

## Normotensive Glaucoma Follow-Up with Incidental Finding of Choroidal Neovascular Membrane: a Teaching Case Report | 1

### Abstract

*Behind cataracts, glaucoma is the second leading cause of blindness worldwide. Patients with glaucoma are followed at regular intervals for testing to confirm stability of the disease; however, providers may need to divert from planned glaucoma testing when clinical findings suggest progression of comorbid ophthalmic conditions. This case report describes a patient presenting for a routine glaucoma follow-up appointment who was subsequently diagnosed with an acute choroidal neovascular membrane due to conversion from non-neovascular to neovascular age-related macular degeneration. The case highlights the management of normotensive glaucoma and both non-neovascular and neovascular macular degeneration.*

**Key Words:** *glaucoma, macular degeneration, optical coherence tomography, fluorescein angiography, visual field*

### Background

Normotensive glaucoma is a progressive optic neuropathy that follows clinical patterns of primary open-angle glaucoma in the absence of elevated intraocular pressure (IOP).<sup>1</sup> Patients with normotensive glaucoma are typically followed at regular intervals several times per year for clinical examination of the optic nerve and for monitoring of IOP, automated visual fields and optical coherence tomography (OCT). The diagnosis and management of glaucoma are often complicated by ocular comorbidities, such as age-related macular degeneration (ARMD). While the exact pathogenesis is unclear, ARMD is characterized by abnormal deposition of acellular, polymorphous debris called drusen between the retinal pigment epithelium and Bruch’s membrane, a condition that represents the leading cause of irreversible blindness in people 65 years of age and older in the developed world.<sup>2</sup> This case report describes a 70-year-old Caucasian female who presented for a visual field test and follow-up for normotensive open-angle glaucoma. Due to a new complaint of a central blurred spot in the right eye as well as a new central depression on visual field testing, the patient, who was also being followed for non-neovascular ARMD, was dilated and incidentally found to have a subretinal macular hemorrhage from an acute choroidal neovascular membrane (CNVM) related to neovascular macular degeneration. The case highlights the importance of a careful case history and the need for clinicians to divert from planned testing based on new information offered by the patient. This case is appropriate for optometry students in years two through four as well as optometry residents. It can be utilized in a seminar, laboratory, classroom or clinical setting.

### Case Description

A 70-year-old Caucasian female presented to the eye clinic for a normotensive glaucoma follow-up appointment, including her annual threshold visual field. Her glaucoma was diagnosed in the right eye in 2012 based on moderate optic nerve cupping, inferior-temporal thinning of the retinal nerve fiber layer (RNFL) on OCT, an early superior nasal arcuate visual field defect, and strong family history (mother). Visual field and OCT findings of the left eye were unremarkable at the time of diagnosis; however, when treatment was discussed, the patient elected to initiate treatment of her left eye prophylactically. The patient’s glaucoma was well-controlled on latanoprost ophthalmic solution 0.005% instilled in both eyes before bedtime. Her pertinent glaucoma findings are summarized in **Table 1**. In addition to glaucoma, her ocular history was significant for intermediate non-neovascular ARMD, a hemorrhagic posterior vitreous detachment in the right eye diagnosed four months prior, non-visually-significant bilateral nuclear sclerotic cataracts, and mild dry eyes. Her medical history was significant for hypertension, asthma, hyperlipidemia, and previous cervical cancer. Her medications included metoprolol tartrate 50 mg BID, ipratropium bromide 20 mcg/albuterol sulfate 100 mcg inhaler QID, and gemfibrozil 600 mg BID. Additionally, she used AREDS2 formula multivitamins BID and was a current daily smoker. Significant allergies included piperacillin and clonidine.

**TABLE 1**  
Summary of Pertinent Glaucoma Findings

	Most Recent Date	Results
Idmann (Ryl)	11/18/11	OD: 18 mmHg OS: 17 mmHg
ann (Ryl)	2011-2016	OD: 10-18 mmHg OS: 10-17 mmHg
	11/18/11	OD: 561 microns OS: 559 microns
	06/26/16	OD: 0.784x0.70x OS: 0.80x0.70x
	01/19/12	OU: flat superior body 360, 1+ trail pigment
	06/26/16	See Figure 1 on
	06/26/16	See Figure 3
Glaucoma		Mother and Male

**Table 1.**  
[Click to enlarge](#)

The patient’s chief complaint was a blurred spot in her right eye for the past week. The spot was most noticeable towards the end of the day and seemed to improve with blink and the use of artificial tears. She reported no complaints with the left eye and observed no other changes to her overall vision. There was no metamorphopsia observed from either eye when using her home Amsler grid.

## Normotensive Glaucoma Follow-Up with Incidental Finding of Choroidal Neovascular Membrane: a Teaching Case Report | 2

Incoming corrected distance visual acuity was OD: 20/30-2 and OS: 20/30+. Previous incoming corrected visual acuities were OD: 20/20- and OS: 20/25-. Pupils were equal, round and reactive to light without afferent pupillary defect. Extraocular motilities were full and concomitant OU. Cover test revealed orthophoria at distance and 6 prism diopters exophoria at near. A manifest refraction of +0.50-1.25×105 corrected the right eye to 20/25 and a manifest refraction of +0.50-1.25×105 corrected the left eye to 20/25. Anterior segment exam was significant for mild punctate epithelial erosions within the inferior one-third of each cornea, with a tear break-up time of 2-3 seconds OU. The 24-2 threshold visual field testing was reliable in both eyes and showed a large central relative defect in the right eye and two non-clustered paracentral relative defects inferiorly in the left eye. **(Figures 1-2)** OCT of the right optic nerve revealed inferior-temporal sector RNFL thinning with borderline quadrant RNFL thinning inferiorly while the left eye demonstrated no significant thinning of the RNFL. **(Figure 3)** Due to the patient's chief complaint, slight reduction in best-corrected visual acuity and visual field findings, a dilated fundus exam was performed. This examination revealed bilateral grade 2 nuclear sclerotic cataracts, clear vitreous OU, optic nerves with cup to disc ratios of 0.70H/0.75V OD and 0.60H/0.70V OS, normal vasculature OU, and a flat and intact peripheral retina bilaterally. Examination of the right macula revealed course mottling with several small and intermediate drusen as well as a subretinal hemorrhage superior to the macula. **(Figure 4)** The left macula showed a mottled appearance with several small and intermediate drusen. **(Figure 5)** OCT of the macula was performed and showed confluent central drusen with a pigment epithelial detachment with overlying subretinal fluid OD, and confluent central drusen without subretinal fluid OS. **(Figures 6-8)**

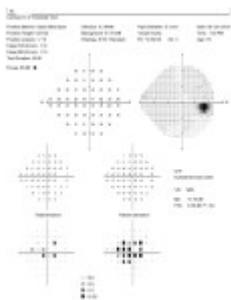


Figure 1. 24-2 Humphrey SITA Standard visual field test OD on 06/28/16 showing good test reliability with a large central relative defect. [Click to enlarge](#)

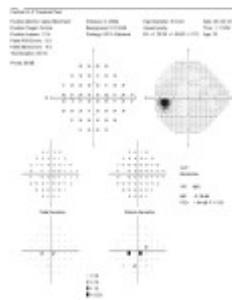


Figure 2. 24-2 Humphrey SITA Standard visual field test OS on 06/28/16 showing good test reliability with two non-clustered paracentral relative defects inferiorly. [Click to enlarge](#)

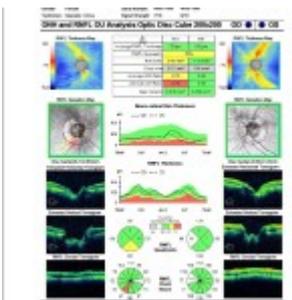


Figure 3. Optic disc OCT OU on 06/28/16 showing borderline RNFL layer thinning inferiorly OD and no significant thinning of the RNFL OS. [Click to enlarge](#)

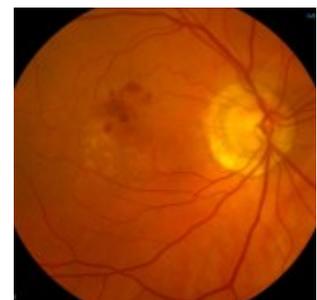


Figure 4. Fundus photograph OD on 06/28/16 showing a mottled appearance of the right macula with several small and intermediate drusen as well as a subretinal hemorrhage slightly superior to the macula. [Click to enlarge](#)



Figure 5. Fundus photograph OS on 06/28/16 showing a mottled appearance of the left macula with several small and intermediate drusen. [Click to enlarge](#)

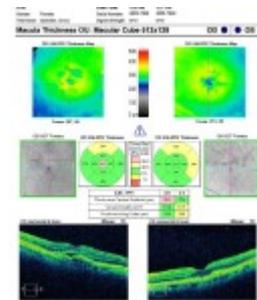


Figure 6. Macular Cube OCT OU on 06/28/16 showing increased central macular thickness of 321 μm OD and normal central macular thickness of 274 μm OS. [Click to enlarge](#)

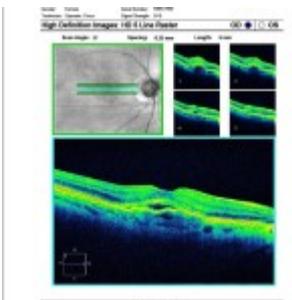


Figure 7. Five Line Raster Macular OCT OD on 06/28/16 showing confluent central drusen and pigment epithelial detachment with overlying subretinal fluid causing macular elevation. [Click to enlarge](#)

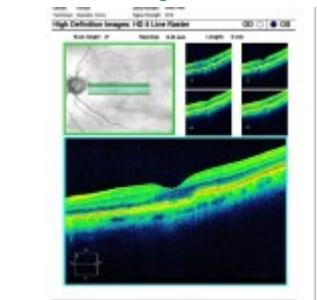


Figure 8. Five Line Raster Macular OCT OS on 06/28/16 showing confluent central drusen with normal macular contour and thickness. [Click to enlarge](#)

**Normotensive Glaucoma Follow-Up with Incidental Finding of Choroidal Neovascular Membrane: a Teaching Case Report | 3**

A same-day consult with a retina specialist was requested, and fluorescein angiography (FA) was performed. **(Figures 9-10)** FA revealed a region of blockage superior to the fovea corresponding to the area of subretinal hemorrhage; however, within this region, specifically the portion superior-nasal to the fovea and corresponding to a pigment epithelial detachment, there was an area of early stippled hyperfluorescence that on the later frame had ill-defined leakage, i.e., occult leakage. Additionally, there was staining of numerous drusen present inferior to the fovea. Based on the FA study, the patient was diagnosed with an occult CNVM in her right eye related to exudative macular degeneration and subsequently treated with a 0.5-cc intravitreal injection of 1.25 mg intravitreal bevacizumab in the right eye. The patient was advised to continue AREDS formula vitamins and to monitor for vision changes at home with an Amsler Grid. Follow-up was scheduled with the retina specialist for four weeks later.

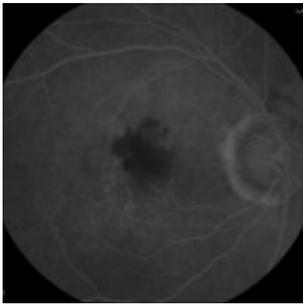


Figure 9. Fluorescein angiography OD at 1:39 showing early-phase blockage superior to the fovea corresponding to the area of subretinal hemorrhage. Superior-nasal to the fovea there is an area of early stippled hyperfluorescence corresponding to the area of pigment epithelial detachment. Additionally, there is staining of numerous drusen present inferior to the fovea.

[Click to enlarge](#)

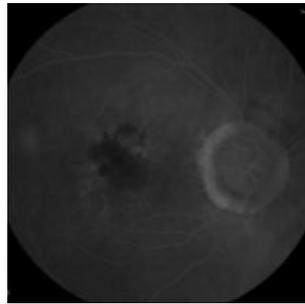


Figure 10. Fluorescein angiography OD at 7:25 showing a late-phase ill-defined area of leakage superior-nasal to the fovea.

[Click to enlarge](#)

**Education Guidelines**

*Key concepts*

1. Diagnosis and management of normotensive glaucoma
2. Diagnosis and management of non-neovascular macular degeneration
3. Diagnosis and management of neovascular macular degeneration
4. Interpretation of OCT for glaucoma and macular degeneration
5. Interpretation of fluorescein angiography

*Learning objectives*

1. To understand and interpret pertinent testing for patients with glaucoma, including visual field and OCT
2. To identify signs of neovascular macular degeneration on OCT
3. To identify signs of neovascular macular degeneration on fluorescein angiography

**Normotensive Glaucoma Follow-Up with Incidental Finding of Choroidal Neovascular Membrane: a Teaching Case Report | 4**

4. To understand how non-neovascular and neovascular macular degeneration are diagnosed
5. To understand how non-neovascular and neovascular macular degeneration are managed

*Discussion questions*

1. Knowledge and concepts required for critical review of the case:
  - a. What are the diagnostic criteria for a patient with normotensive glaucoma?
  - b. What are the risk factors for development and progression of normotensive glaucoma?
  - c. What are the diagnostic criteria for a patient with non-neovascular macular degeneration?
  - d. What are the diagnostic criteria for a patient with neovascular macular degeneration?
2. Differential diagnosis:
  - a. What are the differential diagnoses based on the patient's chief complaint?
  - b. What are the justifications for dilating a patient with a similar chief complaint?
  - c. What other conditions could explain the patient's visual field results?
  - d. What other conditions could explain the patient's optic nerve OCT results?
  - e. What other conditions could explain the patient's macular OCT results?
  - f. How do OCT and visual field findings correlate?
3. Disease management
  - a. Describe the treatment options for glaucoma
  - b. What are the pharmaceutical, non-surgical treatment options for glaucoma?
  - c. Describe the different classes of pharmacological agents. For each agent, describe: drug class, dosage schedule, expected IOP reduction
  - d. What are the surgical treatment options for glaucoma?
  - e. When are AREDS multivitamins clinically indicated for macular degeneration?
  - f. Describe the treatment options for neovascular macular degeneration
4. Patient education
  - a. What lifestyle modifications would be recommended for a patient with macular degeneration?
  - b. How would glaucoma be explained to a patient to facilitate an understanding of the condition?
  - c. How would both neovascular and non-neovascular macular degeneration be explained to a patient to facilitate an understanding of the conditions?
  - d. For a patient acutely diagnosed with neovascular macular degeneration, how would one best explain to the patient what will happen at the exam with the retina specialist?
  - e. What is the long-term visual prognosis for a patient diagnosed with glaucoma?
  - f. What is the long-term visual prognosis for a patient diagnosed with non-neovascular macular degeneration? Neovascular macular degeneration?
5. Critical thinking
  - a. When should surgical treatment be recommend over pharmacological therapy for a patient with glaucoma?
  - b. When should patients with glaucoma be referred to a glaucoma specialist?
  - c. When should patients with macular degeneration be referred to a retina specialist?

*Learning assessment*

1. Clinical skills such as high plus funduscopy, binocular indirect ophthalmoscopy, acquisition of OCT images, automated



## Normotensive Glaucoma Follow-Up with Incidental Finding of Choroidal Neovascular Membrane: a Teaching Case Report | 6

usually preceding the latter.<sup>10</sup> Non-neovascular (also called non-exudative or “dry”) macular degeneration is characterized by the presence and accumulation of yellow lipid deposits called drusen below the retinal pigment epithelium of the retina.<sup>10</sup> Accumulation of drusen damages the retinal pigment epithelium, resulting in large areas of geographic atrophy as well as expression of angiogenic cytokines such as vascular endothelial growth factor (VEGF).<sup>10</sup> In neovascular (also called exudative or “wet”) macular degeneration, VEGF stimulates development of choroidal neovascularization (CNV) causing the characteristic clinical findings of subretinal hemorrhage, fluid exudation, lipid deposition, detachment of the retinal pigment epithelium from the choroid and, ultimately if left untreated, fibrotic scars.<sup>10</sup> Neovascular macular degeneration is responsible for 80-90% of severe visual impairment and blindness, despite only accounting for 10-20% of macular degeneration cases.<sup>10</sup>

The gold standard for diagnosis of neovascular macular degeneration remains fluorescein angiography.<sup>11</sup> FA is a minimally invasive test that involves intravenous administration of dye in conjunction with fundus photography to allow dynamic evaluation of ocular blood flow, including blood leakage and pooling.<sup>11</sup> On FA, CNV is seen as hyperfluorescence that increases in intensity and size over time as the fluorescein leaks from the neovascular membranes.<sup>11</sup> FA patterns of CNV are classified as either “classic,” which shows well-demarcated lesions with early hyperfluorescence and clear leakage in later frames, or “occult,” which is characterized by a fibrovascular pigment epithelial detachment or ill-defined leakage from an undetermined source.<sup>12</sup> In cases where fluorescein is blocked by subretinal hemorrhage, indocyanine green angiography can be useful in identifying and characterizing choroidal neovascular lesions.<sup>11</sup> This patient demonstrated an occult pattern on FA consistent with a fibrovascular pigment epithelial detachment.

In addition to FA, spectral-domain OCT has emerged in recent years as an essential adjunctive test for diagnosing and monitoring non-neovascular and neovascular macular degeneration.<sup>13</sup> Detailed cross-sectional imaging of retinal anatomy allows non-invasive visualization of detachments of the pigment epithelium and subretinal fluid due to choroidal neovascularization.<sup>12</sup> OCT in this patient identified a pigment epithelial detachment with adjacent subretinal fluid.

There is currently no definitive treatment for non-neovascular macular degeneration; however, the Age-Related Eye Disease Study (AREDS) demonstrated that high levels of antioxidants (500 mg vitamin C, 400 IU vitamin E, 15 mg beta carotene, 80 mg zinc, 2 mg copper) reduced progression to advanced AMD by 25% at five years for patients with moderate non-neovascular macular degeneration.<sup>8-9</sup> The AREDS2 expanded on these findings and substituted lutein and zeaxanthin (main components of macular pigment) for beta-carotene. Part of the reasoning for this substitution was that beta-carotene might increase the risk for lung cancer in patients who had a history of smoking.<sup>14</sup> Supplementation with omega-3 fatty acids [docosahexaenoic acid (DHA) and its precursor eicosapentaenoic acid (EPA)] did not appear to slow progression of the condition.<sup>14</sup> As such, patients with intermediate non-neovascular or neovascular macular degeneration should be counseled on supplementation with the AREDS2 formula multivitamin.

In recent years, the treatment for neovascular macular degeneration represents one of the most significant advances in eye care. Current treatment involves intravitreal injection of Food and Drug Administration-approved anti-VEGF agents, such as ranibizumab, aflibercept, and pegaptanib.<sup>11</sup> Bevacizumab, an anti-VEGF medication approved for the treatment of colon cancer, is also currently used off-label to treat neovascular macular degeneration.<sup>10</sup> Several clinical trials (MARINA, ANCHOR, HARBOR, CATT, VIEW1, VIEW2) have demonstrated maintenance or improvement in visual acuity in patients with neovascular macular degeneration receiving regular (usually monthly) treatments of intravitreal anti-VEGF therapy.<sup>15-19</sup> Human clinical trials are currently investigating platelet-derived growth factor (PDGF) antagonists as a promising alternative or combination therapy for treatment of choroidal neovascularization.<sup>20</sup> PDGF is triggered by retinal ischemia and promotes the cascade responsible for neovascular angiogenesis and, as such, inhibiting this factor represents an encouraging new therapeutic possibility for the treatment of choroidal neovascularization.<sup>20</sup> With continued advances in therapies such as anti-VEGF and anti-PDGF, vision can be preserved and even improved with prompt diagnosis and treatment of neovascular macular degeneration.

Smoking represents the only known modifiable risk factor for development and progression of macular degeneration.<sup>12</sup> The AREDS showed the risk for development of neovascular macular degeneration was doubled in patients who had a history of smoking compared to patients who had never smoked. Additionally, the risk of developing any macular degeneration for both males and females was doubled in active smokers, according to The Physicians’ Health Study and Nurses’ Health Study.<sup>21-22</sup> As such, smoking cessation should be strongly encouraged for all patients with macular degeneration.

### Conclusion

This case highlights a patient who presented for a routine glaucoma follow-up visit, but was found to incidentally have a CNVM from neovascular macular degeneration. It reflects the importance of a careful case history to determine if recent

## **Normotensive Glaucoma Follow-Up with Incidental Finding of Choroidal Neovascular Membrane: a Teaching Case Report | 7**

visual changes could be related to progression of ocular pathology. Finally, it underscores the need to be flexible as a clinician to deviate from one's planned exam sequence to address the patient's symptoms.

### **Acknowledgment**

The authors would like to thank Lorne Yudcovitch, OD, MS, FAAO, for his helpful comments during the revision process for this manuscript.

### **References**

1. Mallick J, Devi L, Malik PK, Mallick J. Update on normal tension glaucoma. *J Ophthalmic Vis Res.* 2016;11(2):204-8.
2. Jager RD, Mieler WF, Miller JW. Age-related macular degeneration. *N Engl J Med.* 2008 Jun12;358(24):2606-17.
3. Mi XS, Yuan TF, So KF. The current research status of normal tension glaucoma. *Interv Aging.* 2014;16(9):1563-71.
4. Francoz M, Fenolland JR, Giraud JM, et al. Reproducibility of macular ganglion cell-inner plexiform layer thickness measurement with cirrus HD-OCT in normal, hypertensive and glaucomatous eyes. *Br J Ophthalmol.* 2014;98:322-8.
5. Yenice E, Şengün A, Soyugelen Demirok G, Turaçlı E. Ganglion cell complex thickness in nonexudative age-related macular degeneration. *Eye (Lond).* 2015;29:1076-80.
6. Shields MB. Normal-tension glaucoma: is it different from primary open-angle glaucoma? *Curr Opin Ophthalmol.* 2008;19(2):85-8.
7. Anderson DR; Normal Tension Glaucoma Study. Collaborative normal tension glaucoma study. *Curr Opin Ophthalmol.* 2003;14(2):86-90.
8. Age-Related Eye Disease Study Research Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. *Arch Ophthalmol.* 2001;119(10):1417-36.
9. Age-Related Eye Disease Study Research Group. Risk factors associated with age-related macular degeneration. A case-control study in the age-related eye disease study: Age-Related Eye Disease Study Report Number 3. *Ophthalmology.* 2000;107:2224-2232.
10. Tsilimbaris MK, López-Gálvez MI, Gallego-Pinazo R, Margaron P, Lambrou GN. Epidemiological and clinical baseline characteristics as predictive biomarkers of response to anti-VEGF treatment in patients with neovascular AMD. *J Ophthalmol.* 2016;2016:4367631.
11. Chalam KV, Sambhav K. Optical coherence tomography angiography in Retinal Diseases. *J Ophthalmic Vis Res.* 2016;11(1):84-92.
12. Yonekawa Y, Miller JW, Kim IK. Age-related macular degeneration: advances in management and diagnosis. *J Clin Med.* 2015 Feb 12;4(2):343-59.
13. Health Quality Ontario. Optical coherence tomography for age-related macular degeneration and diabetic macular edema: an evidence-based analysis. *Ont Health Technol Assess Ser.* 2009;9(13):1-22.
14. Age-Related Eye Disease Study 2 Research Group. Lutein + zeaxanthin and omega-3 fatty acids for age-related macular degeneration: the Age-Related Eye Disease Study 2 (AREDS2) randomized clinical trial. *JAMA.* 2013 May 15;309(19):2005-15.
15. Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med.* 2006;355(14):1419-1431.
16. Brown DM, Michels M, Kaiser PK, Heier JS, Sy JP, Ianchulev T. Ranibizumab versus verteporfin photodynamic therapy for neovascular age-related macular degeneration: two-year results of the ANCHOR study. *Ophthalmology.* 2009;116(1):57-65.e5.

**Normotensive Glaucoma Follow-Up with Incidental Finding of Choroidal Neovascular Membrane: a Teaching Case Report | 8**

17. Ho AC, Busbee BG, Regillo CD, et al. Twenty-four-month efficacy and safety of 0.5 mg or 2.0 mg ranibizumab in patients with subfoveal neovascular age-related macular degeneration. *Ophthalmology*. 2014;121(11):2181-2192.
18. Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group, Maguire MG, Martin DF, Ying GS, et al. Five-year outcomes with anti-vascular endothelial growth factor treatment of neovascular age-related macular degeneration: The Comparison of Age-Related Macular Degeneration Treatments Trials. *Ophthalmology*. 2016;123(8):1751-61.
19. Heier JS, Brown DM, Chong V, et al., VIEW 1 and VIEW 2 Study Groups. Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. *Ophthalmology*. 2012;119:2537-48.
20. Sadiq MA, Hanout M, Sarwar S, et al. Platelet derived growth factor inhibitors: a potential therapeutic approach for ocular neovascularization. *Saudi J Ophthalmol*. 2015;29:287-91.
21. Christen WG, Glynn RJ, Manson JE, Ajani UA, Buring JE. A prospective study of cigarette smoking and risk of age-related macular degeneration in men. *JAMA*. 1996;276:1147-1151.
22. Seddon JM, Willett WC, Speizer FE, Hankinson SE. A prospective study of cigarette smoking and age-related macular degeneration in women. *JAMA*. 1996;276:1141-1146.
23. Optometric Clinical Practice Guideline: Care of the Patient with Open Angle Glaucoma (revised 2010) [Internet]. St. Louis, MO: American Optometric Association; c2011. Available from: <http://www.aoa.org/documents/optometrists/CPG-9.pdf>



Dr. Bulson [Ryan.Bulson@pacificu.edu] is an Associate Professor at Pacific University College of Optometry where he teaches optometric procedures and serves as a clinical attending for third- and fourth-year interns in the college's ocular disease and pediatrics clinics. He also serves as a Staff Optometrist at the Portland VA Medical Center where he supervises optometry students and residents.

Dr. Faridi is a medical retina specialist in the VA Portland Health Care System and at Oregon Health & Science University's Casey Eye Institute. In addition, as faculty of the Casey Reading Center, she participates in research on age-related macular degeneration, diabetic retinopathy and inherited retinal degenerations. Dr. Faridi is Director of the Casey Resident Ophthalmic Imaging Conference and she also staffs resident and fellow retina clinics.