Analysis of multivariate longitudinal data from eyes - microperimetry macular sensitivity loss in patients with Stargardt Disease

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Abstract: Microperimetry (MP) is a visual field test for measuring macular sensitivity of human eye. A MP test often involves testing of multiple locations in the visual field (e.g. 68 testing points), and the macular sensitivity is estimated as the mean sensitivity of the testing points. Macular sensitivity may be used as an endpoint in clinical trials for eye diseases. For Stargardt disease (the most common form of inherited juvenile macular degeneration), however, prior data have shown that the mean sensitivity (MS) change within one or two years was small, and thus MS may not be a sensitive measure to use as an endpoint for Stargardt trials. Clinically it has been hypothesized that the testing locations where macular lesions have already developed and are likely to expand, are the locations where function is mostly like to decline. Therefore, we are interested in using the point-level sensitivity data from MP test to characterize the points that are mostly likely to lose sensitivity and to estimate the sensitivity change in these points. Statistically, the data structure can be described as bivariate longitudinal multivariate outcomes, involving repeatedly annual MP tests for the 68 test points in both eyes. Such data structure entails complicated correlations, and simple analysis using generalized estimating equations or random effects models will not address the clinical hypothesis. We will use a point's neighboring points' sensitivity to characterize whether the point is at the lesion's edge, and use a hybrid modeling strategy based on Markov transition models together with pairwise composite likelihood for inference. The method is applied to the international multi-center Progression of Atrophy Secondary to Stargardt Disease (ProgStar) study to test the aforementioned clinical hypothesis and to determine whether the point-specific sensitivity in those points that had faster functional loss could be used as an endpoint for future Stargardt trials.