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Article

A New Graphical Tool for Assessing Visual Field Progression in Clinical Populations

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Purpose: We demonstrate a new approach for assessing and visualizing visual field (VF) progression in clinics.

Methods: Two summary measures for VF progression, Rate of Progression (RP) and Loss of Sight Years (LSY), are combined with a novel visualization (Hedgehog Plots). RP is calculated per eye using linear regression of mean deviation (MD) against time of follow-up. LSY is a novel parameter, linked to actuarial data, which estimates the number of years that a patient will have advanced bilateral VF loss in their predicted remaining lifetime. Every eye is given a rank within the sample based on RP and LSY allowing for "priority" patients to be identified. We illustrate differences between the parameters with an experiment comparing the cases flagged as "priority" by each method using data from 1263 VF records.

Results: RP for every eye in a "clinic" can be visualized and assessed using a Hedgehog Plot. Eyes are ranked against all other eyes by RP and LSY; these parameters provide different and complementary information on a patient's VF progression status. A purpose written interactive application demonstrating the techniques is available in the public domain at https://crabblab.shinyapps.io/hedgehog.

Conclusion: Hedgehog Plots provide a tool for visualizing VF progression in groups of patients and can be used potentially to prioritize monitoring resources.

Translational Relevance: This study illustrates a novel visualization technique and an interactive application that can be used to help determine VF progression in large groups of patients.

Introduction

The primary method for determining functional deterioration in glaucoma is evaluation of series of visual fields (VF) as measured by standard automated perimetry. Treatment for disease progression in glaucoma involves attempting to reduce the only modifiable risk factor, intraocular pressure (IOP).[1,2] Regular monitoring usually is required throughout the course of the disease prompting adjustment of treatment in line with the detection of any worsening in the patient's VF. However, regular VF monitoring of all glaucoma patients results in a huge patient management workload.[3] Hence, a tool for optimizing the use of resources would be beneficial within clinics.

A commonly used summary measure for assessing the severity of VF loss is the mean deviation (MD); this is a measure of the overall VF loss, relative to healthy age-matched observers, with more negative values indicating greater VF loss. Clinicians and researchers in glaucoma are universally familiar with the MD, and its strengths and limitations are well understood.[4] By plotting MD acquired at different examinations over time, it is possible to determine a speed or rate of VF loss per eye. This is not a new idea.[5,6] Ways of doing this in individual eyes exist in some perimetry software.[7] Yet a tool for comparing rate of VF loss of all eyes in a clinic would be useful for prioritizing follow-up resources. Such a tool does not exist. Furthermore, it is important to consider the VF loss in both eyes when evaluating progression. A person's visual function may only become compromised as VFs in both eyes deteriorate.[8] VF progression software has failed to consider this in the past.

We demonstrate a new approach for assessing VF progression in clinics using two parameters designed to be easily understood: Rate of Progression (RP: MD loss [B] per year) and Loss of Sight Years (LSY). These parameters are presented in a novel visualization (Hedgehog Plot) and we illustrated how they might be used to help determine patients requiring more or less monitoring. In this study, we also demonstrated how RP and LSY offer complementary but different information on the patient's VF progression status. Furthermore, we presented a free web-based software application that can demonstrate and implement these techniques.

Materials and Methods

To illustrate our methods we used a sample of data from a population of 88,954 patients extracted from Medisoft VF databases (Medisoft Ltd., Leeds, UK) from four regionally different clinics in England. These data have been described in detail previously[9,10] and were recorded during a period of approximately 12 years before the extraction date in 2012. Data access was granted by the Caldicott Guardians at each center. All patient data were anonymized and transferred to a single secure database. The research procedures followed the tenets set forth in the Declaration of Helsinki and was approved by a research governance committee of City, University of London. For the purpose of this study, only VFs tested by using the Humphrey Field Analyzer (Carl Zeiss Meditec, Dublin, CA) with the 24-2, white-on-white test strategy acquired with the Swedish Interactive Testing Algorithm (SITA Standard or SITA Fast) were included in the analysis. Patients were required to be between the ages of 45 and 90 years and have a follow-up of at least 2 years for inclusion into the present study. Furthermore, each VF series was required to have at least three examinations (visits) after the first was discarded to reduce perimetric learning effects.[11,12] From the eligible data, 200 eyes from 100 individuals (1263 VFs) were selected randomly for our illustrative analyses. Note that all data were anonymized and examination dates were perturbed to ensure anonymity.

Rates of MD loss were calculated per eye in decibels per year (dB/y) using ordinary least squares regression. The regression lines were plotted using a novel data visualization tool, the Hedgehog Plot. Each line in this plot represents an eye, with the length of the line indicating the length of follow-up in years. The location of the line is aligned to the patient's age

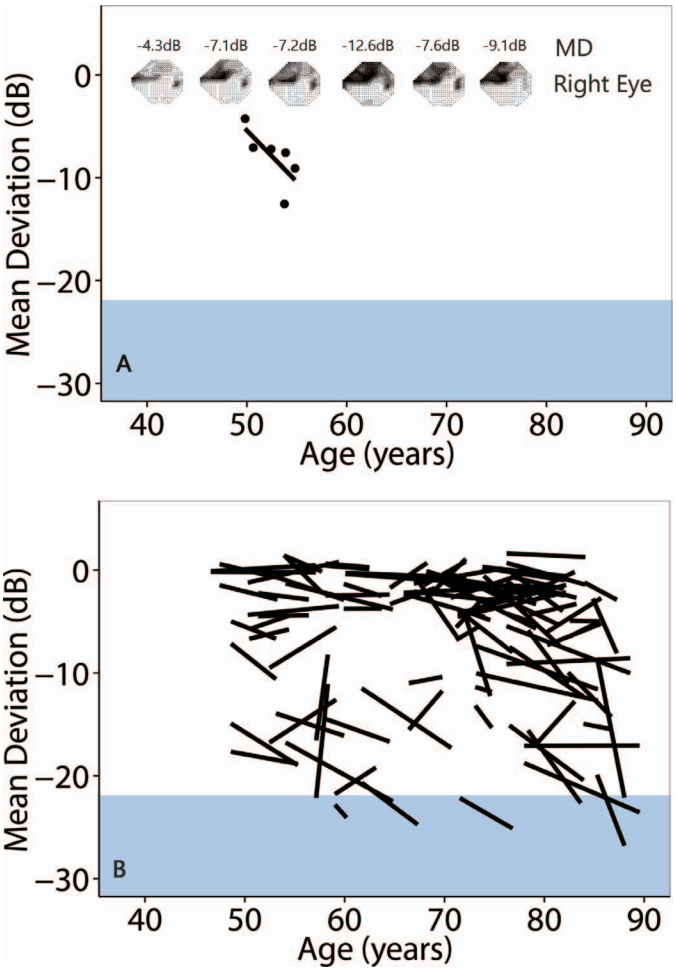

Figure 1. A schematic illustrating how the Hedgehog Plots are created. (A) A real example from the clinic showing the progression rate estimated for one eye. The first and last VFs for this patient were taken at the ages of 50 and 55 years, respectively. (B) Each *line* represents one of the 100 eyes within the clinic.

(horizontal axis) and severity of initial VF loss (vertical axis). The slope of the line indicates the rate of progression with, for example, steeply declining lines indicating rapidly changing eyes. This tool allowed us to visualize the progression rates for all eyes simultaneously. An illustration of this is shown in Figure 1.

Loss of Sight Years (LSY) is a novel parameter, linked to residual life expectancy data. LSY estimates the number of years that a patient will have bilateral VF loss worse than MD of −22 dB (binocular VF impairment) in their predicted remaining lifetime.[13] Both eyes reaching this threshold is considered to be the benchmark for "statutory blindness" by the United States Social Security Administration (US SSA).[14] Assuming the RP remains constant, we

predicted the age at which each patient will reach an MD of −22 dB in their better eye. We then estimated each patient's residual life expectancy, which was expected to differ depending on the current age of the person. For example, a 45-year-old female is expected to live to 84 while a 90-year-old female is expected to live to 94. For the purposes of this work median residual life expectancies, based on age and sex, were collected from the UK Office of National Statistics.[15] These were derived using the latest available English census data. LSY is then calculated as the number of years between the predicted age at which the patient will reach binocular VF impairment and the patient's expected age of death (see Fig. 2).

Using the Hedgehog Plot, we can instantaneously flag the most rapid progressors within the clinic allowing for "at risk" patients to be identified easily. This is based on the progression rate estimated for each eye. However, looking at the progression rates alone does not take into account the disease severity at baseline. LSY considers the patient's age and the patient's baseline measurements. Hence, we also can flag individuals who have a LSY $>$ 0; that is individuals predicted to have binocular VF impairment within their residual expected lifetime.

LSY likely offers different information to RP. For example, an older patient may be flagged as having rapid progression but may never reach predicted binocular VF impairment within their residual expected lifetime. Conversely a younger patient with a moderate progression rate may suffer from significant visual impairment for a prolonged period of time. To test for differences in the information given by RP and LSY we calculated the concordance between the two measures in flagging patients as what we define "priority cases." Individuals are first flagged as a "priority case" based on the RP in their eye with the least VF damage (the least affected eye with the better MD at the last VF examination[16]) progressing faster than a threshold of −1 dB per year. We then calculated the percentage of these patients who are defined as a "priority case" on LSY, that is they have a LSY $>$ 0. We repeated this for a different threshold, namely when RP is worse than −0.5 dB/y. We also compared the baseline ages and MD at presentation of the individuals flagged as a "priority case" by each method.

Results

RP for every eye in a "clinic" is shown in a Hedgehog Plot (Fig. 3A). Here, we demonstrated how

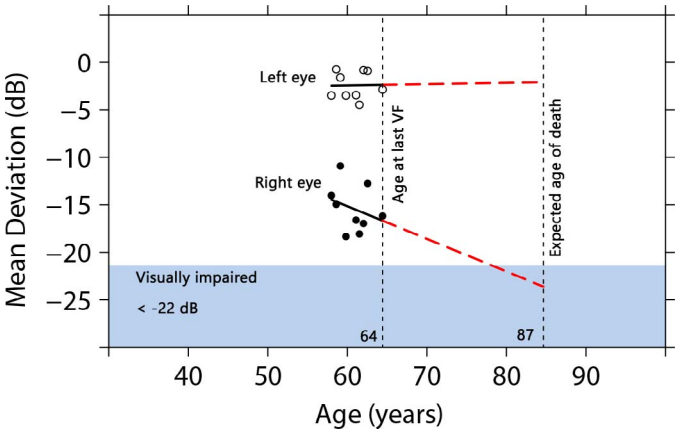

Figure 2. A schematic illustrating the calculation of LSY using a real patient from the clinic. In this example, the right eye was anticipated to have progression to the binocular VF impairment stage by the end of the patient's life. However, given that the VF of the left eye is stable and has less VF damage at diagnosis, this patient would be unlikely to experience visual impairment during their lifetime.

the Hedgehog Plot can be used to visualize data and indicate patients with progression at different rates. Eyes are colored depending on the rate of progression (Fig. 3B–F). Green indicated eyes that are stable/learning (slope $>$ 0 dB/y); gray indicated eyes that with slow progression (−0.5 $<$ slope $<$ 0 dB/y); yellow indicated eyes with moderate progression (−1 $<$ slope $<$ −0.5 dB/y), and red indicated eyes with fast progression (−1 $>$ slope). (An increasing RP [green] is likely due to variability or a learning effect rather than an improvement in MD.) It is interesting to note in our data 39% of eyes have a VF series that is green. These patients are likely stable and may not require increased monitoring, for example.

The application also allows the user to select and highlight individual eyes/patients and compare their progression to data from the entire clinic. Eyes are ranked against all other eyes by RP and LSY. The application can automatically highlight the two lines belonging to an individual patient. Figure 4 shows a patient who has rapid visual progression in one eye (ranked the 10th fastest progressing eye within this clinic). However, since they have slow progression in the second eye (ranked 54th within this clinic), they are not predicted to reach binocular VF impairment within their expected lifetime (LSY of 0 years). In Figure 5, the patient has rapid visual progression in both eyes (ranked the seventh and eighth fastest progressing eyes within this clinic). Due to the age of the patient they are not likely to reach binocular VF impairment within their expected lifetime (LSY of 0

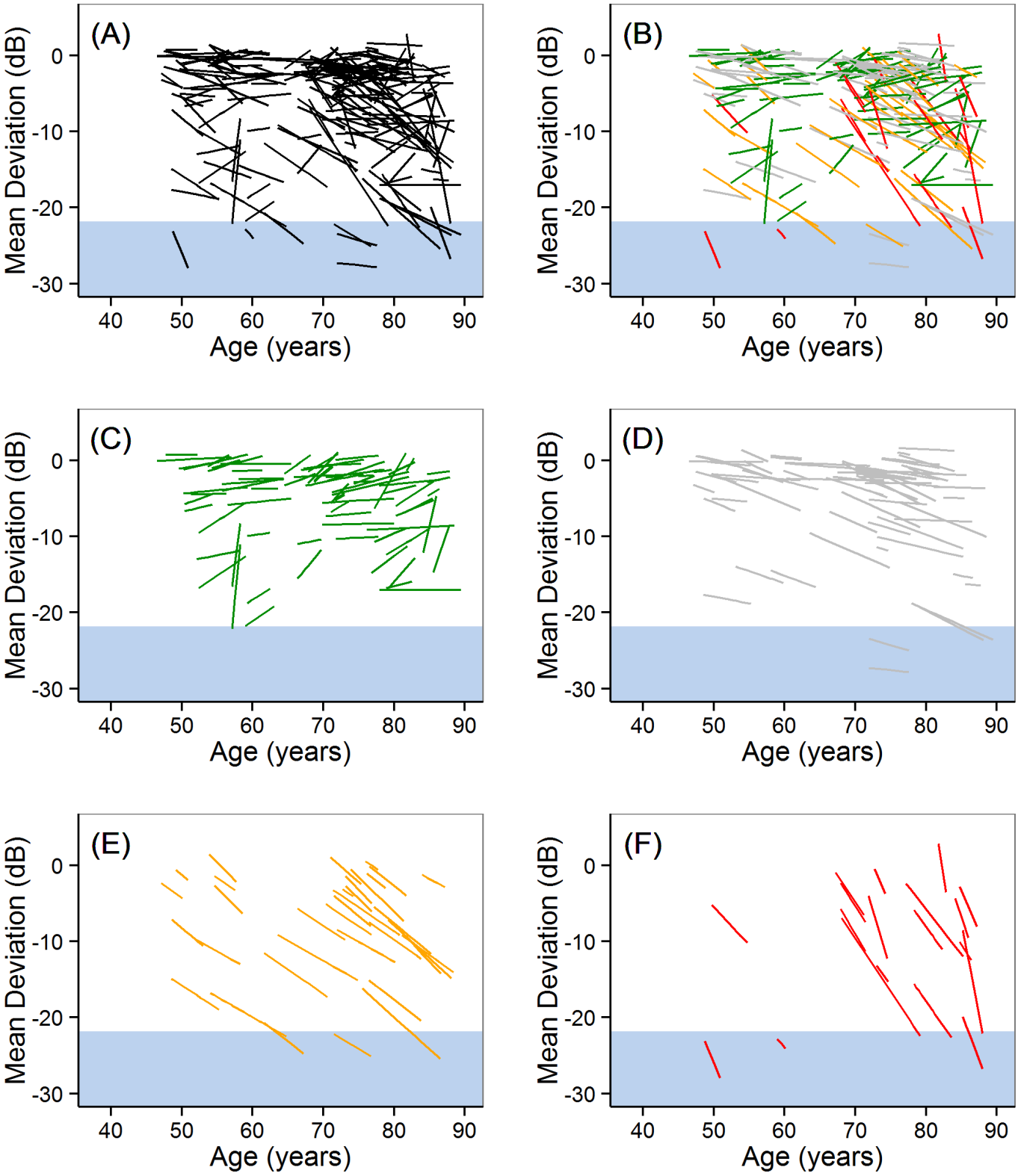

Figure 3. (A) Hedgehog Plot showing rate of VF progression status in a sample of 200 eyes from 100 patients. (B) All eyes are colored depending on the rate of progression. This can be divided into (C) eyes that are stable/improving (slope $>$ 0 dB/y), (D) eyes with slow progression ($-0.5 <$ slope $<$ 0 dB/y), (E) eyes with moderate progressoion ($-1 <$ slope < -0.5 dB/y), and (F) eyes with fast progression ($-1 <$ slope).

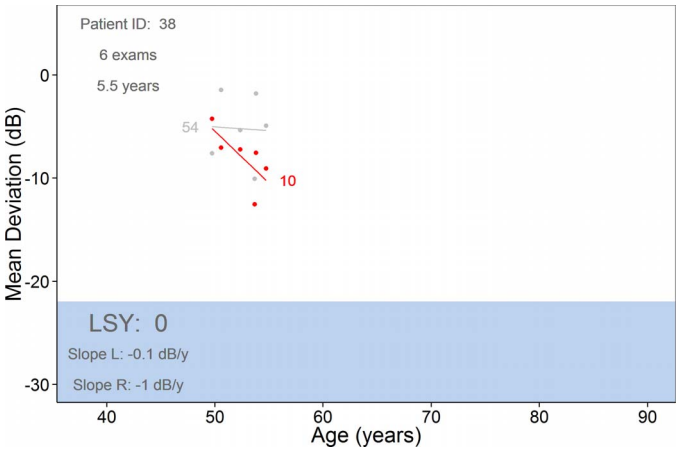

Figure 4. Patient 38 has rapid visual progression in one eye shown in *red* (ranked 10th within this clinic). However, the second eye, shown in *gray*, is progressing slowly (ranked 54th within this clinic), so this patient has a LSY of 0 years.

years). In Figure 6, a younger patient is shown, aged 55 years at the most recent VF examination. This patient has relatively slowly progressing eyes (ranked 23rd and 46th, respectively) but considerable VF damage at diagnosis (worse that −12 dB). This patient is predicted to suffer from binocular VF impairment for 10 years within their expected lifetime. So, this patient might be highlighted to warrant more careful monitoring (more frequent VFs), or intensified treatment.

To compare RP and LSY, we flagged patients as "priority cases" if RP in their better eye was worse than a certain threshold or they were predicted to have LSY > 0. In Figure 7, the individuals flagged according to RP in their best eye are shown in purple.

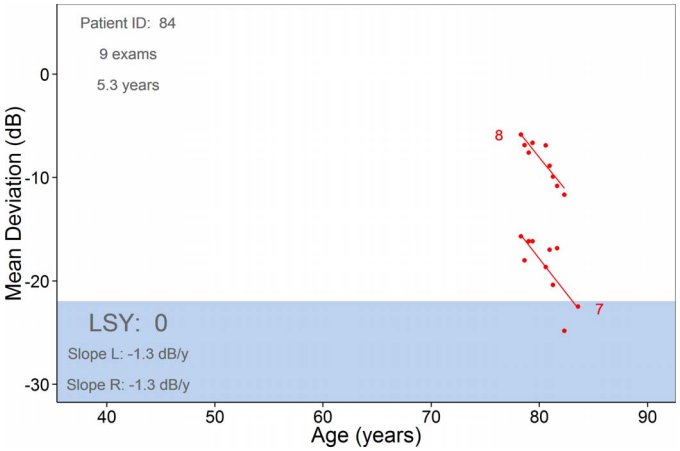

Figure 5. Patient 84 has rapid visual progression in both eyes (ranked seventh and eighth worst eyes within this clinic). However, this patient has a LSY of 0 years.

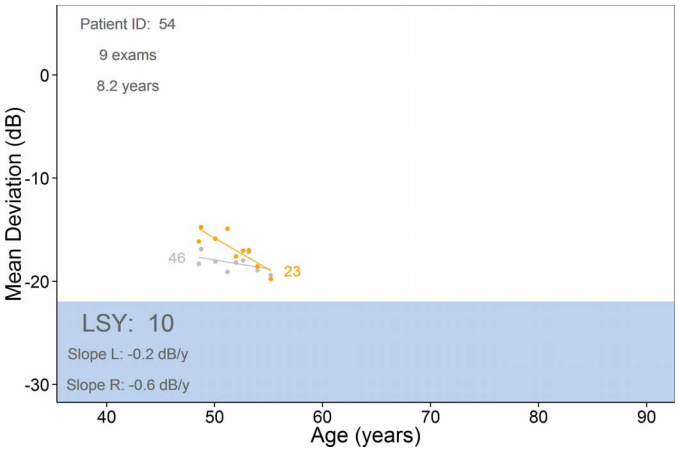

Figure 6. Patient 54 has relatively slowly/moderately progressing eyes (ranked 23rd and 46th, respectively), but considerable visual field damage at diagnosis (worse than −12 dB); the patient is relatively young. This patient is predicted to have bilateral blindness for 10 years within their expected lifetime. So, this patient might be highlighted to warrant more careful monitoring (more frequent VFs), or intensified treatment, to prevent loss of sight.

Figures 7A and 7B highlight individuals flagged based on varying thresholds for the RP (A, < −1 dB/y; B, < −0.5 dB/y). Individuals with a LSY > 0 are shown in cyan. The patients flagged by both parameters are shown in black. (Note, for clarity only the "best eye" per patient is shown as if this eye falls below −22 dB the patient would be considered to have binocular VF impairment.)

To summarize the results from Figure 7, four patients (4%) were identified as being "priority" when a threshold of worse than −1 dB/y was set for the better eye but only two of these (50%) had a LSY > 0. Fourteen (14%) patients were identified as being "priority" when a threshold of worse than −0.5 dB/y was set for the better eye, but only four of these (29%) had a LSY > 0. This showed that the two parameters give different information.

There were differences in the baseline ages and MD at presentation in patients flagged by RP using a threshold of <−1 dB/y and LSY. Mean (SD) age for the individuals flagged as a "priority case" based on RP and on LSY was 76 (7) and 64 (14) years, respectively. Mean baseline MDs were −4.0 dB (3.1 dB) and −10.4 dB (8.9 dB) for individuals flagged based on the RP and LSY, respectively. LSY, therefore, highlights younger patients or patients with more severe damage at presentation.

A purpose written interactive application demonstrating the techniques is available in the public

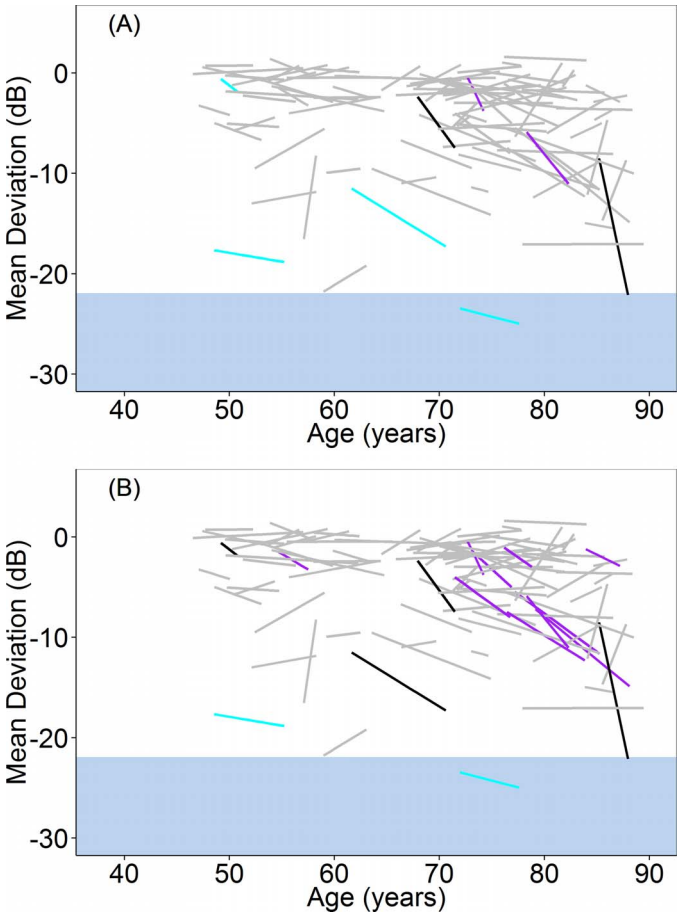

Figure 7. Regression lines with age on the *x*-axis with patients with LSY > 0 highlighted in *cyan*, progressors highlighted in *purple*, and the overlap between the two parameters in *black*. Varying limits for the RP are used: (A) <−1 dB/y, (B) <−0.5 dB/y.

domain at https://crabblab.shinyapps.io/hedgehog. This application contains the demonstration dataset used in this report. However, the application has been written to allow a user to import and analyze their own dataset using the application. A video (available in the public domain at https://youtu.be/zgzEOhfYf4w) as well as a document (available in the public domain at https://crabblab.shinyapps.io/hedgehog README) explaining the results and how to import the data also is provided. In this instance we have not recommended inclusion and exclusion criteria for VFs but prudent use would consider VF reliability indices, for example. This application is intended for informational, educational, and research purposes only. It is not, and is not intended, for use in the diagnosis of disease or other conditions. Health care providers should exercise their own independent clinical judgment when using the application in conjunction with patient care.

Discussion

Previous research from glaucoma clinics in England has suggested most patients get a similar "diet" of VF testing over time.[17] For example, average number of VF examinations over time has been similar for all patients, irrespective of age, severity of VF loss, and rate of MD loss.[17] This "one size fits all" approach to glaucoma follow-up for VF testing is likely suboptimal from a clinical[18] and health economic[19] perspective. Hedgehog Plots provide a potential novel tool for clinicians to visualize all their glaucoma patients simultaneously. Hedgehog Plots could be helpful in selecting patients who should be seen more or less frequently in follow-up, allowing for the prioritization of monitoring resources. In this study, we also present two parameters, RP and LSY. The former is not novel,[5,6] but it is an important concept for clinicians to incorporate into glaucoma management decisions. LSY is novel and we have shown that it offers complementary but different information to RP.

Key to this work and additional to this report is provision of a purpose written interactive application demonstrating the techniques. We hope this application stimulates design of similar software that could be used in clinics. After all, we know software helps provide a way to standardize clinical assessment and has been proven to improve the agreement between clinicians when making decisions about VF progression occurring.[20] Our application is also designed to allow clinicians to analyze data within their own clinics if MD data entry can be completed. Realistically our tool will only be widely adopted if a version is incorporated into clinically used software, like an electronic medical record (EMR) or in ophthalmic data management systems linked to perimeters. At that stage other design features, such as resetting the baseline of a VF series to times of significant changes in therapy in long-term follow-up, could be considered. Moreover, the software ought to be designed such that a clinician can easily exclude unreliable VF examinations or, for example, use published techniques for minimizing the effects of outlier observations.[21]

RP can be ranked for all patients in a clinic to help identify worse cases of VF progression without using inferential statistics. This allows for a comparison between individuals and the general clinical population rather than imposing an arbitrary cutoff based on a *P* value. Such ranking could be useful in

situations where decisions must be made about allocation of VF monitoring resources. For example, more frequent examinations may be allocated to someone with an observed fast rate of progression or a "priority case." Furthermore, a patient who seems to have rapid progression in their better eye would need more monitoring than a person who shows no progression in either eye. Further refinement can be achieved by using LSY. A specific example of this is given in Figure 4, where Patient 84 has rapid visual progression in both eyes (ranked the seventh and eighth worst eyes within this clinic). However, this patient was predicted to have a LSY of 0 years. Patient 54 had relatively slowly progressing eyes (ranked 23rd and 46th, respectively) but considerable VF damage at diagnosis (worse that −12 dB); the patient is relatively young. This patient is predicted to have bilateral blindness for 10 years within their expected lifetime. So, this patient might warrant more careful monitoring (more frequent VFs) or intensified treatment. In addition to the applications we have shown here, the Hedgehog Plot could be used as a tool to compare different clinics by using a large data set as a reference clinic.[10] This would allow clinicians to compare results of their own patients directly to those of others, or could be used for auditing purposes. Hedgehog Plots also might be useful for comparing the entire distribution of VF progression in different arms of a clinical trial.

We used an MD worse than −22 dB as a potential definition of visual impairment, but different cutoff values could be used. This threshold was based on the US SSA benchmark, which defines "statutory blindness" as both eyes reaching this cutoff value.[14] Other criteria, linked to ability to perform functional tasks could be used.[22–25] For example, individuals who reach a MD threshold of worse than −14 dB in both eyes are unlikely to satisfy the VF component for adequate vision to be legally fit to drive in the United Kingdom.[26] Of course this limit will vary by country depending on regulations. Further research in this area would be of interest.

In this study, we used MD measurements, which are well known and well understood by clinicians. The MD is only a summary measure of the VF and is a weighted average across the VF, relative to a group of healthy age-matched individuals. However, the individual VF points may be of greater interest, because of the additional information they provide, such as the spatial nature of VF loss. This information is otherwise lost in global parameters. Although we assume binocular VF impairment at −22 dB, the patient still may have some preserved visual function at this threshold. The remaining visual function may be significantly affected by the location of the VF damage.[27–29] For example, more centrally located progression would arguably affect the patient's quality of life more significantly than peripherally located progression. Additionally, if progression took place in matching locations in each eye, this local progression would likely affect the patient's visual function more significantly than where no such binocular defects existed.[8,30]

The assumption of a linear rate of progression in predicting VF loss is another limitation of this study. While this may not be representative of true glaucomatous VF deterioration, it is used commonly in clinical practice and has been shown to provide more robust estimates of future measurements than more complex models.[31,32] Furthermore, we assumed that the RP is constant throughout the patient's predicted remaining lifetime. This may underestimate true deterioration. It also does not take into account future amelioration of progression by intensified treatment. For example, a glaucoma patient, possibly nonadherent or nonresponsive to treatment, may have a significant reduction in RP after intensified treatment.[33] In turn, this could affect their course to predicted significant LSY because RP and LSY are inherently linked. In this situation it might be prudent to consider a new baseline VF assessment. Conversely an eye that, for example, suffers ocular comorbidity or rapid vision loss due to cataract, even late in life, may result in a rapidly changing RP and unexpected LSY. Our tool, therefore, is limited because it does not solve these unchanging dilemmas of managing glaucoma. Yet, as a visualization tool, used in conjunction with other patient data, it still may offer the managing clinician useful information that may have remained unseen in a series of VF charts.

It also is important to note that our life expectancy data were determined using UK census data and will not be representative of populations in other countries. Furthermore, the clinic data we use were extracted from clinics across England. These may not be representative of different demographics and different health care systems. This should be taken into account particularly for interclinic comparisons.

Conclusions

In conclusion, this study demonstrated a new approach for assessing VF progression in clinics. Differences between selecting patients as "priority"

cases using RP and LSY emphasize the importance of choosing the appropriate criteria for summarizing progression. We illustrated these techniques with a novel visualization tool and provide an interactive application that can be used in clinical practice.

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