CITY UNIVERSITY LONDON

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A study of the role of advanced technologies in glaucoma case-finding

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Submitted for the degree of

Doctor of Philosophy

December 2014

City University London

Division of Optometry and Visual Science

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Acknowledgements

First and foremost, I would like to express my deepest gratitude to my supervisors Professor John Lawrenson and Professor David Edgar for providing me with this opportunity, and encouraging my research with unfounded patience and understanding. It has been my privilege to learn from their knowledge and experience, and I am incredibly proud of what we have achieved together. I am grateful to my co-supervisor from Moorfields Eye Hospital, Professor David Garway-Heath, for offering invaluable advice over the course of the project. A very special thanks to Mr Ian Murdoch for providing the opportunity to collaborate on a study, and for giving so much of his time to guide Chapter 4 with unbounded enthusiasm and words of inspiration.

I am especially grateful to the College of Optometrists for their support and cooperation with the distribution of the surveys, and for providing the funding to conduct this work. To my examiners Dr Mark Dunne and Professor David Crabb, thank you for making the experience so enjoyable, and for enabling the opportunity to learn from your expertise in the field.

I would also like to acknowledge with much appreciation the crucial role of those individuals who were involved in data collection for the studies: Sonal, Shima, Lee, Rinal, Pooja, and in particular Bruno, who performed the technology-based assessment for the open angle glaucoma study with incredible care and diligence over the 12-month period. I am equally thankful to my colleagues at the Fight for Sight Optometry clinic, and Moorfields Eye Hospital (Ealing) for their help in administering data collection for the two main studies. To everyone who has participated in my studies, I will forever be indebted not only for your time, but for your words of encouragement and invaluable help with recruitment. In total, just shy of 2,000 people have been involved in one way or another in providing the data for this thesis! I would particularly like to express my gratitude to Pat Southan who kindly introduced my study to the 'Bridge club' community of East London, and to Simon Brown and the team at Super Being Labs for building a digital tool to allow participants to make online appointment bookings.

A heartfelt thanks to Eva, Irene, Byki and Evgenia, my fellow researchers and good friends, and to all the post-graduate team at City University for keeping me sane when I was most in need. To my other friends and colleagues, too numerous to mention by name, words cannot express how thankful I am for being my tremendous pillar of strength over the past 3 years. Last but not least, to Darsh, for providing me with love and laughter in equal measures and for putting up with my attempts to juggle a PhD with normal life! Your unfounded belief in me gives me the strength to keep believing in myself, and to follow my ambitions without limits.

Declaration

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Abstract

In the UK, 11,000 new cases of open angle glaucoma (OAG) are diagnosed annually in people aged 40 to 70 years. However, two-thirds of UK OAG cases may remain undiagnosed, highlighting the need for improved detection. UK optometrists generate more than 95% of referrals for suspected glaucoma and ocular hypertension. Case-detection of glaucoma may be improved by using screening tests with better diagnostic accuracy, but standardised protocols for advanced technologies used alone, or in combination, to detect glaucoma are lacking.

Chapter 2 reports on two cross-sectional surveys of UK community optometrists, determining the equipment and information technology (IT) used in optometric practice, and exploring the rationale behind the uptake of ophthalmic equipment and IT. UK optometrists are increasingly investing in new ophthalmic equipment and IT, including the latest technology. Longitudinal comparisons with previous surveys revealed an increase in use of Optical coherence tomography (OCT), Goldmann/ Perkins tonometry and pachymetry. Variations in responses reflected differences in General Ophthalmic Services provision across the UK and involvement in community enhanced services. There was general agreement that specialised equipment enhances clinical care and permits increased involvement in enhanced services, but initial costs and ongoing maintenance can be a financial burden.

Chapter 3 summarises a prospective cross-sectional study investigating the diagnostic accuracy of four advanced technologies for detecting POAG, used alone and in combination, in a representative sample (N=505) of the UK primary care population aged ≥60 years, and compared to a reference standard ophthalmic examination. Structural imaging using the iVue SD-OCT provided better discrimination between POAG and non-POAG/ non-OHT subjects than either visual function test (Frequency Doubling Technology or Moorfields Motion Displacement Threshold). The low specificity of visual function tests precludes their use in isolation, but their use together with objective evaluation of optic nerve head structure by SD-OCT should improve case-detection of glaucoma.

Chapter 4 describes a case-control study (N=78) evaluating the diagnostic effectiveness of two slit-lamp based techniques (van Herick and Smith's) and imaging-based systems (Pentacam and Visante OCT) when compared to the reference standard gonioscopic observation, to screen for individuals at-risk of angle closure glaucoma (ACG). Overall, the van Herick test and Visante OCT, used either alone or in combination, showed best discrimination between narrow and open angles. Recording of either the temporal or nasal van Herick grade would be sufficient for case-finding in at-risk individuals.

Chapter 5 summarises preceding chapters and details recommendations for future research.

Abbreviations

ACA	Anterior chamber angle
ACD	Anterior chamber depth
ACG	Angle closure glaucoma
ACV	Anterior chamber volume
AGIS	Advanced Glaucoma Intervention Study
AMD	Age-related macular degeneration
ANOVA	Analysis of variance
AoA	American Optometric Association
AOP	Association of Optometrists
AS-OCT	Anterior segment Optical coherence tomography
AUROC	Area under the receiver operating characteristic curve
BSV	Best Signal Value
CCG	Clinical Communications Gateway
CCT	Central corneal thickness
CET	Continuing Education and Training
CGS	Canadian Glaucoma Study
CH	Corneal hysteresis
CHRPE	Congenital hypertrophy of the Retinal Pigment Epithelium
COAG	Chronic open angle glaucoma
CoO	College of Optometrists
CP	Clinical Practice
CPD	Continued professional development
CRF	Corneal resistance factor
DBR	Diabetic retinopathy
DCT	Dynamic Contour Tonometry
DGH	David Garway-Heath
DOH	Department of Health
ECR	Electronic care records
EGS	European Glaucoma Society
EHEW	Eye Health Examination Wales

EHR	Electronic health record
eReferrals	Electronic referrals
ESTA	Enhanced Standard Threshold Algorithm
ETDRS	Early Treatment Diabetic Retinopathy Study
FDT	Frequency Doubling Technology
FLV	Focal loss volume
GAT	Goldmann applanation tonometry
GCC	Ganglion cell complex
GIST	Glaucoma Inheritance Study in Tasmania
GLV	Global loss volume
GOC	General Optical Council
GON	Glaucomatous optic neuropathy
GOS	General Ophthalmic Services
GP	General Practitioner
HES	Hospital eye service
HFA	Humphrey Field Analyser
HRT	Heidelberg Retina Tomograph
HTA	Health Technology Assessment
IGA	International Glaucoma Association
IOP	Intraocular pressure
IOPcc	Corneal-compensated intraocular pressure
IOPg	Goldmann-correlated intraocular pressure
ISGEO	International Society of Geographical and Epidemiological Ophthalmology
IT	Information Technology
LACD	Limbal anterior chamber depth
LOCS	Lens opacities classification system
LOCSU	Local Optical Committee Support Unit
logMAR	Logarithm of the Minimum Angle of Resolution
LPI	Laser peripheral iridotomy
MD	Mean deviation
MMDT	Moorfields Motion Displacement Threshold test

MPOD	Macular pigment optical density
NAHIT	The National Alliance for Health Information Technology
NCT	Non-contact tonometry
NDB	Normative database
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NRR	Neuro-retinal rim
NSC	National Screening Committee
NTG	Normal tension glaucoma
OAG	Open angle glaucoma
OCT	Optical Coherence Tomography
OHT	Ocular hypertension
OHTS	Ocular Hypertension Treatment Study
ONH	Optic nerve head
ONS	Office for National Statistics
ORA	Ocular Response Analyser
PAC	Primary angle closure
PACG	Primary angle closure glaucoma
PACS	Primary angle closure suspect
PAS	Peripheral anterior synechiae
pAUROC	Partial area under the receiver operating characteristic curve
PCT	Primary Care Trust
PEARS	Primary Eyecare Acute Referral Service or Primary Eyecare Assessment and Referral Service
PhD	Doctor of Philosophy
PHE	Public Health England
PLD	Priya Laxmidas Dabasia
POAG	Primary open angle glaucoma
PPV	Positive predictive value
PSD	Pattern Standard Deviation
QUADAS	Quality Assessment of Diagnostic Accuracy Studies

QS	Quality Score
RCOphth	Royal College of Ophthalmologists
RCT	Randomised controlled trial
RNFL	Retinal nerve fibre layer
ROC	Receiver Operating Characteristic
SAP	Standard automated perimetry
SCI	Scotland's centralized internet
SD	Standard deviation
SD-OCT	Spectral domain Optical coherence tomography
SE	Standard error
SITA	Swedish Interactive Thresholding Algorithm
SLO	Scanning laser ophthalmoscope
SLP	Scanning laser polarimetry
SQI	Scan Quality Index
STARD	Standards for the Reporting of Diagnostic Accuracy Studies
UK	United Kingdom
US	United States
VF	Visual field
VPN	Virtual Private Network
WECI	Welsh Eyecare Initiative
WEHE	Welsh Eye Health Examination
WHO	World Health Organisation
WN	Winnie Nolan
WS	Waveform Score

Chapter 1: Introduction

1.1 Epidemiology of glaucoma

Glaucoma is the second leading cause of blindness worldwide (Quigley & Broman, 2006, WHO, 2012), and is considered a major public health problem. The World Health Organisation (WHO) estimates that 2% of visual impairment and 8% of blindness is attributed to glaucoma (WHO, 2012). The global prevalence for all glaucomas in people aged 40 to 80 years is estimated to be 3.54% (Tham et al., 2014), with open angle glaucoma (OAG) being the commonest cause (Quigley & Broman, 2006, Tham et al., 2014). Worldwide, the number of people with glaucoma (aged 40 to 80 years) is projected to increase by 74% from 64.3 million in 2013 to 111.8 million in 2040 (Tham et al., 2014).

In the UK, glaucoma is responsible for approximately 10% of blindness (severe sight impairment) registrations (NICE, 2009) and is the second commonest cause of certifiable severe sight impairment after age-related macular degeneration in England and Wales (Bunce et al., 2010). However, actual figures for severe sight impairment may be higher still given that the nature of visual morbidity resulting from glaucoma, notably the initial loss of non-central regions of visual field, the preservation of binocular field due to overlap between the nasal visual fields of the right and left eyes, and the asymmetric nature of the disease reduces the likelihood of registration compared to 'more obvious' loss of visual acuity (King et al., 2000). With age being an important risk factor for glaucoma, the number of people affected by the condition in the UK is expected to rise with the changing demographic of the population. The 2011 census demonstrated an increase in the number of people aged 65 years and older from 9.4 million in 2001 rising to 10.4 million in 2011 (ONS, 2011).

A recent meta-analysis determined a pooled prevalence of primary OAG and primary ACG of 3.05% and 0.50% respectively (Tham et al., 2014). The estimated UK prevalence of primary open angle glaucoma is 2.1%, rising from 0.3% in people aged 40 years to 3.3% in people aged 70 years (Burr et al., 2007). Each year, it is estimated that 11,000 new cases of OAG are diagnosed in people aged 40 to 70 years (Burr et al., 2007). However, epidemiological studies in developed countries have demonstrated that approximately half of the population affected by OAG remains undetected using current screening strategies (Tielsch et al., 1991a, Klein et al., 1992, Mitchell et al., 1996, Quigley & Vitale, 1997, Wensor et al., 1998). In fact, Burr et al. predict that two-thirds of the population in the UK affected by OAG may remain undiagnosed

(Burr et al., 2007). These trends may be attributed to the insidious onset of the disease in which symptoms of vision loss due to severe damage of the visual field and/or reduced visual acuity manifest at a more advanced stage.

The WHO estimates that of the 11.2 million people that will be bilaterally blind from glaucoma worldwide by the year 2020, nearly half of these cases will be attributed to angle closure mechanisms (WHO, 2007). These projections are based on the higher incidence of the condition in the populous country of China, together with other East and South East Asian countries where ACG is the predominant form of glaucoma (Foster & Johnson, 2001). The prevalence estimate for Angle Closure Glaucoma (ACG) in European-derived populations aged 40 years and older is 0.4% (Day et al., 2012), which corresponds to 130,000 cases in the UK. Although the condition is considered relatively uncommon in western populations, ACG is predicted to increase by 19% in the UK within the next decade due to increased longevity (Day et al., 2012).

Early detection and administration of treatment reduces the rate of progression of glaucomatous vision loss and visual field defects (2000, Heijl et al., 2002), which is likely to result in a better health-related quality of life for those persons affected by the condition. Long-term treatment is usually administered in the form of medical, laser or surgical interventions aimed to lower eye pressure to a level where further visual loss can be prevented. However, the cost of medical drug treatments for OAG and ocular hypertension (OHT) has seen an increase of 88% from £55.2 million in 2000 rising to £103.7 million in 2012 (Connor & Fraser, 2014). Fiscal factors, together with the need for lifelong review of patients affected by the chronic condition place a substantial burden on the NHS. As the use of resources and the direct costs of glaucoma management increase with worsening severity of disease (Lee et al., 2006b), early identification and treatment of glaucoma may provide potential economic savings.

1.2 Classification and clinical features of glaucoma

The European Glaucoma Society defines glaucoma as "*a group of diseases that result in a progressive optic neuropathy that causes characteristic changes in the optic nerve head and retinal nerve fibre layer*" (EGS 2008). The pathogenesis of glaucoma is likely to be multifactorial (Fechtner & Weinreb, 1994), but the exact mechanism is not fully known.

Glaucoma is usually classified on the basis of the mechanism of damage, or aetiology. Clinically, gonioscopic observation of the anterior chamber angle is used to categorise glaucoma into open or closed angle groups. Further sub-division is based on whether the glaucoma is primary or secondary i.e. whether the glaucoma is the result of an underlying systemic and/ or ocular co-morbidity. Primary glaucomas account for 92% (Quigley & Broman, 2006) of all presentations and, as such, represent the predominant form of glaucoma detected by community optometrists.

For clarification of terminology used in this thesis, the term 'Primary open angle glaucoma (POAG)' is taken to be synonymous with 'Chronic open angle glaucoma (COAG)'. The National Institute for Health and Clinical Excellence (NICE) published a clinical guideline (85) in 2009 (NICE, 2009) which led to the increased use of the term 'COAG'. However, 'POAG' is used much more widely both in publications referenced in this thesis and in publications emerging from this thesis. For this reason, both terms are used in this thesis, to refer to the same condition, depending on the source of publication.

1.3 Primary open angle glaucoma

POAG or COAG is characterised by excavation or cupping of the optic nerve head, often termed 'glaucomatous optic neuropathy' (GON), together with an open and normal appearance of the anterior chamber angle observed using gonioscopy. Elevated intraocular pressure (IOP) above 21mmHg (representing 2 standard deviations above the population mean, and assuming a Gaussian distribution) is no longer included in the definition of POAG, as up to 50% of newly diagnosed glaucoma patients have an IOP ≤21mmHg (Leske, 1983). The progression of glaucomatous damage to the optic disc, from localized thinning of the neuroretinal rim to advanced cupping is associated with the development of typical patterns of visual field loss. Early reduction in visual sensitivity begins with paracentral scotomas, usually contained within 20 degrees from fixation. With progression, scotomata combine to form

arcuate defects. End-stage glaucoma is typified by extension of field loss into the periphery leaving an isolated temporal crescent, and central 5-degree island of vision (Figure 1.1).

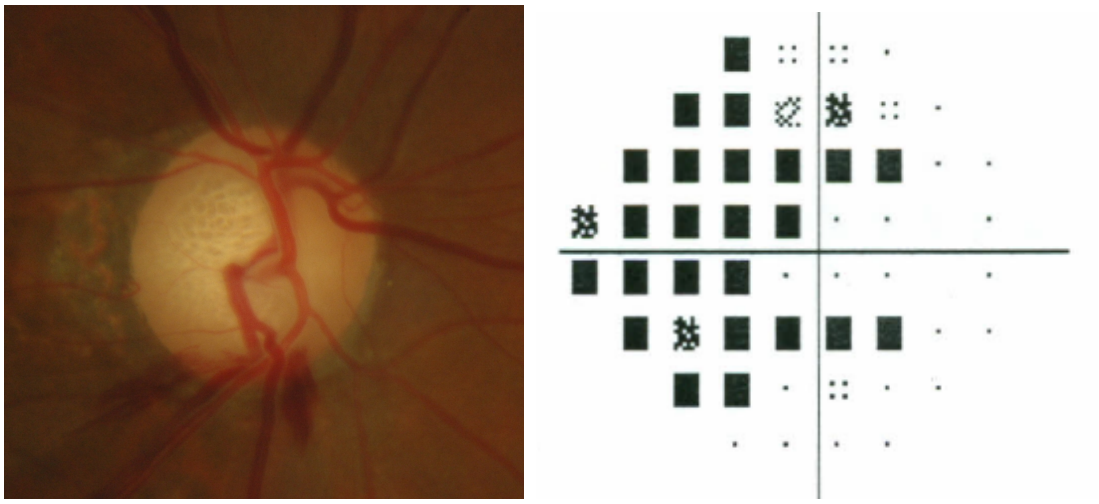


Figure 1.1: A glaucomatous optic disc showing concentric enlargement of the cup and inferior peripapillary haemorrhages (image captured using Topcon TRC-NW8F), with the corresponding Humphrey C24-2 standard visual field plot

POAG is a bilateral condition but the severity of disease is typically asymmetric at the point of diagnosis and during its clinical course. The definitive mechanism of damage to ganglion cell axons is not fully known, but two main theories emerge from the literature. The mechanical theory proposes that loss of ganglion cell axons is the result of direct pressure-induced damage at the level of the lamina cribrosa. The vascular theory describes ischaemia of ganglion cell axons at the level of the optic nerve head as a result of microvascular changes and reduced perfusion. An alternative theory is cell 'apoptosis', or spontaneous degeneration of axons resulting from elevated IOP and impairment to axonal transport of neurotrophic factors (Munemasa & Kitaoka, 2012).

Normal tension glaucoma (NTG) is defined as a type of chronic OAG in which IOP has rarely been recorded above 21mmHg (statistical upper limit of the 'normal' range) (NICE 2009). However, researchers have debated whether NTG is a separate entity, or simply a variable phenotype in the spectrum of OAG (Wilson & Creighton, 2002, Shields, 2008).

Ocular hypertension (OHT) is defined as consistently or recurrently elevated IOP of greater than 21mmHg, in the absence of clinical evidence of optic nerve damage or visual field defect, and open drainage angles on gonioscopy (NICE 2009). The prevalence of OHT in the population ranges from 4.5% to 9.4% in people aged over 40 years (Burr et al., 2012). The

Ocular Hypertension Treatment Study (OHTS) divided patients with OHT into either a treated or an observation group and, after monitoring both groups for 60 months, found a cumulative probability of developing POAG of 4.4% in the medically treated group, compared with 9.5% in the observation group (Kass et al., 2002). In England and Wales, prophylactic treatment is administered based on risk of conversion to manifest disease, determined by the IOP, age, and central corneal thickness in accordance with the NICE clinical guideline 85 (NICE, 2009).

1.3.1 Risk factors for the development of POAG

The onset of POAG is typically over the age of 40 years, with age consistently identified as an important risk factor for development of the disease in epidemiological surveys (Tielsch et al., 1991a, Gordon et al., 2002, Weinreb & Khaw, 2004, Rudnicka et al., 2006, Leske et al., 2008).

The risk of developing glaucoma and progression of the disease increases significantly with elevated IOP and fluctuating IOP (AGIS, 2000, Gordon et al., 2002, Bengtsson et al., 2007, Musch et al., 2011, Rao et al., 2013, Leidl et al., 2014). Moreover, it is presently the only modifiable risk factor for the treatment and management of the condition. Clinically, a reduction in IOP of 20-30% from the untreated pressure for POAG/COAG is considered standard practice (Heijl et al., 2002, Kass et al., 2002, CGS, 2006, NICE, 2009), with greater reductions required for more advanced disease (CGS, 2006).

Another important risk factor is ethnicity, whereby persons of Afro-Caribbean origin are at greater risk of developing glaucoma compared with White populations (Tielsch et al., 1991b, Gordon et al., 2002, Rudnicka et al., 2006, Leske, 2007). Furthermore, OAG presents at an earlier age (Quigley & Vitale, 1997), and demonstrates more rapid disease progression (Wilson et al., 1985) in persons of black origin compared with white populations. Interestingly, Rudnicka et al. reported a steeper increase in prevalence of OAG in white populations with age than compared with black populations (Rudnicka et al., 2006).

A well-recognized risk factor for the development of OAG is family history. Approximately 5% of POAG is attributed to a single-gene, with the majority of presentations being the result of combined effects of a number of genetic and environmental risk factors (Fingert, 2011). Almost 40% of OAG probands recruited in the Barbados Family Study had at least one family member affected by the condition (Leske et al., 2001). In Tasmania, a glaucoma inheritance study of 5 large POAG pedigrees (442 patients), documented that 13% of subjects had a prior diagnosis of POAG or suspect glaucoma, and an additional 16% were newly diagnosed by the

GIST (Glaucoma Inheritance Study in Tasmania (Sack et al., 1996)) examination. Moreover, 27% of previously diagnosed POAG patients were unaware of their true family history of glaucoma, raising the suggestion that a greater proportion of POAG in the adult population may be inherited than is reported (McNaught et al., 2000).

The Ocular Hypertension Treatment Study (OHTS) identified thinner central corneal thickness (CCT) as being a powerful predictor for conversion of OHT to POAG (Gordon et al., 2002). However, Medeiros and Weinreb (2012) have since warned that interpretation of CCT as an independent risk factor for the development of glaucoma may be misleading in view of the dependence of Goldmann tonometry measurements on CCT (Medeiros & Weinreb, 2012). Correction of the OHTS prediction model for CCT confirmed CCT as a risk factor for the development of glaucoma, but showed a lack of evidence to support the claim of CCT being a true independent risk factor for glaucoma (Medeiros & Weinreb, 2012).

Other risk factors identified in epidemiological studies include:

- Myopia (Mitchell et al., 1999, Weinreb & Khaw, 2004) – it has been proposed that structural differences that predispose an eye to myopia may also increase the susceptibility of the optic nerve to glaucomatous damage from elevated or normal IOP.
- Systemic diseases such as diabetes (Bonovas et al., 2004), hypertension (Dielemans et al., 1995, Bonomi et al., 2000b, Mitchell et al., 2004), migraine (Wang et al., 1997, Cursiefen et al., 2000) and Raynaud's phenomenon. Systemic hypertension has been observed to reduce perfusion pressure at the level of the optic nerve head (Fuchsjager-Mayrl et al., 2004, Memarzadeh et al., 2010), while migraine and Raynaud's may be linked to vasospasm.
- Gender – after adjusting for age males have a higher risk of OAG than females in white populations (Rudnicka et al., 2006, Leske et al., 2008).

1.4 Primary angle closure and angle closure glaucoma

The clinical course of the ACG disease process is typically categorized in three stages: primary angle closure suspect (PACS), primary angle closure (PAC) and primary angle closure glaucoma (PACG). A patient is diagnosed as a PACS when anterior chamber angle (ACA) examination by gonioscopy reveals an anatomical predisposition to apposition between the peripheral iris and posterior trabecular meshwork. In accordance with the International Society of Geographical and Epidemiological Ophthalmology (ISGEO) nomenclature, this has typically been defined in

epidemiological research as an ACA in which there is 270 degrees or greater of non-visibility of the posterior (usually pigmented) trabecular meshwork (Foster et al., 2002).

Relative pupillary block is a term used to describe an increased resistance to aqueous flow through the pupil from the posterior to anterior chamber. This leads to increased pressure in the posterior chamber, causing the peripheral iris to bow forward, which narrows or occludes the angle. Relative pupillary block typically occurs in hyperopic eyes and is one of the most common mechanisms of angle closure, reported in approximately 90% of individuals diagnosed with primary ACG (Ritch et al., 1995, Nolan et al., 2000). Repeated contact between the iris and delicate structures of the trabecular meshwork can result in damage and abnormalities at a cellular level, including loss of endothelial cells and fusion of trabecular beams (Sihota et al., 2001, Hamanaka et al., 2011). These result in an elevated intraocular pressure and/ or the formation of irreversible adhesions representing complete obstructions of aqueous flow at points of contact, which are known as goniosynechiae, or, more commonly peripheral anterior synechiae (PAS) (Lee et al., 2006a). The term PACG only applies when PAC progresses to demonstrable glaucomatous optic neuropathy.

In common with all glaucoma disorders, treatment for ACG aims to prevent damage to the optic nerve and subsequent deterioration of the visual field. With timely detection of anatomically narrow angle eyes at risk of occlusion, and the subsequent administration of prophylactic therapy, the progression of the angle closure process to ACG can be arrested. An untreated PACS patient has an estimated 22% (Thomas et al., 2003) to 30% (Wilensky et al., 1996) chance of developing angle closure over 5 years. At the present time, laser peripheral iridotomy (LPI) is considered the most effective treatment to prevent the onset of ACG in predisposed individuals. Once angle closure has been diagnosed in one eye, it is common practice to perform a prophylactic procedure on the fellow eye to prevent it following suit, reducing the chances of an IOP rise in the long-term by over 85% (Ang et al., 2000). However, LPI is demonstrably less effective, and even considered suboptimal where manifest angle closure with evidence of functional damage to the drainage apparatus has already occurred, and in particular where there is evidence of glaucomatous optic neuropathy. The procedure can also be less beneficial in cases where angle closure is predominantly the result of non-pupillary block mechanisms.

1.4.1. Risk factors for the development of angle closure glaucoma

ACG is the result of anomalies in either the size or position of structures in the anterior segment, and assessment of angle width and configuration is an essential part of identifying those individuals at risk. Many population studies have identified common biometric characteristics that crowd the anterior segment, predisposing the eye to ACG (Lowe, 1970a, Congdon et al., 1996). These characteristics include shallow anterior chamber depth (ACD) defined as the distance between the corneal endothelium and anterior lens surface measured along the optical axis, anterior lens positioning, thickening of the crystalline lens, small corneal diameter, short axial length (hypermetropia) and small radius of curvature. Of these characteristics, shallow ACD has been documented as the cardinal risk factor in most ethnic groups (Nolan et al., 2006).

Age is a strong risk factor, as thickening of the crystalline lens with advancing age leads to crowding of anterior segment structures, and shallowing of the ACD by 0.35–0.50mm over a 50-year period (Lowe, 1970b). It has also been postulated that slackening of the zonules over time can induce further anterior movement of both the lens and iris structures (Lowe, 1970b, Markowitz & Morin, 1984).

Higher prevalences of occludable angles have also been repeatedly documented in females, and it is most likely that this can be attributed to an anatomically shallower ACD (Alsbirk, 1986, Oh et al., 1994).

It is well known that characteristics of the anterior chamber differ markedly among ethnic groups, whereby people of European lineage are anatomically distinct from those of both Asian and African descent. The predisposition of East Asian subjects to ACG may be explained by evidence that the iris joins more anteriorly to the scleral wall in this population, slightly more posteriorly in Afro-Americans and most posteriorly in Caucasians (Oh et al., 1994). The predominant pathological mechanism for angle closure also varies markedly with ethnicity (He et al., 2006b). When compared with Caucasians, angle closure in Asians is more likely to be the result of multiple mechanisms rather than pupil block alone. For example, a review paper reported that, in studies examining Chinese subjects, over 50% of cases of ACG were the result of combined mechanisms, including other peripheral non-pupil block mechanisms such as anteriorly positioned ciliary body (Wang et al., 2002). This variability in the mechanism of angle closure may also account for conflicting reports of the effectiveness of both screening tests and interventions for ACG among different ethnic groups (Thomas et al., 1996, Foster et al., 2000).

1.5 Structural changes in glaucoma and their assessment

The progressive loss of vision in glaucoma is the result of damage to retinal ganglion cells and their axons at the level of the optic nerve head. Early damage typically occurs at the inferior and superior poles of the optic disc, observed clinically as focal or diffuse loss of the neuroretinal rim with enlargement of the vertical cup to disc ratio. Comprehensive examination for structural damage requires the use of binocular indirect ophthalmoscopy through a dilated pupil, which affords a stereoscopic view for more sensitive assessment of subtle changes to the optic nerve head and peripapillary retina (Kotecha, 2009). In UK practice, examination of the optic nerve head by community optometrists is a recommended requirement during the course of a routine eye examination of an adult (CoO, 2014e) and child (CoO, 2014c), but the method used to observe the optic disc is at the discretion of the practitioner. In a 2007 survey of community optometrists, 50% of respondents reported use of slit-lamp binocular indirect ophthalmoscopy through undilated pupils for routine checking of the optic disc when case-finding for glaucoma (CoO, 2008). However, the technique is subjective and prone to intra- and inter-observer variability in observations. This may, in part, be accounted for by the overlap in spectrum of optic disc features between glaucoma, suspect glaucoma and normal eyes. Furthermore, ancillary observation of the peripapillary retina surrounding the optic disc for nerve fibre layer defects is also difficult by clinical examination and photography, as visibility of subtle changes can be affected by age, media opacities, and fundal pigmentation (Zangwill & Bowd, 2006).

The past 20 years has seen rapid advancements in technologies for objective examination of the optic disc. Since the initial introduction of conventional ocular imaging, it became apparent that a permanent record afforded better documentation, study and monitoring of clinical features (Harding et al., 1995, Lin et al., 2002, Pirbhai et al., 2005, Jain et al., 2006). Use of fundus imaging in optometric practice has risen from 17% in 2001 (CoO, 2001) to 66% in 2007 (CoO, 2008) and as such, the device is increasingly considered commonplace in optometric practice. Modern devices have evolved to capture 3-dimensional images of ocular structures using laser technology. The optical coherence tomographer (OCT) is the most widely used scanning laser device in the UK, and has been established as a clinical diagnostic tool for detection and monitoring of optic nerve and macular disease that may be difficult to observe using conventional viewing techniques (Chen & Lee, 2007). The use of OCT imaging in community optometric practice is increasing, however, standardized protocols for use of this modality to detect and monitor glaucoma are lacking.

OCT was first described by Huang in 1991 at the Massachusetts Institute of Technology (Huang et al., 1991). OCT methodology is based on the principle of low-coherence interferometry, an optical phenomenon first observed and then developed by Michelson in the late 1800s. Conventional interferometry uses long coherence lengths in which light waves interfere over the distance of a few metres. By using low coherence superluminescent light-emitting diodes, or short pulse femtolaser using infrared wavelengths, the principle has been adapted to suit the shorter dimensions of ocular structures. Tissue depth is evaluated using optical backscatter received from a reference (mirror) and a sample (tissue) path. A series of scans are created to form a reflectivity profile, analogous to an ultrasound A-scan, which in turn, is used to construct a two-dimensional B-scan in real time, representing an in vivo cross-sectional tomograph. More recently, the development of Spectral or Fourier domain technology has enabled faster image acquisition (60x), higher image resolution, and improved retinal layer segmentation compared with the previous version of the technology, known as time-domain systems (Schuman, 2008).

Inbuilt software automatically processes the raw data, converting the optical path lengths to physical dimensions using known refractive indices for ocular media, and adjusting for image distortions, a process known as 'de-warping'. In this way, retinal nerve fibre layer thickness and morphological parameters of the optic nerve head may be derived for the early detection and monitoring of glaucoma. Newer models integrate advanced segmentation algorithms, which enable measurement of inner retinal thickness. The macula contains a high density of cells comprising over 50% of all retinal ganglion cells (Curcio & Allen, 1990). In seeking to improve sensitivity to detect glaucomatous damage, clinically detectable changes in macular inner retinal thickness are identified by combining data from three retinal layers forming the 'ganglion cell complex' (Tan et al., 2009, Schulze et al., 2011, Yoon et al., 2014): the retinal nerve fibre layer (RNFL) representing ganglion cell axons, the ganglion cell layer (GCL; ganglion cell bodies), and the inner plexiform layer (IPL; ganglion cell dendrites) (Figure 1.2).

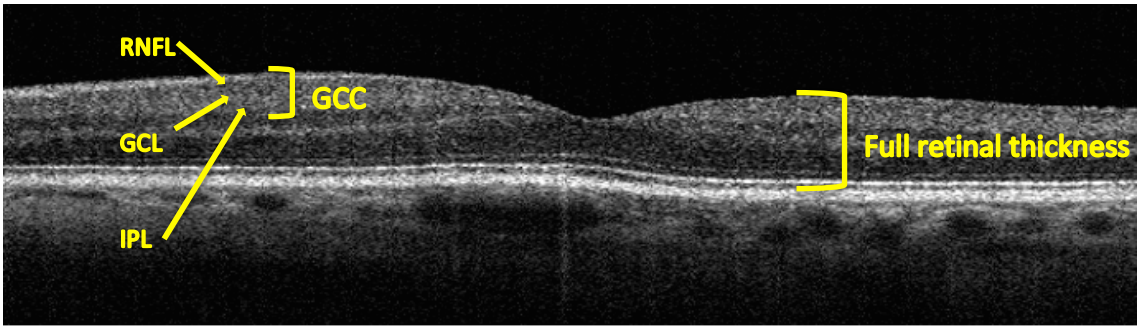


Figure 1.2: Segmentation of the ganglion cell complex (GCC) layer comprised of the retinal nerve fibre layer (RNFL), ganglion cell layer (GCL), and inner plexiform layer (IPL)

Other specialist systems capable of imaging the optic nerve head and surrounding retina include the confocal scanning laser ophthalmoscope (SLO) and scanning laser polarimeter (SLP). An example of a commercially available SLO device is the Heidelberg Retinal Tomograph (HRT) (Strouthidis & Garway-Heath, 2008). The HRT uses the principles of scanning laser confocal microscopy to generate 2-dimensional images of the retina, which are captured at various focal depth planes and combined in series to form a 3-dimensional construct of the ocular tissue. Scanning laser polarimetry e.g. the GDx creates a 3-dimensional image by measuring the retardation or change in polarisation of low intensity polarized light through the retinal nerve fibre layer based on an optical phenomenon known as 'birefringence'.

1.6 Functional changes in glaucoma and their assessment

Glaucoma is known to affect contrast sensitivity (Arden & Jacobson, 1978, Ross et al., 1984), colour vision (Pacheco-Cutillas et al., 1999), motion sensitivity (Shabana et al., 2003), visual acuity (AGIS, 2002), and visual function (Harwerth & Quigley, 2006). Clinically, the loss of visual function manifesting as damage to the visual field is used for the detection and monitoring of glaucoma. A visual field defect is the result of ganglion axon and cell loss exceeding a given threshold. Visual field defects typically caused by glaucoma include paracentral scotomas, arcuate defects, nasal step, and temporal wedge defects.

The Henson perimeter followed by the Humphrey visual field analyser (HFA) are the most widely used instruments for the evaluation of visual field sensitivity by UK community optometrists (Myint et al., 2011). At the present time, static standard automated perimetry (SAP) using the HFA in threshold mode is the acknowledged reference standard for the

assessment of visual function in glaucoma. However, SAP can be time-consuming with typical test durations for a SITA standard program undertaken by a normal patient being 4 to 5 minutes for a 24-2 programme (Wall et al., 2001), and over 6 minutes for a 30-2 test (Bengtsson et al., 1998, Shirato et al., 1999, Budenz et al., 2002). More importantly, a limitation common to all visual function tests is the reliance on patient responses, which limits universal applicability to e.g. people with learning difficulties. It is inevitable that even among able patients, a small proportion will be unable to provide a reliable result. In fact, subjects diagnosed with glaucoma present a further clinical challenge as they show greater short-term and long-term fluctuations in visual field than patients without the disease (Flammer et al., 1984, Heijl et al., 1989, Boeglin et al., 1992, Bengtsson & Heijl, 2000, Fogagnolo et al., 2011). Visual field testing also suffers from a lack of standard agreement as to what constitutes a test failure, and the need for confirmatory testing.

Early reports based on histology and glaucoma modelling suggested that significant loss of ganglion cells of up to 50% may occur before a field defect is significantly detectable (Quigley et al., 1989, Sommer et al., 1991, Kerrigan-Baumrind et al., 2000, Nouri-Mahdavi et al., 2011). However, successive investigators have challenged these findings showing that the curvilinear relationship between visual field measurements in decibels, and structural measures of glaucomatous optic neuropathy may be a consequence of using different units for measuring ganglion cells and visual function (Garway-Heath et al., 2000a, Garway-Heath et al., 2002). A number of researchers support the use of linear units to record both structure and function (Malik et al., 2012). Furthermore, two subsequent reports (Artes & Chauhan, 2005, Strouthidis et al., 2006a) evaluating progression of glaucoma report similar proportions advancing by both structure and function in early glaucoma.

SAP assesses the function of three subtypes of retinal ganglion cells: magnocellular, koniocellular and parvocellular which are subject to degenerative changes in glaucoma (Yucel et al., 2000, Yucel et al., 2003). However, histological studies investigating the pathogenesis of glaucoma have consistently reported preferential damage to large diameter cells, namely parasol ganglion or M_y cells (Quigley et al., 1987, Quigley et al., 1988, Kerrigan-Baumrind et al., 2000). M_y cells comprise 15-20% of the magnocellular pathway, mediating motion detection and scotopic vision. Early reports proposed that preferential loss of these cells may be a function of true selective cell death, or reduced redundancy given the sparser population of M_y cells in the retina. However, the theory of selective damage to M_y cells has been contested based on evidence of non-selective dysfunction of both magnocellular and parvocellular pathways in people with glaucoma (McKendrick et al., 2004). Nonetheless, several

psychophysical tests which aim to isolate M_Y cell activity and provide a more sensitive indicator of early functional loss from glaucoma than SAP have been developed. An example of a commercially available psychophysical device is the Frequency doubling technology (FDT) perimeter. The technology is based on the stimulation of a subset of larger diameter ganglion cells of the magnocellular pathway, which exhibit a non-linear response to stimulus contrast. The frequency doubling illusion was initially observed and reported by Kelly et al. in 1966 (Kelly, 1966). The illusion describes the appearance of twice the number of light and dark vertical stripes than are actually present, when a sinusoidal grating of low spatial frequency is counterphased at a high temporal modulation. Early applications of the phenomenon to assess retinal function were described by Maddess and Henry (Maddess & Henry, 1992), and Johnson and Samuels (Johnson & Samuels, 1997). The FDT perimeter is based on the evaluation of target contrast perceived once the doubling effect has occurred, rather than direct observation of the illusion.

An alternative visual function concept is provided by the Moorfields motion displacement threshold (MMDT) test, which is based on motion perception. The technology uses a temporal form of Vernier acuity in which subjects are required to discriminate positional change of a line stimulus. Prediction of glaucomatous visual field loss by this means was demonstrated in the early 1980's using a single line stimulus presented just above the blind spot (Fitzke et al., 1987). The system has since evolved into a multi-location perimetry program, which integrates an Enhanced Standard Threshold Algorithm (ESTA) program to improve efficiency in screening for glaucoma (Bergin, 2011, Ong et al., 2014), through application of a spatial filter and multisampling methods. The spatial filter uses knowledge of the strengths of correlation of differential light sensitivity between visual field locations and the anatomical location of nerve fibre bundles at the level of the optic nerve head. As a result, the positions of the 31-test stimuli have been selected to correspond with a location field on the Humphrey field analyser (HFA) 24-2 program. More specifically the stimuli locations have been selected in accordance with the Garway-Health anatomical function map, to account for unequal sizing of optic nerve head sectors represented in the visual field and reduce oversampling of optic nerve bundles at the poles of the optic nerve head (Garway-Heath et al., 2000b, Strouthidis et al., 2006b). Multisampling methods refers to the 2 of 3 pass-fail criteria in which locations are classified as 'failed' when all 3 presentations are missed (Artes et al., 2003).

1.7 Measurement of intraocular pressure

Goldmann applanation tonometry is the current reference standard for measurement of IOP. At the present time, the majority (82%) of community optometrists use non-contact 'air-puff' (pneumo) tonometers for routine measurement of IOP to screen for glaucoma. Nonetheless, the use of Goldmann and Perkins applanation tonometry is becoming more commonplace in community practice (CoO, 2008).

When first introduced in 1957, Goldmann and Schmidt acknowledged limitations of their prototype, including the effect of central corneal thickness (CCT) and rigidity on IOP estimates (Goldmann & Schmidt, 1957). Firstly, the device was designed to measure IOP most precisely when applied to a cornea with a central thickness of 520 micrometres, but the developers anticipated little variance of CCT in the absence of disease. Secondly, it was assumed that the effect of corneal rigidity would be negated by surface tension between the device probe and tear film. Overestimation of IOP in eyes with thicker central corneas was documented as early as 1975 (Ehlers et al., 1975). A meta-analysis of corneal thickness and its impact on IOP measures in humans approximated a change in IOP of 3.4±0.9mmHg for a 10% difference in CCT in all eye types (Doughty & Zaman, 2000). Early researchers proposed formulae and nomograms to correct IOP measurements by Goldmann tonometry for the influence of CCT. However, questions were soon raised as to their validity, particularly with emerging evidence of the influence of biomechanical properties of the cornea on variability of IOP measurements between individuals e.g. viscoelasticity, rigidity (stiffness) (Liu & Roberts, 2005, Tonnu et al., 2005).

The Ocular Response Analyser (ORA, Reichert) is a new generation of 'dynamic' tonometer designed to measure and adjust IOP readings for viscoelastic properties of the cornea, termed 'corneal hysteresis' (CH). Lower CH has been consistently reported among individuals diagnosed with OAG (Wells et al., 2008, Mangouritsas et al., 2009, Abitbol et al., 2010, Anand et al., 2010). Researchers have also established a relationship between glaucomatous visual field progression and low CH (Congdon et al., 2006, De Moraes et al., 2012, Medeiros et al., 2013b).

1.8 Screening for glaucoma

The UK National Screening Committee defines 'screening' as "*a process of identifying apparently healthy people who may be at increased risk of a disease or condition"* (NSC, 2013). These individuals are unlikely to have sought medical attention on the basis of having already experienced symptoms of the condition. Screened individuals identified as being at risk of developing the condition are then "*offered information, further tests and appropriate treatment to reduce their risk and/ or any complications arising from the disease or condition"* (NSC, 2013). A universal screening programme requires all individuals within a given population to be screened (e.g. in the case of glaucoma screening, all people aged over 40 years). An alternative approach is to use targeted screening of at-risk groups in the population (e.g. people of Afro-Caribbean origin, and aged over 40 years).

In 1968, Wilson and Jungner outlined ten criteria for appraising the viability, effectiveness and appropriateness of a screening programme (Wilson & Jungner, 1968). The UK National Screening Committee (NSC), which is responsible for advising the NHS on the implementation of screening programmes, has updated the original criteria in line with ongoing developments reported in the scientific literature. As such, they have established an internationally-agreed set of criteria categorized by the condition, test, treatment and screening programme.

1.8.1 Primary open angle glaucoma

In 2001, Spry and Sparrow sought to evaluate whether OAG satisfied UK NSC criteria for the implementation of a screening programme. Using evidence from published literature, the authors surmised that the condition deserved consideration for screening (Spry & Sparrow, 2001). OAG fulfills two important criteria; it is an important public health problem, and effective treatment is available in the form of pressure-lowering therapies. However, currently available screening tests used alone or in combination fail to demonstrate sufficient accuracy to detect OAG (Burr et al., 2007). Moreover, no high quality randomized controlled trials have been undertaken to date to investigate the effectiveness of a screening programme for glaucoma in reducing mortality and morbidity (Fleming et al., 2005, Hatt et al., 2006, Burr et al., 2014). In fact, a recent assessment by Burr et al. of the potential value of a large glaucoma screening RCT to inform glaucoma screening policies deemed it "*unlikely to be the best use of limited NHS research resources*" (Burr et al., 2014). The same author headed a National Institute for Health Research (NIHR) Health Technology Assessment commissioned review to evaluate whether 'opportunity cost of a screening programme for glaucoma would be

economically balanced in relation to expenditure on medical care as a whole'. Using economic modeling of cost-effectiveness and cost-utility, large-scale population screening of POAG selected on the basis of age alone was proved unlikely to be cost-effective, but stronger evidence was found in support of targeted screening e.g. people with a family history of glaucoma (Burr et al., 2014). The review also identified the need for improvements in the efficiency and cost-effectiveness of glaucoma case-finding by e.g. developing better screening tests and promoting the uptake of eye care in the community.

1.8.2 Angle closure glaucoma

Ageing of the population and increasing longevity have raised concerns as to the long-term costs of healthcare, prompting researchers to address the question of whether ACG can be prevented on a population basis. Although the condition is relatively uncommon in western populations, it is the predominant form of glaucoma in many Asian countries (Foster & Johnson, 2001) and it satisfies many of the suitability criteria for the screening for disease specified by Wilson and Jungner (Wilson & Jungner, 1968). In particular, ACG has an early clinically recognisable stage. Furthermore, acceptable instrumentation is available to detect 'at-risk' individuals, and there are standard interventions which may prevent functional loss of vision readily available in the hospital eye service. Community optometrists are well placed to identify the anatomical features that predispose an eye to ACG. Primary angle closure (PAC) is frequently chronic and asymptomatic (He et al., 2006b) and could easily be missed if the anterior chamber configuration has not been evaluated, including an assessment of the anterior chamber angle (ACA) and/or anterior chamber depth (ACD). Each of these anterior chamber features taken in isolation provides a useful indicator of the potential risk of occlusion, but it is logical that a combined analysis based on more than one anatomical characteristic may give diagnostic superiority. The clinical course of the ACG disease process is not yet fully understood, particularly in view of the significant heterogeneity in presentation between ethnic groups (He et al., 2006b). It follows therefore that screening criteria and management programmes would need to be tailored for a given population.

1.9 Case-finding strategies for glaucoma by UK optometrists

In the UK, optometrists play a key role in the detection of glaucoma in primary care, using opportunistic surveillance when people self-select to attend for eye examinations in community practice. A person suspected of having glaucoma or OHT is referred by the optometrist to secondary care for further investigation and administration of treatment. Optometrists are responsible for generating in excess of 95% of referrals for suspected glaucoma and OHT for ophthalmological opinion (Sheldrick et al., 1994, Bell & O'Brien, 1997, Bowling et al., 2005).

1.9.1 Primary open angle glaucoma

Current practice for case-finding of primary open angle glaucoma (POAG) uses a combination of history-taking, and a triad of tests comprising optic disc examination for structural changes, evaluation of functional visual field loss, and measurement of intraocular pressure (Lawrenson, 2013). The decision to refer a patient suspected of glaucoma to secondary care is usually based on one or more abnormal clinical test results, together with the presence of known risk factors for the disease, and guidelines disseminated by local ophthalmologists, optometric bodies and/ or national publications e.g. (NICE, 2009).

A national survey of diagnostic tests used for the detection of COAG demonstrated that UK community optometrists are well equipped for case-finding (Myint et al., 2011). However, questions remain as to whether investment in equipment is cost-effective, how it may be best used for community optometric practice, and whether optometrists are trained sufficiently to use newer technologies. In accordance with NSC UK guidelines, a screening test should be "*simple, safe, precise and validated"*. Test validity refers to the ability of a screening test to accurately identify individuals with the disease and individuals without the disease. A valid test used alone, or in combination may be used to provide an output that alters the pre-test probability of a given subject having the condition. Additional desirable attributes of an ideal screening test may include portability and a high degree of acceptability to patients.

In the context of optometric case-finding for a low prevalence disease such as glaucoma, tests would need to combine high specificity, ideally above 90% (the proportion of those without the disease who are correctly identified as normal by the test), with an acceptably high sensitivity (the proportion of those with the disease correctly identified by the test). However, OAG case-finding presents a diagnostic challenge as no single test, used alone or in

combination, provides a sufficiently high accuracy (Burr et al., 2007). As a result, it is estimated that between 36% and 57% of referrals to the hospital eye service for suspected glaucoma are false positives (Bell & O'Brien, 1997, Vernon, 1998, Theodossiades & Murdoch, 1999, Bowling et al., 2005). The College of Optometrists publish guidance for UK optometrists on the examination of patients at risk of glaucoma based on the standard triad of tests (CoO, 2014a), but there is no statutory requirement to perform visual field assessment and IOP measurement during an eye examination. The accuracy of referrals to secondary care is likely to be improved by combining the results for the three tests, and by repeating tests for consistency (Bell & O'Brien, 1997). Published evidence suggests an increase in the proportion of optometrists carrying out all three tests from 15% in 1999 (Theodossiades & Murdoch, 1999), rising to 66% in 2010 (Lockwood et al., 2010), and 77% in 2011 (Davey et al., 2011).

The positive predictive value (PPV), defined as the percentage of those referred as suspects who actually have the disease, is an important criterion which is often used to describe the diagnostic accuracy of a test. It is determined by the sensitivity and specificity of a test, and the prevalence of the target disease in the population. As such, the PPV for glaucoma is limited by the low prevalence of the disease in the general population, which is approximately 2.1% of over 40 year olds in the UK (Burr et al., 2007). The PPV of referrals by optometrists for suspected glaucoma ranges between 37% and 43% (Newman et al., 1998, Theodossiades & Murdoch, 1999, Lockwood et al., 2010). Although these PPVs may appear modest at first glance, few screening tests could achieve the sensitivity and specificity required to produce higher PPVs for a disease with only 2% prevalence. For example, a screening test with 97% sensitivity and specificity would achieve a maximum PPV of 40% for a disease with 2% prevalence (Harper, 2011, Blakeney, 2012, Lawrenson, 2013). Improvement to the PPV for glaucoma may be achieved by increasing the prevalence of the condition in the population using targeted screening of higher risk populations (e.g. Afro-Caribbean patients with a family history of glaucoma among first-degree relatives), or second tier assessment in a referral refinement clinic (where a typical 40% prevalence of glaucoma would achieve a PPV of 96% for a test with a sensitivity and specificity of 97%).

The success of a targeted screening programme or case-finding strategy is dependent on uptake by the target population. In England, an eye test free to the patient is available to select groups of people considered at higher risk of developing glaucoma:

- People over the age of 60 years
- People over 40 years of age with a family history of an affected first degree relative
- People considered at risk of developing the disease by an ophthalmologist

Nevertheless, evidence of poor uptake of eye care services is apparent in a survey by the College of Optometrists which reported that 5% of people over 40 years age had not attended or could not recall having attended for an eye examination in the last 10 years. This figure rose to 11% for people in minority ethnic groups aged over 40 years (CoO, 2013c), which is cause for substantial concern given the greater risk of glaucoma among Afro-Caribbean groups (Tielsch et al., 1991b, Gordon et al., 2002, Rudnicka et al., 2006, Leske, 2007). Subsequent reports have identified potential deficiencies in the provision of glaucoma (Day et al., 2010) and general eye care services (Leamon et al., 2014) accessible to ethnic minority groups. Leamon et al's report highlighted additional barriers to the uptake of eye care services, including the limited awareness of eye health and eye disease among ethnic minority groups (Leamon et al., 2014). Previous public health campaigns aimed to increase uptake of glaucoma service provision were effective in raising awareness, but made little difference to changing health-seeking behaviour (Baker & Murdoch, 2008).

1.9.2 Angle closure glaucoma

At the present time, gonioscopy is considered the gold-standard assessment for ACA configuration. To date, it remains the only procedure that can adequately quantify features based on direct visualization of the iridocorneal angle. Moreover, with the use of corneal indentation it provides the means to distinguish reversible iridotrabecular contact from permanent PAS. However, the technique requires a considerable level of skill, experience and knowledge to perform the test and to interpret the results, as well as relying on the cooperation of the patient. Even in the hands of experienced examiners and standardized conditions, kappa agreement for angle width estimation between trained observers varies between 0.62 and 0.82 (Thomas et al., 1996, Foster et al., 2000, Jacob et al., 2008, Lavanya et al., 2008). As a result, this clinical reference standard technique is considered unsuitable for large-scale population screening. Furthermore, the physical placement of the lens on the ocular surface induces displacement of anterior structures, which can falsely widen the ACA. Miosis of the pupil as a result of accommodation as the lens approaches the eye and/ or illumination by visible light during the assessment can also affect the ACA. In fact, in recent years, the status of gonioscopy as an ideal reference standard has been brought into question, with suggestions that the technique may be missing cases of angle closure (Nolan et al., 2007).

In the UK, gonioscopy is not a widely adopted technique in community optometric practice for examining the ACA. At the present time, it is not a listed General Optical Council core competency (GOC, 2011) and, as such, the majority of optometrists lack the training to

perform the technique. An estimated 12% of UK community optometrists reported having access to a gonio-lens in a national survey of diagnostic tests for the detection of chronic open angle glaucoma in 2008 (Myint et al., 2011). Fewer still would be performing gonioscopy for routine case-finding for ACG, as the technique is considered invasive, time-consuming and therefore impractical for use in busy high-street practice. Instead, practitioners prefer to use surrogate methods using slit-lamp biomicroscope based techniques such as the van Herick (Van Herick et al., 1969) and/ or Smith's test (Smith, 1979), which are based on the evaluation of limbal ACD and central ACD respectively. The slit-lamp biomicroscope is an item of equipment that is used in the vast majority of optometric practices in the UK, and can be used for both van Herick's and Smith's tests without the need for further auxiliary attachments. Responses to a 2007 cross-sectional survey indicated that 37% of UK community optometrists 'always' use a slit-lamp biomicroscope to examine a patient's external eye or anterior segment during a routine sight test of an adult patient (CoO, 2008).

Given the low prevalence of ACG, it follows that, as per detection of POAG, even when figures for sensitivity and specificity are high, the proportion of individuals testing positive who have angle closure is still likely to be low, particularly in Caucasian groups.

1.10 Increasing demand for glaucoma services in secondary care

In 2009, the NICE clinical guideline 85 reported that over one million outpatient attendances to the hospital eye service each year were glaucoma-related (NICE, 2009). In each clinic, appointments are provided for new referrals, and follow-up of diagnosed and suspect glaucoma/ OHT. It is estimated that one third of patients referred to the hospital eye service for suspected glaucoma are retained for ongoing review (Morley & Murdoch, 2006), usually on the basis of inconclusive clinical findings. Ophthalmologists are often reluctant to discharge these individuals considered at higher risk of developing glaucoma to community practice at the risk of progression being missed until a later stage when significant damage has already occurred. A previous survey revealed that a quarter of consultant ophthalmologists in the south west of England estimated outpatient attendances for glaucoma to be between 25% and 50% (Spry et al., 1999), with absolute numbers expected to rise over time as a result of:

- The ageing population and increasing longevity as per the demographic trends of most developed countries

- Patients becoming increasingly aware of the condition and anxious regarding the disease process after diagnosis
- Consultants aiming for lower target pressures in line with the revised NICE guidelines for the detection and management of glaucoma and OHT (NICE, 2009)
- Improved screening and detection by optometrists using specialised clinical techniques
- Government initiatives to improve care quality in glaucoma e.g. to shorten intervals between review appointments

The NICE clinical guideline 85 created a further opportunity for optometrists to extend their role beyond traditional activities of glaucoma case-finding and detection (NICE, 2009). The past decade has seen integrative changes to the delivery of glaucoma services in the UK in response to the increasing demand on secondary care services, and with a view to prevent a fall in standards where review appointments for less urgent or stable patients are increasingly delayed. Fiscal factors are another driving force to changes in service delivery as estimates for outpatient clinic costs in 2011 were £210 for a new referral, and £65 for a follow-up visit (Devarajan et al., 2011). The concept of 'shared care' in glaucoma has been developed in both the hospital and community settings. Enhanced scheme activities for glaucoma now include repeat measures and glaucoma referral refinement schemes for glaucoma suspects/ OHT, monitoring of suspect glaucoma/ OHT and co-management of stable glaucoma (Kotecha et al., 2014). Many schemes require the use of standardized and modern equipment, serving as potential drivers for upgrade and investment of equipment in community practice.

1.11 Aims of this thesis

The primary aims of this thesis, which are discussed in detail in the next three chapters, are listed as follows:

1. To perform a national survey of UK optometrists' current and anticipated use of equipment and IT

2. To determine whether advanced technologies, alone or in combination, can be used to improve case-detection of primary open angle glaucoma

3. To evaluate the effectiveness of non-contact methods in screening for eyes at risk of developing angle closure glaucoma

Chapter 2 addresses the first primary aim by reporting the findings of a cross-sectional survey of UK community optometrists to determine the equipment and IT currently in use in optometric practice for general use and for the detection of glaucoma, and to identify anticipated purchases in the near future. A secondary aim was to explore the rationale behind the uptake of equipment and IT by eliciting optometrists' views regarding their adoption, and gathering information on the services provided in community practice.

Chapter 3 presents the findings of a cross-sectional study of a sample of subjects aged 60 years and older, to evaluate the diagnostic accuracy of four advanced technologies: Frequency doubling perimeter® (FDT, Carl Zeiss Meditec Inc.), Moorfields motion displacement test (MMDT, Moorfields Eye Hospital, London), iVue Ocular coherence tomographer™ (OCT, Optovue, Inc.), and Ocular Response Analyser ® (ORA, Reichert Inc.) for the detection of POAG, when compared with a reference standard diagnosis.

Chapter 4 addresses the third and final primary aim using a methods comparison study to compare the screening efficacy of slit-lamp biomicroscope techniques and advanced imaging for the detection of narrow anterior chamber angles, when compared with a reference standard gonioscopic observation.

Secondary aims of the studies reported in Chapters 3 and 4 were to determine the acceptability to patients for each index test, and the time taken to perform the examination, in order to provide further evidence of their suitability for use in screening.

Chapter 5 is the concluding chapter. A summary of the main outcomes from studies reported in the preceding three chapters is provided, together with recommendations for future research in this area.

CHAPTER 2: An investigation of the use of standard and specialist equipment by UK optometrists

2.1 Introduction

Over the past 20 years there have been major advances in the scope of optometric practice, including the widespread adoption of sophisticated ophthalmic equipment and information technology (IT). It can be argued that the first steps in this transformation of optometric practice were the introduction of static semi-automated perimetry and non-contact tonometry (NCT) to UK clinical practice in the 1970's. Since these developments, rapid advances in technology allied to initiatives to improve the detection of glaucoma and quality of referrals to secondary care by community optometrists have contributed to developments in the use and uptake of equipment (CoO & RCOphth, 2010). In addition to their traditional role in the detection of eye disease, optometrists are increasingly becoming involved in community-based co-management/ shared care programs for chronic eye disease (Park et al., 2009, Mandalos et al., 2012). In parallel with these developments, greater numbers of optometrists are adopting 'state-of-the-art' equipment for imaging the eye or assessing visual function to enhance the detection and monitoring of eye disease (Myint et al., 2011).

The use of IT in practice is key to the adoption of this advanced equipment as many newer systems are supported by computer software which facilitates data capture and provides more in-depth analysis of clinical data. Alongside the advances in equipment used in ophthalmic practice, IT software has also evolved to facilitate data capture, as well as enabling more complex analysis and more accurate interpretation of clinical results. Examples include computer software developed to aid the detection of visual field progression e.g. Guided Progression Analysis for the Humphrey Visual Field Analyzer (Zeiss, Nouri-Mahdavi et al., 2011)' and automated software analysis integrating normative patient data which is used by advanced imaging systems such as the Heidelberg Retinal Tomograph (Heidelberg, Strouthidis & Garway-Heath, 2008).

An electronic medical (or health) record is a digital documentation of a patient's medical history and care (NAHIT, 2008). A paperless or electronic record facilitates clinical recording, while a practice management system is used to improve the efficiency of practice administration tasks such as functions for appointments and scheduling, billing activities, and communication with patients to generate recalls. Practice management systems can also be

used as a marketing tool by filtering patients and sending up-to-date information on products and services to targeted groups. With rapid advancements in technology, practices are now being promoted online by creating a practice website, use of social media, video marketing, online ordering facilities, and use of email or text messages.

Studies comparing the use of electronic and paper-based records have shown electronic records in a favourable light when applied to optometric practice (McVeigh et al., 2008), and generally across primary care (Hippisley-Cox et al., 2003). Electronic communication has been widely adopted in the NHS, with the ambitious strategic vision for the future set out in Public Health England's *Knowledge Strategy: Harnessing the power of information to improve the public's health* published in October 2013 (PHE, 2013), and driven by targets such as the Department of Health's goal for a "*Paperless NHS by 2018*" (techUK, 2014). Although the efficient electronic collection and sharing of health data is regarded by the NHS as being of paramount importance, electronic communication between primary care optometry and secondary care remains weakly established. The College of Optometrists report "*Better data better care*" (CoO, 2013b) notes that although optometrists are responsible for approximately one million referrals of patients each year to their GP or hospital eye service, most of these referrals continue to be made via an inefficient paper-based system. This is despite the potential benefits of teleophthalmology, which have been demonstrated in a successful referral scheme in Fife in Scotland (Borooah et al., 2013). However, initiatives are underway in parts of the UK in an effort to integrate and centralise IT systems (CoO, 2014f). The College of Optometrists report *Healthy Eyes for All* notes that, for example, optometrists in Northern Ireland may in the near future be able to access patients' Electronic Care Records (ECRs) to obtain information from ophthalmology clinics on patients' screening reports, treatment advice given etc. Also, an electronic Ophthalmic Claims System has been initiated in a number of practices in the province, and optometrists may soon be able to participate in a Clinical Communications Gateway (CCG) which will, among other benefits, allow eReferrals (CoO, 2014f). Similarly, expansion of electronic referral systems in Scotland is proceeding apace via the Eye Care Integration Programme with the support of Optometry Scotland (CoO, 2014f). *Healthy Eyes for All* reports that pilots of eReferral systems are underway across much of Scotland and there are plans that referrals will eventually be submitted through a Virtual Private Network (VPN) with optometrists having access to Scotland's centralised internet portal (SCI Gateway) which will link the data systems from primary and secondary care. Progress towards electronic health communication has been slower in England than in the rest of the UK. One factor holding back progress is that optometrists who are not on NHS secure mail are unable to fully utilise the benefits of electronic communication (CoO, 2013b).

Periodically, the College of Optometrists has carried out Clinical Practice surveys to identify the range of equipment in current use in optometric practice, and to provide a snapshot of community optometric practice. The first Clinical Practice survey was distributed in 2001 to 7846 members from the College of Optometrists' membership database. The second survey was undertaken in late 2007 using a combination of postal and online delivery. This questionnaire was structured using the 2001 version as its basis, and expanded to include questions on the use of specific items of equipment and primary care activities e.g. pre-school testing and patient referrals. Myint et al. carried out a national survey of diagnostic tests used by UK community optometrists for the detection of glaucoma, which found increasing use of modern imaging and visual function tests (Myint et al., 2011). However, this study was specifically focused on equipment used for glaucoma detection. There has been no national survey of optometric equipment as a whole since the Clinical Practice survey conducted in 2007 (CoO, 2008). Information on the use of IT in UK community practice is particularly scant, with the 2007 survey understandably devoting little attention to what was novel technology at that time. This dearth of information on IT use by optometrists was one impetus for the current surveys. In addition, the rationale for optometric practices purchasing such equipment and the views of the profession on its impact on patient care have not been previously investigated in the UK.

Hence, the primary aims of this paper are to present the findings of a cross-sectional survey of UK optometrists to determine the equipment and IT currently in use in optometric practice, and to identify anticipated purchases in the near future. Secondary aims were to gather information about the services provided for patients by community optometry practices, and to elicit optometrists' attitudes regarding the adoption of specialist equipment and IT. Analysis of responses will allow enablers and barriers to the uptake of new technology to be identified. Survey questions were developed, validated, and distributed to a randomized sample of UK optometrists. To the author's knowledge, this is the first cross-sectional survey of UK optometrists aiming to explore the rationale behind the uptake of ophthalmic equipment and IT in community practice. Following distribution of the survey in 2013, the opportunity arose to collaborate with the College of Optometrists in their 2014 Clinical Practice survey. This was the follow-up to the 2001 and 2007 surveys. The author led on the drafting and validation of the survey which was distributed in 2014. Comparison with the previous two Clinical Practice surveys allowed the author to carry out a longitudinal analysis of the use of equipment by optometrists over time.

For the purposes of the current study, 'standard' items of equipment were regarded as those listed in Section B1.02 of the College of Optometrists guideline B1 *Equipment lists for the routine eye examination and dispensing (CoO, 2012).* Newer technologies used to supplement standard equipment for enhanced clinical detection and monitoring are termed 'specialist'.

2.2 Methods: A survey of current and anticipated use of standard and specialist equipment and IT by UK optometrists, 2013

Ethical approval for this research was granted by the City University London School of Health Sciences Research and Ethics Committee and the research was carried out in accordance with the tenets of the Declaration of Helsinki. Participation in the study was voluntary and informed consent was assumed when a participant attempted the questionnaire.

This anonymous cross-sectional survey was conducted using a self-administered questionnaire. An advisory group of nine members was convened to guide the development of the survey instrument. This group included: academic optometrists, practising optometrists working in independent and multiple practices, professional services directors of major optical chains and members of optometric professional organisations. Each member of the advisory group provided feedback on the first draft of the survey, indicating whether the questions were easily understood and clinically relevant. Minor amendments were made based on their feedback, and the resulting survey underwent further piloting by 23 members of the council of the College of Optometrists to further confirm the questionnaire's face validity. The refinements based on their feedback involved minor changes to the wording and placement of questions, plus a few additional multiple-choice options. Results of the pilot survey were not included in the final analysis.

The finalized survey was distributed by email and posted to a sample of UK-based optometrists from the College of Optometrists' membership database. These optometrists were randomly selected in an effort to provide a representative sample from England, Northern Ireland, Scotland and Wales. The required sample size was calculated using Cochran's formula for continuous and categorical data. Based on a margin for error of ±5% and an alpha level of 0.05 (Bartlett et al., 2001) the formula determined that for a population of 10,000 a sample of 370 responses was required. Using an anticipated response rate of 30%, based on response rates to previous surveys (see Table 2.1), 1233 questionnaires should be distributed to members of the College of Optometrists. This total was increased to 1300 to account for 'bounce back' of emails from invalid addresses, or as a result of recipients previously having opted out of receiving online surveys from the College.

Survey topic	Number of items	Was survey piloted?	Incentive offered?	Nature of survey	Response rate (%)
College of Optometrists, Clinical Practice Survey 2001 (CoO, 2001)	8	Not recorded	No	Post	46
College of Optometrists, Clinical Practice Survey 2007 (CoO, 2008)	24	Yes	No	Post & Internet	30
Therapeutic practice by UK optometrists (Needle et al., 2008)	30	Not recorded	No	Internet	24
Referral behaviour among optometrists (Edgar et al., 2010)	23	Yes	No	Internet	12
Attitudes to fitting of rigid gas permeable lenses (Gill et al., 2010)	20	Yes	Not recorded	Post	45
Diagnostic tests for detection of open angle glaucoma (Myint et al., 2011)	27	Yes	No	Internet	28
Habits and attitudes to retinoscopy (Dunstone et al., 2013)	23	Yes	Yes	Internet	30
Advice for people with or at risk of AMD (Lawrenson & Evans, 2013)	19	Yes	Yes	Internet	16 (Optometrists) 6 (Ophthalmologists)
College of Optometrists, Workforce Survey (Unpublished report cited by Dunstone et al., 2013)	59	Yes	Yes	Post & Internet	34
Present survey	**21**	**Yes**	**Yes**	**Post & Internet**	**35**

Table 2.1 – Features of the present study compared with previous UK-based practitioner surveys, ordered by date of publication

The College of Optometrists' membership database contains approximately 76% (10,050 of 13,202) of General Optical Council (GOC) registrants (GOC, 2013). Of the 1300 members captured in the sampling frame, 1215 optometrists had listed an email address and, therefore, received the survey by an email including a hypertext link to the survey homepage. The online version was hosted by a US provider of online surveys, Survey Monkey (http://www.surveymonkey.com). The remaining 85 members without an email contact address were invited to participate in the survey by post, each receiving a questionnaire with a covering letter. Respondents were asked to return the completed questionnaire in the stamped-addressed envelope enclosed within the invitation pack. Both the explanatory email and covering letter accompanying the online and postal surveys respectively detailed information on the purpose of the research. In an effort to maximize survey responses and to minimise bias, the covering letter accompanying the postal invitation included the hyperlink text to the survey homepage to enable the questionnaire to be completed online. Similarly, email recipients were given the option of choosing to complete the questionnaire using a paper version. Settings were adjusted to allow participants to go back to previously completed pages in the survey and update responses. Respondents could exit the survey at any time although all previous responses were automatically saved.

The initial mailing took place at the beginning of February 2013. Two reminder mailings were sent, the first after 10 days and the second after 20 days in an effort to maximize the response rate. As an added incentive, all respondents were also provided with the option of free entry into a prize draw to win one of three sets of shopping vouchers to the value of £100. The use of monetary rewards and reminder mailings has been shown to be an effective way to increase survey responses in a Cochrane systematic review (Edwards et al., 2009). In total, the survey was open for 6 weeks and closed on 15th March 2013 following 2 consecutive days without responses.

The questionnaire was organized into five sections totalling 21 questions: 'Personal details' (4 questions), 'Details of your practice' (4 questions), 'Use of standard ophthalmic equipment' (1 question), 'Use of specialist diagnostic equipment' (3 questions) and 'Use of information technology' (9 questions) (see Appendix A, part i for full survey). Questions within each domain required either Yes/ No responses or the use of 5-point Likert scales for those questions relating to barriers and preferences. The survey was designed to be completed within 20 minutes. The main themes included in the questionnaire and the design of the survey instrument were based on the College of Optometrists' Clinical Practice surveys of 2001 and 2007, together with the outcomes of a literature search of equipment and IT in current

use. The surveys administered to optometrists based in England and Northern Ireland, Scotland, and Wales each differed slightly to account for local variations in NHS terminology and differences in the operation of community optometric services across the UK. The final list of questions is summarized in Table 2.2. Section 1 addressed personal demographic information, as well as ascertaining whether the recipient currently practised community-based optometry. Respondents who had never worked in community optometric practice (e.g. hospital optometrists), or had last worked in this capacity more than 5 years prior to the survey were re-directed to Question 20 (Use of the internet in the workplace), skipping the main body of questions relating to the use of equipment and IT in community optometric practice. This was to encourage all respondents, whether they had recently worked in community practice or not, to complete and return the survey. Sections 3, 4 and 5 related to the use of equipment and IT in practice, and in these sections optometrists were asked to indicate whether the respective item was 'Used', or 'Not available in practice'. The questions relating to optometrists' views on the use of equipment and IT used the Likert scale, one of the most commonly used psychometric response scales to obtain degrees of agreement with a set of statements. A 5-point scale with a middle category was chosen to allow respondents to select a neutral response.

Respondents were provided with several opportunities to add free-text comments in the survey. In particular, they were asked to comment on any additional advantages and/ or disadvantages, not captured by the statements already included in the survey, that they felt may result from the use of specialist equipment in community practice. Another free-text box asked for similar comments on any additional advantages and/ or disadvantages relevant to the use of IT services in community practice. The final survey question asked for any further comments on any aspect of the use of equipment and technology in optometry to be written in the free-text box.

Section	Question Number	Question
About you	1-4	- Year of qualification - University at which optometry training was completed - Gender - To ascertain whether respondent is currently practising as a community optometrist, or has previously worked in this capacity within the last 5 years
About your practice	5-8	- Principal mode of practice – Independent, multiple/ group etc. - Principal practice location – Country and then divided into inner city, rural etc. - Practice involvement in enhanced or additional/separately contracted services (with modifications to account for different modes of practice in different countries)
Standard Ophthalmic equipment	9	- Use of standard ophthalmic equipment
Specialist equipment	10-12	- Use of specialist diagnostic equipment - Views on possible advantages or disadvantages of using specialist equipment (Likert scales) - Items of specialist equipment respondent anticipates buying during the next 12 months
Information Technology	13-21	- Use of computer software for specific clinical applications - Use of IT for the management of patient data and patient education - Use of 'paperless' records and mobile texting for reminders/ collections - Views on possible advantages or disadvantages of using IT (Likert scales) - IT services respondent anticipates buying during the next 12 months - Methods of generating a patient referral or notification letter and whether the results of specific clinical tests are sent together with the referral letter. - Use of internet in the principal workplace - Use of internet in your professional development
N/A	22	Additional comments on any aspect of the survey

Table 2.2: Summary of survey questions from; A survey of current and anticipated use of equipment and IT by UK optometrists (2013)

2.3 Methods: The College of Optometrists (CoO) Clinical Practice survey (2014)

The 2014 Clinical Practice survey was compiled in collaboration with the College of Optometrists based on previous Clinical Practice surveys and using knowledge of current community optometric practice. The draft survey was reviewed by members of the Public Health Research and Communications teams of the College of Optometrists. Following minor amendments to the wording of some questions and the multiple options provided, the survey was piloted by 17 members of the College council to further validate the survey instrument. Based on the responses received from the pilot group, the anticipated time to complete the questionnaire (10-12 minutes) was added to the introductory paragraph for the survey. Two further changes were made to the main body of the survey: an amendment to the wording of one question, and the addition of a single free-text box. As the pilot version of the survey was amended prior to circulation in the survey proper, results of the pilot survey were not included in the final analysis.

The finalised, anonymous, and self-administered survey was distributed to a random sample of 1996 optometrists from the College of Optometrists' membership database. In the first instance, just over 95% (1921 of 1996) of members included in the sampling frame received the survey via a hypertext link to the survey homepage (http://www.surveymonkey.com) detailed in an email. The remaining 75 members of the sampling frame did not have an email contact address on the database. Online respondents were permitted to move back to previously completed pages and to exit the survey at any point. The initial mailing took place in late April 2014, with a first reminder email sent after 2 weeks and a second reminder sent one month following the initial distribution. A paper version of the questionnaire was then sent to all optometrists who had failed to attempt the online survey. This was 2 months after the initial email had been received. At the same time the paper version of the survey was sent to the 75 members in the sampling frame without an email contact address. A stamped-addressed envelope was enclosed, in which members could return the completed questionnaire, together with an accompanying covering letter, which detailed information on the aims of the survey. No incentives were offered to members for completion of the survey.

In common with previous CoO Clinical Practice surveys, the questionnaire was divided into five sections as summarised in Table 2.3 (see Appendix A, part ii for full survey). Several free-text boxes were provided at appropriate points of the survey, in addition to a final box for comments relating to any aspect of the survey. In particular, question 7 required the respondent to indicate their principal work environment (e.g. community independent

practice). This was followed by a request to respondents to answer the remainder of the questionnaire based on their work in their principal practice. Only responses from optometrists working principally in community practice (independent, joint venture/ franchise, multiple/ group or locum practice) were included for this analysis.

Section	Question Number	Question
About you	1-3	- Year of qualification - University at which optometry training was completed - Gender
About your practice	4-7	- Principal practice location – Country and then divided into urban, rural etc. - Half-day sessions worked in a 7-day week in various practice environments - Independent practice, Hospital etc. - Principal work environment – Independent, hospital etc.
Optometric instrumentation	8-10	- Use of instruments for the detection of ocular disease and abnormality - Use of instruments for the measurement of refractive error, and dispensing of optical aids - Frequency of use of a slit-lamp biomicroscope in adult patients

Table 2.3: Summary of survey questions from the CoO Clinical Practice 2014 survey

Section	Question Number	Question
Checking for glaucoma	11-17	- Routine use of equipment to check the patient's optic disc to screen for glaucoma - Frequency of measurement of intraocular pressure in 8 patient categories - Routine use of equipment to measure the patient's intraocular pressure to screen for glaucoma - Frequency of visual field assessment in 8 patient categories - Routine use of equipment to assess the patient's visual field to screen for glaucoma - Likelihood of repeating suspicious test results prior to referral e.g. visual field assessment - Use of tests for repeat assessment of the optic disc, intraocular pressure and visual field
Primary care activities	18-27	- Provision of optometric services amended for variations between countries e.g. Local Optical Committee Support Unit (LOCSU) for respondents working in England and Northern Ireland - Provision of additional and/or enhanced (community) services - Additional and/or enhanced (community) services the respondent would like to provide - Frequency of examination of 9 patient categories e.g. children under 6 months of age - Areas on which to concentrate personal development - Number of patients examined in the last working week - Number of patients referred for further opinion in the last working week - Number of referrals related to suspected ocular hypertension or primary open angle glaucoma, and based on the NICE guidelines published in 2009 for the diagnosis and management of chronic open angle glaucoma - Charging for additional procedures
N/A	28	- Additional comments on any aspect of the survey

Table 2.3 (continued): Summary of survey questions from the CoO Clinical Practice 2014 survey

2.4 Statistical analysis: A survey of current and anticipated use of equipment by UK optometrists (2013), and the CoO Clinical Practice survey (2014)

Results from the online responses to both surveys were exported via Survey Monkey into an Excel spreadsheet, and collated with the manually-entered paper responses to facilitate data analysis. In view of the large number of paper-based responses (388/ 870, 44.6%) to the CoO Clinical Practice (2014) survey, a data entry/ processing company (Eurodata Computer Services Ltd.) was employed to enter the data into an Excel spreadsheet using double-key entry to ensure accuracy. Interval data generated using Likert scales were transcribed into grades from 1 to 5, where 'Strongly disagree' was denoted by 1. The gradings were then described using mode, median and interquartile range. Responses to the free-text responses were coded and assigned to categorical variables by the author. The Chi-squared test was used in the statistical analysis to test for any statistically significant differences between proportions. To reduce the risk of a Type I error arising from multiple statistical comparisons, a p value less than 0.01 was deemed statistically significant. Descriptive data analysis was carried out using SPSS 21.0 software (SPSS Inc, Chicago, Illinois, USA).

2.5 Results; A survey of current and anticipated use of equipment and IT by UK optometrists (2013)

A total of 1300 questionnaires were distributed by email and post. The overall response rate was 35% (455/1300), exceeding our anticipated response rate of 30%. Four hundred and thirty two (out of 455) complete questionnaires were received, representing a completion rate of 95%. Data from the 23 incomplete surveys were not included in the analysis. The remaining 432 respondents were asked to indicate whether they were currently practising as a community optometrist, or had practised in this capacity within the previous 5 years; 16 (4%) of respondents answered 'No' leaving 416 optometrists who answered questions 5 through to 19.

The use of a randomized cohort of optometrists from the College membership database allowed a more representative sample of optometrists to be included in our analysis. A total of 199 male optometrists (46%) and 233 female optometrists (54%) completed the survey, reflecting the 45% male and 55% female gender distribution of registrants on the GOC register for the year 2011-2012 (GOC, 2013).

Of the 416 eligible optometrists who completed the survey, 54% (n=224) worked in independent practices, 24% (n=98) in multiple/ group practices, 9% (n=39) in joint venture/ franchises, and 12% (n=51) were locums. Over 75% of these optometrists worked in England (327/416), 11% in Scotland (47/416), and 5% in both Wales (22/416) and Northern Ireland (20/416).

2.5.1 Provision of services

The remaining analysis is based on the responses from the 416 eligible optometrists who completed the survey. Services provided by optometrists at the time of the survey have been divided into two categories: enhanced services and additional or separately contracted services (Table 2.4). An 'enhanced service' is a locally commissioned scheme to deliver routine or emergency community eye care outside the scope of the standard General Ophthalmic Services (GOS) contract. Enhanced services include PEARS ('Primary Eyecare Acute Referral Service' or 'Primary Eyecare Assessment and Referral Service') schemes, glaucoma referral refinement, cataract direct referral etc. Examples of additional or separately contracted services include domiciliary eye care and screening for diabetic retinopathy.

Enhanced or additional/ separately contracted services were provided by 73% (305/416) of respondents (Table 2.4); however there were marked variations with geographical location. All 22 respondents working in Wales gave a positive response to this question, compared with 85% (40/47), 73% (240/327), and 16% (3/20) of optometrists with practices located in Scotland, England and Northern Ireland respectively (Figure 2.1). 48%, (198/416) of respondents utilised fast-track referrals for exudative (wet) age-related macular degeneration (AMD), and 40% (167/416) provided direct referral for cataract surgery. Glaucoma repeat measures services were provided by 30% of respondents (124/416), and 22% (93/416) were involved in referral refinement schemes. Interestingly, the likelihood of undertaking enhanced and additional/ separately contracted services was statistically significantly greater for males ($p=0.003$). Male respondents were in the majority for 8 of the 12 enhanced and additional/ separately contracted services listed. A greater proportion of those respondents providing enhanced or additional/separately contracted services reported using specialist items of equipment than those who did not provide these services. Specifically, significantly greater proportions of our sample providing these services used Optical Coherence Tomography (OCT) ($p=0.008$) and pachymetry ($p<0.001$) (Figure 2.1). Those participating in enhanced or additional/separately contracted services were also significantly more likely to use electronic delivery for their referrals ($p=0.007$) Figure 2.1).

	Provision of services	A Survey of current and anticipated use of equipment and IT (2013)		CoO Clinical Practice survey (2014)	
		Number of practices providing service (n=416)	Percentage (%)	Number of optometrists providing service (n=749)	Percentage (%)
Enhanced (locally commissioned) services	Glaucoma referral refinement scheme	93	22	178	24
	Funded repeat measurement scheme (repeat IOP and/or fields)	124	30	216	29
	Monitoring of patients with ocular hypertension (OHT) and/ or suspect chronic open angle glaucoma (COAG)	41	10	83	11
	Co-management of patients with stable glaucoma	27	6	41	5
	Post-operative cataract care	79	19	127	17
	Fast-track (Direct referral) cataract programme	167	40	220	29
	Adult community optical low vision services	42	10	44	6
	PEARS-type scheme	48	12	77	10
Additional or separately contracted services	Domiciliary services	64	15	---	---
	Formal programme for screening for Diabetic Retinopathy	59	14	72	10
	Pre-operative and post-operative management of refractive surgery	31	7	---	---

Table 2.4: Provision of enhanced (locally commissioned) and additional/ separately contracted services.

2.5.2 Standard ophthalmic equipment

The majority of respondents (88%, 368/416) indicated that they used NCT for the measurement of intraocular pressure, while 81% (337/416) reported using Goldmann or Perkins contact tonometry (Table 2.5). However, the author did not ascertain how regularly these devices were used in clinical practice. Respondents working in independent practices were significantly less likely to use NCT ($p=0.001$) (Figure 2.1) or an autorefractor compared with optometrists working in multiple/ group practices ($p<0.001$).

2.5.3 Specialist equipment

The most widely used item of specialist equipment was the fundus camera, which was used by 74% (308/416) of respondents, 54% (165/308) of whom charged patients for fundus imaging. This was followed by anterior segment imaging and FDT perimetry (used by 23% and 20% respectively). Newer imaging modalities are usually among the more expensive items listed in the survey, which is probably reflected by the high proportions of optometrists implementing a charge to the patient for the use of the technology; 77%, 48/62, 75%, 9/12 and 76%, 13/17 for use of the OCT, scanning laser polarimeter (SLP), and scanning laser ophthalmoscope (SLO) respectively. The use of OCT was reported by 15% (62/416) of respondents. This device was more likely to be used by respondents working in independent practice compared with multiple/ group practices ($p<0.001$) (Figure 2.1). Practitioners who used OCT were also more likely to use other specialist items of equipment ($p=0.003$). The proportions of those who used OCT and who also reported using a goniolens ($p<0.001$), corneal topographer ($p<0.001$) and macular pigment analyser ($p=0.002$) were all significantly greater than those practitioners who did not use OCT. Furthermore, OCT users were significantly more likely to provide enhanced or additionally/separately contracted services than those who did not use OCT ($p=0.008$) and, specifically, were more likely to provide a glaucoma service alone ($p=0.006$).

A total of 62 respondents reported using gonioscopy, representing 15% of the total sample. A greater proportion of those respondents working in independent practice reported using a goniolens ($p<0.001$) and providing enhanced/separately contracted services ($p=0.001$) than those in multiple/ group practice. The proportion of respondents using NCT ($p=0.001$) and electronic recording ($p<0.001$) was statistically significantly greater in those working in multiple/group practice than independent practice. Practitioners working in independent practice were also significantly less likely to use electronic recording ($p<0.001$) than those working in all other types of practice (Figure 2.1).

Of the 84 respondents who detailed items of specialist equipment they anticipated purchasing in the next 12 months, the greatest number (n=36) noted the OCT, followed by the contact tonometer (n=11), fundus camera (n=9), and pachymeter (n=8).

Item of Equipment or Information Technology	A Survey of current and anticipated use of equipment and IT (2013)		CoO Clinical Practice survey (2014)	
	Frequency item is used in practice (n=416)	Percentage (%)	Frequency item is used in practice (n=761)	Percentage (%)
Non-contact/ pneumo tonometer (NCT)	368	88	---	---
Goldmann/ Perkins applanation tonometer	337	81	---	---
Optical Coherence Tomographer (OCT)	62	15	131	18
Macular Pigment measuring instrument (e.g. MPOD or other)	21	5	---	---
Fundus photography	308	74	645	87
Anterior segment imaging	94	23	370	52
FDT perimetry	82	20	---	---
Advanced tonometer (e.g. iCare, ORA or other)	76	18	---	---
Pachymetry (optical/ ultrasonic)	69	17	107	15
Goniolens	62	15	63	8.9
Computerised/ projection test chart	314	75	529	71.4
Electronic patient record system/ Practice Management System (e.g. Optisoft, Focus, Acuitas or other)	332	80	---	---

Table 2.5: Relative frequency of the use of items of equipment and information technology by community optometrists

2.5.4 Information technology

'Paperless' records were used by 39% (162/416) of respondents, with a further 59% (246/416) reporting that they employed mobile phone texting for patient reminders and collections. Almost 80% (332/416) of practices use a practice management system, and the computerized test chart was the most popular information technology (IT) item listed for clinical use (75% (314/416)). Notably, optometrists working in independent practices were significantly less likely to use a computerized test chart, 'paperless' records (Figure 2.1) or mobile phone texting compared with multiple/ group practices ($p<0.001$). A further nine respondents commented on the use of the Apple iPad and integrated applications in the 'Other' box for clinical testing, patient education and as a dispensing tool.

2.5.5 Views on the use of equipment and IT in optometric practice

A summary of the views of respondents to the questions posed in the survey is presented in Tables 2.6a and 2.6b. In addition there were a number of free-text comments which are considered in the Discussion.

	Views on adoption of specialist equipment	Strongly Disagree % (N)	Disagree % (N)	Neither Agree nor Disagree	Agree % (N)	Strongly Agree % (N)
Positive	Enhances clinical assessment, providing a diagnostic tool to aid management and referral decision-making	2% (7)	0% (1)	3% (12)	40% (166)	55% (230)
	Permits increased involvement in referral refinement and/or co-management schemes	0% (1)	2% (9)	8% (34)	62% (257)	28% (115)
	Provides an opportunity for promoting your practice	1% (4)	1% (5)	11% (44)	57% (239)	30% (124)
	Results can be used as defence in medico-legal cases	0% (2)	2% (10)	29% (119)	53% (219)	16% (66)
	Promotes patient loyalty to the practice	1% (3)	2% (9)	16% (68)	61% (252)	20% (84)
Negative	Can pose a financial burden on the practice due to initial purchase costs and/or continuing maintenance	1% (4)	8% (35)	13% (54)	52% (218)	25% (105)
	Poses a risk of replacing core skills reducing the value of optometric qualifications	22% (91)	48% (198)	21% (87)	9% (36)	1% (4)
	Operator training (initial and on-going) can be inconvenient, time consuming and a drain on resources	7% (30)	35% (146)	33% (136)	22% (90)	3% (14)

Table 2.6a: Views on the adoption of specialist equipment

	Views on adoption of Information Technology	Strongly Disagree % (N)	Disagree % (N)	Neither Agree nor Disagree	Agree % (N)	Strongly Agree % (N)
Positive	Facilitates more efficient administrative flow (tracking records, computerised referrals etc.)	0% (1)	4% (18)	17% (70)	61% (252)	18% (75)
	Enables secure exchange of health information between primary and secondary care	3% (14)	16% (67)	34% (140)	42% (175)	5% (20)
	Gives the impression that the practice is more 'state of the art'	0% (2)	3% (13)	12% (50)	72% (299)	13% (52)
	Reduces the time taken to record information for a routine patient	4% (18)	27% (112)	31% (131)	25% (105)	12% (50)
Negative	Dynamic nature of IT necessitates frequent updates and technical support	0% (1)	5% (20)	19% (79)	59% (246)	17% (70)
	Poses a security risk with storage of confidential patient information online or on databases	3% (13)	23% (97)	42% (174)	29% (120)	3% (12)
	Use of electronic records could impact negatively on patient-practitioner interaction and relations	8% (32)	34% (143)	33% (139)	22% (90)	3% (12)
	There is greater risk of losing data	5% (22)	27% (113)	33% (136)	31% (129)	4% (16)
	Inconvenient to learn new IT skills to operate management systems or software tools	10% (40)	40% (167)	29% (119)	20% (84)	1% (6)

Table 2.6b: Views on the adoption of IT

2.5.6 Referrals

Most respondents (78%, 324/416) use a standard locally adapted form to generate referral or notification letters, with only 17% (71/416) of respondents sending referrals by electronic transfer. Of the respondents using a standard locally adapted form, 58% sent the letter by post/ fax (188/324), 17% (54/324) provided a copy of the letter to hand-deliver to the GP/ specialist, and a further 24% (77/324) used a combination of these delivery options. One in ten respondents reported not including the results of specific tests, notably fundus images, with referrals, citing a lack of the means to send information efficiently as the main reason. Respondents also commented on the inconvenience and poor cost efficacy of printing the results of imaging tests, as well as indicating that colleagues in secondary care did not require this additional information.

2.5.7 Use of the internet

This question applied to all respondents who completed the questionnaire, including those who did not work in community optometric practice. Three in four optometrists use the internet in their workplace. The most popular practice-related use for the internet (83%, 358/432) was for continuing education and training (CET)/ continued professional development (CPD). Fewest respondents used the internet for online discussion groups/ forums (37%, 158/432).

2.5.8 Variations between countries

Some variations between countries were observed for the use of specialist equipment. The proportion of respondents using Goldmann/Perkins tonometry, pachymetry and a goniolens in Scotland was statistically significantly greater than in England & Northern Ireland ($p<0.001$). Respondents from Scotland were significantly more likely to use fundus photography than those from each of the other countries ($p=0.001$). Respondents working in Wales reported significantly greater provision of enhanced/separately contracted services than in England & Northern Ireland ($p=0.002$). There was no significant difference between countries regarding the use of electronic record keeping, use of practice management software and electronic transfer of referral letters ($p>0.1$).

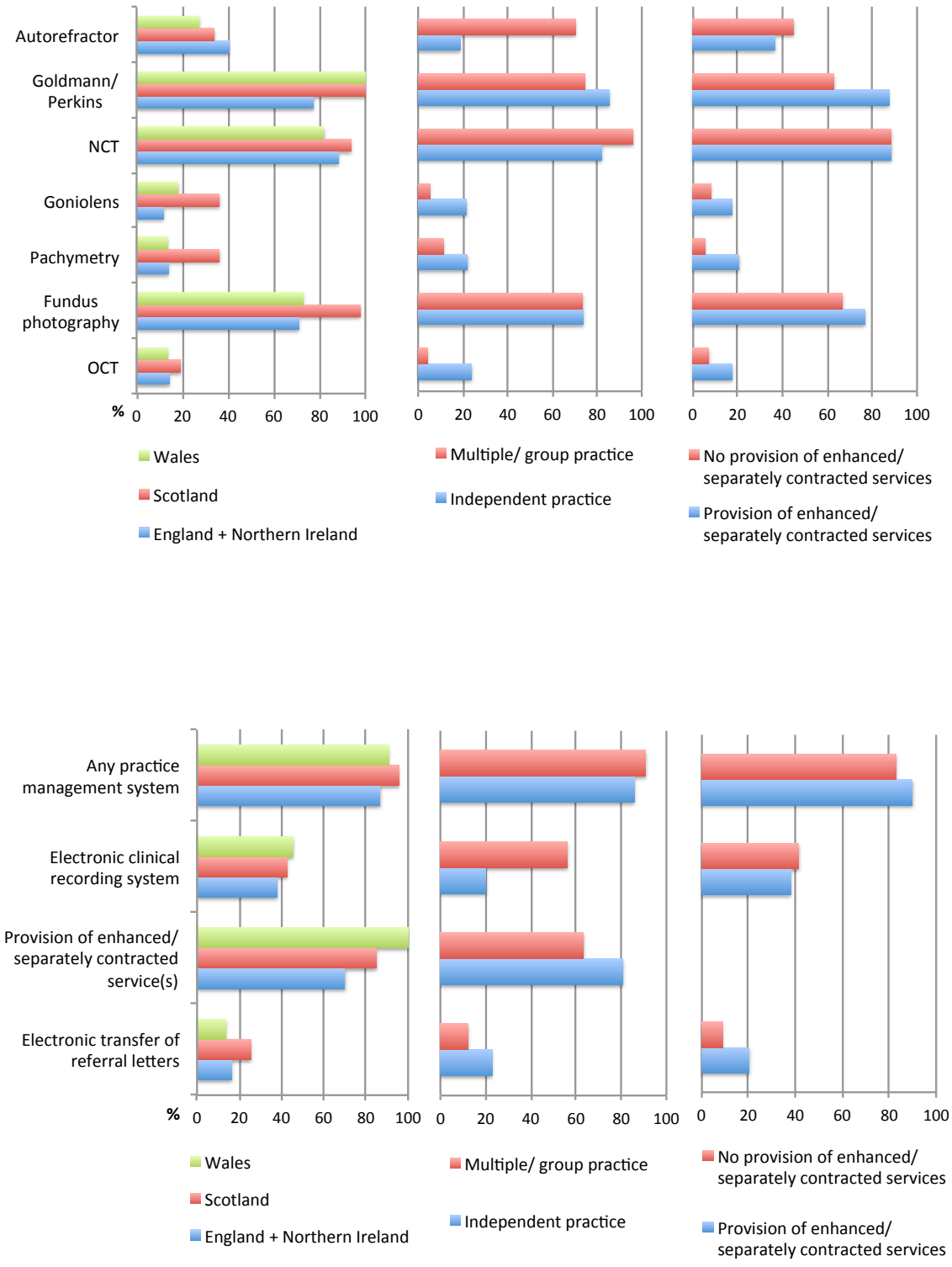


Figure 2.1: Sub-group analysis by country, practice type and provision of services (A survey of current and anticipated use of equipment and IT by UK optometrists, 2013)

2.6 Results; The College of Optometrists (CoO) Clinical Practice 2014 survey

Of the 1996 questionnaires distributed using a combination of postal and online delivery, 870 responses were received representing a response rate of 43.6%, with a completion rate of 76.7%. Data from incomplete surveys were included in the analysis, although all missing entries were ignored when calculating percentage frequencies. The results and discussion that follow are based on the 761 (87.5%) responses received from optometrists who reported their principal place of work to be in community optometric practice (independent, joint venture/ franchise, multiple/ group and locum practice). The remaining respondents who completed a valid response to this question (N=95, 10.9%) reported principally working in hospital, academic/ research, training/ education, management, optometric advisory, domiciliary or 'other' environments.

43.8% (333/761) of respondents were male and 56.2% (427/761) were female, approximately reflecting the 44.7% (6085/13616) male and 55.3% (7531/ 13616) female gender distribution of registrants on the GOC register for the year 2012-2013 (GOC, 2013). A total of 593/761 (78.1%) respondents worked in England, 82/761 (10.8%) in Scotland, 50/761 (6.6%) in Wales and 34/761 (4.5%) in Northern Ireland. Just over half of respondents reported principally working in independent practice (52.8%, 400/761), followed by 24% (182/761) in multiple/ group, 16.8% (127/761) in joint franchise/ venture and 6.5% (49/761) in locum practice. More female optometrists worked in community multiple/ group practice than in independent ($p<0.001$), and joint venture/ franchise ($p=0.009$) practices.

2.6.1 Use of instrumentation for the detection of ocular disease and abnormality, and the measurement of refractive error and dispensing of optical aids (Table 2.5/ Figure 2.2)

For the measurement of refractive error, 44.1% (321/754) of respondents indicated use of an autorefractor in their principal practice. This item of equipment was used by fewer optometrists in independent practice than in joint venture/ franchise and multiple/ group practice ($p<0.001$), together with the computerised test chart (<0.002), automatic phoropter/ refractor head ($p<0.001$) and other equipment for the dispensing of optical aids (automatic focimeter ($p<0.001$), pupillometer ($p<0.001$)).

87.3% (645/754) and 52.0% (370/754) of community optometrists reported use of digital fundus photography and external photography respectively in their community practice. Interestingly, a higher proportion of optometrists working in joint venture/ franchise practice

(124/126, 98.4%) reported use of fundus photography than in independent ($p<0.001$), and multiple/ group ($p=0.001$) practices. A total of 131 respondents reported use of OCT in their practice, representing 18.4% of the total sample. This item of equipment was used more frequently in independent practice than in joint venture/ franchise and multiple/ group practices ($p<0.001$). The same difference in the use of items of equipment between practice types was observed for the contrast sensitivity chart ($p<0.001$), scanning laser ophthalmoscope ($p<0.001$), corneal topographer ($p<0.001$), pachymeter ($p<0.001$), and gonioscope ($p<0.007$). The pachymeter was used in 15% (107/754), and the gonioscope in 8.9% (63/754) of principal community practices. When asked later in the survey whether a fee was charged for listed additional procedures, 33.5% (216/645) and 88.7% (125/141) of respondents who use fundus photography and specialist imaging respectively reported charging patients for use of this equipment. Furthermore, just over 20% (163/744) of respondents indicated an interest in learning more about specialist imaging (in particular practical support and interpretation).

2.6.2 Checking for glaucoma

417 of 751 respondents (55.5%) reported use of conventional fundus photography to routinely check patients' optic discs for glaucoma. Interestingly, 15% (113/751) of optometrists also indicated use of specialist imaging (OCT, SLO, SLP) to check the optic disc, and 14.5% (109/751) reported use of advanced tonometry for the measurement of IOP to case-find for glaucoma. Using a Likert-scale, 63.3% (472/746) of respondents indicated that they were 'likely' or 'very likely' to repeat optic disc assessment prior to referral for further investigation. Of the respondents who then went on to detail the tests used for repeat assessment of the optic disc, 51.9% (384/740) and 15.7% (116/740) reported use of conventional fundus imaging and specialist imaging respectively. A total of 415 respondents (55%) reported use of Goldmann or Perkins applanation tonometry to measure intraocular pressure when case-finding for glaucoma. Use of applanation tonometry showed a marked variation between countries and practice types. A significantly greater proportion of optometrists working in independent practice than in joint venture/ franchise and multiple/ group practice ($p<0.002$), and working in Scotland or Wales than in England/ Northern Ireland ($p<0.001$) reported routine use of Goldmann or Perkins tonometry to case-find for glaucoma.

2.6.3 Primary care activities

58.8% (440/749) of respondents indicated the provision of one or more additional/ and or enhanced (community) service as part of a formally agreed scheme in their principal practice. Of these respondents, between 41.5% and 56.7% reported undertaking training to provide these services. Optometrists providing one or more additional/ and or enhanced (community) service were significantly more likely to work in independent practice than in multiple/ group practice ($p<0.001$). The mean number of services provided by each of these respondents was 3.2, with the maximum number being 11 services. The provision of individual services reported by community optometrists in this survey is summarised in Table 2.4. Some variations were observed between countries and community practice type for the provision of services. A higher proportion of optometrists working in Wales reported provision of adult low vision services ($p<0.001$), PEARS-type schemes ($p<0.001$), and fast-track AMD services ($p<0.007$) than in England/ Northern Ireland and Scotland. In comparison, fewer respondents working in England and Northern Ireland reported provision of post-op cataract assessment ($p<0.001$) and triage schemes ($p<0.001$) than in either Scotland or Wales. A total of 289 of 749 respondents were involved in the provision of one or more glaucoma-related service(s) (repeat measures, referral refinement, monitoring and co-management of stable glaucoma and OHT), representing 38.6% of the sample. Optometrists providing glaucoma-related services were more likely to work in independent practice than in joint venture/ franchise ($p=0.001$) and multiple/ group practice ($p=0.001$). Respondents were also asked to detail any additional/ and or enhanced (community) services they would like to provide. 127 of 749 (17%) optometrists entered one or more additional/ and or enhanced (community) service in this free-text field. Of the services listed, 54 made reference to acute eye services (e.g. PEARS) or dry/ red eye schemes, and 43 to provision of one or more glaucoma service.

2.6.4 Variations between countries

Respondents working in Scotland were more likely to use specialist items of equipment than in England and Northern Ireland, and Wales. These items included external photography ($p<0.005$), fundus photography ($p<0.001$), and the automatic phoropter/ refractor head ($p=0.001$). A significantly higher proportion of optometrists working in Scotland also reported using a gonioscope ($p<0.001$) and pachymeter ($p=0.001$) when compared with respondents working in England and Northern Ireland. Fewer respondents working in England and Northern Ireland reported routine use of Goldmann or Perkins tonometry for glaucoma case-finding than in Scotland and Wales ($p<0.001$). Interestingly, a significantly greater proportion

of respondents working in Wales reported use of a contrast sensitivity chart than in any other country ($p<0.001$).

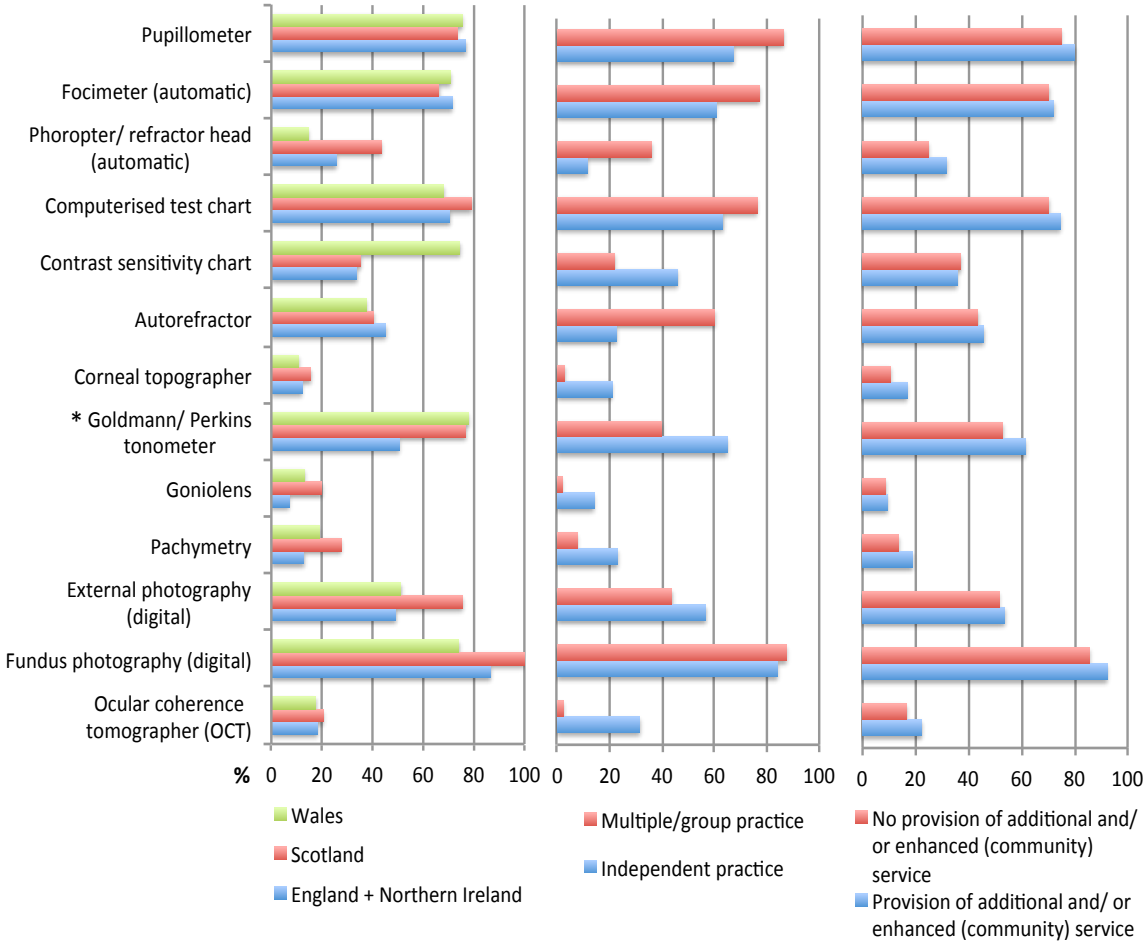


Figure 2.2: Sub-group analysis by country, practice type and provision of services (College of Optometrists (CoO) Clinical Practice survey 2014)

*(*Use of Goldmann/ Perkins tonometry for glaucoma case-finding)*

2.6.5 Additional comments

A total of 34 respondents, representing 4.7% of the total sample, provided a response in the additional comments free-text box. Of these, 3 respondents made reference to the need for revision of the NICE 2009 guideline for the diagnosis and management of chronic open angle glaucoma (NICE, 2009). Moreover, 11 subjects commented on the financial and time pressures of working in community practice, with one respondent indicating the need to 'negotiate a new General Ophthalmic Service contract' to revise the fee structure. A further 6 respondents made reference to the potential for optometrists to use their skills to expand on services provided in the community.

2.7 Discussion

The results of the cross sectional 2013 and 2014 surveys show that UK optometrists are increasingly investing in new ophthalmic equipment and IT, including the incorporation of the latest technology into their practices. The purchase cost of new equipment is largely incurred by practice owners. The business model for community optometry relies heavily on cross-subsidization from sales of optical appliances (Bosanquet, 2010) and the optical market has become a competitive market-driven system for the provision of community eye care. In the UK, optometrists are the first-line eye care providers and play an important role in the detection of early eye disease. Recent developments in ophthalmic equipment, designed for the assessment of structural or functional change have been adopted by community practices to facilitate diagnosis or identify disease progression. In parallel, insufficient capacity and funding issues within secondary care, coupled with the desire to avoid unnecessary referrals and to offer patients care closer to home, have created opportunities to develop new clinical services through the provision of separately commissioned 'enhanced' or 'additional' schemes (CoO, 2013d).

To discuss further how the use of equipment and IT by optometrists has increased over time, data from the current surveys have been compared in Table 2.7 with findings from previous similar surveys (Tuck, 1988a, Tuck, 1988b, Tuck & Crick, 1994a, Tuck & Crick, 1994b, CoO, 2001, CoO, 2008). There are limitations to this approach. The mode of distribution of surveys has progressed from being totally paper-based in the International Glaucoma Association (IGA) survey to largely online in the current surveys, a trend which itself reflects the increasing use of computers and the internet in optometric practice. Also, starting with the 2001 College of Optometrists Clinical Practice Survey, all surveys tabulated in Table 2.7 have been nationwide in their scope whereas the 1987/88 IGA survey targeted specific areas of the UK, resulting in a different respondent demographic. Furthermore, and perhaps the major limitation, although the questions asked in each survey relate to equipment, these questions have often been phrased differently in surveys, which is understandable given the different focus of each survey. To illustrate this point, the data from the 2013 equipment and IT survey shown in Table 2.5 for equipment used in practice were obtained from the following question: "Which of the following items of ophthalmic equipment are used in your practice?" These responses are seeking a response at the practice level, i.e. items of equipment that could be used by any optometrist in the practice or by non-clinical staff. However, in the CoO Clinical Practice survey of 2007 and 2014 the equivalent question relating to equipment asked: "Which of the following instruments are used either by yourself or by non-optometric personnel in your

practice?" The options are "Myself", "Non optometric staff", "Not used", and "No reply". These questions were phrased primarily to establish the responses from an individual optometrist rather than for the practice as a whole. Furthermore, differences in the terminology used for tests may have also introduced some variability between survey results. For example, the 2013 survey asked the respondent to indicate whether 'anterior segment imaging' was used in their principal practice. In contrast, the corresponding question in the CoO CP survey (2014) referred to this item of equipment as 'External photography – digital' as per previous surveys in this series. The proportion of optometrists who reported use of external photography (digital) in the 2014 survey was more than double that of respondents who indicated use of anterior segment imaging in their practice in responses to the 2013 survey. Given the short time interval between survey distributions, it is unlikely that this discrepancy is wholly the result of change in use of this item of equipment. A contributory factor may be that some optometrists interpreted 'anterior segment imaging' as referring to more specialist systems e.g. OCT, and did not provide a positive response to this question to indicate use of conventional digital imaging. In an effort to ensure that data from different surveys are as comparable as possible, the data from previous surveys have been adjusted wherever possible to account for these variations in how questions were phrased. Finally, the frequency of use of equipment data quoted in Table 2.5 is based on those 416 respondents to the 2013 survey, and 753 respondents to the CoO 2014 Clinical Practice survey who answered this question. However, equivalent data quoted in the College of Optometrists 2007 survey are based on the percentage of the "base" figure of 2751 respondents who attempted the survey overall, a total which includes a proportion (more than 20% for some questions) who did not attempt individual questions. Therefore, the College of Optometrists 2007 figures have again been adjusted to give percentages based on those who answered each question in order to bring them into line with the current survey.

Despite these limitations, comparison between surveys reveals some interesting trends (Table 2.7), with the frequency of use of Goldmann/Perkins tonometry in community practices increasing from 47% in 1987/88 to 61% in 2007 and reaching 81% in 2013. NCT, introduced into the UK in the early 1970s, had increased from 44% in 1987/88 to become almost ubiquitous as early as 2001 when it was already in more than 85% of practices, a figure maintained in the 2013 survey. Even more popular were central visual field screeners with threshold control, which are now found in 100% of practices, having increased from around 40% in 1987/88. There has been a remarkable increase in the penetration of fundus photography into community practices. As recently as 2001 they were to be found in only approximately 17% of practices, but this proportion had increased dramatically to

approximately 66% in 2007, 74% in 2013 and further to 87% in 2014. Indirect evidence from Australia published in 2011, from a survey of management by optometrists of patients with diabetes, suggest that at least 55% of Australian optometrists use a fundus camera (Ting et al., 2011). Interestingly, there may be evidence to suggest a levelling off of the use of fundus cameras in the US, where the probability of a fundus photograph being taken by optometrists in glaucoma patients had reached a plateau by 2009 while the probability of the patient undergoing ocular imaging (e.g. OCT, SLO) by optometrists had doubled between 2001 and 2009 (Stein et al., 2012). Some of the factors that have contributed to these trends in equipment usage will be discussed in the following sections.

Item of equipment	**Frequency of respondents (%) in present survey (2014)** n=761 Response rate = 46%	**Frequency of respondents (%) in present survey (2013)** n=416 Response rate = 35%	**Frequency of respondents (%) in CoO 2007 Clinical Practice (CoO, 2008) survey** n=2751 Response rate = 30%*	**Frequency of respondents (%) in CoO 2001 Clinical Practice (CoO, 2001) survey** n=3618 Response rate = 46% *	**Frequency of respondents (%) in 1987/88 IGA survey (Tuck, 1988a, Tuck, 1988b, Tuck & Crick, 1989, Tuck & Crick, 1994a, Tuck & Crick, 1994b)** n=956 Response rate = 66%
Goldmann/ Perkins tonometer	----	81	61	48+	47^
Non-contact tonometer (NCT)	---	88	93	88+	44
Fundus photography	87	74	66~	17+~	N/A
Central visual field perimeter with threshold	100	98	N/A	N/A	41
Autorefractor	44	39	N/A	31	N/A

Table 2.7: Relative frequency of the use of equipment in community optometric practice in present and past surveys

** Data from the two CoO CP surveys have been modified wherever possible to reflect the differences in questions asked when compared with current survey.*

+Estimated figures. Actual figures are likely to be higher than this.

~ Refers to digital and film photography combined

^This figure is likely to include practices owning a Schiotz tonometer in addition to Goldmann and Perkins.

2.7.1 Changes in service provision

GOS provision was essentially uniform across the UK until approximately 10 years ago. However, NHS restructuring, together with the introduction of devolved powers to Scotland and Wales, have led to the development of a greater diversity of provision, with an emphasis on a less prescriptive approach to primary eyecare. These changes are exemplified by the new GOS contract in Scotland, first introduced in 2006, and the Welsh Eye Care Initiative (WECI) which commenced in 2003, and which has evolved into the Eye Health Examination Wales (EHEW), and more recently into the Welsh Eye Care Service (WECS). All optometrists in Scotland who wished to provide GOS services and those in Wales who joined WECI were obliged to provide services for which minimum standards of equipment were stipulated. In Scotland, under the new contract, NHS eye examinations are available to all individuals, not just those belonging to specified groups (i.e. all those over 60 years) as applies in the rest of the UK. Furthermore, the contract stipulates a revised fee structure which includes a fee for supplementary tests to review patients in certain clinical circumstances, notably to carry out Goldmann applanation tonometry, dilated fundus examination and threshold visual fields in glaucoma suspects. Funding was available from NHS Scotland to purchase the equipment needed to allow optometrists to meet the requirements of the new contract. Results from the current equipment survey reflect these GOS changes. The greatest increase in the use of Goldmann/ Perkins tonometry was reported by respondents working in Scotland, rising from 29% in 2001 (CoO, 2001) to 100% in the 2013 survey, compared with 81% for the UK as a whole. A lesser increase in the use of Goldmann/ Perkins tonometry was observed in optometrists working in Wales, rising from 70% in 2001 (CoO, 2001) to 100% in the 2013 survey. A geographical variation across the UK was reported in the 2007 College of Optometrists Clinical Practice survey where 42% of those who responded in England reported using applanation tonometry whereas in Scotland the equivalent figure was 97% (Parkins & Edgar, 2011). The Welsh Eye Health Examination (WEHE), and the PEARS schemes were introduced in 2003 under WECI. WEHE allowed predefined groups of patients considered at risk of eye disease to be eligible for a free eye examination. Optometrists providing WEHE and PEARS services are required to have a minimum standard of equipment, including contact tonometric devices (Sheen et al., 2009). Both the revised GOS services contract implemented in Scotland, and the Welsh PEARS/ WEHE initiatives have been shown to be clinically effective, allow more patients to be retained in community practice, and avoid unnecessary referrals to secondary care (Ang et al., 2009, Sheen et al., 2009).

Some variations between countries were observed for the use of specialist equipment, which may also reflect the differences outlined in the provision of services. In particular, fewer respondents to the 2013 and 2014 surveys from England & Northern Ireland reported using pachymetry and a goniolens than in Scotland. A greater proportion of optometrists working in Scotland reported using fundus photography in both surveys than from any other country. In the 2014 survey, approximately twice the number of optometrists working in Wales reported use of a contrast sensitivity chart compared with any other country. This is likely to be the result of an initiative by the Welsh government in 2004 to implement funded low vision services in optometry practices throughout Wales (Parkins et al., 2014). Participating practices are provided with a kit to the value of approximately £1000, which includes a Pelli-Robson contrast sensitivity chart (Charlton et al., 2011). No significant differences were observed between countries for the use of electronic record keeping or practice management software.

2.7.2 Type of practice

Equipment uptake can be influenced by the practice type, and examples emerging from our study were variations in the use of autorefractors, NCT and OCT with practice type (Figure 2.1 and 2.2). Autorefraction was introduced in the late 1960's and has since become an integral part of many optometric examinations. In our surveys 39% (2013) and 44% (2014) of practices used an autorefractor although, interestingly, autorefractor use is more common in Canada and the USA where they are used by over 75% of survey respondents (Stolee et al., 2011, AoA, 2012). Notably, in the current surveys a statistically significantly greater proportion of optometrists working in multiple/ group practices reported use of an autorefractor, electronic clinical recording (included in 2013 survey only) and computerized test charts when compared with independent practices. In contrast, contact tonometry and specialist diagnostic technologies such as OCT were more widely adopted in independent practices. These findings may reflect the centralized approach to equipment and IT purchase by multiple/ group practices, with standardized items distributed across practices. Furthermore, the patterns of use of these devices may be governed by how eye examinations are delivered in multiple/ group practices (e.g. multiple/ group practices may be more likely to employ optical assistants to undertake autorefraction as part of their standard pre-screening examination).

2.7.3 Involvement in enhanced and additional schemes for service provision

The publication of the Department of Health review of the GOS in England in 2007 provided another catalyst to change in the uptake of modern equipment and IT in community optometric practice (DoH, 2007). This review set out a three-tiered framework for the commissioning of primary care ophthalmic services. The first tier, or essential services which any eligible contractor must provide, includes the provision of NHS sight tests. The second tier includes additional services which all Primary Care Trusts had to commission, notably domiciliary services. However, it is the third tier, the enhanced services which Primary Care Trusts may choose to commission, that had the greatest potential to influence the equipment used in community optometric practice. Such services did exist pre-2007, for example a telephone survey undertaken in 2006 reported 14 community-based schemes for referral refinement or glaucoma monitoring (Vernon & Adair, 2010) but since 2007 there has been a steady increase in the number of locally commissioned enhanced schemes. This increase has been facilitated by input from the Local Optical Committee Support Unit (LOCSU) which has developed a series of pathways for common eye conditions delivering local eyecare services via Local Optical Committees across England. The extent of this expansion is exemplified by the fact that there was a total of 246 LOCSU enhanced schemes in England in July 2013 (LOCSU, 2013). Many other similar locally-led schemes are run in collaboration with eye hospitals. Enhanced schemes have included repeat measures schemes for glaucoma suspects (Parkins & Edgar, 2011), ocular hypertension and glaucoma referral refinement schemes (Henson et al., 2003, Bourne et al., 2010, Vernon & Adair, 2010). Schemes are not limited to glaucoma, however, and there are PEARS type schemes (NHS, 2010) and direct cataract referral schemes (Park et al., 2009, Amin, 2014).

All these enhanced/additional service schemes act as potential drivers for practice development, including purchases of advanced equipment and IT. There are obvious advantages to be gained from standardising the equipment used in primary and secondary care clinics to allow more informed comparisons to be made between clinical baseline measurements captured by optometrists and subsequent examinations performed in the hospital setting. Enhanced or additional/ separately contracted services were provided by 73% of our UK respondents to the 2013 survey, and 59% of respondents to the 2014 survey. The higher percentage in the 2013 survey probably reflects the different focus of the question in the two surveys. The question in the 2013 survey asked whether the practice participated in schemes, unlike the CoO Clinical Practice survey which asked about the individual optometrist's participation in schemes. Nevertheless, these figures are broadly comparable with those from a 2006 survey of US optometrists which reported 65% of their respondents

involved in glaucoma, AMD and retinopathy co-management with an ophthalmologist, and 84% who were co-managing cataract and refractive surgery (Soroka et al., 2006). In the 2013 and 2014 surveys, 29-30% of respondents reported involvement in glaucoma repeat measures schemes, with 22-24% involved in referral refinement schemes, and 11-12% in the monitoring of patients with ocular hypertension, suspect glaucoma or co-management of stable glaucoma in community practice. This exposure to enhanced schemes has led to an upgrade of equipment used by optometrists in practice, partly to meet the requirements of participation in schemes. A greater proportion of our UK respondents (2013 survey) providing enhanced or additional/separately contracted services reported using specialist items of equipment (e.g. OCT, pachymetry and goniolens) than those who did not provide these services (Figure 2.1). Furthermore, optometrists increasing involvement in community-based referral refinement schemes (Henson et al., 2003) or working part-time in general glaucoma outpatient clinics (Banes et al., 2000) or in optometry-led glaucoma assessment clinics in which optometrists examine glaucoma patients (Marks, 2007, Spry, 2008) exposes them to modern equipment for the detection of glaucoma which may encourage them to purchase similar equipment for use in their community practices.

2.7.4 Changes to glaucoma case detection and the influence of the NICE guideline.

Primary open angle glaucoma (POAG) and ocular hypertension (OHT) account for the largest proportion of review appointments in secondary ophthalmic care, with approximately 1 in 4 patients who attend outpatient clinics attending for glaucoma follow-up,(Spry et al., 1999) amounting in total to over 1 million outpatient visits per annum (NICE, 2009). Optometrists are responsible for generating approximately 95% of referrals for suspected glaucoma and OHT for ophthalmological opinion (Sheldrick et al., 1994, Bell & O'Brien, 1997, Bowling et al., 2005). Community optometrists typically rely on a triad of tests for glaucoma case-finding, comprising assessment of the optic nerve head for structural changes, evaluation of functional visual field loss, and measurement of intraocular pressure (Lawrenson, 2013). Glaucoma case-finding by optometrists presents a diagnostic challenge, as does monitoring for progression of glaucoma in secondary care. Many of the recent developments in equipment for ocular imaging, tonometry and perimetry have been driven by the need to improve glaucoma detection and management (e.g. SITA tests on the Humphrey® Field Analyzer/HFA™ (Carl Zeiss Meditec Inc.) (Bengtsson et al., 1997) Henson suite of perimeters (Edgar & Rudnicka, 2007), PASCAL® Dynamic Contour Tonometer (DCT, Swiss Microtechnology AG) and Ocular Response Analyser® (ORA, Reichert Inc.) tonometer (Kotecha, 2009). Optometrists are also aware of the potential risks resulting from failure to detect cases of glaucoma, with glaucoma-related cases

accounting for 30% of 50 consecutive clinico-legal cases involving optometrists reported in a study by Woodward in 2006 (Woodward, 2006). One driver for equipment purchases by optometrists, including automated perimeters, tonometers, OCTs and pachymeters, has been the desire to protect the optometrist in any potential clinico-legal cases. This is supported by the 69% of respondents to the current (2013) survey who agreed or strongly agreed that adoption of specialist equipment could generate results which could be used as evidence in their defence should a case be taken against them.

The College of Optometrists publishes guidance for UK optometrists on the examination of patients at risk of glaucoma based on the standard triad of tests (CoO, 2014a), and the joint guidance from the College of Optometrists and Royal College of Ophthalmologists gives advice on when to refer, based on the results of these three tests together with the patient's age and van Herick estimation of anterior chamber depth (CoO & RCOphth, 2010). There is evidence that the proportion of optometrists carrying out all three tests has increased in parallel with the increase in practices using this equipment revealed by Table 2.7. Moreover, 465 of 749 (62%) of respondents to the 2014 survey reported that they were 'likely' or 'very likely' to repeat optic disc assessment, intraocular pressure measurement and visual field assessment before referring a patient for further investigation. In a study of referrals from optometrists for suspected glaucoma published in 1999 only 15% of referrals contained results of all three standard tests (Theodossiades & Murdoch, 1999). A consistent increase in this proportion has been reported in recent studies e.g. 66% Lockwood et al. (Lockwood et al., 2010) and 77% Davey et al. (Davey et al., 2011). This increased use of modern equipment by optometrists might be expected to increase the quality of their glaucoma-related referrals. However, this is not necessarily the case, as Vernon reported in 1998, where an increase in those referrals for suspected glaucoma which included a visual field assessment from 28% to 48% over a 5-year period was associated with an increase in the false positive rate (Vernon, 1998). Similarly, Lockwood et al noted that although the number of optometrists carrying out a visual field test prior to referral for suspect glaucoma had increased greatly, the Positive Predictive Value (PPV) remained essentially unchanged (Lockwood et al., 2010). However, it should be noted that increasing the PPV above 40% will always be difficult for a disease with a prevalence as low as that of glaucoma whatever equipment is used (Lawrenson, 2013).

A survey of UK optometrists investigated barriers to glaucoma case-finding (Myint et al., 2010). Equipment issues was one of the four major barriers reported to glaucoma case-finding, being noted by 23% of respondents from England, 27% from Scotland, 21% from Wales and 13% from Northern Ireland. It is perhaps surprising that equipment was more of an issue in

Scotland than elsewhere, given the substantial equipment grants available in Scotland. However, Scottish optometrists were concerned more with the absence of more specialized items of equipment, such as pachymeters and gonioscopes, rather than equipment associated with the usual triad of tests for glaucoma. The 2013 survey aimed to identify the equipment used in community practices but did not investigate specifically which items of equipment in the practice were usually employed in the investigation of either patients in general or specific groups of patients suspected of having a particular condition. This latter issue was the focus of another national survey by Myint et al (Myint et al., 2011), who investigated the usual equipment optometrists would use in the investigation of a patient who was a glaucoma suspect. Although the 2013 survey identified that Goldmann/Perkins tonometers (81%) and NCTs (88%) were used almost equally in practice (Table 2.7), when the question asked was a different one, i.e. the usual method of tonometry carried out for a glaucoma suspect, the vast majority (78%) opted for the NCT with only 16% routinely using Goldmann or Perkins applanation tonometry (Myint et al., 2011). A similar, although less marked, trend was observed in the 2014 CoO Clinical Practice survey, in which NCTs were used by 82% of respondents to routinely measure IOP to screen for glaucoma, compared with 55% of respondents who indicated use of Goldmann or Perkins applanation tonometry. It should be noted, however, that the Myint survey was conducted before the publication of the NICE guideline, which reinforces the place of GAT as the current clinical reference standard (NICE, 2009). Despite this, in a post-NICE study of glaucoma referrals to the NHS, Khan et al. (Khan et al., 2012) obtained a similar figure to Myint et al for the use of NCT, which was the tonometer used in almost 75% of referrals.

The publication of the NICE Guidelines for 'Glaucoma diagnosis and management of chronic open angle glaucoma and ocular hypertension' in April 2009 was another important driver for the development of UK optometric practice (NICE, 2009). Notable features of the Guidelines were the validation of a role for optometrists that extended beyond the traditional activities of glaucoma case-finding and detection, and provision of further guidelines for optometrists when not working under the supervision of a consultant ophthalmologist (NICE, 2009). Although the Guidelines provided the possibility for optometrists to extend their traditional roles into, for example, the diagnosis of ocular hypertension and suspect glaucoma (Harper, 2011), they also unintentionally led to an unprecedented increase in the number of glaucoma-related referrals (Edgar et al., 2010, Shah & Murdoch, 2011). For many of these new roles validated by NICE it is essential that optometrists should be able to perform skills such as Goldmann applanation tonometry, gonioscopy and pachymetry. Interestingly, gonioscopy use by optometrists has remained relatively static between 9% (2014) and 15% (2013) compared

with 12% in the Myint et al 2008 survey (Myint et al., 2011), while pachymetry use has more than doubled from 7% in 2008 to 15-17% in 2014 and 2013 respectively. This may reflect the increasing importance placed on central corneal thickness (CCT) when interpreting IOP measurements (CoO and RCOphth, 2010) and the ease with which pachymetry can be included into a routine eye examination. Furthermore, the Ocular Hypertension Treatment Study (OHTS) has highlighted the importance of measuring CCT for the care of OHT, identifying CCT as a powerful predictor for the development of primary open angle glaucoma (Gordon et al., 2002). Increased use of pachymetry by optometrists is also reported in New Zealand where 43% of optometrists reported that the pachymeter was the item of specialist equipment they were likely to acquire in the next five years (Heidarian & Mason, 2013). In 2011 the NICE Glaucoma quality standard was published and recommended that local agreements should be put in place for repeat measures and glaucoma referral refinement (Lawrenson, 2013). All these NICE-stimulated developments have contributed to increasing the number of optometrists working in both community enhanced schemes and in the HES, with the potential impact on equipment purchase already discussed. Improvement in optometrists' equipment and clinical skills are benefits that have emerged from the NICE guidelines and related publications. Some patients may also have benefitted, with one study reporting increasing absolute numbers of patients detected with glaucoma, and more patients being diagnosed with early disease following the introduction of the NICE referral guidelines (de Silva et al., 2013).

2.7.5 Scope for enhanced diagnosis provided by use of OCT.

OCT was first described by Huang in 1991 and this technique has many applications relevant to optometry, including the detection and monitoring of retinal and macular disease and glaucoma. OCT imaging has been established as a clinical diagnostic tool for the non-invasive detection of disorders of the macula and optic nerve that may be difficult to observe using conventional viewing techniques (Chen & Lee, 2007). The upsurge in interest in OCT among UK community optometrists has seen a remarkable rise in its use from a very low base. OCT was available to only 2% of optometrists in a survey conducted in 2008 (Myint et al., 2011), however by 2013 respondents were reporting use in 15% of practices, and in 2014 18% of optometrists/non-optometric personnel were using OCT. Furthermore, OCT was by far the most popular item of specialist equipment in the 2013 survey that respondents anticipated purchasing within the next year (36/84 or 43%). Interestingly, practitioners who used OCT were also more likely to use other specialist equipment, and to provide enhanced or additionally/separately contracted services than those who did not use OCT. A feature of OCT

is that the information derived from a cross-sectional OCT image of the macula may be used by optometrists to screen for early macular disease and, in particular, exudative AMD. OCT has been introduced into shared care schemes in the UK and favourable outcomes of a pilot UK teleophthalmology service based on OCT images have been reported (Kelly et al., 2011). In this study OCT images were captured by one community optometrist and the sample contained 50 patients with a range of retinal conditions. The quality of the images in every case was rated by the ophthalmologists to be at least as good as those recorded in the hospital. Teleophthalmology is an approach that can facilitate prompt responses and in this study the HES ophthalmologists provided responses to the community optometrist or to the patient within the next day in 96% of cases. Notably, the ophthalmologists were content for more than one third of the cases to be managed in community optometry, avoiding unnecessary referrals to secondary care. Fast-track referral services for exudative AMD were used by almost 50% of respondents in the current study, and there is enormous potential to introduce OCT into these schemes.

The rate at which the use of OCT in community optometric practice is increasing suggests it is possible that OCT may follow the example of fundus photography and eventually progress from being classified as an item of specialist equipment to become so widespread in community practices that it can be regarded as almost a standard item. An increase in the use of specialist imaging to check the patient's optic disc to screen for glaucoma was observed from 5% in 2007 (CoO, 2008) up to 15% in 2014. Following the introduction of the fundus camera to clinical practice, evidence soon emerged that posterior segment photography for evaluating and monitoring eye disease permits better documentation, study and monitoring of clinical features (Harding et al., 1995, Lin et al., 2002, Pirbhai et al., 2005, Jain et al., 2006). Early use of film imaging was rapidly superseded by digital imaging, affording the advantage of immediate analysis and facilitating easier storage of data. Optometrists became aware of these advantages and began to invest in fundus cameras from the 1990s onwards. By the time of the 2001 College of Optometrists survey approximately 17% of practices used a fundus camera, increasing to 74% of practices in 2013, and 87% of optometrists/non-optometric personnel in 2014. This rapid increase was partly due to some multiples/ groups making the investment in fundus cameras in all their practices. Further impetus to the advance of fundus cameras came from the introduction in Scotland in April 2009 of NHS-funded digital fundus imaging for patients aged 60 years of age or older, with funding to assist with the purchase of this equipment, providing a further boost to the number of fundus cameras in UK practices.

Two other imaging technologies which can be used for the detection of glaucoma: the SLP (e.g. GDxPro^{TM} (Carl Zeiss Meditec Inc.) and SLO (e.g. Heidelberg Retina Tomograph (HRT, Heidelberg Engineering GmbH)) have been used by community optometrists. In 2007 the SLP (GDx) and SLO (HRT) were available to 3% and 2% of optometrists respectively. Unlike OCT, neither SLP nor SLO have gained significant popularity among UK optometry since 2007. The diagnostic capabilities of specialist imaging for the detection of glaucoma have been extensively evaluated, but research establishing how these data can be integrated for use by optometrists is lacking. A literature search revealed a single study in which suprathreshold visual field assessment was substituted by the HRT II to evaluate the effect on glaucoma case-detection by optometrists. The authors did not observe an improvement in the ability of optometrists to correctly identify subjects with glaucoma using the advanced technology (Ieong et al., 2003). When the findings from the current study are compared with those of international surveys of optometrists, it is apparent that preferences for the use of specialist imaging differs widely between countries. In the United States, the SLO is the most popular specialist imaging technology, with almost 1 in 2 optometrists surveyed reporting owning this device (AoA, 2012), while in Australia, 23-32% of optometrists reported use of OCT in a 2013 survey (Jamous et al., 2014). An earlier survey undertaken in New Zealand identified the SLO as the second most popular item of equipment that optometrists were most likely to acquire over the next five years (Heidarian & Mason, 2013). In contrast, UK-based surveys between 2007 and 2014 indicate that only 2% to 4% of optometrists use a SLO in practice (CoO, 2001, CoO, 2008, Myint et al., 2011). Indirect evidence for the increased use of ocular imaging devices in US optometric practices emerges from a US analysis of diagnostic tests carried out on glaucoma patients and suspects. Comparing 2009 with 2001, the odds ratios of a glaucoma patient or a glaucoma suspect undergoing ocular imaging by an optometrist (method not stipulated) were 2.53 (CI 2.22–2.88) and 1.82 (CI 1.69–1.97) respectively (Stein et al., 2012).

2.7.6 IT in optometric practice (2013 survey)

There has been a significant move towards adoption of electronic patient record (EPR) systems and practice management systems by UK optometrists, evident from the 80% of practices in the current survey with access to these systems. Clinical record keeping is a topic in the College of Optometrists "*Guidance for professional practice*" (CoO, 2014d). The guideline in Section – *Patient records* states "You must keep full, accurate and clear patient records, made at the time of the examination, which provide a history of patient care, including referrals." There are also contractual obligations as regards record keeping imposed on contractors under the GOS Terms of Service (NHS, 2008). Electronic patient records undoubtedly facilitate the

maintenance of legible records and easier storage of data. They also have potential for use as clinical guides by prompting the clinician to ask follow-up questions and perform tests based on the patient's presenting complaint. Among the 2013 survey sample, 39% of practices described themselves as "paperless". Previous UK data on paperless practices is lacking but data from the 2012 American Optometric Association (AOA) survey gives a useful comparator. The AOA survey uses the term "Complete electronic health records (EHR)" to incorporate both electronic record cards and electronic patient management systems, and is taken by the authors to be equivalent to "paperless" practice. Using this definition of paperless practice the proportion of paperless US practices was 49% in 2012 having increased from 41% in the previous AOA survey in 2011, with a marked increase from 2005 US data which estimated that only 5% of practices were paperless (Pieper, 2005). It is perhaps surprising that paperless practice is almost as common in the UK as the US, especially since government financial support for adopting EHRs is provided in the US, together with the threat of penalties for non-compliance. Although there are benefits from electronic recording of patient data in eye care there are also challenges, for example electronic patient record systems are also required to accommodate the entry of clinical diagrams, which can be complex. In free-text survey responses from the current survey there were comments on the difficulty of drawing clinical features, using shorthand, or referring to previous recordings when using electronic patient records, with some respondents raising the suggestion of using an iPad to record notes.

Electronic transmission provides a more efficient means of transferring good quality data from automated perimetry and/or specialist diagnostic tests than paper copies. For optometric practice this is particularly relevant for referrals to secondary care. However, the vast majority of referral or notification letters are still generated using a standard or locally adapted form (e.g. GOS 18), with relatively few optometrists using electronic referrals when not part of an enhanced (locally commissioned) or separately contracted service. NHSmail is a secure national email and directory service available to all NHS staff in secondary care hospital units, and more recently to optometrists in Scotland. The system requires access to N3, the national network replacing the earlier NHSnet and approved for the secure transmission of patient data including referrals and reports. However, NHSmail was not widely used by optometrists in England, Wales and Northern Ireland at the time of the survey, possibly accounting for the low reported use of electronic referrals in our cohort (20%). Kelly et al note that the availability of NHSmail to the profession should be more widely publicised and adopted (Kelly et al., 2011). The benefits of electronic referrals in optometry have been established. In a well-designed pilot study in Fife, the use of a direct electronic referral system, which included transfer of images from optometric practice followed by virtual review of the referrals by a consultant

ophthalmologist, was shown to be safe, fast, efficient, and clinically accurate in most cases (Cameron et al., 2009). Notably, in this study 37% of unnecessary referrals to secondary care were avoided. This successful pilot scheme has been extended across the Fife region and has resulted in reductions in waiting times, in the number of unnecessary referrals, and reductions in patients failing to attend for their appointments which was attributed to the reduced waiting times (Borooah et al., 2013, Khan et al., 2014). Potential cost savings have also been demonstrated but establishing the cost-effectiveness of referral systems of this type is a complex health economics challenge as it is difficult to isolate savings attributed to the use of an electronic referral system alone. By including mandatory fields, standardized electronic referrals may also be used to improve the quality of referrals to secondary care (e.g. reporting on the triad of tests when glaucoma is suspected). The use of electronic medical records could develop into an EHR system in which all medical data are stored centrally. EHRs can improve the efficiency of healthcare by avoiding duplicate testing, and allowing all clinicians to access medical history that may be relevant to eye conditions (Bates & Gawande, 2003, Menachemi & Brooks, 2006, Chiang et al., 2008).

2.7.7 Views and attitudes regarding equipment and IT (2013 survey)

In general the responses given to the 2013 survey statements which invited optometrists' views and attitudes regarding the use of specialist equipment were most positive. For example, 95% of optometrists 'agreed' or 'strongly agreed' that specialist equipment 'enhanced clinical assessment, providing a diagnostic tool to aid management and referral decision-making'. Similar views were obtained from both a recent survey in New Zealand in which 89% of optometrists reported improved patient care as a benefit of health IT and comparable findings (81%) emerged from a US survey (Cole, 2011). Using the same aggregation of results, a similarly high percentage (81% - 90%) of UK optometrists agreed that the use of specialist equipment permitted increased involvement in referral refinement and/ or co-management schemes, and provided an opportunity to both promote the practice and build patient loyalty to the practice. However, the responses also highlighted the negative financial impact of purchasing and maintaining specialist equipment (77% agreed or strongly agreed), a trend which was observed throughout comments detailed in the free-text boxes. Eight respondents, seven from England and one from Northern Ireland commented on the lack of adequate National Health Service (NHS) funding and fee provision for supplementary testing. One respondent stated that NHS fees 'bear no relation to the standard of examination provided by optometrists and the time taken', with another respondent commenting that 'England is falling behind Scotland and Wales'. Recouping equipment costs often requires

patients to be charged for the use of specialist services, which a few respondents stated to be difficult when 'patients are not always willing to pay', particularly when other 'practices offer similar services free of charge'. Bosanquet highlighted the situation in which NHS sight tests are only viable when subsidized by private patients who purchase spectacles and appliances (Bosanquet, 2010). This was attributed to underfunding of sight tests in England and Wales, supported by evidence that overall expenditure on GOS has fallen in real terms since the 1950's, a situation not common to any other service provided across the NHS (Bosanquet, 2010). Concerns about costs are not limited to UK optometrists, as for optometrists in New Zealand costs was the second most commonly stated barrier to adoption of specialist equipment and IT (Heidarian & Mason, 2013).

Interestingly, no statistically significant difference was observed between the proportions of respondents in 2013 reporting financial issues as a barrier to the uptake of equipment in England and Scotland, which was perhaps surprising given the different modes of GOS provision which apply. This contrasts with Myint et al's 2011 study of barriers to detection of POAG in which, although financial issues was one of the four main barriers reported, significantly fewer optometrists in Scotland (34%) reported finance as a barrier than did their English counterparts (50%) (Myint et al., 2010). However, the barriers question regarding finance referred to practice finances in general and was not limited to equipment as in the current survey, so the higher GOS fees in Scotland could have influenced this 2011 finding. Optometry Scotland, which develops and represents the views of the entire optometry sector in Scotland, negotiated two equipment grants to the sum of £8,000 per practice in 2006 and £10,000 per practice in 2008, plus a £1 million training grant (OptometryScotland, 2014). In comparison, optometrists working in England and Wales do not receive funding for equipment, or payment for supplementary repeat testing from the NHS. Even though optometrists can charge patients additional fees for the use of specialist diagnostic equipment, the volume of patients may be insufficient to justify the initial and ongoing investment costs. Another current survey question which alluded to costs was the statement relating to operator training being "inconvenient, time consuming and a drain on resources". Responses were more equivocal to this statement than others regarding equipment, with one third of respondents neither agreeing nor disagreeing. On balance there was more disagreement (42%) than agreement (25%) with this statement, suggesting that the impact of training to use equipment was not a major deterrent to equipment purchase in our sample.

A total of 69% of respondents agreed or strongly agreed that results from specialist equipment could be used as part of the optometrist's defence in any clinico-legal cases. There was minimal disagreement with this statement but 29% of optometrists took the neutral view ("neither agree nor disagree"). This could indicate doubt among these respondees as to whether results of some of these specialist tests would be admissible as evidence. A concern sometimes expressed regarding new specialist equipment is that it can replace existing core skills, thereby reducing the value of optometric qualifications e.g. the use of OCT by optometrists could over time replace assessment of the optic nerve head by ophthalmoscopy. There was little evidence to suggest this is a concern within the survey sample as only 10% agreed with a statement that core skills could be reduced by new equipment.

Views on statements relating to IT in optometric practice were more mixed. There was widespread agreement with the statements that adoption of IT facilitates administrative flow (79%) and creates the impression that the practice is more 'state of the art' (85%). There is probably an element of understandable practice self-interest here but if this is the case then it does not appear to be a purely UK phenomenon because in the New Zealand survey the vast majority (98%) of their respondents believed that health IT in their practices increased patient confidence that their practice was "state-of-the-art" (Heidarian & Mason, 2013). In the 2013 survey, enthusiasm was more guarded regarding the statement that IT "enables secure exchange of health information between primary and secondary care" (with 47% agreement, 19% disagreement and 34% neutral), with the absence of a secure N3 network connection to the NHS being a possible contributory factor to this lack of agreement.

The major negative view on IT related to the need for frequent updates and technical support, a view which found agreement with 76% of respondents and with which only 5% disagreed. Technology updates were the major barrier to health IT adoption reported by optometrists in New Zealand (Heidarian & Mason, 2013). There is clearly a willingness among UK optometrists to learn new IT skills, as evidenced by the minority (21%) of the sample who agreed that they found it inconvenient to learn new IT skills and to operate management systems or software tools.

There was little agreement over the statement that IT reduces the time taken to record information for a routine patient (37% agreed, 31% disagreed, with 31% taking the neutral position). This suggests that on average the time taken to record data for a routine optometric eye examination is probably fairly similar with each of the two methods, which is consistent with the finding in a time and motion study that there was no significant difference between

the time taken for paper-based and electronic optometric record keeping (Shabbir et al., 2010). The speed of ophthalmic documentation has also been observed to be slower for keyboard and mouse electronic strategies when compared with paper-based recording (Chan et al., 2013). McVeigh et al. compared the use of an EHR and clinical automation with health IT advancements with traditional practice modes in an optometric clinic (McVeigh et al., 2008). No statistically significant difference was found between the automated and traditional modes for the authors' measure of efficiency, which was the time taken for different aspects of the patient journey. The transfer of paper records to an electronic file can in itself be a time-consuming and costly process, and this must be considered when weighing up the costs and benefits of IT in healthcare, as it is a cost which is additional to the initial high investment required for software programs. Responses were equally divided regarding the statements that (a) there is a greater risk of losing data with electronic records (35% agreed, 32% disagreed with 33% neutral) and (b) that there is a security risk associated with storage of confidential patient information online or on databases (32% agreed, 26% disagreed with 42% neutral). Free text comments noted that electronic data must be guarded against destruction, and viruses, with some clinicians fearing loss of data and the implications of complete failure (e.g. power loss) in a practice heavily reliant on IT for daily administration. Another emerging theme from the free-text response analysis (n=10) was the issue of training optometrists to proficiently operate specialist equipment and IT, as well as training them to interpret the results correctly, with suggestions that optometric training institutions may need to make amendments to their curricula to address this training need. A survey by Stolee et al. in Canada highlighted the feeling amongst some optometrists of being ill-prepared for the use of IT in practice (Stolee et al., 2011). A further scoping exercise surveyed an academic staff and student group, including representatives from optometry, to determine whether IT training was adequate. Staff survey results suggested that clinical systems training was not necessarily available for many students in placements (where placements are roughly equivalent to the UK pre-registration period), and 61% of students asked for further training in IT systems during their higher education (Bartholomew & Heart, 2011). Recently qualified UK optometrists are expected to be more proficient with operating IT systems as basic IT skills are honed during education in early years, as well as during undergraduate training. One challenge faced by educationalists and the profession alike is that while an optometrist may be exposed to particular technologies during the course of their university training, this may not necessarily prepare them adequately for community practice, especially since a number of different electronic record keeping systems are used. Ongoing instrument-specific training is an inevitable requirement, particularly in practices where locum staff are employed to cover short-term absences or when trained non-optometric staff perform pre-screening duties.

There is scope for optometry CET to target these training issues, particularly with regard to optometrists who qualified when the undergraduate curricula may not have covered these topics.

It has been argued that the use of electronic records could have a negative impact on patient-practitioner interaction and relations, and this statement was tested in the current survey with 25% in agreement, 42% disagreeing and one third neutral. The potential risk is that entering examination results on a computer can interrupt eye contact with the patient and generally interrupt the flow of the examination to a greater extent than would occur with the traditional methods of entering data by hand into paper-based records. For three quarters of the survey sample this was not regarded as a concern but impairment of the patient-practitioner relationship has been reported in other surveys to be an issue associated with the use of electronic patient records (Heidarian & Mason, 2013).

The generally positive views of optometrists to the 2013 survey regarding new equipment and the more guarded but still mainly positive attitudes to IT suggest a profession willing and able to embrace new technology and appreciate the benefits it can bring in both clinical and financial terms. As noted in the limitations section below, the nature of a survey on technology is that those most likely to respond are those with a particular enthusiasm for new technology. This could lead to a positive bias towards IT among the sample. The author attempted to reduce this bias as much as possible by making the survey available in both paper form and online, to encourage those less technologically adept or with particular antipathy to new technologies to complete the survey on paper.

2.7.8 Strengths and limitations

These surveys were distributed to a randomized group of registrants listed on the College of Optometrists' membership database in an effort to achieve a representative sample of optometrists practising in the UK. The survey response rates were 35% (2013) and 46% (2014), surpassing the anticipated return based on experience from previous questionnaires. For the 2013 survey, optometrists who had either last worked in community practice more than five years prior to the survey date, or who had never worked in this capacity (e.g. hospital optometrists) did not complete the bulk of the survey and their results are not presented in this thesis. However, they represented only 3.7% (16/432) of the response sample. While the demographic profile of respondents to the 2013 and 2014 surveys broadly reflects that of optometrists listed on the GOC database in terms of gender and geographical distribution, the

study findings should be considered in light of potential bias inherent in cross-sectional survey designs.

One shortcoming is that respondents self-selected to participate and it is probable that optometrists motivated by an interest in ophthalmic instrumentation were more likely to complete the 2013 equipment questionnaire, leading to a possible overestimation in the use of equipment/ IT. Also, there is some evidence of sampling bias from the higher proportion of independent practices represented in the samples than in the UK as a whole. It is also unclear whether differences between the 2013 and 2014 survey responses represent true changing trends (e.g. increase in the use of conventional and specialist imaging). These observations may also be a function of minor differences in the phrasing of questions, sampling of members from the College of Optometrists' database or survey distribution methods. In particular, the survey of the use of equipment and IT (2013) sought to determine whether items were used at the practice level. However, questions on the use of equipment in the CoO Clinical Practice surveys (2001, 2007 and 2014) identified whether items were used by the individual respondent or by non-optometric personnel, but did not account for use by other optometrists in the practice. It follows, therefore, that CoO CP survey's results may underestimate the use of equipment in comparison with the 2013 survey. As an example of a variation in sampling methods, the 2014 CoO Clinical Practice survey was re-sent as a paper-version to all optometrists who had not responded online, but this method was not used for the earlier 2013 survey.

Optometrists completing the surveys were asked to respond based on equipment used in their practice and it is probable that a number of the 416 (2013) and 753 (2014) optometrists who responded may have been responding on behalf of the same practice. The anonymous nature of the survey makes it impossible to quantify this effect but the numbers affected are likely to be small and to have limited influence on the results or conclusions of the surveys.

Shah et al (2010) noted that questionnaires are prone to sampling bias because more conscientious practitioners will be more likely to complete the questionnaire (Shah et al., 2010). They comment that another potential source of bias is that human nature may induce replies which will report higher standards of practice than may actually apply. There is evidence to support this view in the optometric domain from Theodossiades et al. 2012, who discovered that self-reporting frequently overestimates routine tests undertaken in practice, notably for non-mandatory tests such as visual fields (Theodossiades et al., 2012). This was established by comparing reported practice in an interview with optometrists with their actual

practice, as determined by unannounced standardised patients. Further supporting evidence in the same study came from comparison of results of a national survey in which reported information included in referral letters did not correspond with information actually included in referral letters for tests other than IOP measurement.

2.7.9 Conclusions

To our knowledge, this is the first snapshot of optometry practices in the UK to address the rationale behind the adoption of new technology, and to explore its impact on community practices. Optometrists in our survey samples are increasingly employing newer equipment and IT services to enhance patient care and for practice management. In particular, there was widespread adoption of anterior and posterior digital imaging, with increasing investment in newer technologies, notably OCT, and use of specialist imaging in glaucoma case-finding. The use of specialist equipment is inextricably linked with the need for IT to both collect and analyse clinical data. Optometrists appreciate the benefits of specialist equipment for enhancing clinical assessment and diagnosis, for allowing increased involvement in enhanced services, as evidence for the defence in optico-legal cases, in practice marketing and promotion of patient loyalty. The use of IT facilitates administrative flow and helps to project a state-of-the-art image of the practice. Financial issues remain the main barrier to use of equipment and IT. Questions remain as to whether investment in equipment and IT is cost-effective, how it may be best used for community optometric practice, and whether optometrists are trained sufficiently to use these new services?

Chapter 3: Performance of advanced technologies to improve case-detection of primary open angle glaucoma (POAG)

3.1. Introduction

Glaucoma is the second leading cause of blindness worldwide, with OAG being the commonest cause (Quigley & Broman, 2006, Tham et al., 2014). On a global scale, the number of people with glaucoma (aged 40 to 80 years) is projected to increase by 74% from 64.3 million in 2013 to 111.8 million in 2040 (Tham et al., 2014). The estimated UK prevalence of POAG is 2.1%, rising from 0.3% in people aged 40 years to 3.3% in people aged 70 years (Burr et al., 2007). Each year in the UK, it is estimated that 11,000 new cases of OAG are diagnosed in people aged 40 to 70 years (Burr et al., 2007). However, epidemiological studies in developed countries have demonstrated that approximately half of the population affected by OAG remains undetected using current screening strategies (Tielsch et al., 1991a, Klein et al., 1992, Mitchell et al., 1996, Quigley & Vitale, 1997, Wensor et al., 1998).

POAG is characterised by excavation or cupping of the optic nerve head, often termed 'glaucomatous optic neuropathy' (GON), together with an open and normal appearance of the anterior chamber angle observed using gonioscopy. Elevated IOP above 21mmHg (representing 2 standard deviations above the population mean, and assuming a Gaussian distribution) is no longer included in the definition of POAG, as up to 50% of newly diagnosed glaucoma cases have an IOP ≤21mmHg (Leske, 1983). Early detection and treatment reduces the progression of glaucomatous vision loss and visual field defects (AGIS, 2000, Gordon et al., 2002, Heijl et al., 2002). Treatment for OAG aims to reduce IOP to a level where further visual loss can be prevented, using medical, laser or surgical interventions. However, the cost of medical drug treatments for OAG and OHT has seen an increase of 88% from £55.2 million in 2000 rising to £103.7 million in 2012 (Connor & Fraser, 2014). Potential cost savings may be realised by early identification and treatment of glaucoma, given that use of resources and the direct cost of glaucoma management increase with worsening severity of disease (Traverso et al., 2005, Lee et al., 2006b). This has led researchers to evaluate whether OAG can be identified using population-based screening. OAG satisfies suitability criteria with reference to the condition and treatment that are ideally required to initiate a screening programme (Wilson & Junger, 1968). However, large-scale population screening of POAG selected on the basis of age alone is unlikely to be cost-effective, although there is stronger evidence in support of targeted screening of at-risk individuals (Burr et al., 2007). Moreover, detection of

OAG presents a diagnostic challenge as no single test, used alone or in combination, provides sufficiently high accuracy (Burr et al., 2007).

Current practice for identification of POAG uses a combination of tests comprising optic disc examination for structural changes, evaluation of functional visual field loss, and measurement of intraocular pressure. Comprehensive examination for structural damage requires the use of binocular indirect ophthalmoscopy through a dilated pupil. However, the technique is subjective and prone to intra- and inter-observer variability in observations. This is partly attributed to the overlap in spectrum of optic disc appearance between glaucoma, suspect glaucoma and normal eyes. Over time, technologies to provide more objective examination techniques for structural damage to the optic nerve have seen rapid advances from film-based photography to laser-based devices such as Optical Coherence Tomography (OCT), which is capable of generating 3-dimensional images of ocular structures. The further development and application of segmentation algorithms to OCT cross-sections enables derivation of dimensional data for early detection and monitoring of glaucoma. Previous studies have demonstrated the effectiveness of RNFL thickness and other morphological parameters of the optic nerve head to detect OAG (Bussel et al., 2014). Zeimer et al. first described reduction in macular thickness in glaucoma using the retinal thickness analyser (Zeimer et al., 1998). The macula region contains a high density of cells comprising over 50% of all retinal ganglion cells (Curcio & Allen, 1990). Glaucomatous loss has been shown to preferentially affect innermost retinal layers with ganglion cell loss occurring early in the clinical course of the disease (Glovinsky et al., 1991, Quigley, 1995, Harwerth et al., 1999, Medeiros et al., 2013a, Tatham et al., 2013). Outer retinal layers are less affected by glaucoma and account for two-thirds of the full retinal thickness, potentially confounding diagnostic capability to detect glaucoma if also incorporated into measurements (Tan et al., 2009). It is therefore unsurprising that superior diagnostic performance of inner macular retinal thickness has been observed when compared with full thickness parameters (Tan et al., 2009, Schulze et al., 2011, Yoon et al., 2014). In seeking to improve sensitivity to detect glaucomatous damage, clinically detectable changes in macular inner retinal thickness are identified by combining data from three retinal layers forming the 'ganglion cell complex': the retinal nerve fibre layer representing ganglion cell axons, ganglion cell layer (ganglion cell bodies), and inner plexiform layer (ganglion cell dendrites).

Currently, static standard automated perimetry (SAP) using the HFA in threshold mode is the acknowledged reference standard for the assessment of visual function in glaucoma. However, the HFA in threshold mode is not suitable for screening as the test is time-consuming, a proportion of the population are unable to provide a reliable result, and there is a lack of agreement as to what constitutes a test failure. Moreover, SAP assesses the function of three subtypes of retinal ganglion cells: magnocellular, koniocellular and parvocellular. Early histological studies investigating the pathogenesis of glaucoma have consistently reported preferential damage to large diameter cells, namely parasol ganglion or M_y cells (Quigley et al., 1987, Quigley et al., 1988, Kerrigan-Baumrind et al., 2000), which are responsible for mediating motion detection and scotopic vision. This has led to the development of psychophysical tests aimed to isolate M_y cell activity and provide a more sensitive indicator of early functional loss from glaucoma than SAP. These newer technologies include the Frequency doubling (FDT) perimeter, and the Moorfields motion displacement threshold (MMDT) test. Suprathreshold FDT algorithms have shown favourable diagnostic discrimination for OAG when used in community-based settings (Burr et al., 2007), but evidence for use of MMDT in this setting is lacking. Goldmann applanation tonometry (GAT) is the current reference standard for measurement of IOP. However, overestimation of IOP in eyes with thicker central corneas was documented as early as 1975 (Ehlers et al., 1975). It has since been proposed that variability of IOP measurements between individuals may also be attributed to the influence of other biomechanical properties of the cornea e.g. viscoelasticity, rigidity (stiffness) (Liu & Roberts, 2005, Tonnu et al., 2005). As a result, a new generation of 'dynamic' tonometers has been developed, for example the Ocular Response Analyser (ORA, Reichert), which is designed to measure and adjust IOP readings for the viscoelastic properties of the cornea, termed 'corneal hysteresis' (CH). Lower CH has been consistently reported among individuals diagnosed with OAG (Wells et al., 2008, Mangouritsas et al., 2009, Abitbol et al., 2010, Anand et al., 2010), but few researchers have addressed use of the index to improve detection of OAG.

In the UK, optometrists play a key role in the detection of glaucoma in primary care, and are responsible for generating in excess of 95% of referrals for suspected glaucoma and OHT for ophthalmological opinion (Sheldrick et al., 1994, Bell & O'Brien, 1997, Bowling et al., 2005). Optometrists identify persons suspected of having OAG using opportunistic surveillance when people self-select to attend for eye examinations in community practice. The College of Optometrists publish guidance for UK optometrists on the examination of patients at risk of glaucoma based on the standard triad of tests (CoO, 2014a), but there is no statutory requirement to perform visual field assessment and IOP measurement during an eye

examination. The decision to refer a patient suspected of glaucoma to secondary care is usually based on one or more abnormal clinical test results, together with the presence of known risk factors for the disease, and guidelines disseminated by local ophthalmologists, optometric bodies and/ or national publications (e.g. NICE, 2009). The difficulty in detecting glaucoma is evidenced by the lack of a single test identified as optimal for differentiating individuals with and without OAG. The positive predictive value (PPV) of referrals by optometrists for suspected glaucoma ranges between 37% and 43% (Newman et al., 1998, Theodossiades & Murdoch, 1999, Lockwood et al., 2010). Although these PPVs may appear modest at first glance, few screening tests could achieve the sensitivity and specificity required to produce higher PPVs for a disease with only 2% prevalence. In the context of case-finding for a low prevalence disease in the general population, an ideal screening test would need to be simple, fast and combine high specificity, ideally above 90%, with an acceptably high sensitivity. Researchers have also demonstrated the benefit of combining structural data of the optic nerve head with visual function estimates to enhance differentiation between glaucomatous and normal subjects (Caprioli, 1992, Mardin et al., 2006, Shah et al., 2006, Hong et al., 2007, Bowd et al., 2008, Mwanza et al., 2014).

A national survey of diagnostic tests used for the detection of COAG demonstrated that UK community optometrists are well equipped for case-finding (Myint et al., 2011). Moreover, in Chapter 2, the increase in adoption of specialist equipment by community optometrists was highlighted. In particular, use of OCT has seen a remarkable rise from a low base of 2% in a 2008 survey (Myint et al., 2011) to 18% (CP 2014 survey (Chapter 2), unpublished data). However, the availability of standardized protocols for using OCT to detect and monitor glaucoma is lacking. Literature searching reveals a number of studies that evaluate diagnostic accuracy of traditional and newer structural and functional technologies for the detection of glaucoma. However, in many cases, reliability and applicability of study findings are limited by poor methodology, with failure to satisfy the quality assessment of diagnostic accuracy studies (QUADAS) criteria, a tool used for the quality assessment of studies of diagnostic accuracy included in systematic reviews (Whiting et al., 2003). When a diagnostic test is first introduced, initial validation is usually in the form of a case-control study, focused on whether the test can be used to detect the condition of interest. However, sampling a cohort comprising subjects clearly divided into disease positive and negative status risks overestimation of diagnostic performance (Medeiros et al., 2007). This is compounded further by frequent sampling of subjects from enriched hospital settings, leading to greater numbers of subjects with more advanced disease, and higher levels of perimetric experience, compared with screening populations. For this reason, the next step in the validation of a screening test

would be a cross-sectional study, which includes subjects with glaucoma and suspect glaucoma (Greenhalgh, 2003). Furthermore, the study should be designed to ensure that all subjects receive the same screening tests and reference comparison in the same consistent ophthalmic environment and by the same examiners. Collectively, this provides a truer representation of diagnostic performance in real-world community case-finding, with findings being more applicable to the general population. In fact, an HTA review of the clinical and cost-effectiveness of a screening programme for OAG in the UK identified the need for high-quality studies to evaluate the clinical effectiveness of screening tests in large cross-sectional population-based surveys (Burr et al., 2007).

This study aims to determine the diagnostic accuracy of the Frequency doubling perimeter® (FDT, Carl Zeiss Meditec Inc.), Moorfields motion displacement threshold test (MMDT, Moorfields Eye Hospital, London), iVue Ocular coherence tomographer™ (OCT, Optovue, Inc.), and Ocular Response Analyser ® (ORA, Reichert Inc.) used alone and in combination, for detecting POAG, in a representative sample of the UK primary care population aged 60 years and older, and compared to a reference standard ophthalmic examination. Findings from the current study may be used to optimise case-finding strategies to enhance detection by community optometrists, and to identify tests that may be used in screening programmes of at-risk populations either by technicians or specialist optometrists in community settings.

3.2. Methods

This prospective cross-sectional study was conducted in a single community eye clinic in London, UK during a 12-month period from September 2012 to September 2013. The study protocol was approved by the School of Health Sciences Research and Ethical Committee, City University London. All subjects provided informed consent and the study adhered to the tenets of the Declaration of Helsinki for research involving human subjects. Male and female subjects aged 60 years and older were recruited to participate in the study between July 2012 and September 2013. Information regarding the study, together with an invitation to take part, was distributed to the local population through neighbouring optometry practices and community groups. To ensure a representative sample of the eligible population, no pre-defined exclusion criteria were specified and consequently subjects with known POAG or other ocular co-morbidities were included in the study. Tests were undertaken with the help of interpreters for non-English speakers where necessary.

To avoid verification bias, all subjects underwent a series of technology-based index tests carried out by an independent researcher (Bruno Fidalgo) technician, followed by a reference standard ophthalmic examination, conducted by an experienced clinician who was trained and validated in glaucoma according to UK practice. Both assessments took place on the same day in a consistent ophthalmic clinical setting. A flow diagram for the study is shown in Figure 3.1.

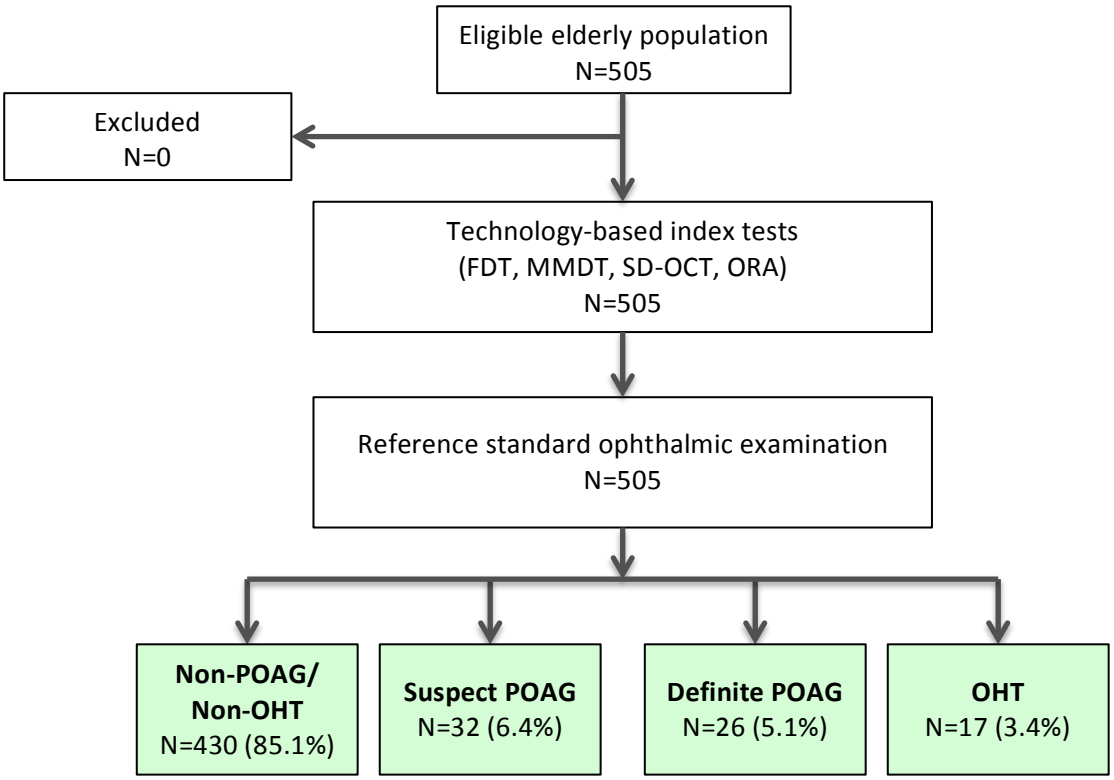


Figure 3.1: Study flow diagram

The technology-based assessment comprised four index tests: FDT perimetry, MMDT, iVue OCT and ORA. The technology-based assessment was performed by an experienced technician who did not have any prior knowledge of the subjects' ocular status, or findings from the reference standard ophthalmic examination. Thresholds for abnormality for the index tests were based on common cut-offs reported in previous literature, manufacturers' suggested cut-offs, and comparisons with internal normative databases, and were specified in the protocol prior to the commencement of the study (Table 3.1). Calibration and diagnostic checks were performed for all index tests and HFA in accordance with manufacturers' guidelines before the start of each clinic day.

Test	Indicators of suitable quality data	Cut-off/ threshold for detection of POAG/ suspected POAG
FDT perimeter	False positives (FP) <15% Fixation errors (FE) <15%	≥1 location missed at any level ≥1 location missed at 1% level
MMDT	False positives (FP) <15% Late responses (LR) <15%	Global PTD ≥2.0 Global PTD ≥3.0
iVue SD-OCT	Scan quality index (SQI) ≥40 and subjective evaluation of scans	P<1% as defined by the normative database
ORA	Waveform score (WS) ≥6.5	Corneal hysteresis (CH) <9.1 Corneal resistance factor (CRF) <9.0

Table 3.1: A summary of index test quality indicators and cut-offs to detect POAG and suspected POAG used in the present study

3.2.1. Index tests

The FDT (C20-5) and MMDT (ESTA 99.5) were used in suprathreshold mode. The order of testing between FDT and MMDT was randomized, and these examinations were never performed in succession to avoid subject fatigue. Each subject was provided with full instructions using a cue card with a preview of the visual task, followed by a short demonstration of the test, with further training provided as needed. The right eye was examined before the left, and rest periods were allowed between tests. FDT and MMDT tests were repeated once if one or more locations had been missed, or if the result was unreliable in

accordance with manufacturers' guidelines. Where a repeat test was performed, the second reliable result was used for analysis. Output data from both tests were stored on an electronic database as Microsoft Access files using FDT Viewfinder and MMDT integral software options.

Near refractive error was determined from a written prescription or by focimetry of spectacles issued within 2 years of the study date. The user manual advises that FDT examination may be undertaken without near correction for refractive errors of less than 7 dioptres (Zeiss, 2000). With an aim to minimize protocol deviations and include limits for cylindrical tolerance, near refractive error was corrected during FDT perimetry and MMDT examination in accordance with limits defined by the manufacturers of the MMDT (>4.50DS hyperopia, >6.00DS myopia, >4.00DC).

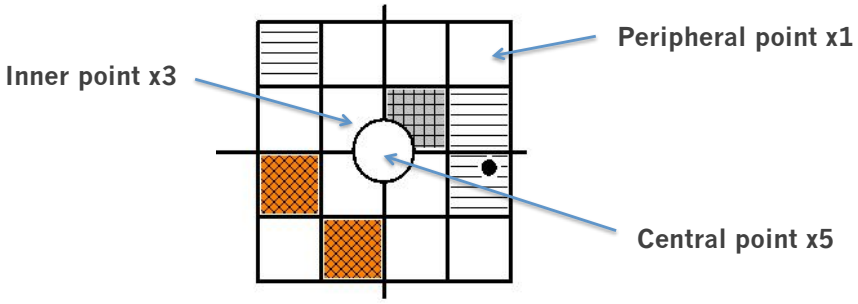
Frequency doubling technology (FDT) perimeter

The frequency doubling illusion was initially observed and reported by Kelly et al. in 1966 (Kelly, 1966). The first generation FDT perimeter was used in C20-5 suprathreshold mode (version 4.00.0). Although the Humphrey matrix perimeter, representing the second generation of the FDT perimeter integrates enhanced features such as smaller and more numerous target presentations, most studies use threshold testing procedures with a testing time of approximately 5 minutes per eye. The aim of the present study was to evaluate the shorter screening protocol for detection of POAG, and use of the first generation FDT perimeter provides more useful comparisons with the literature. Using the C20-5 algorithm, stimuli are initially presented at a contrast that can be detected by 95% of the normal age-matched population. A stimulus perceived at the base level either on first or repeat presentation represents a 'normal' result (P≥5%). Targets missed twice at the 95% level are then tested at the 98% and 99% levels as needed, generating three further levels of shading that represent mild (P<5%), moderate (P<2%) and severe relative loss (P<1%). The C20-5 programme is optimized to detect early or subtle loss in a clinic-setting compared with the C20-1 program which presents initial stimuli at the normal-adjusted 1% level to improve test specificity for large-scale population screening.

Monochrome sinusoidal gratings comprising vertical grey strips (0.25 cycles per degree) are displayed at 17 locations (one central 5-degree circle, and four 10-degree squares distributed one per quadrant) on a video display unit. Each stimulus is presented at a 25Hz counterphase flicker with a maximum duration of 720ms and mean luminance of 50cd/m^2. During the test,

catch trials are assessed three times with one or more false positive or fixation errors being indicative of an unreliable result.

A standard cut-off for an abnormal FDT suprathreshold result has not been established. Researchers have proposed a number of algorithms from counting the number of missed locations, to scoring systems that take account of the position and depth of missed locations.
In the present study, an abnormal result was defined as one or more locations missed at any level, and one or more point missed at the 1% probability level. Further analysis was performed using a scoring system initially described by Patel et al. (Patel et al., 2000). The algorithm allocates an overall score for each FDT result giving increased importance to more severe defects and locations missed closer to fixation (Patel et al., 2000). Figure 3.2 shows score allocation based on the location and depth of a missed location. A final score can be determined by adding scores for all abnormal points with scores ranging from 0 to 87.



Depth of defect	Significance level	Multiplying factor
Within normal limits	P≥5%	0
Mild relative loss	P<5%	1
Moderate relative loss	P<2%	2
Severe loss	P<1%	3

Figure 3.2: Patel et al., 2000 scoring algorithm of FDT suprathreshold results

Moorfields motion displacement threshold test (MMDT)

The MMDT is a novel visual function test based on motion perception. The technology uses a temporal form of Vernier acuity in which subjects are required to discriminate positional change of a line stimulus. Prediction of glaucomatous visual field loss using a single line stimulus presented just above the blind spot was demonstrated in the early 1980's (Fitzke et al., 1987). The system has since evolved into a multi-location perimetry program, which integrates an Enhanced Standard Threshold Algorithm (ESTA) programme to improve

efficiency in screening for glaucoma through application of a spatial filter and multisampling methods.

MMDT testing was performed using the ESTA 99.5 suprathreshold program which has been designed to provide shorter test duration and adjustment for slow responders. Displacements are presented at the 99.5th centile of probability in accordance with normative estimates derived from a UK-based population. The windows-based software program is presented on a 15-inch wide lap-top screen (Lenovo T520i; non-reflective screen) at a distance of 30cm from the subject's eye. 31-white stimuli are presented against a grey background (10cd/m^2) at a constant Michelson contrast of 85%. Each stimulus presentation comprises 3 horizontal oscillations of the target at 200ms per cycle as the vertical bar is displaced towards the central fixation target for 100ms, and moved back to the starting position for 100ms. The four central stimuli of the MMDT display are sized to be resistant to refractive error between a spherical range of +4.50DS and -6.00DS. Peripheral stimuli are scaled in size by estimates of retinal ganglion cell density, and with respect to age and eccentricity.

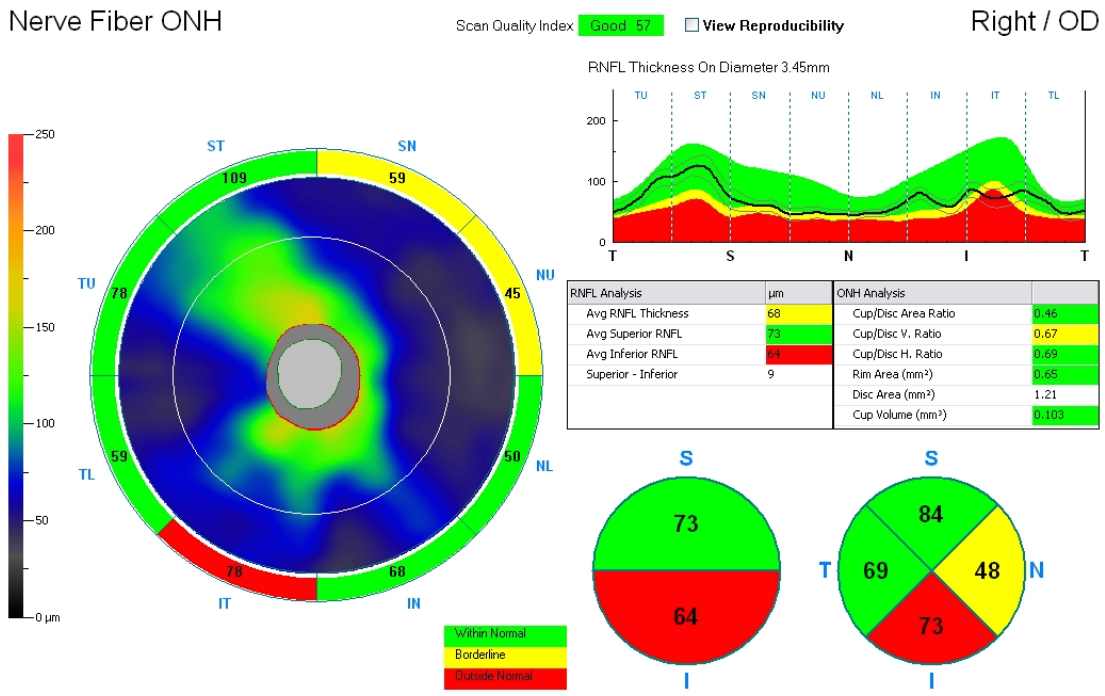
Displacements that are seen or not seen are recorded on a pass-fail plot, and this information is used together with the ESTA spatial filter to generate a probability plot that provides an estimate of the 'probability of true damage' (PTD) at each test location between 0 and 100. A higher global PTD represents a greater probability that the field is damaged. In the present study, an abnormal plot was defined by the manufacturers recommended threshold of a global PTD ≥3.0. A false positive response is recorded when a subject makes a response during the first 180ms of the stimulus presentation, or during the rest period that follows each stimulus presentation. Late responses are recorded when response times fall outside the normal range. A repeat test was performed when false positive or late responses were ≥15%. Following repeat testing, an unreliable plot was defined by false positive responses ≥15%. A late response count ≥15% with false positive recordings <15% were indicative of a 'slow responder' but considered reliable for analysis.

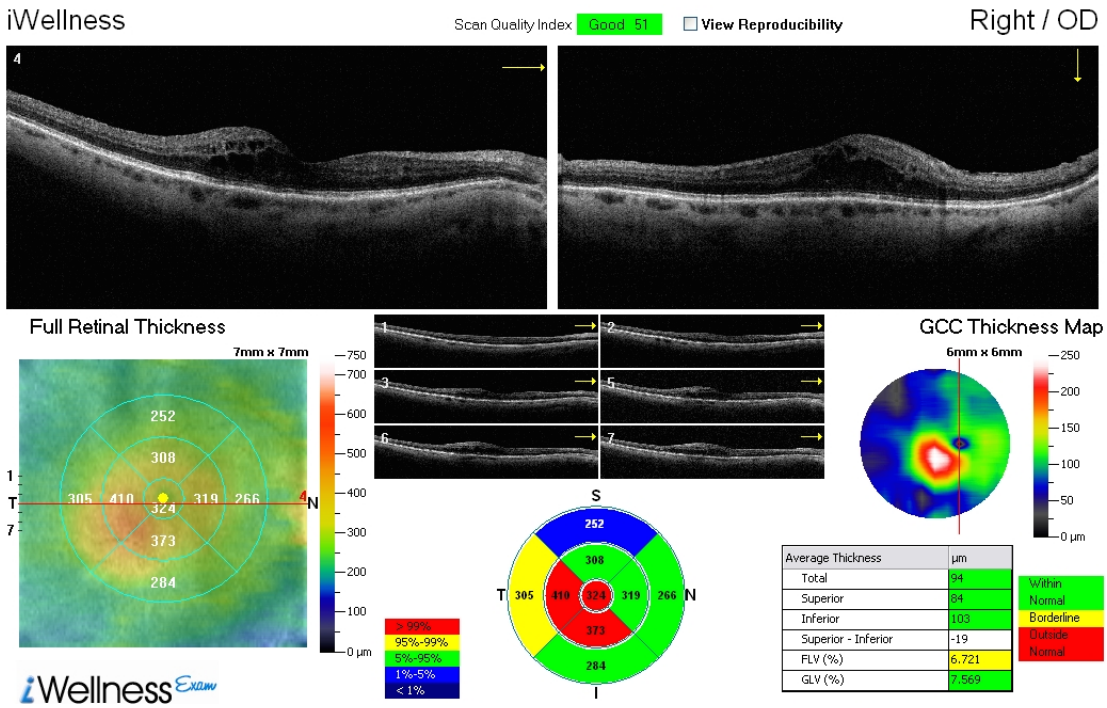
iVue Spectral Domain OCT (SD-OCT)

Optical coherence tomography (OCT) is based on the principle of low-coherence interferometry, in which tissue depth is evaluated using optical backscatter received from a reference (mirror) and a sample (tissue) path. A series of scans are created to form a reflectivity profile, analogous to an ultrasound A-scan which, in turn, is used to construct a two-dimensional B-scan in real time, representing an in vivo cross-sectional tomograph.

Inbuilt software automatically processes the raw data, converting the optical path lengths to physical dimensions using known refractive indices for ocular media, and adjusting for image distortions, a process known as 'de-warping'. In this way, retinal nerve fibre layer (RNFL) thickness and morphological parameters of the optic nerve head may be derived for the early detection and monitoring of glaucoma. More recently, the development of Spectral or Fourier domain technology has enabled faster image acquisition, higher image resolution, and improved retinal layer segmentation compared with the previous version of the technology known as time-domain systems (Schuman, 2008).

The iVue OCT™ (Model iVue 100, Optovue Inc, Fremont CA) is a compact version of the RTVue OCT, which uses spectral domain technology to provide an axial and transverse resolution of 5µm and 15 µm respectively. Scans are captured at a rate of 26,000 A scans per second using a near-infrared scan beam of 840 µm ±10µm wavelength and 50nm bandwidth. The Glaucoma optic nerve head (ONH) scan protocol provides of measure of peripapillary RNFL thickness from the disc margin up to the edge of a circular area of 4.93mm radius from the disc centre (Optovue, 2010). Data from the preceding 3D-glaucoma capture enables the software to automatically demarcate the termination points of the retinal pigment epithelium (RPE), with the option for further manual adjustment to correctly delineate the optic disc margin. The iWellness scan is a composite of the 'ganglion cell complex' (GCC) and 'retina map' scan protocols designed to provide an overall measure of optic nerve and macula function (examples of the Glaucoma ONH and iWellness scan outputs are shown in Figure 3.3a and 3.3b). GCC thickness data are acquired from the inner limiting membrane to the outer plexiform layer in a 7mm by 7mm macula area, centred 1mm temporal to the fovea to sample a greater area of the temporal retina. In addition to standard quantitative parameters (e.g. superior hemifield GCC thickness), Tan et al. developed and introduced two additional parameters to analyse the pattern of GCC loss using differing levels of focality and expressed as a percentage, which are analogous to Humphrey VFA indices of mean deviation (MD) and pattern standard deviation (PSD) (Tan et al., 2009). 'Global loss volume' (GLV) is calculated from a fractional deviation map and represents the average amount of GCC loss over the entire extent of the GCC map. 'Focal loss volume' (FLV) uses the pattern deviation map corrected for absolute changes when compared to normative data to describe focal loss across the GCC map as a percentage of significant tissue loss of volume. In-depth descriptions of procedures used to derive these parameters have been reported previously (Sinai, 2008, Tan et al., 2009, Rao et al., 2012).





Figures 3.3a and 3.3b: iVue SD-OCT scan outputs; a) Glaucoma ONH retinal nerve fibre layer thickness (RNFL), and b) iWellness (composite of GCC and retina map protocols)

In the present study, diagnostic data for OAG detection were obtained using the GCC protocol of the iWellness scan, and glaucoma ONH RNFL scan patterns together with software version V3.2.0.42. Scans were captured in dark-room illumination conditions to encourage pupil dilation and without the use of mydriatic agents. However, imaging was repeated following

pupil dilation if miotic pupils and/ or significant media opacity precluded capture of adequate quality data. Preservative-free artificial lubricants were instilled to promote accurate fixation and data capture where necessary. iVue OCT software generates a Scan Quality Index (SQI) based on the intensity of reflected light from the entire extent of the capture. An SQI under 40 represents a scan of poor quality, but the manufacturer advised that decisions to exclude data should also be based on subjective evaluation. Following each acquisition, the examiner analysed the quality of data observing for e.g. artefacts, poor centration. Rejected scans were reacquired with an aim to capture two images of adequate quality for each scan protocol. The first scan of the two captures was used for analysis unless it satisfied exclusion on the basis of poor quality (SQI <40 and/ or subjective evaluation).

iVue OCT data are automatically compared with the software-integrated normative database providing a colour-coded output for each parameter. 'Within normal limits' is shown in green, representing a result within the 95% confidence interval of the healthy, age-matched population (P≥5%). 'Borderline' (P<5% but ≥1%), and 'outside normal limits' classifications (P<1%) are shown in yellow and red respectively (Figures 3.3a and 3.3b). Of the structural parameters reported for GCC and RNFL thickness, the overall mean, superior hemifield, and inferior hemifield thickness were included for analysis. RNFL thickness was further evaluated by hourglass quadrant: temporal 316 to 45 degrees, superior 46 to 135 degrees, nasal 136 to 225 degrees, and inferior 226 to 315 degrees. GCC thickness data were also represented by FLV and GLV. The defined cut-off for abnormality was any RNFL or GCC parameter falling outside the 99% normal limit based on the manufacturers' integrated normal database.

Ocular response analyzer (ORA)

The ORA is a non-contact air-puff tonometer which applies a rapid, collimated jet of air of increasing intensity to a circular area of the central cornea of 3mm diameter. The 20ms applanation event is monitored by a collimation detection system of electro-optical components comprising an emitting and photoreceptor diode. The unique feature of the 'dynamic' technology is the recording of two IOP readings, each corresponding to an applanation event. Traditional static tonometry observes a single applanation in which the jet of air stops once the cornea has assumed a flattened profile. In contrast, the ORA sequence consists of a bi-directional applanation as the intensity of air continues to rise, deforming the cornea from a flat to concave configuration. The device monitors the air pressure at both applanation events, the first during the force-in applanation when the air pressure rises (P1), and the second after the air pressure falls and stops (P2). It might be expected that two

equivalent IOP values would be obtained if the cornea was perfectly elastic. Instead, energy absorption from viscoelastic 'damping' of the cornea results in a time delay, resulting in a disparity of pressure readings as the outward applanation event occurs at a lower pressure.

The ORA generates two measures of corneal biomechanical properties: corneal hysteresis (CH) and corneal resistance factor (CRF). CH describes the ability of corneal tissue to absorb and dissipate energy, and is represented by the difference between P1 and P2, in which a higher value indicates a 'stiffer' cornea. CRF provides an indication of the overall elastic properties or resistance of the cornea to the air pulse. In the absence of a clinical consensus to define the optimum cut-offs for CH and CRF to detect POAG, the optimal threshold in the present study was determined from the ROC curve using the Youden index (Youden, 1950). IOPg is determined by the mean of P1 and P2, which are calibrated against Goldman applanation tonometry (GAT) to provide a useful comparison. These data are also used to derive a 'truer' IOPcc that is less influenced by corneal properties than IOPg, using the formula P1 - 0.43P2 (Medeiros & Weinreb, 2006).

The ORA software generates a graphical plot comprising 3 curves: pressure of air applied to the cornea, raw signal of applanation detection system, and a filtered version of the latter to identify optimum points of applanation (Figure 3.4). In accordance with the manual, the examiner was required to analyse each output to evaluate, reject and retake poor quality readings (Reichert, 2012). A good quality raw signal is defined by two characteristic spikes corresponding to P1 and P2, which are fairly symmetrical in height and located above the pressure curve in amplitude. The 3.01 version of the ORA used in the present study also incorporates a quality index called the Waveform Score (WS) to objectively assist the operator to select the highest quality measurements. WS scores range between 0 and 10 with higher numbers representing more reliable measurements. The signal with the highest WS is distinguished as the best signal value (BSV). However, the ORA manual does not provide guidance as to the minimum acceptable WS.

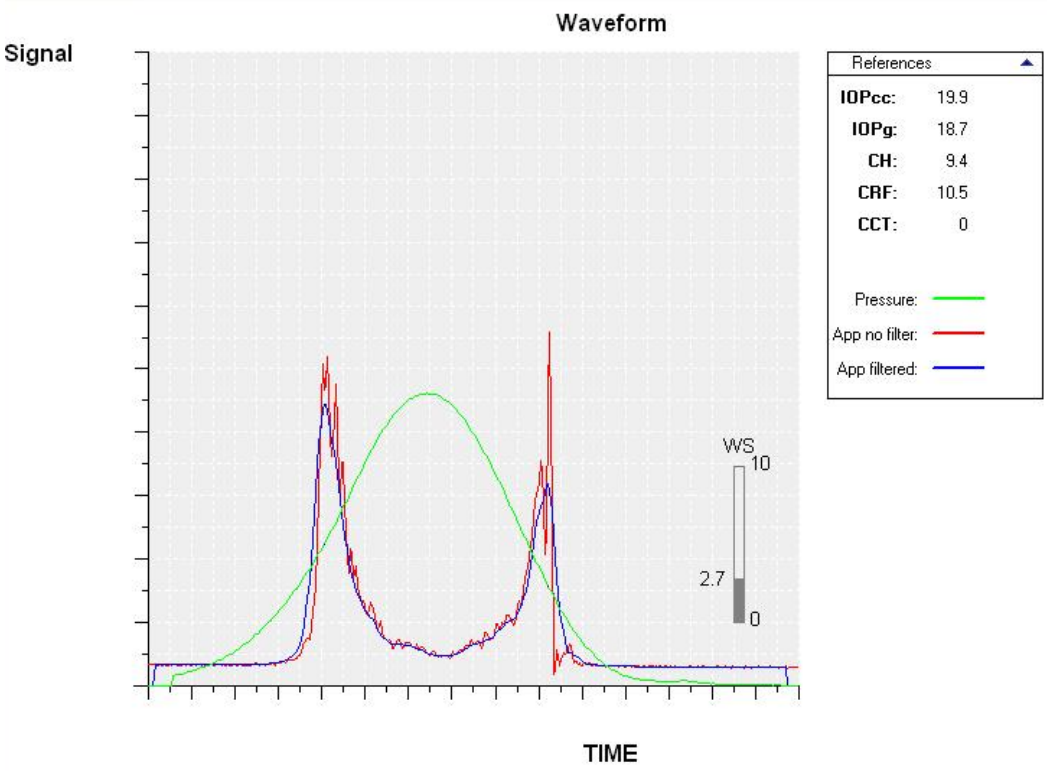


Figure 3.4: Ocular Response Analyser (ORA) graphical plot comprising 3 curves: pressure of air applied to the cornea (green), raw signal of applanation detection system (red), and a filtered version of the latter to identify optimum points of applanation (blue)

A minimum of four ORA measurements from each eye was acquired for each subject using ORA software (version 3.01). A final 5th measurement was captured if preceding readings failed to attain a waveform score (WS) of 6.5 or greater (personal correspondence with David Taylor, Ametec). The highest WS or best signal value (BSV) measurement was used for analysis on the proviso that multiple measurements with similar graphical outputs have been attained (Vantomme et al., 2013). Data were only excluded if deemed unreliable by a WS less than 3.5 (Lam et al., 2010, Vantomme et al., 2013) together with a poor quality graphical output.

3.2.2. Reference standard ophthalmic examination

For the reference ophthalmic examination all subjects underwent a series of standard tests for glaucoma by a clinician masked to the results of preceding index tests. The HFA was used in 24-2 SITA standard mode. The right eye was tested first, and a rest period of at least 5 minutes was allowed before left field examination. Near refractive error was corrected during HFA testing in accordance with the Moorfields Eye Hospital protocol. Where possible, repeat testing was attempted for unreliable results (false negatives >33%, fixation losses >33%, false positives >15%), and Glaucoma hemifield test (GHT) recordings of 'outside normal limits',

either on the same day after a rest period or arranged for another day within a month of the study visit.

Following full assessment of the anterior segment using the slit-lamp biomicroscope (Haag-Streit BS-900, 6-40x magnification), and measurement of IOP by a Goldmann Applanation Tonometer (GAT), eyes with a potentially occludable angle identified by the assessment of limbal anterior chamber depth (van Herick test) were evaluated by gonioscopy. Once the pupils had fully dilated, a detailed optic disc examination and general fundus examination to identify ocular co-morbidities was performed using indirect ophthalmoscopy with the slit-lamp (+60DS and Superfield Volk lenses) and fundus photography (45° optic disc and macula and 30° disc centered image, Topcon TRC-NW8F). Cataract was graded using the LOCS II classification system. Other tests included in the standard protocol included a full history-taking with positive family history of glaucoma recorded if the subject reported a first-degree relative diagnosed with glaucoma, and measurement of visual acuity using a logMAR chart. Whilst the pupils were dilating, subjects were asked to complete a questionnaire regarding the acceptability of each of the index tests.

Based on findings from the reference ophthalmic examination, the clinician classified subjects as non-POAG/ non-OHT, ocular hypertension (OHT), suspect POAG, and definite POAG.
The OHT case definition for subjects who had not been previously diagnosed by an ophthalmologist in this study was based on measurement of IOP above 21mmHg on two separate occasions, with normal visual field results, open anterior chamber angles and healthy optic discs. The following criteria were used for the classification of definite or suspect POAG based on observations from one or both eyes:

- Definite POAG: open anterior chamber angle, presence of glaucomatous optic neuropathy (localised absence of neuro-retinal rim, cup: disc ratio of ≥0.7 or inter-ocular asymmetry in vertical cup to disc ratio of ≥0.2 in similar sized discs) and the presence of a glaucomatous field defect based on criteria amended from Anderson and Patella (Anderson & Patella, 1999) (a cluster of ≥3 points on the pattern deviation plot having P<5% with at least one point with P<1%, none of which can be edge points unless they are located immediately above or below the nasal horizontal meridian, PSD P<5%, and GHT 'outside normal limits'). In contrast with the original Anderson and Patella definition, test failure in the current study was represented by failure of all 3 criteria in order to reduce false positive responses in view of the lack of reproducible

field plots for all subjects. IOP was not used as a criterion for defining the POAG group.

- Suspect POAG: included 'disc suspects' showing features of glaucomatous optic neuropathy but with normal fields and 'field defects' with visual fields suggestive of glaucoma but with normal discs.

Co-morbidities other than POAG, suspect POAG and OHT including anterior segment, media, and retinal disorders were noted and a forced decision was made as to the likelihood of the condition influencing structural and/or functional measurements.

3.2.3. Validation of the reference standard examiner

Following weekly attendance of glaucoma clinics over a 6-month period at Moorfields Eye Hospital (London), validation of the reference standard examiner was confirmed by competency-based assessment. The clinical diagnosis of glaucoma was evaluated for R and L eyes of 50 subjects (all hospital patients who were not part of the main study) and compared with classification by a consultant ophthalmologist (DGH or WN). Each subject was classified as 'normal', 'suspect glaucoma', or 'glaucoma' based on combined observation of the optic disc using binocular indirect ophthalmoscopy, and visual field results. The same classification system was used for further evaluation of the ability to classify glaucoma subjects by visual field assessment alone using 100-HFA C24-2 threshold field plots (50 right and 50 left eye plots). Results were compared with classification by the glaucoma consultant (DGH). The discrimination between normal and glaucomatous eyes based on optic disc evaluation alone was assessed by grading stereoscopic optic disc images against a reference ophthalmological diagnosis. The 110-image set comprised 48 glaucomatous, 40 healthy, 6 ocular hypertensive and 16 duplicate images of the optic disc, and was previously used in a study of over 1200 optometrists (Hadwin et al., 2013). Optic disc image grading was repeated after 2 weeks to evaluate intra-observer repeatability, and then every 6 months until the end of the study to observe for linear drift. Agreement between classifications by the glaucoma-specialist optometrist and ophthalmological opinion were evaluated using Cohen's Kappa statistic (Tables 3.2a and 3.2b). Kappa agreement for optic disc, visual field and combined assessment ranged from 'substantial' to 'almost perfect'. Temporal stability in optic disc image grading was established by Cronbach's alpha statistic. A comparison of image grading performed prior to commencing data collection, and a repeat assessment after two weeks yielded a Cronbach alpha coefficient of 0.867, implying good repeatability. Similar figures were observed when

the first grading was compared to that performed at 6 months (α=0.93), and 12 months (α =0.91) after the start of the study.

Agreement for combined optic disc and visual field (N=50)		Reference standard optometrist					
		Normal		Suspect glaucoma		Glaucoma	
		Right eye	Left eye	Right eye	Left eye	Right eye	Left eye
Consultant ophthalmologist (DGH/ WN)	**Normal**	6	11	3	1	0	0
	Suspect glaucoma	0	0	7	10	5	2
	Glaucoma	1	0	1	2	25	21

Validation assessment	Observed kappa	Standard error	95% confidence interval
Combined optic disc and visual field* (N=50)			
Right eye	0.70	0.09	0.52 to 0.87
Left eye	0.88	0.05	0.77 to 0.98
Visual field plots* (N=50)			
Right plot	0.88	0.05	0.78 to 0.98
Left plot	0.89	0.07	0.75 to 1.00
Optic disc stereo-images (n=110)	0.78	0.06	0.67 to 0.90
** Kappa with linear weighting*			

Tables 3.2a and 3.2b: Kappa agreement for classification of glaucoma between reference standard optometrist and consultant ophthalmologist

3.2.4 The preliminary iVue normal database (NDB) study

A normative database (NDB) is an integral software requirement of modern imaging devices and provides a statistical reference of normality which allows the clinician to compare a given eye's result to a larger group of known healthy eyes. This comparison is based on probability values derived from the normal distribution of data of the healthy eyes. Traditionally, cut-offs based on the normal distribution are set at the 1st (P<1% level) and 5th (P<5% level) percentiles, and are colour-coded for easy interpretation. The aim of the iVue NDB study was to collect data from healthy individuals, establish normal ranges with non-overlapping 1% and 5% cut-offs for normality, and create a normative database for the iVue OCT.

Five clinical sites (four in USA and one in UK) participated in this prospective study with a collective aim to recruit and examine 455 healthy subjects. Subjects were aged 18 years and older and stratified by age to ensure a mean age of approximately 50 years. Recruitment was aimed to sample an approximate gender mix of 50:50 male: female (no more than 60:40 or 40:60). Principal investigators and relevant colleagues were required to adhere to an approved protocol outlining procedures and rigorous inclusion/ exclusion criteria. Each subject attended for a comprehensive clinical examination by an experienced optometrist to verify inclusion for analysis on the basis of normal ocular health. Subjects were considered for inclusion if the examination verified they were free from ocular pathology, had a normal and reliable visual field, and IOP below 22mmHg. Subjects meeting strict inclusion criteria were invited to undergo a full clinical examination including refraction and visual acuity measurement, C24-2 threshold perimetry (HFA), slit-lamp examination of the anterior and posterior eye, digital fundus photography, GAT and measurement of central corneal thickness. iVue OCT scans were acquired of right and left eyes using 6 scan patterns: Glaucoma ONH, Retina map, GCC, 3-dimensional optic disc 512 x 128, 3-dimensional macula 512 x 128 and iWellness. Each scan protocol was repeated 3 times providing a total of 18 scans per eye. All data were collected at a single visit.

Data collection at the UK site took place in the Fight for Sight Optometry clinic of City University London. A total of 54 subjects were enrolled and examined at the London site between December 2011 and February 2012. Subjects had a median age of 38 years ranging from 24 to 69 years, and male:female distribution of 43:57. The study was reviewed and approved by the City University research and ethics committee and was conducted in accordance with the Declaration of Helsinki statement of ethical principles for research involving human subjects. Informed consent was obtained from all subjects.

iVue scans were checked for quality, observing for position within the scan range, artefacts, weak signal data and segmentation failure. Poor quality scans were excluded from analysis. Data captured from R and L eyes of a given subject were averaged to provide a single measurement to account for the correlation between data values. The range and distribution of parameter measurements were described using mean, standard deviation and ranges for each output, and compared to RTVue NDB results with an alpha level $p<0.01$ representing a statistically significant difference. Multivariate regression analysis was used to evaluate the relationship between covariates and each structural parameter. Using these data, 1% and 5% cut-offs for normality were established with adjustments for covariates. A repeatability

(precision) analysis was also performed to evaluate intra-subject variability for a subset of normal, glaucoma, and macular disease subjects.

521 subjects were enrolled between the four sites, with data from 458 subjects meeting NDB study criteria. Mean age was 42.5 ±15.4 years ranging from 18 to 82 years. 47% of subjects were White, followed by 18.6% Asian and 15.3% of Hispanic origin. The majority of subjects within the cohort were female (60.5%). Mean RNFL thickness, disc area, rim area and vertical cup to disc ratio were 99.1±9.5µm, 1.96±0.39mm^2, 1.32±0.35mm^2 and 0.47±0.19 respectively (n=449). Average GCC thickness, GCC FLV and GCC GLV were 94.0±7.1µm, 0.72±0.9, and 2.99±3.57 respectively. Significant differences were observed for RNFL thickness and optic nerve head parameters for variations of age and disc area. Using multivariate regression analysis, mean RNFL and GCC thickness reduced by 0.117µm and 0.115µm per year in this population. ANOVA analysis found no statistically significant gender effect for RNFL, optic nerve head and GCC parameter measurements.

The data were used to establish an iVue normative database, after accounting for several covariates including age, signal strength, and optic disc size, displayed in a colour coded output outlined as follows:

- Within normal limits (within 95% normative level) – green
- Borderline (p<5% level) - yellow
- Outside normal limits (p<1% level) - red

Comparison with the RTVue OCT found similar total number of subjects used to generate their normative database, similar normative values, and similar relationships between parameters and covariates including age, signal strength and optic disc size. Repeatability and reproducibility of iVue measurements were also found to be similar to the RTVue OCT.

3.2.5. Sample size calculation (main study)

The sample size was based on an anticipated sensitivity of the index tests to detect POAG (based on the current case definitions) of 0.75 (Mowatt et al., 2008) with a minimal acceptable precision of ±0.25 with 0.95 probability. This would require 42 cases. Since the prevalence of the target conditions in the local elderly population would be approximately 10% (Reidy et al., 1998) it was estimated that at least 420 subjects needed to be recruited.

3.2.6 Statistical analysis (main study)

Data were exported to a Microsoft Excel spreadsheet and further statistical analysis was performed using SPSS 21.0 software (www.ibm.com/SPSS_Statistics), Medcalc 14.8.1 (www.medcalc.org), and STATA 13.0 (StataCorp. 2013. College Station, TX: StataCorp LP, www.stata.com). Unreliable results acquired by visual function tests (FDT and MMDT), and data from repeatedly poor quality ORA and OCT acquisitions were removed from analysis as previously outlined in the Index test section (3.2.1.). Index data were analysed by a clinician (PLD) masked to findings from the reference ophthalmic examination.

The unit of analysis was the individual, and the comparison was between the 'worse' index test result from either the right or left eye with the overall reference standard classification for a given subject into non-POAG/ non-OHT, OHT, suspect POAG or definite POAG. This screening paradigm addressed potential bias associated with analysing dependent data from both right and left eyes of a given subject.

POAG subjects were classified by disease severity using the Hodapp Parrish Anderson criteria based on Humphrey C24-2 mean deviation values of the worse eye (Hodapp et al., 1993). Categorical variables were compared between subject groups using the chi-squared test. Differences in mean values for demographic characteristics and continuous index test data between diagnostic groups were evaluated by ANOVA and post-hoc tests. Data with skewed distributions were compared between groups using the Wilcoxon signed-rank test and Kruskal-Wallis test with post-hoc analysis for multiple comparisons, and skewed age data were described by the median value and interquartile range. Other summary clinical data between groups were described by the mean value and standard deviation to allow comparison with the literature. $P<0.05$ was considered statistically significant for the majority of tests. However, a p value less than 0.01 was deemed statistically significant for analyses involving multiple comparisons to reduce the risk of a Type I error.

Initial diagnostic accuracy estimates of each index test to detect definite POAG and suspect POAG/ definite POAG combined were evaluated by using the predefined cut-offs for abnormality to generate sensitivity, specificity and likelihood ratios together with associated 95% confidence intervals. Any significant differences between sensitivity and specificity estimates were assessed by the McNemar test. Diagnostic accuracy to discriminate definite and suspect POAG from non-POAG/ non-OHT subjects was explored further by receiver operating characteristic (ROC) curve analysis using raw numerical data for SD-OCT structural and ORA corneal biomechanical parameters. Similarly ROC curves were plotted for the MMDT

using global PTD scores, and for the FDT using the Patel et al. (2000) scoring algorithm. Sensitivity at set specificity, and partial area under the curve (AUC) of ROC plot estimates together with 95% confidence intervals were generated using a bootstrap method. Partial AUROC values were normalized by the false positive rate (Hillis & Metz, 2012). These parameters were evaluated at 90% and 95% specificities to provide a clinically useful range for case detection of a low prevalence disease. Any statistically significant differences between sensitivity at set specificity, and partial AUROC curve estimates were assessed using the Wald test (Pepe et al., 2009). Best performing structural and functional criteria were identified by partial AUROC curve analysis, and combined in series to calculate sensitivity and specificity values, and change from pre-test to post-test probability estimates of a given subject having suspect POAG/ POAG combined and definite POAG using Bayesian reasoning.

User acceptability survey data generated using Likert scales were transcribed into grades from 1 to 7, where 'Strongly disagree' is denoted by 1, and aggregated into summary tables. Chi-squared analysis was used to determine the likelihood that sampling variability or chance could be an explanation for any observed trends between diagnostic subject groups. Responses to the free-text responses were coded and assigned to categorical variables.

3.3 Results

A total of 505 subjects entered the study (59% female and 41% male). Subjects were aged between 60 and 92 years with median age being 68 (IQR 59 to 77) years. Self-reported ethnicities were 88% White, 8% South Asian, and 2% Blacks. Based on the reference standard examination, 26 (5.1%) subjects were classified as having definite POAG, 32 (6.4%) suspect POAG, and 17 (3.4%) OHT. Of the 26 POAG subjects, half were untreated for glaucoma and 31% were newly diagnosed. Using Hodapp Parrish Anderson criteria (Hodapp et al., 1993), 11 (42%) of the definite POAG cases were classified as early (MD -6dB or better), 6 (23%) as moderate (MD worse than -6dB but better than -12dB) and 9 (35%) as advanced (MD -12dB or worse). In the context of case-detection of glaucoma, approximately 12% of subjects were diagnosed with POAG or suspect POAG.

Demographic and summary clinical data for each of the four subject groups are summarised in Tables 3.3a and 3.3b respectively. There were no statistically significant differences between diagnostic groups in terms of age (Kruskal-Wallis, $p=0.512$) and gender (Chi-squared, $p=0.624$). Self-reported family history of glaucoma was greater among POAG subjects than compared with non-POAG/ non-OHT subjects (Chi-squared, $p<0.001$). Means of visual field mean deviation (MD) and pattern standard deviation (PSD) were -9.14dB and 8.32dB respectively for definite POAG subjects, and -1.34dB and 2.29dB for non-POAG/ non-OHT subjects respectively (Table 3.3b), representing a statistically significant difference (Kruskal-Wallis, $p<0.001$). Predictably, significantly higher mean IOP was measured for OHT subjects when compared with any other diagnostic group (Kruskal-Wallis, $p<0.003$), with mean IOP being lowest for non-POAG/ non-OHT subjects (14.4±2.6mmHg). No adverse events were reported for any subject following examination by index tests or gonioscopy.

	All subjects	Non-POAG/ Non-OHT	OHT	Suspect POAG	POAG	P value (Kruskal-Wallis or Chi-squared test)
N (%)	505 (100)	430 (85.1)	17 (3.4)	32 (6.4)	26 (5.1)	---
Age (years) Median (IQR)	68.0±9 (IQR 59 to 77)	68.0±9 (IQR 59 to 77)	70.0±11 (IQR 59 to 81)	70.5±8 (IQR 62 to 78)	68.0±10 (IQR 59 to 78)	0.512
Gender (%)						
Male	206 (40.8)	172 (40.0)	6 (35.3)	16 (50.0)	12 (46.2)	0.624
Female	299 (59.2)	258 (60.0)	11 (64.7)	16 (50.0)	14 (53.8)	
Ethnic group (%)						
White	443 (87.7)	386 (89.8)	14 (82.4)	24 (75.0)	19 (73.1)	---
South Asian	39 (7.7)	28 (6.5)	3 (17.6)	4 (12.5)	4 (15.4)	
Black	10 (2.0)	8 (1.9)	0 (0.0)	2 (6.3)	0 (0.0)	
Chinese	7 (1.4)	3 (0.7)	0 (0.0)	2 (6.3)	2 (7.7)	
Other	6 (1.2)	5 (1.2)	0 (0.0)	0 (0.0)	1 (3.8)	
Positive family history of glaucoma (%)	83 (16.4)	61 (14.2)	3 (17.6)	7 (21.9)	12 (46.2)	<0.001*
*A comparisons between proportions in the diagnostic groups revealed statistically significant differences: *, between non-POAG/ non-OHT and POAG*						

Table 3.3a: Demographic data for each of the four subject groups

	All subjects	Non-POAG/ Non-OHT	OHT	Suspect POAG	POAG	P value (Kruskal-Wallis)
N (%)	505 (100)	430 (85.1)	17 (3.4)	32 (6.4)	26 (5.1)	---
Intraocular pressure (mmHg)						
Mean±SD	14.8±3.3	14.4±2.6	21.9±2.7	14.5±3.6	17.8±5.9	<0.001[a]
Range	8 to 34	8 to 22	15 to 25	10 to 26	11.5 to 34	
Vertical cup:disc ratio						
Mean±SD	0.45±0.17	0.42±0.15	0.43±0.14	0.62±0.17	0.81±0.1	<0.001[b]
Range	0.10 to 0.95	0.10 to 0.80	0.25 to 0.68	0.20 to 0.83	0.70 to 0.95	<0.001[c]
Mean deviation (dB)						
Mean±SD	-1.82±3.3	-1.34±2.4	-1.20±1.4	-2.73±3.0	-9.14±6.8	0.008[b]
Range	-25.4 to 2.58	-20.25 to 2.58	-3.75 to 0.98	-14.18 to 1.20	-25.40 to -0.30	<0.001[c]
Pattern standard deviation (dB)						
Mean±SD	2.64±2.3	2.29±1.6	2.13±0.7	3.18±2.4	8.32±4.2	0.028[b]
Range	1.12 to 16.28	1.12 to 13.16	1.20 to 3.67	1.26 to 13.78	2.04 to 16.38	<0.001[c]

Intraocular pressure, vertical cup:disc ratio, mean deviation and pattern standard deviation data represent the worse result between right and left eye data
Comparisons between diagnostic groups revealed statistically significant differences between means (p<0.05): [a], between non-POAG/ non-OHT and OHT, [b], between non-POAG/ non-OHT and suspect POAG, [c], between non-POAG/ non-OHT and POAG

All clinical data are described by the mean and standard deviation to allow comparison with the literature

Table 3.3b: Summary clinical data for each of the four subject groups

A high proportion of subjects had ocular co-morbidities, as would be expected in a general population of elderly subjects, including 9.5% with moderate or advanced AMD, and 10.7% with clinically significant cataract in one or both eyes. Table 3.4 provides a summary of non-glaucoma related ocular pathology observed during the reference standard ophthalmic examination. The diseases listed are not mutually exclusive.

	N	%
AMD		
Early	155	30.7
Intermediate	27	5.3
Advanced	21	4.2
Diabetic Retinopathy		
R1 (non-proliferative)	26	5.1
R2 (non-proliferative)	4	0.8
R3 (proliferative)	2	0.4
Clinically significant macular oedema	5	1.0
Other macular pathology		
Macular hole (lamellar or full thickness)	8	1.6
Epiretinal membrane: clinically significant	27	5.3
Other macular disorder	5	1.0
Retinal pathology		
Retinal detachment or tear (previous)	20	4.0
Choroiditis	3	0.6
Pigmented fundus lesion (naevus, CHRPE)	55	10.9
Chorioretinal atrophy/ degeneration	25	5.0
Other retinal disorder	9	1.8
Other optic disc disorder	4	0.8
Cataract (clinically significant)	54	10.7
Corneal pathology	19	3.8
Corneal refractive surgery	9	1.8
Vitreal body opacity	10	2.0
Anterior segment disorder		
Primary angle closure suspect/ Primary angle closure	19	3.8
Pigment dispersion/ pseudoexfoliation	9	1.8
Uveitis (previous history)	2	0.4
Neurological disorder	6	1.2
Binocular vision disorder	37	7.3

Table 3.4: Non-glaucoma related ocular pathology observed during the reference standard ophthalmic examination

3.3.1 Basic index test data

504 right eye and 505 left eye examinations were completed using FDT and MMDT testing (right eye assessment for one subject was precluded due to a prosthesis) providing a total of 1009 plots. Following initial testing, 86% of FDT and 97% of MMDT plots were reliable, improving to 96% and 99% respectively on repeat testing (Table 3.5). A greater proportion of FDT plots (42%) were repeated compared with MMDT testing (28%) with 'missed locations' being the most frequent reason for repeat testing. Interestingly, the number of unreliable left eye FDT results following repeat testing (n=28) was almost twice that of right eye data (n=15), representing a statistically significant difference (Wilcoxon signed ranks test, p=0.024).

15% (N=152) of HFA plots were repeated due to poor reliability and/ or a GHT recording of 'outside normal limits', and a further 6 examinations could not be completed providing a total of 978 (97.5%) reliable results. Mean test duration for all subjects was 5.45±0.87 min using the HFA C24-2 SITA standard protocol, compared with 1.83±0.37 and 0.83±0.47 min for MMDT and FDT respectively (Figure 3.5). Significantly longer mean test duration was observed for subjects classified as POAG compared with non-POAG/ non-OHT using FDT (ANOVA, $p<0.001$) and HFA testing (ANOVA, $p<0.001$). Of the 26 subjects classified as definite POAG, two-thirds (17/26) failed both FDT (1 or more location missed at any level of significance) and MMDT (global PTD ≥3.0). Using these index test cut-offs, agreement between HFA and FDT test failure (24/26) was greater than for HFA and MMDT (17/26), with the same trend being observed for definite POAG and suspect POAG groups combined.

	Reliable tests following first examination N (%)	Reliable tests following repeat examination N (%)	Tests repeated N (%)	Reason for repeat testing N (%)
FDT	870 (86.2)	966 (95.7)	426 (42.2)	Missed location – 287 (28.4) Poor reliability – 89 (8.8) Missed location + poor reliability – 50 (5.0)
MMDT*	975 (96.6)	1001 (99.2)	278 (27.6)	Missed location – 235 (23.3) Poor reliability – 15 (1.5) Missed location + poor reliability – 19 (1.9) Late responses – 9 (0.9)
HFA[§]	935 (93.3)	978 (97.5)	152 (15.2)	Visual field defect – 85 (8.5) Poor reliability ± visual field defect – 67 (6.7)

** In accordance with manufacturers' guidelines MMDT tests were repeated if false positive and/ or late responses were ≥15%, but unreliable MMDT data are a function of false positive responses alone.*

[§] *HFA formed part of the reference standard examination*

Table 3.5: Summary data of visual function test reliability and repeat testing

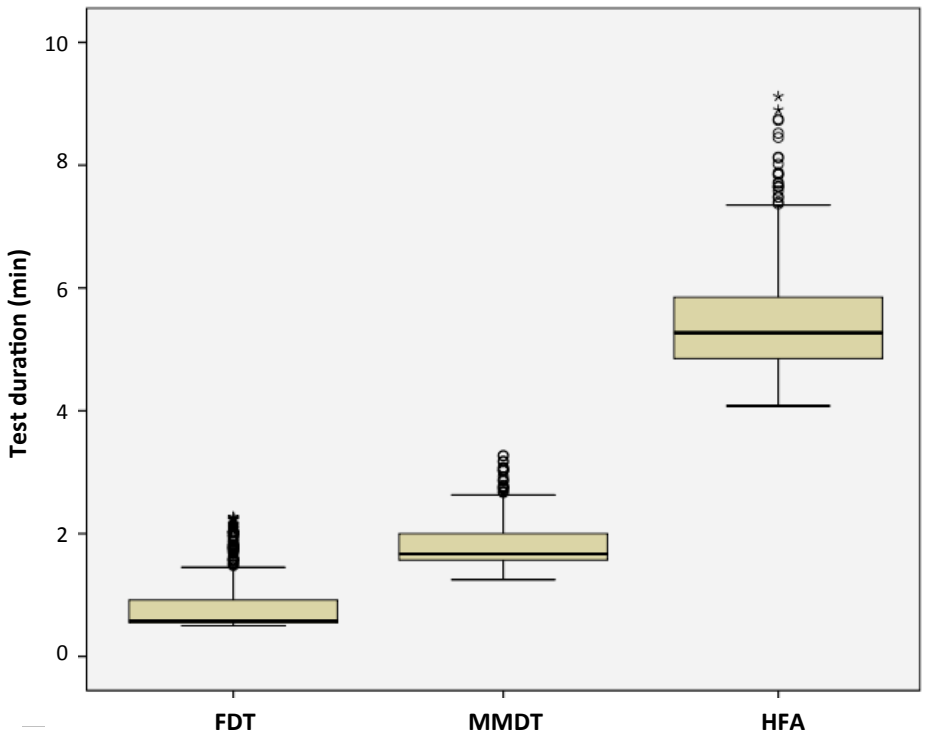


Figure 3.5: Boxplots of the test duration for visual function tests showing the median, upper and lower quartiles, maximum and minimum values (excluding outliers), and outliers (>1.5 times the upper or lower quartile)

Pathological myopia or other significant retinal distortions precluded acceptance of iVue SD-OCT scan quality in a small number of subjects. Following repeat acquisition 98% of glaucoma ONH scans, and 97% of iWellness scans were of sufficient quality to be included in the analysis. Similarly, only 7 ORA best signal value (BSV) measurements were excluded from analysis by virtue of a WS <3.5 and a corresponding poor quality graphical signal output.

Overall mean RNFL and GCC thickness data for all subjects (n=505) were 89.0±11.4 µm and 89.5±9.4 µm respectively (Appendix B, Table i). Mean measurements were significantly lower among subjects diagnosed with definite POAG compared with the non-POAG/ non-OHT group for all GCC and RNFL thickness parameters (ANOVA or Kruskal-Wallis, p≤0.049). Figure 3.6 shows the typical double-hump distribution of RNFL thickness by quadrant with highest mean thickness measured in the superior and inferior positions in all subject groups.

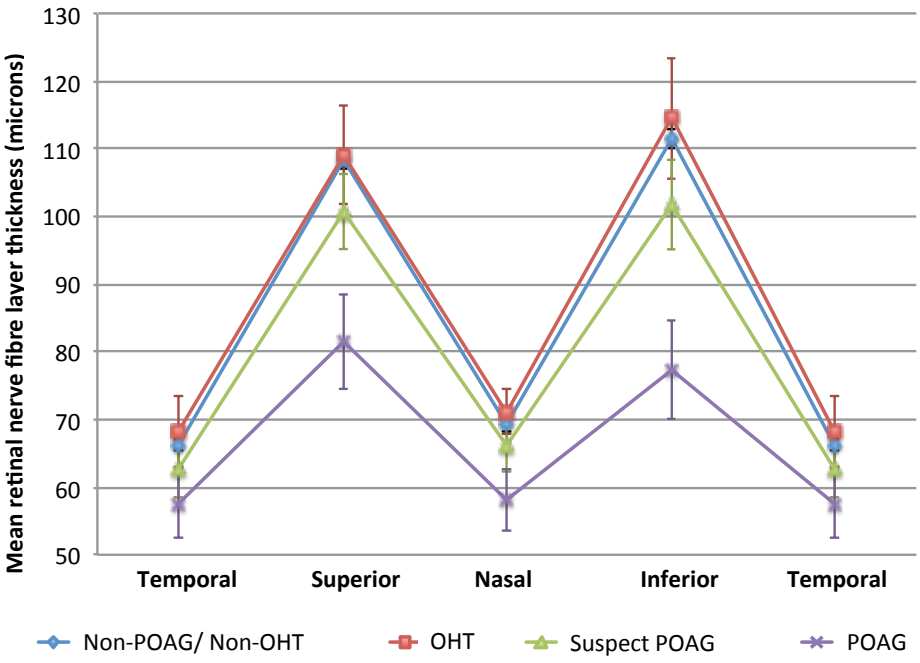
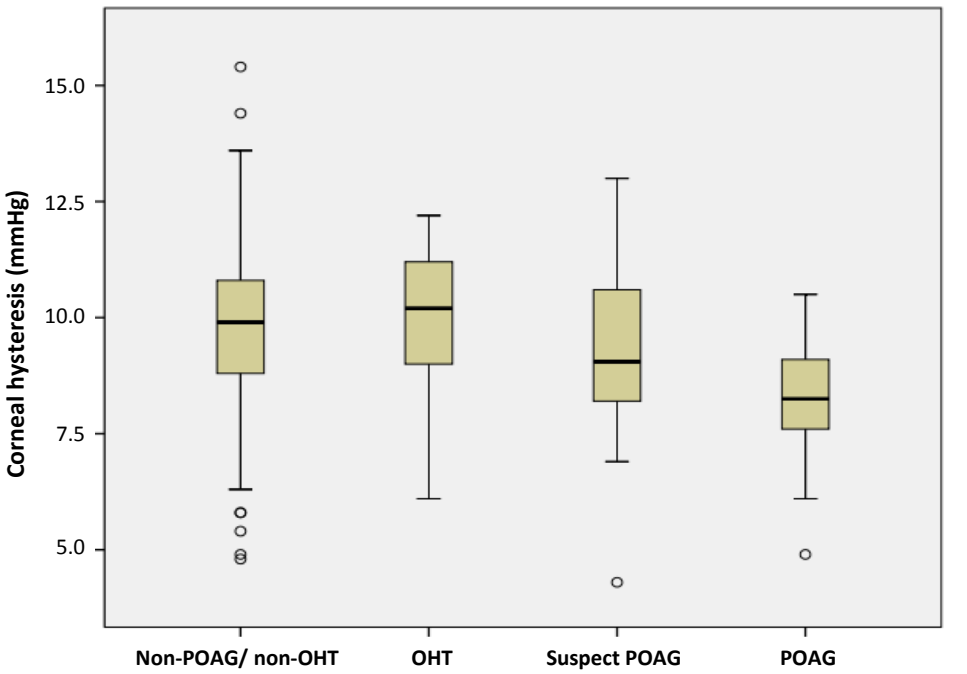
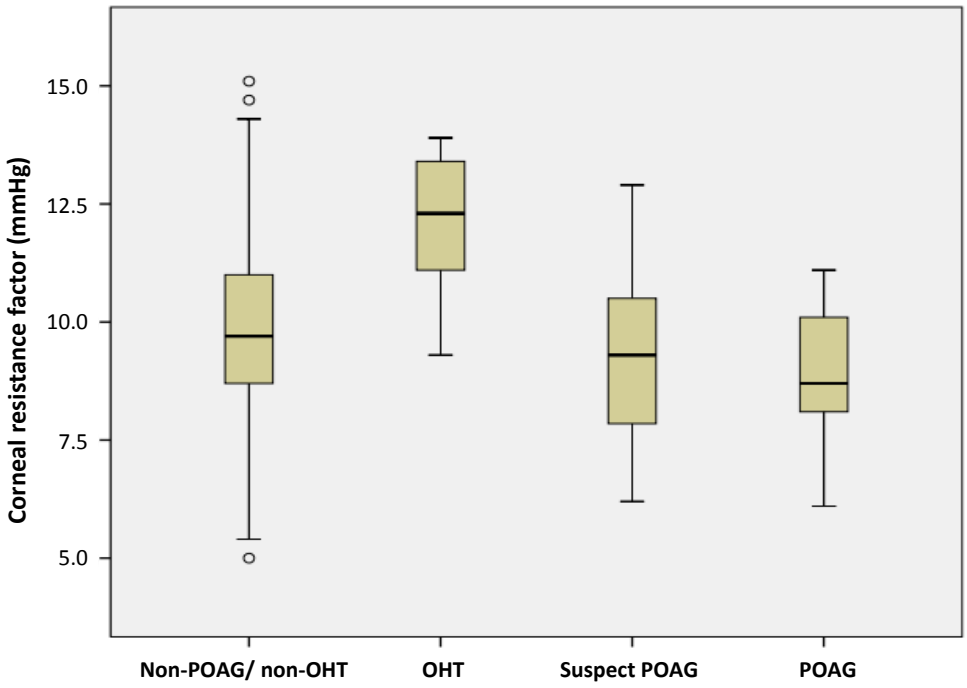


Figure 3.6: Distribution of mean RNFL thickness between quadrants with associated 95% confidence intervals

Mean ORA biomechanical parameters of CH and CRF measurements were 8.2±1.3 and 8.8±1.4 among POAG subjects compared with 9.8±1.5 and 9.8±1.7 for non-POAG/ non-OHT subjects, representing a statistically significant difference (ANOVA, p<0.01) (Appendix B, Table ii). A statistically significantly higher mean CRF of 12.0mmHg was measured in the OHT group than for any other diagnostic group (ANOVA, p<0.001). Figures 3.7a and 3.7b shows boxplots of CH and CRF distribution between the 4 subject groups.





Figures 3.7a and 3.7b: Boxplots of ORA biomechanical parameter measurements between the four diagnostic subject groups; a) CH and b) CRF data showing the median, upper and lower quartiles, maximum and minimum values (excluding outliers), and outliers (> 1.5 times the upper or lower quartile)

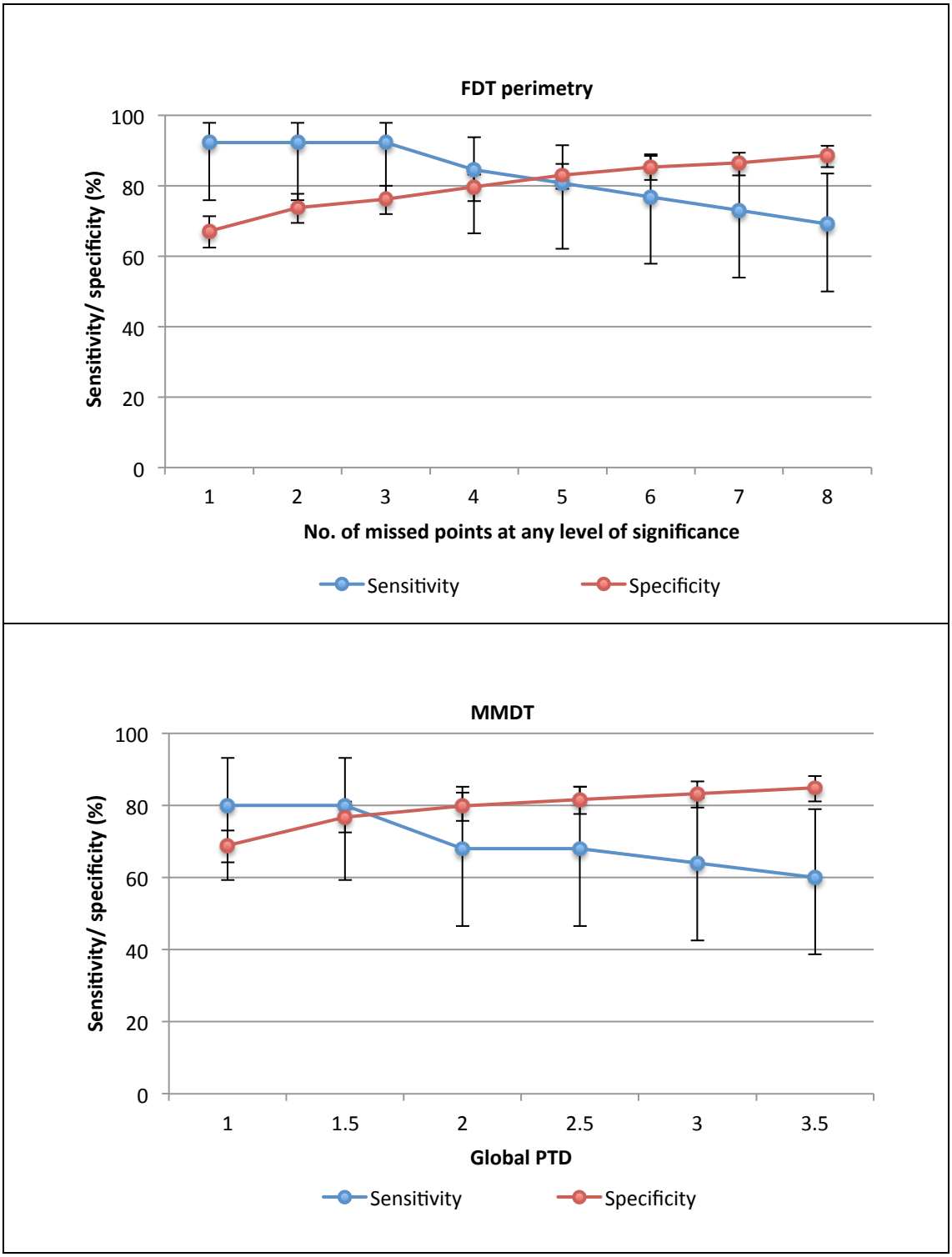
** CH and CRF data are based on the minimum measurement from either the right or left eyes*

3.3.2 Diagnostic performance of index tests

A FDT cut-off of 1 or more missed location at any level of significance, representing the most common threshold for abnormality in published literature, yielded 92.3% (CI 75.9 to 97.9) sensitivity and 67.1% (CI 62.5 to 71.4) specificity for detection of POAG. Test specificity improved to 80.5% (CI 76.4 to 84.0) using a test failure cut-off of 1 or more location(s) missed at the 1% level of significance, while retaining a sensitivity of 88.5%. Figure 3.8a shows the variation in test sensitivities and specificities with number of missed locations at any level of significance. An optimal trade-off of sensitivity and specificity exceeding 80% is achieved using a cut-off between 4 and 5 missed locations at any level of significance.

The manufacturers' recommended MMDT cut-off (global PTD ≥3.0) achieved test specificity of over 80% but lower sensitivity of 64% (CI 44.5 to 80.0). Interestingly, sensitivity and specificity curves plotted as a function of global PTD (Figure 3.8b) suggest that a lower global PTD of 1.5 would improve sensitivity to 80%, but this would be traded off by a reduction in specificity below 80%. ROC curves constructed using the FDT Patel et al. score (2000) and MMDT global PTD values are shown in Figure 3.11.

Predictably, sensitivities for detection of POAG and suspect POAG were lower using FDT (1+ location missed at any level, 72.4%) and MMDT (global PTD ≥3.0, 50.9%) than for detection of definite POAG alone. Notably, all cases of moderate and advanced POAG (mean deviation worse than -6dB) were detected by both index tests; FDT (1 or more location missed at the 1% level or any level) and MMDT (global PTD ≥2.0). Of the 11 POAG subjects classified with early disease (-6dB or better), only 2 subjects (18%) were test positive using MMDT (global PTD ≥3.0) indicating poor sensitivity in this population. Tabulated diagnostic data for FDT and MMDT are shown in Table 3.6 and Tables iii and iv of Appendix B.



Figures 3.8a + b: Sensitivity-specificity plots for the FDT (number of missed locations) and MMDT (global PTD) for detection of POAG

FDT protocol	Sensitivity (%)	Specificity (%)	Positive likelihood ratio	Negative likelihood ratio
1 point missed any level	92.3 (75.9 to 97.9)	67.1 (62.5 to 71.4)	2.8 (2.3 to 3.3)	0.1 (0.0 to 0.4)
1 point missed at 1% level	88.5 (71.0 to 96.0)	80.5 (76.4 to 84.0)	4.5 (3.6 to 5.7)	0.1 (0.0 to 0.4)
Global PTD ≥2.0	68.0 (48.4 to 82.8)	79.8 (75.7 to 83.3)	3.4 (2.4 to 4.7)	0.40 (0.2 to 0.7)
Global PTD ≥3.0	64.0 (44.5 to 79.8)	83.0 (79.2 to 86.3)	3.8 (2.6 to 5.4)	0.43 (0.3 to 0.7)
Any GCC parameter	80.8 (62.1 to 91.5)	88.4 (85.0 to 91.1)	7.0 (5.1 to 9.7)	0.2 (0.1 to 0.5)
GCC overall average	61.5 (42.5 to 77.6)	94.6 (92.0 to 96.4)	11.3 (6.9 to 18.7)	0.4 (0.3 to 0.7)
GCC superior hemifield	46.2 (28.8 to 64.5)	95.0 (92.5 to 96.7)	9.3 (5.2 to 16.8)	0.6 (0.4 to 0.8)
GCC inferior hemifield	69.2 (50.0 to 83.5)	94.3 (91.7 to 96.2)	12.2 (7.7 to 19.5)	0.3 (0.2 to 0.6)
GCC FLV	69.2 (50.0 to 83.5)	91.0 (87.9 to 93.4)	7.7 (5.2 to 11.5)	0.3 (0.2 to 0.6)
GCC GLV	42.3 (25.5 to 61.0)	98.1 (96.3 to 99.0)	22.4 (9.9 to 50.9)	0.6 (0.4 to 0.8)
Any RNFL parameter	88.5 (71.0 to 96.0)	90.7 (87.5 to 93.1)	9.5 (6.8 to 13.1)	0.1 (0.0 to 0.4)
RNFL overall average	69.2 (50.0 to 83.5)	96.0 (93.7 to 97.5)	17.4 (10.2 to 29.7)	0.3 (0.2 to 0.6)
RNFL superior hemifield	61.5 (42.5 to 77.6)	95.1 (92.6 to 96.8)	12.5 (7.5 to 21.0)	0.4 (0.3 to 0.7)
RNFL inferior hemifield	69.2 (50.0 to 83.5)	95.8 (93.4 to 97.3)	16.5 (9.8 to 27.7)	0.3 (0.2 to 0.6)
RNFL superior quadrant	61.5 (42.5 to 77.6)	95.8 (93.4 to 97.3)	14.6 (8.5 to 25.2)	0.4 (0.3 to 0.6)
RNFL inferior quadrant	76.9 (57.9 to 89.0)	96.3 (94.0 to 97.7)	20.6 (12.2 to 34.8)	0.2 (0.1 to 0.5)
Any GCC (5) or RNFL (7) parameter	96.1 (81.1 to 99.3)	82.7 (78.8 to 86.0)	5.6 (4.4 to 6.9)	0.1 (0.0 to 0.3)

Table 3.6: Sensitivity, specificity and likelihood ratios for the FDT, MMDT and iVue SD-OCT presented with 95% confidence intervals for the detection of POAG

Analyses of iVue OCT data were initially performed using software outputs based on the integral normative database with data points outside the 99% limits being indicative of abnormality. Notably, 25 of the 26 subjects classified as POAG in the reference ophthalmic examination were detected by one or more GCC or RNFL parameter exceeding the 99% normative interval (see Table 3.6 and Appendix B, Table v for tabulated diagnostic summary data). Of the 5 GCC parameters included for analysis (overall mean, 2 hemifield, GLV and FLV), highest test sensitivity to detect POAG was achieved by GCC inferior hemifield thickness and GCC FLV (69.2%, CI 50.0 to 83.5). Of the 7 RNFL thickness parameters (overall mean, 2 hemifields and 4 quadrants), inferior quadrant thickness yielded highest test sensitivity of 76.9% (CI 58.0 to 89.0). Figure 3.9 shows the distribution of sensitivities and specificities using thickness measurements for the two best performing GCC and RNFL parameters. In this population, an optimal trade-off between sensitivity and specificity exceeding 80% is achieved by inferior quadrant RNFL thickness at a cut-off of 95 µm.

Notably, all 5 GCC and 7 RNFL parameters individually provided a test specificity exceeding 90%. In particular, GCC GLV was 98% specific for discrimination of definite POAG from non-POAG/ non-OHT subjects, which corresponded to the highest positive likelihood ratio of 22.4 (CI 9.9 to 50.9) of all iVue parameters. However, a threshold of abnormality defined by any of the 7 RNFL parameters (2 hemifields, 4 quadrants and overall average) exceeding the 99% normative level provided further diagnostic value by improving sensitivity to 89% while maintaining a specificity just above 90%. Using the same cut-off, sensitivity improved to 93% for distinguishing POAG subjects with moderate and advanced POAG (MD worse than -6dB) from the non-POAG/ non-OHT group. Predictably, iVue OCT parameters performed less well for detection of POAG and suspected POAG combined.

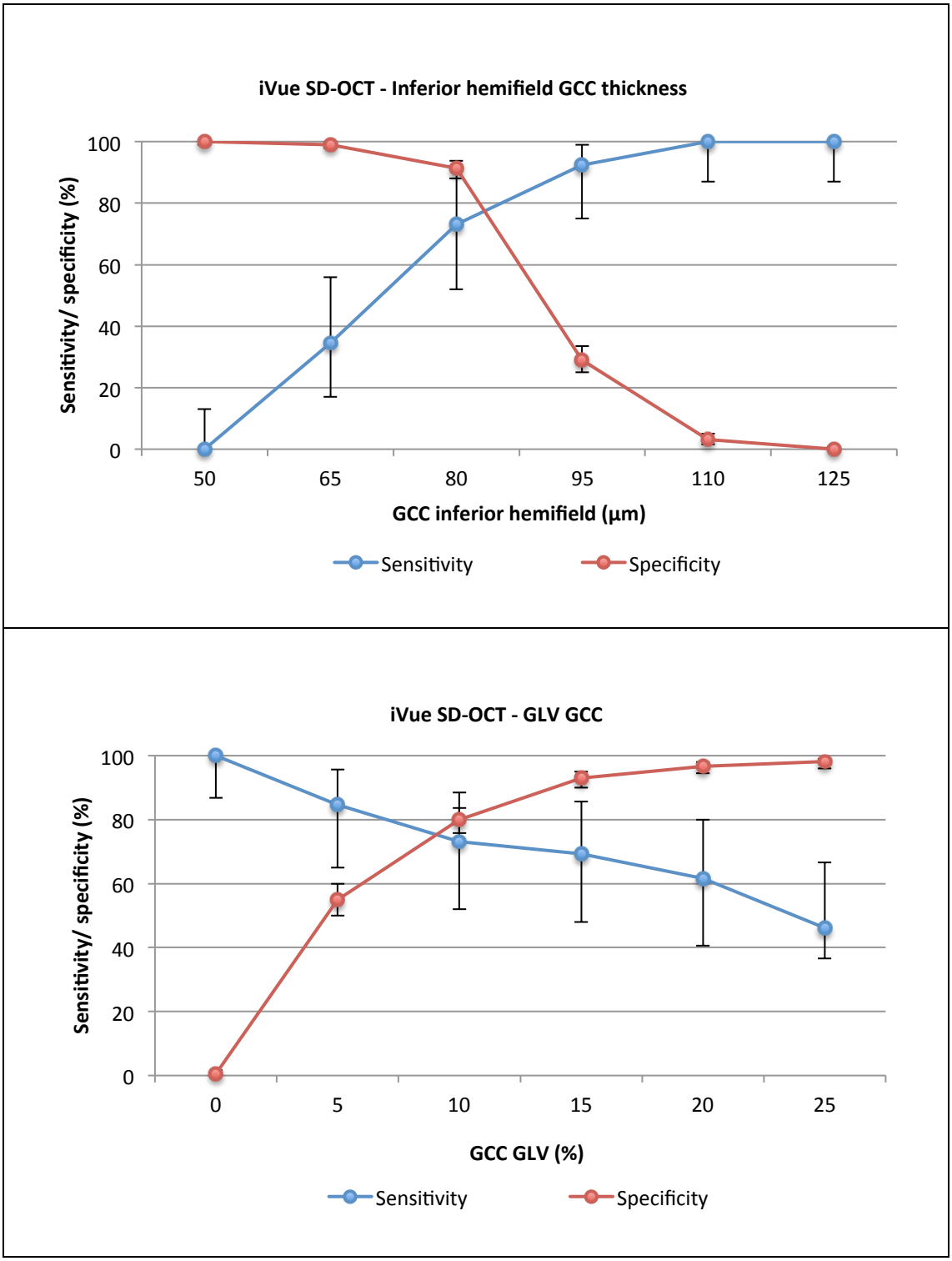


Figure 3.9: Sensitivity-specificity plots for the two best-performing iVue SD-OCT GCC and RNFL parameters for detection of POAG

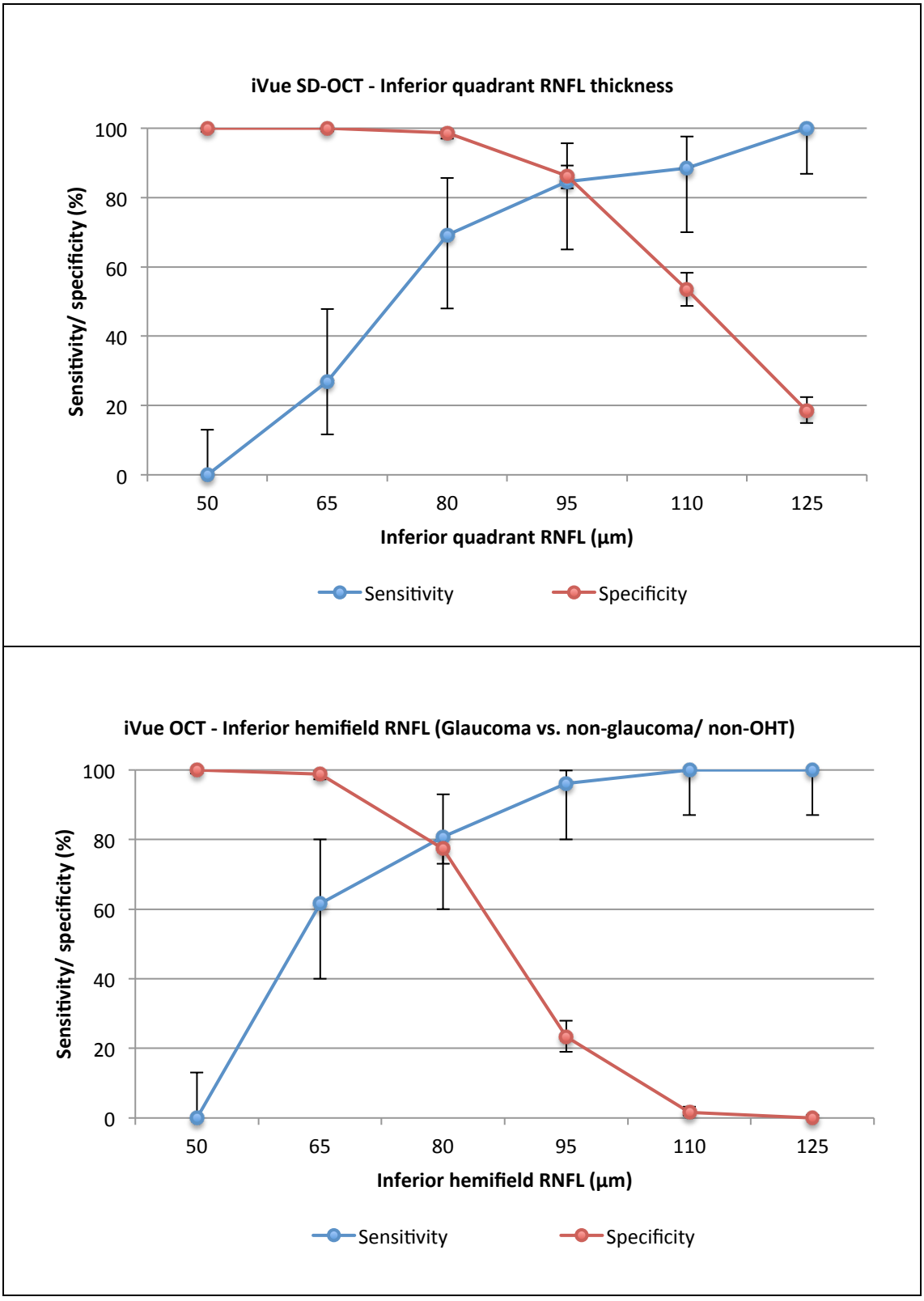


Figure 3.9 (continued): Sensitivity-specificity plots for the two best-performing iVue SD-OCT GCC and RNFL parameters for detection of POAG

IOP estimates of IOPcc and IOPg generated by the ORA were of little diagnostic value for distinguishing POAG subjects from non-POAG/ non-OHT subjects as half the subjects classified with POAG at the time of the study were either receiving topical therapy or reported previous

surgical/ laser interventions to lower IOP. Instead, Figure 3.10 shows diagnostic performance of ORA-corneal biomechanical parameters (CH and CRF). By applying a Youden derived cut-off for abnormality of 9.1, CH achieved higher sensitivity (77%, CI 58 to 89) and specificity (69%, CI 64 to 73) for detection of POAG compared with CRF (Appendix B, Table vi).

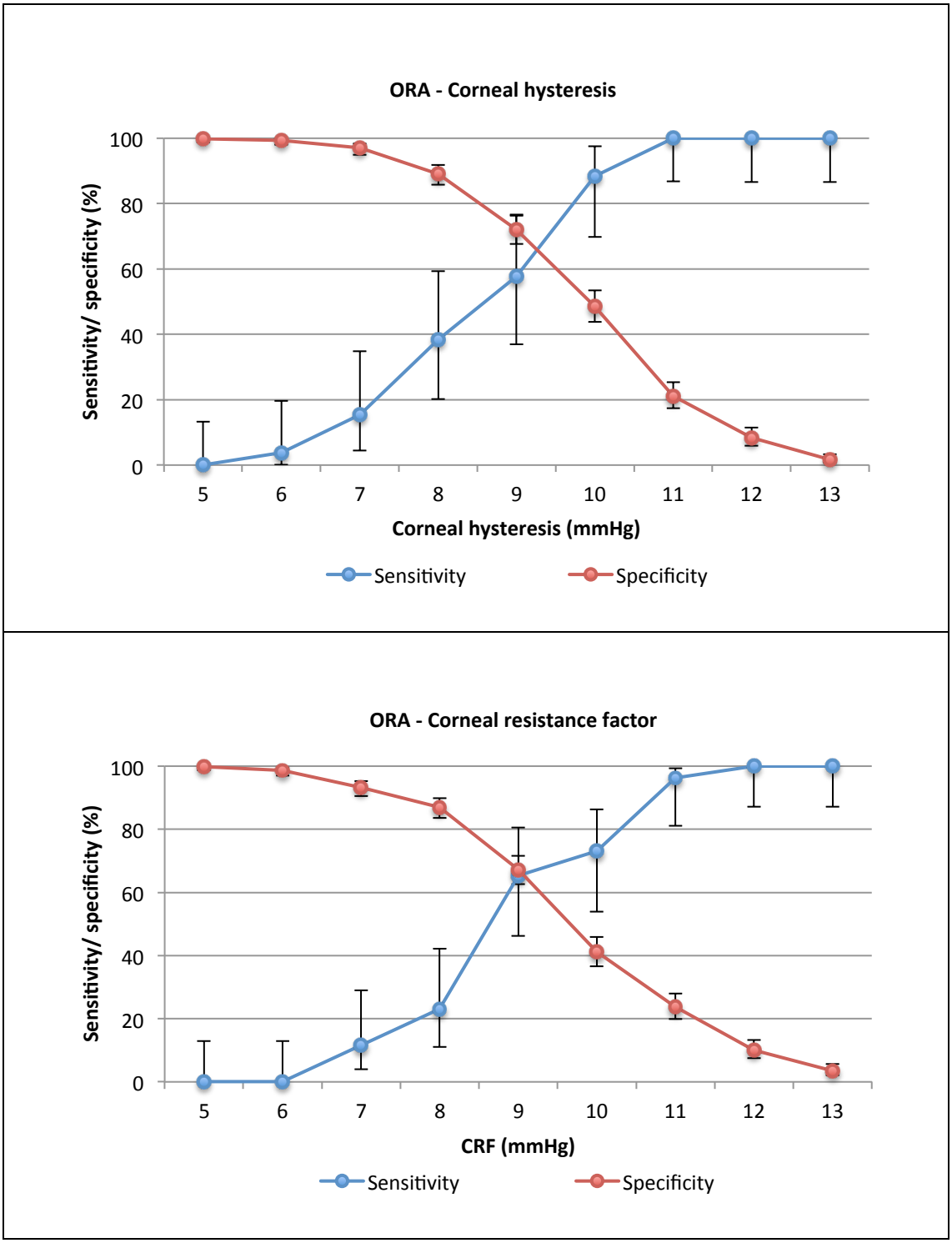


Figure 3.10: Sensitivity-specificity plots for ORA parameters for detection of POAG by corneal biomechanical parameters of a) Corneal hysteresis (CH), and b) Corneal resistance factor (CRF)

Diagnostic performance of index tests detailed in this results section include data from a proportion of subjects identified as having non-glaucoma related ocular morbidities that may have impacted on structural and/ or functional results. These data were included with the aim to provide a truer representation of POAG case-finding in a typical population aged 60 years and older. Following exclusion of subjects classified with comorbid conditions that are likely to affect structure-function tests, test specificities of visual-function tests (FDT and MMDT) improved by 7 to 8% using the pre- specified cut-offs. For example, MMDT test specificity rose from 83% to 90% using a global PTD cut-off of ≥3.0. In comparison, a smaller improvement in test specificity of approximately 2% was observed for iVue SD-OCT RNFL and GCC parameters following exclusion of comorbid subject data (see Appendix B, Table vii for tabulated summary).

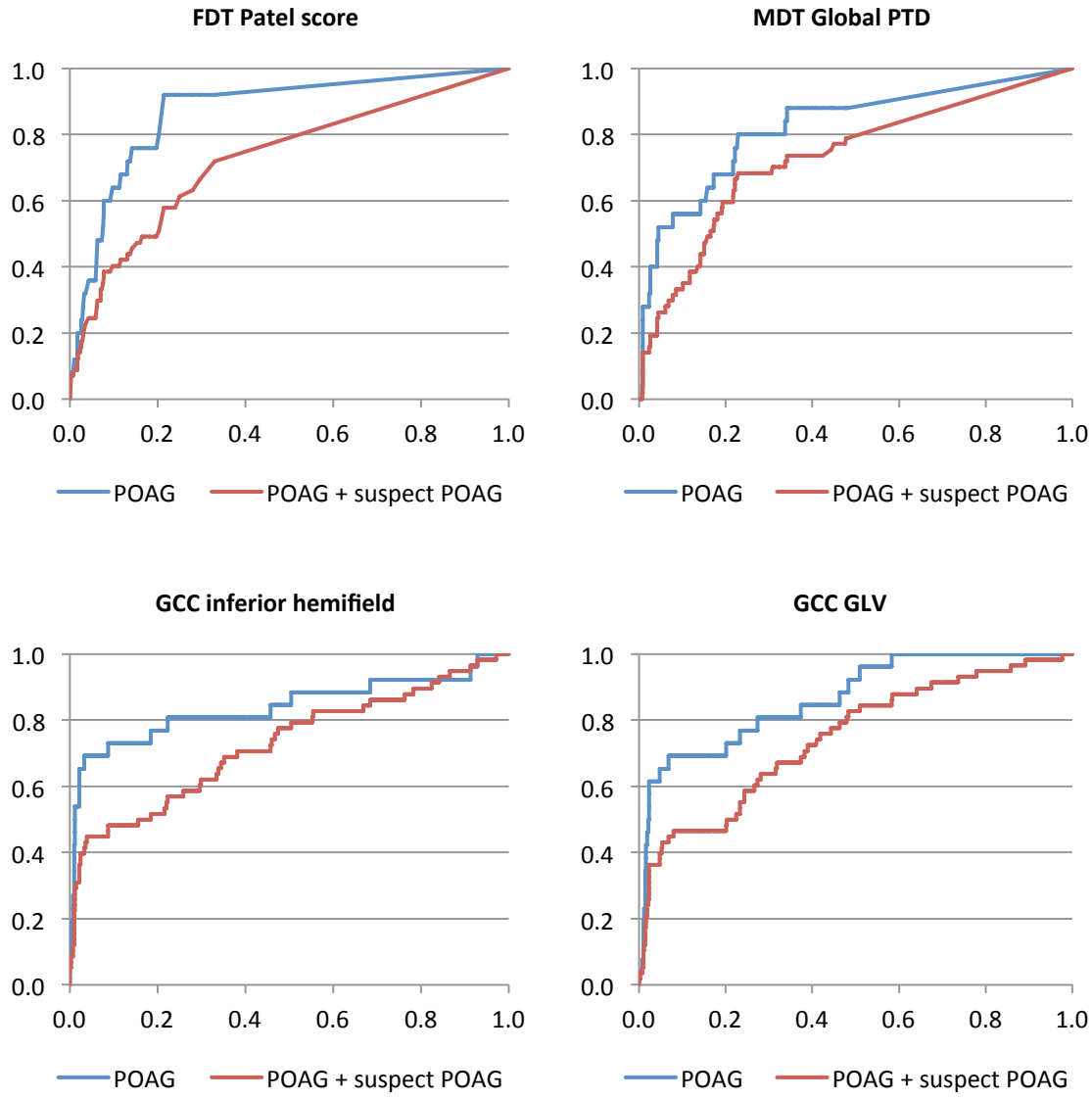


Figure 3.11: ROC curves (plotting sensitivity against 1-specificity) for detection of POAG and POAG/ suspect POAG combined using visual function tests, best performing iVue SD-OCT parameters and ORA corneal hysteresis.

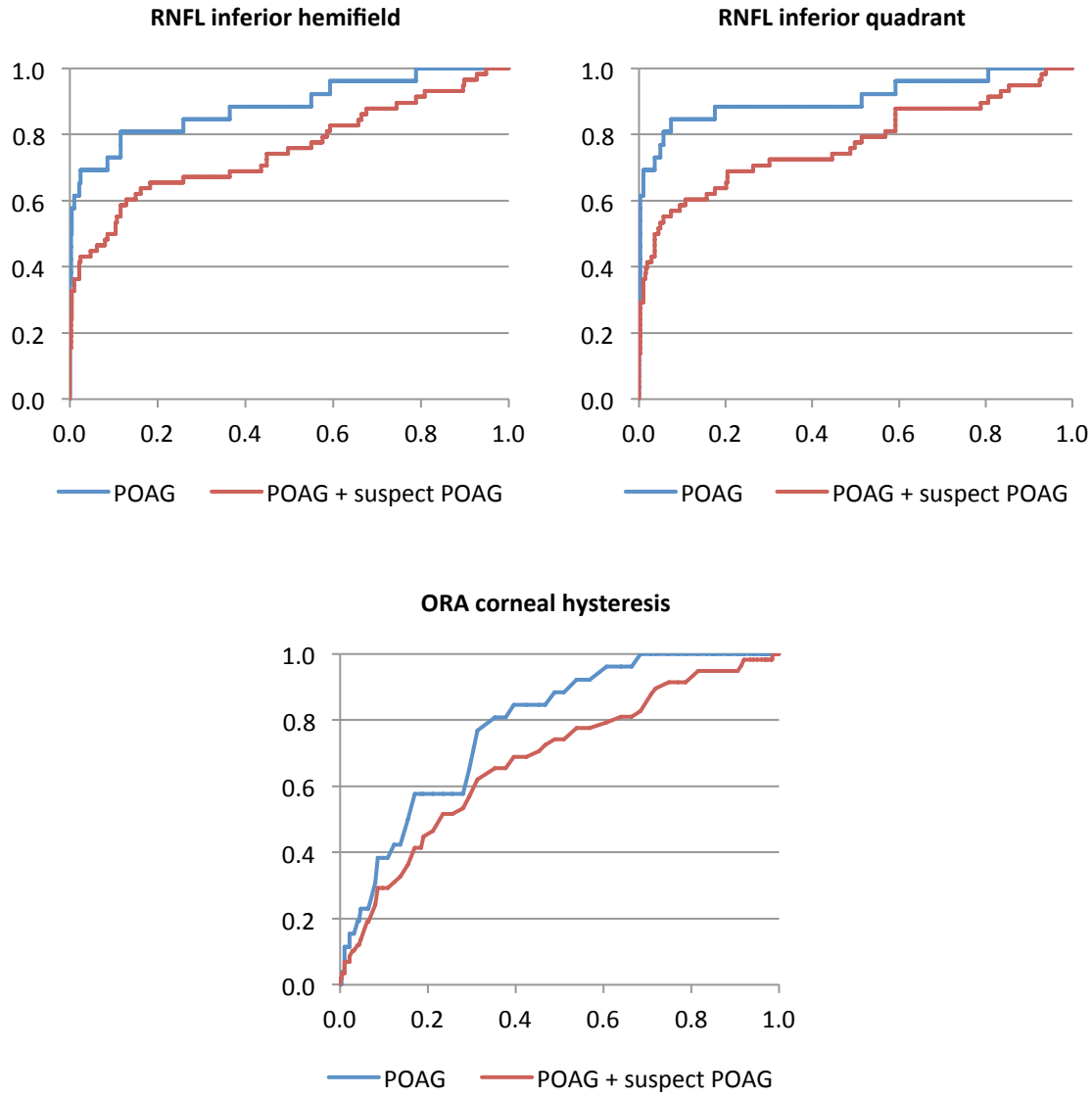


Figure 3.11 (continued): ROC curves (plotting sensitivity against 1-specificity) for detection of POAG and POAG/ suspect POAG combined using visual function tests (FDT, Patel et al. 2000 score and MMDT, global PTD), best performing iVue SD-OCT RNFL and GCC parameters and ORA corneal hysteresis (CH)

Figure 3.11 shows ROC curves plotted using continuous variable data from the best-performing iVue SD-OCT and ORA parameters, and visual-function tests. Analysis of ROC curve data for a false positive rate between 0 and 10% provides a more useful measure of index diagnostic test performance to detect a low prevalence condition such as POAG. Tables 3.7a and 3.7b detail sensitivities at 90% and 95% and partial AUROC curve estimates for ranges starting from 90% and 95% specificities. Overall, inferior quadrant RNFL thickness measured using the iVue SD-OCT was the best performing parameter providing highest sensitivities and partial AUROC curve estimates at 90% and 95% specificity for detection of POAG, and POAG/ suspect POAG combined. At 90% specificity, inferior quadrant thickness achieved 85% sensitivity and a 0.73

normalised partial AUROC curve value. In fact, inferior RNFL thickness was statistically significantly superior at discriminating between POAG and non-POAG/ non-OHT subjects than each of the visual function tests, based on sensitivity at set specificity (90%; FDT p=0.029, MMDT p=0.003 and 95%; FDT p=0.005, MMDT p=0.047) and partial AUROC curve estimates (90% and 95%; FDT and MMDT p<0.001) (see Figures 3.12a and 3.12b for a graphical plot of these comparisons).

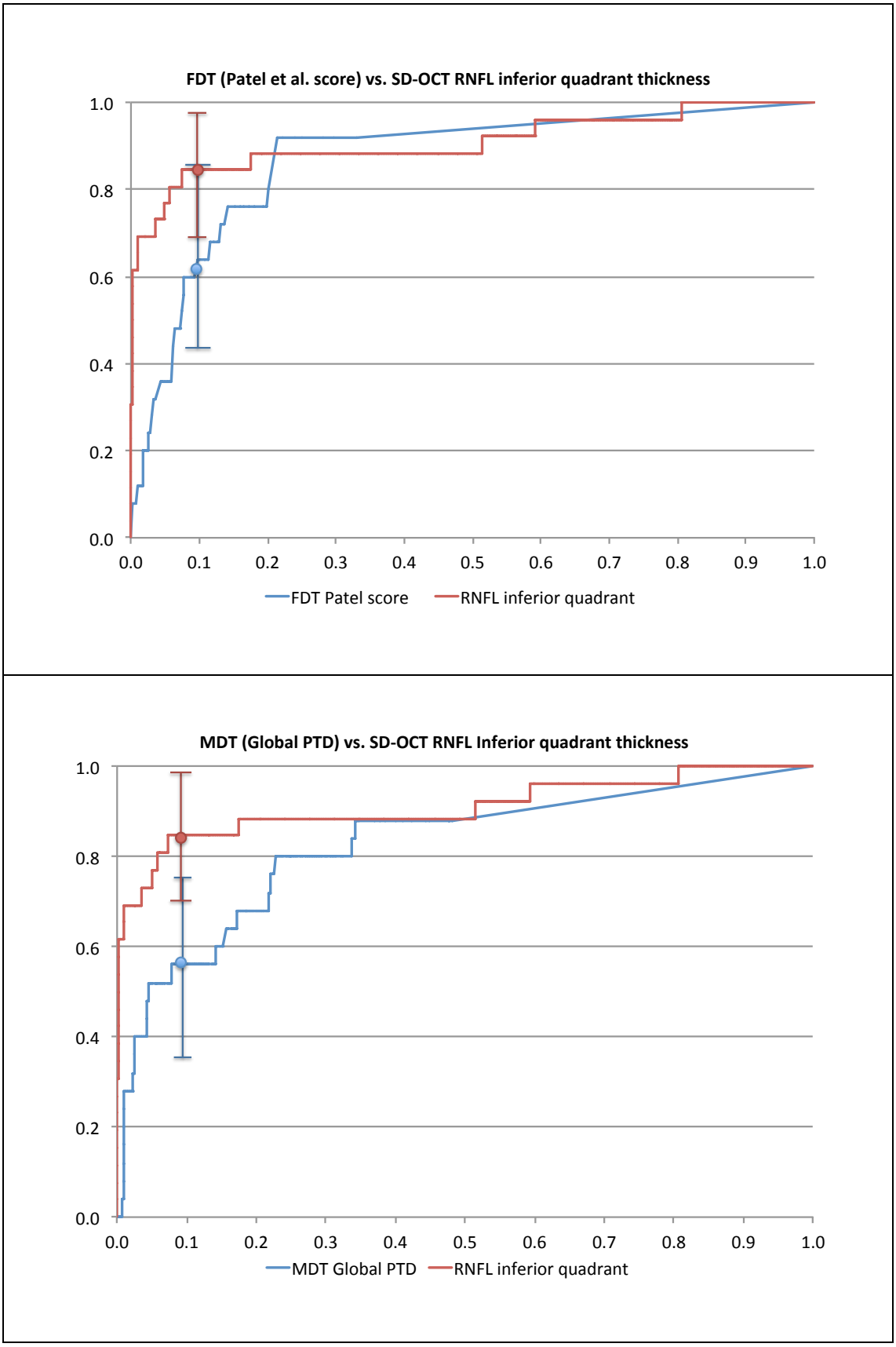
Of the 5 GCC parameters included in the analysis, inferior hemifield GCC thickness achieved highest sensitivities and partial AUROC curve estimates for ranges starting from 90% and 95% specificities for detection of POAG and POAG/ suspect POAG combined. Of the visual-function tests, FDT Patel et al. score (2000) achieved higher sensitivity (64%) but a lower partial AUROC curve result (0.36) compared with MMDT global PTD (56% sensitivity, 0.42 partial AUROC curve) for ranges starting from 90% specificity, but these observations did not represent a statistically significant difference (sensitivity at set specificity p=0.249, partial AUROC curve p=0.438) (Figure 9c).

	POAG		POAG and suspect POAG	
	Sensitivity at 90% specificity (CI)	**Sensitivity at 95% specificity (CI)**	**Sensitivity at 90% specificity (CI)**	**Sensitivity at 95% specificity (CI)**
FDT				
Patel et al. score	64.0 (42.8 to 85.2)	36.0 (13.3 to 58.7)	40.3 (26.6 to 54.1)	24.6 (11.6 to 37.5)
MMDT				
Global PTD	56.0 (36.1 to 75.9)	52.0 (29.4 to 74.5)	33.3 (20.0 to 46.7)	26.3 (12.9 to 39.8)
iVue OCT GCC				
Mean GCC	65.4 (47.1 to 83.6)	61.5 (41.3 to 81.7)	44.8 (32.0 to 57.7)	41.4 (27.3 to 55.4)
Superior hemifield	57.7 (37.9 to 77.4)	50.0 (29.1 to 70.9)	39.7 (25.2 to 54.1)	32.8 (19.7 to 45.8)
Inferior hemifield	73.1 (55.3 to 90.8)	69.2 (51.1 to 87.3)	48.2 (35.2 to 61.4)	44.8 (31.8 to 57.9)
FLV	69.2 (49.7 to 88.8)	50.0 (25.2 to 74.8)	44.8 (31.3 to 58.4)	29.3 (11.3 to 47.3)
GLV	69.2 (51.2 to 87.2)	65.4 (46.9 to 83.9)	46.5 (33.6 to 59.5)	39.6 (25.3 to 54.0)
iVue OCT RNFL				
Mean RNFL	65.4 (46.3 to 84.5)	65.3 (46.0 to 84.7)	46.5 (33.2 to 59.9)	43.1 (29.4 to 56.8)
Superior hemifield	61.5 (40.6 to 82.4)	50.0 (29.2 to 70.8)	41.3 (28.0 to 54.7)	32.8 (19.7 to 45.8)
Inferior hemifield	73.1 (54.7 to 91.4)	69.2 (50.9 to 87.5)	50.0 (35.8 to 64.2)	43.1 (30.6 to 55.6)
Superior quadrant	73.1 (55.9 to 90.2)	61.5 (38.6 to 84.5)	43.1 (30.0 to 56.2)	32.8 (19.3 to 46.2)
Inferior quadrant	84.6 (69.8 to 99.4)	73.1 (54.6 to 91.6)	56.9 (44.1 to 69.6)	50.0 (35.3 to 64.7)
ORA				
Corneal hysteresis	38.5 (18.0 to 58.9)	23.1 (6.4 to 40.0)	29.3 (16.5 to 42.1)	13.8 (3.4 to 24.2)

Table 3.7a: Sensitivity at 90% and 95% specificity for each index test parameter for detection of POAG and POAG/ suspect POAG combined

	POAG		POAG and suspect POAG	
	Partial AUROC from 90% specificity (CI)	**Partial AUROC from 95% specificity (CI)**	**Partial AUROC from 90% specificity (CI)**	**Partial AUROC from 95% specificity (CI)**
FDT				
Patel et al. score	0.36 (0.19 to 0.54)	0.22 (0.06 to 0.37)	0.24 (0.13 to 0.35)	0.15 (0.06 to 0.25)
MMDT				
Global PTD	0.42 (0.25 to 0.59)	0.31 (0.13 to 0.48)	0.23 (0.12 to 0.33)	0.15 (0.05 to 0.25)
iVue OCT GCC				
Mean GCC	0.53 (0.35 to 0.70)	0.41 (0.22 to 0.60)	0.34 (0.23 to 0.46)	0.25 (0.13 to 0.38)
Superior hemifield	0.42 (0.24 to 0.59)	0.29 (0.12 to 0.47)	0.27 (0.16 to 0.38)	0.19 (0.08 to 0.29)
Inferior hemifield	0.62 (0.46 to 0.79)	0.55 (0.36 to 0.73)	0.39 (0.27 to 0.51)	0.33 (0.20 to 0.46)
FLV	0.44 (0.28 to 0.60)	0.26 (0.09 to 0.44)	0.26 (0.15 to 0.38)	0.14 (0.04 to 0.24)
GLV	0.56 (0.39 to 0.73)	0.44 (0.15 to 0.63)	0.35 (0.23 to 0.47)	0.25 (0.12 to 0.38)
iVue OCT RNFL				
Mean RNFL	0.61 (0.42 to 0.79)	0.56 (0.37 to 0.75)	0.39 (0.28 to 0.51)	0.33 (0.21 to 0.45)
Superior hemifield	0.48 (0.29 to 0.67)	0.41 (0.22 to 0.61)	0.30 (0.19 to 0.41)	0.23 (0.12 to 0.34)
Inferior hemifield	0.65 (0.48 to 0.83)	0.61 (0.42 to 0.79)	0.41 (0.30 to 0.53)	0.36 (0.24 to 0.48)
Superior quadrant	0.55 (0.37 to 0.72)	0.41 (0.21 to 0.60)	0.30 (0.19 to 0.41)	0.22 (0.11 to 0.33)
Inferior quadrant	0.73 (0.57 to 0.89)	0.65 (0.47 to 0.83)	0.47 (0.35 to 0.58)	0.38 (0.26 to 0.50)
ORA				
Corneal hysteresis	0.20 (0.06 to 0.34)	0.12 (0.00 to 0.24)	0.14 (0.06 to 0.23)	0.08 (0.01 to 0.15)

Table 3.7b: Partial area under the ROC curve (PAUROC) data for ranges starting from 90% and 95% specificity for each index test parameter for detection of POAG and POAG/ suspect POAG combined



Figures 3.12a and 3.12b: Index test diagnostic effectiveness comparisons using ROC curves with sensitivity at set specificity estimates and associated 95% confidence intervals

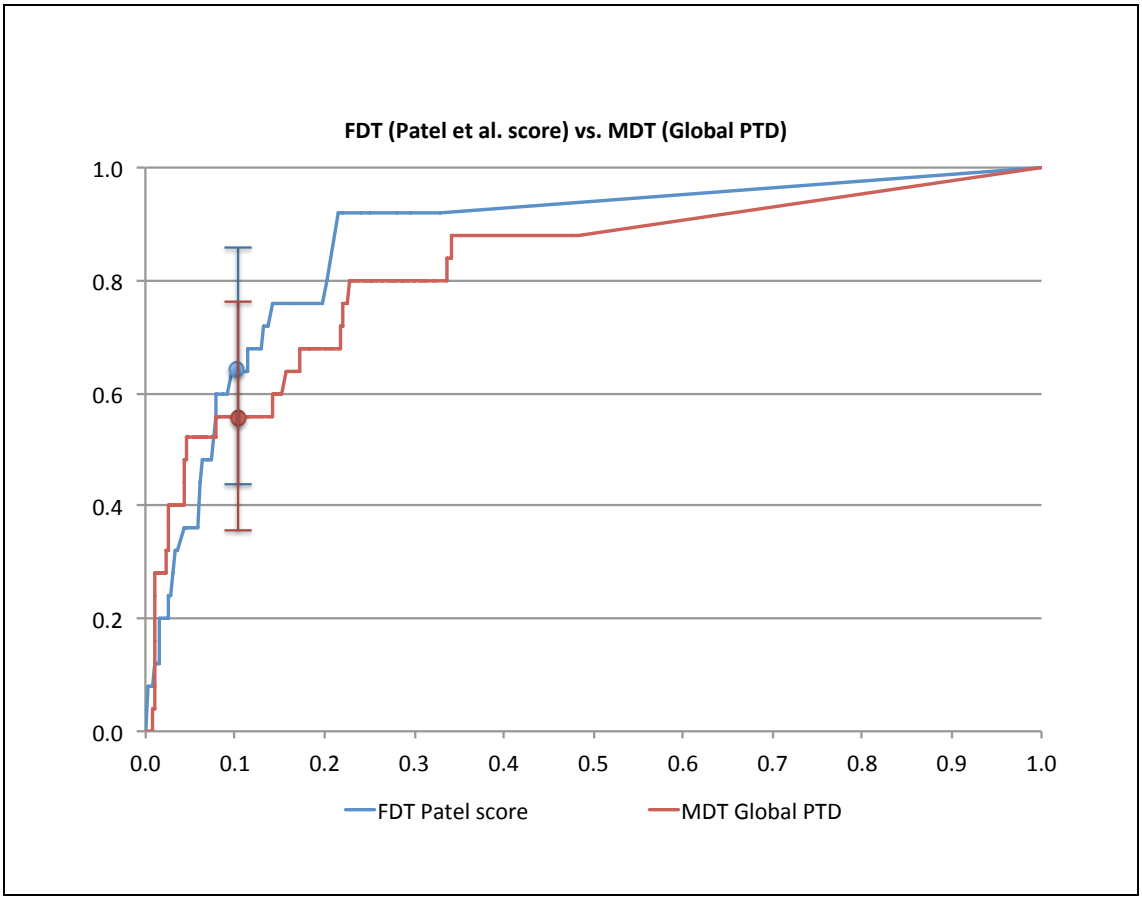


Figure 3.12c: Index test diagnostic effectiveness comparisons using ROC curves with sensitivity at set specificity estimates and associated 95% confidence intervals

3.3.3 Combining index test results for detection of POAG

The diagnostic effectiveness of combining index test results was explored using 2x2 tables to generate sensitivity and specificity estimates. For detection of POAG, the combination of inferior quadrant RNFL thickness (p<1%) with FDT (1 or more location(s) missed at any level) in which failure of either test is indicative of abnormality achieves 100% sensitivity but with a marked reduction in specificity (66%) (Appendix B, Table viii shows a tabulated summary of this test combination). On the other hand, stipulating that failure of both tests were indicative of POAG improved specificity to 98%, but this did not represent a statistically significant improvement above test specificity of 96% achieved by inferior quadrant thickness alone (McNemar, p=1.0).

An alternative approach to the evaluation of the diagnostic value of combining index test data was also explored using Bayesian probabilistic reasoning. Best-performing parameters and cut-offs for abnormality were selected using the highest positive likelihood ratios (+LR). The probability estimate of a given subject having POAG rose from 5% (pre-test probability) to over

90% (post-test probability) when visual function tests (FDT, 1 or more missed location at 1% level and MMDT, global PTD ≥3.0) were combined in series with best performing structural parameters (RNFL inferior quadrant thickness and GCC GLV, p<1%), and ORA CH (<9.1) measurements. Similar results were obtained for POAG/ suspect POAG combined group analysis (Table 3.8).

Test combination					Probability of POAG (%)	Probability of POAG and suspect POAG (%)
FDT (1 or more location missed at 1% level)	+	GCC GLV (p<1%)	+	ORA CH <9.1	93.5	90.3
FDT (1 or more location missed at 1% level)	+	RNFL inferior quadrant (p<1%)	+	ORA CH <9.1	92.9	90.7
MMDT (global PTD≥3.0)	+	GCC GLV (p<1%)	+	ORA CH <9.1	92.3	89.8
MMDT (global PTD≥3.0)	+	RNFL inferior quadrant (p<1%)	+	ORA CH <9.1	91.6	90.2

Positive likelihood ratios for detection of POAG and suspect POAG/ POAG combined:

- *FDT (1 or more location missed at 1% level) +LR = 4.5 (CI 3.6 to 5.7) and 3.2 (CI 2.4 to 4.2)*
- *MMDT (global PTD ≥3.0) +LR = 3.8 (CI 2.6 to 5.4) and 3.0 (CI 2.2 to 4.2)*
- *GCC GLV (p<1%) +LR = 22.4 (CI 9.9 to 50.9) and 11.9 (CI 5.1 to 27.4)*
- *RNFL inferior quadrant thickness (p<1%) +LR = 20.6 (CI 12.2 to 34.8) and 12.4 (CI 7.2 to 21.7)*
- *ORA CH (<9.1) +LR = 2.6 (CI 2.0 to 3.2) and 1.9 (CI 1.5 to 2.3)*

Table 3.8: Summary of combined analysis of index test data using Bayesian probabilistic reasoning for detection of POAG and suspect POAG/ POAG combined

Figure 3.13 constructs Venn diagrams combining visual-function (FDT and MMDT), structural (iVue SD-OCT) and corneal biomechanical (ORA) data for detection of POAG. Notably, the combination of either iVue SD-OCT parameter (GCC inferior hemifield or RNFL inferior quadrant) with FDT (1 or more missed location at any level) and ORA CH (<9.1) detected all 26 subjects classified as POAG in the reference standard ophthalmic examination.

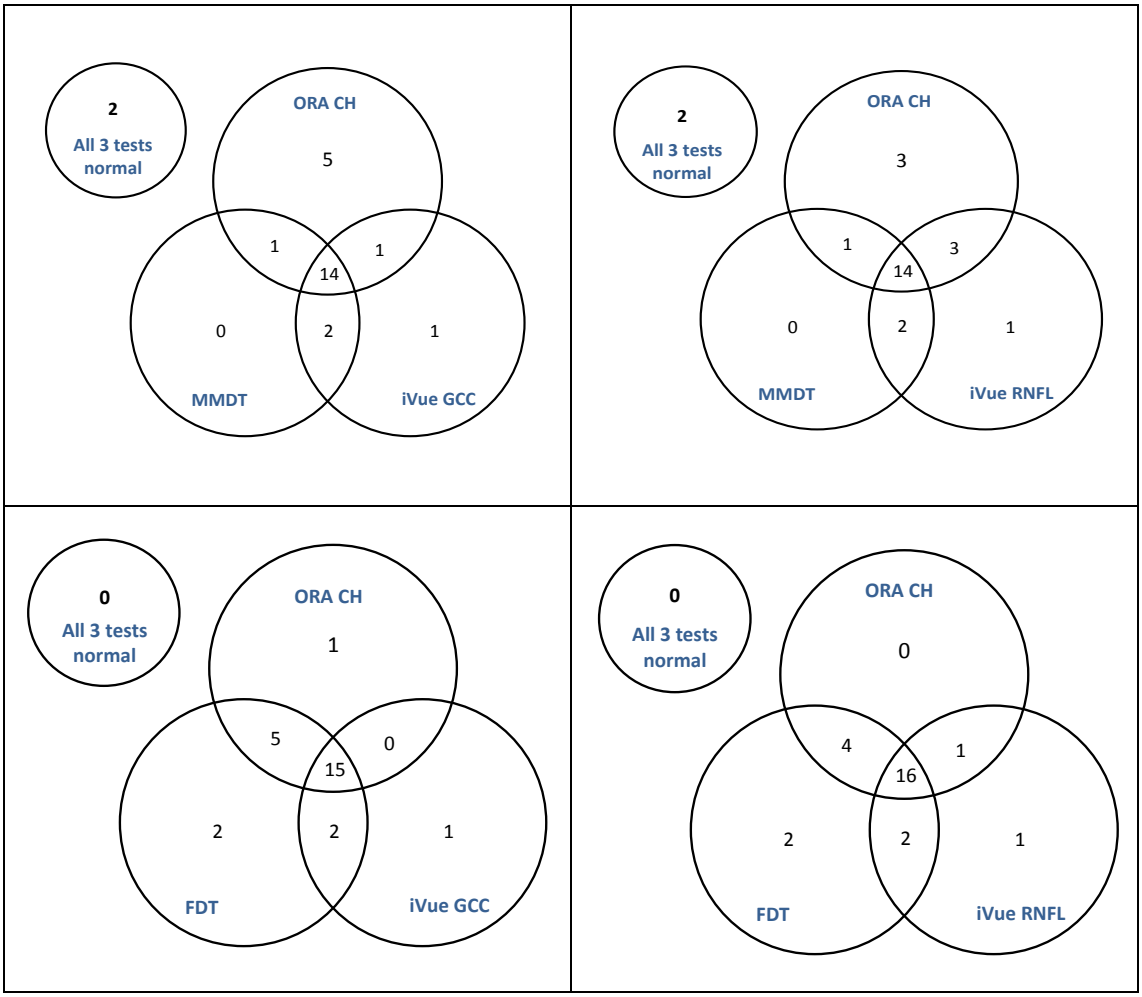


Figure 3.13: Venn diagrams presenting combined index test results for identification of POAG using various cut-offs; FDT (1 or more missed location at any level), MMDT (global PTD ≥3.0), iVue SD-OCT GCC inferior hemifield and RNFL inferior quadrant thickness (P<1%), ORA CH (<9.1). For example the combination of either iVue SD-OCT parameter (GCC inferior hemifield or RNFL inferior quadrant) with FDT (1 or more missed location at any level) and ORA CH (<9.1) detected all 26 glaucoma subjects classified as POAG.

3.3.4 User acceptability survey

Table 3.9 summarises aggregated Likert scale subject responses to the user acceptability survey. Overall, all index tests were well received with over 90% of respondents finding that the tests were comfortable, not too long, and easy to perform. An estimated 5% or fewer respondents agreed that visual function tests (FDT and MMDT) were 'uncomfortable', 'too long' or 'difficult to undertake' compared with 12 to 26% for HFA testing, representing a statistically significant difference (Wilcoxon signed ranks test, p<0.001). Interestingly, of the visual function index tests, a greater proportion of subjects reported difficulty undertaking FDT

perimetry compared with the MMDT, but this did not represent a statistically significant difference at the p<0.01 level (Wilcoxon signed rank test with multiple comparisons, p=0.018). No significant difference was observed between responses to the other statements.

A total of 216 (43%) subjects responded to the 'additional comments' box at the end of the survey. Responses were coded into three main categories: responses relating to screening tests, responses relating to researchers and other comments. Of the 139 comments relating to test experience, 74 (53%) were classified as 'positive' and 54 (39%) 'negative'. Of this 'negative' group, the majority of comments (65%, 24 of 37) made reference to the HFA followed by the FDT (19%, 7 of 37) perimeter. Other more general comments in the 'negative' group referred to tests being 'tiring/ difficult' (n=5), the need for concentration (n=10) and difficulty with posture during examinations (n=7).

	The test was uncomfortable N (%)			**The test was too long N (%)**			**The test was difficult to undertake N (%)**		
	Disagree	**Neither agree nor disagree**	**Agree**	**Disagree**	**Neither agree nor disagree**	**Agree**	**Disagree**	**Neither agree nor disagree**	**Agree**
FDT	477 (94.5)	12 (2.4)	16 (3.2)	479 (94.9)	15 (3.0)	11 (2.2)	467 (92.5)	13 (2.6)	25 (5.0)
MMDT	477 (94.5)	11 (2.2)	17 (3.4)	480 (95.0)	12 (2.4)	13 (2.6)	470 (93.1)	20 (4.0)	15 (3.0)
HFA*	405 (80.2)	39 (7.7)	61 (12.1)	332 (65.7)	42 (8.3)	131 (25.9)	404 (80.0)	32 (6.3)	69 (13.7)
iVue OCT	475 (94.1)	12 (2.4)	18 (3.6)	470 (93.1)	16 (3.2)	19 (3.8)	472 (93.5)	17 (3.4)	16 (3.2)
ORA	433 (85.7)	24 (4.8)	48 (9.5)	476 (94.3)	20 (4.0)	9 (1.8)	477 (94.5)	16 (3.2)	12 (2.4)

**HFA formed part of the reference standard examination with data being presented for comparison.*

Table 3.9: Aggregated Likert scale responses to index test acceptability survey in response to the statements a) 'The test was uncomfortable', b) 'the test was too long', and c) 'the test was difficult to undertake'

3.4. Discussion

Glaucoma is the second leading cause of blindness worldwide (Quigley & Broman, 2006, WHO, 2012). The global prevalence for all glaucomas in people aged 40 to 80 years is estimated to be 3.54% (Tham et al., 2014), with open angle glaucoma (OAG) being the commonest cause (Quigley & Broman, 2006, Tham et al., 2014). The World Health Organisation (WHO) estimates that 2% of visual impairment and 8% of blindness is attributable to glaucoma (WHO, 2012). However, data for the number of severely sight impaired registrations attributed to POAG are likely to be underestimated (King et al., 2000). Moreover, epidemiological studies in developed countries have demonstrated that approximately half of the population affected by OAG remains undetected using current screening strategies (Tielsch et al., 1991a, Klein et al., 1992, Mitchell et al., 1996, Quigley & Vitale, 1997, Wensor et al., 1998).

In 1968, Wilson and Jungner outlined ten criteria for appraising the viability, effectiveness and appropriateness of a screening programme (Wilson & Jungner, 1986). OAG fulfills criteria regarding the condition and treatment, but does not meet requirements for an appropriate diagnostic test or availability of evidence for the effectiveness of a screening programme. OAG is an important public health problem, and effective treatment is available in the form of pressure-lowering therapies. However, currently available screening tests, used alone or in combination, fail to demonstrate sufficient accuracy to detect people at risk of visual impairment due to OAG (Burr et al., 2007). In the context of screening for a low prevalence disease such as glaucoma, tests would need to combine high specificity, ideally above 90%, with an acceptably high sensitivity in order to achieve a reasonable positive predictive value. Moreover, no high quality randomized controlled trials have been undertaken to investigate the value of a screening programme for glaucoma in reducing mortality and morbidity (Fleming et al., 2005, Hatt et al., 2006, Burr et al., 2014).

In the context of the UK healthcare system, Burr et al. (2007) evaluated whether 'opportunity cost of a screening programme for glaucoma would be economically balanced in relation to expenditure on medical care as a whole'. Using economic modeling of cost-effectiveness and cost-utility, large-scale population screening for POAG in a population selected on the basis of age alone was proved unlikely to be cost-effective, but stronger evidence was found in support of targeted screening e.g. people with a family history of glaucoma (Burr et al., 2007). The review also identified the need for high-quality studies to evaluate the clinical effectiveness of screening tests, alone or in combination, in large cross-sectional population-based surveys. Based on the available literature, four tests were recognised as being potentially suitable for

use in a screening programme to detect OAG, including HRT II and Frequency doubling technology (FDT) perimetry. At the time of the review, high quality studies evaluating Optical Coherence Tomography (OCT) technology for OAG detection were lacking. OCT has since been established as a clinical diagnostic tool for the detection of disorders of the macula and optic nerve (Chen et al., 2007), and its popularity in UK community optometric practice has exceeded that of other advanced imaging systems such as the HRT (Dabasia et al., 2014). The current study evaluated the clinical effectiveness and acceptability of structural and functional tests to detect POAG in a representative population. Of the 505-subject cohort, median age was 68 years, male to female distribution was 41:58, and the vast majority (88%) of subjects were White.

3.4.1 Diagnostic effectiveness of visual-function tests (FDT + MMDT)

Static standard automated perimetry (SAP) using the HFA in threshold mode is the acknowledged reference standard for the assessment of visual function in glaucoma. However, the test is of limited use for screening as it is time-consuming, suffers from a lack of standard agreement as to what constitutes a test failure, and is unable to provide reliable results in a subset of the population (Burr et al., 2007). HFA apparatus is also bulky and difficult to transport. As such, researchers have sought to develop alternative tests of visual-function that may be better suited to screening of OAG such as FDT perimetry and the MDT.

A wide range of FDT perimetry cut-offs for detection of glaucoma have been used, with the commonest being one or more location(s) missed at any level of significance. Other authors use scoring systems which account for the number, position and level of significance of missed locations (e.g. Patel et al., 2000). Muskens et al. evaluated 15 algorithms for the FDT based on previous reports and surmised that none performed substantially better than simply counting the number of missed locations at the $p<1\%$ level of significance (Muskens et al., 2004). Using this criterion in our population provided 80.5% sensitivity and 88.5% specificity for detection of glaucoma. Test sensitivity improved above 90% when test failure was defined as one or more location missed at any level of significance, but with an unacceptable reduction in specificity of 67%. Figure 3.14 shows the variation in diagnostic estimates using the common FDT cut-off and C20-5 protocol between the present study and five previous reports; three population-based studies (Detry-Morel et al., 2004, Mansberger et al., 2005, Robin et al., 2005), and two case-control studies (Johnson et al., 1998/1999, Pierre-Filho Pde et al., 2006). Differences may be attributed to characteristics of the populations studied, including demographics, ocular co-morbidity and prevalence and severity of glaucoma. Studies also employed different reference

standards to diagnose glaucoma. In particular, sensitivity estimates ranged between 7% (Mansberger et al., 2005) and 100% (Johnson et al., 1998/1999). Mansberger et al. performed a cross-sectional survey of inhabitants of five rural villages in India, defining glaucoma by ophthalmological assessment of optic disc photographs (Mansberger et al., 2005). In contrast, Johnson et al. reported findings of a case-control study undertaken in the United States (Johnson et al., 1998/1999). Ethnic distribution and criteria for classification of glaucoma are unclear, but the authors did report numbers diagnosed with early, moderate and advanced glaucoma. The inclusion of a high proportion of moderate and advanced OAG (55%) may have led to a non-generalisable estimate of sensitivity for detection of glaucoma. Each study design was subject to differing levels of bias which may have influenced diagnostic estimates. A meta-analysis of two high quality studies for the detection of OAG using the FDT C20-5 protocol and the cut-off of one or more missed locations (Burr et al., 2007), reported a pooled sensitivity of 72% and specificity of 60%, which were lower than those found in the current study.

FDT C20-5 protocol comparison with the literature (cut-off ≥1 location missed at any level of significance)

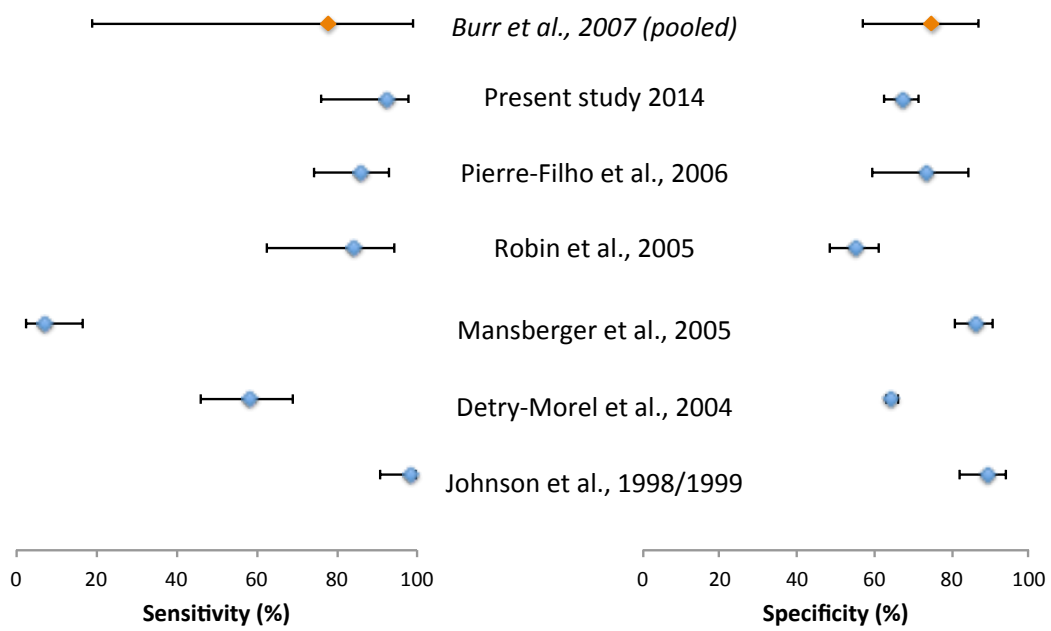


Figure 3.14: Sensitivity and specificity estimates with associated 95% confidence intervals for detection of OAG using FDT C20-5 and a cut-off of one or more location(s) missed at any level of significance

Pooled estimate of 5 studies by Burr et al., 2007 using the C20-5 protocol and common cut-off for abnormality (Johnson et al., 1998/1999, Khong et al., 2001, Detry-Morel et al., 2004, Mansberger et al., 2005, Robin et al., 2005)

FDT perimetry specificity estimates shown in Figure 3.14 vary between 55% and 89%. Khong et al. sought to evaluate whether repeat testing could improve specificity but observed marginal improvement, leading authors to conclude that the C20-5 programme was sensitive but not specific for glaucoma (Khong et al., 2001). Johnson et al. suggested possible improvement in specificity with use of an alternative cut-off of two clustered abnormal points to detect OAG (Johnson et al., 1998/1999). Alternatively, use of the FDT C20-1 protocol in which stimuli are initially presented at a contrast that can be detected by 99% of the normal age-matched population may provide better test specificity for large-scale population screening.

Whilst the concept of using peripheral motion detection thresholds to screen for OAG was explored in the 1990's (Ruben & Fitzke, 1994), it has only recently been incorporated into a device that is suitable for routine clinical testing. Only one full paper on the use of MDT ESTA 99.5 programme for glaucoma detection has been published. Using the developers' recommended cut-off for abnormality based on PTD ≥3.0, Ong et al. reported 81% sensitivity and 96% specificity for detection of OAG (Ong et al., 2014). These estimates are considerably higher than those achieved by the present study population (64% sensitivity and 83% specificity). However, Ong et al. defined glaucoma using two structural tests; clinical observation of glaucomatous optic neuropathy together with HRT-based results described as 'outside normal limits' in any sector (Ong et al., 2014). Their population was enriched with glaucoma subjects, and a greater proportion was classified with moderate or advanced disease (78%) than in the present study (58%). Potentially, these factors may have led to an estimation of test sensitivity which is unachievable in a sample more representative of older people in general. Moreover, examination of an unselected population introduces comorbid conditions likely to reduce specificity when compared with the strict inclusion criteria for normal subjects stipulated by Ong et al. (2014). Interestingly, diagnostic estimates of a previous case-control study, described in a PhD thesis, of 130 glaucoma and 132 age-matched normal subjects using the MDT ESTA protocol provided results more comparable to the current study. The author reported slightly lower sensitivity at 90% and 95% specificity of 50% and 46% respectively for detection of glaucoma than observed in the present study (56% and 52% respectively) (Bergin, 2011).

Overall, FDT perimetry showed higher sensitivity but lower specificity for detection of POAG than MDT. This may in part be attributed to the presentation of initial stimuli at different normal age-adjusted levels (95% FDT and 99.5% MDT). Specificity for detection of OAG by FDT

perimetry was improved to just above 88% using a cut-off of one or more location(s) missed at the 1% level of significance. Similarly, higher sensitivity was achieved by use of a lower MDT PTD cut off of 1.5, but this results in an unacceptable reduction in specificity below 80%. Partial AUROC and sensitivity at set specificity estimates revealed no statistically significant differences for detection of OAG or suspect glaucoma between the FDT and MDT, implying essentially equivalent performance in detection of glaucoma. In the context of test performance in a screening setting, it is notable that FDT and MDT examinations were completed for all eyes. Following repeat testing, 96% of FDT and 99% of MDT plots were reliable. Interestingly, a significantly greater proportion of unreliable FDT plots were observed following repeat examination of the left eye (always tested second) compared with the right eye. This observation has been previously reported (Tatemichi et al., 2003, Iwase et al., 2007), and may be a function of fatigue or delayed light adaptation following occlusion during fellow eye testing (Anderson & Johnson, 2002). While FDT affords the advantage of shorter test duration, this in part is negated by the need to repeat a greater proportion of tests (42% FDT, 28% MDT) on the basis of poor reliability or missed locations. Both tests are portable and easy to administer, but the laptop design of the MDT may provide potential cost savings with implications for screening programmes.

3.4.2 Diagnostic effectiveness of iVue OCT (RNFL and GCC thickness)

iVue OCT data were evaluated for detection of suspect and definite glaucoma using two paradigms; retinal nerve fibre layer (RNFL) and ganglion cell complex (GCC) thickness. The iVue OCT is a recently developed spectral domain OCT, and only one report of diagnostic effectiveness to detect glaucoma was found (Awad et al., 2013). Awad et al. reported sensitivity and specificity of the iWellness screening protocol (a composite of macula cross-section and GCC scan) to detect subjects with confirmed disease (Awad et al., 2013). 42 OAG subjects were included in the analysis, but diagnostic performance was reported for all 50 subjects with optic nerve disorders precluding comparison with present study findings. The iVue OCT is a compact version of the RTVue OCT, so diagnostic comparisons with the literature are based on measurements acquired by RTVue OCT. Initially, data were analysed using normative database colour-banded outputs. A result indicative of OAG was flagged in red to represent data outside the 99% normal confidence interval. The iVue normative database is based on the examination of 521 subjects with mean age of 42.5 years and wide ethnic distribution (which includes 47% White and 19% South Asian).

Average, superior and inferior RNFL thicknesses were better predictors of glaucomatous loss than nasal or temporal measurements, a finding reported previously (Sehi et al., 2009, Rao et al., 2010, Leite et al., 2011). Greater nerve fibre loss superiorly and inferiorly is expected based on their susceptibility to damage in early glaucoma. Using normative database outputs (p<1%), all RNFL parameters provided mean test specificities exceeding 90%. However, inferior quadrant RNFL thickness showed best discrimination between POAG and normal subjects achieving sensitivity and specificity of 77% and 96% respectively. Interestingly, Garas et al. reported equivalent sensitivity and specificity of 84% and 98% respectively for glaucoma detection using a p<5% cut-off (Garas et al., 2011). In the current study, inferior quadrant RNFL thickness also provided greatest sensitivity at set specificity compared with superior quadrant or average RNFL thickness. This observation is consistent with findings of three of the six reports summarised in Table 3.10 (Sehi et al., 2009, Rao et al., 2010, Rao et al., 2012).

Study	**Inferior quadrant RNFL Sensitivity at set specificity (%)**	**Superior quadrant RNFL Sensitivity at set specificity (%)**	**Overall average RNFL Sensitivity at set specificity (%)**
Sehi et al., 2009	94/90	58/90	80/90
Leite et al., 2011	62/95	64/95	62/95
Rao et al., 2012	58/95	33/95	46/95
Rao et al., 2010	71/95	48/95	65/95
Fang et al., 2010	65/95	59/95	73/95
Seong et al., 2010	90/90 86/95	88/90 78/95	94/90 88/95
Present study	85/90 73/95	73/90 61/95	65/90 65/95

Table 3.10a: Sensitivity at set specificity data using best performing RNFL thickness parameters reported in the literature and compared with present study findings for detection of glaucoma

Study	Overall average GCC	Inferior hemifield GCC	GLV GCC	Superior hemifield GCC	FLV GCC
Rao et al., 2012	37/95	44/95	45/95	32/95	53/95
Rao et al., 2010	41/95	49/95	76/95	30/95	78/95
Fang et al., 2010	62/95	65/95	---	38/95	---
Seong et al., 2010	84/90 83/95	84/90 81/95	--- ---	68/90 59/95	---
Present study	65/90 61/95	73/90 69/95	69/90 65/95	58/90 50/95	69/90 50/95

Table 3.10b: Sensitivity at set specificity data using best performing GCC parameters reported in the literature and compared with present study findings for detection of glaucoma

Tan et al. introduced alternative parameters to provide more in-depth analysis of GCC data, namely GLV and FLV (Tan et al., 2009). These provide a measure of the total volume of GCC loss in the macular region using differing levels of focality, which are analogous to Humphrey VFA mean deviation (MD) and pattern standard deviation (PSD) indices (Tan et al., 2009). The authors observed better diagnostic accuracy for detection of glaucoma using these volume parameters than average GCC thickness. In contrast, of the five GCC parameters analysed in the present study, inferior hemifield GCC thickness provided greatest partial AUROC curve estimates (0.61 to 0.55), and highest sensitivities at 90% and 95% specificity (73% and 69%). A true measure of any statistically significant differences in diagnostic performance between test parameters cannot be demonstrated in the current study given the limited number of POAG subjects in the cohort.

Literature searching revealed conflicting reports of the diagnostic effectiveness of RNFL parameters compared with GCC parameters (Fang et al., 2010, Schulze et al., 2011, Arintawati et al., 2013). In view of this heterogeneity between RNFL and GCC diagnostic performance, it is unclear whether one or a combination of diagnostic parameters should be used to improve detection of glaucoma. It is notable that using a combined cut-off for abnormality defined by any RNFL parameter (7 parameters; 2 hemifields, 4 quadrants and average RNFL thickness) exceeding 99% normative limits achieved better sensitivity than any parameter alone (88.5%, see Table 3.6 and Appendix B, Table v, for tabulated diagnostic summary data) while still retaining specificity above 90%. Moreover, combining any RNFL (n=7) or GCC (n=5) parameter

at the p<1% level identifies 25 of 26 glaucoma subjects, representing 96% sensitivity. The diagnostic effectiveness of combining structural measures of peripapillary and macular retinal thickness has been previously demonstated using RTVue OCT (Tan et al., 2009, Fang et al., 2010, Huang et al., 2011) and Status OCT (Lu et al., 2008).

3.4.3 Diagnostic effectiveness of ORA

ORA-derived IOP estimates were of limited diagnostic value in our population as half of the 26 glaucoma subjects were already receiving IOP lowering therapy at the time of the study or had previously undergone surgical or laser interventions. Instead, we opted to explore diagnostic capabilities of ORA-generated corneal biomechanical parameters, namely corneal hysteresis (CH) and corneal resistance factor (CRF). CH is a viscoelastic property of the cornea, which describes the ability of corneal tissue to absorb and dissipate energy. Mean CH has been estimated to be between 9.6mmHg and 12.2mmHg in a normal population (Anand et al. 2010). In accordance with previous reports, statistically significantly lower mean CH (8.2mmHg) was recorded among glaucoma patients in our cohort compared with non-glaucoma/ non-OHT subjects (Sullivan-Mee et al., 2008, Wells et al., 2008, Mangouritsas et al., 2009, Abitbol et al., 2010, Anand et al., 2010). An experimental study of 100 subjects showed a relationship between optic disc compliance (deepening of the optic nerve due to IOP elevation) and CH in subjects with glaucoma (Wells et al., 2008). Researchers have also established a relationship between glaucomatous visual field progression and low CH (Congdon et al., 2006, De Moraes et al., 2012, Medeiros et al., 2013). In particular, Anand et al. observed 0.7mmHg mean difference in CH between the better and worse eye defined by visual field examination of subjects with asymmetric POAG (Anand et al., 2010). However, the cause-effect relationship is debated among researchers as to whether lower CH is the result of glaucomatous damage or an indicator of susceptibility to glaucomatous damage (DeMoraes et al., 2012). The latter proposes that lower corneal CH reflects reduced ability of the optic nerve to absorb increases in IOP and/ or respond to IOP changes.

In the current study, a Youden index-derived CH cut-off of 9.1mmHg for detection of glaucoma yielded 77% sensitivity and 69% specificity. These moderate diagnostic estimates reveal a considerable degree of overlap in CH between glaucomatous and normal subjects, precluding its use as an independent diagnostic tool.

3.4.4 A summary of the diagnostic performance of index tests

Differentiating between eyes with suspicious features of glaucoma and normal eyes presents a significant clinical challenge, as there is a substantial degree of overlap of clinical characteristics between the groups. Using the iVue OCT as an example, a healthy eye can exhibit features that may lead to incorrect classification by normative database algorithms as abnormal (e.g. an eye with a tilted optic disc). All four-index tests evaluated in this study showed poorer discrimination between normal subjects and glaucoma/ suspect glaucoma groups combined than between normal subjects and those with confirmed glaucoma (i.e. excluding the suspect glaucomas). This is unsurprising given that criteria for inclusion of suspect glaucoma were based on either observation of suspect glaucomatous optic neuropathy or a suspect glaucomatous visual field defect. Subjects with suspicious features of the optic disc but an essentially normal visual field are less likely to be detected by visual-function tests (FDT and MDT). Similarly, iVue OCT is less likely to show better discrimination between subjects with evidence of glaucomatous visual field defects and healthy optic discs.

Given that prevalence of glaucoma increases with age, it is important to consider whether index tests were able to accurately detect the condition despite the presence of confounding factors, such as cataract. These comorbidities may have contributed to poorer test specificities for detection of glaucoma using visual-function tests (FDT and MDT) than those obtained for iVue structural parameters. To explore this further, test specificity was recalculated following removal of data acquired from eyes of subjects observed to have comorbidities likely to impact on structure and function. Visual-function test specificity rose by 7- 8%, with lesser improvement for iVue OCT thickness parameters (2 - 3%). Notably, this improved MDT specificity to 90% using the manufacturers recommended cut-off for abnormality (global PTD ≥3.0). Moreover, a greater proportion of subjects with cataract in the non-glaucoma/ non-OHT group passed MDT (62%) than FDT (43%). This suggests FDT is not specific for glaucoma, and/or the MDT is more resistant to the effects of cataract (Bergin et al., 2011).

3.4.5 Combining index test data

Intuitively, combining information from structural and functional tests represents the most appropriate strategy for the detection of glaucoma (Caprioli, 1992, Mardin et al., 2006, Shah et al., 2006, Hong et al., 2007, Bowd et al., 2008, Mwanza et al., 2014). In some people with early disease, structural changes precede functional loss, whilst in others functional abnormalities may be observed before detectable changes in structural parameters (Kass et al., 2002). In our

population, structural imaging alone (specifically inferior quadrant RNFL thickness using the iVue OCT) showed significantly better diagnostic capability to detect glaucoma than either of the visual-function tests (FDT and MDT). Furthermore, sensitivity was not substantially improved by recalculating the 2x2 table based on the presence of a structural imaging parameter outside the 99% confidence interval or a failed functional test. In the context of case-finding for a low prevalence disease, consideration should also be given to maximizing the specificity of the diagnostic strategy. With the aim of improving overall specificity, we evaluated the impact of a criterion based on the combination of a reduced inferior quadrant RNFL thickness ($p<1\%$) together with 1 or more missed locations on the FDT. Although this approach increased specificity to 98%, it did not provide a statistically significant improvement ($p=1.0$, McNemar test) over inferior quadrant RNFL thickness alone (96% specificity), and also led to a corresponding reduction in sensitivity. However, these findings should be interpreted in the light of the diagnostic criteria used in the current study (i.e. based on combined structural and functional damage), and it is possible that these results would not be generalizable to the detection of early OAG defined by either structural or functional damage.

When case-finding for glaucoma, a clinician will typically combine an individual's risk of developing the disease based on age, ethnicity and family history with the results of diagnostic tests to make a decision regarding the likely presence or absence of disease. Consequently, diagnostic test results will be interpreted differently depending on individual's baseline risk. For example, a patient with raised IOP, a suspicious disc and a first degree relative with glaucoma is likely to have a high pre-test probability of disease. The results of diagnostic tests will then be used to modify the probability of disease. It has been suggested that the best way of incorporating diagnostic test results into clinical practice is through the use of likelihood ratios (Deeks & Altman, 2004). The likelihood ratio summarises how many times more (or less) likely it is that a person with the target disease will have a particular test result compared to someone without. A likelihood ratio greater than one indicates that a particular test result is associated with an increased risk of the presence of the disease and a ratio less than one indicates that the test result is associated with a decreased risk of the presence of the disease. The greater the likelihood ratio the more likely a positive test result will predict disease. Likelihood ratios can be translated into probability of disease using Bayes theorem which describes the process of updating beliefs in the light of new evidence. In the context of screening it describes how the results of a diagnostic test (positive or negative) will change the likelihood of disease. By combining the pre-test probability with the likelihood ratio of the diagnostic test, it is possible to calculate the post-test probability. Fagan's nomogram is a graphical tool which can be used to avoid the necessity of performing a mathematical

calculation (Deeks & Altman, 2004). Using this approach, independent diagnostic tests can be combined in series to revise estimates of post-test probability. From the results of the current study with a pre-test probability of OAG of 5% based on our population, a patient with a combined iVue-OCT GCC GLV measurement outside the 99% confidence interval (LR=22.4), one or more points missed on the FDT at the 1% level of significance (LR=4.5), and ORA corneal hysteresis less than 9.1mmHg would have an estimated 93% post-test probability of having glaucoma. This combined approach has significant potential for community-based glaucoma case-finding and could be used to develop diagnostic algorithms and inform referral pathways. Similarly this Bayesian approach could be incorporated into future population screening pathways for at-risk individuals.

3.4.6 Implications for screening and case-finding of POAG

Advances in technologies to identify individuals with POAG may offer increasing opportunities to develop screening programmes, with the purpose being to reduce visual loss and progression to blindness through earlier diagnosis and initiation of therapy. In accordance with NSC UK guidelines, a screening test should be "*simple, safe, precise and validated"*. Additional attributes of an ideal screening test include portability, high degree of acceptability to patients, and the ability to acquire interpretable data in the vast majority of individuals. Perimetry can be challenging, particularly among older subjects, and a significantly greater proportion of subjects in the current study reported the HFA test to be more 'uncomfortable', 'too long' or 'difficult to undertake' than any of the four index tests, which included FDT perimetry. These findings are congruent with a qualitative investigation of patients' views on visual field testing for glaucoma monitoring, in which the test was found to be onerous, time-consuming and tiring (Glen et al., 2014). Acceptability to subjects of the four index tests used in the present study with respect to the three statements on which they were asked to comment was high. Of the four index tests, a greater proportion of subjects reported difficulty undertaking FDT compared with MDT, and the ORA was reported to be the most uncomfortable test.

The present study showed good capability of iVue OCT parameters to discriminate between normal and glaucomatous subjects. Structural automated assessment also satisfies additional criteria for an ideal screening test (e.g. providing rapid objective measurements). The iVue OCT is a compact version of the RTVue OCT, and is more easily transportable using a mobile unit or otherwise. Moreover, measurements were acquired without pupil dilation in the vast majority of subjects, further increasing the ease with which data may be obtained in a

screening setting. In this population, improved estimates of the probability of an individual having glaucoma were obtained when iVue OCT was performed in series with visual-function tests and the ORA. The inclusion of tests for both structure and function for case-detection may also allow for the small proportion of subjects in whom clinically useful structural data acquisition is precluded (e.g. poor quality scans or where dimensions of the optic nerve fall outside the normal range, rendering software outputs of limited value) or when a reliable visual function result cannot be obtained. Presently, evidence from high-quality randomized controlled trials on larger populations to inform clinical practice as to the best use of structural data to screen for glaucoma is lacking. For example, should an RNFL/ GCC parameter exceeding 99% normative limits alert the clinician to the benefit of referring for further ophthalmological investigation, or would use of the p<5% cut-off be more appropriate? Another important factor is that different OCT models are not interchangeable, particularly as each provides software outputs based on different normative databases (Lee et al., 2011).

Currently, a population-based screening programme for OAG has not been implemented in any country. Wilson and Jungner initially documented the need for '*opportunity cost of a screening programme to economically balance in relation to expenditure on medical care as a whole*'. Burr et al. used economic modeling to evaluate the clinical and cost-effectiveness of screening for POAG and concluded that this criterion would not be satisfied using population-based screening (Burr et al., 2007). The Markov model explored by Burr et al. (2007) used a range of POAG prevalences, as higher prevalence is more likely to be cost-effective for screening. They concluded that cost-effectiveness may only be approached if prevalence of OAG was between 3 and 4% at 40 years, with use of a 10-year screening interval. Prevalence of POAG among high-risk populations (e.g. Black ethnicity and family history of glaucoma) is estimated to be between 2 and 5% at 50 years, therefore the authors commented on the possible benefits of targeted screening of these populations with use of a 10-year interval, but acknowledged that a major limitation of this approach is the exclusion of the vast majority of the population in the specified age-group.

Burr et al. also explored methods of implementing a screening programme in a community setting, concluding that while screening by an optometrist with a specialist interest in glaucoma may be more effective, it is also more costly than assessment by a technician, followed by referral to a specialist optometrist for further investigation of test positives (Burr et al., 2007). Based on this assessment, test positives would then be referred for further ophthalmological investigation, and test negatives added to a list for re-screening at a specified interval. Clinical tests for use in both strategies were measurement of IOP with a

26mmHg cut-off, together with an unspecified second test. Based on findings of the present study, the choice for the second test between a structural measurement of RNFL and/ or GCC thickness by OCT or a measurement of vision-function (FDT or MDT) may be governed by consideration of whether the priority is to detect early or moderate/ advanced glaucoma. Sensitivity of both visual-function devices to detect moderate and advanced glaucoma was 100% in the present study, while OCT showed good discrimination of early disease when parameters exceeding the 99% normative interval were considered in combination. Early detection and treatment reduces the rate of progression of glaucomatous vision loss and visual field defects (AGIS et al., 2000, Heijl et al., 2002), which is likely to result in a better health-related quality of life for those affected. The importance of earlier detection and treatment has also been demonstrated on the basis of increased costs associated with advanced disease (Traverso et al., 2005, Lee et al., 2007). On the other hand, screening for very early disease is likely to result in higher numbers of false positive referrals to secondary care, and overtreatment of individuals who may not be at significant risk of developing advanced glaucoma and visual impairment in their lifetime. The net result is increased anxiety among patients, unnecessary exposure to adverse effects of OAG treatments, and the increase in demands on already overburdened hospital eye care units. The mean time for progression of early glaucoma to blindness in at least one eye is approximately 23 years, increasing to 35 years with treatment (Burr et al., 2007). Given that, on average, progression of mild to moderate OAG with treatment will occur in approximately 5 years (Burr et al., 2007), a screening programme that is targeted to identify moderate/ advanced glaucoma may miss an early case in the first cycle, but this individual is likely to be identified in the next screen undertaken in, for example, 5 years. However, use of a shorter interval for screening than the 10 years recommended by Burr et al. will have substantial resource implications (Burr et al., 2007). Other factors to be considered include invitations to participants (e.g. how high-risk individuals may be identified), personnel, training, equipment, and testing sites. Adequate resources and personnel must also be organized to deal with screen positive individuals, and to manage other eye conditions detected during the screening process.

In the UK, optometrists play a key role in the detection of glaucoma in primary care, using opportunistic surveillance when people self-select to attend for eye examinations in community practice. Optometrists are responsible for generating in excess of 95% of referrals for suspected glaucoma and OHT for ophthalmological opinion (Sheldrick et al., 1994, Bell & O'Brien, 1997, Bowling et al., 2005). Current practice for case-finding of POAG uses a combination of history-taking, and a triad of tests comprising optic disc examination for structural changes, evaluation of functional visual field loss, and measurement of intraocular

pressure (Lawrenson, 2013), which are selected at the discretion of the practitioner. However, it is estimated that between 36% and 57% of referrals to the hospital eye service for suspected glaucoma are false positives (Bell & O'Brien, 1997, Bowling et al., 2005, Vernon, 1998, Theodossiades & Murdoch, 1999). Using a combined Bayesian approach to estimate the probability of a given subject having glaucoma has significant potential for community-based glaucoma case-finding. Structural and functional data considered together with information on risk factors (e.g. age, ethnicity and family history) and IOP measurements may be used to develop diagnostic algorithms and inform referral pathways. Notably, the FDT is presently used by 20% of community optometrists in the UK (Dabasia et al., 2014). Moreover, 18% of optometrists responding to a 2014 survey reported use of OCT with numbers expected to rise over time (CoO CP survey 2014, Chapter 2, unpublished data). However, a larger population-based study would be needed to identify and validate the optimal screening paradigm.

Similarly this Bayesian approach could be incorporated into future population screening pathways in the community for at-risk individuals, with tests being performed by a trained technician or a specialist optometrist. The NICE Guidelines for 'Glaucoma diagnosis and management of chronic open angle glaucoma and ocular hypertension' published in April 2009 made reference to roles for optometrists that extended beyond traditional activities of glaucoma case-finding and detection (NICE, 2009). The past decade has seen integrative changes to the delivery of glaucoma services in the UK in response to the increasing demand on secondary care services, and with a view to prevent a fall in standards where review appointments for less urgent or stable patients are increasingly delayed. Enhanced scheme activities for glaucoma now include repeat measure and glaucoma referral refinement schemes for glaucoma suspects/ OHT, monitoring of suspect glaucoma/ OHT and co-management of stable glaucoma.

Improvements in detection of glaucoma may also be addressed by increasing attendance for eye examinations. The success of any targeted screening programme or case-finding strategy is dependent on uptake by the target population. In England, eye examinations free to the patient are offered to persons considered at-risk of developing POAG (e.g. persons with a family history of glaucoma among first degree relatives). However, evidence of poor uptake of eye care services is apparent in a survey by the College of Optometrists, which reported that 5% of people over 40 years age had not attended or could not recall having attended for an eye examination in the last 10 years. This figure rose to 11% for people in minority ethnic groups aged over 40 years (CoO, 2013a), which is cause for substantial concern given the greater risk of glaucoma among Afro-Caribbean groups (Tielsch et al., 1991b, Gordon et al.,

2002, Rudnicka et al., 2006, Leske, 2007). Subsequent reports have identified potential deficiencies in the provision of glaucoma (Day et al., 2010) and general eye care services (Leamon et al., 2014) accessible to ethnic minority groups. Leamon et al's report highlighted additional barriers to the uptake of eye care services, including the limited awareness of eye health and eye disease among ethnic minority groups (Leamon et al., 2014). Previous public health campaigns designed to increase uptake of glaucoma service provision were effective in raising awareness, but made little difference to changing health-seeking behaviour (Baker & Murdoch, 2008). Cross et al. used qualitative methods to identify limitations in access routes to optometrists among African-Caribbean subjects in Birmingham (Cross et al., 2007). Some participants reported being more likely to visit the GP, who would then redirect them to the optometrist as needed. Moreover, 29% of participants felt that 'eye test charges did or would deter people from visiting the optometrist' (Cross et al., 2007). Campaigns to increase awareness may therefore benefit from promotion of the role of optometrists in eye care, and identify their part in educating patients and their families on the benefits of attending for regular sight tests (Eke et al., 1999). There is a need for further research to evaluate the effectiveness of awareness campaigns, and whether the benefits outweigh the costs. Interventions would need to be tailored to increase effectiveness of uptake among lower socioeconomic and/ or black or other ethnic minority (Prior et al., 2012).

3.4.7 Strengths and limitations

The study has a number of strengths. The design, analysis and reporting of the study was compliant with the principles of the STARD statement (Bossuyt et al., 2003). The target population included consecutive subjects who met the inclusion criteria (aged 60 and above) and no subject was excluded on the basis of ocular comorbidity. Although subjects volunteered to participate and it was therefore possible that higher numbers of those with previous or family ocular history were more likely to participate, the prevalence of OAG in our population (5%) was comparable with that expected for the age demographic. Furthermore, a wide spectrum of disease severity was identified. The sample is, therefore, likely to be broadly representative of those presenting for glaucoma case-finding in the community. For this reason, the subjects were generally perimetrically naïve and most had limited experience of electronic screening devices, which increased the generalisability of the results.

The reference standard for OAG corresponded to that used in a typical hospital glaucoma unit and was based on the results of a standard ophthalmic examination by the author (an experienced clinician, whose clinical decision making had been validated prior to the start of

the study and again at intervals during the study). All index tests and the reference standard examination were undertaken on the same day to eliminate disease progression bias, and the clinicians performing the reference and index tests were masked.

The study has a number of limitations. Although the prevalence of glaucoma in our population (5%) was comparable to that expected for the age demographic, the sample size of 505 subjects provided a total of only 26 glaucoma subjects. This resulted in wide confidence intervals around our diagnostic sensitivity estimates, which may have masked real differences between index tests. Furthermore, almost 90% of our study population was of White origin suggesting our findings may not be generalizable to other ethnic groups where glaucoma is more prevalent (e.g. subjects of Black origin). Nevertheless, this study provides useful preliminary data that may be included in meta-analyses in systematic reviews of diagnostic accuracy studies in glaucoma, and to inform the development of larger multi-centre population screening studies.

3.4.8 Conclusions

In our population, the diagnostic performance of structural imaging using the iVue OCT provided better diagnostic accuracy than either of the visual-function tests (FDT and MMDT) in subjects diagnosed with OAG on the basis of structural and functional damage. The low specificity of visual-function tests would preclude their use in isolation, but these findings support the use of visual-function tests together with evaluation of optic nerve head structure to improve case-detection of glaucoma in our population. The detection of individuals with 'suspect' glaucoma presents a significant challenge and the index tests generally performed poorly with respect to this population. It is likely that a Bayesian approach using a combination of diagnostic tests will provide the optimal strategy for this population. Community optometrists are increasingly investing in specialist equipment, and it is anticipated that advanced technologies will play a more significant role in case-finding of glaucoma in the future. Further research is required to evaluate the optimal combination and cut-offs for abnormality of screening tests in a larger population, and in particular, in high-risk groups.

Chapter 4: Non-contact screening methods for the detection of narrow anterior chamber angles

4.1. Introduction

Angle closure glaucoma (ACG) is a major cause of visual morbidity, in which significant and irreversible optic neuropathy and impairment of visual function can occur within a short period following an episode of angle closure. With the ageing population and increasing longevity, the WHO estimates that of the 11.2 million people that will be bilaterally blind from glaucoma worldwide by the year 2020, nearly half of these cases will be attributed to angle closure mechanisms (WHO, 2007). These projections are based on the higher incidence of the condition in the populous country of China, together with other East and South East Asian countries where ACG is the predominant form of glaucoma (Foster & Johnson, 2001). The prevalence estimate for ACG in European-derived populations aged 40 years and older is 0.4% (Day et al., 2012), which corresponds to 130,000 cases in the UK. Although the condition is considered relatively uncommon in western populations, ACG is predicted to increase by 19% in the UK within the next decade due to increased longevity (Day et al., 2012).

With timely detection of anatomically narrow angle eyes at risk of occlusion, and the subsequent administration of prophylactic therapy, the progression of the angle closure process to ACG can be arrested. Reports documenting the nature of ACG presentations in Asia have identified the chronic sub-type as the most common manifestation of the condition, often with no previous evidence of acute or sub-acute episodes (Congdon et al., 1996, Johnson & Foster, 2005, He et al., 2006b). This trend has also been observed in Caucasian populations where chronic ACG has been found to occur more frequently than previously thought (Wilensky et al., 1993, Bonomi et al., 2000a). With fewer symptoms reported at the point of diagnosis, detection of the disease before significant damage has already occurred remains a significant challenge.

The clinical course of the ACG disease process is typically categorized in three stages: primary angle closure suspect (PACS), primary angle closure (PAC) and primary angle closure glaucoma (PACG). A subject is diagnosed with PACS when anterior chamber angle (ACA) examination by gonioscopy reveals an anatomical predisposition to apposition between the peripheral iris and posterior trabecular meshwork. In accordance with the International Society of Geographical and Epidemiological Ophthalmology (ISGEO) nomenclature, this has typically been defined in

epidemiological research as an ACA in which 270° or greater of non-visibility of the posterior (usually pigmented) trabecular meshwork (Foster et al., 2002) has occurred. Without timely intervention, repeated contact between the iris and delicate structures of the trabecular meshwork can result in damage and abnormalities at a cellular level. These result in an elevated intraocular pressure and/ or the formation of irreversible adhesions representing complete obstructions of aqueous flow at points of contact, which are known as goniosynechiae or, more commonly peripheral anterior synechiae (PAS) (Lee et al., 2006a). The term PACG only applies when PAC progresses to demonstrable glaucomatous optic neuropathy.

An untreated PACS subject has an estimated 22% (Thomas et al., 2003) to 30% (Wilensky et al., 1996) chance of developing angle closure over 5 years. Currently, laser peripheral iridotomy (LPI) is considered the most effective evidence-based treatment to prevent the onset of ACG in predisposed individuals. However, LPI is demonstrably less effective, and even considered suboptimal where manifest angle closure with evidence of functional damage to the drainage apparatus has already occurred, and in particular where there is evidence of glaucomatous optic neuropathy (Nolan et al., 2000). This further emphasizes the need for early detection.

The key to the success of an initiative to prevent ACG through early screening is the timely identification of individuals with anatomically narrow angles, considered at-risk of developing the condition. ACG is the result of anomalies in either the size or position of structures in the anterior segment, therefore assessment of angle width and configuration is an essential part of identifying these individuals. Many population studies have identified common biometric characteristics that crowd the anterior segment, predisposing the eye to ACG (Lowe, 1970a, Congdon et al., 1996). These characteristics include shallow anterior chamber depth (ACD), defined as the distance between the corneal endothelium and anterior lens surface measured along the optical axis, anterior lens positioning, thickening of the crystalline lens, small corneal diameter, short axial length (hypermetropia) and small radius of curvature. Of these characteristics, shallow ACD has been documented as the cardinal risk factor in most ethnic groups (Nolan et al., 2006). Community-based screening studies have since established the effectiveness of central ACD for the detection of potentially narrow angles (Congdon et al., 1996, Devereux et al., 2000, Kurita et al., 2009).

Currently, gonioscopy is considered the reference-standard assessment for ACA configuration. However, the technique requires a considerable level of skill, experience and knowledge to perform the test and to interpret the results, as well as relying on the cooperation of the subject. Therefore, this clinical reference-standard technique is considered unsuitable for large-scale population screening. In fact, in recent years, gonioscopy's status as an ideal reference standard has been brought into question, with suggestions that the technique may be missing cases of angle closure (Nolan et al., 2007).

In the UK, community optometrists are responsible for referring the vast majority (>95%) of suspected glaucoma subjects for ophthalmological opinion (Sheldrick et al., 1994, Bell & O'Brien, 1997, Bowling et al., 2005), and are well placed to identify anatomical features that predispose an eye to ACG. However, gonioscopy is not a widely adopted technique in community optometric practice for examining the ACA. Instead, practitioners use surrogate methods using slit-lamp biomicroscope-based techniques such as the van Herick (Van Herick et al., 1969) and/ or Smith's test (Smith, 1979), which evaluate the limbal ACD and central ACD respectively. The slit-lamp biomicroscope is an item of equipment used in the vast majority of optometric practices in the UK, and both the van Herick and Smith's tests can be carried out without the need for further auxiliary attachments.

In particular, the van Herick test fulfills many of the criteria for suitability of an ideal screening test, including, and of particular importance to optometrists, the virtues of being non-invasive and quick to perform. The principle of using LACD as an indicator for predisposition to ACG is supported by a number of studies that confirm increasing prevalence of ACG disease with narrowing peripheral ACD (Törnquist, 1959, Wishart & Batterbury, 1992). A number of reports have been published on the validity of using the technique to estimate peripheral ACD, and its suitability for screening for ACG when compared with gonioscopy (Congdon et al., 1996, Foster et al., 2000, Wirbelauer et al., 2005, Nolan et al., 2006, Baskaran et al., 2007, Park et al., 2011, Andrews et al., 2012).

However, an additional requirement for an ideal screening test is for the technique to be clinician independent. Together with gonioscopy, slit-lamp biomicroscope-based tests are subjective and therefore also prone to errors in interpretation. This has encouraged the search for advanced optical-based methods for assessing the ACA using more objective and quantifiable approaches, including technologies such as anterior-segment optical coherence tomography (AS-OCT) and Pentacam imaging. Newer systems provide non-contact methods for evaluating the ACA, acquiring data rapidly, which can be easily stored thereby making them

suitable for large-scale screening for ACG to identify individuals who may benefit from further investigation by gonioscopy. Both the AS-OCT (Wirbelauer et al., 2005, Nolan et al., 2007, Sakata et al., 2008a, Hong et al., 2009, Pekmezci et al., 2009, Narayanaswamy et al., 2010, Park et al., 2011) and Pentacam imaging (Hong et al., 2009, Kurita et al., 2009, Grewal et al., 2011, Pakravan et al., 2012, Rossi et al., 2012) have been used to image ACA structures and generate quantitative estimates of angle morphology for use in screening for ACG in at-risk populations.

Over time, researchers have reported on the effectiveness to detect persons affected by various clinical stages of angle closure disease using slit-lamp biomicroscope tests such as the van Herick test and optical imaging-based systems. However, the majority of this research has been undertaken in Asia and India, where the prevalences of the condition and mechanisms of angle closure are known to differ significantly from those in Caucasian populations (He et al., 2006b). Moreover, evidence for the use of Smith's test to detect at-risk populations when compared with gonioscopy is lacking. Some reports are limited by examiner bias since observers are not always masked to the findings of previous tests. Furthermore, reference-standard examination is often only performed on selected subject groups considered at-risk during the initial screening investigations.

Our study sought to address the question using an enriched population in whom all tests are undertaken. The inclusion of tests to assess central and peripheral ACD was intended to explore whether combining more than one anatomical characteristic conferred an advantage over an individual parameter for detecting at-risk eyes. We also sought to determine the acceptability to patients of each index test, and the time taken to perform the examination, in order to provide further evidence of their suitability in screening for ACG.

The aim of the present study was to evaluate the diagnostic accuracy of non-contact methods in screening for narrow angles, compared with gonioscopy, the current reference standard. The study was designed, and the findings reported in accordance with the Standards for Reporting of Diagnostic Accuracy (STARD) criteria (Bossuyt et al., 2003). In the context of screening for ACG, the term 'narrow angle' is used to describe an anatomically narrow ACA, and is synonymous with 'occludable' and 'primary angle closure'. The study addresses the question using an enriched population in whom all tests are undertaken. The inclusion of tests to assess central and peripheral ACD, comprising slit-lamp biomicroscope-based examinations (van Herick and Smith's tests), and advanced imaging systems (Pentcam and Visante OCT), was intended to explore whether combining data from more than one anatomical characteristic conferred an advantage over an individual parameter for detecting at-risk eyes. The

acceptability to subjects of each index test, and the time taken to perform the examination, was also determined in order to provide further evidence regarding their suitability in screening for ACG. Ultimately, evidence from the current study on the reliability and validity of non-contact methods is intended to inform good practice guidance for optometrists in the UK.

4.2. Methods

Data collection for this prospective, case-control study took place in Ealing Hospital, Moorfields eye clinic over two days in August 2014. The study was reviewed and approved by the NHS (City Road and Hampstead National Research Ethics Service) and City University London research and ethics committees and was conducted in accordance with the Declaration of Helsinki statement of ethical principles for research involving human subjects. Written informed consent was obtained from all subjects.

Subjects aged 18 years and older were recruited from glaucoma and general ophthalmology clinics in Ealing Hospital, Moorfields eye clinic between March and August 2014. The narrow angle group comprised subjects with suspected and confirmed primary angle closure. The control group included subjects who had no current or previous history of ocular disease, and those who were diagnosed with other eye conditions that do not affect angle configuration including POAG and OHT. Subjects receiving systemic or topical medications known to affect the anterior segment, and in particular those that may influence ACA configuration (e.g. miotics) were not eligible for inclusion in either group. Other exclusion criteria included anomalies of the anterior segment which affect ACA configuration. Subjects with cataract or refractive error were not excluded, but only phakic eyes from both groups were included for analysis. A flow diagram for the study is shown in Figure 4.1.

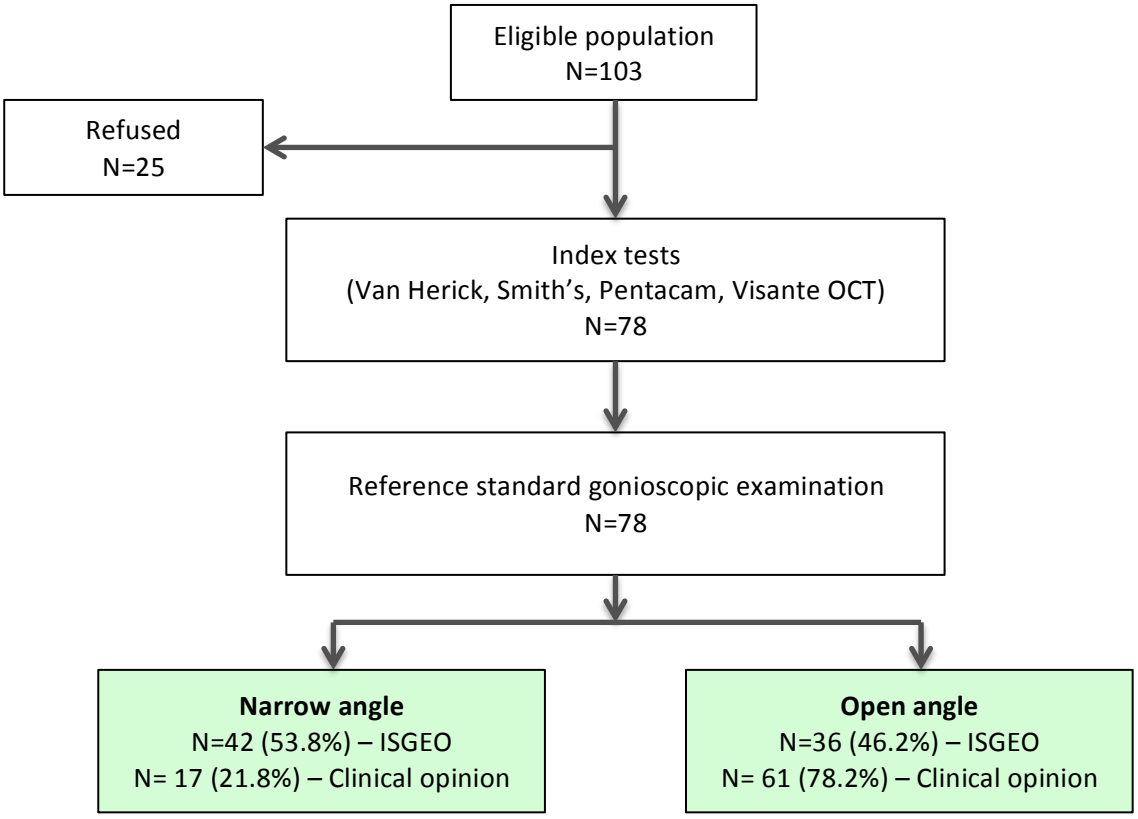


Figure 4.1: Study flow diagram

Enrolled subjects underwent assessment using gonioscopy and a series of index tests comprising van Herick assessment, Smith's test, and imaging using the Pentacam and Visante SD-OCT on the same day, and without use of mydriatic topical drops. All tests were performed in uniform dark-room conditions confirmed using a digital photometer (ISO-TECH ILM 350 digital light meter) as 5 lux or under at the level of the subject's eye, in order to minimize the influence of pupil diameter fluctuations on peripheral iris structures and subsequently the angle width. Subjects were randomized to the starting station, which ensured that not all tests were carried out in the same order. Each test was performed after allowing a minimum of one minute to ensure full recovery of the tear film, and sufficient time for dark adaptation, with further rest periods allowed between assessments as needed. The Goldmann tonometer, slit-lamp biomicroscopes and Visante OCT were calibrated at the beginning of each session in accordance with manufacturers' guidelines.

Each index test was performed by an experienced examiner who did not have any prior knowledge of the subjects' ocular status and was masked to the results of all other tests, including gonioscopy. The time taken to provide an explanation of the test, set the instrument and position the subject correctly, and acquire data from both eyes was recorded by each examiner. On completing the battery of tests and reference standard examination, subjects were asked to complete a short questionnaire regarding the acceptability of each of the index tests. The survey used 7-point Likert scales to ascertain whether a test was 'comfortable' and 'quick', and also included a question to determine self-reported ethnicity.

An objective estimate of refractive error was obtained using the Topcon KR-8100P, recording the result as the mean of three measurements. Visual Acuity was determined for each eye using an ETDRS LogMAR chart positioned 4m from the subject's eye. Measurement of visual acuity was repeated using a pinhole for scorings of 0.20 or greater. Goldmann applanation tonometry (Haag-Streit AT-900) was performed by a consultant ophthalmologist prior to the gonioscopic examination.

4.2.1. Screening methods

Van Herick test

The van Herick technique was originally described as a method of estimating the width of the ACA in 1969 (van Herick et al., 1969). The technique is based on a comparison of the depth of the peripheral anterior chamber to the thickness of the cornea, expressed traditionally as a

fraction. In their initial report, van Herick et al. proposed a 4-point grading scheme (Figure 4.2), to which grade 0, referring to 'slit-like' or 'closed', has subsequently been added to make a fifth grade. In 2000, Foster et al. introduced a modified grading system offering 7-grades by subdividing the traditional Grade 1 into 5% and 15% categories and introducing 40%, 75% and ≥100% categories (Foster et al., 2000).

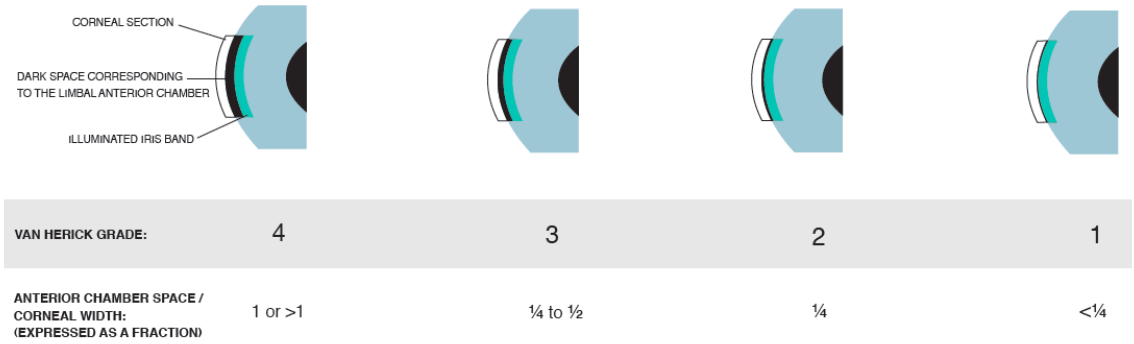


Figure 4.2: Schematic representation of Grade 4 to Grade 1 anterior chamber angles as observed using the van Herick test

Using methodology originally described by van Herick et al. the width of the corneal section was compared to the adjacent anterior chamber space but recorded as a percentage in accordance with Foster and colleagues modified 7-point grading, and using a photographic template for reference comparison where needed (Foster et al., 2000). Measurements were performed using a standard slit-lamp biomicroscope (BQ-900, Haag Streit, Switzerland) and subjects were directed to fixate a distant target to minimize fluctuations of accommodation and pupil size. The slit-lamp was adjusted to 10-16x magnification and high rheostat illumination. The examiner positioned the narrowest visible optical section perpendicular to the cornea (Leung et al., 2012) with the light beam offset at an angle of 60°. Care was taken to ensure the light beam was moved to the outermost corneal aspect as close to the temporal limbus as possible, yet just enabling clear visualization of the dark space between the posterior cornea and the projection of the slit beam on to the peripheral iris. LACD percentage estimates were recorded, first at the temporal limbus and then at the nasal limbus for each eye using the modified 7-point grading scale (0%, 5%, 15%, 25%, 40%, 75% and ≥100%).

Smith's test

Redmond Smith proposed a quantitative method to estimate central ACD that makes use of the calibrated variable slit-height facility on the slit-lamp biomicroscope. In his original report, Smith indicated that the technique could provide an estimate of ACD in a useful clinical range

between 1.4 and 3.0mm, with an accuracy of approximately 0.1mm when compared with pachymetry (Smith, 1979). The procedure involves projecting a horizontal slit across the central cornea with the illumination column set at 60° to the subject's temporal field. The examiner is required to adjust the slit-height until the two light beams: one a focused beam on the corneal surface, and the other a more blurred image at the lenticular-iridal interface just appear to touch, taking care to ensure the beam is focused on the central cornea (Figure 4.3). Smith's report suggested multiplying the slit height registered on the slit-lamp scale by a constant correction factor of 1.40 to determine the estimated ACD in millimetres (Smith, 1979). This constant was originally derived using ACD data from 56 eyes measured by optical pachymetry, but researchers validating Smith's methods have since suggested the use of a smaller constant multiplier of 1.31 when using Smith's method in comparison with ACD obtained by pachymetry and 1.34 in comparison with ACD measured by A-scan ultrasonography (Barrett et al., 1996).

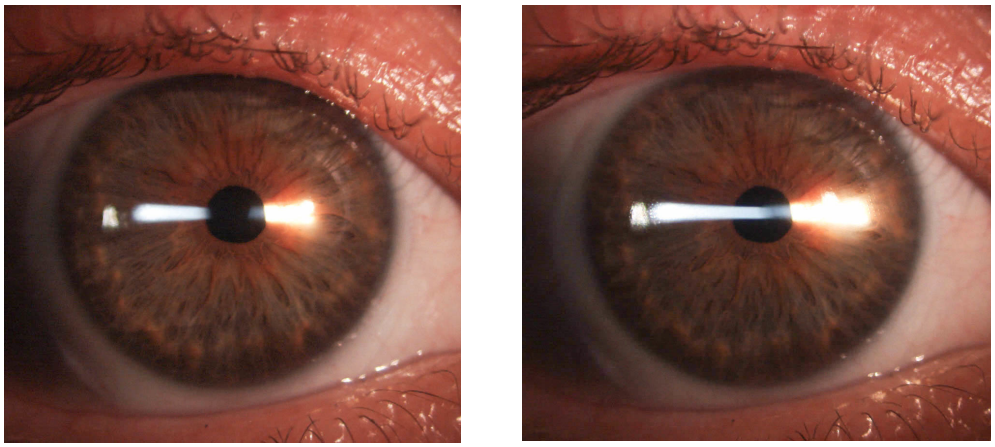


Figure 4.3: Photographic representation of Smith's technique displaying a) separated images on the corneal and lenticular surfaces, and b) at the end-point where the two images appear to just meet

The present study explored use of both the original and alternative multiplication factors by evaluating agreement between central ACD estimates derived using Smith's and imaging-based systems. The technique was performed using a standard slit-lamp biomicroscope (BQ-900, Haag Streit, Switzerland) and subjects were directed to fixate a distant target to relax their accommodative effort. Three readings were taken for each eye, resetting the slit height to 0.5mm between measurements, and recording the result for analysis as the mean of the readings.

Pentacam imaging

The Scheimpflug priniciple was introduced in 1906 to correct perspective distortion in aerial photographs (Scheimpflug, 1906) but has since been adapted for ocular imaging. The technology is based on tilting the camera lens to redirect the plane of sharp focus so that this plane and the film and lens planes all intersect along a line. By illuminating only a thin layer of tissue at any one time, a cross-sectional slit image is created that retains depth. The Pentacam is an example of a device that employs the Scheimpflug principle using monochromatic blue light with a wavelength of 475nm. By rotating the apparatus around the optical axis of the eye, a series of radially orientated images is generated in three dimensions around the 360-degree extent of the anterior segment. Between 12 and 50 real-time sections from the anterior surface of the cornea to the posterior vertex of the lens are acquired within a 2s acquisition frame. Automatic processing of the raw data then allows the detection of tissue boundaries, and corrects for distortions from the camera optics, cornea-lenticular surfaces, and refraction of light at the tissue interfaces. This generates a set of measurements that provide a detailed description of biometric configuration of the anterior segment.

The inbuilt Pentacam software generates three parameters of the anterior chamber: ACA, central ACD and anterior chamber volume (ACV). By selecting individual Scheimpflug images, an examiner can acquire an estimation of the ACA at any position within the anterior chamber (Figure 4.4). The technology is based on the penetration of light through the structure of interest, and is unable to visualize accurately the angle recess, peripheral-most iris, and retroiridal structures. For this reason, the ACA and ACV are computed using an interpolation method where the corneal and iris contour lines are extended to form the angle and anterior chamber boundary. The ACV is calculated using integral calculus by integrating the area bounded by the posterior surface of the cornea, iris and anterior lens surface. ACD is automatically generated as the distance between the posterior vertex of the corneal endothelium and the anterior surface of the crystalline lens along the optical axis. The measurement of central ACD using Pentacam imaging was validated against the IOLMaster (Zeiss) in 100 healthy subjects aged between 21 and 85 years, using study methods described by Dabasia et al (Dabasia et al., 2013). A Bland-Altman difference plot was generated using data obtained from the right eye of the first 50 subjects, and left eye of the next 50 subjects. Mean ACD was 3.42±0.42mm for the IOLMaster, and 3.46±0.43mm for Pentacam imaging with a bias of -0.043±0.08mm. The 95% Wald confidence interval or limits of agreement, was -0.235 to 0.149mm representing 11% of mean ACD, and implying fair agreement.

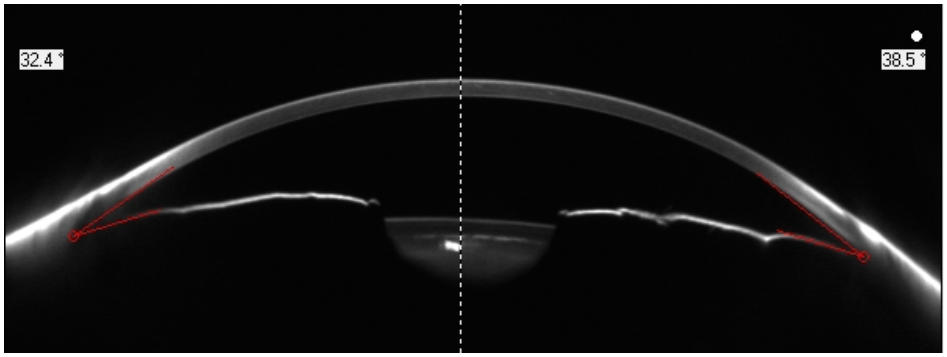


Figure 4.4: Image of Pentacam anterior segment capture with temporal and nasal ACA angle tools

The Pentacam incorporating software version 1.19r11 (Oculus Germany) was used in 25-image acquisition mode. ACA estimates were obtained along the nasal-temporal meridian using Scheimpflug horizontal image segments 16 (184 to 4°), and 17 (176 to 356°). Measurements derived from vertical sections were excluded as these data are more susceptible to variability from distortion following eyelid manipulation and/ or direct eyelid obstruction. Each subject was asked to fixate with both eyes open on a blue LED light, and more specifically a black superimposed target circle, if perceived by the subject, at the centre of the camera. The examiner was required to manually focus the camera on the eye using live indicators generated by the inbuilt software. Images were captured in automatic release mode to reduce operator-dependent variability. Scan acquisition was repeated until two scans of suitable quality, or a maximum of four scans had been captured using manufacturer-recommended quality criteria as guidelines for image acceptance. The software generated quality score (QS) highlights criteria that may influence the accuracy of data such as the loss of segments due to blinks or eye movements. Poor quality scans identified by a red-highlighted QS box satisfied exclusion for analysis. Data acquired with a yellow QS box were considered in more detail using the 'Examination quality specification' option to identify the criterion exceeding the specified threshold. A final decision for inclusion of individual parameter estimates was made following observation of Scheimpflug horizontal segment images 16 and 17. An ACA measurement was included for analysis if the corresponding image was well centered on the pupil, free of eyelid interference, and extrapolated using a correctly positioned angle tool. Analysis was based on the first scan captured, unless it satisfied the listed exclusion criteria on the basis of poor quality data.

Visante SD-OCT

Anterior segment OCT (AS-OCT) is based on the principle of low-coherence interferometry, an optical phenomenon first observed and then developed by Michelson in the late 1800s. AS-OCT employs a method comparable to Ultrasound biomicroscopy (UBM) to evaluate tissue depth, observing optical backscatter in place of acoustic (ultrasonic) signals received from a reference (mirror) and a sample (tissue) path. A series of scans are created to form a reflectivity profile analogous to an ultrasound A-scan, which, in turn, is used to construct a two-dimensional B-scan in real-time, representing an in-vivo cross-sectional tomograph. However, UBM requires direct contact with the cornea as the subject lies supine, and involves a considerable level of operator expertise to acquire good-quality images. In comparison, AS-OCT uses non-contact technology to acquire images within a few seconds as the subject is seated in an upright position, affording the additional advantage of better control of accommodation and pupil size. Inbuilt software automatically processes the raw data, converting the optical path lengths to physical dimensions using known refractive indices for ocular media, and adjusting for image distortions, a process known as 'de-warping'.

The majority of commercially available OCT devices use a shorter wavelength for optimal imaging of the posterior segment than is ideal for imaging the anterior segment. Although images of the ACA can be obtained with these OCTs by using an additional or integral adaptor lens, the detail captured is limited by poor penetration of light through scleral tissue. The Visante OCT provides better visualization of ACA morphology by using longer-wavelength (1310nm) radiation emitted by a super luminescent diode, which is less prone to scatter from limbal and scleral tissues allowing deeper penetration. Moreover, the increased intensity of radiation achieved using this wavelength allows faster image acquisition (0.125 seconds for a standard resolution scan), and a greater signal to noise ratio to enhance the detection of subtle features. Together these features generate an acquisition rate of over 2000 A-scans, and a transverse and axial resolution of 60µm and 18µm respectively of the anterior segment. In the present study, the Visante OCT (Version 2.0.1.88, Carl Zeiss Meditec Inc.) was used in 'Anterior segment single' mode employing wide-field scanning optics to obtain a cross-section of the nasal and temporal angles in a single, 16x6mm image frame between the 3 and 9 o'clock positions. A cross-section was not obtained along the vertical meridian as these data are more susceptible to errors as a result of eyelid obstruction of ACA features or distortion following eyelid manipulation. Each subject's refractive error was entered into the database prior to data capture to allow automatic adjustment of the internal fixation target, which aimed to relax and better control near accommodative effort. Subjects were asked to fixate an internal starburst target with both eyes open, while the examiner centered the camera on the pupil,

and made adjustments to the z axis, saturation, noise and polarization to a level compatible with the highest image quality. Following each acquisition, the experienced examiner analysed the quality of the image for artefacts, poor centration and adequate visibility of the iris recess apex, scleral spur and anterior lens surface. Poor quality scans were reacquired with an aim to capture two images of adequate quality, or until a maximum of 4 scans had been obtained. The first scan acquired for each eye was used for analysis unless it satisfied exclusion criteria on the basis of poor quality data.

All images were analysed using the Visante OCT inbuilt software by one experienced clinician (PLD) masked to the gonioscopy findings and index test results. Accurate qualitative and quantitative assessment of the ACA is dependent on the correct identification of anatomical landmarks within the angle recess. The scleral spur is often used as a point of reference in the ACA, represented by the widest part of the sclera and often observed as an inward protrusion or change in curvature at the inner angle surface. On identification of the scleral spur at the temporal and nasal ACA, angle tool markers (AC-angle-180° and AC-angle-0°) were positioned at the deepest points of the angle recess otherwise known as the apex, adjusting the long arms of the tool at the iris tangential line and posterior corneal surface. Central ACD was measured, using the caliper tool selected from the 'Chamber tool palette', as the distance between the corneal apex in a line perpendicular to the posterior surface of the cornea (endothelium) and anterior lens contour (Figure 4.5).

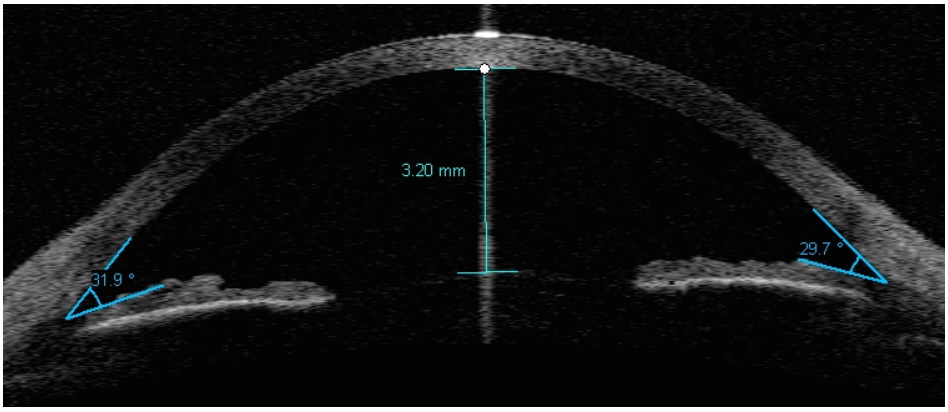


Figure 4.5: A Visante OCT cross-section captured using 'Anterior segment single mode' with angle tool markers; AC-angle-180° and AC-angle-0° and central anterior chamber depth caliper

Gonioscopy

Gonioscopy was defined as the reference standard to assess the screening performance of the slit-lamp and imaging-based tests. Every subject underwent gonioscopy on the same day as the index tests, performed by the same consultant glaucoma sub-specialist ophthalmologist with extensive experience in performing the technique both in research and clinical settings, and previously standardized against another consultant ophthalmologist with a weighted kappa scoring of 0.88 (SE 0.07) for Shaffer angle grading. The ophthalmologist was masked to the subjects' ocular status and results of index tests.

Gonioscopic assessment was performed one minute after dark conditions had been introduced, and confirmed using a digital photometer as being 5 lux or under at the level of the subject's eye. Angle width was estimated using the Modified Shaffer system in each quadrant (superior, inferior, nasal and temporal) using a Goldmann-style 1-mirror lens (Magniview, Ocular Instruments), and with the subjects's eye in primary gaze. Minimal tilting or adjustment to the lens position was permitted to achieve a view over the hill of a steep peripheral iris, taking care to avoid exerting excessive pressure that may distort the image. Modified Shaffer gradings for the 12, 3, 6, and 9 o'clock positions scored on a 5-point scale from grade 0 to 4 were recorded. Using this system, a grade 4 represents observation of the ciliary body (wide open ACA quadrant), grade 3; scleral spur, grade 2; anterior trabecular meshwork, grade 1; Schwalbe's line, and grade 0; Schwalbe's line not visible (closed ACA quadrant) (Figure 4.6). Dynamic assessment by further compression of the corneal surface by the goniolens was performed where the examiner was required to differentiate appositional closure from PAS, which were considered significant when observed in line with or more anterior to the scleral spur. The examiner was also required to make a 'forced' dichotomous choice as to whether the angle of each eye was 'occludable' (a narrow angle with possibility of occlusion) or 'not occludable' (at little risk of occlusion) based on the criteria listed below:

1) Angular approach of the peripheral iris to the recess and peripheral iris configuration (e.g. steep)
2) Angle structures observed with the subject's eye in the primary position (Modified Shaffer grading)
3) 'Openability' – visibility of angle structures on indentation
4) Observation of other features suggestive of irido-trabecular contact e.g. pigment patches

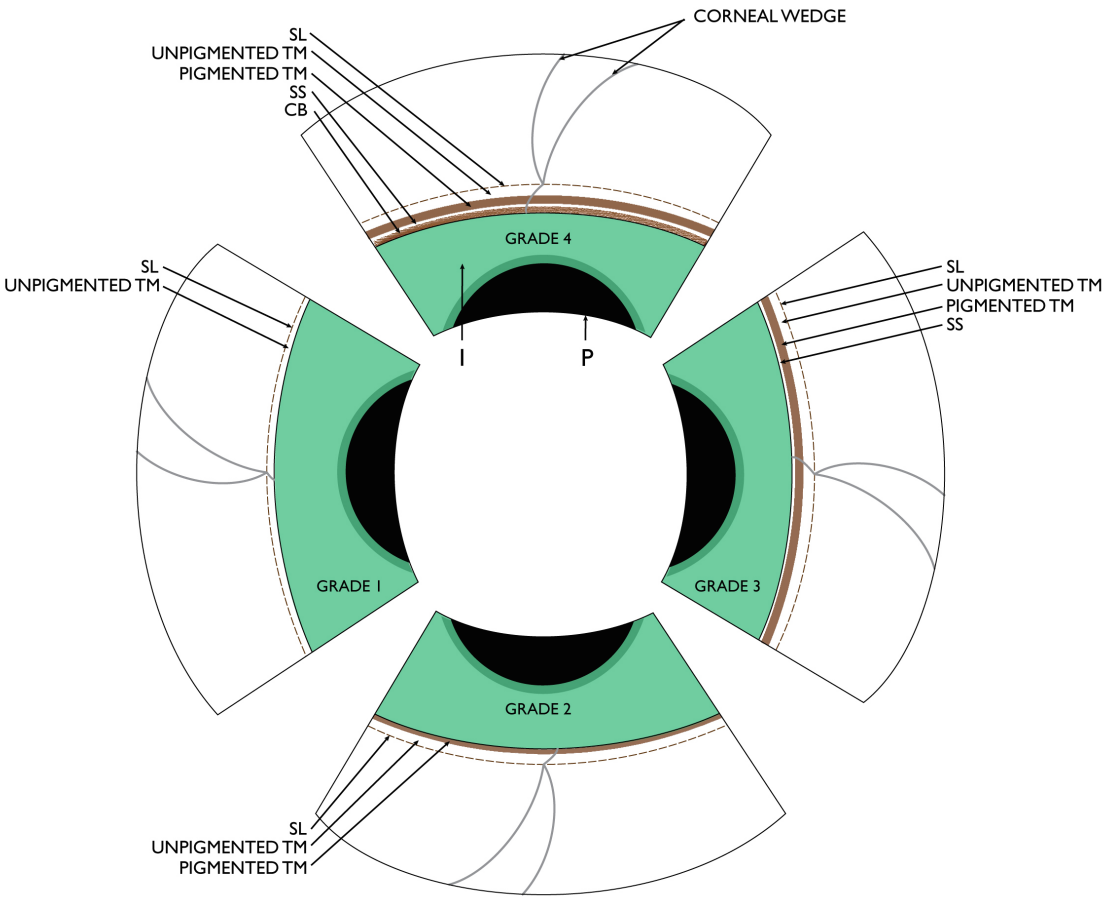


Figure 4.6: A schematic representation of a gonioscopic view of a Grade 4 (open) to Grade 1 (narrow) anterior chamber angle, highlighting the main landmarks. CB = ciliary body; I = iris; SS = scleral spur; TM = trabecular meshwork; SL = Schwalbe's line; P = pupil.

4.2.2 Diagnostic definitions

As the primary aim of this study was to evaluate screening methods for the detection of narrow angles, subjects diagnosed with PACS, PAC and PACG were combined into a single category: 'narrow' or 'occludable' angles. Using gonioscopy as the reference standard, an eye was defined as having a narrow or occludable angle using two criteria:

1) ISGEO definition - if the posterior (usually pigmented) posterior trabecular meshwork was not visible for 270°or more of the angular extent on non-indentation gonioscopy and with the eye in the primary position (Devereux et al., 2000, Foster et al., 2000, Nolan et al., 2006, He et al., 2007, Kurita et al., 2009), corresponding to a Modified Shaffer score of grade 2 or less in 3 or more quadrants
2) Clinical opinion of the consultant sub-specialist ophthalmologist as to whether the angle was 'occludable' based on the structures observed with the subject's eye in the

primary position and following indentation of the corneal surface, angle approach of the peripheral iris insertion, and peripheral iris configuration

For diagnostic purposes, a subject was classified as having narrow angles if one or both eyes was/were graded as narrow.

The diagnostic effectiveness of the index tests was evaluated using two approaches:

- Using the eye as the unit of analysis by selecting the gonioscopy and index test result of the right eye. Left eye data is only included for analysis if the right eye satisfied the exclusion criteria (e.g. pseudophakic)
- Using the individual as the unit of analysis by comparing the smaller index test measurement of the two eyes with the overall gonioscopic classification of narrow/ open angle for a given subject

In this way, both screening paradigms addressed potential bias associated with analyzing dependent data from the right and left eyes of the same subject. For Visante OCT, Pentacam imaging and the van Herick test, ACA was evaluated at the nasal and temporal positions, using the narrower of the two estimates for analysis. However, the screening effectiveness of the nasal and temporal ACA was also explored individually for each test in a secondary level analysis.

4.2.3 Sample size calculation

The sample size was based on an anticipated sensitivity of the van Herick test to detect a narrow angle (based on a gonioscopic case definition) of 0.80 (conservative estimate taken from a study in a population of European descent; (Vargas & Drance, 1973)) with a minimum acceptable precision of ±0.25 with 0.95 probability. This would require 40 cases with narrow angles (Flahault et al., 2005).

4.2.4 Statistical analysis

Data were entered into Excel and further statistical analysis was carried out using SPSS 21.0 software (www.ibm.com/SPSS_Statistics), Medcalc 14.8.1 (www.medcalc.org), and STATA 13.0 (StataCorp. 2013. College Station, TX: StataCorp LP, www.stata.com). Mean/median values for demographic characteristics and quantitative angle measurements were compared between narrow and open angle groups using parametric or non-parametric statistical tests as appropriate. Non-normally distributed data were converted using log transformation where required and an independent t-test applied. Skewed age data were described by the median

value and interquartile range. The chi-squared test was used to compare proportions of categorical variables. For all tests P<0.05 was considered statistically significant.

For imaging-based data, the first scan acquired for each eye was selected for analysis unless it satisfied exclusion criteria on the basis of a) a poor quality scan and/or poor visibility of angle structures or b) manufacturers' recommendations where relevant. Using Pentacam imaging, segments 16 and 17 of the 25 segments corresponded to measurements either side of the horizontal midline. Area under Receiver Operating Characteristic (AUROC) curve analysis at the nasal and temporal positions revealed no statistically significant difference between the AUROCs using both gonioscopy classifications (temporal ISGEO p=0.34, Clinical opinion of occludability p=0.28; nasal ISGEO p=0.37, Clinical opinion of occludability p=0.35) for these two segments. Furthermore, Bland-Altman difference analysis revealed mean bias of 0.11° (CI -4.81 to 5.03) and -0.09° (CI 4.85 to -5.03) for temporal and nasal ACA measurements between the segments respectively (see Appendix C, Figure i). As a result of these similarities between measurements obtained for segments 16 and 17 the ACA data summarized in the results section are those obtained from segment 16 only. For Smith's test a preliminary analysis was carried out to identify the most appropriate choice of multiplication factor to correct slit-height raw data to central ACD. Bland-Altman difference plots were generated (see Appendix C, Figure ii) to evaluate agreement between estimates derived using Smith's test and imaging-based systems. Mean bias was smallest (Pentacam -0.01mm, Visante OCT -0.04mm) for comparisons with both imaging-systems when using a correction factor of 1.31 (Barrett et al. 1996) rather than the original suggested correction factor of 1.40 (Pentacam 0.17mm, Visante OCT 0.15mm) (Smith 1979). Based on this analysis, in the present study Smith's test results including mean central ACD values and optimal cut-offs for diagnostic analysis are based on a 1.31 correction factor applied to slit height readings.

Values for sensitivity, specificity, positive likelihood ratio and negative likelihood ratio and associated 95% confidence intervals were determined for each index test and classification of narrow angles using reference standard, gonioscopic observation. McNemar's test was used to determine any statistically significant differences between sensitivity and specificity values. The ability to discriminate between narrow- and open-angle subjects for continuous data was described using receiver operator characteristic (ROC) curves. For index tests where there is no clinical consensus on the threshold to define a narrow angle, the optimal threshold was determined directly from the ROC curve using the Youden index (J), which represents the point on the curve that maximizes J in the formula (J = max (sensitivity[c] + specificity[c]- 1) where c ranges over all possible criterion values) (Youden, 1950). Sensitivity at set specificity, and

partial area under the curve (AUC) of ROC plot estimates together with 95% confidence intervals were used as an index of global test performance against the reference standard. Any statistically significant differences between sensitivity at set specificity, and partial AUROC estimates were observed using the Wald test (Pepe et al., 2009). Partial AUROC values were normalized by dividing by the false positive rate (Hillis & Metz, 2012). These parameters were evaluated for ranges starting at 90% and 95% specificities to provide a clinically useful range for case-finding.

The diagnostic effectiveness of combining index test results and, in particular, data from non-contact slit-lamp biomicroscope tests was evaluated using 2x2 tables to calculate sensitivity and specificity values. Responses to the user acceptability survey using Likert scales were transcribed into grades from 1 to 7 and aggregated into summary tables. The Chi-squared statistical test was used to determine the likelihood that sampling variability or chance could be an explanation for any observed trends in aggregated Likert scores between subject groups. Free-text responses were coded and assigned to categorical variables.

4.3. Results

78 subjects (34 male and 44 female) attended one of two screening days in Ealing Hospital, Moorfields eye clinic. Subjects were aged between 30 and 83 years with median age being 66 (IQR 53 to 79) years. Self-reported ethnicity was 56% Caucasian, 35% South Asian and 9% other ethnicities. Demographic and summary data for open and narrow angle groups are summarized in Tables 4.1a and 4.1b respectively. Subjects classified with narrow angles were statistically significantly older (p=0.008, ISGEO classification; p=0.046, classification based on clinical opinion of occludability; Mann-Whitney U-test), and measured higher intraocular pressures (p=0.038, ISGEO classification; p=0.009, classification based on clinical opinion; t-test) than those in the open angle group. Mean best vision sphere was 1.82D more hyperopic among subjects classified with narrow angles using the ISGEO system than compared with the open angle group, representing a statistically significant difference between means (p=0.001; t-test). A smaller difference was found for the classification based on clinical opinion (1.28D more hyperopic in the narrow angle group) and this difference failed to reach statistical significance (p = 0.055 t-test). Mean anterior chamber parameters measured using the index tests (ACA, ACD and ACV) were all statistically significantly lower among narrow angle subjects than compared with individuals diagnosed with open angles using either gonioscopy classification ($p \leq 0.002$ t-test or Mann-Whitney U-test). There was no statistically significant difference between groups in terms of White compared with South Asian ethnicity ($p > 0.05$; Chi-Squared test). By defining a narrow angle as ≥270° of non-visibility of the posterior trabecular meshwork (ISGEO classification), 46% (N=36) and 54% (N=42) of subjects were diagnosed with open and narrow anterior chamber angles respectively. The percentage with narrow angles fell to 21.8% (N = 17) if the ophthalmologist's clinical opinion was used as the cut-off criterion. No adverse events were reported for any subject following examination by index tests or gonioscopy.

	All subjects	Classification of narrow anterior chamber angle by gonioscopy					
		≥270° of non-visibility of posterior trabecular meshwork (ISGEO classification)			Clinical opinion of occludability		
		Open anterior chamber angles	Narrow anterior chamber angles	P value	Open anterior chamber angles	Narrow anterior chamber angles	P value
N (%)	78 (100)	36 (46.2)	42 (53.8)	---	61 (78.2)	17 (21.8)	---
Median age (years) [IQR]	66 [IQR 53 to 79]	63 [IQR 49 to 77]	68.0 [IQR 58 to 78]	0.008[b]	65 [IQR 52 to 78]	70 [IQR 59 to 81]	0.046[b]
Gender (%)							
Male	34 (43.6)	20 (55.6)	14 (33.3)	0.048[a]	28 (45.9)	6 (35.3)	0.435[a]
Female	44 (56.4)	16 (44.4)	28 (66.7)		33 (54.1)	11 (64.7)	
Ethnic group (%)							
White	44 (56.4)	19 (52.8)	25 (59.5)	0.477[a]	35 (57.4)	9 (52.9)	0.859[a*]
South Asian	27 (34.6)	14 (38.9)	13 (31.0)		21 (34.4)	6 (35.3)	
Black	1 (1.3)	0 (0)	1 (2.4)		1 (1.6)	0 (0)	
Chinese	1 (1.3)	1 (2.8)	0 (0)		1 (1.6)	0 (0)	
Other Asian	4 (5.1)	1 (2.8)	3 (7.1)		2 (3.3)	2 (11.8)	
Mixed	1 (1.3)	1 (2.8)	0 (0)		1 (1.6)	0 (0)	

Comparisons between narrow and open anterior chamber angle groups produced statistically significant differences (p<0.05): [a]Chi-square test, [b]Mann-Whitney U-test

**** Chi-squared analysis reflects differences in proportions of White and South Asian subjects between diagnostic groups***

Table 4.1a: Demographic data for narrow and open angle subject groups using two different classifications of a narrow anterior chamber angle by gonioscopy

	All subjects	Classification of narrow anterior chamber angle by gonioscopy					
		≥270° of non-visibility of posterior trabecular meshwork (ISGEO classification)			Clinical opinion of occludability		
		Open anterior chamber angles	Narrow anterior chamber angles	P value	Open anterior chamber angles	Narrow anterior chamber angles	P value
N (%)	78 (100)	36 (46.2)	42 (53.8)	---	61 (78.2)	17 (21.8)	---
IOP (mmHg)^	13.9 ±3.22	13.1 ±3.2	14.6 ±3.1	0.038[a]	13.4 ±3.3	15.7 ±2.4	0.009[a]
Best vision sphere	+0.76±2.4	-0.22 ±2.41	+1.60±2.15	0.001[a]	+0.48±2.40	+1.76±2.38	0.055[a]
Smith's ACD (mm)	2.52±0.41	2.77±0.34	2.31±0.35	0.001[a]	2.61±0.40	2.19±0.26	<0.001[a]
Pentacam							
ACA (°)+	29.8±6.0	33.3±5.0	26.8±5.2	<0.001[a]	30.8±5.6	25.9±6.1	0.002[a]
ACD (mm)+	2.54±0.41	2.81±0.35	2.30±0.29	<0.001[a]	2.64±0.39	2.18±0.26	<0.001[a]
ACV (mm^3)+	130.7±38.1	156.7±38.4	108.5±19.2	<0.001[a]	138.3±38.5	103.6±20.4	<0.001[a]
Visante OCT							
ACA (°)+	17.5±13.2	27.9±9.3	8.9±9.1	<0.001[b]	21.0±12.6	5.38±6.40	<0.001[b]
ACD (mm)+	2.58±0.40	2.87±0.32	2.33±0.29	<0.001[a]	2.68±0.38	2.21±0.27	<0.001[a]

Comparisons between narrow and open anterior chamber angle groups produced statistically significant differences (p<0.05): [a] Independent samples t-test, [b]Mann-Whitney U-test

^ Highest measurement between right and left eyes

+ Minimum measurement between right and left eyes

All clinical data are described by the mean and standard deviation to allow comparison with the literature

Table 4.1b: Clinical data for narrow and open angle subject groups using different classifications of a narrow anterior chamber angle by gonioscopy

The distribution of modified Shaffer grades by quadrant are summarized by subject group in Table 4.2. A closed quadrant (Grade 0) was observed most frequently in the superior (45.2%) and temporal angle positions (42.9%). In comparison, the inferior quadrant was most frequently recorded as being 'wide open', represented by a modified Shaffer grade >3 and ≤4.

Gonio cut-off	Superior N (%)		Temporal N (%)		Inferior N (%)		Nasal N (%)	
	Open	Narrow	Open	Narrow	Open	Narrow	Open	Narrow
Grade 0	0 (0)	19 (45.2)	0 (0)	18 (42.9)	0 (0)	10 (23.8)	0 (0)	16 (38.1)
Grade >0 to ≤1	0 (0)	12 (28.6)	0 (0)	13 (31.0)	0 (0)	17 (40.5)	0 (0)	12 (28.6)
Grade > 1 to ≤2	1 (2.8)	11 (26.2)	3 (8.3)	11 (26.2)	0 (0)	14 (33.3)	3 (8.3)	13 (31.0)
Grade >2 to ≤3	23 (63.9)	0 (0)	20 (55.6)	0 (0)	21 (58.3)	1 (2.4)	19 (52.8)	1 (2.4)
Grade >3 to ≤4	12 (33.3)	0 (0)	13 (36.1)	0 (0)	15 (41.7)	0 (0)	14 (38.9)	0 (0)

Table 4.2: Distribution of gonioscopic Shaffer grade by quadrant between subject groups (classified using the ISGEO gonioscopy classification)

An important property of a screening test is its ability to acquire data of suitable quality using a standard protocol. In our cohort, the slit-lamp biomicroscope-based tests (van Herick and Smith's test) and reference comparison gonioscopic examination were able to capture data of suitable quality for analysis in 100% of eyes (n=145). Following repeat acquisition in accordance with the study protocol, the imaging-based systems (Visante OCT and Pentacam) acquired adequate quality data for the measurement of ACA and ACD in 88% to 97%, and 96% to 100% respectively, with Pentacam nasal ACA being the parameter with the greatest proportion of data excluded from analysis (12% for left eye data) (Appendix C, Table i). No bias was observed between narrow and open angle groups for data excluded on the basis of poor quality.

Figure 4.7 shows a box-plot of the time taken to capture data from both eyes using each index test on a subset of bilaterally phakic subjects (N=36). Imaging-based tests took longer to acquire data from both eyes compared with the van Herick technique (1.28±0.44 min) and Smith's test (3.75±0.83 min). In fact, mean time to acquire Pentacam scans (5.11±1.38 min)

was 38 seconds longer than that recorded for the reference standard gonioscopic examination. However, these data must be interpreted with caution as advanced imaging scans were captured in accordance with a strict study protocol, which was aimed to acquire two images of suitable quality for each eye and may not be representative of standard clinical practice.

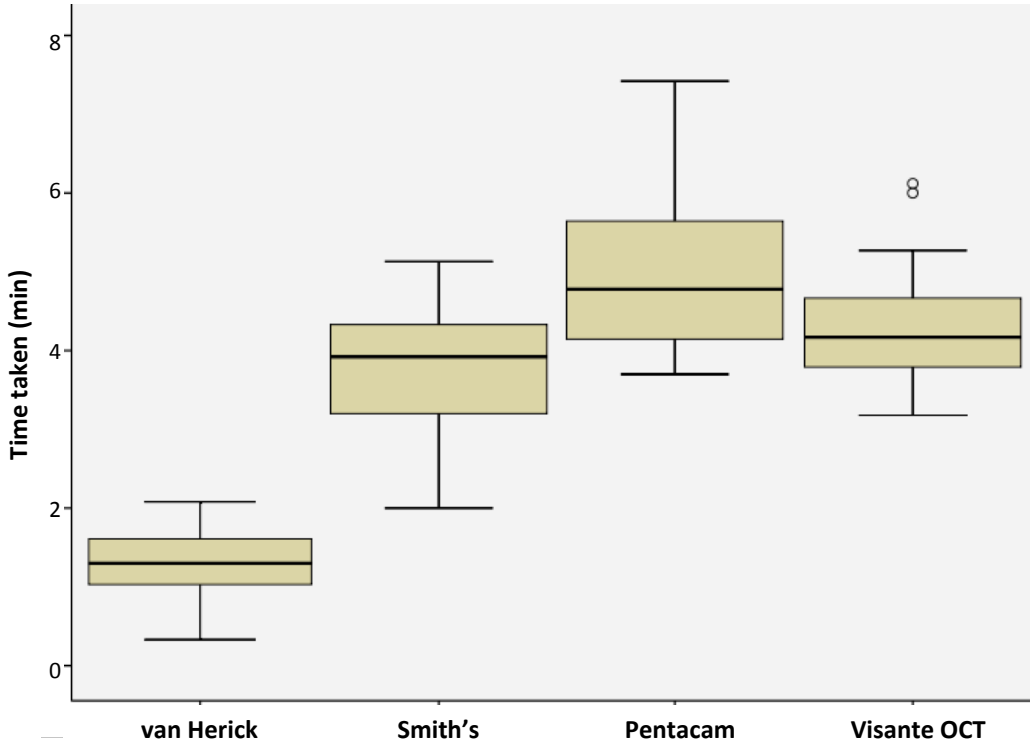
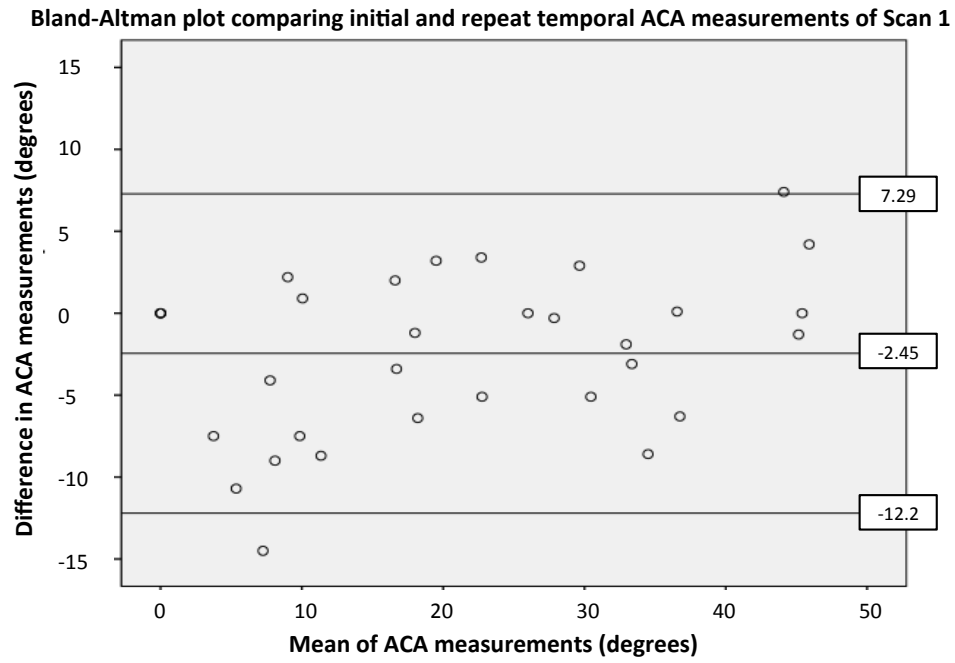


Figure 4.7: Boxplots of the time taken to capture data from both eyes using the four index tests showing the median, upper and lower quartiles, maximum and minimum values (excluding outliers), and outliers (>1.5 times the upper or lower quartile)

To evaluate repeatability of semi-automated Visante OCT anterior chamber analysis, ACA and ACD measurements were repeated using the standard software angle tools for the first scan captured of the right eye in phakic subjects (N=36), excluding poor quality data in accordance with specified guidelines. Using Bland-Altman difference analysis, ACD estimates showed a small mean difference of -0.01mm with narrow 95% confidence limits (CI -0.08 to 0.06), representing 5.5% of mean ACD (0.14/ 2.54), which implies good agreement (Figure 4.8). In comparison, repeatability of ACA measurements using the angle tool showed poorer agreement between initial and repeat observations of Scan 1. Mean bias was -2.45° and -2.60° for temporal and nasal ACA estimates respectively, with wide 95% confidence intervals (CI -12.2 to 7.3 temporal, CI -12.6 to 7.4 nasal) representing just over 90% of mean ACA. No evidence of systematic bias was observed for ACA or ACD.



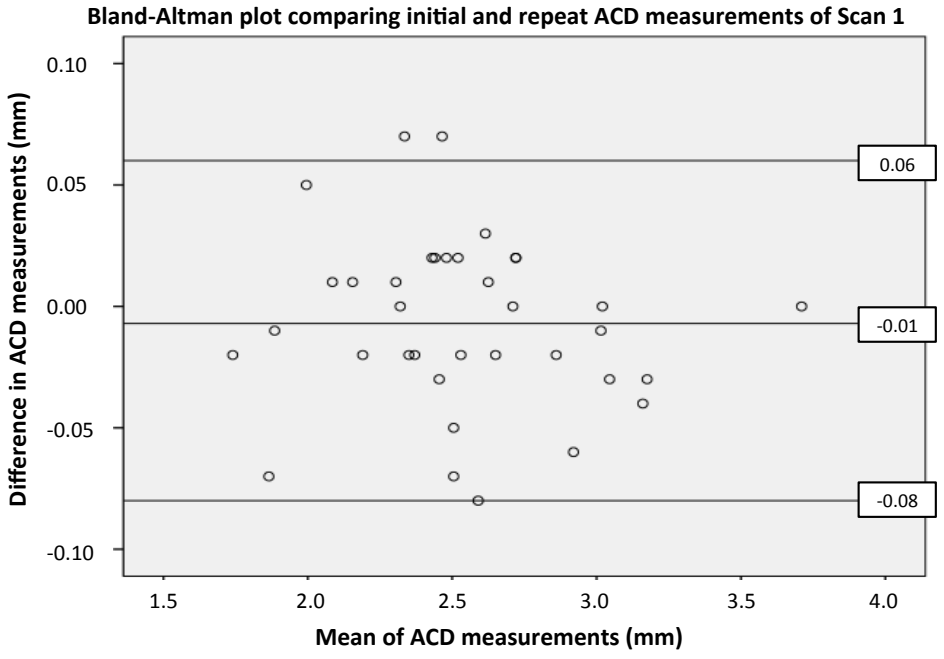


Figure 4.8: Bland-Altman plots evaluating repeatability of semi-automated measurements for the first scan captured of the right eye by Visante OCT (N=36): a) Temporal ACA, b) Central ACD

For the primary analysis the diagnostic performance of each index test was evaluated against a gonioscopy reference standard using the eye as the unit of analysis (data from the right eyes were analyzed, unless the right eye was ineligible e.g. pseudophakia, in which case the left eye was used). The analysis was repeated using the individual as the unit of analysis (as in the study described in Chapter 3). These results are similar to those obtained using the eye as the unit of analysis and are presented in Appendix C, Tables ii and iii)

4.3.1. Diagnostic effectiveness of slit-lamp based index tests

In their original report, van Herick et al. indicated that observation of a Grade 2 LACD (equating to the 25% modified grading) may be suggestive of a narrow anterior chamber angle and should be investigated further using gonioscopy (van Herick et al., 1969). Using the traditional van Herick cut-off criterion of grade 2 (modified LACD ≤25%) and by defining a narrow angle using the ISGEO gonioscopy classification, the van Herick test achieved 79.5% (CI 64.5 to 89.2) sensitivity and 92.3% (CI 79.7 to 97.3) specificity. Figure 4.9 provides a graphical representation of test sensitivities and specificities using various percentage LACD cut-offs (tabulated results are provided in Table 4.3). Interestingly, the ≤25% LACD cut-off point represents a good trade-off between test sensitivity and specificity, providing evidence in support of the use of this traditional threshold to warrant investigation by gonioscopy. In comparison, a similarly high test sensitivity and specificity exceeding 80% was obtained at the ≤15% LACD cut-off when using the gonioscopic classification of an occludable angle based on clinical opinion. The Youden index-derived optimal cut-off for Smith's central ACD was ≤2.6mm based on the ISGEO classification of the angle, yielding lower test sensitivity and specificity of 71.8% (CI 56.2 to 83.5) when compared with LACD observations (Youden cut-off ≤25%). Figure 4.9 illustrates the greater rate of change in sensitivity and specificity either side of this optimal cut-off point. Receiver operating characteristic (ROC) curves constructed using Smith's ACD estimates and modified LACD grades for each gonioscopy classification of a narrow angle are shown in Figure 4.12.

Sub-analysis of the diagnostic effectiveness of nasal and temporal LACD revealed no statistically significant difference for sensitivity or specificity (p=1.0 McNemar test) using the ≤25% cut-off and ISGEO gonioscopic definition of a narrow angle. Test sensitivity was 69.2% (CI 53.6 to 81.4) and 66.7% (CI 51.0 to 79.4) for temporal and nasal observation respectively, while test specificity remained unchanged between limbal positions (94.9%, CI 83.1 to 98.6).

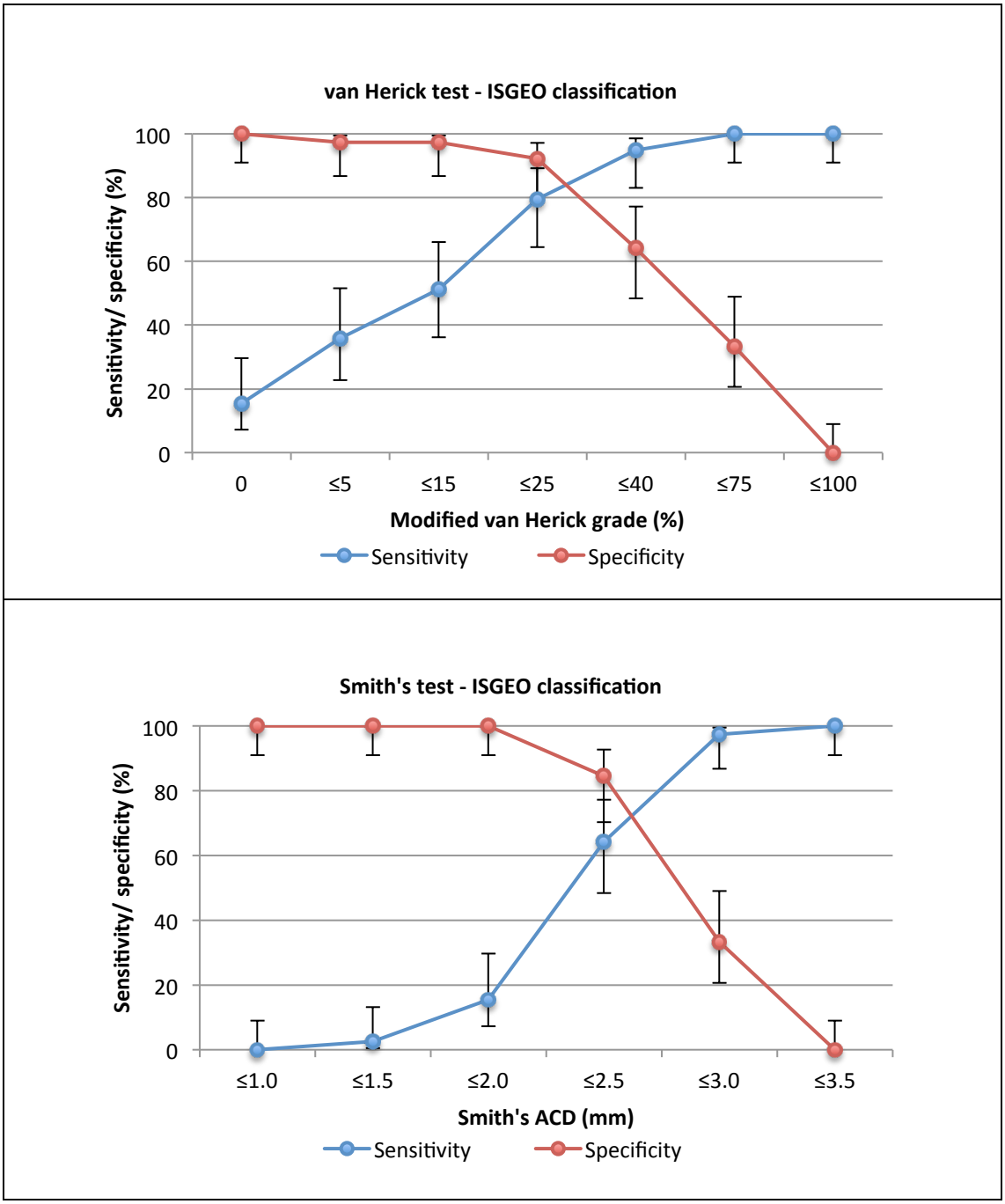


Figure 4.9: Sensitivity-specificity plots for the van Herick technique and Smith's test using the ISGEO gonioscopy classification

Index test	Index test cut-off	Reference standard cut-off	Sensitivity (%)	Specificity (%)	Positive LR	Negative LR
Van Herick	≤25%	ISGEO	79.5 (64.5 to 89.2)	92.3 (79.7 to 97.3)	10.3 (3.4 to 31)	0.2 (0.1 to 0.4)
		Clinical opinion of occludability	94.1 (73.0 to 99.0)	70.5 (58.1 to 80.4)	3.2 (2.1 to 4.8)	0.1 (0.0 to 0.6)
	≤15%	ISGEO	51.3 (36.2 to 66.1)	97.4 (86.8 to 99.5)	20.0 (2.8 to 141.8)	0.5 (0.4 to 0.7)
		Clinical opinion of occludability	82.4 (59.0 to 93.8)	88.5 (78.2 to 94.3)	7.2 (3.5 to 14.9)	0.2 (0.1 to 0.6)
	≤5%	ISGEO	35.9 (22.7 to 51.6)	97.4 (86.8 to 99.5)	14 (1.9 to 101.4)	0.7 (0.5 to 0.8)
		Clinical opinion of occludability	58.8 (36.0 to 78.4)	91.8 (82.2 to 96.4)	7.2 (2.8 to 18.2)	0.4 (0.3 to 0.8)
	0%	ISGEO	15.4 (7.2 to 29.7)	100 (91.0 to 100.0)	---	0.8 (0.7 to 1.0)
		Clinical opinion of occludability	29.4 (13.3 to 53.1)	98.4 (91.3 to 99.7)	17.9 (2.2 to 143.4)	0.7 (0.5 to 1.0)
Smith's	ACD≤2.60mm	ISGEO	71.8 (56.2 to 83.5)	71.8 (56.2 to 83.5)	2.5 (1.5 to 4.4)	0.4 (0.2 to 0.7)
	ACD≤2.50mm	Clinical opinion of occludability	76.5 (52.7 to 90.4)	70.5 (58.1 to 80.4)	2.6 (1.6 to 4.1)	0.3 (0.1 to 0.8)

Table 4.3: Sensitivity, specificity and likelihood ratios for the van Herick technique and Smith's test using various cut-offs and presented with 95% confidence intervals

4.3.2 Diagnostic effectiveness of imaging-based index tests

Youden index-derived cut-offs for ACA were 20.7° and 30.7° using Visante OCT and Pentacam imaging respectively based on the ISGEO gonioscopy classification (Figure 4.10). Using these criteria, Visante OCT ACA showed better sensitivity and specificity (exceeding 85%) than Pentacam-derived estimates (Table 4.4). Central ACD measurements generated by both devices showed similar test sensitivities (71.8%, Visante OCT and 74.4%, Pentacam) compared with Smith's test, but higher specificities (84.6%, Visante OCT and 76.3%, Pentacam) at the ≤2.50mm Youden cut-off. Figure 4.10 shows a similarly high rate of change of sensitivity and specificity either side of the optimal cut-off for ACD with both instruments compared with the best performing imaging-based parameter, the Visante OCT ACA. Of the three Pentacam anterior chamber parameters, ACV (Youden cut-off ≤124mm^3) achieved the highest test sensitivity of 84.6% (CI 69.5 to 94.1) using the ISGEO definition of a narrow angle.

Further analysis of Visante OCT ACA data found similar effectiveness of temporal and nasal measurements to detect narrow angles, with no statistically significant difference observed for either sensitivity or specificity (p= 1.0 McNemar test). Interestingly, Pentacam imaging showed a marked difference in diagnostic performance between temporal and nasal angle positions, with higher mean ACA measured at the temporal limbus compared with the nasal position. Bland-Altman mean difference analysis revealed mean bias of 2.37° (CI -7.18 to 11.93) (Figure 4.11).

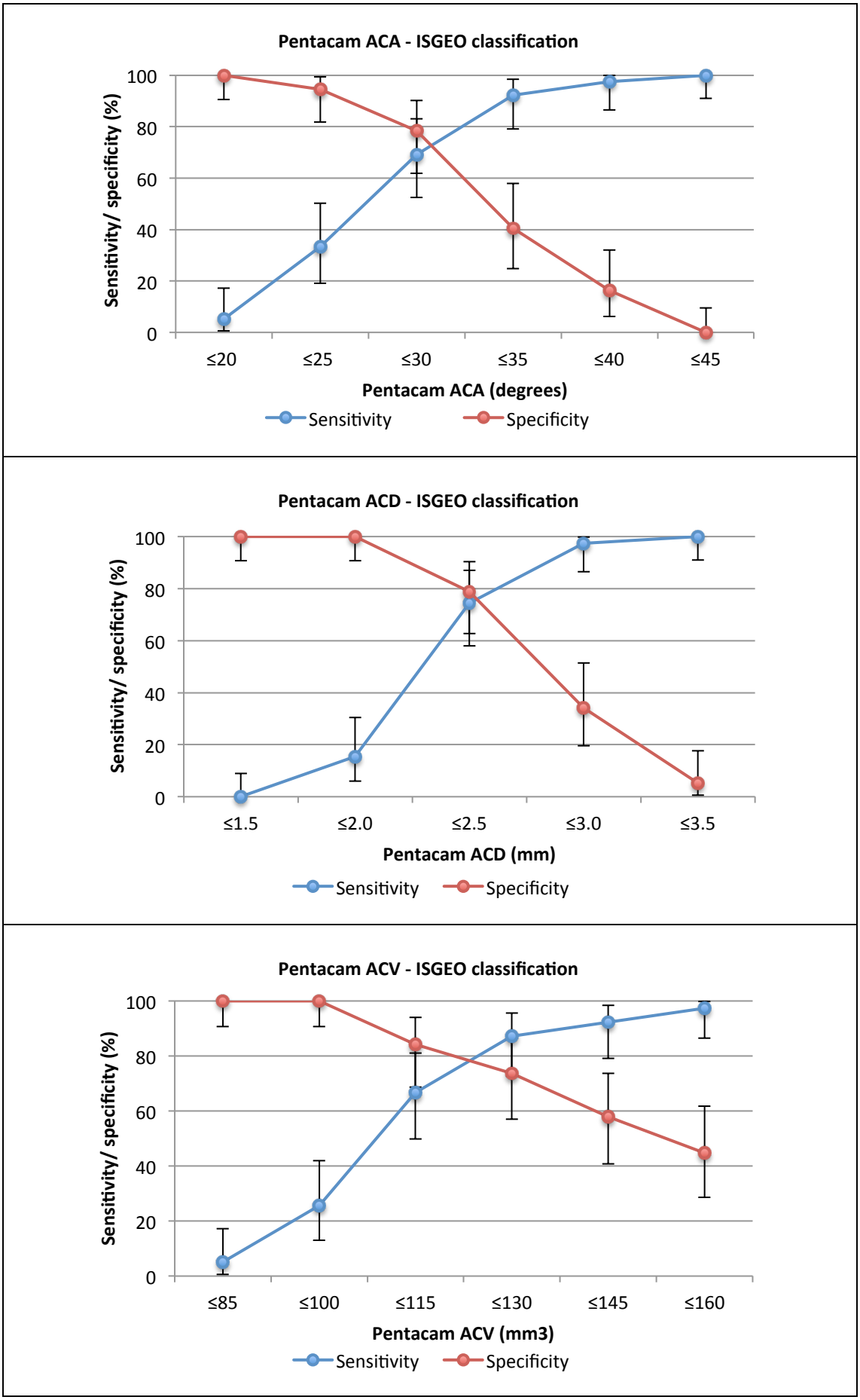


Figure 4.10: Sensitivity-specificity plots for imaging-based parameters using ISGEO gonioscopy classification

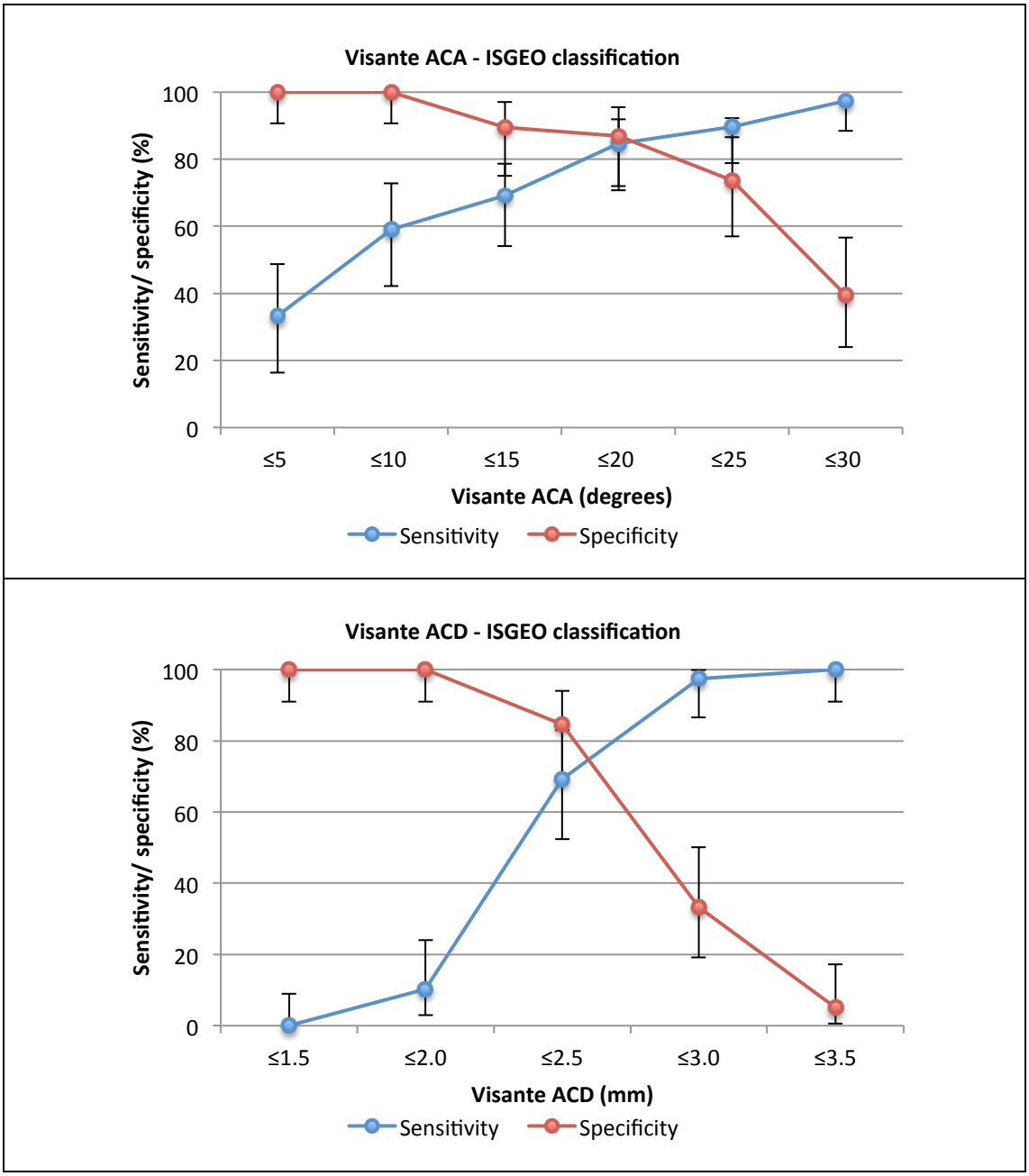


Figure 4.10 (continued): Sensitivity-specificity plots for imaging-based parameters using ISGEO gonioscopy classification

Index test	Index test cut-off	Reference standard cut-off	Sensitivity (%)	Specificity (%)	Positive LR	Negative LR
Visante OCT	ACA≤20.7°	ISGEO	87.2 (72.6 to 95.7)	86.8 (71.9 to 95.6)	6.6 (2.9 to 15.1)	0.15 (0.06 to 0.3)
	ACA≤18.6°	Clinical opinion of occludability	100.0 (80.5 to 100.0)	66.7 (53.3 to 78.3)	3.0 (2.1 to 4.3)	---
	ACD≤2.50mm	ISGEO	71.8 (55.1 to 85.0)	84.6 (69.5 to 94.1)	4.7 (2.2 to 10.0)	0.3 (0.2 to 0.6)
	ACD≤2.38mm	Clinical opinion of occludability	82.3 (56.6 to 96.2)	83.6 (71.9 to 91.8)	5.0 (2.7 to 9.2)	0.2 (0.08 to 0.6)
Pentacam	ACA≤30.7°	ISGEO	71.8 (55.1 to 85.0)	78.4 (61.8 to 90.2)	3.3 (1.7 to 6.3)	0.4 (0.2 to 0.6)
	ACA≤30.2°	Clinical opinion of occludability	82.4 (56.6 to 96.2)	62.7 (49.1 to 75.0)	2.2 (1.5 to 3.3)	0.3 (0.1 to 0.8)
	ACD≤2.50mm	ISGEO	74.4 (57.9 to 87.0)	76.3 (59.8 to 88.6)	3.2 (1.7 to 5.7)	0.3 (0.2 to 0.6)
	ACD≤2.40mm	Clinical opinion of occludability	82.3 (56.6 to 96.2)	76.7 (64.0 to 86.6)	3.5 (2.1 to 5.9)	0.2 (0.1 to 0.6)
	ACV≤124mm^3	ISGEO	84.6 (69.5 to 94.1)	78.9 (62.7 to 90.4)	4.0 (2.1 to 7.5)	0.2 (0.1 to 0.4)
	ACV≤124mm^3	Clinical opinion of occludability	94.1 (71.3 to 99.9)	58.3 (44.9 to 70.9)	2.3 (1.6 to 3.1)	0.1 (0.01 to 0.7)

Table 4.4: Sensitivity, specificity and likelihood ratios for Smith's test, Pentacam imaging and Visante OCT using the Youden cut-off and presented with 95% confidence intervals

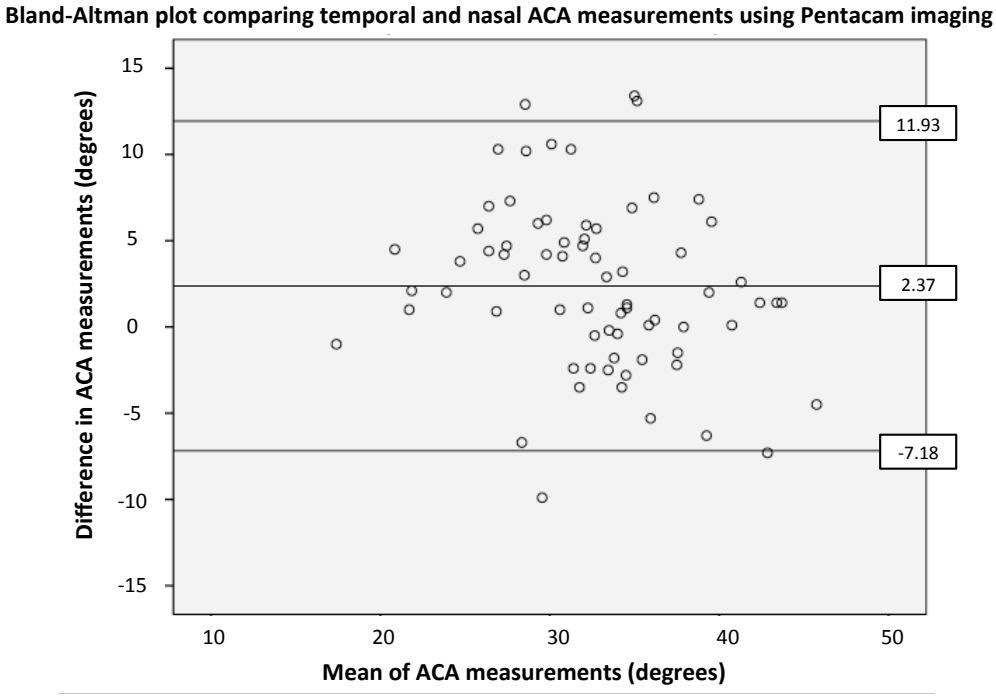


Figure 4.11: Bland-Altman plot comparing temporal and nasal ACA measurements using Pentacam imaging

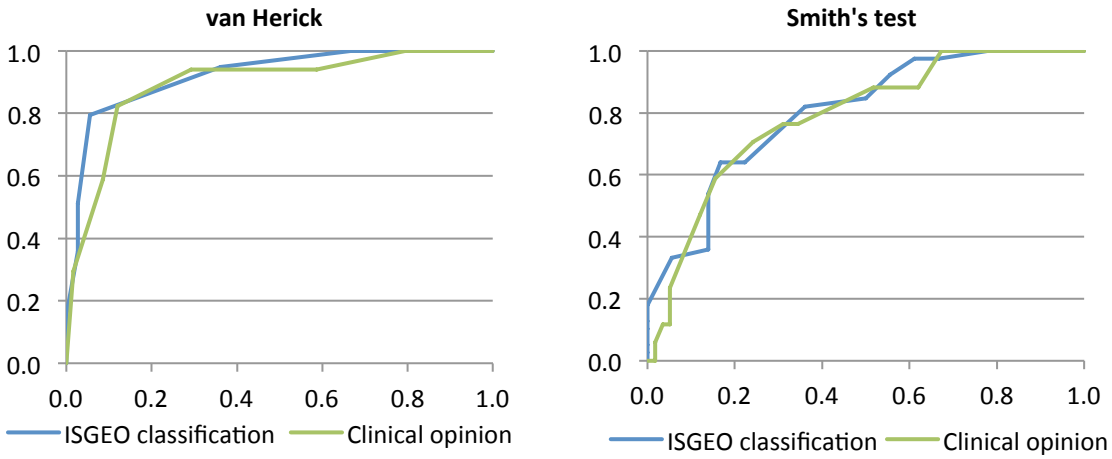


Figure 4.12: ROC curves (plotting sensitivity against 1-specificity) constructed for each index parameter using the two gonioscopic classifications of a narrow angle

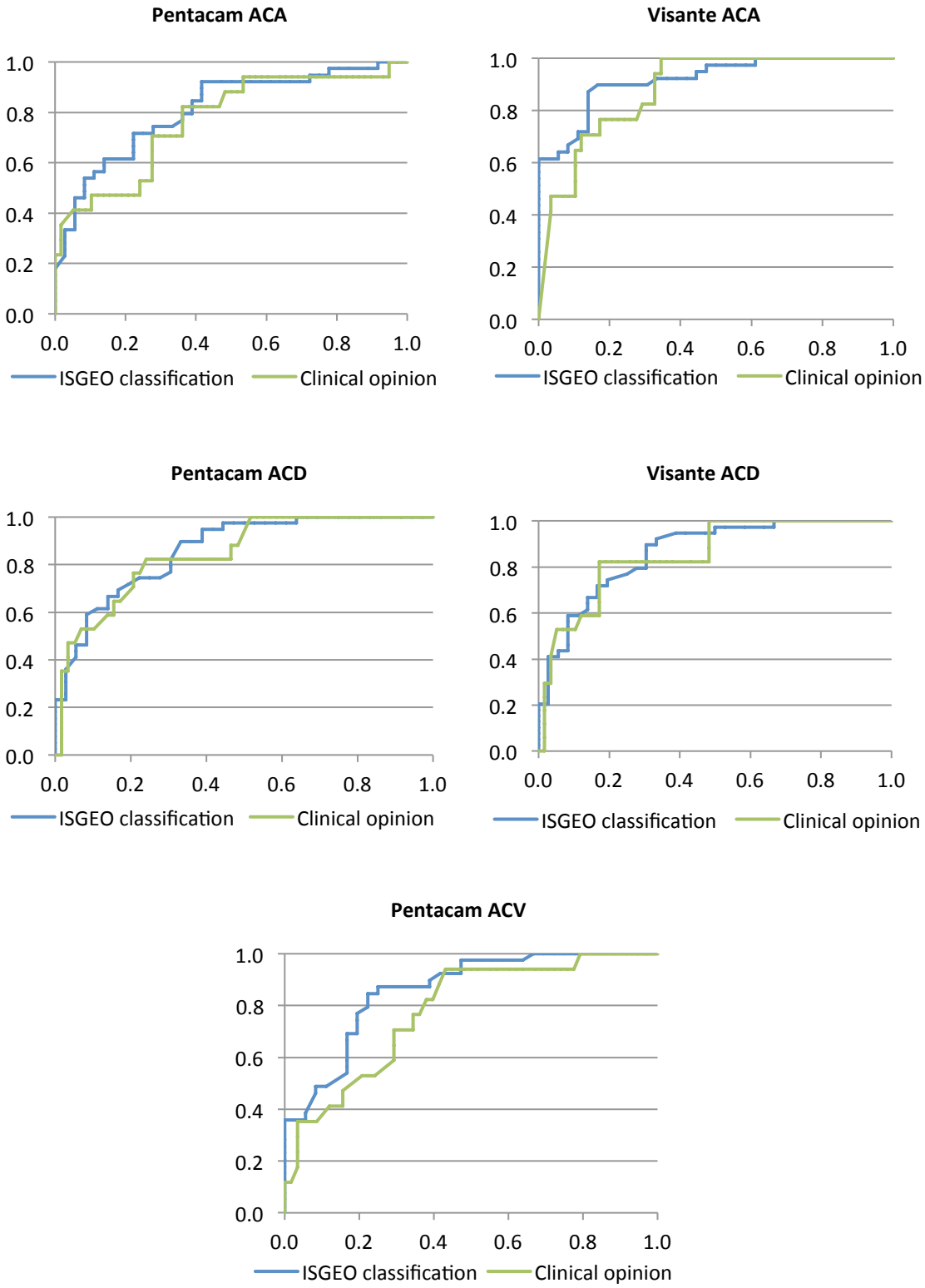


Figure 4.12 (continued): ROC curves (plotting sensitivity against 1-specificity) constructed for each index parameter using the two gonioscopic classifications of a narrow angle

Given the low prevalence of narrow angles in Western populations, a test specificity of 90% or greater is essential to screen for the condition. Tables 4.5a and b detail sensitivities and partial area under the ROC curve estimates at 90% and 95% specificity together with their 95% confidence intervals. At 90% specificity and using the ISGEO definition of a narrow angle, the van Herick test achieved highest sensitivity (79.5%, CI 38.7 to 90.9), and Visante ACA generated the greatest partial area under the ROC curve (0.63, CI 0.48 to 0.84). No significant difference was observed between the two parameters for partial AUROC curve estimates for ranges starting at 90% or 95% specificities ($p>0.14$), or sensitivity at set specificities of 90% or 95% using either gonioscopy classification ($p>0.40$) (Figure 4.13a shows sensitivity for 90% specificity). Using a classification of occludable angle based on clinical opinion, Visante OCT ACA generated the highest sensitivity at 90% and 95% specificities, but notably, partial AUROC estimates were greatest for Pentacam ACD and ACA respectively. These differences were not statistically significantly different ($p>0.44$).

Of the slit-lamp biomicroscope-based tests, the van Herick test yielded a statistically significantly higher sensitivity at 90% specificity using the ISGEO classification of a narrow angle compared with Smith's central ACD estimate ($p=0.02$) (Figure 4.13b). No significant difference was observed for sensitivity at set specificity ($p>0.37$) or partial AUROC curve estimates ($p>0.59$) using either gonioscopy classification between Pentacam parameters.

	ISGEO classification		**Clinical opinion**	
	Sensitivity at 90% specificity (CI)	**Sensitivity at 95% specificity (CI)**	**Sensitivity at 90% specificity (CI)**	**Sensitivity at 95% specificity (CI)**
VH	79.5 (38.7 to 90.9)	51.3 (9.5 to 88.4)	58.8 (15.0 to 94.4)	29.4 (9.1 to 87.5)
Smith's	33.3 (19.2 to 72.9)	30.8 (10.2 to 59.5)	41.2 (11.1 to 76.2)	23.5 (5.0 to 60.0)
Pentacam				
ACA	53.8 (21.4 to 73.4)	33.3 (10.0 to 65.6)	41.2 (17.6 to 70.0)	35.3 (13.6 to 66.7)
ACV	48.7 (26.0 to 84.9)	35.9 (22.4 to 63.1)	35.3 (13.3 to 64.3)	35.3 (6.3 to 60.0)
ACD	59.0 (31.5 to 86.4)	35.9 (13.9 to 70.3)	52.9 (29.4 to 80.9)	47.0 (18.7 to 73.3)
Visante				
ACA	66.7 (51.3 to 95.0)	61.5 (46.5 to 88.6)	64.7 (26.3 to 88.2)	47.1 (22.7 to 77.8)
ACD	59.0 (28.9 to 82.2)	41.0 (13.4 to 75.0)	52.9 (28.0 to 87.5)	41.2 (16.7 to 76.9)

Tables 4.5a: Sensitivity at 90% and 95% specificity for each index test parameter using the two gonioscopic classifications for a narrow angle

	ISGEO classification		Clinical opinion	
	Partial AUROC from 90% specificity (CI)	**Partial AUROC from 95% specificity (CI)**	**Partial AUROC from 90% specificity (CI)**	**Partial AUROC from 95% specificity (CI)**
VH	0.49 (0.20 to 0.82)	0.33 (0.09 to 0.80)	0.30 (0.08 to 0.70)	0.20 (0.0 to 0.54)
Smith's	0.29 (0.14 to 0.53)	0.24 (0.09 to 0.47)	0.19 (0.02 to 0.51)	0.06 (0.0 to 0.40)
Pentacam				
ACA	0.37 (0.16 to 0.61)	0.25 (0.10 to 0.58)	0.36 (0.14 to 0.62)	0.31 (0.1 to 0.58)
ACV	0.39 (0.24 to 0.62)	0.36 (0.22 to 0.55)	0.27 (0.08 to 0.51)	0.19 (0.0 to 0.47)
ACD	0.40 (0.19 to 0.67)	0.29 (0.14 to 0.61)	0.39 (0.15 to 0.67)	0.27 (0.0 to 0.62)
Visante				
ACA	0.63 (0.48 to 0.84)	0.62 (0.46 to 0.80)	0.31 (0.07 to 0.67)	0.16 (0.0 to 0.59)
ACD	0.40 (0.20 to 0.69)	0.30 (0.13 to 0.65)	0.38 (0.13 to 0.70)	0.24 (0.0 to 0.63)

Tables 4.5b: Partial area under the ROC curve (PAUROC) data for each index test parameter using the two gonioscopic classifications for a narrow angle

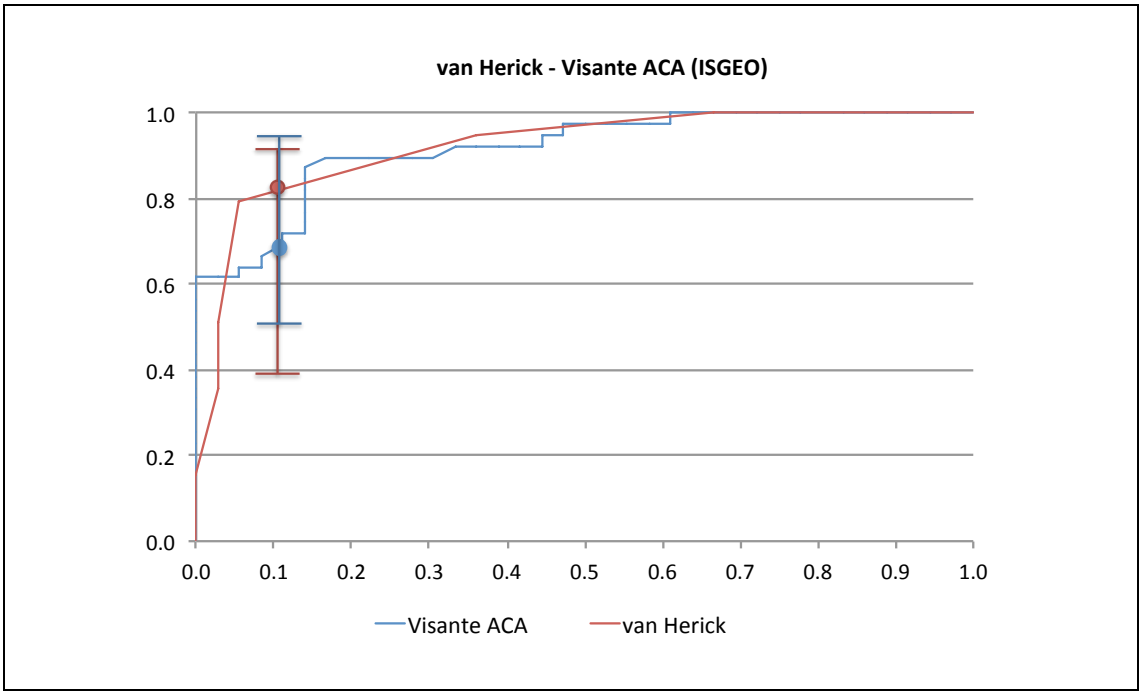


Figure 4.13a: ROC curves showing specificity at 90% sensitivity with 95% confidence intervals for van Herick test and Visante OCT ACA

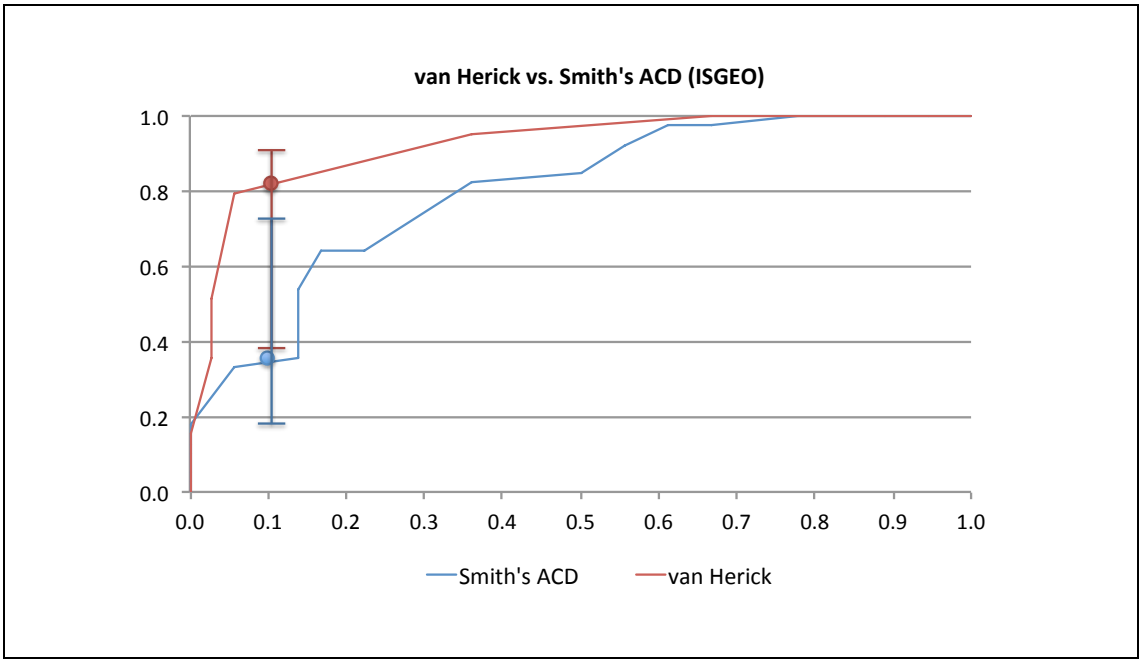


Figure 4.13b: ROC curves showing specificity at 90% sensitivity with 95% confidence intervals for van Herick and Smith's tests

4.3.3. Combining test results

The effectiveness of combining index test results was evaluated using 2x2 tables to generate sensitivity and specificity values. Using the ISGEO gonioscopy classification system and based on failure of both the van Herick test (≤25%) AND Smith's test (≤2.60mm) being suggestive of a narrow angle, test specificity of 95% was achieved but this was traded off against a reduction in sensitivity below 60% (Appendix C, Table iv). Conversely, detection of a narrow angle based on failure of EITHER test using the same criteria improves sensitivity above 90%, but reduces test specificity to just below 70%. Combining the two slit-lamp biomicroscope based tests is logical given that tests may be performed in rapid succession. However, based on failure of both best performing index tests and using the ISGEO gonioscopy classification, the van Herick (≤25%) and Visante OCT ACA (≤20.7°) elicit 97% specificity, while still retaining a sensitivity of 74%.

Figure 4.14 constructs Venn diagrams showing agreement between van Herick, Smith's test, and best performing imaging-based parameters for the detection of narrow angles. Using the ISGEO gonioscopy classification of a narrow angle, 92% of subjects were detected using the van Herick technique (≤25%) and Smith's test (≤2.60mm). Notably, by using a gonioscopic classification based on clinical opinion of occludability, 100% of narrow angle subjects were detected using the van Herick technique (≤25%) together with Smith's test (≤2.50mm).

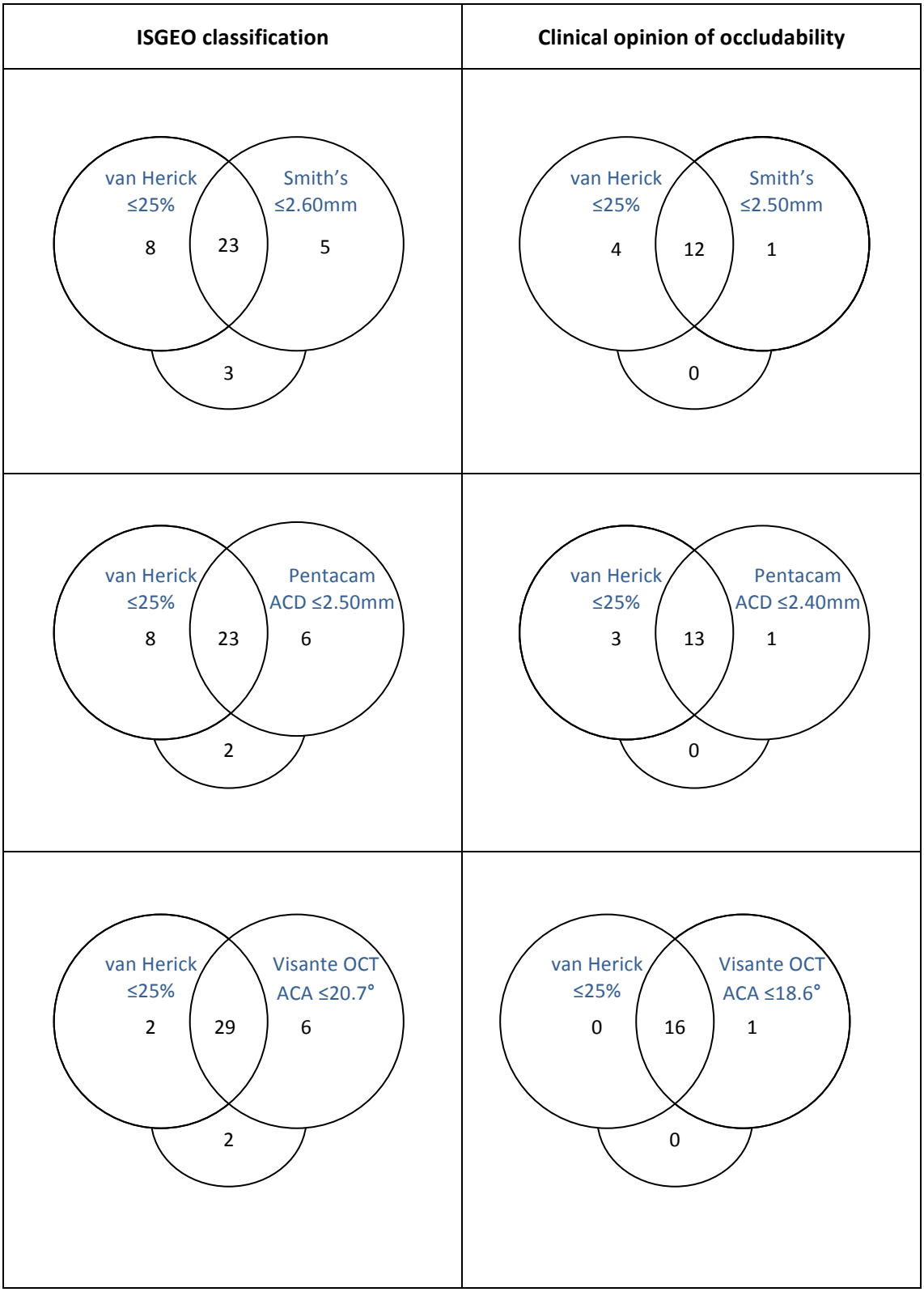


Figure 4.14: Venn diagrams presenting agreement between van Herick and Smith's test, and best performing imaging-based parameters for the detection of narrow angles using gonioscopy classifications based on the ISGEO and clinical opinion *(the number of 'narrow angle' subjects undetected by either index test is detailed beneath the two circles which comprise the main body of the Venn diagram)*

Results of the user acceptability survey are summarized in Table 4.6. Agreement with the statements, 'the test was comfortable' and 'the test was quick' were above 90% for all index tests. Notably, respondents indicated 100% agreement with both statements when providing their view on the van Herick test. Of the index tests, Pentacam imaging was associated with lowest agreement (94%) with the statement 'the test was quick to perform', consistent with longest mean time taken to acquire data from both eyes. Subjects reported gonioscopy as the least comfortable test and most lengthy to undertake despite the fact that the time taken to capture data from both eyes was shorter than for Pentacam imaging. The chi-squared test for differences in proportions between subject groups was not possible because one or more cell(s) had an expected count of less than the minimum acceptable value of 5. 31 subjects responded to the 'additional comments' box at the end of survey. Of these, 11 comments were made with reference to index tests, with the majority (91%) coded as 'positive' or 'neutral'.

	'The test was comfortable'			**'The test was quick'**			**Mean time taken to capture R+L data (min)**
	Disagree % (N)	**Neither agree nor disagree % (N)**	**Agree % (N)**	**Disagree % (N)**	**Neither agree nor disagree % (N)**	**Agree % (N)**	
Van Herick	0 (0)	0 (0)	100 (78)	0 (0)	0 (0)	100 (78)	1.28±0.44
Smith's	0 (0)	0 (0)	100 (78)	1 (1.3)	2.6 (2)	96.2 (75)	3.75±0.83
Pentacam	1 (1.3)	0 (0)	98.7 (77)	3.8 (3)	2.6 (2)	93.6 (73)	5.11±1.38
Visante OCT	0 (0)	1.3 (1)	98.7 (77)	1 (1.3)	1.3 (1)	97.4 (76)	4.29±0.74
Gonioscopy	10.3 (8)	7.7 (6)	82.1 (64)	7.7 (6)	2.6 (2)	89.7 (70)	4.48±1.62

Table 4.6: Aggregated Likert scale responses to index test acceptability survey in response to the statements a) 'The test was comfortable' and b) 'the test was quick, with mean time taken to capture data of both eyes

4.4 Discussion

On a global scale, the WHO estimates that 11.2 million people will be bilaterally blind from glaucoma worldwide by the year 2020, and nearly half of these cases will be attributed to angle closure mechanisms (WHO, 2007). Angle closure glaucoma (ACG) is the predominant form of glaucoma in a number of East and South East Asian countries including China, where it is responsible for 91% of bilateral blindness from glaucoma (Foster and Johnson, 2001).

ACG satisfies many of the suitability criteria for the screening of disease specified by Wilson and Jungner (Wilson & Jungner, 1968). In particular, ACG has an early clinically recognizable stage, acceptable instrumentation to detect at-risk individuals is available, and standard interventions to prevent functional loss of vision are readily available. Laser peripheral iridotomy (LPI) is considered standard practice for treatment of ACG, with strong evidence that early detection of primary angle closure suspect (PACS) eyes can prevent progression to PAC/ PACG in the vast majority of cases (Nolan et al., 2000). Once angle closure has been diagnosed in one eye, it is common practice to perform a prophylactic procedure on the fellow eye to prevent it following suit, reducing the chances of an IOP rise in the long-term by over 85% (Ang et al., 2000). However, LPI is demonstrably less effective, and even considered suboptimal where manifest angle closure with evidence of functional damage to the drainage apparatus has already occurred, and in particular where there is evidence of glaucomatous optic neuropathy (Nolan et al., 2000), highlighting the need for early detection. The procedure can also be less beneficial in cases where angle closure is predominantly the result of non-pupillary block mechanisms.

The low prevalence of ACG of 0.4% in European-derived populations aged 40 years and older (Day et al., 2012) suggests that a population-based screening programme for ACG would not be cost-effective. In the absence of a national screening programme, community optometrists in the UK rely on case-finding to detect ACG, using opportunistic surveillance when people self-select to attend for an eye examination in community practice. Gonioscopy is not widely adopted in community optometric practice, and practitioners use surrogate methods using slit-lamp biomicroscope based techniques such as the van Herick (van Herick et al., 1969) and/ or Smith's test (Smith, 1979). The past 20 years has seen major advances in the scope of optometric practice including increasing use of advanced imaging equipment such as the OCT (Dabasia et al., 2014). Newer systems use non-contact techniques to acquire detailed cross-sections of ocular tissues from which structural data may be derived. Tests need to combine high specificity, ideally above 90%, with an acceptably high sensitivity, in order to achieve a

reasonable positive predictive value when screening for a disease with low prevalence in the target population. A number of cross-sectional surveys have been undertaken to evaluate the effectiveness of surrogate screening tests to identify gonioscopically occludable angles, but the authors present conflicting findings (Congdon et al., 1996, Foster et al., 2000, Nolan et al., 2006, Lavanya et al., 2008, Zhang et al., 2014). Moreover, there is a lack of evidence for the effectiveness of non-invasive tests to screen for gonioscopically narrow angles in Western populations, as the majority of these reports have been undertaken in Asia, where the prevalence and mechanisms for angle closure are known to differ from those in Caucasian populations. For this reason, this study aimed to evaluate how data acquired using advanced technologies may be best used alone, or in combination with traditional tests to improve the accuracy of referrals of individuals at risk of angle closure glaucoma (ACG) for further ophthalmological investigation in a UK population.

4.4.1 Diagnostic performance of slit-lamp biomicroscope based screening tests

In their original paper, van Herick et al. indicated that observation of a limbal anterior chamber depth (LACD) of grade 2 or less (equating to ≤25% of the corneal thickness) may suggest a narrow ACA and these cases should be investigated further by gonioscopy (van Herick et al., 1969). The current study confirmed that this cut-off point provided the optimal balance between sensitivity and specificity (79.5% and 92.3% respectively) for the detection of a narrow angle, as defined by the ISGEO classification. Several studies have reported on the performance of the van Herick test for the detection of gonioscopically occludable angles (Foster et al., 2000, Wirbelauer et al., 2005, Nolan et al., 2006, Baskaran et al., 2007, Park et al., 2011, Andrews et al., 2012). Some have described its superior performance over other non-invasive screening tests, such as ultrasound pachymetry, optical pachymetry or the scanning peripheral anterior chamber depth analyzer (SPAC) (e.g. Nolan et al., 2006, Baskaran et al., 2007). Conversely, others have raised concerns as to the utility of the technique in screening for angle closure. For example, Congdon et al. analysed data from over 500 subjects and concluded that the van Herick test performed less well than ultrasound biomicroscopy (Congdon et al., 1996). Similarly, Thomas et al. cited both low sensitivity (61.9%) and low specificity as the reasons for the inadequacy of van Herick for use in screening for occludable angles, despite the specificity almost reaching 90% (Thomas et al., 1996).

Figure 4.15 compares the results of the current study to sensitivity and specificity estimates from the literature for the detection of narrow anterior chamber angles using the traditional van Herick threshold of grade 2 or less (≤25%). These data should be interpreted with

knowledge of variations in design, population demographics, and sample size between studies. Population-based cross-sectional studies in East Asia (Foster et al., 2000 and Nolan et al., 2006) found higher sensitivities but lower specificities than the present study. Foster and co-workers collected data from 1717 subjects recruited from rural and urban regions of Mongolia, while Nolan et al. examined a representative sample (N=1090) of Chinese Singaporean residents. Foster et al.'s report (2000) described the use of a modified LACD grading scheme that expanded the standard van Herick grading scheme to a seven-point percentage grading scale; including subdividing grade 1 into 5% and 15% subcategories. Using these additional sub-divisions for grading led to improved test specificity when compared with the ≤25% cut-off criterion. Interestingly, mean specificities for the present study exceeded 90% for each of the LACD thresholds ≤25%, ≤15% and ≤5%. Differences in diagnostic performance estimates between studies may be explained by demographic variations between populations. It is widely known that the prevalence and mechanisms of angle closure in Asian populations differ significantly from those in European populations (He et al., 2006b). The predisposition of East Asian subjects to ACG may be explained by anatomical differences whereby the iris joins more anteriorly to the scleral wall in this population, slightly more posteriorly in Afro-Americans and most posteriorly in Caucasians (Oh et al., 1994).

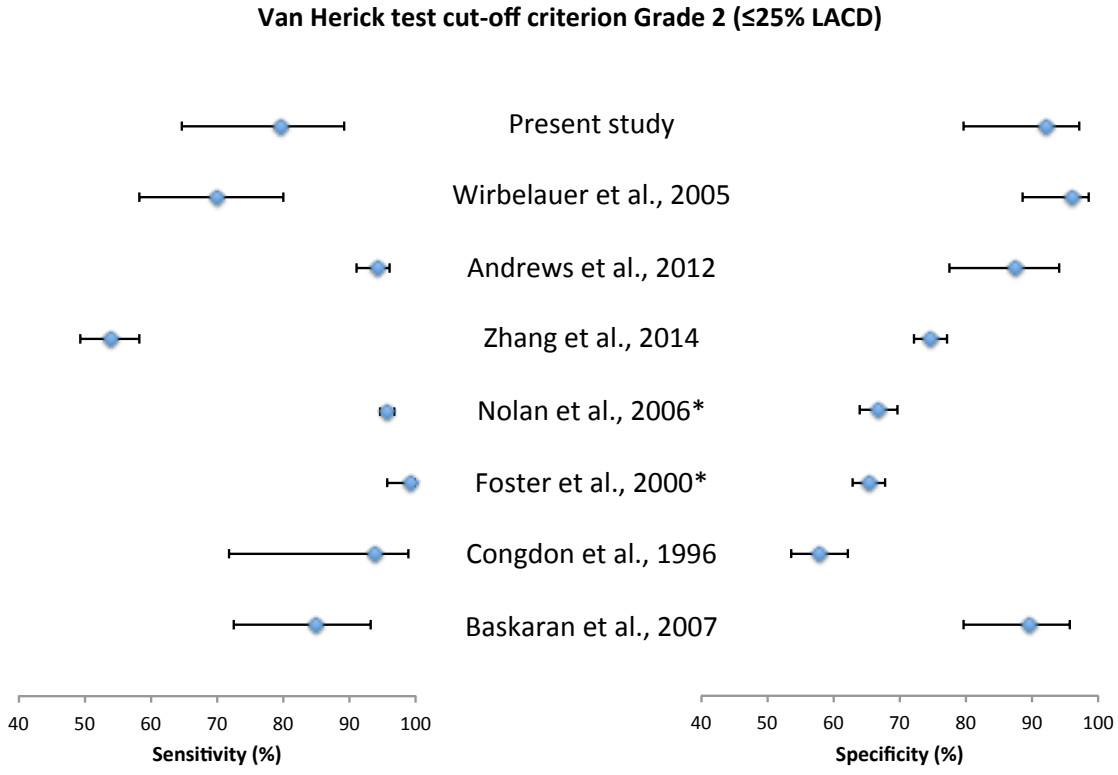


Figure 4.15: Sensitivity and specificity estimates with associated 95% confidence intervals for detection of narrow anterior chamber angles using the van Herick cut-off point of ≤grade 2 (≤25%) *(*Studies that used the ISGEO classification to define a narrow ACA)*

When evaluating the validity of any clinical test, it is important to additionally consider the inter- and intra-observer variability of the measurement itself. In their paper, van Herick et al. compared the results from the same patients over a 2–3-year period, noting that the grading was consistent when made by different examiners, with no greater variation than one grade (van Herick et al., 1969). More recently, weighted kappa statistics have provided a more rigorous quantitative measurement of the inter-rater variability between observers for the technique, with good levels of agreement found, ranging between 0.73 (Thomas et al., 1996) using the traditional grading, and 0.76 using the 7-point percentage scale (Foster et al., 2000). There is only one investigation of intra-observer agreement (Cockburn, 1982) which reported 'high' intra-observer repeatability when using a decimal grading system. There are a number of potential sources of measurement error when performing the van Herick test including; not positioning the beam as close as possible to the limbus and not maintaining a 60° angle between the slit-lamp illumination and observation systems (Leung et al., 2012).

Another important practical consideration of the van Herick test is whether the technique should be performed at the nasal and/or temporal limbal positions. A report by Alsbirk evaluating the effectiveness of the van Herick test observed a marked asymmetry in grades between the temporal and nasal aspects, with shallower LACDs at the temporal limbus (Alsbirk, 1986). This trend was common to both the Inuit and Danish populations evaluated, although the finding was not confirmed by gonioscopy. Alsbirk concluded that, while both quadrants should be evaluated, the temporal side is the more important for screening. Foster et al. suggested that this asymmetry in temporal and nasal grades reported by Alsbirk (1986) may be a reflection of variation in the position of the limbus (Foster et al., 2000). In the current study, we observed similar van Herick grades and diagnostic performances for the detection of gonioscopically narrow angles between nasal and temporal positions. These data suggest that recording of either the temporal or nasal LACD would be sufficient for case-finding in at-risk individuals.

The second slit-lamp biomicroscope-based test evaluated in the present study was Smith's test (Smith, 1979), a non-contact technique that provides an estimate of central anterior chamber depth (ACD). The use of central ACD measurement to screen for ACG is supported by the established relationship between a narrow ACA and a shallow ACD, and the correlation of both these factors with the risk of developing ACG (Wishart & Batterbury, 1992). Community-based screening studies have since established the effectiveness of central ACD for the detection of potentially occludable angles by gonioscopy (Congdon et al., 1996, Devereux et

al., 2000, Kurita et al., 2009). Only one previous report has evaluated the diagnostic performance of Smith's test (Al-Mubrad & Ogbuehi, 2006). Although these authors observed a good correlation between Smith's method and gonioscopy (Spearman rho= 0.938), this does not necessarily imply good agreement between the two techniques. Our findings revealed a statistically significantly lower mean sensitivity for detection of narrow angles at 90% specificity for Smith's test (33%) compared to the van Herick test (80%). In terms of test reproducibility, Osuobeni et al. found acceptable levels of intra- and inter-observer repeatability, with similar results to those found using A-scan ultrasonography for measuring ACD (Osuobeni et al., 2000).

Although Smith's test does not provide a diagnostic advantage over the van Herick test when used alone, a combination of these tests could improve diagnostic performance. In situations where specificity needs to be maximised, for example when case-finding for the low population prevalence of angle closure, a case-detection criterion based on a van Herick grade ≤25% together with a Smith's ACD of ≤2.60mm achieved a specificity of 95% in the current study. However, this would be offset by a fall in sensitivity to below 60%. Since the use of the van Herick test alone achieved sensitivity and specificity estimates of 80% and 92% respectively, combined testing would not provide a notable diagnostic advantage. Furthermore Smith's test takes longer to perform; mean time taken to capture data from both eyes using the van Herick test was 1.28 min compared with Smith's test 3.75 min, although acquisition of three Smith's central ACD estimates for each eye may not represent standard clinical practice. However, there is a case for performing Smith's test when the van Herick is not possible, for example in the presence of a pronounced arcus senilis or in patients with climatic droplet keratopathy (Foster et al., 2000).

4.4.2 Diagnostic performance of imaging-based systems

Advanced imaging systems such as the OCT and Pentacam enable the non-invasive capture of cross-sectional images of the anterior segment. These images can be evaluated qualitatively to identify areas of irido-corneal contact, or analyzed quantitatively using biometric criteria.

In the current study the ACA and central ACD were measured from images obtained with the Visante AS-OCT, and ROC derived cut-points (generated from the Youden index (Youden, 1950)) were used to optimize the balance between sensitivity and specificity. The ACA was the best performing parameter for the detection of narrow angles (based on the ISGEO classification); a ≤20.7° cut-off point being associated with a sensitivity and specificity of 87%. By contrast the ACD yielded an equivalently high specificity but with a lower sensitivity (70%). Wirbelauer et al. have similarly reported a high sensitivity and specificity (86% and 95% respectively) for the ACA measured with the Visante AS-OCT to detect occludable angles in a German clinic-based population (Wirbelauer et al., 2005).

Interestingly, studies conducted in East Asia based on qualitative assessment of AS-OCT images for contact between the peripheral iris and any part of the angle wall anterior to the scleral spur, found equivalently high sensitivities (Nolan et al., 2007, Lavanya et al., 2008, Wong et al., 2009, Sakata et al., 2010, Chang et al., 2011), but reported specificities as low as 51% (Sakata et al. 2010), 55% (Nolan et al., 2007) and 58% (Wong et al., 2009). It is not clear whether these low specificities reflect different use of landmarks and definitions of a narrow angle or if angle closure is being missed by gonioscopy in these populations. Indeed, some authors have questioned the validity of gonioscopy as the reference standard to define angle closure (Nolan et al., 2007), given the known effect of angle distortion caused by surface contact, and the effects of visible light exposure on angle configuration, compared with infra-red radiation used for AS-OCT imaging.

Whilst the AS-OCT shows good potential for identifying individuals at-risk of angle closure, the analysis of OCT images relies on examiner experience to identify features of the ACA correctly and to appropriately position the angle measurement tool. In the current study, intra-observer repeatability of ACA estimates for observations of the initial scan revealed wide 95% confidence intervals which is largely attributed to variability in the positioning of the angle measurement tool. A subset of scans also revealed a marked difference in angle configuration between successive scans captured of the same eye. These observations did not appear to be the result of fluctuations in accommodative status as pupil size remained unchanged. It is not known whether these observations represent true variations in angle width, or artefacts of optical imaging. Reproducibility between individuals was not evaluated in this study, but it is anticipated that Bland-Altman difference plots would generate equivalent if not greater variability for this comparison. Accurate positioning of the central point of the angle marker tool is dependent on correct identification of the deepest angle recess position, which in turn relies on observation of the most important landmark of the ACA, namely the scleral spur. It

has been reported that visualisation of the scleral spur is not possible in an estimated 10–30% of images captured using the Visante OCT due to poor image quality or poor anatomical definition of the spur (Sakata et al., 2008b, Narayanaswamy et al., 2010, Sakata et al., 2010, Chang et al., 2011). Notably, Sakata and colleagues also commented that the scleral spur was less detectable in quadrants with closed angles, and in the superior and inferior positions (Sakata et al., 2008b). The importance of this observation is highlighted by reports of a higher rate of angle closure in the superior quadrant, followed by the inferior quadrant, as predicted by their anatomical predisposition (Sakata et al., 2008a).

Pentacam imaging systems aim to overcome the subjectivity associated with acquiring biometric data of the ACA, by the use of fully automated analysis. In our population, Pentacam parameters showed only moderate ability to distinguish between open and narrow angle subjects. Using the ISGEO gonioscopic definition of a narrow angle, ACA and ACD Youden cut-offs yielded sensitivity and specificity estimates between 70 and 80%. These findings contrast with previous reports of Pentacam ACD being an effective indicator for the detection of gonioscopically narrow angles. Kurita et al. and Alonso et al. both used a 2.6mm cut-off to yield a sensitivity of 100% (Kurita et al., 2009, Alonso et al., 2010), while Hong et al. applied a lower 2.27mm threshold to determine 93% sensitivity and 95% specificity for detection of narrow angles (Hong et al., 2009). Another study favoured use of ACV to partition normal eyes from those at risk of angle closure (Grewal et al., 2011), generating 90% sensitivity and 88% specificity for a ≤113mm^3 cut-off.

The Pentacam acquires images using the Scheimpflug principle, which is based on the penetration of light through the structure of interest. As such, the device is unable to visualize accurately the angle recess, peripheral-most iris and retroiridal structures. Pentacam ACA is critically dependent on the software automatically detecting the apex of the anterior chamber, however this is prone to inaccuracy given the inability of the Pentacam to visualise the most peripheral aspect of the iris. Using a cut-point of 31.7^o, Zhang et al. reported lower sensitivity (67%) and specificity (61%) for detection of gonioscopically occludable angles than was observed in the present study (Zhang et al., 2014). Kurita et al. compared the three Pentacam parameters, revealing significantly poorer performance by Pentacam ACA than ACV and ACD, and poorer correlation of Pentacam ACA with Shaffer's grade determined by gonioscopy (r = 0.65) (Kurita et al., 2009). An interesting observation to emerge from sub-analysis of Pentacam ACA estimates in the present study was the measurement of higher mean ACA temporally compared with the nasal position. This asymmetry between measurements at the two angle positions does not reflect differences in nasal and temporal angle observation using

gonioscopy, or other index tests (van Herick and Visante OCT ACA). These observations are likely to be artefactual, possibly attributed to camera tilting, or adjustments during automatic processing of raw data that allows detection of tissue boundaries, and corrects for distortions.

4.4.3 Case-finding for narrow anterior chamber angles

In the UK, optometrists play a key role in the detection of glaucoma in primary care, and are responsible for referring in excess of 95% of referrals for suspected glaucoma and OHT for ophthalmological opinion (Sheldrick et al., 1994, Bell & O'Brien, 1997, Bowling et al., 2005). Case-finding of individuals at-risk of ACG is also undertaken by optometrists when people self-select to attend for an eye examination in community practice. Gonioscopy is not a widely adopted technique in community optometric practice for examining the ACA. It is not a General Optical Council core competency (GOC, 2011), and the majority of optometrists lack the training to perform the technique. Although an estimated 12% of UK community optometrists reported having access to a gonio-lens in a national survey of diagnostic tests for the detection of chronic open angle glaucoma in 2008 (Myint et al., 2011), a smaller proportion would be performing gonioscopy for routine case-finding for ACG, as the technique is considered invasive, time-consuming and therefore impractical for use in busy high-street practice. Moreover, the technique requires a considerable level of skill, experience and knowledge to perform the test and to interpret the results, as well as relying on the cooperation of the patient.

Instead, practitioners use slit-lamp biomicroscope based methods such as the van Herick (van Herick et al., 1969) and/ or Smith's test (Smith, 1979). The current CoO clinical guideline for examining patients at risk from glaucoma states that "*If you suspect the patient has glaucoma you should assess the anterior eye and angle, for example by slit lamp-van Herick technique"* (CoO, 2014b). Following the publication of the NICE Clinical guideline on the diagnosis and management of chronic open angle glaucoma and ocular hypertension in England and Wales, the College of Optometrists (CoO) and Royal College of Ophthalmologists issued joint guidance on referral of patients with suspect glaucoma which stated that an optometrist should refer patients for further investigation if they identify "*a narrow anterior drainage angle on van Herick testing consistent with a significant risk of acute angle closure within the forseeable future"* (CoO & RCOphth, 2010). In the context of case-finding of a low prevalence disease such as ACG, there is an argument to combine high test specificity ideally above 90% with an acceptably high sensitivity in order to achieve a reasonable predictive value. Sensitivity at 90% specificity identified the van Herick test and Visante OCT ACA as the best-performing index test

criteria for detection of narrow angles defined either by the ISGEO classification or by ophthalmologist's clinical opinion of occludability. Notably, no statistically significant difference was observed between the two parameters for partial AUROC curve estimates for ranges starting at 90% and 95% specificities, or sensitivity at set specificities of 90% and 95%.

In a previous report, Thomas et al. improved specificity to detect occludable angles by combining a positive van Herick test with raised intraocular pressure (Thomas et al., 2002). In the present study, IOP was significantly higher among subjects with narrow angles than compared with open angles, but the diagnostic effectiveness of combining IOP with index test results was of limited value. However, this may be a function of our study population and design. As such, this test combination may be of more value in a cross-sectional screening study.

An ideal screening paradigm is based on good diagnostic performance together with other attributes such as acceptability to patients, the time taken to acquire data etc. In particular, community optometrists are unlikely to invest in advanced imaging devices dedicated solely to anterior segment imaging, such as the Pentacam, given the significant costs, the space taken up by the equipment, and additional training requirements to acquire and interpret images correctly. Financial concerns are frequently reported as a barrier to adoption of equipment by optometrists (Heidarian & Mason, 2013, Dabasia et al., 2014). However, community optometrists are increasingly investing in OCT devices (Dabasia et al. 2014), with the vast majority being optimised for posterior segment imaging. Posterior segment OCT devices use a shorter wavelength than is ideal for imaging of the anterior segment. Although images of the ACA can be obtained with these OCTs by using an additional or integral adaptor lens, the detail captured is limited by poor penetration of radiation through scleral tissue (Figure 4.16). Two authors have commented positively on the ability to qualitatively assess the majority of cross-sections imaged using AS-OCT for angle closure by observing for iridocorneal contact anterior to the scleral spur even when poor image quality precludes sophisticated measurement of angle structure using software tools (Sakata et al., 2008b, Chang et al., 2011). However, Perera et al. reported that 60% of angle quadrants imaged using a posterior segment OCT (RTVue) with corneal adaptor lens could not be assessed for angle closure status due to limited ability to image angle structures (Perera et al., 2012). Quek et al. reported slightly better performance of the iVue OCT, a compact version of the RTVue, in which 25% of eyes could not be assessed for angle status (Quek et al., 2012).

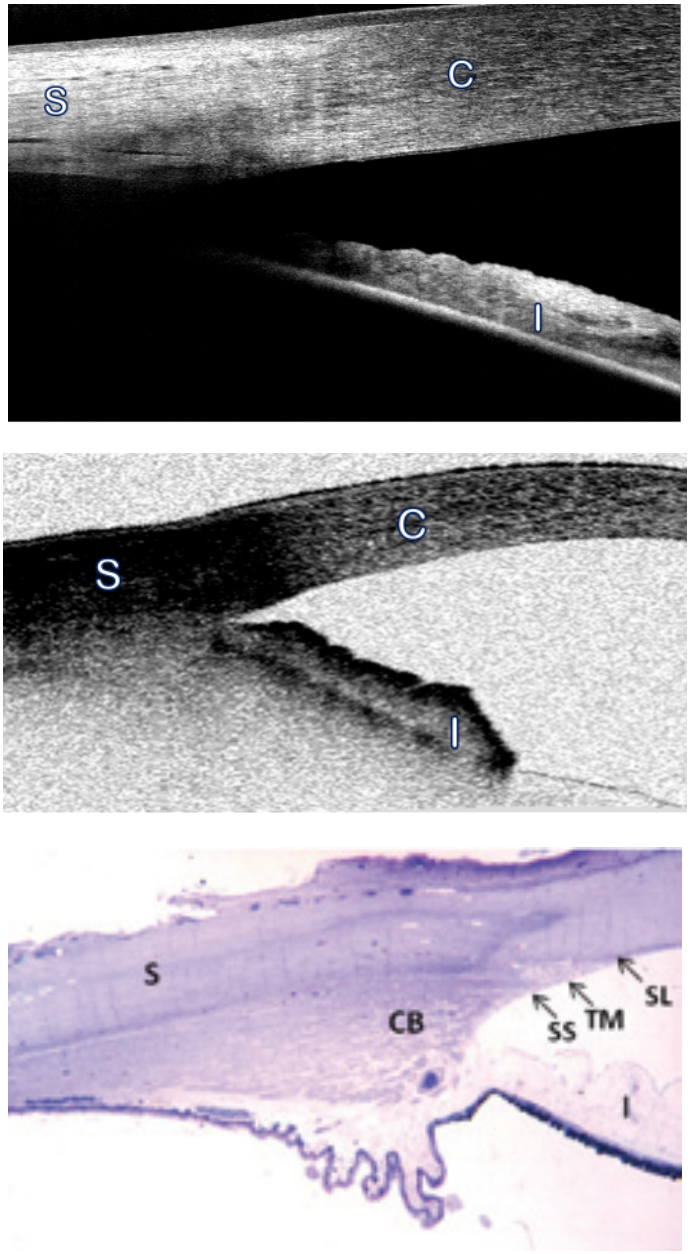


Figure 4.16: Cross-section of an open ACA acquired using a) iVue (800nm) OCT, b) Visante (1310nm) OCT (Image courtesy of Shima Shah, Moorfields Eye Hospital), shown with a histological section of the anterior chamber region, with the angle structures labeled. CB, ciliary body; I, iris; SS, scleral spur; TM, trabecular meshwork; SL, Schwalbe's line; P, pupil; S, sclera; C, cornea

Overall, the van Herick test shows great potential for use in general screening and case-finding of individuals at-risk of ACG who may benefit from definitive gonioscopic examination. In this population, van Herick grades were recorded for both eyes of all 78 subjects, mean time taken to acquire data from both eyes was shortest of all the index tests, and the test would be even quicker in clinical practice as the study has shown that it is only necessary to assess LACD at the temporal limbus. The van Herick test was well received by patients. The test affords

further advantage by using the slit-lamp biomicroscope, an item of equipment found in the vast majority of UK community optometric practices, and the van Herick test does not require any auxiliary attachments. Moreover, optometrists are already trained to perform the technique, and responses to a 2014 cross-sectional survey indicated that 60.2% of UK community optometrists 'always' use a slit-lamp biomicroscope to examine a patient's external eye or anterior segment during a routine sight test of an adult patient (CP 2014 survey (Chapter 2), unpublished data). The UK has seen major changes in recent years to community optometric practice with increasing numbers of optometrists involved in providing additional and enhanced services. Schemes for glaucoma include repeat measures for glaucoma suspects, and glaucoma referral refinement schemes. As such, referrals of individuals identified as being test-positive using the van Herick test from community optometrists may be directed to accredited optometrists for further gonioscopic investigation and management to reduce further the burden on secondary care ophthalmology clinics.

The prevalence of narrow angles in our population was 21.8% based on the ophthalmologist's clinical opinion of occludability, compared with 53.8% using the ISGEO classification of 270° or more of non-visibility of the posterior trabecular meshwork. This means that 25 subjects with gonioscopically narrow angles defined by the ISGEO system would not be eligible for prophylactic treatment at the present time, based on the ophthalmologist's clinical opinion of occludability, but a periodic review appointment for repeat assessment using a goniolens would be arranged to observe for possible conversion to PAC/ PACG. An untreated PACS patient has an estimated 22% (Thomas et al., 2003) to 30% (Wilensky et al., 1996) chance of developing angle closure over 5 years. Risks and benefits of performing prophylactic laser iridotomy on all individuals observed with gonioscopically narrow angles still need to be assessed definitively. Peripheral laser iridotomy is considered a relatively safe procedure but still carries a small risk of complications such as inflammation. Alternatively, lens extraction is considered a reasonable option, where crowding of the ACA by retroiridal structures is thought to be a contributory factor, or when conventional therapies have failed to control IOP suitably. Evidence for the effectiveness of this form of treatment is provided by data from the UK Department of Health's Hospital Episode Statistics, which show a reduction in PACG that corresponds with the increase in cataract procedures undertaken in a period up to 2004 (Day & Foster, 2011). Moreover, ongoing analysis of ACG presentations in the period up to 2010 has revealed a marked decline in acute angle closure presentations and a similar reduction in emergency LPI procedures performed on the same day (Day and Foster, 2011). This has inevitably led researchers to explore the benefits of clear lens extraction for the prevention and management of ACG. However, a Cochrane systematic review considering the risk-to-

benefit ratio for the prophylactic treatment of PACS found no evidence to support the use of clear lens extraction for this purpose (Friedman & Vedula, 2006). More recent reviews drew similar conclusions (Thomas et al., 2011, Walland & Thomas, 2011), and authors commented on the scarcity of randomised controlled trials, as well as a lack of sufficient details included in the few high-quality reports to inform clinical decision-making.

The success of most peripheral iridal prophylactic procedures is dependent on the extent to which the TM can retain normal functioning following damage from previous episodes, highlighting the importance of early detection of at-risk individuals. The clinical course of the ACG disease process is not yet fully understood, particularly in view of the significant heterogeneity in presentation between ethnic groups (He et al., 2006b). It follows therefore that screening criteria and management programmes would need to be tailored for a given population.

4.4.4 Strengths and limitations

The methods used in this study were aimed to improve the reliability and applicability of study findings. The potential for partial verification bias was addressed by performing the same reference standard gonioscopic assessment on every subject. Moreover, all index tests and the reference standard examination were performed on the same day, thereby addressing any risk of disease progression bias. Index-test examiners were masked to findings of other ocular examinations including gonioscopic observations. Furthermore, index test data were interpreted independently without knowledge of the reference standard diagnosis or other test performances. Similarly, results of the reference standard assessment were interpreted masked to index test findings. The proportion of data of inadequate quality acquired using each index test has been reported, and diagnostic data presented using two approaches; using the eye as the unit of analysis, and the individual as the unit of analysis. Diagnostic performance of index tests to identify gonioscopically narrow angles were evaluated on two levels; using the standard epidemiological classification described by the ISGEO (Foster et al., 2002), and a more pragmatic endpoint based on clinical opinion of occludability. The latter serves to identify the proportion of our sample that would qualify for prophylactic intervention.

The study may be subject to spectrum bias as subjects were not sampled using a population-based approach, but recruited from glaucoma and general ophthalmology clinics in Ealing Hospital to form a group of individuals with open and narrow anterior chamber angles. As

such, our cohort is likely to include more cases with extremely narrow angles than in the general population, which may be easier to distinguish from open anterior chamber angles. Demographic data from our population revealed a high proportion of subjects of South Asian origin, which may be typical of the population of Ealing, but does not represent the UK as a whole. Using methodology described by Bland and Altman, a sample size of 100 participants will give a 95% confidence interval with a 0.34 standard deviation (Bland & Altman, 1986). Bland, and McAlinden et al. therefore recommend 100 as a good sample size for a study of the agreement between two methods (Bland, 1986, McAlinden et al., 2011). However, in practical terms it was not possible to recruit such large numbers resulting in wide confidence intervals around the study's diagnostic estimates. While the current data can be compared with the literature, findings may not be generalizable to the UK general population, and they would translate less well to Eastern populations in which the prevalences and mechanisms of ACG are known to differ. Systematic bias may have been introduced by the use of a single examiner to acquire data for each of the index tests (apart from the Visante OCT) and the reference comparison examination. The examiners' knowledge of the higher prevalence of gonioscopically narrow angles in this enriched cohort compared with the general population may have biased observations towards more occludable angles.

The ongoing debate as to whether gonioscopy is an ideal reference standard has been previously mentioned, but gonioscopy was used as the comparator for index test performance in this study. Interestingly, Nolan et al. used AS-OCT as the reference standard and showed a sensitivity of 68.2% with a high specificity of 96.6% for detection of narrow angles by gonioscopy (Nolan et al., 2007).

It is possible that exclusion of angle images captured in the vertical meridian using the Pentacam and Visante OCT may have influenced diagnostic results, in view of the higher prevalence of gonioscopically narrow quadrants observed superiorly both in this study, and in the previous literature (He et al., 2006a, Sakata et al., 2008a). Furthermore, Visante OCT and Pentacam ACA estimates were based on observations of a single-cross section between the temporal and nasal angle positions. As variations in angle morphology can be observed within a sector, it is not known whether test performance for detecting narrow angles would have differed using data from multiple meridional cross-sections. Finally, results of the user acceptability survey showed wide acceptance of all tests, but these data may be biased as they represent views of a hospital-enriched population who have more experience of ocular examinations.

4.4.5 Conclusions

This study provides data on the effectiveness of various non-contact methods to detect at-risk individuals, which may be used to develop case-finding strategies to prevent ACG. Overall, the van Herick test and Visante OCT ACA showed best performance for detection of narrow angles both alone, and in combination. The van Herick test affords a number of advantages over Visante OCT imaging, including less time taken to capture data. However, with continuing advances in OCT imaging supported by advanced analytical tools (e.g automatic detection of angle landmarks), it is anticipated that this technology will play a more significant role over time, particularly as the cost of equipment falls.

Chapter 5: Summary and directions for future work

5.1: Summary

Glaucoma is considered a major public health problem worldwide. With age being an important risk factor, the number of people affected by glaucoma in the UK is expected to rise with the changing demographic of the population. However, Burr et al. predict that two-thirds of the UK population affected by open angle glaucoma (OAG) may remain undiagnosed (Burr et al., 2007), highlighting the need for improved detection.

Both OAG and angle closure glaucoma (ACG) satisfy two important suitability criteria initially outlined by Wilson and Jungner for the implementation of a screening programme: the condition should be an important public health problem, and effective treatment should be available (Wilson & Jungner, 1986). However, a NIHR HTA review of the effectiveness of screening for OAG highlighted some major issues (Burr et al., 2007). Firstly, population screening based on age alone was not proved to be a cost-effective strategy, although more evidence was found in support of targeted screening of, for example, at-risk populations. Secondly, extensive literature searches revealed a lack of screening tests that were sufficiently accurate to detect OAG when used alone or in combination. Although a similar study has not been performed for ACG, a population-based screening programme is unlikely to be cost-effective given the low prevalence of the condition (0.4%) in European-derived populations aged 40 years and older (Day et al., 2012).

In the UK, optometrists are the first-line eye care providers and play an important role in the detection of early eye disease, using opportunistic surveillance when people self-select to attend for an eye examination in community practice. Case-detection of glaucoma may be improved by using screening tests that afford better diagnostic accuracy. In the context of screening for a low prevalence disease such as glaucoma, tests would need to combine high specificity, ideally above 90%, with an acceptably high sensitivity in order to achieve a reasonable positive predictive value.

The primary aims of this thesis were:

- Aim 1: To perform a national survey of UK optometrists' current and anticipated use of equipment and IT.

- Aim 2: To establish whether advanced technologies, alone or in combination, can be used to improve case-detection of POAG

- Aim 3: To evaluate the effectiveness of non-contact methods in screening for eyes at risk of developing ACG

With rapid advancements in ophthalmic equipment and information technology (IT), the author sought to determine the equipment and information technology (IT) currently in use in optometric practice, and to identify purchases anticipated in the near future. Chapter 2 describes the findings of two cross-sectional surveys of UK community optometrists. The first survey, distributed in 2013, additionally aimed to explore the rationale behind the uptake of ophthalmic equipment and IT in community practice. The second survey (CoO Clinical Practice survey, 2014) was drafted and administered in collaboration with the College of Optometrists. Both surveys were validated and sent to a randomized sample of UK College of Optometrists' members using a combination of online and postal delivery. 432 (response rate 35%) and 870 responses (response rate 44%) were received to the 2013 and 2014 surveys respectively. Survey results showed that UK optometrists are increasingly investing in new ophthalmic equipment and IT, including the incorporation of the latest technology into their practices. Variations in responses between parts of the UK reflected differences in the provision of the General Ophthalmic Services contract or community enhanced services. There was general agreement that specialised equipment enhances clinical care and permits increased involvement in enhanced services, but initial costs and ongoing maintenance can be a financial burden.

The past two decades have seen major advances in the scope of optometric practice with increased opportunities for provision of glaucoma services. Enhanced or additional/ separately contracted services were provided by 73% of respondents to the 2013 survey, and 59% of respondents to the 2014 survey. For many glaucoma-related enhanced services it is essential that optometrists should be able to perform skills such as Goldmann applanation tonometry, gonioscopy and pachymetry. However, gonioscopy use by optometrists has remained relatively static between 9% (2014) and 15% (2013) compared with 12% in the Myint et al. survey (Myint et al., 2011), while pachymetry use has more than doubled from 7% in

2008 to 15-17% in 2014 and 2013 respectively. The frequency of use of Goldmann/Perkins tonometry in community practices has increased from 47% in 1987/88 to 61% in 2007 and reached 81% in 2013. Even more popular were central visual field screeners with threshold control, which are now found in 100% of practices, having increased from around 40% in 1987/88. There was a remarkable increase in the penetration of fundus photography into community practices. As recently as 2001 they were to be found in only approximately 17% of practices, but this proportion had increased dramatically to approximately 66% in 2007, 74% in 2013 and further to 87% in 2014.

Another interesting finding to emerge from both surveys was the upsurge in interest in OCT among UK community optometrists, which has seen a remarkable rise in its use from a very low base. OCT was available to only 2% of optometrists in a survey conducted in 2008, however by 2013 respondents were reporting use in 15% of practices, and in 2014 18% of optometrists/non-optometric personnel were using OCT. In parallel, an increase in the use of specialist imaging to check a patient's optic disc to screen for glaucomatous damage was observed, increasing from 5% in 2007 (CoO, 2008) up to 15% in 2014. Furthermore, OCT was by far the most popular item of specialist equipment in the 2013 survey that respondents anticipated purchasing within the next year (36/84 or 43%). The rate at which the use of OCT in community optometric practice is increasing suggests it is possible that OCT may follow the example of fundus photography and eventually progress from being classified as an item of specialist equipment to become so widespread in community practices that it can be regarded as almost a standard item.

OCT has been established as a clinical diagnostic tool for the detection of disorders of the macula and optic nerve (Chen et al., 2007). However, the availability of standardized protocols for using OCT to detect and monitor glaucoma is lacking. Chapter 3 outlines findings of a prospective cross-sectional study to determine the diagnostic accuracy of four advanced technologies (including OCT) used alone and in combination, for detecting POAG, in a representative sample of the UK primary care population aged 60 years and older, and compared to a reference standard ophthalmic examination. The technology-based assessment comprised four index tests: Frequency doubling technology (FDT) perimetry, Moorfields motion displacement threshold test (MMDT), iVue spectral-domain Optical coherence tomography (SD-OCT) and the Ocular Response Analyser (ORA). To avoid verification bias, all 505-subjects underwent the technology-based index tests carried out by a technician, followed by a reference standard ophthalmic examination, conducted by the author who was trained and validated in glaucoma according to UK practice. In the study

population, the diagnostic performance of structural imaging using the iVue SD-OCT provided better diagnostic accuracy than either of the visual function tests (FDT and MMDT) in subjects diagnosed with OAG on the basis of structural and functional damage. The low specificity of visual function tests would preclude their use in isolation, but the study findings support the use of visual function tests together with objective evaluation of optic nerve head structure by SD-OCT to improve case-detection of glaucoma in the study population. Using a Bayesian approach and with a pre-test probability of OAG of 5% based on the study population, a patient with a combined iVue SD-OCT parameter outside the 99% confidence interval (GCC GLV), one or more points missed on the FDT at the 1% level, and ORA corneal hysteresis <9.1mmHg would have an estimated 93% post-test probability of having POAG. This combined structure-function approach has potential for incorporation into community-based glaucoma case-finding by optometrists. These data may be combined with measurement of IOP and information on known risk factors (e.g. age, ethnicity and family history), to develop diagnostic algorithms and inform referral pathways. Similarly, this Bayesian approach could be incorporated into future population screening pathways for at-risk individuals, with tests being performed by a trained technician or a specialist optometrist.

ACG is considered relatively uncommon in western populations, but the prevalence is predicted to increase by 19% in the UK within the next decade due to increased longevity (Day et al., 2012). Over time, researchers have reported on the effectiveness to detect people affected by various clinical stages of angle closure disease using slit-lamp biomicroscope tests, such as the van Herick test, and optical imaging-based systems. However, the majority of this research has been undertaken in Asia, where the prevalences of the condition and mechanisms of angle closure are known to differ significantly from those in Caucasian populations (He et al., 2006b). Chapter 4 reports on a study evaluating the diagnostic effectiveness of two slit-lamp based techniques (van Herick and Smith's) and imaging-based systems (Pentacam and Visante OCT), to screen for individuals at-risk of ACG in an enriched UK population of 78 subjects. Diagnostic performance of index tests was evaluated by comparison with gonioscopy, the current reference standard, using two levels of analysis; the standard epidemiological classification described by the International Society of Geographical and Epidemiological Ophthalmology (Foster et al., 2002), and a more pragmatic endpoint based on a sub-specialist ophthalmologist's opinion of occludability. To improve the reliability and applicability of study findings, the four index-test examiners were masked to findings of other ocular examinations including gonioscopic observations.

Overall, the van Herick test and Visante OCT anterior chamber angle (ACA) showed best discrimination between narrow and open angles both alone, and in combination. Sub-analysis of van Herick grading at the temporal and nasal limbus positions revealed similar results and diagnostic performances. These data suggest that recording of either the temporal or nasal LACD would be sufficient for case-finding in at-risk individuals. Smith's test showed moderate sensitivity and specificity to detect eyes at-risk of ACG, but there is a case for performing Smith's test when the van Herick test is not possible, for example in the presence of a pronounced arcus senilis. The van Herick test affords a number of advantages over Visante OCT imaging, including less time taken to capture data. Moreover it uses the slit-lamp biomicroscope, an item of equipment found in the vast majority of UK community optometric practices, and without need for further auxiliary attachments. Moreover, intra-observer repeatability of ACA estimates for observations of the initial OCT scan revealed wide 95% confidence intervals, largely attributed to variability in positioning of the angle measurement tool. Nonetheless, in view of the current trends in use of equipment by community optometrists and with continuing advances in OCT imaging supported by advanced analytical tools (e.g. automatic detection of angle landmarks), it is anticipated that this technology will play a greater role over time, particularly as the cost of equipment falls.

5.2 Directions for future work

The cross-sectional screening study reported in Chapter 3 determined a prevalence of POAG of 5% in the 505-subject cohort. While this figure was comparable to that expected for the age demographic, the sample provided a total of only 26 glaucoma subjects, resulting in wide confidence intervals around diagnostic estimates. Nonetheless, the study served as a high quality pilot highlighting important findings that should be explored on a larger scale, ideally using a multi-centre population-based screening approach. An additional aim of further work would be to combine OCT and visual function data in series with other clinical results (e.g. measurement of IOP, corneal hysteresis) and information on known risk factors, to establish optimal cut-offs and to develop a screening algorithm to detect POAG. It is likely that using this Bayesian approach may provide a more effective strategy for detection of individuals with 'suspect' glaucoma, as this group presented a diagnostic challenge in the study population. Chapter 3 reports that diagnostic estimates were derived using data from a predominantly Caucasian subject group, and findings may not be generalizable to other ethnic groups where glaucoma is more prevalent (e.g. subjects of Black origin). Therefore, a follow-on study would need to be sufficiently powered to also provide reliable information on the performance of

screening algorithms in ethnic minority groups. Ultimately, study findings may be used to enhance case-detection strategies used by community optometrists and/ or implement screening programmes for at-risk populations in the community setting.

The OCT device (iVue SD-OCT) evaluated in the POAG case-detection study (Chapter 3) acquired ganglion cell complex (GCC) thickness measurements using the iWellness option. The iWellness scan is a composite of GCC and 'retina map' scan protocols. The latter generates 7 cross-sections of the macula together with full macular thickness measurements displayed in a 6mm by 6mm grid. Therefore, the study protocol described in Chapter 3 provided an objective assessment of macula and optic nerve function for each of the 505 subjects examined. Diagnostic effectiveness of the retina map scan to detect macula pathology in our population may be evaluated by comparing these data with findings from the reference standard ophthalmic examination. Moreover, an overall measure of the potential for the iWellness scan to screen for disorders of the optic nerve and macula may be provided by combining diagnostic estimates of GCC and retina map protocols respectively. Further analysis may aim to explore the diagnostic value of performing an iWellness scan in series with a visual function test to case-find/ screen for general eye disease in a community setting. While detection of more than one condition may add value to a community case-finding/ screening strategy, there are considerable cost implications in providing adequate resources and personnel to manage newly diagnosed eye conditions.

A limitation of the study described in Chapter 4 was the use of a case-control approach to evaluate diagnostic effectiveness of screening tests to detect ACG. Recruitment from glaucoma and general ophthalmology clinics in Ealing Hospital to form a group of individuals with open and narrow anterior chamber angles was likely introduce an element of spectrum bias, possibly leading to overestimation of diagnostic performance. The study also sampled a relatively small number of subjects (n=78), and included a high proportion of subjects of South Asian origin, raising questions as to the generalizability of study findings to the UK general population. Therefore, validation of the use of the van Herick test and Visante OCT imaging to screen for individuals who may benefit from further gonioscopic assessment should be investigated using a larger and more representative population. In a previous report, Thomas et al. improved specificity to detect occludable angles by combining a positive van Herick test with raised intraocular pressure (Thomas et al., 2002). In our study, IOP was significantly higher among subjects with narrow angles compared with open angles, but the diagnostic effectiveness of combining IOP with index test results was of limited value. This is likely to be a function of our study population and design, and as such, the value of combining index tests

with other clinical results and information from history taking could be investigated in this larger follow-on study. In the context of community case-finding, optometrists are unlikely to invest in an OCT device designed specifically for anterior segment imaging, such as the model used in Chapter 4. Most OCT devices currently used in optometric practice are optimized for posterior segment imaging. Although images of the ACA can be obtained with these OCTs by using an additional or integral adaptor lens, the detail captured is limited by poor penetration of radiation through scleral tissue. Another focus for further work would be to ascertain whether posterior segment OCT systems can be used to generate images of sufficient quality to allow qualitative or quantitative observation for detection of at-risk individuals.

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Appendices

Appendix A

i) A survey of current and anticipated use of standard and specialist equipment and IT by UK optometrists, 2013

THE COLLEGE OF OPTOMETRISTS

CITY UNIVERSITY LONDON

Survey of Equipment and Eye Care

Over the past 20 years, significant changes have taken place in optometric practice including the widespread adoption of technology for visual assessment, dispensing of optical appliances, patient education and practice management. Periodically, the College of Optometrists has carried out Clinical Practice Surveys to identify the range of specialist equipment in current use; however the rationale for purchasing such equipment and its impact on patient care has not been previously investigated.

This survey has been sent to a randomised sample of optometrists from the College of Optometrists' membership database to seek views on the impact of equipment on eye care. Responses are anonymous, although each response will be assigned a unique code for data entry. The more responses we get from this randomised sample, the better the quality of the research results will be – please try to respond if you possibly can.

The survey should take a maximum of 15 minutes to complete and is divided into 5 sections: Personal details (4 questions), Details of your practice (4 questions), Use of standard ophthalmic equipment (1 question), Use of specialist diagnostic equipment (3 questions) and Use of information technology (9 questions). The majority of questions within each section will consist of Yes/ No responses.

Unless otherwise stated, please fill one circle for each question using only black or blue ink, returning your completed survey in the stamped-addressed envelope enclosed. Alternatively, you may also complete the survey online at [redacted]

If you have any difficulty completing the questionnaire, please email ([redacted]) or telephone ([redacted]) from Monday to Friday, 9am – 5pm.

By participating in the survey, you can choose whether you would like to be entered into a prize draw to win one of 3 sets of John Lewis vouchers to the value of £100.

SECTION 1: About you

Q1 In which year did you qualify?

O	Before 1965	O	1986 – 1995	O	2008 – 2012
O	1965 – 1975	O	1996 – 2001		
O	1976 – 1985	O	2002 – 2007		

Q2 At which University did you complete your initial Optometry training?

O	Anglia Ruskin University/ Anglia Polytechnic University
O	Aston
O	Bradford
O	Cardiff/ UWIST
O	City
O	Glasgow Caledonian University
O	Manchester/ UMIST
O	University of Ulster (Coleraine)
O	Other – please specify university and country:

Q3 What is your gender?

O	Male	O	Female

Q4 Are you currently practising as a community optometrist whether part-time or full-time?

O	YES – Includes optometrists who work in the HES/ Academia but undertake part-time work in community practice
O	NO

If NO, have you ever worked in community practice?

O	YES If you have worked in community practice within the last 5 years, please continue to Question 5 and answer the remainder of the survey based on your work in your LAST PRINCIPAL community practice **If you last worked in community practice 5 or more years ago, please move to Question 20 (Use of IT in workplace)**
O	NO **Please move to Question 20 (Use of IT in workplace)**

SECTION 2: About your practice

Q5 Which of the following do you consider to be your current PRINCIPAL mode of community practice whether part-time or full-time? Please select ONE option only.

O	Independent	O	Multiple/ Group
O	Joint venture/ franchise	O	Locum
O	Other (please specify):		

Q6 Where is your principal practice located?

O	England	O	Wales
O	Scotland	O	Northern Ireland

Q7 Which of the following options best describes where your principal practice is located?

O	Inner city/ town centre
O	Urban but not inner city
O	Rural

Q8 Is your practice involved in undertaking enhanced or separately contracted services?

O	YES	**Please select all those listed that apply below**
O	NO	**Please move to Question 9 (Use of standard ophthalmic equipment)**

O	Formal programme for screening for Diabetic Retinopathy	O	Co-management of patients with stable glaucoma
O	Formal programme for the diagnosis and management of Red Eye	O	Fast-track (Direct referral/ triage/ rapid assessment) screening programme for Exudative (Wet) AMD
O	PCT/ NHS funded repeat measurement scheme (repeat IOP and/or fields)	O	Fast-track (Direct referral) cataract programme
O	PCT/ NHS funded Glaucoma referral refinement scheme	O	Post-operative cataract care
O	Additional Domiciliary services	O	Pre-operative and post-operative management of refractive surgery patients
O	Monitoring of patients with ocular hypertension (OHT) and/ or suspect chronic open angle glaucoma (COAG)	O	Adult community optical low vision services
O	PEARS-type scheme		

Other enhanced service(s) undertaken in your practice but not listed - please specify:

SECTION 3: Use of standard ophthalmic equipment

Q9 Which of the following items of ophthalmic equipment are used in your practice? **Please select all those listed that apply.** Where the item of equipment is not used, please indicate in the final column if it is not available in your practice.

	Used	Not available in the practice
Non-contact/ pneumo tonometer	O	O
Goldmann/ Perkins applanation tonometer	O	O
Keratometer	O	O
Central visual field perimeter with threshold control	O	O
Auto-refractor	O	O
Phoropter head (manual/ automatic)	O	O
Automatic focimeter	O	O
Pupillometer	O	O

SECTION 4: Use of specialist diagnostic equipment

Q10 Is specialist equipment (see list below) used in your practice for the detection and management of ocular disease? **Please select all those listed that apply below and indicate whether patients are normally charged for the test when not part of a funded scheme.** Where the item of equipment is not used, please indicate in the final column if it is not available in your practice.

	Used	Patients normally incur charge for use of the test	Not available in the practice
Optical Coherence Tomographer (OCT)	O	O	O
Scanning laser polarimeter (e.g. GDx or other)	O	O	O
Frequency Doubling Perimeter (FDT)	O	O	O
Scanning laser ophthalmoscope (e.g. HRT, Optomap or other)	O	O	O
Macular Pigment measuring instrument (e.g. MPOD or other)	O	O	O
Fundus photography	O	O	O
Anterior segment imaging	O	O	O
Advanced tonometer (e.g. iCare, ORA or other)	O	O	O
Pachymetry (optical/ ultrasonic)	O	O	O
Corneal Topographer	O	O	O
Goniolens	O	O	O
Other item(s) of specialist equipment used in your practice but not listed – please specify:			

Q11 Please select ONE of the 5 options for each statement relating to your views on the possible advantages and disadvantages of using specialist equipment listed above in optometric practice.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
Enhances clinical assessment, providing a diagnostic tool to aid management and referral decision-making	O	O	O	O	O
Can pose a financial burden on the practice due to initial purchase costs and/or continuing maintenance	O	O	O	O	O
Poses a risk of replacing core skills reducing the value of optometric qualifications	O	O	O	O	O
Permits increased involvement in referral refinement and/or co-management schemes	O	O	O	O	O
Provides an opportunity for promoting your practice	O	O	O	O	O
Operator training (initial and on-going) can be inconvenient, time consuming and a drain on resources	O	O	O	O	O
Results can be used as defence in medico-legal cases	O	O	O	O	O
Promotes patient loyalty to the practice	O	O	O	O	O
Please comment on any additional advantages and/ or disadvantages that you feel may result from the use of specialist equipment in community practice:					

Q12 Are there any items of specialist equipment that you anticipate buying during the next 12 months? If so, please give details of this/ these in the box below.

SECTION 5: Use of IT in practice

Q13 Which of the following computer software for specific clinical applications is in use in your practice? Where the item of equipment is not used, please indicate in the final column if it is not available in your practice.

	Used	Not available in the practice
Computerised/ projection test chart	O	O
Advanced dispensing system - customized free-form lenses (visual behaviour diagnostic/ lifestyle profiling system) - lens or frame fitting system - lens or frame demonstration devices	O	O
Contact lens fitting software tools (EyeSys or other)	O	O
Other item(s) of computer software used in your practice but not listed – please specify:		

Q14 Which of the following are used in your practice for the management of patient data and patient education? Where the item of equipment is not used, please indicate in the final column if it is not available in your practice.

	Used	Not available in the practice
Electronic patient record system/ Practice Management System (e.g. Optisoft, Focus, Acuitas or other)	O	O
Ophthalmic image management software	O	O
Animated software patient education tools (EyeMagination, Insight or other)	O	O
Other IT Service(s) used in your practice but not listed – please specify:		

Q15

	Yes	No
Do you use an electronic system to record clinical notes (i.e. 'paperless' records)?	O	O
Do you use mobile phone texting for appointment reminders and/ or collections?	O	O

Q16 Please select one of the 5 options for each statement relating to your views on the possible advantages and disadvantages of using the IT services listed above in optometric practice.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
Dynamic nature of IT necessitates frequent updates and technical support	O	O	O	O	O
Facilitates more efficient administrative flow (tracking records, computerised referrals etc.)	O	O	O	O	O
Reduces the time taken to record information for a routine patient	O	O	O	O	O
Poses a security risk with storage of confidential patient information online or on databases	O	O	O	O	O
Enables secure exchange of health information between primary and secondary care	O	O	O	O	O
Use of electronic records could impact negatively on patient-practitioner interaction and relations	O	O	O	O	O
There is greater risk of losing data	O	O	O	O	O
Gives the impression that the practice is more 'state of the art'	O	O	O	O	O
Inconvenient to learn new IT skills to operate management systems or software tools	O	O	O	O	O
Please comment on any additional advantages and/ or disadvantages that you feel may result from the use of IT services in community practice:					

Q17 Are there any IT services not listed above that you anticipate acquiring during the next year? If so, please give details of this/ these in the box below.

Q18 How do you generate a non-emergency patient referral/ notification letter when not part of a funded scheme? Please indicate by what means this information is normally delivered to a general medical practitioner or other specialist. **Select all those listed that apply.**

	Given to patient to hand-deliver to GP/ other specialist	Sent by post/ fax	Sent by electronic transfer (e.g. email or other)
Standard/ locally adapted GOS 18, other GOS, or WEHE/ PEARS form	O	O	O
Handwritten free-form letter/ practice-specific proforma	O	O	O
Typed free-form letter/ practice-specific proforma	O	O	O
Electronic referral system	--	--	O
Other – Please specify and indicate by what means this information is normally delivered to a general practitioner or other specialist:			

Q19 Are the results of any specific clinical tests undertaken (e.g. digital images, OCT scans, visual fields plots) sent with the referral/ notification?

O	YES
O	NO **Please specify the reason:**

Q20 Is Internet access available to you in your principal workplace?

O	YES
O	NO

Q21 For which of the following functions is the Internet used in your professional development?

	Used	Not Used
Continuing Education & Training (CET)/ Continuing Professional Development (CPD) activities	O	O
To access practice guidelines on the internet	O	O
To access clinical information on the internet	O	O
Online discussion groups/ forums	O	O
To manage professional membership fees and correspondence by email	O	O

ADDITIONAL COMMENTS

Q22 If you have any further comments on any aspect of the use of equipment and technology in optometry or on this questionnaire, please write them below.

Many thanks for taking the time to complete this survey. Your participation is very much appreciated.

Please indicate below whether you would be happy to be re-contacted to discuss your views and opinions from this survey further:

O	YES	I WOULD be happy to be re-contacted to discuss my views and opinions from this survey further. **Please give details of your contact information in the boxes at the bottom of the page**
O	NO	I WOULD NOT be happy to be re-contacted to discuss my views and opinions from this survey further

By participating in the survey, you can choose whether you would like to be entered into a prize draw to win one of 3 sets of John Lewis vouchers to the value of £100. Please select the appropriate option below:

O	YES	I WOULD like to be entered into a prize draw to win £100 worth of John Lewis vouchers **Please give details of your contact information in the boxes at the bottom of the page**
O	NO	I WOULD NOT like to be entered into a prize draw to win £100 worth of John Lewis vouchers

Three winners will be drawn at random at the end of the submission period. The winners will be notified within 10 days of the draw date by email or telephone, and the prize of £100 worth of John Lewis vouchers forwarded to the address provided.

We require the following details for the purposes of administering the Prize Draw, and/or for re-contacting you if you would be prepared to discuss your views and opinions at a later date.

Name	
Address 1	
Address 2	
City/Town	
Post Code	
Email Address	
Phone Number	

ii) The College of Optometrists (CoO) Clinical Practice survey, 2014

THE COLLEGE OF OPTOMETRISTS
CLINICAL PRACTICE SURVEY 2014

The purpose of this questionnaire is to help the College to understand what is currently happening in UK optometric practice and identify what it can do in the best support of the profession.

The survey should take approximately 10-12 minutes to complete and is divided into 5 sections. Unless otherwise stated, please fill one circle for each question using only black or blue ink, returning your completed survey in the stamped-addressed envelope provided. Alternatively, you may also complete the survey online at [redacted]

Responses are anonymous, although each response will be assigned a unique code for data entry. If you have any difficulty completing the questionnaire, please email [redacted] or telephone [redacted] from Monday to Friday, 9am – 5pm.

This is your 6-digit ID number: ……

SECTION 1: About you

Q1 In what year did you qualify?

O	Before 1965	O	1986 – 1995	O	2008 – 2012
O	1965 – 1975	O	1996 – 2001		
O	1976 – 1985	O	2002 – 2007		

Q2 At which university did you complete your initial optometry training?

O	Anglia Ruskin University/ Anglia Polytechnic University
O	Aston
O	Bradford
O	Cardiff/ UWIST
O	City
O	Glasgow Caledonian University
O	Manchester/ UMIST
O	University of Ulster (Coleraine)
O	Other – please specify university and country:

Q3 What is your gender?

O	Male	O	Female

SECTION 2: About your practice

Q4 Where is the practice located in which you spend most of your time?

O	England – Eastern	O	England – North West	O	England – Yorkshire & Humber
O	England – East Midlands	O	England – South East	O	Northern Ireland
O	England – London Boroughs	O	England – South West	O	Scotland
O	England – North East	O	England – West Midlands	O	Wales

Q5 Which of the following options best describes where your principal practice is located?

O	Other urban (population 100,000 or more)
O	Large rural centre (25,000 – 99,999)
O	Small rural centre (10,000 – 24,999)
O	Remote centre (5,000 – 9,999)
O	Other remote area (less than 5,000)

Q6 Please indicate how many sessions (half-days) you spend during a 7-day week in each of the listed practice environments:

	Mon		Tues		Wed		Thurs		Fri		Sat		Sun	
	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
Community practice – independent	O	O	O	O	O	O	O	O	O	O	O	O	O	O
Community practice – joint venture/ franchise	O	O	O	O	O	O	O	O	O	O	O	O	O	O
Community practice – multiple/ group	O	O	O	O	O	O	O	O	O	O	O	O	O	O
Community practice – locum	O	O	O	O	O	O	O	O	O	O	O	O	O	O
Hospital	O	O	O	O	O	O	O	O	O	O	O	O	O	O
Academic/ research	O	O	O	O	O	O	O	O	O	O	O	O	O	O
Training/ education	O	O	O	O	O	O	O	O	O	O	O	O	O	O
Management	O	O	O	O	O	O	O	O	O	O	O	O	O	O
Optometric advisor	O	O	O	O	O	O	O	O	O	O	O	O	O	O
Domiciliary	O	O	O	O	O	O	O	O	O	O	O	O	O	O
Other – please specify below:	O	O	O	O	O	O	O	O	O	O	O	O	O	O

Q7 Which type of practice do you consider to be your principal work?

O	Community practice – independent	O	Hospital	O	Optometric advisor
O	Community practice – joint venture/ franchise	O	Academic/ research	O	Domiciliary
O	Community practice – multiple/ group	O	Training/ education	O	Other – please specify below
O	Community practice – locum	O	Management		

Please answer the remainder of the questionnaire based on your work in your last principal practice

SECTION 3: Optometric Instrumentation

Q8 Which of the following instruments are used either by yourself, and/or by non-optometric personnel, for the detection of ocular disease and abnormality in your practice? **Please select all those that apply below.** Where the item of equipment is not used, please indicate if it is available or not available in your practice.

	Myself	Non-optometric personnel	Available in the practice but not used	Not available in the practice
Tonometer	O	O	O	O
Visual field screener	O	O	O	O
External photography – digital	O	O	O	O
Fundus photography – digital	O	O	O	O
Ocular coherence tomographer (OCT)	O	O	O	O
Scanning laser ophthalmoscope (e.g. HRT, Optos)	O	O	O	O
Scanning laser polarimeter (e.g. GDx)	O	O	O	O
Corneal topographer	O	O	O	O
Keratometer	O	O	O	O
Pachymeter	O	O	O	O
Gonioscope	O	O	O	O

Q9 Which of the following instruments are used either by yourself, and/or by non-optometric personnel for the measurement of refractive error, and dispensing of optical aids in your practice? **Please select all those that apply below.** Where the item of equipment is not used, please indicate if it is available or not available in your practice.

	Myself	Non-optometric personnel	Available in the practice but not used	Not available in the practice
Auto-refractor	O	O	O	O
Contrast sensitivity chart	O	O	O	O
Computerised test chart	O	O	O	O
Phoropter/ refractor head (manual)	O	O	O	O
Phoropter/ refractor head (automatic)	O	O	O	O
Automatic focimeter	O	O	O	O
Pupillometer	O	O	O	O
Advanced dispensing system	O	O	O	O

Q10 In a routine eye examination of an adult patient (18 years and above), how often would you use a slit-lamp to examine the patient's external eye or anterior segment?

Always	Sometimes	Never
O	O	O

SECTION 4: Checking for Glaucoma

Q11 How do you routinely check the patient's optic disc to screen for glaucoma? Please select all that apply.

O	Direct ophthalmoscopy through undilated pupils	O	Headset indirect ophthalmoscopy through dilated pupils
O	Direct ophthalmoscopy through dilated pupils	O	Conventional fundus photography
O	Slit-lamp binocular indirect ophthalmoscopy through undilated pupils	O	Scanning laser ophthalmoscopy (e.g. HRT)
O	Slit-lamp binocular indirect ophthalmoscopy through dilated pupils	O	Optical Coherence Tomographer (OCT)
O	Headset indirect ophthalmoscopy through undilated pupils	O	Scanning laser polarimeter (GDx)

Q12 Whilst recognising that every patient is different, as a general rule how often would you measure the patient's IOP for each of the following categories? Family history of glaucoma refers to any first-degree relative diagnosed with the condition.

	Always	Sometimes	Never
White adults up to the age of 40 with no family history of glaucoma	O	O	O
White over age 40 with no family history of glaucoma	O	O	O
White adults up to the age of 40 with family history of glaucoma	O	O	O
White over 40 with family history of glaucoma	O	O	O
Black African-Caribbean adults up to the age of 40 with no family history of glaucoma	O	O	O
Black African-Caribbean over 40 with no family history of glaucoma	O	O	O
Black African-Caribbean adults up to the age of 40 with family history of glaucoma	O	O	O
Black African-Caribbean over 40 with family history of glaucoma	O	O	O

Q13 How do you routinely measure the patient's intraocular pressure (IOP) to screen for glaucoma? Please select all that apply.

O	Non-contact/ pneumo tonometer	O	Perkins applanation tonometer
O	Goldmann applanation tonometer	O	Advanced tonometer (e.g. iCare, ORA or other)

Q14 Whilst recognising that every patient is different, as a general rule how often do you perform a threshold-controlled (supra-threshold or full-threshold) visual fields assessment for each of the following categories? Family

	Always	Sometimes	Never
White adults up to the age of 40 with no family history of glaucoma	O	O	O
White over age 40 with no family history of glaucoma	O	O	O
White adults up to the age of 40 with family history of glaucoma	O	O	O
White over 40 with family history of glaucoma	O	O	O
Black African-Caribbean adults up to the age of 40 with no family history of glaucoma	O	O	O
Black African-Caribbean over 40 with no family history of glaucoma	O	O	O
Black African-Caribbean adults up to the age of 40 with family history of glaucoma	O	O	O
Black African-Caribbean over 40 with family history of glaucoma	O	O	O

Q15 How do you routinely assess the patient's visual field to screen for glaucoma? Please select all that apply.

O	Humphrey VFA	O	Dicon
O	Henson	O	Oculus Easyfield
O	FDT	O	Friedmann VFA
O	Other – please specify:		

Q16 If the results of your first tests were suspicious, what is the likelihood that you would repeat the following tests before referring the patient for further investigation?

	Very likely	Likely	Neither likely nor unlikely	Unlikely	Very unlikely
Optic disc assessment	O	O	O	O	O
Intra-ocular pressure measurement	O	O	O	O	O
Visual fields assessment	O	O	O	O	O

Q17 Which test(s) do you routinely use for repeat assessment of the optic disc, IOP, and visual fields? Please select all that apply from the list below.

Optic Disc Assessment		Intraocular pressure measurement		Visual fields assessment	
O	Direct ophthalmoscopy	O	Non-contact (pneumo) tonometer	O	Supra-threshold strategy
O	Indirect ophthalmoscopy (slit-lamp BIO/ Headset)	O	Goldmann/ Perkins applanation tonometer	O	Full-threshold strategy
O	Conventional fundus photography	O	Advanced tonometer (e.g. iCare, ORA, or other)		
O	Specialist imaging (OCT/ GDx, HRT etc.)				

SECTION 5: Primary Care Activities

Q18 In your principal practice, please indicate whether you are involved in undertaking any of the services listed below?

RESPONDENTS WORKING IN ENGLAND AND NORTHERN IRELAND ONLY

O	Local Optical Committee Support Unit (LOCSU) or other enhanced (community) services

RESPONDENTS WORKING IN WALES ONLY

O	Participation in the Welsh Eye Care Service (WECS), formerly known as 'Wales Eye Care Initiative (WECI)

RESPONDENTS WORKING IN SCOTLAND ONLY

O	Provision of new GOS Scotland services (introduced 1st April 2006) funding supplementary examinations for specified circumstances

Q19 In your principal practice, are you involved in providing any of the following additional and/or enhanced (community) services? Please indicate whether the service is provided as part of a locally agreed scheme, and whether you have undertaken any additional training in the area of practice concerned.

	Service provided	Part of a formally agreed scheme	Undertaken additional training to provide service
Glaucoma repeat measures (IOP/ VF)	O	O	O
Glaucoma referral refinement	O	O	O
Ocular hypertension (OHT) and suspect chronic open angle glaucoma (COAG) monitoring	O	O	O
Co-management of stable glaucoma patients	O	O	O
Adult community optical low vision services	O	O	O
Pre-op cataract service/ Direct cataract referral pathway	O	O	O
Post-operative cataract pathway	O	O	O
Primary eye care assessment and referral service (PEARS) pathway	O	O	O
Community eye care for adults and young persons with learning disabilities	O	O	O
Triage scheme (e.g. emergency eye care, red eye)	O	O	O
Screening for diabetic retinopathy	O	O	O
Fast-track (direct referral/ triage/ rapid assessment) screening programme for Exudative (Wet) AMD	O	O	O
Other – please specify (e.g. Children's vision enhanced service/ post screening, specialist contact lenses or binocular vision services, sports vision/ occupational tests):			

Q20 Are there any additional and/or enhanced (community) services you would like to provide in your practice? If so, can you please give details of this/ these in the box below.

Q21 How frequently do you examine patients from the following categories?

	Regularly	Occasionally	Never
Children under 6 months of age	O	O	O
Children aged 6 months to 3 years of age	O	O	O
Children older than 3 years to 5 years of age	O	O	O
Contact lens wearers under 18 years of age	O	O	O
Contact lens wearers 18 years of age and over	O	O	O
Adults with learning difficulties	O	O	O
Patients with dementia (includes Alzheimer's and vasular dementia)	O	O	O
Domiciliary patients (own home)	O	O	O
Domiciliary patients (care home)	O	O	O

Q22 In what areas would you like to concentrate your personal development in the next 12 months?

O	Orthoptics	O	Therapeutics	O	Contact tonometry
O	Glaucoma	O	Mainstream contact lens fitting	O	Examining patients who are sight impaired
O	Diabetes	O	Specialist contact lens fitting	O	Suitable aids and support for patients who are sight impaired
O	AMD	O	Paediatrics	O	Refractive surgery update
O	Slit-lamp BIO technique and Headset BIO technique	O	Specific learning difficulties	O	Specialist imaging – practical support and interpretation
O	Gonioscopy	O	Examining patients with intellectual impairment	O	Computerised record keeping
O	Other – please specify:				

Q23 How many patients did you examine in the last working week? Please enter a whole number only (if you were on holiday, please use the last working week that you were in practice).

Q24 Of the patients you examined in the last working week, how many did you refer for further opinion?

To the patient's GP for management by the GP (e.g. diabetes)			
To an ophthalmologist (non-emergency referral)			
Directly to an Eye Casualty or A+E department as an emergency referral			
To another clinician such as a neurologist (either directly or via the GP including via a local booking/referral management service)			

Q25 Of the patients you referred, how many were related to suspected ocular hypertension or primary open angle glaucoma?

Q26 **RESPONDENTS IN ENGLAND AND WALES ONLY**
Of the patients you referred, how many were based on the NICE guidelines published in 2009 for the diagnosis and management of chronic open angle glaucoma and ocular hypertension, and would not otherwise have been made prior to their introduction?

Q27 Do you ever charge patients for additional procedures that are not included in the GOS sight test or private eye examination fee?

O	Yes – Please select all those that apply from the list below
O	No

O	Fundus photography	O	Dilated retinal exam/ flashes and floaters investigation	O	Contact applanation tonometry
O	Red eye assessment	O	Repeat visual fields	O	Orthoptic assessment and/ or treatment
O	Specialist imaging (e.g. OCT)	O	Repeat IOP	O	Coloured overlay assessment
O	Other – please specify:				

ADDITIONAL COMMENTS

Q28 If you have any comments on the subject matter or questionnaire, please detail them in the box provided:

Thank you very much for taking the time to complete the questionnaire. Please return it to The College of Optometrists, 42 Craven Street, London, WC2N 5NG in the pre-paid envelope provided (no stamp is required).

Appendix B: Performance of advanced technologies to improve case-detection of primary open angle glaucoma (POAG) (additional results)

	All subjects	Non-POAG/ Non-OHT	OHT	Suspect POAG	POAG	P value (Kruskal-Wallis or ANOVA)
N (%)	505 (100)	430 (85.1)	17 (3.4)	32 (6.4)	26 (5.1)	----------
RNFL						
Overall mean (µm)	89.0 ±11.4	90.5 ±10.1	92.4 ±9.6	83.8 ±12.4	69.8 ±11.8	<0.028[bc]
Superior hemifield (µm)	90.7 ±12.0	92.0 ±11.1	93.9 ±9.3	86.0 ±11.9	72.9 ±13.5	<0.049[bc]
Inferior hemifield (µm)	86.3 ±11.8	87.8 ±10.3	89.7 ±11.0	81.1 ±13.5	66.0 ±13.1	<0.001[c]
Temporal quadrant (µm)	65.6 ±10.0	66.2 ±9.4	68.3 ±10.2	62.7 ±11.6	57.6 ±12.8	0.007[c]
Superior quadrant (µm)	106.7 ±16.3	108.5 ±15.0	109.2 ±14.2	100.8 ±15.4	81.5 ±17.3	<0.036[bc]
Nasal quadrant (µm)	68.5 ±11.2	69.2 ±11.0	71.2 ±6.7	66.2 ±11.2	58.0 ±11.5	<0.001[c]
Inferior quadrant (µm)	109.2 ±16.9	111.4 ±14.5	114.5 ±17.6	101.7 ±18.2	77.4 ±18.0	<0.024[bc]
Area cup to disc ratio	0.38 ±0.18	0.35 ±0.16	0.39 ±0.14	0.50 ±0.16	0.64 ±0.18	<0.001[bc]
Vertical cup to disc ratio	0.57 ±0.19	0.55 ±0.19	0.59 ±0.16	0.70 ±0.14	0.80 ±0.18	<0.001[bc]
GCC						
Overall mean (µm)	90.1 ±9.7	91.4 ±8.7	90.5 ±7.4	85.8 ±10.3	75.5 ±12.4	<0.016[bc]
Superior hemifield (µm)	89.7 ±9.5	90.8 ±8.8	89.8 ±7.6	85.1 ±10.3	77.3 ±10.6	<0.008[bc]
Inferior hemifield (µm)	90.1 ±10.5	91.5 ±9.0	91.1 ±7.5	86.2 ±11.3	72.0 ±15.2	<0.001[c]
FLV %	2.5 ±3.6	2.1 ±3.1	1.5 ±1.5	3.1 ±3.9	8.6 ±6.0	<0.001[c]
GLV %	7.1 ±7.4	6.0 ±6.1	6.1 ±5.0	9.9 ±8.8	20.8 ±11.1	<0.04[bc]

Data are expressed as the mean ±SD
Comparisons between diagnostic groups were significantly different (p<0.05): [a], between non-glaucoma/ non-OHT and OHT, [b], between non-glaucoma/ non-OHT and suspect glaucoma, [c], between non-glaucoma/ non-OHT and glaucoma

Table i: Summary data of RNFL and GCC thickness using the iVue SD-OCT for each of the four participant groups

	All subjects	Non-POAG/ Non-OHT	OHT	Suspect POAG	POAG	P value (Kruskal-Wallis or ANOVA)
N (%)	505 (100)	430 (85.1)	17 (3.4)	32 (6.4)	26 (5.1)	
Goldmann applanation tonometry	14.8 ±3.3	14.4 ±2.6	21.9 ±2.7	14.5 ±3.6	17.5 ±5.9	<0.001[a]
ORA IOPg (Goldmann-corrected)	16.5 ±4.1	16.1 ±3.5	24.9 ±3.7	15.8±4.6	18.4 ±6.3	<0.001[a]
ORA IOPcc (cornea-corrected)	17.3 ±4.1	16.8 ±3.4	24.4 ± 4.1	17.3 ±4.8	20.2 ±6.5	<0.038[ac]
ORA CRF	9.8 ±1.7	9.8 ±1.7	12.0± 1.6	9.2 ±1.7	8.8±1.4	<0.01[ac]
ORA CH	9.7 ±1.6	9.8 ±1.5	10.0 ±1.5	9.3 ±1.8	8.2±1.3	<0.001[c]

Data are expressed as the mean ±SD of worse eye data
Comparisons between diagnostic groups were significantly different (p<0.05): [a], between non-glaucoma/ non-OHT and OHT, [b], between non-glaucoma/ non-OHT and suspect glaucoma, [c], between non-glaucoma/ non-OHT and glaucoma

Table ii: Summary ORA data for each of the 4 participant groups

	FDT protocol	Sensitivity (%)	Specificity (%)	Positive likelihood ratio	Negative likelihood ratio
POAG (moderate + advanced)	1 point missed any level 1 point missed at 1% level	100.0 (79.6 to 100.0) 100.0 (79.6 to 100.0)	67.1 (62.5 to 71.4) 80.5 (76.4 to 84.0)	3.0 (2.6 to 3.5) 5.1 (4.2 to 6.21)	--- ---
POAG + suspect POAG combined	1 point missed any level 1 point missed 1% level	72.4 (59.8 to 82.3) 62.1 (49.2 to 73.4)	67.1 (62.5 to 71.4) 80.5 (76.4 to 84.0)	2.2 (1.8 to 2.7) 3.2 (2.41 to 4.2)	0.4 (0.3 to 0.6) 0.5 (0.3 to 0.7)

Table iii: Sensitivity, specificity and likelihood ratios for the FDT presented with 95% confidence intervals

	MDT protocol	Sensitivity (%)	Specificity (%)	Positive likelihood ratio	Negative likelihood ratio
POAG (moderate + advanced)	Global PTD ≥2.0 Global PTD ≥3.0	100.0 (78.5 to 100.0) 100.0 (78.5 to 100.0)	79.8 (75.7 to 83.3) 83.0 (79.2 to 86.3)	4.9 (4.1 to 6.0) 5.9 (4.8 to 7.3)	--- ---
POAG + suspect POAG combined	Global PTD ≥2.0 Global PTD ≥3.0	59.6 (46.7 to 71.4) 50.9 (38.3 to 63.4)	79.8 (75.7 to 83.3) 83.0 (79.2 to 86.3)	2.9 (2.2 to 3.9) 3.0 (2.2 to 4.2)	0.5 (0.4 to 0.7) 0.6 (0.5 to 0.8)

Table iv: Sensitivity, specificity and likelihood ratios for the MDT presented with 95% confidence intervals

	iVue OCT protocol	Sensitivity (%)	Specificity (%)	Positive likelihood ratio	Negative likelihood ratio
POAG (moderate + advanced)	Any GCC parameter	100.0 (79.6 to 100.0)	88.4 (85.0 to 91.1)	8.6 (6.6 to 11.3)	---
	GCC overall average	80.0 (54.8 to 92.9)	94.6 (92.0 to 96.4)	14.7 (9.2 to 23.6)	0.2 (0.1 to 0.6)
	GCC superior hemifield	73.3 (48.0 to 89.1)	95.0 (92.5 to 96.7)	14.8 (8.8 to 24.8)	0.3 (0.1 to 0.6)
	GCC inferior hemifield	93.3 (70.2 to 98.8)	94.3 (91.7 to 96.2)	16.5 (10.9 to 24.9)	0.1 (0.0 to 0.5)
	GCC FLV	100.0 (79.6 to 100.0)	91.0 (87.9 to 93.4)	11.2 (8.2 to 15.1)	---
	GCC GLV	60.0 (35.8 to 80.2)	98.1 (96.3 to 99.0)	31.8 (14.3 to 70.8)	0.4 (0.2 to 0.8)
	Any RNFL parameter	93.3 (70.2 to 98.8)	90.7 (87.5 to 93.1)	10.0 (7.2 to 13.8)	0.1 (0.0 to 0.5)
	RNFL overall average	93.3 (70.2 to 98.8)	96.0 (93.7 to 97.5)	23.5 (14.5 to 38.2)	0.1 (0.0 to 0.5)
	RNFL superior hemifield	80.0 (54.8 to 92.9)	95.1 (92.6 to 96.8)	16.3 (10.0 to 26.6)	0.2 (0.1 to 0.6)
	RNFL inferior hemifield	86.7 (62.1 to 96.3)	95.8 (93.4 to 97.3)	20.6 (12.6 to 33.8)	0.1 (0.0 to 0.5)
	RNFL temporal quadrant	46.7 (24.8 to 69.9)	98.1 (96.4 to 99.0)	25.0 (10.4 to 59.8)	0.5 (0.3 to 0.9)
	RNFL superior quadrant	86.7 (62.1 to 96.3)	95.8 (93.4 to 97.3)	20.6 (12.6 to 33.8)	0.1 (0.0 to 0.5)
	RNFL nasal quadrant	33.3 (15.2 to 58.3)	97.7 (95.7 to 98.7)	14.3 (5.6 to 36.6)	0.7 (0.5 to 1.0)
	RNFL inferior quadrant	93.3 (70.2 to 98.8)	96.3 (94.0 to 97.7)	21.0(15.1 to 41.1)	0.1 (0.0 to 0.5)
	Area cup to disc ratio	66.7 (41.7 to 84.8)	97.2 (95.2 to 98.4)	23.8 (12.3 to 46.1)	0.3 (0.2 to 0.7)
	Vertical cup to disc ratio	80.0 (54.8 to 92.9)	96.0 (93.7 to 97.5)	20.1 (11.8 to 34.2)	0.2 (0.1 to 0.6)
	Any GCC (5) or RNFL (7) parameters	100.0 (79.6 to 100.0)	82.7 (78.8 to 86.0)	5.8 (4.7 to 7.1)	---

POAG + suspect POAG combined	Any GCC parameter	50.0 (37.5 to 62.5)	88.4 (85.0 to 91.1)	4.3 (3.0 to 6.2)	0.6 (0.4 to 0.7)
	GCC overall average	41.4 (29.6 to 54.2)	94.6 (92.0 to 96.4)	7.6 (4.6 to 12.6)	0.6 (0.5 to 0.8)
	GCC superior hemifield	29.3 (19.2 to 42.0)	95.0 (92.5 to 96.7)	5.9 (3.3 to 10.5)	0.7 (0.6 to 0.9)
	GCC inferior hemifield	43.1 (31.2 to 55.9)	94.3 (91.7 to 96.2)	7.6 (4.7 to 12.4)	0.6 (0.5 to 0.8)
	GCC FLV	44.8 (32.7 to 57.5)	91.0 (87.9 to 93.4)	5.0 (3.3 to 7.6)	0.6 (0.5 to 0.8)
	GCC GLV	22.4 (13.6 to 34.7)	98.1 (96.3 to 99.0)	11.9 (5.1 to 27.4)	0.8 (0.7 to 0.9)
	Any RNFL parameter	62.1 (49.2 to 73.4)	90.7 (87.5 to 93.1)	6.6 (4.6 to 9.5)	0.4 (0.3 to 0.6)
	RNFL overall average	44.8 (32.7 to 57.5)	96.0 (93.7 to 97.5)	11.3 (6.5 to 19.5)	0.6 (0.5 to 0.7)
	RNFL superior hemifield	39.7 (28.1 to 52.5)	95.1 (92.6 to 96.8)	8.1 (4.8 to 13.6)	0.6 (0.5 to 0.8)
	RNFL inferior hemifield	43.1 (31.2 to 55.9)	95.8 (93.4 to 97.3)	10.2 (6.0 to 17.6)	0.6 (0.5 to 0.7)
	RNFL temporal quadrant	20.7 (12.2 to 32.8)	98.1 (96.4 to 99.0)	11.1 (4.7 to 25.9)	0.8 (0.7 to 0.9)
	RNFL superior quadrant	36.2 (25.0 to 49.1)	95.8 (93.4 to 97.3)	8.6 (4.9 to 15.2)	0.7 (0.5 to 0.8)
	RNFL nasal quadrant	10.3 (4.8 to 20.8)	97.7 (95.7 to 98.7)	4.4 (1.7 to 11.7)	0.9 (0.8 to 1.0)
	RNFL inferior quadrant	46.6 (34.3 to 59.2)	96.3 (94.0 to 97.7)	12.4 (7.1 to 21.7)	0.6 (0.4 to 0.7)
	Area cup to disc ratio	29.3 (19.2 to 42.0)	97.2 (95.2 to 98.4)	10.4 (5.3 to 20.8)	0.7 (0.6 to 0.9)
	Vertical cup to disc ratio	36.2 (25.0 to 49.1)	96.0 (93.7 to 97.5)	9.1 (5.1 to 16.2)	0.7 (0.5 to 0.8)
	Any GCC (5) or RNFL (7) parameters	67.2 (54.4 to 77.9)	82.7 (78.8 to 86.0)	3.9 (2.9 to 5.1)	0.4 (0.3 to 0.6)

Table v: Sensitivity, specificity and likelihood ratios for the iVue OCT (P<1%) presented with 95% confidence intervals

	ORA protocol	Sensitivity (%)	Specificity (%)	Positive likelihood ratio	Negative likelihood ratio
POAG (all subjects)	CRF <9.0 CH<9.1	65.4 (46.2 to 80.6) 76.9 (57.9 to 89.0)	67.2 (62.6 to 71.5) 68.6 (64.1 to 72.8)	2.0 (1.5 to 2.7) 2.6 (2.0 to 3.2)	0.5 (0.3 to 0.9) 0.3 (0.2 to 0.7)
POAG (moderate + advanced)	CRF <9.0 CH<9.1	66.7 (41.7 to 84.8) 86.7 (62.1 to 96.3)	67.2 (62.6 to 71.5) 68.6 (64.1 to 72.8)	2.0 (1.4 to 3.0) 2.8 (2.2 to 3.5)	0.5 (0.2 to 1.0) 0.2 (0.1 to 0.7)
POAG + suspect POAG combined	CRF <9.0 CH<9.1	53.4 (40.8 to 65.7) 62.1 (49.2 to 73.4)	67.2 (62.6 to 71.5) 68.6 (64.1 to 72.8)	1.6 (1.2 to 2.1) 1.9 (1.5 to 2.3)	0.7 (0.5 to 0.9) 0.6 (0.4 to 0.8)

Table vi: Sensitivity, specificity and likelihood ratios for the ORA presented with 95% confidence intervals

	FDT protocol	Specificity following removal of co-morbidity (%)	Specificity without removal of co-morbidity (%)
POAG (all subjects)	FDT 1 point missed any level	75.1 (70.4 to 79.3)	67.1 (62.5 to 71.4)
	FDT 1 point missed 1% level	88.0 (84.2 to 91.0)	80.5 (76.4 to 84.0)
	MDT global PTD ≥3.0	90.3 (86.8 to 92.9)	83.0 (79.2 to 82.3)
	Any GCC parameter	91.3 (88.0 to 93.8)	88.4 (85.0 to 91.1)
	GCC inferior hemifield	96.4 (94.0 to 97.9)	94.3 (91.7 to 96.2)
	GCC GLV	99.4 (98.0 to 99.8)	98.1 (96.3 to 99.0)
	Any RNFL parameter	92.0 (88.7 to 94.3)	90.7 (87.5 to 93.1)
	RNFL inferior quadrant	97.8 (95.7 to 98.9)	96.3 (94.0 to 97.7)

Table vii: Repeat specificity analysis with 95% confidence intervals following removal of co-morbid conditions likely to influence structure-function results

				Structural Parameters			
				GCC-GLV (P<1%)		RNFL Inferior quadrant (P<1%)	
Functional Parameters				Sensitivity % (CI)	Specificity % (CI)	Sensitivity % (CI)	Specificity % (CI)
		Sensitivity % (CI)	Specificity % (CI)	42.3 (25.5 to 61.0)	98.1 (96.3 to 99.0)	76.9 (57.9 to 89.0)	96.3 (94.0 to 97.7)
OR	**FDT** (1 or more point missed at any level)	92.3 (75.9 to 97.9)	67.1 (62.9 to 71.4)	96.2 (81.1 to 99.3)	67.1 (62.4 to 71.4)	100.0 (87.1 to 100)	65.7 (61.1 to 70.1)
AND	**FDT** (1 or more point missed at any level)	92.3 (75.9 to 97.9)	67.1 (62.5 to 71.4)	42.3 (25.5 to 61.1)	98.6 (96.9 to 99.3)	69.2 (50.0 to 83.5)	97.6 (95.7 to 98.7)
OR	**MMDT** (Global PTD ≥3.0)	64.0 (44.5 to 79.8)	83.0 (79.2 to 86.3)	72.0 (52.4 to 85.7)	83.0 (79.1 to 86.3)	80.0 (60.9 to 91.1)	81.3 (77.3 to 84.7)
AND	**MMDT** (Global PTD ≥3.0)	64.0 (44.5 to 79.8)	83.0 (79.2 to 86.3)	40.0 (23.4 to 59.3)	98.6 (97.0 to 99.3)	60.0 (40.7 to 76.6)	98.4 (96.7 to 99.2)

Table viii: Summary of combined analysis of index tests using a) FDT, b) MMDT, c) iVue SD-OCT parameters (GCC GLV and Inferior quadrant RNFL thickness) for detection of POAG

User acceptability survey: Performance of advanced technologies to improve case-detection of primary open angle glaucoma (POAG)

CITY UNIVERSITY LONDON

Screening Study of Equipment and its Impact in Eye Care

Questionnaire of User Acceptability of Screening Tests

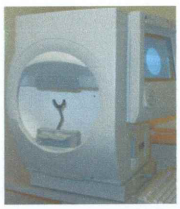
Date of Examination: ..... Subject ID: SEC .....

Unless otherwise stated, please fill one circle for each question using black or blue ink

For Questions 1 – 5, please indicate whether you agree or disagree with the statements relating to your views on the screening tests carried out on you today, using the seven-point scale provided.

	Disagree						Agree
EXAMPLE: The screening test was uncomfortable	O	●	O	O	O	O	O

Question 1 **Humphrey visual fields (Location: small room on Level 4)** – responding to white flashes on a screen

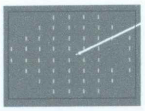


	Disagree						Agree
The screening test was uncomfortable	O	O	O	O	O	O	O
The test was too long	O	O	O	O	O	O	O
The test was difficult to undertake	O	O	O	O	O	O	O

Yellow-orange fixation light

Question 2 **MMDT (Location: larger room on Level 6)** – responding to moving white lines

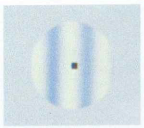
	Disagree						Agree
The screening test was uncomfortable	O	O	O	O	O	O	O
The test was too long	O	O	O	O	O	O	O
The test was difficult to undertake	O	O	O	O	O	O	O



White fixation spot

Question 3 **FDT (Location: larger room on Level 6)** – responding to flickering white and black bars

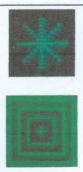
	Disagree						Agree
The screening test was uncomfortable	O	O	O	O	O	O	O
The test was too long	O	O	O	O	O	O	O
The test was difficult to undertake	O	O	O	O	O	O	O



Black fixation square

Question 4 **iVue OCT (Location: larger room on Level 6)** – instrument captures images of the back of your eye

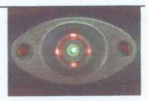
	Disagree						Agree
The screening test was uncomfortable	O	O	O	O	O	O	O
The test was too long	O	O	O	O	O	O	O
The test was difficult to undertake	O	O	O	O	O	O	O



Green star or cross target

Question 5 **ORA (Location: larger room on Level 6)** – 'puff of air' in the eye to measure your eye pressure

	Disagree						Agree
The screening test was uncomfortable	O	O	O	O	O	O	O
The test was too long	O	O	O	O	O	O	O
The test was difficult to undertake	O	O	O	O	O	O	O



Target of green spot within four red lights

Question 6 **How would you describe your ethnicity?** *Your answer to this question will help us to analyse the results of the tests that you have undertaken today*

O	White (British or other background)	O	Black (Caribbean, African, Other background)
O	Mixed (White and Black Caribbean/ White and Black African/ White and Asian/ Other Mixed	O	Chinese
O	Asian (Indian, Pakistani, Bangladeshi, Other background)	O	Other Asian Ethnic group

Question 7 **If you have any further comments on the acceptability of tests undertaken today, or on any other aspect of the study, please write them in the box below:**

Appendix C: Non-contact screening methods for the detection of narrow anterior chamber angles (additional results)

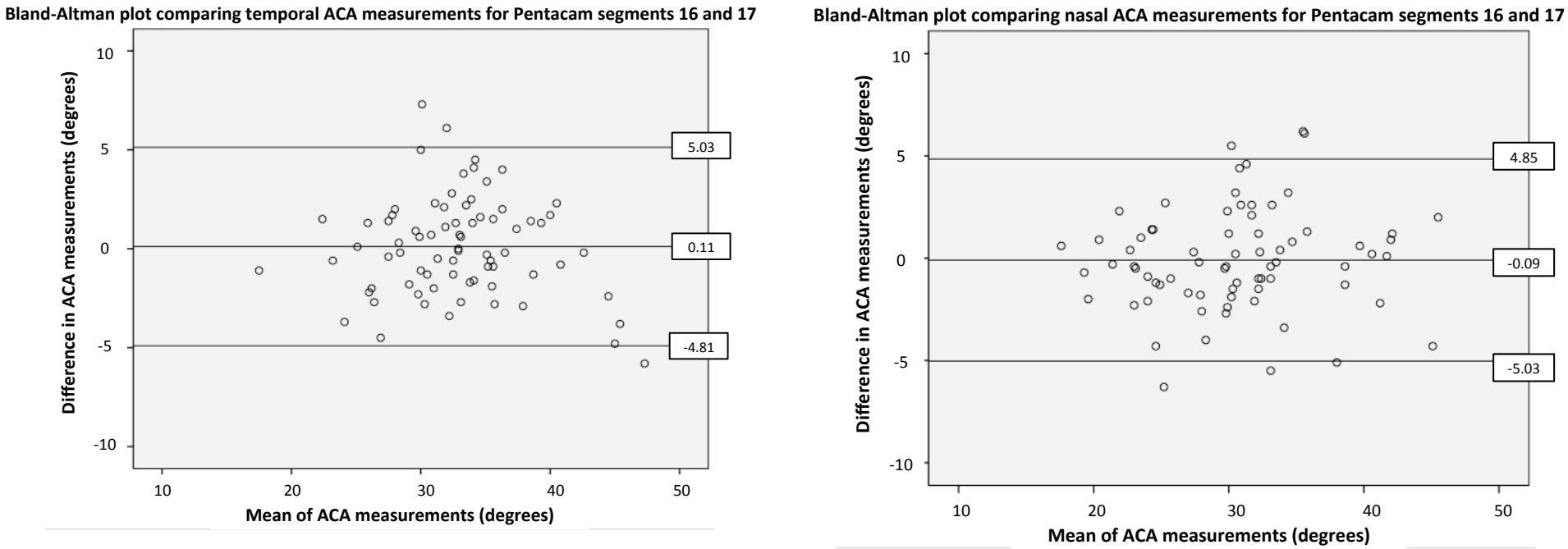


Figure i: Bland-Altman plots to compare temporal and nasal ACA measurements captured by segments 16 and 17 using Pentacam imaging

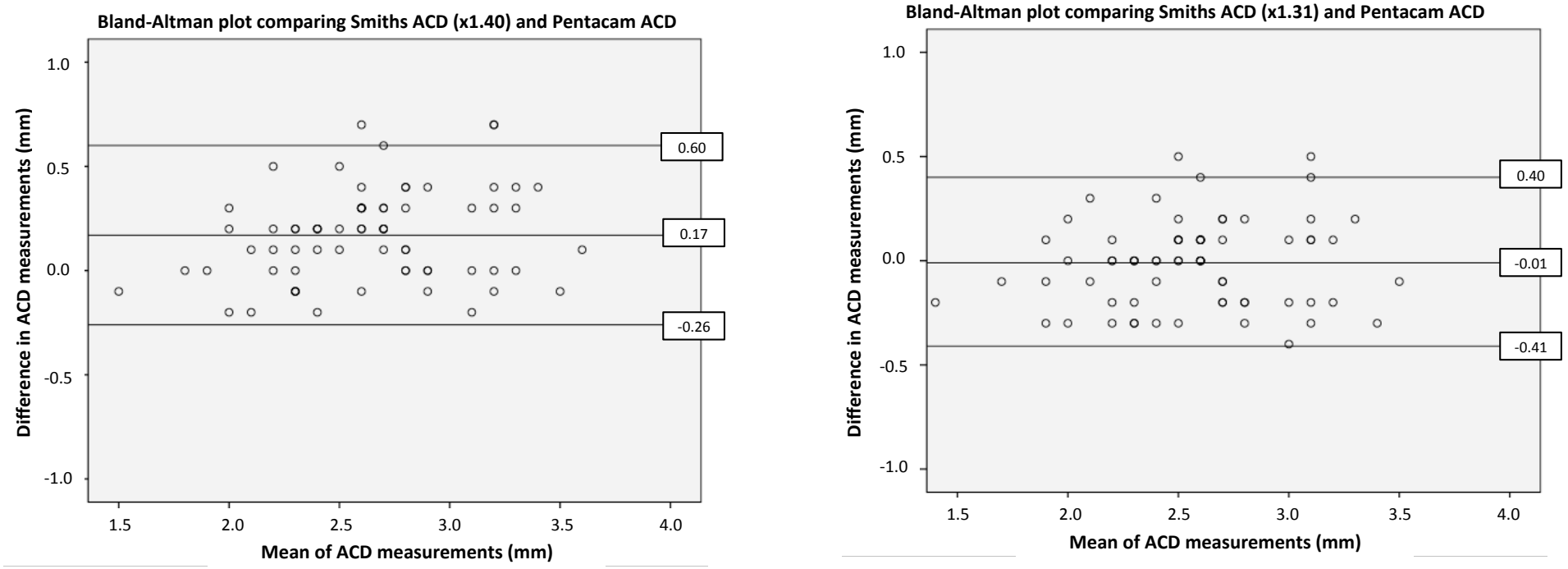
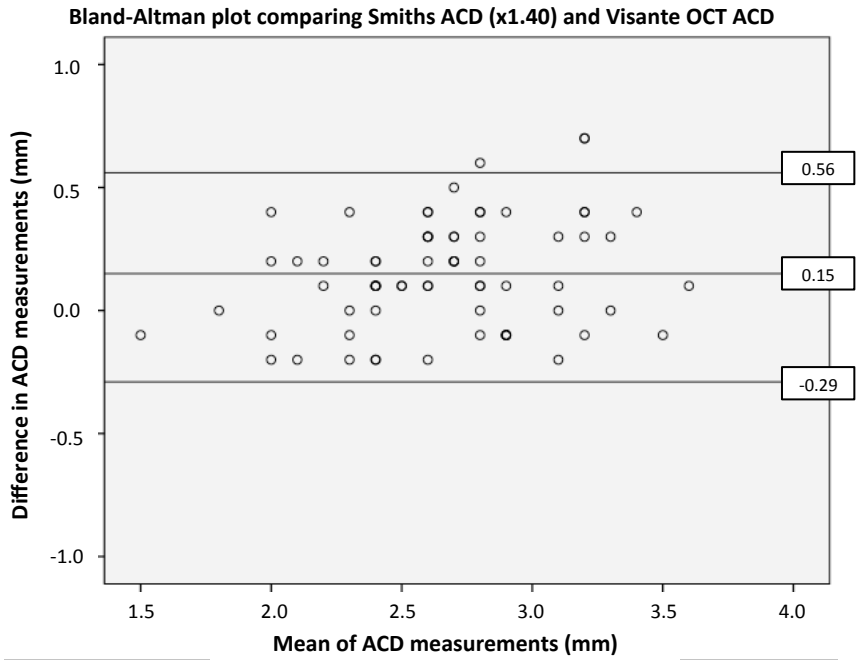


Figure ii: Bland-Altman plots to compare ACD measurements using Smith's test and imaging systems (Pentacam and Visante OCT) to identify the appropriate choice of multiplication factor to correct slit-height raw data



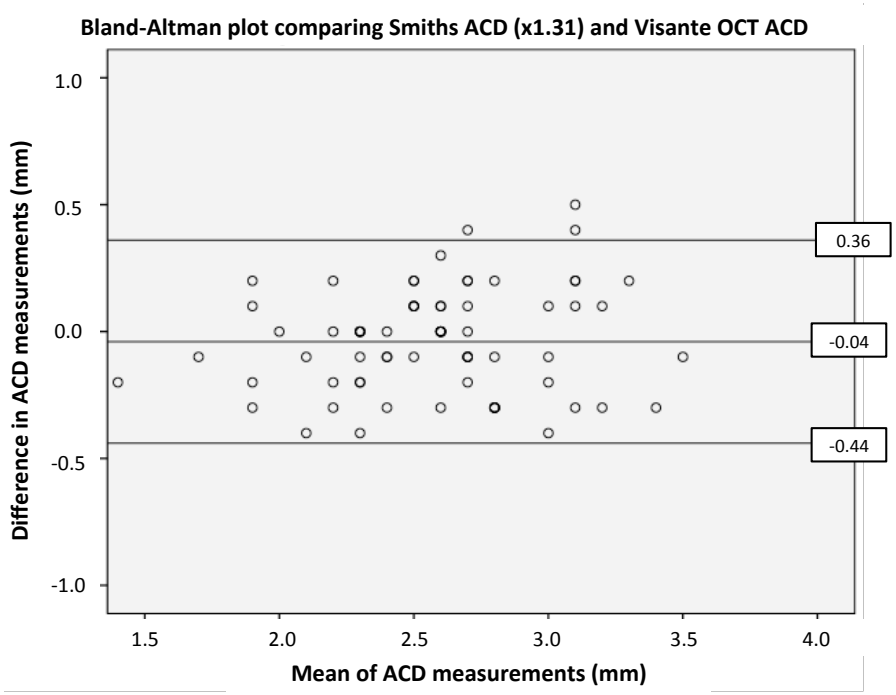


Figure ii (continued): Bland-Altman plots to compare ACD measurements using Smith's test and imaging systems (Pentacam and Visante OCT) to identify the appropriate choice of multiplication factor to correct slit-height raw data

Index test	Right eye following repeat measurement	Left eye following repeat measurement	Right eye following initial measurement	Left eye following initial measurement	Time taken to capture R+L data^
	N=70 (%)	N=75 (%)	N=70 (%)	N=75 (%)	Min/ Sec
Van Herick test	70 (100.0)	75 (100.0)	---	---	1.28±0.44
Smith's test*	70 (100.0)	75 (100.0)	---	---	3.75±0.83
Pentacam **Temporal ACA** **Nasal ACA** **ACV** **ACD**	 66 (94.3) 65 (92.9) 69 (98.6) 69 (98.6)	 67 (89.3) 66 (88.0) 72 (96.0) 72 (96.0)	 65 (92.9) 63 (90.0) 68 (97.1) 68 (97.1)	 66 (88.0) 66 (88.0) 72 (96.0) 72 (96.0)	5.11±1.38
Visante OCT **Temporal ACA** **Nasal ACA** **ACD**	 68 (97.1) 69 (98.6) 70 (100.0)	 73 (97.3) 73 (97.3) 75 (100.0)	 63 (90.0) 68 (97.1) 70 (100.0)	 70 (93.3) 69 (92.0) 75 (100.0)	4.29±0.74
Gonioscopy	78 (100)	78 (100)	---	---	4.48±1.62

** Measurement not possible on pseudophakic eyes (R N=8, L N=3)*
^Mean ±SD (Range). Data for time taken to capture data for both eyes using Smith's test excludes data from pseudophakic eyes

Table i: Proportion of suitable quality measurements obtained using index tests and the time taken to capture data of both eyes

	ISGEO classification		Clinical opinion	
	Sensitivity at 90% specificity (CI)	**Sensitivity at 95% specificity (CI)**	**Sensitivity at 90% specificity (CI)**	**Sensitivity at 95% specificity (CI)**
VH	76.1 (45.2 to 88.1)	52.4 (40.5 to 85.7)	58.8 (17.6 to 94.1)	35.3 (17.6 to 76.5)
Smith's	39.9 (19.0 to 73.8)	31.0 (9.5 to 57.1)	41.2 (5.9 to 70.6)	21.7 (5.9 to 52.9)
Pentacam				
ACA	54.3 (9.5 to 83.3)	26.7 (7.1 to 76.2)	47.1 (17.6 to 70.6)	23.5 (5.9 to 58.8)
ACV	40.5 (28.6 to 86.9)	40.5 (26.2 to 71.4)	35.3 (11.8 to 64.7)	29.4 (5.9 to 58.8)
ACD	61.9 (31.0 to 76.2)	42.9 (11.9 to 69.0)	58.8 (29.4 to 82.4)	35.3 (23.5 to 76.5)
Visante				
ACA	66.7 (42.9 to 95.2)	50.0 (35.7 to 85.7)	52.9 (5.9 to 76.5)	37.9 (13.5 to 64.7)
ACD	64.3 (38.1 to 86.9)	47.6 (31.0 to 78.6)	58.8 (35.3 to 82.4)	41.1 (17.6 to 76.5)

Tables ii: Sensitivity at 90% and 95% specificity for each index test parameter using the two gonioscopic classifications for a narrow angle using the subjects as the unit of analysis

	ISGEO classification		Clinical opinion	
	Partial AUROC from 90% specificity (CI)	**Partial AUROC from 95% specificity (CI)**	**Partial AUROC from 90% specificity (CI)**	**Partial AUROC from 95% specificity (CI)**
VH	0.52 (0.43 to 0.81)	0.42 (0.40 to 0.81)	0.33 (0.11 to 0.68)	0.23 (0.0 to 0.59)
Smith's	0.30 (0.13 to 0.55)	0.23 (0.10 to 0.50)	0.17 (0.02 to 0.47)	0.06 (0.0 to 0.35)
Pentacam				
ACA	0.33 (0.09 to 0.67)	0.25 (0.07 to 0.62)	0.29 (0.09 to 0.55)	0.20 (0.0 to 0.49)
ACV	0.40 (0.29 to 0.66)	0.40 (0.26 to 0.60)	0.26 (0.08 to 0.52)	0.17 (0.0 to 0.45)
ACD	0.40 (0.18 to 0.67)	0.29 (0.12 to 0.63)	0.38 (0.12 to 0.68)	0.21 (0.0 to 0.63)
Visante				
ACA	0.56 (0.39 to 0.82)	0.49 (0.34 to 0.77)	0.39 (0.00 to 0.51)	0.16 (0.0 to 0.42)
ACD	0.50 (0.33 to 0.75)	0.43 (0.30 to 0.69)	0.40 (0.13 to 0.71)	0.23 (0.0 to 0.65)

Table iii: Partial area under the ROC curve (PAUROC) data for ranges starting at 90% and 95% specificity for each index test parameter using the two gonioscopic classifications for a narrow angle using the subjects as the unit of analysis

				Van Herick			
				≤25% temporal or nasal		≤15% temporal or nasal	
				Sensitivity % (CI)	Specificity % (CI)	Sensitivity % (CI)	Specificity % (CI)
		Sensitivity % (CI)	Specificity % (CI)	79.5 (64.5 to 89.2)	92.3 (79.7 to 97.3)	51.3 (36.2 to 66.1)	97.4 (86.8 to 99.5)
OR	**Smiths** ACD≤2.60mm	71.8 (56.2 to 83.5)	71.8 (56.2 to 83.5)	92.3 (79.7 to 97.3)	69.2 (53.6 to 81.4)	84.6 (70.3 to 92.8)	71.8 (56.2 to 83.5)
AND	**Smiths** ACD≤2.60mm	71.8 (56.2 to 83.5)	71.8 (56.2 to 83.5)	59 (43.4 to 72.9)	94.9 (83.1 to 98.6)	38.5 (24.9 to 54.1)	97.4 (86.8 to 99.5)
OR	**Visante OCT** ACA ≤20.7°	87.2 (72.6 to 95.7)	86.8 (71.9 to 95.6)	94.9 (83.1 to 98.6)	78.9 (63.7 to 88.9)	92.3 (79.7 to 97.3)	84.2 (69.6 to 92.6)
AND	**Visante OCT** ACA ≤20.7°	87.2 (72.6 to 95.7)	86.8 (71.9 to 95.6)	74.4 (58.9 to 85.4)	97.4 (86.5 to 99.5)	48.7 (33.9 to 63.8)	97.4 (86.5 to 99.5)

Table iv: Summary of combined analysis using a) van Herick and Smiths test, and b) van Herick and Visante OCT ACA (based on gonioscopic classification of the ISGEO)

User acceptability survey: Non-contact screening methods for the detection of narrow anterior chamber angles

Moorfields Eye Hospital NHS
NHS Foundation Trust

Date of Examination: ..... Subject ID: .....

Unless otherwise stated, please fill one circle for each question using black or blue ink

For Questions 1 – 5, please indicate whether you agree or disagree with the statements relating to your views on the screening tests carried out on you today, using the seven-point scale provided.

	Disagree						Agree
EXAMPLE: The screening test was comfortable	O	●	O	O	O	O	O

Question 1 **Van Herick's test** – red star on the wall

	Disagree						Agree
The screening test was comfortable	O	O	O	O	O	O	O
The test was quick	O	O	O	O	O	O	O

Question 2 **Smith's test** – green star on the wall

	Disagree						Agree
The screening test was comfortable	O	O	O	O	O	O	O
The test was quick	O	O	O	O	O	O	O

Question 3 **Pentacam** – Blue internal light

	Disagree						Agree
The screening test was comfortable	O	O	O	O	O	O	O
The test was quick	O	O	O	O	O	O	O

Question 4 **Visante OCT –** Yellow internal 'starburst' light

	Disagree						Agree
The screening test was comfortable	O	O	O	O	O	O	O
The test was quick	O	O	O	O	O	O	O

Question 5 **Gonioscopy –** 'jelly' on the surface of the eye for approximately one minute or longer **(performed by Mr Ian Murdoch after instillation of a drop in each eye)**

	Disagree						Agree
The screening test was comfortable	O	O	O	O	O	O	O
The test was quick	O	O	O	O	O	O	O

Question 6 **Please list any medications you are currently taking in the box below:**

Question 7 **If you have any further comments on the acceptability of tests undertaken today, or on any other aspect of the study, please write them in the box below:**

2

Publications and Conference Presentations

Conference presentations: Published abstracts

Lawrenson JG, Edgar DF, Fidalgo B, Garway-Heath DF, Dabasia PL. Performance of advanced technologies for community-based glaucoma case-finding. Presentation: European Association for Vision and Eye Research, 2014 (Nice)

Dabasia PL, Edgar DF, Fidalgo B, Garway-Heath DF, Lawrenson JG. Community-based case-finding for primary open angle glaucoma using advanced technologies. Presentation: British Congress of Optometry and Vision Science, 2014 (Cardiff)

Dabasia PL, Edgar DF, Lawrenson JG. A cross-sectional survey of current and anticipated future use of standard and specialist equipment by UK optometrists. Poster presented at: The College of Optometrists, 2014 Research symposium; Optometry Tomorrow (York)

Dabasia PL, Edgar DF, Fidalgo B, Garway-Heath DF, Lawrenson JG. Performance of community-based glaucoma screening using advanced technologies. Presentation: City University, Annual Doctoral Research Conference, 2014 (London)

Dabasia PL, Edgar DF, Fidalgo B, Garway-Heath DF, Lawrenson JG. Performance of community-based glaucoma screening using advanced technologies. Poster presented at: The College of Optometrists, 2014 Research symposium; Optometry Tomorrow (York)

Dabasia PL, Edgar DF, Murdoch I, Lawrenson JG. An evaluation of non-contact screening methods for measuring anterior chamber depth using Pentacam imaging, and the IOL-Master. Presentation: European Academy of Optometry and Optics 2013 (Malaga)

Dabasia PL, Edgar DF, Lawrenson JG. A cross-sectional survey of current and anticipated future use of standard and specialist equipment by UK optometrists. Poster presented at: European Academy of Optometry and Optics 2013 (Malaga)

Dabasia PL, Edgar DF, Fidalgo B, Crabb D, Garway-Heath DF, Lawrenson JG. The effects of spectacle correction of refractive error on results from the Moorfields Motion Displacement Test (MMDT) Enhanced suprathreshold algorithm (ESTA). Poster presented at: City University, Annual Doctoral Research Conference, 2013 (London)

Other Presentations

Dabasia PL, Edgar DF, Fidalgo B, Garway-Heath DF, Lawrenson JG. Performance of community-based glaucoma screening using advanced technologies: City University, Moorfields Eye Hospital, Research seminar (Garway-Heath DF), Feb 2014 (London)

Dabasia PL, Edgar DF, Fidalgo B, Garway-Heath DF, Lawrenson JG. Screening study of equipment and its impact on eye care, an update: City University, Moorfields Eye Hospital, Research seminar (Garway-Heath DF), Nov 2012 (London)

Dabasia PL, Edgar DF, Garway-Heath DF, Lawrenson JG. Equipment and its impact on eye care. Presentation: City University, Moorfields Eye Hospital, Research seminar (Garway-Heath DF), Mar 2012 (London)

Published Papers

Dabasia PL, Edgar DF, Garway-Heath DF, Lawrenson JG. A survey of current and anticipated use of standard and specialist equipment by UK optometrists. Ophthalmic Physiol Opt. 2014;34(5): 592-613

Dabasia PL, Edgar DF, Lawrenson JG. Methods of measurement of the anterior chamber angle Part 3. Optom Pract. 2014;15(1):11-18

Dabasia PL, Edgar DF, Lawrenson JG. Methods of measurement of the anterior chamber angle Part 2. Optom Pract. 2013;14(4):147-154

Dabasia PL, Edgar DF, Lawrenson JG. Methods of measurement of the anterior chamber angle Part 1: Angle closure glaucoma and gonioscopy. Optom Pract. 2013;14(3):107-114