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The Importance of Outcome Measure Research in Stargardt Disease

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In this issue of *JAMA Ophthalmology*, the 2 articles from the Natural History of the Progression of Atrophy Secondary to Stargardt Disease (ProgStar) Study[1,2] focus on outcome measure research in Stargardt disease. Nearly 20 years ago, *ABCA4* was identified as a causative gene for Stargardt disease[3] and its role in photoreceptor function elucidated, leading to potential approaches to intervene clinically on this disease. Critical to the design and success of any interventional study is knowledge about the functional and anatomic parameters defining the disease and information on their rate of change. Based on carefully obtained natural history information, outcome variables can be chosen for a clinical trial of a potential new treatment and study duration and sample size can be calculated. ProgStar has been designed to follow up a large number of *ABCA4*-genotyped patients in a multimodal natural history study. The hope is that these natural history data can be used to develop the reproducible outcome variables that will be critical for use in clinical trials of new treatments for Stargardt disease.

The 2 outcome measures that are the subjects of the 2 ProgStar articles[1,2] in this issue of *JAMA Ophthalmology* hone in on key outcomes of interest for clinical trial design for Stargardt disease. Autofluorescence in Stargardt disease is an imaging modality uniquely suited for tracking the progression of the disease in vivo. In Stargardt disease, causative mutations in *ABCA4* lead to dimerization of A2E, a component of lipofuscin, which accumulates in the retina pigment epithelium. Lipofuscin is a fluorescent pigment that can be excited by light in the visible spectrum, so it is possible to capture and potentially quantitate its fluorescence using non-invasive in vivo in fundus imaging.[4] In Stargardt disease, fundus autofluorescence can document abnormalities and changes in lipofuscin. The degree of these changes in autofluorescence and their rate of change have become important in diagnosing Stargardt disease and following its progression. Several groups have demonstrated longitudinal changes in fundus autofluorescence in Stargardt disease.[5] Quantitating these changes in autofluorescence to include growth of atrophic lesions as well as changes in flecks and background fluorescence could become a key outcome measure in clinical trials because they are noninvasive in vivo biomarkers for disease pathogenesis.

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In this retrospective review, the ProgStar study group[1] highlights aspects of the longitudinal analysis of fundus autofluorescence imaging that focus on but are not limited to atrophic lesions in more than 200 patients. The study provides evidence that autofluorescent images can be reliably graded beyond the measurement of well-defined atrophic lesions to include the pheonotypic entities of flecks, background status (heterogenous or homogenous), and questionable or definite decreases in autofluorescence. Stargardt disease has a wide spectrum of phenotypes including different clinical patterns, diverse age at onset, variable retention of visual acuity, and a wide range of full field electroretinogram effects. Understanding the evolution of varied macular lesions, in addition to atrophy, will provide insight into the disease progression. Using this ProgStar grading paradigm, the study group is poised to use their autofluorescent grading to follow up lesions prospectively in their long-term natural history study. However, caution must be applied when interpreting the incidence rates reported in the article. The study is a retrospective review of visits that preceded and include the enrollment visit into the ProgStar prospective study where the presence of atrophy is an inclusion criterion. The authors point out several limitations of their study including the lack of a common starting point, few (about one-third had only 2 visits) and variably timed visits, and the use of a cohort that was required to have atrophy at the most recent visit.[2] Because the cohort is selected by their development of the outcome of interest (ie, atrophy), the reported rates are dependent on visit sampling and may not be generalizable to incidence rates of atrophy in a nonbiased Stargardt population.

While autofluorescence fundus imaging provides anatomic insights to the disease at the level of the retina pigment epithelium, it will be important to associate these retina pigment epithelium changes with the functional consequences of the disease on macular function. Visual acuity is one aspect of macular function, but in Stargardt as well as in many retinal diseases, it alone does not sufficiently reflect disease progression across stages. As previously demonstrated by the ProgStar Study Group, eyes with Stargardt and moderate to severe vision impairment (visual acuity worse than 20/70) have very little detectable change in visual acuity during a median of 3.6 years of follow-up.[6] With this floor effect on visual acuity measurements in these eyes, it will be important to identify nonfoveal outcome variables, such as those obtained by microperimetry measurements, perhaps in association with fundus imaging. However, the direct association of functional changes and atrophic retinal changes as measured by fundus autofluorescence appears to be more variable in Stargardt disease than that observed in persons with geographic atrophy from age-related macular degeneration.[7] Future reports that correlate long-term structural and functional relationships will be critically important to further our understanding of disease pathogenesis as well as to develop outcome variables for use in phase 3 clinical trials.

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