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Personalized Prediction of Glaucoma Progression Under Different Target Intraocular Pressure Levels Using Filtered Forecasting Methods

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Purpose: To generate personalized forecasts of how patients with open-angle glaucoma (OAG) experience disease progression at different intraocular pressure (IOP) levels to aid clinicians with setting personalized target IOPs.

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

Participants: Participants with moderate or advanced OAG from the Collaborative Initial Glaucoma Treatment Study (CIGTS) or the Advanced Glaucoma Intervention Study (AGIS).

Methods: By using perimetric and tonometric data from trial participants, we developed and validated Kalman Filter (KF) models for fast-, slow-, and nonprogressing patients with OAG. The KF can generate personalized and dynamically updated forecasts of OAG progression under different target IOP levels. For each participant, we determined how mean deviation (MD) would change if the patient maintains his/her IOP at 1 of 7 levels (6, 9, 12, 15, 18, 21, or 24 mmHg) over the next 5 years. We also model and predict changes to MD over the same time horizon if IOP is increased or decreased by 3, 6, and 9 mmHg from the level attained in the trials.

Main Outcome Measures: Personalized estimates of the change in MD under different target IOP levels.

Results: A total of 571 participants (mean age, 64.2 years; standard deviation, 10.9) were followed for a mean of 6.5 years (standard deviation, 2.8). Our models predicted that, on average, fast progressors would lose 2.1, 6.7, and 11.2 decibels (dB) MD under target IOPs of 6, 15, and 24 mmHg, respectively, over 5 years. In contrast, on average, slow progressors would lose 0.8, 2.1, and 4.1 dB MD under the same target IOPs and time frame. When using our tool to quantify the OAG progression dynamics for all 571 patients, we found no statistically significant differences over 5 years between progression for black versus white, male versus female, and CIGTS versus AGIS participants under different target IOPs ($P > 0.05$ for all).

Conclusions: To our knowledge, this is the first clinical decision-making tool that generates personalized forecasts of the trajectory of OAG progression at different target IOP levels. This approach can help clinicians determine appropriate, personalized target IOPs for patients with OAG. *Ophthalmology 2017;■:1–9 © 2017 by the American Academy of Ophthalmology*

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The American Academy of Ophthalmology Preferred Practice Pattern for primary open-angle glaucoma (OAG) emphasizes the importance of setting a target level of intraocular pressure (IOP) for patients with glaucoma. By establishing a target IOP level, clinicians can gauge whether the interventions they are performing are effectively lowering the IOP to a level that is deemed safe or not and whether additional interventions are necessary.

Although there is consensus among the glaucoma community that establishing a target IOP is useful in patient management, it is unclear what the optimal target IOP for a given patient should be. Traditionally, clinicians have used the results of landmark glaucoma clinical trials, past experience, and their gestalt to aid with target IOP selection. However, selecting a target IOP lower than what is required for a particular patient can lead to exposure to unnecessary medical and surgical interventions, which may have side effects, be fraught with complications, and be costly. Likewise, by selecting a target IOP higher than what is actually required, the patient is at risk of experiencing disease progression. Thus, improving the selection of the proper target IOP level can be useful in managing patients with OAG.

An ideal method for selecting the proper target IOP would consider the glaucoma progression dynamics of a population of similar patients to capture how they progress at different IOP levels along with the unique disease progression dynamics of the particular patient in question. This

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would be used to generate personalized forecasts of disease progression under different IOP levels. These assessments can be dynamically updated each time the patient undergoes additional glaucoma testing. Furthermore, because patients vary from one another on a host of factors, including sociodemographic characteristics, overall health and life expectancy, ability to tolerate different interventions, and preferences for aggressiveness of glaucoma control, a decision-making tool that informs clinicians about the glaucoma progression trajectories at different target IOP levels is more valuable than a tool that determines only 1 specific target IOP level for a particular patient. This would enable the clinician and patient to jointly decide on the most appropriate target IOP on the basis of his or her unique circumstances and preferences.

We describe a novel technique using a Kalman Filter (KF) to develop a personalized and dynamically updated menu of target IOPs for patients with OAG. The KF is a technique that has been used for decades by the aerospace industry to help guide flights.[1] More recently, this technique has been used to forecast disease progression in patients with conditions such as diabetes[2,3] and prostate cancer.[4] It incorporates disease progression dynamics from an underlying population of patients with the condition of interest along with past measurements from the specific patient of interest to generate personalized disease forecasts. This technique also allows for updating of the forecasts each time additional readings are obtained.

Methods

Data Sources

We used data from the Collaborative Initial Glaucoma Treatment Study (CIGTS) and the Advanced Glaucoma Intervention Study (AGIS) to parametrize and validate our models. Briefly, the CIGTS is a multicenter clinical trial involving 607 participants with newly diagnosed moderate OAG who were enrolled in 1993−1997 and followed for 5 to 9 years. The patients were randomized to glaucoma medications or trabeculectomy. The AGIS enrolled 591 participants with advanced OAG in 1988−1992 and followed them for 8 to 11 years. The patients were randomized to receive argon laser trabeculoplasty or trabeculectomy. The participants in both trials were followed with tonometry and perimetry measurements obtained every 6 months during their follow-up time. Details about the study methodology of these trials have been described.[5,6] The CIGTS and AGIS data were de-identified before our accessing it, and the University of Michigan Institutional Review Board approved this study.

Inclusion/Exclusion Criteria

Both trials required participants to have a diagnosis of OAG in $\geq$1 eye, with elevated IOP at trial entry. For this study, we included only those persons from the trials who had been randomized to receive medical therapy or argon laser trabeculoplasty. Persons who had been randomized to trabeculectomy were excluded because incisional surgery can dramatically affect IOP and disease progression dynamics, and this adds complexity to the training of our forecasting algorithms. Furthermore, during follow-up, trial participants who later required incisional surgery were censored at the time they underwent trabeculectomy. We also excluded persons who had fewer than 4 IOP measurements or 4 visual field tests using a Humphrey Field Analyzer (Carl Zeiss Meditec, Dublin, CA). When both eyes of a participant met the eligibility criteria, we randomly selected 1 of the 2 eyes for inclusion in our analyses. After these exclusions, there were 571 eyes of 571 participants (266 from CIGTS and 305 from AGIS) who met the eligibility criteria.

Kalman Filter

At the heart of our decision support tool, we harnessed KF methodology.[7] A KF is a powerful statistical method that processes large amounts of quantitative data to forecast the trajectory of a system. This technology has been critical to aerospace engineering, including guiding Apollo missions to the moon.[1] More recently, it has been used to forecast the development or worsening of chronic diseases,[4,8−12] and we have used it to forecast OAG progression.[13]

The following example explains how this method works. Consider the prediction of where a spacecraft, presently in motion at point [*x,y,z*] in space, will be located in the future (e.g., 10, 20, 30, 40 seconds later) relative to a docking bay. Every 10 seconds, a new measurement of the spacecraft's location [x,y,z] is obtained. All measurements possess some error (noise). Traditional regression models use a data set of prior flights using similar spacecrafts and provide a linear relationship between independent (e.g., current location) and dependent (future location [x,y,z]) variables so as to minimize the mean squared error. However, these models were not designed for dynamic updates to the model as new measurements are taken. Instead, with KF, each time a measurement is obtained, the model updates an estimate of the dependent variables based on input variables to minimize mean squared prediction error at each future stage. The effective estimates of current and future locations of the spacecraft require that the functions relating inputs (previously measured locations of the spacecraft) and outputs (future location) are connected over time. This is captured as a dynamic model of internal "state" variable transitions that describes how the process (motion of the spacecraft) changes over time. In addition to the [x,y,z] location, the internal state variables of a good model may include first and second derivatives on [x,y,z] position (velocity and acceleration, respectively). A set of equations relates the measured input variables to the full set of internal state variables, so that the system modeled (current and future motion of the spacecraft) can be optimally updated with each new measurement obtained. Such updating compares the newly obtained measurement (location of the modeled spacecraft) to what would have been expected from the population at that point in time (e.g., prior flights for similar spacecrafts) and what has been learned from the process modeled (e.g., as more measurements are obtained, the technique may reveal that the spacecraft being modeled is faster or slower than average similar spacecrafts). In addition, the method allows the model to include inherent randomness in the "motion" of the state and models of randomness in the observations specific to the measurements (the variability in manually measuring the spacecraft's location).

Forecasting OAG trajectory is analogous to determining a spacecraft's trajectory over time: The type of spacecraft is analogous to sociodemographic characteristics of the patient (e.g., age, sex, race) and other risk factors known to affect OAG progression. The position (or the state of the system) at the past, present, and future is analogous to the mean deviation (MD) and pattern standard deviation (PSD) on standard automated perimetry (SAP), and the IOP at different points in time. These variables help illuminate the disease's current state and how it is changing over time. Moreover, the error or noise in the location measurements of our spacecraft analogy is akin to the error associated with SAP and IOP measurements. Randomness in the motion of the spacecraft (e.g.,

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