Pharmacogenomics of antioxidant supplementation to prevent age-related macular degeneration

Andrew J. Vickers[a,1]

Casual readers of Vavvas et al.'s recent paper in PNAS (1) on the pharmacogenomics of age-related macular degeneration (AMD) may get the impression that the authors have made an important incremental advance based on a logical series of studies, each of which has been moving the science in the same direction. I believe that readers of PNAS should be aware of the chronology of this research.

In 2013, Awh et al. (2) analyzed data from the Age-Related Eye Disease Study (AREDS) trial and claimed that the benefit of supplementation to prevent AMD depended on genotype. As a direct result of this finding, several investigators, including some of the authors of the article by Vavvas et al., advocated the use of genotyping for patients eligible for supplementation. However, the authors of the AREDS trial attempted, but failed, to replicate the findings of Awh et al., concluding that genotyping was not of value (3). An independent panel of statisticians (which included the author of this letter) was commissioned to review and analyze the data. Our findings, published last year, were unequivocal: "We found errors in the data used to support the initial claim of genotype–treatment interaction," were "unable to replicate any genotype–treatment interactions," and recommended that treatment should be given "without consideration of genotype" (4). Brett Zanke, a coauthor on the Vavvas paper, was sent the findings and approached us offering comments. This June 2017 correspondence was absent any suggestion that findings were sensitive to the type of AMD. Several months later, the paper by Vavvas et al. (1) was submitted for publication, claiming that the value of genotyping was endpoint-dependent; that is, genotyping is of value for preventing choroidal neovascular (NV) disease but not geographic atrophy (GA).

Vavvas et al. (1) dismiss the work of our independent panel of statisticians as "inaccurate" because of our "insensitivity to th[e] clinical distinction" between GA and NV. However, the same would be true of the original paper by Awh et al. (2). We also note that for many years, several of the authors of the Vavvas paper recommended the use of genotyping without any reference to this being dependent on the type of AMD. Moreover, Seddon et al. (5) concluded, despite Vavvas et al.'s contrary assertion (1), that genotype influences "effectiveness of . . . treatment [for] risk of progression to overall advanced AMD."

In sum, the Vavvas et al. paper (1) is not a logical extension of prior research indicating the importance of the NV endpoint with respect to genotyping; instead, it is a post hoc data analysis in response to clearly negative findings from an independent group. The results reported by Vavvas et al. (1) may be sound when viewed in isolation but follow a great deal of multiple testing, and thus, at best, are hypothesis-generating. The investigators are advised to conduct appropriate prospective research, for instance, randomizing patients to standard supplements versus genotype-directed supplementation.

1 Vavvas DG, et al. (2018) *CFH* and *ARMS2* genetic risk determines progression to neovascular age-related macular degeneration after antioxidant and zinc supplementation. *Proc Natl Acad Sci USA* 115:E696–E704.

2 Awh CC, Lane AM, Hawken S, Zanke B, Kim IK (2013) CFH and ARMS2 genetic polymorphisms predict response to antioxidants and zinc in patients with age-related macular degeneration. *Ophthalmology* 120:2317–2323.

3 Chew EY, et al.; Age-Related Eye Disease Study Research Group (2014) No clinically significant association between CFH and ARMS2 genotypes and response to nutritional supplements: AREDS report number 38. *Ophthalmology* 121:2173–2180.

4 Assel MJ, et al. (2018) Genetic Polymorphisms of CFH and ARMS2 do not predict response to antioxidants and zinc in patients with age-related macular degeneration: Independent statistical evaluations of data from the Age-Related Eye Disease Study. *Ophthalmology* 125:391–397.

5 Seddon JM, Silver RE, Rosner B (2016) Response to AREDS supplements according to genetic factors: Survival analysis approach using the eye as the unit of analysis. *Br J Ophthalmol* 100:1731–1737.

[a]Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY 10021

Author contributions: A.J.V. wrote the paper.

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[1]Email: vickersa@mskcc.org.

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