Review Article - Narrative Review

Taiwan J Ophthalmol 2024;14:289-298

Access this article online

Quick Response Code:

Website: http://journals.lww.com/TJOP

DOI: 10.4103/tjo.TJO-D-24-00059

Big data in visual field testing for glaucoma

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Abstract:

Recent technological advancements and the advent of ever-growing databases in health care have fueled the emergence of "big data" analytics. Big data has the potential to revolutionize health care, particularly ophthalmology, given the data-intensive nature of the medical specialty. As one of the leading causes of irreversible blindness worldwide, glaucoma is an ocular disease that receives significant interest for developing innovations in eye care. Among the most vital sources of data in glaucoma is visual field (VF) testing, which stands as a cornerstone for diagnosing and managing the disease. The expanding accessibility of large VF databases has led to a surge in studies investigating various applications of big data analytics in glaucoma. In this study, we review the use of big data for evaluating the reliability of VF tests, gaining insights into real-world clinical practices and outcomes, understanding new disease associations and risk factors, characterizing the patterns of VF loss, defining the structure–function relationship of glaucoma, enhancing early diagnosis or earlier detection of progression, informing clinical decisions, and improving clinical trials. Equally important, we discuss current challenges in big data analytics and future directions for improvement.

Keywords:

Artificial intelligence, big data, data science, glaucoma, machine learning, visual field

Introduction

The emergence of "big data" analytics has transformed health care, enabling a paradigm shift toward precision medicine, predictive analytics, and data-driven decision-making. Although there is no universal definition of big data, it is generally accepted as a large data aggregation that cannot be analyzed with traditional methods. However, the concept of big data encompasses more than the sheer size of the data (volume). It is also characterized by the diversity of data types and sources (variety), the speed at which data is generated (velocity), the quality or accuracy of the data (veracity), and the potential insights or benefits derived from analyzing the data (value). For a dataset to be considered "big data", it should exhibit these key attributes.

Ophthalmology is particularly well suited to leverage big data analytics, given the wealth of diagnostic data generated from the advanced technologies used during clinical assessments. Specifically, the development of information technologies has led to the wide adoption of electronic health records, enabling the development of robust clinical registries such as the "IRIS" registry, "Fight Retinal Blindness!" registry, and "Sight Outcomes Research Collaborative" (SOURCE) repository. Other methods of obtaining big data in ophthalmology include genomic databases, large-scale clinical trials, biobanks, administrative and health insurance databases, crowd-source data (social media, mobile applications, wearable devices), and imaging technologies.[1] In glaucoma, sources of big data include clinical examination notes, optical coherence tomography imaging (OCT), visual field (VF) testing, and fundus photography. Among the most important sources of information in

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Submission: 26-05-2024
Accepted: 02-07-2024
Published: 13-09-2024

How to cite this article: Pham AT, Pan AA, Yohannan J. Big data in visual field testing for glaucoma. Taiwan J Ophthalmol 2024;14:289-98.

glaucoma is VF testing through automated perimetry. VF testing is a functional assessment of a patient's central or peripheral vision. Tracing its roots to the 19th century, VF testing has been a cornerstone in diagnosing and tracking glaucoma for the past several decades.[2] Recent technological advancements have significantly enhanced the growing accessibility of VF data from standard automated perimetry machines such as the Humphrey field analyzer (HFA), leading to an influx of glaucoma studies seeking to uncover disease patterns, enhance early diagnosis, improve progression detection, and personalize treatment strategies. In this study, we seek to provide a comprehensive review of the various utilizations of big data from VF testing obtained through standard automated perimetry. We focus on how researchers have used big data to evaluate the reliability and accuracy of VF tests, gain insights into management practices, assess outcomes of real-world interventions, identify disease associations and risk factors, characterize patterns of glaucomatous vision loss, improve our understanding of glaucoma's structure–function relationship, enhance disease detection, monitor progression, provide decision support, and improve clinical trials. Finally, we discuss the advantages and challenges of big data analytics in the setting of VF testing and its potential future directions. A summary of articles referenced is seen in Supplementary Table 1.

Evaluating Reliability and Accuracy of Visual Field Testing

The determination of a "reliable" VF test from an HFA is traditionally based on false positives or false negatives <33% and fixation losses <20%. However, there are limitations to these cutoffs. The cutoffs were based solely on the number of patients who exceeded these thresholds rather than how unlikely VFs above the cutoffs represented the true degree of VF damage. Second, using cutoffs for this approach does not quantify the degree of unreliability. Using large VF datasets, Yohannan *et al*., Tan *et al*., and Aboobakar *et al*. determined the quantitative impact of VF reliability indices on the global VF measurements in large populations of glaucomatous and nonglaucomatous eyes.[3-5] They found that false positives, false negatives, and test duration significantly impacted mean deviation (MD), whereas fixation losses had a minimal or no effect.[3,4] Yohannan *et al*. and Aboobakar *et al*. found that the impact of the reliability indices on MD varied with disease severity in glaucomatous eyes.[3,5] Tan *et al*. found a nonlinear relationship between reliability indices' impact on MD and pattern standard deviation (PSD) in nonglaucomatous eyes.[4] These studies have highlighted the importance of quantitatively considering the systemic effects of VF reliability indices on the degree of VF loss used to detect glaucoma or its progression, even if the VF is considered "reliable" by traditional HFA standards.

Investigators have also used large VF datasets to examine the accuracy of various VF testing strategies. Specifically, multiple studies have evaluated the accuracy of SITA Faster in comparison to its predecessors, SITA Standard, or SITA Fast.[6-12] SITA Faster demonstrates good agreement with SITA Standard or SITA Fast.[6-12] However, SITA Faster tends to underestimate the degree of VF loss compared to its predecessors, especially in the advanced stages of the disease.[6-12] Hence, SITA Faster's time-saving benefits must be weighed against the potential to underestimate VF loss, especially in severe glaucoma.

In addition, researchers have used large databases of VF tests to understand the frequency of testing needed to detect glaucoma worsening accurately. Bradley *et al*. evaluated the accuracy of detecting glaucoma worsening using different numbers of OCT scans or VF tests.[13] They found that the accuracy for OCTs or VFs alone was < 50% when monitoring progression over 2 years.[13] Combining OCT and VF obtained the best accuracy, but at least 12 tests (6 VF and 6 OCT) per year were needed to get an accuracy above 80%.[13]

Insights into Real-world Management Practices

By combining VF databases with large-scale, diverse datasets from electronic health records and insurance claims, big data analytics has given a deeper understanding of glaucoma care in various real-world settings. Sun *et al*. used a nationwide health insurance claims database to investigate whether a temporal association exists between VF testing and management changes.[14] They found that glaucoma patients who received VF testing had increased odds of management change.[14] Specifically, VF testing alone was associated with higher odds of subsequent surgery within 90 days or laser therapy within 30 days.[14] VF and/or OCT were associated with higher odds of medication changes within 30 days.[14] In a large Israel population-based retrospective study, Ben-Artsi *et al*. identified trends in VF testing conducted over 15 years between 2000 and 2014.[15] They discovered a growing trend of VF testing being overused such that nearly 3 out of 4 new VF tests were taken from patients without a glaucoma-related condition (International Classification of Disease [ICD-9] codes for glaucoma or suspect glaucoma diagnosis, or registered glaucoma medication prescription) by 2014.[15] Meanwhile, there was suboptimal adherence to glaucoma monitoring guidelines indicated by underuse of VF testing in patients that did have a glaucoma-related condition. A third of glaucoma-related patients did not perform a single VF test throughout the entire study

period[15] despite good evidence that more frequent testing is needed to detect a change in glaucoma accurately.[13] Moreover, the average time between the first glaucoma-related diagnosis and the first VF test was 2 years.[15] However, once a patient underwent their first VF test, they had VF tests taken annually on average.[15] Similarly, Stagg *et al*. found that VF testing was underused in a United States population of patients diagnosed with open-angle glaucoma (based on ICD-9 or ICD-10 codes).[16] More than 75% of patients with a glaucoma diagnosis in their study population received less than one VF test annually.[16] In a multicenter analysis, Fu *et al*. used electronic health records from 2013 to 2018 in the United Kingdom to evaluate glaucoma-associated health-care resource utilization.[17] They found that over 12 months, patients received an average of 2.0 glaucoma clinic visits and 1.5 VF tests. An important limitation of the studies above is the veracity of the ICD codes obtained from the electronic health records, introducing the potential for misclassification bias.

Assessing Real-world Outcomes

Researchers have analyzed large VF datasets to identify the trends in disease outcomes, factors affecting VF outcomes, and patient responses to therapy across a large, diverse clinical population. Chauhan *et al*. found that in a large treated Canadian population, most patients with a glaucoma-related diagnosis experienced slow rates of VF progression (median MD rate = −0.05 dB/year) and that MD rates of change were worse with increasing age.[18] A minority of patients, 4.3% and 1.5%, experienced fast (MD rate <−1 dB/year) and catastrophic rates of VF progression (MD rate <−2 dB/year), respectively. Similarly, Jammal *et al*. and Kirwan *et al*. found slow rates of VF progression (average MD rate = −0.09 dB/year and = −0.10 dB/year, respectively) in a large treated clinical population in the United States and Portsmouth, respectively.[19,20] Using the same cutoff for the MD rate of change, Jammal *et al*. noted a similar proportion (4.2%) of eyes demonstrating fast progression, leading to significant visual disabilities if sustained over time.[19] Kirwan *et al*. noted that older patients and those with initial VF damage were more likely to have faster rates of VF loss.[20] In contrast to the studies above, Aptel *et al*. found slightly faster rates of VF progression (average MD rate = −0.40 dB/year) in a large French population despite clinical treatment, and rates varied significantly among their subjects.[21] In addition, they found that nearly half of glaucoma patients had significant trend-based or event-based disease progression at the beginning of the follow-up period.[21]

Investigators have also examined the specific factors that affect the rates of glaucomatous VF progression. Shu *et al*. used pharmacy refill data from 2001 to 2014 to quantify the impact of adherence to topical intraocular pressure (IOP) lowering medication, defined by the proportion of days covered, on rates of VF progression in open-angle glaucoma or pseudoexfoliation glaucoma.[22] They found that the average treatment adherence during follow-up was 73%.[22] Using a conditional growth model and controlling confounding variables, they estimated the effect of adherence level on the rates of MD change.[22] Each 10% absolute increase in adherence led to a 0.006 dB/year slower rate of MD change.[22] Concerning IOP control, Villasana *et al*. found that patients who achieved the target IOP set by their clinicians had significantly slower rates than eyes that did not achieve the target.[23] Each 1 mmHg above the target pressure led to a 0.031 dB/year faster rate of MD change.[23] García Caride *et al*. assessed the rates of VF progression in six different glaucoma subtypes (open-angle glaucoma, angle-closure glaucoma, congenital glaucoma, ocular hypertension, pseudoexfoliation glaucoma, and pigmentary glaucoma) in a large Spanish population.[24] They affirmed that most patients with treated glaucoma had slow rates of MD progression regardless of glaucoma subtype.[24] However, they noted that congenital glaucoma had the highest proportions of fast VF progressors.[24] In another study involving a multicenter analysis of glaucoma clinics in the United Kingdom, Liu *et al*. found that rates of MD loss were faster in uveitic glaucoma than in primary open-angle glaucoma, and uveitic glaucoma had nearly double the relative risk of rapid progression.[25] De Moraes *et al*. compared the rates of VF change in ocular hypotensive eyes with and without optic disc hemorrhage and found eyes with disc hemorrhage had more rapid VF deterioration than eyes without disc hemorrhage (average MD rate = −0.17 vs. −0.07 dB/year).[26] Eyes with multiple disc hemorrhages experienced similar rates of global VF loss but more rapid pointwise VF changes when compared to eyes with a single disc hemorrhage.[26]

Disease Associations and Risk Factors

Big data analytics has identified multiple behavioral and socioeconomic risk factors for VF loss in glaucoma. Mahmoudinezhad *et al*. demonstrated that smoking intensity was significantly associated with faster rates of MD loss (−0.05 dB/year per 10 pack-years).[27] Heavy smokers (≥20 pack-years) were more than two times as likely to develop VF progression than patients without a smoking history.[27] Hanyuda assessed the long-term association between low-carbohydrate diets and primary open-angle glaucoma, defined by various VF loss patterns.[28] Although there was no significant association between low-carbohydrate diets and the risk of glaucoma, their data suggested an inverse association between plant-based low-carbohydrate intake and a lower risk of early paracentral VF loss.[28]

Racial and ethnic factors have also been associated with specific patterns of VF loss. Kang *et al*. examined racial differences in VF loss patterns.[29] Compared with non-Hispanic whites, black patients had a higher risk of early central (hazard ratio = 1.98; 95% CI, 1.48–2.66) and advanced VF loss (hazard ratio = 6.17; 95% CI, 3.69–10.32).[29] In addition to racial and ethnic factors, socioeconomic status, Household characteristics, and transportation are associated with functional VF loss. Almidani *et al*. found that the social vulnerability index, a measure that reflects the abovementioned factors, is significantly associated with worse baseline MD and greater VF variability.[30]

Researchers have also identified a variety of health-related risk factors. Diabetes mellitus is a well-known risk factor for many ocular complications. Nonetheless, there is no clear causal relationship between diabetes and glaucoma. Multiple mechanisms have been proposed for how diabetes may increase the risk of glaucoma progression, but the evidence in the literature remains mixed.[31-35] Johnson *et al*. improved on previous studies using the Duke Eye Registry to investigate the relationship between diabetes control, measured by HbA1c levels, and rates of VF loss.[36] They found that HbA1c levels were not significantly associated with rates of MD change over time.[36] In another study, Marshall *et al*. evaluated the relationship between body mass index (BMI) and multiple cross-sectional and longitudinal glaucoma outcomes, including VF progression.[37] They found that lower BMIs were associated with fast rates of VF progression (MD rate >−1.0 dB/year).[37] However, they noted that a limitation of this finding is that due to the study's retrospective nature, it was uncertain whether the recorded BMIs were accurate.[37] Concerning genetic risk factors, Qassim *et al*. used polygenic risk score stratification to examine the effects of common genetic variants linked to IOP on various glaucoma outcomes, including VF measures.[38] No significant difference was found between MD and the IOP-related polygenic risk score groups.[38] Similarly, Kang *et al*. investigated the relationship between vascular-tone regulator genes and primary open-angle glaucoma, defined by early paracentral or peripheral VF loss, and found no significant association.[39] Another genetic risk factor that has been investigated is the *Myocilin* gene. Souzeau *et al*. reported that *Myocilin* mutation was three times more prevalent in glaucoma patients with advanced VF loss than in those with less advanced disease in an Australian population.[40]

Characterizing Patterns of Glaucomatous Visual Field Loss

Unsupervised machine learning methods such as archetypal analysis have helped characterize patterns of VF loss. An advantage of archetypal analysis is that it provides regional stratification of VFs with coefficients that weigh each possible VF loss pattern. In the Ocular Hypertension Treatment Study, Keltner *et al*. offered a VF classification system based on manual inspection of VFs but did not attempt to quantify these patterns.[41] More recently, Elze *et al*. used archetypal analysis to identify and quantify 17 prototypical VF loss patterns without the potential of clinician bias. Their archetypes corresponded well with the previous manual classification scheme from the ocular hypertension study.[42] Wang *et al*. also applied archetypal analysis to identify central 10-2 VF loss patterns.[43] Longitudinal analysis of central VF loss patterns revealed that initial central VF loss was most likely to be from nasal loss, and one of the nasal loss patterns had a substantial chance of shifting to total loss after 2 years.[44] Compared to global indices, archetypal analysis of central VF patterns improved the prediction of central glaucomatous VF loss.[43]

The Structure–Function Relationship in Glaucoma

The structure–function relationship in glaucoma is crucial for understanding the disease's pathophysiology and improving clinical management. This relationship generally refers to the correlation between structural changes in the optic nerve head (often captured as a change in the retinal nerve fiber layer (RNFL) on peripapillary OCT) and functional changes in the patient's field of vision. Deciphering the relationship between structural changes in RNFL and functional VF loss has been challenging due to its nonlinear nature[45] and high interindividual variability.[46] Recent big data analytic studies have attempted to use artificial intelligence (AI) to improve the correlation between structural and functional data. Using AI to predict VF measures from OCT input data is an active area of research as machine learning methods can better model complex, nonlinear relationships than traditional statistical methods.[47-49] Specifically, there has been a growing trend of developing deep learning models using structural data inputs to predict 24-2 or central 10-2 VF measurements.[50-59] VF measurements that investigators have attempted to estimate include global metrics (MD, VF index [VFI]) and focal metrics (individual pointwise thresholds and total deviation values).[47,53-57,60-65] The estimates from these models have modest accuracy with absolute error ranging from 1.5 to 5 dB for global metrics[53,54,57,60,61,63-65] and 3–5 dB for focal metrics.[47,53,55,60,62]

As opposed to mapping structural measurements directly with functional measurements (converting measurements), additional applications of big data analytics in the structure–function relationship involve utilizing large OCT datasets paired with large VF

datasets to gain insights into the concordance between OCT findings and VF findings as it relates to detecting the presence of glaucoma and/or progression. In a large population-based study, Springelkamp *et al*. evaluated the ability of OCT thickness measurements in the peripapillary and macular regions to screen for glaucoma as diagnosed by perimetry.[66] They found that macular abnormalities were as common as RNFL abnormalities in glaucoma cases and that OCT measurements could identify approximately half of the glaucoma cases with evidence of VF loss.[66] Singh *et al*. used a large longitudinal database containing OCT and VFs to challenge the assumption that normative percentiles of RNFL from OCT machines can improve the prediction of glaucomatous VF loss.[67] They found that raw RNFL measurements from OCT predicted current and future VF loss with similar accuracy to normative percentiles of RNFL.[67] Swaminathan *et al*. found that rapid rates of RNFL loss during the initial follow-up period of glaucoma patients were predictive of concurrent or future rapid VF loss.[68] Montesano *et al*. developed a combined Structure Function Index (SFI), and they evaluated the diagnostic ability of SFI to discriminate between glaucomatous eyes (determined from expert evaluation of fundus photographs) and healthy eyes.[69] They found that SFI did not have better discriminative power than RNFL alone but did perform better than MD alone.[69] Given that VF testing requires a patient to fixate on a central target, another critical aspect of their study was assessing the impact of fundus tracking perimetry on the structure–function correlations (R^2 value).[69] Overall, the global structure–function correlations were similar between perimeters that used or did not use fundus tracking.[69]

Improving Glaucoma Diagnosis

Big data analytics involving machine learning holds promising applications for diagnosing glaucoma. As described above, machine learning algorithms can identify the subtle patterns of VF loss and can be clinically valuable in the early detection of glaucoma. Thakur *et al*. demonstrated that convex representations of VF loss through archetypal analysis could better predict glaucoma approximately 4 years before disease onset when compared to the original VF representation.[70] Researchers have built on this by exploring the use of large VF databases to develop deep learning models for glaucoma diagnosis. Li *et al*. conducted a clinical trial that involved developing a deep learning model trained on 3,712 VFs to differentiate glaucoma from non-glaucoma VFs. They demonstrated a convolutional neural network achieves higher accuracy compared to human ophthalmologists and traditional guidelines (Advanced Glaucoma Intervention Study and Glaucoma Staging System 2 of Brusini). Using 300 VFs for validation, their CNN model achieved an accuracy of 0.876. Meanwhile, human ophthalmologists achieved accuracies ranging from 0.585 to 0.626. AGIS and GSS2 criteria achieved accuracies of 0.459 and 0.523, respectively.[71] Compared to conventional statistical analysis methods such as the Glaucoma Hemifield Test, PSD Index, and cluster recognition, Bizios *et al*. demonstrated that deep learning models using VF inputs could diagnose glaucoma with slightly to considerably better accuracy.[72] More recent studies have improved the performance of these machine learning models by incorporating VF data with additional data from OCT scans or fundus images.[73-76]

Improving Detection of Visual Field Progression

Researchers have used big data analytics to explore alternative approaches to detecting glaucoma progression. In a large retrospective longitudinal study of 1,658 eyes with ≥8 reliable VF tests, Leshno *et al*. evaluated the ability of rates of progression in each hemifield of the 24-2 VF to detect rapidly progressing eyes.[77] Hemifield progression rates were more sensitive to focal or faster progression than global progression rates.[77]

Similar to glaucoma diagnosis, there is much interest in utilizing AI approaches to improve the detection of disease progression. Saeedi *et al*. described substantial variation and limited agreement between the existing methods of defining VF progression (MD slope, VFI slope, Advanced Glaucoma Intervention Study, Collaborative Initial Glaucoma Treatment Study, pointwise linear regression, and permutation of pointwise linear regression).[78] To address this issue, Wang *et al*. introduced another method of monitoring VF progression by tracking the changes between archetype weights of longitudinal VF tests; archetypal analysis could be used to detect VF progression and quantify progression patterns.[79] Progression based on archetypal analysis compared well with existing methods of identifying progression such as MD slope, pointwise linear regression, and Collaborative Initial Glaucoma Treatment Study scoring.[79] In a different study, Yousefi *et al*. used archetypal analysis to identify the patterns of VF loss and identified one pattern that predicted future rapid VF progression.[80] Deep learning models have also been effective in predicting progression. Park *et al*. and Kim *et al*. showed that deep learning models such as recurrent neural networks and bidirectional gated recurrent unit algorithms significantly outperformed conventional linear regression when using an initial set of five VFs to predict worsening in the sixth VF.[81,82] Sabharwal *et al*. demonstrated that deep learning models can accurately predict VF progression (area under the curve [AUC] =0.94) when a consensus approach, involving both trend and event-based methods, was used

to define VF progression.[83] Even when the most recent six VFs in the series were removed, the deep learning model had an AUC of 0.78. In contrast, the clinician assessment of worsening (based on electronic health record documentation) had an AUC of 0.64.[83] Moreover, researchers have been able to further improve the predictive accuracy models by incorporating multimodal data.[84,85]

Decision Support Tools

The growing accessibility of large datasets and advances in AI over the past several years have provided researchers with opportunities to build clinical decision support tools to improve glaucoma care. Many studies have focused on forecasting the risk of surgical intervention. Prior work has tried predicting the need for glaucoma surgery using data found in electronic health records, such as clinical progress notes, demographic information, prescribed medications, comorbid diagnoses, vital signs, BMI, and smoking status.[86,87] AI has also been used to aid in risk stratification by forecasting future VF loss.[84,88,89] Since a large number of VFs are needed to accurately determine the rate of VF loss and treatment decisions frequently need to be made after just a few visits, early identification of those at risk for rapid VF loss is difficult. Shuldiner *et al*. demonstrated that machine learning models could predict eyes that underwent fast progression (MD rate <–1 dB/year) using only initial VF data with modest accuracy (AUC $\approx$ 0.70).[88] More recently, there has been increasing interest in building multimodal models incorporating multiple data sources, such as VF tests, into a single predictive model, and many show significantly improved performance.[84,90,91] Other decision support tools researchers are investigating include classification models for managing glaucoma and referral in primary care settings.[92,93]

Improving Clinical Trials Enrollment

Glaucoma neuroprotection trials require demonstrating a significant treatment effect on VF endpoints. Due to the slow rate of progression observed in the majority of treated glaucoma patients and the inherent variability of VF testing, investigators running such clinical trials are burdened by large sample size requirements. Researchers have used computer simulations with large VF datasets to investigate approaches for improving the feasibility of clinical trials and reducing the burden of enrollment. Wu and Mederios demonstrated that different VF testing paradigms, such as clustered VF testing, as opposed to evenly spaced VF testing, can significantly reduce the sample size requirement for glaucoma clinical trials.[94] Moreover, combining OCT and VF endpoints can also help reduce sample size requirements.[95] Recent studies have validated using trend-based VF outcomes over event-based VF outcomes for clinical trials, as trend-based evaluation tends to significantly reduce sample size.[96,97] In addition, Montesano *et al*. found that selecting reliable VF test-takers with low intertest variability can significantly improve the statistical power of glaucoma clinical trials.[98] In a related study, Wang *et al*. demonstrated that clinical trial enrollment could be enhanced by using deep learning models that can identify patients likely to have lower VF variability.[99]

Advantages and Limitations of Big Data in Visual Field Testing

Big data analytics of VF tests offers several advantages for clinical decision-making and research in glaucoma. By analyzing large-scale VF datasets with machine learning and other advanced statistical techniques, researchers can identify the subtle patterns of vision loss, predict disease progression more accurately, and detect glaucoma earlier than conventional methods. The comprehensive analysis of VF data may enable the stratification of glaucoma subtypes and help inform clinicians, so they can develop personalized treatment plans. Analyzing real-world clinical data provides insights into current management practices and can help improve resource allocation.

However, big data analytics also comes with notable limitations. Variability in test administration and patient compliance can lead to noisy and inconsistent VF measurements, complicating analysis. The requirement for large, well-annotated datasets often limits the generalizability of predictive models, as many datasets from the large institutions from which many of these studies were drawn may lack diversity in patient demographics and clinical settings. Ethical and privacy concerns also arise due to the sensitive nature of health data. Implementing these analytics into routine clinical practice often requires significant computational infrastructure and clinician training, posing logistical challenges. Moreover, due to the "black box" nature of some analytic methods, specifically deep learning, the lack of interpretability and resulting ambiguity in clinical accountability are considerable hurdles. Despite these limitations, big data analytics remains a promising approach for enhancing glaucoma care.

Potential Future Directions

Big data analytics in VF testing has the potential to transform glaucoma care. One promising avenue lies in the continued development of multimodal predictive models that integrate VF data with OCT, electronic health records, and genetic information, offering clinicians a comprehensive view of each patient's glaucoma progression risk. Advanced machine learning

techniques, particularly deep learning models, will become increasingly adept at identifying complex patterns in heterogeneous data, leading to more precise early detection and subtype stratification. The advent of home-based VF testing devices and wearable health technology may generate ever-increasing amounts of continuous patient data streams, enabling personalized treatment adjustments and real-time monitoring of disease progression. Furthermore, using federated learning, where models are trained across decentralized data without data sharing, may facilitate collaborations between institutions when addressing privacy concerns, leading to more generalizable predictive models. Developing interpretable models that clinicians can easily understand and trust will be crucial, ensuring that the insights provided by these predictive tools can be seamlessly incorporated into clinical practice. Integrating these analytics into clinical decision support systems will empower clinicians with actionable insights, bridging the gap between data analysis and patient care, ultimately improving outcomes and reducing the global burden of glaucoma.

Acknowledgments

All persons who have made substantial contributions to the work reported in the manuscript (e.g. technical help, writing and editing assistance, general support), but who do not meet the criteria for authorship, are named in the Acknowledgments and have given us their written permission to be named. If we have not included an Acknowledgments in our manuscript, then that indicates that we have not received substantial contributions from nonauthors.

Data availability statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Financial support and sponsorship

This study was financially supported by grants from the National Institute of Health 1K23EY032204-03 and Research to Prevent Blindness Unrestricted Grant.

Conflicts of interest

The authors declare that there are no conflicts of interests of this paper.

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Supplementary Table 1: Summary of articles reviewed

Topic	Author	Sample size	Data source	Study method	Key finding
Evaluating reliability and accuracy of VF testing	Yohannan *et al.*, 2017	10,262 VFs from 1538 eyes (909 subjects)	Institutional database	Mixed-effect modeling	FPs, FNs, and TD significantly impact VF test reliability, and the effect of FPs and FNs varies with disease severity FL has minimal impact on test reliability
	Tan *et al.*, 2017	1828 VFs from 1235 eyes (830 subjects)	Large prospective population-based cohort database	Multivariable regression modeling	Quantified the effects of FP, FN, FL on MD and PSD Clinicians may estimate the impact of varying degrees of unreliability on VF results
	Aboobakar *et al.*, 2020	10,262 VFs from 1538 eyes (909 subjects)	Institutional database	Mixed-effects modeling	FPs, FNs, and TD are the primary measures for predicting VF reliability but VFs with normal reliability indices may still be unreliable
	Le *et al.*, 2022	766 eyes (421 patients)	Institutional database	Unsupervised machine learning (archetypal analysis)	Switching from SITA standard to SITA faster is associated with higher tendency to preserve normal VFs but lower tendency to preserve abnormal VFs compared to consecutive SITA standard examinations
	Pham *et al.*, 2021	766 eyes (421 patients)	Institutional database	Mixed-effects modeling	SITA Faster resulted in similar VF measurements as SITA standard in mild glaucoma. Meanwhile, SITA faster resulted in improved VF measurements in moderate and advanced disease
	Bradley *et al.*, 2023	20,583 eyes (10,958 subjects)	Institutional database	Simulation	OCT and VF each have>50% accuracy for detecting VF worsening Combining OCT and VF results greatly increases the accuracy for detecting VF worsening
Insights into real-world management practices	Sun *et al.*, 2021	12,669,324 outpatient encounters from 1,863,748 subjects	National health-care insurance claims database	Logistic regression	Changes in glaucoma management occurred in a small proportion of outpatient encounters Surgery and laser therapy are more likely to occur following encounters involving VF compared to OCT, but either has higher odds of medication changes
	Ben-Artsi *et al.*, 2019	198,843 VFs from 93,617 subjects	Health-care organization database	Descriptive statistics	Identified a growing trend of VF tests being overused for indications other than glaucoma Observed suboptimal adherence to glaucoma monitoring guidelines
	Stagg *et al.*, 2022	380,029 subjects	National health-care insurance claims database	Negative binomial regression	Observed suboptimal adherence to glaucoma monitoring guidelines>75% of open-angle glaucoma patients received<1 VF annually
	Fu *et al.*, 2023	43,742 subjects	Health-care organization database	Descriptive statistics	Observed patients received an average of 2.0 glaucoma clinic visits and 1.5 VF tests annually
Assessing real-world Outcomes	Chauhan *et al.*, 2014	2324 patients	Institutional database	Robust regression	Most patients under routine glaucoma care have slow rates of VF progression. Meanwhile, a minority of patients experience rapid rates of VF progression
	Jammal *et al.*, 2020	19,812 VFs from 6138 eyes (3669 subjects)	Institutional Database	Mixed-effects modeling	Most patients under routine glaucoma care experience slow rates of VF progression. VF and OCT should be used together for monitoring glaucoma
	Kirwan *et al.*, 2013	4177 eyes (2208 subjects)	Institutional database	Descriptive statistics	The majority of glaucoma VF progressors experience slow or moderate rates of progression while fast progression is rare. Older patients or those with initial VF damage are more likely to have faster rates of VF progression

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Supplementary Table 1: Contd...

Topic	Author	Sample size	Data source	Study method	Key finding
	Aptel *et al*., 2015	441 eyes (228 subjects)	Multicenter database	Descriptive statistics	Observed large variability in rates of VF progression in a sample of the French population
	Shu *et al*., 2021	6343 subjects	Institutional database	Conditional growth model	Greater adherence to topical glaucoma medication may result in slower rates of VF progression
	Villasana *et al*., 2022	2852 eyes (1688 subjects)	Institutional database	Mixed-effects modeling	Failing to achieve target IOP is associated with faster rates of VF progression and this is especially pronounced in eyes with moderate glaucoma
	Sara Garcia Caride *et al*., 2023	1036 eyes	Institutional database	Mixed-effects modeling	Most patients undergoing routine glaucoma care experience slow rates of VF progression regardless of glaucoma subtype
					Congenital glaucoma is more likely to experience faster rates of VF progression
	Liu *et al*., 2018	792,083 VFs from 122,500 subjects	National multicenter database	Descriptive statistics	Uveitic glaucoma has faster rates of VF progression than primary open-angle glaucoma and has nearly double the relative risk of fast progression
	Gustavo De Moraes *et al*., 2012	2607 eyes (1378 subjects)	Clinical trial database	Case-control	Eyes with disc hemorrhage experience more rapid trend-based global and local VF worsening compared to eyes without disc hemorrhage
Disease associations and risk factors	Mahmoudinezhad *et al*., 2022	511 eyes (354 subjects)	Multicenter database	Logistic regression, Kaplan–Meier survival analysis	Heavy smoking ($\geq$20 pack-years) is associated with a higher likelihood of VF loss
	Hanyuda *et al*., 2020	185,638 subjects	Large prospective population-based cohort database	Cox proportional hazard modeling	Low-carbohydrate diets were not associated with a risk of primary open-angle glaucoma
					Observed an inverse associated between plant-based low-carbohydrate diet and lower risk of early paracentral VF loss
	Kang *et al*., 2022	209,036 subjects	Large prospective population-based database from multiple sources	Unsupervised machine learning (archetypal analysis)	Black patients have a higher risk of primary-open angle glaucoma associated with early central and advanced VF loss compared to nonHispanic white patients
	Almidani *et al*., 2024	7897 eyes (4482 subjects)	Institutional database	Mixed-effects modeling	Increased social vulnerability index scores are associated with worse VF loss at baseline and higher VF variability
	Johnson *et al*., 2021	351 eyes (222 subjects)	Institutional database	Mixed-effects modeling	There is no significant association between diabetes control, as measured by HbA1c, and rates of VF loss
	Marshall *et al*., 2022	471 subjects	Large prospective population-based cohort databases and biobank	Multivariate linear regression	BMI is correlated with longitudinal and cross-sectional VF outcomes
	Qassim *et al*., 2020	2154 subjects	National registries	Logistic regression, linear regression	IOP polygenic risk scores were positively correlated with maximum IOP, disease severity, need for surgery, and number of affects members but not VF outcomes
	Kang *et al*., 2014	6548 subjects	Large prospective population-based cohort database from multiple sources	"Pathway analysis by randomization incorporating structure" analysis software	There is no significant association between vascular-tone regulator genes with primary open-angle glaucoma defined by early paracentral or peripheral VF loss
	Souzeau *et al*., 2013	1380 subjects	National registries	Cross-sectional	The prevalence of myocilin mutations in glaucoma associated with advanced VF loss is significantly greater than in nonadvanced glaucoma

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Topic	Author	Sample size	Data source	Study method	Key finding
Characterizing patterns of glaucomatous VF loss	Elze *et al*., 2015	13,231 VFs	Institutional database	Unsupervised machine learning (archetypal analysis)	Identified 17 prototypical patterns of VF loss without clinician bias
	Wang *et al*., 2019	13,951 VFs from 13,951 eyes (8712 subjects)	Multicenter database	Unsupervised machine learning (archetypal analysis)	Quantified central VF loss patterns that may help improve prediction of central VF worsening when compared to global indices
	Wang *et al*., 2020	2912 VFs from 1103 eyes (1010 subjects)	Multicenter database	Unsupervised machine learning (archetypal analysis)	Central VF loss patterns found to exhibit characteristic patterns, specifically initial central VF loss is likely to be nasal, and 1 specific pattern of nasal loss is likely to result in complete total loss
The structure–function relationship in glaucoma	Mariottoni *et al*., 2020	26,499 VF/OCT pairs from 15,173 eyes (8878 subjects)	Institutional database	Supervised machine learning (CNN)	A convolutional neural network predicted VF sensitivity thresholds using OCT measures (MAE=4.25 dB) and generated a structure–function map
	Zhu *et al*., 2010	535 subjects	Multicenter database	Supervised machine learning (RBF)	Bayesian radial basis functions can be used to predict VF sensitivity from structural measurements Bayesian radial basis functions predicted the structure–function relationship better than linear regression (MAE=2.9 dB vs. 4.9 dB)
	Kim *et al*., 2017	499 subjects	Multicenter database	Supervised machine learning (RF, SVM, KNN)	Random forest, support vector machine, and k-nearest neighbors can predict glaucoma diagnosis based on OCT and VF inputs with high accuracy (0.98), sensitivity (0.983), and specificity (0.975)
	Hashimoto *et al*., 2021	597 eyes (367 subjects)	Multicenter database	Supervised machine learning (CNN)	Deep learning models can be used to predict 10-2 VF sensitivities from macular OCT and further corrected using 24-2 or 30-2 VFs (MAE=5.3 dB when using OCT only and MAE=4.3 dB when corrected)
	Xu *et al*., 2020	591 eyes (345 subjects)	Multicenter database	Supervised machine learning (CNN)	Deep learning and tensor regression can be used to predict 10-2 VF sensitivities from OCT thickness measurements (RSME=6.32±3.76 dB)
	Asano *et al*., 2021	753 eyes (430 subjects)	Multicenter database	Supervised machine learning (CNN)	Deep learning can be used to predict 10-2 VF total deviation values from OCT images and further corrected using 24-2 VF (MAE=9.4–9.5 dB when using OCT images only and MAE=~5.5 dB when corrected)
	Hashimoto *et al*., 2021	591 eyes (347 subjects)	Multicenter database	Supervised machine learning (CNN)	Deep learning can be used to predict 10-2 VF sensitivities from SD-OCT measurements (MAE=2.84 dB)
	Huang *et al*., 2021	1796 VF/OCT pairs from 1796 eyes (1796 subjects)	Multicenter database	Supervised machine learning (RF, SVM, CNN)	Artificial neural networks can be used to estimate MD from RNFL measurements (MAE=3.3–5.9 dB) better than multivariable linear regression, random forest, support vector regressor, and 1-D convolutional neural networks
	Park *et al*., 2020	3101 eyes (1819 subjects)	Institutional database	Supervised machine learning (DNN, RF XGBoost, SVM, RBF)	Deep learning can be used to predict global 24-2 VF measurements using optic nerve head (RSME=4.29 dB) and macula (RSME=4.40 dB) OCT images
	Wang *et al*., 2020	691 eyes (691 subjects)	Institutional database	Unsupervised machine learning (NMF)	Nonnegative matrix factorization using RNFL thickness patterns correlated with 24-2 VF total deviation values better than sectoral RNFL thickness

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Topic	Author	Sample size	Data source	Study method	Key finding
	Maetschke *et al.*, 2019	4155 eyes	Institutional database	Supervised machine learning (CNN)	A deep learning model trained on raw optic nerve head OCT volumes can predict 24-2 VF VFI (RMSE=12.2±1.55%) and MD (RSME=4.1±0.35 dB) measurements. This approach outperformed classical machine learning models trained on classical OCT features
	Shin *et al.*, 2021	4634 eyes (2593 subjects)	Institutional database	Supervised machine learning (CNN)	A deep learning model using a wide field SS-OCT image can predict global 24-2 VF measurements better than either optic nerve head or macular SD-OCT images alone (RMSE=4.51±2.54 dB vs. 5.29±2.68 dB)
	Park *et al.*, 2020	2525 eyes (1425 subjects)	Institutional database	Supervised machine learning (CNN)	Deep learning can be used to predict global 24-2 VF using SS-OCT images of the optic nerve head and macula (RSME=4.44±2.09 dB–4.85±2.66 dB)
	Hemelings *et al.*, 2022	1643 VF/OCT pairs from 998 eyes (542 subjects)	Institutional database	Supervised machine learning (CNN)	A deep learning approach can use raw OCT scans to estimate global and pointwise VF sensitivities (MAE=2.89 dB) that fall almost entirely within the 90% test-retest confidence interval of the 24-2 SITA standard test
	Kamalipour *et al.*, 2023	3990 VF/OCTA pairs from 842 eyes (465 subjects)	Clinical trial database	Supervised machine learning (CNN)	A deep learning approach can use en-face optic nerve head and macular OCTA images to predict pointwise VF sensitivities (MAE=2.23 dB)
	Chen *et al.*, 2024	12,915 VF/OCT pairs from 2151 eyes (1129 subjecs)	Institutional database	Supervised machine learning (CNN)	A deep learning approach can be used to generate t-statistic maps for VF sensitivities using raw 3D OCT scans
					Deep learning successfully visualized global trend of pointwise spatial relationships between OCT and VF that aligns well with existing knowledge of structure–function relationship
	Christopher *et al.*, 2020	9765 VF/OCT pairs from 1909 eyes (1194 subjects)	Clinical trial databases	Supervised machine learning (CNN)	Deep learning identify eyes with glaucomatous VF damage and predict the severity of VF loss from SD-OCT images (MD MAE=2.5–3.7 dB)
	Tan *et al.*, 2019	954 subjects	Clinical trial database	Quadratic regression using weighted logarithmic averages	MD estimated from RNFL thickness had better correlation and diagnostic sensitivity with VF MD measurements than average RNFL thickness
	Yu *et al.*, 2021	10,370 VF/OCT pairs from 3014 eyes (1678 subjects)	Multicenter database	Supervised machine learning (CNN)	A deep learning approach can use optic nerve head OCT, macular OCT, or both to predict global VF measurements (MAE=2.7% for VFI and 1.57 dB for MD)
	Springelkamp *et al.*, 2014	1224 subjects	Large prospective, population-based cohort	Case–control study	Macular retinal ganglion cell loss is at least as common as peripapillary RNFL abnormalities in glaucomatous VF loss
	Singh *et al.*, 2023	3016 VF/OCT pairs from 1427 subjects	Institutional database	Machine learning (KNN, SVM, RF, gradient-boosted trees, decision trees, XGBoost)	Normative percentiles of RNFL thickness did not improve glaucomatous VF loss predictions from raw RNFL thickness alone
	Swaminathan *et al.*, 2021	1150 eyes (839 subjects)	Institutional database	Mixed-effects modeling	Rapid RNFL thinning during the initial follow-up period was predictive of concurrent and subsequent rates of VF loss

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Supplementary Table 1: Contd...

Topic	Author	Sample size	Data source	Study method	Key finding
	Montesano *et al.*, 2019	1407 eyes (794 subjects)	Multicenter database	Mixed-effects modeling	VF perimeter with fundus tracking did not have better diagnostic ability using a structure–function index than VF perimeter without fundus tracking
Improving glaucoma diagnosis	Thakur *et al.*, 2020	3272 eyes (1636 subjects)	Clinical trial database	Supervised machine learning (CNN)	Deep learning can predict glaucomatous development before disease onset with reasonable accuracy (AUC=0.88)
	Fei *et al.*, 2018	4,012 VF	Multicenter database	Supervised machine learning (CNN)	A deep model trained on pattern deviation plots differentiated normal from glaucomatous VF with higher accuracy than human ophthalmologists or traditional guidelines
	Bizios *et al.*, 2007	216 subjects	Institutional database	Supervised machine learning (MLP)	Deep learning models using VF inputs can be a useful clinical tool for diagnosing glaucoma (AUC=0.984)
	Yi *et al.*, 2022	502 VF/fundus image pairs from 274 subjects	Institutional database	Supervised machine learning (CNN)	Deep learning models using multimodal inputs can be a useful clinical tool for glaucoma severity diagnosis (AUC=0.992)
	Xiong *et al.*, 2022	2463 VF/OCT pairs from 1083 subjects	Clinical trial database	Supervised machine learning (CNN)	A deep learning model using paired VF/OCT inputs demonstrated better diagnostic ability for detecting glaucoma (AUC=0.950) than VF (AUC=0.868) or OCT (AUC=0.809) alone
	Lim *et al.*, 2022	1155 eyes	Institutional database	Supervised machine learning (RF, SVM, AdaBoost, decision tree, naives bayes, KNN, DNN)	A multimodal deep learning model could differentiate glaucoma, preperimetric glaucoma, and healthy eyes using fundus images with reasonable accuracy (AUC>0.96)
	Song *et al.*, 2022	1395 VF/OCT pairs from 641 subjects	Institutional database	Supervised machine learning (CNN)	A deep learning model using paired VF/OCT inputs demonstrated better diagnostic ability for detecting glaucoma (AUC=0.92) than OCT (AUC=0.87) alone
Improving detection of VF progression	Leshno *et al.*, 2024	1658 eyes (1658 subjects)	Multicenter database	Linear regression	VF hemifield progression rates are more sensitive to focal or faster VF progression than global progression rates
	Saeedi *et al.*, 2019	90,713 VFs rom 13,156 eyes (8499 subjects)	Multicenter database	Cohen's K coefficient, bivariate and multivariate analysis	Existing tend-based and event-based have limited agreements with each other and vary considerably across clinical institutions (kappa range: 0.12–0.52)
	Wang *et al.*, 2019	12,217 eyes (7360 subjects)	Multicenter database	Unsupervised machine learning (archetypal analysis)	Quantified VF progression patterns Archetypal methods compared well with existing methods of defining progression
	Yousefi *et al.*, 2022	2231 VFs from 205 eyes	Clinical trial database	Unsupervised machine learning (archetypal analysis)	Archetypal analysis can identify VF loss patterns objectively with reproducible nomenclature for characterizing early VF defects and rapid VF progression
	Kim *et al.*, 2023	5413 eyes (3321 patients)	Multicenter database	Supervised machine learning (Bi-GRU, LSTM)	Bidirectional gated recurrent unit algorithm outperformed conventional linear regression and long short-term memory algorithms when predicting glaucoma progression from 5 consecutive VF tests
	Park *et al.*, 2019	1689 eyes	Institutional database	Supervised machine learning (RNN)	Recurrent neural network algorithm outperformed conventional linear regression when predicting glaucoma progression from 5 consecutive VF tests

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Supplementary Table 1: Contd...

Topic	Author	Sample size	Data source	Study method	Key finding
	Sabharwal *et al.*, 2023	8705 eyes (5099 subjects)	Institutional database	Supervised machine learning (LSTM)	A deep learning model trained on a consensus method of VF worsening successfully identified VF worsening (AUC=0.94) compared to clinicians assessment of worsening (AUC=0.74)
	Herbert *et al.*, 2023	4536 eyes (2962 subjects)	Institutional database	Supervised machine learning (vision transformer, MLP)	A deep learning model could forecast future rapid VF loss when trained on early baseline multimodal data inputs (AUC=0.87)
Decision support tools	Wang *et al.*, 2022	4512 subjects	Institutional database	Supervised machine learning (CNN)	A deep learning model trained on unstructured electronic health record text could successfully predict glaucoma patients who will need surgery (AUC=0.73)
	Baxter *et al.*, 2019	385 subjects	Institutional database	Supervised machine learning (RF, ANN)	Machine learning models trained on structured electronic health records discriminated glaucoma patients requiring surgery with similar performance to multivariate logistic regression (AUC=0.65 vs. 0.67)
	Shuldiner *et al.*, 2021	175,686 VFs from 14,217 subjects	Multicenter database	Supervised machine learning (RF, SVM)	Machine learning algorithms can predict eyes at risk for future rapid VF worsening based on an initial VF test (AUC=0.68–0.72)
	Berchuck *et al.*, 2019	29,161 VFs from 3832 subjects	Institutional database	Unsupervised machine learning (variational auto-encoder)	A deep learning approach can be used for assessing the rate of VF progression and predict future patterns of VF damage
	Wang *et al.*, 2024	4898 eyes (4038 subjects)	Institutional database	Supervised machine learning (vision transformer)	A deep learning model trained on multimodal baseline VF, OCT, and clinical measurements can successfully predict eyes that will require future glaucoma surgery (AUC=0.92)
	Christopher *et al.*, 2024	961 subjects	Clinical trial databases	Supervised machine learning (RF, gradient-boosting machines, XGBoost, DNN)	Machine learning models trained on VF, OCT, and clinical measurements could successfully predict glaucoma patients requiring future surgical intervention at 1, 2, and 3 years (AUC=0.93, 0.92, and 0.93, respectively)
	Kaskar *et al.*, 2022	3015 subjects	Clinical trial database	Supervised machine learning (SVM, AdaBoost)	Machine learning models trained on baseline clinical features (IOP, demographic, and medical history) could successfully predict eyes that subsequently developed a glaucoma diagnosis in the span of 1–12 years Predictive machine learning classifiers may be a useful screening tool for glaucoma referrals in primary care settings
Improving clinical trial enrollment	Wu *et al.*, 2018	353 eyes (247 subjects)	Institutional database	Simulation	Different VF testing paradigms (clustered VF testing vs. evenly spaced VF testing) can significantly reduce sample size required for glaucoma clinical trials by 17–40%
	Wu *et al.*, 2019	192 eyes (121 subjects)	Institutional database	Simulation	Combining VF and OCT endpoints can reduce the sample size required for glaucoma clinical trials by 31–33%
	Montesano *et al.*, 2023	3352 eyes (3352 subjects)	National multicenter database	Simulation	Trend-based VF outcomes can reduce the sample size required for glaucoma clinical trials when compared to event-based VF outcomes
	Wu *et al.*, 2019	321 eyes (240 subjects)	Clinical trial database	Simulation	Evaluating differences in rate of VF change can reduce the sample size required for glaucoma clinical trials

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Supplementary Table 1: Contd...

Topic	Author	Sample size	Data source	Study method	Key finding
	Montesano *et al*., 2021	2804 subjects	National multicenter database	Simulation	Selecting patients with lower intertest VF variability can significantly reduce the sample size needed for glaucoma clinical trials
	Wang *et al*., 2024	2817 eyes (2817 subjects)	Institutional database	Simulation	Deep learning models can reduce the burden of glaucoma clinical trials by predicting eyes with low interest VF variability based on a single baseline clinic visit

"Machine learning" study methods are those without a closed-form solution. FP: False positive, FN: False negative, TD: Test duration, VF: Visual field, MD: Mean deviation, PSD: Pattern standard deviation, VFI: VF index, SITA: Swedish interactive testing algorithm, OCT: Optical coherence tomography, BMI: Body mass index, IOP: Intraocular pressure, MAE: Mean absolute error, RSME: Root mean squared error, AUC: Area under the curve, RF: Random forest, SVM: Support vector machine, KNN: K-nearest neighbors, RBF: Radial basis function, CNN: Convolutional neural network, DNN: Deep neural network, ANN: Artificial neural network, LSTM: Long short-term memory, RNN: Recurrent neural network, MLP: Multilayer perceptron, bi-GRU: Bidirectional gated recurrent unit, NMF: Nonnegative matrix factorization, RNFL: Retinal nerve fiber layer, HbA1c: Glycated hemoglobin, 1-D: One dimensional, SD-OCT: Spectral domain OCT, SS-OCT: Swept-source OCT, FL: Fixation losses