# PREDICTING GEOGRAPHIC ATROPHY GROWTH WITH SD-OCT

The ability to identify ideal treatment candidates could speed clinical trials.

**BY THEODORE LENG, MD, MS**

Approximately half of eyes with advanced age-related macular degeneration (AMD) have geographic atrophy (GA).[1,2] In patients older than 75 years, GA is the principal cause of severe vision loss.[3] Fortunately, GA often begins outside of the fovea,[4] and central functional areas of vision are often not affected until late in the disease process.

Given the slowly progressive nature of dry AMD with GA, ophthalmologists have an opportunity to preserve vision in these patients. If we could prevent the spread of GA to the center of the fovea, many patients would ultimately end up happier. With the recent success of early clinical trials of pharmacologic agents and cell-based therapies,[5] the ability to intervene may not be too far in the future. So, if we will soon have the power to prevent the growth of GA, to whom should we offer treatment?

## IDENTIFYING IDEAL CANDIDATES

When a new treatment emerges, one should select a few ideal candidates—patients whom one is sure will benefit from the treatment—before casting a wider net and trying it on everyone who might benefit from the therapy. There are two reasons for this. First, if there are unknown side effects of a new treatment that were not uncovered during clinical trials, it would be undesirable for many or all of your patients with GA to be affected by them. Second, you want to have a few "wins" early on to boost your confidence in the efficacy of a new product, so you can continue to use it when indicated. In addition, if you can identify those most likely to benefit—in this case, those most likely to experience GA progression and loss of vision—then you can use that information to help counsel potential treatment candidates and explain to them why they might benefit from the therapy.

Lampalizumab (Genentech) is an antigen-binding fragment of a humanized monoclonal antibody directed against complement factor D. This large molecule is currently being evaluated in two identical phase 3 trials in patients with GA: Spectri (NCT02247531) and Chroma (NCT02247479). The completion date is November 2017 for Spectri and September 2018 for Chroma. If approved, lampalizumab would potentially be the first treatment for GA approved by the US Food and Drug Administration.

When that day comes, to whom should we first administer treatment? I believe that the ideal candidate would be someone we think is at high risk of losing central vision due to the spread and growth of GA. This patient would be the most likely to benefit from this intravitreal therapy and the most likely to agree to a treatment meant to be preventive in nature.

## QUANTITATIVE IMAGING ANALYSIS

Previous studies have shown that the presence of drusen, hyperpigmentation, and reticular pseudodrusen on infrared reflectance images are qualitative risk factors for GA progression.[4,6,7] Spectral-domain optical coherence tomography (SD-OCT) studies have also shown that subretinal drusenoid deposits and abnormalities in the retinal pigment epithelium (RPE) and photoreceptors at the margins of GA may be associated with GA growth.[8,9] While these imaging studies

## AT A GLANCE

- In patients older than 75 years, GA is the principal cause of severe vision loss.
- With the recent success of early clinical trials of pharmacologic agents and cell-based therapies, the ability to intervene in GA may be not too far in the future.
- Patients who are at high risk of GA progression and of movement of that GA into the foveal center would be ideal candidates for emerging therapies for GA.

have given us helpful insights into the progression of dry AMD with GA, none of them describe a method to reliably predict *where* GA is likely to spread and what the pattern of growth will be over a specified time span.

In a recent study,[10] we harnessed the massive amount of data contained in volume SD-OCT scans of the macula (more than 67 million voxels per scan) to create a fully automated algorithm that can quantitatively and accurately identify macular regions where GA is likely to grow. Moreover, the computer model was able to predict if and when the foveal center was likely to be affected by GA—an important clinical issue, as involvement of the foveal center often leads to a precipitous drop in visual acuity and visual function.

## A PREDICTIVE MODEL

In our study, 118 longitudinal SD-OCT volume scans from 38 eyes with GA were used to develop a computer algorithm. A fully automated pipeline was developed to segment the scans, extract imaging features, create a predictive model for GA progression, and test that model using a machine learning approach.

We fed the ground truth about 19 imaging features and regions of GA growth into the model to train it in a pixel-by-pixel fashion. We then tested the ability of the model to predict areas of GA growth in a separate set of data in which the truth was hidden from the model.

We created a two-class classification problem for the artificial intelligence model, asking it to predict whether each pixel in a topographic image was a future GA or non-GA region.

## INFLUENTIAL FEATURES

When the 19 quantitative SD-OCT features were ranked on their predictive ability to identify regions of future GA growth, we found that the most important features were regions of photoreceptor loss, lower reflectivity of OCT band 11, and the height of reticular pseudodrusen. Other influential features included intensity of the GA projection image, retinal thickness between the outer boundary of OCT band 5 and inner boundary of OCT band 11, average intensity between outer boundary of OCT band 7 and inner boundary of OCT band 11, and eccentricity of the existing GA.

Using these features, we were able to predict regions of future GA growth in several testing scenarios with sensitivity ranging from 0.81 to 0.90 and specificity ranging from 0.95 to 0.97, depending on which one of three testing scenarios was used. The area under the receiver operating curve for GA classification was 0.97, with positive predictive values ranging from 0.83 to 0.86 and negative predictive values from 0.96 to 0.97. Correlation coefficients of future GA areas to predictions ranged from 0.97 to 0.99.

Importantly, the ability of our automated algorithm to predict foveal GA involvement had a high level of performance, with correlation coefficients ranging from 0.94 to 0.95 in the various testing scenarios.

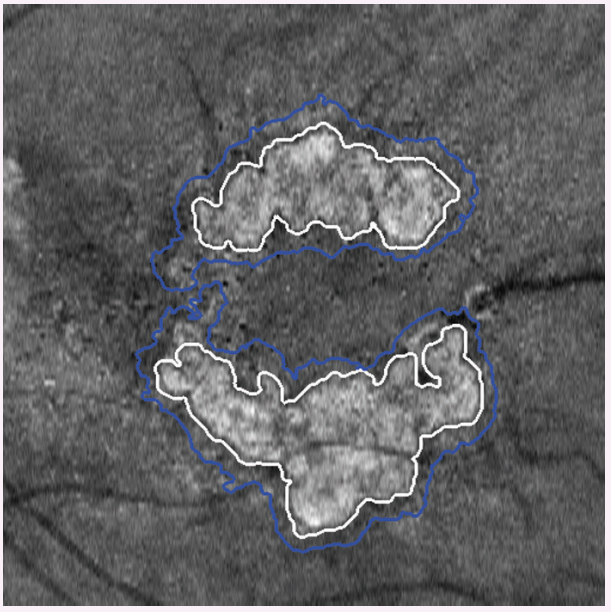

**Figure. GA OCT projection image, with baseline GA outlined in white and predicted GA growth outlined in blue, based on a fully automated prediction model.**

Overall, we found the computer model to be quite robust in predicting areas of future GA growth and whether that growth would involve the foveal center (Figure).

## PUTTING IT ALL TOGETHER

Our algorithm potentially gives us the ability to identify patients who are at high risk of GA progression and of movement of that GA into the foveal center. These patients at risk for vision loss would be ideal candidates for emerging therapies for GA.

Moreover, future GA trials could be designed around these features. If high-risk patients can be recruited into clinical trials, that could potentially shorten trial times and decrease the sample sizes necessary to reach statistical significance in demonstrating the efficacy and safety of a fledgling investigational product. Ultimately, our patients will benefit. ■

1. Chew EY, Clemons TE, Agrón E, et al; Age-Related Eye Disease Study Research Group. Ten-year follow-up of age-related macular degeneration in the age-related eye disease study: AREDS report no. 36. *JAMA Ophthalmol*. 2014;132(3):272-277.
2. Ferris FL, Davis MD, Clemons TE, et al; Age-Related Eye Disease Study (AREDS) Research Group. A simplified severity scale for age-related macular degeneration: AREDS Report No. 18. *Arch Ophthalmol*. 2005;123(11):1570-1574.
3. Schatz H, McDonald HR. Atrophic macular degeneration: rate of spread of geographic atrophy and visual loss. *Ophthalmology*. 1989;96(10):1541-1551.
4. Sunness JS, Gonzalez-Baron J, Applegate CA, et al. Enlargement of atrophy and visual acuity loss in the geographic atrophy form of age-related macular degeneration. *Ophthalmology*. 1999;106(9):1768-1779.
5. Schwartz SD, Regillo CD, Lam BL, et al. Human embryonic stem cell-derived retinal pigment epithelium in patients with age-related macular degeneration and Stargardt's macular dystrophy: follow-up of two open-label phase 1/2 studies. *Lancet*. 2015;385(9967):509-516.

*(Continued on page 66)*

also for neurodegenerative and cardiovascular diseases, cancers, diabetes, and obesity. Mitochondria are becoming the targets for an entire new field of drug development. The future will likely include clinical trials using mitochondria-targeting drugs for retinal diseases, and this will be an exciting, novel area of research with great therapeutic potential. ■


1. Lee C, Yen K, Cohen P. Humanin: a harbinger of mitochondrial-derived peptides? *Trends Endocrinol Metab*. 2013;24(5):222-228.
2. Lee C, Zeng J, Drew BG, et al. The mitochondrial-derived peptide MOTS-c promotes metabolic homeostasis and reduces obesity and insulin resistance. *Cell Metab*. 2015;21(3):443-454.
3. Jones MM, Manwaring N, Wang JJ, Rochtchina E, Mitchell P, Sue CM. Mitochondrial DNA haplogroups and age-related maculopathy. *Arch Ophthalmol*. 2007;125(9):1235-1240.
4. Canter JA, Olson LM, Spencer K, et al. Mitochondrial DNA polymorphism A4917G is independently associated with age-related macular degeneration. *PLoS One*. 2008;3(5):e2091.
5. Udar N, Atilano SR, Memarzadeh M, et al. Mitochondrial DNA haplogroups associated with age-related macular degeneration. *Invest Ophthalmol Vis Sci*. 2009;50(6):2966-2974.
6. SanGiovanni JP, Arking DE, Iyengar SK, et al. Mitochondrial DNA variants of respiratory complex I that uniquely characterize haplogroup T2 are associated with increased risk of age-related macular degeneration. *PLoS One*. 2009;4(5):e5508.
7. Mueller EE, Schaier E, Brunner SM, et al. Mitochondrial haplogroups and control region polymorphisms in age-related macular degeneration: a case-control study. *PLoS One*. 2012;7(2):e30874.
8. Kenney MC, Hertzog D, Chak G, et al. Mitochondrial DNA haplogroups confer differences in risk for age-related macular degeneration: a case control study. *BMC Med Genet*. 2013;14:4.
9. Kenney MC, Chwa M, Atilano SR, et al. Mitochondrial DNA variants mediate energy production and expression levels for CFH, C3 and EFEMP1 genes: implications for age-related macular degeneration. *PLoS One*. 2013;8(1):e54339.
10. Atilano SR, Malik D, Chwa M, et al. Mitochondrial DNA variants can mediate methylation status of inflammation, angiogenesis and signaling genes. *Hum Mol Genet*. 2015;24(16):4491-4503.
11. Thaker K, Chwa M, Atilano SR, et al. Increased expression of ApoE and protection from amyloid-beta toxicity in transmitochondrial cybrids with haplogroup K mtDNA. *Neurobiol Dis*. 2016;93:64-77.
12. Nashine S, Chwa M, Kazemian M, et al. Differential expression of complement markers in normal and AMD transmitochondrial cybrids. *PLoS One*. 2016;11(8):e0159828.
13. Feher J, Kovacs I, Artico M, et al. Mitochondrial alterations of retinal pigment epithelium in age-related macular degeneration. *Neurobiol Aging*. 2006;27(7):983-993.
14. Kenney MC, Atilano SR, Boyer D, et al. Characterization of retinal and blood mitochondrial DNA from age-related macular degeneration patients. *Invest Ophthalmol Vis Sci*. 2010;51(8):4289-4297.
15. Liang FQ, Godley BF. Oxidative stress-induced mitochondrial DNA damage in human retinal pigment epithelial cells: a possible mechanism for RPE aging and age-related macular degeneration. *Exp Eye Res*. 2003;76(4):397-403.
16. Lin H, Xu H, Liang FQ, et al. Mitochondrial DNA damage and repair in RPE associated with aging and age-related macular degeneration. *Invest Ophthalmol Vis Sci*. 2011;52(6):3521-3529.
17. Jarrett SG, Lin H, Godley BF, Boulton ME. Mitochondrial DNA damage and its potential role in retinal degeneration. *Prog Retin Eye Res*. 2008;27(6):596-607.
18. Karunadharma PP, Nordgaard CL, Olsen TW, Ferrington DA. Mitochondrial DNA damage as a potential mechanism for age-related macular degeneration. *Invest Ophthalmol Vis Sci*. 2010;51(11):5470-5479.
19. Terluk MR, Kapphahn RJ, Soukup LM, et al. Investigating mitochondria as a target for treating age-related macular degeneration. *J Neurosci*. 2015;35(18):7304-7311.
20. Ferrington DA, Kapphahn RJ, Leary MM, et al. Increased retinal mtDNA damage in the CFH variant associated with age-related macular degeneration. *Exp Eye Res*. 2016;145:269-277.



**M. Cristina Kenney, MD, PhD**
- a professor and director of laboratory research at the Gavin Herbert Eye Institute of the University of California, Irvine, School of Medicine
- financial interest: none acknowledged

**Baruch D. Kuppermann, MD, PhD**
- a professor of ophthalmology and biomedical engineering, chief of the retina service, and vice chair of academic affairs at the Gavin Herbert Eye Institute of the University of California, Irvine, School of Medicine
- member of the *Retina Today* editorial advisory board
- financial interest: none acknowledged
- +1-949-824-6256; bdkupper@uci.edu


*(Continued from page 62)*

# GA BY THE NUMBERS


GA affects more than **5 million people** worldwide,[11] including almost **1 million Americans**.[12]

For patients with advanced AMD (neovascular AMD or GA involving the center of the macula) in one eye, the risk of progression to an advanced stage in the fellow eye ranged from **35%** to **50%** at 5 years.[2]

Of patients with GA, **42%** are legally blind.[13]


6. Pumariega NM, Smith RT, Sohrab MA, et al. A prospective study of reticular macular disease. *Ophthalmology*. 2011;118(8):1619-1625.
7. Zweifel SA, Imamura Y, Spaide TC, et al. Prevalence and significance of subretinal drusenoid deposits (reticular pseudodrusen) in age-related macular degeneration. *Ophthalmology*. 2010;117(9):1775-1781.
8. Fleckenstein M, Schmitz-Valckenberg S, Martens C, et al. Fundus autofluorescence and spectral-domain optical coherence tomography characteristics in a rapidly progressing form of geographic atrophy. *Invest Ophthalmol Vis Sci*. 2011;52(6):3761-3766.
9. Bearelly S, Chau FY, Koreishi A, et al. Spectral domain optical coherence tomography imaging of geographic atrophy margins. *Ophthalmology*. 2009;116(9):1762-1769.
10. Niu S, de Sisternes L, Chen Q, Rubin DL, Leng T. Fully automated prediction of geographic atrophy growth using quantitative spectral-domain optical coherence tomography biomarkers. *Ophthalmology*. 2016;123(8):1737-1750.
11. Wong WL, Su X, Li X, et al. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. *Lancet Glob Health*. 2014;2(2):e106-116.
12. Friedman DS, O'Colmain BJ, Muñoz B, et al; The Eye Diseases Prevalence Research Group. Prevalence of age-related macular degeneration in the United States. *Arch Ophthalmol*. 2004;122(4):564-572.
13. Klein R, Wang Q, Klein BE, et al. The relationship of age-related maculopathy, cataract and glaucoma to visual acuity. *Invest Ophthalmol Vis Sci*. 1995;36(1):182-191.



**Theodore Leng, MD, MS**
- director, clinical and translational research, at the Byers Eye Institute at Stanford, Stanford University School of Medicine, Palo Alto, Calif.
- financial interest: none acknowledged
- vision.md@gmail.com