

Beyond BCVA: In Search of Better Biomarkers for Geographic Atrophy  
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- I. Geographic Atrophy
  - a. Clinical presentation
    - i. Characterized by the presence of retinal atrophy that arises as a result of progressive and irreversible loss of the photoreceptors, retinal pigment epithelium (RPE) and choriocapillaris
  - b. Pathophysiology
    - i. Complement factor pathway
      1. C3, C5, Membrane Attack Complex
  - c. Status of the fellow eye in risk assessment
  - d. Risk factors for progression
    - i. GA size- GA lesions that are large at baseline, have a higher rate of progression
    - ii. Number of GA lesions- multifocal lesions have increased rates of GA growth
    - iii. Shape- Irregularly shaped lesions grow more rapidly than circular lesions
    - iv. Location of the atrophy (foveal versus extrafoveal)- GA can present with or without foveal involvement. Foveal involvement is believed to be a strong predictor of growth rate and progression. Extrafoveal lesions progress more rapidly than foveal lesions
    - v. OCT and FAF findings
    - vi. Outer Retinal Tubulation (ORT)- ORT is a distinct finding identified on OCT. ORT correlate with an area of damaged photoreceptors that take on a circular or tubular pattern. They have a characteristic outer ring of hyper-reflectivity with a central core of hypo-reflectivity on OCT. Presence of ORT is correlated with a more rapid rate of GA progression. Patients that have ORT and neovascular AMD are at higher risk of developing atrophy as well.
    - vii. Type of drusen- Reticular pseudodrusen or subretinal drusenoid deposits reside in the subretinal space (versus regular drusen that exist between the RPE and Bruch's membrane). These drusen have a "saw-tooth" appearance and resemble small triangular projections on OCT. Reticular pseudodrusen are highly linked to GA progression.
    - viii. Hyper-reflective foci- Hyper-reflective dots or round lesions within retinal layers on OCT. These foci are biomarkers for disease progression and prognosis including macular atrophy.
  - e. Multi-modal imaging
    - i. Color fundus photography
    - ii. OCT (CAM Classification Criteria)
      1. Complete RPE and outer retinal atrophy (cRORA)
        - Loss of outer retinal layers
        - RPE loss

- Choroidal hypertransmission of at least 250 um: Choroidal hypertransmission (increased signal penetration into the choroid) occurs as a result of the atrophy or attenuation of the overlying sensory retina and RPE.
  - 2. Incomplete RPE and outer retinal atrophy (iRORA)
    - Earlier stage of atrophy
    - Patchy loss of the RPE (less than 250 um)
    - Choroidal hypertransmission (less than 250 um)
  - 3. Complete outer retinal atrophy (cORA)
    - Continuous non-visibility of the ellipsoid zone and interdigitation zone
    - Severe thinning of the outer retina
    - Intact RPE band
    - Choroidal hypertransmission is intermittent
  - 4. Incomplete outer retinal atrophy (iORA)
    - Continuous external limiting membrane (ELM)
    - Detectable ellipsoid zone disruption
    - Thinning of outer retina
    - Intact RPE band
    - No hypertransmission defects
- iii. Fundus Autofluorescence (FAF)
  1. Patterns (seen in the junctional zone of GA)
    - a. None
    - b. Focal- Evidence of one or more small spots of elevated FAF at the edge of the lesion
    - c. Patchy-Lesions show some FAF spots outside the GA lesion area, with spread toward the posterior pole
    - d. \*Banded - increased autofluorescence is characterized by a continuous stippled band of increased FAF surrounding the entire atrophic area
    - e. Diffuse: (Reticular, branching, fine-granular with peripheral punctate spots, or \*diffuse trickling); Diffuse trickling- lesions demonstrate gray (rather than black) hypoautofluorescence and lobular atrophic patches with high intensity at the margins
  - iv. Near Infrared Reflectance Imaging
- II. Treatment?
  - a. Syfovre: pegcetacoplan injection
    - i. First FDA approved intravitreal injection to halt progression of GA
    - ii. Targeted C3 therapy
    - iii. Up to 36% reduction rate when used monthly
  - b. avacincaptad pegol (ACP): on the pipeline
    - i. Complement 5 inhibitor
      1. observed efficacy rates of up to 35%