Pharmacogenetics for Genes Associated with Age-related Macular Degeneration in the Comparison of AMD Treatments Trials (CATT)

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Purpose: To evaluate the pharmacogenetic relationship between genotypes of single nucleotide polymorphisms (SNPs) known to be associated with age-related macular degeneration (AMD) and response to treatment with ranibizumab (Lucentis; Genentech, South San Francisco, CA) or bevacizumab (Avastin; Genentech) for neovascular AMD.

Design: Clinical trial.

Participants: Eight hundred thirty-four (73%) of 1149 patients participating in the Comparison of AMD Treatments Trials (CATT) were recruited through 43 CATT clinical centers.

Methods: Each patient was genotyped for SNPs rs1061170 (CFH), rs10490924 (ARMS2), rs11200638 (HTRA1), and rs2230199 (C3), using TaqMan SNP genotyping assays (Applied Biosystems, Foster City, CA).

Main Outcomes Measures: Genotypic frequencies were compared with clinical measures of response to therapy at one year, including mean visual acuity (VA), mean change in VA, 15-letter or more increase in VA, retinal thickness, mean change in total foveal thickness, presence of fluid on OCT, presence of leakage on fluorescein angiography (FA), mean change in lesion size, and mean number of injections administered. Differences in response by genotype were evaluated with tests of linear trend calculated from logistic regression models for categorical outcomes and linear regression models for continuous outcomes. To adjust for multiple comparisons, \( P \leq 0.01 \) was considered statistically significant.

Results: No statistically significant differences in response by genotype were identified for any of the clinical measures studied. Specifically, there were no high-risk alleles that predicted final VA or change in VA, the degree of anatomic response (fluid on OCT or FA, retinal thickness, change in total foveal thickness, change in lesion size), or the number of injections. Furthermore, a stepwise analysis failed to show a significant epistatic interaction among the variants analyzed; that is, response did not vary by the number of risk alleles present. The lack of association was similar whether patients were treated with ranibizumab or bevacizumab or whether they received monthly or pro re nata dosing.

Conclusions: Although specific alleles for CFH, ARMS2, HTRA1, and C3 may predict the development of AMD, they did not predict response to anti–vascular endothelial growth factor therapy.

Financial Disclosure(s): The author(s) have no proprietary or commercial interest in any materials discussed in this article. Ophthalmology 2013;120:593–599 © 2013 by the American Academy of Ophthalmology.

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The treatment of neovascular age-related macular degeneration (AMD) has been improved dramatically by the development of the anti–vascular endothelial growth factor (VEGF) therapies bevacizumab (Avastin) and ranibizumab (Lucentis). The Comparison of AMD Treatments Trials (CATT) showed that bevacizumab was equivalent to ranibizumab in improving visual acuity (VA) of patients with neovascular AMD when treatment was administered either monthly or pro re nata (PRN).1 At 1 year, participants treated monthly with bevacizumab or ranibizumab gained 8.0 and 8.5 letters, respectively, and those treated as needed gained 5.9 and 6.8 letters, respectively. Most CATT participants (>92%) had stable or improved VA relative to baseline. However, despite this remarkable clinical effect, there was a wide range in treatment response.

Pioneering developments in AMD genetics research have identified numerous single nucleotide polymorphisms (SNPs) in multiple genes associated with the prevalence of the early or late stages of AMD, or both.5,3 Although the risk associated with these SNPs is well characterized, the
The influence of these genetic variants on response to therapy is inconclusive. To date, a limited number of studies investigating small numbers of patients have explored this topic, and their results are inconsistent. Reports investigating either bevacizumab or ranibizumab indicate that patients homozygous for the risk allele at the CFH Y402H polymorphism experienced worse visual outcomes or required more injections than patients with other genotypes. However, other studies report no association with the risk genotype. Results from studies evaluating the ARMS2 A69S and HTRA1 promoter polymorphisms also conflict with regard to treatment response, and no definitive conclusions can be drawn. Nevertheless, these studies introduce the idea that SNPs associated with the development of AMD may play a role in predicting treatment response and outcome.

The large cohort of patients treated with anti-VEGF drugs for neovascular AMD in the CATT along with the many outcome variables that were collected following standardized protocols makes this study population an ideal group to evaluate the effects of a number of genetic polymorphisms on treatment response. This study investigated whether a pharmacogenetic relationship exists between response to treatment and SNPs rs1061170 (CFH Y402H), rs10490924 (ARMS2 A69S), rs11200638 (HTRA1 promoter), and rs2230199 (C3 R80G). Although other susceptibility genes have been reported, these 4 SNPs have been shown consistently to have the strongest associations with the development and progression of AMD and have been postulated to influence response to therapy. A comprehensive analysis of genotypic associations with visual and anatomic outcomes evaluated by treatment group, drug, and dosing regimen is described.

**Patients and Methods**

Study procedures for CATT have been reported previously and are provided on ClinicalTrials.gov (study identifier, NCT00593450). Written informed consent was obtained from all CATT study participants involved in the genetics ancillary study. Institutional review board approval was obtained by the Cleveland Clinic and all participating CATT centers.

**Patients**

Between February 2008 and December 2009, 1185 patients with neovascular AMD were enrolled in CATT at 43 clinical centers in the United States. Patients were assigned randomly to 1 of the 4 treatment groups: (1) ranibizumab monthly, (2) bevacizumab monthly, (3) ranibizumab PRN, and (4) bevacizumab PRN. Between July 2010 and September 2011, 834 (73%) of the 1149 patients who were alive were enrolled in the genetics study.

The CATT protocol specified that eligible patients needed to be at least 50 years of age, to have untreated active choroidal neovascularization (CNV) resulting from AMD in the study eye (1 eye per patient), and to have VA in the study eye between 20/25 and 20/320, inclusive, on electronic VA testing. Active CNV was defined as the presence of leakage on fluorescein angiography and the presence of fluid on time-domain optical coherence tomography (OCT). Fluid could be located either within or below the retina or below the retinal pigment epithelium. Neovascularization or the sequelae of neovascularization, that is, pigment epithelium detach-ment, subretinal hemorrhage or hemorrhage below the retinal pigment epithelium, blocked fluorescence, macular edema, or intraretinal fluid or fluid below the retinal pigment epithelium, needed to be present under the fovea. Patients were evaluated every month and were treated according to their randomly assigned schedule of either monthly or as needed treatment.

**Measures of Response to Treatment**

Clinical measures of the response to treatment were based on VA, anatomic features of AMD assessed by OCT and fluorescein angiography, and the total number of injections given in 1 year. Visual acuities were measured with an electronic VA testing system. Mean VA, mean change from baseline in VA, and the proportion of patients with a 15-letter or more increase from baseline were the visual measures. The OCT parameters were determined by readers using a prospectively defined assessment protocol at the OCT reading center. The proportions of patients with a thin (<120 μm), normal (120–212 μm), and thick (>212 μm) retina; mean change from baseline in total foveal thickness; and the proportion of patients with no fluid (“dry”) on OCT were used as the indicators of response to treatment. Lesion size and leakage on fluorescein angiography was determined by readers using a prospectively defined assessment protocol at the fundus photograph reading center. All examiners and readers were masked to treatment assignment.

**Genotype Determination**

Approximately 20 ml of peripheral blood was collected from each patient. DNA was extracted and purified from leukocytes by means of the Gentra Systems PUREGENE DNA Purification Kit (Qiagen, Valencia, CA). The following 4 AMD-associated SNPs were evaluated in each patient: (1) complement factor H (CFH) Y402H (rs1061170) in exon 9 of the CFH gene on chromosome 1q31, resulting in a substitution of histidine for tyrosine at codon 402; (2) age-related maculopathy susceptibility 2 (ARMS2, also called LOC387715) A69S (rs10490924) in the chromosome 10q26 region, a nonsynonymous coding SNP variant in exon 1, resulting in a substitution of the amino acid serine for alanine at codon 69; (3) high temperature requirement factor A1 (HTRA1; rs11200638) in the chromosome 10q26 region, altering the promoter sequence; and (4) complement component 3 (C3) R80G (rs2230199), the nonsynonymous coding SNP variant in exon 3 resulting in the amino acid glycine to arginine at codon 80. Genotyping was performed using a custom made TaqMan OpenArray loaded with TaqMan SNP genotyping assays (Applied Biosystems). Typing of SNPs with OpenArray uses TaqMan nanofluidic genotyping chemistry supported on a metal-based array. DNA samples were loaded and were amplified by polymerase chain reaction on arrays as recommended by the manufacturer. Arrays were scanned on the OpenArray NT imager and genotypes were identified using the OpenArray SNP Genotyping analysis software. The allele identification of the SNP assays was verified by direct DNA sequence analysis from 10 samples for each assay yielding 100% concordance. Primer and probe sequences are available on request. All laboratory personnel were masked to treatment assignment and patient clinical data.

**Data Analysis**

Clinical outcomes were compared among genotypes to determine if there was an association between genotype and response to treatment. The number of risk alleles for each genotype was counted as 0, 1, or 2, and associations of genotype (in terms of number of risk alleles) with outcomes were evaluated using tests of linear trend calculated from logistic regression models for categorical outcomes and linear regression models for continuous outcomes at 1 year. Additionally,
Results

Eight hundred thirty-four CATT study participants who were treated with anti-VEGF therapy were evaluated across 4 of the most consistent and important AMD-associated genetic risk variants. Baseline demographic and ocular characteristics of all genetic study participants are shown in Table 1. The mean age ± standard deviation of the patients at study entry was 78.5 ± 7.5 years, and 61.2% of patients were female. Mean baseline VA was 61.3 ± 13.3 letters (Snellen equivalent, approximately 20/63). The genetic study participants generally were comparable with those who were still alive but chose not to participate (n = 315), except that the genetic study participants were 2 years younger (P < 0.001) and had better baseline VA (P = 0.005) and a higher percentage of them had hypertension (P = 0.045) and occult lesions (P = 0.04; Table 1).

The genotypic frequencies for each SNP analyzed were balanced across treatment groups, drug, and dosing regimen (data not shown). As expected, the frequency of the high-risk alleles among CATT participants was higher than in the general population because the SNPs examined are known to be associated with AMD. For each measure of response to treatment, the interaction between genotypes and treatment group was assessed. The effect of risk alleles on each measure did not differ by treatment group, drug, or regimen. Therefore, all treatment groups were collapsed and the findings on the entire 834 patients are reported as a single group (Tables 2 and 3). The genotypic associations for each treatment group are shown in Tables 4, 5, 6, and 7 (available at http://aaojournal.org).

Visual Outcomes by Genotype

For each of the 3 visual measures evaluated at 1 year, there was no association with any of the genotypes or with the number of risk alleles from the 4 SNPs. The strongest association was for mean VA with C3 (P = 0.03); however, the association was for better VA among those homozygous for the risk allele (GG). Furthermore, when additional time points (12, 24, and 36 weeks) were evaluated using longitudinal models, there was no association between genotype and mean change in VA from baseline (smallest P = 0.30).

Anatomic Outcomes by Genotype

For each of the 5 anatomic outcomes evaluated at 1 year, there was no significant association with any of the genotypes or with the number of alleles from the 4 SNPs. The strongest association was for mean change in total retinal thickness with CFH (P = 0.03), where the association was for less improvement (decrease, 142 μm) among those homozygous for the risk allele (CC) and largest improvement (decrease, 188 μm) among those heterozygous for the risk allele (CT). Furthermore, when additional time points (12 and 24 weeks) were evaluated using longitudinal models, there was no association between genotype and mean change in total foveal thickness from baseline (smallest P = 0.27).

Number of Injections in the Pro Re Nata Treatment Groups

Among the participants in the 2 PRN groups, no statistically significant difference was found in the number of injections among the different genotypes for any of the 4 SNPs or for the total number of risk alleles from the 4 SNPs (Table 2). The strongest association was for HTRA1 (P = 0.25), where the highest mean number of injections (n = 8.0) was among those homozygous for the risk allele (AA) and an equal mean number of injections (n = 7.3) was required among those heterozygous for the risk allele (AG) or homozygous for the nonrisk allele (GG).

Table 1. Comparison of Baseline Demographic and Ocular Characteristics between Participants and Nonparticipants in the Genetic Study (n = 1149)

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Subjects in Genetic Study (n = 834)</th>
<th>Alive Subjects Not in Genetic Study (n = 315)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD), yrs</td>
<td>78.5 (7.5)</td>
<td>80.9 (7.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female (%)</td>
<td>510 (61.2)</td>
<td>204 (64.8)</td>
<td>0.28</td>
</tr>
<tr>
<td>Former or current cigarette smoker (%)</td>
<td>483 (57.9)</td>
<td>169 (53.7)</td>
<td>0.36</td>
</tr>
<tr>
<td>Presence of hypertension (%)</td>
<td>563 (67.5)</td>
<td>232 (73.7)</td>
<td>0.045</td>
</tr>
<tr>
<td>Taking AREDS supplement (%)</td>
<td>536 (64.3)</td>
<td>189 (60.0)</td>
<td>0.21</td>
</tr>
<tr>
<td>Mean baseline VA (SD), no. of letters</td>
<td>61.3 (13.3)</td>
<td>58.8 (13.7)</td>
<td>0.005</td>
</tr>
<tr>
<td>Mean baseline area of CNV (SD), disc area</td>
<td>1.70 (1.69)</td>
<td>1.91 (1.90)</td>
<td>0.096</td>
</tr>
<tr>
<td>Mean baseline total area of CNV lesion (SD), disc area</td>
<td>2.47 (2.55)</td>
<td>2.49 (2.54)</td>
<td>0.87</td>
</tr>
<tr>
<td>Presence of occult lesion (%)</td>
<td>505 (60.6)</td>
<td>169 (53.7)</td>
<td>0.04</td>
</tr>
<tr>
<td>Presence of RAP lesion (%)</td>
<td>80 (9.6)</td>
<td>41 (13.0)</td>
<td>0.12</td>
</tr>
<tr>
<td>Mean total foveal thickness (SD), μm</td>
<td>462 (190)</td>
<td>456 (180)</td>
<td>0.60</td>
</tr>
</tbody>
</table>

AREDS = Age-Related Eye Disease Study; CNV = choroidal neovascularization; RAP = retinal angiomatosus proliferation; SD = standard deviation; VA = visual acuity.
The principal aim of this study was to investigate whether 4 strongly associated AMD-risk genotypes predict response to treatment with bevacizumab or ranibizumab for neovascular AMD. The CATT patient cohort is an ideal population to study the pharmacogenetic relationship between genetic variants and anti-VEGF therapy. Most previous published studies involve small, retrospective reviews of a limited number of outcomes determined from routine clinical visits. The CATT is a large, prospectively defined cohort of patients with neovascular AMD drawn from multiple clinical sites with all follow-up treatment and outcomes carried out under well-defined protocols. Specifically, all VAs were determined by masked examiners using electronic Early Treatment Diabetic Retinopathy Study testing, all OCT measurements were determined in a masked fashion by an independent OCT reading center, and all photographic and fluorescein angiographic outcomes were determined by masked assessment at an independent fundus photographic reading center. The SNPs chosen for evaluation in this study represent the genes with the strongest and most consistent association with the development and progression of AMD. In addition, these SNPs have been targeted as potential markers to guide disease management.

This study found no statistically significant pharmacogenetic association between these SNPs and VA outcomes, anatomic outcomes, or the number of injections required. There were 2 instances in which borderline significance was present. First, better VA was seen in patients who were homozygous for the risk allele at C3 (P = 0.03). This is the opposite of what would be expected if C3 risk alleles negatively influence treatment response. Second, the lowest mean change in total foveal thickness (less clinical response) was seen in patients who were homozygous for the CFH risk allele.
vascularization resulting from increased levels of VEGF. Any allele has been hypothesized to favor recurrence of new vessels in patients harboring complement-related AMD-risk alleles and is located in the promoter region and is predicted to increase expression levels of the gene. It has been hypothesized that overexpression of \textit{HTRA1} may alter the integrity of Bruch’s membrane and favor the development of CNV. This may suggest that \textit{HTRA1} would play a role in regulating CNV and therefore would affect response to anti-VEGF therapy. The precise mechanisms by which these genetic variants affect AMD susceptibility are still not understood fully, and the present data indicate that alteration of either \textit{ARMS2} or \textit{HTRA1} via these SNPs does not influence anti-VEGF therapy strongly.

This study provides convincing evidence that the major risk alleles that influence the development of AMD do not affect clinical response to therapy strongly. This lack of

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|c|c|}
\hline
& \textbf{Genotype*} & \textbf{No.} & \textbf{Retinal Thickness (\%), $\mu m$} & \textbf{Mean Change in Total Foveal Thickness from Baseline (Standard Error), $\mu m$} & \textbf{Dry on Optical Coherence Tomography (\%)} & \textbf{Leakage on Fluorescein Angiography (\%)} & \textbf{Mean Change in Lesion Size from Baseline (Standard Error, Disc Area)} \\
\hline
\textbf{Single Nucleotide Polymorphism} & & & \textbf{<120} & \textbf{120–212} & \textbf{>212} & & & \\
\hline
\textit{CFH}, rs1061170 & \textit{CC} & 270 & 46 (17.2) & 187 (70.0) & 34 (12.7) & -142 (9.9) & 72 (27.3) & 120 (46.2) & 0.2 (0.2) \\
& \textit{TC} & 391 & 85 (22.1) & 262 (68.2) & 37 (9.6) & -188 (9.4) & 112 (29.6) & 173 (47.1) & 0.2 (0.1) \\
& \textit{TT} & 173 & 37 (21.9) & 116 (66.3) & 20 (11.8) & -174 (16.3) & 55 (33.5) & 71 (43.8) & 0.4 (0.1) \\
& Linear trend & & & & & 0.62 & 0.03 & 0.18 & 0.71 & 0.48 \\
& $P$ value & & & & & & & & & \\
\hline
\textit{ARMS2}, rs10490924 & \textit{TT} & 170 & 34 (20.5) & 114 (68.7) & 18 (10.8) & -184 (16.3) & 46 (28.0) & 79 (48.8) & 0.5 (0.2) \\
& \textit{GT} & 398 & 79 (20.2) & 275 (70.2) & 38 (9.7) & -176 (9.0) & 129 (33.4) & 164 (43.5) & 0.0 (0.1) \\
& \textit{GG} & 266 & 55 (21.0) & 172 (65.6) & 35 (13.4) & -152 (10.8) & 64 (24.9) & 121 (48.4) & 0.4 (0.2) \\
& Linear trend & & & & & 0.33 & 0.06 & 0.30 & 0.89 & 0.80 \\
& $P$ value & & & & & & & & & \\
\hline
\textit{HTRA1}, rs11200638 & \textit{AA} & 162 & 34 (21.5) & 107 (67.7) & 17 (10.8) & -178 (15.8) & 45 (28.8) & 76 (49.4) & 0.5 (0.2) \\
& \textit{AG} & 398 & 79 (20.2) & 273 (69.6) & 40 (10.2) & -179 (9.2) & 128 (33.1) & 162 (43.0) & 0.1 (0.1) \\
& \textit{GG} & 274 & 55 (20.4) & 181 (67.0) & 34 (12.6) & -152 (10.8) & 66 (25.0) & 126 (48.8) & 0.3 (0.1) \\
& Linear trend & & & & & 0.64 & 0.10 & 0.23 & 0.84 & 0.42 \\
& $P$ value & & & & & & & & & \\
\hline
\textit{C3}, rs2230199 & \textit{GG} & 56 & 11 (20.4) & 37 (68.5) & 6 (11.1) & -182 (24.8) & 19 (35.8) & 27 (50.0) & 0.0 (0.4) \\
& \textit{CG} & 318 & 69 (22.0) & 217 (69.1) & 28 (8.9) & -161 (10.4) & 90 (23.1) & 135 (45.3) & 0.1 (0.1) \\
& \textit{CC} & 460 & 88 (19.5) & 307 (67.9) & 57 (12.6) & -174 (8.7) & 121 (27.1) & 202 (46.2) & 0.3 (0.1) \\
& Linear trend & & & & & 0.51 & 0.67 & 0.07 & 0.85 & 0.28 \\
& $P$ value & & & & & & & & & \\
\hline
\textbf{No. of risk alleles*} & 0–1 & 123 & 27 (22.5) & 75 (62.5) & 18 (15.0) & -153 (15.3) & 30 (25.9) & 63 (54.8) & 0.2 (0.2) \\
& 2 & 141 & 26 (18.6) & 101 (72.1) & 13 (9.3) & -157 (15.2) & 33 (24.1) & 60 (45.1) & 0.5 (0.2) \\
& 3 & 175 & 36 (20.9) & 116 (66.9) & 21 (12.2) & -200 (15.6) & 51 (29.8) & 63 (38.4) & 0.1 (0.1) \\
& 4 & 170 & 41 (24.6) & 113 (67.7) & 13 (7.8) & -174 (14.8) & 61 (37.0) & 71 (43.8) & 0.0 (0.2) \\
& \geq 5 & 225 & 38 (17.2) & 157 (71.0) & 26 (11.8) & -160 (11.7) & 64 (29.4) & 107 (49.8) & 0.3 (0.2) \\
& Linear trend & & & & & 0.29 & 0.68 & 0.30 & 0.93 & 0.80 \\
& $P$ value & & & & & & & & & \\
\hline
\end{tabular}
\caption{Genotypic Associations with Anatomic Outcome Measures at 1 Year (n = 834)}
\end{table}

(P = 0.03). However, patients who were heterozygous for the risk allele had the highest mean change in total foveal thickness (best clinical response), which would not be expected if the presence of the risk allele truly influences clinical response. Further, both of these instances were isolated and, because of the adjustments for multiple comparisons, did not reach the prespecified significance level of $P<0.01$.

The lack of any association is provocative. Although these SNPs clearly influence AMD risk, they seem to have no impact on the response or durability of anti-VEGF therapy. \textit{CFH} and \textit{C3} encode genes involved in the complement cascade. Dysregulation of the complement system manifest by genetic polymorphisms clearly plays an important role in the pathogenesis of AMD. The increased inflammation found in patients harboring complement-related AMD-risk alleles has been hypothesized to favor recurrence of neovascularization resulting from increased levels of VEGF. In addition, inflammation has been postulated to reduce response to anti-VEGF treatment. However, there is little biologic evidence to support this idea, and the present data provide convincing evidence that the complement pathway, or at least these SNPs in the complement pathway, do not influence response to therapy strongly. \textit{ARMS2} and \textit{HTRA1} both lie in the AMD susceptibility locus identified on chromosome 10q26 and are expressed in the retina.\textsuperscript{19} Genetic variation at this locus has been shown to confer a differential risk for CNV versus geographic atrophy.\textsuperscript{21} The \textit{ARMS2} gene product has been localized to the mitochondrial outer membrane, and it has been proposed that the A69S polymorphism alters \textit{ARMS2} function and increases susceptibility of photoreceptor cells to oxidative damage and aging.\textsuperscript{22} As such, it is understandable that it would increase the risk of developing AMD, but the mechanism by which it would influence response to anti-VEGF treatment is not obvious. The SNP evaluated in \textit{HTRA1} is located in the promoter region and is predicted to increase expression levels of the gene.\textsuperscript{23} It has been hypothesized that overexpression of \textit{HTRA1} may alter the integrity of Bruch’s membrane and favor the development of CNV.\textsuperscript{2} This may suggest that \textit{HTRA1} would play a role in regulating CNV and therefore would affect response to anti-VEGF therapy. The precise mechanisms by which these genetic variants affect AMD susceptibility are still not understood fully, and the present data indicate that alteration of either \textit{ARMS2} or \textit{HTRA1} via these SNPs does not influence anti-VEGF therapy strongly.

This study provides convincing evidence that the major risk alleles that influence the development of AMD do not affect clinical response to therapy strongly. This lack of
association is supported by the high power provided by the large sample size and the rigorously assessed outcome variables. The possibility that other SNPs that are less predictive of AMD risk may be associated with response to therapy cannot be excluded. Additional studies are underway, including investigations targeting biologic pathways that directly modulate cytokine behavior in neovascular AMD, such as VEGF and other growth factor pathways. Identification of markers that do affect clinical response may result in optimization of anti-VEGF therapy.

References


Footnotes and Financial Disclosures

Originally received: July 13, 2012.
Final revision: November 16, 2012.
Accepted: November 16, 2012.
Available online: January 18, 2013.
Manuscript no. 2012-1051.

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Financial Disclosure(s):
The author(s) have no proprietary or commercial interest in any materials discussed in this article.

Supported by the National Eye Institute, National Institutes of Health, Bethesda, Maryland (cooperative agreement nos.: U10 EY017823, U10 EY017825, U10 EY017826, and U10 EY017828). The sponsor or funding organization had no role in the design or conduct of this research.

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