

# How Do Patients Respond to Genetic Testing for Age-related Macular Degeneration?

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**SIGNIFICANCE:** The American Academy of Ophthalmology currently recommends against routine genetic testing for complex diseases such as age-related macular degeneration (AMD). The results of this study demonstrate that patients are very interested in predictive genetic testing for AMD, find the information useful, and make behavioral changes as a result of the information.

**PURPOSE:** The goal of this project was to conduct a pilot AMD genomic medicine study.

**METHODS:** Eligible patients were aged 50 to 65 years with no personal history of AMD. DNA samples were genotyped for five single-nucleotide polymorphisms (SNPs) in the *CFH* gene, one SNP in the *ARMS-2* gene, one SNP in the *C3* gene, and one SNP in the mitochondrial *ND2* gene. A risk score was calculated utilizing a model based on odds ratios, lifetime risk of advanced AMD and known population prevalence of genotype, haplotype, and smoking risk. The study optometrist provided the patient's risk score and counseling for personal protective behaviors. Telephone interviews were conducted 1 to 3 months after the counseling visit.

**RESULTS:** One hundred one subjects (85%) participated in the genetic testing; 78 (77.2%) were female. Follow-up interviews were conducted with 94 participants (93.1%). More than half ( $n = 48$ ) of the participants said that they were motivated to participate in the study because they had a family member with AMD or another eye or genetic disorder. Despite low risk levels, many participants reported making changes as a result of the genetic testing. Twenty-seven people reported making specific changes, including wearing sunglasses and brimmed hat and taking vitamin supplements. Another 16 people said that they were already doing the recommended activities, including wearing glasses, quitting smoking, and/or taking vitamins.

**CONCLUSIONS:** Interest in genetic testing for future risk of AMD was high in this population and resulted in support to continue current health behaviors or incentive to improve behaviors related to eye health.

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Age-related macular degeneration is the leading cause of blindness in the elderly.<sup>1</sup> Age-related macular degeneration was one of the early success stories for genomic discoveries using genome-wide association study approaches, with complement factor H polymorphisms consistently shown to predict prevalence and progression of age-related macular degeneration.<sup>2–5</sup> Gene/environment associations have been demonstrated for modifiable risk factors including smoking and body mass index.<sup>6,7</sup> Risk prediction models for age-related macular degeneration have been developed and validated that include both genetics and environmental factors.<sup>8–15</sup> In 2014, the American Academy of Ophthalmology recommended that ophthalmologists “avoid routine genetic testing for genetically complex diseases like age-related macular degeneration and late-onset primary open-angle glaucoma until specific treatment or surveillance strategies have been shown in one or more published prospective clinical trials to be of benefit to individuals with specific disease-associated genotypes. In the meantime, confine the genotyping of such patients to research studies” (<https://www.aao.org/clinical-statement/recommendations-genetic-testing-of-inherited-eye-d>, accessed June 27, 2017). Despite this recommendation from the American Academy of Ophthalmology, a

number of tests are available clinically and direct-to-consumer, with highly variable results in estimated lifetime risk of age-related macular degeneration and calls for inclusion of more genetic information and environmental risk factors to improve age-related macular degeneration prediction accuracy.<sup>16,17</sup> A pilot study in 49 smokers demonstrated that people given high genetic risk information were more likely to quit smoking than generic or low genetic risk groups.<sup>18</sup>

The overall goal of this project was to investigate the patient perspective of predictive genetic testing for age-related macular degeneration. The specific aims were (1) to document reasons that people elect or do not elect to enroll in a study to learn their genetic risk of age-related macular degeneration and (2) to document behavioral changes patients make after receiving information about genetic risk of age-related macular degeneration.

## METHODS

The project was reviewed and approved by the Essentia Health Institutional Review Board and all subjects gave written informed consent prior to participation.

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**TABLE 1.** Interview questions

Can you tell me a little about the whole process (genetic testing with Dr. Fuchs to learn about future risk of age-related macular degeneration)
Why did you decide to participate in this study and have the genetic test about risk of age-related macular degeneration?
Has your opinion about genetic testing changed since you first agreed to participate? If so, why?
Do you remember what the genetic test results were?
What information did you find out about yourself that was interesting or useful?
What information did you find out that was not useful?
Did it matter to you how you received the information about the genetic test results?
Would you like to have gotten the information another way?
Were you glad you decided to have the genetic test? Why or why not?
Have you made any changes as a result of the test result?
Do you expect your doctor to make any changes as a result of the test result?
Now I would like to talk with you about genetic testing more broadly. If you had the chance, would you have another blood test to see if genes affect how you react to the medicine you take or whether you are more likely to develop other diseases? Why or why not? What would be the benefits and drawbacks of such a test?
Would you be willing to have a genetic test that told you a wide variety of general genetic information (e.g., risks for several different diseases or medication responses), even if scientists still know very little about how that information actually affected your health? Why or why not? What would be the benefits and drawbacks of such a test?
If you had to decide about whether or not to receive information about genetic risk for disease, where would you go to get information to help you decide? (options provided: your doctor, other people who faced similar decisions, scientific journals or websites, internet, your insurance company, other___, no one—I already know what I would do)
Would you be willing to pay for the cost of a genetic test out of pocket? Why or why not? How much would you be willing to pay for the test?
Is there anything else that you would like to share about your experience?

Eligible patients, aged 50 to 65 years with no personal history of age-related macular degeneration, of the participating optometrist were mailed letters of invitation over a 6-month time frame. The goal was to recruit 100 participants for this pilot study. No formal sample size calculations were conducted. The invitation letters were followed by a phone call from a research nurse to answer any questions and schedule an appointment if interested. At the initial study appointment, patients provided written informed consent, and then genomic DNA was extracted from a blood sample. The DNA samples were sent to an external laboratory for genotyping. Participants were offered \$20 for participation. The study covered all costs, including phlebotomy, DNA extraction, and genotyping.

DNA samples were genotyped for five single-nucleotide polymorphisms in the *CFH* gene, one single-nucleotide polymorphism in the *ARMS2* gene, one single-nucleotide polymorphism in the *C3* gene, and one single-nucleotide polymorphism in the mitochondrial *ND2* gene. A risk score was calculated by the genotyping company utilizing

a model based on odds ratios, lifetime risk of advanced age-related macular degeneration and known population prevalence of genotype, haplotype, and smoking risk (risk score = [CFH factor] [ARMS2 factor] [C3 factor] [mtND2 factor] [smoking factor]).<sup>9</sup>

The optometrist provided the patient's risk score and counseling for personal protective behaviors at a separate appointment. The optometrist did not use a script or template, instead tailoring the discussion to the participant as with any usual clinical encounter.

Telephone interviews were conducted 1 to 3 months after the counseling visit by two of the investigators to ascertain reactions to genetic testing and any behavior changes made as result of the testing. The interviewers introduced themselves as members of the research team calling to follow-up on their participation in the age-related macular degeneration genetic testing project. They did not use the title of "doctor." Questions asked are included in Table 1. The interviewers entered responses to the questions directly into a database at the time of the interview; they were not recorded verbatim. Interview responses were coded and analyzed with NVivo version 10.0 (QSR International, Melbourne, Australia). Two people coded the responses after first reading through all of the interviews to identify themes. The coders met to resolve discrepancies. Content analysis was done to identify and quantify common themes within and between interview questions.<sup>19</sup>

## RESULTS

Letters of invitation were sent to 151 individuals; 32 could not be reached after multiple attempts, and 18 people refused to participate. Of the people who could be reached, 101 chose to participate (84.9%). Interview times ranged from 8 to 20 minutes (median, 12 minutes). Seventy-eight (77.2%) were female, and the mean age was 57.4 (SD, 4.6) years. Ninety-nine participants were white, and one was American Indian. Race/ethnicity was not available for one participant.

The smoking status of the participants was as follows: 67 (66.3%) never smoked, 31 (30.7%) were former smokers, and three (3.0%) were current smokers. Body mass index ranged from 17.9 to 53.0 kg/m<sup>2</sup> (mean, 27.9 [SD, 6.7] kg/m<sup>2</sup>). Education level of the participants was as follows: 10 (9.9%) high school, 33 (46.6%) some college or associate of arts, 35 (34.7%) bachelor's degree, and 23 (22.8%) graduate or professional degree.

Family history of age-related macular degeneration was as follows: 29 (28.7%) maternal, 14 (13.9%) paternal, 7 (6.9%) maternal grandmother, 3 (3.0%) maternal grandfather, 6 (5.9%) paternal grandmother, 1 (1.0%) paternal grandfather, and 4 (4%) siblings. Calculated 10-year age-related macular degeneration risk is shown in Table 2. Genetic subscores ranged from 0 to 98 (median, 79). Frequencies of recommendations for three different

**TABLE 2.** Ten-year age-related macular degeneration (AMD) risk of study participants

10-y Risk of AMD	No. participants	%
0	22	22
3	1	1
21	64	64
32	12	12
53	1	1

**TABLE 3.** Frequency of antioxidant supplement recommendations provided to 73 patients based on CFH and ARMS2

CFH risk	ARMS2 risk	Recommended antioxidants without zinc	Recommended antioxidants with zinc	Recommended zinc alone
High	High	1 (1.4%)		
	Moderate	6 (8.2%)		1 (1.4%)
	Low		18 (24.7%)	
Moderate	High			1 (1.4%)
	Moderate		1 (1.4%)	
	Low	9 (12.3%)	9 (12.3%)	
Low	High			3 (4.1%)
	Moderate			6 (8.2%)
	Low	1 (1.4%)		17 (23.3%)
Total		17 (23.3%)	28 (38.4%)	28 (38.4%)

vitamin/mineral supplement combinations based on genotype are summarized in Table 3. Antioxidants with zinc were recommended for 38.4% of patients, and zinc alone was recommended for another 38.4% of patients.

Follow-up telephone interviews were conducted with 94 (93.1%) of the 101 participants. Five areas were explored in the interviews: (1) motivation to participate in the research study, (2) experience participating in the current study, (3) results of the research project, (4) behavior changes made as a result of the genetic testing, and (5) genetic testing more generally. More than half ( $n = 48$ ) of the participants who completed follow-up interviews said that they were motivated to participate in the study because they had a family member with age-related macular degeneration (one of the initial inclusion criteria) or another eye or genetic disorder and often listed specific family members who had age-related macular degeneration and the impact of the disease on their lives. A typical comment about personal family age-related macular degeneration history as a motivator to participate was: “Because my Dad had really bad macular degeneration and was almost blind from it.” Twenty-five participants indicated that they chose to participate in the study because their optometrist had suggested the study to them and they respect him. Stated simply by one of the participants, “cause you asked me to” and by another “I did it because Dr. F. was personally involved in the testing.” Altruistic reasons for study participation, such as “I hope it helps somebody” and “Partly because I really believe in clinical trials and studies,” were given 26 times. Patient curiosity was also a common reason for study participation, with comments specific to genetics such as “just interested in the whole genetic thing.”

Response to the experience of participating in the study was overwhelmingly positive, with many people saying that the process was simple and the results were interesting. Only four negative emotions were expressed, two because of inaccurate billing (participants were not supposed to be billed for any costs related to the study). Overwhelmingly, people found the information received useful, with 77 specific positive comments provided such as “nothing was a waste of time,” “the genetic information was definitely useful,” and “yep, learned some prevention measures.” Five people expressed some confusion about the information they received.

Genetic results and counseling were provided by the optometrist, and 70 participants said they preferred that genetic results be returned face-to-face with a doctor or other health care professional because it allowed patients to ask questions. A number of people specifically mentioned that the optometrist who provided the information was very good at explaining the information. A number of people mentioned that it would be especially important if the results were not good. Phone calls with results were mentioned by a number of people as another option to receive genetic test results.

Participants were asked, “Do you remember what the genetic test results were?” As expected from the actual genetic risk scores displayed in Table 2, the majority of patients reported low or no risk of developing visually impairing age-related macular degeneration in the next 10 years.

Despite low levels of risk, many participants reported making changes as a result of the genetic testing. Seven people reported that their doctor would be watching them because of the genetic results. Twenty-seven people reported making specific changes, such as wearing sunglasses and brimmed hat and taking vitamin supplements. Another 16 people said that they were already doing the recommended activities, including wearing glasses, quitting smoking, and/or taking vitamins.

Fifty-nine people (62.8%) indicated that they would participate in additional genetic testing for other diseases, citing a variety of reasons for their interest. A specific comment that “knowledge is power” reflected a number of comments from people about using information from additional genetic testing to give them warning about diseases that might develop so they could be prepared. One person did mention the “double-edged sword” of knowledge of increased risk of development of conditions in the future that could not be prevented. A couple of people mentioned being supportive of additional testing to help out other people.

## DISCUSSION

Advancements in our understanding of genetic and environmental contributions and their interaction to risk of age-related macular degeneration provide opportunities for early intervention to prevent vision loss. The scientific authors of two recent reviews of direct-to-consumer genetic testing for age-related macular degeneration concluded that routine testing for future risk of age-related macular degeneration is not warranted currently, in part because of the wide variation in cost and scope for existing clinical genetic tests and in part because of questions of clinical utility.<sup>16,17</sup> Authors of a cost-utility analysis found that genetic screening for age-related macular degeneration that would allow for early treatment with ranibizumab therapy for neovascular macular degeneration would be cost effective.<sup>20</sup> To our knowledge, our study is the first of its kind to evaluate response to predictive genetic testing from a patient perspective. We found strong support for this study and future genetic testing in this primarily white, educated patient population.

Behavioral response to predictive genetic testing for various conditions has varied in prior studies.<sup>16–18,21</sup> A recent review and meta-analysis found no support in the literature for behavior change as a result of communicating genetic-based risk prediction.<sup>21</sup> Exceptions have been seen for improved health behaviors after risk communication for genetic risk of colorectal cancer,<sup>22</sup> lung cancer,<sup>23</sup> and Alzheimer disease.<sup>24</sup> Perhaps significant behavior

change in response to genetic testing is associated with fear of the disease being predicted. We have shown previously that, when given five options, the majority of people would first choose to provide treatment and support for total blindness.<sup>25</sup> In the Collaborative Initial Glaucoma Treatment Study, researchers reported that more than one-third of patients had a fear of blindness after receiving a glaucoma diagnosis.<sup>26</sup> Blindness was found to be a key motivational factor in smoking cessation programs.<sup>27</sup>

Knowledge about motivation to participate in genetic studies is important for future research and ultimately clinical practice. More than one-quarter of study participants indicated that they participated in the study because of the good relationship that they have with their optometrist. A study of patient attitudes toward recruitment and participation in clinical trials found that patients are interested in participating in clinical trials if they get information from their treating physician and get personal results returned to them.<sup>28</sup> Similar to a study of patients in retinal trials, in the current study we also found that many participants chose to participate for altruistic reasons.<sup>29</sup> Early adopters of personalized genomics are motivated to participate to learn about their disease risk and improve their health through speaking with their physicians to request specific recommendations.<sup>30</sup>

The Behavior Change Wheel may be useful to understand how the information gained from the current study can be used to understand the components necessary for successful implementation of behavior change, in this case behaviors related to age-related macular degeneration risk.<sup>31</sup> In the inner core of this wheel, the

personal sources of behavior including capability, motivation, and opportunity are already in place as demonstrated by the positive responses to age-related macular degeneration genetic testing observed. The middle layer of the Behavior Change Wheel comprises intervention functions, such as education, persuasion, training, enabling, and incentivizing that we have shown can be successfully implemented in a single optometry practice. The outer layer of the wheel includes guidelines. Notably, the American Academy of Ophthalmology currently recommends against genetic screening for age-related macular degeneration because of a lack of immediate clinical utility. Furthermore, fiscal measures including payment for genetic testing are not standardized. Communication/marketing is taking place through direct-to-consumer testing and marketing.

Strengths of the current pilot study include the high response rate. Limitations include the study population being representative of the limited geographic area, but not representative of the more diverse United States in terms of race/ethnicity and education levels. The personal connection with the one provider may limit generalizability.

In summary, we found a very positive response to predictive genetic testing for age-related macular degeneration in this study population with a family history of age-related macular degeneration, with many people reporting adoption or maintenance of positive eye health behaviors. Further research is needed in other patient populations and over time to determine long-term impact of genetic testing.

## ARTICLE INFORMATION

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