Definitions of Final Age-Related Macular Degeneration (AMD) Phenotype Categories

The final age-related macular degeneration (AMD) phenotype for participants in the Age-Related Eye Disease Study (AREDS) is based on fundus photographs that were graded by a central Reading Center located at the University of Wisconsin, Madison. These photographs were obtained both during the clinical trial portion of AREDS as well as subsequently when participants were followed for natural history data. During the clinical trial, fundus photographs were taken at baseline and annually thereafter starting at Year 2. In addition, a photograph was taken for each participant at the last clinic visit prior to the conclusion of the clinical trial. The median length of follow-up in the clinical trial was 6.5 years. During the natural history follow-up period, fundus photographs were obtained on an annual basis. Some AREDS participants who chose not to participate in the natural history follow-up came back prior to its conclusion for one final clinic visit at which a fundus photograph was obtained.

There were 1,699 participants in AREDS in whom either geographic atrophy (GA) or one or more of the abnormalities characterizing neovascular AMD (NV AMD) were graded as definitely present in photographs from any visit during the study or who had treatment for NV AMD. GA was defined as any GA definitely present within the grid. NV AMD was defined as the presence of one or more of the following 5 neovascular characteristics (NVC): non-drusenoid retinal pigment epithelial detachment, serous sensory retinal detachment, subretinal or subpigment epithelial hemorrhage, subretinal fibrous tissue or fibrin, or hard exudates. An algorithm that looked at all gradable photographs for each participant was used to categorize each eye as having strong or weak NV AMD and strong or weak GA when they were present.

NV AMD was defined as strong for an eye if the density of NV AMD was > 60%. Density of NV AMD was the sum of all 5 NVC at all visits divided by twice the number of visits completed (with gradable photographs), beginning with (and including) the first visit at which any NVC was graded definitely present, expressed as percent. The density calculation ignored gradings of GA prior to the first visit with any NV AMD so that eyes with GA that subsequently developed NV AMD would have an equal opportunity to meet the > 60% threshold for the strong NV AMD category. Eyes whose NV AMD density was greater than 0 and ≤ 60% were categorized as having weak NV AMD.

GA was defined as strong for an eye if it was definitely present at the last two visits (with gradable photographs) and the density of GA was > 50%. Density of GA was the sum of all visits at which GA was definitely present divided by the number of visits completed, beginning with (and including) the first visit at which GA, NV AMD, or treatment for choroidal neovascularization (CNV) was recorded. Eyes with some GA present that did not meet the definition of strong GA were categorized as having weak GA.

Participants with strong NV AMD or treatment for CNV in one or both eyes were categorized as having NV AMD, those with strong GA alone in one or both eyes were categorized as having GA and those with strong NV AMD or treatment for CNV in one eye and strong GA in the other were categorized as having both NV AMD and GA, without review of the grading summaries or of the photographs. The grading summaries, and when necessary, the photographs for eyes with weak NV AMD or GA were reviewed when the status of this eye was likely to contribute to the phenotype of the participant. For example, if one eye had strong NV AMD or treatment for CNV and the second eye had weak GA, review of the grading summaries was needed and, in many cases, the photographs as well, in order to determine whether this participant should be classified as NV AMD only or as having both NV AMD and GA. If the second eye had weak NV AMD only, review was not necessary, and the participant’s phenotype would be NV AMD only.
When a review of either grading summaries or photographs was carried out and evidence was considered too weak in both eyes for both NV AMD and GA, the phenotype of ‘Questionable Advanced AMD’ was assigned to avoid mixing these cases with those free of any suggestion of NV AMD or GA. In occasional cases (e.g. a participant in whom the only eye with any NV AMD or GA had photocoagulation scars from treatment of a branch retinal vein occlusion that were graded as GA) this participant was considered to have no advanced AMD. All reviews of grading summaries and photographs were conducted by Dr. Matthew Davis of the AREDS Reading Center. (Note that any grading errors found by Dr. Davis in the course of his review only affected the assignment of the AMD phenotype, the database with the fundus photograph data was not changed.)

AREDS participants who were not assigned a final AMD phenotype of NV AMD, GA, both NV AMD and GA, or Questionable Advanced AMD were categorized by the AREDS Coordinating Center using the algorithm described below:

- **Large Drusen**: Large drusen (≥ 125 microns in diameter) in at least one eye at the last study visit and in at least one other study visit (in the same eye).
- **Large Drusen Questionable 1**: Large drusen in at least one eye at 2 or more visits (other than the last visit).
- **Large Drusen Questionable 2**: Large drusen in at least one eye only at the last study visit. This includes participants who only have a baseline visit if one or both eyes have large drusen.
- **Large Drusen Questionable 3**: Large drusen in at least one eye at just one study visit (other than the last visit).
- **Control**: AMD Category 1 (no drusen or small [< 63 microns in diameter] non-extensive drusen) in both eyes at all visits. This includes participants who only have a baseline visit if both eyes were graded as AMD Category 1.
- **Control Questionable 1**: AMD Category 1 in both eyes at last visit and at all previous visits, except that one eye is AMD Category 2 (non-extensive intermediate [≥ 63 microns to < 125 microns in diameter] drusen or extensive small drusen) at one visit.
- **Control Questionable 2**: AMD Category 1 in both eyes at last visit and at all previous visits, except that each eye is AMD Category 2 at one visit.
- **Control Questionable 3**: AMD Category 1 in both eyes at last visit, no worse than AMD Category 2 in either eye at all other visits, at least one eye is Category 2 at 2 or more visits prior to last visit.
- **Control Questionable 4**: AMD Category 1 in one eye at last visit and AMD Category 2 in fellow eye at last visit; AMD Category 1 at all other visits. Participant must have at least one visit post-baseline.
- **Other, Non-control**: Does not meet any of the criteria of categories noted above.