Using large-scale visual field data to gain insights into management of patients with glaucoma

Stephen Richard Kelly

A thesis submitted for the degree of Doctor of Philosophy

Division of Optometry and Visual Science

School of Health Sciences

September 2019

Table of Contents

List of Tables

List of Figures

List of Abbreviations

AARR: Age-Adjusted Risk Ratio

AMD: Age-Related Macular Degeneration

COAG: Chronic Open Angle Glaucoma

EGPS: European Glaucoma Prevention Study

EGRET: European Glaucoma Research and Training

EMGT: Early Manifest Glaucoma Treatment Study

EMR: Electronic Medical Records

GHT: Glaucoma Hemifield Test

GSS: Glaucoma Staging System

HES: Hospital Eye Service

HFA: Humphrey Field Analyzer

HR: Hazard Ratio

IMD: Index of Mean Deprivation

IOP: Intraocular Pressure

IQR: Interquartile Range

MAE: Mean Absolute Error

MD: Mean Deviation

NICE: National Institute for Health and Care Excellence

OCT: Ocular Coherence Tomography

OHT: Ocular Hypertension

OHTS: Ocular Hypertension Treatment Study

OLS: Ordinary Least Squares

ONS: Office for National Statistics

POAG: Primary Open Angle Glaucoma

PoPLR: Permutation of Pointwise Linear Regression

PSD: Pattern Standard Deviation

RGC: Retinal Ganglion Cells

RR: Risk Ratio

SAP: Standard Automated Perimetry

SITA: Swedish Interactive Testing Algorithms

UKGTS: United Kingdom Glaucoma Treatment Study

VF: Visual Field

Acknowledgements

I would like to sincerely thank my supervisor David Crabb for the support, advice and opportunities provided to me throughout my three years in the lab. The skills I have learned under your guidance have been invaluable. I would also like to thank my external supervisor Anthony Khawaja for his encouragement and advice, both within my studies and without.

I want to acknowledge my friends, colleagues and collaborators in the Crabb Lab, in the UMCG and elsewhere. Not only for putting up with my near-constant distractions but also for never hesitating to lend a hand when it was needed. Every beer, coffee and chat was a pleasure. Thank you LLLADs and thank you G1, G2, BH & JE.

I would like to thank everyone involved in the Marie Curie EGRET and EGRET+ programmes as well as the EU itself. The right to live, work and experience different parts of Europe is an amazing opportunity and one that I hope continues long into the future. The friends and memories that I've made during this PhD have been incredible.

I want to thank my friend and mentor Susan Bryan, without whom much of this work would literally not have happened. I'll miss London but at least I know I'll always have a friend to go back and visit.

Despite being hundreds of miles away, my friends from Ireland have never let me feel alone and for that, I will forever be grateful. The late-night chats, gaming sessions and HCOL debates helped me to weather many storms. I'm looking forward to us all being in the same place together soon.

I owe Allie Loiselle more than can be put into words. Thank you for helping me (re)discover my love of research, life and good food.

Finally, I want to thank all of my parents and my families for keeping me grounded and always reminding me that I had a home waiting for me.

Declaration

The work contained in this thesis was completed by the candidate, Stephen Richard Kelly (SRK) under the supervision of Professor David Crabb. It has not been submitted for any other degrees, either now or in the past. Where work contained within has previously been published, this has been stated in the text. All sources of information have been acknowledged and references have been given. The University Librarian of City, University of London is permitted to allow the thesis to be copied in whole or in part without further reference to the author. This permission covers only single copies made for study purposes, subject to normal conditions of acknowledgement.

Support

The work carried out in this thesis would not be possible without the European Glaucoma Research Training Programme Plus (EGRET+). I want to acknowledge and thank the organisers for their work in managing the programme since it began in 2016. The EGRET+ programme received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Sklowdowska-Curie grant agreement No. 675033.

Abstract

Electronic medical records (EMRs) are increasingly being used for patient management in eye clinics in the UK. Glaucoma clinics in particular have an increasing capacity to store and link patient data from a variety of sources, including perimetric visual field (VF) records, intraocular pressure records, medication and surgical records. The studies detailed in this thesis aim to show, for the first time, the versatility of these data through a range of proof-of-concept examples. The studies were designed to show the different levels of scope that these data can be used for, from an individual patient level (patient performance), to a clinic level (auditing clinic performance) to disease level (retrospective cohort studies). The studies took advantage of two data extractions from EMRs from regionally different National Health Service (NHS) Hospital Trust glaucoma clinics in England. The first (2012) and second (2015) extraction yielded records from 88954 and 73994 people respectively. Central to these studies was the use of more than 1.2 million individual VF examinations. The first study tested the hypothesis that perimetric fatigue effects are greater in the eye examined second. The results showed that the second eye tested (usually the left eye) showed slightly reduced sensitivity (0.13 dB, $p < 0.001$) in mean deviation (MD) compared to the first eye. There was also a small but significant relative increase (3%) in the longitudinal variability of the second eye. This study provides evidence for statistically significant fatigue effects on the second eye tested in routine clinics. Although the average effect was small, there was a large variation among patients and as such, to keep any order effect consistent, eye testing should be carried out in the same order for each visit. The second study took routinely collected clinic data and audited aspects of service delivery of glaucoma. Metrics predicting loss of sight years and reliability of examinations varied between the centres ($p < 0.001$) indicating that some clinics may be performing better than others. This study illustrates the feasibility of assessing aspects of health service delivery in glaucoma clinics through analysis of VF databases and the proposed metrics could be useful for blindness prevention from glaucoma in secondary care centres. In the third study, the real-world conversion rates from ocular hypertension (OHT) to primary open angle glaucoma (POAG) were estimated. Within the study population ($n = 3163$), 17.5% (95% CI: 15.4% - 19.6%) were predicted to convert within 5 years. The use of intraocular pressure (IOP) lowering treatment was associated with a lower change of conversion with a Hazard Ratio of 0.45 (95% CI: 0.35 – 0.57, $p < 0.001$). Previously, it had only been in the context of clinical trials that OHT conversion rates and efficacy of IOP-lowering treatment have been reported, however this study shows the feasibility of using EMR data as an alternative. In the fourth study, the outcomes of patients with a combination of uveitis and glaucoma were compared with that of POAG only patients. The uveitis and glaucoma eyes were almost twice more likely to have rapidly declining VF function than the POAG only eyes (age-adjusted risk ratio of 1.9 [95% CI: 1.8 – 2.0]). It can be difficult to study the outcomes of a combination of diseases such as this due to the low incidence rate. However, when patient visits are recorded in EMRs in such large numbers it becomes feasible to carry out these retrospective cohort studies. In the fifth study, both previous datasets were assessed to investigate how socioeconomic factors affect likelihood of glaucoma detection and progression. People in the most deprived regions presented to the clinic with worse VFs than those in the more affluent regions. Once patients were diagnosed and treated under the management of the hospital eye services these dipartites dissipated. For example there was no evidence of differences in the rates of progression (worsening) of VF based on socioeconomic factors. In conclusion, the results from these studies show the breadth of research that is possible if EMR data from glaucoma clinics were to be fully utilised. Insights into individual patient care, the performance of clinics, and the prognosis of diseases could all be gained through the analysis of routinely collected data in eye clinics as well as an insight into the public health aspect of glaucoma.

1 Introduction to thesis

This introductory chapter gives an overview of relevant background information that underpins the research contained in the thesis. This will begin with a brief introduction to glaucoma, highlighting some clinical information that will be helpful in understanding the glaucoma-related studies. Following this, a more detailed section describing visual fields (VFs) and some approaches to analysing longitudinal VF data. Finally, a section detailing the two main electronic medical record (EMR) datasets used in the studies is included.

1.1 Glaucoma definition and epidemiology

Glaucoma is the term used to identify a group of irreversible progressive diseases that cause vision loss through damage of the optic nerve. It is one of the most common causes of irreversible blindness in the world.[1,2] Accelerated death of retinal ganglion cells (RGC), which play a vital role in the transfer of visual information from the photoreceptors to the optic nerve, is the primary mechanism of glaucomatous damage.

Glaucoma affects around 3% of the worldwide population aged between 40 and 80 with the prevalence of the disease rising as age increases. The number of people living with glaucoma is expected to be 76 million by 2020.[3] In primary open angle glaucoma (POAG), this damage usually occurs slowly over time, often over decades, requiring routine contact with the hospital eye service to ensure adequate management. As the life expectancy (and hence population of over 40s) of the UK is increasing, the burden on glaucoma clinics is steadily increasing. This thesis is focused on what is happening within English clinics only although the findings can broadly be related to the rest of the UK.

1.1.1 Risk factors & Treatment

While glaucoma encompasses several different diseases, the work in this thesis will focus on the most common type, primary open angle glaucoma. A related term, chronic open angle glaucoma (COAG) is a term used that covers variants of OAG with elevated eye pressure (POAG), normal pressure (normal tension glaucoma; NTG) and causes of secondary open angle glaucoma associated with pigment dispersion and pseudoexfoliation.[4] The NICE guidelines are evidence-based recommendations for health and care in England. They set out the care and services suitable for most people with a specific condition or need, and people in particular circumstances or settings. Glaucoma is often characterised by a raised intra-ocular pressure (IOP), optic nerve head damage and reduced VF sensitivity. There are several known risk factors for POAG. In short, these include older age, race, family history, diabetes, systemic vascular diseases, ocular perfusion pressure and optic disc area.[5–10] Some genetic factors have also been proposed such as the MYOC and OPTN genes.[11–13] The only modifiable risk factor however is the IOP.[7,14] In the general population, the mean IOP is around 16 mmHg and two standard deviations either side of this gives a ‘normal’ IOP range.[15] People with IOP above this normal range

but without detectable glaucomatous damage are referred to ocular hypertensives or glaucoma suspects. Conversely, it is possible for patients to have normal IOP but still develop glaucomatous optic disc damage and VF loss. This is referred to as normal tension glaucoma (or low-tension glaucoma).

At present, the detection of glaucoma primarily relies on opportunistic identification with optometrists responsible for nearly all referrals to hospital eye service for suspected cases. Referral guidelines for ocular hypertension (OHT) or other glaucoma include an IOP of 24 mmHg or more (as measured with Goldmann applanation tonometry) as one of the possible diagnostic criteria. [4] Previous guidelines set this IOP threshold at 21 mmHg and the EPIC-Norfolk study reported a prevalence of 10% for OHT in the English county of Norfolk using this IOP cut-off.[15] Current guidance recommends that IOP-lowering eye drops or selective laser trabeculoplasty (SLT) may be offered to patients with high IOP if they are at risk of visual impairment in their lifetime. A large randomised clinical trial, the Ocular Hypertension Treatment Study, showed the efficacy of IOP-lowering treatment on delaying (or even preventing) conversion from OHT to POAG.[5,16] Patients with OHT were assigned either to ocular hypotensive medication or to a placebo arm. The cumulative 5-year probability of developing POAG was reduced in the treatment arm by 60%. When a patient has already progressed to POAG, two other large clinical trials, the Early Manifest Glaucoma Trial and the United Kingdom Glaucoma Treatment Study, showed that IOP-lowering medication can slow down the progression of VF damage.[7,17] In both of these studies, patients with "early" glaucoma were assigned to either a placebo group or to a treatment group receiving ocular hypotensive medication. The frequency of progression as measured by VF or optic disc changes was reduced in both intervention arms. These results show the efficacy of using IOP-lowering drugs in the treatment of OHT and POAG to reduce progressive VF loss.

As of 2017, the current National Institute for Health and Care Excellence (NICE) guidelines recommend referral to secondary care for glaucoma related conditions under certain criteria. This involves assessment for glaucoma-associated signs in the VF (perimetry), IOP (applanation tonometry), optic nerve (slit lamp biomicroscopy/OCT) or anterior angle (gonioscopy) measurements. A repeat VF assessment and IOP measurement should then be considered before referral, to confirm a VF defect or an IOP of 24 mmHg or more. Patients who have been previously discharged from hospital eye services for COAG-related conditions should not be referred unless clinical circumstances have changed. Treatment may be offered in the form of one or more IOP-lowering eye-drops, surgery or laser treatment to lower IOP. Several classes of eye drops are available, all with the aim of reducing IOP by either reducing the production of aqueous humour in the eye or by increasing its outflow. Several studies have shown the clinical efficacy of these various different types of eyedrops.[17–19] Laser treatment, which can often be considered for an initial treatment (a so-called laser first approach), can also reduce IOP by increasing outflow.[20] A major trial showing the efficacy and cost effectiveness of SLT concluded that it should be offered as a first-line treatment.[20,21] Glaucoma surgery for refractory IOP is a relatively last resort option compared to less invasive treatments, of which, trabeculectomy is

considered the gold standard. A hole is cut into the wall of the eye (sclera) to allow for additional drainage of the aqueous humour.

1.1.2 Detecting and monitoring POAG

The structure-function relationship between changes in the optic nerve and how that translates into functional VF changes is unclear.[18] In certain cases, structural damage can be severe with only a mild change in VF function. Even when there is significant VF loss, the patient might not experience any difference in their day-to-day vision until it is very severe.[19] In this way, early to moderate glaucoma is said to be asymptomatic. Many glaucoma patients do not notice loss of their VF due to the nature of the damage: VF loss in the one eye can also be compensated by better vision in the fellow eye. As such, routine contact with primary eye care professionals is the most important way of catching glaucoma early and retarding loss of vision function. The number of cases of glaucoma worldwide is expected to increase with population increases.[3,20,21] As such, efficient referral schemes and efficient management of patients in glaucoma clinics will become increasingly important in years to come.

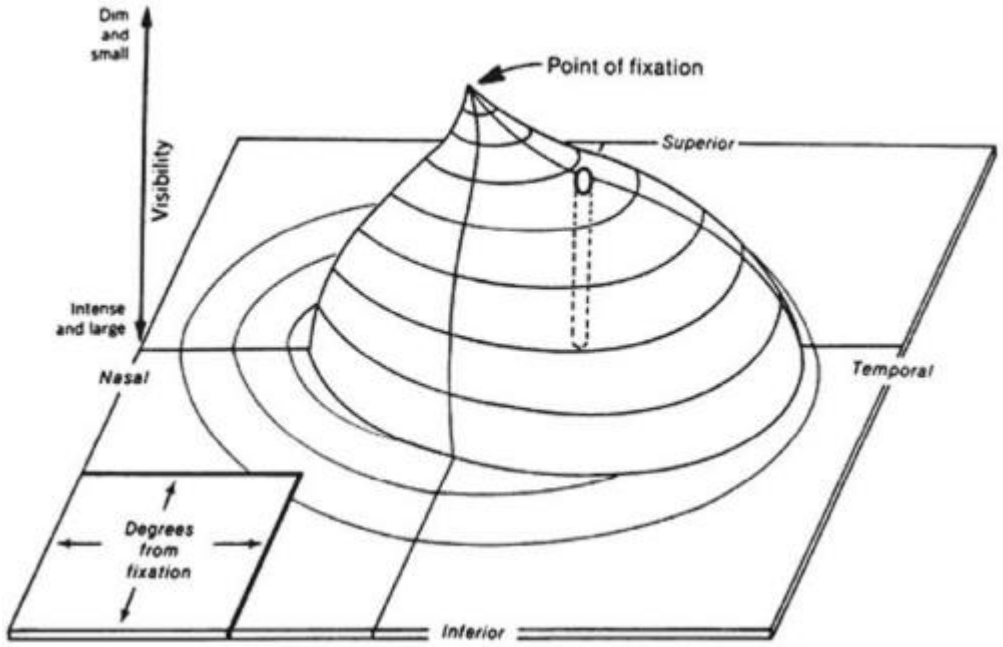
Diagnostic evaluation of glaucoma severity consists of an examination of the anterior chamber angle using gonioscopy, IOP measurements (ideally using applanation tonometry), examination of the visual field with perimetry and imaging of the retinal nerve fibre layer and of the optic nerve head.[22] After diagnosis, glaucoma requires lifelong monitoring which is typically carried out in secondary care. As glaucomatous damage is irreversible, the management aim is to delay the progression of the disease. IOP is currently the only modifiable risk factor for glaucoma and, as such, the main aim of glaucoma care is to lower IOP. After a patient is diagnosed with glaucoma, a target IOP pressure is decided upon. This is an estimate of IOP that, given the patient's age and disease severity, should be enough to prevent progressive VF loss that could cause a reduction in quality of life. As mentioned above, there are several options available to manage IOP levels. Functional and structural measurements are also taken at each clinic visit, typically through the use of standard automated perimetry and fundus photography/ocular coherence tomography, respectively. Ideally the monitoring interval should reflect the patient's individual condition, with higher risk patients being seen more frequently and low risk patients less so.[22] It is not clear however whether this is the case.[23]

1.2 A primer on visual fields

Simply put, the VF is the entire area that can be seen when the eye is directed forward.at a single object. The maximum extent of the VF is about 65 degrees superiorly 75 degrees inferiorly, 100 degrees temporally and 60 degrees nasally.[24] Within this range, and under photopic conditions, the greatest sensitivity corresponds to the fovea, with a decline in sensitivity as with increase in sensitivity. This can be helpfully depicted as an "island" or "hill" of vision with a steep central peak (Figure 1.1). Measuring this "hill" helps to detect when VF sensitivity is different from that which would be expected

for a patent's age. The hill of vision naturally reduces with age and as such, perimetry machines will require input of the age of the patient, so that it can compare against a database of correct "normal" values.

Figure 1.1: The normal hill of vision. The hill is highest at fixation, where visual sensitivity is greatest. The height of the hill of vision declines toward the periphery as visual sensitivity diminishes. (Image from Anderson DR: Perimetry with and without Automation. 2nd ed. St Louis, MO: Mosby, 1987.)



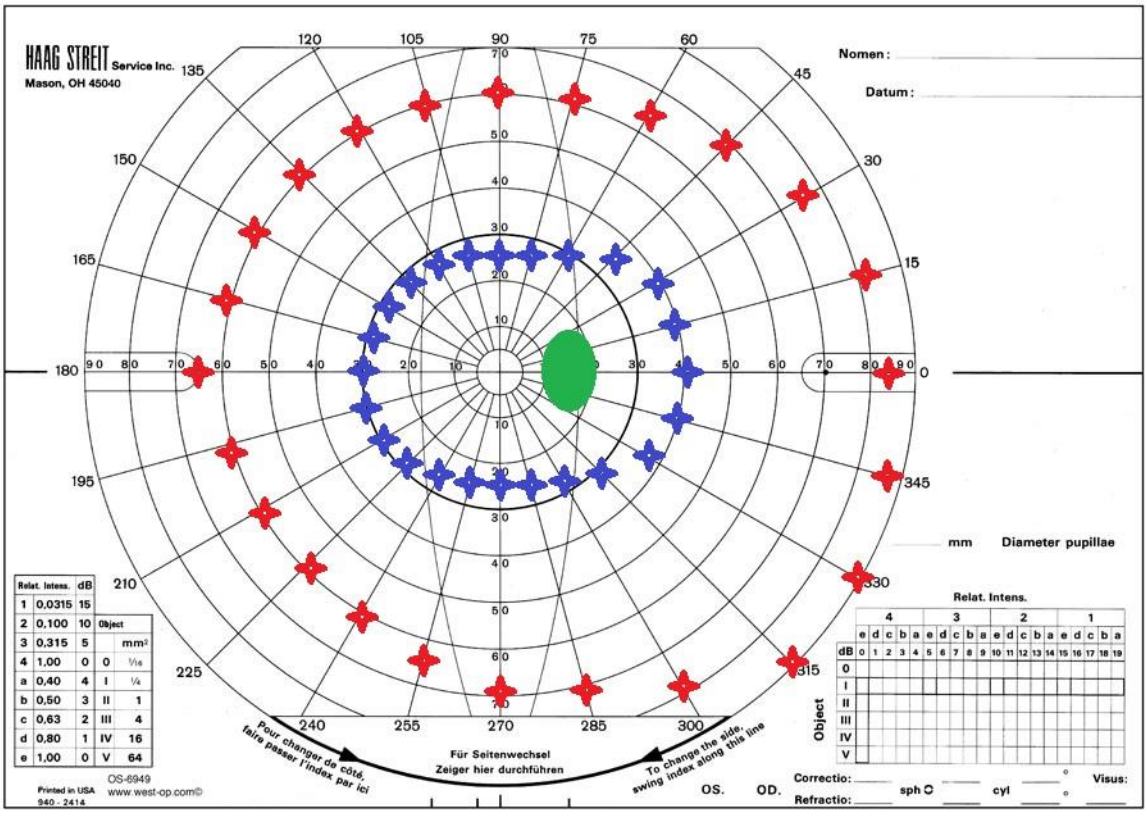
While any loss of the VF may be cause for concern, there are particular patterns of loss that are characteristic of glaucoma. Early glaucomatous damage is associated with either a paracentral loss, a nasal step, or a combination of both, in one hemifield.[25] As the disease progresses, the field loss becomes arcuate and then altitudinal by which time, the remaining hemifield has generally become affected.

1.2.1 Short history on VF testing

Perimetry as a method to test for visual field loss has been around for decades. The process involves determining if the sensitivity of the patients' VF is different to normal, as represented in the hill of vision (Figure 1.1). This can be done with the horizontal approach (marking isopters using kinetic perimetry) or with the vertical approach (separately testing fixed locations but varying the stimulus luminance). Traditionally the horizontal approach using the Goldmann Bowl Perimeter was the gold standard. This involved the patient placing their head in a large bowl while the technician controlled an arm that projected a stimulus onto its surface. The operator moved the stimulus, beginning in an unseen region such at the periphery into a central view. The patient pressed a buzzer when the stimulus became visible, marking the border of their visual field at a given stimulus brightness. The operator then moves

the stimulus radially towards fixation to verify that the stimulus remains visible. This is generally repeated along each 15 degree meridian around the visual field at a fixed brightness and the location at which the stimulus is first seen is taken as threshold. A line joining all the threshold points is known as an isopter. This is then repeated using different stimulus luminances and/ or different stimulus sizes to form additional isopters. As the operator controlled the position and movement of the stimulus by hand, this is known as manual kinetic perimetry. An example of an output of this is in Figure 1.2. The vertical approach, known as static perimetry, where a stimulus is presented at a single position in the field of view was also possible on the Goldmann perimeter but was very time consuming. This process became much quicker with the introduction of computers, leading to automated perimetry. Software enables control of the stimulus parameters, such as the uniform luminance white background, the stimulus size, duration and location and the stimulus algorithm (strategy) for the estimation of threshold . Smart algorithms (such as the SITA family of algorithms discussed later) allowed for an even further reduction in testing time. This approach has been so successful that it is still considered the gold standard for visual field testing today.

Figure 1.2: Mock example of a Goldmann Perimetry test result. The red crosses represent one isopter with a high luminance and the blue crosses represent another isopter with a lower luminance. The blind spot is marked in green.



1.2.2 Current state of VF testing

When using perimetry to monitor or test for glaucoma, examinations are done monocularly with the contralateral eye being covered with an eye patch. The patient's head is placed on the chin rest and they are instructed to keep their eye fixated on a single central point. White circular stimuli are then presented and the participant presses a button on a handheld remote when they see a presented stimulus. Different locations within a given region of the VF are tested until the threshold (defined below) is estimated at each point. The luminance of the stimuli on the Humphrey Field Analyzer (HFA) can vary between 0.08 to 10,000 apostlibs (abs; a measure of luminosity). This is reported in decibels (dB; a unit of measurement to express the ratio of one value to another on a log scale) of dimming from 0 dB (the brightest stimulus) to 51 dB (the dimmest stimulus). The formula to calculate the decibels from apostlibs (A) is:

$$dB = 10 \log_{10}\left(\frac{10000}{A}\right)$$

VF tests can employ either threshold or suprathreshold algorithms. In suprathreshold perimetry the stimulus is presented at aa luminance brighter than the age-corrected normal value and the response is either "seen" or "not seen". With this method, the depth of the any defect is unknown. Moreover, the suprathreshold increment is such that it can fail to detect loss which lies inside the increment.[26]

In thresholding tests, the stimulus brightness is varied with the goal of determining the luminance at which there is a 50% chance of the participant seeing the stimulus. This is carried out by using a psychophysical technique, usually by up-and-down staircase or bracketing methods. The original comprehensive VF testing algorithm was known as the (Full) Threshold strategy. This general principle of this strategy was to start with a luminance which was either infrathreshold or suprathreshold relative to the expected normal value and then to present the subsequent luminance 4 dB brighter or dimmer, depending upon the response of the patient. Once the threshold had been crossed the direction of the staircase was reversed and the stimulus was presented in 2 dB steps. The threshold at any given point was either the mean of the last "unseen" and "seen" values or the last "seen" value depending upon the type of perimeter. This meant there was a resolution of 2 dB and a difference from the "true" threshold of around 1 dB. On the Octopus system, the order of VF points was determined randomly. With the HFA, one "seed" point at 9,9 degrees in each quadrant were threshold initially and the starting value for their adjacent points were derived from these values.[26] Another earlier algorithm of the HFA, known as the FASTPAC algorithm was an attempt to make VF testing even faster and is designed to achieve threshold in two thirds the time of Full Threshold. It uses a single crossing with a 3 dB step size. While quicker, there is an increase in within-test variability (short term fluctuation) and underestimation of focal loss in glaucoma.

A “smarter” family of strategies, known as the Swedish Interactive Threshold Algorithms (SITA) that were developed in the 1990s, use additional information to allow for more rapid analysis without trading off accuracy.[27] The two versions of the SITA algorithm that are relevant to this thesis are the SITA Standard and SITA Fast strategies. They are designed to replace the Full Threshold and FASTPAC strategies respectively. These algorithms use likelihood functions for each location. A likelihood function measures the “goodness of fit” of a statistical model to a sample of data for given values of the unknown parameters. The functions are adjusted after each positive or negative response at a stimulus location. As the test proceeds, the height of the function estimates the most likely threshold value and the width measures the certainty of the estimate. SITA Standard uses a 4-2 step size like Full Threshold whereas SITA Fast uses a 4 dB step size. The testing stops when a specific level of accuracy is obtained, measured by the Error Related Factor.[28] The SITA algorithms are 50% faster than the algorithms they sought to replace. Depending on the eccentricity that requires testing, each algorithm examines out to 27 degrees, 21 degrees or 10 degrees, and are named 30-2, 24-2 and 10-2 respectively. The former provide locations based upon a 6 degree square grid whilst the latter provides location based upon a 2 degree square grid. The -2 refers to the fact that the locations do not lie on the horizontal or vertical meridians but are offset by 3 or 2 degrees. See Figure 1.3 (Section 2, left) for the grid layout on a sample subject.

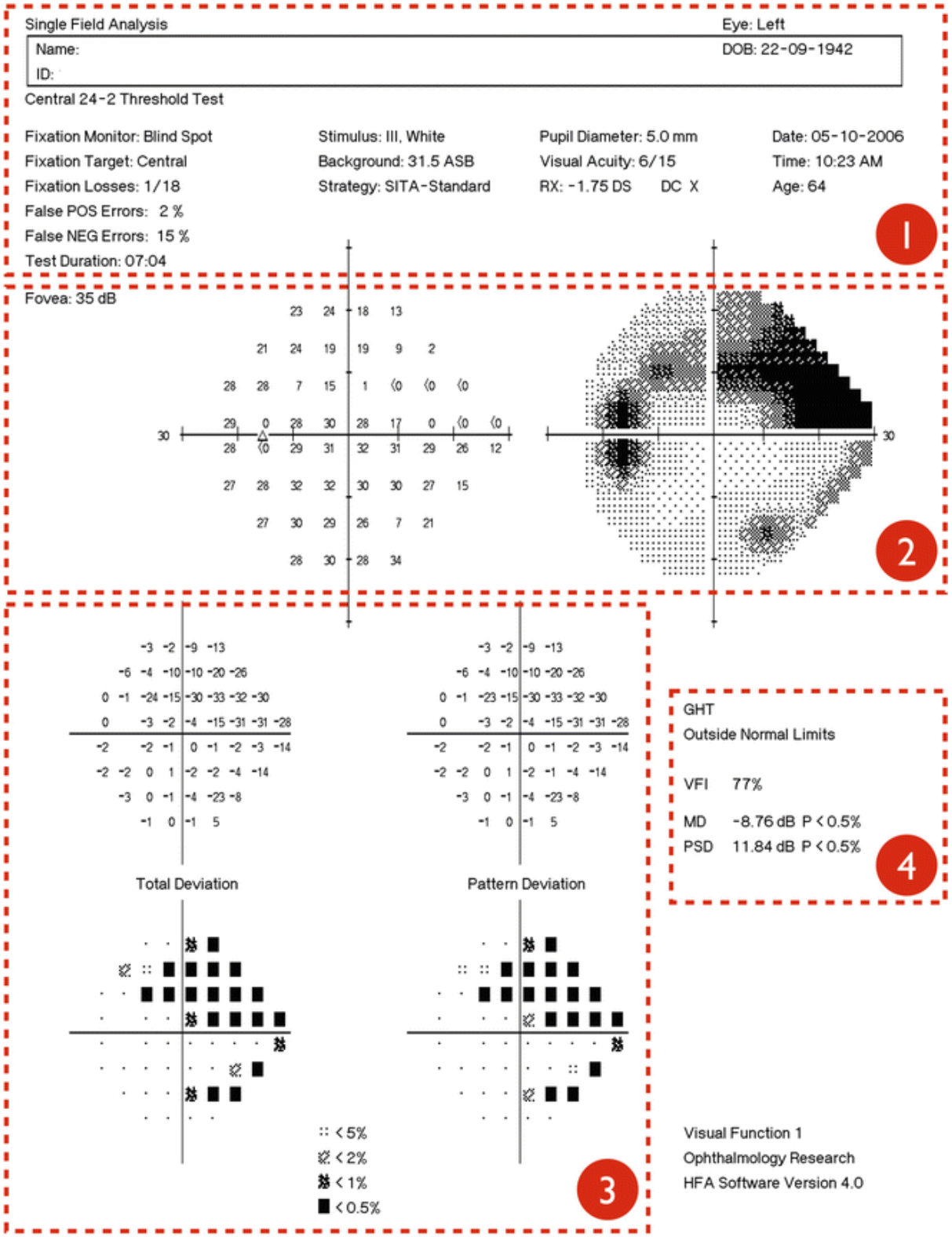
The SITA Standard strategy tends to take around 7 minutes per eye for Program 24-2 and the SITA Fast strategy, as its name might suggest, is slightly faster at around 4 minutes per eye. The SITA Fast strategy has been shown to slightly underestimate VF defects and so it is recommended more for screening purposes and the SITA Standard strategy is recommended for closer monitoring. Despite this, discrepancy, it has been shown that there is little difference in the time to detect glaucoma progression using either strategy.[29] Newer strategies are constantly being developed, even within the SITA family. The SITA Faster strategy, which looks to replace SITA Fast, is currently being rolled out and a clinical evaluation shows it to be around 30% faster with little difference in results.[30]

The printout of the results from automated perimetry are relatively standardised between the different types of perimetry and an example printout can be seen in Figure 1.3. In section 1 various fields of information, such as patient data, information about the settings of the test (stimulus size, strategy name, refractive error correction etc.) as well as the reliability indices are visible. These reliability metrics, False Positives, False Negatives and Fixation Loss attempt to quantify how well the participant was complying with the testing procedure. Every time the subject presses the button when no stimulus was presented (false positive) or didn’t press the button when a stimulus that should be visible was presented (false negative), this information is recorded and presented in the printout. To attempt to control for fixation, a stimulus is sometimes presented to the blind spot (an area that should not be visible). If the participant can see this presentation and presses the button, it may mean that they were not fixating at the central target. Of these three reliability indices, the literature tends to show that false positives are

the most significant predictor of performance.[31] In Figure 1.3, Section 2 the raw pointwise sensitivity values (in dB) and the corresponding greyscale plot can be seen. The greyscale plot visually represents scotomas (area of partial visual function loss) and VF defects, with the darker areas representing regions with more severe VF loss (i.e. regions that are less sensitive) regions. In Figure 1.3, Section 3 the patients' results compared to age-matched normative data is also visible. In the total deviation plot (top, left) the numbers represent how the subjects VF sensitivity differs to a healthy normal population. The pattern deviation plot (top, right) attempts to represent focal depressed areas when accounting for a blanket/diffuse reduction in sensitivity (as estimated by the total deviation plot). Conditions such as media opacities caused by cataracts or vitreous haemorrhages can cause an general reduction in sensitivity across the whole VF which is not representative of glaucomatous damage, and the pattern deviation plot tries to correct for this.

Finally, but arguably most importantly, at least for the analyses described in this thesis, in Figure 1.3, Section 4 is where the summary metrics are. From top to bottom is the Glaucoma Hemifield Test (GHT), the Visual Field Index (VFI), Mean Deviation (MD) and Pattern Standard Deviation (PSD). The GHT compares the upper and lower hemifields for differences and then reports whether the difference is within normal limits, borderline or outside of normal limits (indicating possible glaucoma damage). The VFI outputs a percentage from 100% (indicating a perfect, age-adjusted VF) to 0% (no visual function). It weighs the central points more heavily than the peripheral points when calculating the percentage score as these are typically more useful for visual function. The MD value gives a simple, average difference from normal values in the subject's age group, where a lower (more negative) score represents more damage. For example, a value of -8.76 dB means that the subject's VF was an average of 8.76 dB lower than that from a visually healthy control across all the points. The PSD value provides information about localised loss, with a high value indicating a non-uniform sensitivity loss (i.e. not from cataracts, which could cause a largely negative (bad) MD value). While PSD in theory sounds like a better measure of VF worsening, it has a couple of drawbacks. Namely, the PSD value may seem to improve even when VF sensitivity is worsening due to it attempting to correct for global depressions. For this reason, most of the research in this thesis uses the MD value as a summary measure for visual function (although PSD is used in some chapters in conjunction with MD).

Figure 1.3: Example of a HFA VF printout. The printout is made up of 1) Patient information, test settings and reliability indices, 2) Sensitivity and greyscale printouts, 3) Total deviation and pattern deviation plots and 4) The GHT, VFI, MD and PSD summary measures.



As with any psychophysical testing, a large source of unreliability or variability (noise) comes from the participants themselves. Even with a young, healthy and perfectly compliant subject, the test-retest reliability of VF exams can be large.[32–34] One main factor that introduces unwanted variability into VF testing (especially over time) is a "learning effect". A learning effect (with regards to VF testing) is a process in which a subject's results may seem to be improving (their VF sensitivity increasing, for example) but in reality the subject is just becoming more familiar with (and better at) the testing process. This effect has been shown to happen over several visits. It is for this reason that often times, the first (or first few) VF exams of a series are excluded as they could be artificially worse due to inexperience with the testing process.[35,36] In this thesis, any study that deals with longitudinal data excludes the first VF in a participant's series to attempt to mitigate this learning effect. A complement to the learning effect is a so-called fatigue effect. In many of the older (and slower) testing strategies, it was shown that as the duration of the test increased, the VF sensitivity tended to decrease (and variability increased) as patients became fatigued. Often a short break of a few minutes was not enough to combat this. Very little research of a fatigue effect had been done to date on the more recent (and quicker) testing strategies (SITA family). In Chapter 2 of this thesis, a short-term fatigue effect using the SITA strategies is investigated.

In real terms, even though SAP is the gold standard of VF testing, it is far from perfect. As mentioned earlier, due to the subjective nature of psychophysical testing, results tend to have a lot of noise. Even with the most compliant patients, it can take many tests over time before a clear picture of how the VF is changing becomes clear. Taking the test itself can be unpleasant too, especially for older people (which happens to be the demographic that most frequently uses it).[37] Sitting on a stool that is incorrectly adjusted can be uncomfortable and staring at the fixation target can be tiresome.[37] This perhaps may be a thing of the past as newer forms of VF measurements become available. In recent years, a lot of work has been done to make VF testing less strenuous. Laptop and tablet-based tests (possibly suited to home testing) are being trialled as are eye tracking approaches that require no input from the participant.[38] It is possible that some day, the laborious act of balancing your head in a white dome will be a thing of the past. Until then however, SAP is a necessity as are techniques to analyse the data it produces. There are many groups around the world working on this problem.[39–46]

1.2.3 Analysis of VF data

Collecting the VF data is only one of the challenges when it comes to understanding visual function. Once the raw sensitivity values are collected (using for example a 24-2 SITA strategy) there are numerous approaches one can take to analyse the data to glean some insights from it. A common approach is to try to distil much the available information into one, easy to understand summary number, such as mean sensitivity (MS) which is just the mean of all the sensitivity values. Other slightly more involved metrics are more commonly used, some of which are mentioned above. Measures such as MD,

PSD, VFI and GHT are useful for an "at a glance" summary of the status of the eye. When only considering one VF exam in isolation, this is usually called single field analysis. What tends to be more important is how this VF changes over time. There are two main approaches to evaluate the progression of VF defects, event-based change analysis and trend-based analysis.

Event-based analysis tries to answer the question, "has either glaucomatous field loss become manifest or has existing glaucomatous field loss worsened?". A common example of event-based analysis software is the in-built guided progression analysis (GPA) included with the HFA perimeter. This software looks at a series of VFs over time (minimum of 3) and tries to detect if progression has occurred. It does this by looking at the individual pointwise pattern deviation value and checking for repeated consecutive significant reductions in sensitivity from the baseline value. The approach is based on the Early Manifest Glaucoma Trial (EMGT) criteria for VF progression. The outcomes are "possible progression" and "likely progression". Possible progression is defined as three or more VF points that deviate beyond the 95% confidence interval for expected test-retest variability for two consecutive visits. Likely progression is the same criteria but for three consecutive visits. A major drawback of GPA is the high rate of false positives it can produce. Artes et al found that by randomly arranging 12 VF tests in a three month period, there was an 18.5% false-positive rate for "possible progression".[47] While event-based analysis is useful for checking if a patient has progressed, it does not say anything about the rate of progression, or how quickly visual function is being lost over time. For this type of information, trend-based analyses are needed. A very simplistic trend-based analysis is to take one of the VF measures, and model it over time using a linear regression. The slope of the fitted line, measured in dB/year, gives an estimation of how much dB would be lost per year at the current rate with no intervention. Many of the studies in this thesis utilise this type of analysis using ordinary least squares (OLS) linear regression models. Linear regression can be applied to the summary metrics (such as MD or PSD), to clusters or to individual points. Knowing an estimate of the rate of VF loss can give an indication of when a patient may experience severe VF loss (or even blindness) and so is useful for informing a clinician of what course of treatment to take. VFI is a trend analysis that scores the VF from 100% (normal, healthy eye) to 0% (end stage glaucoma). A linear regression of VFI over time can be used to measure the rate of VFI deterioration.

The Medisoft PROGRESSOR software is frequently used in a research setting to evaluate glaucoma progression.[48,49] A linear regression is fitted for each test location and the slope and p-values are used to detect how many locations are "significantly" progressing. The criteria of an eye progressing is usually determined by a number of statistically significant progressing test locations. The downside of this approach is that confounding factors such as a diffuse media opacity (cataracts) can result in a false-positive for glaucoma progression.

The above highlights that with linear regression, the progression criteria (slope and p-value of varying locations) is somewhat arbitrary. The permutation of pointwise linear regression (PoPLR) approach combines the pointwise statistics into a single statistic using the Truncated Product method and then calculates the p-value for overall change through permutation analysis.[50] This method is an individualised approach that assumes the ordering of the VF tests does not matter unless actual VF deterioration has taken place. It is independent of factors such as baseline VF damage, number of test locations, length of follow-up and dB scale making it useful to compare VF progression across different types of protocols.

Other more sophisticated models exist that can be used to model VF progression. Multi-level models are statistical models that vary on more than one level. For example, a model of a patient that contains measures for individual patients as well as the clinics they attend. They are extensions of linear models that are useful for dealing with "nested" data. When using this type of model, researchers must decide what parameters will be included in the model and whether they will be "fixed" or "random". Fixed effects are constant across groups whereas random effects can be different across groups. These types of models are also known as mixed-effects models as they can contain both fixed and random effects. In the context of modelling VF progression over time, there are two main variables that a researcher must be concerned with, they are the intercept and slope. The slope is the rate of progression over time (dB/year) and the intercept is the MD value at time zero (baseline). These two criteria can be fixed or random across groups. It's possible to have a model where slopes are modelled as fixed but intercepts are modelled as random. In the above example, this model would assume that the rate of VF progression is the same across the clinics and that only presentation (intercept) can vary. The most realistic (but most complex) models are usually when the slopes and intercepts (and other possible variables) are modelled as random. Increasing complexity does not always provide a better model and so there are model fit statistics available to judge how well the model balances complexity and accuracy. These include the chi-square likelihood-ratio rest which can be used to build/compare nested models, and the Akaike or Bayesian information criteria (AIC and BIC respectively). There are many more types of perimetry and many things that need to be considered when analysing VF data that are not listed here. To find out more about recent developments in perimetric testing and analysis, the reviews by Wu and Hu respectively provide a more complete picture.[51,52]

1.3 Datasets

1.3.1 Electronic Medical Records

Once the various examinations are administered and treatments are prescribed, it is useful to have these data stored somewhere for easy patient management. Historically this has been done manually using paper records, with electronic tests being stored on individual machines. A more efficient solution to this was the Electronic Medical Record (EMR) system. These EMRs are computer-based record keeping systems that have the long-term aim of replacing paper records within medicine. Traditional paper medical records would be replaced with structured, digital data stores which could be easily searched for, exported and analysed. The interested reader can find out more about using EMRs in health outcomes research in the review by Dean et al.[53] An ideal EMR would be connected to the various instruments in a clinics and any examinations could be easily (or automatically) added to the patients' records. If set up and utilised correctly, a clinician would have full access to any and all patient information or results from a single computer. An example view of the Medisoft EMR is shown in Figure 1.4. These EMRs have been introduced into many ophthalmology clinics and studies investigating their impact are beginning to emerge.[54–67]

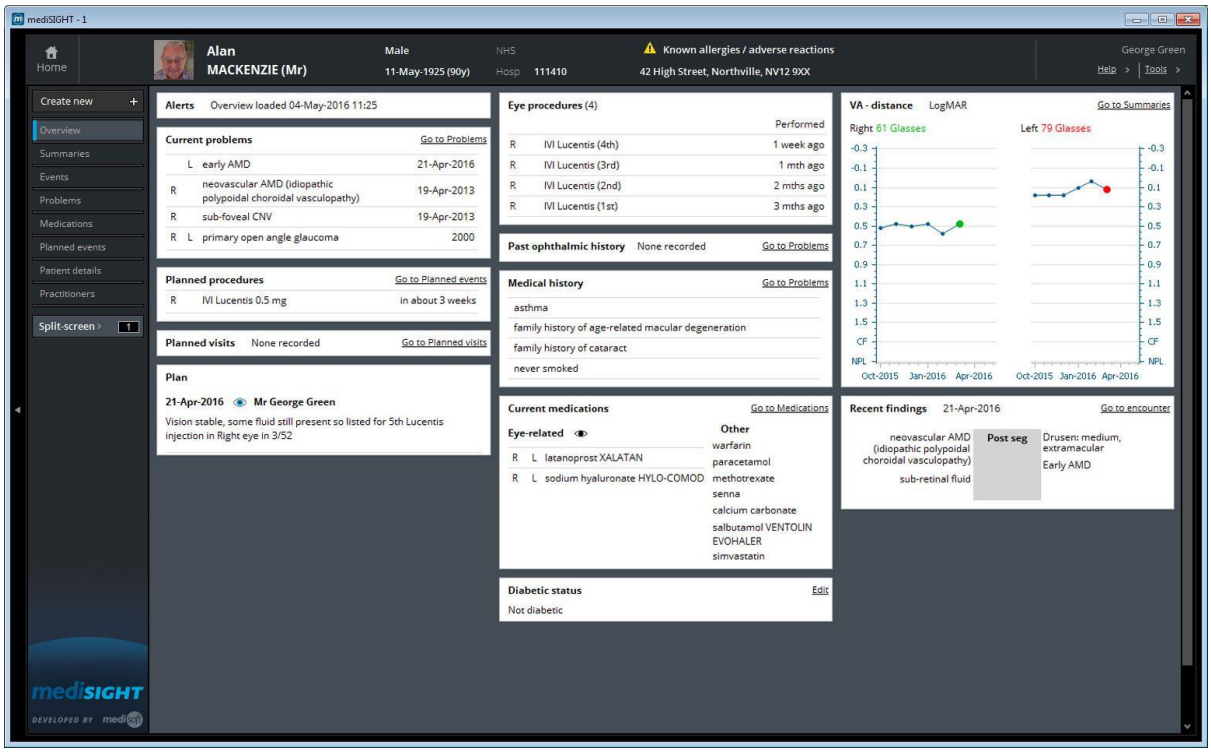
Across the UK, EMR systems are slowly being rolled out to healthcare providers. There were plans for the National Health Service (NHS) to go fully digital by 2020 although for a variety of reasons this has not been achieved.[68] One reason for the delay is a lack of funding support. Another may be a lack of clinical engagement. In 2002, The National Programme for Information Technology (NPfIT) was a £12.4 billion initiative to revamp the English NHS with IT. Despite some successes, it was discontinued in 2011 and dubbed a "fiasco" in the media. The main consensus for this was that without the involvement of clinics, the focus was on merely getting computer systems into the NHS and not on service change. Clinicians were forced to adapt to these changes without being given reasons for why they were happening and without any strategy for engagement.[69]

While the introduction of computer systems to hospitals has been fraught with issues, GP practices in England are almost completely digital, working with some form of EMR system. The benefits of these systems are numerous but a few that have been cited are: less space required for paper notes, helpful and customisable decision support programmes and improved quality of care demonstrated by less errors, reduced variability and the ability to easily compare practices.[70] A number of drawbacks include a lack of training and user interfaces that are cumbersome and inflexible. There is a whole field of research around user interfaces (UX design) and finding out the best approaches for getting users to use software appropriately.[71–73] It is not always the case that the users know best. What users might prefer (free text boxes for notes, drop down menus) or what may be familiar to them, in all likelihood

will not be the most efficient way to do things. Striking a balance between ease of use and efficient use will be the main factor that holds back EMR uptake.

In an ideal world, all aspects of healthcare would be digitised and available for all those involved in health service delivery. The possibilities for further integration are numerous. If general practitioners and pharmacies were added to an EMR network, it could streamline the prescription of drugs as well as recording a more thorough medical history.[74,75]

Figure 1.4: Example view of an EMR system entry (image sourced from the Medisoft Medisight website. The data is not from a real patient.)



1.3.2 Using VF data to help in glaucoma management

SAP is widely used in research settings but is possibly underutilised within clinical practice.[76] As IOP is the only modifiable risk factor for disease progression, it becomes the centre of attention in the follow-up and management of glaucoma patients. While recommendations state that new glaucoma patients should receive 6 VF tests within the first two years of diagnosis, this is often not met.[6] A clinical audit of glaucoma clinics in England found that most newly-diagnosed patients received less than three VF tests within in the first two years. [77] Many of the sophisticated methods to analyse VF defects mentioned previously are not available to the clinician and so they must rely on pre-packaged software such as the GPA on the HFA. This is slowly changing as EMR systems that have ophthalmology packages are being introduced into practices. Control of IOP is usually the main factor in deciding treatment adequacy. This over-reliance on IOP may contribute to glaucoma patients

becoming visually impaired or blind while under care.[78,79] If the goal of treatment is to preserve visual function and prevent visual disability, then the measures of *function* must be given equal if not more consideration than IOP. As POAG can present with normal (low) IOP in the form of NTG, it does not make sense to measure adequacy of treatment with a measure that is not necessary nor sufficient in glaucoma.

The possible reasons for underuse of VF testing are numerous. SAP generates large volumes of data that can be time consuming to collect and even more so to interpret without adequate software. Patients, too, are not fond of the procedure but accept that it is a part of their routine care.[23] Despite this, having sufficient VF data and analysis methods are crucial in providing the clinician with the tools that are needed to provide more targeted care and better functional outcomes. Results from a study looking at the frequency of VF testing in the UK found that increased early testing may in fact be cost-effective. This is even more so when gains to society rather than just the NHS are considered.[23] Despite this, many glaucoma specialists consider increased surveillance of the VF would be impossible with current resources.

Functional testing, particularly binocular testing, is the best approximation as to how disease will affect daily life. This makes it all the more important to put in place measures to make use of as much VF data as possible. Smart EMR systems that can incorporate decision support algorithms could improve clinical management. The introduction of newer/improved VF analysis could make better use of the limited resources glaucoma clinics possess. If increased VF testing would be impossible within clinics, perhaps at-home monitoring could play a role in future glaucoma management.[38] If these at-home tests were able to connect to a hospitals EMR, it could free up time and resources for clinic visits.

1.3.3 Data used in this thesis

The two sources of patient data used for the studies in this thesis both come from EMR extractions of glaucoma clinics in England. Both of the datasets were collated and stored on Medisoft (Medisoft Ltd., Leeds, UK) EMR systems.

The first of these, the VF only dataset, contains 473,252 VFs from 88,954 patients extracted from three different glaucoma centres in England. These are Cheltenham General Hospital Gloucestershire (2000-2011), Queen Alexandra Hospital in Portsmouth (1999-2011) and the Calderdale and Huddersfield NHS Foundation Trust (2000-2011). Data access was granted by the Caldicott Guardians (person responsible for protecting the confidentiality of peoples healthcare information in hospitals in England) at each centre. As well as the usual data that is recorded on a HFA (date of birth, time of test, VF results etc.) it also contains patient postcode data. This dataset has previously been used by others to explore aspects of VF testing including measurement precision, frequency of testing and health economic

factors related to glaucoma.[23,34,77,80–84] The data was used in various studies investigating the health economics of glaucoma, the variability of perimetric testing and the use of perimetry in the fitness to drive test. This dataset is used in Chapters 2 and 6 of this thesis to investigate additional aspects of VF testing. While many interesting studies can be designed using the data contained in this dataset (VF data plus additional postcode data), it would be also useful to know more about the subjects. If this dataset could be linked to other related datasets (such as one containing medications or IOP measurements) it would greatly increase the range of studies possible.

The second dataset used in this thesis, contains data from several linked sources. As well as VF test records, there are records of patient demographics, history of diagnoses, medications, IOP measurements, visual acuity records, recorded co-pathologies and glaucoma surgeries. There are also records of cataract surgeries and diabetes status. The data were extracted from Gloucestershire Hospitals NHS Foundation Trust, Hinchingbrooke Health Care NHS Trust, Peterborough and Stamford Hospitals NGS Trust, Portsmouth Hospitals NHS Trust and the University Hospitals Bristol NHS Foundation Trust. These data were recorded between April 2000 and March 2015. The National Ophthalmology Database (NOD) was established under the auspices of the Royal College of Ophthalmologists (RCOphth) in 2010. The NOD aimed to collate pseudonymised data collected as a by-product of routine clinical care using EMR systems for the purposes of national audit, research and establishing meaningful measures for revalidation of ophthalmologists.[85] In 2014, the Healthcare Quality Improvement Partnership (HQIP) commissioned NOD to do a feasibility study to investigate the use of VF data to audit activity in glaucoma clinics. The results of the study are reported in Chapter 3, with the specific aim of examining the viability of extracting meaningful metrics of health service delivery that might in future allow comparison between glaucoma clinics. A further look at the other research outputs from NOD are also discussed in Chapter 3. A data sharing agreement between NOD and City, University of London was established to allow additional future studies relating to various aspects of glaucoma management in the hospital eye services. The work generated from these studies appear in Chapters 3 to 5.

Supplementary data from various sources are also used in the studies contained in this thesis. Statistics from the UK government Office of National Statistics (ONS) on socioeconomic deprivation were sourced from the GOV UK website (https://data.gov.uk/dataset/8f601edb-6974-417e-9c9d-85832dd2bbf2/english-indices-of-deprivation-2015-lsoa-level). Census data relating to the age and ethnicity of populations in parts of England were also sourced from the GOV UK website (https://data.gov.uk/dataset/150b43db-10ce-465d-9961-29e679350a9d/2011-census). Additional data such as shapefiles (the files used to store mapping data) and location of optometrists (used to draw the maps in Chapter 6) were also sourced from the UK GOV website.

1.4 Aims:

The prime objective of Big Data analysis is to process data of high volume, velocity, variety and veracity using traditional and novel computational techniques.[86] According to IBM, 90% of the data that exists in the world today was created in the last two years. This data is coming from all sorts of sources, from YouTube videos to social media updates and now increasingly, medical data. At this rate of growth, a proper understanding of how to manage electronic medical Big Data will be crucial to extracting useful insights in the future. The main aim of this thesis is to determine what can be done with regards to analysing existing large databases of routinely collected ophthalmic data. Chapters 2 through 6 are a selection of studies that show the broad range of research that can be carried out using data available in glaucoma clinics. They highlight the current opportunities in ophthalmic research, specifically gaining insights about glaucoma testing, the progression of ocular hypertension, how glaucoma is affected by uveitis and the relationship between glaucoma and socioeconomic status using Big Data. As well as opportunities, this thesis also involves highlighting where data-related challenges had to be overcome to achieve these results.

Chapter 2 answers the question of whether there is a clinically meaningful difference in the results of the first and second eyes tested with SAP. Often if there is a real effect, no matter how small, an increasing amount of data will eventually produce a statistically significant result. If the effect is too small however, it may not be clinically relevant. This chapter highlights the difference between a highly significant result (due to the sheer amount of data) and usefulness in clinic.

The remaining chapters (3 to 6) use a second dataset in their analyses. This dataset comes from multiple sources and is linked together using the anonymised patient ID. With additional demographic information it is possible to analyse the large volume of data from each clinic and compare them to each other. Chapter 3 compares five English glaucoma clinics based on selected VF (severity, reliability and frequency), demographic (age, gender) and mixed (predicted loss of sight years) metrics. The amount of data from clinics is drastically increasing and smart management of these data is crucial to be able to identify its utility. In Chapter 4, VF data is linked with diagnostic, demographic, IOP, surgical, medication and comorbidity data to predict the in-clinic conversion rate from OHT to visual field loss. The real world is quite different to clinical trials and it is not a guarantee that results from trials are easily transferable to a clinic setting. This study combines various different sources of data to model OHT conversion and compares it with prominent trial results to determine if there is a difference. Chapter 5 looks at a subset of patients with both uveitis and glaucoma. As this a relatively rare combination within glaucoma clinics, a population size of almost 100,000 is needed to find 200 patients fitting the inclusion criteria. This study emphasises the power of using Big Data to carry out studies on rarer conditions or combinations of conditions. In Chapter 6, socioeconomic and VF data are linked to investigate the association between deprivation and glaucoma presentation and progression. Other

studies have shown a link between socioeconomic deprivation and late glaucoma presentation but this study highlights that once these patients are monitored within the health service, they have similar outcomes to affluent populations.

Finally, Chapter 7 provides a brief summary of the key findings from the previous studies and discusses them in the context of past and potential future work. The findings will be disseminated to glaucoma care providers and policy makers through direct and indirect channels.

The works contained in this thesis have been presented at national and international conferences by myself and colleagues and have been positively received. Many of the contacts made during the course of this PhD have been with academics who sit on scientific committees or are a part of groups/charities that campaign for policy change. It is my hope that these works can affect some positive change for those who are afflicted by glaucoma.

Dataset 1 primer – The visual field dataset

The data used in Chapter 2 is an extraction of VF data (along with postcode data) from several glaucoma clinics across England. Medisoft VF databases (Medisoft Ltd., Leeds, UK) containing 473,252 VFs from 88,954 patients were extracted in 2012 from glaucoma clinics at Moorfields Eye Hospital in London; Cheltenham General Hospital Gloucestershire Eye Unit; Queen Alexandra Hospital in Portsmouth and the Calderdale and Huddersfield NHS Foundation Trust [81,84,87]. Data access was granted by the Caldicott Guardians (person responsible for protecting the confidentiality of people's healthcare information in hospitals in England) at each centre. The data was anonymised at the point of extraction, so that no identifying information was transferred to City, University of London. The data was transferred via encrypted flash storage to the secure City, University of London database. Access is restricted to only those that possess an account that is flagged for access. The studies using these data adhered to the Declaration of Helsinki and all analyses of the data were approved by a research ethics committee of City, University of London.

These data have previously been used in several studies investing various aspects of glaucoma and VF progression. Saunders et al. published several studies using these data revolving around the precision of measurement of VF testing, the relationship between MD and the legal fitness to drive and predicting VF loss of patients based on their remaining lifetime.[29,82,87,88] Boodhna et al. published two longitudinal studies investigating the change in trends in glaucoma clinics over time.[81,84] Russell et al. used the data to investigate the variability and sensitivity of VF testing.[34,89]

One limitation of using this type of data is the lack of diagnosis labelling for patients. Although they are in glaucoma clinics and receiving VF testing, many patients may only be there for a once off test or for a false positive referral. As such, if one is trying to develop a surrogate label of patients with POAG, additional criterial, such as a minimum number of visits would be needed. In Chapter 2 date and time recorded on the VF machine is used to differentiate which eyes were tested in what order.

2 Does the eye testing order for visual fields matter?

The work presented in this chapter has formed a paper published in *Acta Ophthalmologica* (Kelly et al., 2019); see list of supporting publications. The co-authors on this paper are Susan Bryan (SB) and David Crabb (DC). The analysis contained in the study (including the R code and production of figures) and the drafting of the manuscript was carried out by SRK which was reviewed and edited by SB and DC. This work was presented at the Association for Research in Vision and Ophthalmology 2018 conference.

2.1 Introduction

The primary method for determining functional deterioration in glaucoma is an evaluation of VF series over time, as measured by standard automated perimetry (SAP). Examination results from SAP are susceptible to high levels of measurement variability from different sources, including the patient themselves. Good examination procedures and instructions produce usable results in the vast majority of patients.[6,90] Nevertheless, measurement variability in SAP hampers clinical interpretation of the VF. For example, several examinations need to be considered before progression or stability of the VF can be confirmed with confidence against this background of measurement variability.[6,91]

The fatigue effect mentioned in Chapter 1 has been shown in studies to also exist within a single session of perimetry, decreasing sensitivity in the second eye tested.[92,93] Studies reporting these effects were conducted at a time before better perimetry algorithms were developed to reduce test time. More efficient examination techniques, like the Swedish Interactive Testing Algorithms (SITA Standard or SITA Fast) on the Humphrey Field Analyzer (HFA; Carl Zeiss Meditec, Dublin, CA), have become a clinical standard and are assumed to be less susceptible to fatigue effects.[80,94,95]

SAP necessitates testing both eyes separately and sequentially. Conventionally, the right eye is usually tested first so that any examination order effects will be as constant as possible from visit to visit. Few studies have considered this testing order effect in SITA testing. One study examined patients with two prior sets of SITA Standard 24-2 test results performed on the right eye first.[96] A subsequent test was performed on the left eye first. No significant differences in summary measures of the VF were found suggesting that, on average, it probably does not matter which eye is tested first. These findings might be corroborated by comparing right eye with left eye perimetry results among a large number of patients whose right eyes had been tested first. This is an idea examined in this study. If the VF sensitivity in the second tested (left) eye is worse than in the first tested (right) eye then this may suggest a testing order effect. Measurement variability from fatigue effects in the second tested eye may also possibly accumulate over a series of follow-up visits; this is also explored.

This study investigates an eye testing order effect in retrospectively observed large-scale VF data from glaucoma clinics. First, the hypothesis that average VF sensitivity is worse in the second tested (left) eye compared to the first tested (right) eye in HFA SITA VFs is tested. Second, a surrogate of measurement variability in the second tested (left) eye compared to the first tested (right) eye in series of HFA SITA VFs is examined. Furthermore, to what extent any detectable order effect is associated with patient age and the length of rest time between first and second eye examinations is analysed. As measurement variability is inherently linked to the number of VFs required to estimate the likelihood of progression, these findings could help determine if detection is being delayed due to a second-eye fatigue effect.

2.2 Materials and Methods

As mentioned in the VF dataset 1 primer, this data uses a multi-centre Medisoft VF dataset. No other clinical data was made available other than each patient's age. Subsequent analyses of the data were approved by a research ethics committee of City, University of London and this study adhered to the Declaration of Helsinki.

Patients aged 30 years or older with VFs from the HFA using Goldmann size III (white-on-white) stimuli with the 24-2 test pattern acquired with either SITA Standard or SITA Fast testing algorithms were included in the study. Patients were only included if they had at least six recorded VF examinations (consistently with SITA Fast or consistently with SITA Standard) where both eyes were tested on the same day. Patients were not excluded on the basis of longer follow-ups but for these analyses, only the first six examinations were considered. The first VF in each series was then omitted in order to attempt to account for perimetric learning effects.[97,98] This left a total of 6,901 patients for analysis. These data represent a population of people receiving routine follow-up in glaucoma clinics in England.

For these analyses, only patients where eyes were tested in the same order at each examination, with right eye tested first, were included. The first VF examination of each series was defined as the baseline VF. HFA mean deviation (MD) values were extracted for each VF for each eye. MD estimates overall VF sensitivity, relative to healthy age-matched observers, with more negative values indicating greater VF sensitivity reduction. Average MD for first eye tested (right) and second eye (left) tested, from the baseline examinations only, were compared; no difference in these values would suggest no average systematic eye testing order effect.

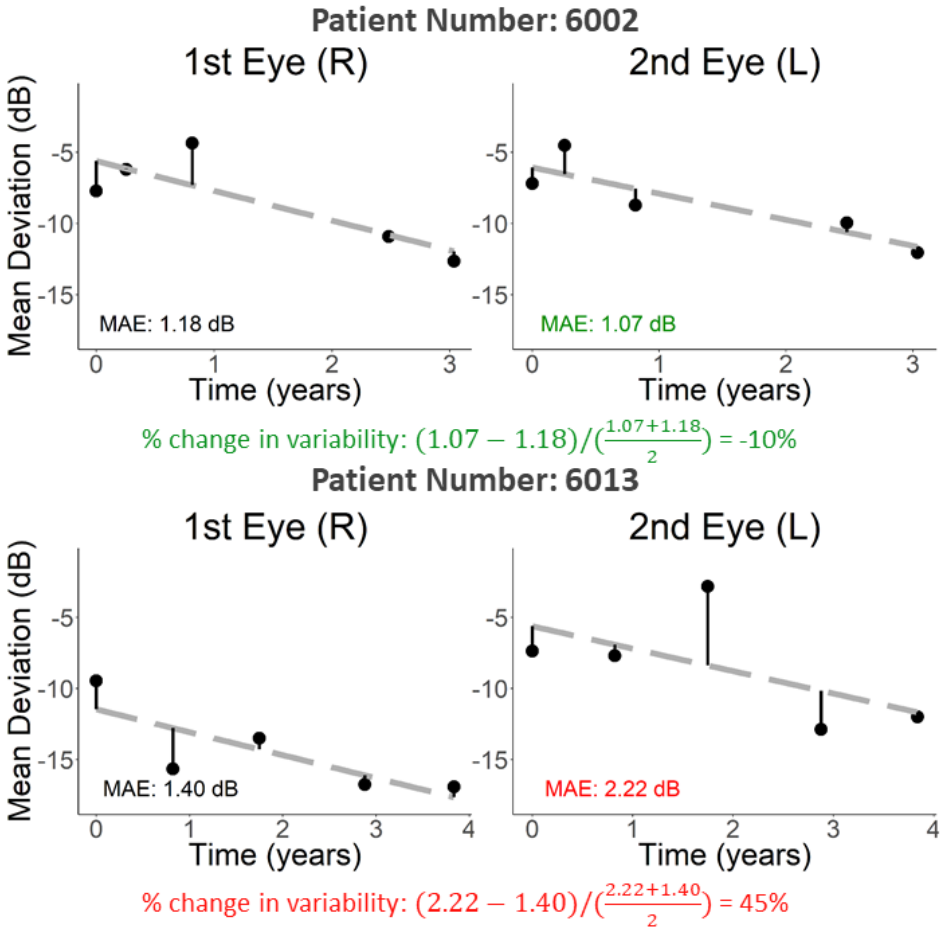
To investigate differences in long-term measurement variability in the eye tested first or second, MD over the five examinations was analysed for each patient. Ordinary least-squares linear regression of MD against time was used to extract errors (predicted values minus the observed sensitivity [dB] values) at each examination (Figure 2.1). The mean of these absolute errors (MAE) was used as the estimate of long-term measurement variability. For example, a series exhibiting high measurement variability

would have variable MD values (after removing any trend for change over time) yielding a high MAE value. The increase (or decrease) in MAE for the second tested eye compared to the first tested eye, relative to the average MAE in both eyes, was calculated; this effect, expressed as a percentage, was the surrogate used for long-term measurement variability due to an eye testing order effect (See Figure 2.1). VF measurement variability is directly related to the amount of VF loss.[89] For example, a patient with early VF loss in their first tested eye but advanced loss in their second tested eye will likely have more measurement variability in the latter regardless of any fatigue effects. Therefore, in order to minimise noise the analyses were repeated on a subset of patients where overall VF loss was similar in both eyes (left and right eye baseline MD within 3 dB of each other).

Furthermore, it was also examined if this potential order effect was associated with the age of a patient or the rest time between the first and second eye exam. All analyses were done using R (R Development Core Team, R: A Language and Environment for Statistical Computing, R Foundation for Statistical Computing, Vienna, Austria, URL: http://www.R-project.org, 2008).

Figure 2.1: Calculation of absolute errors (vertical lines) and relative MAE increase (%) for two different patients. Patient 6013 has more long-term measurement variability in the second eye tested

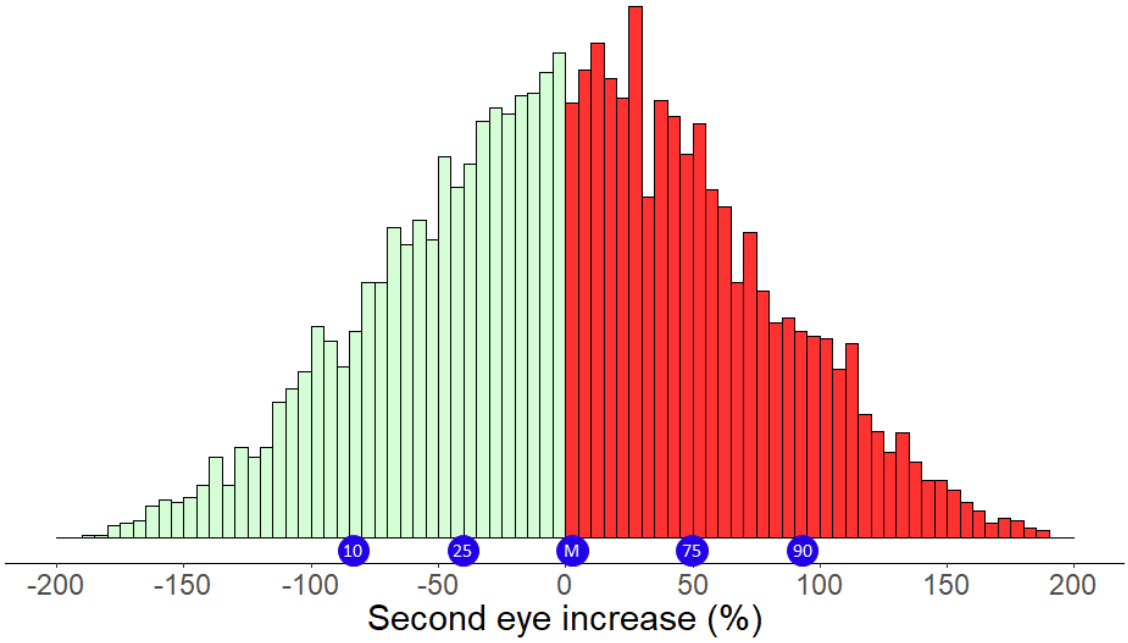
with a 45% increase in the surrogate measure. In patient 6002, the long-term variability is more similar in both eyes.



2.3 Results:

Median (interquartile range [IQR]) age of the patients and length of follow-up for the five examinations was 66 (56, 73) and 4.5 (3.5, 5.8) years respectively. From the population of 6,901 patients with sufficient VF follow-up, 6,320 (91.6%) had consistently been examined in a right eye then left eye sequence at each SAP examination. Only seven (0.1%) patients had been consistently examined in left then right eye sequence. The remaining patients (574; 8.3%) were excluded due to the eye testing order not being consistent (not always right eye first). These numbers illustrate the remarkable adherence to the convention of testing the right eye first in perimetric examination in the clinic.

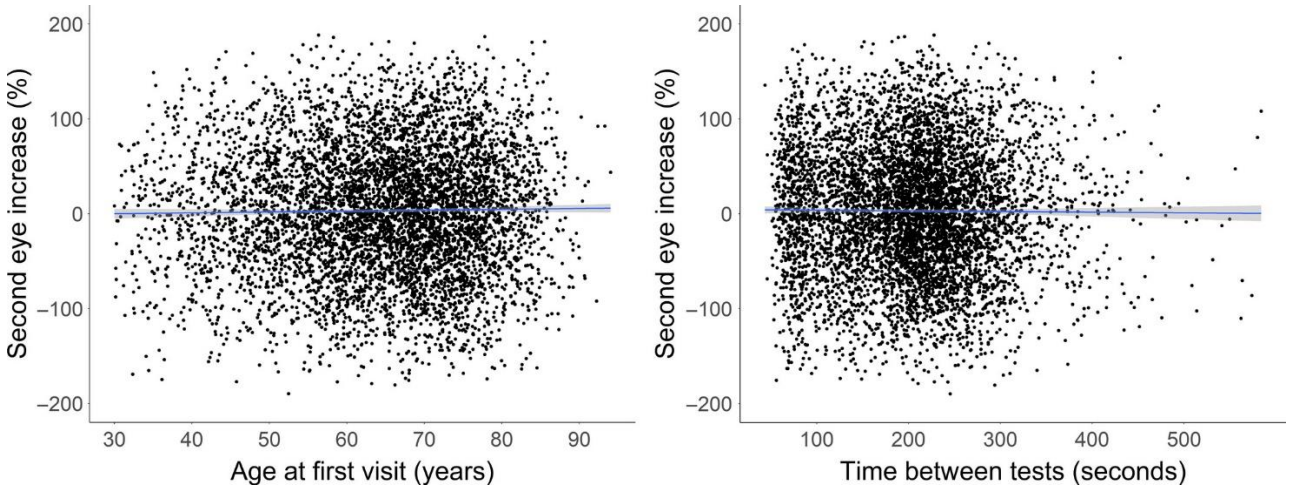
Figure 2.2: Distribution of the percentage change in second eye variability with labelled median and 10th, 25th, 75th and 90th percentiles.



Median (IQR) MD in the first tested (right) eye and second tested (left) eye was -2.57 (-6.15, -0.58) dB and -2.70 (-6.34, -0.80) dB respectively. This average decrease in MD from first to second tested eye was statistically significant (Wilcoxon signed rank test; $p<0.001$) but small in magnitude (median difference of 0.13 dB, 95% CI: -0.26, -0.02). This average worsening in VF sensitivity in the second eye tested could be explained by a fatigue effect but the magnitude of the average effect is small.

Measurement variability in MD values from series of VFs performed in clinics, as measured by relative change in MAE, varies considerably between eyes in the same patient (Figure 2.2). Relative median (IQR) increase in second tested (left) eye measurement variability (order effect) was 3% (-43, 50%) and this was statistically significant ($p<0.001$). This effect was small and obviously not consistent across all patients. Yet, it does indicate that on average the second tested eye in SAP accumulates slightly more measurement variability during a follow-up in a routine clinic. This average effect remained unchanged (median = 3%) when analysis is restricted to patients with similar overall VF loss in both eyes (n=4,528). Yet, as would be expected, the IQR narrowed, but only moderately (-39, 48%). The analysis was also repeated using series of 10 VFs, the IQR narrowed again to (-30, 33%).The eye testing order measurement variability effect was not associated with the age of a patient ($p=0.20$), nor was it associated with the time (seconds) between testing the first and second eye ($p=0.53$) with $R^2 \sim 0$ in both cases. (Figure 2.3). So, any accumulative measurement variability in the second tested eye is not inflated in older patients or associated with the period between each eye examination.

Figure 2.3: Scatter plots showing the change in variability as a function of baseline age (left) and rest time between exams (right) with fitted linear model (blue). The blue line would slope upwards (or downwards) to indicate a change in effect size with age or rest time. The time between tests is censored at 600 seconds resulting in 0.3% of patients being excluded.



2.4 Discussion:

Several factors contribute to measurement variability in automated perimetry. For some patients this perimetric variability may be inflated by examination fatigue, which will worsen during prolonged testing. Therefore, the second eye examined may be more susceptible to fatigue induced variability. This leads to at least two scenarios in the clinic: an instruction to examine the eye of interest first or examining eyes in a consistent order so that any fatigue effects will be as constant as possible from visit to visit. More simply, the right eye is always tested first following a convention for most eye examinations; this was supported by the results from this study with over 90% of patients consistently being tested right eye first.

The results of this study indicate that average VF sensitivity, as estimated by HFA MD, was slightly worse in the second eye examined (left eye) in a large sample of over 6,000 people. Assuming no physiological reason for left-right eye VF sensitivity differences this sensitivity decline might be attributed to a fatigue effect. This study also explored the accumulation of measurement variability in the second eye tested using a novel serial analysis of MD variability. Results from this analysis suggests some evidence of more measurement variability in the second eye tested. It is important to note this order effect is an 'average' effect and likely too small (3% increase) to impact on results from routine clinics. For example, it has been suggested that a decrease in longitudinal variability of about 20% is needed to detect a progression one visit earlier using linear regression of sensitivity values over time.[99] Still, in situations where small differences in average precision could affect the statistical power to detect an outcome measure, such as in a group of participants in a clinical trial, it might be worthwhile to test the "study eye" first.

Most studies highlighting perimetric fatigue were done when automated perimetry was hampered by longer exam times.[92,93,100] SITA strategies halved testing times compared to the full threshold algorithms and have become the standard for HFA examinations.[27,94,101,102] One study, with a similar aim to ours, recruited patients from clinics with two prior sets of SITA Standard 24-2 test results performed on the right eye first and then deliberately examined them once with the left eye first. There was no statistically significant difference in the MD, or the test reliability measures, among the three test results for either eye. The results in this study contradict these findings. It is however important to reiterate that the average sensitivity decline between first and second eye tested is very small and it probably still does not matter which eye is tested first when considering MD. A series of factors thought to influence SITA HFA VF measurement variability, or spurious changes in VF sensitivity, were thoroughly investigated by Montolio et al.[31] Not-so-obvious factors such as *the time of day* and *the season* (time of year) when examinations are performed were considered. The effects were real and statistically significant but similar in small magnitude to the eye examination order effect on longitudinal variability that was observed. Fatigue in the second eye tested, then, does slightly increase measurement variability in that eye during follow-up but in context of other minor factors, it is relatively similar.[31,103–105] Ultimately, to minimise VF variability patients should be encouraged to produce reliable results by making sure they understand what to expect, and what they need to do during an examination, even if they have done them several times before.[6,37,90]

No association was found between change in between eye measurement variability (order effect) against age of patient, or against the rest period between right and left eye examination. These results indicate that older age or a shorter rest period between examinations did not explain any of the increase in between eye variability. Whilst the latter is interesting, interpretability is very limited by the retrospective nature of this data. For example, decisions about how long to 'rest' patients between examinations may be made because the patient is already tiring, complaining or asking for a rest. In Frequency Doubling Technology (FDT) perimetry, an experiment showed the existence of a "second eye" effect, where there was reduced sensitivity in the eye tested second (compared to a monocular baseline) when using an opaque eye-patch. This effect was abolished when a translucent patch was used, showing the changes were less to do with fatigue and more to do with adaptation.[110,111]

This study was multi-centre and utilised a Big Data approach to the analysis by incorporating anonymised data from several thousands of patients. Using a large repository of electronically stored VF data is useful for auditing different aspects of glaucoma related healthcare such as testing hypotheses about the management of patients. Moreover, these data represent unselected people in glaucoma clinics that are receiving routine care and therefore estimates are directly meaningful to in-clinic or 'real-world' practice. When using Big Data it is important to be able to differentiate between statistically significant and clinically meaningful outcomes. This study highlights a highly significant, but very small, relative change in sensitivity between the first and second eye tested. The distinction is important to note

because as larger and larger datasets become available to use for medical research, statistical significance will become easy to reach. The importance in results then becomes the clinical utility and not just a measure of significance.

This study has some key limitations. The dataset used in this study is missing the false positives reliability indices due to an unknown (and likely input) error in handling the data before it was transferred. Poor practices around data storage and transfer can result in missing or corrupted data. In these instances, it is important to evaluate whether or not the omission of these data introduces bias into the study.[112] In this instance, while it may have been of interest to carry out a secondary analysis looking at the unreliability indices such as FP, there is evidence to show that the metrics themselves are unreliable. [6,107,113] As datasets become larger and sourced from multiple locations, these types are errors could become more frequent if proper data management practices are not maintained.

Another limitation is that the study only considers data retrospectively. As such, there was no control over the data used for assessing change in long-term variability; for example, some patients might have deliberately not been followed with VFs in these clinics because they fatigued so badly during the testing. These people would not be represented in this study.

The order effect we detected is an average effect and it varies enormously between patients. A suggestion for future work would be to design a study that can help determine how well a particular patient can remain vigilant and avoid fatigue. Clinics certainly need better ways of determining which individuals are more likely to produce reliable perimetric results so we can better use perimetry resources.[114] Better use of eye tracking to measure surrogates of vigilance, like pupil diameter, might better estimate fatigue during perimetry.[115] Moreover, occlusion of one eye while testing the first could also affect variability in the second tested eye in perimetry in some people. This might be the result of perceptual deprivation (ganzfeld) effects whilst the eye is occluded.[116] It would need a prospective study to study this hypothesis.

In conclusion, statistically significant average perimetric fatigue effects were observed in the second eye tested in routine clinics using HFA SITA examinations. However, the effects were very small and there was enormous variation meaning some patients may experience a perimetric fatigue effect by the time their second eye is examined, whilst others are unaffected. Clinically it therefore seems reasonable to continue to start with a right eye examination so that any perimetric fatigue effects, if they exists in an individual, will be as constant as possible from visit to visit. Perhaps, in situations where measurement precision needs to be maximised, such as in a clinical trial using VF measures as an outcome or endpoint, it may be worthwhile to examine a “study eye” first.

Dataset 2 primer - New opportunities and challenges using linked datasets

Anonymised recorded data between April 2000 to March 2015 were extracted from the Medisoft (Medisoft Ltd., Leeds, UK) EMR from five regionally different NHS trusts in England and linked to the Royal College of Ophthalmologists' (RCOphth) National Ophthalmology Database (NOD).[113] These centres were Gloucestershire Hospitals NHS Foundation Trust, Hinchingbrooke Health Centre NHS Trust, Peterborough and Stamford Hospitals NHS Trust, Portsmouth Hospitals NHS Trust and University Hospitals Bristol NHS Foundation trust.

The NOD was established under the auspices of the RCOphth in 2010. The NOD aimed to collate pseudonymised data collected as a by-product of routine clinical care using EMR systems for the purposes of national audit, research and establishing meaningful measures for revalidation of ophthalmologists.[85] In 2014, the Healthcare Quality Improvement Partnership (HQIP) commissioned NOD to do a feasibility study to investigate the use VF data to audit activity in glaucoma clinics. The results of the study are reported here with the specific aim of examining the viability of extracting meaningful metrics of health service delivery that might in the future allow comparison between glaucoma clinics. The resulting database contained records from 71,404 patients. As with Dataset 1, Dataset 2 was anonymised at the time of extraction/collation by NOD before being shared with City, University of London. The dataset was transferred to City via encrypted flash storage before being added to the secure database that is password protected.

The database contains linked medical and demographic data such as diagnosis labelling, medications, glaucoma surgeries, IOP measurements, copathologies, cataract surgeries as well as information on diabetes status, retinal detachments and race/age/sex. This data also included socioeconomic deprivation scores as measured by the Index of Multiple Deprivations (IMD). While the breadth of the dataset is impressive, it could also pose a challenge if scaled up to more than a few clinics. As each visit for each patient is potentially another entry in each of the datasets, the amount of data balloons rapidly with for each patient. The amount and complexity of data being collected is increasing with time and how this will affect hospital record systems needs to be considered. Many hospitals use computers and servers that were not designed to handle Big Data. This could potentially lead to a slowdown (and potential crashing) of computer systems if not dealt with appropriately.

This dataset is used for studies in the following four chapters. In Chapter 3 and Chapter 6, only the VF data and VF data plus socioeconomic data (IMD score) were used respectively. In Chapter 4, linked diagnostic labels are used to define three groups (POAG, OHT and Glaucoma suspect). Copathology data and visual acuity (VA) data were used to include or exclude patients. Treatment status (IOP lowering treatment or surgery) was used to classify patients into different arms for a survival analysis.

In Chapter 5, diagnosis and copatholgy labels were used to define the two study groups (POAG and POAG plus uveitis). The linked IOP records were used to investigate the relationship between IOP and VF progression within the two groups. A further look at some of the other studies produced using the NOD are also discussed in Chapter 3.

3 Using electronic medical records to audit service delivery in glaucoma clinics

The work presented in this chapter has formed a paper published in *BMJ Open Ophthalmology* (Kelly et al., 2019); see list of supporting publications. The co-authors on this paper are Susan Bryan (SB), John Sparrow (JS) and David Crab (DC). The entire content of analysis contained in the study (such as the R code and the production of figures 3.1, 3.2 and 3.2) and the drafting of the manuscript was carried out by SRK. The code for Figure 3.4 (the hedgehog plot) was produced by SB. The draft manuscript was subsequently reviewed and edited by SB, JS and DC.

3.1 Introduction

EMRs have potential to form a repository of data on patient encounters that can be directly used in research and clinical audit.[60] The latter can be used as a first step towards improving health service delivery and improving patient care. Indeed, it is only possible to gauge improvements in a process after it has been measured in the first place.

Glaucoma clinics in Hospital Eye Services (HES) in England handle more than one million patient visits per year.[4,110] Most of these visits are for monitoring people with established glaucoma. Once diagnosed, all patients with glaucoma require lifelong monitoring so that any worsening of disease can be detected and treatment intensified accordingly. Patient management focuses on monitoring the VF, assessment of the optic nerve and measurement of the IOP. The latter is critical because it is the only modifiable risk factor for the condition worsening (progression).[7] Research evidence from clinics in England suggest measures of IOP are the main determinant of how often a patient is monitored over a period of time.[23,77] In contrast to IOP, a measurement of the VF is the closest surrogate to what matters to the patient in the glaucoma clinic, that is, preservation of their vision.[76] VF monitoring is therefore recognised to be critically important for the clinical management of the patient but it is also perceived to be difficult to do unless it is well implemented.[6,37,114] The computerised technology used to measure VFs (standard automated perimetry; SAP) has been in clinics for 20-30 years and has remained largely unchanged. Data from SAP are stored electronically, often in an EMR. These records, which are likely to be historically rich, should be amenable to easy electronic auditing. Therefore, at different clinical centres it might be possible, for example, to audit measures of disease severity (VF loss) of patients at diagnosis. Moreover, it might be possible to audit speed at which patients in different clinics might be losing vison and, for example, whether frequency of VF monitoring is consistent across clinics. It is these ideas that are explored in this report. Additional information regarding the source of the data can be found in the preceding primer for Dataset 2.

The “hedgehog plot” (Figure 3.4) is a novel approach by Bryan et al. of assessing and visualising VF progression within populations, in this case, in glaucoma clinics. It allows clinics or even individual clinicians to analyse their data easily.[115] It can also be used to swap between population level and individual patient level to see individual rates of progression or “loss of sight years” (a metric to estimate loss of vision in a person’s remaining lifetime). An online web app to visualise your own data can be found at https://crabblab.shinyapps.io/hedgehog.

3.2 Methods

The VF data were extracted from the Medisoft EMR system (Medisoft Ltd., Leeds, UK) from five regionally different National Health Service (NHS) Hospital Trust glaucoma clinics in England. The extraction was done in November 2015 and data transferred to the RCOphth NOD. All patient data were anonymised and subsequently transferred to a single secure database held at City university. For the purpose of this report the five centres are anonymised. No other clinical data were used in this study other than the patient’s age, gender and the dates of the VF examinations. Subsequent analyses of the data were approved by a research ethics committee of City, University of London; the study adhered to the Declaration of Helsinki and the General Data Protection Regulation of the European Union. The database material contained 602,439 separate VF records from 73,994 people (Table 3.1) recorded between April 2000 and March 2015.

Table 3.1: Total number of VFs per centre. Each centre is simply labelled 1-5 and represented by a specific colour. This colour coding is used throughout this report. (Every centre had data recorded between April 2000 and March 2015 except from centre 5 where data were first recorded in May 2000)

	Centre 1	Centre 2	Centre 3	Centre 4	Centre 5
Number of people	3,423	8,459	27,921	18,636	15,555
Number of VF records	16,162	65,355	285,552	113,847	121,523

3.2.1 Inclusion and exclusion criteria

SAP in these clinics, and most others in England, is routinely performed on a Humphrey Visual Field Analyzer (HFA, Carl Zeiss Meditec, Dublin, CA, USA). Only VFs recorded on the HFA using a Goldmann size III stimulus with a 24-2 test pattern acquired with the Swedish Interactive Testing Algorithm (SITA Standard or SITA Fast) were included, reducing the aggregated database to 576,615 VFs from 71,361 people. SITA fast is commonly used in clinics in England. (Although SITA Standard is a more precise testing algorithm than SITA Fast at lower VF sensitivities, it is unlikely to make a

sizeable difference to improving the time to detect VF progression.[80]) In this specific study population, 83% of the recorded VFs were SITA Fast and the rest were SITA Standard.

For the purpose of this report, the study population was defined as people in glaucoma clinics with measurable and sustained VF loss in at least one eye. This definition aims to exclude people suspected of having possible glaucoma (glaucoma suspects) and people with normal VFs and raised eye pressure (ocular hypertension [OHT]). Therefore, patients were only included if they had a VF with a HFA mean deviation (MD) flagged as outside the 95% normative limits in the HFA VF analysis software in at least one eye. (MD is a standard measure of the overall severity of VF loss, relative to healthy peers, with more negative values indicating greater VF loss). Moreover, this proxy criterion for measurable VF loss had to be satisfied for both of the first two VFs recorded in the clinic; this was done in order to improve the precision of the estimate of an individual likely to have real VF loss at their presentation to secondary care. The number of patients satisfying these criteria expressed as a percentage of the total number of people with a VF record was calculated. This can be thought of as a simple count of people in clinics with actual VF loss at presentation to secondary care (diagnosis) as opposed to, for example, being a glaucoma suspect, a false positive referral or having OHT.

3.2.2 Metrics for assessing service delivery

Six different metrics were calculated to characterise and estimate aspects of patient monitoring and outcomes in the clinics.

Age at presentation was estimated by the age of the patient (years) at the time of their first VF record.

Reliability of VFs was estimated by using the HFA false positive (FP) measure. It is accepted that HFA FP is a useful measure of a reliable examination.[31] The HFA-II flags VFs as unreliable if there are more than 33% FP errors. As these VFs were recorded using the HFA-II the FP cut-off used was 33%, although there are other potential values that could have been used. The more recent HFA-III, for example, sets the FP unreliable rate at 15%. Percentage of all VFs considered as unreliable due to FP errors was therefore determined for each centre.

Stage of VF loss at presentation was estimated by MD in the worse eye (the one with the more negative MD) at the second VF examination. The second VF was used to ameliorate the bias of the perimetry learning effect.[97,98] The worse eye was chosen as a surrogate of the most 'detectable' level of VF loss at the stage of case finding in primary care. Patients with MD worse than -12 dB in this eye were defined as having advanced VF loss. Patients with MD better than -6 dB in this most affected eye were defined as having early VF loss, with all other patients classified as having moderate VF loss. These VF criteria have been used in health economic investigations of service delivery of glaucoma.[116,117] The proportion of patients within each of these three categories (early, moderate, advanced) can be summarised in a *traffic-light waffle plot* (green, yellow, red) for each centre.

Next, a subset of the study patients with sufficient series of VF examinations were defined as those with at least five VFs recorded over a period of four or more years. This subset of data were used for three more metrics summarising patient follow-up activity at each clinic.

Speed (rate) of VF loss in clinics was determined by using simple linear regression of MD against time of follow-up (dB/year) and was only calculated in patients with series of data. The first VF examination in each series was removed to account for perimetric learning effects. These rates were then graphed for each centre by fitting a smoothing line to the peaks of a histogram (kernel density estimation vis the geom_density() function in ggplot2).

Risk of VF loss blindness in clinics was estimated by a Loss of Sight Years (LSY) metric as described elsewhere.[115] In short, LSY estimates the number of years that a patient will have bilateral VF loss worse than MD of -22 dB (binocular VF impairment) in their predicted remaining lifetime.[87] The metric considers rate of VF loss in both eyes and the patient's residual life expectancy based on age and sex as reported in UK Office of National Statistics.[118] Residual life expectancy takes into account that a person aged, for example, 80 years is more likely to live to age 81 years than someone aged 70 years and is a useful measure of relative life expectancy. For patients with two eligible eyes with series of VF data it was determined whether LSY would be predicted to be longer than three years. The percentage of patients in each centre with this attribute was then calculated.

Frequency of VF examination in clinics was simply estimated as the average interval (months) between recorded VF examinations during the follow-up period in those patients with series of VF data.

Summary measures and distributions of these metrics were evaluated and compared for the five glaucoma clinics. Medians and interquartile ranges (IQRs) were used along with conservative non-parametric tests to make simple, illustrative comparisons between clinics. All analyses were done using R (R Development Core Team, R: A Language and Environment for Statistical Computing, R Foundation for Statistical Computing, Vienna, Austria, URL: http://www.R-project.org, 2008).[119]

3.3 Results

Table 3.2: This table shows the summary measures of a number of metrics across the five centres (and a total column). The six main metrics highlighted in the methods section are given in bold font. Median (and interquartile range [IQR]) values or percentages are given in bold font. Median (and interquartile range [IQR]) values or percentages are reported as summary measures.

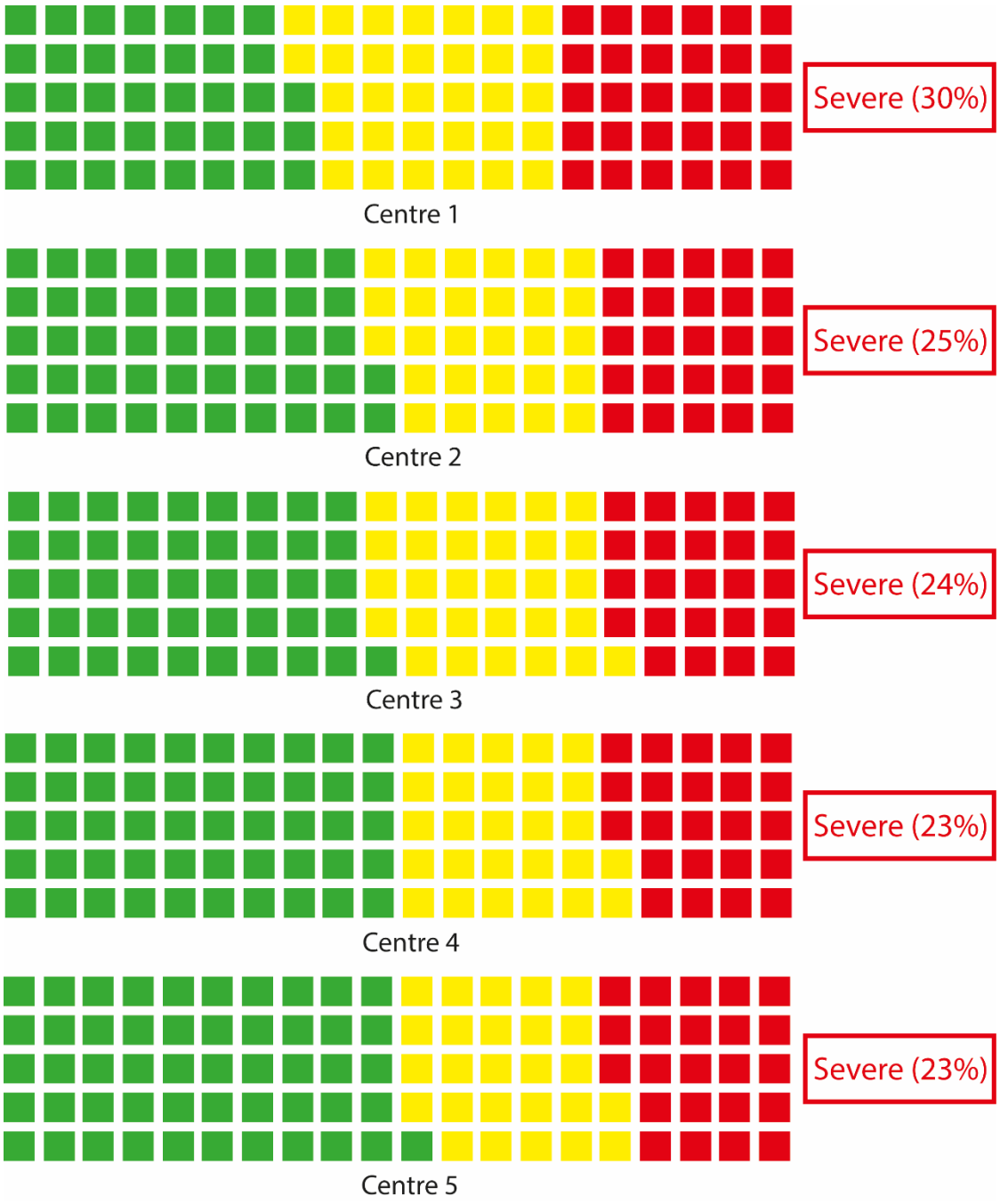
	Centre 1	Centre	Centre 3	Centre 4	Centre 5	TOTAL
Number of Patients with VF loss	1,373	2,404	11,589	5,713	4,681	25,760
Number of VFs	7,813	19,654	121,939	36,011	35,737	223,379
Sex (% men)	45.6	45.2	47.1	47.7	44.8	46.5
Median (IQR) Age (years) at presentation	**75 (67, 80)**	**71 (61, 78)**	**71 (61, 78)**	**71 (62, 79)**	**69 (58, 77)**	**71 (61, 78)**
% of unreliable VFs	**3.0**	**4.4**	**5.1**	**4.3**	**4.1**	**4.6**
Median (IQR) MD at presentation (dB)	-6.5 (-11.7, -3.9)	-5.8 (-10.6, -3.6)	-5.7 (-10.1, -3.6)	-5.4 (-9.9, -3.5)	-5.4 (-9.9, -3.5)	-5.6 (-10.2, -3.6)
% patients with advanced VF loss at presentation	**29.6**	**25.0**	**24.2**	**23.0**	**22.8**	**24.0**
Number of Patients* with VF series >4 years	843	1,786	9,208	3,917	3,480	19,264
Median (IQR) MD loss per year (dB/y)*	**-0.37 (-1.2, 0.32)**	**-0.26 (-0.90, 0.20)**	**-0.23 (-0.83, 0.21)**	**-0.19 (-0.81, 0.27)**	**-0.10 (-0.71, 0.37)**	**-0.21 (-0.83, 0.26)**
% Patients LSY > 3 years	**12.5**	**12.9**	**11.8**	**10.1**	**10.0**	**11.2**
Median (IQR) interval between VFs (months)	**12.6 (8.6, 18.1)**	**10.3 (7.6, 13.6)**	**9.5 (7.2, 13.0)**	**15.4 (11.5, 21.1)**	**12.3 (9.6, 16.5)**	**11.2 (8.1, 15.8)**

Application of the inclusion and exclusion criteria resulted in 223,379 VFs from 25,760 patients. Therefore 65.2% (n = 48,234) of people were excluded because they only had one VF examination or normal VFs in both eyes in their first or second VF examination. These people were excluded from further analysis. Series of VFs (more than 4 years of follow up) were available for 19,264 patients. Summary measures of the metrics for assessing glaucoma service delivery for the five centres (and the aggregate data) are given in Table 3.2.

There was a statistically significant difference in the **median age at presentation** between the centres ($p<0.001$; Kruskal-Wallis test). Centre 1 had slightly older patients with little difference between the other centres. There was also a statistically significant difference between centres for **percent of unreliable VFs** ($p<0.001$; Chi Square test). Centre 1 (despite having older test takers) returned the lowest proportion of unreliable VFs. Differences between centres were generally small. Yet, for example, the rate of unreliable VFs recorded at Centre 3 was 1.7 times higher than that of Centre 1 (95% confidence interval for the relative risk of 1.4 to 1.9). It is noteworthy that around 1 in 20 VF examinations were unreliable according to this proxy measure across all centres.

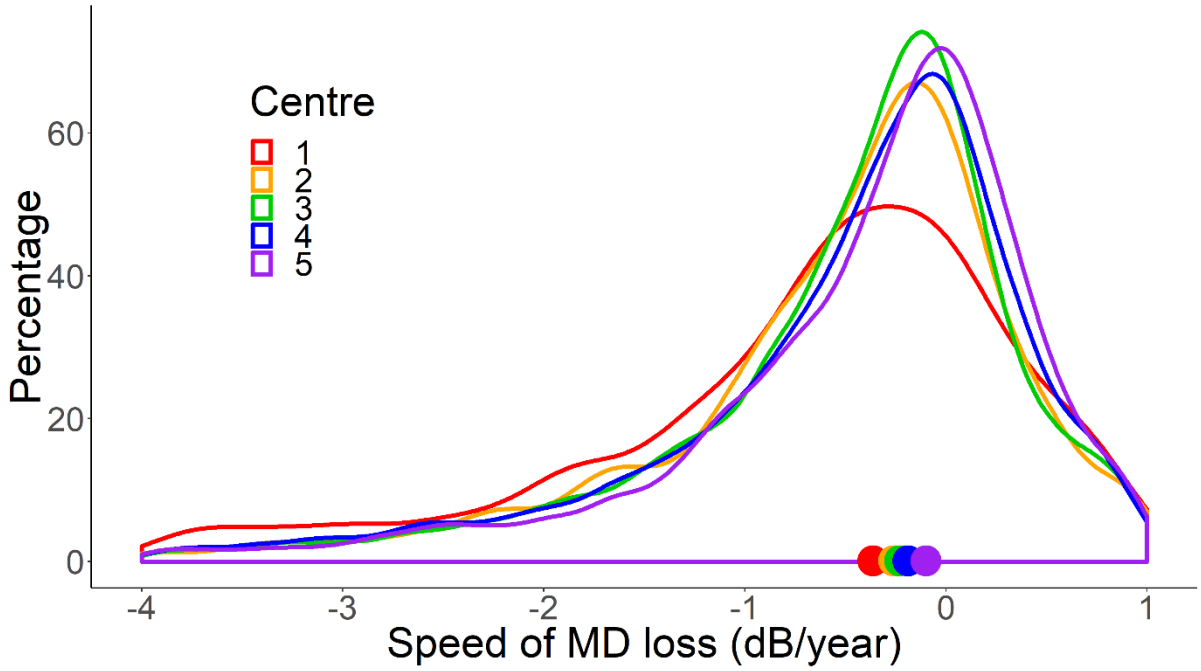
Stage of VF loss at presentation is also summarised as a series waffle (traffic light) plots for each centre in Figure 3.1. Centre 1 had notably more patients presenting with advanced VF loss when compared to the other centres. (Note this value summarises percent with advanced loss for those who present with some sort of VF loss. The value would be lower if the denominator was all people in the clinics.[81])

Figure 3.1: A traffic-light (waffle) plot showing the classification of VF loss of newly presenting patients in each of the five centres. Each square represents 1% of the patients being classified as early (green), moderate (yellow) or advanced (red) VF loss on presentation.



Speed (rate) of VF loss in the five clinics are summarised as distributions in Figure 3.2. The distributions were generally similar with the exception of centre 1 (and to a lesser extent centre 2); these distributions exhibited much heavier tails which means there were more eyes experiencing faster speed of loss VF loss at these centres compared to the others.

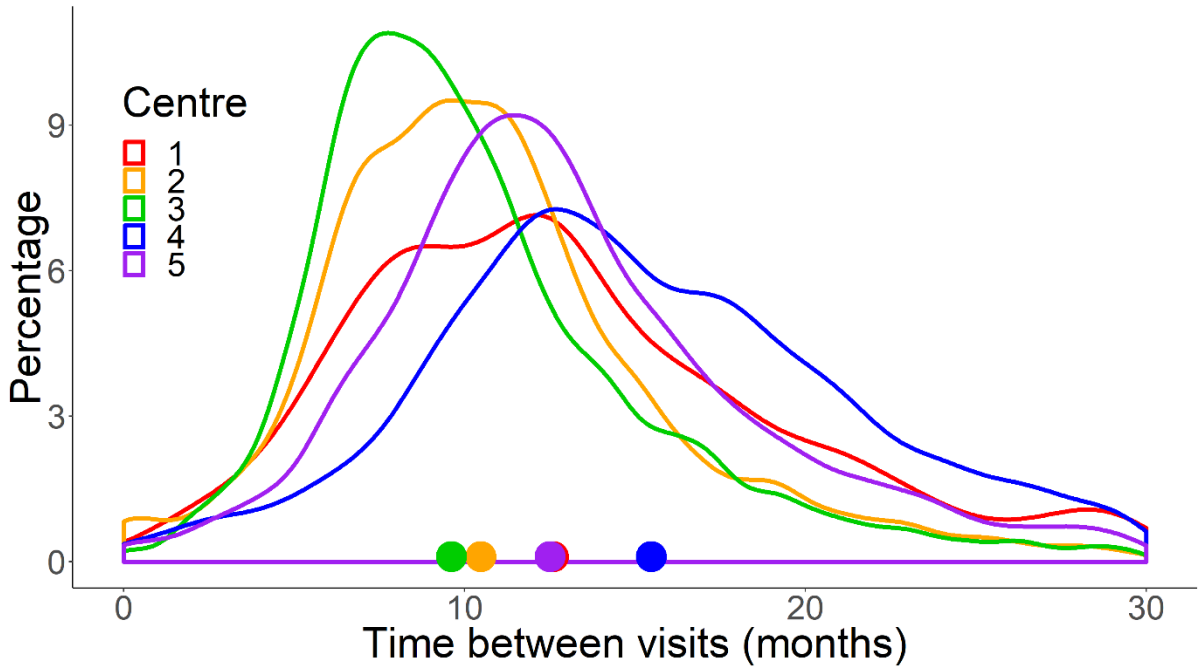
Figure 3.2: A plot showing the distribution of the speed of mean deviation (MD) loss (dB/year) in each of the five centres. Each line represents one of the centres. The distribution curves are obtained by using kernel density estimation to fit a smoothed curve to a histogram. Centre 1 (red) has a heavier tail compared with the other centres, indicating a higher proportion of patients with higher speeds of loss. Centre 1 also has a lower kurtosis (tail-to-peak ratio) and more negative skewness than the others. The coloured symbols on the x-axis indicate the median value for each centre (see Table 3.2).



Risk of VF loss blindness as estimated by percentage of patients predicted to have LSY > 3 years was slightly greater in centre 2 (12.9%) when compared to the other centres and this was statistically significant ($p < 0.001$; Kruskal-Wallis test).

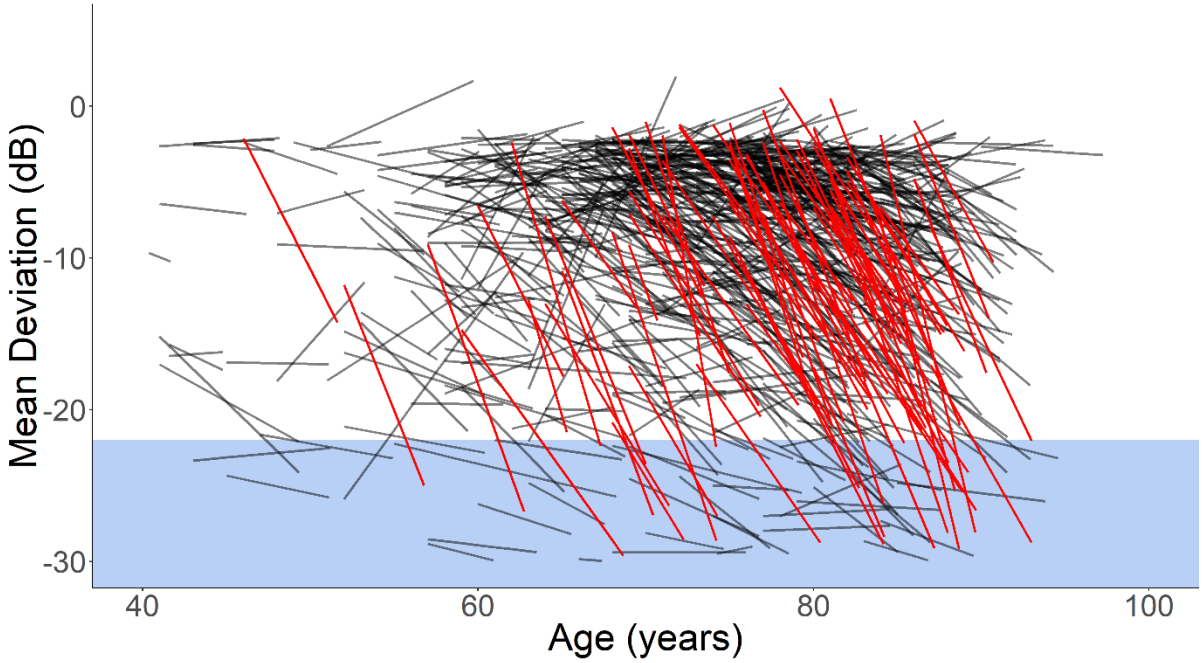
Frequency of VF examination at the five clinics is summarised by distributions of the time interval in months between VF tests in Figure 3.3. Centre 4 had a noteworthy longer median time interval between VF tests (15.4 months) compared to the other centres and this was statistically significant ($p < 0.001$; Kruskal-Wallis test).

Figure 3.3: A plot showing the distributions of the time interval between patient visits (in months) in each of the five centres. Each line represents one of the centres. Centre 4 is more positively skewed, indicating a higher proportion of patients with longer intervals between visits. The coloured symbols indicate the median time interval between visits for each centre (see Table 3.2).



One way of visualising speed of VF loss in clinics is to use a Hedgehog plot. [115] One of these is shown for Centre 1 in Figure 3.4.

Figure 3.4: A hedgehog plot showing the mean deviation loss over time of each eye in centre 1. Eyes highlighted in red indicate a speed of loss worse than −1.5 dB/year. The region marked in blue is a threshold for a severely impaired VF. More detail on these plots can be found in Bryan et al.[115]



3.4 Discussion

This work confirms that routinely collected VF data from glaucoma clinics can be downloaded, aggregated and anonymised from an EMR and be made available for analysis. This has previously been done for research purposes yet, here int this study it is illustrated how it could be done to potentially monitor and compare health service delivery at different glaucoma clinics.[80,81,84,87,120] For this exercise, assessments were done on anonymised centres with a key point of this work showing that this approach is feasible for future implementation. The logistics of the VF data extraction, which in this instance was carried out as part of the NOD work commissioned by HQIP, was not assessed. The amount of work carried out by NOD must not be understated, however. Even though only five centres are included in this study (and the other studies using this dataset) the actual NOD database contains records from 28 different hospitals and clinics. It takes an incredible amount of work to download, homogenise, clean, and collate the data from one database with linked patient data on surgeries, medications, demographics and so on. To do so with multiple centres is an impressive task and it is clear that a lot of care and diligence would have been needed to reduce the number of errors (missing data, incorrect data), a common trend in Big Data. Outside of the studies contained in this thesis, the group behind NOD have published a series of their own studies on the topic of cataract surgery as well as annual reports .[85,121–123] These highlight findings such as the (lack of) evidence of equity in

gaining access to cataract eye surgery as well as results surrounding the outcomes and complications of cataract surgery.

This study has shown that assessment of VF records in glaucoma clinics could provide a first step towards quality improvement of services; this is a novel idea. For example, it has now been demonstrated how VF metrics of late presentation of glaucoma, or speed of loss of VF in people in glaucoma clinics during follow-up could be easily summarised for a clinical centre. It has also shown how it might be possible to compare the reliability and use of VF measurement between centres – for instance, it is feasible to identify centres that are doing more or fewer VF exams compared to others. The latter is important because it has been shown previously, via health economic modelling of retrospective data, that optimising use of VF resources could improve clinical management of patients and save money at the same time.[110] Since VF data can be held in EMRs this makes them amenable to automated and live analysis. This feasibility study indicates that this approach could be used to monitor what happens to people in different glaucoma clinics in real time. Assessment of quality improvement of glaucoma services with an implementation of this idea could be the subject of future work.

The results from this report illustrate the feasibility of calculating metrics for assessing service delivery between centres using VF records alone. Nevertheless, some discussion about the differences in these metrics between the five anonymous centres is worthwhile. For example, centre 1 had more patients presenting with advanced VF loss and had more patients losing VF at a faster speed than other centres. These variables are highly associated in people with glaucoma and are, in turn, positively associated with older age.[1,84,110] It is noteworthy that patients in centre 1 were generally older than those in the other centres and this might, at least in part, explain these observations. Still, the chosen metric for risk of VF loss blindness as estimated by percentage of patients predicted to have LSY > 3 years was 12.5% in centre 1. This observation underlines the importance of preventing late detection of VF loss for prevention of avoidable blindness.[87] The spread of time between visits also fluctuated quite significantly between centres. Centre 4 had the longest median time between visits and also had the widest range of IQR, indicating that follow-up times are highly variable between patients. This may be seen as a bad thing but when considering their performance metrics (VF rate of progression, presenting MD, reliability etc.) they are performing average or slightly above average compared to the other clinics. Why is that? It's possible that the clinic has its own local guidelines in determining how long to wait before seeing a patient again. In Chapters 4 and 5, it will be shown that patients tend to have similar follow-up times irrespective of if they are a glaucoma suspect, OHT, POAG or POAG and uveitis. This "one size fit all" approach is not optimal and ideally the frequency with which patients are seen should be based on the suspected need (more severe = seen sooner, less severe = seen less soon). If Centre 4 was implementing something such as this, it could lead to the sort of results reported. An additional discussion on the variability between centres and possible effect on findings is in Chapter 7.

This report reveals some other interesting subsidiary findings. The population for this report is people with measurable VF loss in glaucoma clinics (at least two VFs with actual VF loss as measured by MD). These inclusion criteria reduced the sample by 65.2%. In other words, around two-thirds of people with HFA 24-2 VF records in these data sets had single 'one-off' VFs or had normal VFs at presentation to the clinics. This figure illustrates the huge volume of likely false positive glaucoma referrals, glaucoma suspects and ocular hypertensive that glaucoma clinics deal with on a daily basis. Moreover, around 1 in 20 VFs are recorded with reliability indices outside normal limits. In addition, the median interval between VF tests in people being followed over time was 11.2 months and as high as 15.4 months in one centre. This supports previous findings that annual VF testing is the norm for most patients in glaucoma clinics in England.[77] Heath economic modelling has highlighted the benefits of stratifying patients to more or less VF monitoring based on age and stage of disease at diagnosis; a prospective study is needed to prove these findings.[110]

Using EMRs for research or audit is not a new idea, having been implemented in many fields of medicine to study diseases such as diabetes, heart failure, cancer and asthma.[53] In eye clinics EMRs have been used for audit of cataract surgical outcomes but importantly also have potential for making health care delivery more efficient by facilitating more streamlined clinical work flow, better patient management and improved data tracking.[61,62,85,124–127] However, ideas and implementation are different entities and meaningful use of EMRs in ophthalmology is still a work in progress.[54,55,128] Presently, certainly in clinics in England, there are challenges about how clinical data are recorded, archived and stored. Moreover, issues such as non-collated datasets, duplicate IDs and differing databases add to the challenge of moving towards comprehensive use of EMRs.

This approach to the concept of assessing service delivery in glaucoma clinics has several strengths. In theory, VF records should be easily stored on EMRs making them amenable to easy extraction, analysis and audit. Whether this happens in practice is dependent on the motivation of implementing electronic archiving of VF examinations and use of EMRs in hospital eye services. Another rational for using VF metrics is their relevance to measuring vision. IOP is the only modifiable risk factor for glaucoma progression and is crucial to patient management but VF metrics will best estimate the status of people's vision loss in the clinic. The approach in this audit does not consider everyone in glaucoma clinics but centres on those with a proxy measure of sustained VF loss. These patients are at higher risk of further significant vision loss in their lifetime when compared, for example, to people with ocular hypertension.[55,87,128,129]

There are limitations to the ideas reported in this study. The main problem is reliance on the VF data alone. A more complete assessment of what is happening in a glaucoma clinic would be achieved by considering exact diagnosis, treatment regimens, intraocular pressure, optic nerve head characteristics, individual patient history, or other risk factors. For example, much can be learnt about what is happening

in glaucoma clinics by reviewing repositories of data on prescribed medications. [130] However, EMRs need an established and standardised minimum data set for glaucoma care and this is the subject of future work. This idea will also be limited to how well VF records can be archived at a centre. The five sites chosen for this study were all EMR enabled and known to run large glaucoma services with aggregated electronic VF databases. Alternative options could include separate data extractions from individual machines with subsequent aggregation into a single database, but this would be time consuming and carry significant cost, in particular if these services were delivered in different settings such as outreach clinics. A possible limitation of this approach in general is that not all clinics/centres are the same. When comparing large numbers of centres, it's important to note whether they are primary, secondary or tertiary care centres and compare appropriately.

There are also limitations to some of the proposed metrics for assessing service delivery. First, while MD is a useful summary measure of how much sensitivity loss there is in a VF and particularly convenient to monitor changes over time, it is not a perfect measure for glaucomatous VF loss. MD can be affected by non-glaucomatous changes such as a general reduction in VF sensitivity caused by, for example, cataract. Second, as noted previously, only the FP reliability index was used as a measure of patient test taking performance.[31] Of course this measure, or any other similar measure, would not capture patients failing to complete an exam or those excluded because of a previous failure to reliably conduct a VF examination. Third, the measure of "risk of blindness" (LSY) makes a number of assumptions around residual life expectancy and progression of VF loss being constantly linear. Fourth, when comparing metrics it will also be important to consider some centres simply differ in terms of population factors (e.g. racial and socio-economic profile) and audits using the methods proposed in any report would have to take this into account. Finally, if this approach were to be extended into a national audit, as I believe should be an eventual goal of the NHS, several challenges would first need to be overcome. The integration of every centre into a national database would take a considerable amount of time and money. It may also involve the learning or re-learning of the new systems put in place by both clinicians and technical staff. Maintaining adequate upkeep of this sort of database, implementing offline and offsite backups as well as ensuring high levels of security/data protections would itself take additional time and resources. Issues around data protection and data sharing within ophthalmology have been highlighted recently, whereby anonymised patient data is assumed to be available for research. Patients are unable to opt out of certain research projects (such as ones being carried out by large multinational corporations) but opt into research being carried out at a more local level. Going forward, clarification around this data sharing and perhaps a more stratified opt-out system will be needed. If these issues are overcome however, such a sophisticated network would have benefits for clinicians and researchers, allowing for real-time audit of how clinics are performing. The outcomes of changes in policy or guidelines would be easy to measure allowing for rapid feedback.

The amount of data and the complexity of data being collected within healthcare is constantly increasing. Newer imaging paradigms, while incredibly useful also take up large amounts of storage space. All of these images and records need to be stored somewhere. They need to be accessible from anywhere on a network. The end result of this is an exponential increase in the amount of data throughput hospital servers need to handle. Smart techniques to handle data can only go so far and many systems currently are not ready to deal with the increases in requirements. A multi-pronged approach will be needed in the future.

In conclusion, this study illustrates the feasibility of assessing some aspects of quality of care in glaucoma clinics through analysis of VF databases from EMR enabled centres. This approach, which is outcome focussed, is a potentially useful method for assessing blindness prevention from glaucoma in secondary care centres. VF testing technology is standardised in the UK NHS and although in many centres the electronic VF tests will be distributed across several VF testing machines it is feasible to aggregate these fields into a central database located in each centre for central analysis. Ideally, such a central field database would reside within a specialty specific EMR implementation serving both clinical and quality assurance needs. Secondary benefits from such an approach would include the ability to more easily detect patients whose VF loss is progressing rapidly in order to intensify their treatment as well as detection of those patients whose VFs are stable who may require less intensive monitoring once VF stability has been documented. By shifting focus towards those in most need, health services resources can be more effectively utilised. In the current NHS digital environment, a variety of challenges would need to be overcome in order to extend this audit approach into a national audit of vision preservation in people with glaucoma.

4 Using electronic medical records to investigate the conversion from ocular hypertension to primary open angle glaucoma

The work presented in this chapter has formed a paper submitted to the *British Journal of Ophthalmology*; see list of supporting publications. The authors on this paper are SRK, Susan Bryan (SB), Anthony Khawaja (AK), John Sparrow (JS), Augusto Azuara-Blanco (AAB) and David Crabb (DC). The entire analysis contained in the study (including coding and production of figures) was carried out by SRK as well as the drafting of the manuscript. The manuscript was then reviewed and edited by SB, AK and DC. AAB and JS acted as advisors during the manuscript review process but were not involved directly in the study.

4.1 Introduction

Referral guidelines for ocular hypertension (OHT) or other glaucoma related conditions in England currently require evidence of optic nerve head damage, a VF defect consistent with glaucoma or an IOP of 24 mmHg or more measured using Goldmann-type applanation tonometry.[4] Before referring, the clinician may repeat the IOP measurement or VF assessment to confirm glaucomatous-type signs before referral. The EPIC-Norfolk study recently reported a prevalence of 10% for OHT (IOP >21 mm Hg, based on previous guidelines) in the English county of Norfolk.[15] This is based on a mostly Caucasian population and there is evidence that OHT is more prevalent among other ethnic groups, specifically blacks. Specifically the Barbados Eye Study found the incidence of IOP above 22 mmHg to be five times higher in blacks than in whites.[131] Current guidance states that IOP-lowering eye drops may be offered to patients with high IOP if they are at risk of visual impairment in their lifetime.[4] The reported rate of conversion from OHT to POAG is variable in the literature.[5,132–134] Robust data on the likelihood of developing glaucoma for those with OHT are required to inform monitoring guidelines in terms of effectiveness, cost-effectiveness and acceptability to all patients, eye care providers and commissioners of NHS services.

Since there is a risk of developing glaucoma, patients with OHT are monitored using a similar testing regime that POAG patients receive. Standard UK practice as such is to monitor in secondary care. This places a strain both on eye care services and the people affected as monitoring in specialist eye clinics can be inconvenient, may lead to ‘over treatment’ and is expensive for the NHS.[15] As up to half of POAG is characterised as normal tension glaucoma (NTG) in Europeans, high IOP is neither a necessary nor a sufficient condition of glaucoma.[15,135] Therefore, it is likely that a proportion of patients with OHT are receiving unnecessarily close follow-up or treatment. With an aging population and an increase in optometric screening, the number of patients being seen in clinics with glaucoma related conditions is expected to rise, placing further strain on these services.[20]

Healthcare clinics in the UK are transitioning to some form of EMR system to store patient data digitally, although progress is slow.[69,136] Glaucoma clinics in particular have the ability to store data relevant to OHT patients such as IOP readings, VF test results and which medications (if any) they are taking. The aims of this study were to use EMR data from five glaucoma clinics in England to retrospectively analyse OHT patients. The primary aim was to estimate the proportion of OHT cases that progressed to VF loss within 5 years and to examine factors associated with this progression. The secondary goal was to consider the burden that OHT patients have on glaucoma clinics, relative to other conditions such as POAG and glaucoma suspects.

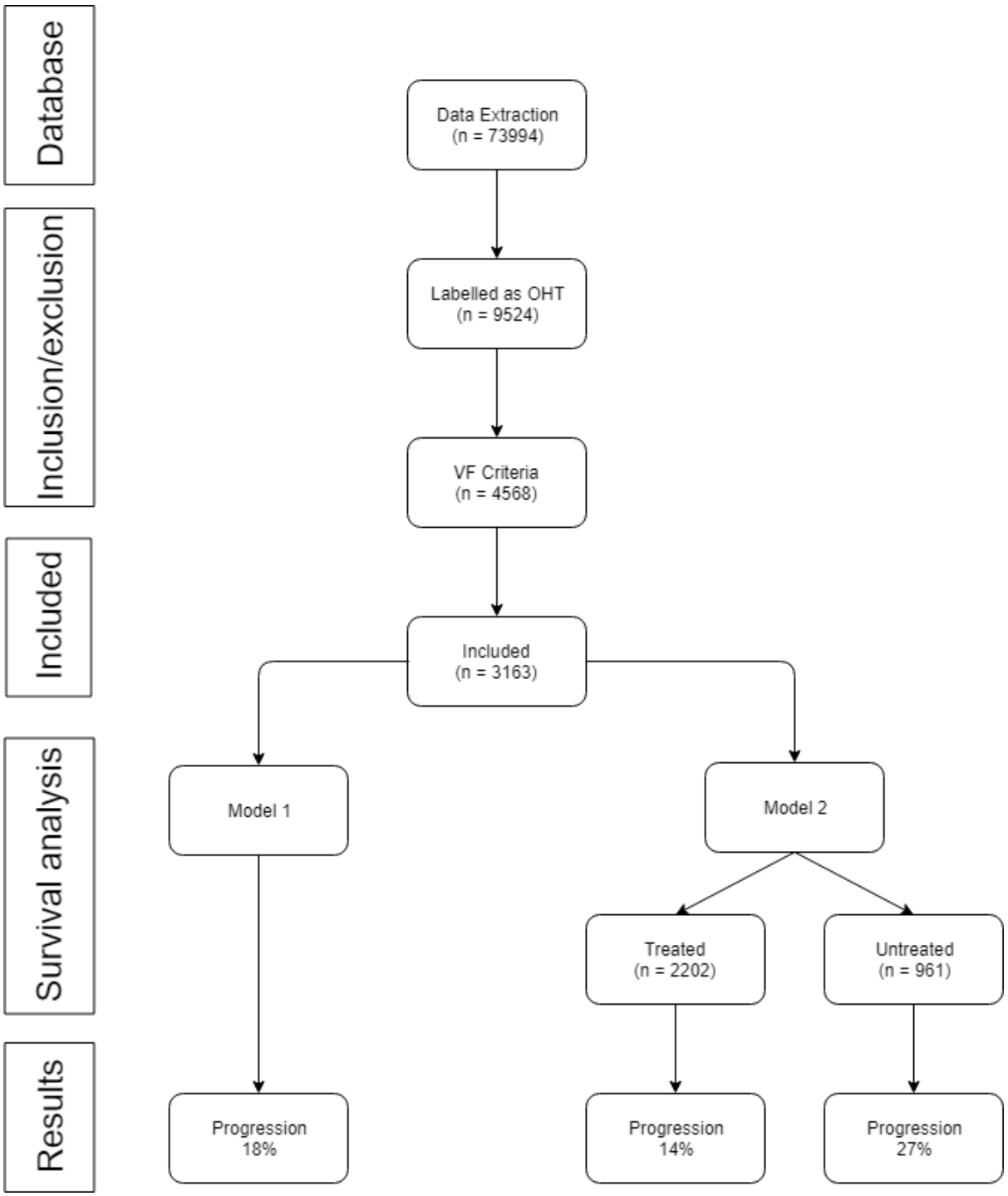
4.2 Materials and methods:

Information on the source of the data can be found in preceding Dataset 2 primer. The study adhered to the Declaration of Helsinki and all analyses of the data were approved by a research ethics committee of City, University of London. All patient data were anonymised and securely held on the university database.

4.2.1 Inclusion criteria

In this analysis, only one eye per patient was included. To be included, a patient needed an eye with a clinical diagnosis label of OHT with no prior glaucoma-related diagnoses (similarly for the fellow eye) and with no disallowed comorbidities. Eyes with a visual acuity (VA) worse than 6/19 were excluded. Eyes were also excluded if they were labelled with a diagnosis label of cataract, corneal condition or eye casualty. Eyes with age-related macular degeneration (AMD), for example, were included if they had a VA better than 6/19. If both eyes were eligible, the eye with the highest baseline IOP was chosen. As the risk of VF loss is being considered at a patient level, VF loss to either eye would qualify. As such the eye with the higher IOP was picked for this analysis as it is at a higher risk of VF loss. If both eyes had the same baseline IOP, one eye was chosen at random. For the purpose of this study, only VFs tested by using the Humphrey Field Analyzer (Carl Zeiss Meditec, Dublin, CA) with the 24-2, white-on-white test strategy acquired with the Swedish Interactive Testing Algorithm (SITA Standard or SITA Fast) were included in the analysis. A minimum of 3 reliable VF tests were needed, one to measure the baseline readings and two consecutive reliable examinations showing potential repeated VF loss.

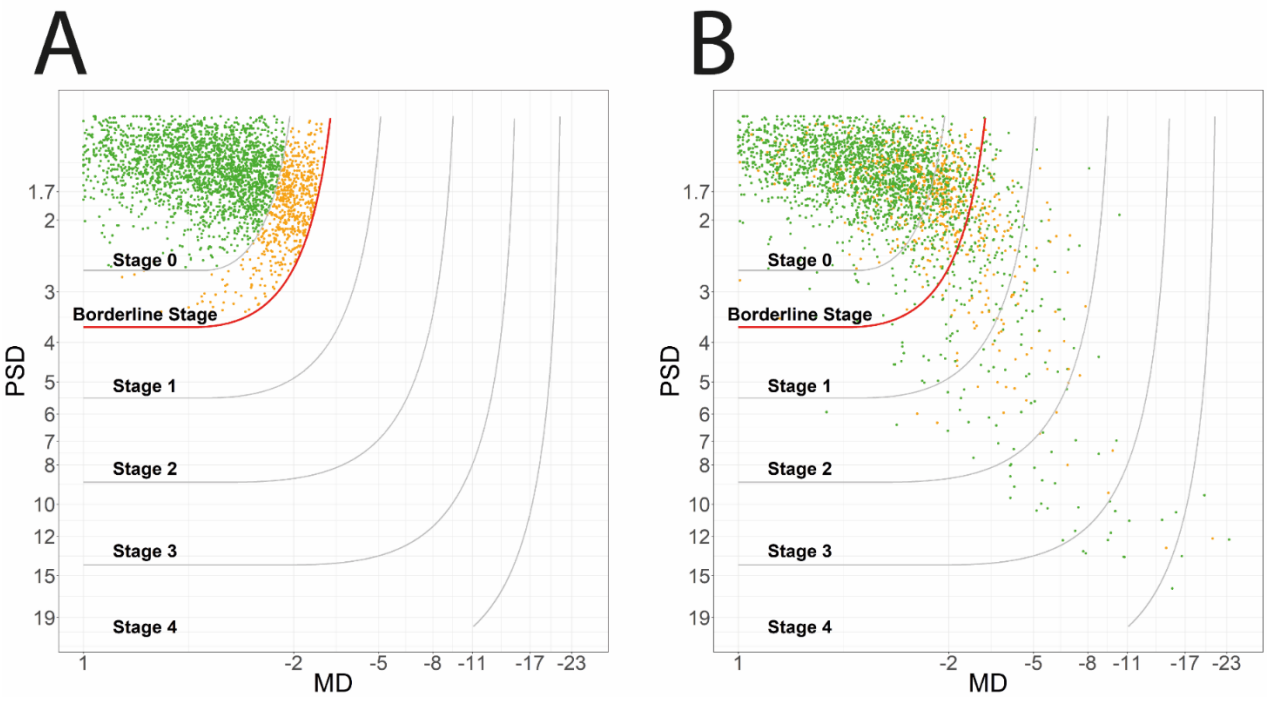
Figure 4.1: Flowchart of where patients were included/excluded. The flowchart also shows the predicted proportion of progression for model 1 (all-cause survival analysis) and model 2 (segregated by treatment group).



To classify patients into different levels of VF damage the glaucoma staging system 2 (GSS2) described by Brusini and colleagues was used.[137] This system classifies VF damage into one of seven progressively worsening categories based on MD and PSD values. There are situations where a person

may have a poor MD value (highly negative) but a normal or mild PSD value. This can occur due to diffuse VF suppression from eye conditions such as cataracts. If using MD alone, these patients would have resembled glaucoma patients despite not having typical glaucomatous VF damage. By incorporating PSD into the staging system, the patient population can more accurately be filtered for those with no/early glaucomatous VF damage. The GSS2 was adapted for use with the 24-2 SITA testing strategies (the original GSS2 uses values from full threshold strategies). The desired study population was "true" OHT patients (i.e. with little-to-no VF damage). As such only patients classified as one of the two early stages (Stage 0 or Borderline) were included. If an eye is diagnosed as OHT but has a high GSS2 stage (usually indicating a high level of VF loss), this could mean that either the diagnosis was not updated, or the patent was unable to reliably perform VF testing. Baseline VF was defined as the VF closest to the time of diagnosis labelling, with a maximum of one year between the diagnosis and VF test. Baseline stages as measured by the GSS2 for all included eyes can be seen in Figure 4.2A. The measurement of the last recorded follow-up visit is also shown in Figure 4.2B. There was no upper limit set for this plot so some patients visible have over 5 years of follow-up.

Figure 4.2: A glaucoma staging system 2 scatterplot showing the eyes included for analysis. Only eyes with a baseline measurement in the early stages (stage 0 [green] or borderline [orange] stage, demarked by a red curve) were included (Figure 4.2A). A second scatterplot illustrating the GSS2 stage of the last recorded follow-up visit (some of which have over 5 years of follow-up) for the same data is also shown (Figure 4.2B).



4.2.2 Statistical Analysis

Follow up VF data was considered for up to 5 years following diagnosis of OHT. Any visits after this 5-year window were excluded. Two consecutive reliable VF exams with a GSS2 classification of stage 1 or worse was used to define VF loss. The VF with the earlier date was considered as the date of progression. Patients with less than 5 years follow-up were included in the analysis but censored.

Cox Proportional-Hazards regression analysis was used to examine the factors associated with incident VF loss and several models were fitted. Baseline age (years), sex (man vs woman), baseline IOP (mm Hg) and treatment group (treated vs untreated) were examined both univariably and then together. The treated group was defined as eyes that had a record of IOP-lowering medication or surgery, while being labelled as an OHT patient. The untreated group was defined as eyes that were recorded in the medication database but did not have any glaucoma medication listed and had no recorded glaucoma surgeries. Three models were selected for reporting. A simple (no predictor variables) all-cause survival curve and a survival curve with treatment group as a predictor variable are shown in Figure 4.2. The results for the multivariable cox regression are shown in Table 4.2.

The relative burden of glaucoma suspect patients, OHT patients and POAG patients on the glaucoma clinics was estimated. This was defined as the relative proportion of unique clinic visits (for IOP or VF measurements) for each of the three clinical diagnosis labels. A visit for one of the labels, say OHT, was defined as a visit date that occurred in the range of dates while the eye of interest was labelled as OHT. If the diagnosis label was updated at a later date, for example from OHT to POAG, then subsequent visits would be counted as POAG visits. A visit where both eyes had the same label, would be counted as one visit for that label. A visit where both eyes had different labels, would be counted as a visit for the more “serious” label (where POAG is considered more serious than glaucoma suspect, which is considered more serious than OHT). The average number of months between VF tests for patients with at least 4 visits was calculated. All analyses were performed within the open-source statistical programming environment R.[119]

4.3 Results:

4.3.1 Baseline Characteristics

From the initial cohort of 9524 patients with a clinician diagnosis label of OHT, 3163 were included in the final analysis (see Figure 4.1 for inclusion flow chart). Of these, 1716/3163 (54%) were women, 2202 (70%) were on IOP lowering treatment during their OHT diagnosis and 1531 (48%) of the eyes were right eyes. Other descriptive statistics can be found in Table 4.1.

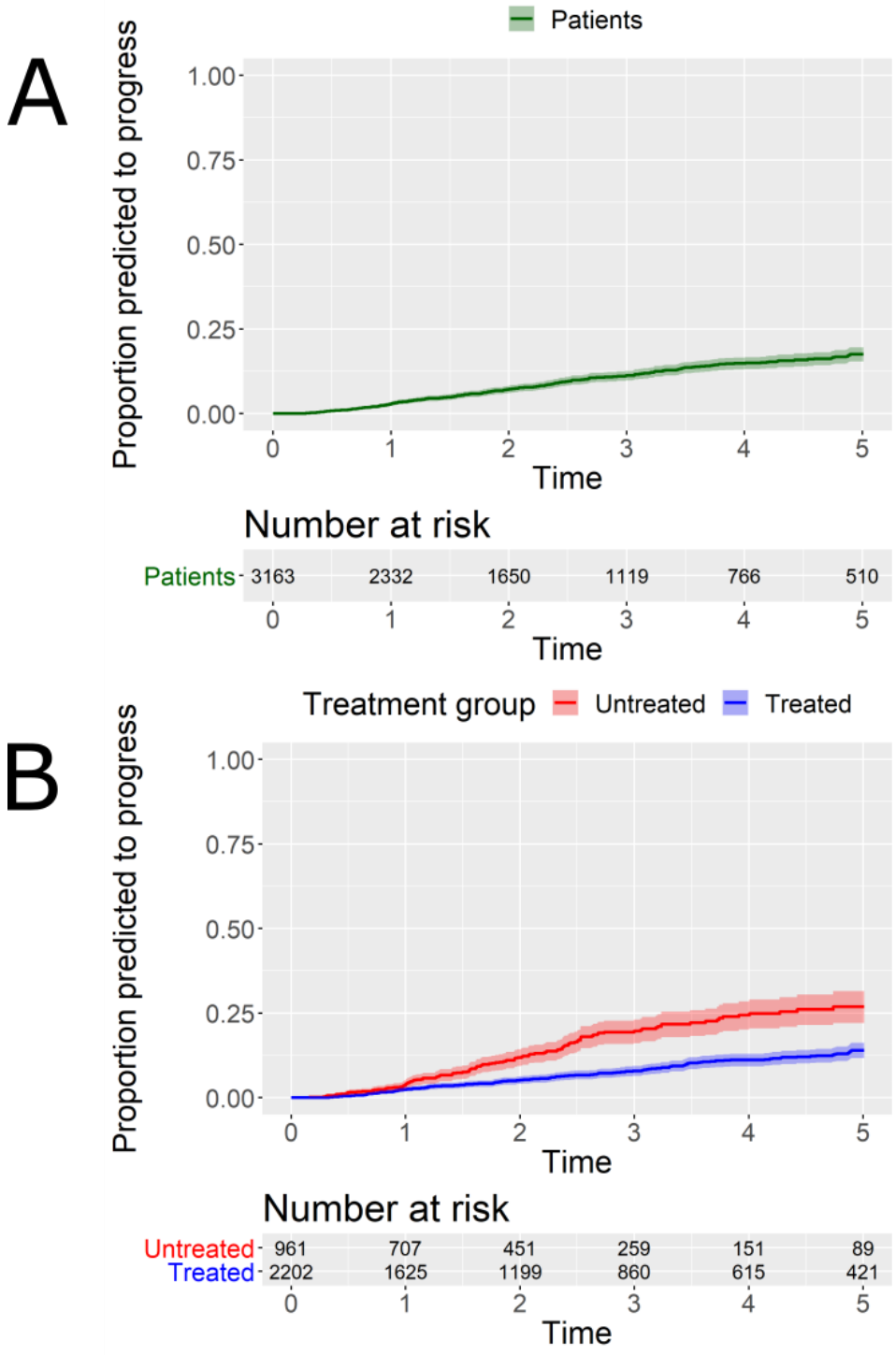
Table 4.1: Statistics of included patients

Included (n)	Median (IQR) age at diagnosis (years)	Median (IQR) Baseline IOP (mmHg)	Median (IQR) follow-up IOP (mmHg)	Median (IQR) Baseline MD (dB)
3,163	60 (51, 66)	24 (20, 27)	20.75 (18.33, 23.00)	-0.45 (-1.32, 0.34)

4.3.2 Cox PH analysis

The survival analysis curves can be seen in Figure 4.3. All-cause predicted progression after 5 years was 17.5%. (Figure 4.3A). When stratified by treated and untreated groups, the predicted progression after 5 years was 14.0% and 26.9% respectively (Figure 4.3B). Results of the Cox multivariable regression can be found in Table 4.2. The hazard ratio of VF progression while on IOP-lowering treatment versus no treatment was 0.45 (95% CI: 0.35 – 0.57). The hazard ratio of VF progression per year increase of baseline age was 1.03 (95% CI: 1.02 – 1.04). The hazard ratios of both baseline IOP and sex were both close to 1 and were not statistically significant.

Figure 4.3: Cox PH survival curve of 5-year progression predictions for (A) all patients (green) and (B) the treated (blue) and untreated (red) groups with the 95% confidence intervals. The risk table shows the number of patients still included in the analysis for a group at each 1-year interval. The cumulative probability of progression was higher in the untreated group than the treated group ($p < 0.01$, Figure



4.3B).

Table 4.2: Results of Cox PH survival analyses

Variable Name	Hazard Ratio	P value
Baseline Age (years)	1.03	< 0.001
Baseline IOP (mmHg)	1.00	0.87
Sex (F)	1.01	0.95
Treatment (Yes)	0.45	< 0.001

4.3.3 Burden on clinics

Of the total number of unique visits (recording either a VF or IOP measurement) for the three clinical labels included for analysis, 21% were recorded for glaucoma suspect patients, 22% for OHT patients and 57% for POAG patients. If only VF measurements are considered, the distribution is 23%, 23% and 54% for glaucoma suspects, OHT and POAG patients respectively. For IOP measurements the distribution is 20%, 23% and 57%.

The survival analysis predicts that around one in six (17.5%) OHT patients will have detectable VF loss within five years. Of these, 70% are receiving IOP-lowering treatment. OHT patients receiving IOP-lowering treatment have a lower rate of predicted progression of around one in eight (14%). This indicates that there are many OHT patients in the clinic, especially those who are being treated, that are unlikely to lose much VF function within a five-year window. If only 3163 patients that were included in the survival analysis are considered, 11727 of 15464 (76%) of the visits within the five-year study window were recorded while the eye was receiving IOP-lowering treatment. This corresponds to 76% and 74% of the IOP and VF measurements respectively. For patients with at least 4 VF visits, the average time between VF tests was 10.9, 9.7 and 9.6 months for glaucoma suspects, OHT patients and POAG patients respectively, showing that OHT patients are seen as frequently as POAG patients.

4.4 Discussion:

The aim of this study was to estimate the likelihood that a newly diagnosed OHT patient would suffer from VF loss within five years. The figures in Table 4.1 show that a relatively high number of eyes

(3163) were included in the analysis, despite a reasonably strict inclusion criterion. The results from the survival analysis predicts that 17.5% of patients in the data would progress to a worse VF stage (per the GSS2) within the study period of five years (Figure 4.2A). Although not all included patients had at least 5 years of follow up time, the survival analysis handles these data with right-censoring. When comparing treated eyes and untreated eyes, it was found that 70% (2202/3163) of the OHT eyes had some form of IOP-lowering medication or surgery during their OHT diagnosis. The survival curve analyses show that the treated eyes were predicted to progress to VF loss significantly less than the untreated eyes with 14% and 26.9% respectively (Hazard ratio: 0.45, 95% CI: 0.35 – 0.57) (Figure 4.2B). A caveat of using this retrospective observational data is that it cannot be said for sure that the treatment and lower rate of progress had a cause-effect relationship. Instead, it is more sensible to report that there was a significant association. Baseline age was also a statistically significant predictor, with a one-year increase indicating a hazard ratio of 1.03 (95% CI: 1.02 – 1.04).

According to these data, more than one in five (22%) unique clinic visits were for OHT patients, relative to POAG and glaucoma Suspects. If only 17.5% of patients are predicted to have detectable VF loss within five years, is it necessary that they be seen in secondary care clinics this frequently, considering that the risk of significant vision loss is very low (only 1.75% of this study population reaching severe VF loss)? There are several alternative options available that would reduce the burden on hospitals and glaucoma clinics, such as monitoring patients in primary care practices or in virtual clinics. So-called 'shared care' schemes could be a possible approach for low risk OHT patients.[20,138,139] Notably, OHT patients had VF testing as frequently as both POAG and glaucoma suspect patients further emphasising that OHT patients are using a disproportionate amount of resources, relative to the immediate risk of VF loss. One suggestion to reduce the burden of OHT patients could be to increase the follow-up period between appointments.[20] Morley and Murdoch estimated that increasing time between follow-up visits by a factor of 1.5 could reduce the relative clinic workload by 30%. If the follow-up time was increased by a similar factor for stable, low-risk OHT patients, it could free up resources for high-risk or new patients.

According to the National Institute for Health and Clinical Excellence (NICE) glaucoma guidelines, 1.3 million people over aged 40 in the UK have high eye pressure (above 24 mmHg) and those who have this condition are monitored in hospital eye services.[4] The rate of progression from OHT to POAG is variable in the literature. In a large multicentre clinical trial, the Ocular Hypertension Treatment Study (OHTS), the cumulative probability of developing POAG at 5 years was 9.5% in the untreated group and 4.4% in the treated group.[16] In another study, the European Glaucoma Prevention Study (EGPS), the progression rates were 13.7% and 16.4% for the treated and untreated groups respectively [133]. The results in this chapter likely underestimates the number of OHT patients converting to POAG, since the dataset lacked any sort of structural data (including CCT) and could only consider VF outcomes. Also, only patients with no comorbidities and a baseline VF stage of 0 or borderline using the GSS2

were considered, which could further skew results. The results, however, still seem to be relatively high when compared with the above trials.

When designing the study protocol, one option was to consider a change of diagnosis label as an outcome for progression. The centres varied significantly in their labelling conventions and often, labels were not being updated (to say, POAG) despite there being obvious, repeatable VF defects. Moreover, one centre had little-to-no diagnosis labelling, while another had a much higher rate of label changing. As such, it was decided to opt for the more objective approach of looking at VF loss alone. While still relying on these subjective labels to define the study population, the labels are only used once to establish a baseline, instead of twice to also mark progression. For added a baseline VF measurement indicating no VF damage, as classified by the GSS2 was also required. As the dataset did not include any biometric data (such as optic nerve measurements) this study does not examine OHT patients progressing to POAG in a clinical sense, but rather investigating the likelihood of developing VF loss in OHT patients.

The diagnosis labels and dates of diagnosis used in this study to select OHT patients are to be interpreted as surrogates of disease presentation. For this analysis, the first recorded date in the EMR was used as a surrogate of when the disease began. However, it is sometimes the case that patients come into a clinic previously diagnosed with OHT and already are being treated for some time before being entered into the EMR.

Retrospective analyses such as this are only possible if the data is recorded electronically in a structured way. If this data were recorded via an open text box (as opposed to mandatory text fields) or on pen and paper, this type of study would not be feasible. Today, most medical record systems are being digitised which makes the possibility of large, multi-centre studies using Big Data much more feasible.[69] As these data are already being recorded routinely, there is an opportunity of relatively cheap and accessible healthcare research to be gained from exploring them. Moreover, as this data comes straight from clinics, it can tell us more about what goes on in real-world scenarios, which could inform how we organise our healthcare systems.

The results from this study highlights an important issue recently experienced in glaucoma clinics around the UK. Since primary care facilities for the most part only have the facilities to measure IOP, large numbers of patients were being referred to secondary care clinics on IOP alone. The vast majority of these patients are at no risk of sight loss in the near future and yet they take up a large portion of time and resources. This can hopefully help to inform clinicians for OHT-specific guidelines with regards to the frequency of which these patients are being seen and the potentially unnecessary burden they have on secondary care facilities.

5 Using electronic medical records to investigate patients with uveitis and POAG

The work presented in this chapter has formed a paper published in the *American Journal of Ophthalmology (Liu et al. 2019)*; see list of supporting publications. The authors on this paper are SRK, Xiaoxuan Liu (XL, who was a joint-first author with SRK), Giovanni Montesano (GM), Susan Bryan (SB), Robert Barry (RB), Pearse Keane (PK), Alastair Denniston (AD) and David Crabb (DC). Most of the statistical analysis (as well as all the related code and figures) contained in the study were carried out by SRK. GM contributed to the development of the mixed-effects model. The drafting of the manuscript was carried out by SRK (methods and results) and XL (introduction and discussion) which was reviewed and edited by GM, SB, AD and DC. RB and PK acted as advisors during the manuscript review phase but were not involved directly in the study. This work was presented as a paper presentation at several conferences by XL (ARVO 2018, UKÉGS 2018 and EURETINA 2019).

5.1 Introduction:

Uveitis remains the fourth most common cause of blindness in the working-age population throughout the developed world, with visual impairment affecting between 2.8 and 10% of uveitic patients.[140–143] Reduced visual function may result from direct damage to uveal tract structures, but more commonly occurs due to secondary tissue damage, with the most prevalent complications being cataract, macular oedema and glaucoma.[67] Of these, both cataract and macular oedema can be considered at least partially reversible, however visual impairment due to glaucoma is irreversible and thus early diagnosis and appropriate management of uveitic glaucoma is of paramount importance.

Glaucoma in the presence of uveitis can develop via a number of mechanisms.[144] Increases in intraocular pressure (IOP) can occur due to mechanical obstruction of aqueous outflow, presenting with secondary angle closure due to pupillary block from posterior synechiae, or more chronically following development of peripheral anterior synechiae or angle rubeosis. Secondary open angle glaucoma may develop due to chronic inflammatory damage to the trabecular meshwork, or in response to corticosteroid therapy. In addition, specific uveitis entities are associated with elevation of IOP, such Posner-Schlossmann syndrome, Fuch's heterochromic iridocyclitis and herpetic uveitis. Active inflammation, corticosteroid usage, increasing age, and number of years since diagnosis have each been demonstrated to be associated with raised IOP in uveitic patients.[145]

The prevalence of raised IOP in uveitis remains poorly defined, since increases in IOP may be transient and may not progress to true glaucomatous optic neuropathy. The prevalence of treated glaucoma varies from 20-30% in most cohorts.[67,145–147] Accurate stratification of patients at risk of uveitic

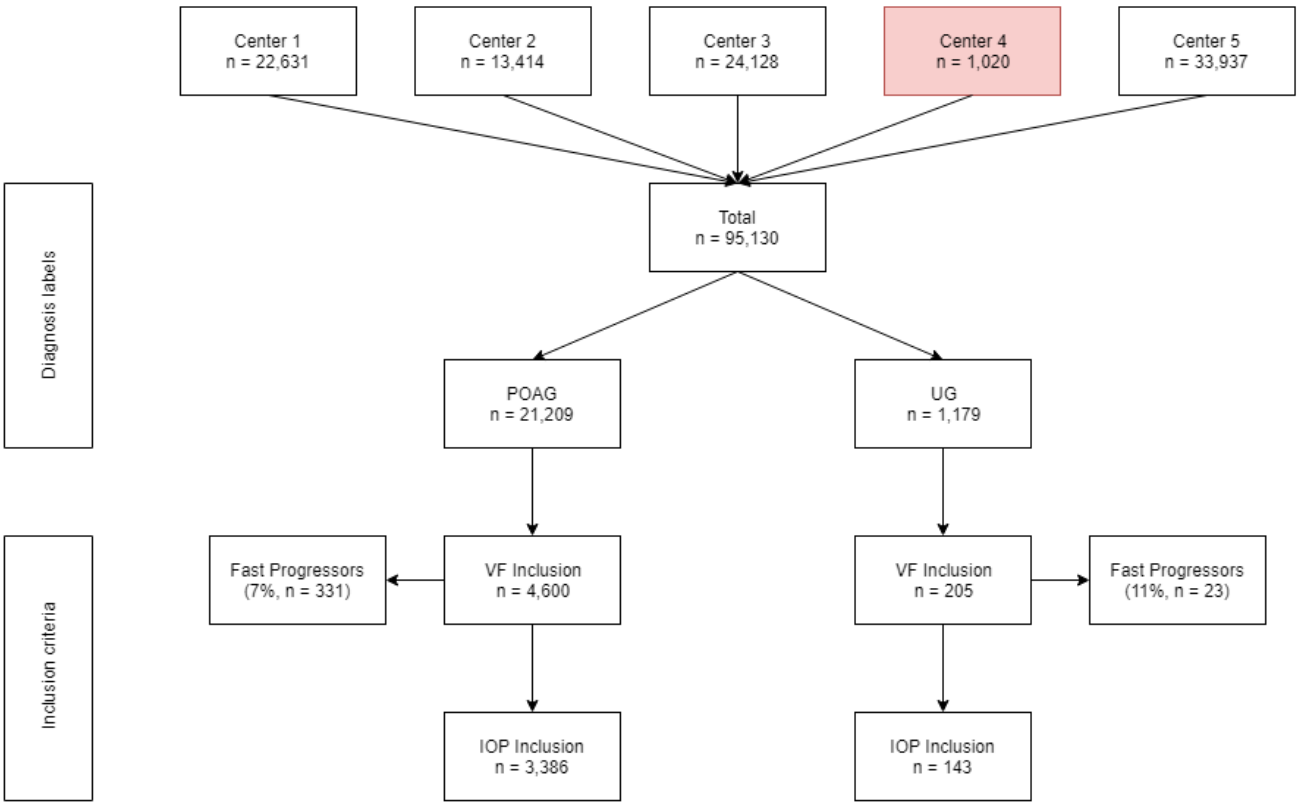
glaucoma is necessary to identify those at high risk of irreversible vision loss. Intensive monitoring and active intervention are important to prevent irreversible visual impairment in these patients.[6]

With the widespread adoption of EMRs, it is now possible to collect clinical data from large patient populations, identifying trends in disease progression and treatment response which have not been possible with traditional paper-based records. Such Big Data approaches have been successfully used to characterise the population and predict outcomes in other ophthalmic diseases.[29,64,65,84,87] This study aims to utilise large-scale EMR data for comparing the rate of VF loss in uveitis patients with glaucoma, compared to those with POAG, and explore whether this is associated with IOP.

5.2 Methods

Information regarding the dataset can be found in the preceding Dataset 2 primer.

Figure 5.1: Flow chart showing the inclusion criteria leading to a study sample of 4,600 POAG eyes and 205 UG eyes for the VF analysis and 3,386 POAG eyes and 143 UG eyes for the IOP analysis. Number of "fast progressors" in the VF analysis are also shown. Centre 4 is highlighted in red as it was missing a large amount of diagnosis data.

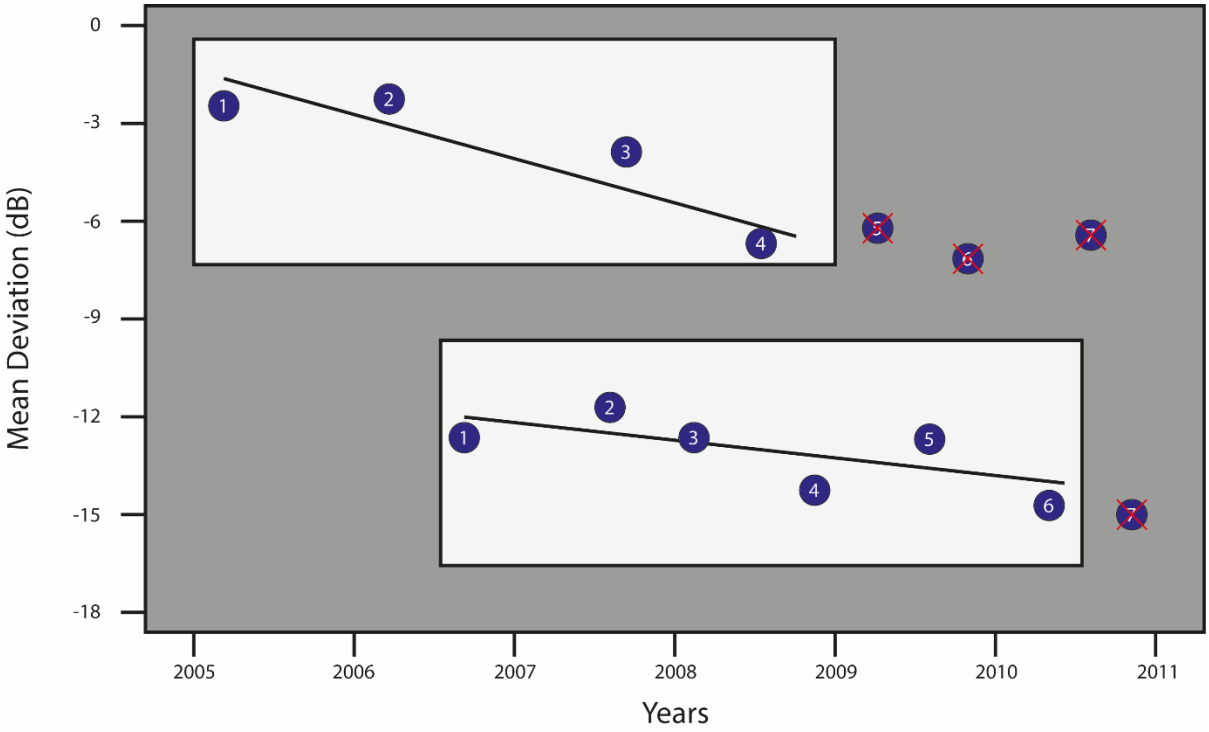


5.2.1 Inclusion criteria

Eyes were sorted into two groups based on EMR diagnostic labelling: a POAG group and a group of patients with both a 'uveitis' and 'glaucoma' diagnosis. POAG was defined by having a diagnostic label of 'POAG' or 'chronic open angle glaucoma (COAG)' without any uveitis co-pathologies. Uveitis plus glaucoma was defined as having both a label of POAG or COAG plus a uveitis label. A variety of anatomical and disease-specific labels for uveitis were included. Initial extraction by diagnosis found 1,179 eyes with uveitic glaucoma and 21 209 eyes with POAG (Figure 5.1). The inclusion criteria for each eye was a minimum of 4 VF tests over 4 years, with at least 4 of the included tests being performed within the initial 4 years (Figure 5.2). Often times the first visual field is excluded to mitigate potential learning effects. The first visit is included in this study as the power of the linear regressions was higher

with it included, despite the potential underestimation of VF sensitivity. Only VFs from the Humphrey Field Analyser (HFA) using Goldmann size III (white-on-white) stimuli with the 24-2 test pattern acquired with either SITA Standard or SITA Fast testing algorithms were included.

Figure 5.2: A schematic illustrating the VF series inclusion criteria and method for calculating rates of MD loss (dB/year) for two example eyes. Eyes were excluded if <4 VF examinations of <4 years of follow-up. Rates of VF loss were calculated from ordinary least squares linear regression of the baseline VF and the series of exams that fell within a 4-year window period after it (white window). In the top example, the 5th, 6th and 7th recorded VFs fall outside of the window and were not used in the calculation. In the bottom example, only the seventh exam was excluded. This ensures that all rates are estimated with equivalent precision, allowing for comparisons over time.



A secondary analysis on the association between IOP behaviour and VF progression was also carried out. In addition to the above inclusion criteria, a minimum of 4 IOP measurements in the first 4 years were needed.

5.2.2 Statistical analysis

Analysis was carried out on one eye per patient; if a patient had two eligible eyes, one was chosen at random. The first VF examination of each series was defined as the baseline measurement. HFA pointwise sensitivity values and mean deviation (MD; an estimate of average VF sensitivity relative to healthy age matched controls) values were extracted for each VF for each eye. Pattern deviation (PD) pointwise values were calculated using the visualFields package in R.[148]

Ordinary least-squares (OLS) linear regression of MD over time was used to estimate rates of progression (dB/year). As with previous studies, a fast progressing VF series was defined as having a rate of progression slope of ≥1.5 dB/year.[84,110] A crude relative risk (RR) was calculated as the ratio of the proportion of fast progressors in the uveitis and POAG groups, for each 10-year age group from 40 to 100 years, as estimated by the OLS regression slopes. An overall age-adjusted RR was calculated using the direct method.[149]

Two secondary VF progression analyses were also performed. First, a linear mixed-effects model analysis**,** which can estimate the regression coefficient while including both fixed and random effects was fitted.[150] A brief explanation of mixed-effects models can be found in Chapter1 .MD was treated as a response variable, time (years since first visit), group (POAG or uveitis) and baseline age were treated as fixed effects and individuals as a random effect.

Second, the permutation of pointwise linear regression (PoPLR) technique was used to analyse the pointwise sensitivities and PD values of each VF series.[151–153]A summary of this is also given in Chapter 1. The outcome of interest is simply the proportion of eyes showing statistically significant progression (at $p = 0.05$) in the uveitic and POAG groups.

IOP data were analysed using longitudinal metrics: mean, range and mean absolute error (MAE). Mean IOP was defined as the mean of all recorded IOP values in the series. IOP range was defined as the highest value (peak) minus the lowest value (trough) in the IOP series. MAE, as a measure of IOP variability, was estimated by fitting an OLS linear regression to IOP values over time, then extracting errors (predicted values minus the observed IOP) at each visit. The mean of the absolute values of these errors was the MAE value. Univariate associations between rates of progression and IOP metrics were analysed. Statistical comparisons were made using the Mann-Whitney U test.

Analysis was caried out using R (R Development Core Team, R Foundation for Statistical Computing, Vienna, Austria).

5.3 Results:

5.3.1 Baseline Characteristics

From a starting population of 1,179 eyes, 205 (17%) eyes with uveitis plus glaucoma satisfied the inclusion criteria and were included in further analysis. From a starting population of 21,209 eyes, 4,600 (22%) eyes with POAG were included in further analysis (Figure 5.2). Median (interquartile range [IQR]) age of the patients was 64 (53, 73) and 70 (62, 76) years in the uveitis and POAG groups respectively. Baseline MD model estimates in the uveitis and POAG groups were –5.55 (95% CI: -6.39, -4.47) dB and –4.47 (95% CI: -4.31, -4.63) dB respectively. Median (IQR) Intensity (frequency) of VF testing was the same, with an interval of 10 months between each VF test, for both groups.

5.3.2 Rate of Visual Field loss

The uveitis and POAG groups had 23/205 (11%) and 331/4 600 (7%) eyes which progressed at ≥1.5 dB/year respectively. The crude RR of a fast rate of progression for uveitis/POAG was 1.6 (95% confidence interval [CI] 1.1 – 2.3) and age-adjusted RR was 1.9 (95% CI: 1.8 - 2.0). This indicates that, for a similarly aged population, a patient in the uveitis group was 1.9 times more likely to be a fast progressor than patients in the POAG group.

Further analysis using the mixed effects model showed that, the age-adjusted rate of progression was -0.49 dB/year for the uveitis group and -0.37 dB/year for the POAG group. The estimated average age-corrected difference in rate of progression between the groups at the mean age was -0.12 dB/year ($p < 0.01$)

VF progression analysis using PoPLR on PD values indicates that the uveitis group has a higher proportion of significantly progressing eyes (21.2%), compared to the POAG group (18.5%).

5.3.3 Longitudinal intraocular pressure (IOP) analysis

A total of 143 eyes with uveitis plus glaucoma and 3,386 eyes with POAG met the additional inclusion criteria for longitudinal IOP analysis. A summary of longitudinal IOP measurements can be found in Table 5.1. There was no statistically significant difference in mean IOP (within 1 mmHg) between the two groups, yet there was wider range and higher MAE in the uveitis group ($p<0.001$). A comparison between fast and non-fast progressors found the mean IOP difference to be within 1 mmHg for all groups. IOP range was wider in the fast progressors of both POAG and uveitis groups (both $p<0.05$), and widest in the fast progressing uveitis group (21 mmHg). Similarly, MAE was higher in fast progressors of both diseases ($p<0.01$), but highest in the fast progressing uveitis group (3.5 mmHg).

Table 5.1: Longitudinal Intraocular Pressure Metrics: Comparison Between Primary Open-Angle Glaucoma and Uveitis Plus Glaucoma Groups

IOP (mm Hg), Median (IQR)	**POAG (N = 3386)**	**Uveitis Plus Glaucoma (N = 143)**			
Mean	16.5 (14.5, 18.8)	15.9 (13.5, 19.3)	P = .445		
Range	10.5 (7.0, 15.0)	13.3 (8.0, 23.5)	P < .001*		
Mean absolute error	2.1 (1.6, 2.8)	2.6 (1.9, 4.4)	P < .001*		
	Normal Progressors	**Rapid Progressors**		**Normal Progressors**	**Rapid Progressors**	
Mean	16.6 (14.6, 18.6)	16.0 (13.7, 17.9)	P < .001*	15.9 (12.6, 19.2)	16.4 (12.1, 21.0)	P = .827
Range	10.0 (7.0, 15.0)	12.0 (8.5, 17.0)	P < .001*	13.0 (8.0, 22.0)	21.0 (12.0, 30.8)	P = .040*
Mean absolute error	2.1 (1.6, 2.8)	2.3 (1.7, 3.2)	P < .001*	2.6 (1.8, 2.9)	3.5 (2.3, 6.1)	P = .051

5.4 Discussion:

This is the first study to utilize real world EMR data to compare rates of VF loss in uveitis patients with glaucoma and those with POAG. It was demonstrated that uveitis patients with a diagnosis of glaucoma were likely to be younger and have a worse MD at baseline than those with a diagnosis of POAG. The uveitis group were more likely to lose VF at a rapid rate (≥1.5 dB/year loss in MD) compared with the POAG group, with an age-adjusted RR of 1.9 (95% CI: 1.8 - 2.0). Despite this, the data show that the average frequency of VF monitoring is the same for both diseases. The longitudinal IOP analysis suggests IOP range and variability had a stronger association with rapid VF loss than mean IOP.

These findings suggest that patients with a combination of uveitis and glaucoma lose vision more rapidly than POAG, yet on average they are monitored with VFs at the same intensity. These estimates

of rate of VF loss in POAG (-0.37 dB/year) is higher than previously been reported in the literature, however these estimates differ in that were adjusted for age.[84,154] The observed proportion of fast progressors in the POAG cohort is also similar to previous studies: defined thresholds for 'fast' or 'rapid' progression in published literature range from ≥1 to 2 dB/year loss in MD, and reported prevalence of patients progressing rapidly varies between 3-17% in previous studies.[154–159]

The main strength of this study is the large starting sample size compared to others in the literature. Although only 205 uveitic eyes were included in the final VF progression analysis, a sufficiently large starting sample was required to reach the final 205 included samples. This highlights the strength of Big Data in carrying out this type of retrospective study. Inclusion of patients was restricted to those with a minimum of 4 VF tests over at least 4 years. Additionally, at least 4 of the included VF tests must have been performed within 4 years of the first test. As with previous work, the minimum inclusion criteria was a compromise between maximising sample size whilst still ensuring robustness of the rate of progression estimates.[84,87] Reasons for this are given in the additional discussion section in Chapter 7.

This study also has several limitations. Firstly, the data were reliant upon accurate recording in the EMR. Diagnostic labelling within the Medisoft EMR is not a mandatory field and can be entered as free-text, or not entered at all. A large list of diagnostic labels commonly found in the presence of uveitis was included to widen the capture of uveitis subjects. However, a large portion of uveitis subjects in this analysis were lacking in anatomical or disease-specific diagnostic labels in the EMR, thus limiting the ability to explore patterns in specific uveitis subtypes. Steps were taken in the analyses to mitigate the confounding effects of ocular comorbidities. For example, PoPLR VF progression analysis with PD values is designed to identify localised VF change and not just general reduction in VF sensitivity that might be attributed to developing cataract. Results from the PoPLR analysis supported the main findings. Nevertheless, its not possible with this data to fully account for the effects of ocular comorbidities on perimetric performance of the patients. Uveitic patients are susceptible to a range of complications such as cataract, cystoid macular edema, fibrin deposition, band keratopathy and epiretinal membrane, all of which may affect VF performance. Acute inflammatory processes may cause temporary drops in visual acuity, which subsequently resolves. This may explain why some patients' MD seems to improve over time (i.e. perhaps due to cataract surgery or resolution of inflammatory disease such as cystoid macular oedema), although this could also be attributed to patient variability and learning effect.[97,98,160] On the other hand, progressive loss of visual acuity from longstanding uveitic damage (such as scarring and retinal atrophy) may also confound the apparent loss of MD in the uveitic group. Structural information such as retinal nerve fibre layer thickness, cup-to-disc ratio or the inclusion of imaging data would be useful for differentiating between true glaucomatous VF loss and global loss due to other causes. Although not available in this dataset, linkage of structural information would be of interest for future studies.

An important finding is the worse presenting MD in the uveitic group, suggesting early VF loss may be under-detected. Additionally, the baseline age in the uveitis plus glaucoma group was younger, which also supports the hypothesis that uveitic glaucoma may progress faster. Detecting early VF loss is clinically difficult if perimetric testing is not performed routinely, particularly in the absence of a deranged IOP. In the context of uveitis, controlling the inflammation may require more clinical urgency and early glaucomatous damage can be easily overlooked. On the other hand anti-inflammatory treatment, of which corticosteroids is the preferred first-line agent, can precipitate raised IOP in up to a third of patients.[161,162] Steroid implants have been shown to increase the risk of developing glaucomatous optic neuropathy by four times compared to those taking systemic therapy.[163] A comparison of VF progression in uveitis patients receiving steroid treatment versus those without would be of interest for future studies. Such an analysis would require accurate data on frequency, duration and formulation of steroid use, which is not routinely captured by the Medisoft EMR. Successful management of glaucoma in uveitis requires simultaneous treatment of inflammation and IOP elevation. In some cases, controlling the inflammation also helps to reduce IOP and there is evidence to suggest those treated with aggressive anti-inflammatory therapy have better outcomes.[144] Anti-glaucomatous drugs such as beta-blockers and carbonic anhydrase inhibitors can be used to lower the IOP. Some controversy exists around the use of prostaglandin analogues (PGAs) as a first-line agent due to the theoretical risk of blood-aqueous barrier disruption and cystoid macular oedema, however multiple studies have found no differences in the rate of inflammatory recurrences and it is considered safe to use PGAs as first-line therapy in quiescent uveitis.[164,165] The management options for glaucoma in uveitis are predominantly with an aim to decrease IOP, but it is unclear whether these treatments influence IOP variability.

The exact pathological process behind glaucoma in different uveitic subtypes is difficult to define, as there are often multiple co-existing mechanisms driving IOP changes and glaucomatous damage. Yet, elevated IOP has been considered the main modifiable risk factor. This study, albeit based on retrospective data, represents the largest published longitudinal analysis of IOP behaviour in uveitis patients with glaucoma. The mean longitudinal IOP was found to be similar in uveitis and POAG. However, IOP range and MAE was higher in uveitis patients. In both uveitic and POAG groups, IOP range and MAE are consistently higher in those progressing rapidly compared to those losing less than 1.5 dB/year in MD. It is unclear whether the fluctuant IOP is a contributing factor to glaucomatous damage, or whether it is simply a more prevalent finding in those with more severe glaucoma, representing those with the poorest controlled IOP and therefore receiving the most aggressive treatment. The published literature on POAG is inconsistent in this area, with some studies reporting a strong relationship between ocular hypertension and glaucomatous field loss, whilst others suggest that long-term IOP variability is associated more strongly with progression than mean IOP.[166,167] Lee et al. suggest a 1 mmHg increase in standard deviation of IOP is associated with a four-fold increase in

risk of POAG progression.[168] In uveitis, published long-term data on IOP is limited and understanding of IOP behaviour in the context of inflammation, secondary structural damage and anti-inflammatory treatment remains poor.

Glaucoma secondary to uveitis is an important cause of irreversible sight loss, which is challenging to detect and manage. The main finding from retrospective analysis of clinical data from multi-centre glaucoma services in England shows that uveitis patients with glaucoma are almost twice as likely to lose VF rapidly when compared to patients with POAG. Therefore, clinicians managing patients with uveitis should remain vigilant for glaucomatous damage in these high-risk patients. In England, there is evidence that most patients get a similar diet of VF examinations during follow-up, and the findings support this.[84,110] These results at least highlight that uveitis patients require closer attention in order to rule out rapid loss of VF during treatment. IOP variability is more common in uveitic eyes and the findings of the current study suggest that IOP fluctuates across a wider range in this group than in POAG. An appropriate change would be to consider implementing a low threshold for glaucoma screening in patients with uveitis, even if IOP is within normal limits and particularly in the presence of a fluctuating IOP.

6 Using electronic medical records to study socioeconomic status and outcomes in glaucoma clinics

The co-authors of this work are Yusrah Shweikh (YS), Susan Bryan (SB) and David Crabb (DC). The analysis contained in the study (i.e. the R code for the models and the maps as well as the fusion table management), the production of the figures and the drafting of the manuscript was carried out by SRK. YS was the clinical co-author and wrote much of the introduction. The manuscript was then reviewed and edited by all of the authors.

6.1 Introduction

Glaucoma is a common eye condition with significant public health implications. It affects around 2% of Caucasians over 40 and is more prevalent with increasing age and in Black populations.[169] Glaucoma is the most common cause of optic neuropathy and second largest cause of blindness in the UK, accounting for 7.6% of registration for sight impairment and 11% of severe sight impairment.[170] VF defects resulting from optic nerve damage are irreversible. Late presentation with significant VF defects is a common problem and is a major risk factor for subsequent visual loss.[87,171,172] Glaucoma is mostly asymptomatic in its early stages and early detection relies on regular eye tests with optometrists. Over 90% of referrals to hospital eye services in the UK are generated by optometrists.[173]

It is widely recognised that deprivation adversely affects health. In studies of all-cause mortality it is suggested that the effects of deprivation are mediated through 'health-related behaviours' including health-seeking behaviour, smoking, diet, alcohol consumption and physical activity.[174] The link between deprivation and late glaucoma presentation is well established.[175–177] There is no formal screening programme for glaucoma in the UK and individuals with lower socioeconomic status, lower educational attainment and less awareness of eye disease and are less likely to engage with primary healthcare services for "opportunistic" eye health screening, recommended once every 2 years.[178] Fraser and colleagues reported that the risk of late glaucoma presentation was proportional to the number of years since the patient last visited an optometrist and also found a strong association between lower socioeconomic status and late glaucoma presentation.[171] Further evidence has since emerged to corroborate the latter finding.[175,177,179–182] Less is known about the effect of socioeconomic status on the speed (rate) of VF progression in patients who are diagnosed and receiving long-term treatment from Hospital eye services. Previous studies have found that the extent of VF loss at presentation is associated with more rapid VF loss.[183,184] However, the impact of socioeconomic status *per se* on VF progression has not been evaluated.

An EMR allows collection of clinical data from large patient populations. In turn these data can be used for identifying trends in disease progression and treatment response on a large scale.[53,66,85,185–

187] Linking these Big Data to other public health data like those developed for measuring a person's socioeconomic status opens up interesting areas of research and this study serves as an example of this. One such data set is the index of multiple deprivation (IMD), which is the most widely used English measure of socio-economic status, aimed at assisting policy makers. IMD is based on 7 metrics: income, employment, education, health, crime, living environment and access to housing and services.[188]

The purpose of this study is to present large-scale multisite data on glaucoma severity at presentation to secondary eye care services in England and to see how this varies across the socioeconomic spectrum. The novel hypothesis that rates of VF progression in diagnosed patients do not vary with socioeconomic status is also tested, which might suggest greater equity once people are diagnosed.

6.2 Methods

This study involved retrospective analysis of large-scale data extracted from EMRs form several glaucoma clinics in England.

For additional information regarding the datasets used in this study, see the primers for Dataset 1 and Dataset 2. These data included VF results as measured on the Humphrey Visual Field Analyzer (HFA, Carl Zeiss Meditec, Dublin, CA, USA) as well as age (years) and a minimum data set of other clinical records. Eyes with other ocular comorbidities (impeded fundal view etc.) were excluded based on coding in the EMR database. At source the EMR includes data on residential address as standard. Each postcode was identified and allocated to the IMD score for that area (LSOA; lower layer super output area) based on the English Indices of Deprivation 2015 (https://www.gov.uk/government/statistics/english-indices-of-deprivation-2015). The LSOA conversion was undertaken at source to avoid transfer of patient-identifiable data. The English Indices of Deprivation 2015 uses the LSOAs defined in the 2011 census, with evaluation of deprivation being primarily based on data taken from 2012 to 2013.

Anonymised data were collected from five regionally different National Health Service (NHS) Hospital Trust glaucoma clinics in England. Only VFs recorded using the 24-2 Swedish Interactive Testing Algorithm (SITA Standard or SITA Fast) were included for analysis.

The study adhered to the Declaration of Helsinki and all analyses of the data were approved by a research ethics committee of City, University of London. All patient data were anonymized and securely held on the university database. The resulting database contained records from 71,404 patients.

Cross-Sectional analysis

Age, VF and IMD data were available for a total of 69,588 patients. Patients with ≥2 HFA VFs (recorded using the 24-2 SITA algorithm) were included for analyses on glaucoma severity at presentation (n=45,973). Presenting VF was defined as the VF of the second examination. This was done to ameliorate the bias of a perimetry learning effect. Only one eye was included per patient. The eye with the worse (more negative) presenting MD was chosen for inclusion. This is to be interpreted as a surrogate of disease presentation. The worse eyes were chosen as a surrogate of the most "detectable" level of VF loss. Eyes were excluded if they had an impeded fundal view, vitreous opacities or previous retinal detachments, resulting in 324 eyes being removed (n=45,649).

Patients were stratified into their IMD quintiles (1-5). Quintile 5 corresponds to the most deprived group. Odds ratios were calculated to estimate the relative likelihood that patients in the different quintiles presented with severe MD loss (-12 dB or worse) relative to the middle (third) quintile. To do this, a logistic regression model, adjusted for age, was fitted with the third IMD quintile set as the reference group. A higher odds ratio (>1) for a more deprived quintile would indicate a relationship between deprivation and late presentation (Figure 6.1). Secondary analyses using IMD deciles (1-10) were also carried out. In these analyses, the fifth IMD decile was set as the reference group (Figure 6.2).

Longitudinal analysis

Patients with ≥6 VFs were included for analyses on VF progression (n=16,507). As with the cross-sectional analysis, only one eye was included per patient (the eye with the lower MD value at presentation).

Speed (rate) of MD loss per year was calculated by ordinary least squares linear regression of MD over time, for those with sufficient follow-up visits to be included in the progression analyses. As before, patients were stratified into IMD quintiles (1-5). Odds ratios were used to estimate the relative likelihood that patients in different IMD quintiles had a rapid rate of MD loss (-1.5 dB per year or worse) relative to the third quintile. A logistic regression model, adjusted for age, was fitted with the third IMD quintile set as the reference group. A positive odds ratio (>1) would indicate that a particular quintile is more likely to have a rapid rate of MD loss relative to the reference group (Figure 6.3).

Secondary longitudinal analyses replacing IMD quintiles with IMD deciles were also completed. The reference group of the logistic regression model was set to the fifth decile (Figure 6.4).

All statistical analyses were done using R (R Development Core Team, R: A Language and Environment for Statistical Computing, R Foundation for Statistical Computing, Vienna, Austria, URL: http://www.R-project.org, 2008).[119]

6.3 Results

A total of 45,694 (65.6%) patients were included for the analysis of glaucoma severity at presentation. Summary measures of patients included in the cross-sectional analysis are given in Table 6.1.

Table 6.1: Table showing summary statistics of patients included in the cross-section analysis.

	Quintile 1	*Quintile 2*	***Quintile 3***	*Quintile 4*	*Quintile 5*	*Total*
Median age at presentation (IQR) (years)	69 (60, 77)	68 (59, 77)	69 (59, 77)	69 (58, 77)	69 (60, 77)	69 (59, 77)
Median MD at presentation (IQR) (dB)	-2.76 (-6.45, -0.98)	-2.9 (-6.61, -1.02)	-3.15 (-7.31, -1.19)	-3.64 (-7.73, -1.5)	-3.89 (-8.54, -1.56)	-3.07 (-7.01, -1.14)
% of patients presenting worse than -12 dB MD	11.8	12.5	14.4	14.6	17.0	13.3

A total of 16,507 (23.7%) patients were included for the rates of progression (longitudinal) analysis. Summary measures of the patients included are given in Table 6.2.

Table 6.2: Table showing the summary statistics of patients included in the longitudinal analysis.

	Quintile 1	*Quintile 2*	***Quintile 3***	*Quintile 4*	*Quintile 5*	*Total*
Median age at presentation (IQR) (years)	68 (60, 76)	68 (59, 75)	68 (60, 76)	68 (60, 76)	68 (59, 76)	68 (60, 75)
Median rate of progression (IQR)	-0.11 (-0.5, 1.19)	-0.08 (-0.47, 0.22)	-0.09 (-0.5, 0.21)	-0.1 (-0.53, 0.25)	-0.07 (-0.51, 0.28)	-0.09 (-0.5, 0.22)
% of patients progressing faster than -1.5 dB/year	11.3	11.1	12.0	12.5	11.5	11.6

The odds ratio of presenting with a MD of ≤-12dB was 1.3 for the most deprived quintile (quintile 5, relative to reference quintile 3) versus an odds ratio of 0.8 for patients in least deprived quintile (quintile 1, relative to reference quintile 3), $p<0.01$ (Figure 6.1). This shows that patients from deprived regions are significantly more likely to present with severe MD loss than patients from more affluent regions.

Figure 6.1: Ratio of patients presenting with severe glaucoma (worse than -12 dB MD in worse eye) per IMD quintile relative to the middle (third) quintile. The numbers of stars at the top of the plot indicate the level of significance, with three stars (***) representing a value of $p < 0.001$.

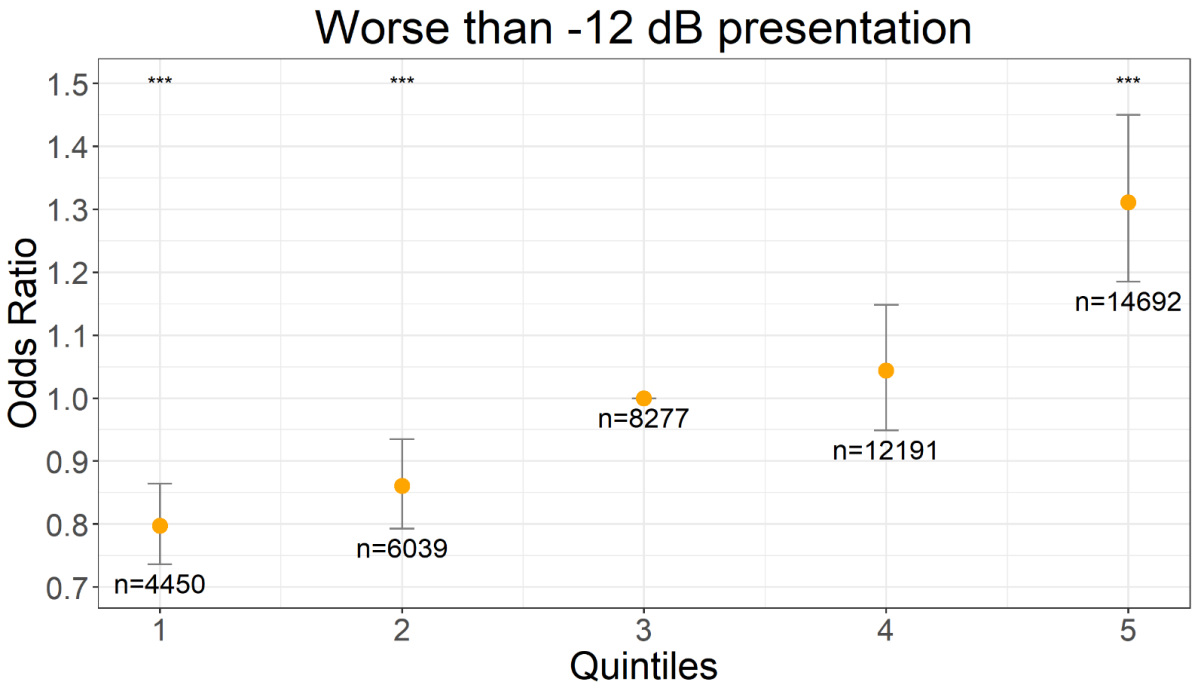
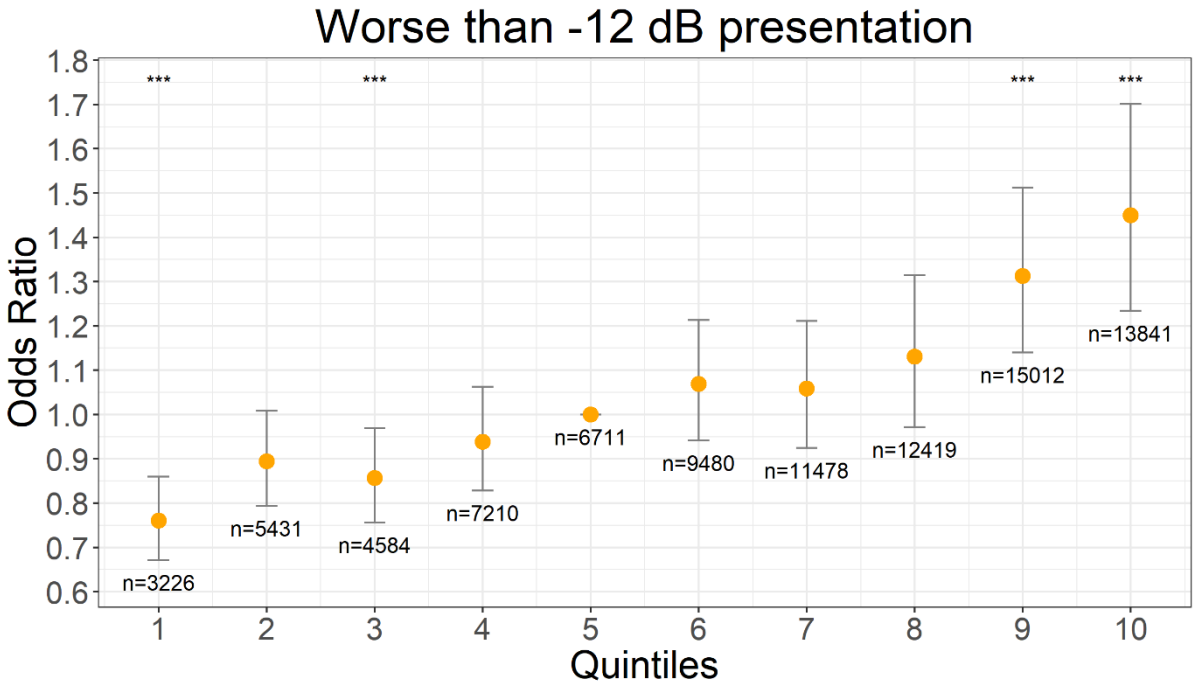


Figure 6.2: Ratio of patients presenting with severe glaucoma (worse than -12 dB MD in worse eye) per IMD quintile relative to the fifth decile. The numbers of stars at the top of the plot indicate the level of significance, with three stars (***) representing a value of $p < 0.001$.



A total of 16,507 patients were included for the analysis of VF progression. Figure 6.3 shows that IMD segregated by quintiles had no significant effect relative to the central quintile on rapid VF progression.

This indicates that although presenting MD is associated with deprivation, once patients are in the glaucoma clinics, deprivation does not affect their progression.

Figure 6.3: Ratio of patients with a fast (<-1 dB/year) rate of VF loss per IMD quintile relative to the middle (third) quintile. The lack of stars (***) indicate that none of the quintiles were statistically significantly different from the middle quantile.

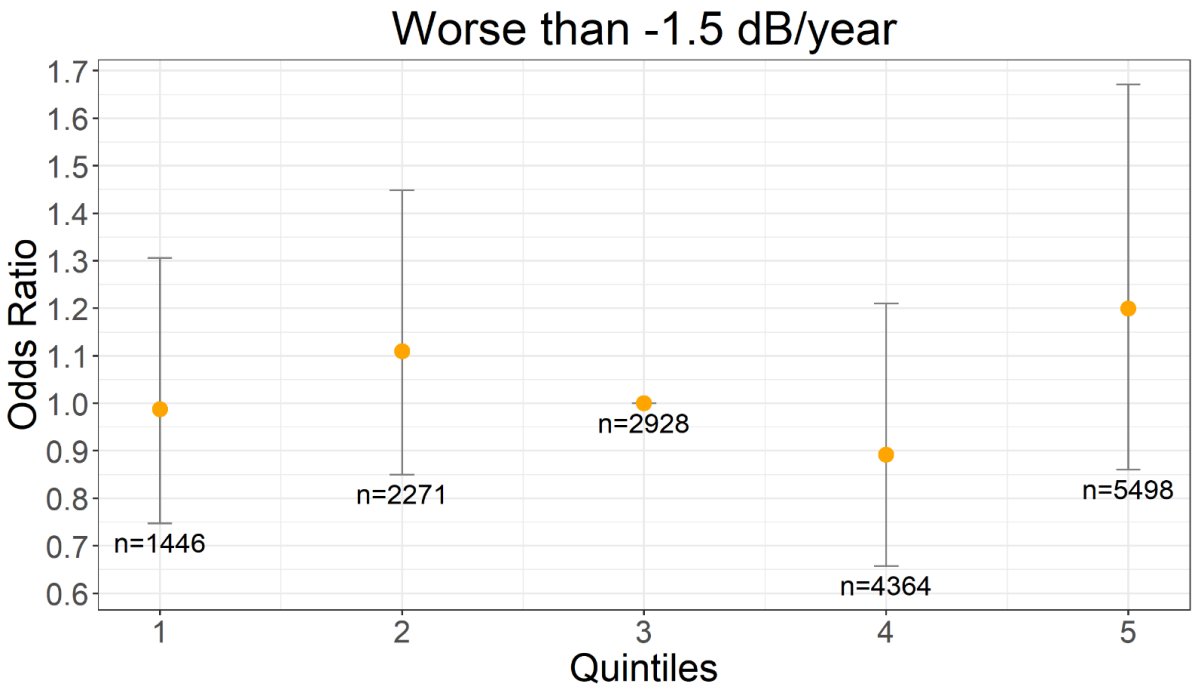
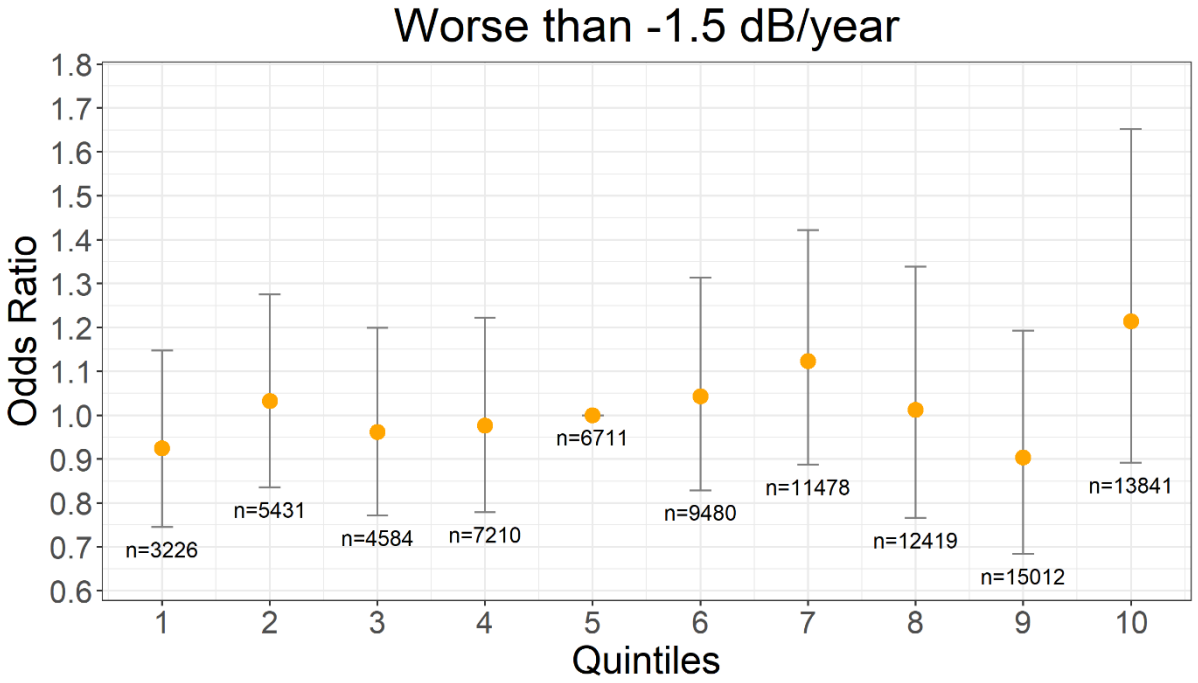


Figure 6.4: Ratio of patients with a fast (<-1 dB/year) rate of VF loss per IMD decile relative to the fifth decile. The lack of stars (***) indicate that none of the deciles were statistically significantly different from the fifth decile.



6.4 Discussion

Using data from 45,649 patients in glaucoma clinics across the UK, this study has shown that people with greater deprivation are more likely to present to hospital eye services with more advanced glaucoma. An analysis of VF progression was carried out using data from 16,507 patients, which revealed that IMD had no significant impact on rates of progression . Deprivation as indicated by IMD segregated by quintiles also had no significant effect on rates of progression (Figure 6.3).

A strength of this study is the sample size, allowing us to detect and quantify small effects. Patients with obvious confounders including patients with no fundal view and those with a history of retinal detachment were excluded. However, data on systemic and ocular comorbidities are incomplete and have made an assumption that the VF defects of patients in glaucoma clinics are reliable and are secondary to glaucoma. Another source of potential bias is the assumption that initial VFs represent those of a new patient in every case when they may be those of a patient transferred from a different glaucoma unit. However, the number of transferred cases is expected to be relatively low and expect that this would not diminish the overall patterns seen in the data.

Analysis of large-scale data in this study supports the previously published finding that patients with greater deprivation are more likely to present to hospital eye services with more severe glaucoma.[175,177,189] Fraser and colleagues reported a case control study in 1999 in which an association between lower socioeconomic status and late glaucoma presentation was identified.[171] In 2009 and 2010 supporting evidence was published by two UK groups.[177,189] Limitations of the study by Fraser and colleagues are the small sample size of 110 cases and the relative lack of resolution of the Jarman index used which is a composite measure of 3 factors (occupation, housing and access to a car). The relatively low power of this study may explain the reported lack of statistical significance in some domains. The studies published in 2009 also report small sample sizes of 126 and 113 patients respectively.[177,189] The theory that deprivation is linked to late glaucoma presentation is also supported by literature from Canada, where patients from more affluent neighbourhoods were statistically less likely to have moderate or severe glaucoma at initial presentation.[181] As a novel finding, this study has also identified no significant relationship between the rate of VF progression and socioeconomic deprivation (Figure 6.3). This may be a result of care in the NHS being free at the point of service. In countries where patients must pay out of pocket for care, it's possible that this relationship wouldn't hold. A systematic review found that the cost of illness for glaucoma increases with severity, so presenting with late stage disease would further compound the burden of disease.[190] Further discussion on this can be found in Chapter 7.

Results from this study suggest that patients with lower socioeconomic status are at no greater risk of glaucomatous VF progression while under the care of glaucoma clinics compared to patients with less deprivation, despite a greater likelihood of presenting with severe glaucoma. Late glaucoma

presentation can be explained by less frequent attendance to optometrists, failure of glaucoma detection by optometrists or inherently more aggressive disease.[171,175] The evidence that there is a mismatch between the locations of optometrists and areas of deprivation within the UK is inconclusive, but it is possible that a limited access to primary care services in socioeconomically disadvantaged areas is contributing to these findings.[191,192] Previous research also links deprivation and lower educational attainment to diminished access to eye care services.[193,194] Reasons underpinning poor access to regular eye testing with optometrists in the UK are varied and may include poor knowledge of eye health, fear, inertia, perceived costs, limited mobility and challenging geographical access.[195,196] Directing resources into case-finding and strengthening links between primary and secondary eye care may help reduce the disparity in severity at presentation between socioeconomic groups. For the most economically disadvantaged areas, there may be a role for non-commercial primary eye care that is not funded by examination fees or product sales.[191] The choice of service locations could be facilitated by interactive maps generated by further work in this area. The costs of such services would be offset by the resultant utility gain from the earlier detection of treatable, blinding conditions.[196]

7 Overview, further discussion of main findings and future work

7.1 Overview of findings

Firstly, I want to start with a general critique and discussion of the studies conducted in this thesis. In any of the chapters that make use of a longitudinal analysis of visual fields, the inclusion criteria of which visits and how many visits to include changes seemingly at random. One could be forgiven for thinking that the intent behind this was some form of "p-hacking" or other untoward data manipulation. In Chapter 2 and 6, I chose to include six visits and then excluded the first one to mitigate learning effects. In Chapter 3, there is a requirement of at least four visits but without an upper limit on how many to include, so that some patients have four and others have ten. In Chapter 5 it is at least four visits in a four-year window, but the first is not excluded. The obvious question is why? The answer lies in trying to strike a balance between statistical power and inclusion. If one assumes that VF loss is linear then the number of visits needed to detect the rate of progression is determined by the rate of progression itself (steeper slopes are easier to detect), the variability (less noise makes for a more accurate model) and the length of time between visits (longer time makes it easier to detect change). For a single visual field series, it takes about six evenly spaced VF measurements over two years to detect a rate of progression with a relatively moderate level of variability with 80% power.[6] It's possible to get the same power with four VF measurements but spaced out over a longer time period (say 3 or 4 years). To emphasise the point I'm trying to make, imagine a scenario where it's only possible to schedule two VF visits. To use two VF measurements to detect VF loss, those two VFs need to be spread out far enough apart to be able to detect a certain level of change but not far enough that the person being measured could have reasonably lost a large chunk of VF function. This is in essence the basis of recommendations for setting guidelines on the intervals between VF visits. When carrying out comparisons of these slopes, another level of variability arises. When comparing two groups, each group will have an underlying distribution of these slopes. The more observations (patients) in each of these groups, the easier it is to determine what that underlying distribution is. How close the study sample can get to the "true" underlying distribution using a limited number of observations is a process that can be tweaked by choosing particular inclusion criteria and statistical methods.

If there is an abundance of data, it doesn't really matter what your inclusion criteria is. If the slopes (that is, the rates of progressions) really are different, then a change will be detected given enough data (provided it isn't systematically biased in some way). In Chapters 3 and 6, the subpopulations that are being studied (patients in clinics and patients in different SES groupings respectively) are so large that not much thought needs to go into how many VFs are needed to be included. With thousands of patients in each group, even with high levels of variability a crude mean estimate will be decently accurate. In Chapter 5 however, the subgroup is much smaller than in the previous chapters. A mixed effects model is used so that no useful information about intra-patient variability is lost. If all the chapters had used

this approach, the results might not have changed much but the certainty would have gone up. There are two main reasons that this was not done. The first is for interpretability, simple linear models are more easily understood than mixed effects models. If the goal of this thesis is to demonstrate how useful Big Data is, it's important that readers are easily able to understand the methods and results. Secondly, it highlights (albeit indirectly) the power of large data sets. In clinical trials, a lot of effort goes into planning the analysis that will be carried out, how many patients are needed, how far apart and how frequently to test the VF etc.[91,197] This is because clinical trials are expensive. In studies using Big Data (i.e. an abundance of data), a blunt tool (OLS linear models) can be used and still come away with a statistically significant result. This further emphasises a need to move away from relying on p-values and instead focus on how meaningful a result is in context. The issue of significance versus relevance arises in Chapter 2.In the chapter, several aspects of perimetry procedure were analysed using a large VF dataset. Patients who had a series of at least 6 pairs of monocular VF tests, where the right eye was consistently tested first were included in the study (n=6320 One of the aims of the study was to determine if the testing order of eyes effected their perimetric performance, and if so, by how much. The results showed a small decrease (0.13 dB, 95% CI: -0.26, -0.02) in MD in the second eye tested compared to the first and a small relative (3%) increase in variability. The effect is small but is also an average across thousands of patients. The spread of variability is large and so does not say much on how any individual patient might vary. While statistically significant, this result is not directly clinically useful although in situations where measurement precision and intrapatient variability needs to be kept constant, it may be beneficial to keep the order of testing constant.

A criticism that was raised about the usefulness of the type of clinic-based Big Data found in this thesis is of its veracity. A reviewer commenting on the now-published version of Chapter 5 argued that relying on diagnostic information contained in EMRs alone is not a basis for a study and needs to be validated by reviewing charts. I think criticisms such as these are a part of a series of growing pains associated with moving towards electronic based systems. Issues around clinicians recording conditions in different ways (such as the different subtypes of uveitis) can be overcome by implementing standardised criteria such as The Standardisation of Uveitis Nomenclature criteria in all clinics. Most specialists are aware of these and once EMRs have the appropriate labels in their systems, it is then just a case of adaptation. There is a potential for systematic biases between centres due to different systems and practices (discussed below). A national unified standardisation of EMR systems and procedures would address this in the future, but for the time being, as long as centres are measuring and recording the same data, it's possible to collate them into a single dataset with some harmonisation. Chapter 5 investigated cases of patients with uveitis and glaucoma. A treatment for uveitis (steroids) can increase IOP and lead to glaucoma, making it difficult to manage patients who have both. The results of a mixed effects model showed that the uveitis and glaucoma group had a higher rate of progression when adjusted for age (-0.49 dB/year vs -0.37 dB/year, $p < 0.01$). The uveitis and glaucoma group also had

twice the risk (Age-adjusted Risk Ratio: 1.9) of being "fast progressors" (progressing faster than -1.5 dB/year). Many of the IOP metrics showed a statistically significant association with the combination group and the fast progressors. Namely, the combination group had a higher variability (MAE) compared to the POAG group and the fast progressors had a wider range of IOP values compared to the non-fast progressors. It would have been of interest to do an analysis of the subtypes of uveitis but the sample sizes were too small. This was due to (in part) almost half of the patients being labelled as having a uveitis comorbidity, but not specifying the subtype. If standardised criteria as mentioned previously had been implemented previously, this data may have been available.

The study in **Chapter 3** looked at how Big Data coming from glaucoma clinics can be used to audit health service delivery of the clinics themselves. This was done by proposing 6 metrics that could be used to get a snapshot view of how a clinic or sample population is performing. One-third of people (34.8%) in the EMRs had measurable and repeatable VF loss and were subject to analyses (n=25 760 patients). The median (IQR) age and presenting MD in these patients were 71 (61, 78) years and −6 (–10, –4) dB, respectively. In the 19,264 patients with more than 4 years follow-up, the median (IQR) rate of MD loss was −0.2 (−0.8, 0.3) dB/year and the median (IQR) intervals between VF examinations was 11 (8, 16) months. Metrics predicting loss of sight years and reliability of examinations varied between centres ($p<0.001$). This study illustrates the feasibility of assessing aspects of health service delivery in glaucoma clinics through analysis of VF databases. Proposed metrics could be useful for blindness prevention from glaucoma in secondary care centres. In the discussion section it was noted that there was a significant variability in results between the centres. There are essentially two main reasons that there would be measurable VF differences between the centres. With everything else equal, either the underlying populations are different, or the management of the patients is different. In this study take Centres 1 and 5 as examples and compare their rates of progression (-0.37 vs -0.10 dB/year). The reason for this difference *could* be because Centre 5 is much better at managing glaucoma patients *or,* more likely, it is because of a demographic difference. Centre 1 has an older population and a higher percentage of patients presenting with later stage VF damage. Both of these could be contributory factors to patients in that centre progressing at a faster rate compared to Centre 5. The true answer is likely a combination of both factors. For a true fair combination between centres, a multivariable model correcting for demographic factors would need to be used. This raises a broader point on creating data sets from multiple sources, such as in clinical trials with multiple centres or indeed observational data from multiple clinics. Systematic biases arise when there is a non-random reason for changes in the measurement or recording of data in a sample. A common example given is of a response bias in surveys. With regards to VF testing, if some centres used an opaque eyepatch and others used a translucent patch, this could (and likely would) lead to a difference in MD (see discussion of Chapter

2). When collating data from different centres such as in this study, it is important to keep this in mind when carrying out analyses.

The work in Chapter 4 replicates the findings of several large-scale clinical trials on the conversion from OHT to POAG. Clinical trials are of course the gold standard in determining the efficacy of medical treatments, but it is not clear how well the results from trials are replicated in clinics. For the sake of rigor, clinical trials are stringently monitored but the "real world" in-clinic conditions tend to be a bit messier. Studies using Big Data to replicate the results of clinical trials using a population from clinics undergoing routine treatment are a useful resource in determining the utility of interventions outside of a clinical trial. The cumulative risk of conversion to POAG was 17.5% (95% CI: 15.4% – 19.6%) at 5 years for this in-clinic population. Older age (HR: 1.35 per decade, 95% CI: 1.22 – 1.50, P < 0.001) was associated with a higher risk of conversion. IOP-lowering therapy (HR: 0.45, 95% CI: 0.35 – 0.57, P < 0.001) was associated with a lower risk of conversion. The discussion in **Chapter 4** compares these results to that of the OHTS study. Both in this study and in the OHTS, IOP lowering treatment was associated with around a 50% reduction in conversion to POAG over five years. In this instance, the in-clinic efficacy lined up with that of a major clinical trial but this is not guaranteed. Further replication studies in the same vein are needed and could be the topics of future work.

In **Chapter 6,** the two main datasets in the thesis were used in combination with census statistics to take a closer look at socioeconomic factors and how they affect certain aspects of glaucoma diagnosis and management. The linked dataset (Dataset 2, which contains IMD data) was used to calculate odds ratios. Different socioeconomic groups were grouped into quintiles and their relative odds of late presentation to clinic were calculated (n=45649). Secondary analysis comparing their rates of progression was also carried out (n=16507). The most deprived quintile of the population presented to clinics with a statistically significantly worse baseline MD than the reference (middle) quantile ($p < 0.001$). There was no difference in rates of progression between quintiles. This indicates that once patients were in the hospital eye services, socioeconomic status did not affect outcomes. It is possible that the UK (England) is a special case in that the NHS provides care free at the point of service. One study for Korea found similar results. Those with lower incomes were more likely to have glaucoma related visual impairment but that there was no significant difference in impairment after they were diagnosed and managed.[198] Like the UK, Korea has a universal health scheme and the cost of treatment was mostly covered. In countries where patients must pay out of pocket this may not necessarily be true. One American study found that ethnic minorities (black race and Latino ethnicity) were much more likely to be inconsistent with follow-up glaucoma appointments.[199] While self-reported ability to pay for medications was not reported to be predictive of irregular follow-up patterns, the sample size was small and most participants had the same government-provided insurance. Of the 152 patients only 9 had private insurance or no insurance making it difficult to draw any definite conclusions. The author echoes the above hypothesis that ability to pay may be a factor in glaucoma adherence. Reiterating a US

department of health and human services report stating that “patients of lower socioeconomic status are more likely to have limited access to care” the authors conclude: “whether similar patterns are evident in patients with glaucoma … is an area for future investigation”.

7.2 Ideas for future work

The studies in this thesis go some of way towards demonstrating the breadth of analysis that can be carried out with these types of large-scale clinic data. Much of the data, particularly in Dataset 2 has the potential to be used in numerous more studies. Many additional projects were touched upon during the course of compiling the work in this thesis and several of the studies and could potentially lead to interesting and impactful work. A systematic review analysing the challenges of Big Data in healthcare listed issues around data structure, security, data standardisation and storage/transfers as the biggest barriers to effective research.[200] Several of these challenges needed to be overcome to produce the work contained in this thesis.

One study, for example, was to investigate how well the whole point-wise VF could be predicted by only using the first (or first few) examination results. There were several potential approaches ranging from simple linear models to more complicated deep learning techniques. A recent paper used deep learning techniques to create a model that could predict a patient’s pointwise VF results.[201] This work had around 30,000 patients with VF records while the two datasets used in this thesis alone amounts to well over four times that (>120000), as well as a large portion of them including additional linked data. These datasets (in particular Dataset 2) would be incredibly useful in any sort of deep learning not only for the sheer number of patients/VFs but also the linked data which adds additional dimensionality. As many of these sophisticated computer-science techniques are relatively new to ophthalmology, many simple but useful studies could be readily done and be of high interest.

Another example which would benefit from large scale VF data would be a study of perimetric variability based on age. Large sample sizes are needed to better understand small variation in populations based on factors like age or ethnicity. When there are large sets of data available, monitoring and treatment could potentially be personalised to some extent to make the process more efficient. The linked dataset for example contains information on conditions such as cataract surgery, diabetes status, previous retinal detachment and mortality status (at the time of extraction in 2015). Many short and interesting studies could be carried out looking at factors such as these and what association, if any, they have on glaucoma metrics (VF, IOP, etc.).

In Chapter 2, an order effect was investigated using one measure of longitudinal variability, namely MAE. Many other measures of reliability (such as false-positives, false-negatives and fixation loss) could be used to explore slightly different aspects of the variability. Perimetric variability is associated disease severity and it’s also possible that it is associated with age. A more complex model, such as a

mixed-effects model, could be used to further investigate factors behind this order effect. It is likely, however, that any subsequent effect found would be similarly small and possibly not of clinical relevance.

In Chapter 3, six metrics were chosen to try to quantify how well clinics were performing and how well patients' outcomes were. To an extent, these metrics were chosen arbitrarily and other outcomes could have been chosen instead. One example of a different metric would be to analyse the rates and outcomes of glaucoma surgeries in the clinics. Other data from Dataset 2, such as rates of medical treatment, ethnicity and IOP measures could also be included to gain insights about different aspects of the clinic.

In Chapter 4, clinic data was used to estimate the "real-world" conversion rate from OHT to POAG in the HES. What was not reported were the differences, if any, that existed between the clinics in rates of conversion. Health economic factors, such as the cost of monitoring/treating OHT patients and epidemiological factors such as the numbers of OHT patients needed to treat to prevent an additional conversion could also be estimated using these data. Additional medications (such as systemic medications like Acetazolamide) or combinations of medications could also be explored to see what effect they have on OHT conversion rates.

In Chapter 5, a broad umbrella term of "uveitis" was used to categories the groups. Uveitis itself has several subtypes based on where inflammation occurs (anterior, posterior etc.). It is likely the case that some of these sub-types have a more profound effect on VF outcomes than others and additional work to explore this could prove to be fruitful. Unfortunately, due to a low number of patient data with these anatomical subtypes in this dataset, it wasn't possible to consider this during the course of the study. Future ophthalmology clinic extractions, especially clinics that specialise in uveitis, may provide the additional patients needed for this type of sub-analysis. Further work could also be done to expand on the IOP metrics, as well as to include information about medications and surgeries into the model. Qualitative work on the experience of uveitis patients with this condition could be carried out in the future. Dealing with glaucoma or uveitis alone can be a burden for patients so it's likely that a combination of both would be more so. Reaching out to uveitis support groups could be a potential avenue for further study.

In Chapter 6, one measure of socioeconomic deprivation (IMD) was used to investigate the effect of socioeconomic status on glaucoma presentation and progression. This metric, while useful, hides a lot of underlying information. The score itself is made up of seven sub-scores relating to factors like education and crime. When using IMD alone it may obfuscate a specific aspect of deprivation that is driving the late presentation. One idea to tackle this would be to instead use the original seven scores, increasing the resolution of study and potentially teasing out the specific factors affecting late presentation to eye clinics. Another and potentially more interesting metric would be to use the ACORN (A Classification Of Residential Neighbourhoods) segmentation tool, which categorises the UKs

population into demographic types based on behaviour as well as where they live.[202] Often used commercially for marketing purposes, it combines several public and private datasets to attempt to capture insights about populations. Categories such as “First time buyers in small, modern homes”, “Semi-skilled workers in traditional neighbourhoods” or “elderly people in social rented flats” would be a much more intuitive way to convey the lifestyles of people interacting with eye services than a single number.

Hopefully it is clear that Big Data and the inclusion of more sophisticated analyses have the potential to change the way providers leverage modern computing power to make more informed clinical decisions. To make this transition as easy as possible, the large amounts of data being collected within healthcare need to be organised and structured in such a way to make it accessible to clinicians and researchers. This will pave the way to a future where Big Data analytics is synonymous with healthcare and enable us to extract the most amount of useful information as possible.

8 List of supporting publications

8.1 Peer-reviewed manuscripts

Kelly, S.R., Bryan, S.R, Crabb, D. P., Does eye examination order for standard automated perimetry matter? *Acta Ophthalmologica 2019;97;e833-e838.*

Liu, X., **Kelly, S.R.**, Montesano, G., Bryan, S.R., Barry, R.J., Keane, P.A., Denniston, A.K., Crabb, D.P., Evaluating the Impact of Uveitis on Visual Field Progression Using Large Scale Real-World Data. *American Journal of Ophthalmology 2019;207;144-150.*

Kelly, S.R., Bryan, S.R., Sparrow, J.M., Crabb, D.P., Auditing service delivery in glaucoma clinics using visual field records – a feasibility study. *BMJ Open Ophthalmology 2019;4:e000352.*

Kelly, S.R., Khawaja, A.P., Bryan, S.R., Azuara-Blanco, A., Sparrow, J.M., Crabb, D.P., 2019 Progression from ocular hypertension to visual field loss in the English hospital eye service. *British Journal of Ophthalmology 2020;0;1-6.*

8.2 Conference presentations

5th Annual School of Health Sciences Doctoral Research Conference - City, University of London 2017 - London, England. Does the testing order of visual fields matter? **Stephen Kelly,** Susan Bryan, David Crabb.

The Association of Research in Vision and Ophthalmology (ARVO) 2018 – Honolulu, HA. Does the testing order of visual fields matter? **Stephen Kelly**, Susan Bryan, David Crabb.

The work in Chapter 5 was presented in several conferences by my co-author Xiao Liu. These conferences include **The United Kingdom and Éire Glaucoma Society meeting 2018, The Association of Research in Vision and Ophthalmology meeting (ARVO) 2018** and **EURETINA 2019**, where it scored the highest paper presentation in the uveitis section.

9 References:

1 Quigley HA, West SK, Rodriguez J. The Prevalence of Glaucoma in a Population-Based Study of Hispanic Subjects- Proyecto VER. *Arch Ophthalmol* 2001;**119**:1819–26.

2 Resnikoff S, Pascolini D, Etya D, *et al.* Global data on visual impairment in the year 2002. *Bull World Heal Organ* 2004;**012831**. doi:/S0042-96862004001100009

3 Tham Y-C, Li X, Wong TY, *et al.* Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. *Ophthalmology* 2014;**121**:2081–90. doi:10.1016/j.ophtha.2014.05.013

4 National Institute for Health and Clinical Excellence. Glaucoma: Diagnosis and management of chronic open angle glaucoma and ocular hypertension (NG81). 2017. http://www.nice.org.uk/guidance/cg85

5 Gordon MO, Beiser JA, Brandt JD, *et al.* The Ocular Hypertension Treatment Study: Baseline factors that predict the onset of primary open-angle glaucoma. *Arch Ophthalmol* 2002;**120**:714–20. doi:10.1001/archopht.120.6.714

6 Chauhan BC, Garway-Heath DF, Goñi FJ, *et al.* Practical recommendations for measuring rates of visual field change in glaucoma. *Br J Ophthalmol* 2008;**92**:569–73. doi:10.1136/bjo.2007.135012

7 Garway-Heath DF, Crabb DP, Bunce C, *et al.* Latanoprost for open-angle glaucoma (UKGTS): a randomised, multicentre, placebo-controlled trial. *Lancet* 2015;**385**:1295–304. doi:10.1016/S0140-6736(14)62111-5

8 Coleman AL, Miglior S. Risk Factors for Glaucoma Onset and Progression. *Surv Ophthalmol* 2008;**53**:2–10. doi:10.1016/j.survophthal.2008.08.006

9 Leske MC, Heijl A, Hyman L, *et al.* Predictors of Long-term Progression in the Early Manifest Glaucoma Trial. *Ophthalmology* 2007;**114**:1965–72. doi:10.1016/j.ophtha.2007.03.016

10 Racette L, Wilson MR, Zangwill LM, *et al.* Primary open-angle glaucoma in blacks: A Review. *Surv Ophthalmol* 2003;**48**:295–313. doi:10.1016/S0039-6257(03)00028-6

11 Fingert JH. Primary open-angle glaucoma genes. *Eye (Lond)* 2011;**25**:587–95. doi:10.1038/eye.2011.97

12 Allingham RR, Liu Y, Rhee DJ. The genetics of primary open-angle glaucoma: A review. *Exp Eye Res* 2009;**88**:837–44. doi:10.1016/J.EXER.2008.11.003

13 Libby RT, Gould DB, Anderson MG, *et al.* Complex Genetics of Glaucoma Sussceptibility. *Annu Rev Genomics Hum Genet* 2005;**6**:15–44. doi:10.1146/annurev.genom.6.080604.162209

14 Heijl A, Leske MC, Bengtsson B, *et al.* For the Early Manifest Glaucoma Trial Group: Reduction of intraocular pressure and glaucoma progression. *Arch Ophthalmol* 2002;**120**:1268–79. doi:10.1001/archopht.120.10.1268

15 Chan MPY, Broadway DC, Khawaja AP, *et al.* Glaucoma and intraocular pressure in EPIC-Norfolk Eye Study: cross sectional study. *BMJ* 2017;**358**:j3889. doi:10.1136/BMJ.J3889

16 Kass MA. The Ocular Hypertension Treatment Study. *Arch Ophthalmol* 2002;**120**:701. doi:10.1001/archopht.120.6.701

17 Leske MC, Heijl A, Hussein M, *et al.* Factors for glaucoma progression and the effect of treatment: The early manifest glaucoma trial. *Arch Ophthalmol* 2003;**121**:48–56. doi:10.1001/archopht.121.1.48

18 Malik R, Swanson WH, Garway-Heath DF. 'Structure-function relationship' in glaucoma: Past thinking and current concepts. *Clin Exp Ophthalmol* 2012;**40**:369–80. doi:10.1111/j.1442-9071.2012.02770.x

19 Crabb DP, Smith ND, Glen FC, *et al.* How does glaucoma look?: Patient perception of visual field loss. *Ophthalmology* 2013;**120**:1120–6. doi:10.1016/j.ophtha.2012.11.043

20 Morley AMS, Murdoch I. The future of glaucoma clinics. *Br J Ophthalmol* 2006;**90**:640–5. doi:10.1136/bjo.2005.085522

21 Tuck MW, Crick RP. The projected increase in glaucoma due to an ageing population. *Ophthalmic Physiol Opt* 2003;**23**:175–9. doi:10.1046/j.1475-1313.2003.00104.x

22 King A, Azuara-Blanco A, Tuulonen A. Glaucoma. *BMJ* 2013;**346**. doi:10.1136/bmj.f3518

23 Crabb DP, Russell RA, Malik R, *et al.* Frequency of visual field testing when monitoring patients newly diagnosed with glaucoma: mixed methods and modelling. *Heal Serv Deliv Res* 2014;**2**:1–102. doi:10.3310/hsdr02270

24 Spector RH. *Visual Fields*. 3rd ed. Butterworths, Boston 1990. https://www.ncbi.nlm.nih.gov/books/NBK220

25 Crabb DP, Smith ND, Glen FC, *et al.* How does glaucoma look?: Patient perception of visual field loss. *Ophthalmology* 2013;**120**:1120–6. doi:10.1016/j.ophtha.2012.11.043

26 Wild JM. Techniques and developments in automated perimetry: A review. *Ophthalmic Physiol Opt* 1988;**8**:295–308. doi:10.1111/j.1475-1313.1988.tb01059.x

27 Bengtsson B, Olsson J, Heijl A, *et al.* A new generation of algorithms for computerized threshold perimetry, SITA. *Acta Ophthalmol Scand* 1997;**75**:368–75. doi:10.1111/j.1600-0420.1997.tb00392.x

28 Olsson J, Rootzén H. An Image Model for Quantal Response Analysis in Perimetry. *Scand J Stat* 1994;**21**:375–87.http://www.jstor.org/stable/4616324

29 Saunders LJ, Russell RA, Crabb DP. Measurement precision in a series of visual fields acquired by the Standard and Fast versions of the Swedish Interactive Thresholding Algorithm: Analysis of large-scale data from clinics. *JAMA Ophthalmol* 2015;**133**:74–80. doi:10.1001/jamaophthalmol.2014.4237

30 Heijl A, Patella VM, Chong LX, *et al.* A New SITA Perimetric Threshold Testing Algorithm: Construction and a Multicenter Clinical Study. *Am J Ophthalmol* 2018;**198**:154–65. doi:10.1016/j.ajo.2018.10.010

31 Montolio FGJ, Wesselink C, Gordijn M, *et al.* Factors that influence standard automated perimetry test results in glaucoma: Test reliability, technician experience, time of day, and season. *Investig Ophthalmol Vis Sci* 2012;**53**:7010–7. doi:10.1167/iovs.12-10268

32 Heijl A, Lindgren A, Lindgren G. Test-retest variability in glaucomatous visual fields. *Am J Ophthalmol* 1989;**108**:130–5. doi:10.1016/0002-9394(89)90006-8

33 Keller KE, Bradley JM, Vranka JA, *et al. Segmental versican expression in the trabecular meshwork and involvement in outflow facility*. 2011. doi:10.1167/iovs.10-6948

34 Russell RA, Crabb DP, Malik R, *et al.* The relationship between variability and sensitivity in large-scale longitudinal visual field data. *Investig Ophthalmol Vis Sci* 2012;**53**:5985–90. doi:10.1167/iovs.12-10428

35 Wild JM, Dengler-Harles M, Searle AE, *et al.* The influence of the learning effect on automated perimetry in patients with suspected glaucoma. *Acta Ophthalmol* 1989;**67**:537–45.http://www.ncbi.nlm.nih.gov/pubmed/2589053 (accessed 23 Apr 2018).

36 Heijl A, Lindgren G, Olsson J. The effect of perimetric experience in normal subjects. *Arch Ophthalmol* 1989;**107**:81–6. doi:10.1001/archopht.1989.01070010083032

37 Glen FC, Baker H, Crabb DP. A qualitative investigation into patients' views on visual field testing for glaucoma monitoring. *BMJ Open* 2014;**4**. doi:10.1136/bmjopen-2013-003996

38 Jones PR, Smith ND, Bi W, *et al.* Portable perimetry using eye-tracking on a tablet computer—A feasibility assessment. *Transl Vis Sci Technol* 2019;**8**. doi:10.1167/tvst.8.1.17

39 Murray IC, Fleck BW, Brash HM, *et al.* Feasibility of Saccadic Vector Optokinetic PerimetryA Method of Automated Static Perimetry for Children Using Eye Tracking. *Ophthalmology* 2009;**116**:2017–26. doi:10.1016/j.ophtha.2009.03.015

40 McTrusty AD, Cameron LA, Perperidis A, *et al.* Comparison of Threshold Saccadic Vector Optokinetic Perimetry (SVOP) and Standard Automated Perimetry (SAP) in Glaucoma. Part II: Patterns of Visual Field Loss and Acceptability. *Transl Vis Sci Technol* 2017;**6**:4. doi:10.1167/tvst.6.5.4

41 Wroblewski D, Francis BA, Sadun A, *et al.* Testing of visual field with virtual reality goggles in manual and visual grasp modes. *Biomed Res Int* 2014;**2014**:206082. doi:10.1155/2014/206082

42 Tahir HJ, Murray IJ, Parry NRA, *et al.* Optimisation and assessment of three modern touch screen tablet computers for clinical vision testing. *PLoS One* 2014;**9**:e95074. doi:10.1371/journal.pone.0095074

43 Bodduluri L, Boon MY, Dain SJ. Evaluation of tablet computers for visual function assessment. *Behav Res Methods* 2017;**49**:548–58. doi:10.3758/s13428-016-0725-1

44 Anderson AJ, Bedggood PA, George Kong YX, *et al.* Can Home Monitoring Allow Earlier Detection of Rapid Visual Field Progression in Glaucoma? *Ophthalmology* 2017;**124**:1735–42. doi:10.1016/j.ophtha.2017.06.028

45 Kong YXG, He M, Crowston JG, *et al.* A Comparison of Perimetric Results from a Tablet Perimeter and Humphrey Field Analyzer in Glaucoma Patients. *Transl Vis Sci Technol* 2016;**5**:2. doi:10.1167/tvst.5.6.2

46 Schulz AM, Graham EC, You Y, *et al.* Performance of iPad-based threshold perimetry in glaucoma and controls. *Clin Experiment Ophthalmol* 2018;**46**:346–55. doi:10.1111/ceo.13082

47 Artes PH, O'Leary N, Nicolela MT, *et al.* Visual field progression in glaucoma: What is the specificity of the guided progression analysis? *Ophthalmology* 2014;**121**:2023–7. doi:10.1016/j.ophtha.2014.04.015

48 De Moraes CG V, Juthani VJ, Liebmann JM, *et al.* Risk Factors for Visual Field Progression in Treated Glaucoma. *Arch Ophthalmol* 2011;**129**:562–8. doi:10.1001/archophthalmol.2011.72

49 Fitzke FW, Hitchings RA, Poinoosawmy D, *et al.* Analysis of visual field progression in glaucoma. *Br J Ophthalmol* 1996;**80**:40 LP – 48. doi:10.1136/bjo.80.1.40

50 O'Leary N, Chauhan BC, Artes PH. Visual field progression in glaucoma: Estimating the overall significance of deterioration with permutation analyses of pointwise linear regression (PoPLR). *Investig Ophthalmol Vis Sci* 2012;**53**:6776–84. doi:10.1167/iovs.12-10049

51 Wu Z, Medeiros FA. Recent developments in visual field testing for glaucoma. *Curr Opin Ophthalmol* 2018;**29**:141–6.

52 Hu R, Racette L, Chen KS, *et al.* Functional Assessment of Glaucoma Progression: Uncovering Progression. *Surv Ophthalmol* Published Online First: 2020.

doi:10.1016/j.survophthal.2020.04.004

53 Dean BB, Lam J, Natoli JL, *et al.* Use of Electronic Medical Records for Health Outcomes Research. *Med Care Res Rev* 2009;**66**:611–83. doi:https://doi.org/10.1177/1077558709332440

54 Boland M V., Chiang MF, Lim MC, *et al.* Adoption of electronic health records and preparations for demonstrating meaningful use: An american academy of ophthalmology survey. *Ophthalmology* 2013;**120**:1702–10. doi:10.1016/j.ophtha.2013.04.029

55 Sanders DS, Read-Brown S, Tu DC, *et al.* Impact of an electronic health record operating room management system in ophthalmology on documentation time, surgical volume, and staffing. *JAMA Ophthalmol* 2014;**132**:586–92. doi:10.1001/jamaophthalmol.2013.8196

56 Jackson TL, Donachie PHJ, Sparrow JM, *et al.* United Kingdom National Ophthalmology Database Study of Vitreoretinal Surgery: Report 1; Case mix, complications, and cataract. *Eye* 2013;**27**:644–51. doi:10.1038/eye.2013.12

57 Knox Cartwright NE, Johnston RL, Jaycock PD, *et al.* The Cataract National Dataset electronic multicentre audit of 55 567 operations: when should IOLMaster biometric measurements be rechecked? *Eye* 2009;**24**:894.https://doi.org/10.1038/eye.2009.196

58 Jaycock P, Johnston RL, Taylor H, *et al.* The Cataract National Dataset electronic multi-centre audit of 55 567 operations: Updating benchmark standards of care in the United Kingdom and internationally. *Eye* 2009;**23**:38–49. doi:10.1038/sj.eye.6703015

59 Sparrow JM, Taylor H, Qureshi K, *et al.* The Cataract National Dataset electronic multi-centre audit of 55 567 operations: Risk indicators for monocular visual acuity outcomes. *Eye* 2012;**26**:821–6. doi:10.1038/eye.2012.51

60 Timmis A, Hawking MKD, Janjuha S, *et al.* Feasibility of real-time capture of routine clinical data in the electronic health record: a hospital-based, observational service-evaluation study. *BMJ Open* 2018;**8**:e019790. doi:10.1136/bmjopen-2017-019790

61 Nghiem AZ, Canning C, Eason J, *et al.* Going paperless: improved cataract surgery outcome data quality in a new fully electronic unit. *Eye* Published Online First: 2019. doi:10.1038/s41433-019-0350-1

62 Chiang MF, Boland M V., Brewer A, *et al.* Special requirements for electronic health record systems in ophthalmology. *Ophthalmology* 2011;**118**:1681–7. doi:10.1016/j.ophtha.2011.04.015

63 The RCOphth NOD Audit Team. National Electronic Glaucoma Surgery and Visual Field Preservation Audit: Feasibility Report. 2017. https://www.nodaudit.org.uk/u/docs/20/joxmqddqpu/Glaucoma Surgery and Visual Fields Audit Feasibility Report.pdf (accessed 18 Jul 2019).

64 Lee CS, Lee AY, Baughman D, *et al.* The United Kingdom Diabetic Retinopathy Electronic Medical Record Users Group: Report 3: Baseline Retinopathy and Clinical Features Predict Progression of Diabetic Retinopathy. *Am J Ophthalmol* 2017;**180**:64–71. doi:10.1016/j.ajo.2017.05.020

65 Egan C, Zhu H, Lee A, *et al.* The United Kingdom Diabetic Retinopathy Electronic Medical Record Users Group, Report 1: baseline characteristics and visual acuity outcomes in eyes treated with intravitreal injections of ranibizumab for diabetic macular oedema. *Br J Ophthalmol* 2017;**101**:75–80. doi:10.1136/bjophthalmol-2016-309313

66 Liu X, Kelly SR, Montesano G, *et al.* Evaluating the Impact of Uveitis on Visual Field Progression Using Large Scale Real-World Data. *Am J Ophthalmol* 2019;**207**:144–50. doi:10.1016/j.ajo.2019.06.004

67 Jones NP. The Manchester Uveitis Clinic: The first 3000 patients, 2: Uveitis Manifestations, Complications, Medical and Surgical Management. *Ocul Immunol Inflamm* 2015;**23**:127–34. doi:10.3109/09273948.2014.968671

68 Honeyman M, Dunn D, McKenna H. A digital NHS? An introduction to the digital agenda and plans for implementation. 2016. http://www.kingsfund.org.uk/publications/digital-nhs

69 National Advisory Group on Health Information Technology in England. Making IT work : harnessing the power of health IT to improve care in England. 2016. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/550866/Wachter_Review_Accessible.pdf

70 Schade CP, Sullivan FM, de Lusignan S, *et al.* e-Prescribing, Efficiency, Quality: Lessons from the Computerization of UK Family Practice. *J Am Med Informatics Assoc* 2006;**13**:470–5. doi:10.1197/jamia.M2041

71 Hackos JT, Redish J. *User and task analysis for interface design*. Wiley New York, New York 1998.

72 Laurel B, Mountford SJ. *The art of human-computer interface design*. Addison-Wesley Longman Publishing Co., Inc, Boston 1990.

73 Mayhew DJ, Mayhew D. *The usability engineering lifecycle: a practitioner's handbook for user interface design*. Morgan Kaufmann, Burlington 1999.

74 McInnes DK, Saltman DC, Kidd MR. General practitioners' use of computers for prescribing and electronic health records: results from a national survey. *Med J Aust* 2006;**185**:88–91.

75 Ludwick DA, Doucette J. Adopting electronic medical records in primary care: lessons learned from health information systems implementation experience in seven countries. *Int J Med Inform* 2009;**78**:22–31.

76 Crabb DP. A view on glaucoma - Are we seeing it clearly? *Eye* 2016;**30**:304–13. doi:10.1038/eye.2015.244

77 Fung SSM, Lemer C, Russell RA, *et al.* Are practical recommendations practiced? A national multi-centre cross-sectional study on frequency of visual field testing in glaucoma. *Br J Ophthalmol* 2013;**97**:843–7. doi:10.1136/bjophthalmol-2012-302903

78 Zahari M, Mukesh BN, Rait JL, *et al.* Progression of visual field loss in open angle glaucoma in the Melbourne Visual Impairment Project. *Clin Experiment Ophthalmol* 2006;**34**:20–6. doi:10.1111/j.1442-9071.2006.01142.x

79 Kwon YH, Kim CS, Zimmerman MB, *et al.* Rate of visual field loss and long-term visual outcome in primary open-angle glaucoma. *Am J Ophthalmol* 2001;**132**:47–56. doi:10.1016/S0002-9394(01)00912-6

80 Saunders LJ, Russell RA, Crabb DP. Measurement Precision in a Series of Visual Fields Acquired by the Standard and Fast Versions of the Swedish Interactive Thresholding Algorithm: Analysis of Large-Scale Data From Clinics. *JAMA Ophthalmol* 2015;**133**:74–80. doi:10.1001/jamaophthalmol.2014.4237

81 Boodhna T, Crabb DP. Disease severity in newly diagnosed glaucoma patients with visual field Loss: trends from more than a decade of data. *Ophthalmic Physiol Opt* 2015;**35**:225–30. doi:10.1111/opo.12187

82 Saunders LJ, Russell RA, Kirwan JF, *et al.* Disease Severity in Newly Diagnosed Glaucoma Patients with Visual Field Loss: Trends From More Than a Decade of Data. *Investig Ophthalmol Vis Sci* 2012;**53**:225–30. doi:10.1371/journal.pone.0083595

83 Hu S, Smith ND, Saunders LJ, *et al.* Patterns of Binocular Visual Field Loss Derived from Large-Scale Patient Data from Glaucoma Clinics. *Ophthalmology* 2015;**122**:2399–406. doi:10.1016/j.ophtha.2015.08.005

84 Boodhna T, Saunders LJ, Crabb DP. Are rates of vision loss in patients in English glaucoma clinics slowing down over time? Trends from a decade of data. *Eye (Lond)* 2015;**29**:1613–9. doi:10.1038/eye.2015.161

85 Day AC, Donachie PHJ, Sparrow JM, *et al.* The Royal College of Ophthalmologists' National Ophthalmology Database study of cataract surgery: Report 1, visual outcomes and complications. *Eye* 2015;**29**:552–60. doi:10.1038/eye.2015.3

86 Kakhani MK, Kakhani S, Biradar SR. Research issues in Big Data analytics. *Int J Appl or Innov Eng Manag* 2013;**2**:228–32.www.ijaiem.org

87 Saunders LJ, Russell RA, Kirwan JF, *et al.* Examining visual field loss in patients in glaucoma clinics during their predicted remaining lifetime. *Investig Opthalmology Vis Sci* 2014;**55**:102–9. doi:10.1167/iovs.13-13006

88 Saunders LJ, Russell RA, Crabb DP. Practical landmarks for visual field disability in glaucoma. *Br J Ophthalmol* 2012;**96**:1185–9. doi:10.1136/bjophthalmol-2012-301827

89 Russell RA, Garway-Heath DF, Crabb DP. New insights into measurement variability in glaucomatous visual fields from computer modelling. *PLoS One* 2013;**8**:e83595. doi:10.1371/journal.pone.0083595

90 Kutzko KE, Brito CF, Wall M. Effect of instructions on conventional automated perimetry. *Invest Ophthalmol Vis Sci* 2000;**41**:2006–13.http://iovs.arvojournals.org/article.aspx?articleid=2123623 (accessed 2 Jul 2018).

91 Crabb DP, Garway-Heath DF. Intervals between visual field tests when monitoring the glaucomatous patient: wait-and-see approach. *Invest Ophthalmol Vis Sci* 2012;**53**:2770–6. doi:10.1167/iovs.12-9476

92 Hudson C, Wild JM, O'Neill EC. Fatigue effects during a single session of automated static threshold perimetry. *Investig Ophthalmol Vis Sci* 1994;**35**:268–80. doi:10.1364/AO.27.001030

93 Searle AE, Wild JM, Shaw DE, *et al.* Time-related variation in normal automated static perimetry. *Ophthalmology* 1991;**98**:701–7.http://www.ncbi.nlm.nih.gov/pubmed/2062504 (accessed 13 Sep 2017).

94 Bengtsson B, Heijl A. SITA Fast, a new rapid perimetric threshold test. Description of methods and evaluation in patients with manifest and suspect glaucoma. *Acta Ophthalmol Scand* 1998;**76**:431–7. doi:10.1034/j.1600-0420.1998.760408.x

95 Bengtsson B, Heijl A, Olsson J. Evaluation of a new threshold visual field strategy, SITA, in normal subjects. *Acta Ophthalmol Scand* 1998;**76**:165–9. doi:10.1034/j.1600-0420.1998.760208.x

96 Barkana Y, Gerber Y, Mora R, *et al.* Effect of eye testing order on automated perimetry results using the Swedish Interactive Threshold Algorithm Standard 24-2. *Arch Ophthalmol* 2006;**124**:781–4. doi:10.1001/archopht.124.6.781

97 Wild JM, Searle AET, Dengler-Harles M, *et al.* Long-term follow-up of baseline learning and fatigue effects in the automated perimetry of glaucoma and ocular hypertensive patients. *Acta Ophthalmol* 1991;**69**:210–6. doi:10.1111/j.1755-3768.1991.tb02713.x

98 Gardiner SK, Demirel S, Johnson CA. Is there evidence for continued learning over multiple years in perimetry? *Optom Vis Sci* 2008;**85**:1043–8. doi:10.1097/OPX.0b013e31818b9b40

99 Turpin A, McKendrick AM. What reduction in standard automated perimetry variability would improve the detection of visual field progression? *Investig Ophthalmol Vis Sci* 2011;**52**:3237–45. doi:10.1167/iovs.10-6255

100 Johnson CA, Adams CW, Lewis RA. Fatigue effects in automated perimetry. *Appl Opt* 1988;**27**:1030. doi:10.1364/AO.27.001030

101 Bengtsson B, Heijl A. Evaluation of a new perimetric threshold strategy, SITA, in patients with manifest and suspect glaucoma. *Acta Ophthalmol Scand* 1998;**76**:268–72. doi:10.1034/j.1600-0420.1998.760303.x

102 Wild JM, Pacey IE, O'Neill EC, *et al.* The SITA perimetric threshold algorithms in glaucoma. *Investig Ophthalmol Vis Sci* 1999;**40**:1998–2009.

103 Bengtsson B, Heijl A. False-negative responses in glaucoma perimetry: Indicators of patient performance or test reliability? *Investig Ophthalmol Vis Sci* 2000;**41**:2201–4. doi:10.1016/S0002-9394(00)00758-3

104 Bryan SR, Eilers PHC, Lesaffre EMEH, *et al.* Global visit effects in point-wise longitudinal modeling of glaucomatous visual fields. *Investig Ophthalmol Vis Sci* 2015;**56**:4283–9. doi:10.1167/iovs.15-16691

105 Gardiner SK, Demirel S, Gordon MO, *et al.* Seasonal Changes in Visual Field Sensitivity and Intraocular Pressure in the Ocular Hypertension Treatment Study. *Arch Ophthalmol* 2009;**127**:213–5. doi:10.1001/archophthalmol.2008.599

106 Anderson AJ, Johnson CA. Effect of dichoptic adaptation on frequency-doubling perimetry. *Optom Vis Sci* 2002;**79**:88–92. doi:10.1097/00006324-200202000-00009

107 Anderson AJ, McKendrick AM. Quantifying adaptation and fatigue effects in frequency doubling perimetry. *Investig Ophthalmol Vis Sci* 2007;**48**:943–8. doi:10.1167/iovs.06-0685

108 Altman DG, Bland JM. Missing data. *Br Med J* 2007;**334**:424. doi:10.1136/bmj.38977.682025.2C

109 Bengtsson B. Reliability of computerized perimetric threshold tests as assessed by reliability indices and threshold reproducibility in patients with suspect and manifest glaucoma. *Acta Ophthalmol Scand* 2000;**78**:519–22. doi:10.1034/j.1600-0420.2000.078005519.x

110 Boodhna T, Crabb DP. More frequent, more costly? Health economic modelling aspects of monitoring glaucoma patients in England. *BMC Health Serv Res* 2016;**16**:1–13. doi:10.1186/s12913-016-1849-9

111 Henson DB, Emuh T. Monitoring vigilance during perimetry by using pupillography. *Investig Ophthalmol Vis Sci* 2010;**51**:3540–3. doi:10.1167/iovs.09-4413

112 Fuhr PS, Hershner TA, Daum KM. Ganzfeld blankout occurs in bowl perimetry and is eliminated by translucent occlusion. *Arch Ophthalmol* 1990;**108**:983–8. doi:10.1001/archopht.1990.01070090085045

113 Health Quality Improvement Partnership. National Electronic Glaucoma Surgery and Visual Field Preservation Audit: Feasibility Report. 2017.https://www.hqip.org.uk/wp-content/uploads/2018/04/Glaucoma-Surgery-Audit-Feasibility-Report.pdf

114 Malik R, Baker H, Russell RA, *et al.* A survey of attitudes of glaucoma subspecialists in England and Wales to visual field test intervals in relation to NICE guidelines. *BMJ Open* 2013;**3**:1–5. doi:10.1136/bmjopen-2012-002067

115 Bryan SR, Crabb DP. A New Graphical Tool for Assessing Visual Field Progression in Clinical Populations. *Transl Vis Sci Technol* 2018;**7**:22–22. doi:10.1167/tvst.7.1.22

116 Mills RP, Budenz DL, Lee PP, *et al.* Categorizing the stage of glaucoma from pre-diagnosis to end-stage disease. *Am J Ophthalmol* 2006;**141**:24–30. doi:10.1016/j.ajo.2005.07.044

117 Burr J, Mowatt G, Hernández R, *et al.* The clinical effectiveness and cost-effectiveness of screening for open angle glaucoma: a systematic review and economic evaluation HTA Health Technology Assessment NHS R&D HTA Programme www.hta.ac.uk Feedback. *Health Technol Assess (Rockv)* 2007;**11**.http://www.hta.ac.uk

118 ONS. National life tables, UK - Office for National Statistics. January. 2016;:3.https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/bulletins/nationallifetablesunitedkingdom/2014to2016%0Ahttps://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/bulletins/na

119 R Core Team. R Core Team. R A Lang. Environ. Stat. Comput. R Found. Stat. Comput. Vienna, Austria. 2016;**55**:ISBN 3-900051-07-0, URL http://www.R-project.org/.http://www.mendeley.com/research/r-language-environment-statistical-computing-96/%5Cnpapers2://publication/uuid/A1207DAB-22D3-4A04-82FB-D4DD5AD57C28

120 Crabb DP, Saunders LJ, Edwards LA. Cases of advanced visual field loss at referral to glaucoma clinics – more men than women? *Ophthalmic Physiol Opt* 2017;**37**:82–7. doi:10.1111/opo.12328

121 Day AC, Donachie PHJ, Sparrow JM, *et al.* The Royal College of Ophthalmologists' National Ophthalmology Database Study of cataract surgery: Report 2, relationships of axial length with ocular copathology, preoperative visual acuity, and posterior capsule rupture. *Eye* 2015;**29**:1528–37. doi:10.1038/eye.2015.198

122 Day AC, Donachie PHJ, Sparrow JM, *et al.* United Kingdom National Ophthalmology Database Study of Cataract Surgery: Report 3: Pseudophakic Retinal Detachment. *Ophthalmology* 2016;**123**:1711–5. doi:10.1016/j.ophtha.2016.04.002

123 Johnston RL, Day AC, Donachie PHJ, *et al.* The Royal College of Ophthalmologists' National Ophthalmology Database study of cataract surgery: report 4, equity of access to cataract surgery. *Eye* 2020;**34**:530–6. doi:10.1038/s41433-019-0524-x

124 The Center for Accelerating Medical Solutions. Think Research: Using Electronic Medical Records to Bridge Patient Care and Research. 2005. http://www.providersedge.com/ehdocs/ehr_articles/Think_Research-Using_EMRs_to_Bridge_Patient_Care_and_Research.pdf

125 Sparrow JM, Taylor H, Qureshi K, *et al.* The Cataract National Dataset electronic multi-centre audit of 55 567 operations: Risk indicators for monocular visual acuity outcomes. *Eye* 2012;**26**:821–6. doi:10.1038/eye.2012.51

126 Johnston RL, Taylor H, Smith R, *et al.* The Cataract National Dataset Electronic Multi-centre Audit of 55 567 Operations: variation in posterior capsule rupture rates between surgeons. *Eye* 2009;**24**:888.https://doi.org/10.1038/eye.2009.195

127 Jaycock P, Johnston RL, Taylor H, *et al.* The Cataract National Dataset electronic multi-centre audit of 55 567 operations: updating benchmark standards of care in the United Kingdom and internationally. *Eye* 2007;**23**:38.https://doi.org/10.1038/sj.eye.6703015

128 Boland M V. Electronic Health Records and Ophthalmology. *JAMA Ophthalmol* 2015;**133**:633. doi:10.1001/jamaophthalmol.2015.0913

129 Boland M V., Chiang MF, Lim MC, *et al.* Adoption of electronic health records and preparations for demonstrating meaningful use: An american academy of ophthalmology survey. *Ophthalmology* 2013;**120**:1702–10. doi:10.1016/j.ophtha.2013.04.029

130 Rotchford AP, Hughes J, Agarwal PK, *et al.* Prevalence of treatment with glaucoma medication in Scotland, 2010–2017. *Br J Ophthalmol* 2019;:bjophthalmol-2019-314206. doi:10.1136/bjophthalmol-2019-314206

131 Wu MA S-Y, Nemesure PhD B, Hennis PhD, FRCP A, *et al.* Open-angle Glaucoma and Mortality, The Barbados Eye Studies. *Arch Ophthalmol* 2008;**126**:365.

132 Medeiros FA. Validation of a Predictive Model to Estimate the Risk of Conversion From Ocular Hypertension to Glaucoma. *Arch Ophthalmol* 2005;**123**:1351. doi:10.1001/archopht.123.10.1351

133 Miglior S. Results of the European Glaucoma Prevention Study. *Ophthalmology* 2005;**112**:366–75. doi:10.1016/j.ophtha.2004.11.030

134 Salvetat ML, Zeppieri M, Tosoni C, *et al.* Baseline factors predicting the risk of conversion from ocular hypertension to primary open-angle glaucoma during a 10-year follow-up. *Eye* 2016;**30**:784–95. doi:10.1038/eye.2016.86

135 Prokofyeva E, Zrenner E. Epidemiology of major eye diseases leading to blindness in Europe: A literature review. *Ophthalmic Res* 2012;**47**:171–88. doi:10.1159/000329603

136 Honeyman M, Dunn D, McKenna H. A digital NHS? An introduction to the digital agenda and plans for implementation. *King's Fund* Published Online First: 2016.http://www.kingsfund.org.uk/publications/digital-nhs

137 Brusini P, Filacorda S. Enhanced Glaucoma Staging System (GSS 2) for classifying functional damage in glaucoma. *J Glaucoma* 2006;**15**:40–6. doi:10.1097/01.ijg.0000195932.48288.97

138 Gray SF, Spry PGD, Brookes ST, *et al.* The Bristol shared care glaucoma study: Outcome at follow up at 2 years. *Br J Ophthalmol* 2000;**84**:456–63. doi:10.1136/bjo.84.5.456

139 Vernon SA, Adair A. Shared care in glaucoma: A national study of secondary care lead schemes in England. *Eye* 2010;**24**:265–9. doi:10.1038/eye.2009.118

140 Suttorp-Schulten MS, Rothova A. The possible impact of uveitis in blindness: a literature survey. *Br J Ophthalmol* 1996;**80**:844–8.

141 Bodaghi B, Cassoux N, Wechsler B, *et al.* Chronic severe uveitis: Etiology and visual outcome in 927 patients from a single center. *Medicine (Baltimore)* 2001;**80**:263–70. doi:10.1097/00005792-200107000-00005

142 Darrell R, Wagener H, Kurland L. Epidemiology of uveitis. Incidence and prevalence in a small urban community. *Arch Ophthalmol (Chicago, Ill 1960)* 1962;**68**:502–14.

143 Goldstein H. The reported demography and causes of blindness throughout the world. *Adv Ophthalmol* 1980;**40**:1–99.

144 Siddique SS, Suelves AM, Baheti U, *et al.* Glaucoma and Uveitis. Surv. Ophthalmol. 2013;**58**:1–10. doi:10.1016/j.survophthal.2012.04.006

145 Herbert HM, Viswanathan A, Jackson H, *et al.* Risk factors for elevated intraocular pressure in uveitis. *J Glaucoma* 2004;**13**:96–9.

146 Sallam A, Sheth HG, Habot-Wilner Z, *et al.* Outcome of raised intraocular pressure in uveitic eyes with and without a corticosteroid-induced hypertensive response. *Am J Ophthalmol* 2009;**148**:207-213.e1. doi:10.1016/j.ajo.2009.02.032

147 Takahashi T, Ohtani S, Miyata K, *et al.* A clinical evaluation of uveitis-associated secondary glaucoma. *Jpn J Ophthalmol*;**46**:556–62.

148 Marin-Franch I, Swanson WH. The visualFields package: A tool for analysis and visualization

of visual fields. *J Vis* 2013;**13**:10–10. doi:10.1167/13.4.10

149 Fay MP, Feuer EJ. Confidence intervals for directly standardized rates: a method based on the gamma distribution. *Stat Med* 1997;**16**:791–801.

150 Bates D, Mächler M, Bolker B, *et al.* Fitting Linear Mixed-Effects Models using lme4. Published Online First: June 2014. doi:10.18637/jss.v067.i01

151 O'Leary N, Chauhan BC, Artes PH. Visual field progression in glaucoma: Estimating the overall significance of deterioration with permutation analyses of pointwise linear regression (PoPLR). *Investig Ophthalmol Vis Sci* 2012;**53**:6776–84. doi:10.1167/iovs.12-10049

152 Garway-Heath DF, Zhu H, Cheng Q, *et al.* Combining optical coherence tomography with visual field data to rapidly detect disease progression in glaucoma: a diagnostic accuracy study. *Health Technol Assess (Rockv)* 2018;**22**:1–106. doi:10.3310/hta22040

153 Garway-Heath DF, Quartilho A, Prah P, *et al.* Evaluation of Visual Field and Imaging Outcomes for Glaucoma Clinical Trials (An American Ophthalomological Society Thesis). *Trans Am Ophthalmol Soc* 2017;**115**:T4(1-23).

154 Chauhan BC, Malik R, Shuba LM, *et al.* Rates of glaucomatous visual field change in a large clinical population. *Investig Ophthalmol Vis Sci* 2014;**55**:4135–43. doi:10.1167/iovs.14-14643

155 Chan TCW, Bala C, Siu A, *et al.* Risk Factors for Rapid Glaucoma Disease Progression. *Am J Ophthalmol* 2017;**180**:151–7. doi:10.1016/j.ajo.2017.06.003

156 De Moraes CG V., Prata TS, Tello C, *et al.* Glaucoma with early visual field loss affecting both hemifields and the risk of disease progression. *Arch Ophthalmol* 2009;**127**:1129–34. doi:10.1001/archophthalmol.2009.165

157 Heijl A, Buchholz P, Norrgren G, *et al.* Rates of visual field progression in clinical glaucoma care. *Acta Ophthalmol* 2013;**91**:406–12. doi:10.1111/j.1755-3768.2012.02492.x

158 Aptel F, Aryal-Charles N, Giraud J-M, *et al.* Progression of visual field in patients with primary open-angle glaucoma - ProgF study 1. *Acta Ophthalmol* 2015;**93**:615–20. doi:10.1111/aos.12788

159 Medeiros FA, Zangwill LM, Mansouri K, *et al.* Incorporating risk factors to improve the assessment of rates of glaucomatous progression. *Invest Ophthalmol Vis Sci* 2012;**53**:2199–207. doi:10.1167/iovs.11-8639

160 Heijl A, Bengtsson B. The effect of perimetric experience in patients with glaucoma. *Arch Ophthalmol (Chicago, Ill 1960)* 1996;**114**:19–22.

161 Tripathi RC, Parapuram SK, Tripathi BJ, *et al.* Corticosteroids and glaucoma risk. *Drugs Aging* 1999;**15**:439–50.

162 Becker B. Intraocular Pressure In Response to Topical Corticosteroids. *Invest Ophthalmol* 1965;**4**:198–205.

163 Friedman DS, Holbrook JT, Ansari H, *et al.* Risk of elevated intraocular pressure and glaucoma in patients with uveitis: Results of the multicenter uveitis steroid treatment trial. *Ophthalmology* 2013;**120**:1571–9. doi:10.1016/j.ophtha.2013.01.025

164 Markomichelakis NN, Kostakou A, Halkiadakis I, *et al.* Efficacy and safety of latanoprost in eyes with uveitic glaucoma. *Graefe's Arch Clin Exp Ophthalmol* 2009;**247**:775–80. doi:10.1007/s00417-009-1036-3

165 Horsley MB, Chen TC. The Use of Prostaglandin Analogs in the Uveitic Patient. *Semin Ophthalmol* 2011;**26**:285–9. doi:10.3109/08820538.2011.588650

166 Caprioli J, Coleman AL. Intraocular Pressure Fluctuation. *Ophthalmology* 2008;**115**:1123-1129.e3. doi:10.1016/j.ophtha.2007.10.031

167 Nouri-Mahdavi K, Hoffman D, Coleman AL, *et al.* Predictive factors for glaucomatous visual field progression in the Advanced Glaucoma Intervention Study. *Ophthalmology* 2004;**111**:1627–35. doi:10.1016/j.ophtha.2004.02.017

168 Lee PP, Walt JW, Rosenblatt LC, *et al.* Association Between Intraocular Pressure Variation and Glaucoma Progression: Data from a United States Chart Review. *Am J Ophthalmol* 2007;**144**:901–7. doi:10.1016/j.ajo.2007.07.040

169 Rudnicka AR, Mt.-Isa S, Owen CG, *et al.* Variations in primary open-angle glaucoma prevalence by age, gender, and race: A Bayesian meta-analysis. *Investig Ophthalmol Vis Sci* 2006;**47**:4254–61. doi:10.1167/iovs.06-0299

170 Quartilho A, Simkiss P, Zekite A, *et al.* Leading causes of certifiable visual loss in England and Wales during the year ending 31 March 2013. *Eye (Lond)* 2016;**30**:602–7. doi:10.1038/eye.2015.288

171 Fraser S, Bunce C, Wormald R. Risk Factors for Late Presentation in Chronic Glaucoma. *Investig Opthalmology Vis Sci* 1999;**40**:2251–7.

172 Grant WM, Burke JF. Why Do Some People Go Blind from Glaucoma? *Ophthalmology* 1982;**89**:991–8. doi:10.1016/S0161-6420(82)34675-8

173 Sheldrick JH, Ng C, Austin DJ, *et al.* An analysis of referral routes and diagnostic accuracy in cases of suspected glaucoma. *Ophthalmic Epidemiol* 1994;**1**:31–9. doi:10.3109/09286589409071443

174 Sánchez-Santos MT, Mesa-Frias M, Choi M, *et al.* Area-Level Deprivation and Overall and Cause-Specific Mortality: 12 Years' Observation on British Women and Systematic Review of Prospective Studies. *PLoS One* 2013;**8**:1–11. doi:10.1371/journal.pone.0072656

175 Fraser S, Bunce C, Wormald R, *et al.* Deprivation and late presentation of glaucoma: case-control study. *BMJ* 2001;**322**:639–43. doi:10.1136/bmj.322.7287.639

176 Ng WS, Agarwal PK, Sidiki S, *et al.* The effect of socio-economic deprivation on severity of glaucoma at presentation. *Br J Ophthalmol* 2010;**94**:85–7. doi:10.1136/bjo.2008.153312

177 Sukumar S, Spencer F, Fenerty C, *et al.* The influence of socioeconomic and clinical factors upon the presenting visual field status of patients with glaucoma. *Eye* 2009;**23**:1038–44. doi:10.1038/eye.2008.245

178 McCarty C. Knowledge and beliefs about common eye diseases. Aust. N. Z. J. Ophthalmol. 1997;**25**:253–4. doi:10.1111/j.1442-9071.1997.tb01511.x

179 Tielsch J, Sommer A, Katz J, *et al.* Socioeconomic status and visual impairment among urban Americans. *Arch Ophthalmol* 1991;**109**:637–641.

180 Dandona R, Dandona L. Socioeconomic status and blindness. *Br J Ophthalmol* 2001;**85**:1484–1488.

181 Buys YM, Jin Y-P, Canadian Glaucoma Risk Factor Study Group. Socioeconomic status as a risk factor for late presentation of glaucoma in Canada. *Can J Ophthalmol / J Can d'Ophtalmologie* 2013;**48**:83–7. doi:10.1016/j.jcjo.2012.10.003

182 Shweikh Y, Ko F, Chan MPY, *et al.* Measures of socioeconomic status and self-reported glaucoma in the UK Biobank cohort. *Eye* 2015;**29**. doi:10.1038/eye.2015.157

183 Wilson R, Dueker DK, Walker AM, *et al.* Risk Factors for Rate of Progression of Glaucomatous Visual Field Loss: A Computer-Based Analysis. *Arch Ophthalmol*

1982;**100**:737–41. doi:10.1001/archopht.1982.01030030741002

184 Mikelberg FS, Schulzer M, Drance SM, *et al.* The rate of progression of scotomas in glaucoma. *Am J Ophthalmol* 1986;**101**:1–6. doi:10.1016/0002-9394(86)90457-5

185 Kelly SR, Bryan SR, Sparrow JM, *et al.* Auditing service delivery in glaucoma clinics using visual field records: a feasibility study. *BMJ Open Ophthalmol* 2019;**4**:e000352. doi:10.1136/bmjophth-2019-000352

186 Denniston AK, Lee AY, Lee CS, *et al.* United Kingdom Diabetic Retinopathy Electronic Medical Record (UK DR EMR) Users Group: report 4, real-world data on the impact of deprivation on the presentation of diabetic eye disease at hospital services. *Br J Ophthalmol* 2019;**103**:837–43. doi:10.1136/bjophthalmol-2018-312568

187 Jackson TL, Donachie PHJ, Sparrow JM, *et al.* United Kingdom National Ophthalmology Database Study of Vitreoretinal Surgery: Report 1; Case mix, complications, and cataract. *Eye* 2013;**27**:644–51. doi:10.1038/eye.2013.12

188 Smith T, Noble M, Noble S, *et al.* The English Indices of Deprivation 2015 Technical report. 2015.

189 Ng WS, Agarwal PK, Sidiki S, *et al.* The effect of socio-economic deprivation on severity of glaucoma at presentation. *Br J Ophthalmol* 2010;**94**:85–7. doi:10.1136/bjo.2008.153312

190 Fiscella RG, Lee J, Davis EJH, *et al.* Cost of illness of glaucoma: A critical and systematic review. *Pharmacoeconomics* 2009;**27**:189–98. doi:10.2165/00019053-200927030-00002

191 Day F, Buchan JC, Cassells-Brown a, *et al.* A glaucoma equity profile: correlating disease distribution with service provision and uptake in a population in Northern England, UK. *Eye (Lond)* 2010;**24**:1478–85. doi:10.1038/eye.2010.73

192 Legge R, Strang NC, Loffler G. Distribution of optometric practices relative to deprivation index in Scotland. *J Public Heal (United Kingdom)* 2018;**40**:389–96. doi:10.1093/pubmed/fdx074

193 Zhang X, Beckles GL, Chou C-F, *et al.* Socioeconomic Disparity in Use of Eye Care Services Among US Adults With Age-Related Eye Diseases. *JAMA Ophthalmol* 2013;**131**:1198. doi:10.1001/jamaophthalmol.2013.4694

194 Cox A, Blaikie A, MacEwen CJ, *et al.* Visual impairment in elderly patients with hip fracture: Causes and associations. *Eye* 2005;**19**:652–6. doi:10.1038/sj.eye.6701610

195 Shickle D, Griffin M. Why don't older adults in England go to have their eyes examined? *Ophthalmic Physiol Opt* 2014;**34**:38–45.

196 Shickle D, Todkill D, Chisholm C, *et al.* Addressing inequalities in eye health with subsidies and increased fees for General Ophthalmic Services in socio-economically deprived communities: a sensitivity analysis. *Public Health* 2015;**129**:131–7. doi:10.1016/j.puhe.2014.07.010

197 Wu Z, Medeiros FA. Impact of Different Visual Field Testing Paradigms on Sample Size Requirements for Glaucoma Clinical Trials. *Sci Rep* 2018;**8**:4889. doi:10.1038/s41598-018-23220-w

198 Sung H, Shin HH, Baek Y, *et al.* The association between socioeconomic status and visual impairments among primary glaucoma: The results from Nationwide Korean National Health Insurance Cohort from 2004 to 2013. *BMC Ophthalmol* 2017;**17**:1–9. doi:10.1186/s12886-017-0551-y

199 Murakami Y, Lee BW, Duncan M, *et al.* Racial and ethnic disparities in adherence to

glaucoma follow-up visits in a county hospital population. *Arch Ophthalmol* 2011;**129**:872–8. doi:10.1001/archophthalmol.2011.163

200 Kruse CS, Goswamy R, Raval Y, *et al.* Challenges and Opportunities of Big Data in Health Care: A Systematic Review. *JMIR Med Informatics* 2016;**4**:e38. doi:10.2196/medinform.5359

201 Wen JC, Lee CS, Keane PA, *et al.* Forecasting future humphrey visual fields using deep learning. *PLoS One* 2019;**14**:1–14. doi:10.1371/journal.pone.0214875

202 Morgan M, Chinn S. ACORN group, social class, and child health. *J Epidemiol Community Health* 1983;**37**:196–203. doi:10.1136/jech.37.3.196

Quod Erat Demonstrandum

■