Early detection of glaucomatous progression is crucial to prevent vision loss and to maintain patients’ good quality of life. A clinician’s decision to intensify treatment therefore strongly depends on the presence and rate of progression. The detection of progression, however, is challenging as current strategies are imprecise and not sensitive to early glaucomatous changes. Standard automated perimetry, the current clinical standard for monitoring glaucoma, is limited by high test-retest variability. As a result, a longer follow-up period or more frequent testing is required in order to accurately identify visual field deterioration. This results in delays in detecting glaucomatous progression. Advances in structural assessment are promising, particularly the development of OCT.

In contrast to the commonly held opinion that structural progression occurs first, studies have shown that functional deterioration can be detected before structural loss in some patients. Furthermore, mounting evidence suggests that functional changes may be present in the absence of structural changes. These observations provide the motivation to investigate joint structure-function strategies with the goal of improving the detection of progression. Several sophisticated attempts have been developed, including integrating structure and function into a single index, using structural data as prior information to identify visual field deterioration, and utilizing machine learning classifiers.

**AN INDIVIDUALIZED JOINT STRUCTURE-FUNCTION APPROACH**

We developed a dynamic structure-function (DSF) model that uses structural and functional data jointly to monitor glaucomatous progression. This model has two components: (1) centroids that characterize the state of the disease and (2) velocity vectors that assess the rate of change (worsening or improvement). The model reassesses the state of the disease as new data are obtained and can predict subsequent measurements using the series of data available. In a previous study, we demonstrated that the DSF model predicts future measurements with more precision than ordinary least square linear regression for short follow-up series. This finding suggests that the model could be clinically useful when few measurements are available, possibly translating to earlier detection of progression.

Although there is currently no consensus on the most suitable strategy for the joint use of structural and functional information, our approach has several features that distinguish it from others. Equal importance of structure and function. The DSF model gives equal importance to both structure and function, regardless of disease severity. A challenge for the early detection of progression is the poor relationship between structural and functional measurements. Disagreements between structural and functional assessments impair clinicians’ ability to confidently identify the progression status of an eye. An advantage of our model is that it makes no assumptions about the relationship between structure and function, nor does it make assumptions about whether change should first be identified on structure or on function. Our overarching goal is to have a
robust model that uses structural and functional information jointly to identify progression.

Individualized assessment of progression. We are striving to develop an individualized assessment of progression. This approach is promising because of the known differences in variability observed between patients. When a patient exhibits highly reliable measurements over time, small changes may be indicative of true change. In contrast, when a patient exhibits highly variable measurements over time, larger changes may be needed before progression can be identified. In other words, a certain amount of change (eg, -1 dB/year on mean deviation) may be indicative of progression in one patient but not necessarily in another patient.

Our aim, therefore, is to implement a customized approach that takes into account the level of variability within each patient’s data. This approach is in contrast to conventional approaches in which patient data are evaluated against a normative database or progression is defined as the presence of a significantly negative slope without considering the heterogeneity among patients.

We have been exploring a number of methods to individualize the detection of progression. Permutation analysis is one of these methods and involves shuffling measurements in a longitudinal series to generate thousands of different series of the same data. The reshuffling process disrupts the temporal sequence in which the data were obtained, and slopes can be obtained for each of these series. The slope of the original series of measurements is then assessed to determine whether it is sufficiently different from the permutations to warrant making a determination of progression. This approach is individualized because this determination is derived from each patient’s own data. Finally, individualized structure-function relationship maps can be modelled into our approach to improve the detection of progression.

Newer, more sensitive parameters. Although the DSF model was developed using rim area for structure and mean sensitivity from standard automated perimetry for function, it can easily be expanded to include more than two parameters. We are now testing the model using newer and more sensitive structural and functional parameters. Recent work has focused on identifying the most sensitive combination of structural and functional parameters for early detection of progression. To this end, we are developing a statistical framework to assess progression with two or more parameters jointly. In addition, the model’s performance could be enhanced by including patient information that is predictive of progression. For example, IOP could be included to further enhance the detection of progression. Similarly, the status and rate of progression in one eye could be used to modulate the detection of progression in the fellow eye.

CONCLUSION

Early detection of glaucomatous progression remains a complex task for both clinicians and researchers. New strategies are needed to overcome the current limitations associated with the early detection of progression. We have developed an individualized model that uses structural and functional measurements jointly to identify progression. Our current efforts focus on optimizing this model to identify progression, with the goal of reducing the time to detection.

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