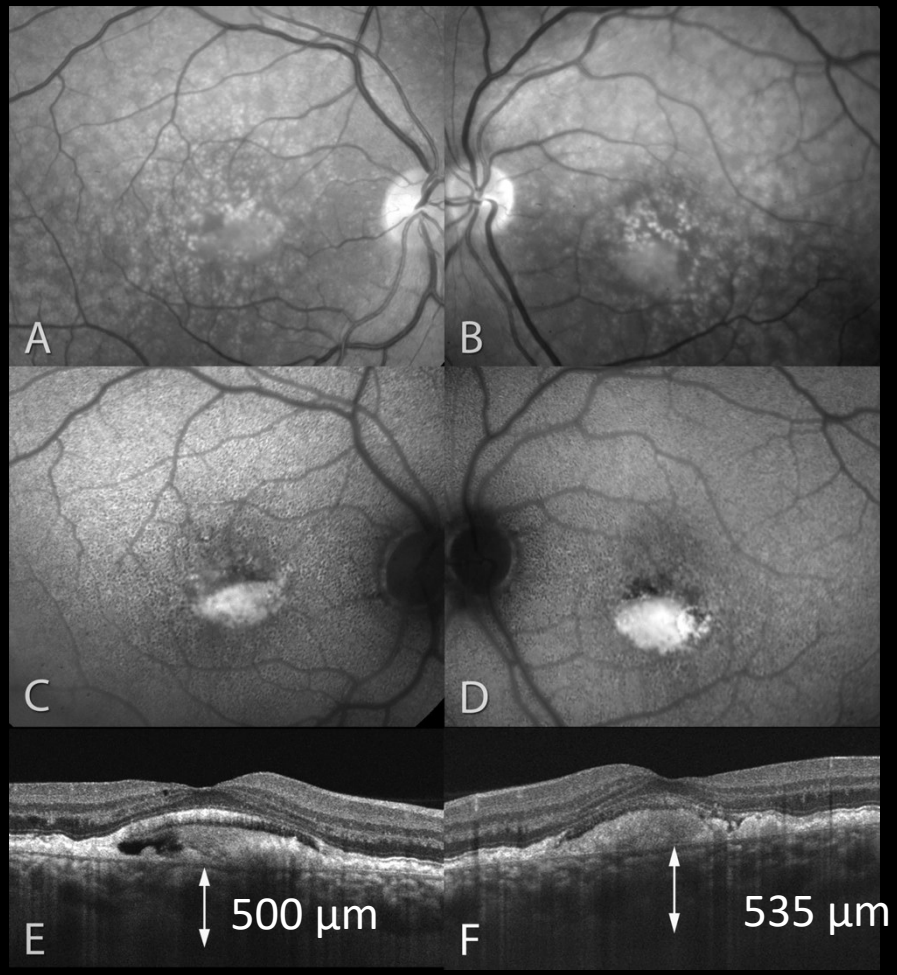
Balaratnasingam, Cherepanoff, Dolz-Marco, Killingsworth, Chen, Mendis, Mrejen, Curcio, Freund, Yannuzzi. Cuticular drursen: clinical phenotypes and natural history defined using multimodal imaging. Ophthalmology. Accepted. 2017

Cuticular Drusen

Acquired Vitelliform Lesions

24% of 240 eyes (1)

Choroidal thickening associated with vitelliform in 24 eyes (2)



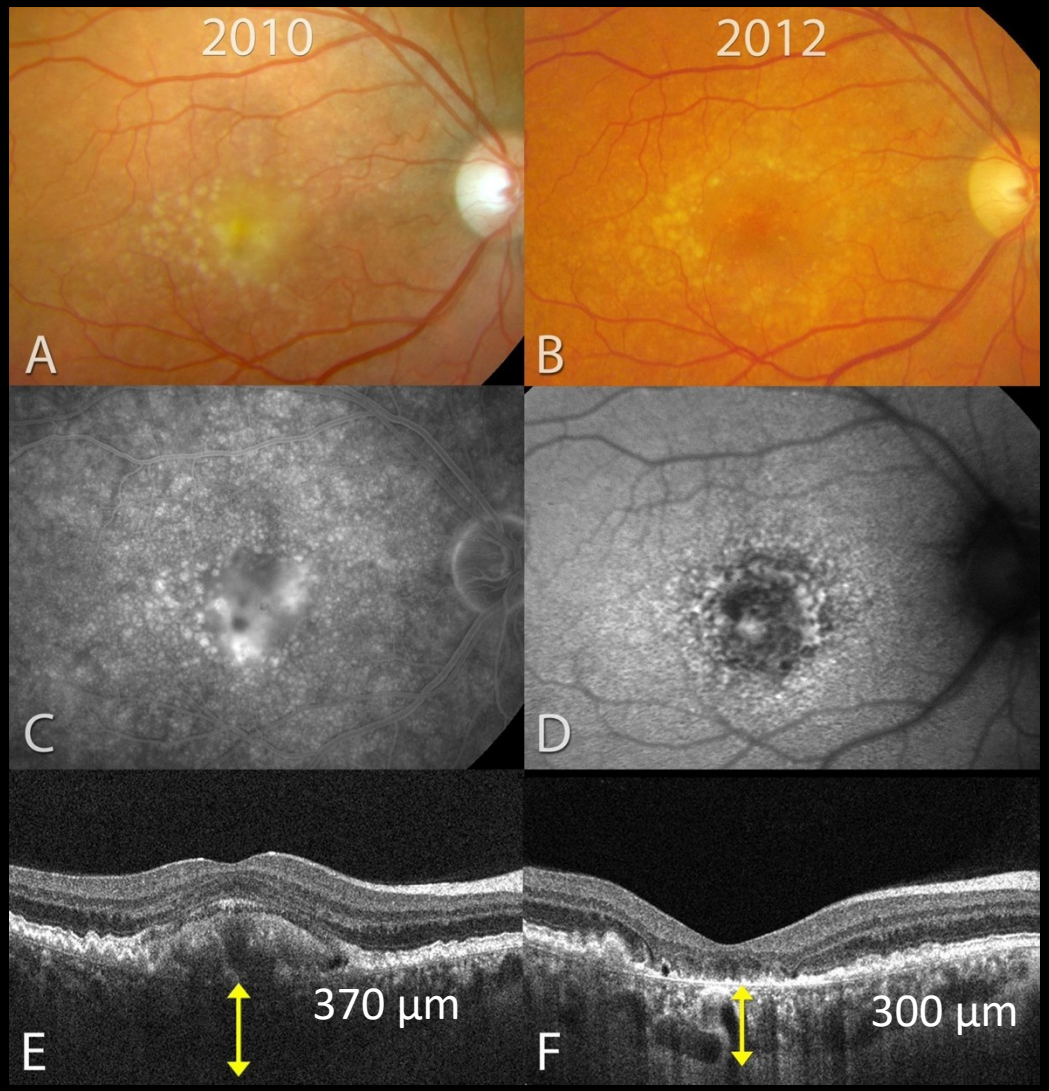
47-year-old female

1. Balaratnasingam, Cherepanoff, Dolz-Marco, Killingsworth, Chen, Mendis, Mrejen, Curcio, Freund, Yannuzzi. Cuticular drursen: clinical phenotypes and natural history defined using multimodal imaging. Ophthalmology. Accepted. 2017

2. Mrejen-Uretsky S, Ayrault S, Nghiem-Buffet S, Quentel G, Cohen SY. Choroidal thickening in patients with cuticular drusen Combined with vitelliform macular detachment. Retina, 2016.

Cuticular Drusen

Acquired Vitelliform Lesion and Evolution to RPE Atrophy

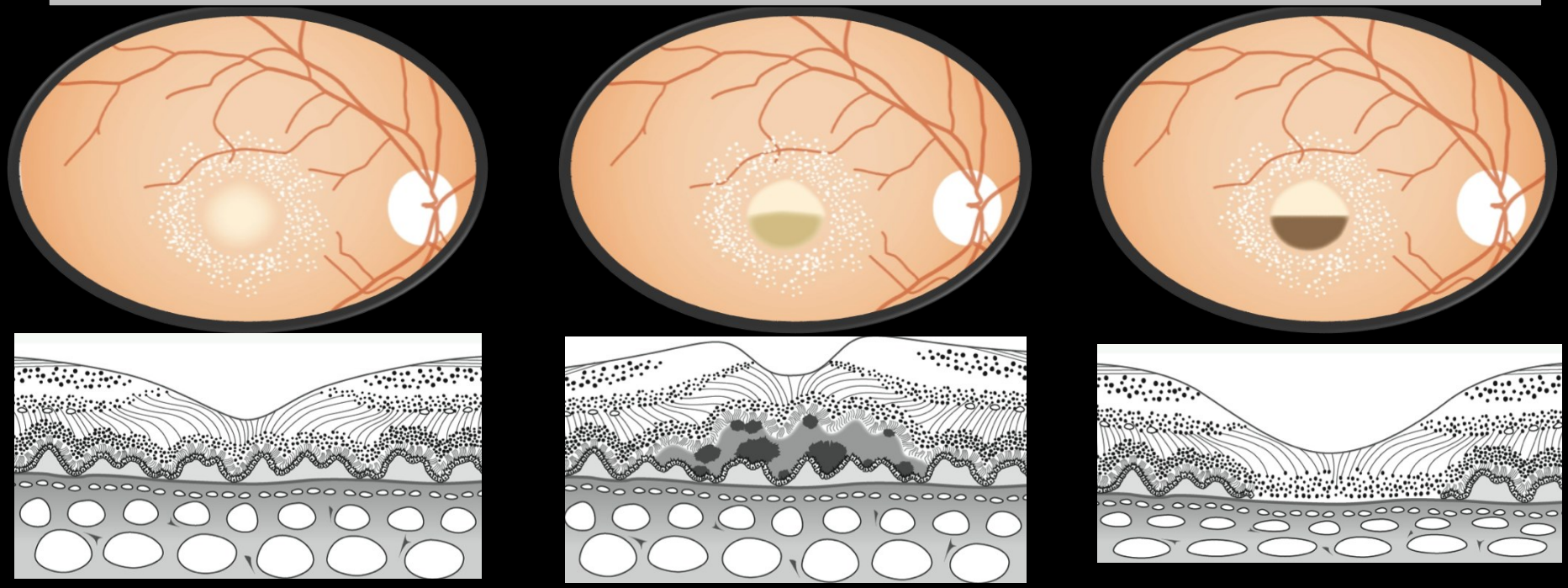


Mrejen-Uretsky S, Ayrault S, Nghiem-Buffet S, Quentel G, Cohen SY. Choroidal thickening in patients with cuticular drusen Combined with vitelliform macular detachment. Retina, 2016.

Cuticular Drusen

Acquired Vitelliform Lesion and Evolution to RPE Atrophy

- **Significant choroidal tickening in 12 eyes with cuticular drusen associated with vitelliform lesions compared to 12 eyes without**
- **Significant choroidal thinning after a follow-up of 3,3 years**

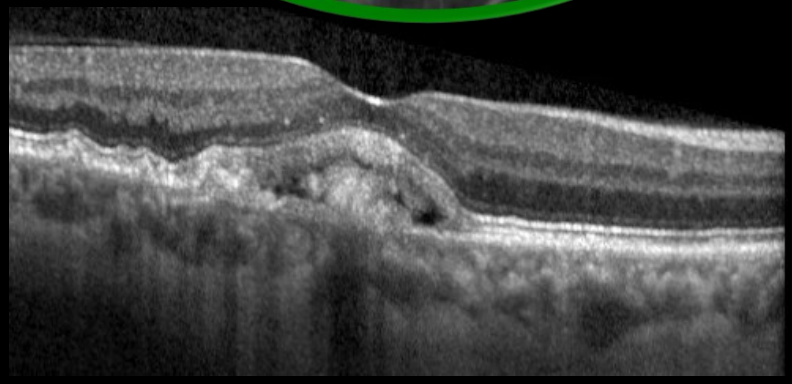


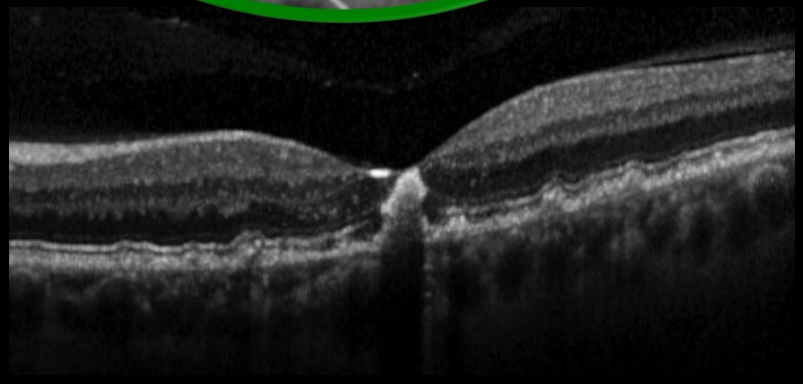
- **Cuticular drusen → outer blood retinal barrier dysfunction**
- **Choroidal vascular hyperpermeability→ serous retinal detachment → vitelliform**
- **Vitelliform → RPE atrophy → vitelliform resorption and choroidal thinning**

Mrejen-Uretsky S, Ayrault S, Nghiem-Buffet S, Quentel G, Cohen SY. Choroidal thickening in patients with cuticular drusen Combined with vitelliform macular detachment. Retina, 2016.

Cuticular Drusen

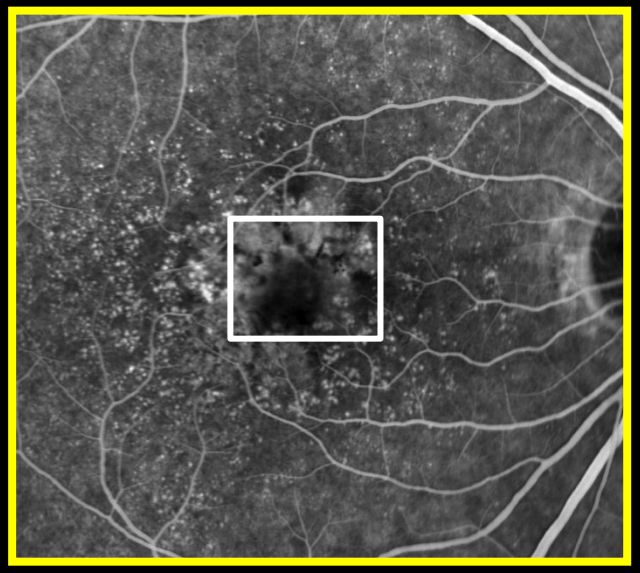
Acquired Vitelliform Lesion and Pigmentary Changes

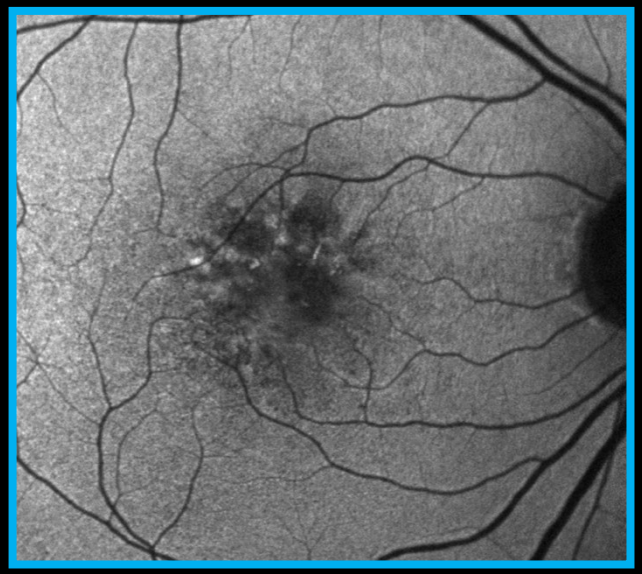


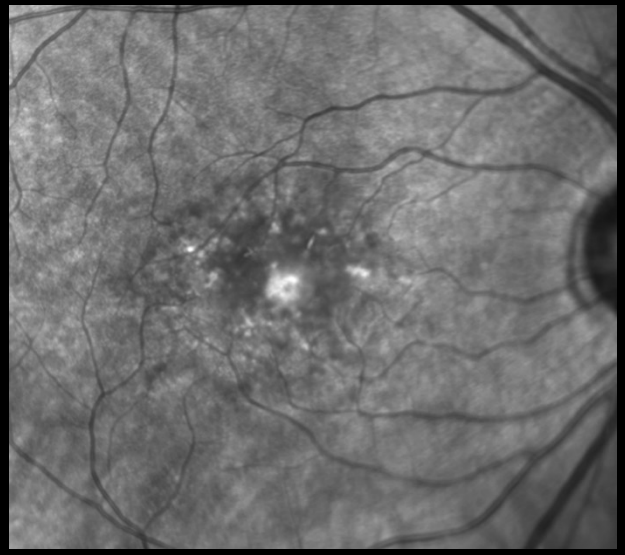


Cuticular Drusen

Acquired Vitelliform Lesion and Pigmentary Changes

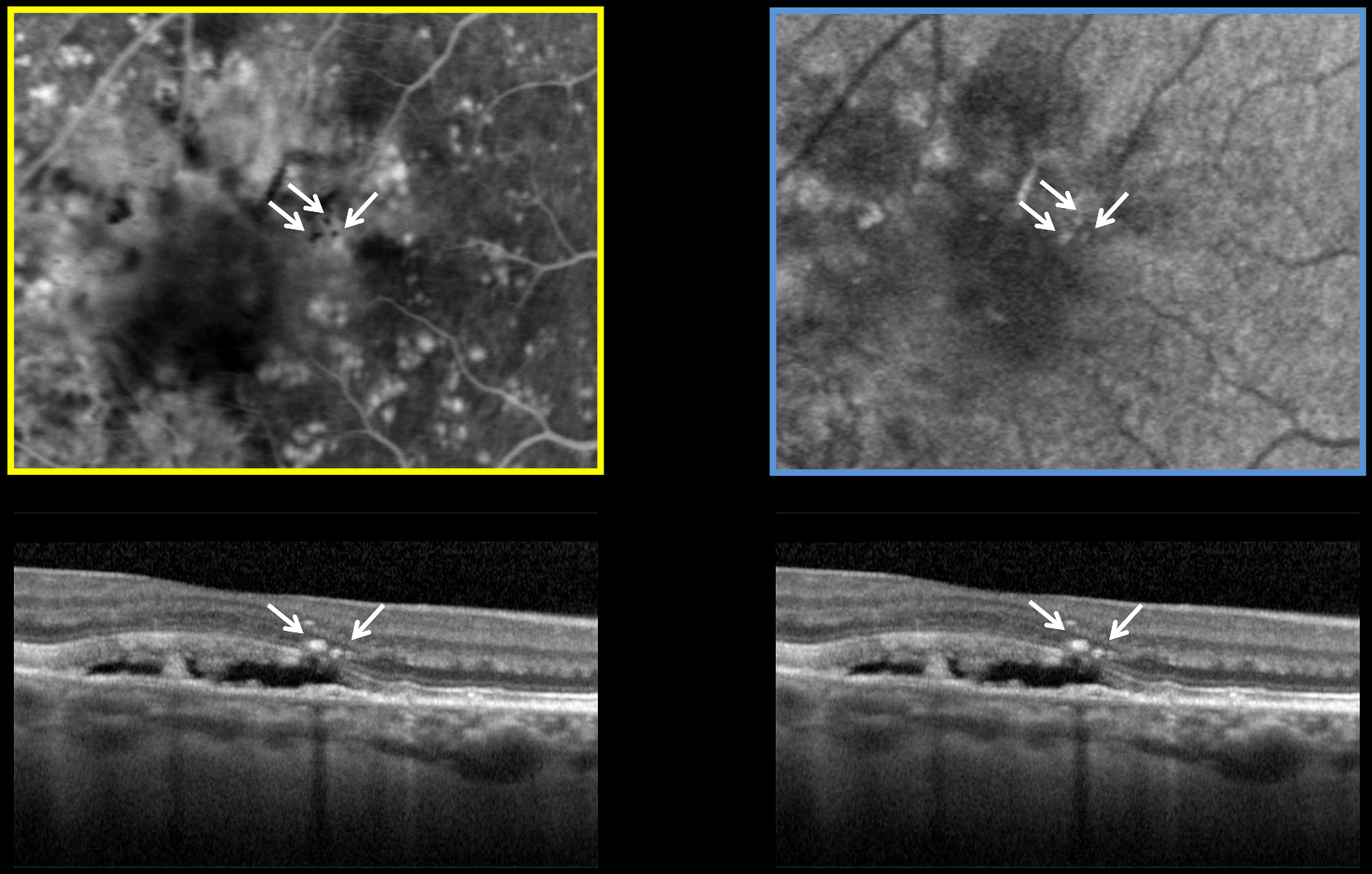






Cuticular Drusen
Pigmentary Changes

47% of 240 eyes



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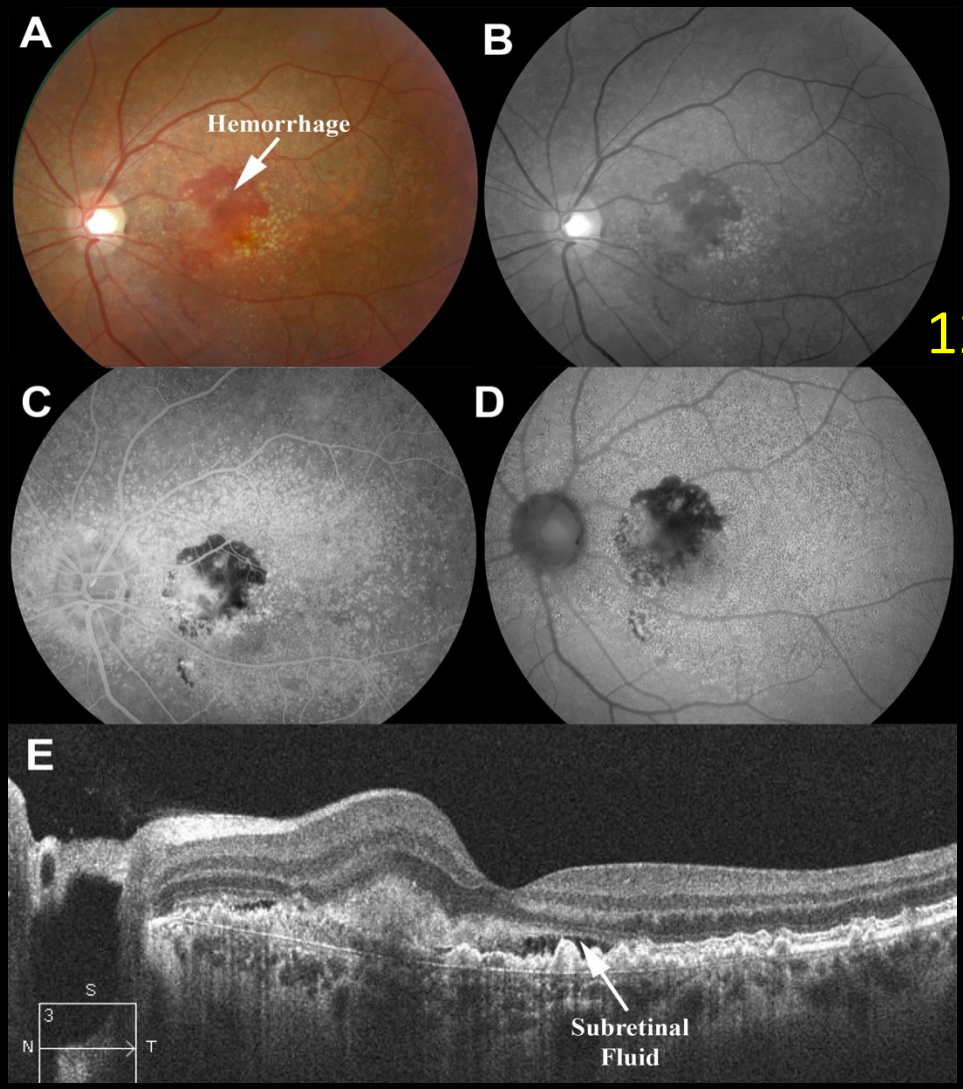
Cuticular Drusen

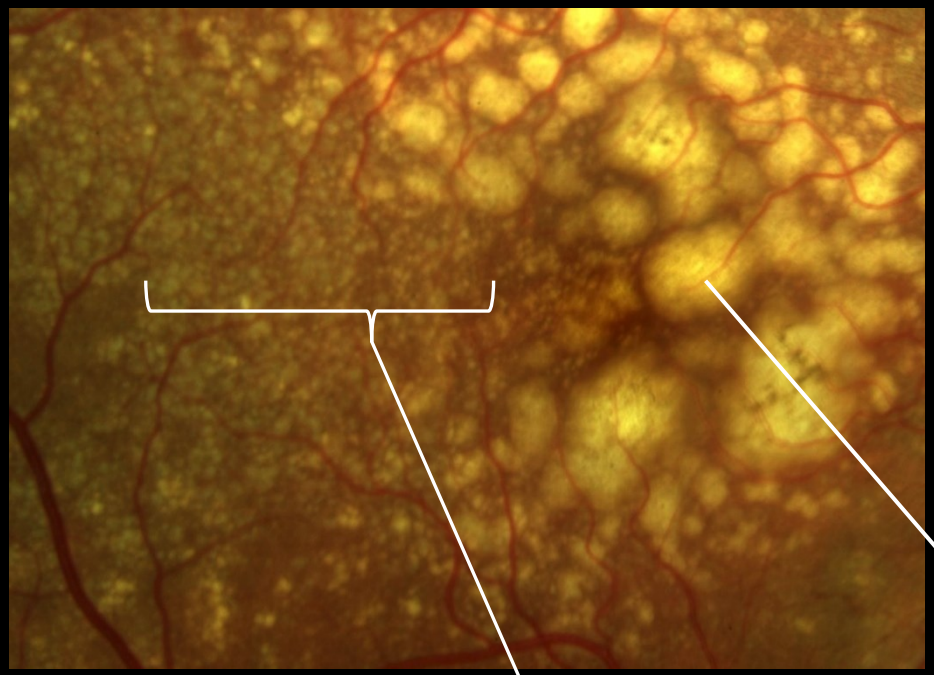
Choroidal Neovascularization

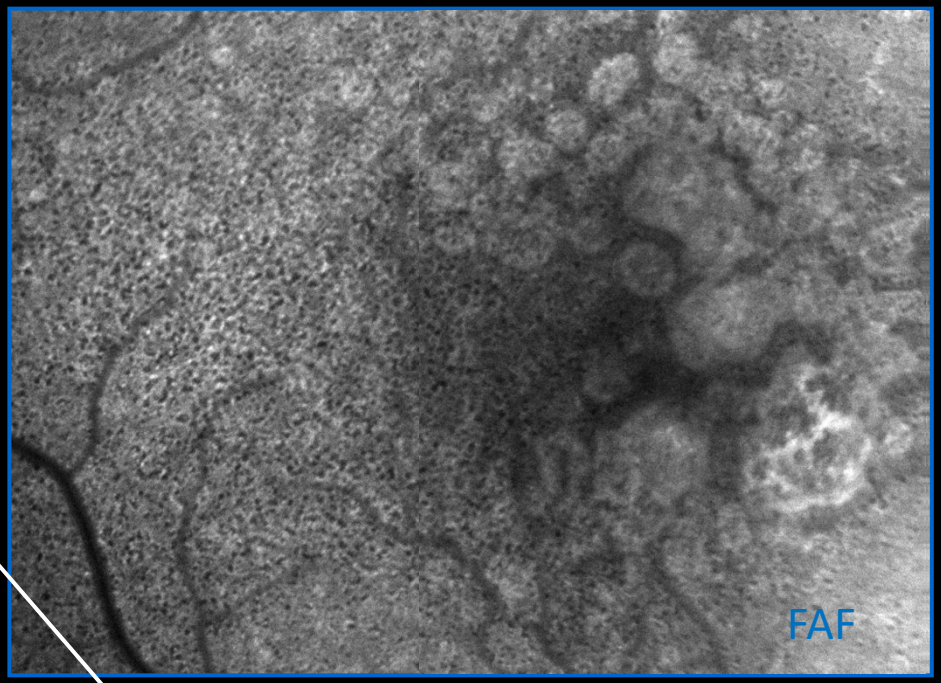


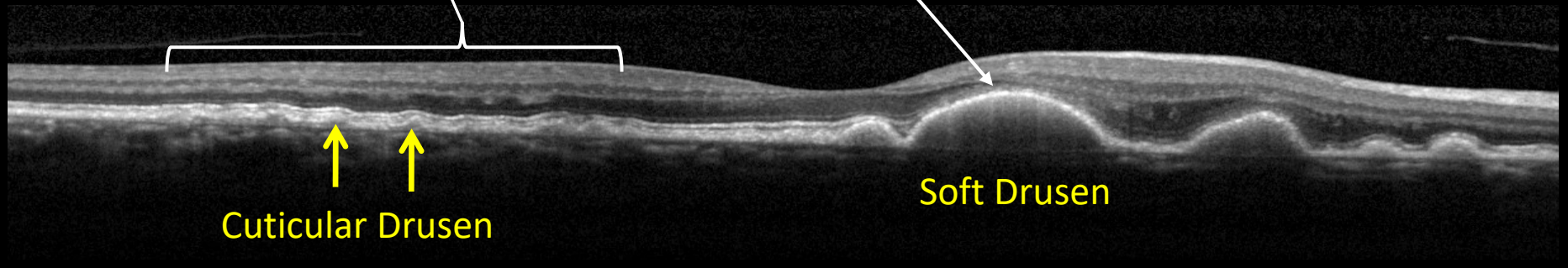
12% of 240 eyes

Balaratnasingam, Cherepanoff, Dolz-Marco, Killingsworth, Chen, Mendis, Mrejen, Curcio, Freund, Yannuzzi. Cuticular drursen: clinical phenotypes and natural history defined using multimodal imaging. Ophthalmology. Accepted. 2017

Cuticular Drusen
Mixed Pattern with Soft Drusen







Lawrence Yannuzzi

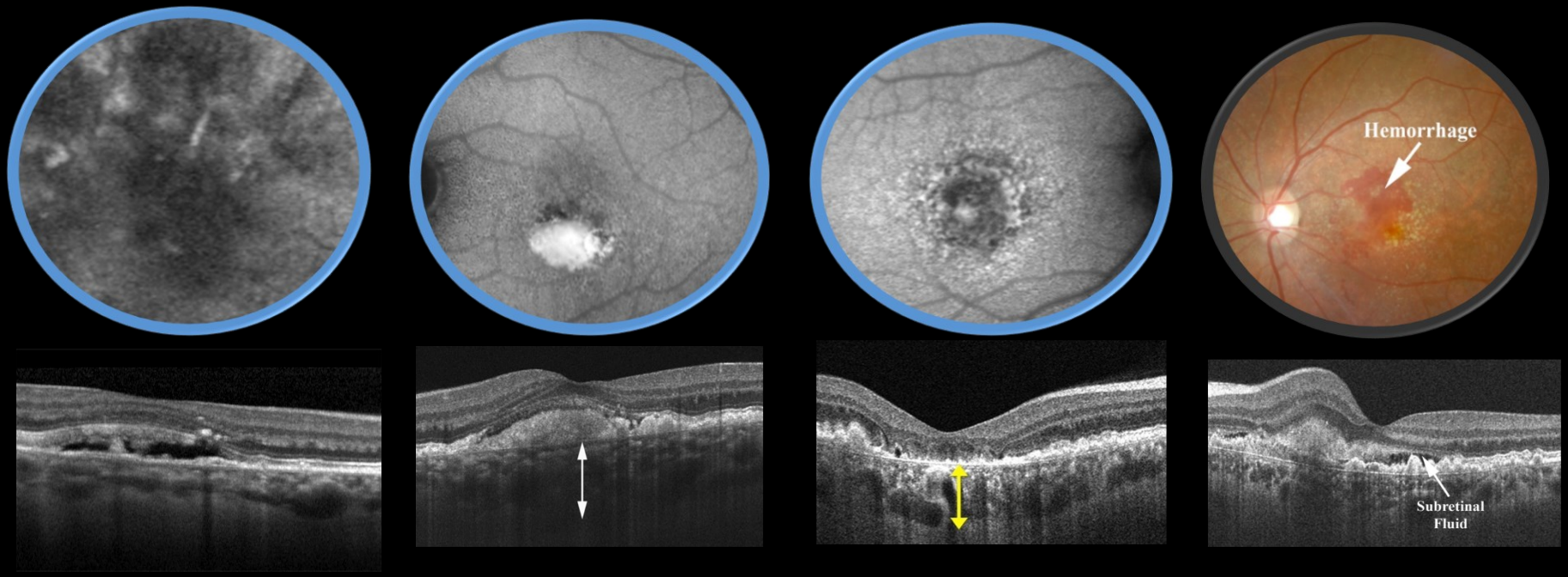
Cuticular Drusen

Conclusions

120 patients
58 years

follow-up 3,7 years

Pigmentary changes	Acquired vitelliform	RPE atrophy	Neovascularization
47%	24%	25%	12%

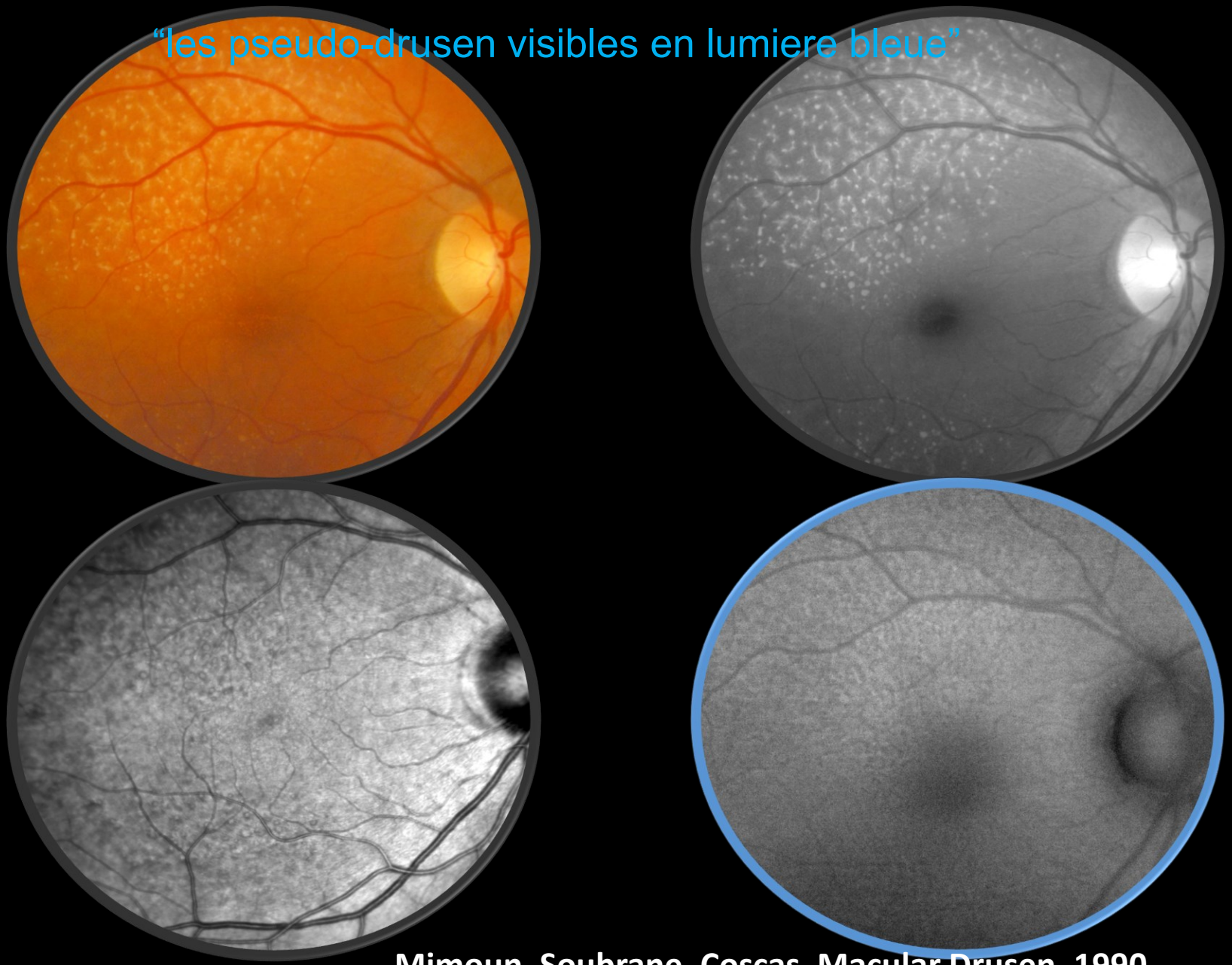


Same long-term complications than other drusen types but better prognosis
The neovascular and atrophic complications are more frequent after the age of 60 years

Balaratnasingam, Cherepanoff, Dolz-Marco, Killingsworth, Chen, Mendis, Mrejen, Curcio, Freund, Yannuzzi. Cuticular drursen: clinical phenotypes and natural history defined using multimodal imaging. Ophthalmology. Accepted. 2017

Reticular Pseudodrusen

"les pseudo-drusen visibles en lumiere bleue"



Mimoun, Soubrane, Coscas. Macular Drusen. 1990

Reticular Pseudodrusen
Population based studies

- **Beaver Dam Eye Study**: risque X 5 de progression vers stades tardifs de DMLA à 5 ans en présence de pseudodrusen, comparé aux autres phénotypes de DMLA précoce
- **Blue Mountain Eye Study**: risque X 4
- Mêmes FdR environnementaux que DMLA
- Mêmes FdR génétiques que DMLA (HTRA1, CFH, ARMS2)
- Composition biochimique vs aux drusen séreux
  - Cholestérol non estérifié SDD et estérifié drusen séreux
- Distribution périfovéolaire vs centrale pour les drusen séreux

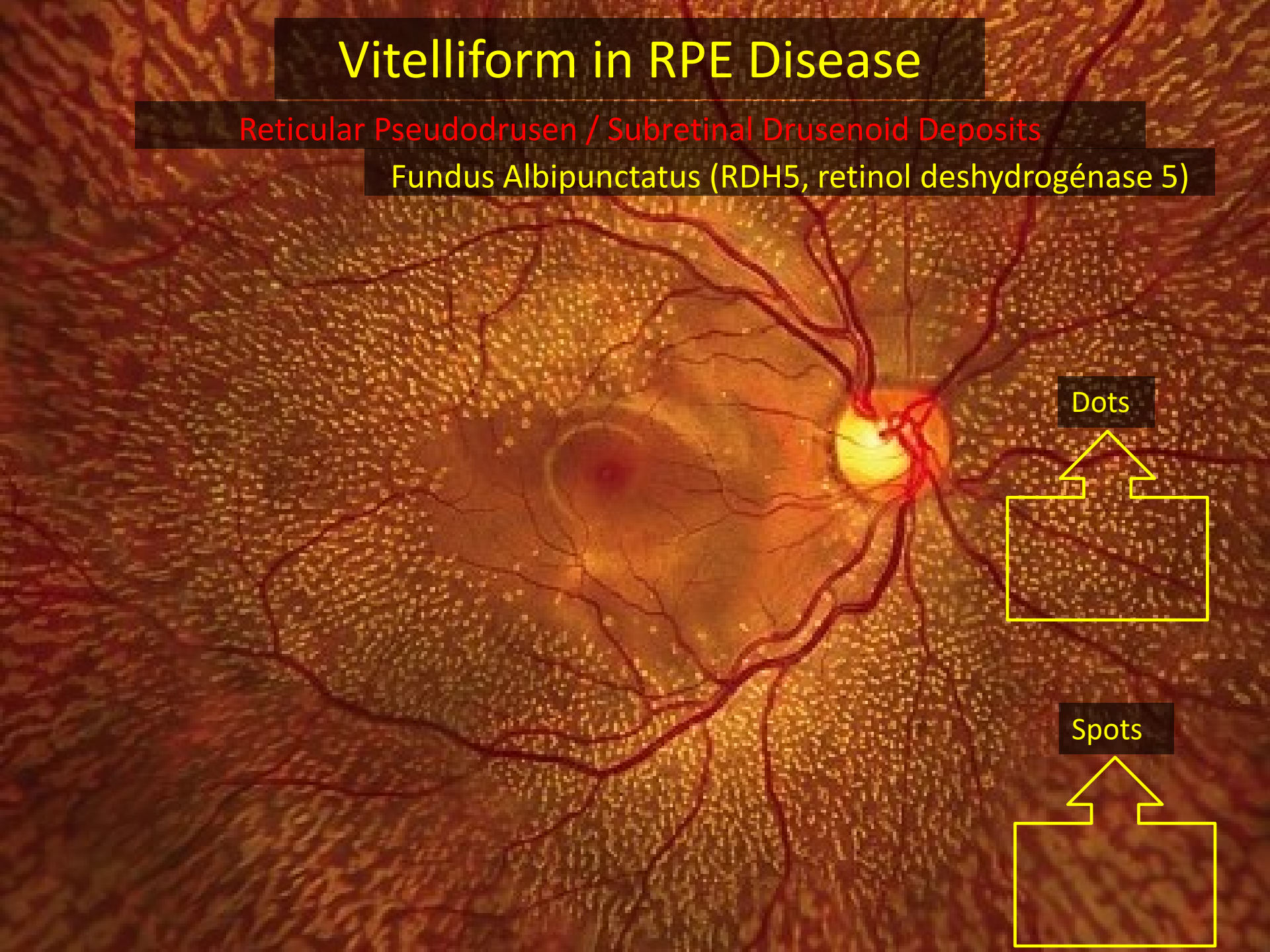
Pseudodrusen Réticulés

- Peuvent être isolés sans autre signe de DMLA
- Peuvent être associés à certaines dystrophies
  - Sorsby fundus dystrophy (TIMP3)
  - Pseudoxanthoma Elasticum (ABCC6)
  - Fundus albipunctatus (RDH5)

Vitelliform in RPE Disease

Reticular Pseudodrusen / Subretinal Drusenoid Deposits

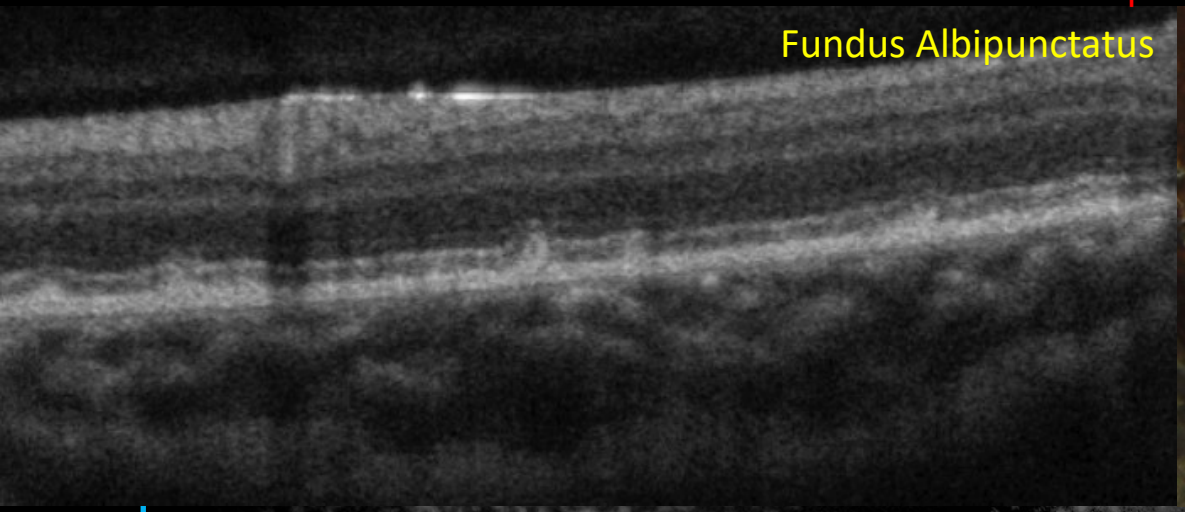
Fundus Albipunctatus (RDH5, retinol deshydrogénase 5)

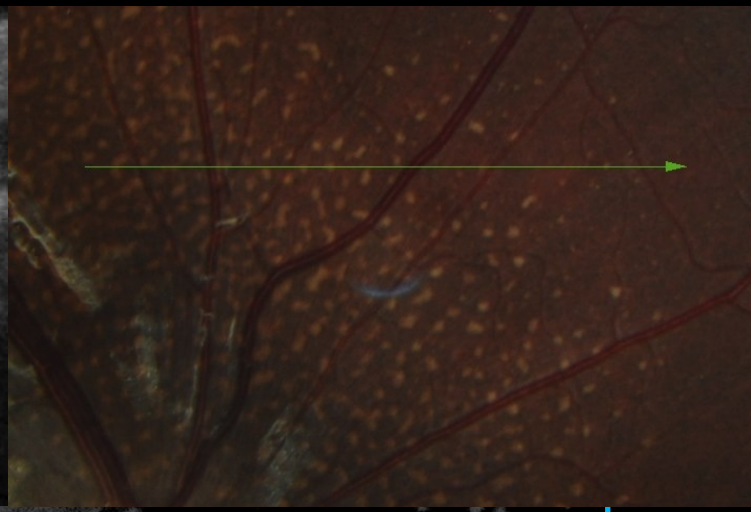


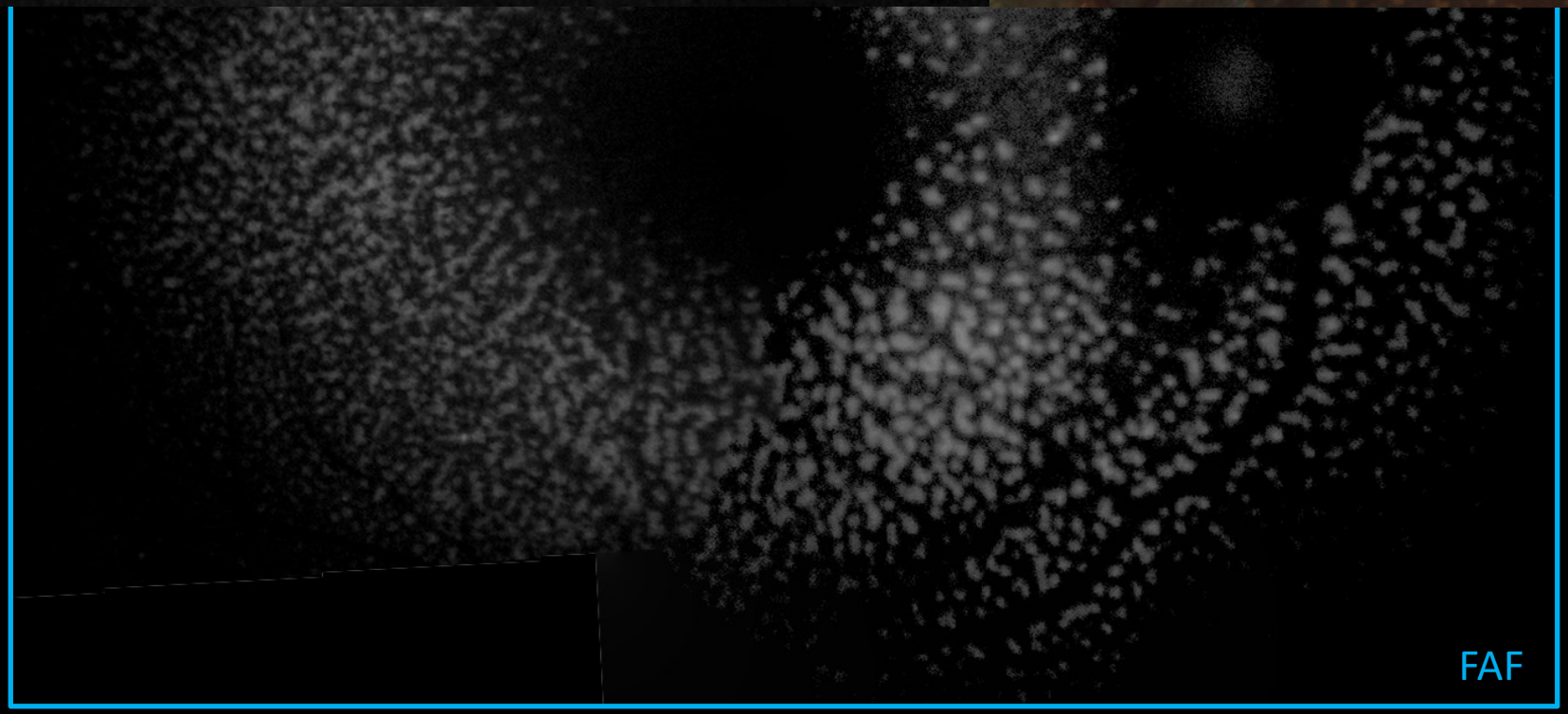
Vitelliform in RPE Disease

Subretinal Drusenoid Deposits

Fundus Albipunctatus



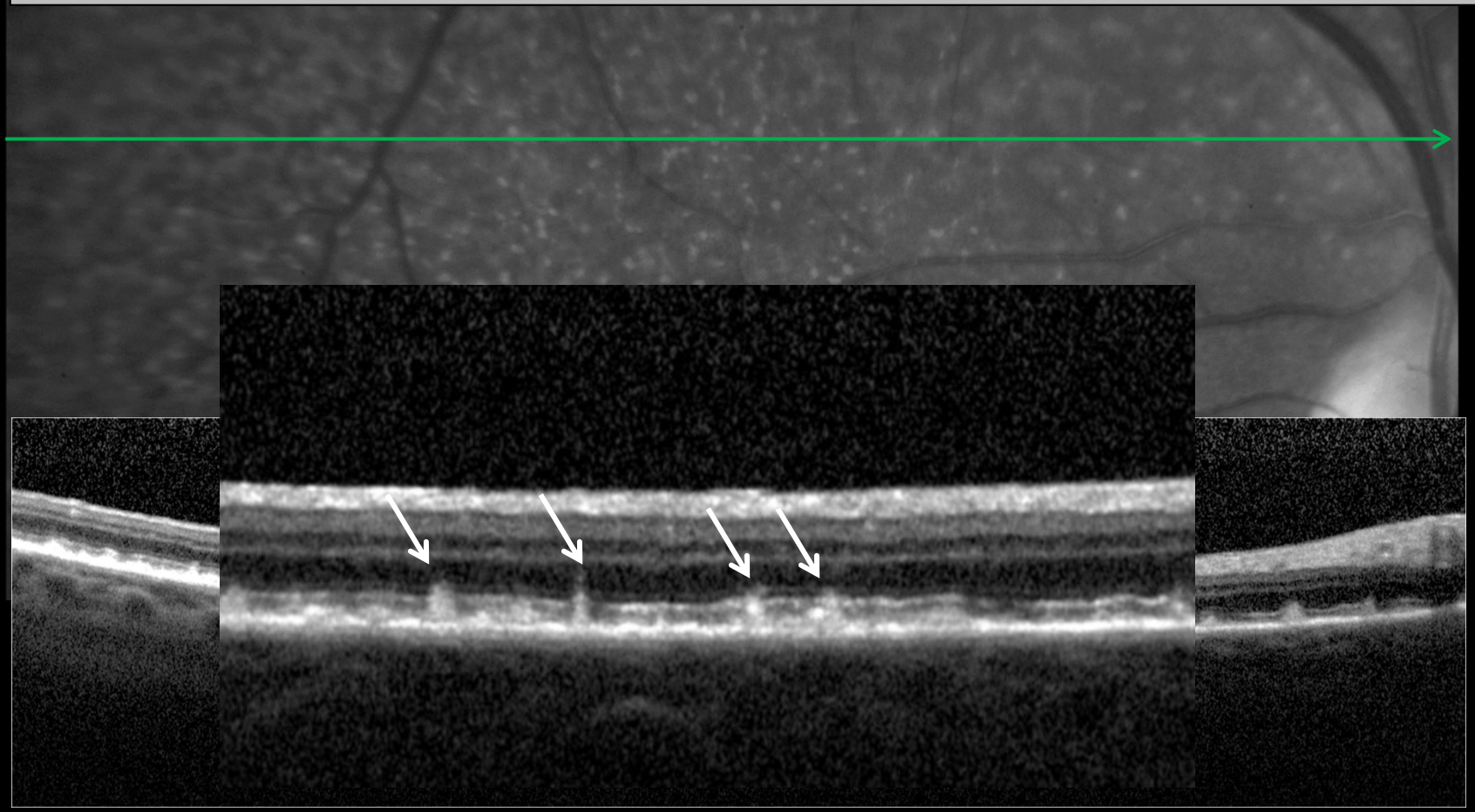




J. Sherman

Reticular Pseudodrusen

Reticular pseudodrusen are “Subretinal Drusenoid Deposits (SDD)”

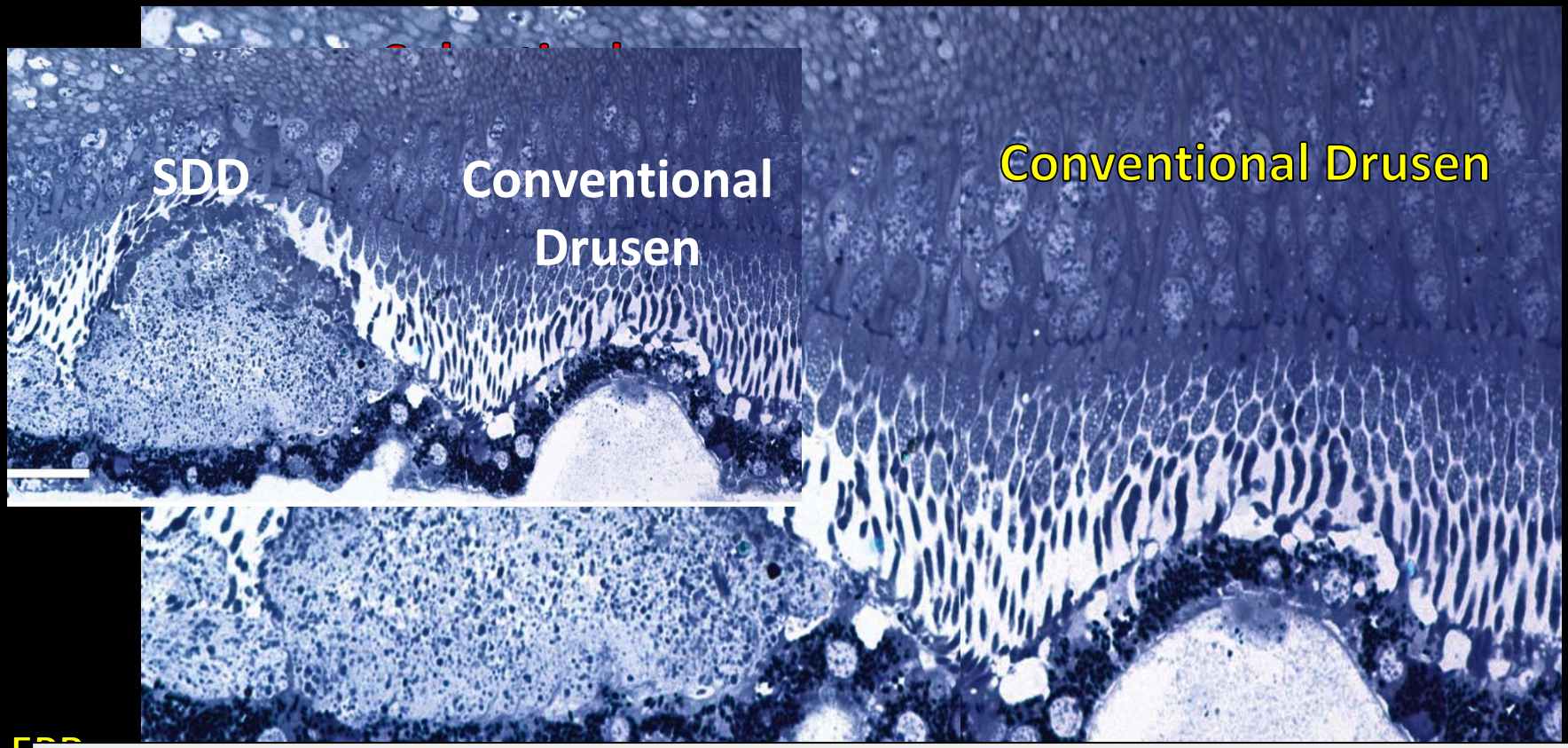


Reticular Pseudodrusen Are Subretinal Drusenoid Deposits

Sandrine A. Zweifel, MD,[1,2] Richard F. Spaide, MD,[2] Christine A. Curcio, PhD,[3] Goldis Malek, PhD,[4] Yutaka Imamura, MD[1,2]

Ophthalmology, 2010

Reticular Pseudodrusen



Reticular Pseudodrusen are subretinal

Similar composition as conventional drusen

Differential Impact on photoreceptors

Reticular Pseudodrusen
Prevalence discrepancies

- Fellow eyes of neovascular AMD
  - Smith et al: 36% on color fundus photography and FAF (55 patients)
  - Finger et al: 58% on combined IR-SLO and SD OCT imaging (200 patients)
- Newly diagnosed neovascular AMD
  - Cohen et al: 24% on bue light photography (100 patients)
- Newly-diagnosed late AMD
  - Ueda-Arakawa et al: 14% on combined SD OCT and IR SLO (249 patients)
  - low prevalence (included PCV, younger and less female, ethnic differences?)

Smith RT, Chan JK, Busuoic M, Sivagnanavel V, Bird AC, Chong NV. Autofluorescence characteristics of early, atrophic, and high-risk fellow eyes in age-related macular degeneration. IOVS 2006.
Cohen SY, Dubois L, Tadayoni R, et al. Prevalence of reticular pseudodrusen in age-related macular degeneration with newly diagnosed choroidal neovascularisation. Br J Ophthalmol. 2007
Finger RP, Wu Z, Luu CD, et al. Reticular pseudodrusen: a risk factor for geographic atrophy in fellow eyes of individuals with unilateral choroidal neovascularization. Ophthalmology. 2014
Ueda-Arakawa N, Ooto S, Nakata I, et al. Prevalence and genomic association of reticular pseudodrusen in age-related macular degeneration. Am J Ophthalmol. 2013.

Reticular Pseudodrusen

SD-OCT

Reticular Pseudodrusen Are Subretinal Drusenoid Deposits

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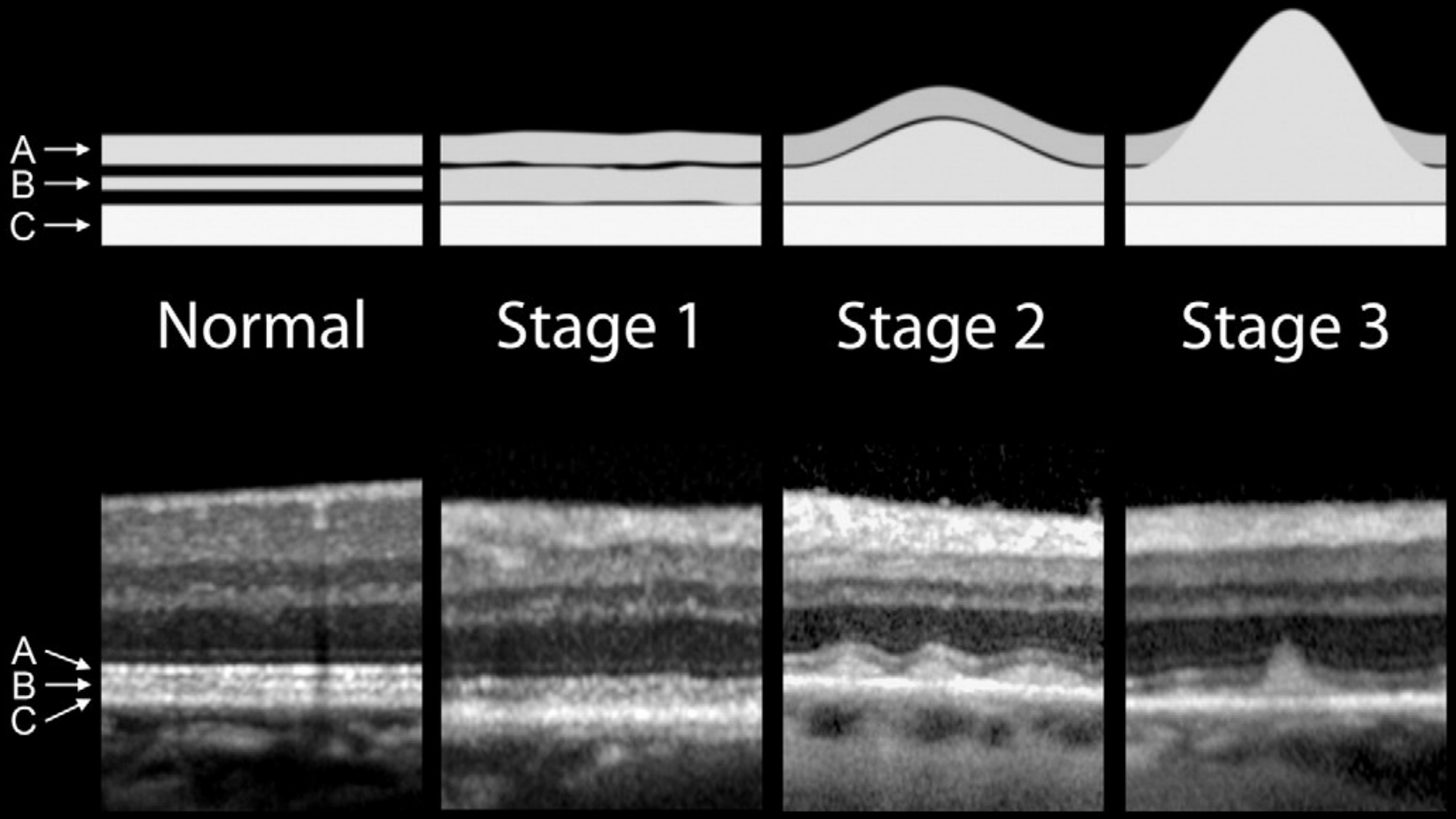
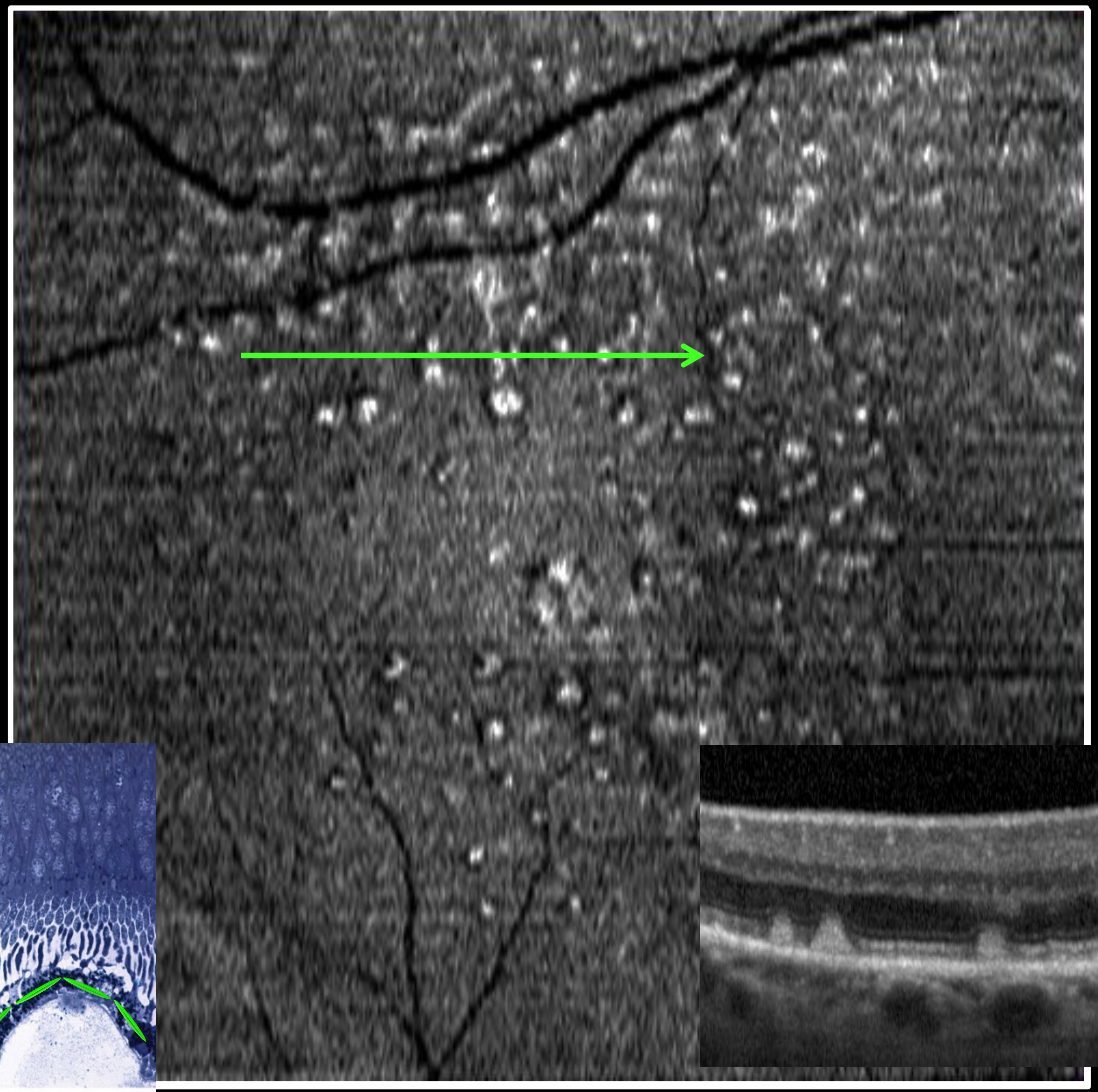
Ophthalmology, 2010

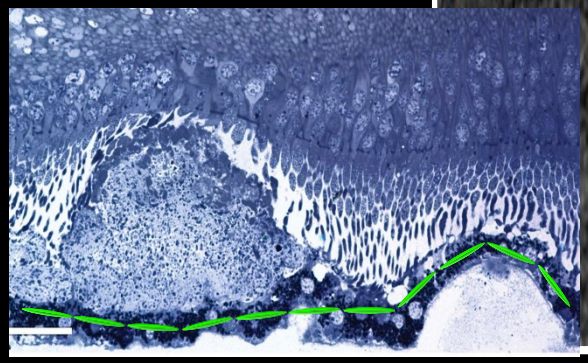


Reticular Pseudodrusen

En Face SD-OCT

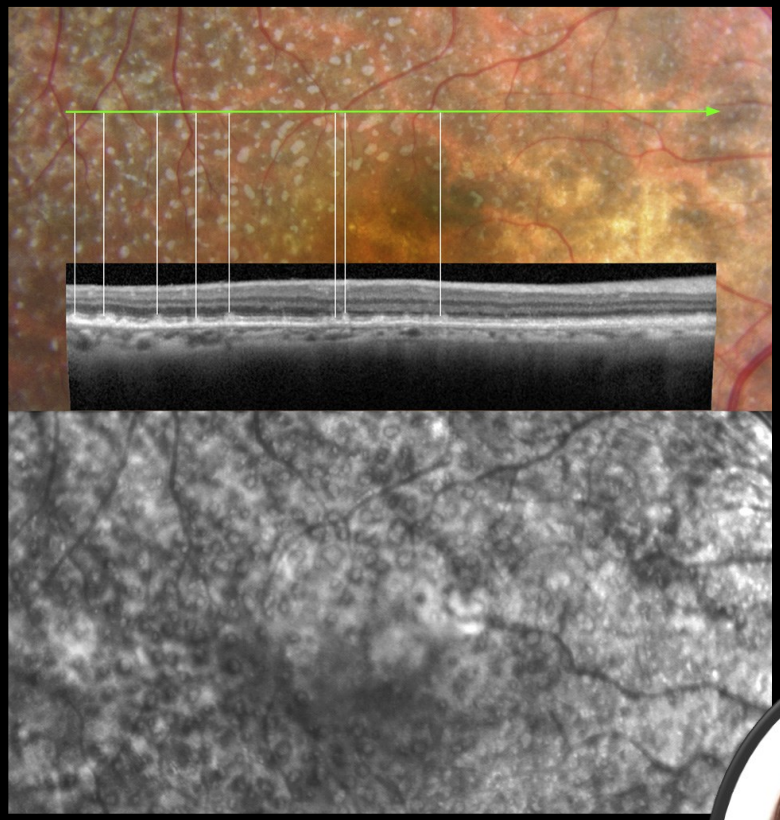


C-Scan Plane



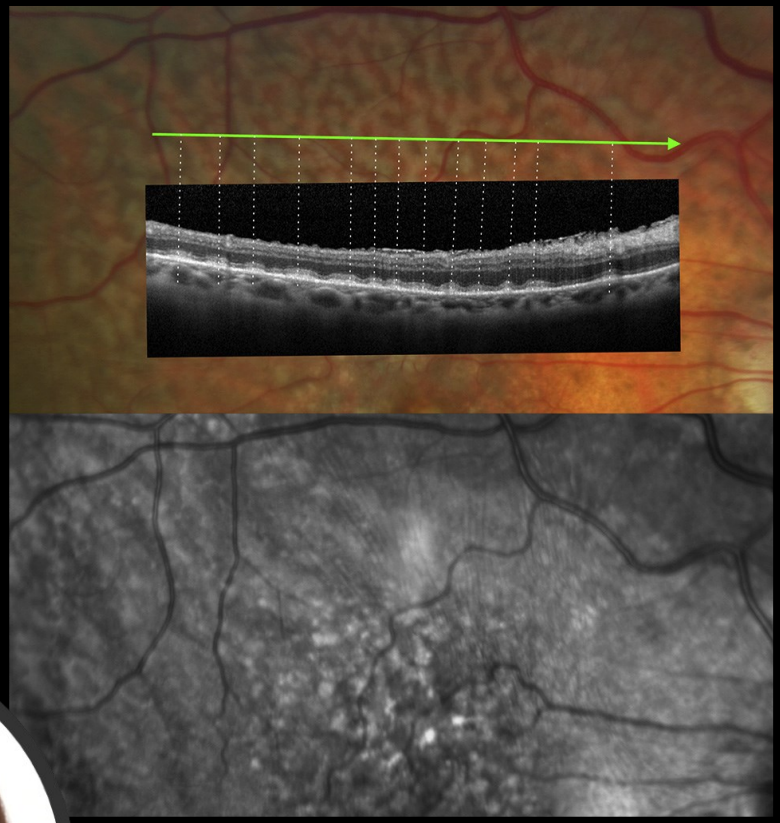
Switzer, Engelbert, Freund. Eye, 2011

Reticular Pseudodrusen Subtypes



Dot pseudodrusen
more frequent
Visualized on IR-SLO: target lesion
SD-OCT: peaked

Mihoko Suzuki



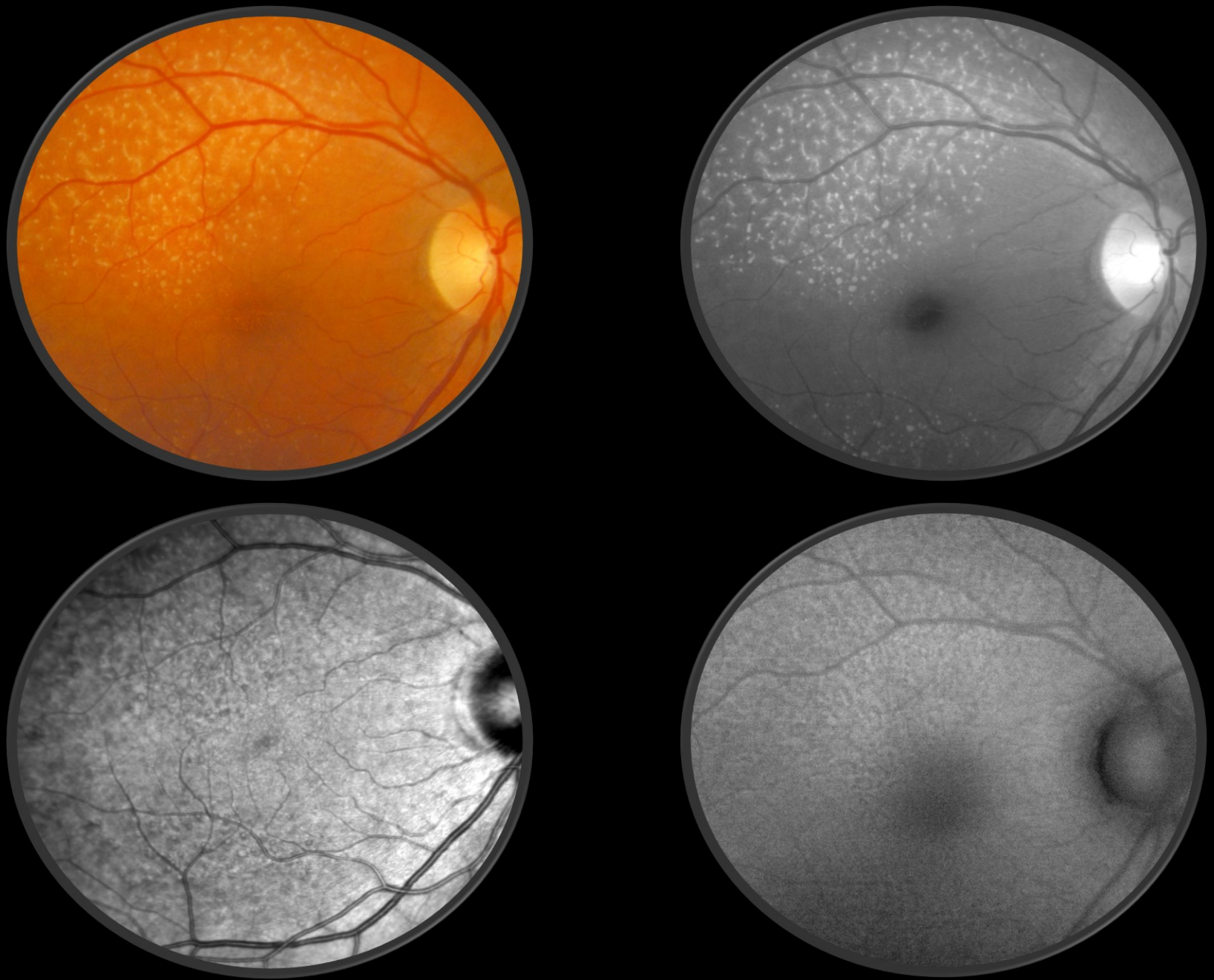
Ribbon pseudodrusen
Best visualized on color photo
SD-OCT: broader mounds

Pseudodrusen Subtypes as Delineated by Multimodal Imaging of the Fundus

MIHOKO SUZUKI, TAKU SATO, AND RICHARD F. SPAIDE

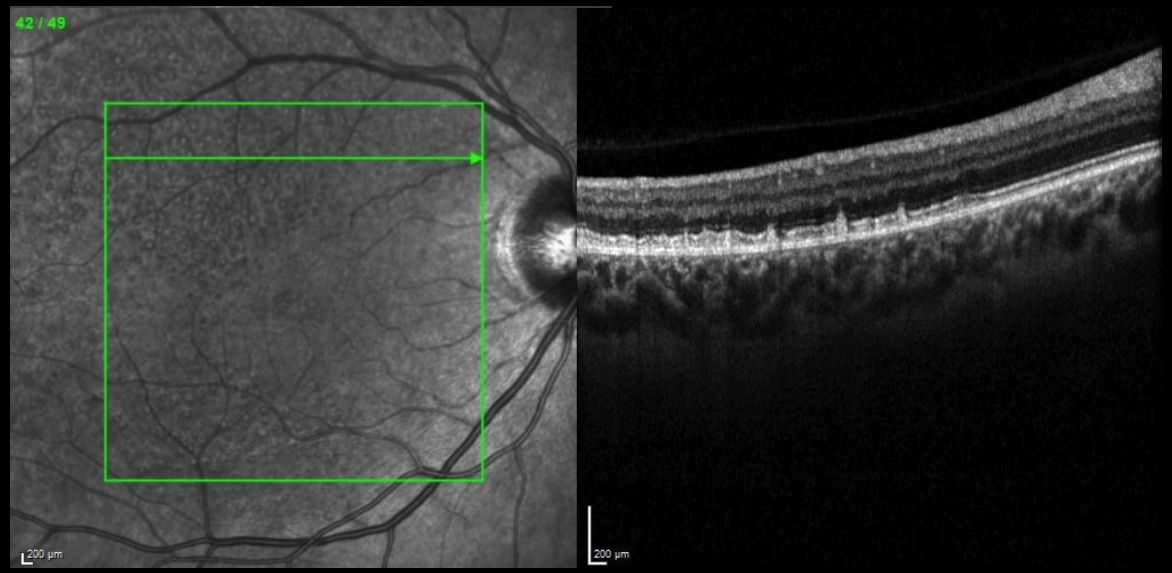
AJO, 2014

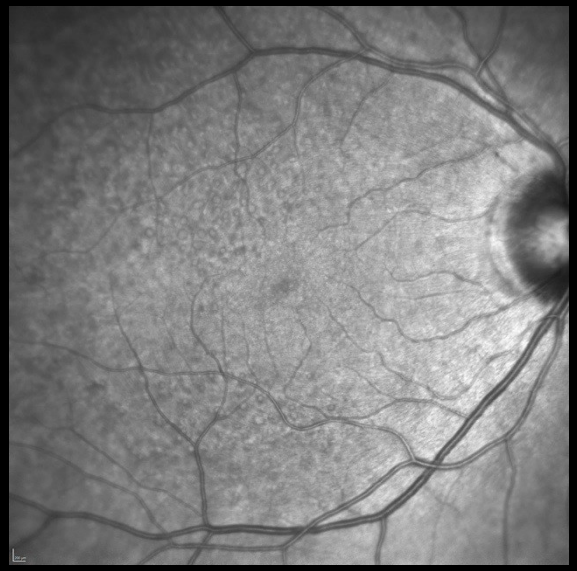
Reticular Pseudodrusen

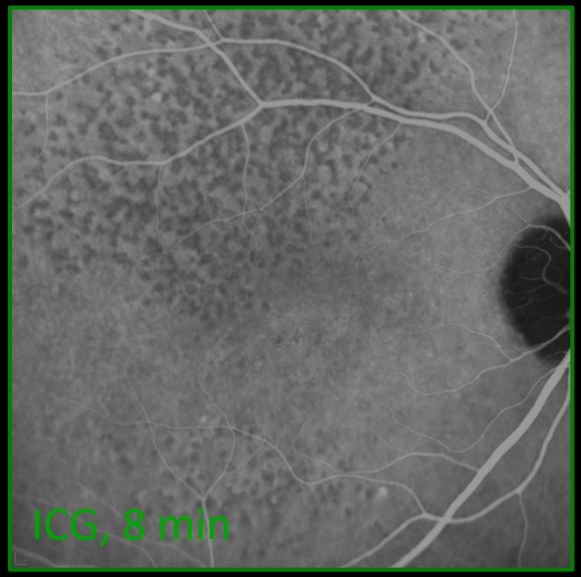


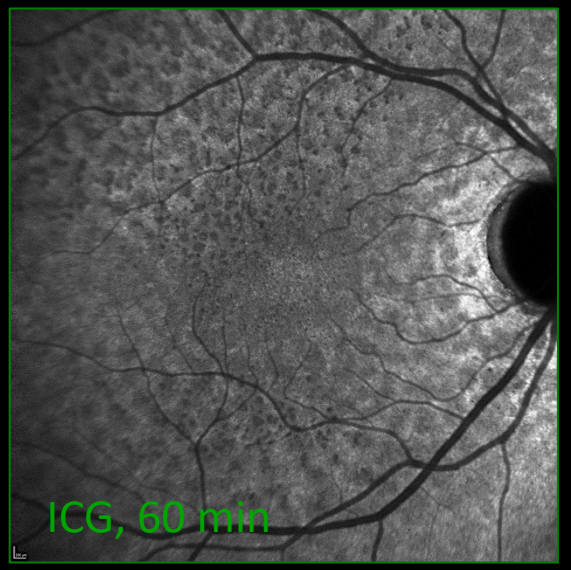
Reticular Pseudodrusen Subtypes

Multimodal Imaging



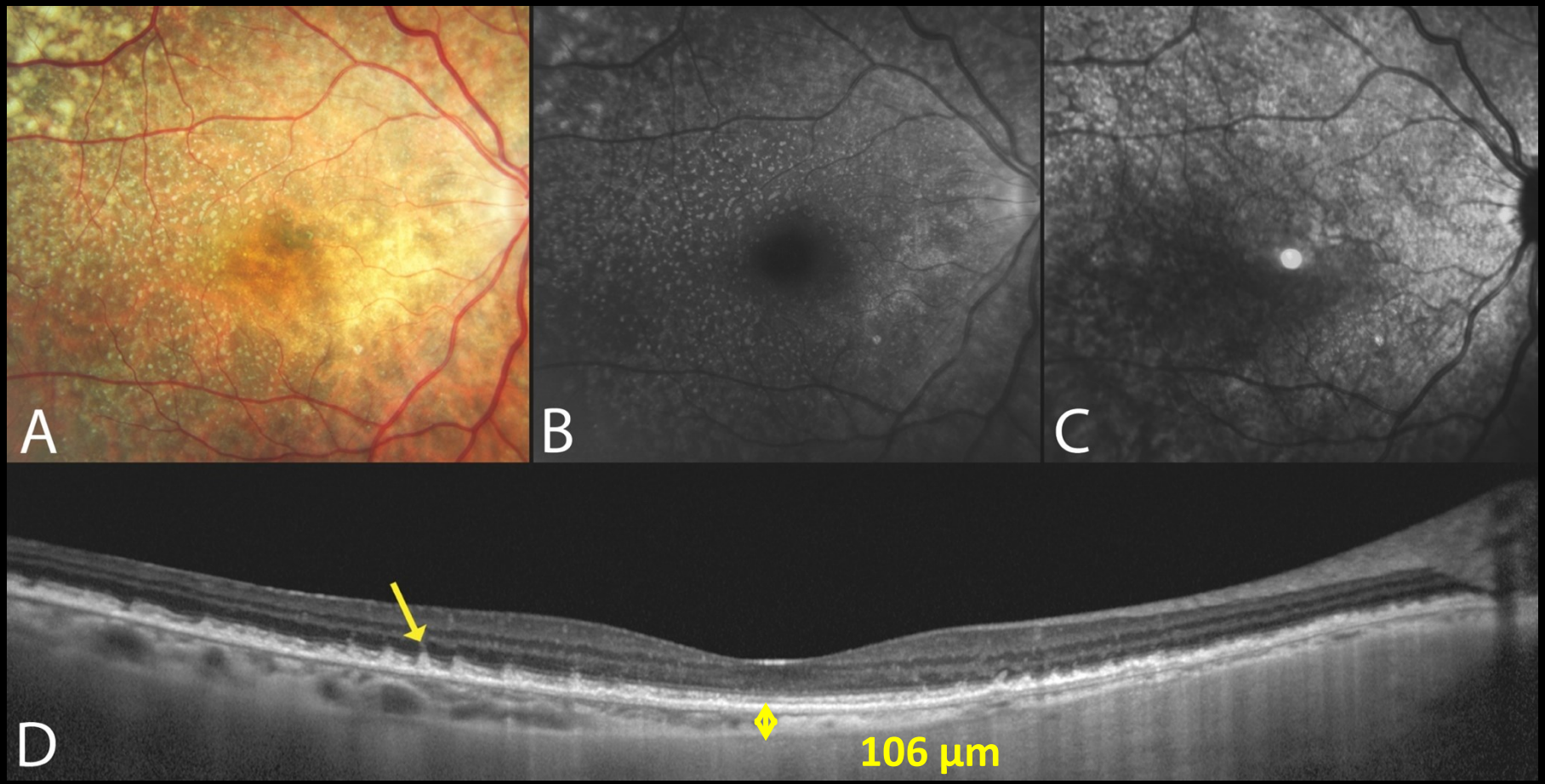






Reticular Pseudodrusen

Choroidal Thinning



Retina

Choroidal Changes Associated with Reticular Pseudodrusen

Giuseppe Querques,[1,2] Lea Querques,[1,2] Raimondo Forte,[1] Nathalie Massamba,[1] Florence Coscas,[1] and Eric H. Souied[1]

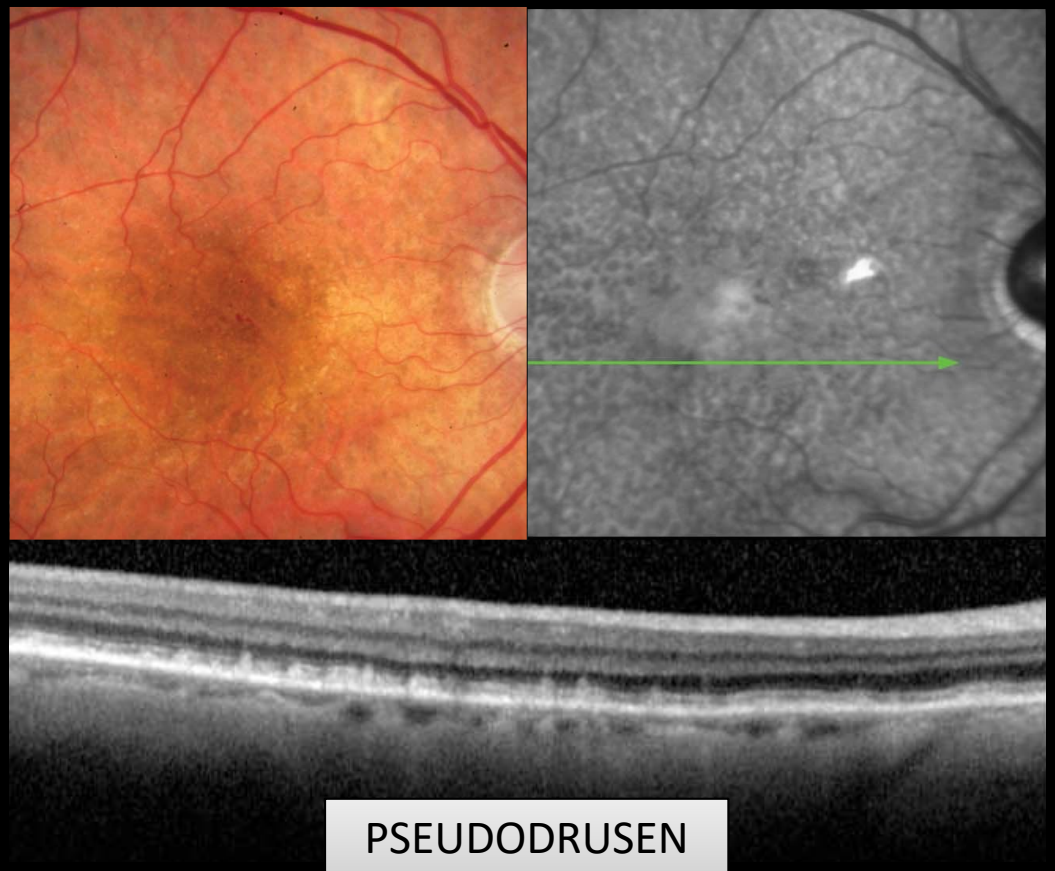
2012

SEGREGATION OF OPHTHALMOSCOPIC CHARACTERISTICS ACCORDING TO CHOROIDAL THICKNESS IN PATIENTS WITH EARLY AGE-RELATED MACULAR DEGENERATION

DAVID W. SWITZER, JR, MD, LUIS S. MENDONÇA, MD, MASAAKI SAITO, MD, SANDRINE A. ZWEIFEL, MD, RICHARD F. SPAIDE, MD

Reticular Pseudodrusen

Choroidal Thinning



PSEUDODRUSEN
Choroidal thinning

Soft drusen
Relatively thicker choroid

SEGREGATION OF OPHTHALMOSCOPIC CHARACTERISTICS ACCORDING TO CHOROIDAL THICKNESS IN PATIENTS WITH EARLY AGE-RELATED MACULAR DEGENERATION

DAVID W. SWITZER, JR, MD, LUIS S. MENDONÇA, MD, MASAAKI SAITO, MD, SANDRINE A. ZWEIFEL, MD, RICHARD F. SPAIDE, MD

Retina, 2012

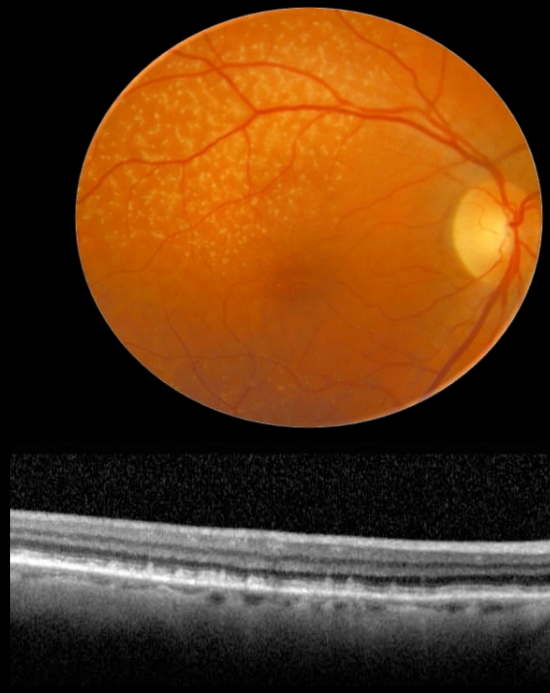
La choroïde module l'expression de la DMLA

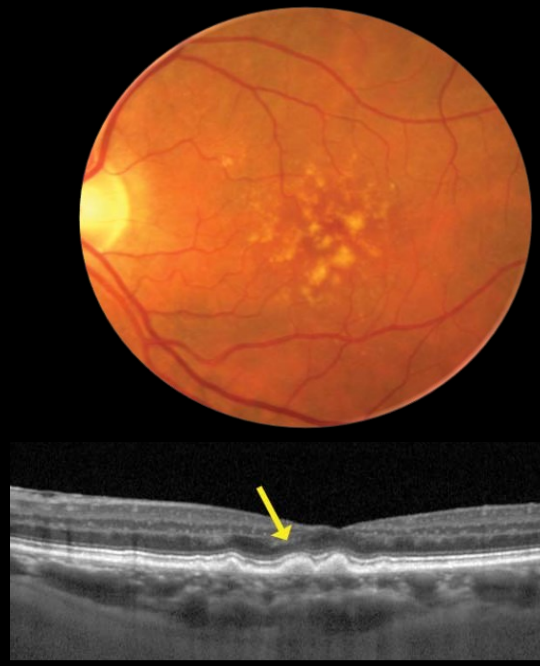
Drusen

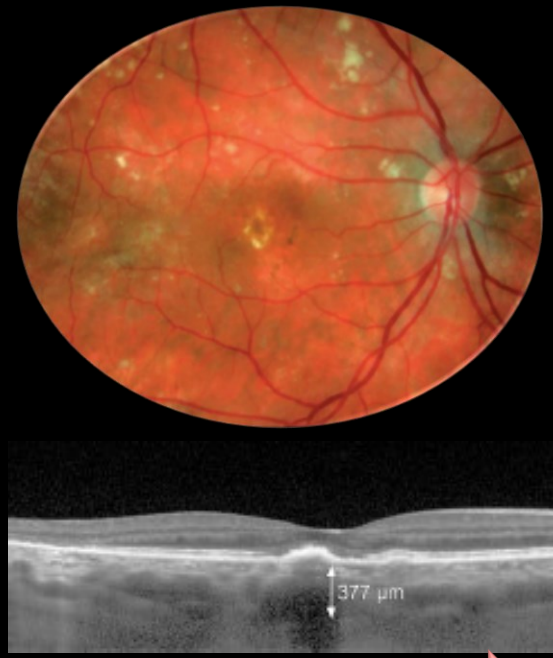
Pseudodrusen réticulés

Drusen séreux

Pachydrusen







< 120 µm

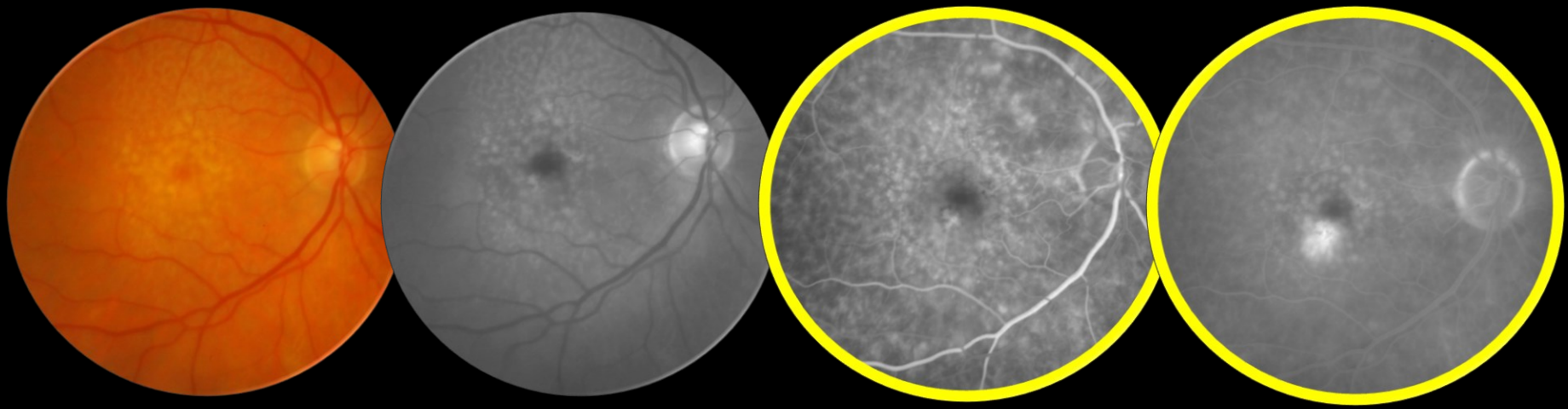
Epaisseur choroïdienne

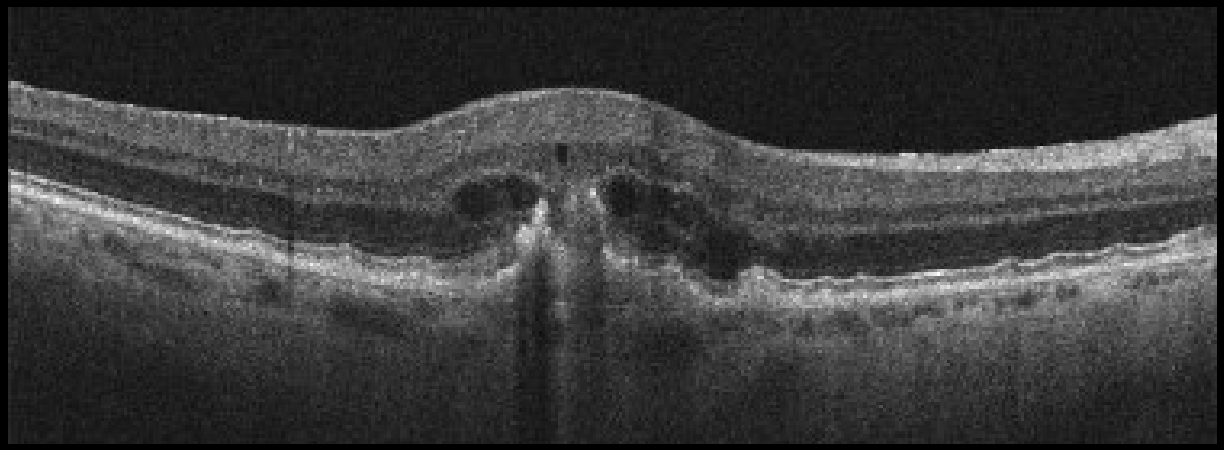
> 300 µm

Spaide RF. Disease expression in nonexudative AMD varies with choroidal thickness. Retina 2017

Reticular Pseudodrusen

Association with RAP lesions



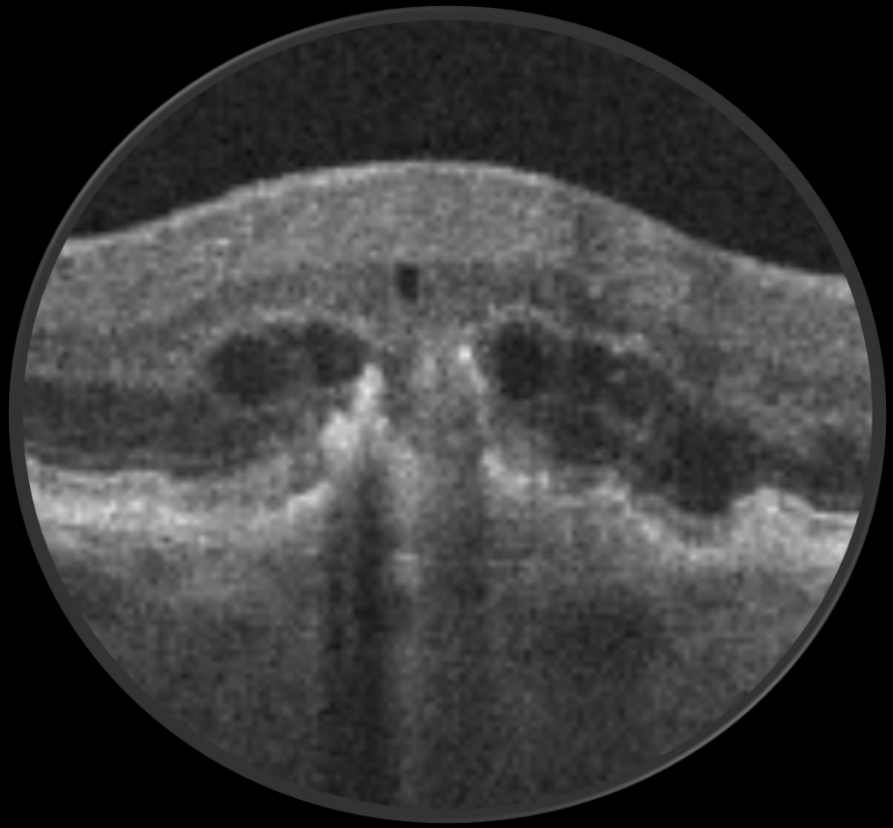


90% of eyes with Type 3 NV have reticular pseudodrusen

Hogg RE, Silva R, Staurenghi G, Murphy G, Santos AR, Rosina C, Chakravarthy U. Clinical characteristics of reticular pseudodrusen in the fellow eyes of patients with unilateral AMD. Ophthalmology 2014.

Reticular Pseudodrusen

Association with RAP lesions



« Kissing sign »

Querques G, Atmani K, Berboucha E, Martinelli D, Coscas G, Soubrane G, Souied EH. Angiographic analysis of retinal-choroidal anastomosis by confocal SLO technology and eye-tracked SD OCT. Retina 2010.

Reticular Pseudodrusen

Association with RAP lesions and choroidal thinning

CORRELATION BETWEEN NEOVASCULAR LESION TYPE AND CLINICAL CHARACTERISTICS OF NONNEOVASCULAR FELLOW EYES IN PATIENTS WITH UNILATERAL, NEOVASCULAR AGE-RELATED MACULAR DEGENERATION

RETINA, THE JOURNAL OF RETINAL AND VITREOUS DISEASES • 2014 •

MARCELA MARSIGLIA, MD, PHD,*†‡ SUCHARITA BODDU, BA, BS,*†§
CHRISTINE Y. CHEN, MD, PHD,*†¶** JESSE J. JUNG, MD,*†‡§ SARAH MREJEN, MD,*†
ROBERTO GALLEGO-PINAZO, MD, PHD,*††† K. B. FREUND, MD*†‡§

< 120 µm — Choroidal Thickness — > 120 µm

Type 3 NV (RAP)

Reticular Pseudodrusen
Choroidal thickness < 120 µm
Central RPE atrophy

Type 1 NV (occults)

Less pseudodrusen
Choroidal thickness > 120 µm

Reticular Pseudodrusen

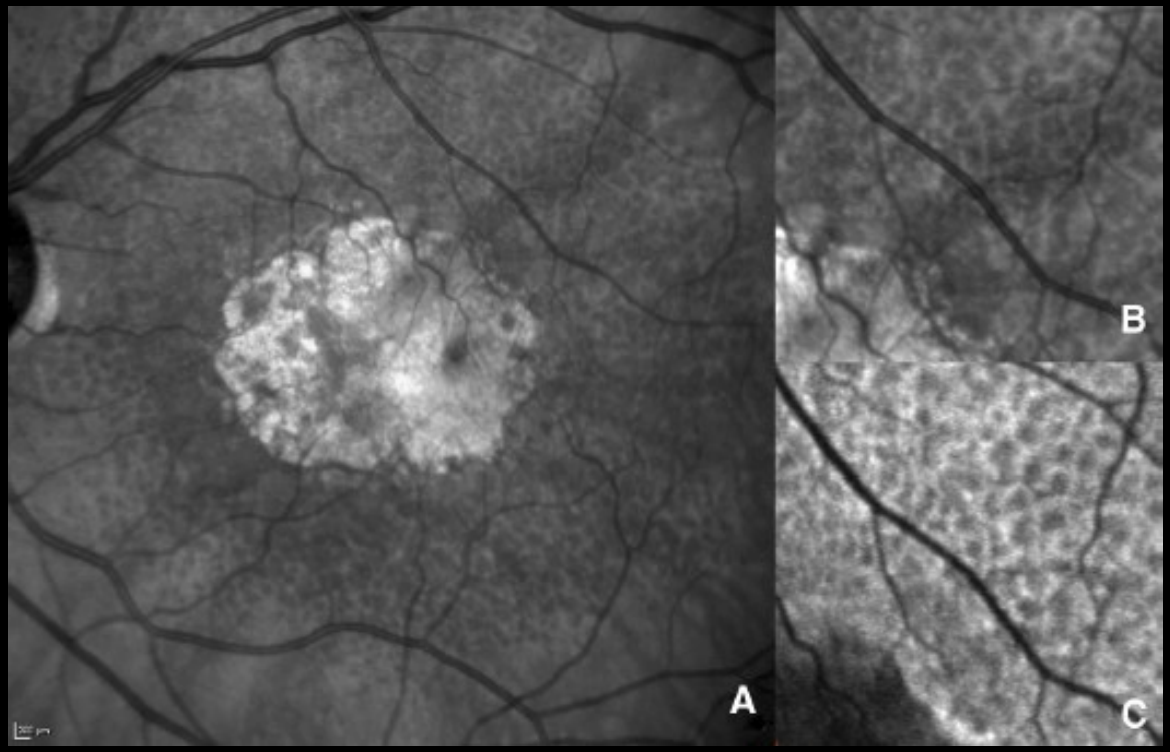
Hallmark of Geographic Atrophy

Clinical Trials

Reticular Drusen Associated with Geographic Atrophy in Age-Related Macular Degeneration

Steffen Schmitz-Valckenberg,[1] Florian Alten,[1] Julia S. Steinberg,[1] Glenn J. Jaffe,[2] Monika Fleckenstein,[1] Bickol N. Mukesh,[3] Thomas C. Hohman,[3] and Frank G. Holz[1] for the Geographic Atrophy Progression (GAP) Study Group[4]

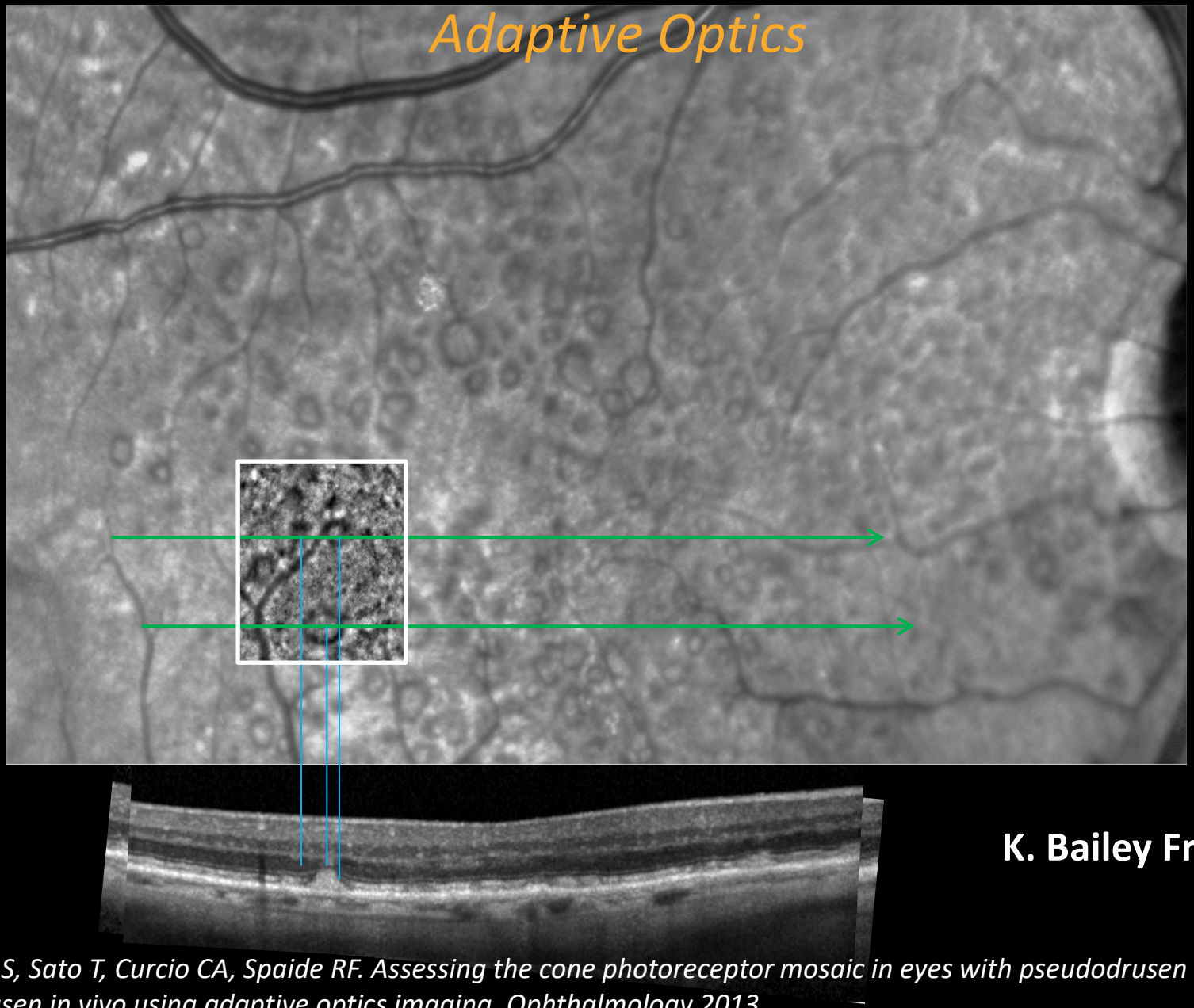
IOVS, 2011



62% of 458 patients with GA had pseudodrusen

Reticular Pseudodrusen

Adaptive Optics



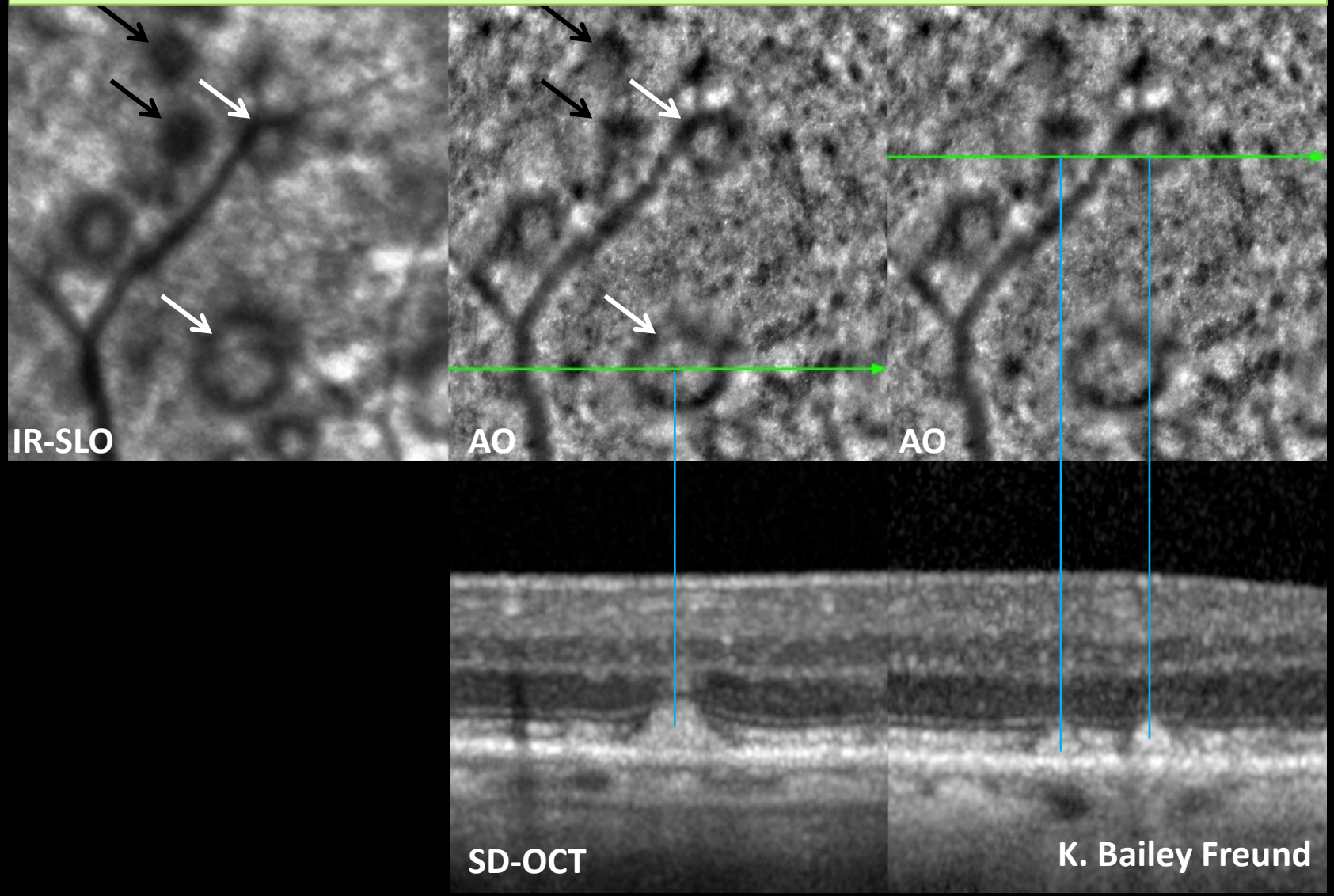
K. Bailey Freund

Mrejen S, Sato T, Curcio CA, Spaide RF. Assessing the cone photoreceptor mosaic in eyes with pseudodrusen and soft drusen in vivo using adaptive optics imaging. Ophthalmology 2013.

Reticular Pseudodrusen

Adaptive Optics

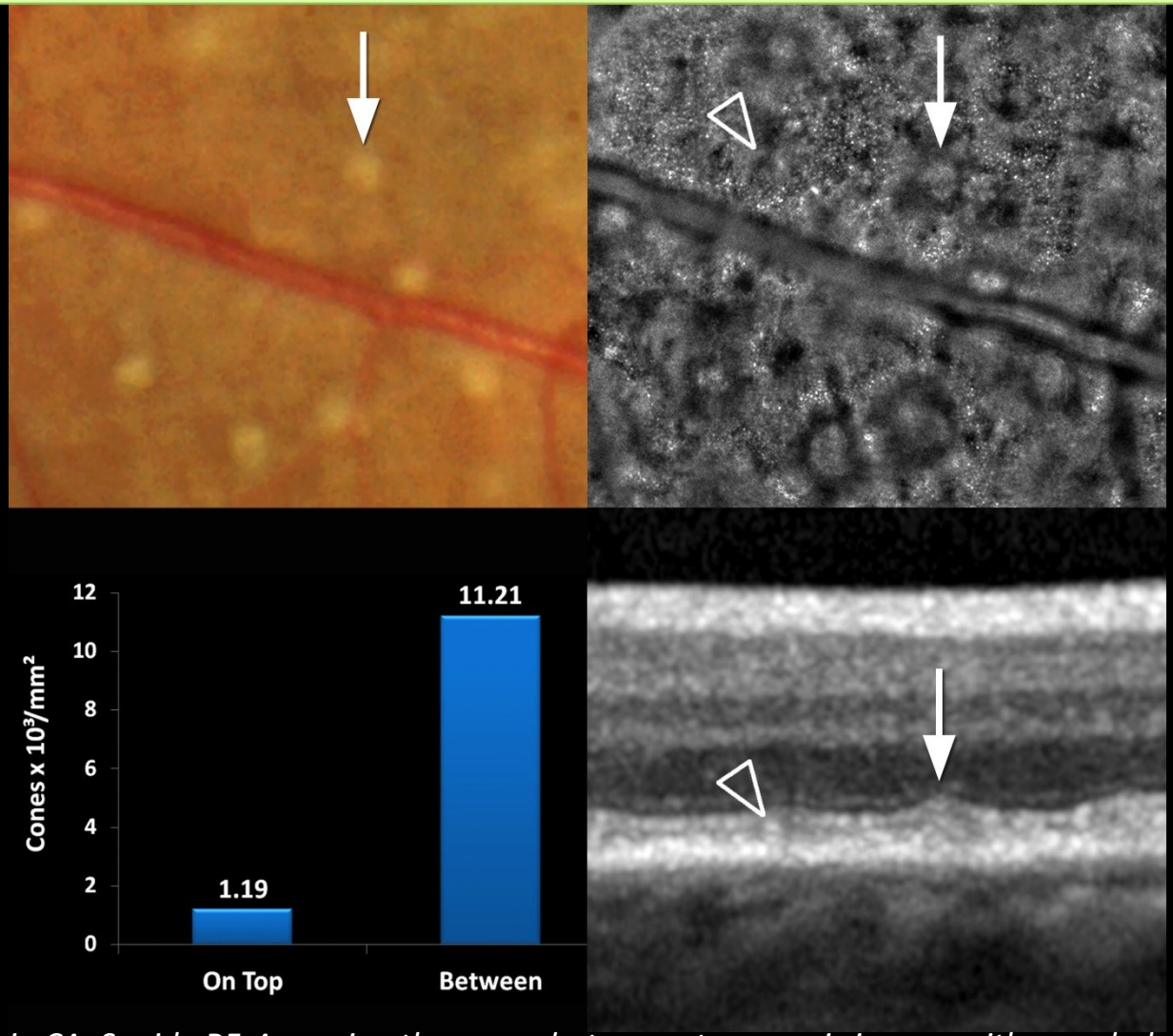
Co-localization of SDD with IR-SLO, SD-OCT and AO



Results

Cone Packing Density Analysis

Comparison of cone densities over and between SDD

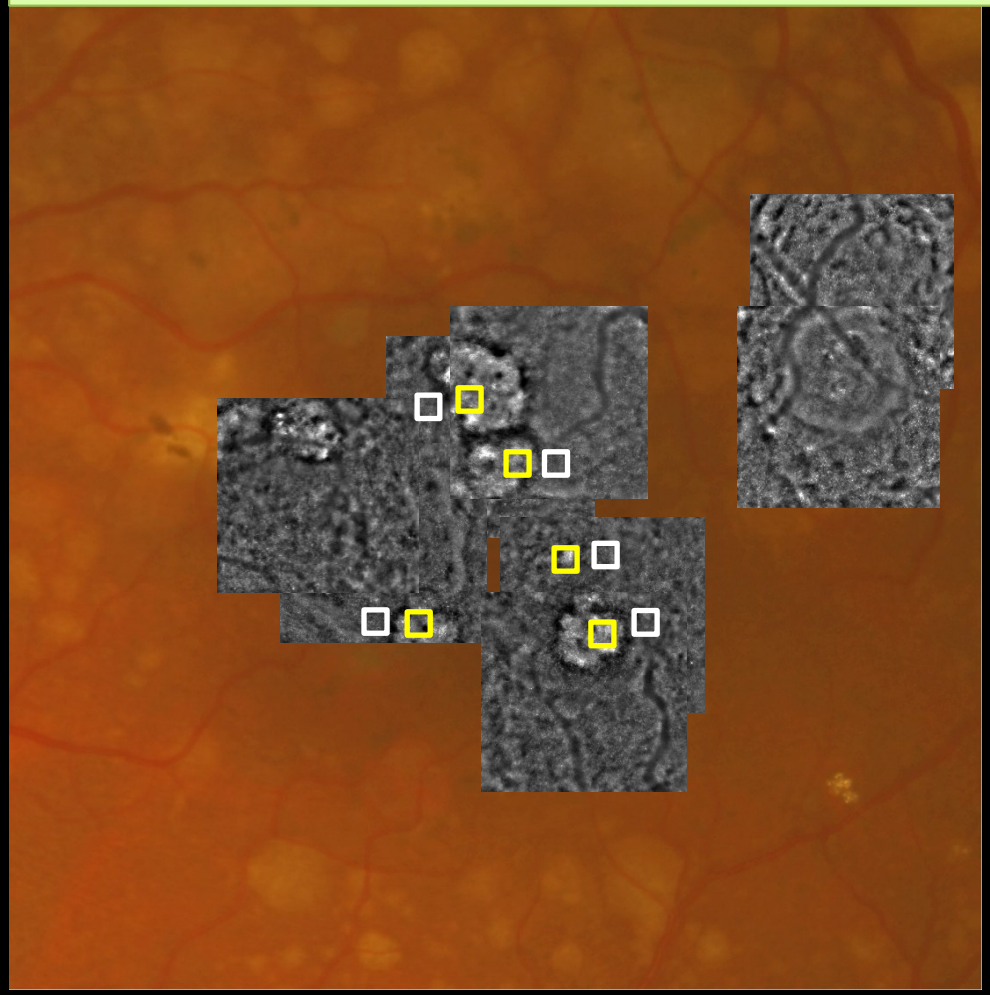


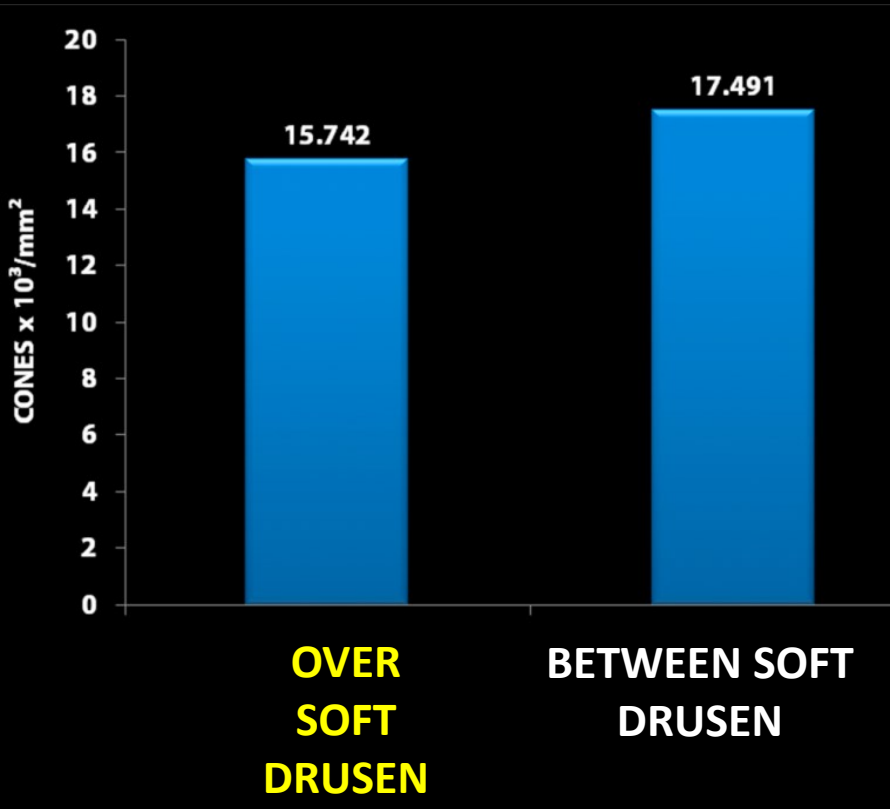
Mrejen S, Sato T, Curcio CA, Spaide RF. Assessing the cone photoreceptor mosaic in eyes with pseudodrusen and soft drusen in vivo using adaptive optics imaging. Ophthalmology 2013.

Results

Cone Packing Density Analysis

Comparison of cone densities over and between soft drusen





Mrejen S, Sato T, Curcio CA, Spaide RF. Assessing the cone photoreceptor mosaic in eyes with pseudodrusen and soft drusen in vivo using adaptive optics imaging. Ophthalmology 2013.

Reticular Pseudodrusen

Perturbations to Photoreceptors on Adaptive Optics

Comparison of cone densities over and between SDD vs soft drusen

	SDD	Conventional Drusen	*P* Multivariate GEE
Mean density over drusen (±SD)	863 (±388)	9,838 (±3,723)	
Mean density between drusen (±SD)	8,964 (±2,793)	12,592 (±3,323)	
Ratio of density over and between drusen	**9.6%**	**78.1%**	**<<0.001**

Observed densities between drusen are within the range of densities determined histologically from grossly normal older donor retinas from similar eccentricities.

Aging of the Human Photoreceptor Mosaic: Evidence for Selective Vulnerability of Rods in Central Retina

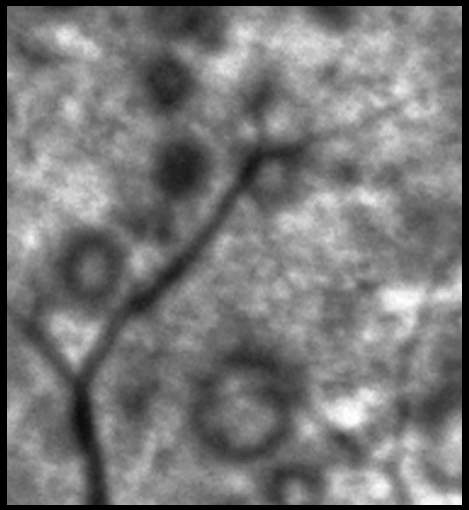
Christine A. Curcio,† C. Leigh Millican,* Kimberly A. Allen,‡ and Robert E. Kalina‡*

Reticular Pseudodrusen

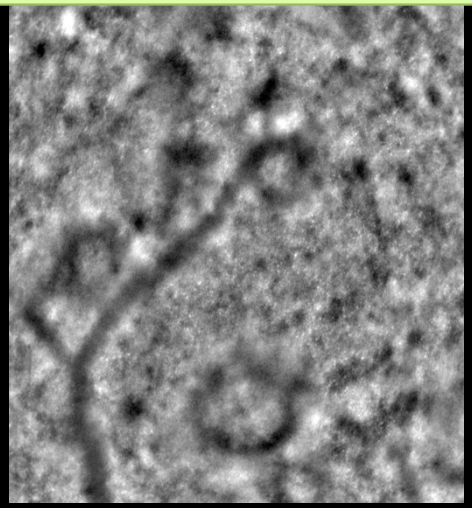
Perturbations to Photoreceptors on Adaptive Optics

Comparison of SDD reflectivity on IR-SLO and AO

Dark annulus constant width



IR-SLO



AO

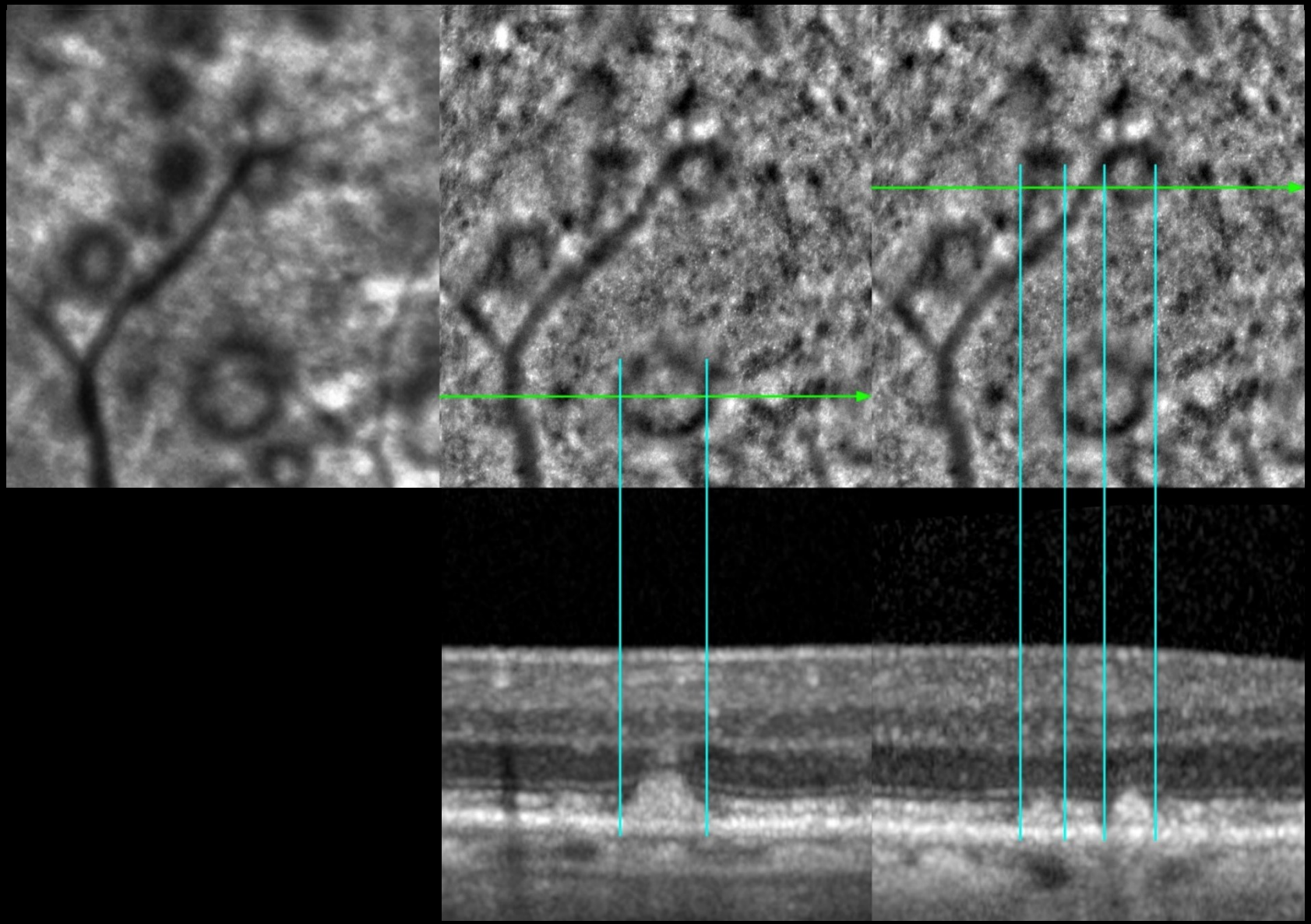
Schematic

Different imaging characteristics may correspond to different stages of progression of SDD

Analysis of Progression of Reticular Pseudodrusen by Spectral Domain–Optical Coherence Tomography

Giuseppe Querques,[1] Florence Canoui-Poitrine,[2,3] Florence Coscas,[1] Nathalie Massamba,[1] Lea Querques,[1,4] Gerard Mimoun,[3] Francesco Bandello,[4] and Eric H. Souied[1]

SDD - Dark Annulus - Multimodal Imaging



K. Bailey Freund

Reticular Pseudodrusen

Perturbations to Photoreceptors on Adaptive Optics

Causes of the lack of visualization of cones over SDD on AO

change in their orientation
absence of inner segments
absence of outer segments
loss of cones in totality

} **Decreased cone function**

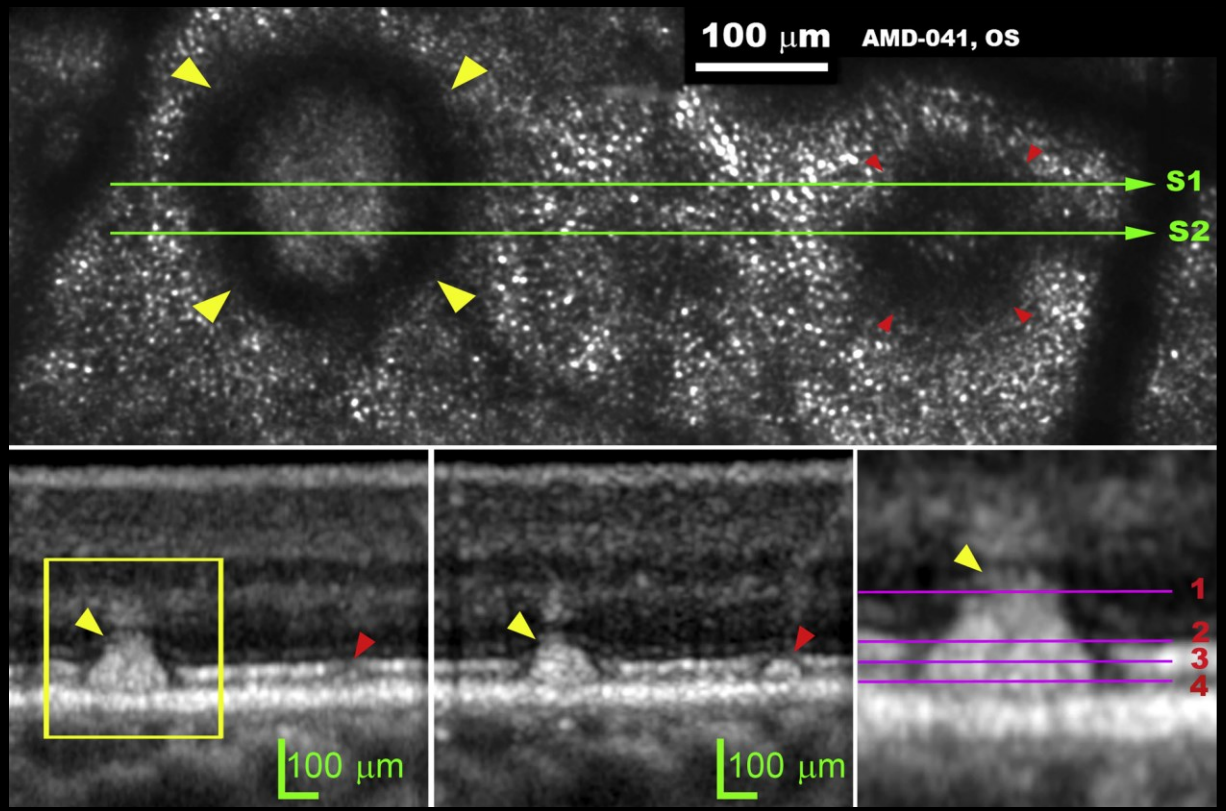
No difference in the heights of SDD vs soft drusen → true structural difference in photoreceptor configuration

SDD → ↓ cone density → ↓ photopic visual function
Rods not visualized in his study but may be affected before cones in both aging and AMD

Mrejen S, Sato T, Curcio CA, Spaide RF. Assessing the cone photoreceptor mosaic in eyes with pseudodrusen and soft drusen in vivo using adaptive optics imaging. Ophthalmology 2013.

Photoreceptor Perturbation Around Subretinal Drusenoid Deposits as Revealed by Adaptive Optics Scanning Laser Ophthalmoscopy

YUHUA ZHANG, XIAOLIN WANG, ERNESTO BLANCO RIVERO, MARK E. CLARK, CLARK DOUGLAS WITHERSPOON, RICHARD F. SPAIDE, CHRISTOPHER A. GIRKIN, CYNTHIA OWSLEY, AND CHRISTINE A. CURCIO



Depth discrimination

SDD visualized in the plane of photoreceptors

SDD are associated with perturbations to photoreceptors

Reticular Pseudodrusen

Decreased retinal sensitivity

IMPACT OF RETICULAR PSEUDODRUSEN ON MACULAR FUNCTION

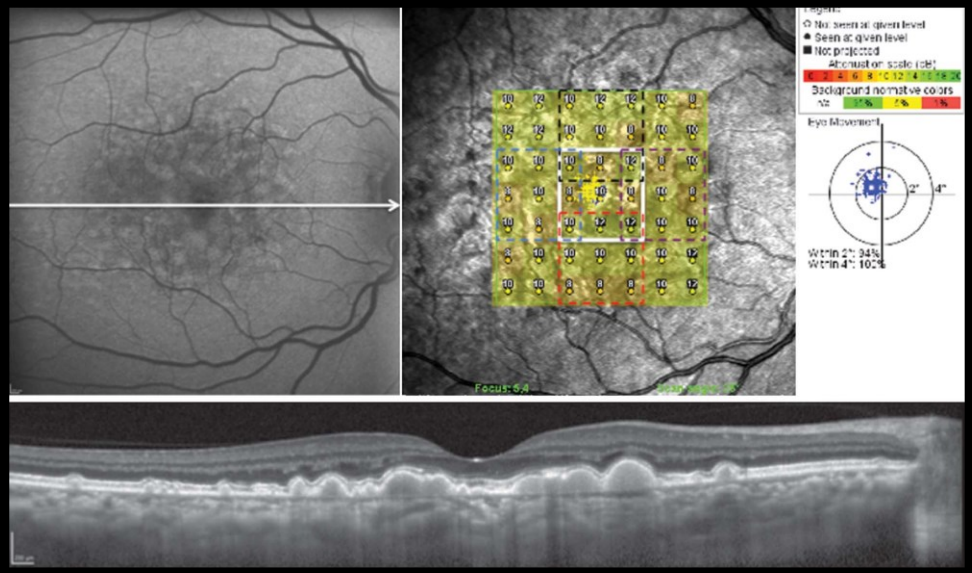
GIUSEPPE QUERQUES, MD, PHD,*† NATHALIE MASSAMBA, MD,* MAYER SROUR, MD,* ELISE BOULANGER, MD,* ANOUK GEORGES, MD,* ERIC H. SOUIED, MD, PHD*

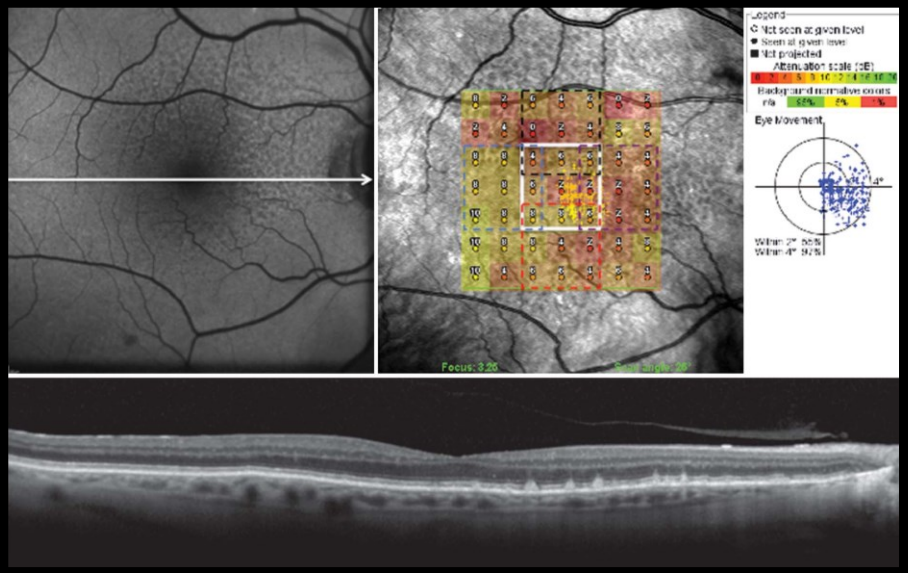
2013

Reduction of Retinal Sensitivity in Eyes With Reticular Pseudodrusen

SOTARO OOTO, ABDALLAH A. ELLABBAN, NAOKO UEDA-ARAKAWA, AKIO OISHI, HIROSHI TAMURA, KENJI YAMASHIRO, AKITAKA TSUJIKAWA, AND NAGAHISA YOSHIMURA

2013





Pseudodrusen are associated with major decrease in retinal sensitivity compared to soft drusen
Major impact on macular function without RPE loss, due to outer retinal atrophy

Reticular Pseudodrusen

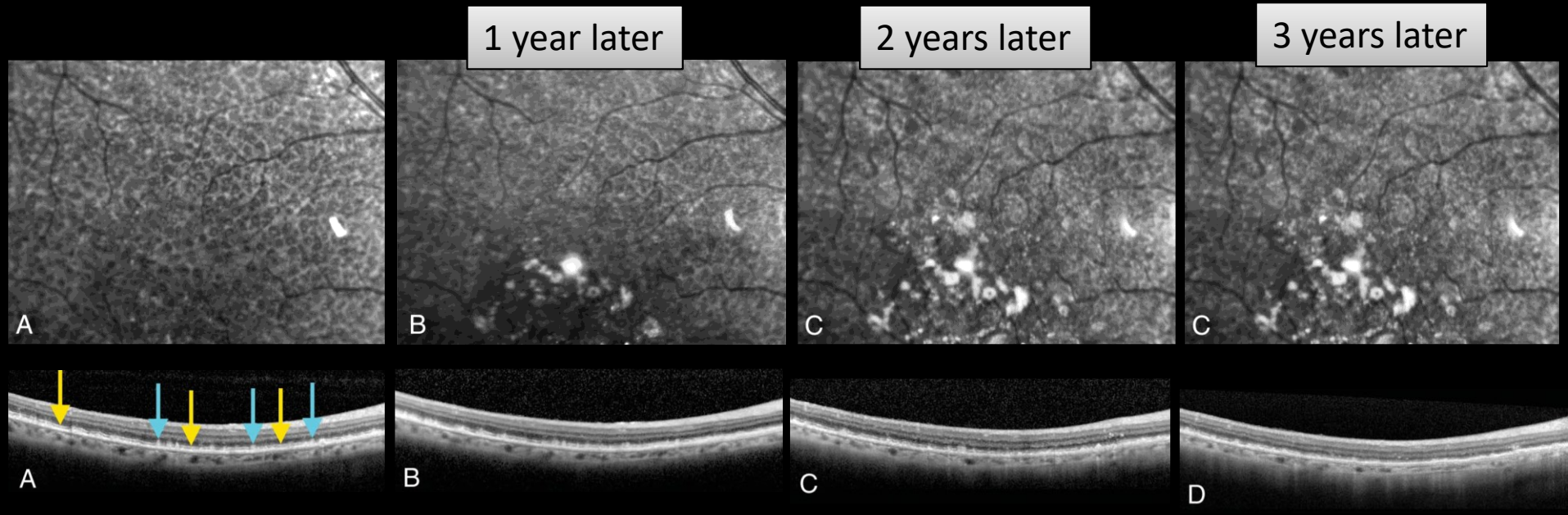
Regression and Outer Retinal Atrophy

21 eyes with pseudodrusen, mean follow-up 2,9 years

Regression of pseudodrusen in 43% of cases associated to:

- Decrease in the photorecptor length and choroidal thickness on OCT
- Loss of the ellipsoid band

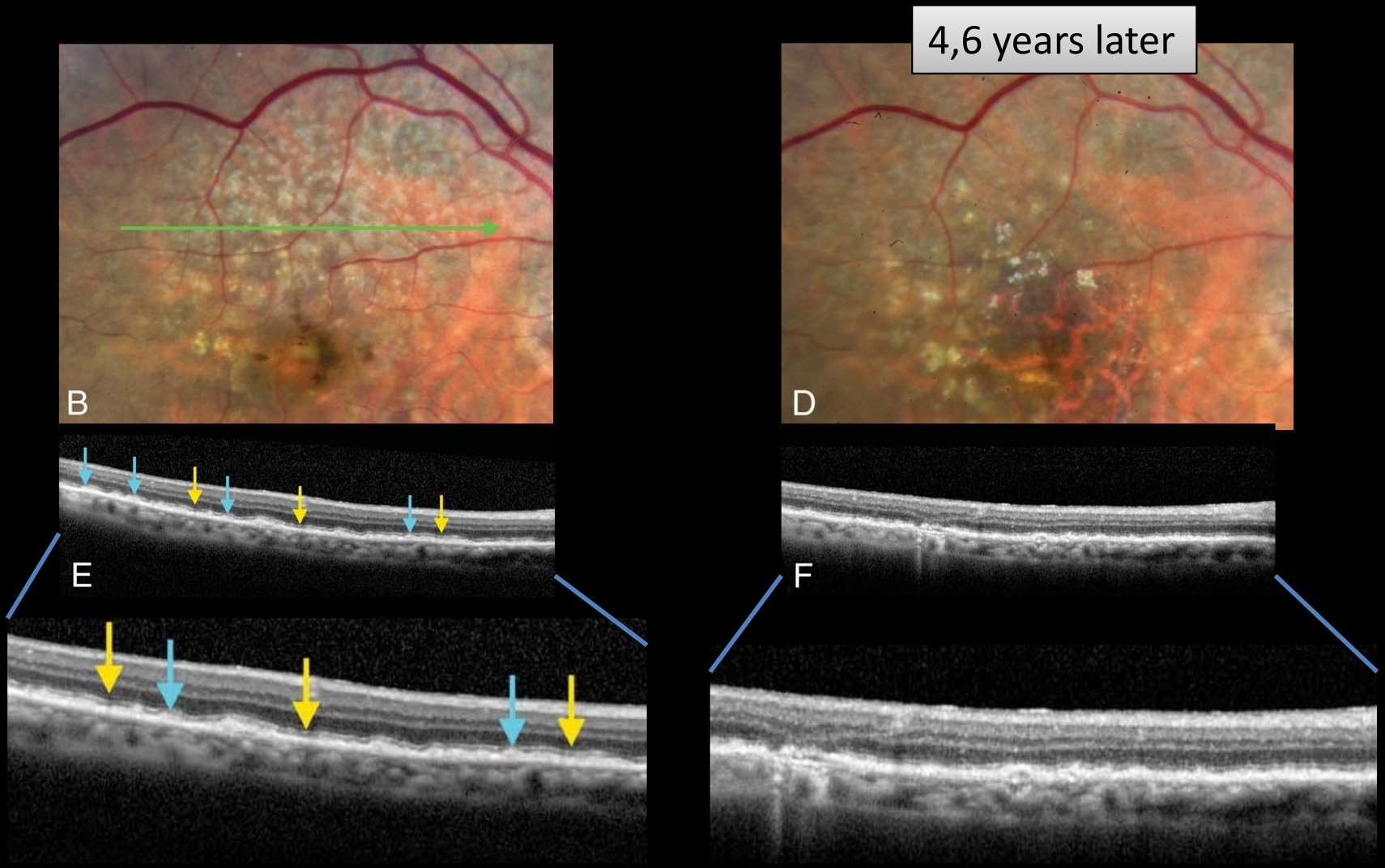
Eyes without regression of pseudodrusen → no change in the overlying retina or underlying choroid



Spaide RF. Outer retinal atrophy after regression of subretinal drusenoid deposits as a newly recognized form of late AMD. Retina. 2013 Oct;33(9):1800-8.

Reticular Pseudodrusen

Regression and Outer Retinal Atrophy

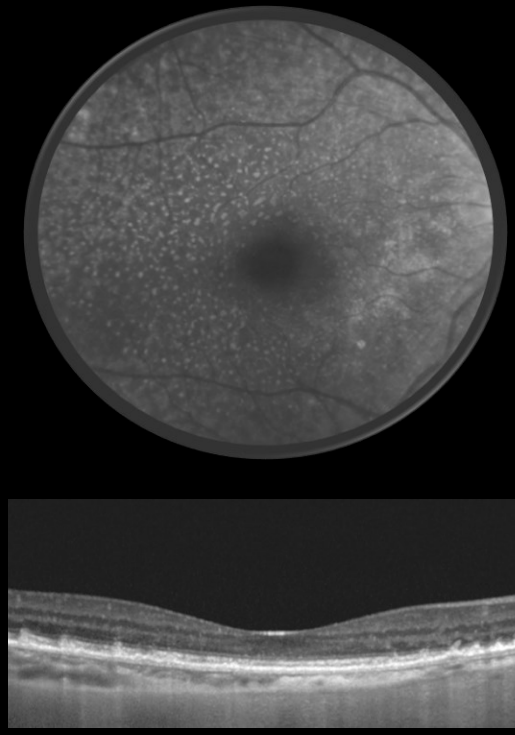


Spaide RF. Outer retinal atrophy after regression of subretinal drusenoid deposits as a newly recognized form of late AMD. Retina. 2013 Oct;33(9):1800-8.

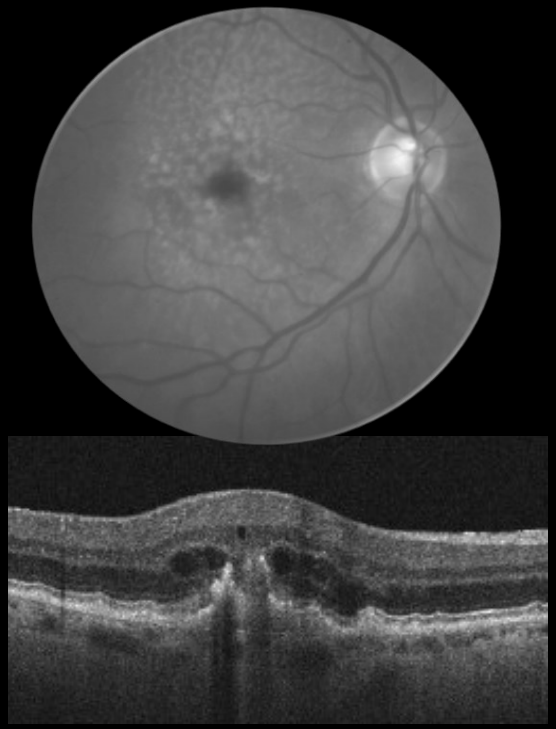
Reticular Pseudodrusen

Associated Features

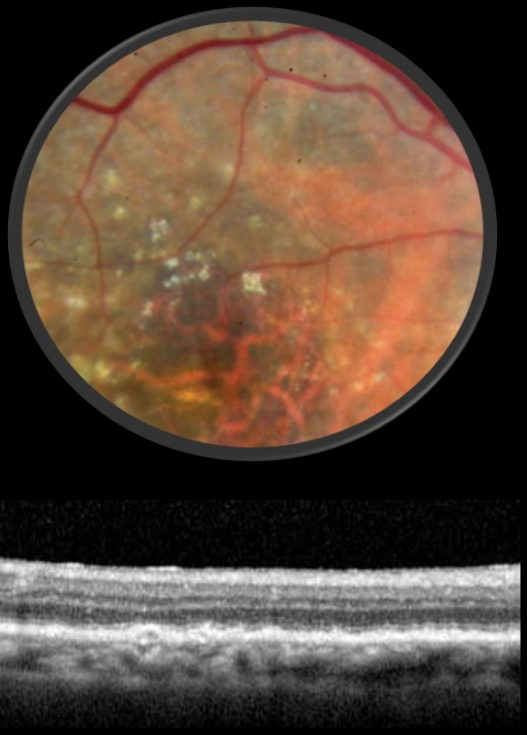
Choroidal thinning



Type 3 NV
RAP lesion



Regression and
Outer retinal atrophy



Reticular pseudodrusen are subretinal drusenoid deposits

- Hallmark of geographic atrophy
- Intraretinal neovascularization – Type 3
- Outer retinal atrophy
- More threatening for vision and quality of life than conventional drusen

Reticular Pseudodrusen

Relationship between outer retinal atrophy and GA?

- Areas of PR degeneration extend beyond areas of RPE loss
  - Fleckenstein et al, IOVS 2008 (SD OCT)
  - Bird et al, JAMA Ophthalmology 2014 (Histopathology)
  - Takayashi et al, AJO 2016 (SD OCT)

- Histopathology and imaging studies
  - 2 patterns of GA
    - With photoreceptor loss in the perilesional area
    - With intact photoreceptors in the perilesional area

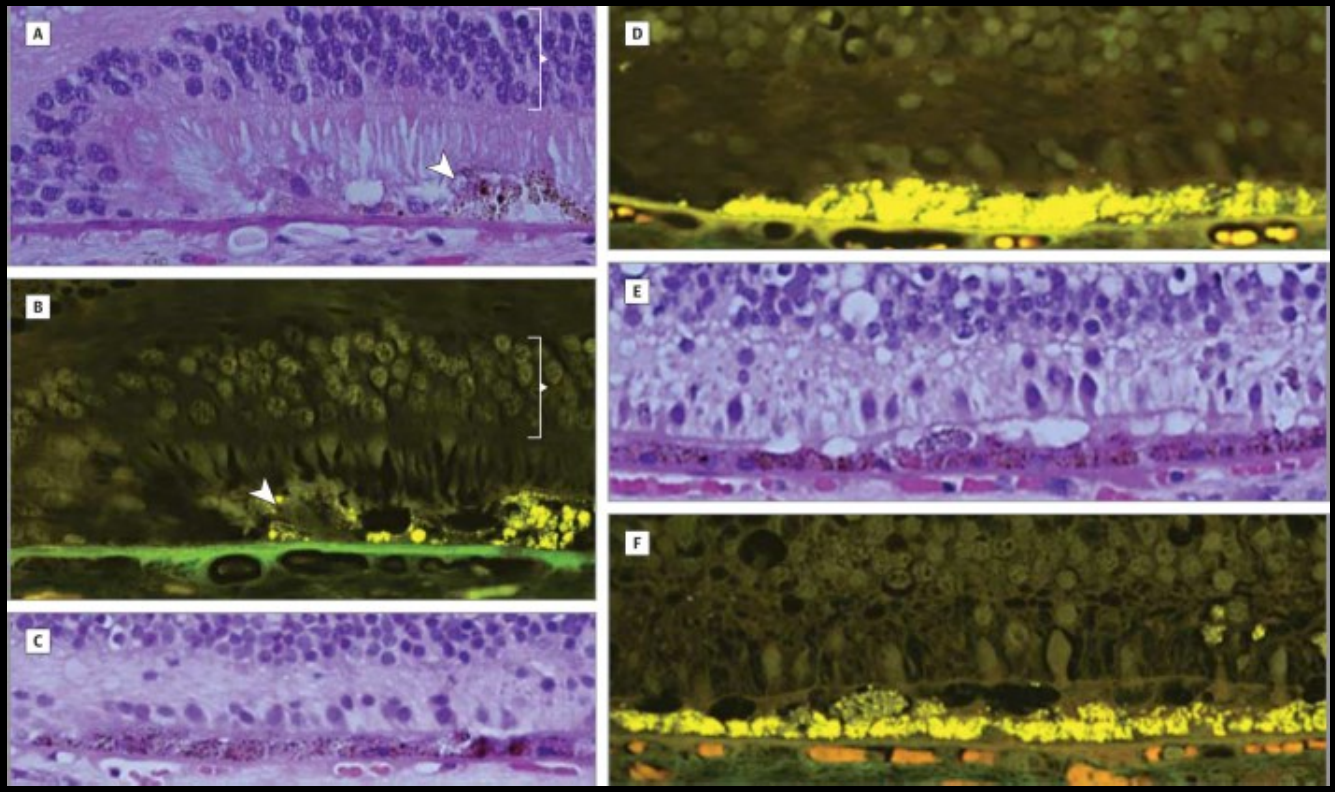
Fleckenstein M, Charbel Issa P, Helb HM, Schmitz-Valckenberg S, Finger RP, Scholl HP, Loeffler KU, Holz FG. High-resolution SD OCT imaging in GA associated with AMD. IOVS 2008.

Takahashi A, Ooto S, Yamashiro K, Oishi A, Tamura H, Nakanishi H, Ueda-Arakawa N, Tsujikawa A, Yoshimura N. Photoreceptor damage and reduction of retinal sensitivity surrounding GA in AMD. AJO 2016.

Bird AC, Phillips RL, Hageman GS. Geographic atrophy: a histopathological assessment. BJO 2014.

Reticular Pseudodrusen

Relationship between outer retinal atrophy and GA?



2 patterns of RPE loss?

One primarily starting at the level of the RPE may be associated with soft drusen

One preceded by photoreceptor loss may be associated with pseudodrusen

Bird AC, Phillips RL, Hageman GS. Geographic atrophy: a histopathological assessment. BJO 2014.

Multimodal Imaging of Drusen
Key Points

- Multimodal imaging is necessary to classify drusen
  - Important for providing visual prognosis
- Soft drusen
  - Drusen volume, hyperreflective foci and acquired vitelliform lesions are biomarkers of RPE atrophy
  - Hyperreflective foci on SD OCT correspond to migrated RPE cells
- Cuticular drusen
  - Part of the AMD spectrum
  - Younger patients, better prognosis
- Reticular pseudodrusen are subretinal and associated with processes starting intrinsic to the retina
  - Intraretinal neovascularization – Type 3
  - Outer retinal atrophy
- Hypothesis: 2 patterns of atrophy in AMD
  - Primary RPE loss associated associated with soft conventional drusen
  - Primary photoreceptor loss associated with reticular pseudodrusen
- Research into therapeutics targeting photoreceptor loss could be considered for certain subtypes of AMD

Paris Adaptive optics Retinal Imaging and Surgery (PARIS) group

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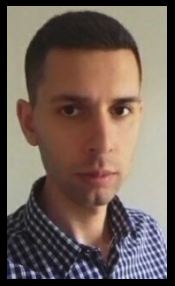

Thank you for your attention