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Predicting Development of Glaucomatous Visual Field Conversion Using Baseline Fourier-Domain Optical Coherence Tomography

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Abstract

Purpose—To predict the development of glaucomatous visual field (VF) defects using Fourier-domain optical coherence tomography (FD-OCT) measurements at baseline visit.

Design—Multi-center longitudinal observational study. Glaucoma suspects and pre-perimetric glaucoma participants in the Advanced Imaging for Glaucoma Study.

Methods—The optic disc, the peripapillary retinal nerve fiber layer (NFL), and macular ganglion cell complex (GCC) were imaged with FD-OCT VF was assessed every 6 months. Conversion to perimetric glaucoma was defined by VF pattern standard deviation (PSD) or glaucoma hemifield test (GHT) outside normal limits on 3 consecutive tests. Hazard ratios were calculated with the Cox proportional hazard model. Predictive accuracy was measured by the area under the receiver-operating-characteristic curve (AUC).

Results—Of 513 eyes (309 participants), 55 eyes (46 participants) experienced VF conversion during 41 ± 23 months of follow-up. Significant ($p < 0.05$, Cox regression) FD-OCT risk factors included all GCC, NFL, and disc variables, except for horizontal cup-to-disc ratio. GCC focal loss volume (FLV) was the best single predictor of conversion (AUC=0.753, $p < 0.001$ for test against

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Dr. Huang and Dr. Tan have a significant financial interest in Carl Zeiss Meditec, Inc (Dublin, CA). Oregon Health & Science University (OHSU, Portland, OR), Dr. Huang and Dr. Tan have a significant financial interest in Optovue, Inc. (Fremont, CA), a company that may have a commercial interest in the results of this research and technology. These potential conflicts of interest have been reviewed and managed by OHSU. Dr. Huang and Dr. Schuman receive royalties for an optical coherence tomography patent owned and licensed by the Massachusetts Institute of Technology (Cambridge, MA) and Massachusetts Eye & Ear Infirmary to Carl Zeiss Meditec, Inc. Dr. Greenfield receives research support from Optovue, Inc., Carl Zeiss Meditec, Inc., and Heidelberg Engineering (Carlsbad, CA). Dr. Varma has received research grants, honoraria and/or travel support from Carl Zeiss Meditec, Inc., Heidelberg Engineering, and Optovue, Inc. Dr. Zhang and Dr. Loewen have no financial interest.

AUC = 0.5). Those with borderline or abnormal GCC-FLV had a 4-fold increase in conversion risk after 6 years (Kaplan-Meier). Optimal prediction of conversion was obtained using the glaucoma composite conversion index (GCCCI) based on a multivariate Cox regression model that included GCC-FLV, inferior NFL quadrant thickness, age, and VF PSD. GCCCI significantly improved predictive accuracy (AUC=0.783) over any single variable ($p=0.04$).

Conclusions—Reductions in NFL and GCC thickness can predict the development of glaucomatous VF loss in glaucoma suspects and pre-perimetric glaucoma patients.

Introduction

A fundamental challenge with glaucoma suspects is to estimate glaucoma progression risks and to intervene before significant damage to vision occurs. The appearance of risk factors on initial presentation can vary greatly. For instance, an individual with ocular hypertension may have a normal appearing disc while another patient might have an abnormal high cup-disc ratio (CDR) but a low to normal intraocular pressure (IOP). Several studies have tried to identify and combine anatomic, visual field (VF) and epidemiological variables to create a risk calculator. Investigators in the Ocular Hypertension Treatment Study (OHTS) ¹ and in OHTS validation studies^{2,3} developed a formula that tries to predict the onset of primary open angle glaucoma (POAG) using a number of standard glaucoma variables: IOP, central corneal thickness (CCT), CDR, and VF indices. Although this formula summarizes standard clinical observations, the accuracy of predicting glaucoma conversion, i.e., development of definitive glaucomatous damage in a suspect, was only fair, with the area under the receiver-operating curve (AUC) of 0.68, according to an independent study.² The accuracy of the OHTS calculator is limited by the variability of component variables, especially IOP, VF and the CDR derived from subjective clinician grading. Song et al found that within the same individual, the estimated risk can vary almost 10-fold. ⁴

Using digital imaging-derived variables to predict glaucoma conversion may provide greater accuracy due to their objective and automated nature. Imaging also requires less sustained attentiveness from the test subject, a consideration that is especially relevant in the older age group affected by glaucoma.^{1,5} In this study, we investigate the use of Fourier-Domain optical coherence tomography (FD-OCT) anatomic measurements to predict the development of glaucomatous VF damage.

Methods

Participants

The data used for the study was taken from participants enrolled in the Advanced Imaging for Glaucoma (AIG) Study, a multi-site bioengineering partnership and longitudinal prospective clinical study sponsored by the National Eye Institute (ClinicalTrials.gov identifier: NCT01314326). The study design and baseline participant characteristics have been published in a separate paper,⁶ and the Manual of Procedures is available online (www.AIGStudy.net). Clinical data for the AIG Study was collected from three clinical centers, including the Doheny Eye Institute then at the University of Southern California (Now at University of California, Los Angeles), the University of Pittsburgh Medical

Center, and Bascom Palmer Eye Institute at the University of Miami. The study procedures adhered to the Declaration of Helsinki that guides studies involving human subjects. Written consent was obtained from all of the participants and proper institutional review board approvals were obtained from all of the participating institutions.

One of the specific aims of the study was to predict conversion in glaucoma suspect and pre-perimetric glaucoma (GSPPG) eyes. The eyes categorized as glaucoma suspect (GS) do not have abnormal VF pattern standard deviation (PSD) or glaucoma hemifield test (GHT), and either ocular hypertension (IOP ≥ 22 mmHg) or the fellow eye had perimetric glaucoma. Pre-perimetric glaucoma (PPG) eyes do not have abnormal VF PSD or GHT, but have a glaucomatous appearance of the disc or NFL on dilated ophthalmoscopy defined as vertical cup-disc asymmetry greater than 0.2, notch or thinning of the neuroretinal rim, optic disc hemorrhage, or NFL defect. GS and PPG participants were seen every 6 months and received a comprehensive eye exam, VF tests, and imaging using FD-OCT that was included in the AIG Study as a standard imaging procedure in 2006. Cataract patients were not excluded from the AIG study. Details about inclusion and exclusion criteria are available online (www.AIGStudy.net). The VF tests were done on Standard Automated Perimetry and repeated at least twice to get a reliable reading.

Optical coherence tomography imaging

Three anatomic regions - the optic disc, peripapillary nerve fiber layer (NFL), and macular ganglion cell complex (GCC) - were imaged and measured by FD-OCT (RTVue, Optovue, Inc., Fremont, CA, USA). During each visit, participants had three GCC and optic nerve head (ONH) scans. Only ONH scans with a signal strength index (SSI) above 37 and GCC scans above 42 were selected for analysis. Measurements in qualified scans in the same visit were averaged.

The macular GCC scan covered a 7 by 7 mm square area in the macula. Scans were centered 0.75 mm temporal to the fovea to improve the coverage of the temporal macula. The macular GCC thickness was defined as the combination of NFL, GCL, and inner plexiform layer.⁷ The automated Optovue software derived a 6 mm diameter GCC thickness map centered 0.75 mm temporal to fovea.

The ONH scans consisted of concentric (1.3–4.9 mm diameter) scans and radial scans (3.4 mm length) centered on the optic disc and automatically registered with the 3D disc scan to provide the disc margin information. The NFL thickness profile at D=3.4 mm was resampled on the NFL map recentered according to detected optic disc center. The radial scans were segmented to calculate the CDRs and optic disc rim area.

The RTVue software (version 6.12) was used to provide the following OCT image-derived measurements: (1) the overall, superior, and inferior hemisphere averages of the GCC thickness map; (2) the overall, superior, and inferior quadrant averages of the NFL thickness profiles; (3) CDRs and rim area; and (4) the pattern analysis of the GCC thickness map. In pattern analysis, the global loss volume (GLV) was used to measure a pattern of diffuse loss, whereas the focal loss volume (FLV) was used to measure more focal losses.⁷ Pattern analysis was also applied to the NFL using custom software by coauthor Ou Tan. The NFL

pattern analysis is analogous to the RTVue GCC pattern analysis, but based on the NFL profile instead of the GCC map.⁸

Glaucoma Conversion Event

The primary outcome event for participants in the GSPPG group was conversion to a confirmed abnormal VF, where PSD became abnormal ($P < 5\%$) or GHT fell outside of normal limits on 3 consecutive tests. This required minimum of 4 total visits including the baseline visit, equivalent to minimum of 1.5 years in follow-up time. Confirmation of VF conversion also required the clinical investigator to review the most recent eye examinations and determine that the VF change was likely due to glaucoma rather than confounding conditions such as cataract, macular disease, or other non-glaucomatous conditions. The conversion time was defined at the time of final confirmation.

Statistical Analysis

All statistical analyses were performed by SAS 9.3 (SAS Institute, Cary, NC, USA). The primary analysis used Cox regression⁹ which is suitable for time-to-event data. The participants had to have at least three follow-up visits to be eligible for inclusion in the analysis. For each of the covariates in the analysis, we provided a hazard ratio (HR) estimate and the corresponding p-value. We also provided the AUC for the covariate to compare its relative predictive power in glaucomatous conversion.

For each of the FD-OCT measurements such as GCC overall thickness, borderline and abnormal categories were defined against normal values. Such categories are shown in yellow (borderline), red (abnormal), and green (normal) on the printout from the Optovue device. These categories were determined by cutoff values based on the proprietary database maintained by Optovue, Inc. Typically “borderline” represents values between 1–5 percentile of the normal population, and “abnormal” represents values below the 1 percentile cutoff.

For categorical covariates, Kaplan-Meier survival curves were produced, and log-rank tests were used to compare risks among categories. We also provided HRs for IOP analysis, which unlike other covariates, were recorded at baseline visit. Four of the five IOP covariates were summaries from the baseline to the time of the conversion event or censoring (described below), including average, peak, range and variation. It should be noted that the IOP were measured from a mix of treated and untreated eyes, according to the decision of the patient and treating physician, as the treatment regimen is not mandated or randomized in the AIG Study.

Because many participants had both eyes enrolled in this study, we used a robust sandwich covariance estimation method in the Cox regression to adjust for this potential correlation.¹⁰ For other analyses, the generalized estimating equations method¹¹ was used when applicable to adjust for inter-eye correlation.

All of the potential covariates were evaluated to build an optimal multivariate Cox regression model through a combination of manual elimination and automatic stepwise selection processes. When the optimal combination of the covariates was determined, the

linear form was transformed through a logistic function. The resulting value, which ranged from 0 to 1, was defined as the glaucoma composite conversion index (GCCCI). Values closer to 1 implied a higher risk of conversion. To avoid overestimate prediction accuracy of the GCCCI, leave-one-out-cross-validation (LOOCV) was used to calculate the AUC for GCCCI.

All statistical analyses were performed with SAS 9.3 software package (Cary, NC, USA). The level of significance was set at $p < 0.05$.

Results

Among the GSPPG group consisting of 664 eyes from 394 participants, 513 eyes of 305 participants were included in the analysis while 151 eyes from 89 participants were excluded due to less than three follow-up visits. In 21 participants, data following glaucoma surgeries were censored, while data preceding the surgeries were used. These surgeries included trabeculectomy, laser trabeculoplasty, glaucoma drainage device implantation, or laser iridotomy. After 41 ± 23 months of follow-up, 55 eyes from 46 participants experienced VF conversion.

The Venn diagram (Figure 1) details the distribution of PPG and perimetric glaucoma (PG) participants based on enrollment criteria. Notably, the cohort had a majority of PPG ($n = 359$, 70%). Most GS participants ($n = 154$) had ocular hypertension with a small fraction having PG in the fellow eye.

Table 1 summarizes the demographic characteristics of the cohort. Glaucomatous converters were significantly more likely to be female and to be treated with topical glaucoma medication. Older age was a risk factor of borderline significance. Race, systemic hypertension, diabetes, and family history of glaucoma were not significantly associated with conversion. Univariate Cox analysis also showed that these covariates were not significant risk factors.

Table 2 describes ocular characteristics. Univariate Cox regression analysis showed that female gender ($HR = 2.0$, $p = 0.04$) was a significant risk factor. CCT and axial length were similar in converters and non-converters. There were also no differences between IOP averages and peaks of either group, but participants who converted had a wider IOP range and variation. Visual field stage, mean deviation (MD), PSD, and visual field index (VFI) were worse in participants who converted. Except for horizontal CDR, all FD-OCT variables under study were significantly worse among converters.

Among the continuous baseline clinical variables (Table 3), age and VFI were significant risk factors. Baseline IOP and CCT were not significant risk factors. Judging by the AUC, the VFI was the strongest non-OCT baseline predictive factor.

All FD-OCT variables were significant predictive factors except horizontal CDR and Among disc variables, vertical CDR had the highest predictive value by AUC, while among NFL variables, overall average, GLV, and FLV were the strongest predictors. All GCC variables were strong predictors except the superior hemispheric average. The strongest single predictive variable was the GCC-FLV.

Clinicians often rely on the classification of OCT variables such as “normal”, “borderline”, and “abnormal” using the criteria based on the manufacturer-supplied normative reference. The FD-OCT manufacturer (Optovue) provides normative classification for most GCC and NFL variables, but not disc variables. Supplemental Table 1 analyzes the conversion risk associated with the normative classifications of the key GCC and NFL variables. Among all GSPPG eyes analyzed, 42.6% had at least one abnormal or borderline FD-OCT variable at baseline. Of those eyes, 16.7% experienced VF conversion, at 23 ± 17 (mean $\pm$ SD) months of follow-up. In comparison, only 3.1% of those with normal FD-OCT measurements at baseline had VF conversion.

When we analyzed all eyes that converted, 70.9% of those had an abnormal or borderline FD-OCT variable at baseline visit, and 81.8% had an abnormal or borderline FD-OCT variable at the time of conversion

Consistent with the analysis of the continuous variables above, GCC-FLV was again the most predictive of the FD-OCT variables. A borderline GCC-FLV classification raised the conversion risk 3.8 fold, while an abnormal classification raised the risk 5 fold in the univariate Cox regression model. Based on Kaplan-Meier survival curves, eyes with borderline or abnormal reading in GCC-FLV at baseline had almost 4 times as much risk after 6 years compared to those with normal GCC-FLV at baseline (Figure 2). A borderline or abnormal GCC-FLV predicted conversion during the AIG study period with a sensitivity of 40% and a specificity of 88.4% with an overall accuracy of 83.2%. The positive predictive value (PPV) was 29.3% and the negative predictive value (NPV) was 92.5%.

Of all eyes that converted, 40.0% of those had an abnormal or borderline GCC-FLV at the baseline visit, and 50.9% had an abnormal or borderline GCC-FLV at the time of conversion. In contrast, of eyes that did not convert, only 11.6% had an abnormal or borderline GCC-FLV reading at baseline and 14.7% had an abnormal or borderline GCC-FLV at the last follow-up.

Since clinical glaucoma management is based on using all available diagnostic information, we combined the available demographic, clinical, and FD-OCT continuous variables together to construct the Glaucoma Composite Conversion Index (GCCCI). First, baseline covariates with univariate Cox regression HRs at a significance level of $p < 0.1$ were included: age, gender, ophthalmoscopic rim/NFL defect, MD, PSD, VFI, and all of the FD-OCT measures (Table 3) except for horizontal CDR. Next, these candidate covariates were run through an automatic stepwise selection/elimination process, where the p-value for elimination was set at 0.05. The final components that made up the GCCCI included VF PSD, age, inferior NFL, and GCC-FLV. The components were then added together with the optimized weight coefficients (Table 4) to produce the composite index with a value ranging from 0 to 1. The GCCCI AUC of 0.783 performed marginally better ($p = 0.04$) than the best performed single variable, including GCC-FLV, which had an AUC of 0.753 ($p < 0.001$ for test against AUC = 0.5, Table 3). We applied exact same model selection procedure on all available candidate variables except for the OCT variables, the resulting model included baseline age, PSD and MD, with AUC = 0.708. Finally we applied the procedure on OCT variables only, the resulting model under this selection included only GCC-FLV and inferior

NFL, with AUC = 0.760. Both models from the sub-selection provided less AUC than the model from full-selection.

Using the Cox regression model, the probability of VF conversion could be predicted as a function of time and GCCI (Figure 3). Eyes with GCCI below 0.6 had low conversion risk (<5%) while those with a GCCI above 0.8 had high conversion risk (>80%) after 6 years of follow-up. We also looked at the actual conversion rate among the GSPPG eyes analyzed and found that GCCI was highly predictive (Table 5). The eye with the lower half of GCCI values (<0.72) had less than 4.4% conversion rate, while those with the highest quartile of GCCI values (>0.84) had a highly elevated conversion risk of 29.7% during the AIG study period. Using a value of 0.84 as the cutoff for the entire GSPPG group, GCCI predicted VF conversion with a sensitivity of 60% and a specificity of 83%, with an overall accuracy of 80.5%. The PPV was 29.7% and the NPV was 94.5%. Using the same cutoff, for the PPG subgroup, the GCCI had sensitivity of 58% and specificity of 80.7%, with an overall accuracy of 78%; for the GS subgroup, the GCCI had sensitivity of 66.7% and specificity of 88%, with an overall accuracy of 86.4%.

Discussion

The management of glaucoma in the early stages presents a dilemma. On the one hand, it is desirable to start treatment early to prevent irreversible damage to the optic nerve and visual disability. On the other hand, all treatment options have significant cost and side effects which are best avoided in patients who do not have glaucoma or have such a slowly progressive disease that debilitating VF loss is highly unlikely within their lifetime. To offer greater ease and consistency in the management of glaucoma suspect participants, risk calculators have been developed that include anatomical, epidemiological, and functional data. The most established risk calculator is based on data from the OHTS and the European Glaucoma Prevention study.³ It includes the IOP, CCT, age, CDR, and VF PSD. The OHTS-derived model has been tested in an independent study population.² The AUC ranged from 0.68 to 0.73, indicating a moderate predictive value. One of the challenges of using the OHTS risk model is that there is considerable variability in the measurement of its component variables. IOP, vertical CDR, VF PSD, and even CCT⁴ can all differ significantly in the same individual between visits and when assessed by different examiners and instrumentation. As a result, the estimated 5-year risk of glaucoma conversion can vary up to 10 times between follow-up visits.⁴ Therefore, it is desirable to assess conversion risk using FD-OCT, which offers relatively reproducible anatomic measurements. Various studies put the NFL reproducibility in term of coefficient variation at 1.5–4%¹² and GCC at 0.4% - 2.8%.^{13,14} In the normal participants of the AIG Study, the reproducibility, measured as the coefficient of variation, for overall average thickness was 2.1% for NFL and 1.5% for GCC (unpublished data).

Our study did show that many baseline OCT anatomic measurements had a significant predictive value ($p < 0.001$ for testing against AUC = 0.5). While there were participants with an abnormal OCT who did not convert during follow up, GSPPG eyes with a borderline or abnormal FD-OCT finding in the listed NFL or GCC variables had 5 times the chance of conversion of those with all normal FD-OCT findings. In general, the macular GCC

variables were the most reliable predictors, with the GCC-FLV being the most reliable of all. The AUC of the GCC-FLV was 0.753, which by itself was higher than that of the OHTS risk calculator at 0.73.² By adding NFL information, age, and VF PSD in a Cox model, the GCCI had a marginally higher AUC of 0.783. We must caution, however, that no direct conclusion can be based on comparisons of the GCC-FLV and GCCI in the AIG Study with the results of the OHTS and other studies because of differences in the study design and participant population. Further studies that use both risk models and calculators are needed for a fair comparison of predictive accuracy. Another caveat is that, although the leave-one-out cross validation method was used, the GCCI was not developed and tested on entirely differently populations. It is possible that the performance may see variation on independent test groups.

A notable negative finding in the AIG Study was that the CCT, baseline IOP, and mean follow-up IOP were not significant risk factors. This is probably due to the fact that treatment was not randomized in our study and the clinicians made treatment decisions based on these known risk factors. The intensity of treatment might therefore have been influenced by insights gained in the OHTS. Therefore our study design does not allow us to make any conclusion on the predictive value of CCT or IOP. Therefore our results do not contradict the OHTS and other studies that confirmed the predictive values of CCT and IOP. A recent study highlighted the importance of lowering IOP even at the pre-perimetric stage by showing with linear regression analysis a significant negative association between the percent reduction in intraocular pressure and rate of change in standard automated perimetry mean deviation.¹⁵ We did find that IOP peak, range, and variation were predictors of conversion, which supports the finding of these same IOP indices as risk factors for VF progression in the Advanced Glaucoma Intervention Study.¹⁶ One reason that we did not mask IOP, VF, and CCT information information or randomize glaucoma treatment in the AIG Study was because these risk factors were already well established by OHTS, therefore denying the use of this information in patient management would have been unethical. It should be noted that the OCT measurements were masked to the clinical investigators/ treating physicians and patients during the AIG Study. Therefore we are able to make valid inferences on the predictive value of OCT variable without any direct confounding effect.

The reason that FD-OCT anatomic measurements were predictive of subsequent VF conversion is probably because the instrument was detecting early glaucoma damage that was at the cusp of being detectable on a VF test. In most patients, anatomic damage can be detected earlier than the appearance of VF defects.^{17,18} When objective, topographic optic disc measurements were obtained in participants of the OHTS validation study² using confocal scanning laser ophthalmoscopy, a larger CDR, cup depth and volume, and smaller rim area and rim volume were found to predict POAG with a PPV of 14% to 40% (NPV not given).¹⁹ In comparison, PPV and NPV in our study were 29.7% and 94.5%, using a GCCI cutoff value of 0.84. This cutoff value worked well for both the GS and PPG subgroups. Of the predicted VF conversions, FD-OCT findings (abnormal or borderline NFL or GCC) preceded by 23 months on the average. This is a significant period of time in which earlier treatment could have had an impact on the course of disease.

Of all predictors in our study, GCC-FLV was the most reliable by far. One possible explanation is that the focal structural loss may be a more reliable indication of early glaucoma damage than diffuse thinning, which is more likely to be a normal anatomic variant. This is consistent with a recent study by Mwanza et al in which the authors found that the minimal radial sector of focal macular loss can be a powerful approach to diagnose glaucoma²⁰ and with a glaucoma structural diagnostic index from the AIG Study, which also found GCC-FLV useful.⁸

Furthermore, the macular GCC is mapped over a wider area than the peripapillary NFL, which may allow for a more accurate detection of focal loss. In the AIG Study, VF conversion was defined by PSD or GHT but not by MD. The PSD and GHT indices are more sensitive to focal VF defects that may correspond better to macular structural loss measured by GCC-FLV. Finally, focal loss that involves the macula may be a common pattern of glaucoma damage and reflective of the increased vulnerability of the inferotemporal disc^{21,22} and inferior macula or superior visual field²³ respectively.

OCT results were masked to the treating clinicians during the study period, therefore the structural changes detected by OCT do not affect treatment decisions. Of course, optic disc cupping and rim defects, RNFL bundle defect, and disc hemorrhages that are ophthalmoscopically visible would affect treatment decisions since these standard clinical information cannot be ethically masked. To the extent these ophthalmoscopic evidences of glaucoma damage could be partially correlated with OCT evidence of damage, the predictive performance of OCT could be decreased. Therefore the hypothetical AUC values of OCT variables and composite indices could be higher in a hypothetical study where there is no treatment or if the treatments are randomized. This does not detract from the conclusion that OCT provides useful prognostic information.

Our finding that more than 70% of converters had abnormal or borderline GCC or NFL variables at baseline in contrast to non-converters suggests that the GCC and NFL defects often seen on FD-OCT scans may be true glaucomatous damage even in the absence of concurrent VF defects. We propose that OCT measurements, especially GCC-FLV, may be valuable surrogate endpoints in studying the benefit of treatments in preventing glaucomatous progression in the early stages of the disease. Using such OCT endpoints would address the need for better, standardized, and objective glaucoma testing that is less dependent on the examiner's experience and the participant's performance.

In conclusion, FD-OCT variables are useful to assess the risk of conversion to PG. Individuals who have abnormal or borderline OCT parameters, especially those affecting the macula, may require closer follow-up and initiation of treatment to avoid the vision loss. Combining anatomic and VF variables appears to be synergistic in the assessment of glaucoma conversion risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Biography

Dr. Xinbo Zhang received his PhD in Biostatistics in 2009 from University of Southern California. Since 2010, Dr. Zhang has been working at Oregon Health & Science University as a Research Assistant Professor. His research focus has been longitudinal trials in glaucoma, including researching statistical methodology to improve diagnosis and progression tracking of glaucoma.

Figure 1. Glaucoma Suspect and Pre-Perimetric Glaucoma Group Composition

The percentage in the parenthesis is the percentage of conversion, and the number in the parenthesis is the length of follow-up in months. Those with ophthalmoscopic optic nerve head/nerve fiber layer (ONH/NFL) defect (entire top circle) represents the pre-perimetric glaucoma (PPG) subgroup, while the remainder represents the glaucoma suspect (GS) subgroup. PG, perimetric glaucoma.

Figure 2. Kaplan-Meier Curves Stratified by Ganglion Cell Complex Focal Loss Volume
 GCC-FLV = macular ganglion cell complex focal loss volume status according to the OCT manufacturer's normative classification.

Figure 3. Visual Field Conversion Probability Curve Stratified by Glaucoma Composite Conversion Index
GCCCI = glaucoma composite conversion index (range 0 to 1).

Table 1

Demographic Summary of the Glaucoma Suspects and Pre-perimetric Glaucoma Participants in the Advanced Imaging for Glaucoma Study

	No Conversion	Conversion	
	N= 458	N= 55	p-value *
Age	61.0 ± 9.3	63.8 ± 8.5	0.058
Female	271 (59.2%)	41 (74.5%)	0.0027
African origin	55 (12.0%)	8 (14.5%)	0.82
Hispanic ethnicity	40 (8.7%)	6 (10.9%)	0.69
Systemic hypertension	128 (27.9%)	18 (32.7%)	0.46
Diabetes mellitus	28 (6.1%)	5 (9.1%)	0.4
Family history of glaucoma	215 (46.9%)	24 (43.6%)	0.19
Baseline Eye drops used: 0	314 (68.6%)	23 (41.8%)	<0.001
1	98 (21.4%)	27 (49.1%)	
2 or more	46 (10%)	5 (11%)	
Average number of Eye drops used	0.43 ± 0.72	0.67 ± 0.64	0.02

* p-values were calculated from chi-square tests, significance level set at 0.05

Table 2

Comparison of Ocular Characteristics between Participants with Visual Field Glaucoma Conversion and Participants with no Conversion

	No Conversion	Conversion	
	N= 458	N= 55	p-value
Anatomic Variables			
Central Corneal Thickness (μm)	557.11 ± 39.70	558.80 ± 36.30	0.860
Axial Length (mm)	24.19 ± 1.32	24.28 ± 1.52	0.946
IOP			
Ocular Hypertension (frequency)	154 (33.6%)	17 (30.9%)	0.57
Baseline IOP (mmHg)	16.10 ± 3.93	16.78 ± 4.35	0.0755
IOP Average (mmHg)	15.53 ± 3.30	15.32 ± 2.87	0.2226
IOP Peak (mmHg)	18.60 ± 4.55	19.71 ± 5.02	0.2106
IOP Range (mmHg)	5.72 ± 3.41	8.37 ± 5.23	0.0062
IOP Variation (mmHg)	1.96 ± 1.12	2.69 ± 1.69	0.0066
Visual Field			
GSS II VF Stage 0	213 (46.5%)	15 (27.3%)	<0.001
Borderline	158 (34.5%)	15 (27.3%)	
1	80 (17.5%)	21 (38.2%)	
2	7 (1.5%)	4 (7.3%)	
MD (dB)	-0.27 ± 1.27	-1.05 ± 1.39	<.0001
PSD (dB)	1.62 ± 0.39	1.92 ± 0.70	0.0033
VFI (%)	98.99 ± 1.89	98.32 ± 1.26	0.0008
FD-OCT			
Rim Area (mm ²)	1.09 ± 0.32	0.90 ± 0.36	0.0013
CDR, Vertical (ratio)	0.66 ± 0.16	0.74 ± 0.16	0.0001
CDR, Horizontal (ratio)	0.74 ± 0.18	0.80 ± 0.16	0.0883
CDR, Area (mm ²)	0.45 ± 0.17	0.53 ± 0.20	0.0005
NFL Overall (μm)	94.25 ± 10.09	88.72 ± 8.97	0.0002
NFL Inferior Q (μm)	115.70 ± 14.82	107.13 ± 14.95	0.0003
NFL Superior Q (μm)	114.56 ± 14.43	107.79 ± 14.52	0.0006
NFL Nasal Q (μm)			
NFL Temporal Q (μm)			
NFL GLV (%)	9.31 ± 6.75	13.55 ± 6.82	<.0001
NFL FLV (%)	2.70 ± 2.85	4.08 ± 2.99	<.0001
GCC Overall (μm)	93.43 ± 8.17	88.87 ± 6.04	<.0001
GCC Inferior H (μm)	93.72 ± 8.53	88.47 ± 6.58	<.0001
GCC Superior H (μm)	93.15 ± 8.47	89.29 ± 7.41	<.0001
GCC GLV (%)	4.81 ± 4.82	7.63 ± 4.62	<.0001
GCC FLV (%)	1.00 ± 1.33	2.38 ± 2.14	<.0001

Cell contents are mean $\pm$ standard deviation. CCT=central corneal thickness; IOP=intraocular pressure; VF= visual field; MD=mean deviation, PSD=pattern standard deviation; VFI=visual field index; CDR=cup-to-disc ratio, Q=quadrant average thickness; H=hemispheric average thickness; NFL=nerve fiber layer; GCC=ganglion cell complex; GLV=global loss volume; FLV=focal loss volume; IOP Range = max IOP - min IOP during follow-up; IOP variation = standard deviation of IOP during the follow-up.

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Table 3

Results of Univariate Cox Regression of Continuous Variables as Visual Field Conversion Risk Factors and their Predictive Power

	Unit	Hazard Ratio	p-value	AUC (95% CI)
Age (years)	10	1.45	0.012	0.586 (0.508, 0.665)
Axial Length (mm)	1	1.06	0.566	0.509 (0.425, 0.593)
Central Corneal Thickness (μm)	-10	0.98	0.643	0.504 (0.410, 0.576)
IOP Baseline (mmHg)	1	1.04	0.256	0.534 (0.454, 0.614)
IOP Average (mmHg)*	1	0.99	0.749	0.516 (0.442, 0.591)
IOP Peak (mmHg)*	1	1.05	0.108	0.565 (0.489, 0.640)
IOP Range (mmHg)*	1	1.13	<.001	0.676 (0.601, 0.751)
IOP Variation (mmHg)*	1	1.48	<.001	0.646 (0.571, 0.722)
VF MD (dB)	-1	1.57	<.001	0.664 (0.584, 0.744)
VF PSD (dB)	1	2.25	<.001	0.691 (0.625, 0.757)
VFI (%)	-5	1.46	0.011	0.714 (0.644, 0.784)
FD-OCT				
Rim Area (mm ²)	-0.05	1.08	0.010	0.646 (0.559, 0.734)
CDR, Vertical	0.1	1.44	0.016	0.657 (0.567, 0.748)
CDR, Horizontal	0.1	1.15	0.156	0.586 (0.498, 0.674)
CDR, Area	0.1	1.27	0.024	0.623 (0.536, 0.713)
NFL Overall (μm)	-10	1.58	0.001	0.662 (0.587, 0.736)
NFL Inferior Q (μm)	-10	1.41	0.001	0.653 (0.573, 0.733)
NFL Superior Q (μm)	-10	1.29	0.038	0.635 (0.553, 0.717)
NFL Nasal Q (μm)	-10	1.38	0.017	0.600 (0.522, 0.678)
NFL Temporal Q (μm)	-10	1.33	0.046	0.598 (0.519, 0.677)
NFL GLV %	1	1.06	<.001	0.667 (0.594, 0.740)
NFL FLV %	1	1.12	0.004	0.655 (0.583, 0.728)
GCC Overall (μm)	-10	2.04	<.001	0.677 (0.609, 0.745)
GCC Inferior H (μm)	-10	2.15	<.001	0.689 (0.621, 0.756)
GCC Superior H (μm)	-10	1.70	0.004	0.634 (0.556, 0.711)
GCC GLV %	1	1.09	<.001	0.696 (0.631, 0.761)
GCC FLV %	1	1.49	<.001	0.753 (0.683, 0.814)

AUC = area under receiver operating characteristics curve; IOP=intraocular pressure; VF= visual field; MD=mean deviation, PSD=pattern standard deviation; VFI=visual field index; CDR=cup-to-disc ratio, NFL= peripapillary nerve fiber layer; GCC=macular ganglion cell complex; Q=quadrant average thickness; H=hemispheric average thickness; GLV=global loss volume; FLV=focal loss volume CI = confidence intervals.

* These IOP covariates are summaries of longitudinal follow-up, not just baseline. Variation was measured by standard deviation.

Table 4

Components from the Best Multivariate Cox Regression Model to Construct the Glaucoma Composite Conversion Index

	Unit	Coefficient	Hazard Ratio	p-value
Age	10 years older	0.321	1.39	0.041
VF PSD	1 dB higher	0.836	2.26	<.0001
NFL Inferior Q	10 μ m thinner	0.224	1.25	0.046
GCC FLV	1% higher	0.303	1.36	<.0001

Multivariate Cox regression analysis. VF PSD=visual field pattern standard deviation; NFL Inferior Q=nerve fiber layer inferior quadrant; GCC FLV=ganglion cell layer focal loss volume.

Table 5

List of Glaucoma Composite Conversion Index Quartiles and Corresponding Rates of Visual Field Glaucoma Conversion from

Quartiles	GCCI Range	Actual Conversion Rate
0% – 25%	0.33 – 0.62	3.6%
25%–50%	0.62 – 0.72	4.4%
50%–75%	0.72 – 0.84	8.9%
75%–100%	0.84 – 0.99	29.7%

GCCI = glaucoma composite conversion index