Simfield: A Computer Simulated Visual Field Test to Screen for Glaucoma

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Abstract: *Objective:* To evaluate the efficacy of a computer simulated visual field test (Simfield) as a screening tool for glaucoma.

Design/Participants/Methods: 36 glaucoma or glaucoma suspect patients (53 eyes) from one ophthalmology clinic between October 2013 and May 2014 used the Simfield program within six months of a reliable performance on a 24-2 SITA standard Humphrey Visual Field Analyzer Exam. The exam measured threshold values at the same 54 points as the 24-2 SITA standard software as well as false positives, false negatives, and fixation losses. Two glaucoma specialists and one general ophthalmologist analyzed the Simfield results in masked fashion and determined whether there was evidence of a glaucomatous defect in any of the 4 quadrants of each field. These results were compared to the corresponding HFA tests to determine sensitivity and specificity.

Results: The sensitivity of Simfield ranged from 51-76% and the specificity was 67-88%. In a subanalysis that eliminated mild defects, defined as defects in a field with mean deviation < 7.0, sensitivity improved to 75-91% and specificity was 69-91%. The average false positive rate was 5.2%, the average false negative rate was 3.7%, and the average fixation loss rate was 27.7%.

Conclusions: Simfield is an effective test for identifying moderate to severe glaucomatous visual field loss and can be accessed from any home computer. While the cost to detect glaucoma in one patient using current screening methods is estimated at $1000, Simfield can be used for free anywhere that a computer is available.

Keywords: Glaucoma screening, visual fields, Simfield, glaucoma, Humphrey.

1. INTRODUCTION

An estimated 60 million people worldwide have glaucoma, and that number will increase by 20 million in 2020. At that time, glaucoma will cause bilateral blindness in a projected 11.1 million people [1]. The most common form in North America, primary open angle glaucoma, has a prevalence of 2.6% and often goes undetected due to its slow progression and a lack of obvious symptoms [2]. Though effective treatments that slow the rate of vision loss are available, [3] fewer than 50% of patients in developed countries are aware of their condition [4]. Clearly a cost effective screening method is needed to make earlier diagnoses, before too much irreversible damage has taken place. Unfortunately, there is no current population screening method that is cost effective [5].

The current clinical standard for primary open angle glaucoma screening is evaluation by an ophthalmologist with examination of intraocular pressure, the optic disc and retinal nerve fiber layer, and visual fields *via* standard automated perimetry (SAP) [6]. Current recommendations are for patients with a combination of risk factors such as family history, black race, and advanced age to receive regular examinations by an ophthalmologist [2]. It is understood that this selective screening won't detect all cases of glaucoma, but it is the best option available.

Perhaps the most important part of the current screening process is the examination of the visual fields *via* SAP, which has been shown to detect the presence and stage of glaucoma *via* well-documented patterns of visual field loss [7-13]. Automated perimetry is generally performed on a Humphrey Visual Field Analyzer (HFA, Carl Zeiss Meditex, Dublin, CA) using the SITA standard 24-2 algorithm and measures the threshold value for 54 points in the central 24 degrees of the visual field. Though effective in detecting glaucomatous visual field loss, Gottelib's study found SAP to only be cost effective in the screening of very elderly people [14]. Frequency doubling technology, a newer version of SAP that takes only a minute, has shown some promise as a screening tool [15] but is not commonly used for population screening. Though cheaper than a HFA, it still requires use of a specific machine and cannot be done at home.

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Though some studies recommend tonometry as a screening tool [14, 16], the increasing prevalence of normal tension glaucoma and cost make it inadequate as a single screening test, and the lack of training with tonometry in generalist physicians makes it less feasible. One study reported the sensitivity of tonometry to be 47.1% [17]. Examination of the fundus with the ophthalmoscope, which generalist physicians do receive some training in, has also been shown to be relatively ineffective due to low sensitivity and inter-observer variability [2, 18]. Newer technologies which assess the optic nerve head and retinal nerve fiber layer can detect glaucoma but aren't ideal screening tools due to extremely high costs [19].

In 2005 researchers at USC developed a program called Peristat with sensitivity from 80-83% and specificity from 94-97% to detect scotomas [20]. This program is available as a screening tool online, though it hasn't become ubiquitous in the world of glaucoma screening. As computer use becomes more prevalent, home screening processes are becoming more and more realistic, and several other yet unpublished programs are being developed at various institutions. Our program, Simfield, was developed as a tool to reduce unreliability in visual field tests but has evolved into a program capable of detecting visual field loss. With features not seen in other programs, we hope that this program will be an effective tool for glaucoma screening that is more widely adopted by the general medical community.

2. MATERIALS AND METHODS

2.1. Sample Size Calculation

The intention of the study was to show that the sensitivity of Simfield is roughly equivalent to the sensitivity of the Humphrey Visual Field Analyzer. Blackwelder offers an equation appropriate for determining an appropriate sample size in such a situation with alpha of 0.05 and beta of 0.20 (power = 80%):

$$n= (Z_{0.95} + Z_{0.80})^2 [Ps(1-Ps) + Pn(1-Pn)] / (Ps-Pn-D)^2$$

In this equation, Ps is the sensitivity of the Humphrey Visual Field Analyzer, which we have set to be 1 as this is the clinical standard. Pn is the estimated sensitivity of Simfield, which we estimate to be 0.85 based on results of the Peristat study [15]. D is the difference that we are willing to tolerate between the sensitivities, which we set to 0.21 as a sensitivity of 79% would make Simfield a good option as an inexpensive screening tool. With these calculations n = 372 per group. Since each eye was evaluated in all 4 quadrants of the visual field and performs a Simfield exam and a HFA exam, this required 47 eyes in the study.

2.2. Methods

36 patients (53 eyes) who were referred to the ophthalmology clinic at the Duchossois Center for Advanced Medicine were recruited for the study, which was approved by the institutional review board at the University of Chicago. Informed consent was obtained from all individual participants included in the study.

Inclusion criteria consisted of glaucoma or glaucoma suspect patients who had performed reliably on a 24-2 SITA standard HFA exam within the previous 6 months. Reliability was defined as having the two most recent HFA exams with absolute value of the difference in mean deviation ≤ 1 and fixation losses, false positives, and false negatives all < 15%. Patients with corrected vision worse than 20/100 were excluded. Patients ranged from having no visual field defects to advanced glaucoma. Glaucoma suspects were most often referred to the clinic for a suspicious optic nerve or elevated intraocular pressure.

After oral and written consent were obtained, subjects were taken into a dark exam room in our ophthalmology clinic. After placing a patch on the subject's left eye and having them put on their reading glasses, the test administrator measured 30cm from the 19 inch screen and instructed the subjects to place their right eye at that point, lined up with the central focus point on the screen. A stimulus was presented in the blind spot and if the subject was not able to see it they could begin the test. If they could see the stimulus, the distance from the screen to the subject was measured again and if accurate the blind spot could be adjusted using the arrow keys until the true blind spot was determined. Subjects were told to focus on the orange light and to press the spacebar whenever they saw a light flash on the screen. A sound accompanied the pressing of the spacebar to verify that they had pressed it correctly. When the program instructed them that the exam was complete, the process was repeated on the other eye.

Simfield measures the same 54 points in the visual field as the 24-2 SITA standard software. After inputting the screen size and resolution in the control panel, the program projects stimuli with a diameter of 2.26 mm. The stimuli are spaced at 6° intervals on the x and y

axes, with the 4 central stimuli constituting the points of a square around the central focus point at a distance of 3° from the center. The background color has an RGB value of 30, and the 5 different intensity values have RGB values that range from 39 to 255 RGB with a differential in light intensity from 23 to 320cd/m^2. Each stimulus is presented for 200 milliseconds and the time between stimuli varies randomly between 1 and 2.25 seconds. The response times are calculated for 50 responses and a variance is calculated for the square root of those times. Each point is removed and if the variance changes by more than 1, the point is considered a false positive and is retested. All response times less than 180 ms are also considered false positives and are eliminated and not retested. Stimuli that are more intense than a stimulus that was previously detected in the same location are used to test false negative rate. Stimuli presented at the previously confirmed blind spot are used to test fixation loss. Variance, RGB values, stimulus duration, and minimum and maximum stimulus delay can be altered in the control panel.

The algorithm is modeled as closely as possible to the 24-2 SITA standard software. Initially, 4 points located 9° from center, one from each quadrant, are tested at various intensities to determine a baseline value for each quadrant. Then points are tested randomly at the baseline value for their quadrant, and the intensity is altered based on the subject's results until a threshold value is determined. These threshold values (0-5) are then reported in a figure that resembles the figure in the results of SAP with areas of greater field loss appearing in a darker color (see Figure **1**).

To determine the sensitivity and specificity of the program, we compared its ability to detect a scotoma vs the clinical standard 24-2 SITA SAP test on the HFA. On the HFA, a scotoma was defined as a pattern typical of glaucoma in a field with five or more points of $p < 5\%$, with a cluster of three or more abnormal points of $p < 5\%$, or two or more points of $p < 1\%$ [21]. On Simfield, the definition of a scotoma was left up to three different ophthalmologists, who each analyzed the results to determine if the patterns were indeed typical

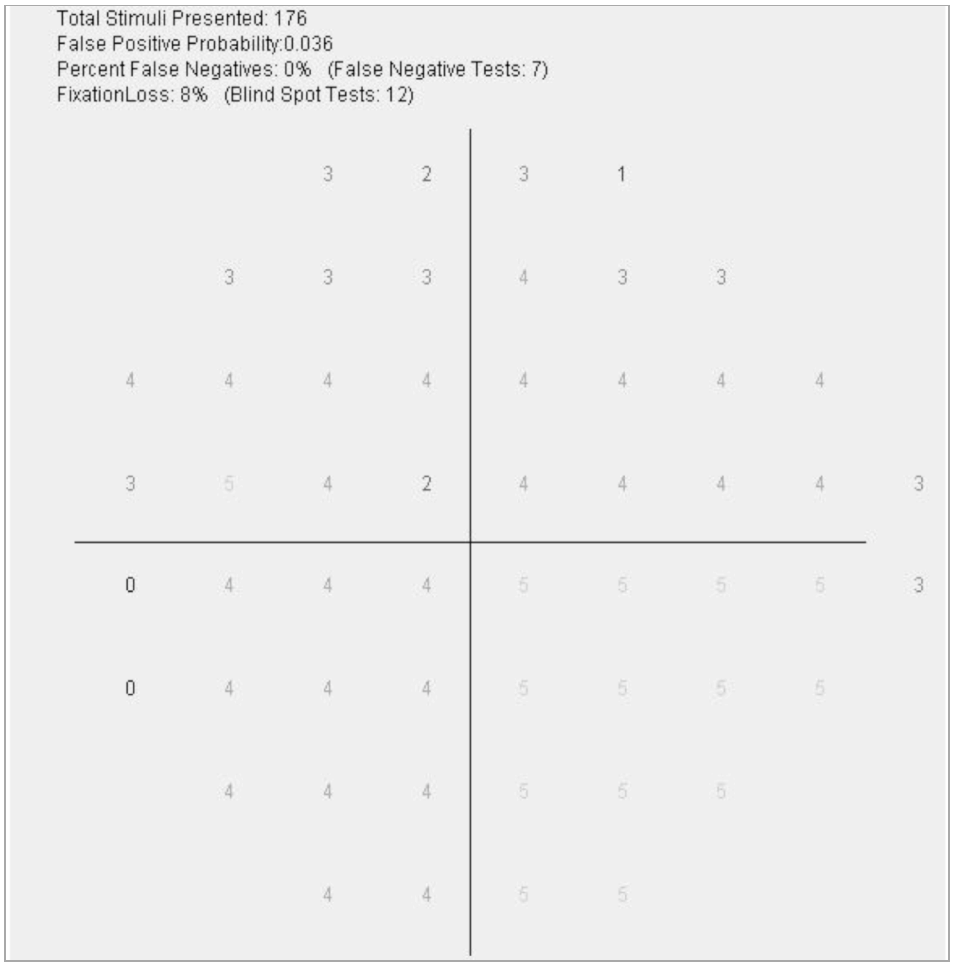

Figure 1: Sample Simfield result, showing the threshold value at 54 different points as well as false positive probability, false negative percentage, and fixation loss rate.

of glaucoma and decided whether scotomas were present. Each set of results was divided into 4 quadrants and the physicians marked yes or no for whether there was a defect in each quadrant analyzed. A scotoma detected on the HFA but not on Simfield was considered a false negative while a scotoma detected on Simfield but not the HFA was considered a false positive.

Study data were collected and managed using REDCap electronic data capture tools hosted at University of Chicago [22]. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies.

3. RESULTS

The mean age of patients in the study was 71.5 (SD = 11.65) with 18 males and 18 females. Other patient demographics are displayed in Table **1**. Patients were recruited between October 2013 and May 2014. 20% (11) of the Humphrey visual fields had no defect, 53% (28) had a mild defect, 13% (7) had a moderate defect, and 13% (7) had an advanced defect. The sensitivity varied between the three reviewers from 51-76% with a mean of 63%, and the specificity ranged from 67-88% with a mean of 78% (Figure **2**). A sub analysis which removed mild defects, defined as defects in fields with mean deviation < 7, increased the sensitivity to 84% with a specificity of 77%. This analysis included 162 of the original 212 quadrants. Figure **3** displays the combined results of all three reviewers and includes the sub analysis. The mean false positive rate was 5.2%, and the mean false negative rate was 3.7%. The mean fixation loss rate was 27.7%. The mean test duration of the Simfield exam was 6 minutes.

Table 1: Patient Demographics (n = 53)

Mean Age	71.5 (SD = 11.65)
Gender	50% male, 50% female
Mean Best Corrected Visual Acuity	20/30
Mean Days Since Last Visual Field Test	98 (SD = 58)

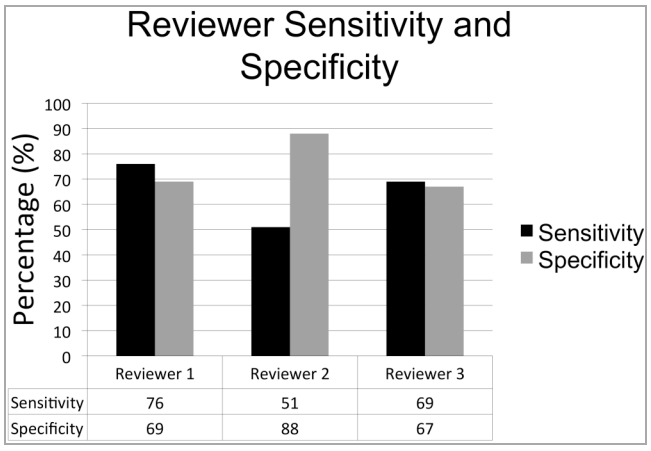

Figure 2: Sensitivity and specificity of Simfield as determined by 3 masked reviewers.

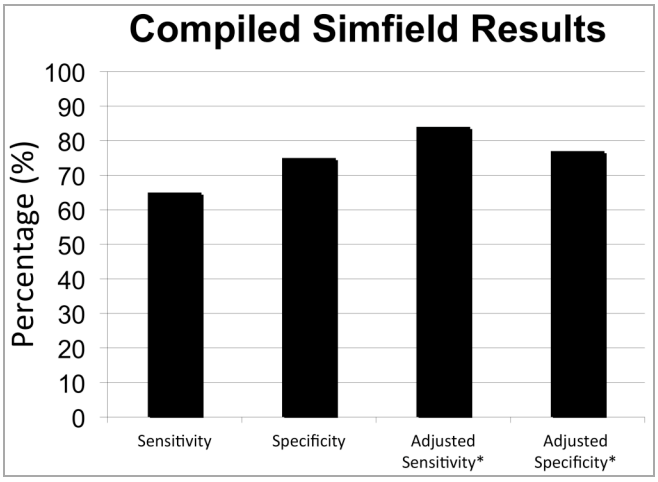

Figure 3: Compiled Simfield results, including adjusted sensitivity and specificity. *Mild defects, defined as defects in a field with mean deviation < 7.0, were not included in adjusted sensitivity and specificity calculations.

4. DISCUSSION

Our study shows a moderate degree of correlation between the results on a Simfield exam and on the clinical standard HFA exam. When considering only moderate or severe defects, Simfield is a reliable way to detect glaucomatous defects and has better sensitivity (84%) and specificity (77%) than any other widely used screening method. An ideal screening tool will detect mild defects, however early detection is challenging even with the clinical standard HFA and there are several patients with undetected moderate disease due to lack of a cost effective screening tool.

One feature seen in Simfield that is not available in Peristat is a customization of screen size and resolution, which ensures that appropriately sized stimuli will appear in the correct locations on any screen that is at least 15 inches. Also, rather than using the older style of presenting catch trials to look for false positives, we incorporated the newer method which uses response time windows and has been shown to reduce both test time and test-retest variability [23]. Finally, the control panel allows for greater control in cases where Simfield is used for research purposes.

A key challenge with Simfield is fixation loss. At a mean of 27%, many of the Simfield results would have been considered unreliable on the HFA. The apparatus used to hold the head in place on the HFA is an ideal way to avoid fixation loss but isn't a realistic option for a program designed to be used on home computers. Our group is currently working on applying Simfield to an inexpensive head-mounted device to resolve this issue.

There was also a great deal of variation on results between the 3 reviewers. While one had a sensitivity of 76% with a specificity of 69%, another had a sensitivity of 51% and a specificity of 88%. Before doing their analyses of the results, each reviewer was shown 3 random Simfield results and their corresponding HFA results. Studying all of our data would likely make a reviewer much more accurate at interpreting Simfield data as there is likely a learning curve in interpreting the results. With only 3 examples to look at, it was difficult for reviewers to develop a system and it is clear from the results that each one used a slightly different method. An objective definition of a socotoma on Simfield would improve inter-reviewer consistency, sensitivity, and specificity. We have since developed such a definition and have incorporated it into the latest version of Simfield.

Some of the differences in the results between Simfield and SAP can be accounted for by the inter-test variability that is an accepted imperfection in SAP results due to physiologic threshold fluctuation [24, 25]. Also, the fact that we allowed up to 6 months between the previous SAP exam and the Simfield exam means that glaucoma progression may have occurred in some patients.

Other variability can be accounted for by the fact that patients were allowed to use their own glasses, which may have varied in shape and size. Additionally, Simfield uses a computer screen. The HFA has curved sides to test peripheral points, which we were unable to emulate on a flat computer screen. This problem will also be addressed by the head-mounted device. Similarly, the computer screen wasn't able to produce stimuli that were as bright as the stimuli produced on the HFA. We overcame this shortcoming by using a darker background. The additional contrast allowed patients to see stimuli that they couldn't have seen had we used the white background of the HFA. Future efforts to compare results from different computer screens may be challenging as each display monitor may have different dynamic ranges and gamma functions.

While there are some issues involved in the use of a computer screen, we feel that the benefits outweigh the shortcomings. The primary advantage is in reducing cost. Considering the estimated costs of $60 per patient screened for glaucoma and $1000 for each case of detected glaucoma [20], an effective computer based screening technique makes population based screening much more feasible. We will continue to improve the program and hope that physicians will begin to use this resource to screen for glaucoma.

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COMPLIANCE WITH ETHICAL STANDARDS

No financial disclosures were reported by any of the authors of this paper. This study was approved by the institutional review board at the University of Chicago and all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later ammendments or comparable ethical standards.

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