Using Filtered Forecasting Techniques to Determine Personalized Monitoring Schedules for Patients with Open-Angle Glaucoma

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Purpose: To determine whether dynamic and personalized schedules of visual field (VF) testing and intraocular pressure (IOP) measurements result in an improvement in disease progression detection compared with fixed interval schedules for performing these tests when evaluating patients with open-angle glaucoma (OAG).

Design: Secondary analyses using longitudinal data from 2 randomized controlled trials.

Participants: A total of 571 participants from the Advanced Glaucoma Intervention Study (AGIS) and the Collaborative Initial Glaucoma Treatment Study (CIGTS).

Methods: Perimetric and tonometric data were obtained for AGIS and CIGTS trial participants and used to parameterize and validate a Kalman filter model. The Kalman filter updates knowledge about each participant's disease dynamics as additional VF tests and IOP measurements are obtained. After incorporating the most recent VF and IOP measurements, the model forecasts each participant's disease dynamics into the future and characterizes the forecasting error. To determine personalized schedules for future VF tests and IOP measurements, we developed an algorithm by combining the Kalman filter for state estimation with the predictive power of logistic regression to identify OAG progression. The algorithm was compared with 1-, 1.5-, and 2-year fixed interval schedules of obtaining VF and IOP measurements.

Main Outcome Measures: Length of diagnostic delay in detecting OAG progression, efficiency of detecting progression, and number of VF and IOP measurements needed to assess for progression.

Results: Participants were followed in the AGIS and CIGTS trials for a mean (standard deviation) of 6.5 (2.8) years. Our forecasting model achieved a 29% increased efficiency in identifying OAG progression ($P<0.0001$) and detected OAG progression 57% sooner (reduced diagnostic delay) ($P = 0.02$) than following a fixed yearly monitoring schedule, without increasing the number of VF tests and IOP measurements required. The model performed well for patients with mild and advanced disease. The model performed significantly more testing of patients who exhibited OAG progression than nonprogressing patients (1.3 vs. 1.0 tests per year; $P<0.0001$).

Conclusions: Use of dynamic and personalized testing schedules can enhance the efficiency of OAG progression detection and reduce diagnostic delay compared with yearly fixed monitoring intervals. If further validation studies confirm these findings, such algorithms may be able to greatly enhance OAG management. *Ophthalmology 2014;■:1–8 © 2014 by the American Academy of Ophthalmology.*

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When evaluating patients with glaucoma to assess for disease progression, clinicians must be able to assimilate past and present information from standard automated perimetry and other functional tests, intraocular pressure (IOP) measurements, and careful assessments of the optic nerve and retinal nerve fiber layer to decide whether patients are stable or exhibit disease progression and require changes in management. Complicating such an assessment is the presence of measurement error and variability in testing performance that is known to exist for many of these testing modalities. Studies have shown that the difficulties associated with evaluating patients with glaucoma to assess for disease progression have led to undertreatment[1,2] and that decision aids, such as risk calculators,[3] are useful supplements to clinician judgment. In this article, we present pilot data from a validation study of a decision aid tool that we hope someday will be able to assist clinicians with the management of patients with glaucoma. The tool assimilates data from past and present visual fields (VFs) and IOP measurements to determine whether a patient's disease is stable and helps guide the timing of when the patient should next be examined to assess for disease progression.

At the core of this decision aid is a powerful statistical tool called "Kalman filtering," which models the motion of a dynamic system, forecasting the future trajectory and combining multiple measurements for optimal noise reduction.[4] This technique is useful for accurately extracting state/position estimates from multiple noisy data sources. In the 1960s, the

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National Aeronautics and Space Administration used Kalman filtering to "optimally" guide Apollo missions to the moon. More recently, there has been interest in applying it to the management of chronic diseases, such as monitoring glucose levels in patients with diabetes mellitus[5] and prostate-specific antigen levels in patients with prostate cancer.[6] This approach builds a model that optimizes the timing of future tests by integrating a population-based understanding of the natural history of the disease of interest with the individual patient's disease dynamics. When applied to glaucoma management, the model can be used to forecast future perimetric and tonometric measurements for individual patients. Unlike traditional approaches that identify glaucoma progression by comparing test results with a normative database, this approach generates personalized information on the disease state for each patient and forecasts how that state changes over time. By applying this to glaucoma management, it can be used to predict future values of the "positions" and respective velocities and accelerations of VF global indices, such as mean deviation (MD), pattern standard deviation (PSD), visual functional index, and IOP levels. One would expect these estimates to have increased accuracy over raw observations because the Kalman filter can optimally correct for measurement noise in the forecasts.

The purpose of this study is to determine whether the use of Kalman filtering to obtain personalized monitoring schedules of VF testing and IOP measurements for patients with open-angle glaucoma (OAG) results in an improvement in disease progression detection compared with 1-, 1.5-, and 2-year fixed interval schedules for performing these tests. By using longitudinal data from 2 randomized controlled trials of patients with OAG, we developed, parameterized, validated, and tested an algorithm that can determine whether each patient with OAG is stable or experiencing disease progression. The algorithm also dynamically determines the optimal time to perform the next test to monitor for OAG progression on the basis of information from the population that is integrated with past test results from the individual patient.

Methods

Data Sources

Data from 2 large, multicenter, randomized, controlled clinical trials, the Collaborative Initial Glaucoma Treatment Study (CIGTS) and Advanced Glaucoma Intervention Study (AGIS), were used for parameterization and validation of a Kalman filter and scheduling algorithm. These clinical trials were chosen because they included multiple measurements of IOP (by Goldmann applanation tonometry) and VF results (using a Humphrey Field Analyzer; Carl Zeiss Meditec, Dublin, CA) for patients with mild to advanced OAG over a period of up to 11 years and because they had highly structured follow-up examination regimens, with perimetry and tonometry performed every 6 months throughout the trials. In the CIGTS, 607 adults with newly diagnosed, early to moderate OAG were randomized to trabeculectomy or medical therapy and followed for up to 11 years to assess for disease progression.[7,8] In the AGIS, 591 adults with advanced OAG were randomized to treatment with argon laser trabeculoplasty or trabeculectomy and followed for at least 5 years to check for OAG progression.[9] The information contained in both the CIGTS and AGIS datasets was de-identified before we accessed it, and the University of Michigan Institutional Review Board determined that this study was exempt from requiring its approval.

Inclusion and Exclusion Criteria

To be included in our study, individuals from the 2 trials were required to have $\geq$4 examinations with VF and IOP readings. From both trials, we included only those participants who were treated with medical therapy or laser trabeculoplasty. Because incisional intraocular surgery can abruptly change glaucoma progression dynamics, we opted in this pilot study not to include data from those who were randomized to initial treatment with trabeculectomy, and those who underwent trabeculectomy during the course of either trial were censored at the time of their first trabeculectomy.

Data Elements

For each trial participant, we gathered demographic information on their age, sex, and race along with information on the IOP and VF performance at each visit. From every VF test performed on each patient throughout the trial, we extracted the MD and PSD values. By assessing global indices from serial VFs from the same patient over time, we calculated rates of change (i.e., velocity and acceleration) for MD and PSD. Velocity was computed per month, and acceleration was computed as the difference of the velocities from one period to the next period. We also calculated velocity and acceleration for IOP in a similar manner for each participant.

To validate and test our methodology, we divided the study's CIGTS and AGIS trial data equally into a training set (for parameterizing models) and testing set (for validating and testing the models). We randomly assigned CIGTS/AGIS participants to these sets to ensure equal representation of both groups in the training and testing sets. We performed this randomization process 25 times and calibrated the Kalman filter for each randomization. The prediction error of the Kalman filter was consistently unbiased across the randomizations. We present the numeric results of one of these randomizations.

Probability of Progression

Progression Criterion. We characterized a participant in the dataset as exhibiting progression at a particular visit if he or she experienced a loss of MD of at least 3 decibels from their baseline MD and this loss was confirmed on a subsequent VF test.[8] Because there is presently no gold standard for identifying progression on perimetric testing, we compared our progression definition with other progression measures, such as pointwise linear regression[10] and changes in Hodapp–Anderson–Parrish (HAP) classification[11] (e.g., change from a HAP classification of moderate to a HAP classification of severe) and found strong similarities in progression identification (data not shown), suggesting robustness of the definition of progression we chose to use. Other progression definitions could easily be incorporated into the algorithm, contingent on the availability of all of the necessary data elements.

Logistic Regression

We developed a probability of progression function using generalized estimating equations with a logit link function and exchangeable correlation structure using the training data as inputs. This binary logistic regression approach accounted for noise in VF and IOP measurements and allowed us to assess the likelihood of a patient experiencing OAG progression at a particular visit given the patient's specific characteristics (sex, age, race, baseline MD, present MD, MD velocity, MD acceleration, baseline PSD, present